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Disulfide Bond Creates a Small Connecting Loop in Aminoxy Peptide Backbone

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Abstract: Disulfide-bond formation between the side chains of cysteine–cysteine pairs is often critical to the folding behavior, stability, and functionality of proteins. In this paper, we report that sulfur atoms can be introduced into the amide groups of aminoxy peptides to form a novel type of disulfide bridge, which creates a connecting loop in the peptide backbone.

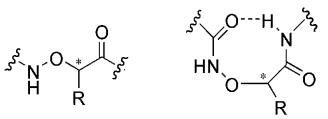
Keywords: aminoxy peptides · disulfide bonds · foldamers · loop motifs · peptides · protein folding

Introduction

Protein folding, which intimately reflects protein function, is a highly complex process controlled by a series of noncovalent (e.g., hydrogen bonds, and electrostatic and hydrophobic interactions) and covalent (e.g., disulfide bonds) interactions.[1] The presence of disulfide bonds between the side chains of pairs of cysteine residues is often critical to the folding behavior, stability, and functionality of some membrane proteins and secreted proteins in both bacteria and eukaryotes.[2,3] We report that a novel type of disulfide bridge can be formed in the peptide backbone (in lieu of the side chains) by introducing sulfur atoms into the amide groups of aminoxy peptides.

Thioamides as peptide-bond surrogates have attracted great attention in biological recognition and peptide-based drug design[4] by virtue of their improved proteolytic stability and modified hydrogen bonding ability.[5,6] In comparison to regular amide NH, a thioamide NH exhibits higher acidity and is thus expected to form stronger intramolecular or intermolecular hydrogen bonds. In fact, novel secondary structures have been obtained by introducing thioamide groups into peptide backbones. For example, the N-terminal thionated β-hexapeptides reportedly adopt 3_{14}-helix.[5a] Therefore, insertion of thioamides at specific positions in a peptide sequence has gained acceptance as a general approach to peptidomimetics design.

Aminoxy peptides, which are a family of peptidomimetic foldamers,[7] adopt predictable and well-defined secondary structures, such as N–O turns (e.g. α N–O turn adopted by α-aminoxy diamide unit), N–O helices, 7/8 helices, reverse turns and sheets, that are independent of the nature of their side chains.[8] On the basis of their unique conformational preferences, functional molecules such as anion receptors and synthetic chloride channels have been constructed from aminoxy acids.[9] To further explore new secondary structures of aminoxy peptides, we have initiated a study on the conformational features of thioamide analogs of aminoxy peptides in which sulfur atom(s) is/are used to replace the oxygen atom(s) of the peptide bond(s) in α-aminoxy oligomers. The results of this study are disclosed herein.



Results and Discussion

Synthesis of disulfide-bonded aminoxy peptides: As outlined in Scheme 1, we have prepared compounds **8a** and **8b** by

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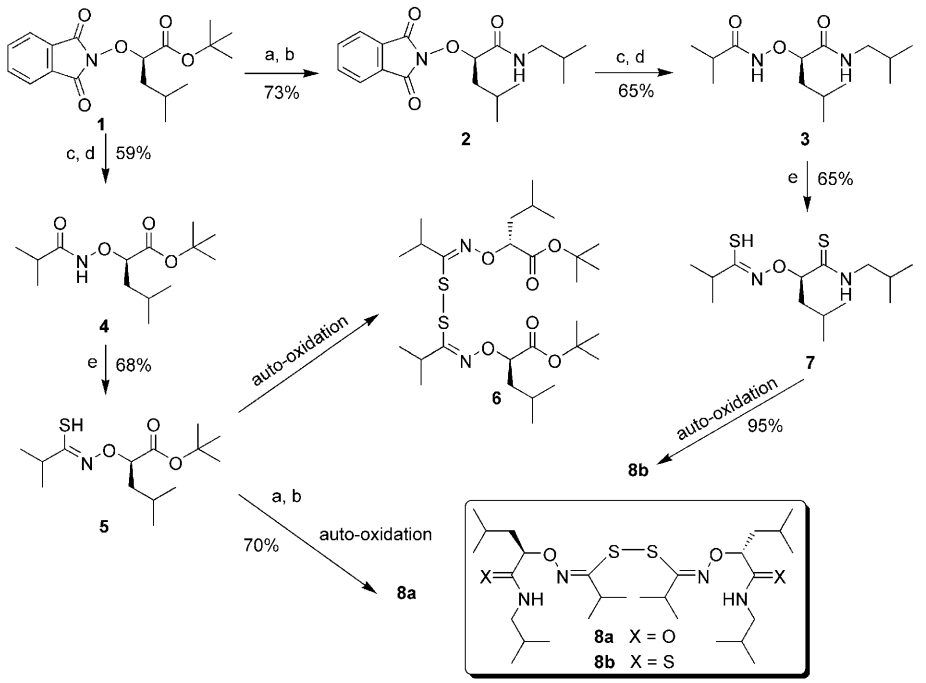

