Foldamer Structures

$\beta^{2,3}$-Cyclic Aminoxy Acids: Rigid and Ring-Size-Independent Building Blocks of Foldamers**

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The exploration of foldamers having rigid conformations is an area of intensive research.[1] Recently, the research groups led by Seebach and Gellman discovered independently that peptides of β-amino acids can fold into defined secondary structures.[2] One special series of β-peptides, comprising cyclic ring-constrained β-amino acids, which were developed by Gellman and co-workers, form significantly stable helical structures in the solid state, in organic solvents,[3] and even in aqueous solution.[4] Increasing the number of cyclic ring-constrained residues can enhance the helical content of such β-peptides;[5] this approach has become an important and powerful tool for structure–activity studies of the peptides.[5b] Gellman et al. also found that the size of the side-chain rings in the β-peptides has significant impact on the secondary structures. The β-peptides of cyclohexane-containing amino acids prefer to form 14-helix structures, while those of cyclopentane-containing amino acids favor a very different helix, the 12-helix; these conformations result from the different torsional preferences of the C_α–C_β bonds in the cyclic rings of the individual residues.[3b,6] To investigate whether this "ring-size effect" also plays an important role in determining the conformations of our aminoxy peptides, which represent another class of foldamers,[7] we have explored, and report herein, the potential of $\beta^{2,3}$-cyclic aminoxy acids, a subclass of β-aminoxy acids in which the α- and β-carbon atoms are part of an aliphatic ring (either a cyclopentane and cyclohexane unit), to behave as new chiral building blocks for turns and helices.

Compounds **1** and **2**, which are derived from (*R,R*)-2-aminoxycyclopentanecarboxylic acid, and **3** and **4** derived from (*R,R*)-2-aminoxycyclohexanecarboxylic acid, were synthesized by following the standard methods of peptide coupling. Table 1 summarizes the chemical shifts of all the amide protons in ^{1}H NMR spectra (5 mM in $CDCl_3$ at room temperature). To confirm that intramolecular hydrogen bonds are formed, we also performed [D_6]DMSO titration studies and dilution studies with those four compounds; the chemical-shift changes of all the amide protons are presented in Table 2.

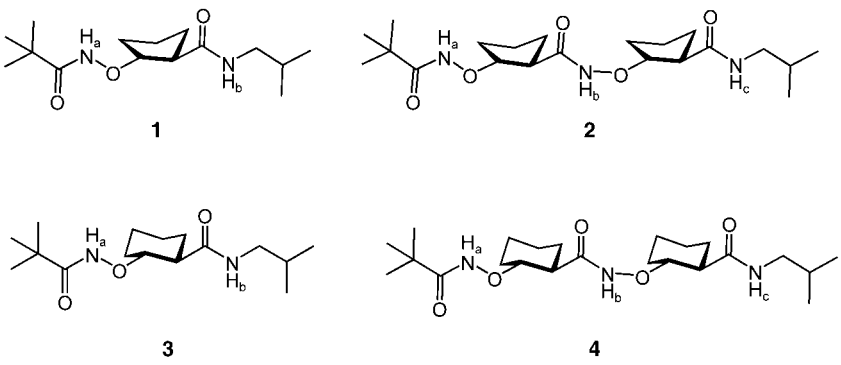

Table 1: ^{1}H NMR chemical shifts of the amide NH protons of **1**–**4** (5 mM in $CDCl_3$ at room temperature).[a,b]

Cmpd.	$\delta(NH_a)$ [ppm]	$\delta(NH_b)$ [ppm]	$\delta(NH_c)$ [ppm]
1	8.45 (s)	7.33 (t)	
2	8.48 (s)	10.99 (s)	7.61 (t)
3	8.44 (s)	7.54 (t)	
4	8.58 (s)	11.78 (s)	8.58 (t)

[a] Abbreviations: s, singlet; t, triplet. [b] There is little change for chemical shifts of the amide NH protons of **1**–**4** below 5 mM (see the Supporting Information).

