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Synthesis of linear and cyclic aromatic peptides with fixed conformation owing to intramolecular hydrogen bonding by condensation polymerization method

Tomoyuki Ohishi^a, Toshiya Suzuki^a, Tetsurou Niiyama^a, Koichiro Mikami^a, Akihiro Yokoyama^a, Kosuke Katagiri^b, Isao Azumaya^b, Tsutomu Yokozawa^{a,*}

^a Department of Material and Life Chemistry, Kanagawa University, 3-27-1 Rokkakubashi, Kanagawa-ku, Yokohama 221-8686, Japan ^b Faculty of Pharmaceutical Sciences at Kagawa Campus, Tokushima Bunri University, 1314-1 Shido, Sanuki, Kagawa 769-2193, Japan

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ABSTRACT

Chain-growth condensation polymerization of 3-(4-octyloxybenzylamino)benzoic acid esters bearing an alkoxy group on the benzene ring was investigated for the synthesis of polyamides having a specific conformation owing to intramolecular hydrogen bonding of CONH...OR. The 4-octyloxybenzyl group on the nitrogen of the amide linkage was easily removed with trifluoroacetic acid after polymerization to afford the desired polyamides, which had lower solubility than expected. Furthermore, we found that a cyclic triamide was selectively obtained by slow addition of the base to a solution of the monomer.

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In recent years, there has been intense interest in developing unnatural aromatic peptides in which intramolecular hydrogen bonding leads to macrocycle formation or folding into helical structures (Scheme 1A).¹ These oligomers, however, have been synthesized by time-consuming stepwise condensation reactions. On the other hand, we have developed chain-growth condensation polymerization (CGCP) to afford aromatic tertiary polyamides with controlled molecular weight and low polydispersity.² Poly(p-benzamide)s and poly(naphthalenecarboxamide)s with a chiral side chain on the amide nitrogen can be easily synthesized by CGCP,³ and they adopt helical conformation on the basis of the high cis conformational preference of the tertiary amide linkage⁴ and the syn arrangement of the three consecutive aromatic units connected by two amide linkages. These helical structures are different from those in Scheme 1A, in that the aromatic rings in the polymer are almost perpendicular to the amide carbonyl plane. However, polyamides with a sheet or curved structure, in which the aromatic rings and the amide carbonyl are in the same plane, similar to the oligomers in Scheme 1A, could be synthesized by CGCP of alkoxy-substituted monomers, followed by conversion of the tertiary amide to secondary amide by removal of the protecting group on the amide nitrogen (Scheme 1B). Indeed, the structure of N-o-methoxyphenylbenzamide was studied by means of crystallographic analysis, and this amide has a highly planar structure owing to intramolecular hydrogen bonding of CONH…OR.⁵ In this Letter, we synthesized well-defined aromatic polyamides that exhibit intramolecular hydrogen bonding between CONH and an alkoxy group by means of CGCP of 4-alkoxy-3-(4-octyloxybenzylamino)benzoic acid phenyl esters **1** in the presence of base and initiator **2**, followed by removal of the 4-octyloxybenzyl (OOB) group. Furthermore, we also found that cyclic trimers of these monomers were selectively formed under certain conditions.

The CGCP of monomer **1a** was first carried out in the presence of 10 mol % of initiator **2**, 1.1 equiv of lithium 1,1,1,3,3,3-hexamethyldisilazide (LiHMDS), and 5.5 equiv of LiCl, which is effective for the stabilization of anions,^{6,7b} in THF ([**1a**]₀ = 0.40 M) at 0 °C. The polymerization proceeded homogeneously and was completed within 2 h after slow addition of **1a** to the reaction mixture (40–60 min). The obtained poly**1a** possessed low polydispersity as well as welldefined molecular weight based on the feed ratio of monomer **1a** to initiator **2** (M_n (calcd) = 4870, M_n = 4200, M_w/M_n = 1.11) (Fig. 1a). The ¹H NMR spectrum of poly**1a** showed the methyl signal of **2** attached to the polymer, and there was no signal of a terminal amino **1a** unit not attached to **2**. These results indicate successful CGCP of **1a** from **2** without self-polycondensation of **1a**. However, when the polymerization of **1a** was carried out at the feed ratio (**1a**]₀/[**2**]₀ of 29, the gel-permeation chromatogram (GPC) elution





^{*} Corresponding author. Tel.: +81 45 481 5661; fax: +81 45 413 9770. *E-mail address:* yokozt01@kanagawa-u.ac.jp (T. Yokozawa).

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Scheme 1. Synthesis of folding oligoamides and polyamides by means of (A) stepwise condensation reactions and (B) chain-growth condensation polymerization.



Figure 1. GPC profiles of the crude products of polymerization of **1** with **2** (eluent: THF). The polymerization was carried out with (a) $[1a]_0/[2]_0 = 10$, (b) $[1a]_0/[2]_0 = 29$, (c) $[1b]_0/[2]_0 = 10$, (d) $[1b]_0/[2]_0 = 29$, (e) $[1c]_0/[2]_0 = 10$ and (f) $[1c]_0/[2]_0 = 30$.

curve of the obtained polymer showed a small peak in the lowermolecular-weight region, as well as the peak corresponding to poly**1a** (M_n = 8850, M_w/M_n = 1.12) (Fig. 1b). The ¹H NMR spectrum of this tiny peak product, which was separated by a preparative HPLC, showed only the signals of the repeat unit of the polymer. Furthermore, the observed molecular weight determined by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectroscopy was consistent with the expected molecular weight of a cyclic trimer of **1a**. Accordingly, it turned out that a small amount of **1a** underwent self-condensation at high feed ratio to afford the cyclic trimer.



