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The relevance of the relative configuration in the folding of hybrid peptides containing β-cyclobutane amino acids and γ-amino-L-proline residues

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ABSTRACT

Four new series of diastereomeric β,γ-di- and β,γ-tetrapeptides derived from conveniently protected (1*R*,2*S*)- and (1*S*,2*S*)-2-aminocyclobutane-1-carboxylic acid and *cis*- and *trans*-γ-amino-L-proline joined in alternation have been synthesized. High resolution NMR experiments show that peptides containing *trans*-cyclobutane amino acid residues adopt a more folded structure in solution than those containing a *cis*-cyclobutane residue, which adopt a strand-like structure. The *cis*/*trans* relative configuration of the cyclobutane residue is the origin of the folding pattern of each peptide due to either intra- or inter-residue hydrogen-bonded ring formation, whereas the *cis*/*trans* isomerism of the γ-amino-L-proline residue does not have a significantly relevant role on the folding ability of these peptides.

1. Introduction

The structural organization of peptides and proteins has a very important impact on their function. Nevertheless, the use of naturally occurring α-amino acids for the synthesis of peptides with a potential pharmacological application is limited due to their instability to enzymatic degradation. Various alternatives have been thought out to overcome this problem while reproducing the structural disposition of natural peptides.[1] For example, the appearance of the peptide-based foldamers,[2] which are synthetic oligomers containing unnatural amino acids or equivalent building blocks, has allowed the preparation of folded structures that mimic natural occurring ones: helices, strands, turns, ribbons, amongst others.[3] These structures are generally generated by intra-molecular non-covalent interactions, mainly hydrogen bonds. Some of these non-natural peptides and analogues have been used for various applications,[4] with special interest in biological and biomedicinal ones.[5]

In particular, β-amino acids emerged as privileged scaffolds for the preparation of various foldamers.[6] The backbone of the β-amino acids can be either linear or cyclic. These β-amino acids can serve as building blocks for the synthesis of homopeptides. Otherwise, hybrid peptides can be obtained by alternate combination of their stereoisomers or with other α, β, or γ-amino acids.[7] Our group has worked extensively on the synthesis and structural study of peptides constituted by β-cyclobutane amino acids (CBAA). For homopeptides containing all *cis*-CBAA (from di-to octapeptides), an intraresidual six-membered hydrogen-bonded ring (6-strand) was described, as well as for the protected parent amino acid.[8] In contrast, a 12-helix arrangement was described by Aitken et al. for the all-*trans*-CBAA hexa- and octapeptides.[9] The study of di-peptides composed of various combinations of the *cis* and *trans* isomers of this amino acid revealed the predominance of an eight-membered hydrogen-bonded ring in those cases where a *trans* amino acid is at the N-terminus of the peptide whereas a six-membered ring is preferred for those cases where a *cis* amino acid is at the N-terminus.[10] Moreover, a detailed computational and NMR study of small β-CBAA-containing oligopeptides demonstrated that the chirality of the monomeric residues, in any position of the peptide sequence, controls and determines their prevalent folding. The *cis*-CBAA gives rise to two conformers that generate zig-zag structures from six- and eight-membered hydrogen-bonded rings, Z6 and Z8, while the *trans* form manifests uniquely as a helical promoter eight-membered hydrogen-bonded ring, H8

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(Fig. 1).[11] These findings allowed the rational design of new folding structures using these monomers.

Hybrid oligomers have also been prepared from β-CBAA residues joined in alternation with glycine, β-alanine, and γ-amino butyric acid (GABA), respectively. Results accounted for the spacer length effect on the folding and showed that the conformational preference for these hybrid peptides could be tuned from a β-sheet-like folding for those containing a glycine or a GABA residue, to a helical folding for those with a β-alanine between cyclobutane residues.[12] The intra-residue 6-membered hydrogen bond (Fig. 1) was observed in the β-CBAA in the hybrid peptides containing glycine and GABA residues. Some of these β-CBAAs and the peptides in which they have been incorporated have found application as functional organofibers,[13] as organogelators,[14] as neuropeptide Y inhibitors[15] and as surfactants.[16]

Proline is a naturally occurring amino acid which is conformationally constrained due to the pyrrolidine ring, and which induces well defined secondary structures in peptides that contain it.[17] γ-Aminoproline is a derivative of proline, which has been used in the synthesis of peptide foldamers acting as either an α-amino acid[18] or as a γ-amino acid.[19,20] In both types of peptides, the presence of the additional amino group, which is not involved in the peptide bond formation, allows its functionalization and, thus, the introduction of side-chains.[18,19,21]

In our group, a detailed structural study was carried out with hybrid peptides prepared with γ-CBAAs and N^{α}-Boc-protected *cis*-γ-amino-L-proline joined in alternation.[20] It revealed that a strong intra-residue 7-membered ring was formed within the proline residues and an inter-residue one was observed between the carbonyl of the *tert*-butyl carbamate group and the NH of the subsequent γ-CBAA residue (see Fig. 2).

