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All-Thioamidated Homo-α-Peptides: Synthesis and Conformation

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Replacement of a peptide bond with its thioamide surrogate is a classical method for the generation of a peptidomimetic with altered spectroscopic, conformational, physicochemical, and biological properties. In this context, we synthesized short series of terminally protected homo-α-oligopeptides based on the α-amino acids Gly, Ala, and Nle, as well as their corresponding fully thioamidated analogues. For the first time, the preparation of the latter compounds was achieved in single-step fashion through direct thionation of their oxygenated precursors. Using X-ray diffraction analysis and NMR spectroscopy we were also able to confirm that the thioamidated α-amino acid residues can easily adopt either folded or fully extended conformations.

Introduction

Thionated peptides are members of an interesting class of backbone-modified peptidomimetics[1] that have been utilized in a variety of fields, including medicinal chemistry, spectroscopy, and photophysics (*cis*/*trans* thioamide isomerization).[1–25] Their preferred conformations have been extensively investigated, in particular by X-ray diffraction, NMR, and electronic and energy calculations.[2,3,7,13,15,17,26–59] Most of these studies have involved compounds with single, site-specific peptide bond modifications. These targets have typically been achieved by regioselective thionation of very short peptides (e.g., terminally protected tripeptides), followed by extension of the amino acid chain by chemical synthesis.[2,3,30,60–65] The classical protecting functionalities used in peptide synthesis (urethanes at N termini and esters at C termini) are not modified under the experimental conditions almost universally employed for thionation of an amide group (Lawesson reagent[60] in an organic solvent of low polarity). Moreover, additional regioselectivity between two (or three) amide groups can frequently be achieved by taking advantage of the differences in steric hindrance exerted by the side chains of the pairs of surrounding amino acids.

In contrast, only a very limited number of articles dealing with synthesis and conformation of all-thioamidated peptides have appeared in the literature.[2,28] This observation is rather surprising in view of the great potential interest of this class of peptidomimetics as new foldameric structures and the increasing number of naturally occurring poly-α- and -β-peptides containing up to five consecutive thioamide groups in their amino acid chains, that have been isolated and sequenced.[66–68] In this work we decided to fill this gap at least partially by synthesizing a large set of all-thioamidated, selected peptide foldamers, by use of the single-step direct thionation methodology, and by investigating their conformational preferences by detailed X-ray diffraction and 2D-NMR analyses.

Results and Discussion

Peptide Synthesis and Characterization

We used classical solution-phase methods to prepare three short series (from dimer through tetramer) of terminally protected homo-α-oligopeptides based on the Gly, Ala, and Nle (norleucine) residues. These amino acids differ in their linear, but increasingly bulkier, side chains (R), where R = H for Gly, R = $–CH_3$ for Ala, and R = $–CH_2–(CH_2)_2–CH_3$ for Nle. The syntheses and characterizations of these nine peptides had already been reported.[69–72]

Thionation of the Gly dipeptide with Lawesson reagent (LR)[60] under typical conditions [anhydrous THF at room temperature; Procedure A (see the Exp. Section)] proceeded fairly smoothly in about 1 hour to afford the monothioamidated compound **2a** (Scheme 1) after chromatographic purification (no special efforts were made to optimize the yields in our thionation reactions).

To obtain the desired Gly bis-thioamidated product **3a** and the tris-thioamidated product **4a**, a further aliquot of LR (to a total of 1.8–3.0 equiv.) was added after 24 hours in each case. The reaction mixtures were left whilst stirring for additional 24 hours.

The preparations of the Ala bis-thioamidated tripeptide **3b** and the tris-thioamidated tetrapeptide **4b** (but not that

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Z-Gly-ψ[CSNH]-Gly-OMe	**2a**
Z-Gly-ψ[CSNH]-Gly-ψ[CSNH]-Gly-OMe	**3a**
Z-Gly-ψ[CSNH]-Gly-ψ[CSNH]-Gly-ψ[CSNH]-Gly-OMe	**4a**
Z-Ala-ψ[CSNH]-Ala-OMe	**2b**
Z-Ala-ψ[CSNH]-Ala- ψ[CSNH]-Ala-OMe	**3b**
Z-Ala-ψ[CSNH]-Ala- ψ[CSNH]-Ala- ψ[CSNH]-Ala-OMe	**4b**
Z-Nle-ψ[CSNH]-Nle-OMe	**2c**
Z-Nle-ψ[CSNH]-Nle- ψ[CSNH]-Nle-OMe	**3c**
Z-Nle-ψ[CSNH]-Nle- ψ[CSNH]-Nle-ψ[CSNH]-Nle-OMe	**4c**

Scheme 1. Amino acid sequences of the nine all-thioamidated homo-α-peptides synthesized and studied (Z is benzyloxycarbonyl, OMe is methoxy, and ψ[CSNH] is the widely used representation of a thioamidated peptide surrogate[1]).

of the monothioamidated dipeptide **2b**) required larger excesses of LR (up to a total of 2.4–3.6 equiv.) and longer reaction times (up to 9 d). Thionation of the Nle dipeptide proved to be much more sluggish.

To obtain the monothioamidated compound **2c**, 9 days under reflux were found to be necessary with multiple additions of LR to a total of 3 equiv. Thionation of the Nle tri- and tetrapeptides under comparable conditions could barely be achieved, however. Eventually, syntheses of the bis-thioamidated product **3c** and the tris-thioamidated product **4c** were accomplished by use of Procedure B, which involves treatment of the oxygenated peptides with P_2S_5[64] in anhydrous tetrahydrofuran under ultrasound irradiation conditions for 3–5 hours, with addition of a total of 5–10 equiv. of the sulfur donor reagent in three to six aliquots.

Selective thionations of the peptide functionalities were achieved in all cases, because urethane and ester groups do not react under all conditions tested.[2,3,60–62,64] The various synthetic steps ultimately leading to the all-thioamidated tri- and tetrapeptides (in particular those affording the intermediate monothionated tripeptides and mono- and bis-thionated tetrapeptides) were not investigated in detail because our goal was solely to obtain sufficient amounts of the final materials for use in our subsequent conformation studies. As already reported in the literature for partially and fully thionated α- and β-peptides, peptide solubilities were observed to have increased markedly relative to those of their oxygenated counterparts.[2] In our study, this effect is best demonstrated by the sparingly soluble Z-$(Gly)_4$-OMe tetrapeptide. Indeed, we found that its suspension in tetrahydrofuran became a clear solution as the thionation reaction proceeded to afford **4a**.

