The Structural Characterization of Folded Peptides Containing the Conformationally Constrained β-Amino Acid Residue $\beta^{2,2}Ac_6c$

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Dedicated to Prof. *Dieter Seebach* on the occasion of his 75th birthday

Backbone alkylation has been shown to result in a dramatic reduction in the conformational space that is sterically accessible to α-amino acid residues in peptides. By extension, the presence of geminal dialkyl substituents at backbone atoms also restricts available conformational space for β and γ residues. Five peptides containing the achiral $\beta^{2,2}$-disubstituted β-amino acid residue, 1-(aminomethyl)cyclohexanecarboxylic acid ($\beta^{2,2}Ac_6c$), have been structurally characterized in crystals by X-ray diffraction. The tripeptide Boc-Aib-$\beta^{2,2}Ac_6c$-Aib-OMe (**1**) adopts a novel fold stabilized by two intramolecular H-bonds (C_{11} and C_9) of opposite directionality. The tetrapeptide Boc-[Aib-$\beta^{2,2}Ac_6c$]$_2$-OMe (**2**) and pentapeptide Boc-[Aib-$\beta^{2,2}Ac_6c$]$_2$-Aib-OMe (**3**) form short stretches of a hybrid $\alpha\beta$ C_{11} helix stabilized by two and three intramolecular H-bonds, respectively. The structure of the dipeptide Boc-Aib-$\beta^{2,2}Ac_6c$-OMe (**5**) does not reveal any intramolecular H-bond. The aggregation pattern in the crystal provides an example of an extended conformation of the $\beta^{2,2}Ac_6c$ residue, forming a 'polar sheet' like H-bond. The protected derivative Ac-$\beta^{2,2}Ac_6c$-NHMe (**4**) adopts a locally folded *gauche* conformation about the C_β–C_α bonds ($\theta = -55.7°$). Of the seven examples of $\beta^{2,2}Ac_6c$ residues reported here, six adopt *gauche* conformations, a feature which promotes local folding when incorporated into peptides. A comparison between the conformational properties of $\beta^{2,2}Ac_6c$ and $\beta^{3,3}Ac_6c$ residues, in peptides, is presented. Backbone torsional parameters of H-bonded $\alpha\beta/\beta\alpha$ turns are derived from the structures presented in this study and earlier reports.

Introduction. – Short peptides composed of the 20 α-amino acids that occur naturally in proteins are characterized by an ensemble of conformational states in solution. In the solid state, short α-peptide sequences invariably adopt extended conformations, with intermolecular H-bonds, favoring sheet-like arrangements of peptides. The incorporation of proline residues into short sequences facilitates local folding, permitting characterization of β-turn conformations, stabilized by $4 \rightarrow 1$ H-bond in Pro-Xxx sequences [1]. This feature is a consequence of the locking of the rotation about the N–C_α (ϕ) bond by side-chain backbone cyclization, necessitated by the pyrrolidine ring of the Pro residue. Secondary-structure formation resulting in helical folds have been shown to be chain-length-, solvent-, and sequence-dependent [2][3]. In large polypeptides, exemplified by the remarkable range of folded structures in proteins, local secondary structures are often stabilized by long-range tertiary interactions [4]. The design of shorter α-peptide sequences with well-defined

conformational preferences is readily achieved by the incorporation of guest residues which impose local conformational restraints, thereby facilitating the nucleation of secondary structures [5][6]. In works dating back to the 1970s [7][8], the α,α-dialkylated residues, of which α-aminoisobutyric acid (Aib) residue is a prototype, were shown to be extraordinarily efficient promoters of helix formation in short sequences composed of α-amino acids [9–15]. Limiting conformational heterogeneity in solution had an unanticipated effect of promoting peptide crystallizability, permitting definitive structural characterization by X-ray diffraction [10][12]. Over the last 35 years, Aib-containing linear peptide sequences constitute the largest group of peptide crystal structures available in the *Cambridge Crystallographic Data Centre*, Cambridge, England.

The principle of stereochemical constraints to engineer local folding nuclei may be extended to the construction of peptide hairpins, where ^{D}Pro-Xxx sequences strongly promote hairpin formation with H-bond-registered antiparallel strands [16–19]. Considering the local conformational flexibility of the 19 non-proline α-amino acids found in proteins, conventional wisdom in the field of peptide structures might have suggested an even greater backbone conformational variability for β-amino acids, in which an additional degree of torsional freedom has been introduced. While conformational space for α-residues may be defined, by using the *Ramachandran* angles ϕ (N–C_α) and ψ (C_α–C=O) [20], three torsional variables, ϕ (N–C_β), θ (C_β–C_α), and ψ (C_α–C=O), define the structure space for β residues [21]. In the early 1990s, few researchers in the field would have ventured to suggest that well-ordered folded structures could indeed be formed in sequences containing backbone-homologated β-amino acid residues. *Dieter Seebach*'s 1996 report on the folded conformation of a hexapeptide composed of six β-amino acids in solution raised the intriguing possibility that the backbone-homologated residues, especially β- and γ-residues, may indeed have an intrinsic propensity to support folded structures [22]. Locally folded conformation require *gauche* or near *gauche* conformations about the C_β–C_α (θ) bonds in β-residues. *Sam Gellman*'s use of constrained β-residues, in which the C_β–C_α (θ) bond was locked into five- and six-membered rings, resulted in the first characterization of helical structures in β oligopeptides in the crystalline state [23][24]. Most importantly, the early reports on β-peptides raised the intriguing possibility that H-bonded helical structures, hitherto unknown in α-peptides, may be constructed using β- and γ-residues [25–30].

Can backbone-homologated ω-amino acid residues be incorporated into designed secondary structures formed by α-amino acid sequences? Accommodattion of additional backbone CH_2 groups into canonical helical folds was realized in solution, in the peptide Boc-Leu-Aib-Val-δ-Ava-Leu-Aib-Val-OMe [31]. The construction of helical structures with hybrid backbones was demonstrated in the crystal structures of eleven and fourteen residue peptides containing internal β-Ala-γ-Abu segments [32]. (The term β-alanine (β-Ala) was used in the literature for the amino acid β-aminopropionic acid. In subsequent years, following the explosion of interest in β-homologs of protein amino acids, it is preferable to use the description β-Gly or β-hGly suggested by *Seebach et al.* [28].) These structures contained unsubstituted β- and γ-residues which may be formally viewed as higher homologs of the Gly residue. By analogy with α-amino acids, it may then be anticipated that the introduction of

backbone substituents would significantly reduce sterically accessible conformational space, a feature best understood by comparing *Ramachandran*-allowed regions for Gly and Ala residues [33]. Furthermore, geminal dialkyl substituents on backbone atoms may be expected to dramatically limit allowed regions of conformational space, a feature apparent by comparing the *Ramachandran* maps for Ala and Aib residues [9][34]. In the extensive work that emanated from *Seebach*'s laboratory, multiply substituted β-amino acids quickly became the objects of study. A 1998 paper first reported the synthesis and structural characterization of peptides containing geminally disubstituted $\beta^{2,2}$- and $\beta^{3,3}$-amino acids [35]. The residues chosen were the homologs of the well-characterized, conformationally constrained amino acid 1-aminocyclohexane-1-carboxylic acid (Ac_6c) [36][37]. *Fig. 1* shows the structures of the three related residues, Ac_6c, $\beta^{2,2}Ac_6c$, and $\beta^{3,3}Ac_6c$. In all three amino acid residues, both possible chair conformations of the cyclohexane ring are observed. *Seebach et al.* reported crystal structures of the protected amino acid Boc-$\beta^{2,2}Ac_6c$-OH and tripeptide Boc-$\beta^{2,2}Ac_6c$-$\beta^{2,2}Ac_6c$-$\beta^{2,2}Ac_6c$-OMe. A novel ten-atom H-bond $NH_i \cdots CO_{i+1}(1 \rightarrow 2)$ with a directionality opposite to that normally observed in α-peptide structures was established in the tripeptide ester.

