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Conformational Analysis of Some C_2-Symmetric Cyclic Peptides Containing Tetrahydrofuran Amino Acids†

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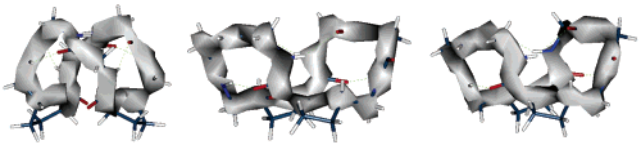
Received March 4, 2006



Cyclic oligomers of tetrahydrofuran amino acids, *cyclo*-(Taa1-Leu-Val)$_2$ (left), *cyclo*-(Taa2-Leu-Val)$_2$ (middle), and *cyclo*-(Taa2-Phe-Leu)$_2$ (right), displayed well-defined intramolecularly hydrogen-bonded structures with distorted "$\beta-\beta$ corner" motifs similar to the tennis ball seam.

Since they were first reported, as useful peptide building blocks, the pyranoid[1] and furanoid[2] sugar amino acids have been used extensively by many research groups worldwide as conformationally constrained scaffolds in peptidomimetic studies. They form an important class of synthetic monomers, leading to many de novo oligomeric libraries, and versatile multifunctional templates, to create many designer molecules.[3] As part of our ongoing project on sugar amino acids, we were interested in synthesizing cyclic peptides containing furanoid sugar amino acids and natural α-amino acids.[4] Cyclization of linear peptides is a widely used method to restrict their conformational degrees of freedom and induce desirable structural biases essential for their biological activities, such as tubular structures for transporting ions or molecules across membranes.[5] Furthermore, cyclic peptides, devoid of charged termini, enhance passive membrane permeability and provide structures for assessing structure−activity relationships in ligand−receptor interactions.[6] It was envisaged that insertion of furanoid sugar amino acids, known as turn inducers, into cyclic peptides would lead to structures stabilized by intramolecular hydrogen bonds rather than the intermolecular hydrogen bonds between the stacked rings seen in tubular structures.[7] The idea was to construct cyclic peptides that have polar interior

† IICT Communication No. 060304.

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10.1021/jo060470x CCC: $33.50
Published on Web 07/07/2006

TABLE 1. ^{1}H NMR Chemical Shifts (δ, ppm) and Coupling Constants (J, Hz) of 1[a]

residue/ protons	Taa1	Leu	Val
NH	7.85 (dd) (J = 3.2, 9.7)	8.97 (d) (J = 10.4)	8.09 (d) (J = 9.6)
CαH	4.17 (dd) (J = 2.3, 8.7)	4.66 (ddd) (J = 6.5, 9.5, 10.4)	4.25 (dd) (J = 9.6, 11.2)
CβH	2.18 (m)	1.76 (ddd), *pro-S* (J = 6.4, 9.5, 13.5)	2.19 (m)
Cβ'H	2.15 (m)	1.71 (ddd), *pro-R* (J = 6.5, 7.0, 13.5)	-
CγH	1.99 (m), *pro-R*	1.60 (m)	1.00 (d) (J = 6.7)
Cγ'H	1.35 (m), *pro-S*		1.00 (d) (J = 6.7)
CδH	3.95 (dddd) (J = 3.8, 5.4, 9.6, 10.6)	0.97 (d), *pro-S* (J = 6.7)	
Cδ'H		0.93 (d), *pro-R* (J = 6.7)	
CϵH	3.65 (ddd), *pro-S* (J = 9.7, 10.6, 14.0)		
Cϵ'H	3.10 (ddd), *pro-R* (J = 3.2, 3.8, 14.0)		

[a] 500 MHz, $CDCl_3$, 289 K.

