Synthesis and conformational investigation of hetero-chiral sequential oligopeptides based on the (α Me)Aze/Ala dyad

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Introduction

Methylation at the C α -position of a Pro residue is known to lock the preceding tertiary amide (ω) torsion angle of the resulting (α Me)Pro (Fig. 1) residue to the trans disposition and to restrict the α,ψ surface mainly to the region where the 310-/ α -helices are found [1]. Moreover, the known high propensity for β -turn formation of the Pro residue is further enhanced in peptides based on its C α -methylated derivative. A few years ago some of us developed a practical, multigram scale synthesis of both (α Me)Aze (Fig. 1) enantiomers[2]. This residue is characterized by a ring contraction (from five to four atoms) with respect to (α Me)Pro. Herein, we discuss synthesis and conformational analysis of the following set of hetero-chiral sequential oligopeptides based on the -(S)-Ala-(R)-(α Me)Aze- dyad:

- (a) Boc-[(S)-Ala-(R)-(α Me)Aze] $_n$ -OMe ($n = 1-3$)
- (b) Boc-[(S)-Ala-(R)-(α Me)Aze] $_n$ -(S)-Ala-OMe ($n = 1,2$)

Figure 1: Chemical structures of (R)-(α Me)Pro, left, and (R)-(α Me)Aze, right.

Results and Discussion

Peptide syntheses were achieved in acceptable yields by use of the HATU coupling reagent.

Results from our combined X-ray diffraction and solution studies of terminally protected, hetero-chiral sequential oligopeptides based on the -(S)-Ala-(R)-(α Me)Aze- dyad support the view that this type of oligopeptide sequence strongly favors folding of the main chain into turns. In particular, the occurrence of a type-II β -turn has been unambiguously demonstrated for the -(S)-Ala-(R)-(α Me)Aze- sequence in the crystal state (Fig. 2). This finding matches that published for the strictly related -(S)-Ala-(R)-(α Me)Pro- sequence [1] (Fig. 2).

However, FT-IR absorption and 2D-NMR data provide evidence that in CDCl₃ solution the tripeptide ester is mainly folded in a γ -turn conformation. As for its higher homologs, in solution they seem to be involved in conformational equilibria to which both β - and γ -turn conformations may contribute. It is worth recalling here that the γ -turn promoting ability of (α Me)Aze was previously documented by us with the crystal structure of the homo-chiral tetrapeptide Boc-[(S)-MeAze-(S)-Ala]₂-OMe [3]. In any case, even if β -turns may prevail over γ -turns in the longest hetero-chiral oligomers, the resulting overall structure would be a "flat" β -turn ribbon [4], distinct from the (helical) β -turn ribbon spiral typical of sequential oligopeptides based on the -Aib-Pro- dyad [5].

References

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