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Hybrid Peptide Design. Hydrogen Bonded Conformations in Peptides Containing the Stereochemically Constrained γ-Amino Acid Residue, Gabapentin

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Abstract: The crystal structure of 12 peptides containing the conformationally constrained 1-(aminomethyl)-cyclohexaneacetic acid, gabapentin (Gpn), are reported. In all the 39 Gpn residues conformationally characterized so far, the torsion angles about the $C^{\alpha}-C^{\beta}$ and $C^{\beta}-C^{\gamma}$ bonds are restricted to the *gauche* conformation ($\pm 60°$). The Gpn residue is constrained to adopt folded conformations resulting in the formation of intramolecularly hydrogen-bonded structures even in short peptides. The peptides Boc-Ac_6c-Gpn-OMe **1** and Boc-Gpn-Aib-Gpn-Aib-OMe **2** provide examples of C_7 conformation; peptides Boc-Gpn-Aib-OH **3**, Boc-Ac_6c-Gpn-OH **4**, Boc-Val-Pro-Gpn-OH **5**, Piv-Pro-Gpn-Val-OMe **6**, and Boc-Gpn-Gpn-Leu-OMe **7** provide examples of C_9 conformation; peptide Boc-Ala-Aib-Gpn-Aib-Ala-OMe **8** provides an example of C_{12} conformation and peptides Boc-βLeu-Gpn-Val-OMe **9** and Boc-βPhe-Gpn-Phe-OMe **10** provide examples of C_{13} conformation. Gpn peptides provide examples of backbone expanded mimetics for canonical α-peptide turns like the γ (C_7) and the β (C_{10}) turns. The hybrid $\beta\gamma$ sequences provide an example of a mimetic of the C_{13} α-turn formed by three contiguous α-amino acid residues. Two examples of folded tripeptide structures, Boc-Gpn-βPhe-Leu-OMe **11** and Boc-Aib-Gpn-βPhg-NHMe **12**, lacking internal hydrogen bonds are also presented. An analysis of available Gpn residue conformations provides the basis for future design of folded hybrid peptides.

Introduction

The observation of novel intramolecularly hydrogen-bonded structures in peptides containing β-amino acids[1] has stimulated considerable interest in the conformational properties of hybrid peptide sequences containing α, β and higher ω amino acid residues.[2] The insertion of additional atoms into the backbone of synthetic polypeptides greatly enhances the repertoire of stable, internally hydrogen-bonded folded structures. The creation of new classes of foldamers has been facilitated by the use of conformationally constrained residues. In the case of β-peptides, the cyclic β-amino acids *trans*-2-aminocyclopentanecarboxylic acid (ACPC) and *trans*-2-aminocyclohexanecarboxylic acid (ACHC) provide an entry into novel families of α-peptide helices.[1c,d,3] Backbone substitution restricts the stereochemically allowed conformations generated by rotation

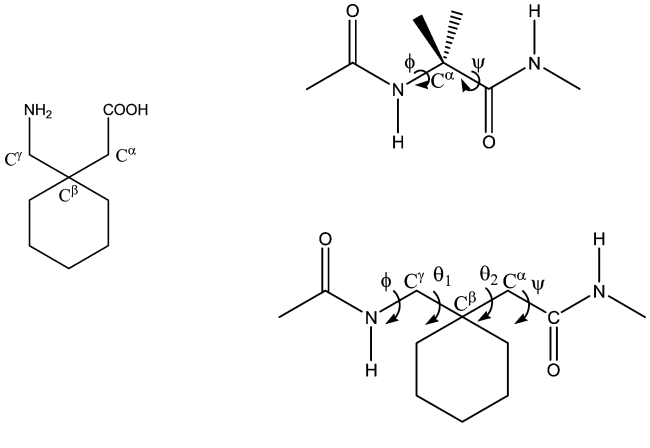

Figure 1. (a) Gabapentin (1-(aminomethyl)cyclohexaneacetic acid, Gpn). (b) Definition of the backbone torsion angles of (top) Aib residue and (bottom) Gpn residue.

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Table 1. Unit Cell Parameters and Final *R*-factor for the Peptides **1**−**12**[a]

	empirical formula	space group	*a* (Å)	*b* (Å)	*c* (Å)	α (deg)	*β* (deg)	*γ* (deg)	*R* (%)
Boc-Ac$_6$c-Gpn-OMe **1**	$C_{22}H_{38}N_2O_5$	$P2_1/c$	10.869(5)	9.944(4)	22.199(10)	90	90.30(1)	90	4.90
Boc-Gpn-Aib-Gpn-Aib-OMe **2**	$C_{32}H_{56}N_4O_7$	$C2/c$	30.027(4)	12.182(2)	20.453(3)	90	109.26(1)	90	6.94
Boc-Gpn-Aib-OH **3**	$C_{18}H_{32}N_2O_5$	$P2_1$	9.846(7)	10.339(7)	10.806(7)	90	110.97(1)	90	3.87
Boc-Ac$_6$c-Gpn-OH **4**	$C_{21}H_{36}N_2O_5$	Pc	18.445(7)	9.743(4)	12.405(5)	90	98.97(1)	90	6.99
Boc-Val-Pro-Gpn-OH **5**	$C_{24}H_{41}N_3O_6 \cdot H_2O$	$P1$	6.813(4)	7.416(4)	14.072(8)	81.12(1)	76.35(1)	83.50(1)	5.14
Piv-Pro-Gpn-Val-OMe **6**	$C_{25}H_{43}N_3O_5$	$P2_12_12_1$	6.712(3)	15.323(7)	26.306(12)	90	90	90	5.57
Boc-Gpn-Gpn-Leu-OMe **7**	$C_{30}H_{53}N_3O_6 \cdot 0.5H_2O$	$C222_1$	19.762(2)	20.478(2)	16.381(2)	90	90	90	8.04
Boc-Ala-Aib-Gpn-Aib-Ala-OMe **8**	$C_{29}H_{51}N_5O_8$	$P2_1$	9.418(1)	23.186(2)	15.417(1)	90	90.80(1)	90	8.55
Boc-*β*Leu-Gpn-Val-OMe **9**	$C_{27}H_{49}N_3O_6$	$P4_1$	11.074(1)	11.074(1)	25.464(2)	90	90	90	8.55
Boc-*β*Phe-Gpn-Phe-OMe **10**	$C_{34}H_{47}N_3O_6$	$P2_12_12_1$	9.140(6)	15.953(10)	22.952(15)	90	90	90	5.41
Boc-Gpn-*β*Phe-Leu-OMe **11**	$C_{31}H_{49}N_3O_6$	$P2_12_12_1$	15.814(2)	22.153(3)	9.570(1)	90	90	90	7.86
Boc-Aib-Gpn-*β*Phg-NHMe **12**	$C_{28}H_{44}N_4O_5 \cdot H_2O$	$P2_12_12_1$	99.352(1)	13.554(1)	24.864(2)	90	90	90	5.10

[a] Full details of the crystal and diffraction data and details of refinement are provided as Supporting Information (Table S1).