Scheme 1. Synthetic routes toward disulfide-bridged aminoxy peptides. a) CF_3COOH, CH_2Cl_2; b) isobutylamine, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI), 1-hydroxy-1*H*-benzotriazole (HOBt), CH_2Cl_2, overnight; c) $NH_2NH_2{\cdot}H_2O$, MeOH; d) isobutyric acid, EDCI, HOBt, CH_2Cl_2, overnight; e) Lawesson's reagent, THF.

means of standard peptide coupling reactions by using Lawesson's reagent (LR) to substitute a sulfur atom for the amide oxygen atom.[10] Additionally, we have synthesized compound **6** as a reference for conformational studies.

After substituting a sulfur atom for the oxygen atom of the carbonyl group in the aminoxy amide units, we obtained compounds **5** and **7** in their thioimidic acid forms, rather than their thioamide forms; during storage, these compounds were spontaneously oxidized in air to give the disulfide-bridged dimers **6** and **8b**, respectively. We also prepared compound **8a** from **5**. In this case, auto-oxidation occurred spontaneously under the reaction conditions (Scheme 1).

The structures of compounds **5**–**7**, **8a**, and **8b** were subsequently confirmed by means of NMR spectroscopy and theoretical studies. For compound **7**, the ^1H and ^{13}C NMR spectra displayed signals for the C-terminal regular thioamide NH proton and thiocarbonyl carbon atom at $\delta = 7.95$ and 203.0 ppm, respectively (Figure 1). At the N-terminus, signals were observed at $\delta = 4.05$ ppm in the ^1H NMR spectrum and $\delta = 159.1$ ppm in the ^{13}C NMR spectrum, suggesting the presence of a thioimidic acid unit (HS–C=N–O–) in **7**, rather than the tautomeric structure **7′**. After oxidation, we observed chemical shifts in the ^1H and ^{13}C NMR spectra of the disulfide-bridged dimers **6** and **8b**, which were almost identical to those of the corresponding thioimidic acid monomers **5** and **7**, respectively, except for the disappearance of the SH protons.

Theoretical calculations of the model compounds thioamide **I** and thionated aminoxy amide **II** using DFT methods indicate that while the thiono form is more stable than the thioimidic acid form by ≈8 kcal mol^{-1} for a regular thioamide (Figure 2, see **Ia** with **Ib** and **Ic**), the thioimidic acid form is more stable than the thiono form by ≈7 kcal mol^{-1} for a thionated aminoxy amide (Figure 2, see **IIb** with **IIa**),[11] presumably because a) the NH proton of an aminoxy thioamide is more acidic than that of a regular thioamide, as a result of the inductive effect of the adjacent oxygen atom, and b) the presence of an intramolecular hydrogen bond between the SH proton and the N–O oxygen atom (Figure 2, see **IIb** and **IIc**). In the thioimidic acid form, the Z isomer is more stable than the E

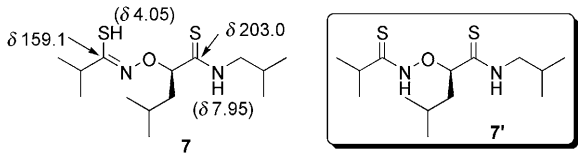

Figure 1. Some ^1H and ^{13}C NMR chemical shift data for compound **7**.