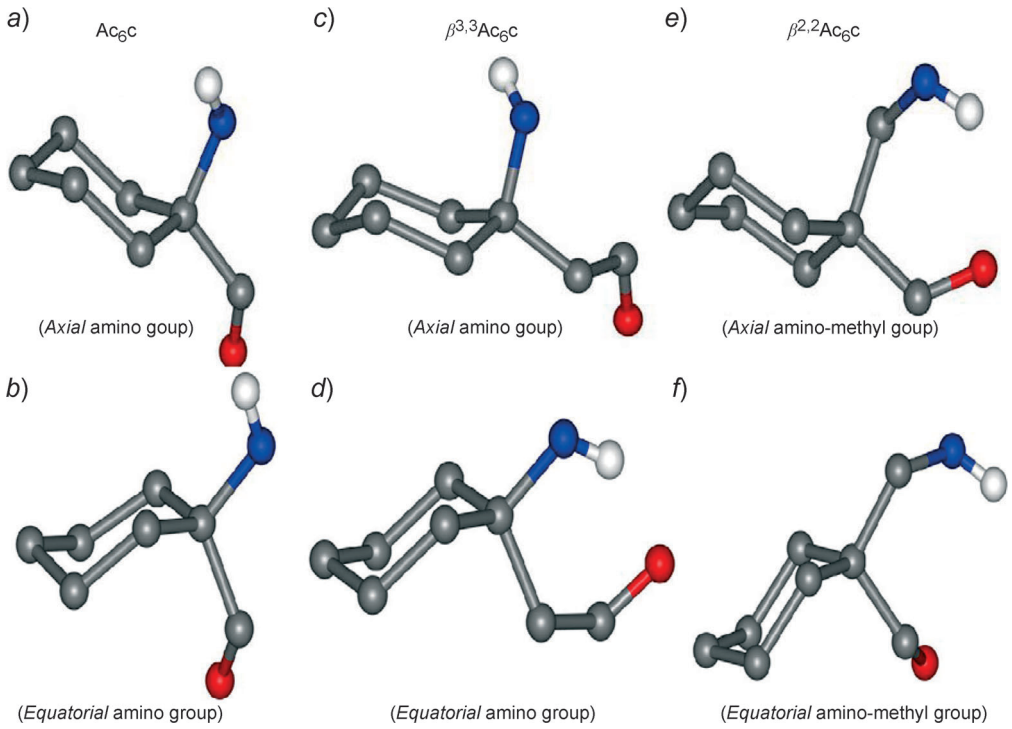

Fig. 1. *Chair conformations of the 1,1-disubstituted cyclohexane moieties in the amino acid residues Ac_6c, $\beta^{3,3}Ac_6c$, and $\beta^{2,2}Ac_6c$.* Conformations represented are from previously published crystal structures. *a*) Boc-Aib-Ac_6c-OMe [37], *b*) N-[1-(3,5-Dimethylbenzoyl)cyclohexyl]-3-methoxy-2-methylbenzamide–methanol solvate [41], *c*) Boc-Phe-$\beta^{3,3}Ac_6c$-NHMe [40], *d*) Boc-$\beta^{3,3}Ac_6c$-$\beta^{3,3}Ac_6c$-NHMe [38], *e*) Boc-$\beta^{2,2}Ac_6c$-$\beta^{2,2}Ac_6c$-$\beta^{2,2}Ac_6c$-OMe [35], *f*) Boc-$\beta^{2,2}Ac_6c$-OH [35].

A later study from in our laboratory provided several crystal structures of short peptides containing the $\beta^{3,3}$Ac$_6$c residue [38][39]. Only one example of an internally H-bonded $\alpha\beta$-turn, which is a backbone-expanded analog of β-turn in the peptide was observed [39]. We, therefore, turned to a more extensive structural characterization of peptides containing the $\beta^{2,2}$Ac$_6$c residue [40]. *Fig. 2* shows the structures of the peptides studied. In this paper, intramolecularly H-bonded folded structures of hybrid $\alpha\beta$-peptides, Boc-Aib-$\beta^{2,2}$Ac$_6$c-Aib-OMe (**1**), Boc-[Aib-$\beta^{2,2}$Ac$_6$c]$_2$-OMe (**2**), and Boc-[Aib-$\beta^{2,2}$Ac$_6$c]$_2$-Aib-OMe (**3**), are described. In addition, structures of Ac-$\beta^{2,2}$Ac$_6$c-NHMe (**4**) and Boc-Aib-$\beta^{2,2}$Ac$_6$c-OMe (**5**) are also reported.

