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Prevalence of Eight-Membered Hydrogen-Bonded Rings in Some Bis(cyclobutane) β-Dipeptides Including Residues with Trans Stereochemistry†

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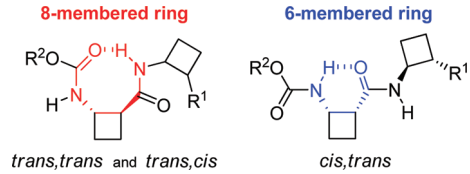
ABSTRACT



Three new bis(cyclobutane) β-dipeptides have been synthesized from appropriate derivatives of *cis*- and *trans*-2-aminocyclobutane-1-carboxylic acid, respectively. The predominance of eight-membered hydrogen-bonded rings has been manifested for (*trans,trans*)- and (*trans,cis*)-β-dipeptides while the formation of six-membered rings is preferred for the (*cis,trans*)- β-dipeptide similarly to the previously described (*cis,cis*)-diastereomer.

β-Peptides offer unique possibilities to fold, prompted by the formation of intramolecular hydrogen bonds leading to helices, strands, or sheets as the most usual conformations. These defined secondary structures are often responsible for the biological activities found in oligomers containing β-amino acid residues.[1] Sometimes, secondary structures coexist with substructures resulting from interresidual hydrogen-bonds between N*H*(*i*) and C*O*(*i* + 1), (*i*) and (*i* + 1) being two consecutive residues in the peptide backbone. This confers high rigidity on these oligomers.[1] For this reason, the investigation of hydrogen-bonding in small peptides is crucial to understand complex conformations in larger oligomers.

Carbocycle[1] and heterocycle[2] $\beta^{2,3}$-disubstituted β-peptides are particularly prone to adopt well-defined conformations in solution. However, besides several examples on 12- and 14-helical-foldings,[1,3] there are only a few instances on eight-helices.[4−7] An eight-membered ring with hydrogen-bonding between next neighbors has been described as the characteristic secondary structural motif in β-oligopeptides consisting of 1-(aminomethyl)-cyclopropanecarboxylic acid. These hydrogen-bonded rings arrange in a ribbon-type secondary structure in solution.[5] Moreover, the formation of consecutive eight-membered hydrogen-bonded ring helices (8-helix) has

† Dedicated to Professor Josep Font on the occasion of his 70th birthday.
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(1) For recent reviews, see: (a) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chemistry & Biodiversity* **2004**, *1*, 1111. (b) Gelman, M. A.; Gellman, S. H. In *Enantioselective Synthesis of β-Amino Acids,* 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; John Wiley and Sons: New York, 2005; pp 527−585. (c) Fülöp, F.; Martinek, T. A.; Tóth, G. K. *Chem. Soc. Rev.* **2006**, *35*, 323. (d) Seebach, D.; Hook, D. F.; Glattli, A. *Biopolymers* **2006**, *84*, 23. (e) Le Grel, P.; Guichard, P. In *Foldamers: Structure, Properties, and Applications*; Hecht, S., Huc, I., Eds.; Wiley-VCH: New York, 2007; pp 35−74. (f) Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366. (g) Horne, W. S.; Gellman, S. H. *Acc. Chem. Res.* **2008**, *41*, 1399.

(2) See, for instance: Claridge, T. D. W.; Goodman, J. M.; Moreno, A.; Angus, D.; Barker, S. F.; Taillefumier, C.; Watterson, M. P.; Fleet, G. W. *Tetrahedron Lett.* **2001**, *42*, 4251.

(3) Izquierdo, S.; Kogan, M. J.; Parella, T.; Moglioni, A.; Branchadell, V.; Giralt, E.; Ortuño, R. M. *J. Org. Chem.* **2004**, *69*, 5093.

