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Reliable folding of hybrid tetrapeptides into short β-hairpins

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ABSTRACT

Five hybrid tetrapeptides, each consisting a central dipeptide segment of α-amino acid residues flanked by two aromatic γ-amino acid residues, are found to fold into well-defined β-hairpin conformations as shown by NMR, computational study, and X-ray structures. The turn loop of this β-hairpin motif accommodates different two-residue α-amino acid sequences from the highly flexible Gly-Gly, to the more restricted D-Pro-Gly. The presence of α-amino acid side chains enhances the stabilities of the β-hairpins with the exception of D-Pro-Gly-which results in destabilization. Based on this hairpin/turn motif, a variety of different dipeptide sequences of α-amino acids which rarely occur in β-turns can be introduced and presented as two-residue loops.

As a major class of protein secondary structures, reverse turns are sites of chain reversal responsible for the globular character of a protein [1,2]. β-Turns, *i.e.*, tight turns consisting of two amino acid residues, are frequently found in hairpin loops of globular proteins [3-5]. The design of type II' D-Pro-Gly β-turn [6-9], type I' Asn-Gly [10-12], Aib-D-Ala [13] β-turns, and other such as aza-amino acids [14] have facilitated the formation and stabilization of isolated β-hairpins consisting of α-amino acids, and have played crucial roles in initiating the folding of peptides and proteins [15,16]. Stable β-turns also exhibit important biological functions such as serving as epitopes in protein–protein [17-20] and protein–nucleic acid [21-25] interactions.

Interests in developing foldamers have led to the creation of many folding oligomers containing unnatural building blocks that adopt defined conformations including sheets and turns [26-30]. For example, aromatic residues derived from 5-amino-2-methoxybenzoic acid were incorporated into β-strands by Nowick to enhance the stability of templated and cyclized β-sheets [31]. β-Turns based on nipecotic acid developed and those containing $\beta-2,3$-amino acid residues reported by Seebach [32,33] were shown to facilitate the formation of β-hairpin structures of β-peptides. Besides, β-hairpins containing centrally located α/γ- and α/δ-hybrid dipeptide loops that connect oligopeptide strands of α-amino acid residues were also reported [34].

We created oligoamide strands consisting of alternating *meta*-linked aromatic units and α-amino acid residues [35]. Such oligoamides strands, as mimics of β-strands, associate into double-stranded sheets with stabilities proportional to the number of inter-strand H-bonds [36-38]. A recent attempt to enhance the diversity of our H-bonded duplexes, based on the incorporation of glycine and β-alanine, the most flexible α- and β-amino acid residues, into the oligoamide strands, led to hybrid peptide **1** (Fig. 1a) that was found to adopt a stably folded hairpin, *i.e.*, an expanded β-turn, containing a β-Ala-Gly-dipeptide loop flanked by two doubly H-bonded aromatic γ-amino acid residues [39]. Subsequent studies revealed that such an expanded β-turn motif is capable of accommodating a variety of different combinations of α/β-dipeptide sequences [40,41].

To probe whether the β-turn motif adopted by **1** and its analogous hybrid peptides could be extended to constructing two-residue loops consisting of α-amino acid residues, four-residue hybrid peptides **2**, which differ in the α-amino acid sequences of their central dipeptide segments, are designed (Fig. 1b). Each of peptides **2**, if folding into the conformation as shown, will give a

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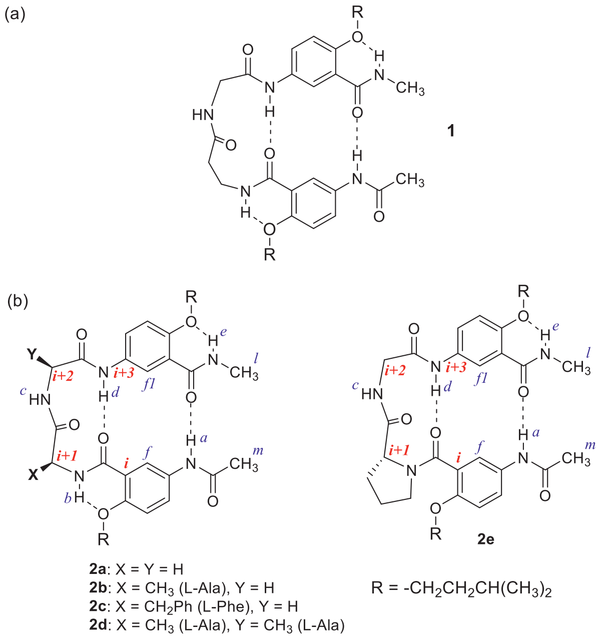