about backbone single bonds. Substituted *β*- and *γ*- amino acid residues, which are prepared with considerable synthetic effort, have proved valuable in characterizing well defined conformations in short synthetic peptides.[2b,f,g,4] We describe in this report the conformational characteristics of the gabapentin (Gpn) residue, a readily accessible achiral *β*,*β*-disubstituted *γ*-amino acid.[5] Gabapentin, 1-(aminomethyl)cyclohexaneacetic acid, is a widely used antiepileptic drug which has also been advanced as a potential therapeutic in deep neuropathic pain.[6]

The conformation of *γ*-residues incorporated into peptides is described by four torsion angles, ϕ, θ_1, θ_2, and ψ (Figure 1).[2h] The *gem* dialkyl substituents at the C$^\beta$ atom restrict the allowed values for θ_1 and θ_2, in a manner entirely analogous to the conformational restrictions imposed by the dialkyl substituents at the C$^\alpha$ atom in the well studied residue α-aminoisobutyric acid (Aib).[7] In order to define the conformational properties of the Gpn residue, we have undertaken a systematic characterization of the conformations of Gpn-containing peptides in crystals by X-ray diffraction. The observation of conformations with 7 (C_7), 9 (C_9), 12 (C_{12}), and 13 (C_{13}) atom hydrogen-bonded rings is described below. An analysis of 14 Gpn residues from 12 independent peptide structures reveals that *gauche* conformations are exclusively populated about the C$^\beta$−C$^\gamma$ (θ_1) and C$^\beta$−C$^\alpha$ (θ_2) bonds. The observed structures illustrate the potential utility of the Gpn residue in promoting the formation of diverse hydrogen-bonded structures and in the design of reverse turn mimetics.[8]

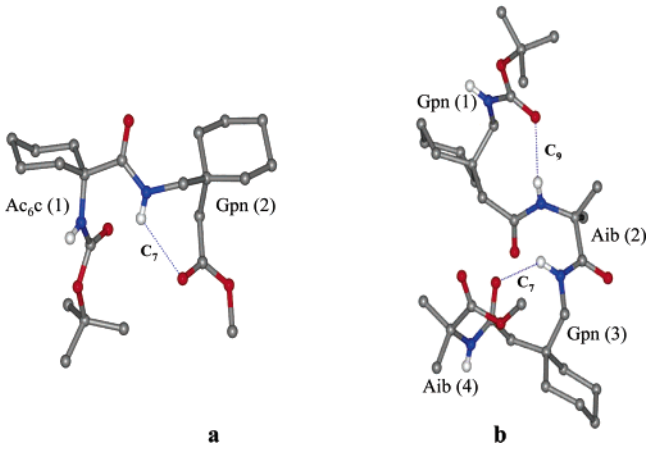

Figure 2. Molecular conformation of Gpn peptides with C_7 and C_9 hydrogen bonds. (a) Boc-Ac$_6$c-Gpn-OMe **1** stabilized by a C_7 hydrogen bond. (b) Boc-Gpn-Aib-Gpn-Aib-OMe **2** stabilized by C_9 and C_7 hydrogen bonds.

Experimental Procedures

Peptide Synthesis. Peptides were synthesized by conventional solution-phase chemistry using a racemization-free fragment condensation strategy using the *tert*-butyloxycarbonyl (Boc) or pivaloyl (Piv) groups and the methyl ester or *N*-methyl amide groups for blocking N- and C-termini, respectively.[5b] All the intermediates were characterized by ^{1}H NMR spectroscopy (80 MHz) and thin-layer chromatography (TLC) on silica gel. The final peptides were purified by reversed phase, medium-pressure liquid chromatography (C_{18}, 40−60μ) and high performance liquid chromatography (HPLC) on a reversed phase C_{18} column (5−10 μ, 7.8 mm × 250 mm) using methanol/water gradients. The final peptides were characterized by electrospray ionizaion mass spectrometry (ESI-MS) on an HP-1100 mass spectrometer and by complete assignment of 500 MHz ^{1}H NMR spectra. Gabapentin was obtained from the Hikal R&D Centre, Bangalore (India).

Structure Solution and Refinement. Single crystals of peptides **1**−**12** for X-ray data collection were grown by slow evaporation from an organic solvent/water mixture. X-ray intensity data were collected at room temperature on a Bruker AXS SMART APEX CCD diffractometer, using Mo Kα radiation (λ = 0.710 73 Å). ω scan type was used. Structures were solved by direct methods of phase determination using the program SHELXS-97[9] and were refined against F^2 by the full matrix least-squares method using SHELXL-97.[10] Table 1 sum-

(3) We will use the terms α-peptides, *β*-peptides ... *ω*-peptides to denote peptides composed entirely of α, *β*···*ω* amino acids, respectively. The general designation *ω*-amino acids is used for the higher homologues of the α-amino acids that contain additional backbone atoms. Inevitable nomenclature confusion that arises when the Greek letters α, *β*, *γ*, etc. are also used for describing polypeptide secondary structures is unavoidable. The generalized nomenclature for backbone dihedral angles has been presented in ref 2h.

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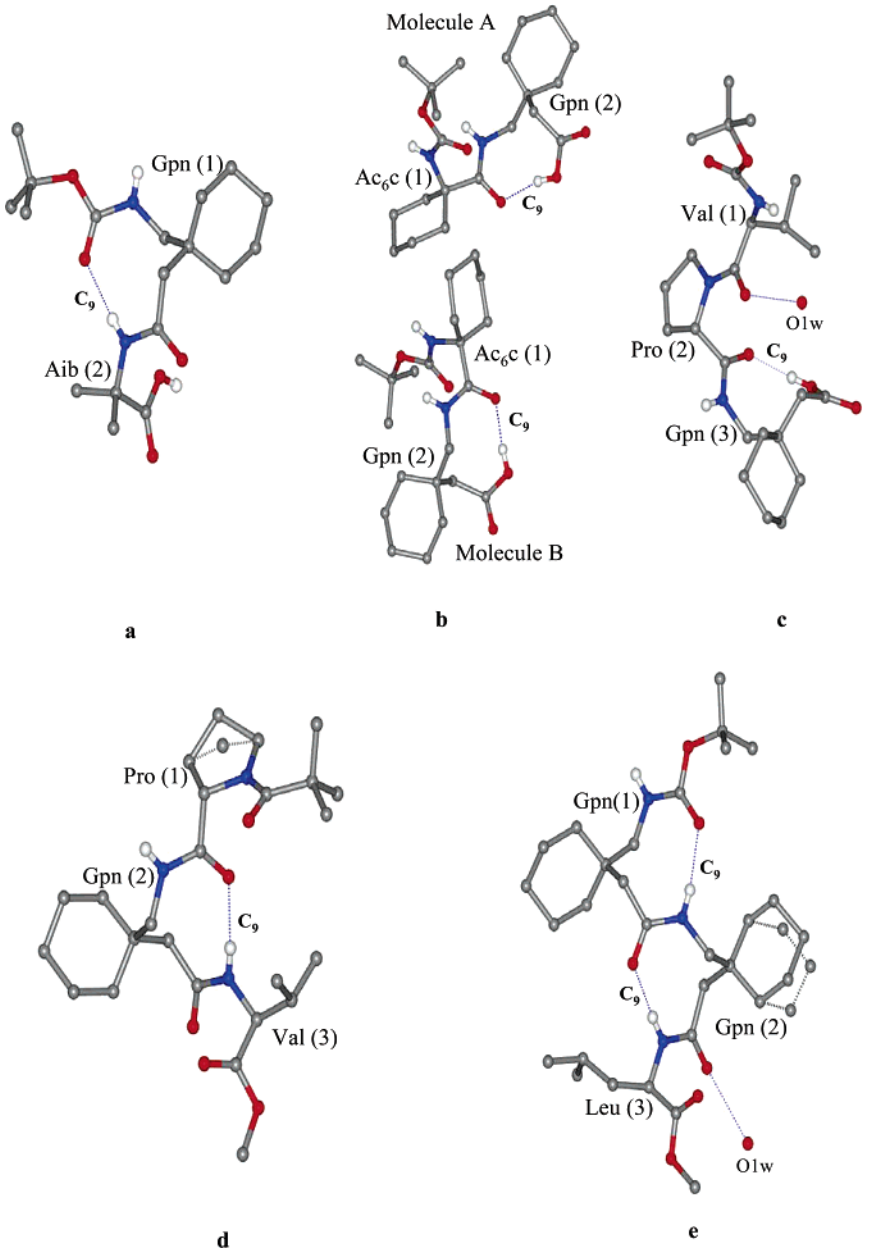