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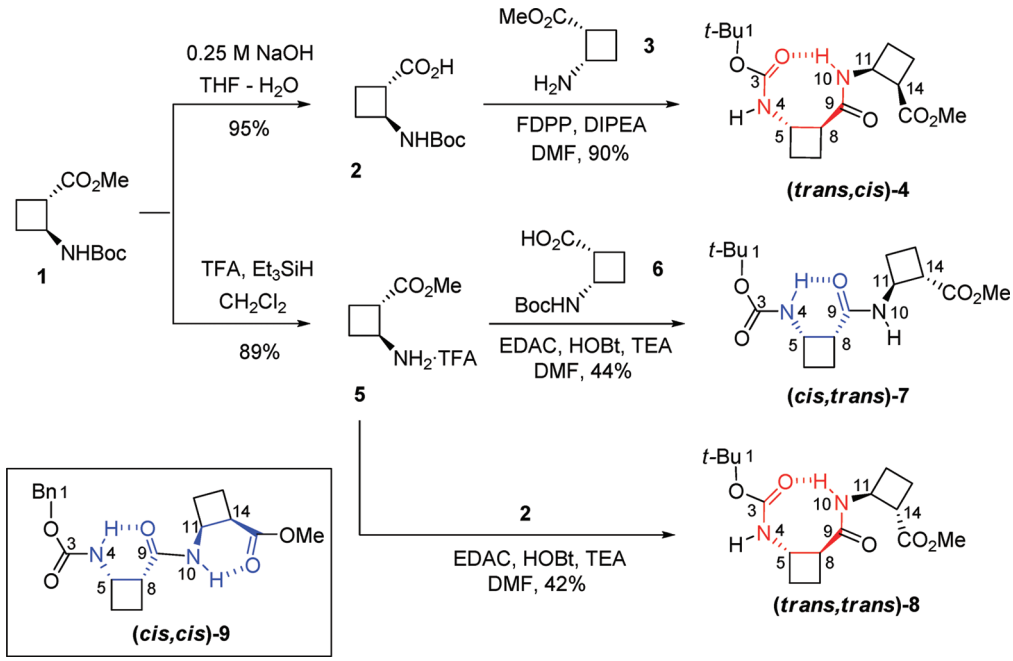
Scheme 1. Synthesis of β-Dipeptides **4**, **7**, and **8**. Structure of Peptide **9**



been described for oxanorbornene β-peptides,[6] and for peptides derived from nucleoside β-amino acids.[7] In the last two cases, a conformationally constrained ring and $\beta^{2,3}$-trans-stereochemistry is a common structural feature which accounts for the propensity to fold into a 8-helix.

We have recently described the formation of intraresidue hydrogen bonds affording cis-fused [4.2.0]octane structural units in β-dipeptides made up by monomers derived from *cis*-2-aminocyclobutane-1-carboxylic acid.[8] One example of these β-dipeptides is compound (*cis,cis*)-**9** in Scheme 1. This substructure is retained in a related tetramer, which adopts a strand-mimicking secondary structure in solution.[9]

In this Letter we report on our preliminary results on the synthesis and structural study of a new family of cyclobutane β-dipeptides. They consist of two monomers of trans stereochemistry, (*trans,trans*)-**8,** or one cis- and one trans-monomer, (*cis,trans*)-**7** and (*trans,cis*)-**4** (Scheme 1). The secondary structures of these compounds in solution have been investigated and compared with (*cis,cis*)-**9**.[8] The combined results from NMR experiments and theoretical calculations show the predominance of an 8- over a 6-membered hydrogen-bonded structure for diastereomers **4** and **8**.

Compounds **4**, **7**, and **8** were synthesized as described in Scheme 1. Trans-derivative **1** was prepared by epimerization of the cis-isomer as previously described in the literature.[10] Monoprotected cis-intermediates **3** and **6** had been already prepared in our laboratory.[8,11] Removal of the *N*-Boc protection in **1** under treatment with TFA and triethylsilane afforded amine **5** in 89% yield. Amine **5** was coupled with acid **6** in the presence of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDAC) as a dehydrating agent and hydroxybenzotriazole (HOBt) as a catalyst providing **7** in 44% yield. Similarly, acid **2** was reacted with amine **5** to give **8** in 42% yield. Alternatively, saponification of the methyl ester in **1** with diluted NaOH provided acid **2** in 95% yield. Subsequent coupling of acid **2** with amine **3** in the presence of pentafluorophenyl diphenylphosphinate (FDPP) afforded **4** in 90% yield showing the efficiency of FDPP in peptide coupling reactions.

