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 nanovaccine development. Two distinct types of hydrogen bonded helical structures were demonstrated in these studies for oligomeric β peptides. The Cγ helix which is an analog of the canonical 3α helical structure in “all α” sequences, has the same hydrogen bond directionality (C = O– H-Nγ). The second helical form, the C14 helix, has the opposite directionality (C = O– H-Nγ), 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 a 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-aminomethylcyclohexanecacetic 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 Cβ-Cα(θ1), and Cα-Cγ(θ2) bonds. A large body of crystallographic evidence has been presented, which suggests that in the case of Gpn θ1, and θ2, are largely restricted to gauche conformations (θ1 ≤ 60°, θ2 ≤ 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 (β3,3Ac6c)c, and 1-aminocyclohexanecacetic acid (β4,3Ac6c). Figure 3 shows the structures of the four related residues, all of which possess 1,1-disubstituted cyclohexane rings. The parent a amino acid residue 1-aminomethylcyclohexane 1-carboxylic acid (Ac6c)c has been conformationally characterized in a number of synthetic peptides [6,12,14]. The Ac6c residue strongly favors helical conformations, with ψ ~ 60 ± 30, and χ ~ 30 ± 20. Thus, both β-turn and 3α/α-helical structures can readily accommodate the Ac6c residue. Two β amino acid homologs may be considered viz β3,3Ac6c, and β4,3Ac6c. Earlier studies from Appavu et al., focused on the more readily synthetically accessible residue β3,3Ac6c [7,10-13]. X-ray crystallographic characterization of a number of small peptides containing the β3,3Ac6c residue revealed that internally hydrogen bonded conformations were rarely observed. The overwhelming majority of the β-amino acid residues (149) adopt gauche conformation (θ = ± 60°). Out of a total of 210 examples, 61 residues adopt the trans conformation (θ = -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 β3,3Ac6c amino acid residue fall 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 βC11 turn has been observed in the peptide Piv-Pro-β3,3Ac6c-NHMe [7,12-14]. These results suggest that the intrinsic conformational preferences of the β3,3Ac6c residue may not readily facilitate its incorporation into folded, intramolecularly hydrogen bonded structures in short peptides. Therefore, an examination of the conformational properties of the isomeric β2,3Ac6c residue was undertaken. The characterization of folded structures in model peptides containing the β2,3Ac6c 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 β2,2Ac6c residue. Figure 5 shows a view of the structure of the tripeptide Boc-β2,2Ac6c-β2,2Ac6c-β2,2Ac6c-OMe which was already reported at the time these studies undertaken. In this structure the unusual ββ C10 hydrogen bond with reverse directionality and a C6 hydrogen bond were observed. The hydrogen bonded C11 turns obtained in αβ hybrid sequences incorporating the β2,2Ac6c residue.

References


