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Stereoselectivity in dehydrative cyclic trimerization of substituted 4-alkylaminobenzoic acids†

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The cyclic trimerization of substituted 4-alkylaminobenzoic acids was investigated. From NMR analyses of **DiMeO_C3A** with two methoxy groups, which was obtained by using $SiCl_4$ as a dehydrative condensation reagent and purified by preparative GPC, a *syn*/*anti* ratio of 60/40 was obtained. On the other hand, **3Br_C3A** with one bromine group at the *ortho*-position relative to the amide nitrogen was synthesized by using PPh_3/Cl_3CCCl_3 as a dehydrative condensation reagent and isolated by SiO_2 column chromatography. **3Br_C3A** showed an inverse stereoselectivity, namely, a *syn*/*anti* ratio of 25/75 was calculated based on the comprehensive NMR analyses. The population of stereoisomers had no relationship with the dehydrative condensation reagent and reaction temperature. The solvent character also had a negligible influence on the *syn*/*anti* ratio in solution reflecting the rigid structure of **3Br_C3A**.

Introduction

Since the accidental preparation of crown ethers and their complexation with alkali and alkaline earth metal ions developed by Pedersen in 1967,[1] many synthetic macrocyclic compounds have been investigated due to the specific and selective host–guest complexation. In addition to the fundamental chemistry related to the host–guest interaction, this molecular recognition event stimulated the research activity associated with supramolecular chemistry, organic catalysis, polymer formation, and so on. From this point of view, cyclic oligomers including calixarenes,[2] resorcinarenes,[3] cucurbiturils,[4,5] cyclodextrins[6,7] and pillararenes[8–10] with unique cavities have been drawing much attention in the past few decades. The design and synthesis of new cyclic oligomers is of high importance and allows chemists to explore novel science.[11] Furthermore, cyclic oligomers having a well-defined conformation can provide the molecular system for studying the through-space interactions between segments to which the cyclic oligomer is covalently bound. Cyclic oligomers can also serve as a building block to construct supramolecular architectures leading to the development of materials with smart functions. For example, calix[4]arene scaffolds have been applied to organize perylene bisimide chromophores in zigzag-type arrangements providing defined distances and angles between chromophores.[12,13] The zigzag-type arrangement of dyes gave rise to the efficient sequential energy transfer process along the oligomeric chain.

Calix[3]amide classified by Azumaya and co-workers is a cyclic trimer having a meta-linked *N*-alkylated benzanilide skeleton[14,15] and is efficiently synthesized by the condensation reaction of 3-alkylaminobenzoic acid derivatives due to the preferential *cis* conformation of *N*-alkylated benzanilides.[16] Calix[3]amides having functional groups on the benzene ring were also synthesized.[17–19] We have achieved the chiral three dimensional alignment of π-conjugated chromophores with triple-stranded helicity, in which three bithiophene chromophores are sandwiched by two calix[3]amides.[20] However, the helicity of bithiophenes was dynamic to only show the strong Cotton effect in selected solvents or at low temperature. Subsequently, we have reported the synthesis and chiroptical properties of new cyclic tri(benzamide) carrying bis(phenylethynyl)benzene chromophores arranged in a triple-stranded helical fashion.[21] It is to be noted that the diastereoselective synthesis of cyclic tri(benzamide) having six bromo groups (**DiBr_C3A**) proceeds exclusively (Fig. 1).

Because the introduction of functional groups is highly demanded for the post-modification of cyclic oligomers (*vide supra*), our previous finding gave invaluable information about the stereoselective cyclization of 4-alkylaminobenzoic acids. On the other hand, the role of the bromine group is not fully understood and the incorporation of other substituents has not

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† Electronic supplementary information (ESI) available: Synthetic schemes, GPC chromatograms, ESI-MS charts, NMR spectra, and computational results. See DOI: 10.1039/d0nj05368f

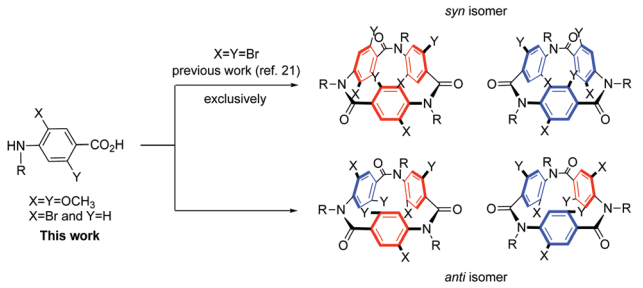


Fig. 1 Dehydrative cyclic trimerization of 4-alkylaminobenzoic acids.

been investigated in detail. In this contribution, we describe the stereoselectivity in the dehydrative cyclic trimerization of two monomers to address this issue (Fig. 1). The comprehensive NMR analyses and preliminary theoretical calculations are reported.