Figure 3. Molecular conformation of Gpn peptides with C_9 hydrogen bonds. (a) Boc-Gpn-Aib-OH **3**, (b) Boc-Ac$_6$c-Gpn-OH **4**, (c) Boc-Val-Pro-Gpn-OH **5**, (d) Piv-Pro-Gpn-Val-OMe **6**, and (e) Boc-Gpn-Gpn-Leu-OMe **7**. The C$^\gamma$ atom of Pro(1) in peptide **6** is disordered over two positions, with the occupancy ratio 0.58:0.42.

marizes the sequences and cell parameters for all 12 peptides. Crystal and diffraction data and details of refinement are provided as Supporting Information (Table S1).

Results and Discussion

Figures 2−6 illustrate the observed molecular conformations in crystals for peptides **1**−**12**. The structures are grouped together to highlight specific intramolecular hydrogen-bonding patterns. The observed backbone torsion angles for peptides **1**−**12** are listed in Table 2. The hydrogen bond parameters averaged over the observed structures in each group are shown in Figure 7.

C$_7$ Conformations. The structures of peptides **1** and **2** reveal an intramolecular seven-atom hydrogen-bonded ring in which the N−H group of Gpn residue is internally bonded to the Gpn C═O group. This feature is observed in the protected dipeptide

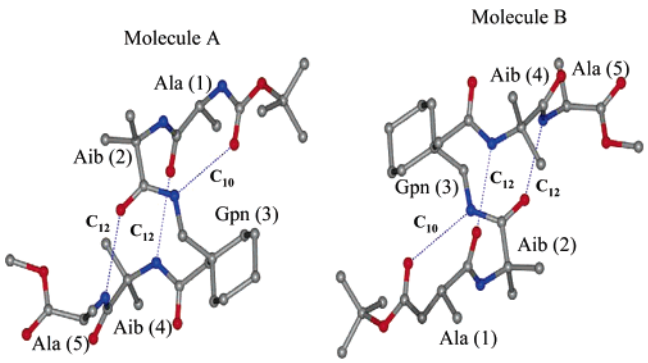

Figure 4. Two molecules in the asymmetric unit of Boc-Ala-Aib-Gpn-Aib-Ala-OMe **8**, forming a C_{12} helix.

(10) Sheldrick, G. M. *SHELXL-97, A program for crystal structure refinement*; University of Göttingen: Göttingen, Germany, 1997.

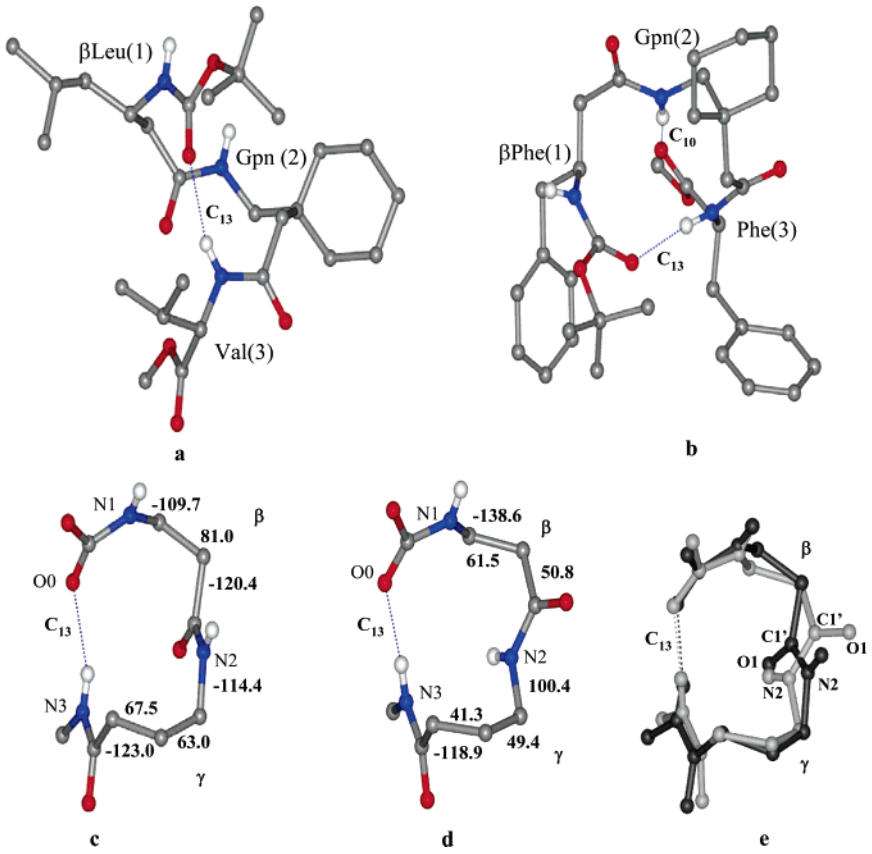

Figure 5. (Top) Molecular conformation of peptides with a C_{13} hydrogen bond in crystals: (a) Boc-βLeu-Gpn-Val-OMe **9**, (b) Boc-βPhe-Gpn-Phe-OMe **10**. (Bottom) The $\gamma\beta$ C_{13} turn segments in (c) peptide **9** and (d) peptide **10**. Backbone torsion angles for the C_{13}-turn are indicated for peptides **9** and **10**. (e) Superposition of the backbone atoms of the two turns (Dark, βLeu-Gpn segment of **9**; light, βPhe-Gpn segment of **10** (rmsd = 0.43 Å)).

structure, **1**, where alternative hydrogen-bonding patterns are precluded. The tetrapeptide Boc-Gpn-Aib-Gpn-Aib-OMe **2** constitutes an interesting example where Gpn (3) forms a C_7 hydrogen bond, despite the possibility of forming a C_9 hydrogen bond between Aib (2) C═O and Aib (4) N—H groups. The C_7 structure in a γ-amino acid may be considered as a formal expansion of the C_5 hydrogen bond proposed in the fully extended conformations of α-peptides.[11] In the C_5 conformation of an α-residue, the C═O and N—H vectors are parallel, resulting in a N—H···O angle which is nearly 90°. This is a situation in which the interaction must deviate considerably from the conventional hydrogen bond in which a much larger N—H···O angle is expected.[12] The C_7 structure in the γ-residues, illustrated by the experimentally determined conformations shown in Figure 2, is characterized by significantly improved angular parameters as compared to the C_5 hydrogen bond (Figure 7).

