Pergamon

Tetrahedron Letters 39 (1998) 7841–7844

TETRAHEDRON LETTERS

β-Turn Modulation by the Cyclohexane Analogues of Phenylalanine

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Received 26 June 1998; accepted 17 August 1998

Abstract: *X-ray diffraction experiments have evidenced that the orientation of the aromatic side chain determine the folding tendencies of ^{t}BuCO-Pro-c_6Phe-NH^{i}Pr, where c_6Phe denotes the (S,S) and (R,R) cyclohexane analogues of phenylalanine. In the solid state, both dipeptides are β-folded, the β-turn type being dictated by the stereochemistry of the cyclohexane ring.*

The introduction of α,α-disubstituted amino acids into peptide chains reduces the conformational freedom of the backbone, providing a powerful means of restricting their inherent flexibility. The simplest member of this familly of constrained residues, the α-aminoisobutyric acid (Aib), strongly stabilizes helical structures.[1,2] In contrast, longer linear alkyl chains favour fully extended conformations,[1] whereas their homologous cyclic derivatives (Ac_nc, 1-aminocycloalkanecarboxylic acids) exhibit a marked preference for folded structures.[1,3]

The structural versatility of symmetrically α,α-disubstituted glycines has been extensively explored but, due to synthetic difficulties, chiral residues have been much less investigated. We have recently reported the β-turn preferences of model dipeptides containing the cyclopropane analogues of phenylalanine.[4] The observed dependence of the β-turn type on the side chain orientation prompted us to evaluate the effect of the ring size on the folding mode. To this end, we undertook the synthesis and the structural analysis of Piv-Pro-c_6Phe-NH^{i}Pr, where c_6Phe stands for (*S,S*)- and (*R,R*)-1-amino-2-phenylcyclohexanecarboxylic acid. Although the unsubstituted 1-aminocyclohexanecarboxylic acid (Ac_6c) has been extensively studied,[1,3a,5] this is, to the best of our knowledge, the first example of peptides incorporating the cyclohexane analogues of phenylalanine.

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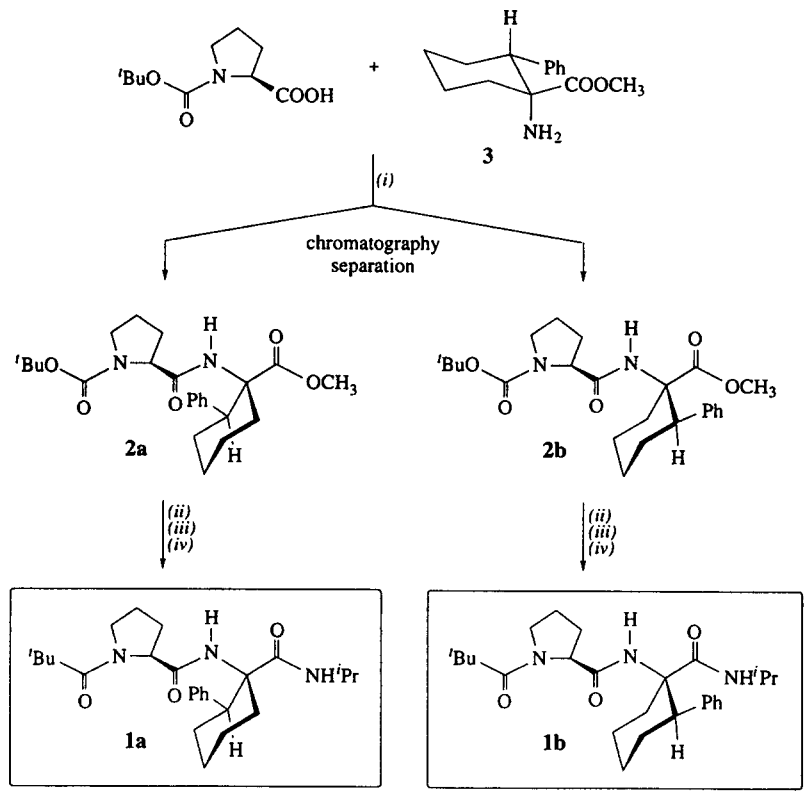
0040-4039/98/$ - see front matter
PII: S0040-4039(98)01723-7