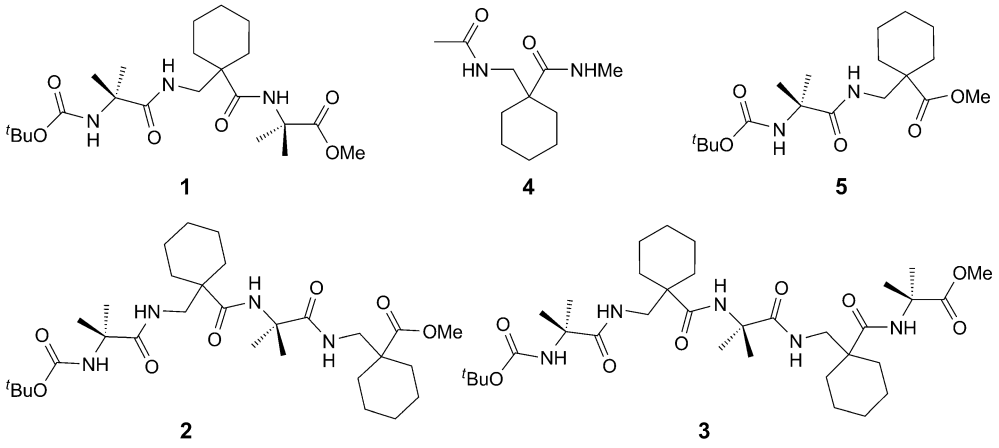

Fig. 2. *Structures of the peptides* **1**–**5**

Results. – *Fig. 3* shows the molecular conformations determined in crystals for the peptides Boc-Aib-$\beta^{2,2}$Ac$_6$c-Aib-OMe (**1**), Boc-[Aib-$\beta^{2,2}$Ac$_6$c]$_2$-OMe (**2**), and Boc-[Aib-$\beta^{2,2}$Ac$_6$c]$_2$-Aib-OMe (**3**). In all three cases, the molecules adopt folded conformations in the solid state, stabilized by intramolecular C=O $\cdots$ HN H-bonds. *Fig. 4*, shows the structures of the protected amino acid derivative Ac-$\beta^{2,2}$Ac$_6$c-NHMe (**4**) and protected dipeptide ester Boc-Aib-$\beta^{2,2}$Ac$_6$c-OMe (**5**), both of which adopt conformations lacking intramolecular H-bonds. The backbone torsion-angle parameters are compiled in *Table 1*, and the H-bond parameters are collected in *Table 2*.

Boc-Aib-$\beta^{2,2}$Ac$_6$c-Aib-OMe (**1**). In this protected tripeptide, two internal H-bonds of opposite directionality are observed. The Aib(1)-$\beta^{2,2}$Ac$_6$c(2) ($\alpha\beta$) segment forms a C_{11} H-bonded turn, which is a backbone-expanded analog of $4\rightarrow1$ H-bonded C_{10} β-turns observed in $(\alpha\alpha)_n$ sequences. The C-terminus dipeptide segment $\beta^{2,2}$Ac$_6$c(2)-Aib(3) ($\beta\alpha$) forms a C_9 H-bonded structure ($\beta^{2,2}$Ac$_6$c(2)NH $\cdots$ O=C Aib(3)). This H-bonded conformational feature has been previously characterized in solution [42][43] and in the solid state [44] for short peptides containing β-amino acids. A notable feature of this structure is that both Aib(1) and Aib(3) residues adopt polyproline (P_{II}) conformations ($\phi\approx-60^\circ,\psi\approx120^\circ$). P_{II} Conformations at Aib are extremely rare in folded oligopeptides [12], where helical conformations (α_L/α_R) ($\phi\approx\pm60^\circ,\psi\approx\pm30^\circ$) are invariably observed [5][6]. Clearly, the energy penalty for forcing Aib residues into

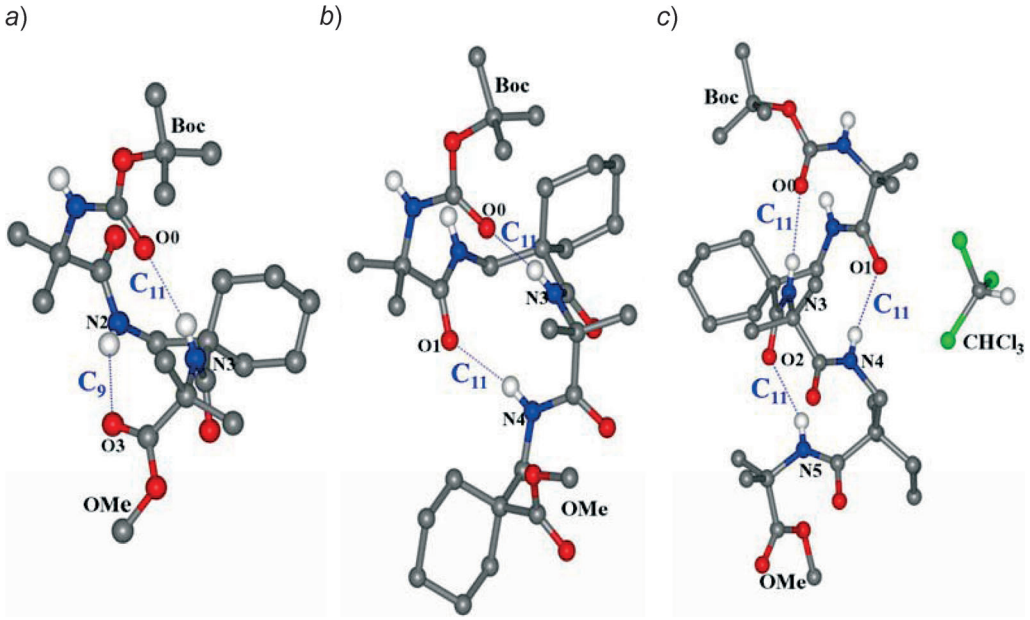

Fig. 3. *Molecular conformations in crystals. a*) Boc-Aib-$\beta^{2,2}$Ac$_6$c-Aib-OMe (**1**), *b*) Boc-[Aib-$\beta^{2,2}$Ac$_6$c]$_2$-OMe (**2**), *c*) Boc-[Aib-$\beta^{2,2}$Ac$_6$c]$_2$-Aib-OMe (**3**) (a lone solvent molecule ($CHCl_3$) is also observed in the crystal).

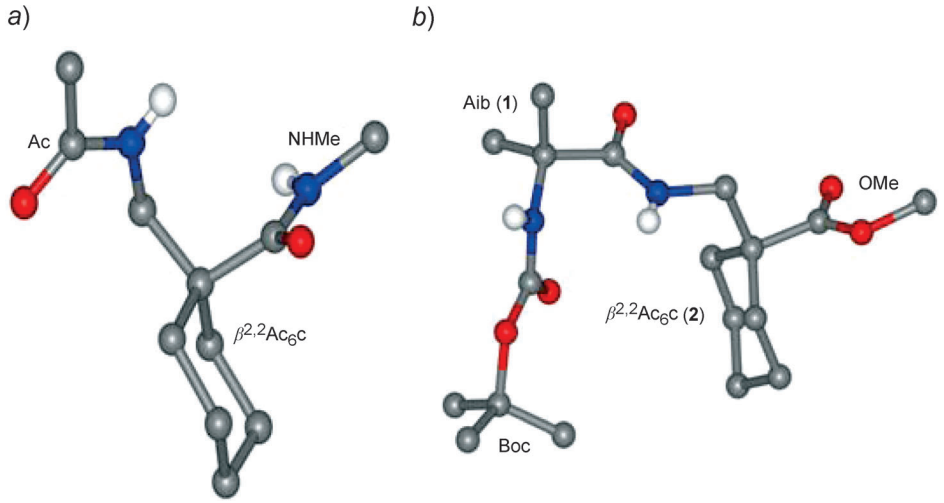

Fig. 4. *Molecular conformations in crystals. a*) Ac-$\beta^{2,2}$Ac$_6$c-NHMe (**4**), *b*) Boc-Aib-$\beta^{2,2}$Ac$_6$c-OMe (**5**).

an unfavorable P_{II} conformation has been paid by the simultaneous formation of the C_{11} and C_9 intramolecular H-bonds.

