

Synthesis and structural studies of peptides containing a glucose-derived furanoid sugar amino acid

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Received 29 January 2005; revised 23 February 2005; accepted 1 March 2005

Available online 16 March 2005

Abstract—Conformational analysis of peptides containing a glucose-derived furanoid sugar amino acid (Gaa) by detailed NMR and constrained MD studies revealed that peptides with repeating Gaa-Leu-Val units had conformational signatures very similar to those of linear homooligomers of Gaa.

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The usefulness of sugar amino acids as conformationally constrained multifunctional scaffolds in peptidomimetic studies has been amply demonstrated by many researchers worldwide.¹ Besides, they have also emerged as an important class of synthetic monomers leading to many de novo oligomeric libraries.^{2,3} We have shown earlier that the linear tetramer of a glucose-derived furanoid sugar amino acid (Gaa) had a well-defined structure in CDCl₃ with repeating β -turns, each involving a 10-membered ring structure with intramolecular hydrogen bonds between NH_{*i*} → C=O_{*i-2*}.^{3b} In the present communication, we have studied the conformational tolerance of the structure of Gaa homooligomers by replacing alternate Gaa units with dipeptides from natural amino acids that gave peptides **1–3** with repeating Gaa-Leu-Val units (Fig. 1). It was assumed that such assemblies might nucleate the formation of β -hairpin structures as the Leu-Val units being more flexible than Gaa were expected to disrupt the interwoven (10/10/10...)-H-bonded structure of Gaa-oligomers.⁴ However, detailed NMR and constrained MD studies showed that the peptides **1–3** had conformational signatures very similar to those of homooligomers of Gaa with repetitive H-bonding patterns reminiscent of the helical structures of natural amino acid-containing peptides.

Peptides **1–3** were synthesized following standard solution phase peptide synthesis methods⁵ using 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride

(EDCI) and 1-hydroxybenzotriazole (HOBt) as coupling agents and dry DMF and/or CH₂Cl₂ as solvents. While the *tert*-butoxycarbonyl (Boc) group was used for N-protection, the C-terminal was protected as a methyl ester (OMe). Deprotection of the former was done in TFA–CH₂Cl₂ (1:1) and saponification of the latter was performed using LiOH in THF–MeOH–H₂O. In the racemization-free fragment condensation strategy that was followed, Boc-Gaa(Bn₂)-OH⁶ was first coupled with the dipeptide H-Leu-Val-OMe as efficiently as with any normal amino acid using the reagents mentioned above to give the tripeptide Boc-Gaa(Bn₂)-Leu-Val-OMe in 90% yield. After removal of the Boc protection, the resulting tripeptide, H-Gaa(Bn₂)-Leu-Val-OMe, was reacted with Boc-Leu-Val-OH to furnish the peptide **1** in 85% yield.⁷ Coupling of Boc-Gaa(Bn₂)-Leu-Val-OH with H-Gaa(Bn₂)-Leu-Val-OMe gave **2** in 80% yield.⁷ Finally, Boc deprotection of **2** followed by coupling with Boc-Leu-Val-OH provided the third peptide **3**.⁷ The peptides were purified by silica gel column chromatography and fully characterized by spectroscopic methods before conformational studies.

Peptide **1** is equivalent to a hexapeptide containing one unit of the dipeptide isostere Gaa and two dipeptide units of Leu-Val at both ends. Extensive NMR study⁸ showed that peptide **1** folds into a stable repetitive β -turn conformation similar to that observed for homooligomers of furanoid sugar amino acids. The spectral parameters are given in Table 1. Three out of five-amide protons, GaaNH (6.89 ppm), Leu(2)NH⁹ (7.84 ppm) and Val(2)NH (7.04 ppm), indicate their likely participation in intramolecular H-bonding (Fig. 2). However, a solvent titration study showed that only Leu(2)NH

Keywords: Sugar amino acids; H-bonding; Conformation; NMR.

