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A γ-turn induced by a highly constrained cyclopropane analogue of phenylalanine ($c_3$diPhe) in the solid state

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Abstract

In order to evaluate the possible influence of the side chain orientation on the backbone conformation we have synthesized the model dipeptides ^{t}BuCO-L-Pro-$c_3$diPhe-NH^{i}Pr, where $c_3$diPhe represents (2*S*,3*S*)- and (2*R*,3*R*)-1-amino-2,3-diphenylcyclopropanecarboxylic acid, two cyclopropane analogues of phenylalanine. In the solid state, the (2*S*,3*S*)$c_3$diPhe-containing compound adopts a classical βII-turn disposition. In contrast, the dipeptide incorporating the (2*R*,3*R*) enantiomer exhibits an *open* βII-turn structure that lacks the usual *i*+3 to *i* hydrogen bond, together with a γ-turn centred at the $c_3$diPhe residue. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: phenylalanine cyclopropane analogues; X-ray diffraction; crystal structures; β-turn; γ-turn.

Structure–activity relationship studies in bioactive peptides pursue the understanding of the biological processes at the molecular level with the aim to establish their bioactive conformation and thereafter to develop peptide analogues with improved pharmacological properties. In this context, the side chain moieties deserve special attention since they are directly involved in peptide–receptor recognition phenomena and determine biological specificity. Moreover, some side substituents may modulate to a certain extent the backbone conformation due either to steric factors or to specific side chain–main chain interactions.[1–5]

We have been working on the study of the conformational tendencies of 1-amino-2-phenylcycloalkanecarboxylic acids (c_nPhe, Fig. 1) when incorporated into model dipeptides RCO-L-Pro-c_nPhe-NHR′.[6–9] In particular, we have reported[6,7] that the four stereoisomers of the phenylalanine cyclopropane analogue (c_3Phe, Fig. 1) exhibit different preferences to occupy the *i*+2 position of a βI- or a βII-turn, depending both on the side chain orientation and on the environment. In order to further investigate the conformational behaviour of phenylalanine cyclopropane surrogates, we have now undertaken the study of ^{t}BuCO-L-Pro-$c_3$diPhe-NH^{i}Pr where $c_3$diPhe stands

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for (2*S*,3*S*)- and (2*R*,3*R*)-1-amino-2,3-diphenylcyclopropanecarboxylic acid (Fig. 1). Recently, both enantiomers of this amino acid have been shown to impart very different backbone conformations to a midsize peptide.[10]

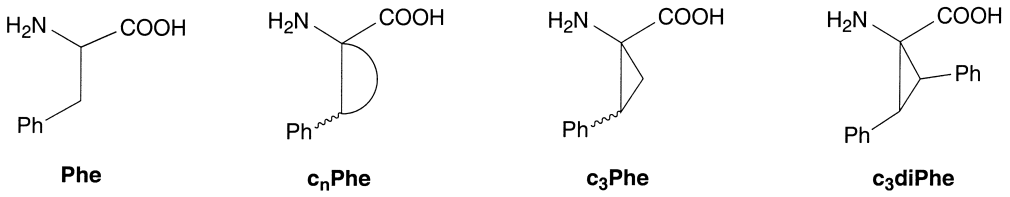

Figure 1. Structure of cyclic constrained analogues of phenylalanine

Racemic $c_3$diPhe was prepared by 1,3-dipolar cycloaddition of phenyldiazomethane to (*Z*)-2-phenyl-4-benzylidene-5(4*H*)-oxazolone.[11] Oxazolone ring opening with methanol and further transformations of the benzamido and methyl ester groups provided **1** in good yield. Racemic **1** was coupled to Boc-Pro-OH (*N-tert*-butyloxycarbonyl-L-proline) by the mixed anhydride method using isobutyl chloroformate as the coupling agent[12] (Fig. 2). Diastereomeric dipeptides **2a** and **2b** were separated by column chromatography on silica gel. The Boc group was removed with trifluoroacetic acid and the proline amino group was acylated with pivaloyl chloride (pivaloyl = *tert*-butylcarbonyl, Piv) to afford enantiomerically pure **3a** and **3b**.