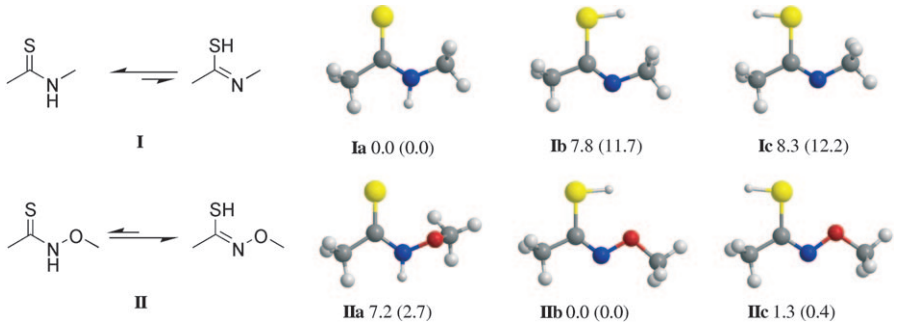

Figure 2. B3LYP/6-311+G**-optimized structures of the thioimidic acid and thiono forms of a regular thioamide and a thionated aminoxy amide, with their MP2/6-311+G** relative energies (kcal mol^{-1}) in the gas phase and in CH_2Cl_2 (in parentheses).

isomer because of less steric interactions and possible intramolecular hydrogen bonding in the former.[11]

Conformational studies of disulfide-bonded aminoxy peptides 8a and 8b. We used ^{1}H NMR spectroscopy to characterize the secondary structures of the disulfide-bridged dimers **8a** and **8b**. As summarized in Table 1, dilution and [D_6]DMSO titration resulted in almost no changes in the chemical shifts of their NH protons ($\Delta\delta < 0.1$ ppm), suggesting that these protons are involved in intramolecular hydrogen bonds.

Table 1. Chemical shifts of thioamide protons of **8a** and **8b** at 25 °C and their chemical shift changes ($\Delta\delta$) in ^{1}H NMR dilution (dilu.) and [D_6]DMSO titration (DMSO) studies.

Compound	NH [ppm]		
	δ[a]	$\Delta\delta$[b](dilu.)	$\Delta\delta$[c](DMSO)
8a	6.21	0.03	0.05
8b	7.94	0.01	0.08

[a] The value of δ refers to the chemical shift observed in the ^{1}H NMR spectrum of the indicated compound in $CDCl_3$ at a concentration of 1.56 mM. [b] The values of $\Delta\delta$ were calculated according to the expression δ_{NH}(200 mM)$-\delta_{NH}$(1.56 mM). [c] The values of $\Delta\delta$ were calculated according to the expression δ_{NH}(5 mM in $CDCl_3$/9% [D_6]DMSO)$-\delta_{NH}$(5 mM in $CDCl_3$).

Theoretical studies have supported these chemical shift phenomena.[11] Figure 3 indicates that an intramolecular five-membered-ring hydrogen bond exists between the amide NH proton and the N–O oxygen atom of the Z isomer model **III** (thioimidic acid form) in its six lowest-energy conformations (free energies within 0.7 kcal mol^{-1} in CH_2Cl_2).