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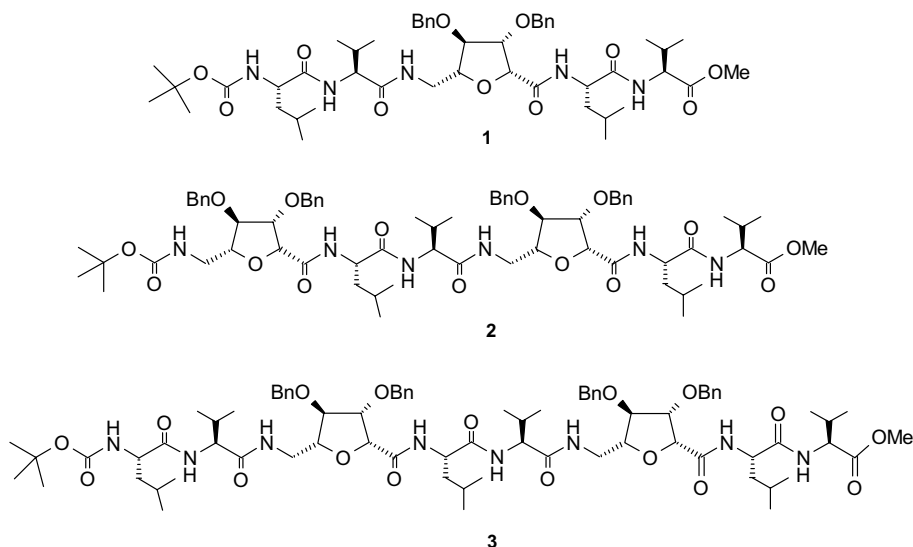


Figure 1. Structures of peptides 1–3.

Table 1. Chemical shift values of peptide 1 in CDCl₃, 500 MHz at 30 °C

Protons	Leu(1)	Val(1)	Leu(2)	Val(2)
NH	4.85 (d, $J = 7.4$)	6.60 (d, $J = 8.8$)	7.84 (d, $J = 9.3$)	7.04 (d, $J = 8.6$)
C α H	4.05 (m)	4.18 (dd, $J = 6.9, 8.8$)	4.70 (dt, $J = 5.0, 9.3$)	4.47 (dd, $J = 5.6, 8.6$)
C β H	1.65 (m)	2.19 (m)	1.83 (m)	2.05 (m)
C β' H	1.50 (m)	—	1.75 (m)	—
C γ H	1.50 (m)	0.91 (d) ^a	1.71 (m)	0.88 (d) ^a
C γ' H	—	0.91 (d) ^a	—	0.88 (d) ^a
C δ H	0.93 (d) ^a	—	0.96 (d) ^a	—
C δ' H	0.93 (d) ^a	—	0.96 (d) ^a	—

Others: 6.89 (dd, $J = 4.9, 7.5$, GaaNH), 4.67 (d, $J = 4.2$, GaaC2H), 4.26 (d, $J = 4.2$, GaaC3H), 3.67 (d, $J = 5.5$, GaaC4H), 4.15 (ddd, $J = 1.2, 5.5, 9.3$, GaaC5H), 3.14 (m, GaaC6H), 3.88 (m, GaaC6'H), 1.47 (s, Boc), 3.58 (s, OMe), 4.66–4.21 (m, 4H, OCH₂Ph), 7.15–7.35 (m, aromatic protons).

^a The J value could not be determined due to the overlapping of signals.

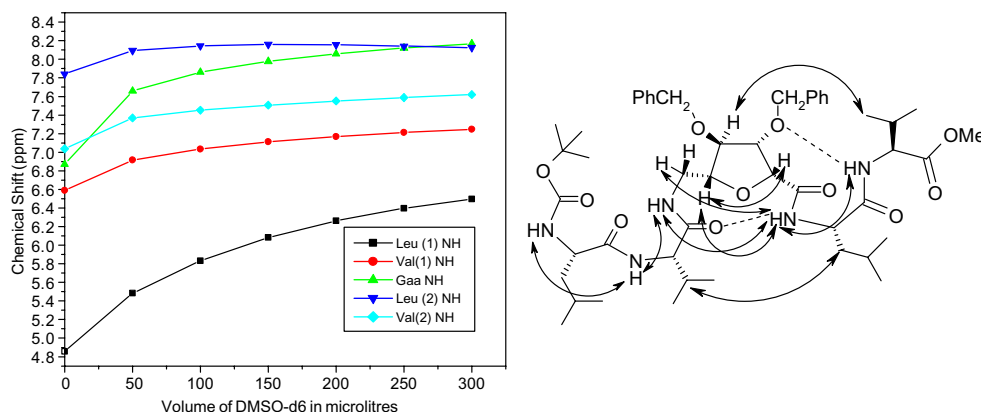


Figure 2. Solvent titration plot and schematic representation of the H-bonding and long-range NOE correlations observed for peptide 1.

and Val(2)NH participate in intramolecular H-bonding, because of the small change of 0.28 and 0.59 ppm, respectively, in their chemical shifts when 33% v/v DMSO-*d*₆ was added. The cross-correlations, Leu(1)-NH ↔ Val(1)NH, Val(1)NH ↔ GaaNH, GaaNH ↔ Leu(2)NH, Leu(2)NH ↔ Val(2)NH, GaaC2H ↔ GaaC5H, GaaNH ↔ GaaC5H, GaaNH ↔ GaaC6H, Val(2)NH ↔ GaaC4H, Val(2)CH₃ ↔ GaaC4H, in the

ROESY spectrum (Fig. 2) suggest possible H-bonds between Leu(2)NH → Val(1)CO with a 10-membered β-turn structure and a 9-membered pseudo-β-turn structure between Val(2)NH → GaaC3OBn. In addition, the cross-peaks between Leu(1)NH ↔ Val(1)NH and Val(1)NH ↔ GaaNH hint at a significant population of molecular structures with a β-turn between GaaNH → BocCO.