Racemic *cis* 1-amino-2-phenylcyclohexanecarboxylic acid was prepared by Diels-Alder reaction between (Z)-2-phenyl-4-benzylidene-5(4H)-oxazolone and 1,3-butadiene according to our previously reported methodology.[6] Methyl ester **3**, obtained by diazomethane addition on the amino acid hydrochloride, was coupled to N-*tert*-butyloxycarbonyl-*L*-proline by the classical mixed anhydride method using isobutyl chloroformate as coupling agent (Scheme 1). Diastereomeric dipeptides **2a** and **2b** were separated by column chromatography on silicagel. Subsequent treatment with isopropylamine in the presence of $AlMe_3$ allowed the transformation of methyl esters into the corresponding amides.[7] After Boc elimination with trifluoroacetic acid, acylation with pivalic anhydride afforded enantiomerically pure **1a** and **1b**.



Scheme 1.[8] (*i*) ^{t}BuOCOCl / NMM / CH_2Cl_2 / -15°C; (*ii*) ^{i}PrNH$_2$ / $AlMe_3$ / toluene; (*iii*) TFA / CH_2Cl_2; (*iv*) Piv_2O / DMAP / NEt_3 / CH_2Cl_2.

The absolute configurations of the c_6Phe residues in **1a** and **1b** were assigned on the basis of X-ray diffraction experiments.[9] In the crystal state, both dipeptides exhibited a β-folded[10] conformation stabilized by a NH(^{i}Pr) to CO(^{t}Bu) intramolecular hydrogen bond (N···O = 3.04 and 3.09 Å in **1a** and 3.35 Å in **1b**), closing a ten-membered pseudocycle. However, the two structures differed in the orientation of the middle amide group. Thus, **1a** accommodated a type I β-turn,[11] characterized by the *syn* disposition of the proline C=O and $C^{\alpha}H$ bonds, whereas **1b** adopted a type II β-turn,[12] with the above two bonds *anti*-orientated (Figure 1).