Fig. 1. (a) Hybrid peptide **1** shown as its expanded β-turn conformation. (b) Hybrid peptides **2a-2e** shown as their likely β-turn conformations. The amino acid residues are labeled in red. The selected hydrogens are labeled in blue.

Table 1
Chemical shifts of protons *a*, *d*, *f*, and *f1* in $CDCl_3$.[a]

Peptide	δ (ppm)			
	a	*d*	*f*	*f1*
2a	9.759	9.223	8.396	8.311
2b	9.825	9.294	8.432	8.291
2c	9.791	9.331	8.376	8.282
2d	9.895	9.195	8.527	8.289
2e	9.551	9.224	7.915	7.403

[a] ^1H NMR spectra (400 MHz, 298 K) were recorded in $CDCl_3$ (5 mmol/L).

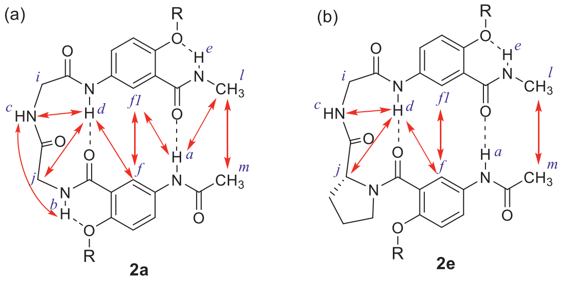

Fig. 2. NOEs shown as double-headed arrows, between remote (non-adjacent) protons revealed by the NOESY spectra of (a) **2a** and (b) **2e** in $CDCl_3$ (5 mmol/L, 298 K, 400 MHz, mixing time 0.3 s).

β-hairpin consisting of, from the N- to the C-termini, four consecutive residues with position *i* being an aromatic γ-amino acid, positions *i* + 1 and *i* + 2 being two α-amino acid, and *i* + 3 being another aromatic γ-amino acid, residues. By studying the folding of **2**, we hope to address the following questions: Could such a β-turn motif accommodate different α-amino acid residues? How do different α-amino acid residues influence the stability of the corresponding β-turns?

Herein we report that the folding of peptides **2a-2e**, with residues *i* + 1 and *i* + 2 being Gly-Gly, L-Ala-Gly, L-Phe-Gly, L-Ala-L-Ala and D-Pro-Gly, follows a general pattern by adopting β-hairpin conformations as shown by results from 1D and 2D ^1H NMR studies and confirmed by the crystal structures of **2a-2d**. The stabilities of the hairpin conformations are found to vary with the α-amino acid sequences of the dipeptide loops.

The ^1H NMR spectra of **2a-2e** from 0.1 mmol/L to 25 mmol/L in $CDCl_3$ reveal sharp peaks, except for proton *a* of **2e** (Fig. S1 in Supporting information). The well dispersed ^1H resonances of these hybrid peptides indicate that, although having multiple H-bond donors and acceptors, peptides **2a-2e** do not engage in noticeable self-aggregation and most likely exist as discrete species adopting defined conformations in solution. Consistent with the adoption of β-turn conformations by **2a-2e**, amide protons *a, b, d* and *e* show insignificant changes in their chemical shifts, indicating their involvement in intramolecular H-bonding; in contrast, protons *c* of all five peptides show much larger downfield shifts, suggesting their engagement in intermolecular H-bonding.