Table 2. Chemical shift values of peptide **2** in CDCl₃, 500 MHz at 30 °C

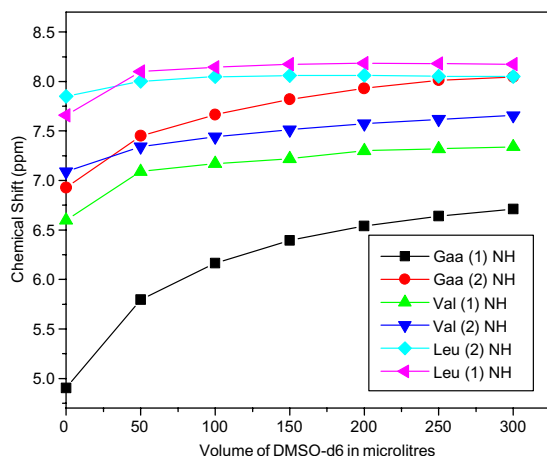
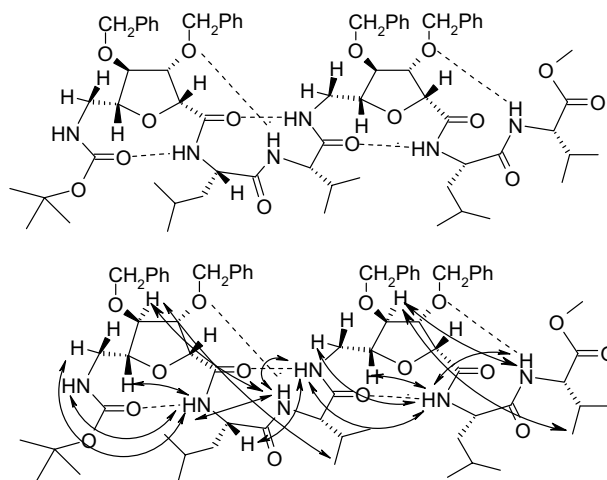
Protons	Leu(1)	Val(1)	Leu(2)	Val(2)
NH	7.69 (d, $J = 8.5$)	6.66 (d, $J = 8.7$)	7.85 (d, $J = 9.1$)	7.09 (d, $J = 8.6$)
C α H	4.61 (m)	4.21 (m)	4.65 (m)	4.47 (dd, $J = 5.7, 8.6$)
C β H	1.86 (m)	2.21 (m)	1.78 (m)	1.98 (m)
C β' H	1.71 (m)	—	1.71 (m)	—
C γ H	1.71 (m)	0.90 (d) ^a	1.67 (m)	0.83 (d) ^a
C γ' H	—	0.90 (d) ^a	—	0.83 (d) ^a
C δ H	0.92 (d) ^a	—	0.91 (d) ^a	—
C δ' H	0.92 (d) ^a	—	0.91 (d) ^a	—

Others: 4.91 (dd, $J = 5.4, 7.9$ Hz, Gaa(1)NH), 4.68 (d, $J = 4.2$, Gaa(1)C2H), 4.23 (m, Gaa(1)C3H), 3.50 (m, Gaa(1)C4H), 4.03 (m, Gaa(1)C5H), 3.68 (m, Gaa(1)C6H), 2.97 (m, Gaa(1)C6'H), 6.94 (dd, $J = 5.1, 7.1$, Gaa(2)NH), 4.63 (d, $J = 4.23$, Gaa(2)C2H), 4.23 (d, $J = 4.23$, Gaa(2)C3H), 3.58 (m, Gaa(2)C4H), 4.05 (m, Gaa(2)C5H), 3.72 (m, Gaa(2)C6H), 3.02 (m, Gaa(2)C6'H), 1.44 (s, Boc), 3.53 (s, OMe), 4.70–4.18 (m, 8H, OCH₂Ph), 7.11–7.35 (m, aromatic protons).

^a The J value could not be determined due to the overlapping of signals.