Experimental

Instruments

Microwave-assisted reactions were performed in a Biotage microwave reactor (Initiator) using 0.5–2.0 mL microwave reaction vials. Melting points (Mps) were determined on a Yanaco micro melting point apparatus MP-500D. Elemental analyses (EA) were performed on an Elementar vario EL cube in the CHN mode. Gel permeation chromatography (GPC) analyses were carried out with a Shodex 104 system using tandem LF-404 columns (THF as the eluent, flow rate = 1.0 mL min^{-1}, 40 °C) equipped with refractive index (RI) and ultraviolet (UV) detectors. Purifications with preparative GPC were carried out on a Japan analytical industry LC-9210 system using tandem JAIGEL 1H, 2H, and 2.5H columns ($CHCl_3$ as an eluent, flow rate = 3.8 mL min^{-1}) equipped with an UV detector monitored at 254 nm. High resolution electrospray ionization mass spectra (HR ESI-MS) were obtained on a Waters Synapt G2 HDMS (Nagoya Institute of Technology, NIT) and Thermo Fisher Scientific LTQ Orbitrap XL (Hiroshima Univ). One dimensional NMR spectroscopy and nuclear Overhauser effect spectroscopy (NOESY) were performed on a Bruker Avance III HD NanoBay 400 FT-NMR spectrometer (NIT). Heteronuclear single quantum correlation (HSQC), double quantum filtered COSY (DQF-COSY), diffusion ordered spectroscopy (DOSY), and valuable temperature NMR (VT-NMR) were performed on a JEOL JNM-ECA500 spectrometer (Hiroshima Univ). Theoretical calculations were performed using Gaussian 09 (Revision E.01) package of programs at Research Center for Computational Science, Okazaki, Japan. The ground state structures were optimized with density functional theory (DFT) calculations at the B3LYP/6-31G(d) level of theory.

Methods

Chloroform-d_1 solution of **Br_C3A** (0.03 mmol mL^{-1}) was placed in an NMR sample tube (3 mmϕ). The pulse-field gradient diffusion NMR spectra were recorded using a bipolar pulse pair stimulated echo pulse sequence on a JEOL JNM-ECA500 spectrometer with a three mm inverse H3X/FG probe at 24 °C. The resulting DOSY data were analyzed using the MestReNova program to obtain the diffusion coefficient values discussed in the main text. The signal decay of selected aromatic protons was fit to a mono-exponential fitting function (eqn (1)).

$$I = I_0 e^{-xD} \quad (1)$$

I and I_0 denote the NMR signal intensities in the presence and absence of gradient pulses, respectively. D is the diffusion coefficient value. The x indicates $[-\gamma^2 g^2 \delta^2 (\Delta - \delta/3)]$, where γ, g, δ, and Δ denote the gyromagnetic ratio, gradient strength, its duration gradient, and separation between the edges of the gradient pulses, respectively.[22]

Materials

All materials were obtained from commercial suppliers and used as received. Anhydrous tetrahydrofuran (THF) and dichloromethane (DCM) were purchased from Kanto Chemical. Other solvents were dried and distilled following the standard methods, and stored under a nitrogen atmosphere.

Synthesis

*2,5-Dimethoxy-4-nitrobenzoic acid methyl ester (**1**).* A mixture of 2,5-dihydroxy-4-nitrobenzoic acid methyl ester (2.77 g, 13.1 mmol),[23] K_2CO_3 (3.98 g, 28.8 mmol), and iodomethane (1.80 mL, 28.8 mmol) in acetone (80 mL) was heated to reflux for 48 h under a nitrogen atmosphere. After cooling, acetone was evaporated and then ethyl acetate and water were added. An aqueous phase was extracted with ethyl acetate, and the combined organic phase was rinsed with brine and dried over $MgSO_4$. After evaporating solvents, the obtained crude product was used for the next reaction without purification (2.95 g, 99%). ^{1}H-NMR ($CDCl_3$, ppm) 3.91 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 7.45 (s, 1H), 7.51 (s, 1H).

