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Short Note

Methyl 2-[(2-{2-[(2-acetamidophenyl)ethynyl]benzamido} phenyl)ethynyl]benzoate

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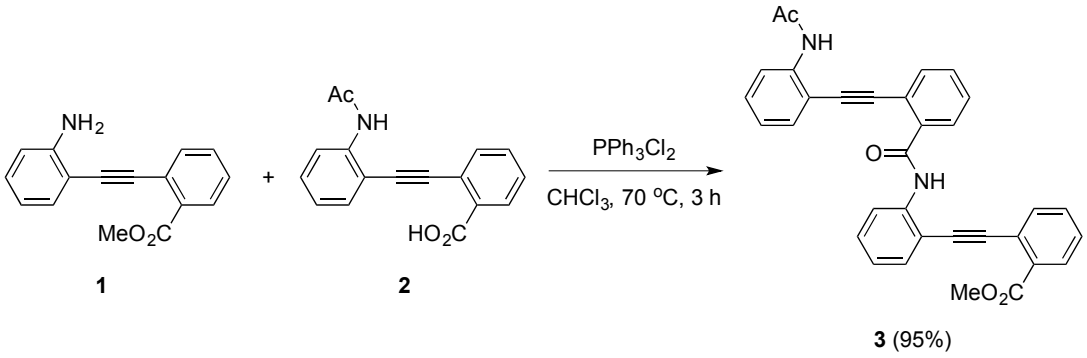
Abstract: The title compound was prepared by inducing amide bond formation between methyl 2-[(2-aminophenyl)ethynyl]benzoate and 2-[(2-acetamidophenyl)ethynyl]benzoic acid in the presence of dichlorotriphenylphosphorane. The structure of the synthesized compound was determined on the basis of its ^{1}H-nuclear magnetic resonance (NMR), ^{13}C-NMR, and mass spectral data. Furthermore, the compound's crystal structure is also reported.

Keywords: foldamer; aromatic amide; X-ray crystallographic analysis

Introduction

The *de novo* design of oligomers that form well-defined three-dimensional conformations is of extraordinary importance in the fields of biotechnology, nanotechnology, and medicinal chemistry. Such conformationally ordered molecules are called foldamers [1], and amide, urea, arene, and acetylene units are often utilized as templates for constructing such foldamers [2–10]. In this note, we report the synthesis of the hybrid foldamer methyl 2-[(2-{2-[(2-acetamidophenyl)ethynyl]benzamido}phenyl)ethynyl]benzoate (**3**), which possesses both amide and acetylene units. Its dominant conformation in the crystalline state was also analyzed by X-ray crystallographic analysis.

During the synthesis of the molecule, the coupling of methyl 2-[(2-aminophenyl)ethynyl]benzoate (**1**) [11] and 2-[(2-acetamidophenyl)ethynyl]benzoic acid (**2**) [12] was induced with dichlorotriphenylphosphorane in $CHCl_3$ to give the target molecule **3** in a 95% yield. The structure of **3** was subsequently determined on the basis of its ^{1}H-nuclear magnetic resonance (NMR), ^{13}C-NMR, and mass spectral data.



Scheme 1. Synthesis of methyl 2-[(2-{2-[(2-acetamidophenyl)ethynyl]benzamido} phenyl)ethynyl]benzoate (**3**).

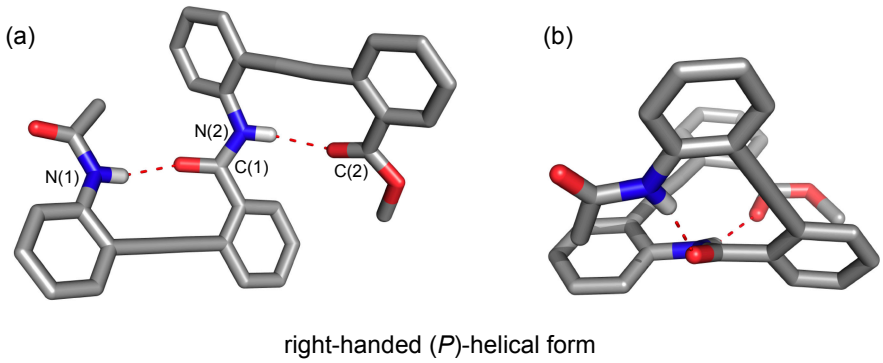


Figure 1. X-ray diffraction structure of **3** as viewed (**a**) perpendicular to and (**b**) along its helical axis. The left-handed folded structure and hydrogen atoms have been omitted for clarity.