Peptide **2** contains two sugar amino acid residues and two dipeptide (Leu-Val) templates, with the molecular formula Gaa(1)-Leu(1)-Val(1)-Gaa(2)-Leu(2)-Val(2). The spectral parameters obtained from a ca. 8 mM solution in CDCl₃ are given in Table 2. The hydrogen bonding studies indicate that five out of six amide protons are involved in intramolecular H-bonding as they appear downfield in the ¹H NMR spectrum. In addition, Gaa(2)NH, Leu(1)NH, Leu(2)NH, Val(1)NH and Val(2)NH showed very small shifts in the solvent titration studies in agreement with their participation in H-bonding (Fig. 3).

The long-range cross-correlations between Gaa(1)NH $\leftrightarrow$ Leu(1)NH, Leu(1)NH $\leftrightarrow$ Val(1)NH, Val(1)NH $\leftrightarrow$ Gaa(2)NH, Gaa(2)NH $\leftrightarrow$ Leu(2)NH, Leu(2)NH $\leftrightarrow$ Val(2)NH, Leu(1)NH $\leftrightarrow$ Gaa(1)C6H, Leu(1)NH $\leftrightarrow$ Gaa(1)C5H, Leu(2)NH $\leftrightarrow$ Gaa(2)C6H, Leu(2)NH $\leftrightarrow$ Gaa(2)C5H, Boc $\leftrightarrow$ Gaa(1)C5H, Val(1)NH $\leftrightarrow$ Leu(2)C β H and Val(1)C β H $\leftrightarrow$ Leu(2)C β H (Fig. 4) coupled with the intramolecular H-bonding of Leu(1)NH, Gaa(2)NH and Leu(2)NH suggest the presence of possible H-bonds between Leu(1)NH $\rightarrow$ BocCO, Gaa(2)NH $\rightarrow$ Gaa(1)CO and Leu(2)NH $\rightarrow$ Val(1)CO resulting in repetitive three 10-membered β -turn like structures around Gaa(1), Leu(1)-Val(1) and Gaa(2) residues. The equal intensities of the cross-peaks between

**Figure 3.** Solvent titration plot of peptide **2**.**Figure 4.** Schematic representation of the H-bonding pattern (10/10/9-) and the long-range NOE correlations observed for peptide **2**.

Val(1)NH $\leftrightarrow$ Leu(1)C α H compared to Gaa(2)NH $\leftrightarrow$ Val(1)C α H support the existence of a type-I β -turn between Leu(1)-Val(1) residues, which results in the proximity of Val(1)NH towards Gaa(1)C3OBn and the formation of a nine-membered intramolecular H-bond between them. In addition, the C-terminal cross-peaks between Val(2)NH $\leftrightarrow$ Gaa(2)C4H and Val(2)-Me $\leftrightarrow$ Gaa(2)C4H indicate the possibility of a nine-membered pseudo β -turn structure between the Val(2)NH $\rightarrow$ Gaa(2)C3OBn H-bond. Thus, the resulting structure possesses a repetitive 10/10/9-intramolecular H-bonding pattern.

The constrained MD study of peptide **2** using distance constraints was performed for 600 ps totalling 100 cycles of the simulated annealing protocol. During the process, 20 structures were collected after each and every 5-cycle intervals and these were energy minimized again by removing the constraints. One of these 20 low-energy conformations is shown in Figure 5.

Peptide **3** is larger than peptide **2**, containing two Gaa residues and three dipeptide Leu-Val units, with the molecular formula Leu(1)-Val(1)-Gaa(1)-Leu(2)-Val(2)-Gaa(2)-Leu(3)-Val(3) and is similar to a decapeptide.

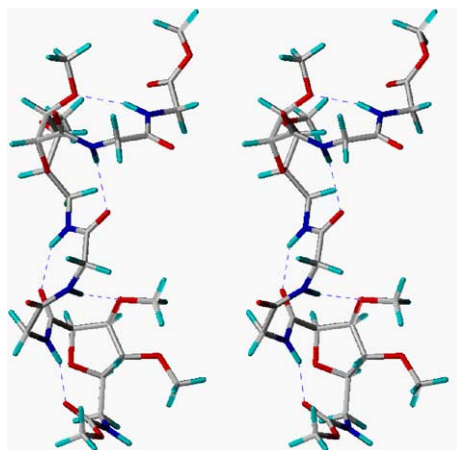


Figure 5. Stereoview of one of the 20 low-energy conformations of peptide **2** (for clarity the side chains are not shown).