TABLE 2. ^{1}H NMR Chemical Shifts (δ, ppm) and Coupling Constants (J, Hz) of 2[a]

residue/ protons	Taa2	Leu	Val
NH	6.90 (dd) (J = 3.9, 8.6)	7.93 (d) (J = 7.9)	7.18 (br)
CαH	4.39 (m)	4.26 (ddd) (J = 6.2, 7.9, 9.4)	3.63 (dd) (J = 7.2, 8.0)
CβH	2.40 (m), *pro-R*	1.88 (ddd), *pro-S* (J = 5.5, 9.4, 13.3)	2.35 (m)
Cβ'H	2.00 (m), *pro-S*	1.69 (ddd), *pro-R* (J = 6.2, 7.2, 13.3)	
CγH	2.00 (m), *pro-S*	1.67 (m)	1.00 (d), *pro-S* (J = 6.7)
Cγ'H	1.44 (m), *pro-R*		0.96 (d), *pro-R* (J = 7.0)
CδH	3.94 (m)	0.93 (d), *pro-R*, (J = 6.3)	
Cδ'H		0.91 (d), *pro*-S (J = 6.5)	
CϵH	3.86 (ddd), *pro-S* (J = 2.3, 8.6, 13.9)		
Cϵ'H	2.71 (ddd), *pro-R* (J = 3.9, 9.5, 13.9)		

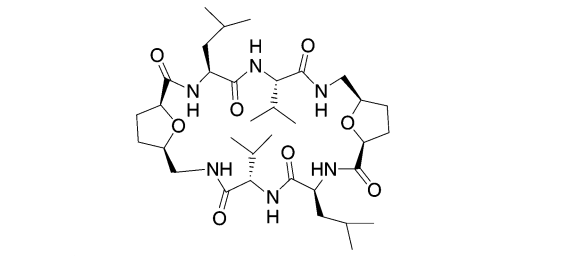
[a] 500 MHz, $CDCl_3$, 303 K.

TABLE 3. ^{1}H NMR Chemical Shifts (δ, ppm) and Coupling Constants (J, Hz) of 3[a]

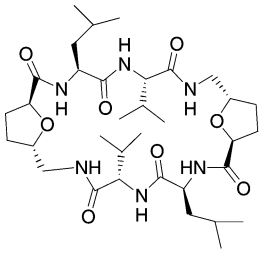
residue/ protons	Taa2	Phe	Leu
NH	7.21 (dd) (J = 4.4, 8.5)	8.57 (d) (J = 6.8)	6.81 (d) (J = 7.2)
CαH	4.30 (dd) (J = 7.9, 8.0)	4.26 (ddd) (J = 6.3, 6.8, 10.0)	3.46 (ddd) (J = 4.1, 7.2, 10.7)
CβH	2.38 (m), *pro-S*	3.55 (dd), *pro-S* (J = 10.0, 13.7)	1.90 (ddd), *pro-S* (J = 4.4, 10.7, 14.6)
Cβ'H	1.73 (m), *pro-R*	3.26 (dd), *pro-R* (J = 6.3, 13.7)	1.82 (ddd), *pro-R* (J = 4.1, 10.0, 14.6)
CγH	1.98 (m), *pro-S*		0.88 (m)
Cγ'H	1.33 (m), *pro-R*		
CδH	4.07 (dddd) (J = 2.2, 4.7, 8.8, 11.2)		0.76 (d), *pro-S* (J = 6.7)
Cδ'H			0.67 (d), *pro-R* (J = 6.7)
CϵH	3.91 (ddd), *pro-S* (J = 2.2, 8.5, 14.0)		
Cϵ'H	2.49 (ddd), *pro-R* (J = 4.4, 8.8, 14.0)		
others		phenyl protons, 7.28 (m)	

[a] 500 MHz, $CDCl_3$, 303 K.

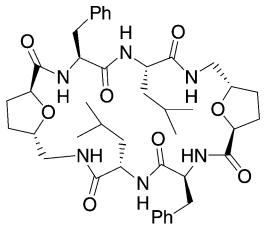
and hydrophobic groups around the periphery mimicking the natural ionophores.[8] Herein, we describe the synthesis and conformational studies of three cyclic peptides **1**−**3** containing "2,5-*cis*" (2*S*,5*R*)-tetrahydrofuran amino acid[9] (Taa1, in **1**) and "2,5-*trans*" (2*S*,5*S*)-tetrahydrofuran amino acid[9] (Taa2, in **2** and **3**).



1



2



3

Compounds **1**−**3** were synthesized by cyclodimerization of the corresponding H-(Taa-Aa1-Aa2)-OH using pentafluorophenyl diphenylphosphinate (FDPP)[10] in CH_3CN under dilute conditions to give the desired cyclic products in 55−60% yields.[11] The final products were purified by standard silica gel column chromatography and fully characterized by spectroscopic methods before using them in the conformational studies.

