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A new peptide motif in the formation of supramolecular double helices†

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The single crystal X-ray diffraction studies of a new tripeptide motif Boc-Tyr-Aib-Xaa-OMe (Xaa = Leu/Ile/Ala) reveal that the peptides adopt β-turn conformations which self-assemble to form a supramolecular double helical structure using various non-covalent interactions in the solid state and the peptides exhibit a type-III N_2 sorption isotherm.

Double helical structures are ubiquitous in nature and have exclusive biological functions like information storage, transcription and formation of ion channels.[1] Hence there is a general interest for designing biomimetic materials like double helical structures of biopolymers by self-assembly of the synthetic organic moiety.[2] This interest stems from their structural versatility, biocompatibility, robustness and a relative experimental simplicity. In recent years considerable progress has been achieved in the design and characterization of artificial oligomers that can wind around one another based on the intrinsic nature of the motifs.[3] Different kinds of duplex structures have been developed, for example, on the basis of metal–ligand interactions,[4] H-bonds,[5] ion pairing,[6] aromatic–aromatic interactions,[7] hydrophobic interactions[8] or π–π interactions.[9] Although plenty of supramolecular duplexes held together by hydrogen bonds have been reported, most of them are from large macromolecules and characterized as ladder- or zipper-like linear structures.[10] In this context, the supramolecular double helix from self-assembling small peptide building blocks by a combination of several non-covalent interactions is highly interesting. Görbitz has made a seminal contribution in structures of left-handed double helices from hydrophobic dipeptides based exclusively on α-amino acids (Val-Ala class structures).[11] Banerjee and coworkers have reported the formation of a double helix from dipeptide containing N-terminal β-amino acids.[12]

As a part of our program aiming the investigation of helices from synthetic oligomers,[13] herein we present the formation of supramolecular double helical structures in crystals from a series of synthetic tripeptides (**1–3**), each containing N-terminal L-tyrosine and central Aib (α-amino isobutyric acid) residues. The new molecular scaffold Boc-Tyr-Aib-Xaa-OMe (Xaa = Leu/Ile/Ala) adopts β-turn conformations in the solid state and forms the supramolecular double helix in higher order assembly, mainly directed by intermolecular N–H···O and O–H···O hydrogen bonds.

A series of terminally protected tripeptides, Boc-Tyr-Aib-Xaa-OMe, containing N-terminal L-tyrosine and central Aib (α-amino isobutyric acid) residues (Xaa = Leu(**1**)/Ile(**2**)/Ala(**3**)) have been synthesized by conventional solution-phase methodology, purified, characterized, and studied (Fig. 1). Colorless orthorhombic crystals of peptides **1**, **2** and colorless monoclinic crystals of peptide **3** suitable for X-ray diffraction studies were obtained from their methanol–water solutions by slow evaporation.‡ Peptides **1** and **2** crystallize with one peptide molecule in the asymmetric unit (Fig. S1, ESI†). However, peptide **3** crystallizes with two molecules of water in the asymmetric unit (Fig. S1, ESI†). Interestingly, the torsion angle around the conformationally constrained Aib residue appears to play a critical role in dictating the overall turn-like structural features.

From the crystal structure of peptide **1**, it is evident that there is an intramolecular hydrogen bond between BOC C=O and Leu NH resulting in a ten member hydrogen bonded β-turn conformation in the solid state. The backbone torsion angles of peptide **1** (Table 1) reveal that the turn is of distorted type II β-turn. In comparison with peptide **1**, peptide **2** contains one additional chiral centre (Ile residue). The dihedral angles around the Cα of Aib of peptide **1** are in the

