Participation of Non-Aminoisobutyric Acid (Aib) Residues in the 3_{10} Helical Conformation of Aib-Rich Foldamers: A Solid State Study

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The solid state conformational preferences of a series of 2-aminoisobutyric acid (Aib) foldamers bearing a single N-terminal tertiary amino acid (Cbz-L-phenylalanine (Cbz-L-Phe)) have been investigated by X-ray crystallography. The type of β-turns present at the N-terminus and the global screw-sense preferences of the Aib foldamers were determined by analysis of intramolecular hydrogen-bonds and peptide torsion angles. The contrasting influence of a C-terminal ester or amide on the 3_{10} helical conformation of the foldamers was established by identifying the hydrogen-bonding motifs adopted in the solid state. The ability of non-Aib achiral quaternary residues in the middle of the chain to stabilise the 3_{10} helix was similarly confirmed. Combining these structural features, which promote the formation of consecutive $i \rightarrow i + 3$ β-turns in Aib foldamers, permitted the formation of long chain oligomers which display 3_{10} helical conformations which extend over 21 Å.

Introduction

Peptaibols are a class of antibiotics whose potent biological activity is realised through the self-association of well-folded structures to induce the formation of membrane-spanning aggregates. These aminoisobutyric acid (Aib) rich peptides are thought to be $3_{10}$ or α-helical when embedded in the bilayer membrane, so understanding how the helical conformation contributes to the biological activity of these Aib-rich peptides is essential. Accordingly, gaining insight into how different residues produce structural motifs that stabilise or destabilise the folded structures adopted by peptaibols should provide greater understanding of how the biological properties of these peptides arise.

The presence of the quaternary achiral amino acid Aib in peptides promotes the formation of helical conformations and synthetic oligomers (foldamers) consisting exclusively of Aib residues demonstrate well-defined folding behaviour. Peptide chains containing four or more Aib residues are able to mimic the conformational behaviour of peptaibols through the adoption of stable $3_{10}$ helices in the solid state and solution. Achiral Aib oligomers have no preferred screw sense and rapid interconversion between $M$ and $P$ helicity occurs at ambient temperature. However the incorporation of a single chiral amino acid at the N-terminus of an Aib oligomer induces a screw-sense preference. Our group has demonstrated that the nature of the N-terminal chiral amino acid influences both the magnitude and direction of the screw-sense preference of the foldamer in solution and the solid state. We have shown that N-terminal acetyl (Ac) or benzoyloxyacarbonyl (Cbz) protected tertiary residues of L configuration, of which Ac-L- valine was representative, induce a left-handed helix by stabilising an initial Type II β-turn. Conversely, N-terminal Ac or Cbz protected quaternary residues, of which Ac-L-α-methylvaline was representative, induce a right-handed helix by stabilising a Type III β-turn.

In this paper, we report an investigation of the influence of N-terminal Cbz-Phe residues, C-terminal esters and amides, and mid-chain quaternary residues and the adoption of $3_{10}$ helical conformations of both short and long chain Aib oligomers in the solid state. X-ray crystallography was employed to characterise the intramolecular hydrogen-bonding network, and analysis of the $\phi$ and $\psi$ torsion angles provided information about the type of β-turn adopted by these Aib foldamers at the termini and at the non-Aib mid-chain residues. The long chain Aib foldamers incorporate terminal groups and central quaternary linker residues that promote intramolecular $i \rightarrow i + 3$ helical interactions.
hydrogen-bonding interactions, leading to examples of $3_{10}$ helices over 21 Å in length.

**Results and Discussion**

**Design of Aib Foldamers**

Two classes of peptides were studied, all with a minimum of four residues to ensure the formation of a stable $3_{10}$ helix.\(^9^{,11}\)

![Diagram of Aib Foldamers](image)

**Fig. 1.** a) Class 1: Tetramers with N-terminal Cbz-L-Phe residues and C-terminal ester or amide functionalities, b) Class 2: Extended Aib foldamers with quaternary linking amino acids and N-terminal Cbz-L-Phe residues and C-terminal GlyNH$_2$, c) Representation of a $3_{10}$ helix adopted by Aib oligomers and $\phi$ and $\psi$ torsion angles adopted in an ideal $3_{10}$ helix ($\phi = 57.9^\circ$, $\psi = 30.9^\circ$).