Notably, the signals of the NH_b protons of **1**–**4** and the NH_c protons of **2** and **4** are unusually downfield (Table 1), and they undergo little change when solutions of **1**–**4** are titrated gradually with [D_6]DMSO or diluted from 200 mM to 1.56 mM

Table 2: Changes in the ^{1}H NMR chemical shifts of the amide NH protons of **1**–**4**.[a,b]

Cmpd.	$\Delta\delta(NH_a)$ [ppm]		$\Delta\delta(NH_b)$ [ppm]		$\Delta\delta(NH_c)$ [ppm]	
	[D_6]DMSO	Dil.	[D_6]DMSO	Dil.	[D_6]DMSO	Dil.
1	1.82	0.74	0.48	0.31		
2	2.01	1.43	0.31	0.30	0.14	0.23
3	1.68	0.68	1.01	0.33		
4	2.04	1.60	0.47	0.52	0.15	0.31

[a] Titration study: [D_6]DMSO (50 μL) was added gradually to a solution of the peptide (5 mM) in $CDCl_3$ (0.5 mL) at room temperature ($\Delta\delta_{titration} = \delta_{50\,\mu L\ DMSO} - \delta_{0\,\mu L\ DMSO}$). [b] Dilution study: solutions of the peptides in $CDCl_3$ were diluted from 200 mM to 1.56 mM at room temperature ($\Delta\delta_{dilution} = \delta_{200\,mM} - \delta_{1.56\,mM}$).

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[**] This work was supported by The University of Hong Kong, Hong Kong University of Science and Technology, Hong Kong Research Grants Council (HKU7098/01P and HKUST6083/02M), HKU-Fudan Joint Laboratory on Molecular Design and Synthesis, and the National Natural Science Foundation of China (project no. 20202001). D.Y. acknowledges the Bristol-Myers Squibb Foundation for an Unrestricted Grant in Synthetic Organic Chemistry.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/ange.200454140

(Table 2). In contrast, the chemical shifts of N-oxy amide protons NH_a of **1**–**4** are rather upfield (Table 1) and change dramatically upon dilution or addition of [D_6]DMSO (Table 2). These results suggest that the NH_b protons of **1**–**4** and the NH_c protons of **2** and **4** form intramolecular hydrogen bonds, but that the NH_a protons of **1**–**4** are not hydrogen-bonded and are solvent accessible. Similar conclusions were drawn from FT-IR spectroscopic studies (see the Supporting Information). This hydrogen-bonding pattern is very similar to that observed in $\beta^{2,2}$-aminoxy peptides and, hence, suggests the presence of a β N–O turn in each peptide, in other words, an intramolecular hydrogen bond between C=O_i and NH_{i+2} to form a nine-membered ring, which is stabilized by an extra hydrogen bond between NO_{i+1} and NH_{i+2} to form a six-membered ring.[8]

Interestingly, the values of the chemical shifts of the NH_c protons of dimers **2** and **4** are much higher than those of the NH_b protons of monomers **1** and **3** (Table 1). In addition, the chemical-shift changes of the NH_c protons of dimers **2** and **4** that are caused by dilution or addition of [D_6]DMSO are much smaller than those of the NH_b protons of monomers **1** and **3**. This observation suggests that hydrogen bonding is enhanced by increasing the number of N–O turns, that is, a cooperative effect exists.

Suitable crystals of **3** and **4** were obtained from $CHCl_3$/*n*-hexane solutions; their solid-state structures, obtained by X-ray crystallography, are presented in Figure 1.[8] Similar to the $\beta^{2,2}$-aminoxy peptides[9] compound **3** adopts a β N–O turn that is characterized by a nine-membered-ring hydrogen bond between the C=O_i and NH_{i+2} units (O···H distance = 2.20 Å) that is stabilized further by a six-membered-ring hydrogen bond between the NO_{i+1} and NH_{i+2} units (Figure 1a). The N–O bond is *anti* to the C_α–C_β bond with a dihedral angle $\sphericalangle NOC_\alpha C_\beta$ of 172°. Analogous to the 1.7_9-helix present in $\beta^{2,2}$-aminoxy peptides,[9] the solid-state structure of **4** (Figure 1b) indicates the presence of a well-defined 1.8_9-helix composed of two consecutive β N–O turns with a basic hydrogen-bonding pattern similar to that existing in **3**. In the first N–O turn, the O···H distance in the hydrogen bond between the C=O_i and NH_{i+2} units is 1.93 Å, which reflects the higher acidity of aminoxy amide protons relative to typical amide protons. In the second N–O turn, the O···H distance in the hydrogen bond between the C=O_{i+1} and NH_{i+3} units (2.07 Å) is shorter than that in **3** (2.20 Å); this observation further corroborates the existence of the cooperative effects suggested by the ^{1}H NMR study.