Comparing the chemical shifts of amide protons *a* and *d* of **2a-2d** (Table 1) at 5 mmol/L provides for a qualitative assessment on the relative stabilities of the corresponding H-bonds and thus those of the β-turns. Compared to that of **2a**, the signals of proton *d* of **2b** and **2c** move downfield, which imply that the H-bonded loops of **2b** and **2c** are stabilized due to the presence of the L-Ala-and L-Phe-side chains; the signal of proton *d* of **2d** moves slightly upfield, suggesting that the two L-Ala-residues more or less twist the H-bonded loop and weakens the H-bond involving proton *d*.

The chemical shifts of protons *a* which are away from the H-bonded loops indicate the strength of the H-bonds and also indicate the stability of the β-turns. Relative to that of **2a**, the signals of protons *a* of **2b-2d** move downfield. The resonance of **2d** shows the largest downfield shift, followed by that of **2b**, and then by **2c**, based on a stability order of **2d** > **2b** > **2c** > **2a** results. Thus, the presence of α-amino acid sidechains in hybrid peptides **2b-2d** seems to enhance the stability of the hairpins, most likely by imposing stereochemical constraints that limit the conformational flexibility of the turn loops.

Compared to the sharp resonances of protons *a* of **2a-2d**, proton *a* of **2e**, which contains a D-Pro-Gly-loop that strongly promotes turn and hairpin conformation in peptides of α-amino acids [6], gives a broadened peak (Fig. S1e) that moves upfield to 9.551 ppm (Table 1). Besides, the peaks of protons *f* and *f1* of **2e** also move upfield to 7.915 and 7.403 ppm, respectively, relative to those of protons *f* and *f1* of **2a-2d** (Table 1). Thus, the H-bond involving proton *a* of **2e** seems to be weakened, resulting in a conformation of **2e** in which the two aromatic residues and the *N*- and *C*-termini undergo dynamic relative motion.

Peptides **2a-2e** were then examined with 2D NMR (NOESY) in $CDCl_3$ (Fig. S2 in Supporting information). The NOEs observed with **2a** (Fig. 2a) are those between protons *a* and *l*, *a* and *f1*, *d* and *f*, and *f* and *f1*, indicating that the two aromatic rings are brought into close proximity by H-bonding involving amide protons *a* and *d*. Besides, the NOE between protons *l* and *m* demonstrates that the two termini of **2a** are in close proximity, which is consistent with the expected hairpin conformation. NOEs involving the protons of the Gly-Gly-segment of **2a** include those between protons *c* and *b*, *c* and *d*, and *d* and *j*, which indicate the presence of a well-defined loop. The NOESY spectra of **2b-2d** (Figs. S2b-d) reveal that NOEs share the same overall pattern observed in that of **2a**, suggesting that **2b-2d** also adopt well-defined β-turn conformations in $CDCl_3$.

The NOEs revealed for **2e** (Fig. 2b) include those between protons *c* and *d*, *d* and *j*, *d* and f, *f* and *f1*, and *l* and *m*, indicating that **2e** also adopts a β-turn conformation. That no NOE between protons *a* and *f1*, or *a* and *l* is observed, along with the significant upfield shift of this proton resonance relative to the signals of protons *a* of **2a-2d**, is consistent with the weakening of the H-bond involving proton *a* of **2e**.

Single crystals of **2a-2d** were obtained, which led to the determination of the X-ray structures of these hybrid peptides. As