After chromatographic purifications, the nine all-thioamidated peptides synthesized were spectroscopically characterized by IR absorption, UV absorption, circular dichroism (chiral compounds only), and ^1H and ^{13}C NMR techniques. FTIR absorption analysis in $CDCl_3$ solution showed the peptide C=O stretching band near 1650 cm^{-1} to be missing[2,3,60] in each case (only bands at wavenumbers higher than 1690 cm^{-1}, associated with the ester and urethane C=O stretching modes, are seen).[73] In the UV absorption spectra in methanol or 2,2,2-trifluoroethanol solutions, an intense maximum near 265 nm, accompanied by an extremely weak maximum at about 330 nm, is found in each case. These two bands, which are absent in the spectra of the corresponding oxygenated peptides, are attributable to the π→π* and n→π* transitions, respectively, of the thioamide chromophore.[2,30,60] In the 250–400 nm region of the CD spectra in the same solvents, two well-separated Cotton effects at about 260–270 nm and 345–350 nm are typically displayed.[2,3,11–14,16–21,24,25,74] The longer-wavelength band is positive and weaker, whereas the shorter-wavelength band is negative and much more intense. The ^1H (and ^{13}C) spectra in $CDCl_3$ solution exhibit significant downfield shifts for the thioamide and α-carbon protons (and for the thiocarbonyl and α-carbons as well) with respect to their corresponding amide analogues, consistently with previously reported values for similar compounds.[2,30,60]

Crystal-State Conformation Analysis

Out of the all-thioamidated homo-α-peptides synthesized in this work, we were able to grow single crystals from Z-Gly-ψ[CSNH]-Gly-ψ[CSNH]-Gly-OMe (**3a**). The X-ray diffraction structure is illustrated in Figure 1. Selected torsion angles are listed in Table 1, intra- and intermolecular H-bond parameters are reported in Table 2, and crystal data and structure refinement parameters are given in Table 3. The achiral thiopeptide crystallizes in a centrosymmetric space group, so molecules of both handedness are present in the unit cell. In Table 1 and in the following discussion, reference is made to the molecule characterized by a negative value of the ϕ_1 torsion angle, arbitrarily chosen as the asymmetric unit.

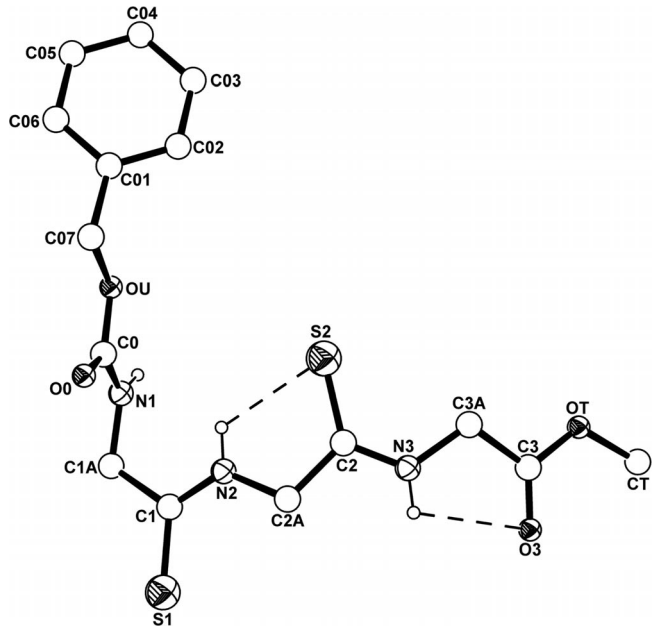

Figure 1. X-ray diffraction structure of Z-Gly-ψ[CSNH]-Gly-ψ[CSNH]-Gly-OMe (**3a**) with atom numbering. The two intramolecular H-bonds are indicated by dashed lines.

Table 1. Selected torsion angles [°] for Z-Gly-ψ[CSNH]-Gly-ψ[CSNH]-Gly-OMe (**3a**).

C02–C01–C07–OU	–69.2(3)
C06–C01–C07–OU	113.5(2)
C01–C07–OU–C0	174.5(2)
C07–OU–C0–N1	178.8(2)
OU–C0–N1–C1A	–173.98(16)
C0–N1–C1A–C1	–86.3(2)
N1–C1A–C1–N2	–3.4(3)
N1–C1A–C1–S1	176.63(15)
C1A–C1–N2–C2A	179.38(18)
C1–N2–C2A–C2	168.95(18)
N2–C2A–C2–N3	–159.90(16)
C2A–C2–N3–C3A	176.40(17)
C2–N3–C3A–C3	–159.38(17)
N3–C3A–C3–OT	167.61(18)
C3A–C3–OT–CT	–179.4(3)

Table 2. Intra- and intermolecular H-bond parameters for Z-Gly-ψ[CSNH]-Gly-ψ[CSNH]-Gly-OMe (**3a**).

Donor (D–H)	Acceptor (A)	Distance [Å] D···A	Distance [Å] H···A	Angle[°] D–H···A	Symmetry equivalence of A
N2–H2	S2	2.9348(16)	2.44	118	*x, y, z*
N3–H3	O3	2.715(2)	2.39	103	*x, y, z*
N1–H1	S1	3.4183(18)	2.62	155	*x*, ½-*y*, ½ + *z*
N3–H3	O3	3.039(2)	2.19	169	2-*x*, –*y*, –*z*

Table 3. Crystal data and structure refinement for Z-Gly-ψ[CSNH]-Gly-ψ[CSNH]-Gly-OMe (**3a**).

