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Right-handed 14-Helix in β^3-Peptides from L-Aspartic Acid Monomers

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Abstract

β-Peptides made from L-aspartic acid monomers form a new class of β^3-peptides. Here we report the first three-dimensional NMR solution structure of a β^3-hexapeptide (**1**) from L-aspartic acid monomers in 2,2,2-trifluoroethanol (TFE). We show that **1** forms a *right-handed* 14-helical structure in TFE. α-peptides from naturally occurring L-amino acids adopt a right-handed α-helix whereas β^3-peptides formed from β^3-amino acids derived from naturally occurring L-amino acids form left-handed 14-helices. The right-handed 14-helical conformation of **1** is a better mimic of α-peptide conformations. Using the NMR structure of **1** in TFE, we further study the conformation of **1** in water, as well as two similar β^3-peptides (**2** and **3**) in water and TFE by molecular dynamics (MD) simulations. NMR and MD results suggest loss of secondary structure of **1** in water and show that it forms a fully extended structure. **2** and **3** contain residues with oppositely charged side chains that engage in salt-bridge interactions and dramatically stabilize the 14-helical conformation in aqueous media.

Keywords: β-Peptides; 14-Helical conformation; Solution structure; MD simulations

1. Introduction

β-peptide foldamers are interesting from a pharmaceutical standpoint as mimics of α-peptides since they are not susceptible to proteolysis and metabolism [1–6]. β-peptides contain one additional methylene group in the backbone compared to the α-peptides. They are subdivided into mainly three types, namely, β^3-, β^2-, and β^{2,3}-peptides, depending upon the substitution of the backbone carbon. The substitution pattern dictates the solution conformation of these peptidomimetics. In general, monosubstituted β^3- or β^2-peptides form 14-helical structures and alternating β^2/β^3-peptides prefer 10/12 helices. β^3-peptides that fold into stable 14-helical conformations have received particular attention [7–12]. The helical secondary structure is enhanced by the presence of organic solvents, such as methanol and 2,2,2-trifluoroethanol (TFE), and efforts have been made to stabilize this conformation in aqueous solutions [13–17]. Introduction of constraints like cyclic ring systems, salt-bridge formation, or neutralization of the helix macrodipole have been utilized to obtain stable helical structures in aqueous media [13,18,19].

β^3-peptides are made from β^3-amino acid monomers using solid-phase synthesis, while the β^3-amino acids themselves are synthesized by homologotion of α-amino acids [12,20]. We have recently reported the synthesis of novel β^3-peptides from L-aspartic acid monomers [21]. The synthetic strategy employed allowed easy access to a wide variety of side chains by coupling of a free amine to the side chain α-carboxylic group of aspartic acid. This procedure introduces an extra amide bond in the side chain of the β-peptide scaffold making them more polar than the previously reported β-peptides (Fig. 1a). However, this extra amide bond provides opportunities for more hydrogen-bonding capabilities and is speculated to give unprecedented secondary structure in this class of β-peptides. Furthermore, the stereochemistry at the β^3 carbon is opposite in these two classes of β^3-peptides (Fig. 1a).

Abbreviations: CD, circular dichroism; MD, molecular dynamics; NMR, nuclear magnetic resonance spectroscopy; NOE, nuclear Overhauser effect; NOESY, two-dimensional NOE spectroscopy; ns, nanosecond; pbc, periodic boundary conditions; ps, picosecond; RMSD, root mean square deviation; TFE, 2,2,2-trifluoroethanol; SPC, simple point charge

