THE SYNTHESIS AND STRUCTURAL STUDY OF ISO-Aß(1-42)

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Aß(1-42) is prone to aggregate in aqueous solution. The solubility of the peptide is poor and it cannot be stored for prolonged time in solution. Sohma and Kiso [*J. Pept. Sci*., 11: 441] attached Gly^{25} to the hydroxyl side chain of the Ser^{26} via an ester bond in their synthesis using Fmoc-chemistry. The solubility of the '*O*-acyl isopeptide' is greater than that of the Aß(1-42), and it can be stored in acidic solution for days. This isopeptide will be rearranged at pH 7.4 to Aß(1-42) through an *O→N* acyl shift. Thus this peptide can be used as a precursor of Aß(1-42).

The Aß(1-42) peptide is difficult to synthesize, because of its high tendency for aggregation during the synthesis. Both the couplings and the Fmoc-removal can be troublesome, due to the steric hindrance. If the peptide would be synthesized using Boc-chemistry the removal of the alpha-amino protecting group would be less problematic, because the 50% TFA/DCM mixture solubilizes well the peptide chain. Thus a Boc-strategy was devised for the synthesis of iso-Aß(1-42).

The purified peptide was studied with CD-spectroscopy, dynamic light scattering, transmission electron microscopy and atomic force microscopy. It was shown that isopeptide has some ß-sheet content and small aggregates are present even in a pH 2 solution. After altering the pH to 7.4, the ß-sheet content of the peptide increases and aggregation take place. With the use of the isopeptide, Aβ oligomers and - with prolonged incubation - fibrillar structures can be formed for biological studies.