Parameter	Data	
Empirical formula	$C_{15}H_{19}N_3O_4S_2$	
Formula weight	369.45	
Temperature	293(2) K	
Wavelength	0.71069 Å	
Crystal system	monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 9.1152(3) Å	α = 90°
	b = 21.7511(6) Å	β = 108.153(3)°
	c = 9.8888(3) Å	γ = 90°
Volume	1863.03(10) Å^3	
Z	4	
Density (calculated)	1.317 Mgm^{-3}	
Absorption coefficient	0.309 mm^{-1}	
F(000)	776	
Crystal size	0.50 × 0.20 × 0.20 mm^3	
θ Range for data collection	2.35 to 28.27°.	
Iindex ranges	$-12 \le h \le 12$, $-29 \le k \le 29$, $-13 \le l \le 13$	
Reflections collected	33002	
Independent reflections	4627 [R(int) = 0.0246]	
Completeness to θ = 28.27°	100.0%	
Absorption correction	semiempirical from equivalents	
Max. and min. transmission	1.00000 and 0.83404	
Refinement method	full-matrix, least-squares on F^2	
Data/restraints/parameters	4627/0/205	
Goodness-of-fit on F^2	1.042	
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0480, $wR2$ = 0.1194	
R indices (all data)	$R1$ = 0.0610, $wR2$ = 0.1300	
Largest diff. peak and hole	0.453 and –0.498 eÅ^{-3}	

Interatomic distances and angles are in general agreement with literature values for the benzyloxycarbonyl-amino[75] and methyl ester groups[76] and the thioamide linkage.[27] Specifically, the C1=S1 and C2=S2 bond lengths are 1.659(2) Å and 1.6623(19) Å, respectively, and the C1–N2 and C2–N3 bond lengths are 1.306(2) Å and 1.315(2) Å, respectively. The C′=S bonds are significantly longer that the corresponding C′=O bond length in peptides (1.20 Å),[26,27] whereas the C′–N bonds are slightly shorter than in the peptide unit (1.34 Å). This latter finding suggests a more pronounced double bond character for C′–N bonds in thioamides than for those in peptides.[26,27,41,51,52]

Both thioamides, as well as the urethane and ester units, are in the common *trans* disposition, with deviations from *trans* planarity [|Δω|] not exceeding 6°.

The conformation adopted by the N-terminal Gly(1) residue, characterized by ϕ_1 = –86.3(2)° and ψ_1 = –3.4(3)°, falls in the region of the Ramachandran map between the helical and extended conformations, termed the "bridge" region.[77] Conversely, the Gly(2) and Gly(3) residues, with ϕ_2,ψ_2 = 168.95(18)°, –159.90(16)° and ϕ_3,ψ_3 = –159.38(17)°, 167.61(18)°, are essentially fully extended.[78] As a result, two intramolecularly H-bonded forms of the C_5 type[79] are observed at the level of the Gly(2) and Gly(3) residues, involving the N2–H and N3–H groups, respectively, as the donors, and the (thioamide) S2 and (ester) O3 atoms, respectively, as the acceptors. Interestingly, the τ (N–C^α–C′) bond angle for Gly(1) is 114.86(16)°, but those for the Gly(2) and Gly(3) residues involved in the C_5 structures are 110.05(15)° and 109.99(15)°, respectively. For comparison, the values of the τ bond angle of Gly averaged from small-molecule[80] and protein[81] X-ray diffraction structures are 112.5° and 112.1°, respectively. The expansion of τ above the standard tetrahedral value to about 114° for amino acids in the "bridge" region of the conformation map was noted by Karplus[81] in his statistical survey of protein structures. This author ascribed it to the existence of a short contact between the nitrogen atom of residue *i* and the amide H atom of the subsequent (*i* + 1) residue in the peptide chain.

The C′=S bond is significantly longer than a C′=O bond, so the geometric parameters of the C_5 structure at the level of Gly(2) differ from the corresponding average values reported for N–H···O=C intra-residue H-bonds of the C_5 type.[79] In the case of the C-terminal C_5 structure, the N–H···O angle is narrower and the N···O and H···O distances are longer than the average in C_5 structures, as a result of the deviation of the ϕ,ψ backbone torsion angles from the ideal values (180°, 180°) of the fully extended conformation. In addition, and at variance with the observation that the N–H and C=O groups involved in regular C_5 structures do not take part in any intermolecular hydrogen bonding, in this structure the N3–H and C3=O3 groups are also intermolecularly H-bonded to each other (see below).

In the packing mode (not shown), both N–H···S=C[41] and N–H···O=C intermolecular H-bonds are observed. Specifically, the N1–H group is H-bonded to an (*x*, ½ – *y*, ½ + *z*) symmetry equivalent of the C1=S1 group, connecting molecules in a zigzag motif along the *c* direction. A second intermolecular H-bond is found between the N3–

H3 group and the (2 – *x*, –*y*, –*z*) equiv. of the C3=O3 group, thus generating a doubly H-bonded, centrosymmetric pair of molecules. In addition, a C–H···S contact with a H···S distance of 2.79 Å (less than the sum of the van der Waals radii of S and H, 2.90 Å)[82,83] is observed between the CT-HT1 group and the (2 – *x*, –*y*, –*z*) symmetry equivalent of S1. Packing is then completed through van der Waals interactions.

Solution Conformation Analysis

Our 2D-NMR study was performed on tripeptides **3a**, **3b**, and **3c** and tetrapeptides **4a**, **4b**, and **4c** in $CDCl_3$ solution. The assignments of all of the resonances for these compounds were achieved by DQF-COSY,[84] TOCSY,[85,86] and HMQC and HMBC[87] experiments.

As examples, Figure 2 shows that, for each of the three tripeptides, both NH(*i*)→NH(*i* + 1) sequential connectivities, characteristic of helical conformations,[88] can be seen in the NOESY spectra. However, the NH(1)→NH(2) cross-peak is weak and the NH(2)→NH(3) cross-peak is hardly even visible. Moreover, an analysis of the relative intensities of the intraresidue αCH(*i*)→NH(*i*) and interresidue αCH(*i* – 1)→NH(*i*) connectivities in the NOESY spectra of all six tripeptides and tetrapeptides investigated provided a useful hint of the conformations adopted. Firstly, we did observe all of the expected intra- and interresidue cross-peaks in the spectrum of each compound. Secondly, in some cases the interresidue cross-peak is more intense than the intraresidue cross-peak. This informative observation, combined with the general weakness of the sequential NH(*i*)→NH(*i* + 1) connectivities described above, represents a clear indication of the presence of fully extended structures.[89] In summary, in the conformational equilibrium mixtures of the all-thioamidated homo-oligopeptides studied in this work, fully extended and folded residues occur concomitantly, with the latter prevailing near the N terminus of the chain. Interestingly, this conclusion from our solution conformation analysis fits nicely with the results of the X-ray diffraction study on peptide **3a** in the crystalline state discussed above.

In our 2D-NMR analysis, specific attention was given to the TOCSY experiments. These were conducted on the six all-thioamidated tri- and tetrapeptides and also, for comparison, on the oxygenated Z-$(Gly)_3$-OMe and Z-$(Gly)_4$-OMe. An unanticipated behavior pattern was noted, but was limited to the TOCSY spectra of the all-thioamidated Gly peptides **3a** and **4a**.

