Selective Cyclic Trimerization of 4-(Alkylamino)benzoic Acid Dimer Phenyl Esters

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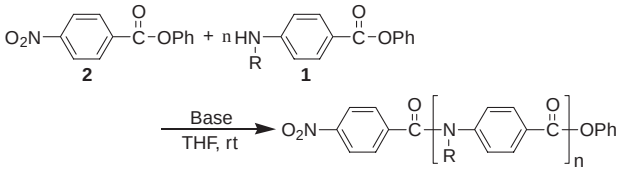
Treatment of 4-(alkylamino)benzoic acid dimer phenyl esters with a base, under conditions where monomeric 4-(alkylamino)benzoic acid phenyl esters polymerize to give well-defined aromatic polyamides, affords not polymers, but cyclic trimers in good yield.

Cyclic amide compounds have received much attention due to their interesting characteristics such as molecular recognition[1] and formation of functional organic nanotubes.[2] In order to put functional amide macrocycles to practical use, it is important to develop novel and convenient procedures for the synthesis of cyclic amide compounds. We report here a one-pot synthesis of aromatic amide macrocycles having alternating *N*-alkyl groups under conditions conventionally used for polymerization. The macrocycles obtained by this method not only have a potential to self-assemble in a unique manner without hydrogen bonding because of different nature of two side chains, but also will be used as a novel multifunctional components such as two functional initiator for the synthesis of miktoarm star polymers.

We previously investigated chain-growth polycondensation for the synthesis of aromatic polyamides, and demonstrated that the polycondensation of phenyl 4-(alkylamino)benzoate **1** in the presence of a base and an initiator **2** proceeded in a chain-growth polymerization manner (Scheme 1).[3] At the first step of the polycondensation, deprotonated **1** reacts selectively with the monofunctional initiator **2**, not with other monomers. Therefore, one end of the propagating polymer is capped with the inactive initiator unit, and the polycondensation proceeds without formation of cyclic compounds. The success of controlled polymerization of **1** led us to focus our attention on the polycondensation of a two-aromatic monomer, the phenyl ester of 4-(alkylamino)-benzoic acid dimer **3**. In this communication, we show that condensation of **3** in the presence of a base results not in polymerization, but in cyclization to afford the cyclic trimer of **3** in good yield. Recently, Azumaya reported a one-pot synthesis of the cyclic trimer and hexamer of *N*-(methylamino)benzoic acid.[4] However, our result is very interesting because the reaction reported here provides a new synthetic method for cyclic aromatic oligoamides having alternating *N*-alkyl groups. There are several reports of isolation of single-sized aromatic macrocycles by one-pot oligomerization of monomer units,[4,5] but switching between polymerization and cyclization by changing the number of monomer repeating units is unique, to our knowledge.

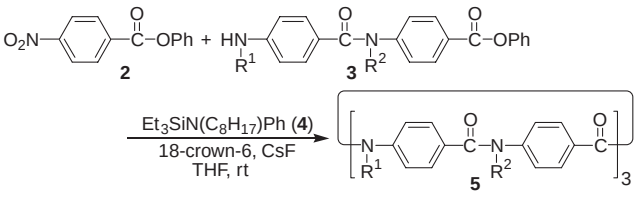
Condensation of the two-aromatic monomer **3a** ($R^1 = C_8H_{17}$, $R^2 = CH_3$) was investigated in the presence of 5 mol % of initiator **2** and 1 equiv. of base (*N*-triethylsilyl-*N*-octylaniline **4**/CsF/18-crown-6) in THF ($[\mathbf{3a}]_0 = 0.16$ M) at room temperature (Scheme 2). Under similar conditions, **1** polymerized quantitatively to give a well-defined polyamide in 1–3 h.[3a] However, when **3a** was used as a monomer, **3a** still remained after 24 h in spite of complete consumption of the initiator **2** within 10 min.



Scheme 1.

The gel permeation chromatography (GPC) profile of the crude product showed a sharp peak in the oligomeric region accompanied with a broader peak in the higher molecular weight region (Figure 1a). The oligomer corresponding to the sharp peak in the GPC profile was isolated by preparative HPLC. The ^{1}H NMR spectrum of the oligomer revealed the presence of repeating units of the aromatic polyamide without the signals of the initiator or terminal unit, indicating that the oligomer had a cyclic structure. As shown in Figure 1b, matrix-assisted laser desorption ionization-time of flight mass spectroscopy (MALDI-TOF MS) analysis confirmed that the oligomer was a single compound with a molecular weight corresponding to that of the cyclic trimer **5a** (m/z Calcd for $[\mathbf{5a} + \mathrm{Ag}]^+$ 1200, found 1200), the isolated yield being calculated as 26%. The MALDI-TOF MS experiment also revealed that the higher molecular weight region in the GPC elution curve contained cyclic oligomers larger than the trimer, as well as chain oligomers with and without the initiator unit. The cyclization occurred independently of the initiator: the reaction in the absence of the initiator gave **5a** in similar yield (33% for 48 h).

