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Design, Synthesis and Development of Stereo Chemical Constraints into β -Amino Acid Residues: Gabapentin Structural Data Role in Nerve Pain Medication

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Abstract

Over the last 15 years, a growing body of work in the literature has focused on the folded structures formed by peptide sequences containing backbone homologated residues. The work of Seebach in Zurich, and Gellman in Madison, established that oligomers of β amino acid residues can form novel helical structures in solution and in the solid state. These peptides are highly useful for nnaovaccine development. Two distinct types of hydrogen bonded helical structures were demonstrated in these studies for oligomeric β peptides. The C_{12} helix which is an analog of the canonical 3_{10} helical structure in "all α" sequences, has the same hydrogen bond directionality ($C = O_i \cdots H\text{-}N_{i+3}$). The second helical form, the C_{14} helix, has the opposite directionality ($C = O_i \cdots H\text{-}N_{i+4}$), which is unprecedented in α peptide sequences.

Keywords: Amino acids; Peptides; β Amino acids; Gabapentin; Peptide folding

The β, And γ Amino Acids Role in Protein Folding

These reports sparked a flurry of activity on the conformational properties of β peptide oligomers. The unsubstituted β, and γ amino acid residues can be incorporated into oligopeptide helices, without disturbing the overall helical fold [1-4]. This study suggested that hybrid sequences with expanded hydrogen bonded, rings could indeed be constructed. A very large number of recent studies have greatly expanded our understanding of the conformational properties of substituted β and γ residues, when incorporated into α peptide host sequences [2-17]. One approach that has been investigated by Appavu et al. [18] is to examine the role of *gem* dialkyl substitution on the conformational properties of β, and γ residues [2,12,14]. The ready availability of the achiral β, β′-disubstituted γ amino acid, gabapentin (1-aminomethylcyclohexaneacetic acid, Gpn), has permitted detailed exploration of the structural chemistry of gabapentin peptides (Figure 1). The presence of *gem* dialkyl substituents at the central β carbon atom, limits the accessible conformations about the $C^{\beta}\text{-}C^{\gamma}(\theta_1)$, and $C^{\beta}\text{-}C^{\alpha}(\theta_2)$ bonds. A large body of crystallographic evidence has been presented, which suggests that in the case of Gpn θ_1, and θ_2, are largely restricted to *gauche* conformations ($\theta_1 \pm 60$, $\theta_2 \pm 60$), a property that favors locally folded conformation at this residue. Consequently, a very large number of folded peptides have been characterized, in which diverse hydrogen bonded rings are facilitated by the gabapentin residue. Figure 2 provides a summary of the conformational characteristics for the gabapentin residue.

The success in generating folded structures in hybrid peptides containing, the gabapentin residue prompted an examination of the related β-amino acid residues 1-aminomethylcyclohexane carboxylic acid ($\beta^{2,2}Ac_6c$), and 1-aminocyclohexane acetic acid ($\beta^{3,3}Ac_6c$). Figure 3 shows the structures of the four related residues, all of which posses 1,1-disubstituted cyclohexane rings. The parent α amino acid residue 1-aminocyclohexane 1-carboxylic acid (Ac_6c) has been conformationally characterized in a number of synthetic peptides [6,12,14]. The Ac_6c residue strongly favors helical conformations, with φ ~ 60 ± 30, and ψ ~ 30 ± 20. Thus, both β-turn and 3_{10}/α-helical structures can readily accommodate the Ac_6c residue. Two β amino acid homologs may be considered *viz* $\beta^{2,2}Ac_6c$, and $\beta^{3,3}Ac_6c$. Earlier studies from Appavu et al., focused on the more readily synthetically accessible residue $\beta^{3,3}Ac_6c$ [7,10-13]. X-ray crystallographic characterization of a number of small peptides containing the $\beta^{3,3}Ac_6c$ residue revealed that internally hydrogen bonded conformations were rarely observed. The overwhelming majority of the β-amino acid residues (149) adopt *gauche* conformation ($\theta = \pm 60°$). Out of a total of 210 examples, 61 residues adopt the *trans* conformation ($\varphi = -180°$). Figure 4 provides a summary of the observed φ,ψ values for all β amino acid residues in which θ values of ~ ± 60° have been obtained. Most $\beta^{3,3}Ac_6c$ amino acid residue fall out outside the region, expected for intra molecularly hydrogen bonded structures, which have been characterized for other β amino acid residues. Only one example of a hydrogen bonded hybrid αβ C_{11} turn has been observed in the peptide Piv-Pro-$\beta^{3,3}Ac_6c$-NHMe [7,12-14]. These results suggest that the intrinsic conformational preferences of the $\beta^{3,3}Ac_6c$ residue may not readily facilitate its incorporation into folded, intramolecular hydrogen bonded structures in short peptides. Therefore, an examination of the conformational properties of the isomeric $\beta^{2,2}Ac_6c$ residue was undertaken. The characterization of folded structures in model peptides containing the $\beta^{2,2}Ac_6c$ residue [2,10-14]. Advancing the fundamental structures of alpha amino acids to homologation would significantly impact the nanovaccine development for infectious and non-infectious diseases [17-20].

