Parallel sheet structure in cyclopropane γ-peptides stabilized by C–H···O hydrogen bonds†

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A three-residue *trans*-cyclopropane γ-peptide adopts an infinite parallel sheet structure in the solid state stabilized by intermolecular C–H···O hydrogen bonds, as demonstrated by single crystal X-ray diffraction.

Hydrogen bonding is ubiquitous in biological systems; its role encompasses the reactivity and specificity of enzymatic reactions, the stability of proteins, and the formation and stabilization of secondary structural elements.[1] Although the factors influencing the folding of proteins are manifold, hydrogen bonding between NH and C=O functional groups plays a pivotal role. The design of non-natural oligomeric species that emulate protein-like folding into secondary structural elements relies on an understanding and manipulation of these NH···CO hydrogen bonding patterns.[2] This has been elegantly demonstrated in β- and γ-amino acid derivatives[3] that adopt specific helix[4] and sheet conformations.[5] The role of other hydrogen bonding interactions, such as C–H···O hydrogen bonds[6] has been recognised in proteins,[7] and in particular, sheets,[8] but there are few examples of the exploitation of this interaction in the development of novel folding backbones.[9] As part of a programme investigating the factors that affect the preference for *inter*- rather than *intra*-molecular hydrogen bonding in short γ-peptides, we have designed a simple γ-amino acid derivative **1** with a cyclopropane ring constraint in the backbone and examined the conformation of simple oligomeric species **2** (Fig. 1).

Recrystallization of a trimeric derivative of **1** from methanol and chloroform provided crystals of sufficient quality for X-ray diffraction; the structure of this compound **3** is pictured in Fig. 2A. Examination of the single crystal X-ray data‡ demonstrates that the trimeric γ-peptide **3** adopts an extended conformation, and self-assembles into an infinite sheet structure through an intermolecular hydrogen bond network in which the amide N–H protons and the C–H bond on the cyclopropane adjacent to the amide group function as hydrogen bond donors (Fig. 2B).[10] This

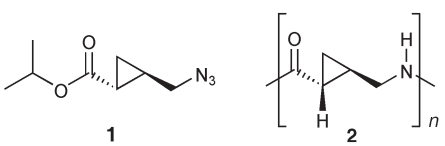

Fig. 1 γ-Amino acid building block and oligomeric derivatives.

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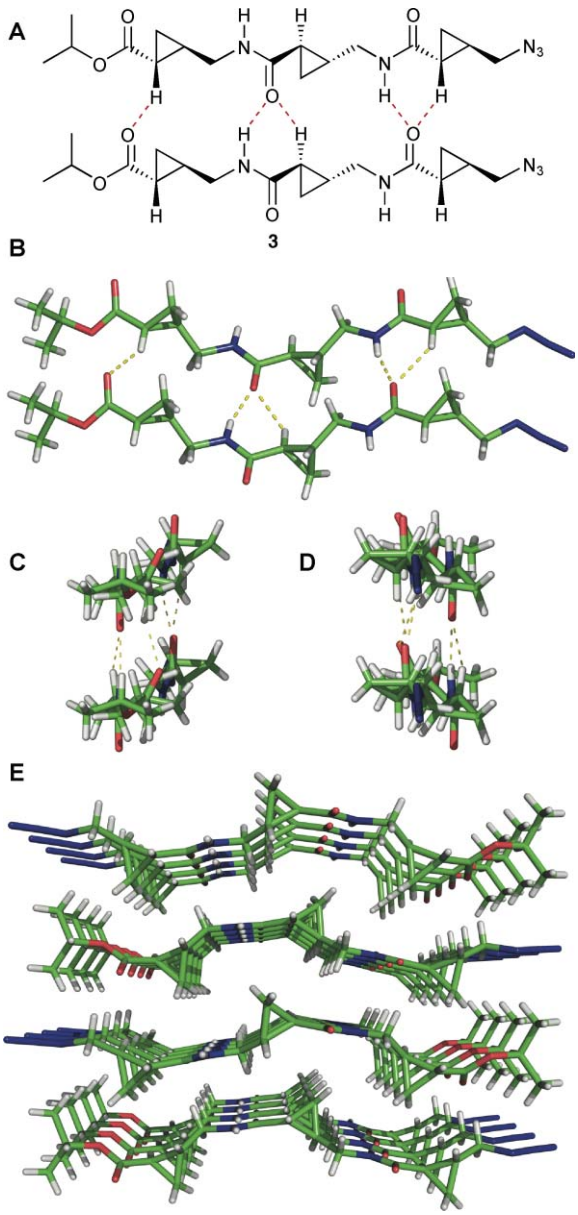
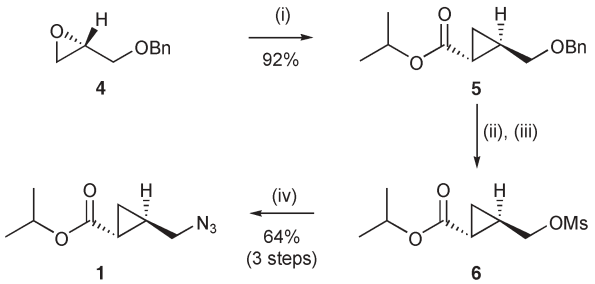