Conformational studies of these cyclic peptides were carried out first by studying their circular dichroism (CD) spectra in various solvents, CH_3CN, MeOH, EtOH, and trifluoroethanol (TFE). The CD spectra of all of them, shown in the Supporting Information, indicated the presence of prominent secondary

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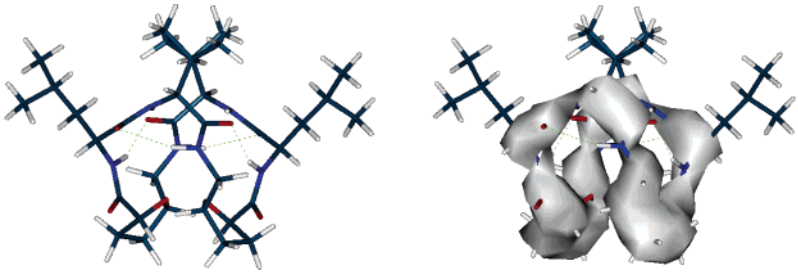

FIGURE 1. Lowest-energy structure of **1** (left) and its backbone highlighted with a pseudo-Connolly surface using Insight II (right), obtained from MD calculations.

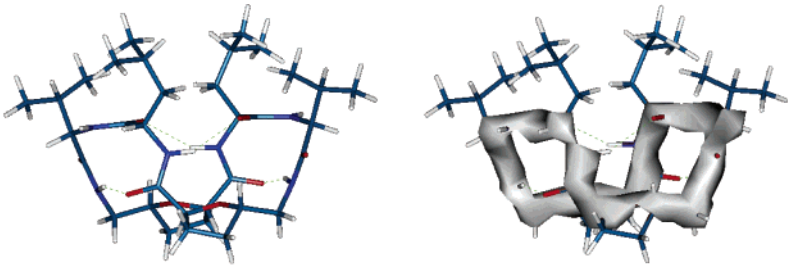

FIGURE 2. Lowest-energy structure of **2** (left) and its backbone highlighted with a pseudo-Connolly surface using Insight II (right), obtained from MD calculations.

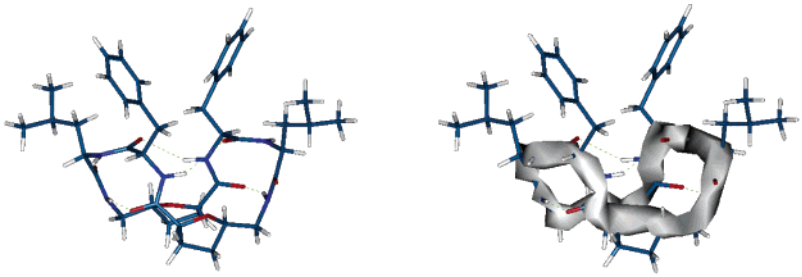

FIGURE 3. Lowest-energy structure of **3** (left) and its backbone highlighted with a pseudo-Connolly surface using Insight II (right), obtained from MD calculations.

structures in the different solvent systems used. The CD spectra of **1** in all the solvents showed bands characteristic of a typical helical structure[12] with almost two times more ellipticity in TFE. Compound **2** showed bands typical of β-sheet structures, especially in TFE with a positive peak at 200 nm and a negative peak at 217 nm.[12] The CD spectra of **3** indicated the presence of some kind of β-turn structures, especially in TFE, with the shifting of maxima and a change in patterns in other solvents.