The TOCSY method gives a total correlation for all protons of a peptide chain with one another. Rotating frame experiments produce coherence transfer through *J* coupling and through cross-relaxation simultaneously. This phenomenon can lead to undesired interference and ambiguities between TOCSY and ROESY effects. The pulse program with MLEV17 used in our experiments provides clean TOCSY spectra, in which contributions from cross-relaxation are suppressed. This procedure guarantees that the spin system will evolve solely under the influence of the scalar coupling. Accordingly, no peaks of negative sign due to cross-relaxation are present in our spectra. However, quite surprisingly, cross-peaks (although rather weak) attributable to interresidue signals were detected. It is well known that, dur-

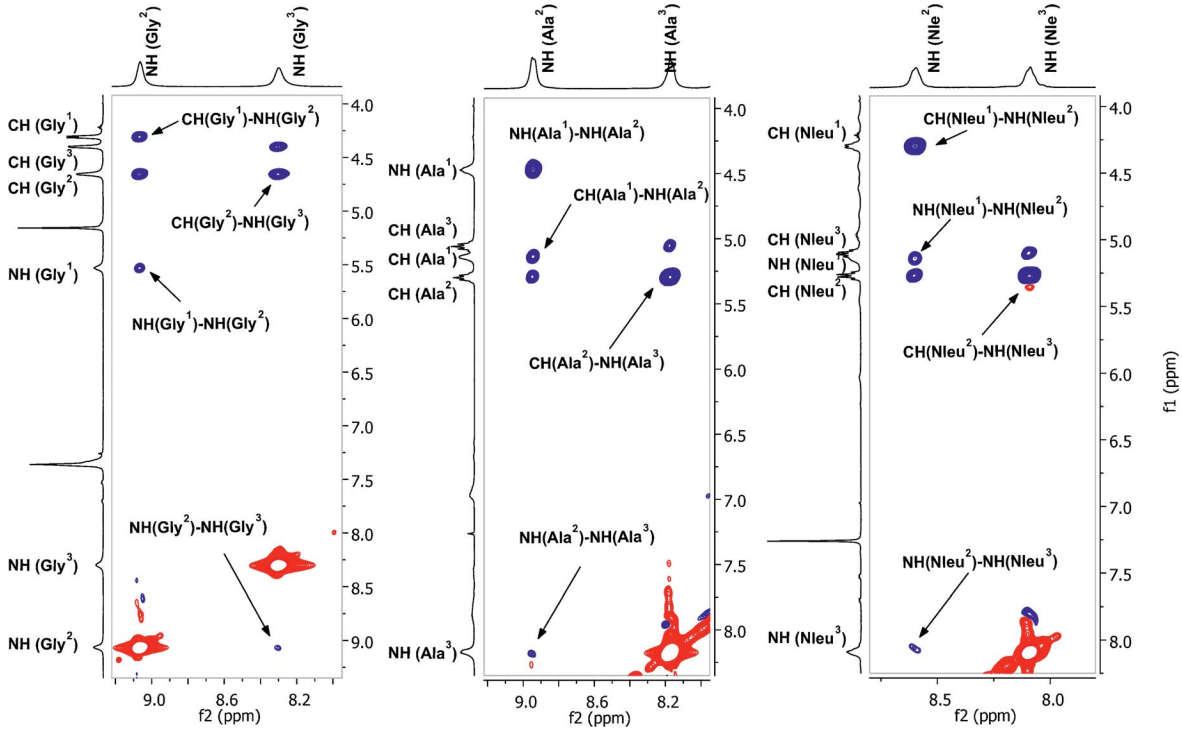

Figure 2. NH→NH and αCH→NH regions of the NOESY spectra of the all-thioamidated tripeptides **3a** (left), **3b** (center), and **3c** (right) in $CDCl_3$ solution. The intraresidue αCH→NH cross-peaks are not labeled.

ing the mixing time in a TOCSY experiment with a peptide substrate, magnetization, occurring through *J* coupling, normally does not pass through different residues (it is "stopped" by the amide bonds).[88] Surprisingly, in our all-thioamidated Gly tripeptide **3a** and tetrapeptide **4a**, couplings between $\alpha CH_2(i) \rightarrow NH(i + 1)$, $\alpha CH_2(i) \rightarrow \alpha CH_2(i + 1)$, and $\alpha CH_2(i) \rightarrow NH(i - 1)$ are seen. With use of increasing mixing times (45, 64, 70, 100, and 140 msec) to record the spectra, the intensities of the anomalous cross-peaks increase correspondingly. Strictly comparable experiments performed on the all-thioamidated tri- and tetrapeptides derived from Ala (**3b** and **4b**) and Nle (**3c** and **4c**), and also on the corresponding oxygenated Z-Gly_3–OMe and Z-Gly_4–OMe, did not reveal any abnormal cross-peak even at the longest mixing time considered. The $\alpha CH_2 \rightarrow NH$ region in the TOCSY spectra of the all-thioamidated Gly tripeptide **3a** (with 70 and 140 msec mixing times), with most of the anomalous cross-peaks highlighted, is shown in Figure 3 (this figure also shows the corresponding TOCSY spectra for the non-thioamidated tripeptide Z-Gly_3–OMe). Two additional, anomalous cross-peaks (not shown) occur in the $\alpha CH_2 \rightarrow \alpha CH_2$ region of the TOCSY spectrum of this same tripeptide **3a**. Analogous cross-peaks were also found in the TOCSY spectra of the all-thioamidated Gly tetrapeptide **4a** (not shown). From our TOCSY experiments, it seems safe to conclude that this seemingly unprecedented phenomenon is correlated with the presence of thioamidated bonds in the peptide sequence. However, the lack of this observation in the all-thioamidated Ala and Nle homopeptides needs further experiments on related peptide substrates before a definitive conclusion. These words of caution are justified by the weakness of the observed abnormal interresidue signals and by the fact that all protein amino acids but Gly are characterized by one αCH proton (only Gly has two). In other words, this effect might also occur in all thioamidated Ala and Nle homopeptides, but might simply be below the level of a possible observation.

