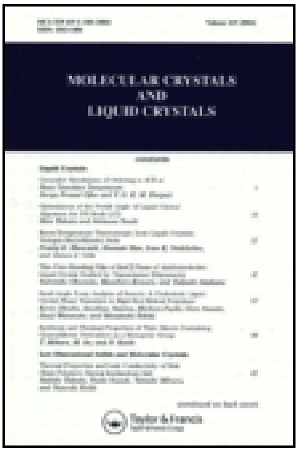

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Conformational Study of Structurally Constrained 18-Membered Cyclic Peptide Containing N,N′-Ethylene-Bridged-(S)-Alanyl-(S)-Alanine

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

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Abstract The detailed conformation of macrocyclic pseudopeptide, cyclo[(2*S*,3'*S*)-2-(3'-methyl-2'-oxopiperazin-1'-yl)-propanoyl-glycyl]$_2$, has been reported in crystal and has been examined by ^{1}H NMR measurement in CD_3CN in comparison with its solid state conformation.

INTRODUCTION

Macrocyclic molecules have unique properties in inclusion phenomena and complexations with metal and organic substrates.[1,2] As a new type of host molecule, we have studied the macrocyclic pseudopeptides containing *N,N'*-ethylene-bridged-dipeptide.[3] We previously succeeded in the crystal structural analysis of cyclo[(2*S*,3'*S*)-2-(3'-methyl-2'-oxopiperazin-1'-yl)-propanoyl-glycyl]$_2$ **1** and reported its structure preliminary (Figure 1).[4] In this paper, we describe the conformation of **1** in crystal and solution in detail.

SOLID STATE CONFORMATION

Our previous X-ray crystallographic study on the crystal of **1** from CH_3CN revealed that there are two independent molecules of **1** (**1a** and **1b**) and the bond lengths and torsion angles of these molecules are similar. These molecules are stabilized by three intermolecular hydrogen bondings (C=O---H-N) in crystal packing, but no intramolecular hydrogen bonding was observed. **1** has one cis and five trans peptide

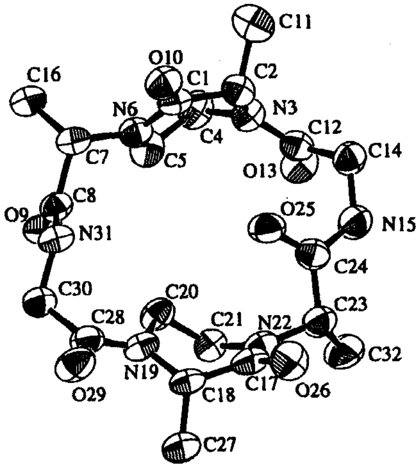

FIGURE 1 ORTEP drawing[5] of **1a** at 50% probability level.

bonds, and one piperazin-2-one ring is in distorted-form and the other is in pseudo-boat-form.[4] The cavity of **1a** is open like a nest and on this cavity is a *N,N'*-bridged ethylene (C4 and C5) in the piperazin-2-one ring of another **1a** (Figure 2). The distance of O25 of **1a** and C5 and C4 of another **1a** is 3.287(8) and 3.822(8) Å, respectively, indicating that the cavity of **1** can act as a hydrophobic hole where the planes of amide bonds and two piperazin-2-one- rings are perpendicular to the 18-membered ring. This inclusion of ethylene on the cavity is stabilized by hydrogen bonding between O13 and N31 of another **1a**. These observations are also shown in the relationship of **1b** and its environs. CH_3CN molecule is not in or on the cavity of **1**, but in the extramolecular space (Figure 3). A water molecule (H-O33-H) is hydrogen bonded to O13 of **1a** and O29 of **1b** as donors. The distances of O33 and O13 of **1a**, and O29 of **1b** are 2.921(8) and 2.99(1) Å, respectively.

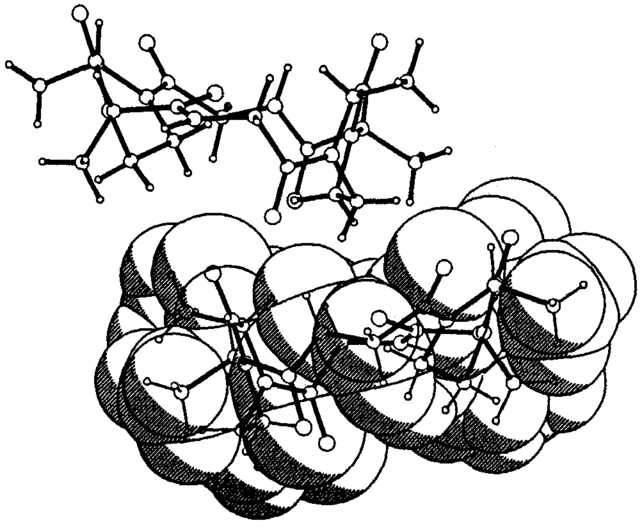

FIGURE 2 Perspective view of the nest-like cavity of **1a**.