The three new β-dipeptides **4**, **7**, and **8** were fully characterized and their secondary structures in solution were investigated by using experimental techniques and molecular modeling (see the Supporting Information). The most relevant features are listed in Table 1 where one can observe that the same trends are followed by **4** and **8.** Thus, a complete set of standard 1D and 2D NMR experiments was done for each β-dipeptide. The high-resolution ^{1}H NMR spectra in $CDCl_3$ for **4** and **8** exhibit a high deshielded chemical shift (8.28−8.47 ppm) for the NH_{10} proton (compare with the 5.90 ppm value found for **7**). That suggests

(4) (a) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 1054. (b) Winkler, J. D.; Piatnitski, E. L.; Mehlmann, J.; Kasparec, J.; Axelsen, P. H. *Angew. Chem. Int. Ed* **2001**, *40*, 743. (c) Gademann, K.; Häne, A.; Rueping, M.; Jaun, B.; Seebach, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 1534. (d) Li, X.; Yang, D. *Chem. Commun.* **2006**, 3367, and references therein.

(5) Abele, S.; Seiler, P.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1559.

(6) Doerksen, R. J.; Chen, B.; Yuan, J.; Winkler, J. D.; Klein, M. L. *Chem. Commun.* **2003**, 2534.

(7) Threlfall, R.; Davies, A.; Howartz, N. M.; Fisher, J.; Cosstick, R. *Chem. Commun.* **2008**, 585.

(8) Izquierdo, S.; Rúa, F.; Sbai, A.; Parella, T.; Álvarez-Larena, Á.; Branchadell, V.; Ortuño, R. M *J. Org. Chem.* **2005**, *70*, 7963.

(9) Rúa, F.; Boussert, S.; Parella, T.; Díez-Pérez, I.; Branchadell, V.; Giralt, E.; Ortuño, R. M. *Org. Lett.* **2007**, *9*, 3643.

(10) Fernandes, C.; Gauzy, C.; Yang, Y.; Roy, O.; Pereira, E.; Faure, S.; Aitken, D. J. *Synthesis*, **2007**, 2222.

(11) Martín-Vilà, M.; Muray, E.; Aguado, G. P.; Álvarez-Larena, Á.; Branchadell, V.; Minguillón, C.; Giralt, E.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2000**, *11*, 3569.

Table 1. Significant Experimental NMR and Calculated Parameters for β-Dipeptides **4**, **7**−**9**

	δ^a	δ^a	exptl δ		calcd δ		qualitative interresidue NOEs			calcd distance[b]		calcd hydrogen-bond length[b]				
dipeptide	NH_{10}	NH_4	$NH_{10}-\delta$	NH_4	$NH_{10}-\delta$	NH_4	$H_{10}-H_5$	/	$H_{10}-H_8$	$H_{10}-H_5$	$H_{10}-H_8$					
(*trans,cis*)-**4**	8.28	4.88	3.40		3.81		strong	/	weak	2.53	2.96	CO_3	−	NH_{10}	1.93
(*trans,trans*)-**8**	8.47	4.92	3.55		3.84		strong	/	weak	2.47	3.02	CO_3	−	NH_{10}	1.93
(*cis,trans*)-**7**	5.90	5.25	0.65		0.69		weak	/	strong	4.51	2.23	CO_9	−	NH_4	2.24
(*cis,cis*)-**9**	6.41[c]	5.44[c]	0.97[c]		--		weak[c]	/	strong[c]	4.51[c]	2.23[c]	CO_9	−	NH_4	2.22[c]

[a] In ppm, from $CDCl_3$ solutions. [b] In angstroms. [c] Reference 8.

that the NH_{10} proton is implied in a strong hydrogen-bond in those β-dipeptides.