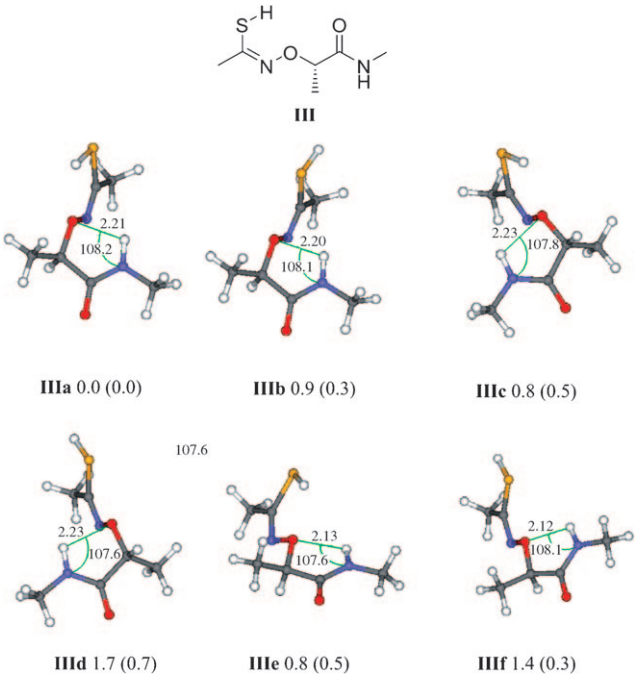

Figure 3. B3LYP/6-31G**-optimized structures of the *Z* isomer model **III**, with their MP2/6-31G** relative energies (kcal mol^{-1}) in the gas phase and in CH_2Cl_2 (in parentheses).

To characterize the -(O–N=C–S)$_2$- chromophore, compound **9** (Figure 4a), an achiral disulfide-bonded dimer of (*Z*)-*N*-methoxy-2,2-dimethylpropanethioimidic acid, has

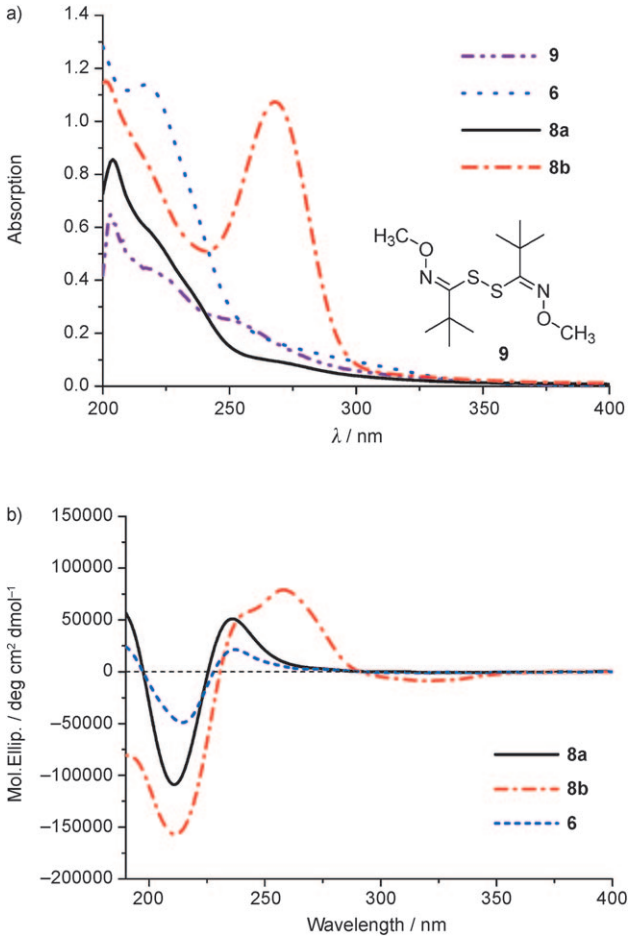

Figure 4. a) UV absorption spectra of **6**, **8a**, and **8b**, and **9** in methanol solutions at $\lambda = 200$–400 nm (0.04–0.1 mM). b) CD spectra of **6**, **8a**, and **8b** in trifluoroethanol (TFE; 0.4 mM).

been prepared.[12] The UV spectra of compounds **6**, **8a**, **8b** and **9** were shown in Figure 4a. In the UV absorption spectra, the -(O–N=C–S)$_2$- chromophore of compound **9** was characterized by a main absorption peak at $\lambda = 203$ nm and shoulders at $\lambda = 214$ and 243 nm. Among these peaks, the $\lambda = 243$ nm absorption is presumably contributed by the S–S bond.[13a] Similarly, a main UV absorption peak at $\lambda = 204$ nm and shoulders at $\lambda = 214$ and 255 nm were observed for **8a**. Compound **6** was characterized by a main absorption peak at $\lambda = 217$ nm, which is presumably contributed by the S–C=N–O chromophore. Other than the thioamide **8b**, besides an absorption at $\lambda = 201$ nm, a main absorption peak was found at $\lambda = 268$ nm which is possibly contributed by the strong π–π^* transition of the C=S chromophore.