Firstly (Class 1, Figure 1a), oligomers incorporating either N-terminal racemic or enantiopure Cbz-Phe residues, and with differing C-terminal functionalities, were investigated: Cbz-Phe-(Aib)$_4$-OtBu 1 and Cbz-L-Phe-(Aib)$_4$-NH$_2$ 2.\(^{16c}\) These were compared with an oligomer carrying an N-terminal azido group N$_2$-(Aib)$_4$-GlyNH$_2$ 3.\(^{18}\) Secondly (Class 2, Figure 1b), a series of longer linked Aib foldamers incorporating the alternative achiral quaternary residues L-aminocyclopentanecarboxylic acid (Ac$_C$),\(^{19}\) L-aminocyclohexanecarboxylic acid (Ac$_C$C$_6$),\(^{20}\) and the biphenyl-based Bip,\(^{4,6}\) were investigated (Figure 1b). These oligomers also incorporated N-terminal Cbz-L-Phe and C-terminal glycynamide (GlyNH$_2$) residues, allowing us to explore the influence of these three factors on the $3_{10}$ helical conformational preferences of extended Aib foldamers. The achiral quaternary residues, Ac$_C$, Ac$_C$C$_6$ and Bip, were selected as they have been previously studied in solution and shown to perform as effective conductors of conformational preference in long linked Aib oligomers.\(^{16}\) Furthermore, our solution-based studies demonstrated that they display levels of stereochemical control comparable to those achieved with Aib residues.\(^{16,27}\) The efficiency of chirality transfer achieved by the achiral quaternary amino acids, Ac$_C$, Ac$_C$C$_6$ and Bip, as determined by NMR spectroscopy, implicates the adoption of a global stable $3_{10}$ helical conformations, in solution, despite the presence of these non-Aib residues. Ac$_C$C$_6$ and Ac$_C$ residues display the propensity to induce folding and the conformational preferences of these residues are known to support either $3_{10}$/$\alpha$-helices in synthetic oligomers.\(^{19,20}\) The formation of oligomers exclusively from pro-atropoisomeric Bip residues or the incorporation of the achiral biaryl residue into peptide chains bearing chiral tertiary amino acids, such as valine\(^{11}\) and alanine,\(^{17d}\) creates structures which exhibit the ability to adopt stable $3_{10}$ helical conformations.\(^{21c}\)

X-ray crystallographic analysis was carried out on peptides 1 – 6. The $3_{10}$ helix is characterised by a series of $i$ $\rightarrow$ $i$ $+$ 1 Type III (or Type III’) $\beta$-turns with ideal torsion angles of $\phi = 30^\circ$ and $\psi = 57^\circ$ (Figure 1c). Analysis of intramolecular hydrogen bonds and torsion angles allowed us to identify the extent to which the oligomers adopt $3_{10}$ helical conformations, and to locate any helix reversal induced by the C-terminal groups. The C-terminal GlyNH$_2$ residue was of particular significance as part of a research programme developing $^1$H NMR spectroscopic probes that are able to report on the conformational preferences of Aib oligomers in solution.\(^{13c,16a}\) All the NH and carbonyl positions in the chain are described in relation to the N-terminus and the torsion angles are reported in the same manner, from N-terminus to C-terminus.

