

Short Note

# 1,4-Bis[(*N*-acetyl-*L*-phenylalanyl-glycyl-*L*-alanyl)aminomethyl]benzene

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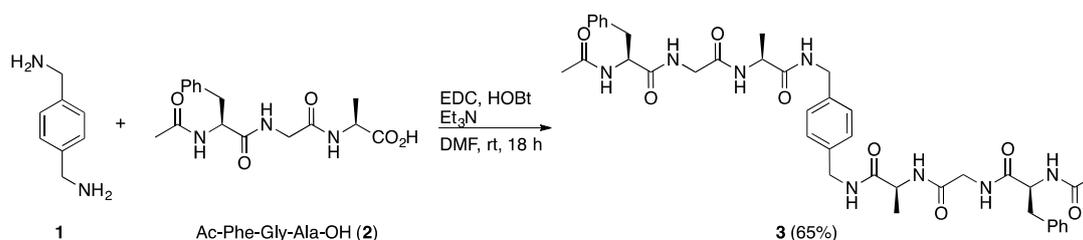
**Abstract:** The title compound was prepared by inducing amide bond formation between 1,4-bis(aminomethyl)benzene and tripeptide Ac-Phe-Gly-Ala-OH. The structure of the synthesized compound was determined on the basis of its <sup>1</sup>H-nuclear magnetic resonance (NMR), <sup>13</sup>C-NMR, and mass spectral data. Furthermore, the compound's preferred structure in solution and calculated conformation are also reported.

**Keywords:** peptide; foldamer; NMR analysis

## 1. Introduction

Oligomers composed of rigid building blocks, such as amino acids, aromatic amides, urea, and arenes, are capable of forming well-defined three-dimensional structures [1–9]. They are collectively called foldamers [10] and play important roles in biological, organic, material, and medicinal chemistry. In this note, we report the synthesis of the hybrid molecule 1,4-bis[(*N*-acetyl-*L*-phenylalanyl-glycyl-*L*-alanyl)aminomethyl]benzene (**3**), which contains an aromatic unit and peptide units. Its preferred conformation was analyzed based on its 2D ROESY (rotating-frame Overhauser spectroscopy) spectrum in solution, and its global-minimum energy conformation was calculated using MacroModel.

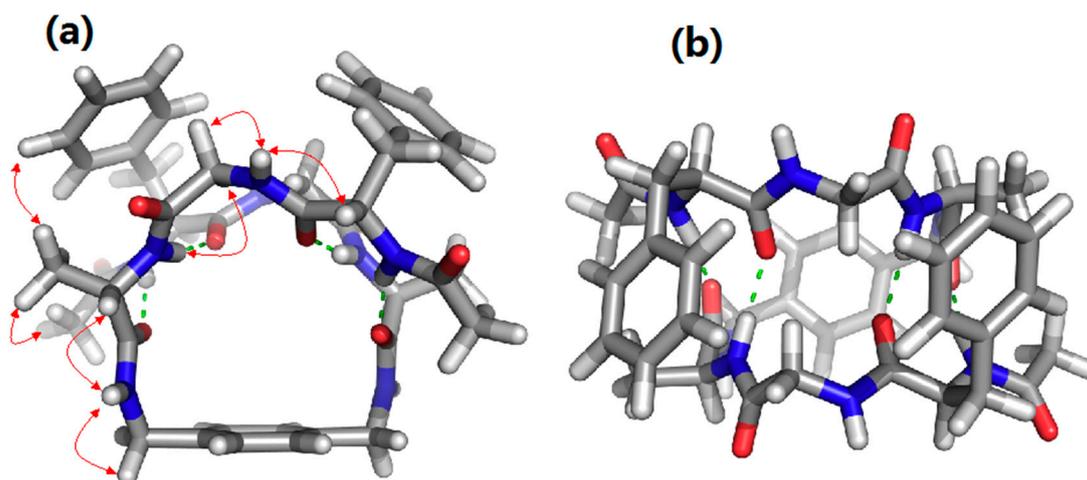
During the synthesis of the molecule, the coupling of methyl 1,4-bis(aminomethyl)benzene (**1**) and tripeptide Ac-Phe-Gly-Ala-OH (**2**) was induced with 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (EDC), 1-hydroxybenzotriazole hydrate (HOBT), and triethylamine (Et<sub>3</sub>N) in dimethylformamide (DMF) to give the target molecule **3** in a 65% yield (Scheme 1). The structure of **3** was subsequently determined on the basis of its <sup>1</sup>H-nuclear magnetic resonance (NMR), <sup>13</sup>C-NMR, and mass spectral data.