Circular dichroism (CD) spectroscopy has been widely used to characterize the secondary structures of α-, β-, and γ-peptides and unnatural oligomers.[14] In the CD spectrum of compound **6**, we observed Cotton effects at 214 nm (negative) and 237 nm (positive), corresponding to the absorption of the C=N bond and S–S bond, respectively, of the -(O–N=C–S)$_2$- chromophore. A similar curve, albeit of stronger intensity, was observed in the CD spectrum of compound **8a** in the range of $\lambda = 200$–250 nm. The maximum molar ellipticity of compound **8a** at either $\lambda = 211$ nm or 236 nm was almost twice of that of compound **6**, suggesting that the regular amide group of dimer **8a** is a critical feature affecting the folding of the disulfide-bridged aminoxy dimer. In the CD spectrum of compound **8b**, we observed in the range of $\lambda = 200$–250 nm both negative and positive Cotton effects that are similar to those of **6** and **8a**, but with a much stronger absorption peak at 211 nm. In addition, the CD spectrum of **8b** reveals strong positive and weak negative Cotton effects at 258 nm and 319 nm arising from the π–π* and n–π* transitions, respectively, of the C=S group in the regular thioamide chromophore at the C-terminus.[5a,11]

It is known that a disulfide unit preferentially adopts a skewed conformation with a dihedral angle of around ±90° and a rotational barrier of 5–15 kcal mol^{-1} at room temperature.[13] In compound **6**, the interconversion between the *M* (left-handed) and *P* (right-handed) conformations of the disulfide unit is possible at room temperature, which results in moderate CD absorption. The observed increase in intensity of the Cotton effects (progressively from compound **6** to compounds **8a** and **8b**) at $\lambda \approx 214$ and 237 nm can be explained conceptually on the basis that the formation of an intramolecular hydrogen bond between the C-terminal amide/thioamide NH proton and the N–O oxygen atom within one aminoxy acid residue restricts the rotation of the disulfide bond in **8a** and **8b**. Additional evidence was obtained by analysis of the ^{1}H NMR data in the range $\delta = 2$–9 ppm for the three compounds, as shown in Figure 5. Compounds **8a** and **8b** display only one conformation as shown by ^{1}H NMR. However, although the α proton (H_α, marked in blue) of compound **6** appears only at $\delta = 4.54$ ppm with an integration of 1H, there are two sets of signals centered at $\delta = 3.15$ and 3.35 ppm with the integration values of 0.4H and 0.6H, respectively, corresponding to the signals of the proton of C*H*C(–S)=NO- moiety (marked in red).

Our single-crystal X-ray diffraction study indicates that, in the solid state, compound **8b** exists in a C_2 symmetric conformation with its C_2 axis being perpendicular to the S–S bond (Figure 6).[11] The dihedral angle $\measuredangle C_{11}S_2S_3C_{15}$ (−105.1°) indicates a left-handed orientation of the disulfide bond with the two C–S bonds positioned in an almost perpendicular arrangement. Each thioamide NH proton is hydrogen bonded to the N–O oxygen atom of its adjacent aminoxy acid residue, consistent with our theoretical predictions. The *i*Bu side chain is positioned almost anti to the N–O bond ($\measuredangle N_3O_2C_{19}C_{20} = -169.3°$). The dihedral angle $\measuredangle N_3O_2C_{19}C_{24}$ (+69.3°) is similar to that of the right-handed N–O turns that we reported previously.[8c] Collectively, these