The detailed solution conformational study was carried out in CDCl_3 solution and the majority of the spectral parameters are given in Table 3. The intramolecular H-bonding information was derived from the downfield appearance of amide proton chemical shifts as well as a solvent titration study. Five out of the eight amide protons, Leu(2)NH (7.79 ppm), Leu(3)NH (8.0 ppm), Gaa(2)NH (7.56 ppm), Val(2)NH (6.73 ppm) and Val(3)NH (7.17 ppm) appear in the downfield region. Also, their chemical shifts changed by small amounts—0.19 ppm for Leu(1)NH, 0.06 ppm for Leu(2)NH, 0.51 ppm for Gaa(2)NH, 0.63 ppm for Val(2)NH and 0.48 ppm for Val(3)NH, on addition of 33% v/v $\text{DMSO}-d_6$ to the CDCl_3 solution of **3**, thereby confirming their involvement in H-bonding (Fig. 6).

The long-range cross-correlations of the amide protons throughout the length of the chain, Leu(1)NH $\leftrightarrow$ Val(1)NH, Val(1)NH $\leftrightarrow$ Gaa(1)NH, Gaa(1)NH $\leftrightarrow$ Leu(2)NH, Leu(2)NH $\leftrightarrow$ Val(2)NH, Val(2)NH $\leftrightarrow$ Gaa(2)NH, Gaa(2)NH $\leftrightarrow$ Leu(3)NH, Leu(3)NH $\leftrightarrow$ Val(3)NH, indicate that there is a well-defined folded conformation in solution. Additional long-range cross-correlations between Leu(2)NH $\leftrightarrow$ Gaa(1)C α H, Leu(2)NH $\leftrightarrow$ Gaa(1)C β H, Leu(2)NH $\leftrightarrow$ Val(1)C α H, Val(1)C γ Me $\leftrightarrow$ Leu(2)C α H, Val(1)C β H $\leftrightarrow$ Leu(2)C β H,

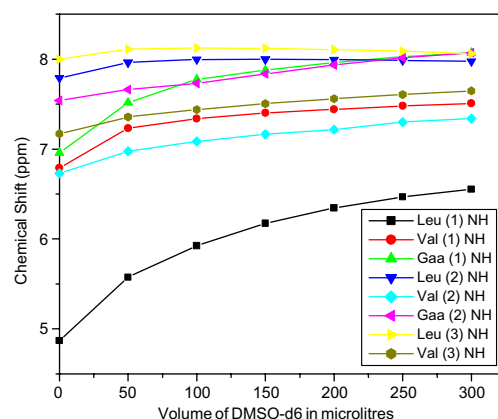


Figure 6. Solvent titration plot of peptide **3**.

Gaa(2)NH $\leftrightarrow$ Leu(2)C α H, Val(2)C β H $\leftrightarrow$ Leu(3)C β H (Fig. 7) unequivocally support the formation of the above-mentioned H-bonds between Leu(2)NH $\rightarrow$ Val(1)CO, Gaa(2)NH $\rightarrow$ Gaa(1)CO and Leu(3)NH $\rightarrow$ Val(2)CO. The comparable strong cross-correlations between Val(1)NH $\leftrightarrow$ Leu(1)C α H and Val(2)NH $\leftrightarrow$ Leu(1)C α H to Gaa(1)NH $\leftrightarrow$ Val(1)C α H and Gaa(2)NH $\leftrightarrow$ Val(2)C α H indicates that the turns involving Leu-Val residues are type-I β -turns, which result in the close proximity of Val(2)NH towards Gaa(1)-C3OBn and formation of a nine-membered pseudo- β -turn structure between Val(2)NH Gaa(1)C3OBn. This was confirmed by the observation of cross-correlations between Val(2)NH $\leftrightarrow$ Gaa(1)C4H and Val(2)-Me $\leftrightarrow$ Gaa(1)C4H in the ROESY spectrum. Similarly, at the C-terminus correlations between Val(3)NH $\leftrightarrow$ Gaa(2)C4H and Val(3)Me $\leftrightarrow$ Gaa(2)C4H confirmed the nine-membered pseudo β -turn conformation between Val(3)NH $\rightarrow$ Gaa(2)C3OBn. The resulting structure contains a repetitive 10/10/9-H-bonding pattern.

The constrained MD studies were carried out by using various distance constraints obtained from NMR experiments. During the simulation, 20 low-energy conformations were sampled after each and every 5 ps interval and these were energy minimized again by removing the constraints. A stereoview of one of the 20 low-energy conformations is shown in Figure 8.