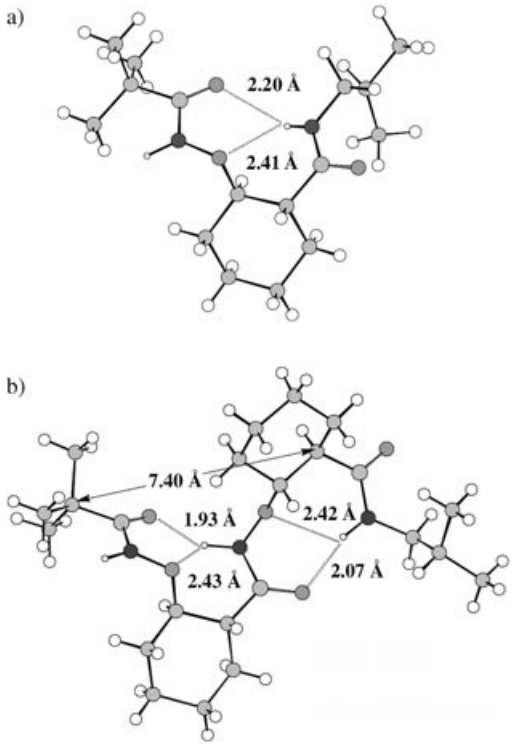

Figure 1. Pertinent hydrogen bonds present in the crystal structures of a) **3** and b) **4**.

Since suitable crystals of compounds **1** and **2** for X-ray analysis were not obtained, we utilized computational methods to calculate the most stable conformations of **5** and **6**,[10] which are model compounds for **1** and **3**, respectively (Figure 2). The calculated structure of **6** and the crystal structure of **3** are almost superimposable, which strongly supports the correlation between the computational simulation and solid-state structure. The β N–O turn structures are found in the most stable conformations of both **5** and **6**, with little changes in the φ and μ angles but significant changes in the ϕ and θ angles (Table 3). In order to maintain the intramolecular hydrogen bonds of the N–O turns, the tor-

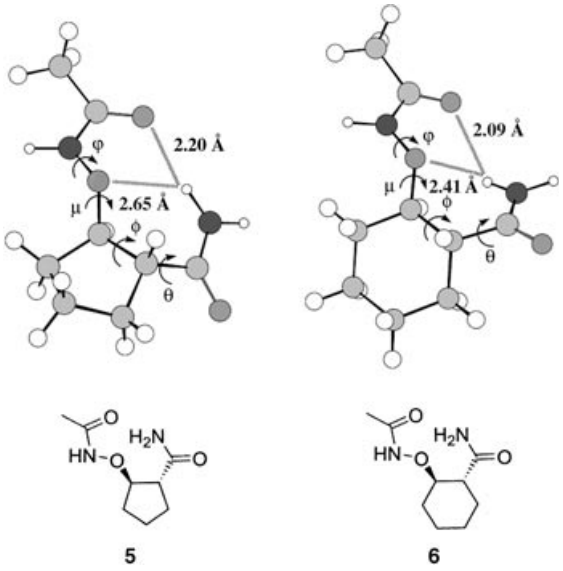

Figure 2. Pertinent hydrogen bonds present in the most stable conformations of **5** and **6**.

Table 3: Representative dihedral angles of the N–O turns of the most stable conformations of **5** and **6**.

Cmpd.	Dihedral angle [°]			
	φ	μ	ϕ	θ
5	−103.8	163.5	−101.0	51.8
6	−100.8	172.0	−59.6	−12.0

sional angle θ is adjusted accordingly to compensate for the changes in the torsional angle ϕ caused by the difference in ring size. As a result, the relative orientations of the two amide carbonyl groups ($C{=}O_i$ and $C{=}O_{i+1}$) are distinct in the most stable conformations of **5** and **6**. This difference is also reflected in the CD spectra of **1**–**4** (see the Supporting Information).

