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Conformational Study of Structurally Constrained 18-Membered Cyclic Peptide Containing N,N′-Ethylene-Bridged-(S)-Phenylalanyl-(S)-Phenylalanine

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CONFORMATIONAL STUDY OF STRUCTURALLY CONSTRAINED 18-MEMBERED CYCLIC PEPTIDE CONTAINING *N,N'*-ETHYLENE-BRIDGED-(*S*)-PHENYLALANYL-(*S*)-PHENYLALANINE

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Abstract The conformation of cyclo[(2*S*,3'*S*)-2-(3'-benzyl-2'-oxopiperazin-1'-yl)-3-phenyl-propanoyl-glycyl]$_2$ crystallized with two water molecules ($C_{44}H_{46}N_6O_6 \cdot 2H_2O$) is compared with its solution structure and those of cyclo[(2*S*,3'*S*)-2-(3'-methyl-2'-oxopiperazin-1'-yl)-propanoyl-glycyl]$_2$.

INTRODUCTION

Cyclic pseudopeptide containing *N,N'*-ethylene-bridged-dipeptides is a new concept of a novel host molecule in cyclic peptides.[1] These pseudopeptides can bind to metal and ammonium cations, and 27- and 36-membered pseudopeptides in particular exhibit effective transport properties of amino acid ester salts through organic liquid membrane.[2] The *N,N'*-bridged-ethylenes provide simple conformations for macrocyclic peptides. To obtain more detailed information on their cyclic conformation requires a the structural examination in solid state. This paper describes the conformation of cyclo [(2*S*,3'*S*)-2-(3'-benzyl-2'-oxopiperazin-1'-yl)-3-phenyl-propanoyl-glycyl]$_2$ **1** in solid state and solution in comparison with those of cyclo[(2*S*,3'*S*)-2-(3'-methyl-2'-oxopiperazin-1'-yl)-propanoyl-glycyl]$_2$ **2**.[3]

SOLUTION CONFORMATION OF 1

^{1}H NMR measurement of **1** at room temperature gives broad signals in several solvents such as dimethyl sulfoxide-d_6, methanol-d_4 and acetonitrile-d_3. These signals become

sharper as the temperature is lowered. Figure 1 shows ^{1}H NMR spectra of **1** in CD_3CN, suggesting that **1** is primarily in C_2-symmetry and that other minor conformers exist too. The chemical shifts of Phe αH (5.43 and 4.70 ppm in Table I) of major **1** at -40°C show that the conformation of all peptide bonds in this cyclic molecule is trans referred to our previous data.[1] The sum of vicinal constants of glycyl $HNC^{\alpha}H_2$ protons (H14A and B) is 11.0 Hz and the glycine $H\text{-}C^{\alpha}\text{-}H$ geminal constant is 13.7 Hz, suggesting the torsion angles ϕ^5 and ψ^5 are +130° and -120°, respectively, for the same reason as for the solution conformation of **2**. Thus, the difference of side chain in the *N,N'*-ethylene-bridged-dipeptides cannot change the conformation of 18-membered ring.

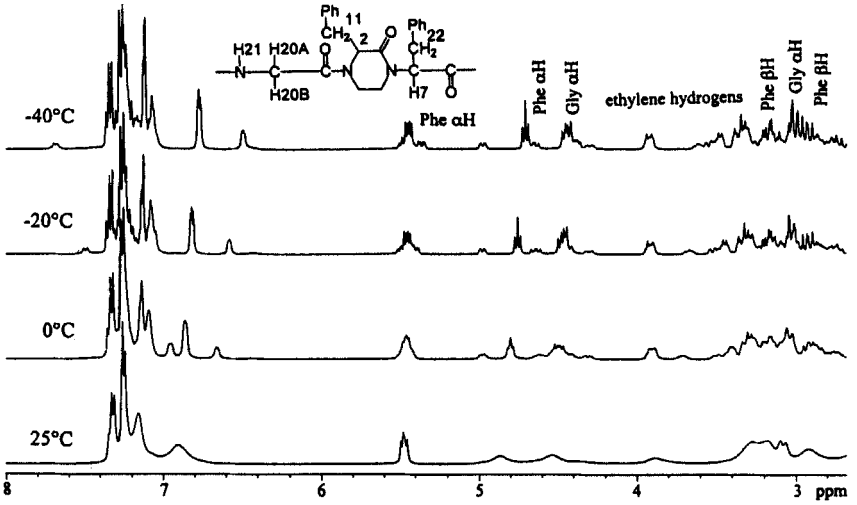


FIGURE 1 ^{1}H NMR spectra of **1** in CD_3CN.