A tentative explanation of this phenomenon might reside in the different electronic properties of carboxylic thioamides in relation to amides.[26,27,41,51,52] The well-known

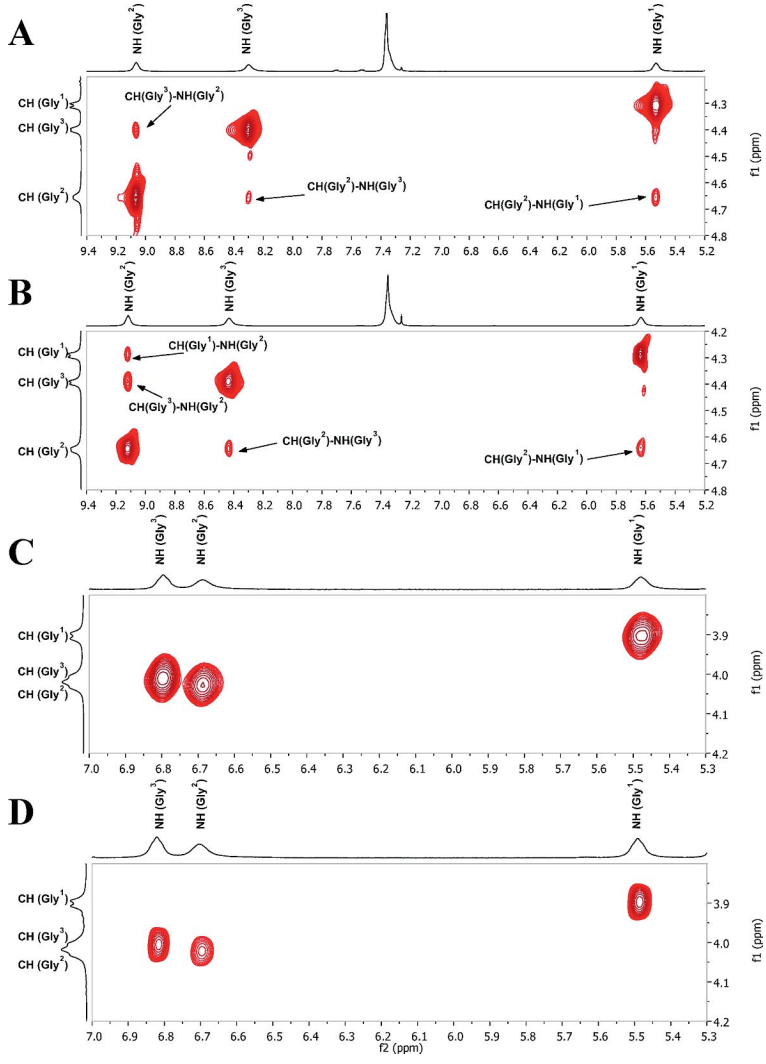

Figure 3. $\alpha CH_2 \rightarrow NH$ region of the TOCSY spectra for: i) the all-thioamidated Gly tripeptide **3a** at A) 70 msec, and B) 140 msec mixing times, and ii) the corresponding oxygenated Z-$(Gly)_3$-OMe at C) 70 msec, and D) 140 msec mixing times.

restricted rotation around the C(=O)–NH bond in an amide is associated with the partial double bond character between the C^{α} and N atoms. In a thioamide, the rotation barrier (more than 21 kcal mol^{-1} in amides) requires about 5 kcal mol^{-1} more than in an amide. This property is in turn related to a greater contribution of the dipolar resonance structure C(–S^-)=N^+H in thioamides, which enhances their double bond character. The presence of these successive (although partial) C=N double bonds might be responsible for the transfer of magnetization taking place through protons belonging to different residues in the amino acid sequence.

Conclusions

The replacement of an amide bond in a peptide by a thioamide bond is one of the most valuable backbone modifications for the generation of new and useful compounds in bioorganic stereochemistry and biology. In most of the examples in the literature the polypeptide chain is selectively modified at the level of a single amide function. Recently, however, interest in multiply thioamidated or even all-thioamidated compounds has been steadily increasing.[2,28,66–68]

In this work, with the aim of determining the conformation effects induced in peptides by complete thionation of their –C(=O)–NH– bonds, we synthesized a set of nine all-thioamidated homo-oligopeptides, based on three α-amino acids with side chains of enhanced steric hindrance. For the first time, we succeeded in preparing bis- and tris-thioamidated tri- and tetrapeptides, respectively, in single-step fashion, starting from their corresponding oxygenated analogues. Complete thionation was observed to become increasingly more difficult as the peptide is elongated and as the amino acid side chain becomes bulkier. To thionate the most resistant substrates fully, we were forced to replace the classical LR[60] with the more efficient procedure based on the P_2S_5 reagent assisted by ultrasonication.[64]

A literature search on the conformational propensities of thionated (usually monothionated) peptides revealed that, despite the well-established, individual geometric properties of the thiopeptide unit (in particular of thiocarbonyl vs. carbonyl bond length), both folded and fully extended conformations are stereochemically favorable and commonly found for the thionated residues.[2,3,7,13,15,17,26–59] In this article we have extended these conclusions to all-thioamidated α-peptides both in the crystalline state and in solution, as assessed by detailed X-ray diffraction and 2D-NMR analyses, respectively. These results pave the way for the exploitation of the all-thioamidated peptidomimetics as a new class of foldameric compounds and functional modifications of bioactive peptides.

Experimental Section

Synthesis and Characterization: Materials and reagents were of the highest commercially available grade and were used without further purification. Melting points were determined in open capillaries with a Leitz Laborlux 12 apparatus. The solid-state (KBr disk) and solution ($CDCl_3$) IR absorption spectra were recorded with a Perkin–Elmer model 1720X FTIR spectrophotometer. TLC was performed with Merck Kieselgel 60F_{254} pre-coated plates and the following solvent systems: 1) chloroform/ethanol 9:1, 2) butanol/acetic acid/water 3:1:1; and 3) toluene/ethanol 7:1. The chromatograms were visualized by UV fluorescence or developed by chlorine/starch/potassium iodide or ninhydrin chromatic reaction as appropriate. All compounds were obtained in a chromatographically homogeneous state. Flash chromatography was carried out with a Merck silica gel 60 (40–63 μm mesh) stationary phase. MS (ESI mode) spectra were measured with a Perseptive Biosystems (Mariner model) ESI-ToF instrument. The UV absorption spectra were recorded with a Shimadzu model UV-2501 spectrophotometer. The CD spectra were measured with a Jasco model J-715 spectropolarimeter equipped with a Haake thermostat.

The Z-$(Gly)_n$-OMe,[69] Boc-$(Ala)_n$-OMe,[70,71] and Boc-$(Nle)_n$-OMe[72] peptides are known compounds.