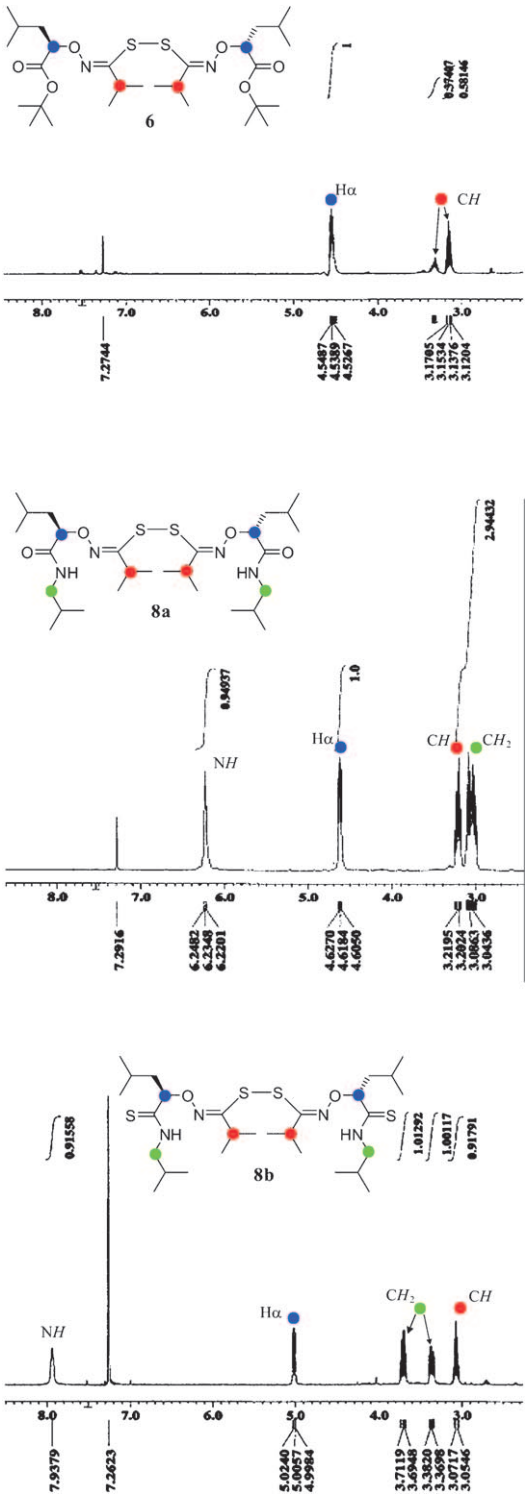

Figure 5. ^{1}H NMR spectra of compounds **6**, **8a** and **8b** in the range of $\delta =$ 2–9 ppm.

results indicate that the conformation around the α-carbon atom of the thioimidic acid backbone is similar to that of typical α-aminoxy peptides. This finding is also in agreement with the positive Cotton effect observed for the thioamide chromophore in the CD spectrum. Figure 6b,c show the