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Conclusion

Thus far, relatively few structural reports are available for the $\beta^{2,2}Ac_6c$ residue. Figure 5 shows a view of the structure of the tripeptide Boc-$\beta^{2,2}Ac_6c$-$\beta^{2,2}Ac_6c$-$\beta^{2,2}Ac_6c$-OMe which was already reported at the time these studies undertaken. In this structure the unusual ββ C_{10} hydrogen bond with reverse directionality and a C_6 hydrogen bond were observed. The hydrogen bonded C_{11} turns obtained in αβ hybrid sequences incorporating the $\beta^{2,2}Ac_6c$ residue.

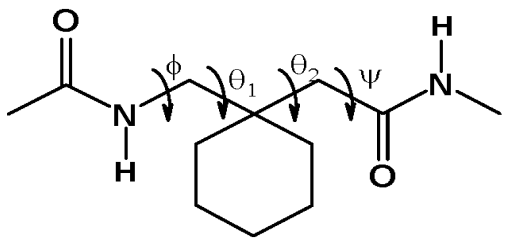

Figure 1: Chemical structure of Gabapentin (Gpn).

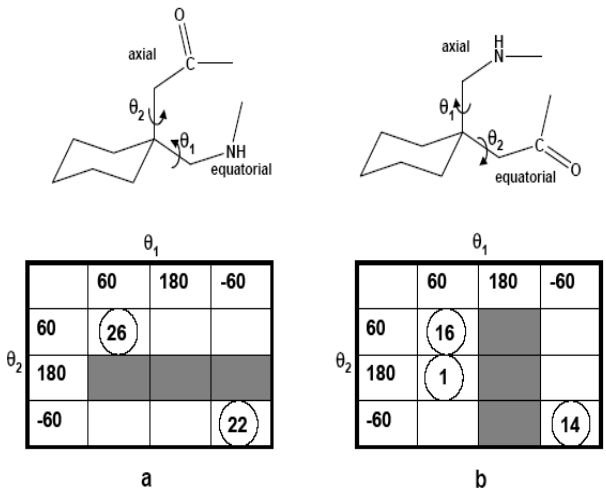

Figure 2: Nine combinations of the torsion angles θ_1 and θ_2 in gabapentin. (a) Gpn with chair conformation of the cyclohexane ring in which the aminomethyl group is equatorial and carboxymethyl group axial, (b) the inverted chair conformation of the cyclohexane ring with respect to (a), in which the aminomethyl group is axial and carboxymethyl group is equatorial. Sterically disallowed combinations are shaded dark. Numbers of Gpn residues crystallographically characterized are shown in circles in the respective cells. In the case of achiral structures both the combinations, (+60°, +60°) and (-60°, -60°) are indicated. (21achiral structures in (a) and 11 in (b)).

