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Mini Review

Introduction of Stereo Chemical Constraints into β -Amino Acid Residues

Introduction

Over the last 20 years, a large body of work in the literature has focused on the folded structures formed by peptide sequences containing backbone homologated residues. Currently increasing interest in peptide based vaccines for several infectious diseases, and non-infectious diseases. The work of Seebach in Zurich [1] and Gellman in Madison [2], established that oligomers of β amino acid residues can form novel helical structures in solution and in the solid state. 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 ($C{=}O_i\cdots H{-}N_{i+3}$). The second helical form, the C_{14} helix, has the opposite directionality ($C{=}O_i\cdots H{-}N_{i+4}$), which is unprecedented in α peptide sequences [3,4]. These reports sparked a flurry of activity on the conformational properties of β peptide oligomers. An early study from Appavu et al. [3-7], had demonstrated that unsubstituted β and γ amino acid residues can be incorporated into oligopeptide helices, without disturbing the overall helical fold [4].

β-amino acid residues

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 [5]. One approach that has been investigated in this laboratory is to examine the role of *gem* dialkyl substitution on the conformational properties of β and γ residues. The ready availability of the achiral β,β-disubstituted γ amino acid, gabapentin (1-aminomethylcyclohexaneacetic acid, Gpn), has permitted detailed exploration of the structural combinations, (+60°, +60°) and (-60°, -60°) are indicated. (21 structures in (a) and 11 in (b)) (Figure 1).

The presence of *gem* dialkyl substituents at the central β carbon atom, limits the accessible conformations about the C^{β}-$C^{\gamma}(\theta_1)$, and C^{β}-$C^{\alpha}(\theta_2)$ 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 [2-7]. 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 possess 1,1-disubstituted cyclohexane rings. The parent α amino acid residue 1-aminocyclohexane 1-carboxylic acid (Ac_6c) has been conformational characterized in a number of synthetic peptides [8]. The Ac_6c residue strongly favors helical conformations, with φ60±30,

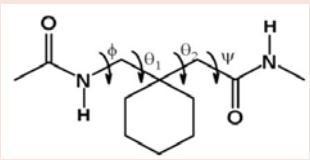

Figure 1: Chemical structure of Gabapentin (Gpn).

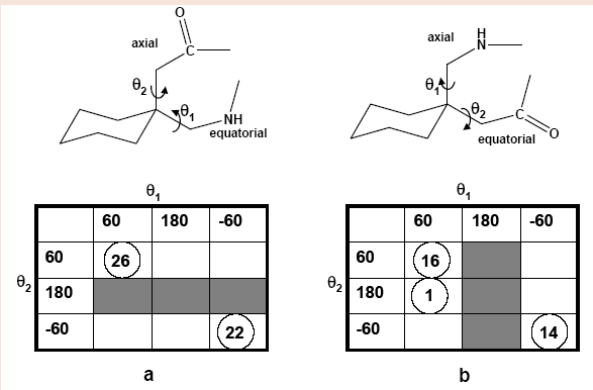

Figure 2: Nine torsion angles θ1 and θ2 in gabapentin. (a) Gpn with chair conformation of the cyclohexane ring in which the aminomethyl group is equatorial and carboxymethyl group axial, (b) the inverted chair conformation of the cyclohexane ring with respect to (a), aminomethyl group is axial and carboxymethyl group is equatorial.

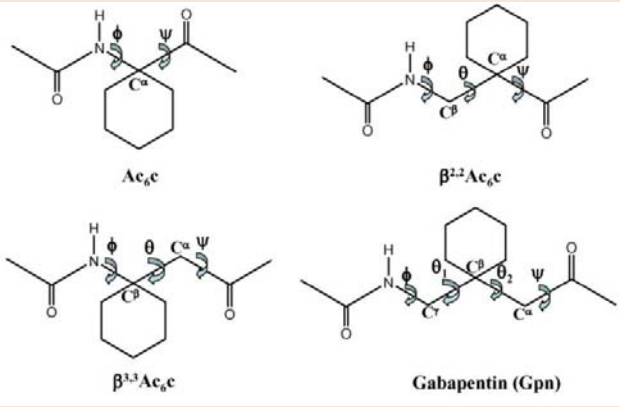

Figure 3: Definition of backbone torsion angles in , β and γ amino acid residues.

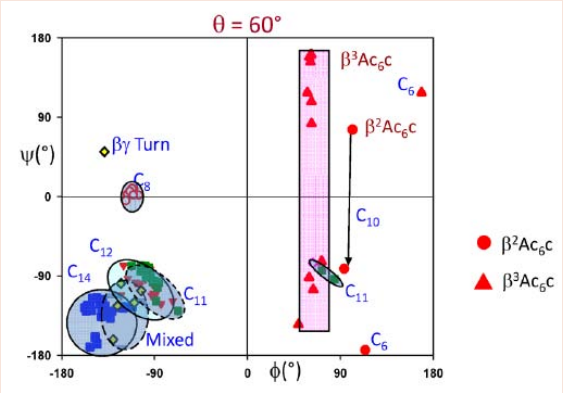

Figure 4: The scatter plot in 2D space (θ = ±60°) for intramolecular hydrogen bonded β-residues. Regions accommodating C_{12} and C_{14} helices (ββ) and C_{11} helices (αβ) are shaded.

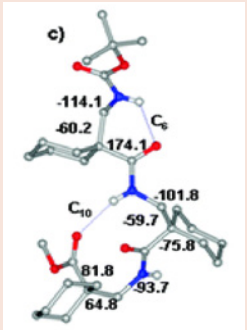

Figure 5: Molecular conformation of the peptide Boc-β2,2Ac6c-β2,2Ac6c-β2,2Ac6c-OMe, which has a single C_6 hydrogen bond at β2,2Ac6c(1) and a non-helical ββ C_{10} hydrogen bond with reversed directionality, at the β2,2Ac6c(2)- β2,2Ac6c(3) segment. The backbone dihedral angles are marked [10-12].

and ψ30±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 this laboratory focused on the more readily synthetically accessible residue $\beta^{3,3}Ac_6c$.[3,4,5,6,7,8] 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 (θ=±60°). Out of a total of 210 examples, 61 residues adopt the *Trans* conformation (φ=-180°). Figure 4 provides a summary of 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 intramolecularly 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 Piv-Pro-$\beta^{3,3}Ac_6c$-NHMe. 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.

Thus far, relatively few structural reports are available for $\beta^{2,2}Ac_6c$ residue. Figure 5 shows a view of the structure of the peptide 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 [9,10]. Chapter 5 describes hydrogen bonded C_{11} turns obtained in αβ hybrid sequences incorporating the $\beta^{2,2}Ac_6c$ residue.

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