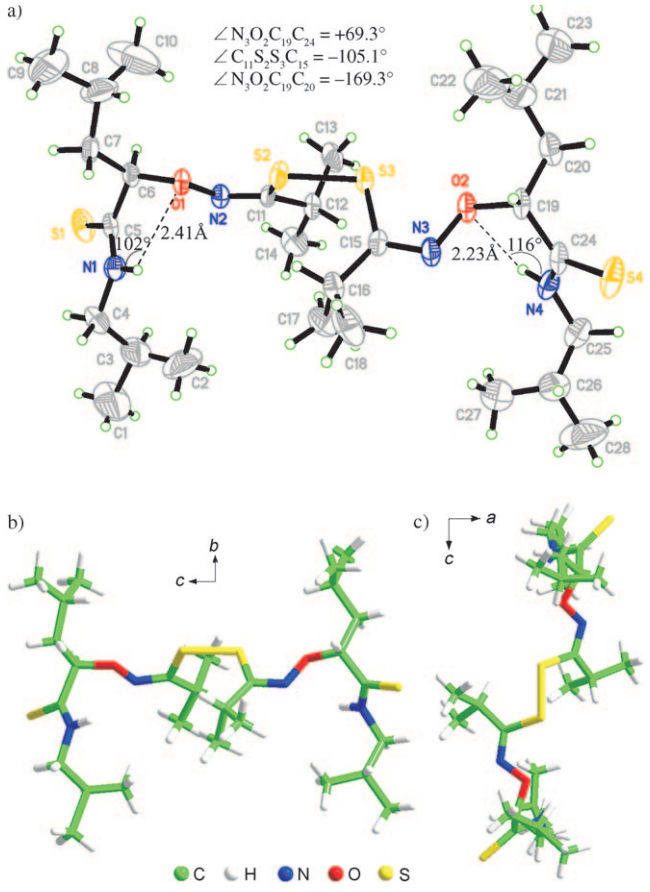

Figure 6. Solid state structure of **8b**. a) ORTEP structure of compound **8b** with atom labels and intramolecular hydrogen bonds; b) Stick model of the solid structure of **8b** viewed along direction *a*; c) Stick model of the solid structure of **8b** viewed along direction *b*.

solid-state structures of compound **8b** viewed along the directions *a* and *b*, respectively. By taking a perspective along direction *a*, we can clearly see that the two peptide chains are extended in the same direction and are almost parallel to each other with a distance of 11.8 Å between them. Overall, a novel loop structure is adopted by these disulfide-bridged dimers. This scaffold promises the opportunity to design predictable, well-defined secondary or even super-secondary and tertiary structures with a small loop as the covalent linkage.

Conclusion

In summary, disulfide-bridged dimers can be readily obtained by substituting a sulfur atom for the oxygen atom of an N-oxy amide carbonyl group. These C_2-symmetric disulfide-bonded dimers adopt a rigid loop conformation characterized by one disulfide bond and two five-membered-ring intramolecular hydrogen bonds. Putting these into perspective, we believe that thionated α-aminoxy acid residues hold great potential, as useful building blocks for the preparation of new peptide mimics featuring loop motifs.

Experimental Section

General methods: All reagents and solvents for the reactions were of analytical grade and were dried and distilled where necessary. Melting points (m.p.) were determined by using a Reichert Thermovar Kofler microscope and the values were uncorrected. Optical rotations were measured by using an AUTO POL IV automatic polarimeter. NMR spectra were recorded by using Jeol ECA-400 or Bruker DMX-400. IR spectra were recorded by using a NICOLET FTIR-360 spectrometer as a thin film unless otherwise noted. Mass spectra were recorded by using a Finnigan MAT 95 mass spectrometer for both low resolution and high resolution mass spectra. Circular dichroism spectroscopic studies were carried out by using a JASCO J-715 spectropolarimeter. UV absorptions were recorded by using an Agilent HP8453 spectrometer.

Compound 5: A pale yellow oil, auto-oxidized to compound **6**; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 4.58$ (dd, $J = 8.8$, 4.9 Hz, 1H), 4.51 (s, 1H), 2.73–2.62 (m, 1H), 1.93–1.73 (m, 2H), 1.63–1.53 (m, 1H), 1.46 (s, 9H), 1.19 (d, $J = 6.8$ Hz, 6H), 0.97 ppm (d, $J = 5.4$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 171.6$, 157.4, 81.1, 80.8, 40.0, 35.7, 28.1, 24.8, 23.2, 22.2, 21.0, 20.8 ppm.

Compound 6: A colorless oil; $[\alpha]_D^{20} = +165.5°$ ($c = 1.00$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (two conformers around the disulfide bond) $\delta = 4.56$–4.50 (m, 2H), 3.36–3.30 (m, 0.4×2H), 3.19–3.12 (m, 0.6×2H), 1.85–1.73 (m, 4H), 1.63–1.53 (m, 2H), 1.46 (s, 18H), 1.26–1.19 (m, 0.4×12H), 1.14 (d, $J = 6.8$ Hz, 0.6×6H), 1.13 (d, $J = 6.8$ Hz, 0.6×6H), 0.96 (d, $J = 6.4$ Hz, 6H), 0.95 ppm (d, $J = 6.4$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) the major conformer $\delta = 171.4$, 159.2, 81.6, 81.2, 39.8, 29.6, 28.1, 24.9, 23.1, 22.2, 21.2, 21.1 ppm; IR: $\tilde{\nu} = 3375$, 1730, 1669 cm^{-1}; LRMS (EI, 20 eV): m/z: 576 (M^+, 2), 288 (100), 171 (25); HRMS (EI) for $C_{28}H_{52}N_2O_6S_2$ (M^+): calcd 576.3267, found 576.3291.