**Influence of N-Terminal Cbz-Phe Residues and C-Terminal Esters and Amides on Conformational Preferences**

The crystal structure of peptide 1 incorporating an N-terminal racemic Cbz-Phe residue has two molecules in the unit cell, one of each screw-sense preference. Both molecules contain stable $3_{10}$ helices supported by three intramolecular $i$ $\rightarrow$ $i$ $+$ 3 hydrogen-bonding interactions (2.89 - 3.06 Å) (see Supporting Information). The torsion angles $\phi = -71.9^\circ$, $-54.9^\circ$ and $\psi = -12.7^\circ$, $-25.2^\circ$ for $i$ + 1 and $i$ + 2 respectively (Table 1) indicate the initial $\beta$-turn formed at the N-terminus was ‘Type III’ with a slight distortion at $i$ + 1. In the unit cell, molecules bearing L-amino acids possess $M$ helicity due to the presence of an initial Type III’ $\beta$-turn whilst those incorporating D-amino acids adopt $P$ helices. Interestingly, this Type III’ $\beta$-turn is in contrast to the
Type II turn that have been previously identified in solution and solid-state structures for Aib oligomers bearing single N-terminal tertiary amino acids.\textsuperscript{16} N-terminal amino acids bearing the aromatic Phe residue may induce a change in sign in conformation through intermolecular π–π stacking (see Supporting Information).\textsuperscript{22} In 1, the crystal packing shows the presence of intermolecular edge-to-face π–π stacking interactions, of 3.60 Å between the Phe residues of opposite enantiomers (see Supporting Information). In 2, the two sets of conformers of opposing screw-sense display edge-to-face π–π stacking interactions, of relatively short distances; 3.72 – 4.18 Å, between the aromatics of Phe residues of adjacent molecules (see Supporting Information). Additionally, there are edge-to-face π–π stacking interactions, 3.90 – 4.72 Å, between the aromatics of N-terminal Cbz protecting groups of adjacent molecules of opposite screw-sense. The longer linked peptides, 4-6 display no π–π stacking interactions (inter- or intra-molecular) between the aromatics of the Phe residue and/or the Cbz group. Whilst we have previously generalised that N-terminal amino acids, give rise to initial Type II β-turn\textsuperscript{16} it appears that this is true of non-aromatic chiral residues and the behaviour of aromatic residues is more complex. In 1, Aib residues 1 - 3 possess torsion angles close to those expected for an ideal 3\textsubscript{10} helix (Table 1) but the bulky non-hydrogen bonded C-terminal ester group leads to helix reversal\textsuperscript{23} denoted by the change in sign (Table 1 ). The ω torsion angles of 172.6°, 172.2°, 176.0°, 175.0°, 177.7° and 178.9° show only slight deviation from the ideal trans planar peptide bond (see Supporting Information).

Table 1. Torsion angle ϕ and ψ for foldamers 1-3.

<table>
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<tr>
<th>Cpd.</th>
<th>Torsion Angle</th>
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<th>Aib (2)</th>
<th>Aib (3)</th>
<th>Aib (4)/GlyNH₂</th>
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<td>24.0(2)</td>
<td>7.9(2)</td>
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</table>

*For foldamers 1 and 2 the first residue refers to Phe but for foldamer 3 the initial residue bears an azido group, \(^{26}\) For foldamers 1 and 2 the C-terminal residue is Aib but for foldamer 3 the C-terminal residue is GlyNH₂. \(^{27}\) For foldamers 1 and 3 the torsion angles for left-handed helix only are given although in the unit cell both left and right-handed helices are observed and the torsion angles are of equal magnitude but opposite sign.