Table 3. Chemical shift values of peptide **3** in CDCl_3 , 500 MHz at 30 $^\circ\text{C}$

Protons	Leu(1)	Val(1)	Leu(2)	Val(2)	Leu(3)	Val(3)
NH	4.87 (d, $J = 7.8$)	6.79 (d, $J = 9.4$)	7.79 (d, $J = 8.3$)	6.73 (d, $J = 9.3$)	8.00 (d, $J = 9.4$)	7.17 (d, $J = 8.6$)
C α H	4.08 (m)	4.50 (m)	4.63 (m)	4.28 (m)	4.70 (ddd, $J = 4.6, 10.2$)	4.43 (dd, $J = 5.8, 8.6$)
C β H	1.63 (m)	2.18 (m)	1.69 (m)	2.12 (m)	1.83 (m)	2.03 (m)
C β' H	1.48 (m)	—	1.69 (m)	—	1.73 (m)	—
C γ H	1.48 (m)	0.90 (d) ^a	1.69 (m)	0.91 (d) ^a	1.65 (m)	0.88 (d) ^a
C γ' H	—	0.87 (d) ^a	—	0.89 (d) ^a	—	0.88 (d) ^a
C δ H	0.90 (d) ^a	—	0.95 (d) ^a	—	0.92 (d) ^a	—
C δ' H	0.90 (d) ^a	—	0.95 (d) ^a	—	0.92 (d) ^a	—

Others: 6.96 (t, $J = 5.3$, Gaa(1)NH), 4.66 (d, $J = 4.2$, Gaa(1)C2H), 4.26 (m, Gaa(1)C3H), 3.59 (m, Gaa(1)C4H), 4.18 (m, 1H, Gaa(1)C5H), 3.81 (m, 1H, Gaa(1)C6H), 3.17 (m, 1H, Gaa(1)C6'H), 7.56 (dd, $J = 4.7, 7.2$, Gaa(2)NH), 4.66 (d, $J = 4.23$, Gaa(2)C2H), 4.24 (m, Gaa(2)C3H), 3.59 (m, Gaa(2)C4H), 4.09 (m, 1H, Gaa(2)C5H), 3.89 (m, 1H, Gaa(2)C6H), 2.98 (m, 1H, Gaa(2)C6'H), 4.11–4.68 (m, OCH_2Ph), 7.11–7.35 (m, aromatic protons), 3.54 (s, OMe), 1.44 (s, Boc).

^a The J value could not be determined due to the overlapping of signals.

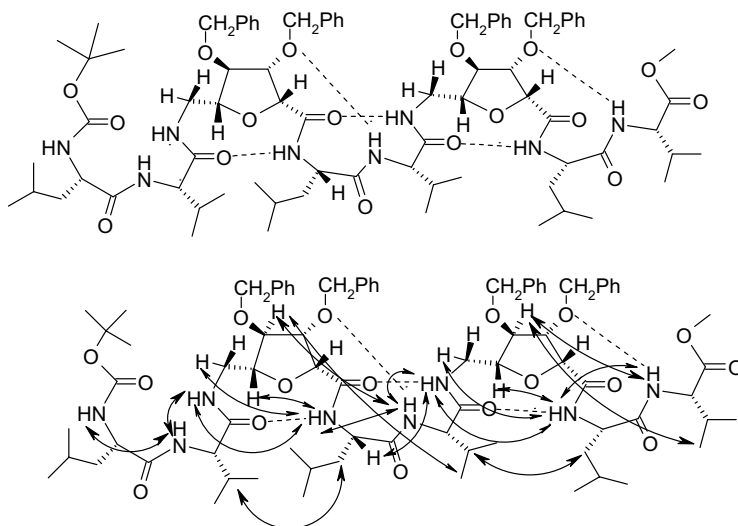


Figure 7. Schematic representation of the H-bonding and long-range NOE correlations observed for peptide 3.

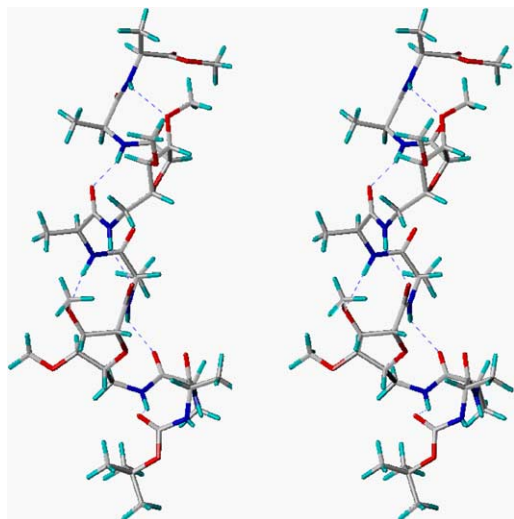


Figure 8. Stereoview of one of the 20 low-energy conformations of peptide 3 (for clarity the side chains are not shown).