C_9 Conformations. The C_9 hydrogen bond is readily formed in Gpn peptides as evidenced by the examples in Figure 3 and in the earlier structures reported in the literature.[13] Indeed, in Gpn oligomers the C_9 ribbon appears to be the favored conformation. While conventional C_9 N—H···O hydrogen bonds are observed in peptides Boc-Gpn-Aib-OH **3**, Piv-Pro-Gpn-Val-OMe **6**, and Boc-Gpn-Gpn-Leu-OMe **7**, C_9 O—H···O hydrogen bonds are established in Boc-Ac$_6$c-Gpn-OH **4** and Boc-Val-Pro-Gpn-OH **5**. In peptides **4** and **5** the Gpn residue occurs at the C-terminus. Interestingly, intramolecular hydrogen bonds involving the C-terminus carboxylic acid groups are observed less frequently in the case of α-peptide structures. The formation of intramolecular O—H···O hydrogen bonds in the peptide structures **4** and **5** is thus noteworthy. Notably, in both cases, the carboxylic acid group adopts an unusual *anti* conformation.[14] The C_9 structure of the Gpn residue may be considered as a formal expansion of the C_7 (γ-turn) conformation characterized for α-amino acid residues, in proteins and peptides. Once again, the linearity of the hydrogen bond, as evidenced by the N—H···O angle, is considerably improved over its C_7 (γ-turn) counterpart.

C_{12} Conformations. An α−γ or γ−α hybrid sequence can, in principle, give rise to the formation of C_{12} hydrogen bonds. Such C_{12} structures may be viewed as a backbone expanded version of the widely studied two-residue β-turn formed in αα sequences. Repetitive C_{12} structures formed in the $(\alpha\gamma)_n$ sequence may be considered as a C_{12} helix, which is a formal

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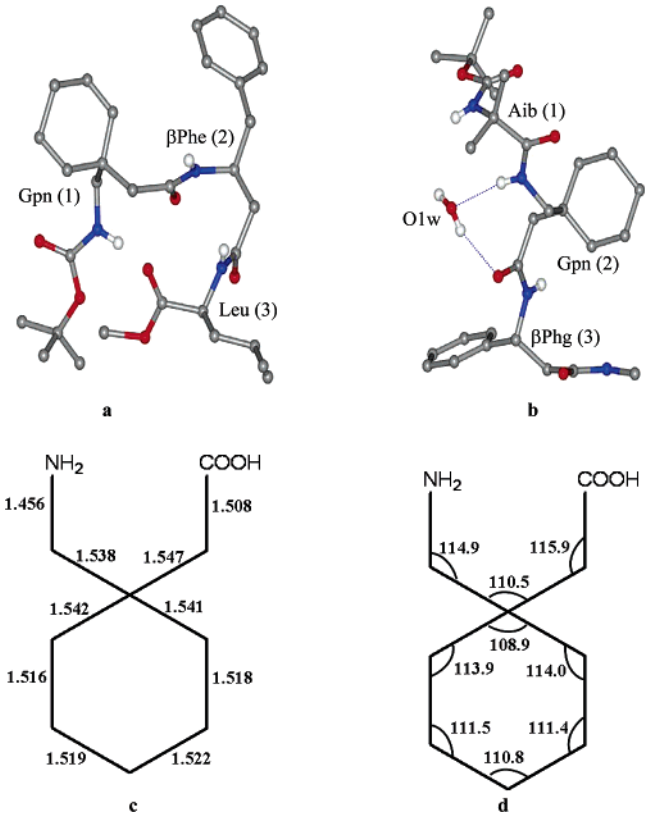

Figure 6. Non-hydrogen-bonded, folded molecular conformation determined in crystals of (a) Boc-Gpn-βPhe-Leu-OMe **11** and (b) Boc-Aib-Gpn-βPhg-NHMe **12**. Average geometry of Gpn residue determined so far in crystal structures (number of residues = 37), (c) bond lengths (esd $\approx$ 0.015 Å), and (d) bond angles (esd $\approx$ 1°)

two-atom expansion of the 3_{10} helical structure in an all α-sequence.[15] The recently characterized structure of Boc-Aib-Gpn-Aib-Gpn-OMe constitutes the first example of the observation of an incipient C_{12}-helix in a hybrid $\alpha\gamma$ oligopeptide.[16] An isolated C_{12} turn has also been crystallographically established in the model $\alpha\gamma$ sequences Boc-Ac_6c-Gpn-Ac_6c-OMe (Ac_6c: 1-aminocyclohexane-1-carboxylic acid).[17] Figure 4 illustrates the molecular conformations characterized in crystals for the pentapeptide Boc-Ala-Aib-Gpn-Aib-Ala-OMe **8**. Both the independent molecules in the asymmetric unit form folded conformations stabilized by three intramolecular hydrogen bonds. In Molecule A, the Ala(1)-Aib(2) segment forms a type III′ β-turn, while the segment Aib(2)-Gpn(3)-Aib(4)- forms two C_{12} helical hydrogen bonds, corresponding to approximately one helical turn. In Molecule B, the segment Ala(1)-Aib(2) forms a C_{10} Type I/III turn with Aib(2)-Gpn(3)-Aib(4) once again forming two C_{12} hydrogen bonds. In both molecules A and B, the two terminal Ala residues adopt helical conformations of opposite handedness. Furthermore, the handedness of the local helical conformation is reversed in molecules A and B. It may be noted parenthetically that both of the Ala residues have the same configuration[18] and the reversal of the signs of all the torsion angles in the structure of **8** leaves the crystal structure unaffected. Similar examples of the reversal of handedness of the conformation of chiral residues in asymmetric units containing multiple molecules have been noted earlier.[19]

Table 2. Backbone Torsion Angles (deg) for the Peptides **1**−**12**[a]