General Procedures for Thionation of Peptides

Procedure A: LR (0.6–1.0 mmol for a dipeptide, 1.8–2.4 mmol for a tripeptide, 3.0–3.6 mmol for a tetrapeptide) was added at room temperature under nitrogen to a solution of the peptide (1 mmol) in anhydrous tetrahydrofuran. The course of the reaction (with stirring at room temperature) was monitored by TLC. After 1–3 d, further LR (0.6–1.0 mmol) was added. After completion of the reaction and removal of the solvent under reduced pressure, the crude product was directly purified by flash chromatography.

Procedure B: P_2S_5 (2.4 mmol) was added at room temperature under nitrogen to a solution of the peptide (1 mmol) in anhydrous tetrahydrofuran. The reaction mixture was subjected to ultrasound and stirred for 3–5 h, during which the bath temperature was increased gradually to 45 °C. The course of the reaction was monitored by TLC. Further additions of P_2S_5 (total amount of 5–10 mmol) were performed over 3–5 h. After completion of the reaction and removal of the solvent under reduced pressure, the crude product was directly purified by flash chromatography.

Z-Gly-ψ[CSNH]-Gly-OMe: Flash chromatography eluent: EtOAc (ethyl acetate)/PE (petroleum ether) 1:1, yield 35%, m.p. 93–95 °C [from EtOAc/PE]. R_f1 = 0.90; R_f2 = 0.95; R_f3 = 0.50. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.44 (br., 1 H, CSNH Gly^2), 7.36 (m, Z CH), 5.45 (br., 1 H, NH Gly^1), 5.14 (s, 2 H, Z CH_2), 4.40 (d, 2 H, Gly CH_2), 4.29 (d, 2 H, Gly CH_2), 3.81 (s, 3 H, OCH_3) ppm. ^{13}C NMR (200 MHz, $CDCl_3$): δ = 200.01 (CS), 168.93 (COOMe), 156 (Z CO), 135.86–128.59–128.36–128.17 (Z), 67.56 (Z CH_2), 52.71 (OCH_3), 52.16 (Gly CH_2), 46.81 (Gly CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3396, 3364, 3295, 1748, 1717, 1706, 1548 cm^{-1}. MS (ESI$^+$): *m/z* = 297.09 [M + H]$^+$.

Z-Gly-ψ[CSNH]-Gly-ψ[CSNH]-Gly-OMe: Flash chromatography eluent: CH_2Cl_2/EtOH (ethanol) 98:2, yield 57%, m.p. 101–103 °C [from EtOAc/PE]. R_f1 = 0.90; R_f2 = 0.95; R_f3 = 0.50. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.01 (br., 1 H, CSNH Gly^2), 8.19 (br., 1 H, CSNH Gly^3), 7.36 (m, Z CH), 5.46 (br., 1 H, NH Gly^1), 5.16 (s, 2 H, Z CH_2), 4.65 (br. d, 2 H, Gly^2 CH_2), 4.40 (d, *J* = 3.48 Hz, 2 H, Gly^3 CH_2), 4.31 (d, *J* = 5.68 Hz, 2 H, Gly^1 CH_2), 3.82 (s, 3 H, OCH_3) ppm. ^{13}C NMR (200 MHz, $CDCl_3$): δ = 199.40 (CS Gly^1), 197.32 (CS Gly^2), 168.77 (COOMe), 156.95 (Z CO), 135.87–128.60–128.35–128.15 (Z), 67.64 (Z CH_2), 54.03 (Gly^2 CH_2), 52.88 (OCH_3), 52.32 (Gly^1 CH_2), 47.06 (Gly^3 CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3294, 1718, 1541 cm^{-1}. MS (ESI$^+$): *m/z* = 370.09 [M + H]$^+$.

Z-Gly-ψ(CSNH)-Gly-ψ[CSNH]-Gly-ψ[CSNH]-Gly-OMe: Flash chromatography eluent: $CHCl_3$/MeOH (methanol) 97:3, yield 56%,

m.p. 56–58 °C [from EtOAc/PE]. R_f1 = 0.90; R_f2 = 0.95; R_f3 = 0.40. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.93 (br., 2 H, CSNH Gly^2 CSNH Gly^3), 8.06 (br., 1 H, CSNH Gly^4), 7.37 (m, Z CH), 5.55 (br., 1 H, NH Gly^1), 5.17 (s, 2 H, Z CH_2), 4.72 (d, 2 H, Gly^2 CH_2), 4.65 (d, *J* = 3.56 Hz, 2 H, Gly^3 CH_2), 4.41 (d, *J* = 4.64 Hz, 2 H, Gly^4 CH_2), 4.33 (d, *J* = 6.00 Hz, 2 H, Gly^1 CH_2), 3.82 (s, 3 H, OCH_3) ppm. ^{13}C NMR (200 MHz, $CDCl_3$): δ = 200.13 (CS), 196.95 (CS), 196.78 (CS), 168.90 (COOMe), 156.95 (Z CO), 135.77–128.62–128.41–128.15 (Z), 67.72 (Z CH_2), 54.51 (Gly^2 Gly^3 CH_2), 52.86 (OCH_3), 52.39 (Gly^1 CH_2), 46.92 (Gly^4 CH_2) ppm. IR (KBr): ṽ = 3358, 1735, 1696, 1585, 1561 cm^{-1}. MS (ESI$^+$): *m*/*z* = 443.08 [M + H]$^+$.

Boc-Ala-ψ[CSNH]-Ala-OMe: Flash chromatography eluent: EtOAc/PE (1:3), yield 67%, oil. R_f1 = 0.90; R_f2 = 0.95; R_f3 = 0.80. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.37 (br., 1 H, CSNH Ala^2), 5.12 (br., 1 H, NH Ala^1), 5.09 (m, 1 H, α-CH), 4.45 (m, 1 H, α-CH), 3.79 (s, 3 H, OCH_3), 1.54 (d, 3 H, CH_3 Ala), 1.54 (d, 3 H,CH_3 Ala), 1.45 (s, 9 H, 3 × CH_3 Boc) ppm. ^{13}C NMR (200 MHz, $CDCl_3$): δ = 205.27 (CS), 172.60 (COOMe), 155.90 (COBoc), 79.50 (C_4 Boc), 68.34 (Ala^1 CH), 53.30 (Ala^2 CH), 52.84 (OCH_3), 28.44 (3 × CH_3 Boc), 21.65 (Ala^1 CH_3), 17.17 (Ala^2 CH_3) ppm. IR (KBr): ṽ = 3261, 1746, 1689 cm^{-1}. MS (ESI$^+$): *m*/*z* = 291.13 [M + H]$^+$.