A Cbz-L-Phe residue at the N-terminus of an Aib oligomer induces \(M\) helicity in solution.\textsuperscript{16c} However, both \(M\) and \(P\) helices are present in the solid state structure of the enantiopure oligomer 2 and the torsion angles for all four molecules observed in the unit cell are reported in Table 1.\textsuperscript{28} Clearly, screw-sense preference is finely balanced in the solid state and can presumably be readily dictated by crystal packing. As with 1, the β-turn at the N-terminus is Type III (or Type III\textsuperscript{+}) with only slight distortion from the expected \(ψ\) and \(ϕ\) torsion angles at \(i + 1\) and \(i + 2\) (Table 1 ).\textsuperscript{22} The Aib residues 1 - 3 show no significant deviation from the ideal torsion angles of the Type III β-turns that form 3\textsubscript{10} helices (Table 1). Surprisingly, the C-terminal amide-bearing residue displayed helix reversal in a fashion analogous to the bulky ester group of 1 (Figure 2a). This is particularly surprising as examples have been reported of C-terminal amide-functionalised, both primary\textsuperscript{26} and
secondary\textsuperscript{27} Aib residues and bulkier quaternary residues,\textsuperscript{28} which do not induce helix reversal but participate in intramolecular hydrogen-bonding interactions. The magnitude of the torsion angles were comparable for 1 and 2 (Table 1). The absence of an expected intramolecular hydrogen-bond between the C-terminal amide and Aib (3) in 2 is most likely a consequence of subtle crystal packing effects in the solid-state which influences the nature of the hydrogen-bonding interactions involving the AibNH\textsubscript{2} C-terminal residue. In the four conformers of 2 observed in the solid-state, there are seven hydrogen-bonding interactions which involve either the NH or the carbonyl of the AibNH\textsubscript{2} residue, (see Supporting Information). Six intermolecular hydrogen-bonding interactions involving the NH of AibNH\textsubscript{2} are observed, three of which display unusual tail-to-tail interactions with the carbonyl of the AibNH\textsubscript{2} (2.26 – 2.68 Å) (see Supporting Information), one displays a head-to-tail interaction with the NH at position i + 2 from the N terminus of an adjacent molecule (3.18 Å) (see Supporting Information) and two involve tail-to-centre interactions between adjacent molecules with the carbonyl at i + 3 position from the N-terminus (2.71 and 2.68 Å) (see Supporting Information). The head-to-tail intermolecular H-bonding interaction involving the carbonyl of AibNH\textsubscript{2} exists with the NH at the i + 2 position from the N-terminus (3.18 Å). Finally, an intramolecular interaction involving the NH of AibNH\textsubscript{2} and the carbonyl of i + 4 from the N-terminus (3.01 Å) (see Supporting Information) is observed Presumably, the formation of these inter- and intra-molecular hydrogen-bonding interactions in 2 prevent the adoption of the anticipated stable Type III β-turn at the C-terminus involving the AibNH\textsubscript{2} residue and the carbonyl of Aib (3).

In N\textsubscript{3-}(Aib)\textsubscript{4}-GlyNH\textsubscript{2} 3 the C-terminal glycineamide participates in an additional i → i + 3 intramolecular hydrogen-bonding interaction, with a C=O…HN distance of 3.05 Å between the Aib (3) carbonyl and GlyNH\textsubscript{2} (Figure 2a).\textsuperscript{18} Interestingly, unlike in 2, the C-terminal amide does not induce helix reversal in the ϕ torsion angle, although the ψ angle is closer to zero (Table 1). At the N-terminus, the azido group causes significant destabilisation of the 3\textsubscript{10} helix due to its inability to participate in the i → i + 3 hydrogen bond motif (Table 1). The central Aib residues (Aib 1-3) display torsion angles close to those expected in a 3\textsubscript{10} helix.

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{figure2}
\caption{Side view of the X-ray structure of a) Cbz-L-Phe-(Aib)\textsubscript{4}-NH\textsubscript{2} 2 and b) N\textsubscript{3-}(Aib)\textsubscript{4}-GlyNH\textsubscript{2} 3 highlighting the intramolecular hydrogen-bonding interactions present in the solid state and the stable formation of a 3\textsubscript{10} helical conformation. The hydrogen atoms have been removed for simplicity C atoms are shown in grey, N in light blue and O in red; some H atoms have been removed for clarity. One chloroform solvent molecule has been removed for clarity from 3.}
\end{figure}