Some additional NMR experiments were performed to rule out the possibility of N−*H* hydrogen-bonds to solvent and to exclude the existence of intermolecular aggregates Thus, the chemical shift of NH_{10} was not concentration dependent in a range of 60−5 mM in $CDCl_3$. Moreover, when methanol-d_4 was added to both concentrate and dilute respective solutions of **4** and **8**, in the concentrate sample, the NH_4 signal rapidly disappeared while the NH_{10} signal remained. Analogous behaviors were found in the dilute sample. These results pointed out the involvement of NH_{10} in an intramolecular hydrogen bonding. 1D selective NOESY(EXSY) experiments also led to the same conclusion (see Figures S21−S24 in the Supporting Information for details).

IR spectroscopy reinforces these findings. Two bands of comparable intensity at about 3447 and 3280 cm^{-1} corresponding to free and associated N−H stretching, respectively, were observed in the spectra of **4** and **8** in dilute chloroform solutions (ca. 5 mM).[5]

Analogously, the same reasoning applies to explain the NH_4 chemical-shift behavior. Thus, a more deshielded position is found for the NH_4 proton of **7** and **9**[8] (5.25−5.44 ppm) with respect to the same proton in **4** and **8** (4.88−4.92 ppm). That indicates that the formation of the hydrogen bond through NH_4 is only present in β-dipeptides with 5,8-*cis* stereochemistry.

Moreover, by means of 1D selective TOCSY experiments, the isolated selection of NH_{10} and NH_4 protons and posterior magnetization transfer to the whole spin system permits the editing of the ^{1}H NMR spectrum of each residue into two separated subspectra. Furthermore, the spatial disposition between residues was disclosed by performing a 1D selective NOE experiment on H_{10} in every case. Figure 1 shows, as an example, the experiments performed on **8**.

Interestingly, for all β-dipeptides herein studied, two interresidue NOE contacts are observed between the NH_{10} proton and H_5/H_8 protons (Table 1). However, the strength of the NOE observed clearly depends upon the adopted spatial arrangement. In **4** and **8**, strong interresidue NOE contacts are observed between NH_{10} and H_5 and weak ones are detected between NH_{10} and H_8 (Table 1).

Opposite results are obtained for **7**, showing a weak interresidue NOE contact between NH_{10} and H_5 while a stronger one is observed between NH_{10} and H_8. A similar result had been obtained for **9**.[8]

Theoretical calculations at the B3LYP/6-31G (d) level of theory nicely support these experimental data. Figure 2 shows the calculated structures for the most stable conformers of **7** and **8**.

For these structures, the calculated difference between the ^{1}H NMR shifts of NH_4 and NH_{10} compares fairly with the experimental data as observed in Table 1. Moreover, the electronic CD spectra calculated for these compounds (gas phase) predict bands that are in qualitative agreement with the experimental spectra in methanol (see the Supporting Information).

Table 1 shows the interatomic distances between NH_{10} proton and H_5/H_8 calculated for the most stable conformers of the four β-dipeptides considered, which are in very good accordance with the observed NOE contacts (Figure 2).

Furthermore, the calculated CO_3-NH_{10} distance for **4** and **8** (1.9 Å) is shorter than the calculated CO_9-NH_4 distance