In order to obtain **5a** more effectively, the reaction conditions were optimized without the initiator. When the initial concentration of monomer ($[\mathbf{3a}]_0$) and base ($[\mathbf{4}]_0$) was 0.71 M, the reaction for 2 d gave cyclic trimer **5a** in 39% yield. In contrast, the reaction of the one aromatic monomer **1** without initiator under almost identical conditions ($[\mathbf{1}]_0 = 0.67$ M) for 23 h gave a well-defined polyamide with 90% conversion of **1**.[6] These results indicate that the selective cyclization of **3a** would be induced by intrinsic nature of **3a**. The different condensation nature of **3a** from that of **1** would result from the slow polymerization of **3a**: the fast reaction of **1** with the polymer propagating end prevents the intramolecular reaction, but the opposite situation occurs in the condensation of **3a**. As $[\mathbf{3a}]_0$ decreased from 0.67 M to 0.13, 0.063, 0.042, and 0.025 M, the condensation of **3a** with 1 equiv. of the base proceeded more slowly, but the



Scheme 2.

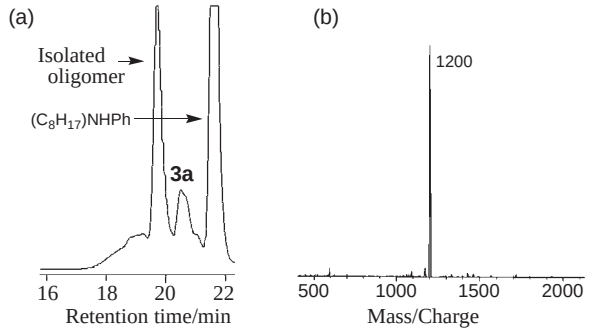


Figure 1. (a) GPC profile of the crude product in the reaction of **3a** with **2** (5 mol %) in the presence of **4**, CsF and 18-crown-6 in THF at room temperature for 24 h ($[\mathbf{3a}]_0 = [\mathbf{4}]_0 = 0.16$ M, $[CsF]_0 = 0.17$ M, $[18\text{-crown-6}]_0 = 0.33$ M), and (b) MALDI-TOF mass spectrum of the isolated product.

yields of **5a** were not improved (35–45%). We speculated that the low concentration of the base would retard the intra- and intermolecular reaction due to the ineffective deprotonation of the monomer amino group. In order to carry out the reaction with low concentration of the monomer as well as high concentration of the base, monomer **3a** was added slowly to a THF solution of base (pseudo-high-dilution condition). This method was very effective in this cyclization and the results are listed in Table 1. As the addition period was prolonged from 1 h to 4.5 h, the yield of **5a** increased up to 67% (Entries 1–3). However, further prolongation resulted in a decrease of the yield (Entries 4–6). Therefore, we determined that the optimum conditions for cyclization involved addition of a THF solution of **3a** to the base at room temperature over a period of 4.5 h.

Table 1. Effect of addition period of **3a**[a]

Entry	Addition time/h	Conversion of **3a**/%[b]	Yield of **5a**/%[c]
1	1	84	48
2	3	88	52
3	4.5	87	67
4	6	85	60
5	12	nd[d]	45
6	24	nd[d]	40

[a]Conditions: a THF solution (0.5 mL) of **3a** (0.27 mmol) was added dropwise to a mixture of **4** (1 equiv.), 18-crown-6 (2 equiv.) and CsF (1 equiv.) in THF (0.4 mL) at room temperature, and the mixture was stirred for 24 h at room temperature. [b]Determined by HPLC. [c]Isolated yields. [d]Not determined.

We next investigated the effect of the *N*-alkyl substituents, and found that the cyclization occurred independently of the length of the *N*-alkyl chains. As shown in Table 2, reaction of 4-(alkylamino)benzoic acid dimer phenyl esters having methyl or octyl substituents on the nitrogen (**3a**–**3d**) afforded cyclized products **5a**–**5d**. Among them, the *N*-methyl dimer **3d** gave the cyclic trimer **5d** (13%), along with the 4-(methylamino)-benzoic acid cyclic pentamer (22%).[7] On the other hand, when the terminal amine of **3** was primary (**3e**), consumption of the monomer was completed within 2 h to afford a mixture of linear oligomers, but cyclic oligomers were not observed by MALDI-TOF MS analysis. We did not examine the reaction of **3** in which R^2 was H, because we have already shown that condensation of such amide compounds does not proceed.[8]