\textbf{Optimised Systems: Extended Linked Aib Foldamers}

A short series of extended Aib foldamers 4-6 were also characterised in the solid state, each having the general formula Cbz-L-Phe-(Aib)\textsubscript{4}-Xaa-(Aib)\textsubscript{4}-GlyNH\textsubscript{2} where Xaa is the achiral quaternary residue Acsc, Acâ€ or Bip, respectively (Figure 1b). The four Aib residues lying between the Xaa residue and the termini ensure a stable 3\textsubscript{10} helix is established both before and after the central non-Aib residue.
Foldamers 4-6 display a preference for $M$ helicity in solution as a result of the N-terminal tertiary Cbz-L-Phe residue. However, as found for 2, in the solid state the unit cells of all three contain equal numbers of left and right-handed helices (Table 2). The first reported example of an Aib oligomer bearing a single chiral C\textsuperscript{\textsuperscript{\textsuperscript{\textsuperscript{\textcircled{N}}}}}trisubstituted amino acid which displays screw sense indifference in the solid state through the presence of both $M$ and $P$ helices was reported for Ac-(Aib)$_\text{S}$-Iva-(Aib)$_\text{S}$-OMe by Toniolo and co-workers.

More recently, there has been a report in which the incorporation of a single chiral residue at the N-terminus displays both screw senses in the unit cell in the solid state has been reported for Cbz-L-Dab($\rho$BrBz)-(Aib)$_\text{S}$-NHMe.$^{27a,29}$ Foldamer 4 is pseudo-centrosymmetrical with a non-crystallographic $C_2$ axis (see Supporting Information) whilst, interestingly foldamer 5 shows no pseudo-centrosymmetry in the solid-state. This is most likely due to the two head-to-tail intermolecular hydrogen-bonding interactions in 5 between adjacent molecules of opposite screw-sense preference combined with the anti-parallel packing observed in the crystal (see Supporting Information) which prevents a pseudo-symmetrical arrangement from being adopted. The intermolecular hydrogen-bonding interactions in 5 are between two molecules involving the NH at $i + 2$ from the N-terminus in one molecule and the carbonyl of the amide of the GlyNH$_2$ residue of an adjacent molecule (2.88 Å) and the NH at $i + 1$ from the N-terminus and the carbonyl of the C-terminal Aib residue, (2.83 Å). Foldamer 4 displays only one intermolecular head-to-tail interaction between the NH closest to the N-terminus in one molecule and the carbonyl of the amide of the GlyNH$_2$ residue of an adjacent molecule (2.85 Å) of opposite enantiomers along the c axis but, unlike 5, a parallel arrangement of the molecules along the axis is observed. Foldamer 6 displays pseudo-centrosymmetry with a non-crystallographic $C_2$ axis (see Supporting Information) and an anti-parallel arrangement of the molecules is adopted in the crystal packing. As in Cbz-Phe tetramers 1 and 2 the presence of a Type III (Type III') $\beta$-turn was evident at the N-terminus of all three extended Aib foldamers with the torsion angles deviating only slightly from ideal values ($\phi$ and $\psi$ torsion angles at $i + 1$ and $i + 2$ residues in Table 2). The $\phi$ and $\psi$ angles in 4-5 show a series of Type III $\beta$-turns in the Aib tetramer chains, but in both 4 and 5 there is a slight distortion away from those angles expected of a $3_10$ helix in the Aib residue preceding the non-Aib quaternary amino acid Xaa (-

<table>
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<th>Aib (3)</th>
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$^a$Xaa refers to Ac$_\text{c}$ and Ac$_\text{c}$ residues situated in the centre of foldamers 4-5 respectively.