Table 1. *Backbone Torsion Angles of Peptides* **1**–**5**

Peptides	Residues	Backbone torsion angles [°]		
		ϕ	θ	ψ
Boc-Aib-$\beta^{2,2}$Ac$_6$c-Aib-OMe (**1**)	Aib(1)	– 56.9		122.1
	$\beta^{2,2}$Ac$_6$c(2)	97.5	61.9	– 94.3
	Aib(3)	– 51.5		141.8
Boc-[Aib-$\beta^{2,2}$Ac$_6$c]$_2$-OMe (**2**)	Aib(1)	– 58.4		– 36.7
	$\beta^{2,2}$Ac$_6$c(2)	– 108.6	80.7	– 72.4
	Aib(3)	– 53.2		– 44.6
	$\beta^{2,2}$Ac$_6$c(4)	93.4	– 68.8	94.6
Boc-[Aib-$\beta^{2,2}$Ac$_6$c]$_2$-Aib-OMe (**3**)	Aib(1)	– 67.0		– 27.2
	$\beta^{2,2}$Ac$_6$c(2)	– 108.5	82.9	– 68.8
	Aib(3)	– 53.1		– 34.4
	$\beta^{2,2}$Ac$_6$c(4)	– 103.5	70.6	– 98.1
	Aib(5)	49.2		42.7
Ac-$\beta^{2,2}$Ac$_6$c-NHMe (**4**)	$\beta^{2,2}$Ac$_6$c	– 100.8	– 55.7	– 63.0
Boc-Aib-$\beta^{2,2}$Ac$_6$c-OMe (**5**)	Aib(1)	– 65.5		– 26.8
	$\beta^{2,2}$Ac$_6$c(2)	– 102.5	170.0	81.1

Boc-(Aib-$\beta^{2,2}$Ac$_6$c)$_2$-OMe (**2**). The structure of the tetrapeptide reveals two consecutive C_{11} H-bonded $\alpha\beta/\beta\alpha$-turns, corresponding to a single turn of a C_{11} helix. This is a backbone-expanded analog of the incipient 3_{10}-helical structures characterized in short α-peptides [7–9][45]. In this case, both Aib residues adopt the anticipated helical conformations, in sharp contrast to the observations for the peptide **1**.

Boc-(Aib-$\beta^{2,2}$Ac$_6$c)$_2$-Aib-OMe (**3**). Extension of peptide chain length results in a further propagation of the C_{11} helix, with three consecutive C_{11} H-bonds being observed in the $\alpha\beta\alpha\beta$-segment. This structure is analogous to previously determined short C_{10} H-bonded 3_{10} helices in all α-pentapeptides [8]. Here again, all three Aib residues adopt helical conformation with a helix sense reversal at the C-terminus, a feature commonly observed in helical Aib peptides [12].

Ac-$\beta^{2,2}$Ac$_6$c-NHMe (**4**) *and Boc-Aib-$\beta^{2,2}$Ac$_6$c-OMe* (**5**). The protected derivative **4** and dipeptide ester **5** do not possess any intramolecular H-bonds in the observed conformations (*Fig. 4*), with all donor and acceptor groups participating in intermolecular interactions in the crystals. *Fig. 5*, *a*, shows a view of the molecular packing in the crystals of **5**. A pair of intermolecular H-bonds link adjacent molecules in rows in a direction parallel to the crystallographic '*c*' axis (*Fig. 5*, *b*). The $\beta^{2,2}$Ac$_6$c residue adopts a *trans* conformation about the C_β–C_α bond ($\theta = 170^\circ$), which orients the C=O groups of the N-terminus peptide unit and C-terminus ester group in the same direction, facilitating formation of a motif refered to as a 'polar sheet' arrangement [46][47]. The helical conformation of the Aib(1) residue orients the NH groups of the N-terminus urethane and C-terminus amide in the same direction, resulting in intermolecular H-bonds between adjacent molecules, forming an infinite chain along the direction of the crystallographic '*c*' axis.

Conformation of $\beta^{2,2}$Ac$_6$c Residues. With the exception of the dipeptide ester Boc-Aib-$\beta^{2,2}$Ac$_6$c-OMe (**5**), the $\beta^{2,2}$Ac$_6$c residues in all other cases adopt *gauche*

Table 2. *H-Bond Parameters of Peptides* **1**–**5**

Peptides	Donor	Acceptor	$d(D\cdots A)$ [Å]	$d(H\cdots A)$ [Å]	$\angle(D\text{–}H\cdots A)$ [°]
Boc-Aib-$\beta^{2,2}$Ac$_6$c-Aib-OMe (**1**)	Intramolecular H-bonds				
	N(2)	O(3)	3.30	2.48	156.7
	N(3)	O(0)	3.03	2.20	165.0
	Intermolecular H-bonds				
	N(1)	O(2) [$x-1/2$, $-y+3/2$, $z+1/2$]	2.99	2.18	166.5
Boc-[Aib-$\beta^{2,2}$Ac$_6$c]$_2$-OMe (**2**)	Intramolecular H-bonds				
	N(3)	O(0)	3.00	2.20	159.9
	N(4)	O(1)	2.92	2.06	169.3
	Intermolecular H-bonds				
	N(1)	O(2) [$x+1/2$, y, $-z+3/2$]	2.92	2.09	167.9
	N(2)	O(3) [$x+1/2$, y, $-z+3/2$]	2.88	2.07	155.6
Boc-[Aib-$\beta^{2,2}$Ac$_6$c]$_2$-Aib-OMe (**3**)	Intramolecular H-bonds				
	N(3)	O(0)	3.07	2.23	168.1
	N(4)	O(1)	3.09	2.26	167.7
	N(5)	O(2)	2.86	2.17	140.3
	Intermolecular H-bonds				
	N(1)	O(3) [$x-1/2$, $-y+1/2$, $z+1/2$]	3.01	2.16	171.5
	N(2)	O(4) [$x-1/2$, $-y+1/2$, $z+1/2$]	3.10	2.35	148.7
Ac-$\beta^{2,2}$Ac$_6$c-NHMe (**4**)	Intermolecular H-bonds				
	N(1)	O(1) [x, $-y+1$, $z+1/2$]	2.87	2.03	168.0
	N(2)	O(0) [$x-1/2$, $-y+1/2$, $z-1/2$]	2.89	2.03	165.4
Boc-Aib-$\beta^{2,2}$Ac$_6$c-OMe (**5**)	Intermolecular H-bonds				
	N(1)	O(1) [x, $-y$, $z-1/2$]	3.05	2.16	172.2
	N(2)	O(2) [x, $-y$, $z-1/2$]	3.06	2.25	156.2