*4-Amino-2,5-dimethoxybenzoic acid methyl ester (**2**).* A CH_3OH solution (35 mL) of $SnCl_2$ (27.5 g, 140 mmol) was added dropwise to **1** (6.60 g, 29.3 mmol) in CH_3OH/THF mixed solution (70 mL, 1/1 in volume), and the mixture was heated to reflux overnight. After neutralizing with saturated Na_2CO_3 solution, an aqueous phase was extracted with DCM. The combined organic phase was rinsed with saturated $NaHCO_3$ solution and dried over $MgSO_4$. The crude product was purified by SiO_2 column chromatography (DCM : acetone = 6 : 1, Rf = 0.70) to give a brown solid (4.10 g, 67%). ^{1}H-NMR ($CDCl_3$, ppm) 3.83 (s, 6H), 3.85 (s, 3H), 4.25 (br, 2H), 6.30 (s, 1H), 7.34 (s, 1H).

*2,5-Dimethoxy-4-hexylaminobenzoic acid methyl ester (**3**).* After dissolving **2** (4.10 g, 19.5 mmol), hexanal (3.66 mL, 30.0 mmol), and AcOH (0.74 mL, 12.9 mmol) in THF (90 mL), $NaBH(OAc)_3$ (7.50 g, 35.3 mmol) was added and the mixture was stirred at room temperature overnight. After adding the saturated $NaHCO_3$ solution, an aqueous phase was extracted with DCM. The combined organic phase was rinsed with brine and dried over $MgSO_4$. The crude product was purified by SiO_2 column chromatography (ethyl acetate : hexane = 2 : 3, Rf = 0.35) to give brown oil (3.22 g, 56%). ^{1}H-NMR ($CDCl_3$, ppm) 0.89 (br, 3H),

1.21–1.67 (8H), 3.16 (t, J = 6.82 Hz, 2H), 3.84 (s, 6H), 3.89 (s, 3H), 6.12 (s, 1H), 7.29 (s, 1H).

*2,5-Dimethoxy-4-hexylaminobenzoic acid (**4**).* A mixture of **3** (3.22 g, 10.9 mmol) and 2 M NaOH solution (45 mL) in CH_3OH (100 mL) was heated at 40 °C for 24 h. After concentrating, 2 M HCl solution was added to acidify the solution. The precipitated solid was collected by filtration and washed with water to give a pale yellow solid (1.68 g, 56%). M.p. 88–90 °C. ^{1}H-NMR ($CDCl_3$, ppm) 1.35 (6H), 1.43 (3H), 1.69 (2H), 3.18 (t, J = 6.82 Hz, 2H), 3.87 (s, 3H), 4.03 (s, 3H), 6.13 (s, 1H), 7.43 (s, 1H). ^{13}C-NMR ($CDCl_3$, ppm) 14.0, 22.6, 26.8, 29.1, 31.5, 43.1, 55.9, 56.9, 92.1, 102.9, 111.9, 141.0, 144.4, 155.1, 166.3. Anal. calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98%. Found: C, 63.90; H, 8.48; N, 4.71%.

DiMeO_C3A. $SiCl_4$ (230 mg, 1.34 mmol) was added to **4** (250 mg, 0.89 mmol) in pyridine (5 mL) at 0 °C, and the mixture was heated at 120 °C under microwave irradiation for 24 h. After evaporating pyridine, 2 M HCl was added and an aqueous phase was extracted with DCM. The combined organic phase was rinsed with brine and dried over $MgSO_4$. The crude product was purified by SiO_2 column chromatography (ethyl acetate, Rf = 0.85) to give viscous oil (189 mg, 27%). After purification with preparative GPC, the target compound was isolated. ^{1}H-NMR ($CDCl_3$, ppm) 0.89 (9H), 1.26 (18H), 1.48 (6H), 3.28–4.10 (24H), 6.17–6.75 (6H). HR-ESI-MS calcd for $C_{45}H_{63}N_3O_9$ + Na: 812.4464. Found: 812.4438.