Figure 2. GPC profiles of the crude product obtained by the cyclization of 1b in THF at 0 $^\circ \text{C}.$

Other monomers **1b** and **1c** with a bulkier alkoxy group on the benzene ring were similarly polymerized. A small peak was observed in the lower-molecular-weight region even in the polymerization with 10 mol % of **2** (Fig. 1c and e), and this peak became larger at the feed ratio $[1]_0/[2]_0$ of about 30 (Fig. 1d and f). We confirmed that these peak products were the cyclic trimers of **1b** and **1c** from the ¹H NMR spectra and the MALDI-TOF mass spectra. The accompanying cyclization of monomer **1** is a feature of the CGCP of **1**, because the CGCP of *meta*-substituted monomers without the



Scheme 2. Deprotection of cycle1b.



Figure 3. ¹H NMR spectrum (600 MHz, CDCl₃) of cycle1b'.

alkoxy group did not afford cyclic triamides.⁷ The difference may be accounted for by the lower acidity of the amino group of **1** due to intramolecular hydrogen bonding between the amine proton and the alkoxy oxygen; slow proton abstraction of the amino group would induce the reaction of deprotonated **1** with nondeprotonated **1**, leading to self-condensation. Actually, the amino proton of **1** appears at higher magnetic field (4.64–4.57 ppm), compared to that of *meta*-substitute monomers without the alkoxy group (4.09–4.02 ppm).^{7b}

Removal of the OOB group on the amide nitrogen of the obtained poly1b and poly1c was conducted with trifluoroacetic acid (TFA) in CH₂Cl₂ at ambient temperature for 3 days.^{7b,8} The reaction proceeded homogeneously, and the products were purified by precipitation into a large amount of hexane. In the ¹H NMR spectra of the products, the signal of the benzylic protons of the OOB group at around 4.90 ppm was absent. The FT-IR spectra of the products showed *N*-H stretching bands at 3290 cm⁻¹. Therefore, the OOB group was quantitatively removed, resulting in the desired secondary polyamides. However, both the N-H polybenzamides were only soluble in TFA and CH₂Cl₂ and had lower solubility than poly(N-H-m-benzamide), which is soluble in dimethylsulfoxide (DMSO) and N,N-dimethylacetamide (DMAc).^{7b} This result is considered to be due to intramolecular hydrogen bond formation between amide N-H and the oxygen atom at the ortho position of the benzene ring in poly1, which favours the formation of a sheet structure, such as a planar zigzag or a curved structure (Fig. S2), resulting in strong π - π interaction between polymer chains. Furthermore, density functional theory (DFT) calculations at the B3LYP/6-31G(d) level showed that a zigzag structure of 3-(N-benzoylamino)-4-methoxybenz-2'-methoxyanilide, as a model compound of the polyamide, was more stable than a curved structure (ca. 2.1 kcal/mol). This implies that poly**1** would preferentially adopt a planar zigzag conformation rather than a curved conformation, and the former conformation is likely to have stronger intermolecular interaction among polymer chains.

Since the cyclic triamide was obtained as byproduct in the polymerization of **1**, we next tried to selectively synthesize the cyclic triamide of **1b**. Contrary to the case of cyclic trimerization of Nalkylated *p*-aminobenzoic acid esters,⁹ when LiHMDS was added to a solution of **1b**,¹⁰ the GPC profile of the product obtained after 4 h showed a sharp peak due to cyclic triamide (Fig. 2). Purification on a silica gel column afforded the cyclic triamide of **1b** in a 70% yield.

Deprotection of the cyclic triamide was attempted with TFA, but the OOB group was not removed. Then, the cyclic triamide was refluxed in neat TFA with triisopropylsilane (TIPS) as a scavenger, as reported by Wilson et al. (Scheme 2).¹¹ In the ¹H NMR spectrum of the product, the signal of the benzylic protons of the OOB group at around 4.90 ppm had disappeared, and a new signal due to amide *N*-H proton was observed at around 7.27 ppm (Fig. 3). The MALDI-TOF mass spectrum contained only one peak corresponding to the Na⁺ adduct of *N*-H cyclic triamide (cycle**1b**').

In conclusion, we have demonstrated that well-defined poly(*m*benzamide)s having a specific conformation arising from intramolecular hydrogen bonding between CONH and an alkoxy group can be obtained by means of CGCP of **1** bearing alkoxy groups on the benzene ring, followed by removal of the OOB group with TFA. Furthermore, we found that the cyclic trimer of **1** was selectively obtained by the slow addition of LiHMDS to a solution of **1**; the obtained cyclic tertiary triamide was converted to the secondary triamide by the removal of the OOB group with TFA/TIPS.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.071.

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