Table 2. Effect of *N*-alkyl substituents on cyclization of **3**[a]

3	R^1	R^2	**5**	Yield/%[b]
3a	C_8H_{17}	CH_3	**5a**	67
3b	CH_3	C_8H_{17}	**5b** (=**5a**)	45
3c	C_8H_{17}	C_8H_{17}	**5c**	58
3d	CH_3	CH_3	**5d**	13[c,d]
3e	H	C_8H_{17}	**5e**	0[e]

[a]Conditions: a THF solution of **3** was added over 4.5 h to a mixture of **4** (1 equiv.), 18-crown-6 (2 equiv.) and CsF (1 equiv.) in THF at room temperature, and the whole was stirred at room temperature for 24 h. [b]Isolated yields. [c]Ethyl (trimethylsilyl)acetate was used instead of **4**. [d]4-(Methylamino)-benzoic acid cyclic pentamer was obtained in 22% yield. [e]18-Crown-6 (4 equiv.) in THF was added to a mixture of **3e**, **4** (2 equiv.), and CsF (2 equiv.) in THF.

In conclusion, we investigated the condensation of 4-(alkylamino)benzoic acid dimer phenyl esters, and found that the cyclic trimer was formed selectively. When all the *N*-alkyl substituents were methyl groups, the reaction afforded the cyclic hexamer of 4-(methylamino)benzoic acid, as well as its cyclic pentamer. We are now examining the detail mechanism of this selective cyclization.

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References and Notes

1 a) A. P. Bisson, V. M. Lynch, M.-K. C. Monahan, and E. V. Anslyn, *Angew. Chem., Int. Ed. Engl.*, **36**, 2340 (1997). b) A. Andrievsky, F. Ahuis, J. L. Sessler, F. Vögtle, D. Gudat, and M. Moini, *J. Am. Chem. Soc.*, **120**, 9712 (1998). c) S. Kubik, R. Kirchner, D. Nolting, and J. Seidel, *J. Am. Chem. Soc.*, **124**, 12752 (2002). d) K. Choi and A. D. Hamilton, *J. Am. Chem. Soc.*, **125**, 10241 (2003).

2 a) M. R. Ghadiri, J. R. Granja, R. A. Milligan, D. E. McRee, and N. Khazanovich, *Nature*, **366**, 324 (1993). b) M. R. Ghadiri, J. R. Granja, and L. K. Buehler, *Nature*, **369**, 301 (1994). c) D. T. Bong, T. D. Clark, J. R. Granja, and M. R. Ghadiri, *Angew. Chem., Int. Ed.*, **40**, 988 (2001). d) D. Ranganathan, *Acc. Chem. Res.*, **34**, 919 (2001).

3 a) T. Yokozawa, T. Asai, R. Sugi, S. Ishigooka, and S. Hiraoka, *J. Am. Chem. Soc.*, **122**, 8313 (2000). b) T. Yokozawa and A. Yokoyama, *Polym. J.*, **36**, 65 (2004).

4 a) I. Azumaya, T. Okamoto, F. Imabeppu, and H. Takayanagi, *Tetrahedron*, **59**, 2325 (2003). b) I. Azumaya, T. Okamoto, F. Imabeppu, and H. Takayanagi, *Heterocycles*, **60**, 1419 (2003).

5 a) Cyclic ether ketones: M. Chen and H. W. Gibson, *Macromolecules*, **29**, 5502 (1996); M. F. Teasley, D. Q. Wu, and R. L. Harlow, *Macromolecules*, **31**, 2064 (1998). b) Cyclic sulfides: K. Miyatake, Y. Yokoi, K. Yamamoto, E. Tsuchida, and A. S. Hay, *Macromolecules*, **30**, 4502 (1997). c) Cyclic phenylazomethines: M. Higuchi, A. Kimoto, S. Shiki, and K. Yamamoto, *J. Org. Chem.*, **65**, 5680 (2000).

6 T. Yokozawa, R. Sugi, T. Asai, and A. Yokoyama, *Chem. Lett.*, **33**, 272 (2004).

7 The formation of the cyclic pentamer in the reaction of **3d** can be interpreted in terms of a "backbiting" mechanism due to the small steric repulsion induced by the methyl groups. For an example of cyclodepolymerization of poly(ether sulfone)s by the backbiting mechanism, see: H. M. Colquhoun, D. F. Lewis, P. Hodge, A. Ben-Haida, D. J. Williams, and I. Baxter, *Macromolecules*, **35**, 6875 (2002), and references cited therein.

8 T. Yokozawa, M. Ogawa, A. Sekino, R. Sugi, and A. Yokoyama, *Macromol. Symp.*, **199**, 187 (2003).

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