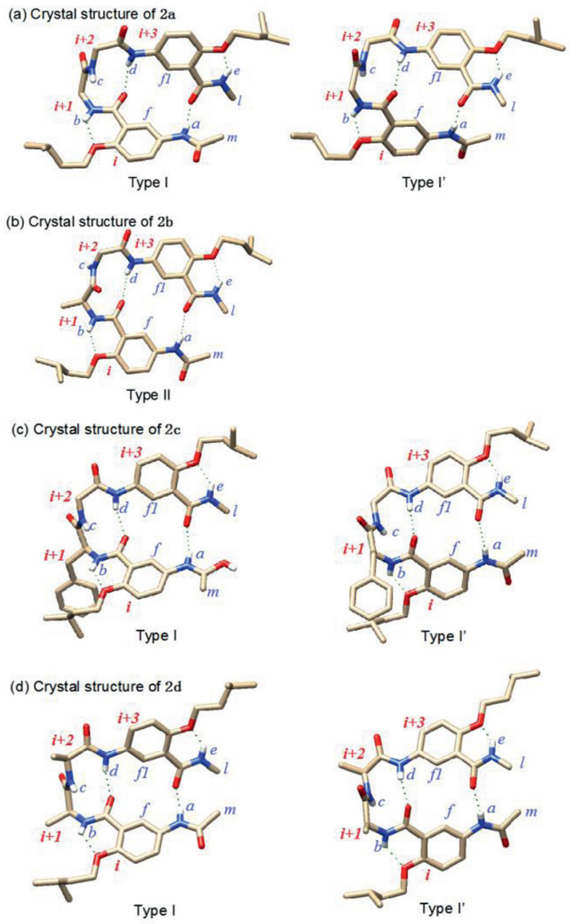

Fig. 3. Crystal structures of (a) **2a**, (b) **2b**, (c) **2c**, and (d) **2d** Two independent molecules with their main chain atoms adopting enantiomeric turn types having are found for **2a, 2c**, or **2d** For clarity, all hydrogen atoms except for those of the amide groups, are removed.

shown in Fig. 3, each of the four hybrid peptides, regardless of its two-residue sequence involving residues *i* + 1 and *i* + 2, folds into a typical β-hairpin conformation that is held together by two intramolecular H-bonds involving amide protons *a* and *d* of residues *i* and *i* + 3. Although the two-residue sequences Gly-Gly, L-Ala-Gly, L-Phe-Gly and L-Ala-L-Ala-do not have high β-turn propensities [4,5], peptides **2a-2d** nevertheless fold into β-hairpins, which demonstrate the general applicability of this β-turn motif for accommodating different loop sequences.

Based on the crystal structures of **2a-2d**, dihedral angles φ and ψ of residues *i* + 1 and *i* + 2 in the turns are obtained, which reveal the β-turn types (Fig. 3). The crystal structure of achiral **2a** (CCDC: 2,053,064) reveals two independent molecules adopting the enantiomeric type I and type I' β-turn conformations (Fig. 3a). With its chiral L-Ala-residue, peptide **2b** (CCDC: 2,053,065) exists as two independent molecules with very similar φ and ψ angles and folds into a type II β-turn (Fig. 3b). Interestingly, peptides **2c** (CCDC: 2053066) (Fig. 3c) and **2d** (CCDC: 2053067) (Fig. 3d), although having one (L-Phe) and two (L-Ala) chiral residues, respectively, still fold into both types I and I' β-turns, *i.e.*, the presence of chiral α-amino acid residues is incapable of biasing the main chain atoms of **2c** or **2d** to settle on one of the two enantiomeric turn types.

Attempts to grow single crystals of peptide **2e** have been unsuccessful. The conformation of **2e** was computationally probed using the ADF and VASP software packages with revPBE-D3 [42-44]. The most stable conformation of **2e** is a β-hairpin in which the planes of the two aromatic residues have a sharp dihedral angle of ~60° (Fig. 4a). Besides, the benzene ring of residue *i* and the amide group linking residues *i* and *i* + 1 deviate from coplanarity, with a dihedral angle of ~50°. In contrast, the optimized conformation of **2b** shows a much less curved structure, with a dihedral angle of ~117° between the benzene rings of the two aromatic residues (Fig. 4b). The benzene ring of residue *i* and the amide group between residues *i* and *i* + 1 are coplanar. The twisted conformation of **2e** seems to be caused by the need to avoid steric hindrance between the five-membered ring of the Pro-residue and the adjacent methoxy sidechain of aromatic residue *i*. As a result, the two H-bonds involving protons *a* and *d* are slightly longer, and thus weaker, in **2e** than those in **2b**.