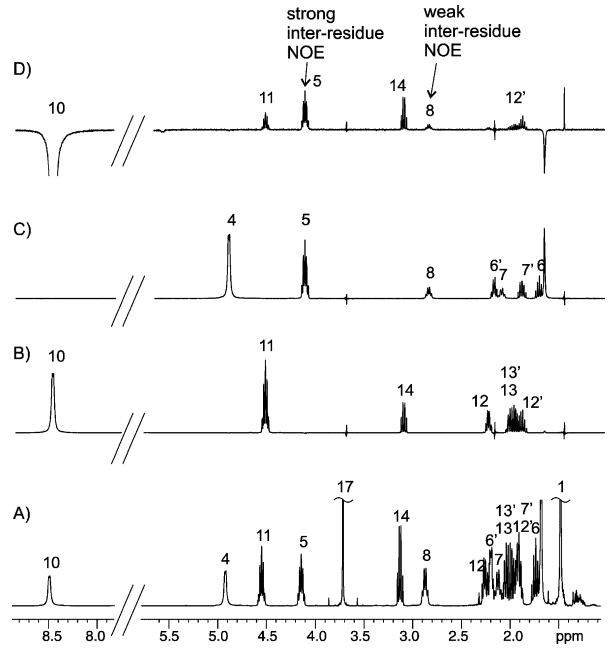


Figure 1. (A) ^{1}H NMR spectrum of **8** recorded at 500 MHz in $CDCl_3$. (B) Selective 1D TOCSY experiment selecting NH_{10} proton. Magnetization is transferred to the whole spin system by using 60 ms mixing time. (C) Selective 1D TOCSY experiment selecting NH_4 proton. Magnetization is transferred to the whole spin system by using 60 ms mixing time. (D) Selective 1D NOE experiment on NH_{10} proton (NOE mixing time was set to 500 ms).

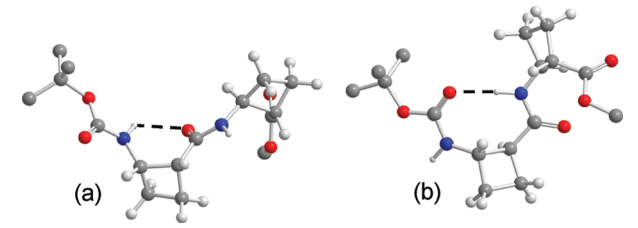


Figure 2. Structures of **7** (A) and **8** (B) optimized at the B3LYP/6-31G(d) level of calculation. Methyl hydrogen atoms have been omitted for clarity.

for **7** and **9** (2.2 Å). These data suggest an eight-membered hydrogen-bonding for β-dipeptides **4** and **8**. The existence of a six-membered hydrogen-bonded structure is predicted for **7**, similarly to the previously described **9**.[8]

To summarize, from the combined results obtained by means of experimental techniques and theoretical calculations, we can state the prevalent secondary structures for the β-dipeptides studied. For **4** and **8,** an eight-membered cycle through a hydrogen bond between the NH_{10} proton and CO_3 is established. Differently, in the 5,8-*cis*-β-dipetide **7**, as well as in **9**,[8] a six-membered hydrogen-bonded ring conformation involving the NH_4 proton and CO_9 is favored.

Thus, in conclusion, we have reported herein on a novel family of β-oligomers made, totally or in part, of (*trans*)-2-aminocyclobutanecarboxylic acid residues. In these β-dipeptides, the presence of rigid cyclobutane rings together with 5,8-*trans* stereochemistry ($\beta^{2,3}$-*trans*), through the constraints it imposes on the torsions around C_5-C_8, accounts for the formation of eight-membered hydrogen-bonded rings. This structural motif prevails over six-membered rings, a characteristic of the cis series.[8,9]

It is noteworthy that the cis/trans stereochemistry in the *N*-Boc cyclobutane residue (5,8-relative configuration) governs the conformational bias of these β-dipeptides. Therefore, the combined or alternative use of cyclobutane residues with cis and trans stereochemistry, respectively, can be a good tool for the design of secondary structures in small β-peptides. In larger oligomers, this would give rise to helical structures not accessible from carbocyclic cyclopentane and cyclohexane derivatives.[1] Active investigations are in progress to confirm this hypothesis.

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Supporting Information Available: Synthetic procedures and full characterization of **4**, **7**, and **8**, detailed NMR experiments, and theoretical studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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