NMR studies of **1**−**3** were carried out in about 4−6 mM solutions in $CDCl_3$. The spectra were well resolved, and most of the spectral parameters could be obtained easily and are reported in Tables 1−3. The presence of only one set of resonance peaks from Taa, Aa1, and Aa2 residues was due to the 2-fold molecular symmetry in these molecules. Although the assignments were carried out with the help of total correlation spectroscopy (TOCSY),[13] nuclear Overhauser effect spectroscopy (NOESY)/rotating frame nuclear Overhauser effect spectroscopy (ROESY)[14] experiments provided the information on the proximity of protons, the details of which are provided in the Supporting Information. The volume integrals of the cross-peaks in the ROESY spectra along with the use of two-spin approximation provided the restraints in the simulated molecular dynamics (MD) calculations.[15]

For compound **1**, all the amide protons appeared at low field (chemical shifts (δNH) > 7.85 ppm), whereas solvent titration studies, by adding up to 33% v/v of DMSO-d_6, showed a very small change in δNH of Taa1 and Leu residues ($\Delta\delta$NH < 0.42 ppm), thereby confirming their involvement in H bonding. $^3J_{NH-C\alpha H} = 9.6$ Hz (Val) and 10.4 Hz (Leu) strongly support an anti-periplanar arrangement of NH and CαH for Val and Leu, corresponding to a value of $\varphi \sim -100°$, which falls in the β-region of the Ramachandran plot. Similarly, the $^3J_{NH-C\alpha H(pro-S)} = 9.7$ and $^3J_{NH-C\alpha H(pro-R)} = 3.2$ Hz for Taa1 correspond to a $\varphi \sim 100°$.

Four β-turnlike features were deduced from the nOe data. Strong LeuNH/ValNH and medium intensity LeuCαH/Taa1′NH nOe cross correlations along with the involvement of Taa1NH

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in H bonding support a β-turn around Leu-Val residues. Similarly, a turn, involving a pseudo 10-membered H-bonded ring, involving LeuNH, around the Taa1 residue was deduced from the nOe's, LeuNH/Taa1CϵH(*pro-S*), and Taa1CδH/LeuCαH. MD calculations were carried out using constraints derived from the ROESY data (Supporting Information). The structures that emerged (Figure 1) are very rigid and show the four turns along with the presence of H bonds between LeuNH and ValCO and Taa1NH and Taa1′CO (10-membered H bonds). The structures can be viewed as a distorted $\beta-\beta$ corner motif with the corners deviating significantly from the standard 90°,[16] resembling a tennis ball seam.

The structural features of **2** and **3** are very similar. The participation of amide protons of Taa2 and the next residue (Leu for **2** and Phe for **3**) has been deduced from their low-field shifts as well as the solvent titration studies. The $^3J_{NH-C\alpha H}$ values are not as distinctive as those in **1**, with values ~8 Hz in **2** and even smaller values in **3**. Yet, we presume the 24-membered macrocycle with four H bonds is quite rigid and thus the backbone couplings arise from predominantly a single rigid conformation. This is born out from the MD studies, which show for **2** (Figure 2) and **3** (Figure 3) essentially one family of structures with the dihedral angle φ differing considerably from 120° giving a distorted $\beta-\beta$ corner structure.

One special feature of these molecules is very restricted rotations of the side chains. For Val in **1**, $^3J_{C\alpha H-C\beta H} = 11.2$ Hz, suggesting the presence of predominantly a single conformer, with CαH in trans disposition with respect to CβH. Additionally, the presence of the nOe correlation Val-NH/Val-βH permits deducing that $\chi1$ (N−Cα−Cβ−Cγ(*pro-R*)) ~ 180°. Similarly for Leu, $^3J_{C\alpha H-C\beta H(pro-S)} = 9.5$ and $^3J_{C\alpha H-C\beta H(pro-R)} = 6.5$ Hz suggesting large populations of rotamers with $\chi1$ (N−Cα−Cβ−Cγ) ~ 180° (*t*), with significant populations of rotamers with $\chi1 \sim -60°$ (g^-). Using the relations[17] from the literature, we found populations of *t* and g^- isomers to be about 64% and 33%, respectively. For **2**, $^3J_{C\alpha H-C\beta H(pro-S)} = 9.4$ and $^3J_{C\alpha H-C\beta H(pro-R)} = 6.2$ Hz, showing the *t* and g^- isomer populations of about 63% and 30%, respectively. For Val, on the other hand, a nondescript value of 6.0 Hz for $^3J_{C\alpha H-C\beta H}$ did not permit us to make definitive conclusions on the rotamer populations about $\chi1$. For **3**, $^3J_{C\alpha H-C\beta H(pro-S)} = 10.0$ and $^3J_{C\alpha H-C\beta H(pro-R)} = 6.3$ Hz for the Phe residue, suggesting rotamer populations for *t* and g^- isomers of about 69% and 30%, respectively, whereas for Leu, $^3J_{C\alpha H-C\beta H(pro-S)} = 10.7$ and $^3J_{C\alpha H-C\beta H(pro-R)} = 4.1$ Hz implying the predominance of *t* isomers (77%). It was however interesting to note that for **3** there are significant restrictions even about $\chi2$, with $^3J_{C\beta H(pro-S)-C\gamma H} = 4.4$ and $^3J_{C\beta H(pro-R)-C\gamma H} = 10.0$ Hz, which corresponds to a predominance of a rotamer with CβH in trans disposition with respect to CγH.