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44.4 and 47.2 for φ in Ac_{10} residue of 4 and -32.0 and 27.0 for ψ in Ac_{10} residue of 4, -44.7 and 41.8 for φ in Ac_{10} residue of 5 and -49.0 and 48.5 for ψ, in Ac_{10} residue of 5). The achiral quaternary amino acid residues in 4-5, Ac_{10} and Ac_{6}, do not impede the continuation of the 3_{10} helical structure in these extended Aib foldamers, and the torsion angles around these residues are close to those expected (Table 2): φ from -55.3 to -62.5 and from 53.8 to 58.1 and ψ from -22.9 to -28.3 and from 28.3 to 28.8. The observation that these achiral quaternary residues promote 3_{10} helical conformations in the solid state correlates well with solution studies that ascribe the long-range propagation of screw-sense in extended Aib foldamers to the adoption of a stable 3_{10} hydrogen-bonding network. In 4 and 5, the 3_{10} helical motif is formed of ten i → i+3 intramolecular hydrogen-bonding C=O…HN interactions, (2.84 - 3.05 Å for 4, 2.98 - 3.16 Å for 5, see Figure 3 and Supporting Information).

In these oligomers the C-terminal GlyNH$_2$ residue participates in an additional intramolecular interaction with the C=O of Aib (8) (Figures 3a and b), giving rise to the C-terminal 3_{10} helical conformation that was also seen in 3 (Figure 2b). In 6, the C-terminal GlyNH$_2$ residue is not in the correct orientation to form an additional interaction with the C=O of Aib (8) (Figure 3c) presumably a consequence of subtle interactions established in the crystal packing of 6. As in 3, the C-terminal GlyNH$_2$ does not cause helix reversal in the φ angle but values close to zero are observed for the ψ torsion angle in 4-5 (Table 2). In 6, the pro-atropoisomeric residue Bip, adopted an axial conformation of M helicity in the molecules with overall P helicity in the solid-state and an axial conformation of P helicity in the molecules with overall M helicity in the solid state. As the central quaternary linker residue, the N-terminal Cbz-L-Phe amino acid and C-terminal GlyNH$_2$ residue in 4 and 5 all form i → i+3 hydrogen-bonds, the total length of the 3_{10} helix adopted in these foldamers is ~21 Å (Supporting Information). The longest reported solid state structure of a 3_{10} helix is the extended foldamer Cbz-L-Phe-(Aib)$_8$-Gly-(Aib)$_8$O' Bu, in which the central Gly residue distorts, but does not fully break, the intramolecular hydrogen-bonding network. In this compound over five full turns of the helix are observed.  

**Fig. 3.** Side-on view of the X-ray structure of peptides a) Cbz-L-Phe-(Aib)$_8$-Ac$_{10}$-Gly$_2$NH$_2$ 4 b) Cbz-L-Phe-(Aib)$_7$Ac$_{10}$-(Aib)$_7$-Gly$_2$NH$_2$ 5 and c) Cbz-L-Phe-(Aib)$_6$-Bip-(Aib)$_6$-Gly$_2$NH$_2$ 6 highlighting the intramolecular hydrogen-bonding interactions present in the solid state. The hydrogen atoms have been removed for simplicity C atoms are shown in grey, N in light blue and O in red; some H atoms have been removed for clarity. In 6 one methanol solvent molecule has been removed for clarity.

**Conclusions**

By appropriate choice of the functional groups at the N and C termini, the 3_{10} helical structure of Aib foldamers can be stabilised. The surprising discovery that, unlike other N-terminal tertiary amino acids, N-terminal Cbz-Phe gives rise to a Type III (or Type III’) β-turn in the solid-state is thought to be a consequence of crystal packing effects including intermolecular aromatic interactions between the Phe residues of adjacent molecules in the cases of foldamers 1 and 2. The presence of both left- and right-handed helices in the structures of Aib oligomers bearing N-terminal benzoxycarbonyl-L-phenylalanine (Cbz-L-Phe) amino acids are indicative of the finely balanced energetics of the conformational preferences of these foldamers in the solid state. Bulky C-terminal esters and 2-aminoisobutyric acid (Aib) AibNH$_2$ amides are unable to participate in the intramolecular 3_{10} helical conformation and in the former case act as non-hydrogen bonding groups and in the latter participate in predominantly intermolecular hydrogen-bonding interactions, which can in some cases consequently induce helix inversion. Some amides, such as glycaminamide, accommodate an additional intramolecular i → i+3 hydrogen-bonding interaction, stabilising the 3_{10} helical structure.
Combination of these 3\textsubscript{10} helix-promoting structural features promotes the formation of long chain Aib foldamers whose well defined intramolecular hydrogen-bonding network extends over 21 Å.