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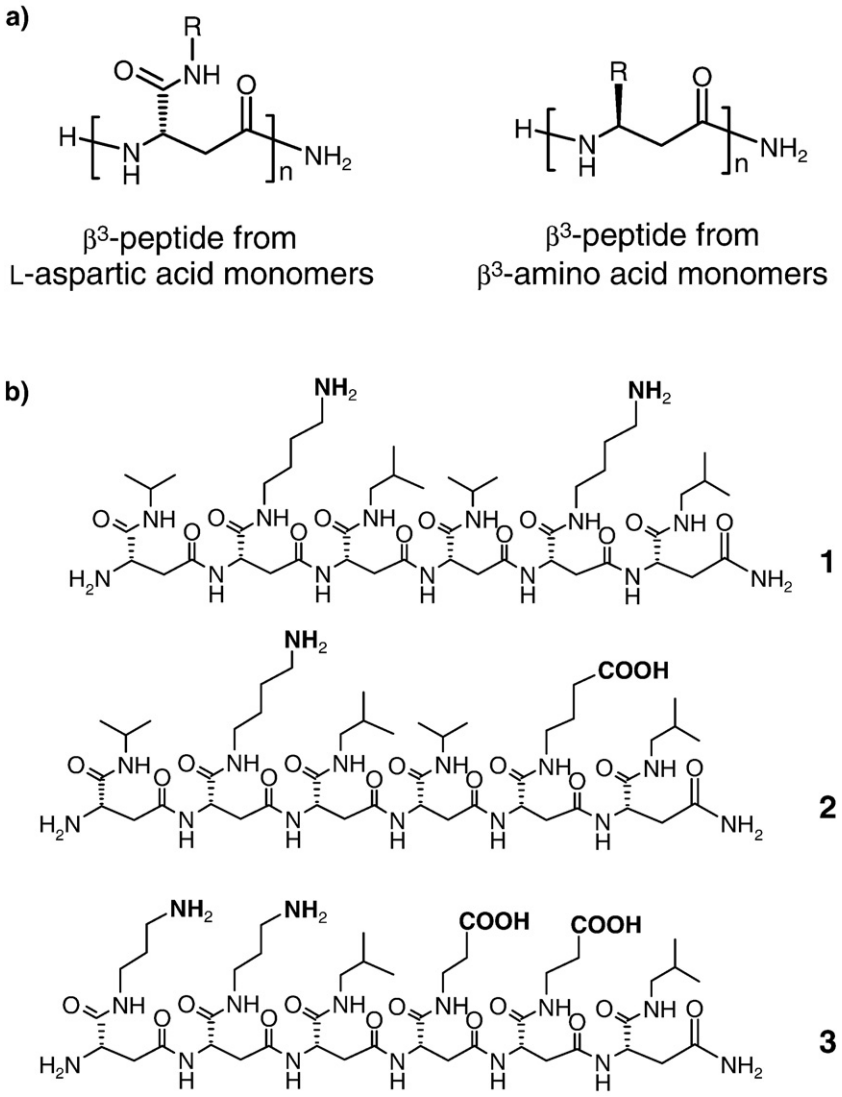

Fig. 1. (a) Chemical structure of β^3-peptide from L-aspartic acid monomers (left) and β^3-peptides from β^3-amino acids derived from natural L-amino acids (right). (b) Chemical structure of β^3-peptides from L-aspartic acid monomers (**1**, **2**, and **3**) studied here.

Here, we study the solution conformation of few representative β^3-peptides (Fig. 1b) from L-aspartic acid monomers. Using NMR spectroscopy and MD simulations, we have determined the three-dimensional structure of a β^3-hexapeptide **1** in 2,2,2-trifluoroethanol (TFE). We show that **1** forms a *right-handed* 14-helical structure in TFE. In contrast, the reported β^3-peptides formed from β^3-amino acids derived from naturally occurring L-amino acids form left-handed 14 helices [1,4]. The right-handed 14-helical conformation of **1** is a better mimic of right-handed α-helix of α-peptides (Fig. 2). The NMR solution structure of **1** in TFE is further used to study the conformation of **1**, as well as two similar β^3-hexapeptides (**2** and **3**) in water and TFE by molecular dynamics (MD) simulations. Six independent simulations, each of 10 or 20 ns duration, were conducted with β^3-peptides immersed in water or TFE with appropriate salt concentrations. The results from these simulations suggest that a salt-bridge interaction between the side chain residues is required for maintaining the helical conformation in

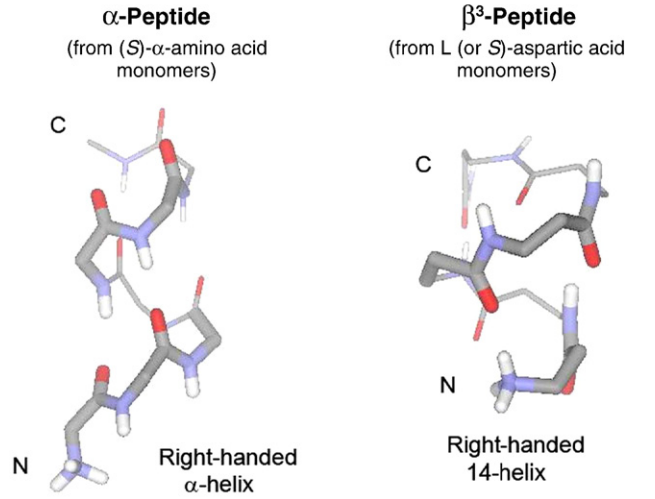

Fig. 2. Backbone conformation of right-handed α-helix in an α-peptide and 14-helix in a β-peptide from L-aspartic acid monomers. N and C stand for N- and C-terminus of the peptides, respectively.