In summary, *cyclo*-(Taa1-Leu-Val)$_2$ (**1**), *cyclo*-(Taa2-Leu-Val)$_2$ (**2**), and *cyclo*-(Taa2-Phe-Leu)$_2$ (**3**) displayed well-defined distorted $\beta-\beta$ corner structures. Such oligomeric assemblies, with intramolecularly hydrogen-bonded structures, can play significant roles in recognizing and binding to suitable ligands mimicking biological systems. These efforts should permit the design of compounds that will successfully mimic the structures and functions of biological receptors.

Experimental Section

The peptides were synthesized following standard solution-phase peptide coupling methods[18] using 1-ethyl-3-(3-(dimethylamino)-propyl)carbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt) as coupling agents and dry DMF and/or CH_2Cl_2 as solvents. In the racemization free fragment condensation strategy that was followed, the Boc-Taa1-OH[9] 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-Taa1-Leu-Val-OMe. Saponification of the tripeptide using LiOH in THF−MeOH−H_2O was followed by Boc deprotection using TFA−CH_2Cl_2 to give the fully deported TFA·H-Taa1-Leu-Val-OH, which was then subjected to cyclodimerization. It was dissolved in CH_3CN (10^{-2} M) and treated with FDPP (1.5 equiv) at 0 °C, followed by the slow addition of *N*,*N*-diisopropylethylamine (DIPEA, 5 equiv). After aqueous workup, chromatographic purification furnished the product **1** in 55% yield. Compounds **2** and **3** were similarly prepared from Boc-Taa2-OH.[9]

Spectral Data of Peptide 1. IR (KBr): ν_{max} 3353, 3257, 3091, 2960, 2929, 2874, 1645, 1520, 1088 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): see Table 1. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.5, 173.5, 173.4, 81.5, 79.1, 59.6, 53.2, 44.9, 42.7, 31.3, 29.3, 28.2, 25.3, 22.6, 22.04, 19.5, 18.4. MS (ESI): *m*/*z* (%) 680 (100) [M + H]$^+$.

Spectral Data of Peptide 2. IR (KBr): ν_{max} 3334, 2959, 2927, 1638, 1537, 1085 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): see Table 2. ^{13}C NMR ($CDCl_3$, 50 MHz): δ 175.3, 173.4, 171.1, 79.6, 77.9, 61.0, 53.5, 43.7, 40.2, 30.7, 29.4, 28.7, 24.9, 22.7, 21.9, 20.7, 19.0. MS (ESI): *m*/*z* (%) 680 (100) [M + H]$^+$, 702 (27) [M + Na]$^+$.

Spectral Data of Peptide 3. IR (KBr): ν_{max} 3300, 3065, 2956, 2927, 2865, 1654, 1536, 1084 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): see Table 3. ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.4, 172.1, 171.6, 136.9, 129.2, 128.8, 126.9, 79.7, 77.9, 57.7, 53.9, 44.5, 36.3, 36.0, 31.4, 30.0, 24.1, 23.7, 20.7. MS (ESI): *m*/*z* (%) 776 (100) [M + H]$^+$.

Acknowledgment. The authors wish to thank CSIR, New Delhi, for research fellowships (S.R., D.K., and S.K.D.) and DST, New Delhi, for financial support (SR/S1/OC-21/2003).

Supporting Information Available: General experimental procedures, the detailed protocols for NMR and MD studies, ^{1}H NMR, ^{13}C NMR, NOESY/ROESY, TOCSY, and CD spectra of **1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060470X

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