Application of $\alpha$-chloroglycine residues for the modification of oligopeptides

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Abstract: New reactions of peptides incorporating electrophilic glycine equivalents are described including cycloadditions and a novel dimerization reaction. The stereochemistry of the addition of nucleophiles to this type of compounds is discussed.

1. INTRODUCTION

Electrophilic glycine equivalents within oligopeptide chains are easily generated from the corresponding seryl and threonyl peptides $1$ by treatment with lead tetraacetate. The resulting $\alpha$-acetoxyglycyl peptides $2$ can be transformed into the more reactive $\alpha$-chloroglycyl derivatives $3$ by successive treatment with ethanethiol/NEt$_3$ and sulfuryl chloride.

Compounds $2$ and $3$ react with nucleophiles by an elimination/addition mechanism to yield a range of $\alpha$-substituted glycine derivatives $5$. Reactive intermediates are the dehydroglycyl peptides $4$. These transformations occur under mild conditions and in the presence of most proteinogenic amino acids.
2. STEREOCHEMICAL ASPECTS

Chiral amino acid residues attached to the prochiral dehydroglycine centre should influence the steric outcome of these additions. We have found that achiral nucleophiles like benzyl alcohol, benzyl mercaptane, benzylamine, and higher order cuprates add to oligopeptide derivatives with low steric preference, e.g.

\[
\begin{align*}
\text{Z-} & \begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\text{Cl}
\end{array}
\begin{array}{c}
\text{H} & \text{H} \\
\text{N} \\
\text{O} \\
\text{CO}_2\text{Me}
\end{array}
\text{ } & \overset{\text{BnXH}}{\text{BnXH}} & \text{Z-} \begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\text{X} \\
\text{X}
\end{array}
\begin{array}{c}
\text{H} & \text{H} \\
\text{N} \\
\text{O} \\
\text{CO}_2\text{Me}
\end{array}
\text{ } \overset{\text{NET}_3}{\text{NET}_3} & (60-80\%) \text{ (d.e. } 5-15\%) \\
\end{align*}
\]

Even some nucleophiles with chiral centres behave similarly and yield the \(\alpha\)-substituted glycyl peptides without notable stereoselectivity. This is illustrated by the reactions of \(\alpha\)-hydroxy acid esters and sugar derivatives with \(\alpha\)-acetoxy- and \(\alpha\)-chloroglycine derivatives.

\[
\begin{align*}
\text{Z-} & \begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\text{Cl}
\end{array}
\begin{array}{c}
\text{H} & \text{H} \\
\text{N} \\
\text{O} \\
\text{CO}_2\text{Me}
\end{array}
\text{ } & \overset{\text{H} \text{O-} \text{CO}_2\text{Me}}{\text{NET}_3, \text{CH}_2\text{Cl}_2, -78^\circ \text{C}} & \text{Z-} \begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\text{Me}
\end{array}
\begin{array}{c}
\text{H} & \text{H} \\
\text{N} \\
\text{O} \\
\text{CO}_2\text{Me}
\end{array}
\text{ } \overset{\text{NET}_3, \text{CH}_2\text{Cl}_2, -78^\circ \text{C}}{\text{NET}_3, \text{CH}_2\text{Cl}_2, -78^\circ \text{C}} & (65\%) \text{ (d.e. } 2\%)
\end{align*}
\]

In contrast, \(\alpha\)-amino acid esters, enamines, and \(N\)-Boc-\(L\)-serine methyl ester react with peptide derivatives like \(Z-L-Va\text{l-Gly(Cl)}-\text{OMe} \) with high stereoselectivity (d.e. 68-90\%). In the case of serine derivatives the stereochemistry of the prevailing diastereomers has still to be determined.