peptide	residue	ϕ	θ_1	θ_2	ψ	hydrogen bond[b]
1	Ac_6c	−80.4			1.5	
	Gpn	−94.9	−47.5	−53.6	−113.6	C_7 (N2···O2)
2	Gpn	114.4	−69.9	−74.3	93.1	C_9 (O0···N2)
	Aib	−69.1			−13.5	
	Gpn	−100.6	−44.4	−54.2	−99.7	C_7 (N3···O3)
	Aib	−49.2			−39.8	
3	Gpn	−99.1	68.0	75.4	−94.4	C_9 (O0···N2)
	Aib	−63.2			−31.0	
4 Mol. A	Ac_6c	53.8			50.0	
	Gpn	105.0	−57.9	−75.4	74.0	C_9 (O1···O3)
4 Mol. B	Ac_6c	58.1			44.8	
	Gpn	104.3	−56.3	−76.3	74.2	C_9 (O1···O3)
5	Val	−94.5			142.9	
	Pro	−59.8			144.7	
	Gpn	95.2	−64.3	−73.3	80.6	C_9 (O2···O4)
6	Pro	−65.9			160.9	
	Gpn	−90.3	72.8	70.6	−85.0	C_9 (O1···N3)
	Val	−62.2			159.2	
7	Gpn	−99.7	72.3	70.8	−98.4	C_9 (O0···N2)
	Gpn	−111.4	64.5	74.7	−84.4	C_9 (O1···N3)
	Leu	−68.9			157.9	
8 Mol. A	Ala	50.8			43.8	C_{10} (O0···N2)
	Aib	62.1			27.0	C_{12} (O1···N4)
	Gpn	137.5	−50.4	−59.1	107.1	C_{12} (O2··N5)
	Aib	57.9			36.8	
	Ala	−73.8			−32.6	
8 Mol. B	Ala	−61.4			−31.4	C_{10} (O0···N2)
	Aib	−56.6			−27.7	C_{12} (O1···N4)
	Gpn	−140.3	54.6	58.2	−108.2	C_{12} (O2···N5)
	Aib	−63.8			−32.4	
	Ala	50.8			40.7	
9	βLeu	−109.7	81.0		−120.4	
	Gpn	−114.4	63.0	67.5	−123.0	C_{13} (O0···N3)
	Val	−77.1			−26.3	
10	βPhe	−138.6	61.5		50.8	C_{13} (O0···N3)
	Gpn	100.4	49.4	41.3	−118.9	C_{10} (N2···O3)
	Phe	−112.3			−174.8	
11	Gpn	112.7	41.2	63.4	122.4	
	βPhe	−106.5	47.0		−111.9	none
	Leu	−102.0			145.9	
12	Aib	−56.9			−47.2	
	Gpn	−113.7	−60.4	−65.3	−105.3	none
	βPhg	−135.0	67.4		−138.6	

[a] For definition of torsion angles, see refs 2h and 5a. [b] Average hydrogen bond parameters for each turn type are shown in Figure 7. Full details are given in Supporting Information (Table S2).

C_{13} Conformations. The 13-atom (C_{13}) structure in all α-peptide sequences is formed by a three residue $\alpha\alpha\alpha$ segment and is stabilized by a 5→1 C═O···H—N hydrogen bond. Historically, the discovery of the α-helical structure of polypeptides by Pauling was based on considerations of maximization of intramolecular hydrogen bonding, with the 3.6_{13} (α) helix emerging as the candidate that best fitted available fiber X-ray diffraction data.[20] Pauling's insights have ensured that the C_{13} structure occupies a central place in discussions of hydrogen-bonded polypeptide motifs. Nonhelical α-turns stabilized by

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(18) The identity of the configuration of both Ala residues (L-Ala was used in synthesis) in the structure shown is established by the value of the dihedral angle C′−N−C^α−C^β (κ) which is −79° and 162° for Ala(1) and Ala(5) of Molecule 1 and 175° and −77° for Ala(1) and Ala(2) of Molecule 2. The value of κ for an L-residue is ϕ−120°.
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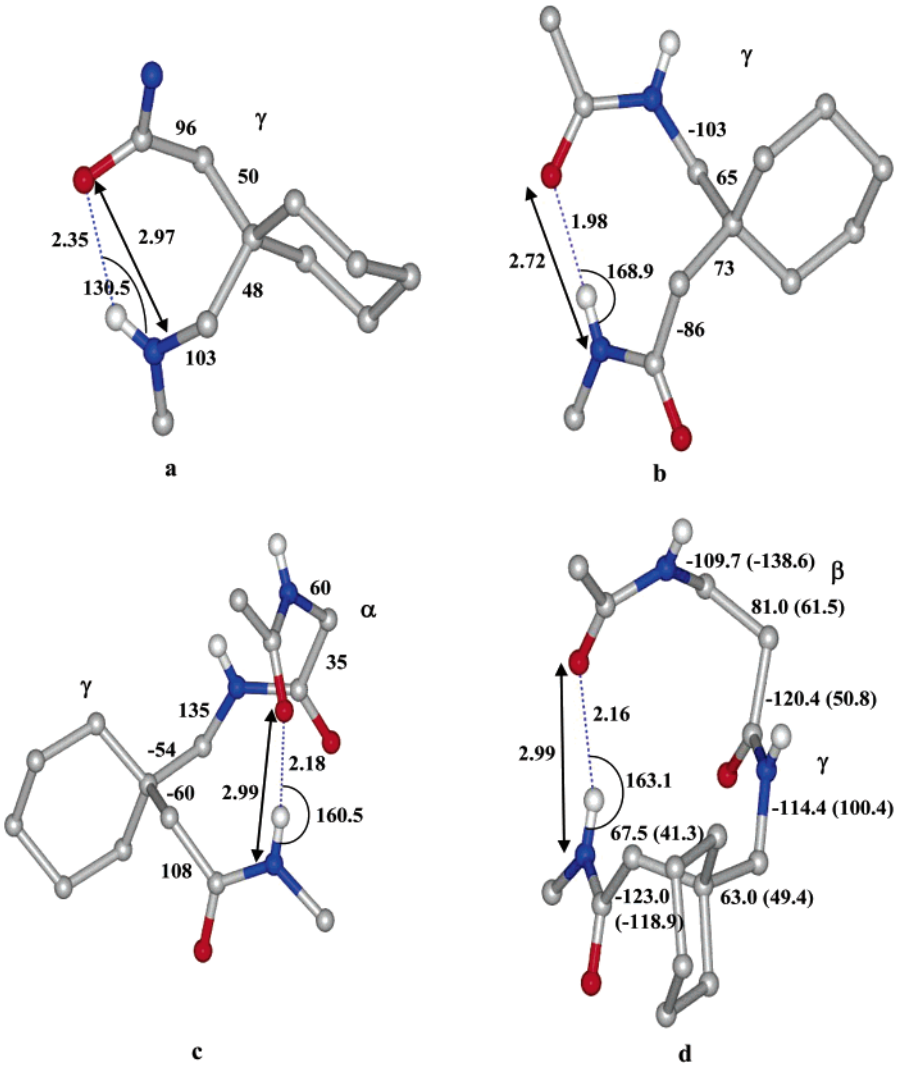

Figure 7. Average hydrogen bond parameters for the C_7, C_9, C_{12}, and C_{13} hydrogen bonded conformations in Gpn peptides. Average values of dihedral angles are also shown for 7, 9, and 12 atom hydrogen bonds. For the C_{13} hydrogen bond, torsion angles characterizing the two types of 13-atom turns are indicated. (a) C_7 hydrogen bond (esd's: dihedral angles ≈ 5°, hydrogen bond lengths ≈ 0.1 Å, hydrogen bond angle ≈ 3°). (b) C_9 hydrogen bond (esd's: dihedral angles ≈ 5°, hydrogen bond lengths ≈ 0.25 Å, hydrogen bond angle ≈ 6°). (c) C_{12} hydrogen bond (esd's: dihedral angles ≈ 5°, hydrogen bond lengths ≈ 0.1 Å, hydrogen bond angle ≈ 11°). (d) C_{13} hydrogen bond (esd's: hydrogen bond lengths ≈ 0.1 Å, hydrogen bond angle ≈ 10°).

isolated 5→1 hydrogen bonds have also been identified in globular protein structures.[21] Curiously, isolated α-turns have not been crystallographically characterized in small peptides, although short α-helices have been established in crystals.[7,22] Hybrid peptide mimics of the C_{13} turn can, in principle, be generated by two residue $\beta\gamma/\gamma\beta$ sequences. The $\beta\gamma$ C_{13} structure may also be viewed as an expanded analogue of the two residue β-turn structure formed in αα segments. The successful incorporation of an unsubstituted βAla-γAbu segment into the center of a forced α-peptide helix has been reported.[2i] Figure 5 illustrates the crystallographic characterization of two C_{13} turns in the hybrid sequences, Boc-βLeu-Gpn-Val-OMe **9** and Boc-βPhe-Gpn-Phe-OMe **10**. In both cases, a C_{13} hydrogen bond between the Boc C═O and the Val/Phe NH groups is observed. Inspection of the hydrogen bond parameters summarized in Figure 7 reveals almost ideal geometry for these interactions.