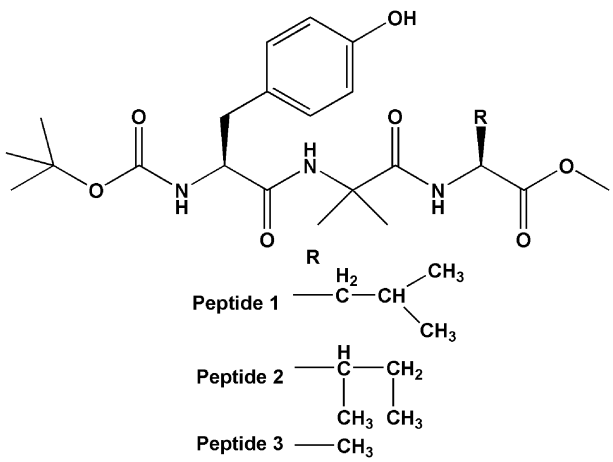

Fig. 1 The schematic presentation of the reported peptide motifs **1–3**.

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† Electronic supplementary information (ESI) available: Synthesis and characterization of peptides, ^{1}H NMR, ^{13}C NMR, solid state FTIR spectra, Table S1, TGA data, Fig. S1–S13. CCDC 797096–797098. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc04244g

Table 1 The important backbone torsion angles of peptides **1–3**

	ϕ_1/°	ψ_1/°	ϕ_2/°	ψ_2/°	ϕ_3/°	ψ_3/°
Peptide **1**	−50.7	119.1	62.4	26.4	−123.3	−17.6
Peptide **2**	52.1	−125.7	−64.2	−21.8	128.0	38.6
Peptide **3**	−59.0	134.7	67.3	21.6	−151.8	−178.6

right handed α-helical region (ϕ_2 62.4; ψ_2 26.4°) and those for peptide **2** are in the left handed α-helical region (ϕ_2 −64.2; ψ_2 −21.8°). For peptide **2**, the type II′ β-turn conformation has been stabilized by a ten member intramolecular hydrogen bond between BOC C═O and Ile NH. Though the backbone torsion angles (Table 1) of peptide **3** are similar to that of peptide **1** and are in the type II β-turn region of the Ramachandran diagram, the peptide fails to form a ten member intramolecular hydrogen bond. Moreover, peptide **3** exhibits a water mediated turn-structure in the solid state (Fig. S1, ESI†).

Each peptide **1** and **2** molecules is then stacked one on top of the other maintaining the proper registry to form an intermolecular hydrogen bonded helical strand along the crystallographic *c* axis (Fig. 2). There are two intermolecular hydrogen bonds (Tyr)N–H···O═C(Leu/Ile) and side chain phenolic–OH functionality of Tyr (O–H···O═C) with Aib C═O (ESI†, Tables S1 and S2) connecting individual peptide molecules to form the supramolecular helical strand for peptides **1** and **2** respectively.

The crystal structure further revealed that the two individual helical strands are connected *via* non-covalent interactions to form the double helical superstructure along the axis parallel to the crystallographic *c* axis. Fig. 3 clearly demonstrates that the individual β-turn subunits are stacked by maintaining proper registry between the subunits, generating a supramolecular individual helical strand which forms a double helical structure upon further self-assembly. The diameter of the supramolecular double helix is 36 Å and rise per turn of the helix is 77 Å. The double helical structures share some crystal packing similarities with the Görbitz Val-Ala dipeptide.[11]

For peptide **3**, the individual right handed helical strands are formed by intermolecular hydrogen bonds between (Tyr)N–H···O═C(Tyr) and by intervening bridging water molecules through intermolecular hydrogen bonding interactions between Aib C═O and side chain phenolic–OH functionality of Tyr (ESI†, Table S3) of properly arranged

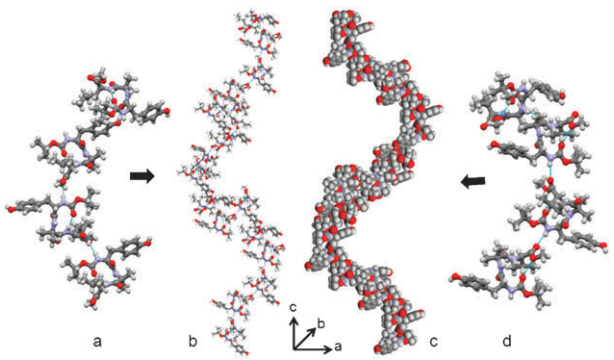

Fig. 2 The formation of hydrogen bonded helical strand (a) and (b) from peptide **1** and (c) and (d) from peptide **2**.