Compound 7: A pale yellow oil, auto-oxidized to compound **8b**; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.95$ (br s, 1H), 5.03 (dd, $J = 10.2$, 2.9 Hz, 1H), 4.05 (s, 1H), 3.72–3.66 (m, 1H), 3.38–3.32 (m, 1H), 2.74–2.66 (m, 1H), 2.03–1.95 (m, 2H), 1.94–1.85 (m, 1H), 1.73–1.66 (m, 1H), 1.19 (d, $J = 6.8$ Hz, 3H), 1.18 (d, $J = 6.8$ Hz, 3H), 0.99 (d, $J = 6.8$ Hz, 3H), 0.97–0.95 ppm (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 203.0$, 159.1, 89.3, 52.2, 43.6, 36.2, 27.6, 25.4, 23.5, 21.6, 20.9, 20.8, 20.3 ppm.

Compound 8a: A white solid; m.p. 78–81 °C; $[\alpha]_D^{20} = +29.0°$ ($c = 1.00$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 6.23$ (t, $J = 5.4$ Hz, 2H), 4.62 (dd, $J = 8.3$, 4.9 Hz, 2H), 3.25–3.19 (m, 2H), 3.10–2.99 (m, 4H), 1.89–1.69 (m, 8H), 1.16 (d, $J = 6.8$ Hz, 12H), 0.97 (d, $J = 6.4$ Hz, 12H), 0.92 ppm (d, $J = 6.4$ Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 172.1$, 159.8, 83.8, 46.3, 40.6, 30.0, 28.6, 25.0, 23.4, 21.8, 21.3, 20.8, 20.1, 20.0 ppm; IR: $\tilde{\nu} = 3370$, 1736, 1665 cm^{-1}; LRMS (EI, 20 eV): m/z: 574 (M^+, 1), 255 (100), 170 (31); HRMS (EI): m/z calcd for $C_{28}H_{54}N_4O_4S_2$: 574.3586 (M^+), found 574.3621.

Compound 8b: a white solid, m.p. 107–110 °C; $[\alpha]_D^{20} = +28.4°$ ($c = 1.00$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.94$ (t, $J = 4.9$ Hz, 2H), 5.01 (dd, $J = 10.2$, 2.9 Hz, 2H), 3.75–3.68 (m, 2H), 3.40–3.34 (m, 2H), 3.11–3.04 (m, 2H), 2.06–1.96 (m, 4H), 1.94–1.84 (m, 2H), 1.74–1.67 (m, 2H), 1.15 (d, $J = 6.8$ Hz, 6H), 1.14 (d, $J = 6.8$ Hz, 6H), 1.00–0.95 ppm (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 202.5$, 160.7, 90.2, 52.2, 43.5, 30.1, 27.7, 25.4, 23.5, 21.6, 21.4, 20.7, 20.3 ppm; IR: (CH_2Cl_2) $\tilde{\nu} = 3377$, 1736, 1662 cm^{-1}; LRMS (EI, 20 eV): m/z: 606 (M^+, 10), 303 (100), 186 (40), 147 (48); HRMS (EI): m/z calcd for $C_{28}H_{54}N_4O_2S_4$: 606.3130 (M^+), found 606.3163.

Theoretical calculations: Structures of model compounds **I**–**III** were optimized by using the B3LYP/6-31G** method by harmonic vibration frequency calculations to ensure that each structure was a minimum. Energies were evaluated by MP2/6-31G** calculations on B3LYP/6-31G** geometries. Solvent effect was evaluated by using the PCM model using the B3LYP/6-31G** method. The relative free energies of the structures were also calculated in terms of the MP2/6-31G** energies plus the enthalpy and entropy corrections along with solvent energy corrections. All calculations were conducted with the use of the Gaussian 98 software package.[15]

Acknowledgements

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