Regarding their applications, proline- and γ-aminoproline-based peptides have been reported to have excellent cell penetration abilities.[19,21,22] In our preliminary studies with γ,γ-peptides as cell penetrating agents, we showed that the chirality of the amino acids plays a role in their biological activity[21] and very recently it has been demonstrated that the preorganization of the side-chains of these sorts of peptides is crucial for their adequate performance.[18]

For this reason and aimed by the development of new oligopeptides with pharmacological properties, in this work we describe the synthesis and structural study of eight diastereomeric hybrid di- and tetrapeptides containing β-CBAAs and N^{α}-Boc-protected γ-amino-L-proline of various relative and absolute configurations (Chart 1). The relevance of the relative configuration of the β- and γ-amino acids in the folding propensity of the resulting peptides has been analyzed by means of high resolution NMR spectroscopy.

2. Results and discussion

The synthesis started with the coupling of the adequate cyclobutane-containing *N*-Cbz-protected β-amino acid, *cis*-(1*R*, 2*S*)-**9**23 or *trans*-(1*S*, 2*S*)-**10** (see the experimental section for its preparation), respectively, with the N^{α}-Boc-protected *cis*- or *trans*-γ-amino-L-proline methyl ester, respectively, using PyBOP as coupling agent (see Scheme 1). The protected dipeptides **1**–**4** were obtained in good yields (66–85%). The N-terminal protecting group of each dipeptide (**1**–**4**) was removed by Pd-catalyzed hydrogenation in excellent yields. In parallel, the *C*- terminus methyl ester of dipeptides **1**–**4** was saponified under mild conditions to yield the corresponding carboxylic acids in quantitative yields. The coupling between these monodeprotected dipeptides, using similar conditions as described above, rendered tetrapeptides **5**–**8** in moderate to good yields (42–65%).

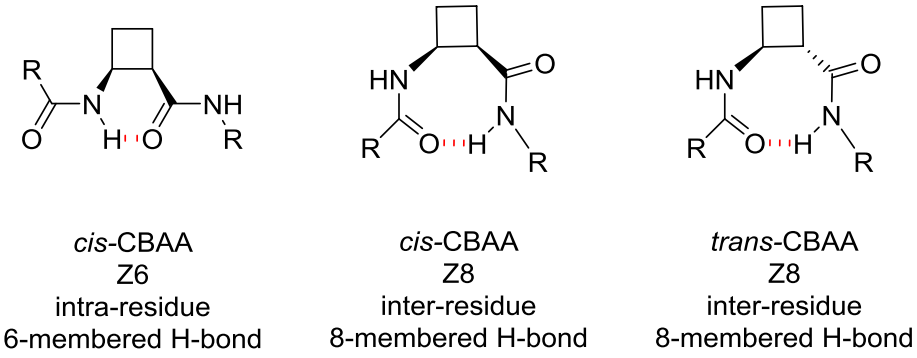

Fig. 1. Intra- and inter-residue hydrogen bonds in peptides that incorporate either *cis*-β-CBAA or *trans*-β-CBAA.

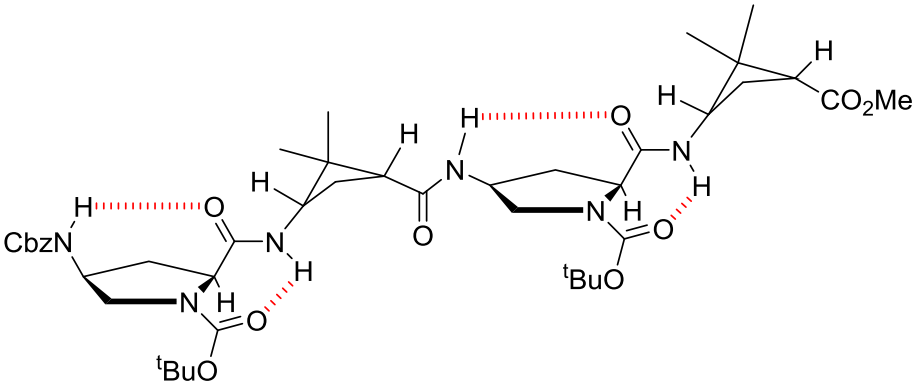

Fig. 2. Intra- and inter-residue hydrogen bonds described in hybrid peptides consisting of γ-CBAAs and *cis*-γ-amino-L-proline joined in alternation.