Fig. 2 **A**, Parallel sheet structure (H-bonds in red); **B**, X-ray structure of trimer **3** showing arrangement of strands in an infinite hydrogen bonded parallel sheet (the cyclopropane ring of residue C is disordered over two sites but for clarity only one of the disordered groups has been depicted); **C**, view of sheet unit from *C* to *N* terminus; **D**, view of sheet unit from *N* to *C* terminus; **E**, crystal packing. (H-bonds are in yellow throughout.)

bifurcated hydrogen bonding pattern—when one oxygen lone pair interacts with an amidic NH proton, and another with a $C^{\alpha}H$ proton[11]—has been observed in adjacent peptide strands in β-sheets. The planarity of the hydrogen bonding interaction stabilizing the sheet structure can be seen in Fig. 2C and Fig. 2D; there is little elevation from the amide plane to the donor group. Although the strength of the CH···O interaction in proteins is not conclusively known, a series of theroretical studies has suggested that it may play a significant role in determining both protein conformation[12] and stability.[13] The close CH···O contacts in **3** involve hydrogen atoms attached to the α-position of the peptide backbone that are also a component of the cyclopropane. The enhanced hydrogen bonding capabilities of this functional group may be ascribed to the electron-withdrawing carbonyl group acting in concert with the increased acidity of the cyclopropane system (relative to an acylic hydrocarbon).[14] Crystal packing in the trimer **3** (Fig. 2E) clearly shows the two molecules in the unit cell and illustrates the infinite sheet structure. This also serves to demonstrate how substitution adjacent to the amino group could affect the overall structure. In general, angle and distance criteria are used to classify close heteroatom contacts as hydrogen bonds,[15] though there are examples of CH···O hydrogen bonds that do not satisfy these demands.[16] High resolution protein structures have been demonstrated to contain β-sheet regions with short CH···O distances, and in these examples, the average CH···O distances and CH···O angles are 3.29 Å and 143° respectively.[8] The values for the peptide **3** are presented in Table 1.

These show a remarkably close correspondence to the average values in proteins and are consistent with the similarity of these interactions to those observed in nature. β-Peptides containing cyclopropanes have been demonstrated to fold into a ribbon-type arrangement,[17] though the geminal nature of the substitution in these materials precludes the cyclopropane from acting as a hydrogen bond donor.

The synthesis of oligomeric materials such as **2** requires efficient access to enantiopure γ-peptide building blocks on a multigramme scale. The key step in the generation of the ring-constrained backbone of the γ-peptide is a Wadsworth–Emmons cyclopropanation[18] (Scheme 1). Treatment of commercially available (*S*)-benzyl glycidol **4** with triisopropylphosphonoacetate and sodium hydride in the presence of catalytic isopropyl alcohol gave exclusively *trans*-cyclopropane **5** (as confirmed by nOe studies) in 92% yield on 10 g scale. It has been demonstrated that this transformation proceeds with inversion of configuration at the epoxide stereocentre.[19,20] The efficiency of this transformation is



Scheme 1 *Reagents and conditions:* (i) $(^{i}PrO)_2POCH_2CO_2{}^{i}Pr$, NaH, toluene, $^{i}PrOH$ (cat.), 60 to 90 °C; (ii) H_2, Pd/C, EtOH; (iii) MsCl, Et_3N, CH_2Cl_2; (iv) NaN_3, DMF, 90 °C.

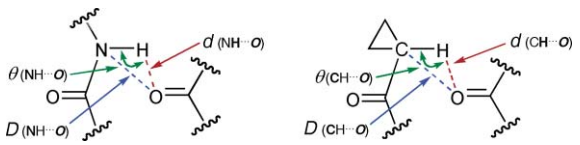
dependent on the reaction temperature,[20] and it was found that heating at 60 °C for 2 h led to consumption of the epoxide starting material (presumably to give an intermediate phosphonate) and subsequent heating to 90 °C afforded the *trans*-cyclopropane **5**. Debenzylation was achieved by hydrogenolysis with palladium on carbon in ethanol to give a primary alcohol (98% yield) that could be converted to mesylate **6** in 90% yield by treatment with methanesulfonyl chloride in the presence of triethylamine. Subsequent dispacement of this sulfonate ester by sodium azide in DMF at 90 °C afforded the γ-amino acid derivative **1** in 64% overall yield from cyclopropane **5**. In this fashion, multigramme quantities of enantioenriched **1** can be prepared in 60% overall yield in four steps from (*S*)-benzyl glycidol.