Boc-Ala-ψ[CSNH]-Ala-ψ[CSNH]-Ala-OMe: Flash chromatography eluent: $CHCl_3$/EtOH (97:3), yield 43%, m.p. 115–117 °C [from EtOAc/PE]. R_f1 = 0.90; R_f2 = 0.95; R_f3 = 0.80. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.96 (br. d, *J* = 5.72 Hz, 1 H, CSNH Ala^2), 8.17 (br. d, *J* = 5.20 Hz, 1 H, CSNH Ala^3), 5.30 (m, 1 H, α-CH Ala^2), 5.14 (br., 1 H, NH Ala^1), 5.06 (m, 1 H, α-CH Ala^3), 4.47 (m, 1 H, α-CH Ala^1), 3.80 (s, 3 H, OCH_3), 1.56 (d, *J* = 6.64 Hz, 3 H, CH_3 Ala^2), 1.52 (d, *J* = 7.12 Hz, 3 H, CH_3 Ala^3), 1.47 (d, *J* = 6.96 Hz, 3 H, CH_3 Ala^1), 1.44 (s, 9 H, 3 × CH_3Boc) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 203.65 (CS Ala^1), 202.65 (CS Ala^2), 172.21 (COOMe), 155.12 (CO Boc), 80.53 (C_4 Boc),59.19 (α-CH), 57.20 (α-CH), 53.41 (α-CH), 52.83 (OCH_3), 28.32 (CH_3 Boc), 21.61 (CH_3Ala), 20.76 (CH_3Ala), 19.95 (CH_3Ala) ppm. IR (KBr): ṽ = 3262, 1726, 1691, 1595 cm^{-1}. MS (ESI$^+$): *m*/*z* = 378.15 [M + H]$^+$.

Boc-Ala-ψ[CSNH]-Ala-ψ[CSNH]-Ala-ψ[CSNH]-Ala-OMe: Flash chromatography eluent: $CHCl_3$/MeOH (97:3), yield 49%, m.p. 150–151 °C (from EtOAc/PE). R_f1 = 0.90; R_f2 = 0.95; R_f3 = 0.80. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.91 (br., 1 H, CSNH Ala^2), 8.70 (br. d, *J* = 5.72 Hz, 1 H, CSNH Ala^3), 8.15 (br. d, *J* = 5.92 Hz, 1 H, CSNH Ala^4), 5.26 (m, 2 H, α-CH Ala^2 α-CH Ala^3), 5.18 (br., 1 H, NH Ala^1), 5.07 (m, 1 H, α-CH Ala^4), 4.48 (m, 1 H, α-CH Ala^1), 3.80 (s, 3 H, OCH_3), 1.58 (2 × d, *J* = 6.04 Hz, 6 H, CH_3 Ala^2 CH_3 Ala^3), 1.54 (d, *J* = 7.16 Hz, 3 H, CH_3 Ala^4), 1.48 (d, *J* = 6.92 Hz, 3 H, CH_3 Ala^1), 1.44 (s, 9 H, 3 × CH_3 Boc) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 203.81 (CS Ala^1), 202.22 (CS Ala^3), 201.26 (CS Ala^2), 172.21 (COOMe), 155.47 (COBoc), 80.75 (C_4 Boc), 59.19 (2α-CH), 57.44 (α-CH), 53.53 (α-CH), 52.84 (OCH_3), 28.32 (CH_3 Boc), 21.52 (CH_3 Ala), 20.78 (2 × CH_3Ala), 16.97 (CH_3 Ala) ppm. IR (KBr): ṽ = 3259, 1730, 1691, 1595 cm^{-1}. MS (ESI$^+$): *m*/*z* = 465.16 [M + H]$^+$.

Boc-Nle-ψ(CSNH)-Nle-OMe: Flash chromatography eluent: EtOAc/PE (1:9), yield 27%, oil. R_f1 = 0.95; R_f2 = 0.95; R_f3 = 0.85. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.24 (br. d, *J* = 7.26 Hz, 1 H, CSNH Nle^2), 5.14 (m, 1 H, α-CH),5.12 (br., 1 H, NH Nle^1), 4.29 (m, 1 H, α-CH), 3.77 (s, 3 H, OCH_3), 1.44 (s, 9 H, 3 × CH_3 Boc), 2.04 (m, 4 H, 2 × Nle β-CH_2), 1.35–1.26 (m, 8 H, 2 × Nle γ-CH_2, δ-CH_2), 0.89 (m, 9 H, 2 × CH_3 Nle) ppm. ^{13}C NMR (200 MHz, $CDCl_3$): δ = 205.13 (CS), 172.60 (COOMe), 155.90 (COBoc), 80.21 (C_4Boc), 61.48 (α-CH Nle), 57.62 (α-CH Nle), 52.62 (OCH_3), 35.13 (2 × Nle β-CH_2), 28.44 (3 × CH_3 Boc), 28.01 (Nle γ-CH_2), 27.23 (Nle γ-CH_2), 22.53 (2 × Nle δ-CH_2), 13.93 (2 × CH_3 Nle) ppm. IR (KBr): ṽ = 3274, 1748, 1691 cm^{-1}. MS (ESI$^+$): *m*/*z* = 375.24 [M + H]$^+$.

Boc-Nle-ψ[CSNH]-Nle-ψ[CSNH]-Nle-OMe: Flash chromatography eluent: EtOAc/PE (2:9), yield 27%, oil. R_f1 = 0.95; R_f2 = 0.95; R_f3 = 0.90. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (br. d, *J* = 7.04 Hz, 1 H, CSNH), 8.02 (br. d, *J* = 7.56 Hz, 1 H, CSNH), 5.27 (m, 1 H, α-CH), 5.10 (m, 1 H, α-CH), 5.10 (br., 1 H, NH Nle^1), 4.29 (m, 1 H, α-CH), 3.78 (s, 3 H, OCH_3), 2.01 (m, 2 H, Nle^2 β-CH_2), 2.00 (m, 2 H, Nle^3 β-CH_2), 1.93 (m, 2 H, Nle^1 β-CH_2), 1.94 (m, 2 H, Nle^2 γ-CH_2), 1.84 (m, 2 H, Nle^3 γ-CH_2), 1.71 (m, 2 H, Nle^1 γ-CH_2), 1.44 (s, 9 H, 3 × CH_3Boc), 1.34 (m, 2 H, Nle^2 δ-CH_2), 1.32 (m, 4 H, Nle^1 Nle^3 δ-CH_2), 0.89 (m, 9 H, 3 × CH_3 Nle) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 204.01 (CS Ala^1), 202.16 (CS Ala^2), 171.60 (COOMe), 155.57 (COBoc), 80.21 (C_4Boc), 64.18 (α-CH Nle), 63.94 (α-CH Nle), 61.59 (α-CH Nle), 52.62 (OCH_3), 35.14 (Nle β-CH_2), 34.43 (Nle β-CH_2), 30.70 (Nle β-CH_2), 28.34 (3 × CH_3Boc), 27.83 (Nle γ-CH_2), 27.30 (2 × Nle γ-CH_2), 22.27 (3 × Nle δ-CH_2), 13.90 (3 × CH_3 Nle) ppm. IR (KBr): ṽ = 3295, 1731, 1691 cm^{-1}. MS (ESI$^+$): *m*/*z* = 504.29 [M + H]$^+$.