Understanding the influence of these subtle structural modifications on the adoption of stable helical conformations in these Aib foldamers, which are mimics of antibiotic peptaibols, will facilitate future design of synthetic oligomers with tunable and programmable physical and biological properties.

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Experimental
Synthesis
Compounds 1-6 were made by reported methods\textsuperscript{17,18} or simple modifications thereof. Full characterisation data for the new compound 1 is given in the Supporting Information.

X-ray Crystallography
Crystalllographic data for the compounds 1-6 were collected at T = 293 K. Full crystal data and refinement details are summarised in the Supporting Information. Peptide 1 is racemic and peptide 3 is achiral and so the unit cell contains equal numbers of molecules of both screw-senses (see Supporting Information). X-ray data for foldamers 1-5 have been deposited with the Cambridge Crystallographic Data Centre. Deposition numbers 1: 1023512, 2: 982058, 3: 986573, 4: 8595485: 1023515.

Crystal data for 1. Crystals of Cbz-Phe-(Aib)\textsubscript{4}-OrBu are triclinic, space group P-1 with unit cell dimension a = 11.3070 (4), b = 13.8002 (4), c = 17.3410 (5) and angles are α = 70.683 (2), β = 73.734 (2), γ = 71.237 (2).

Crystal data for 2. Crystals of Cbz-L-Phe(Aib)\textsubscript{2}NH\textsubscript{2} are triclinic, space group P1 with unit cell dimension a = 11.357 (2), b = 16.271 (3), c = 18.895 (4) and angles are α = 80.846 (4), β = 87.004 (4), γ = 89.866 (4).

Crystal data for 3. Crystals of N\textsubscript{2}(Aib)\textsubscript{2}-GlyNH\textsubscript{2} are triclinic, space group P1 with unit cell dimension a = 11.4534 (8), b = 11.6801 (9), c = 14.4308 (11) and angles are α = 71.838 (7), β = 82.558 (6), γ = 74.669 (7).

Crystal data for 4. Crystals of Cbz-L-Phe-(Aib)\textsubscript{2}-Ac-c-(Aib)\textsubscript{2}-GlyNH\textsubscript{2} are monoclinic, space group P2\textsubscript{1} with unit cell dimension a = 13.774 (7), b = 9.540 (5), c = 48.58 (2) and angle β = 94.375 (9)

Crystal data for 5. Crystals of Cbz-L-Phe-(Aib)\textsubscript{2}-Ac-c-(Aib)\textsubscript{2}-GlyNH\textsubscript{2} are monoclinic, space group P2\textsubscript{1} with unit cell dimension a = 18.316 (6), b = 17.553 (6), c = 20.359 (7) and angle β = 96.012 (6).

Crystal data for 6. Crystals of Cbz-L-Phe-(Aib)\textsubscript{2}-Bip-(Aib)\textsubscript{2}-GlyNH\textsubscript{2} are monoclinic, space group P2\textsubscript{1} with unit cell dimension a = 19.474 (6), b = 13.389 (4), c = 28.731 (9) and angle β = 95.638 (5).

Notes and references
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\textsuperscript{†} Electronic Supplementary Information (ESI) available. See DOI: 10.1039/b000000x/


24. In ref 16c, the X-ray structure for 2 was mistakenly reported to show exclusively a left-handed screw-sense in its unit cell.

25. In ref 16c, the X-ray structure for 2 was mistakenly reported to show an initial β-turn lying between a Type II and Type III’.


29. For the first example of an Aib oligomer bearing only one chiral amino but which displays both enantiomers in the solid state see: G. Valle, M. Crisma, C. Toniolo, R. Beisswenger, A. Rieter, G. Jung, J. Am. Chem. Soc., 1989, 111, 6828.