*4-Octylaminobenzoic acid (**5**).* $NaCNBH_3$ (1.1 g, 15 mmol) was added to an EtOH (55 mL) solution of *p*-aminobenzoic acid (2.0 g, 15 mmol) and octanal (2.3 mL, 15 mmol) at 0 °C. The mixture was stirred overnight while returning to room temperature. 1 M HCl solution was added to acidify the solution. The precipitated solid was collected by filtration and washed with water. The crude product was recrystallized from water/EtOH (1/4 in volume) to give a colorless solid (3.2 g, 88%). ^{1}H-NMR ($CDCl_3$, ppm) 0.85 (t, J = 6.60 Hz, 3H), 1.26 (br, 10H), 1.53 (m, 2 H), 3.03 (m, 2H), 6.41 (t, J = 5.26 Hz, 1H), 6.54 (d, J = 8.56 Hz, 2H), 7.65 (d, J = 8.56 Hz, 2H), 12.0 (br, 1H).

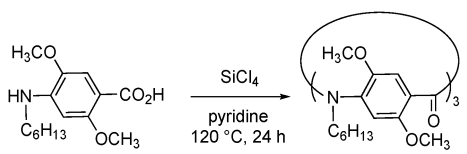
*3-Bromo-4-octylaminobenzoic acid (**6**).* A mixture of **5** (7.4 g, 30 mmol) and *N*-bromosuccinimide (5.4 g, 30 mmol) in DCM (180 mL) was stirred at room temperature for 20 h. The precipitated solid was filtered off, and the solution was rinsed with 1 M HCl solution and the solvent was evaporated to dryness to give a colorless solid (4.4 g, 46%). M.p. 120–122 °C. ^{1}H-NMR ($CDCl_3$, ppm) 0.89 (t, J = 6.72 Hz, 3H), 1.29 (br, 10H), 1.69 (m, 2H), 3.23 (br, 2H), 4.86 (br, 1H), 6.60 (d, J = 8.56 Hz, 1H), 7.92 (dd, J = 8.56, 1.96 Hz, 1H), 8.17 (d, J = 1.96 Hz, 1H). ^{13}C-NMR ($CDCl_3$, ppm) 14.1, 22.7, 27.0, 29.0, 29.2, 29.3, 31.8, 43.5, 108.4, 109.5, 117.5, 131.5, 134.7, 149.1, 171.3. Anal. calcd for $C_{15}H_{22}BrNO_2$: C, 54.89; H, 6.76; N, 4.27%. Found: C, 54.86; H, 6.76; N, 4.19%.

3Br_C3A. A mixture containing **6** (0.20 g, 0.61 mmol), PPh_3 (0.19 g, 0.73 mmol), Cl_3CCCl_3 (0.17 g, 0.73 mmol) in pyridine (4.6 mL) was heated at 120 °C under microwave irradiation for 24 h. After evaporating pyridine, 1 M HCl was added and an aqueous phase was extracted with DCM. The combined organic phase was rinsed with brine and dried over $MgSO_4$. The crude product was purified by SiO_2 column chromatography (DCM, Rf = 0.44) to give a pale yellow gummy solid (57 mg, 30%). ^{1}H-NMR ($CDCl_3$, ppm) 0.87 (9H), 1.25 (30H), 1.65 (6H), 3.18 (3H), 4.23 (3H), 6.68–7.64 (9H). ^{13}C-NMR ($CDCl_3$, ppm) 14.1, 22.6, 26.9, 27.1, 27.3, 27.5, 27.6, 29.1, 29.2, 29.7, 31.7, 47.5, 47.6, 47.8, 123.2, 123.4, 123.9, 124.0, 124.3, 124.4, 126.3, 126.8, 130.7, 131.1, 131.7, 131.9, 132.0, 132.3, 132.8, 137.8, 138.1, 138.2, 138.4, 141.1, 141.2, 168.8 (some signals are overlapped). HR-ESI-MS calcd for $C_{45}H_{60}N_3O_3Br_3$ + H: 928.2258. Found: 928.2266.