TABLE I ^{1}H NMR data of major **1** in CD_3CN at -40°C.[a]

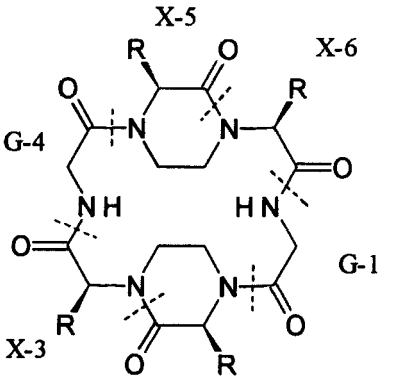
Chemical shift / ppm, (coupling constant / Hz)								
H21	H20A	H20B	Phe αH (H2 or H7)		Phe βH (H11A, H11B, H22A or H22B)			
7.16 (br)	4.44 (dd, 13.4, 7.9)	3.00 (dd, 14.0, 3.1)	5.43 (dd, 11.0, 5.5)	4.70 (t, 7.0)	3.17 (dd, 14.3, 5.2)	2.92 (dd, 14.7, 11.0)	2.51 (dd, 13.7, 7.0)	2.42 (*)

[a] ^{1}H NMR spectra of **1** was obtained by Jeol GX-400 under the conditions of 1.9×10^{-2} mol dm^{-3} in CD_3CN at -40°C.

* Overlapped signal

COMPARISON OF CONFORMATION OF 1 WITH THAT OF 2

We obtained crystals of cyclic hexa-pseudopeptide **1**.[4] X-ray crystallographic study has shown that the two piperazin-2-one rings are perpendicular to the 18-membered ring thus producing a molecular cavity, and that a water molecule is located in this cavity and interacts with the macrocyclic ring. The conformation of only one peptide bond on the *N*-terminal of *N,N'*-ethylene-briged-dipeptide is cis, those of all others are trans. Table II shows the torsion angles of cyclic



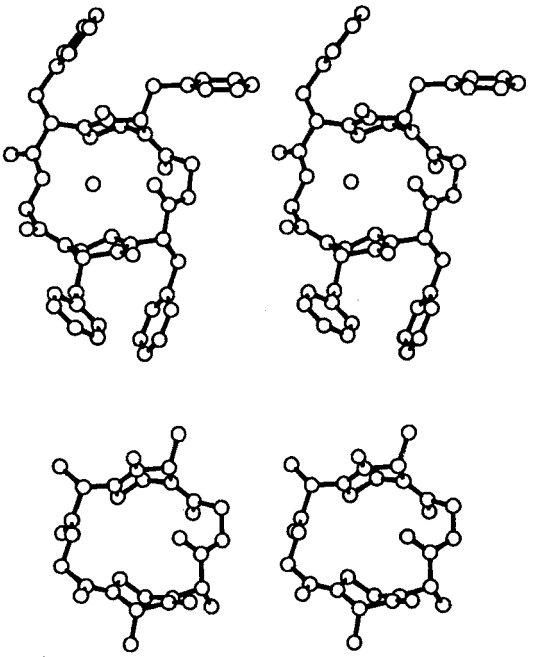


FIGURE 1 Stereoview of macrocyclic pseudopeptides **1** (above) and **2** (below).

pseudopeptides **1** and **2**, indicating similar results between them except for the ϕ angle on the G-4. This difference is induced by the hydrogen-bonded water molecule in **1**, that is to say, amide group participating in the hydrogen bond to water molecule leans slightly toward the center of the ring . These results and the studies in solution lead to the conclusion that the overall conformation in 18-membered ring containing *N,N'*-ethylene-bridged-dipeptides is not influenced by the side chains on *N,N'*-ethylene-bridged-dipeptides.

TABLE II Torsion angles of cyclic skeleton.

	1		**2**	
	ϕ	φ	ϕ	φ
G-1	-80.9(5)	116.4(4)	-66.6(7)	118.2(5)
X-2	-130.8(4)	-10.7(5)	-135.6(5)	1.5(7)
X-3	-128.5(3)	62.1(4)	-131.4(5)	106.3(5)
G-4	-169.0(4)	-87.2(4)	127.6(6)	-67.1(7)
X-5	-134.0(4)	-19.4(5)	-151.4(5)	-40.1(6)
X-6	-111.8(4)	-133.4(3)	-99.4(6)	-166.6(5)

REFERENCES

1. H. Miyake and Y. Kojima, Coord. Chem. Rev., in press.
2. H. Miyake, T. Yamashita, Y. Kojima, and H. Tsukube, submitted for publication.
3. Y. Kojima, T. Yamashita, and H. Miyake, Chem. Lett., 201 (1995).
4. H. Miyake, T. Yamashita, K. Hirotsu, and Y. Kojima, submitted for publication.
5. IUPAC-IUB Commission on Biochemical Nomenclature, Biochemistry, 9, 3471 (1970).