Foldamers derived from nucleoside beta-amino acids: a new twist on the DNA helix

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ABSTRACT

Peptides derived from a thymidine beta-amino acid have been prepared by solid-phase synthesis and their conformation investigated by NMR. Interestingly, NMR and modelling studies indicate that the tetramer and octamer form an unusual 8-helical conformation. Studies are currently underway to investigate the synthesis of peptides derived from the other deoxyribonucleosides with the intention of examining the association between helices capable of nucleobase-pairing.

RESULTS AND DISCUSSION

The target monomer (2, Scheme 1), was synthesised from the previously reported\textsuperscript{5} fluorenylethoxycarbonyl (Fmoc)-protected amino alcohol (1) by oxidation with bis-acetoxyiodobenzene (BAIB)\textsuperscript{6} and 2,2,6-tetramethylhexyloxyloxy (TEMPO) in aqueous acetonitrile. Although the oxidation proceeds in relatively low yield (46%) the method is advantageous in that the Fmoc-protected amino acid precipitates out of reaction mixture and is obtained pure after filtration and washing with diethylether.


We were struck by the fact that nucleosides can be readily converted to \(\beta\)-amino acids which are closely related to Gellman’s helix-forming trans-2-aminoacylpeptanocarbonylic acid monomer\textsuperscript{7} and now report the synthesis of peptides derived from the thymidine beta-amino acid (Scheme 1) and their structural properties.\textsuperscript{8} The analogous amino acid derived from 2’-deoxyadenosine has also been prepared.

Choice of resin for Fmoc solid-phase peptide synthesis (SPPS) was influenced by the sensitivity of the glycosidic bond to acid. With this in mind, the hyper acid-labile Sieber amide resin was chosen which on cleavage, produces peptides with a primary amide at the carboxylate terminus. The peptide assembly used HBTU in N,N-dimethylacetamide as the coupling agent and followed standard Fmoc protocols. Using this procedure dimers, tetramers and octamers, both with and without the Fmoc
group, were prepared (Scheme 1). In all cases the oligomers were sufficiently pure for analysis following cleavage from the support and washing with water.

Structural NMR studies were performed on both the Fmoc-protected tetramer and the deprotected octamer. Detailed NMR studies on the tetramer established a series of NOE connectivities which were utilized to build a model using Macro-Model. The model produced was consistent with an 8-membered ring between the backbone amide groups corresponding therefore to an "8-helix". This helical arrangement places the thymine bases on the outside of the helix where they could potentially H-bond to a complementary adenine base. With this in mind, we have therefore embarked on the synthesis of the corresponding adenine-derived oligomers in order to explore the possibility of helix association driven by base pairing.

The synthesis of the 2'-deoxyadenosine monomer (6) starts from the previously reported azidonucleoside (3, Scheme 2) and utilizes benzoyl protection of the adenine base. In this case, the most efficient reduction of the azide was obtained using hydrogen sulfide. Current studies are underway on the solid-phase synthesis of peptides derived from adenine monomer (6).

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\begin{align*}
\text{HO} & \rightarrow \text{TEMPO, BAIB,} \\
& \quad \text{MeCN/H}_2\text{O} \rightarrow \text{HO} \\
& \quad \begin{array}{c}
N_3 \\
\begin{array}{c}
\text{305} \rightarrow \text{82}\% \\
\end{array}
\end{array} \\
& \quad \begin{array}{c}
N_3 \\
\begin{array}{c}
\text{40} \rightarrow \text{82}\% \\
\end{array}
\end{array} \\
& \quad \begin{array}{c}
\text{H}_2\text{S, Pyridine,} \\
& \quad \text{NEt}_3 \\
\end{array} \\
& \quad \begin{array}{c}
\text{HO} \rightarrow \text{FmocCl,} \\
& \quad \text{dioxane/H}_2\text{O} \rightarrow \text{HO} \\
& \quad \begin{array}{c}
\text{NHFmoc} \\
\begin{array}{c}
\text{50} \rightarrow \text{56}\% \\
\end{array}
\end{array}
\end{array}
\end{align*}
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Scheme 2, Synthesis of 2'-deoxyadenosine-derived beta-amino acid.

CONCLUSION

In conclusion, peptides derived from a thymidine beta-amino acid have been prepared and their conformation studied by NMR. Interestingly, the tetramer forms an 8-helix, which differs considerably from the 12-helix derived from the related trans-2-aminocyclopentanecarboxylic acid. Studies are currently underway on the synthesis of the complementary adenine peptides in order to investigate association between helices capable of nucleobase-pairing, such systems would offer a new motif in the search for innovative macromolecular architectures.

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REFERENCES


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