In peptide **10**, an additional hydrogen bond between Gpn (2) NH and Phe (3) C═O groups is observed in the Gpn-Phe ($\gamma\alpha$) segment. This corresponds to a C_{10} ($\gamma\alpha$) hydrogen bond with reversed directionality; i.e., the NH group lies toward the N-terminus, and the C═O group is at the C-terminus. Hydrogen bonds with reverse hydrogen bond directionality have also been characterized in $\beta\beta$ segments, which contain the same number of backbone atoms.[23] The analogous hydrogen bond in an αα segment will result in the C_8 structure, which is schematically illustrated in Figure 8. The C_8 structure requires a central *cis* peptide bond and has been proposed in spectroscopic studies[24] but has not been observed crystallographically.

Non-Hydrogen-Bonded Structures in Gpn Peptides. Two interesting conformations have been crystallographically determined in the hybrid tripeptides Boc-Gpn-βPhe-Leu-OMe **11** ($\gamma\beta\alpha$) and Boc-Aib-Gpn-βPhg-NHMe **12** ($\alpha\gamma\beta$). Peptide **11** adopts a compact, folded conformation without any intramo-

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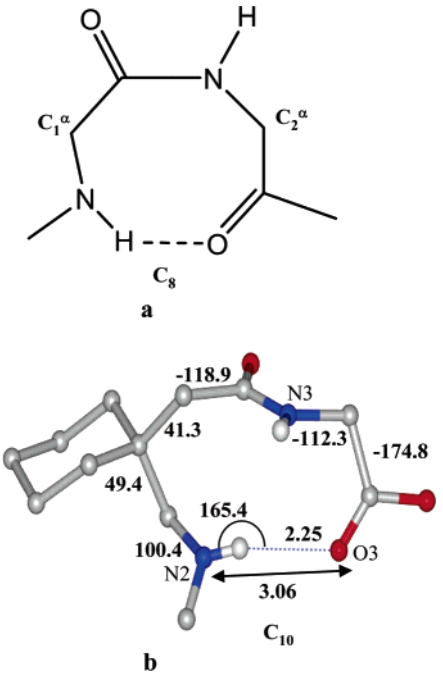

Figure 8. (a) The C_8 conformation in αα sequences. (b) The γα (C_{10})-turn, which is a backbone expanded analogue of the C_8 conformation in α-peptides, observed in peptide **10**.

lecular hydrogen bonds. In principle, the Gpn (1) residue could have participated in a wide variety of intramolecular hydrogen bonds. Inspection of the molecular conformation in Figure 6 reveals that the Gpn NH is pointed inward, suggesting that the observed conformation may be close to those necessary for forming hydrogen bonds with reverse directionality, i.e., C_7 (Gpn C═O), C_{11} (*β*Phe C═O), and C_{14} (Leu C═O). The observed N—O distances corresponding to these potential interactions are 3.05, 5.58, and 5.22 Å, respectively. An observed H···O distance of 2.51 Å and a N—H···O angle of 121° for the C_7 interaction are somewhat smaller than the optimum values. Folded conformations devoid of intramolecular hydrogen bonds are almost never observed in short all α oligopeptides. In short sequences containing all α-residues, the absence of intramolecular hydrogen bonds is observed only in extended sequences, which then associate in the crystal by forming sheetlike structures. Figure 9 shows a view of the intermolecular hydrogen bond interactions observed in the crystals of peptides **11** and **12**. In both cases, polar sheet formation is observed, involving the *β* residues, *β*Phe in peptide **11** and *β*Phg in peptide **12**. The residue (1) NH group, Gpn in **11** and Aib in **12**, is not involved in any hydrogen bonding interactions. In peptide **12**, the Gpn(2) NH group interacts with a water molecule. In these cases, the *β*-residue adopts a *gauche* conformation. The observed motif is relevant for delineating features of sheet formation in *β*-peptides.[25] Clearly, the tendency for backbone substituted *ω*-amino acids to adopt the *gauche* conformation about the additional C—C bonds may provide a driving force for the formation of compact structures. Notably, intramolecularly hydrogen-bonded C_{13} structures are observed for the *βγ* segments in peptides **9** and **10** (Figure 5, Table 2), whereas the *γβ* unit in peptide **11** is devoid of strong hydrogen bonds. In peptide **12**, the absence of intramolecular hydrogen bonds involving the Gpn residue may be ascribed to the effect of hydration. A lone water molecule interacts with both the Gpn NH and C═O groups, resulting in a conformation, which may be viewed as arising by water insertion into a precursor C_7 structure.

Backbone Conformation of Gpn Residues. Table 3 summarizes the torsion angles for the Gpn residue observed thus far in crystal structures of amino acid derivatives and peptides. Of the 39 independent residues characterized, all examples adopt the *gauche* conformation about the $C^\gamma-C^\beta$ (θ_1) and $C^\beta-C^\alpha$ (θ_2) bonds. Since Gpn is an achiral residue, there is no intrinsic preference for a specific sign of the torsion angles. Importantly, in all cases, the signs of θ_1 and θ_2 are the same. Furthermore, the distribution of values for ϕ is centered very close to ±100°. A wider distribution is observed for the torsion angle ψ, with a clustering observed near ±80°. The average torsion angles for the structurally characterized hydrogen-bonded C_7, C_9, and C_{12} types are illustrated in Figure 7. Notably, the Gpn conformation in the C_9 ($\phi = -103°$, $\theta_1 = 65°$, $\theta_2 = 73°$, $\psi = -86°$) is very close to that required for the C_{12} hydrogen bond formation ($\phi = 135°$, $\theta_1 = -54°$, $\theta_2 = -60°$, $\psi = 108°$). Transitions between C_9 and C_{12} conformations may therefore be achieved relatively easily. The average geometry of the Gpn residue determined by averaging over 37 examples is summarized in Figure 6c and d.

Hydrogen-Bonded Turn Types in Hybrid Sequences. An important milestone in the development of peptide conformational analysis was the recognition that two-residue αα sequences can give rise to C_{10} hydrogen bonded (*β*-turn) conformations, which vary in the backbone torsion angles at residues $i + 1$ and $i + 2$.[26] The conformational diversity of the turn types has important consequences in protein folding, since specific turns are associated with nucleation of secondary structures like helices and hairpins. While the 3_{10}-helix is generated by successive Type III *β*-turns, the *β*-hairpin formation is facilitated by Type I′ and II′ *β*-turns.[7c,f] Conformational diversity is therefore expected to have important consequences in the case of backbone expanded hybrid turns.