In summary, although peptides with repeating Gaa-Leu-Val units did not nucleate the expected β -hairpin structures, they displayed well-defined turn structures with repetitive 10/10/9-H-bonding patterns, very similar to those seen earlier in Gaa-oligomers^{3b} and other Gaa-containing peptides.¹⁰ Such oligomeric assemblies with large propensity for helical structures can play significant roles in recognizing and binding to suitable receptors in biological systems. These efforts should permit the design of compounds that will successfully mimic the structures and functions of biopolymers.

Acknowledgements

We thank CSIR (S.R. and S.K.K.), New Delhi for research fellowships and DST, New Delhi for financial support.

References and notes

- For reviews on sugar amino acids see: (a) Chakraborty, T. K.; Srinivasu, P.; Tapadar, S.; KrishnaMohan, B. *J. Chem. Sci.* **2004**, *116*, 187–207; (b) Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491–514; (c) Chakraborty, T. K.; Ghosh, S.; Jayaprakash, S. *Curr. Med. Chem.* **2002**, *9*, 421–435; (d) Chakraborty, T. K.; Jayaprakash, S.; Ghosh, S. *Comb. Chem. High Throughput Screening* **2002**, *5*, 373–387; (e) Schweizer, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 230–253; (f) Peri, F.; Cipolla, L.; Forni, E.; La Ferla, B.; Nicotra, F. *Chemtracts Org. Chem.* **2001**, *14*, 481–499.
- For some important work on cyclic oligomers and homooligomers of sugar amino acids and related compounds see: (a) Bornaghi, L. F.; Wilkinson, B. L.; Kiefel, M. J.; Poulsen, S.-A. *Tetrahedron Lett.* **2004**, *45*, 9281–9284; (b) Mayes, B. A.; Stetz, R. J. E.; Ansell, C. W. G.; Fleet, G. W. J. *Tetrahedron Lett.* **2004**, *45*, 153–156; (c) Mayes, B. A.; Simon, L.; Watkin, D. J.; Ansell, C. W. G.; Fleet, G. W. J. *Tetrahedron Lett.* **2004**, *45*, 157–162; (d) Mayes, B. A.; Cowley, A. R.; Ansell, C. W. G.; Fleet, G. W. J. *Tetrahedron Lett.* **2004**, *45*, 163–166; (e) Chakraborty, T. K.; Srinivasu, P.; Bikshapathy, E.; Nagaraj, R.; Vairamani, M.; Kumar, S. K.; Kunwar, A. C. *J. Org. Chem.* **2003**, *68*, 6257–6263; (f) van Well, R. M.; Marinelli, L.; Erkelens, K.; van der Marel, G. A.; Lavecchia, A.; Overkleeft, H. S.; van Boom, J. H.; Kessler, H.; Overhand, M. *Eur. J. Org. Chem.* **2003**, 2303–2313; (g) Stöckle, M.; Voll, G.; Günther, R.; Lohof, E.; Locardi, E.; Gruner, S.; Kessler, H. *Org. Lett.* **2002**, *4*, 2501–2504; (h) Campbell, J. E.; Englund, E. E.; Burke, S. D. *Org. Lett.* **2002**, *4*, 2273–2275; (i) Gruner, S. A. W.; Truffault, V.; Voll, G.; Locardi, E.; Stöckle, M.; Kessler, H. *Chem. Eur. J.* **2002**, *8*, 4365–4376; (j) Locardi, E.; Stöckle, M.; Gruner, S.; Kessler, H. *J. Am. Chem. Soc.* **2001**, *123*, 8189–8196; (k) Gruner, S. A. W.; Kéri, G.; Schwab, R.; Venetainer, A.; Kessler, H. *Org. Lett.* **2001**, *3*, 3723–3725; (l) van Well, R. M.; Overkleeft, H. S.; Overhand, M.; Carstenen, E. V.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2000**, *41*, 9331–9335; (m) Lohof, E.; Planker, E.; Mang, C.; Burkhardt, F.; Dechantreiter, M. A.; Haubner, R.; Wester, H.-J.; Schwaiger, M.; Hölzemann, G.; Goodman, S. L.; Kessler, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2761–2764.