3Br_C3Ared. To $LiAlH_4$ (46 mg, 1.2 mmol) and $AlCl_3$ (0.16 g, 1.2 mmol) in ether (2.4 mL) was added dropwise a THF solution (1.2 mL) of **3Br_C3A** (93 mg, 0.10 mmol) at 0 °C, and the mixture was stirred for 2 h at room temperature. After quenching with cold 2 M aq. NaOH, an aqueous phase was extracted with DCM. The combined organic phase was washed with brine and dried over $MgSO_4$. The crude product was purified by preparative GPC ($CHCl_3$ as an eluent) to give pale yellow oil (45 mg, 51%). ^{1}H-NMR ($CDCl_3$, ppm) 0.86 (9H), 1.26 (30H), 1.65 (6H), 2.87–4.39 (12H), 6.42–7.57 (9H). ^{13}C-NMR ($CDCl_3$, ppm) 14.1, 22.6, 26.7, 26.8, 27.0, 27.2, 29.3, 29.5, 29.7, 31.8, 54.6, 55.1, 55.5, 56.2, 56.5, 56.9, 121.6, 123.2, 123.6, 124.8, 125.2, 126.0, 126.2, 126.8, 127.1, 128.3, 133.1, 133.3, 133.6, 133.7, 134.6, 135.3, 135.7, 145.2, 145.6. (some signals are overlapped). HR-ESI-MS calcd for $C_{45}H_{66}N_3Br_3$ + H: 886.2885. Found: 886.2863.

Results and discussion

In the first part of this paper, the stereoselectivity in the dehydrative cyclic trimerization of 2,5-dimethoxy-4-hexylaminobenzoic acid (**4**) was investigated (Scheme 1). The monomer was synthesized in four steps starting from 2,5-dihydroxy-4-nitrobenzoic acid methyl ester[24] prepared by Kilbinger and co-workers (Scheme S1, ESI†). Following our previous paper,[23] the cyclization of **4** was carried out using $SiCl_4$ as a dehydrative condensation reagent in pyridine at 120 °C under microwave heating for 24 h. After purifying by SiO_2 column chromatography, the product was analyzed by GPC to find out that higher molecular weight oligomers (peak B) are contaminated to the target compound (peak A) (Fig. S1, ESI†). A cyclic trimer **DiMeO_C3A** was finally isolated by the preparative GPC and the purity was unambiguously confirmed by the HR ESI-MS measurement (Fig. S2, ESI†). The detected mass number



4 DiMeO_C3A

Scheme 1 Cyclic trimerization of 2,5-dimethoxy-4-hexylaminobenzoic acid (**4**).

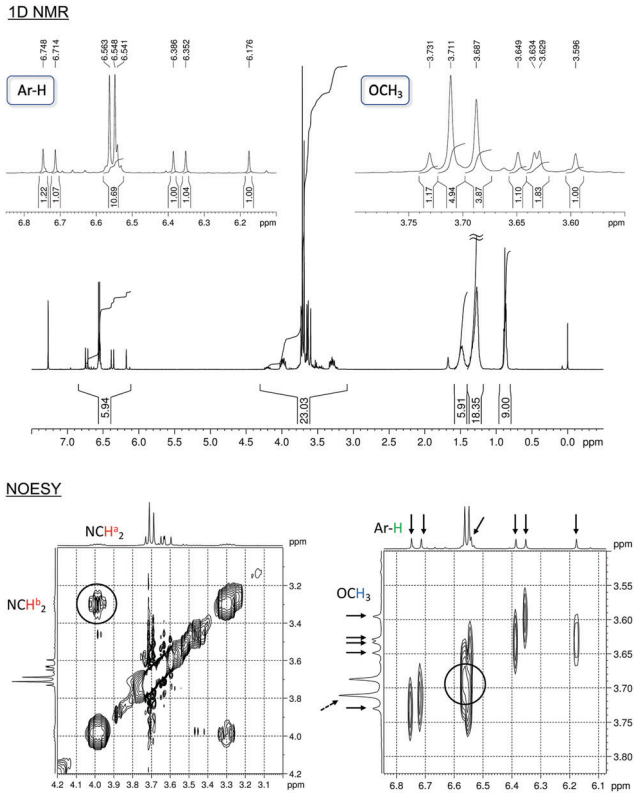


Fig. 2 1D NMR spectra and NOESY charts of **DiMeO_C3A** in $CDCl_3$.