**Scheme 1.** Synthesis of 1,4-bis[(*N*-acetyl-*L*-phenylalanyl-glycyl-*L*-alanyl)aminomethyl]benzene (**3**).

The global minimum energy conformation of **3**, which was calculated using MacroModel with the OPLS\_2005 force field, is shown in Figure 1. The global minimum energy conformation of **3** was

found to be a capsule-like structure, and the two peptides within the molecule formed an anti-parallel  $\beta$ -sheet structure via hydrogen bonds. The preferred structure of **3** was analyzed based on its  $^1\text{H-NMR}$  spectrum in dimethyl sulfoxide ( $\text{DMSO-}d_6$ ) (peptide concentration: 10 mM). On the basis of its 1D  $^1\text{H-NMR}$  spectrum, **3** was found to display a  $\text{C}_2$ -symmetric conformation in solution (equivalent sets of protons were seen in its spectrum) (Figure S1). Seven dipolar interactions that supported the calculated conformation were observed in the 2D ROESY spectrum of **3** (Figure 1a) (Figure S3). The hybrid molecule described in this study is expected to be useful for designing foldamer scaffolds.



**Figure 1.** The calculated minimum energy conformation of **3** from (a) the side view and (b) the overhead view. Dipolar interactions are indicated as red arrowed lines, and hydrogen bonds are indicated as green dashed lines.

## 2. Experimental Section

### 2.1. General Information

The molecule's  $^1\text{H-}$  and  $^{13}\text{C-NMR}$  spectra were recorded on a Varian AS 400 spectrometer (Agilent, Santa Clara, CA, USA) after it had been dissolved in  $\text{DMSO-}d_6$ . The molecule's coupling constants ( $J$ ) are reported in Hz, and apparent peak multiplicities are indicated (s = singlet, d = doublet, t = triplet, m = multiplet). The molecule's melting point was determined using a Yanako MP-13 (Yanako, Kyoto, Japan). High-resolution mass spectra (HRMS) were recorded on a SHIMADZU LCMS-IT-TOF spectrometer (Shimadzu, Kyoto, Japan). A conformational search calculation was performed using the MCMM method of MacroModel (Schrödinger, Inc., New York, NY, USA) and the OPLS\_2005 force field to obtain several local-minimum energy conformations. An extended structure was used as the initial structure, and more than 20,000 structures were optimized.

### 2.2. Synthesis of 1,4-Bis[(N-acetyl-phenylalanyl-glycyl-alanyl)aminomethyl]benzene (**3**)

A mixture of 1,4-bis(aminomethyl)benzene (**1**) (27 mg, 0.2 mmol), Ac-Phe-Gly-Ala-OH (**2**) (168 mg, 0.5 mmol), EDC (115 mg, 0.6 mmol), HOBT (81 mg, 0.6 mmol), and  $\text{Et}_3\text{N}$  (84  $\mu\text{L}$ , 0.6 mmol) in DMF (5.0 mL) was stirred for 18 h at room temperature. AcOEt (50 mL) and MeOH (5.0 mL) were added to the solution, which was then washed with 3% aqueous HCl (10 mL), 3% aqueous  $\text{NaHCO}_3$  (10 mL), and brine (10 mL), before being dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed in vacuo, and the resultant product was purified by chromatography on silica gel (5% MeOH in AcOEt) to give **3** (100 mg, 65%) as a white solid.

Mp: 262–263  $^\circ\text{C}$ ;  $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ , 400 MHz)  $\delta$ 8.35 (t, 2H,  $J = 6.0$  Hz), 8.29 (t, 2H,  $J = 5.6$  Hz), 8.18 (d, 2H,  $J = 5.6$  Hz), 7.98 (d, 2H,  $J = 7.2$  Hz), 7.16–7.28 (m, 14H), 4.46 (m, 2H), 4.28 (t, 2H,  $J = 7.2$  Hz), 4.23 (d, 4H,  $J = 6.0$  Hz), 3.80 (dd, 2H,  $J = 5.6, 16.4$  Hz), 3.67 (dd, 2H,  $J = 5.6, 16.4$  Hz), 3.03 (dd, 2H,  $J = 4.4,$

14.0 Hz), 2.74 (dd, 2H,  $J = 10.0, 14.0$  Hz), 1.75 (s, 6H), 1.23 (d, 6H,  $J = 6.8$  Hz);  $^{13}\text{C}$ -NMR (DMSO- $d_6$ , 100 MHz):  $\delta$  18.7, 37.4, 42.2, 42.5, 49.1, 52.5, 54.3, 127.0, 127.3, 128.8, 129.0, 129.7, 136.9, 137.7, 169.5, 170.8, 172.5, 173.3; HRMS (ESI-TOF):  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{40}\text{H}_{51}\text{N}_8\text{O}_8$ : 771.3830; found: 771.3851.

**Supplementary Materials:** The molefiles and the other supplementary materials can be found at <http://www.mdpi.com/1422-8599/2016/2/M893>.

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**Author Contributions:** The listed authors contributed to this study in the following ways: K. Tsutsui and T. Misawa performed the synthesis and identification, and Y. Demizu and M. Kurihara prepared the manuscript. All of the authors have read and approved the final manuscript.

**Conflicts of Interest:** The authors declare that no conflicts of interest exist.

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