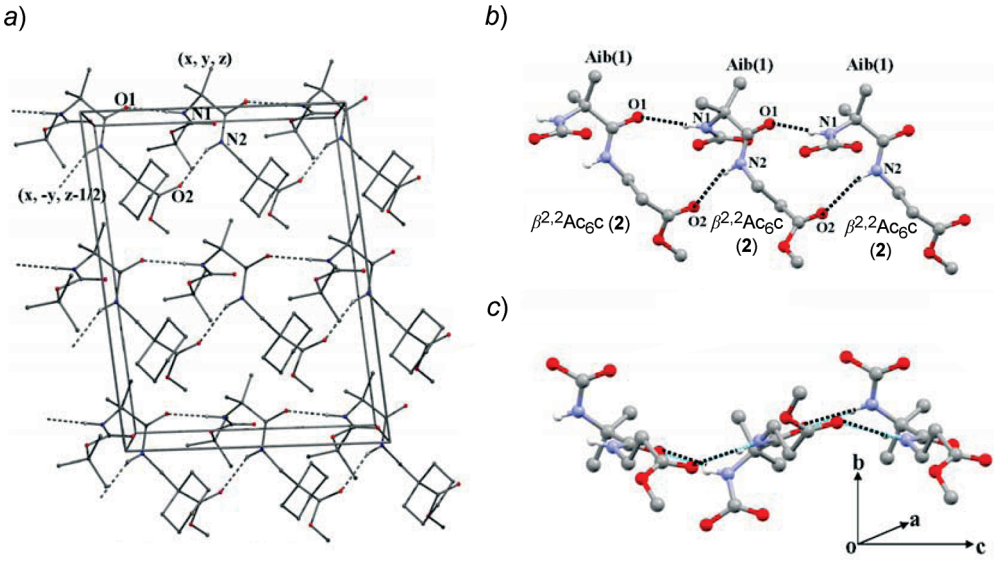

Fig. 5. *Packing of the molecules in the crystal of Boc-Aib-$\beta^{2,2}$Ac$_6$c-OMe* (**5**). *a*) A projection down the crystallographic '*b*' axis, *b*) Intermolecular H-bonding network, in a direction parallel to the crystallographic '*c*' axis, *c*) A different projection, showing the intermolecular H-bonding network.

conformations, with θ values ranging from 55.7° to 82.9°. Thus far, a total of 13 $\beta^{2,2}$Ac$_6$c residues have been crystallographically characterized from nine independent molecules (eight different peptides and derivatives). Three of these peptide structures containing $\beta^{2,2}$Ac$_6$c residues were reported earlier, two by *Seebach et al.* in 1998 [35] and one from Bangalore [40]. Interestingly, of these 13 residues twelve reveal *gauche* conformations about the C$_\beta$–C$_\alpha$ bond (θ). The sole example of a *trans* conformation was observed in the dipeptide ester **5**, discussed above. This may be compared with the case of the isomeric $\beta^{3,3}$Ac$_6$c residue, where a survey of 23 examples revealed 18 cases of *gauche* and five cases of *trans* conformations. Folding into the intramolecularly H-bonded structures, is facilitated by adoption of *gauche* conformation about the C$_\beta$–C$_\alpha$ bond (θ). The gem-dialkyl substituents at C$_\alpha$ in $\beta^{2,2}$Ac$_6$c may also be expected to restrict the range of the torsion angle ψ about the C$_\alpha$–CO bond. A scatter plot in ϕ, ψ space for crystallographically characterized $\beta^{2,2}$Ac$_6$c residues is shown in *Fig. 6*. Twelve out of the thirteen residues represented, adopt ψ values which are clustered about $\pm 60°$ to $\pm 90°$.

The sole example of an extended value of $\psi \approx 180°$ is observed in the tripeptide Boc-$\beta^{2,2}$Ac$_6$c-$\beta^{2,2}$Ac$_6$c-$\beta^{2,2}$Ac$_6$c-OMe, reported by *Seebach et al* [35]. In this case a C$_{10}$ H-bond, $\beta^{2,2}$Ac$_6$c(2) NH$\cdots$OC $\beta^{2,2}$Ac$_6$c(3), is observed. This reverse directionality $1 \rightarrow 2$ C$_{10}$ H-bond in the $\beta\beta$-segment is analogous to the $1 \rightarrow 2$ C$_9$ H-bond discussed earlier, for the $\beta\alpha$ segment in the tripeptide **1**. Presumably, the formation of the H-bond compensates energetically for an unfavorable value of the ψ torsion angle.

H-Bonded Turns Involving $\beta^{2,2}$Ac$_6$c Residues. Fig. 7,a and *b*, illustrate two distinct families of $4 \rightarrow 1$ H-bonded C$_{11}$ turns observed in the peptides **1** to **3**, described in the present study. Of these, the C$_{11}$-helical $\alpha\beta/\beta\alpha$-turn is formed for backbone torsion-angle

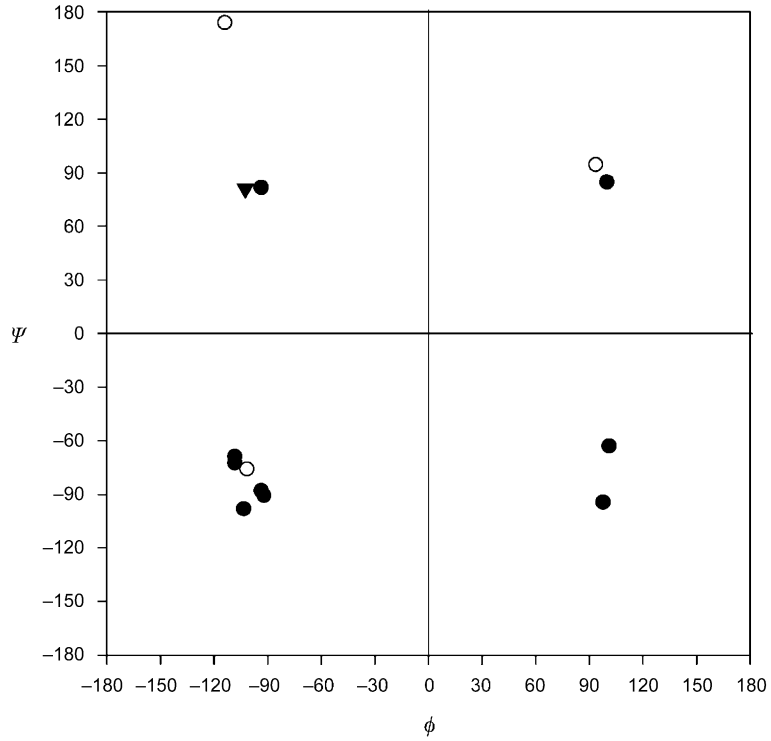

Fig. 6. *Scatter plot in ϕ,ψ space of crystallographically characterized $\beta^{2,2}$Ac$_6$c residues.* For three distinct classes of torsion-angle values about the C_β–C_α bond (θ), with ●: $\theta \approx +60°$; ○: $\theta \approx -60°$, and ▼: $\theta \approx 180°$.