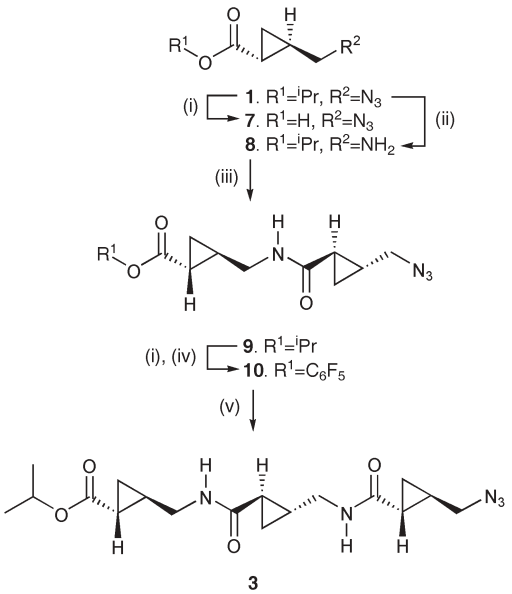
An iterative approach was adopted for the generation of oligomeric derivatives, and this necessitated the formation of amino and carboxylate components. With this in mind, isopropyl ester **1** was converted to its respective acid **7** by treatment with aqueous sodium hydroxide followed by protonation with 3N HCl. Hydrogenation of azide **1** with hydrogen in the presence of palladium black gave amine **8**, which was characterized as an *N*-acyl derivative.[21] A range of peptide coupling protocols was investigated for the formation of the dimeric derivative **9** (Scheme 2) but it was found that coupling of fragments **7** and **8** with TBTU and Et_3N in a CH_2Cl_2–DMF mixture was most effective, and afforded compound **9** in 73% yield. The formation of a trimeric derivative was inefficient using diimide reagents, and it was more useful to generate pentafluorophenyl ester **10** (72% yield from the ester **9**) prior to coupling with the amine **8**; this afforded the trimeric derivative **3** in 80% yield. The oligomer **3** is sparingly soluble in non-polar solvents such as chloroform (at concentrations below 15 mM), forming gel-like structures at higher

Table 1 Interstrand distances (Å) and hydrogen bond angles (°)[a]

Residue	*D* (C**H**···***O***)	*D* (N**H**···***O***)	*θ* (C**H**···***O***)	*θ* (N**H**···***O***)	*d* (C**H**···***O***)	*d* (N**H**···***O***)
A	3.3	—	143	—	2.3	—
B	3.2	2.9	142	160	2.3	2.0
C	3.2	2.9	142	165	2.3	2.0

[a] Residues are labelled alphabetically from the *N* to the *C* terminus. Measurements are defined according to the donor group on the appropriate residue. Angles and distances are defined below:





Scheme 2 *Reagents and conditions:* (i) NaOH (aq.), EtOH; then 3N HCl; (ii) H_2 (g), Pd black, EtOH; (iii) TBTU, Et_3N, CH_2Cl_2–DMF (2 : 1 v/v), 1 equiv. of **7**; (iv) pentafluorophenol, EDCI, CH_2Cl_2, sonication; (v) HOBt, CH_2Cl_2, Na_2CO_3, 1 equiv. of **8**.

concentrations, presumably due to the formation of extended sheet arrangements and aggregation; however, it readily dissolves in more polar solvent mixtures, such as chloroform–methanol (9 : 1) or DMSO. At concentrations of less than 15 mM in $CDCl_3$ there is no evidence of *inter*- or *intra*-molecular hydrogen bonding, on the basis of the chemical shifts of the amide protons of **3**.†

Elegant syntheses of γ-substituted variants of **1** have been recently reported,[22] and materials such as these may prove useful in further design iterations based on this backbone. The sheet structure of trimer **3** offers a glimpse of the potential of such supramolecular building blocks,[23] and suggests that this bifurcated hydrogen bonding motif may be useful in the generation of catalytic molecules[24] and higher order structures.

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Notes and references

‡ Crystal data for **9**: $C_{18}H_{27}N_5O_4$, M = 377.45, monoclinic, $P2_1$, a = 4.8023(1), b = 8.6693(2), c = 24.1050(5) Å, β = 93.793(2)°, V = 1001.36(4) Å^3, Z = 2, μ = 0.090 mm^{-1}, $F(000)$ = 404, T = 220(2) K. Of 8057 reflections collected, 2142 were unique (R_{int} = 0.033), F^2 refinement: R_1 = 0.045, wR_2 = 0.107 [$I > 2\sigma(I)$], and R_1 = 0.048, wR_2 = 0.111 on all data. CCDC 617972. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b611882h

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