The *βγ* C_{13} turn formed in the tripeptides Boc-*β*Leu-Gpn-Val-OMe **9** and Boc-*β*Phe-Gpn-Phe-OMe **10** provides a clear example of structural diversity. Inspection of the torsion angles in the two structures reveals that ψ ($i + 1$) and ϕ ($i + 2$) show a very large difference between the two structures, corresponding to the reorientation of the central peptide bond between the *β* and *γ* residues. The backbone superposition shown in Figure 5 reveals that the two *βγ* C_{13} turns differ from one another by an approximately 180° flip of the central peptide unit. The resemblance to the Type I—Type II *β*-turn interconversion in αα sequences is striking. Theoretical studies on *β*-turn transitions suggest a low barrier concerted flip of the central peptide unit facilitates conformational interconversion.[27]

A recent modeling study has provided backbone conformational parameters for an ideal C_{13}-helix formed by a repetitive $(\beta\gamma)_n$ polypeptide.[16] The calculated parameters for the *βγ* helix are as follows: *β*-residue, $\phi = -106°$, $\theta = 75°$, and $\psi = -115°$; *γ*-residue, $\phi = -117°$, $\theta_1 = 66°$, $\theta_2 = 62°$, and $\psi = -120°$.

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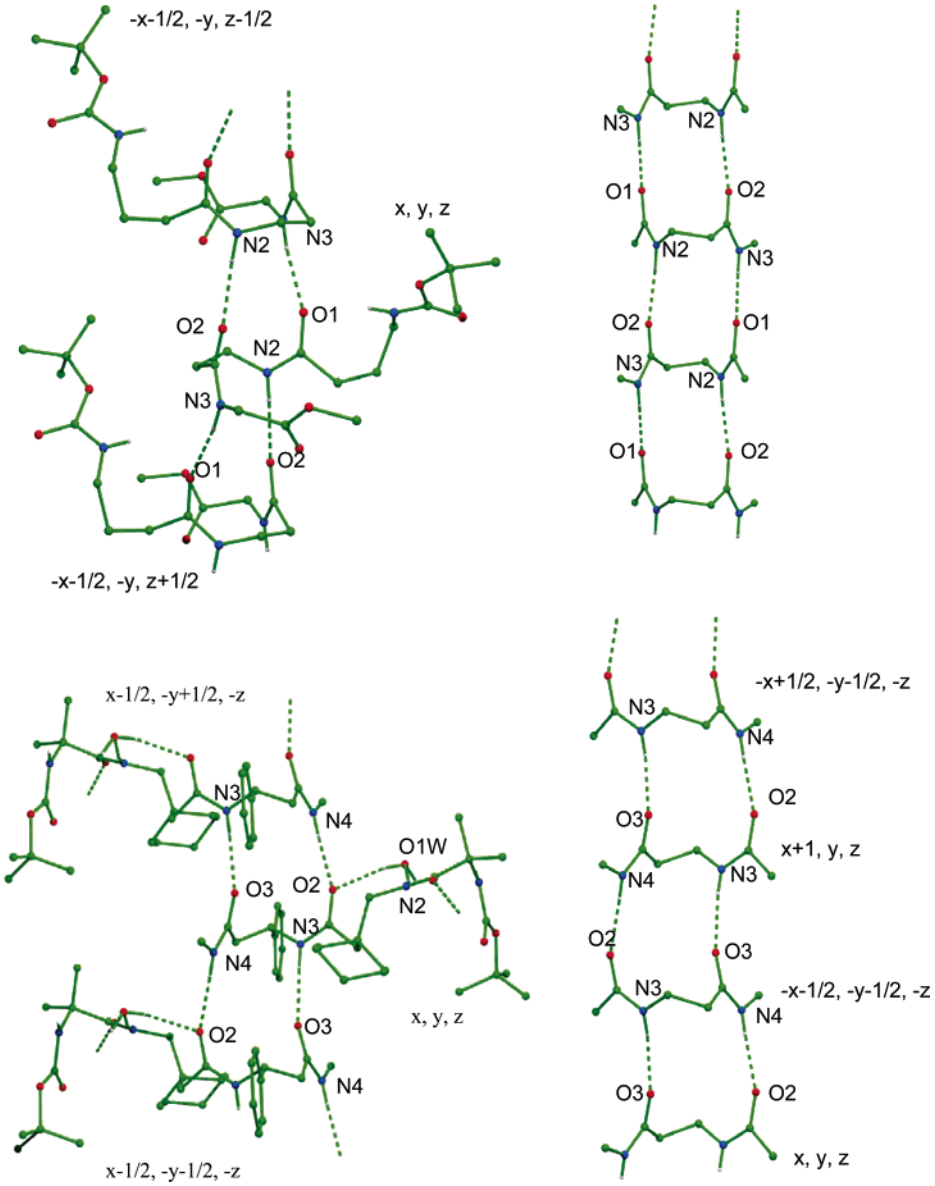

Figure 9. Intermolecular hydrogen bonds in the crystals of (top) Boc-Gpn-βPhe-Leu-OMe, **11** (Side chain atoms are not shown), and (bottom) Boc-Aib-Gpn-βPhg-NHMe, **12**.

The values observed for βLeu ($\phi = -109°$, $\theta = 81°$, $\psi = -120.4°$) and Gpn ($\phi = -114°$, $\theta_1 = 63.1°$, $\theta_2 = 67.6°$, $\psi = -123°$) in the structure of peptide **9** are very close to those suggested for the ideal helix. Thus the structures of peptides **9** and **10** have provided examples of both an isolated $\beta\gamma$ helical turn and a nonhelical $\beta\gamma$ C_{13} turn.

Conformation of the Cyclohexane Ring in the Gpn Residue. In all the structures determined thus far, the cyclohexane ring adopts an almost perfect chair conformation. Since Gpn is a 1,1-disubstituted cyclohexane, the barrier for interconversion between the two chair forms is likely to be of the order of 10−12 kcal/mol, in solution.[28] The energy difference between the two forms which have the aminomethyl group axial and equatorial has been established as 0.01−0.19 kcal/mol, for protected Gpn derivatives in methanol solution.[5a] Table 3 lists the orientation of the aminomethyl group in the Gpn containing amino acid derivatives/peptides determined thus far. It is observed that both axial and equatorial orientations occur almost equally. The conformation of the six-membered ring and the orientation of the substituents do not seem to influence the observed conformations of the Gpn backbone. Notably, in the structure of Boc-Gpn−Gpn-Leu-OMe **11**, both orientations of the cyclohexane rings are observed.