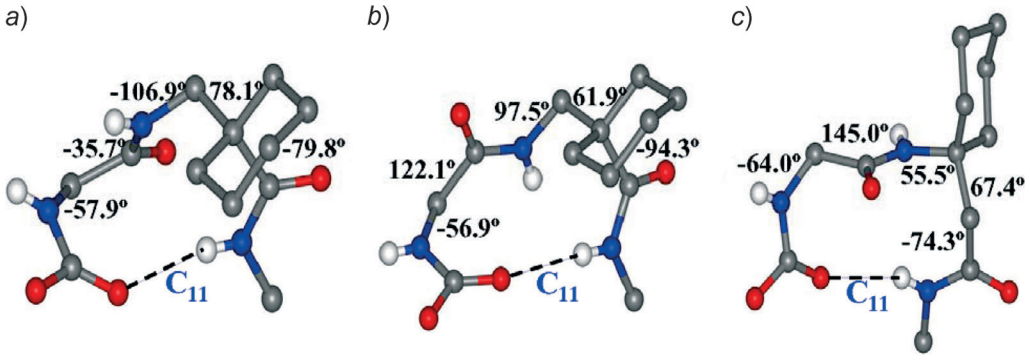

Fig. 7. *Two different types of 4 → 1 C_{11} ($\alpha\beta$) H-bonded turns observed in the present study. a*) Helical turn (torsion-angle values averaged over all helical peptides of the present study are shown). *b*) Non-helical turn (torsion-angle values are taken from peptide **1**, the sole example of this type discussed in the present study). *c*) Non-helical turn in Boc-Phe-$\beta^{3,3}$Ac$_6$c-NHMe [40] (torsion-angle values are shown).

values of $\phi \approx -100°$, $\theta \approx 80°$, and $\psi \approx -80°$ at the $\beta^{2,2}$Ac$_6$c residue. The C_{11} $\alpha\beta$ non-helical turn observed in the tripeptide **1** (*Fig. 7,b*) may be compared with the C_{11} turn observed in the peptide Boc-Phe-$\beta^{3,3}$Ac$_6$c-NHMe (*Fig. 7,c*), in which the geminal-

dialkyl substitution is effected at C_β (*Fig. 7,c*). In both cases, the α-residue adopts a polyproline (P_{II}) conformation. The $\beta^{2,2}Ac_6c$ residues at the *$I+2$ position in the two peptides may be considered to belong to the same conformational family: $\phi \approx 70^\circ \pm 30^\circ$, $\theta \approx 60^\circ \pm 10^\circ$, and $\psi \approx -80^\circ \pm 20^\circ$. The two classes of C_{11} turns shown in Fig. 7* may be formally viewed as backbone expanded analogs of type-I/III and type-II β-turn structures commonly observed for $\alpha\alpha$-sequences [48][49]. While the C_{11} turn in *Fig. 7,a*, upon repetition generates a continuous C_{11} helix, the C_{11} conformations depicted in *Fig. 7,b* and *c*, can serve as isolated chain reversals in larger sequences.

Conclusions. – The structural studies presented in this report point to the utility of the $\beta^{2,2}Ac_6c$ residue in generating folded conformations in $\alpha\beta$-hybrid sequences. The comparison with previously reported structural work on the related $\beta^{3,3}Ac_6c$ residue suggests that the positioning of the geminal dialkyl substituents on the β-residue backbone can be used to modulate local conformational preferences. Synthetically accessible achiral geminally disubstituted β residues may prove valuable in the design of hybrid peptide foldamers.

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Experimental Part

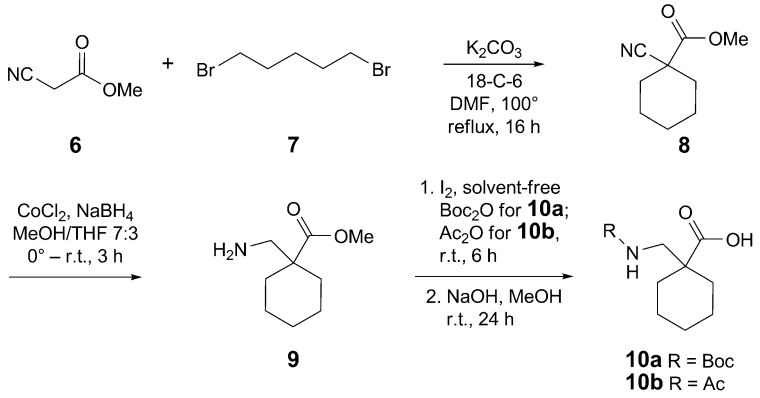
General. Abbreviations: Boc_2O, di(*tert*-butyl)dicarbonate; DCC, *N,N′*-dicyclohexylcarbodiimide; BtOH, 1-hydroxy-1*H*-benzotriazole; HATU, 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyuroniumhexafluorophosphate; NMM, *N*-methylmorpholine; Aib, α-aminoisobutyric acid; $\beta^{2,2}Ac_6c$, 1-(aminomethyl)cyclohexanecarboxylic acid. THF was distilled over Na/benzophenone before use. $CHCl_3$ employed for the coupling reactions was filtered over Al_2O_3. All other reagents were used as received from *Fluka* and *Sigma-Aldrich*. The peptides were synthesized following standard solution-phase procedures. TLC: silica gel *60 F_{254}* plates (SiO_2; *Merck*) using hexanes/AcOEt as eluent; visualization on exposure to I_2 vapor or UV light. HPLC: Reversed-phase (RP) *C18* column (5–10 μm, 7.8 mm × 250 mm) using MeOH/H_2O gradients. M.p.: *Stuart Biocote SMP10* melting-point apparatus; uncorrected. IR Spectra: *JASCO* spectrometer; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker AV400* FT-NMR spectrometer (400 MHz); δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. ESI-MS: *Bruker Daltonics Esquire-3000* instrument; in *m*/*z*.

Synthesis of N- *and* C-*Protected $\beta^{2,2}Ac_6c$ Residue* (*Scheme*). *Methyl 1-(aminomethyl)cyclohexanecarboxylate* (H-$\beta^{2,2}Ac_6c$-OMe; **9**) was prepared using a previously published procedure *via* bisalkylation of *methyl 2-cyanoacetate* (**6**) with *1,5-dibromopentane* (**7**) [50–53]. The cyano ester **8** thus obtained was hydrogenated using $CoCl_2 \cdot 6\,H_2O$ to yield **9** [52][53]. Boc-Protection of **9** under solvent-free condition in the presence of cat. amount of I_2 [54], followed by saponification with 1N NaOH in MeOH, furnished the Boc-protected amino acid **10a**.