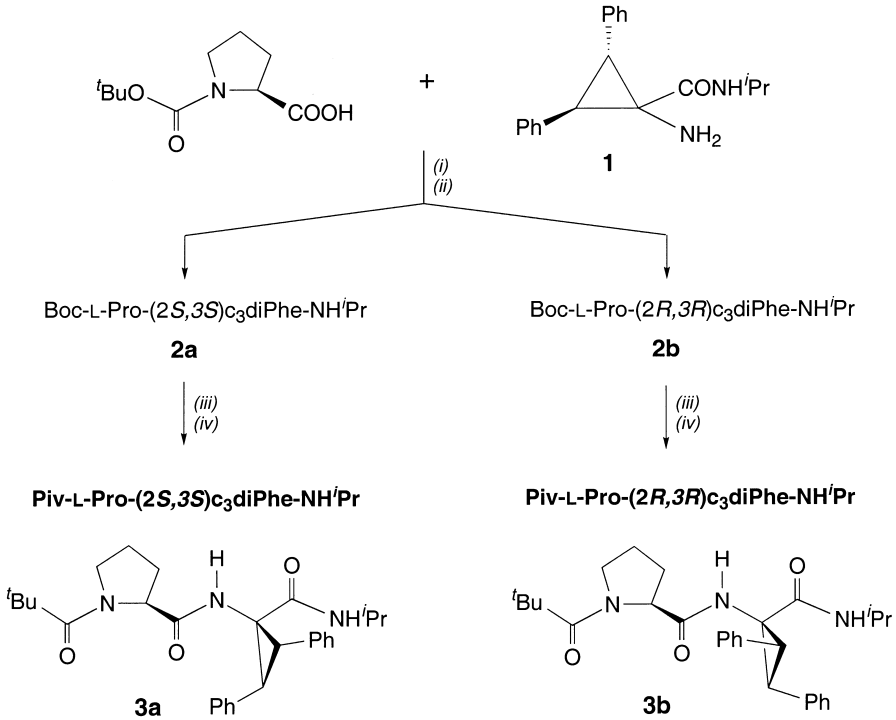

Figure 2. (i) ^{i}BuOCOCl/*N*-methylmorpholine/THF/–15°C; (ii) column chromatography CH_2Cl_2:AcOEt, 9:1; (iii) CF_3COOH/CH_2Cl_2/rt; (iv) ^{t}BuCOCl/*N*-methylmorpholine/$CHCl_3$/0°C

Both **3a** and **3b** yielded single crystals, which were subjected to X-ray diffraction analysis.† In this way, and taking L-proline as a reference, the absolute configuration of the $c_3$diPhe residue was established as (2*S*,3*S*) in **3a** and (2*R*,3*R*) in **3b** (Fig. 3).