3. For some important work on acyclic oligomers and homooligomers of sugar amino acids and related compounds see: (a) Chandrasekhar, S.; Reddy, M. S.; Jagadeesh, B.; Prabhakar, A.; Ramana Rao, M. H. V.; Jagannadh, B. *J. Am. Chem. Soc.* **2004**, *126*, 13586–13587; (b) Chakraborty, T. K.; Srinivasu, P.; Madhavendra, S. S.; Kumar, S. K.; Kunwar, A. C. *Tetrahedron Lett.* **2004**, *45*, 3573–3577; (c) Sharma, G. V. M.; Reddy, K. R.; RadhaKrishna, P.; Sankar, A. R.; Narsimulu, K.; Kumar, S. K.; Jayaprakash, P.; Jagannadh, B.; Kunwar, A. C. *J. Am. Chem. Soc.* **2003**, *125*, 13670–13671; (d) Hunter, D. F. A.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2003**, *14*, 3831–3839; (e) Smith, M. D.; Claridge, T. D. W.; Sansom, M. S. P. *Org. Biomol. Chem.* **2003**, *1*, 3647–3655; (f) Vescovi, A.; Knoll, A.; Koert, U. *Org. Biomol. Chem.* **2003**, *1*, 2983–2997; (g) Suhara, Y.; Yamaguchi, Y.; Collins, B.; Schnaar, R. L.; Yanagishita, M.; Hildreth, J. E. K.; Shimada, I.; Ichikawa, Y. *Bioorg. Med. Chem.* **2002**, *10*, 1999–2013; (h) Chakraborty, T. K.; Jayaprakash, S.; Srinivasu, P.; Chary, M. G.; Diwan, P. V.; Nagaraj, R.; Sankar, A. R.; Kunwar, A. C. *Tetrahedron Lett.* **2000**, *41*, 8167–8170; (i) Brittain, D. E. A.; Watterson, M. P.; Claridge, T. D. W.; Smith, M. D.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3655–3665; (j) Hungerford, N. L. H.; Claridge, T. D. W.; Watterson, M. P.; Aplin, R. T.; Moreno, A.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3666–3679; (k) Hungerford, N.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3680–3685; (l) Smith, M. D.; Long, D. D.; Martin, A.; Marquess, D. G.; Claridge, T. D. W.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *40*, 2191–2194; (m) Long, D. D.; Hungerford, N. L.; Smith, M. D.; Brittain, D. E. A.; Marquess, D. G.; Claridge, T. D. W.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *40*, 2195–2198; (n) Claridge, T. D. W.; Long, D. D.; Hungerford, N. L.; Aplin, R. T.; Smith, M. D.; Marquess, D. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *40*, 2199–2202; (o) Smith, M. D.; Long, D. D.; Marquess, D. G.; Claridge, T. D. W.; Fleet, G. W. J. *Chem. Commun.* **1998**, 2039–2040; (p) Smith, M. D.; Claridge, T. D. W.; Tranter, G. E.; Sansom, M. S. P.; Fleet, G. W. J. *Chem. Commun.* **1998**, 2041–2042.
4. Dhanasekaran, M.; Prakash, O.; Gong, Y. X.; Baures, P. W. *Org. Biomol. Chem.* **2004**, *2*, 2071–2082, and references cited therein.
5. (a) Bodanszky, M.; Bodanszky, A. *The Practices of Peptide Synthesis*; Springer: New York, 1984; (b) Grant, G. A. *Synthetic Peptides: A User's Guide*; WH. Freeman: New York, 1992; (c) Bodanszky, M. *Peptide Chemistry: A Practical Textbook*; Springer: Berlin, 1993.
6. Chakraborty, T. K.; Ghosh, S.; Jayaprakash, S.; Sarma, J. A. R. P.; Ravikanth, V.; Diwan, P. V.; Nagaraj, R.; Kunwar, A. C. *J. Org. Chem.* **2000**, *65*, 6441–6457.
7. Selected physical data of **1**: ^1H NMR (CDCl_3 , 500 MHz): see Table 1. MS (MALDI): m/z (%): 919.4 (100) $[\text{M}+\text{Na}]^+$, 935 (80) $[\text{M}+\text{K}]^+$. Selected physical data of **2**: ^1H NMR (CDCl_3 , 500 MHz): see Table 2. MS (LSIMS): m/z (%): 1136 (10) $[\text{M}+\text{H}-\text{C}_5\text{H}_8\text{O}_2]^+$. Selected physical data of **3**: ^1H NMR (CDCl_3 , 500 MHz): see Table 3. MS (MALDI): m/z (%): 1471.3 (45) $[\text{M}+\text{Na}]^+$, 1487.0 (25) $[\text{M}+\text{K}]^+$.
8. For details of the NMR and MD protocol see: Chakraborty, T. K.; Reddy, V. R.; Sudhakar, G.; Kumar, S. U.; Reddy, T. J.; Kumar, S. K.; Kunwar, A. C.; Mathur, A.; Sharma, R.; Gupta, N.; Prasad, S. *Tetrahedron* **2004**, *60*, 8329–8339.
9. The individual units of amino acids are numbered in ascending order from N- to C-termini.
10. Chakraborty, T. K.; Jayaprakash, S.; Srinivasu, P.; Madhavendra, S. S.; Sankar, A. R.; Kunwar, A. C. *Tetrahedron* **2002**, *58*, 2854–2859.