Conclusions

The ability to generate folded intramolecularly hydrogen-bonded structures in short peptides is essential for peptide design strategies, which rely on the use of folding nuclei in the construction of secondary structure modules like helices and hairpins.[29] In these approaches, conformational choices at selected positions are biased, using local stereochemical constraints that limit the range of accessible backbone torsion angles.[7c,f] Hybrid polypeptide sequences provide an opportunity to expand the range of polypeptide structures by introducing variability in the number of backbone atoms at each residue. The generation of folded structures in hybrid sequences suggests

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Table 3. Backbone Torsion Angles (deg) and Orientation of Substituents on the Gpn Residue Determined in Crystal Structures

	compounds	ϕ	θ_1	θ_2	ψ	orientation of amino methyl group	reference
1	gabapentin		59.7	51.1		axial	
2	Boc-Gpn-OH	119.6	57.4	40.0	79.7	equatorial	
3	Ac-Gpn-OH	−101.3	59.0	75.9	−79.4	equatorial	
4	Piv-Gpn-OH	99.8	45.3	53.1	100.9	axial	5a
5	Tosyl-Gpn-OH	144.6	66.7	63.8	−86.8	axial	
	(Mol. A)						
	(Mol. B)	146.9	69.0	65.3	−88.4	axial	
	(Mol. C)	−124.7	59.9	61.7	−171.1	axial	
	(Mol. D)	−124.1	59.6	60.9	−169.4	axial	
6	Boc-Gpn-OSu	−102.4	−61.1	−68.2	94.6	equatorial	
7	Boc-Gpn-NHMe	−125.5	−68.7	−52.8	118.5	disordered ring	
8	Piv-Pro-Gpn-OH	92.9	−66.7	−70.7	84.6	equatorial	
9	Boc-Aib-Gpn-OH	−103.9	57.3	75.5	−73.5	equatorial	5b
10	Boc-Gly-Gpn-OH	−103.7	−44.9	−48.7	−94.3	axial	
11	Boc-Aib-Gpn-OMe	−102.1	−48.2	−50.3	−90.0	axial	
12	Boc-Gpn-Gpn-NHMe						
	(Gpn1)	108.9	−63.2	−76.6	87.2	axial	
	(Gpn2)	108.2	−61.9	−78.2	88.0	equatorial	
13	Boc-Gpn-Gpn-Gpn-Gpn-NHMe						13
	(Gpn1)	100.5	−69.6	−72.8	84.5	equatorial	
	(Gpn2)	−103.8	69.9	73.4	−90.5	axial	
	(Gpn3)	−112.2	66.8	72.6	−88.4	axial	
	(Gpn4)	104.6	−70.7	−71.5	97.2	equatorial	
14	Boc-Aib-Gpn-Aib-Gpn-OMe						
	(Gpn2)	126.8	−52.1	−63.8	107.9	equatorial	16
	(Gpn4)	−109.9	−60.8	−62.7	−146.3	axial	
15	Boc-Ac_6c-Gpn-Ac_6c-OMe	135.7	−58.4	−58.6	107.8	equatorial	17
16	Boc-Ac_6c-Gpn-OMe	−94.9	−47.5	−53.6	−113.6	equatorial	
17	Boc-Gpn-Aib-OH	−99.1	68.0	75.4	−94.4	axial	
18	Boc-Ac_6c-Gpn-OH	105.0	−57.9	−75.4	74.0	equatorial	
	(Mol. A)						
	(Mol. B)	104.3	−56.3	−76.3	74.2	equatorial	
19	Boc-Val-Pro-Gpn-OH	95.2	−64.3	−73.3	80.6	axial	
20	Piv-Pro-Gpn-Val-OMe	−90.3	72.8	70.6	−85.0	axial	
21	Boc-Gpn-Gpn-Leu-OMe						
	(Gpn1)	−99.7	72.3	70.8	−98.4	equatorial	present study
	(Gpn2)	−111.4	64.5	74.7	−84.4	disordered ring	
22	Boc-βLeu-Gpn-Val-OMe	−114.4	63.0	67.6	−123.0	equatorial	
23	Boc-βPhe-Gpn-Phe-OMe	100.4	49.4	41.3	−118.9	axial	
24	Boc-Gpn-βPhe-Leu-OMe	112.7	41.2	63.4	122.4	axial	
25	Boc-Aib-Gpn-βPhg-NHMe	−113.7	−60.4	−65.2	−105.3	axial	
26	Boc-Gpn-Aib-Gpn-Aib-NHMe						
	(Gpn 1)	114.4	−69.9	−74.3	93.1	axial	
	(Gpn 3)	−100.6	−44.4	−54.2	−99.7	axial	
27	Boc-Ala-Aib-Gpn-Aib-Ala-OMe	137.5	−50.4	−59.1	107.1	axial	
	(Mol A)						
	(Mol B)	−140.3	54.6	58.2	−108.2	axial	

that the overall fold of all α peptide sequences can be mimicked by appropriately chosen hybrid sequences. The growing body of evidence for the conformational preferences of heteropolypeptides containing diverse ω-amino acids suggests that the design of globular structures from non-α-peptide backbones is achievable. Hybrid peptide design will be facilitated by the availability of building blocks with well-defined conformational properties. With this end in view, we have extensively characterized the conformational preferences of the achiral, β,β-disubstituted γ-amino acid residue, gabapentin (Gpn). The crystallographic results described here establish that the Gpn residue is almost exclusively constrained to adopt *gauche* conformations about the $C^{\gamma}-C^{\beta}$ and $C^{\beta}-C^{\alpha}$ bonds, resulting in an intrinsic preference for the Gpn residue to adopt locally folded conformations. The characterization of intramolecularly hydrogen-bonded C_7 and C_9 conformations, which involve only the Gpn residue and the establishment of the C_{12} and C_{13} conformations in $\alpha\gamma$ and $\beta\gamma$ sequences, clearly demonstrates the potential of this stereochemically constrained residue to stabilize mimics of canonical turn structures in all α sequences, which have been widely characterized in proteins and peptides. The ready availability of Gpn as a bulk drug, and the absence of chirality, together with its conformational properties should make the Gpn residue a valuable addition to the area of peptide research. Preliminary results on Gpn oligomers suggest that C_{14} structures may also be populated in $\gamma\gamma$ sequences. The conformational angles determined in crystals for a 2.6_{14} helix in a model peptide sequence, by Seebach and co-workers, are $\phi = 140 \pm 23°$, $\theta_1 = -67 \pm 5°$, $\theta_2 = -55 \pm 5°$, and $\psi = 134 \pm 15°$.[30] Notably, these values are very close to those established in the present study for the C_9 and C_{12} conformations of the Gpn residue (See Table 2). Thus, the Gpn conformations necessary to form C_9, C_{12}, and C_{14} structures cluster quite closely in four-dimensional ϕ, θ_1, θ_2, ψ space and may be selectively populated by the appropriate choice of flanking residues. The structure space of polypeptide conformations is rapidly expanding as the confor-

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mational characteristics of hybrid $\alpha\omega$ sequences are established. The principle of "equal backbone atoms" will undoubtedly be useful in the further design of hybrid sequences. The availability of constrained ω-amino acids will be critical in the rational design of hybrid sequences with predictable folding patterns.

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Supporting Information Available: X-ray crystallographic information files for peptides **1**−**12** (CIF format), crystal and diffraction data and details of refinement (Table S1), intramolecular hydrogen bond parameters (Table S2), and the packing diagrams for peptides **1**−**10** (Figures S1−S7).The X-ray crystallographic files (CIF) have also been deposited with the Cambridge Structural Database with accession numbers CCDC 630099−630110. This material is available free of charge via Internet at http://pubs.acs.org.

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