Peptide Synthesis. General Procedure (*GP*). *i*) Peptides **1** and **5** were synthesized *via* coupling mediated by DCC/BtOH. DCC (1 equiv.) was added to an ice cold soln. of the Boc-protected amino acid and peptide acid (1 equiv.) in dry THF/$CHCl_3$, followed by the addition of BtOH (1.1 equiv.), and the soln. was stirred for 30 min. After complete activation of the acid, the amino component (free amino acid ester or dipeptide ester) was added dropwise, and the mixture was allowed to attain r.t. with stirring continued for 24 h under N_2. After completion of the reaction (TLC), dicyclohexylurea obtained as by-product was filtered, and the filtrate was concentrated, diluted with $CHCl_3$, and washed with 1N Na_2CO_3, followed by sat. aq. NaCl soln. The org. layer was dried ($MgSO_4$) and evaporated under *vacuo*.

ii) Peptides **2**, **3**, and **4** were synthesized *via* the HATU/BtOH-mediated coupling method. HATU (1 equiv.) was added to an ice cold soln. of Boc-protected amino acid (1 equiv.) in dry DMF, followed by

Scheme



the addition of BtOH (1 equiv.) and EtN^iPr_2 or NMM (3 equiv.). After complete activation of the acid, the free amino ester (1.2 equiv.) was added dropwise, and the mixture was allowed to stir at r.t. for 24 h under N_2. The reaction was monitored using TLC. After completion of the reaction, DMF was evaporated under reduced pressure. The crude product was dissolved in $CHCl_3$, and washed with sat. aq. $NaHCO_3$, $KHSO_4$ and NaCl solns. The org. layer was dried ($MgSO_4$) and evaporated *in vacuo*. Following the procedure described above, **9** was coupled with Boc-Aib-OH to yield the dipeptide ester **5**. Saponification of **5**, followed by coupling with H-Aib-OMe, provided the tripeptide ester **1**. The dipeptide ester **5** was deprotected at the N-terminus and coupled with N-protected dipeptide acid to afford the tetrapeptide ester **2**. The Boc-protected dipeptide acid derived from **5** was coupled with the free tripeptide ester derived from **1** to provide the pentapeptide **3**. Deprotections of N- and C-termini were achieved with 98% HCOOH and 2N NaOH/MeOH, resp.

Boc-Aib-$\beta^{2,2}$Ac$_6$c-OMe (**5**). The ester **9** (0.84 g, 4.9 mmol) was coupled with Boc-Aib-OH (0.5 g, 2.5 mmol) according to *GP*. Flash chromatography (FC) yielded **5** (0.684 g, 78%). Crystalline white solid. M.p. 108–110°. R_f (Hexane/AcOEt 8:2) 0.34. IR ($CHCl_3$): 3344*w*, 2979*m*, 2934*s*, 2862*w*, 1718*s*, 1667*s*, 1520*s*, 1453*m*, 1367*m*, 1162*s*, 1078*m*, 1019*w*, 755*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.41 (*s*, 3 Me); 1.47 (*s*, 2 Me); 3.40 (*d*, $J = 6.4$, CH_2); 3.67 (*s*, MeO); 4.97 (*s*, NH); 6.78 (*s*, NH). ESI-MS: 379 ($[M+Na]^+$), 395 ($[M+K]^+$).

Boc-Aib-$\beta^{2,2}$Ac$_6$c-Aib-OMe (**1**). H-Aib-OMe (0.21 g, 1.8 mmol) was coupled with Boc-Aib-$\beta^{2,2}$Ac$_6$c-OH (0.5 g, 1.5 mmol) derived by saponification of **5** according to *GP*. FC yielded **1** (0.432 g, 67%). White powder. M.p. 168–169°. R_f (Hexane/AcOEt 6:4) 0.38. IR ($CHCl_3$): 3365*w*, 3306w, 2931*s*, 2863*w*, 1745*m*, 1693*s*, 1526*s*, 1455*m*, 1364*m*, 1286*s*, 1078*m*, 1018*w*, 756*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.42 (*s*, 3 Me); 1.51 (*s*, 2 Me); 1.54 (*s*, 2 Me); 3.30 (*d*, $J = 6.4$, CH_2); 3.42 (*d*, $J = 6.4$, CH_2); 3.70 (*s*, MeO); 5.19 (*s*, NH); 6.73 (*s*, NH); 7.4 (*s*, NH). ESI-MS: 464 ($[M+Na]^+$), 480 ($[M+K]^+$).

Boc-Aib-$\beta^{2,2}$Ac$_6$c-Aib-$\beta^{2,2}$Ac$_6$c-OMe (**2**). H-Aib-$\beta^{2,2}$Ac$_6$c-OMe (0.45 g, 1.8 mmol) derived by deprotection of Boc group of **5** was coupled with Boc-Aib-$\beta^{2,2}$Ac$_6$c-OH (0.5 g, 1.5 mmol) derived by saponification of **5** according to *GP*. FC yielded **2** (0.458 g, 54%). White powder. M.p. 209–210°. R_f (Hexane/AcOEt 1:1) 0.31. IR ($CHCl_3$): 3274*w*, 2936*m*, 1726*m*, 1692*m*, 1647*s*, 1527, 1447*m*, 1384*w*, 1157*m*, 1080*m*, 1021*w*, 715*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.42 (*s*, 3 Me); 1.51 (*s*, 2 Me); 1.54 (*s*, 2 Me); 3.39 (*d*, $J = 5.6$, CH_2); 3.43 (*d*, $J = 5.6$, CH_2); 3.70 (*s*, MeO); 5.19 (*s*, NH); 6.73 (*s*, NH); 7.02 (*s*, NH); 7.4 (*s*, NH). ESI-MS: 603 ($[M+Na]^+$), 619 ($[M+K]^+$).

Boc-Aib-$\beta^{2,2}$Ac$_6$c-Aib-$\beta^{2,2}$Ac$_6$c-Aib-OMe (**3**). H-Aib-$\beta^{2,2}$Ac$_6$c-Aib-OMe (0.55 g, 1.6 mmol) derived by deprotection of Boc group of **1** was coupled with Boc-Aib-$\beta^{2,2}$Ac$_6$c-OH (0.5 g, 1.5 mmol) derived by saponification of **5** according to the general procedure. FC yielded **3** (0.21 g, 21%). White powder. M.p. 220–221°. R_f (Hexane/AcOEt 1:1) 0.31. IR ($CHCl_3$): 3393*w*, 2934*s*, 2862*w*, 1716*s*, 1668*s*, 1521*s*, 1455*m*, 1367*m*, 1170*s*, 1076*m*, 1048*w*, 782*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.41 (*s*, 3 Me); 1.44 (*s*, 2 Me); 1.55 (*s*, 2