Boc-Nle-ψ(CSNH)-Nle-ψ[CSNH]-Nle-ψ[CSNH]-Nle-OMe: Flash chromatography eluent: EtOAc/PE (2:8), yield 33%, oil. R_f1 = 0.95; R_f2 = 0.95; R_f3 = 0.90. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.64 (br., 1 H, CSNH Nle^2), 8.37 (br. d, *J* = 7.00 Hz, 1 H, CSNH Nle^3), 8.06 (br. d, *J* = 5.18 Hz, 1 H, CSNH Nle^4), 5.23 (m, 2 H, α-CH Nle^2 α-CH Nle^3), 5.16 (br., 1 H, NH Nle^1), 5.13 (m, 1 H, α-CH Nle^4), 4.31 (m, 1 H, α-CH Nle^1), 3.78 (s, 3 H, OCH_3), 1.98 (m, 2 H, Nle^2 β-CH_2), 2.01 (m, 2 H, Nle^3 β-CH_2), 2.00 (m, 2 H, Nle^4 β-CH_2), 1.93 (m, 2 H, Nle^1 β-CH_2), 1.90 (m, 2 H, Nle^2 γ-CH_2), 1.91 (m, 2 H, Nle^3 γ-CH_2), 1.83 (m, 2 H, Nle^4 γ-CH_2), 1.71 (m, 2 H, Nle^1 γ-CH_2), 1.44 (s, 9 H, 3 × CH_3Boc), 1.31 (m, 2 H, Nle^3 δ-CH_2), 1.30 (m, 4 H, Nle^1 Nle^4 γ-CH_2), 1.28 (m, 2 H, Nle^2 δ-CH_2), 0.89–0.88 (m, 12 H, 4 × CH_3 Nle) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 203.86 (CS), 201.81 (CS), 201.25 (CS), 171.59 (COOMe), 155.57 (COBoc), 80.33 (C4Boc), 64.18 (α-CH Nle), 63.94 (α-CH Nle), 61.59 (α-CH Nle), 57.60 (α-CH Nle), 52.62 (OCH_3), 35.07 (Nle β-CH_2), 34.41 (2 × Nle β-CH_2), 30.87 (Nle β-CH_2), 28.44 (3 × CH_3Boc), 27.83 (Nle γ-CH_2), 27.40 (Nle γ-CH_2), 27.29 (Nle γ-CH_2), 27.20 (Nle γ-CH_2), 22.35 (4 × Nle δ-CH_2), 13.81 (4 × CH_3 Nle) ppm. IR (KBr): ṽ = 3286, 1729, 1691 cm^{-1}. MS (ESI$^+$): *m*/*z* = 633.33 [M + H]$^+$.

^{1}H NMR Spectroscopy: All NMR experiments were performed at 298 K with a Bruker AVANCE DRX-400 instrument operating at the frequency of 400 MHz for ^{1}H, with use of the TOPSPIN software package. The homonuclear 2D-spectra were recorded in $CDCl_3$ as solvent. The DQF-COSY[84] spectra were acquired in the magnitude mode, and CLEAN-TOCSY[85,86] (spin lock period 45, 64, 70, or 140 ms) and NOESY (mixing time 400 ms) spectra were recorded in the phase-sensitive mode. All homonuclear 2D-spectra were acquired by collecting 400 experiments of 32 scans each, with a relaxation delay of 1–1.2 s and 2000 data points. The spectral width was 11 ppm in each dimension. The assignments of the chemical shifts of each residue were obtained by means of 2D ^{1}H,^{13}C correlation spectra. HMBC[87] experiments with selective excitation in the CO region were performed with use of a long-range coupling constant of 7.5 Hz and a spectral width in F1 of 60 ppm centered at δ = 190 ppm.

X-Ray Diffraction: Single crystals of Z-Gly-ψ[CS-NH]-Gly-ψ[CS-NH]-Gly-OMe were grown by slow evaporation of a methanol solution. X-ray diffraction data were collected with an Oxford Diffraction Gemini E four-circle kappa diffractometer fitted with a 92 mm EOS CCD detector, with use of graphite-monochromated

Mo-K_α radiation (λ = 0.71069 Å). The sample-to-detector distance was 50 mm. A total of 876 frames were collected by 1.0° ω oscillation with exposure times of 6 or 25 s, depending on the θ values, in the 2.35°–28.27° θ range. Data collection and reduction were performed with the CrysAlisPro software (version 1.171.35.19, Agilent Technologies). A semiempirical absorption correction based on the multi-scan technique using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm, was applied. Overall, 33002 reflections were integrated, of which 4627 are independent (R_{int} = 0.0246). The structure was solved by direct methods with use of the SIR 2002 program[90] and refined by full-matrix, least-squares procedures on F^2, with use of all data, by application of the SHELXL-97 program.[91] H atoms were calculated at idealized positions and refined by use of a riding model. Relevant crystal data and structure refinement parameters are listed in Table 3.

CCDC-914716 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Copies of the mass, ^{1}H NMR, and ^{13}C NMR spectra.

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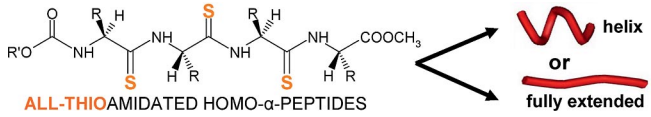

ALL-THIOAMIDATED HOMO-α-PEPTIDES

Short series of terminally protected, fully thioamidated, homo-α-peptides were synthesized. For the first time, their preparation was achieved in single-step fashion through direct thionation of their oxygen-ated precursors. Conformation analysis confirms that the thioamidated α-amino acid residues can easily adopt either folded or fully extended conformations.

Keywords: Conformation analysis / Synthetic methods / Peptides / Peptidomimetics