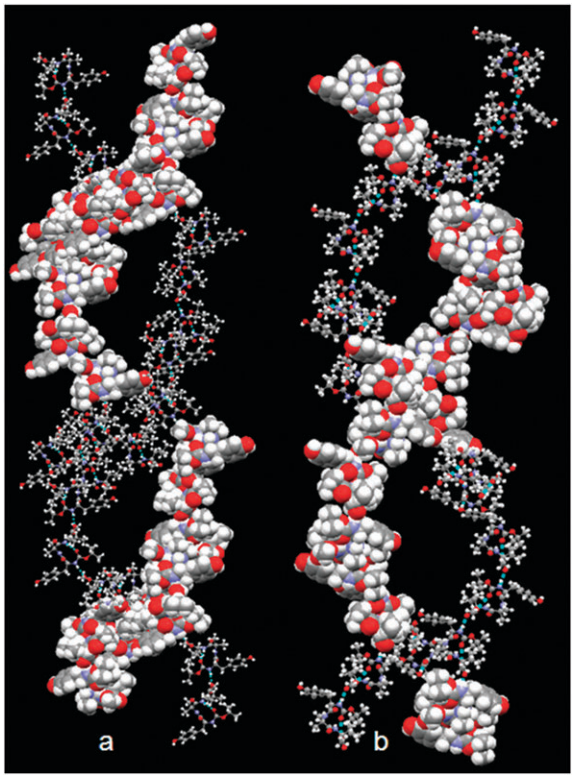

Fig. 3 The double helical structures obtained from (a) peptide **1** and (b) peptide **2**.

peptide molecules along the axis parallel to the crystallographic *a* axis. There are previous reports on the role of water molecules in stabilizing supramolecular single stranded helical structures in short peptides.[14] The individual supramolecular helical strand of peptide **3** further self-assembles to form a double helical architecture along the crystallographic *c* axis through non-covalent interactions (Fig. 4).

The TGA-DTA experiments show that the supramolecular double helices have significant thermal stability (ESI†, Fig. S2–S4). These tripeptides **1**, **2** and **3** showed no decomposition, phase transitions, or mass loss up to 196 °C

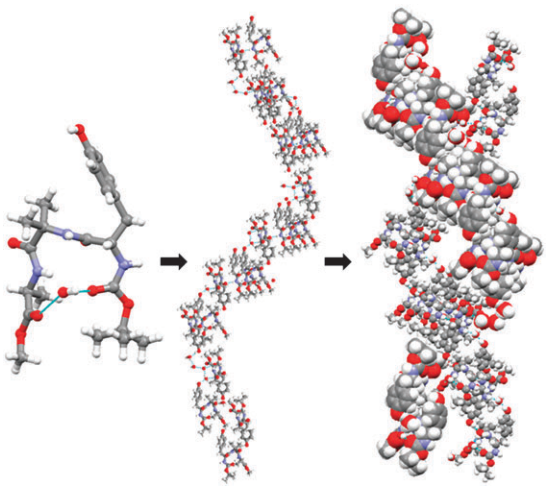

Fig. 4 Formation of a water mediated double helix from peptide **3**.