Table 3. *Crystal Data and Structure-Refinement Parameters*

Peptide	Boc-Aib-$\beta^{2,2}$Ac$_6$c-Aib-OMe (**1**)	Boc-[Aib-$\beta^{2,2}$Ac$_6$c]$_2$-OMe (**2**)	Boc-[Aib-$\beta^{2,2}$Ac$_6$c]$_2$-Aib-OMe (**3**)	Ac-$\beta^{2,2}$Ac$_6$c-NHMe (**4**)	Boc-Aib-$\beta^{2,2}$Ac$_6$c-OMe (**5**)
Empirical formula	$C_{22}H_{39}N_3O_6$	$C_{30}H_{52}N_4O_7$	$C_{34}H_{59}N_5O_8 + CHCl_3$	$C_{11}H_{20}N_2O_2$	$C_{18}H_{32}N_2O_5$
Crystal habit	rectangular	rectangular	rectangular	rectangular	thin rod
Crystal size [mm]	$(0.35 \times 0.12 \times 0.09)$	$(0.25 \times 0.22 \times 0.16)$	$(0.50 \times 0.12 \times 0.06)$	$(0.35 \times 0.31 \times 0.20)$	$(0.62 \times 0.06 \times 0.04)$
Crystallizing solvent	AcOEt/hexane	MeOH/H_2O	$CHCl_3$/hexane	$CHCl_3$/hexane	AcOEt/hexane
Space group	$P2_1/n$	*Pbca*	$P2_1/n$	*Cc*	*Cc*
a [Å]	10.4777(4)	16.7818(5)	13.3449(3)	14.6179(7)	14.7174(5)
b [Å]	20.1709(7)	18.3808(5)	20.2511(5)	11.7791(5)	11.6076(4)
c [Å]	11.9697(4)	21.7457(6)	15.7334(4)	7.9299(4)	12.1060(4)
β [°]	98.358(1)		90.988(1)	119.368(2)	96.163(2)
V [Å^3]	2502.9(2)	6707.7(3)	4251.3(2)	1189.9(1)	2056.2(1)
Z	4	8	4	4	4
Molecules/asymmetric unit	1	1	1	1	1
Co-crystallized solvent	None	None	Chloroform	None	None
Molecular weight	441.56	580.76	785.23	212.29	356.46
Calculated density [g/cm^3]	1.172	1.150	1.227	1.185	1.151
$F(000)$	960	2528	1680	464	776
Radiation	CuK_α (1.54178 Å)	CuK_α (1.54178 Å)	MoK_α (0.71073 Å)	CuK_α (1.54178 Å)	MoK_α (0.71073 Å)
Temp. [K]	296(2)	296(2)	296(2)	296(2)	296(2)
$2\theta_{max}$ [°]	140.12	144.22	56.60	143.62	56.60
Measured reflections	16468	26248	39528	4100	15793
R_{int}	0.0068	0.0198	0.0317	0.0220	0.0223
Unique reflections	4504	6340	10478	1140	2553
Observed reflection [$\lvert F \rvert > 4\sigma(F)$]	4305	5678	5904	1140	1993
Final R/$wR2$ [%]	3.95/11.98	4.26/13.20	6.58/22.38	3.20/8.98	3.61/8.68
Goodness-of-fit on F^2 (S)	1.044	1.043	1.027	1.144	1.030
$\Delta\rho$ (max; min) [e Å^{-3}]	0.23; −0.18	0.47; −0.15	0.81; −0.69	0.12; −0.14	0.115; −0.135
No. of restraints/parameters	0/340	0/491	7/590	2/195	2/282
Data-to-parameter ratio	12.66 : 1	11.56 : 1	10.00 : 1	5.85 : 1	7.10 : 1

Me); 3.22 (*d*, *J* = 6.4, CH_2); 3.28 (*d*, *J* = 6.4, CH_2); 3.75 (*s*, MeO); 5.23 (*s*, NH); 6.94 (*s*, NH); 7.09 (*s*, NH); 7.33 (*s*, NH); 7.50 (*s*, NH). ESI-MS: 688 ($[M+Na]^+$), 704 ($[M+K]^+$).

Ac-β^{2,2}Ac$_6$c-NHMe (**4**). Acetylation of **9** (1 equiv.) with Ac_2O (1 equiv.) in the presence of cat. amount of I_2 (10 mol %) under solvent-free conditions furnished *Ac-β^{2,2}Ac$_6$c-OMe*. Saponification followed by coupling of the resulting acid **10b** (0.5 g, 2.5 mmol) with $MeNH_2 \cdot HCl$ (0.12 g, 3.8 mmol) mediated by HATU in the presence of EtN^iPr_2 afforded **4** (0.15 g, 36%). White solid. M.p. 199–200°. R_f (Hexane/AcOEt 1:1) 0.45. IR ($CHCl_3$): 3321*w*, 2934*s*, 2862*w*, 1723*s*, 1535*s*, 1249*s*, 1161*s*, 1355*m*, 1367*m*, 1170*s*, 976*m*, 620*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.97 (*s*, Me); 2.82 (*d*, *J* = 4.8, CH_2); 3.67 (*d*, *J* = 4.8, CH_2); 5.96 (*s*, NH); 6.22 (*s*, NH). ESI-MS: 235 ($[M+Na]^+$), 251 ($[M+K]^+$).

X-Ray Diffraction. Suitable single crystals of all the peptides and amino acid derivatives **1**–**5** were obtained by the slow-evaporation method. Single crystals for peptides **1** and **5** were grown by dissolving *ca.* 8 mg of the peptide in 200 µl of AcOEt and 50 µl of hexane. Colorless single crystals of tetrapeptide **2** were obtained by dissolving 6–8 mg of the peptide in 300 µl of MeOH and 50 µl of H_2O. Pentapeptide **3** and **4** were crystallized by dissolving 6–8 mg of the peptides in 400 µl and 300 µl of $CHCl_3$, resp., and then 2–3 drops of hexane were added to both solns. Peptides **1** and **3** crystallized in the monoclinic space group $P2_1/n$. Ac-β^{2,2}Ac$_6$c-NHMe (**4**) and the dipeptide **5**, both crystallized in the monoclinic space group *Cc*, with one molecule in the asymmetric unit. The tetrapeptide **2** crystallized with one peptide molecule in the asymmetric unit, in the orthorhombic space group *Pbca*. A cocrystallized solvent molecule ($CHCl_3$) was observed only in the case of **3**.

For peptides **1**, **2**, and **4**, X-ray data were collected on *Bruker AXS ULTRA APEXII CCD* (rotating anode X-ray generator) with CuK_α (λ 1.54178 Å) radiation. For peptides **3** and **5**, the X-ray data were collected on *Bruker AXS KAPPA APEXII CCD* with MoK_α (λ 0.71073 Å) radiation. All the X-ray diffraction data sets were collected at r.t. (296 K). In all these cases, the X-ray data were acquired in φ and ω scan mode. The structures were solved by using iterative dual-space direct methods in SHELXD [55]. The structures were refined against F^2 isotropically, followed by full-matrix anisotropic least-squares refinement using SHELXL-97 [56][57]. The solvent molecule in peptide **3** were located from difference *Fourier* map. All H-atoms, with the exception of the terminal Me groups (Boc, MeO, Ac, MeNH), were located from difference *Fourier* maps. For the terminal Me groups, the H-atoms were fixed geometrically in idealized position and allowed to ride with the respective C-atoms, to which each H-atom was bonded, in the final cycles of refinement. Details of crystal data and structure refinement parameters are compiled in *Table 3*.

CCDC Deposition Nos. for peptides and derivative are 899142 (**1**), 899143 (**2**), 899144 (**3**), 899139 (**4**), and 899141 (**5**), which contain the crystallographic data of the peptides mentioned in this manuscript and can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif.

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