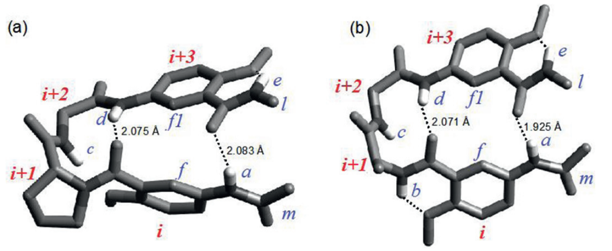

Fig. 4. Energy-minimized structures of the hairpin conformations of (a) **2e** and (b) **2b**. The isopentyloxy side chains are replaced with methoxy groups. For clarity, all hydrogen atoms except for those of the amide groups, are removed.

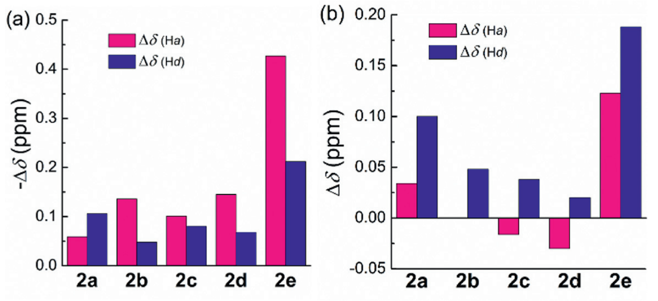

Fig. 5. Changes in chemical shifts ($\Delta\delta$) amide protons *a* and *d* (400 MHz) of **2a-d** (5 mmol/L) (a) from 0–45 °C in $CDCl_3$ ($\Delta\delta = \delta_{(45\ ^\circ C)} - \delta_{(0\ ^\circ C)}$) and (b) in mixed solvents containing 0 to 20% DMSO–d_6 in $CDCl_3$ at 25 °C ($\Delta\delta = \delta_{(20\%\ DMSO)} - \delta_{(0\%\ DMSO)}$).

Quantum molecular dynamics calculations on **2b** and **2e** in a *NVT* ensemble (298 K, Supporting information for movies) revealed that the length of the H-bond involving proton *a* of **2b** fluctuated in a narrow range (~1.7–2.5 Å), while the H-bond of **2e** involving proton *a* was drastically more dynamic and fluctuated over a much larger range (~1.7–3.8 Å) (Fig. S7 in Supporting information). Thus, structural deformation caused by the D-Pro-residue results in weakened H-bonding interactions and thus lowered stability for the hairpin of **2e**.

The stabilities of the folded structures of **2a-2e** were further examined by comparing the effects of temperature and solvent polarity on the strength of H-bonds involving protons *a* and *d* (Figs. S3 and S4, Table S1 in Supporting information). As shown in Fig. 5a, from 0 to 45 °C, the signals of protons *a* and *d* all move upfield. The signal of proton *a* of **2e** shows an upfield shift (0.43 ppm) that is significantly larger than those of the other four peptides, and those of protons *a* of **2a-2d** shift within a much narrower range of 0.06 to 0.14 ppm. Among protons *d*, that of **2e** shows the largest upfield shift (0.21 ppm), while those of **2a-2d** are much smaller, ranging from 0.05 to 0.10 ppm. The temperature-dependent upfield shifts of amide protons *a* and *d* indicate that, the presence of the D-Pro-residue in **2e** weakens the H-bonds involving protons *a* and *d* much more significantly than in **2a-2d**. Among **2a-2d**, the presence of side chains in the β-turn loops of **2b-2d** slightly weakens

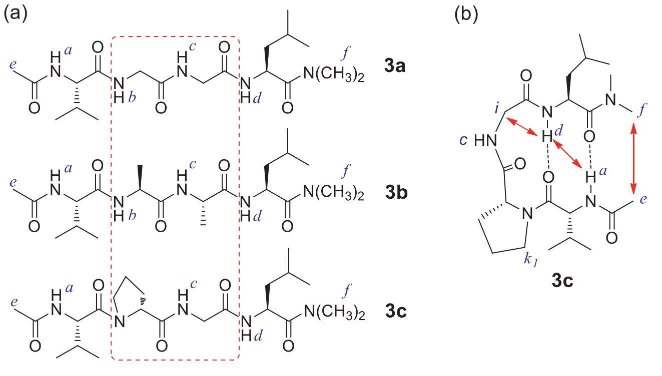

Fig. 6. (a) Tetrapeptides **3a-c** differing in their central residues (highlighted in red-dashed box) flanked by the same L-Val-and L-Leu-residues. (b) NOEs (red double-headed arrows) between remote protons revealed by the NOESY spectrum of **3c** (5 mmol/L in $CDCl_3$, 400 MHz, mixing time: 0.3 s).

the H-bonds involving protons *a*, while enhancing the H-bonds involving protons *d*.