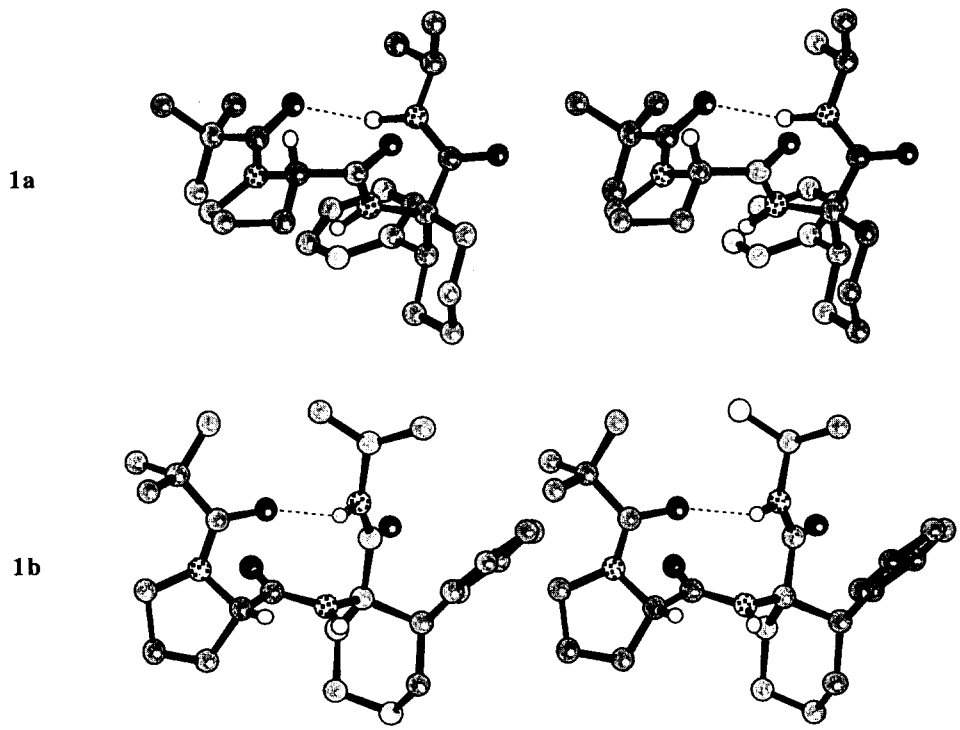


Figure 1. Stereoviews of the crystal molecular structures of **1a** (molecule A, type I β-turn) and **1b** (type II β-turn). The intramolecular hydrogen bonds are represented as dashed lines.

The disposition of the amide bond is probably governed by the fact that the π-orbitals of the rigidly oriented c_6Phe aromatic ring exert an attractive interaction with the c_3Phe N-H bond and a repulsive interaction with the Pro carbonyl. Both effects tend to favour the type I β-turn for **1a**, where the middle amide bond is free from intermolecular hydrogen bonding, and the type II β-turn for **1b**, where the c_6Phe N-H bond interacts with the c_6Phe carbonyl of a neighbouring molecule (N···O = 3.06 Å). At variance, the Piv-*L*-Pro-*L*-Phe-NHMe and Piv-*L*-Pro-*D*-Phe-NHMe dipeptides, where the phenyl ring may rotate with reference to the peptide backbone, have been shown to adopt the same βII-folding mode in the solid state.[13,14]

The type I and II β-turns found in the crystal molecular structures of **1a** and **1b**, respectively, where the cyclohexane ring rigidly holds the aromatic side chain, evidences the value of the c_6Phe residues in modulating the β-folding mode and therefore in the design of peptide analogues with predetermined conformational features. Studies to evaluate whether the folded structures observed in the solid state are maintained in solution are currently in progress.

***Acknowledgements**: The authors thank Dr C. Didierjean for technical assistance. Financial support from Ministerio de Educación y Cultura (project PB94-0578 and acción integrada HF-9746) and Ministère des Affaires Etrangères (action intégrée 97039) is gratefully acknowledged.*

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8. The following abbreviations are used: Boc, *tert*-butyloxycarbonyl; ^{i}Bu, isobutyl; ^{t}Bu, *tert*-butyl; ^{i}Pr, isopropyl; Pro, *L*-proline; c_6Phe, 1-amino-2-phenylcyclohexanecarboxylic acid; NMM, N-methylmorpholine; Piv, pivaloyl (*tert*-butylcarbonyl); DMAP, 4-dimethylaminopyridine.
9. Single crystals of **1a** (dihydrate) and **1b** were grown by slow evaporation of a cyclohexane/diethyl ether solution. **1a**: P1; a = 10.165(2) Å, b = 10.536(2) Å, c = 12.664(1) Å, α = 86.27(1)°, β = 78.62(1)°, γ = 87.52(1)°; Z = 2 (2 independent molecules per asymmetric unit); $d_{calc.}$ = 1.15 g.cm^{-3}; 4688 reflections; R = 0.039. **1b**: $P22_12_1$; a = 17.166(2) Å, b = 23.613(3) Å, c = 6.347(1) Å; Z = 4; $d_{calc.}$ = 1.14 g.cm^{-3}; 2514 reflections; R = 0.039.
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11. Torsional angles: Pro-ϕ,ψ = -56°, -38° (molecule A) and -69°, -28° (molecule B); c_6Phe-ϕ,ψ = -62°, -17° (molecule A) and -81°, -5° (molecule B).
12. Torsional angles: Pro-ϕ,ψ = -61°, 144°; c_6Phe-ϕ,ψ = 66°, 19°.
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