Figure 3 summarizes the observed nuclear Overhauser effects (NOEs) of compounds **1**–**4** obtained in 2D-NOESY experiments. All of the 2D NMR experiments were performed using 5 mM solutions in $CDCl_3$ at room temperature,

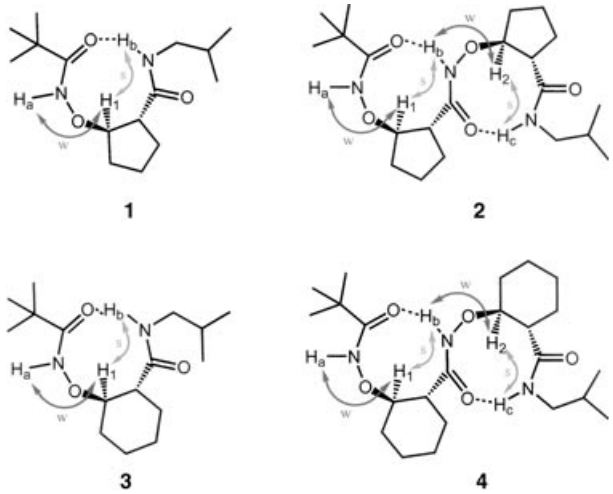

Figure 3. Summary of NOEs observed for compounds **1**–**3** (5 mM) and compound **4** (10 mM) in $CDCl_3$ at room temperature (s, strong NOE; w, weak NOE).

except for those for compound **4** (recorded at 10 mM to avoid overlap of the signals of the NH_a and NH_c protons). Compounds **1**–**4** exhibit very similar NOE patterns: weak NOEs exist between the NH_i and $C_\beta H_i$ protons, but strong NOEs exist between the NH_{i+1} and $C_\beta H_i$ protons. Moreover, these NOE patterns match well with the corresponding distances between protons of the N–O turns observed in the calculated structure of **5** and crystal structures of **3** and **4** (Table 4). This correlation suggests that, although the ring size of the side chain varies from five to six atoms, to a great extent compounds **1**–**4** adopt similar N–O turn structures in $CDCl_3$, in contrast to Gellman's β-peptides.

Our β-aminoxy peptides can be considered as analogues of γ-peptides in which the γ-carbon is replaced by an oxygen atom. In fact, nine-membered-ring hydrogen-bonded structures have been observed for several γ-peptides. Dado and Gellman studied a diamide of an unsubstituted γ-amino acid and found that a nine-membered-ring hydrogen-bonded conformation and a seven-membered-ring hydrogen-bonded conformation are in equilibrium in CH_2Cl_2 solution.[11] Seebach et al. observed a nine-membered-ring hydrogen-bonded structure for a $\gamma^{2,3,4}$-dipeptide in the solid state.[12] However, a $\gamma^{2,3,4}$-tetrapeptide was found to form a 2.6_{14}-helix (or 14-helix),[12] which is also observed in several other types of γ-peptides.[13] Theoretical calculations on α- and β-aminoxy acids have indicated that the N–O bond has a very strong conformational preference,[7,9b] which contributes to the fact that peptides formed by α- and β-aminoxy acids have a tendency to form hydrogen bonds between adjacent residues.[7,9] On the other hand, β- and γ-peptides have more flexible backbones and tend to form helical structures with hydrogen bonds involving more distant amino acid residues.[2,12,13]

In summary, peptides of $\beta^{2,3}$-cyclic aminoxy acids adopt rigid β N–O turns and 1.8_9-helix structures. These secondary structures exist independently of the ring size of the aliphatic side chains (either five or six atoms), unlike the case of the β-peptides having cyclically constrained backbones. The strong local conformational control exerted by the $\beta^{2,3}$-cyclic aminoxy acids provides a powerful tool that allows the preparation of short peptides having rigid and predictable conformations.

Table 4: Characteristic distances between the amide NH protons and β-protons of **5** in its most stable conformation as well as **3** and **4** in their crystal structures.

Cmpd.	H_a–H_1 [Å]	H_1–H_b [Å]	H_b–H_2 [Å]	H_2–H_c [Å]
5	3.27	2.50		
3	3.46	2.28		
4	3.15	2.35	3.02	2.14

Received: February 28, 2004
Revised: September 20, 2004 [Z54140]

Keywords: foldamers · helical structures · peptides · secondary structure · structure elucidation

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