In mixed solvents containing 0 to 20% DMSO–d_6 in $CDCl_3$ (Fig. 5b), the signals of both protons *a* and *d* of **2a-2e** show downfield shifts. The shifts of protons *a* and *d* of **2e**, being 0.12 and 0.19 ppm, respectively, are much larger than those of the other four peptides, confirming that the protons *a* and *d* are more exposed in **2e**, *i.e.*, the corresponding H-bonds are less shielded, leading to a confirmation of **2e** that is less stable than those of **2a-2d**. The downfield shifts of protons *a* and *d* of **2a** are larger than those of protons *a* of **2b-2d**, indicating that the α-amino acid side chains of **2b-2d** enhance the stabilities of these three β-turns, a conclusion that is consistent with the one based on comparing the chemical shift values of protons *a*.

The critical role played by the aromatic γ-amino acid residues in promoting the folding of peptides **2** was demonstrated by comparing **3a-3c** which differ in their central dipeptide sequences but share the same L-Val-and L-Leu-terminal residues (Fig. 6a). Peptide **3c** is known to fold into a β-hairpin conformation that is promoted by its D-Pro-Gly-loop sequence [6]. As shown in Fig. S5 and Table S2 (Supporting information), from 0.1 mmol/L to 25 mmol/L in $CDCl_3$, the signals of amide protons *b, c*, and *d* of **3a** show noticeable downfield shifts of ~0.56 to 0.77 ppm and that of proton *a* shows a very small shift (~0.02 ppm); while all four amide protons of **3b** undergo very large downfield shifts from ~1.61 to 1.74 ppm. Consistent with the folding of **3c** into a β-hairpin, the downfield shifts of amide protons *a* and *d* of **3c**, being 0.13 and 0.05 ppm, are much smaller than those of **3a** and **3b** (except for proton *a* of **3a**), which also suggests that **3a** and **3b** undergo intermolecular H-bonding interaction and do not fold like **3c**.

The NOESY spectrum of **3c** (Fig. S6 in Supporting information) reveals NOEs between remote protons *a* and *d, d* and *i*, and *e* and *f*. In contrast, no NOEs between the corresponding remote protons, especially between protons *a* and *d*, and *e* and *f*, are found in the NOESY spectra of **3a** and **3b**, showing that **3a** and **3b**, unlike **3c**, do not fold into β-hairpin conformations.

In summary, hybrid tetrapeptides **2a-2e**, each has a central dipeptide segment of α-amino acid residues and two aromatic γ-amino acid residues, fold into well-defined β-turn hairpins. Results from 1D and 2D NMR, and computational studies, along with crystal structures, demonstrate that the five different two-residue sequences of α-amino acid residues are all incorporated as the turn loops of the β-hairpins. D-Pro-Gly, a turn sequence that strongly promotes the adoption of β-hairpin conformations by peptides of α-amino acids, results in a β-turn with the lowest stability. Compared to peptide **2a** which has a Gly-Gly-loop, peptides **2b-2d** with L-Ala-Gly, L-Phe-Gly and L-Ala-L-Ala-loops, showed enhanced stabilities. The inability of peptides **3a** and **3b**, which shares their central dipeptide segments with **2a** and **2d**, respectively, demonstrates the critical importance of the two aromatic γ-amino acid residues in ensuring the adoption of hairpin conformations by peptides **2a-2e**. The same folding pattern of the five hybrid peptides has offered a reliable hairpin motif capable of accommodating different two-residue sequences of α-amino acids, which will greatly enhance the diversity of β-turns and β-hairpins.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.06.019.

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