The three-dimensional structure of **3** was determined by X-ray crystallographic analysis [13,14]. Single crystals of **3** were obtained via the slow evaporation of tetrahydrofuran. The X-ray crystallographic structure of **3** was solved with a *Cc* spacer group, resulting in left- and right-handed folded structures containing 1.5 residues per turn (Figure 1). In the crystal structure of **3**, two hydrogen bonds were observed between H-N(1) and C(1)=O(1) [N(1)···O(1) = 3.15 Å; N-H···O 165.9°] and between H-N(2) and C(2)=O(2) [N(2)···O(2) = 3.10 Å; N-H···O 159.9°]. The new folding molecule described in this study is expected to be useful for designing foldamer scaffolds.

Experimental Section

General Information

The molecule's ^{1}H and ^{13}C-NMR spectra were recorded on a *Varian AS 400* spectrometer (Agilent, Santa Clara, CA, USA) after being dissolved in $CDCl_3$, and tetramethylsilane was used as an internal standard. The molecule's coupling constants (*J*) are reported in Hz and refer to the apparent peak multiplicities (s = singlet, d = doublet, t = triplet, m = multiplet, br s= broad singlet). The molecule's melting point was determined using a *Yanako MP-13* (Yanako, Kyoto, Japan). High resolution mass spectra were recorded on a SHIMADZU *LCMS-IT-TOF* spectrometer (SHIMADZU, Kyoto, Japan). The data collection for the X-ray diffraction analysis was performed on Rigaku RAXIS-RAPID and Bruker AXS SMART APEX imaging plate diffractometers (Bruker, Yokohama, Japan) using graphite-monochromated Mo*K*α radiation.

Synthesis of Methyl 2-[(2-{2-[(2-acetamidophenyl)ethynyl]benzamido}phenyl)ethynyl]benzoate (**3**)

Dichlorotriphenylphosphorane (1.0 g, 3.0 mmol) and 2-[(2-aminophenyl)ethynyl]benzoate (**1**) (376.9 mg 1.5 mmol) were added to a solution of 2-[(2-acetamidophenyl)ethynyl]benzoic acid (**2**) (279.3 mg, 1.0 mmol) in chloroform (5.0 mL). The reaction mixture was stirred for 3 h at 70 °C under an argon atmosphere. Chloroform (50 mL) was added to the solution, which was then washed with water (30 mL × 2) and brine (10 mL), before being dried over Na_2SO_4. The solvent was removed in vacuo, and the resultant product was purified by chromatography on silica gel (30% AcOEt in hexane) to give **3** (486 mg, 95%) as a colorless crystal.

Mp: 161–163 °C

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.73 (br s, 1H), 8.81 (br s, 1H), 8.48-8.51 (m, 2H), 7.98 (d, 2H, *J* = 8.0 Hz), 7.85 (d, 1H, *J* = 7.2 Hz), 7.67 (d, 1H, *J* = 6.8 Hz), 7.57 (t, 2H, *J* = 7.6 Hz), 7.47–7.53 (m, 2H), 7.35–7.43 (m, 3H), 7.31 (t, 1H, *J* = 8.4 Hz), 7.15 (t, 1H, *J* = 7.6 Hz), 6.97 (t, 1H, *J* = 7.6 Hz), 3.34 (s, 3H), 2.29 (s, 3H).

^{13}C-NMR ($CDCl_3$, 400 MHz) δ 24.6, 51.9, 89.8, 90.4, 93.9, 95.1, 111.5, 113.1, 119.6, 120.6, 122.2, 122.7, 123.8, 123.9, 127.9, 128.2, 129.0, 129.7, 129.9, 130.1, 130.5, 130.6, 131.6, 132.1, 132.3, 133.0, 133.7, 137.6, 140.2, 140.7, 165.4, 167.3, 170.1.

HRMS (ESI-TOF): $[M + Na]^+$ calcd for $C_{33}H_{24}N_2NaO_4$ 535.1628; found 535.1634.

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Author Contributions

The listed authors contributed to this study in the following ways: T. Misawa and N. Yamagata performed the synthesis and identification; M. Doi performed the X-ray crystallographic analysis; 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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12. Compound **2** was prepared by N-acetylation of compound **1** and the subsequent alkaline hydrolysis of the methyl ester.

13. CCDC-784138 (**3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
14. *Crystal data for* **3**: $C_{33}H_{24}N_2O_4$; *M*r = 512.54; Monoclinic; *Cc*, *a* = 18.3920, *b* = 9.0316, *c* = 15.1378 Å; α = 90, *β* = 114.054, γ = 90°; V = 2513.2 Å^3; *Z* = 4; D_{calc} = 1.355 g/cm^3; μ (MoK_α) = 0.90 cm^{-1}; No. of observations ($I > 2\sigma(I)$) = 4457; No. of variables = 352; R_1 = 0.0658, and R_w = 0.1753.