\[
\begin{align*}
\text{Z-} & \begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\text{Cl}
\end{array}
\begin{array}{c}
\text{H} & \text{H} \\
\text{N} \\
\text{O} \\
\text{CO}_2\text{Me}
\end{array}
\text{ } & \overset{\text{H}_2\text{N-} \text{CO}_2\text{Me}}{\text{NET}_3, \text{CH}_2\text{Cl}_2, -78^\circ \text{C}} & \text{Z-} \begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\text{H}
\end{array}
\begin{array}{c}
\text{H} & \text{H} \\
\text{N} \\
\text{O} \\
\text{CO}_2\text{Me}
\end{array}
\text{ } \overset{\text{NET}_3, \text{CH}_2\text{Cl}_2, -78^\circ \text{C}}{\text{NET}_3, \text{CH}_2\text{Cl}_2, -78^\circ \text{C}} & (72\%) \text{ (d.e. } 86\%)
\end{align*}
\]

\[
\begin{align*}
\text{Z-} & \begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\text{Cl}
\end{array}
\begin{array}{c}
\text{H} & \text{H} \\
\text{N} \\
\text{O} \\
\text{CO}_2\text{Me}
\end{array}
\text{ } & \overset{\text{H} \text{O-} \text{CO}_2\text{Me}}{\text{NET}_3, \text{CH}_2\text{Cl}_2, -78^\circ \text{C}} & \text{Z-} \begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\text{MeO}_2\text{C}
\end{array}
\begin{array}{c}
\text{H} & \text{H} \\
\text{N} \\
\text{O} \\
\text{CO}_2\text{Me}
\end{array}
\text{ } \overset{\text{NET}_3, \text{CH}_2\text{Cl}_2, -78^\circ \text{C}}{\text{NET}_3, \text{CH}_2\text{Cl}_2, -78^\circ \text{C}} & (95\%) \text{ (d.e. } 68\%)
\end{align*}
\]
Modification of oligopeptides

The same group of compounds exhibits a remarkably strong reagent control as indicated by their reactions with methyl α-bromohippurate 7:

![Chemical structure image](attachment:image1)

An interesting difference between O- and S-nucleophiles is observed in the reaction of 7 with N-Boc-L-cysteine methyl ester. Whereas the serine derivative leads to a diastereomeric excess of 91%, the corresponding cysteine ester affords only a 1:1 mixture of the diastereomers.

These results point to a highly ordered transition state for the reaction of 4 with α-amino acid esters, enamines, and serine derivatives. The factors responsible for the complex stereochemical behaviour of α-chloroglycyl peptides towards chiral nucleophiles are under investigation.

3. CYCLOADDITIONS

Cycloaddition reactions offer an attractive possibility for the modification of the secondary structure of peptides containing dehydroglycine residues. We found that the latter compounds react with cyclopentadiene to yield the cycloadducts with high diastereoselectivity. This technique allows the conversion of serine residues within peptide chains into secondary amino acids which imposes conformational restrictions.
4. A Novel Method for the Dimerization of Peptide Chains

Treatment of peptides containing α-acetoxy- or α-chloroglycine residues with triethylamine and a catalytic amount of triphenylphosphine constitutes an efficient method for the synthesis of dimers in which two identical peptide chains are connected by a C=C-double bond between two glycine residues. As seen from the examples the position of the activated glycine within the peptide chain has no influence on the success of the reaction. The appearance of a NH-signal at $6 - 9$ ppm in the $^1$H NMR spectrum indicates strong hydrogen bonding between the central NH- and the CO-groups and seemed to be in accord with the (E)-configuration at the double bond.$^5$ However, the X-ray analysis of dimethyl 2,3-bis(benzoylamino)-maleinate proved to have a (Z)-configuration in its crystalline state.

![Chemical Structures]

The dimers can be catalytically hydrogenated to compounds in which the two peptide chains are connected by a C-C-bond between two glycine residues.

![Chemical Structures]

Acknowledgements
Support for this work was provided by the Deutsche Forschungsgemeinschaft. M. J. thanks the Studienstiftung des Deutschen Volkes and S. J. the Fonds der Chemischen Industrie for scholarships.

References and Notes:
4. The stereochemistry given in the formulas for the main diastereomers is in accord with the NMR data but has still to be confirmed by X-ray structural analyses.
5. A simple example of this reaction has been described: R. Kober, W. Steglich, Liebigs Ann. Chem. 599 (1983).