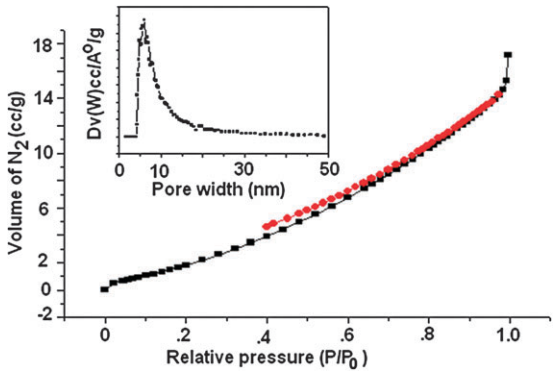

Fig. 5 N_2 sorption isotherm of peptide **1** at 77 K (P_0 = 1 atm). Black square: sorption; red circle: desorption. Inset: mesoporous size distribution of peptide **1** exhibits one peak at 6.50 nm.

(mp 164 °C), 187 °C (mp 137 °C) and 177 °C (mp 158 °C) for peptides **1**, **2**, and **3**, respectively.

In order to examine their double helix hollow, gas absorption studies have been performed.[15] The N_2 sorption studies with an evacuated sample of peptide **1** indicate that it exhibits a type-III isotherm (Fig. 5). The pore size distribution curve of tri-peptide showed one peak at 6.50 nm. The N_2 uptake of peptide **1** crystal was found to be 18.31 cc g^{-1}. Peptide **2** exhibits a similar N_2 sorption isotherm but sorption for peptide **3** is not satisfactory. Space between two helical strands is *ca.* 3 nm for peptide **1** or **2** and *ca.* 1 nm for peptide **3** in crystal.

In summary, we have shown that the self-assembly of a series of tripeptides in a well-defined pattern may be directed by similar intermolecular N–H···O and O–H···O hydrogen bonds. In crystals the reported tripeptides adopt β-turn conformations which further self-assemble to form a supramolecular double helical architecture. Boc-Tyr-Aib-Xaa-OMe (Xaa = Leu/Ile/Ala) can be considered as a new molecular scaffold for supramolecular double helix formation in the solid state. Moreover, the peptides adsorb N_2 in the double helix hollow. The results presented here may foster new studies for the design of useful nanoporous materials.

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Notes and references

‡ Crystallographic data: peptide **1**: $C_{25}H_{39}N_3O_7$, M_w = 493.59, orthorhombic, space group $P2_12_12_1$, a = 10.650(5), b = 14.144(5), c = 18.399(8) Å, U = 2771 Å^3, Z = 4, dm = 1.183 Mg m^{-3}. Peptide **2**: $C_{25}H_{39}N_3O_7$, M_w = 493.59, orthorhombic, space group $P2_12_12_1$, a = 10.724(5), b = 14.233(5), c = 18.202(9) Å, U = 2778 Å^3, Z = 4, dm = 1.180 Mg m^{-3}. Peptide **3**: $C_{22}H_{32}N_3O_7{\cdot}2H_2O$ M_w = 486.54, monoclinic, spacegroup C_2, a = 27.262(12), b = 8.137(4), c = 13.415(6) Å, U = 2675 Å^3, Z = 4, dm = 1.208 Mg m^{-3}. Intensity data were collected with MoKα radiation at room temperature using a Bruker APEX-2 CCD diffractometer. The crystal was positioned at 70 mm from the Image Plate. 100 frames were measured at 2° intervals with a counting time of 5 min to give 5000 independent reflections. Data were processed using the Bruker SAINT package and the structure solution and refinement procedures were performed using SHELX97.[16] The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. The final R values were for peptide **1**: R_1 0.0445 and wR_2 0.1276 for 3641 data with $I > 2\sigma(I)$. Peptide **2**: R_1 0.0409 and wR_2 0.1482 for 4251 data with $I > 2\sigma(I)$. Peptide **3**: R_1 0.0461 and wR_2 0.1880 for 4397 data with $I > 2\sigma(I)$. CCDC 797098, 797097 and 797096 for peptides **1**, **2** and **3** respectively.

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