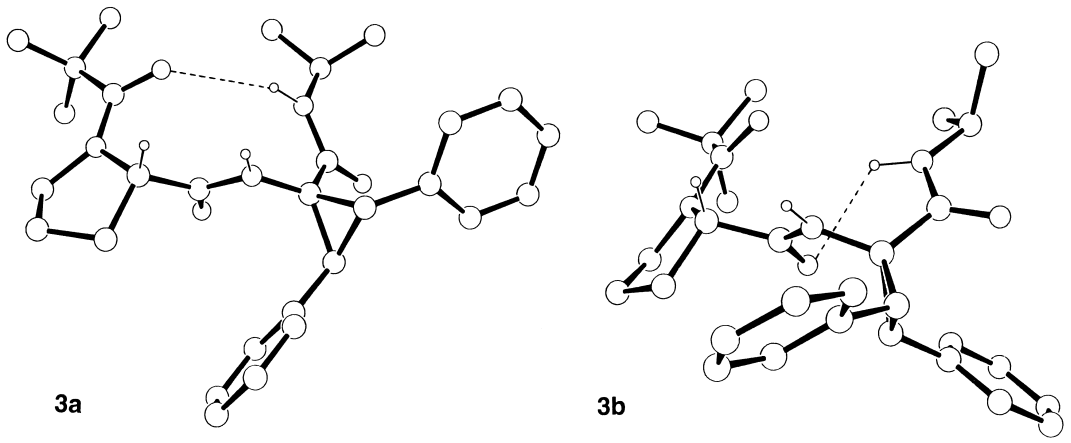

Figure 3. Crystal molecular structures of **3a** (βII-turn) and **3b** (*open* βII-turn and γ-turn). Most hydrogen atoms are omitted for clarity. The intramolecular hydrogen bonds are represented as dashed lines

In the crystal state, dipeptide **3a** assumes a β-folded conformation[13] stabilized by an intramolecular *NH*(^{i}Pr) to Piv-*C′O* hydrogen bond, closing a ten-membered pseudocycle (Fig. 3). The N···O distance of 3.37 Å is at the upper limit for hydrogen bonding.[14] The orientation of the middle amide group, with the proline C=O and C^{α}–H bonds in an *anti* disposition,‡ corresponds to the type II β-turn.[13] This result was not unexpected since, in the solid state, the βII form has proven to be the preferred conformation for most L-Pro-Xaa sequences.[5,7,13,15]

In contrast, the crystal structure of the (2*R*,3*R*)$c_3$diPhe-containing dipeptide exhibits some striking features (Fig. 3). Thus, **3b** adopts a distorted γ-turn[13,16] around the $c_3$diPhe residue, with Pro-*C′O* and *NH*(^{i}Pr) intramolecularly hydrogen-bonded (N···O distance = 3.25 Å). The γ-turn or the C7 structure is less widely distributed than the β-turn disposition and has only rarely been observed in crystallized small linear peptides.[13,15,17–19] The molecule is globally β-folded, the β-turn being of the II type,§ but the *i*+3 to *i* hydrogen bond generally observed in β-folded structures is absent. The distance between the pivaloyl O and the isopropylamide N of 3.74 Å is indeed inappropriate to allow hydrogen bonding, as is the unfavourable alignment of the C=O and N–H bonds. In spite of this, the distance between the extreme C_i^{α} and C_{i+3}^{α} carbons (6.20 Å) is inferior to 7 Å, thus satisfying the requirement generally accepted to be considered as a β-turn.[20,21] It may be assumed that the global β-folded structure observed for **3b** is due to the proline residue, which is known to adopt with high preference the disposition found in position *i*+1 of a β-turn.[22]

† Single crystals of **3a** were grown by slow evaporation of a methanol solution: monoclinic, $P2_1$; $a = 5.995(3)$ Å, $b = 10.763(4)$ Å, $c = 21.832(10)$ Å, $\beta = 92.13(3)^\circ$; $Z = 2$; $d_{calc.} = 1.12$ g/cm^{-3}; 5162 unique reflections; $R = 0.0621$. Single crystals of **3b** were grown by slow evaporation of a dichloromethane/ethyl acetate solution: orthorhombic, $P2_12_12_1$; $a = 12.085(6)$ Å, $b = 13.827(7)$ Å, $c = 17.024(10)$ Å; $Z = 4$; $d_{calc.} = 1.11$ g/cm^{-3}; 5293 unique reflections; $R = 0.0663$.

‡ Torsion angles: Pro-ϕ, $\psi = -59^\circ$, 140°; $c_3$diPhe-ϕ, $\psi = 67^\circ$, 25°.

§ Torsion angles: Pro-ϕ, $\psi = -60^\circ$, 154°; $c_3$diPhe-ϕ, $\psi = 86^\circ$, -20°.

These results suggest that (2*R*,3*R*)$c_3$diPhe may have a strong tendency to induce γ-turn conformations. Studies in solution are in progress in order to discern whether the behaviour observed in the solid state is an intrinsic characteristic of this residue or rather a consequence of the crystal packing.

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