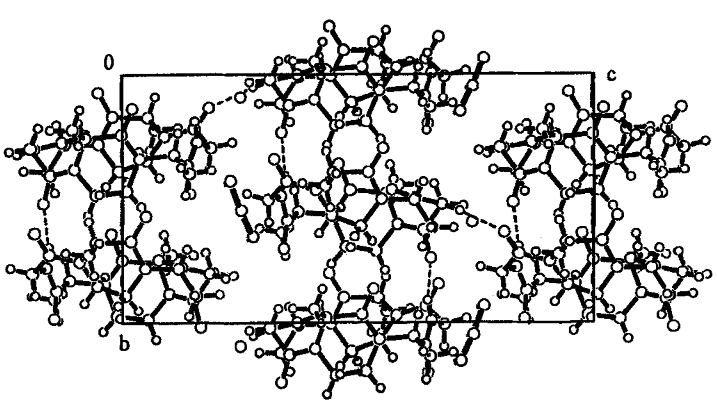

FIGURE 3 Crystal packing of $1\cdot 1/2H_2O\cdot 1/2CH_3CN$ viewed down the a axis.

SOLUTION CONFORMATION OF 1

^1H NMR spectra of 1 in CD_3CN are shown in Figure 4, revealing that at -40°C the major conformer (ca. 67% abundance) of 1 is in C_2-symmetry and conformation of all peptide bonds are trans as expected by our previous studies,[3,6] and that at room temperature the signal is very broad. This confirms that 1 exists in equilibrium between the C_2-conformer and other conformers, and that one cis and five trans conformer is easily crystallized in CH_3CN at room temperature.

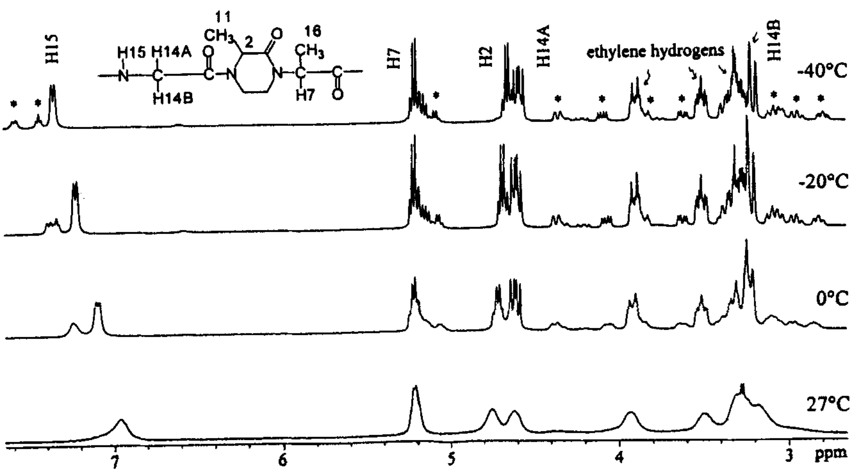

FIGURE 4 ^1H NMR spectra of 1 in CD_3CN. *; Minor conformer.

The torsion angles are estimated using Bystrov's function.[7] The sum of vicinal constants (see H14A and B in Table I) of glycyl HNC$^{\alpha}$H$_2$ protons is 10.7 Hz, suggesting ±50° or ±130° on the torsion angle ϕ.[8] The glycine H-C$^{\alpha}$-H geminal constant is 13.6 Hz, suggesting ±60° or ±120° on the torsion angle ψ.[8] Corey-Pauling-Koltun modeling and assumption that the compound prefers the most extensive structure in solution determine the angles $\phi = +130°$ and $\psi = -120°$.

TABLE I ^{1}H NMR data of major **1** in CD$_3$CN at -40°C.

Chemical shift / ppm, (coupling constant / Hz)					
H15	H14A	H14B	H2	H11	bridged ethylene
7.34 (bd, 6.7)	4.57 (dd, 14.0 8.6)	3.19 (dd, 13.1 2.1)	4.64 (q, 7.3)	1.27 (d, 7.3)	3.88 (dt, 12.8, 4.3, 1H) 3.49 (ddd, 13.1, 8.9, 4.0, 1H) 3.29 (m, 2H)

H7	H16
5.19 (q, 7.3)	1.20 (d, 7.3)

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