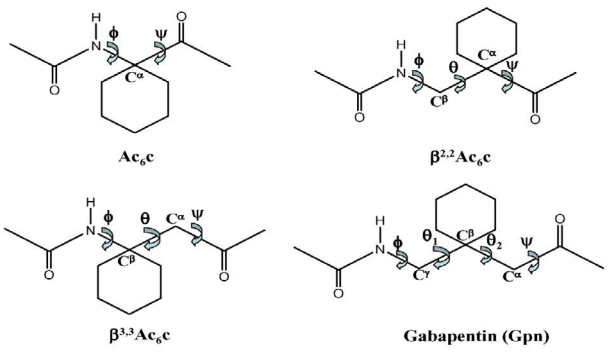

Figure 3: Definition of backbone torsion angles in α, β and γ amino acid residues.

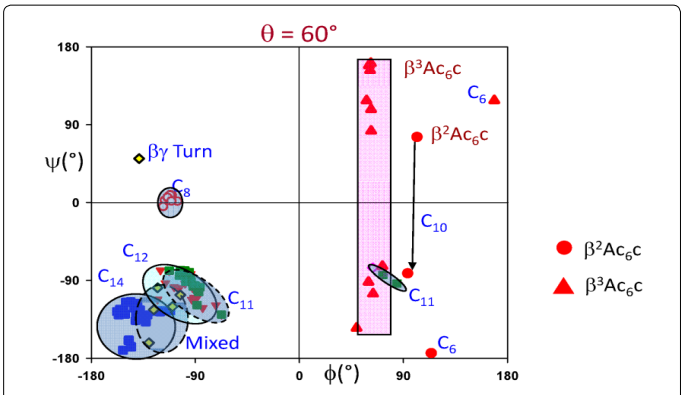

Figure 4: Two - dimensional scatter plot in φ - ψ space (θ = ± 60°) for intramolecularly hydrogen bonded β-residues determined in several peptide crystal structures. Specific intramolecular hydrogen bond types and the space for non - hydrogen bonded $\beta^{3,3}Ac_6c$ residue are marked. The arrow indicates the position of the N- and C- terminus residues of the ββ C_{10} turn. Regions accommodating C_{12} and C_{14} helices (ββ) and C_{11} helices (αβ) are shaded.

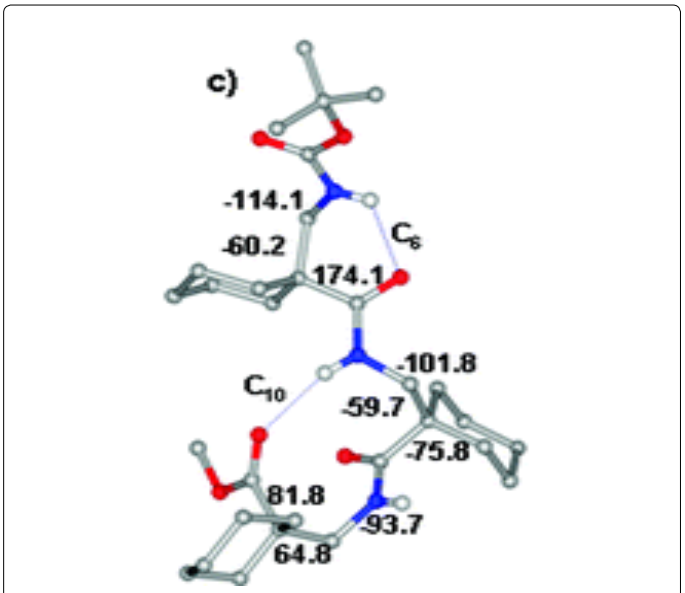

Figure 5: Molecular conformation of the tripeptide Boc-$\beta^{2,2}Ac_6c$-$\beta^{2,2}Ac_6c$-$\beta^{2,2}Ac_6c$-OMe, which has a C_6 hydrogen bond at $\beta^{2,2}Ac_6c(1)$ and a non-helical ββ C_{10} hydrogen bond with reversed directionality, at the $\beta^{2,2}Ac_6c(2)$- $\beta^{2,2}Ac_6c(3)$ segment. The backbone dihedral angles are marked [9-14].

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