m/z = 812.4438 agreed well with the theoretical value of the Na adduct of **DiMeO_C3A** (m/z = 812.4464). No higher molecular weight oligomer such as a cyclic tetramer (m/z = 1075.5986) was observed at all. Although the chemical purity of **DiMeO_C3A** was ensured, the ^{1}H-NMR spectrum showed a complex peak splitting at around 3.7 ppm and 6.5 ppm region, which can be assigned to methoxy and aromatic protons, respectively (Fig. 2, top). In order to contemplate the result, the NOESY measurements were performed in $CDCl_3$ at room temperature. As indicated in the bottom left chart of Fig. 2, the cross-peak was observed between NCH_2 protons at 3.3 ppm and 4.0 ppm (marked with circle), and the integral ratio of these signals was 1 : 1. This signal separation would be ascribed to the diastereotopic environment of methylene protons due to the chirality of **DiMeO_C3A** as in the case of bromo-substituted derivative (**DiBr_C3A**).[23] On the other hand, a cross-peak was clearly observed for methoxy and aromatic protons

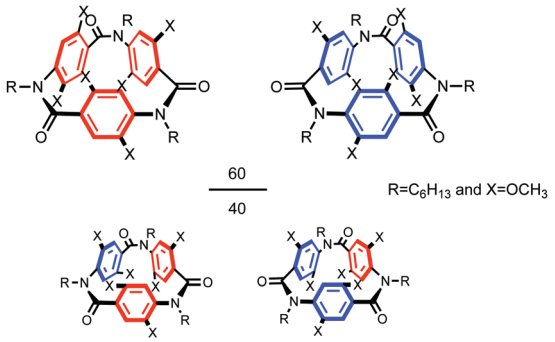
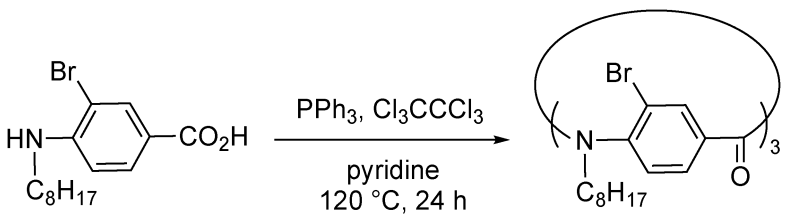


Fig. 3 Population of *syn*/*anti* stereoisomers in **DiMeO_C3A**.

in the bottom right chart of Fig. 2. More importantly, similar cross-peaks were also observed for minor six proton signals as highlighted with the arrow although some of them were overlapped each other or with major peaks. Taking the comparable integral ratio of six proton signals into consideration, these minor peaks are most likely derived from the *anti*-stereoisomer and the *syn*/*anti* ratio was calculated as 60/40 (Fig. 3). This fact is in sharp contrast to the diastereoselective cyclic trimerization of the bromo counterpart (*syn*/*anti* = 100/0).[23] We have preliminarily performed the DFT calculations for **DiMeO_C3A** and **DiBr_C3A**. The geometry optimization was executed using the B3LYP/6-31G(d) level of theory. For both compounds, the *syn*-stereoisomer exhibited a lower energy compared to the *anti*-stereoisomer due to the steric repulsion of substituents (Fig. S3, ESI†). The energy difference between *syn* and *anti* was somewhat larger for **DiMeO_C3A** contrary to our expectations. Because the separation of *syn*- and *anti*-stereoisomers was difficult by the chromatographic technique and **DiMeO_C3A** was relatively unstable under the ambient conditions, we gave up carrying out further characterization and experiments.

In the second part of this paper, the stereoselectivity in the dehydrative cyclic trimerization of 3-bromo-4-octylaminobenzoic acid (**6**) was investigated (Scheme 2). The monomer was synthesized in two steps starting from commercially available 4-aminobenzoic acid (Scheme S2, ESI†). The cyclization of **6** was carried out using $SiCl_4$ and PPh_3/Cl_3CCCl_3 as a dehydrative condensation reagent in pyridine at 120 °C under microwave heating for 24 h. Although higher molecular weight oligomers are contaminants of the target compound on using $SiCl_4$ similar to the synthesis of **DiMeO_C3A**, the selective cyclic trimerization proceeded by using PPh_3/Cl_3CCCl_3 (Fig. S4, ESI†).



5 **3Br_C3A**

Scheme 2 Cyclic trimerization of 3-bromo-4-octylaminobenzoic acid (**6**).

Thus **3Br_C3A** could be easily isolated by SiO_2 column chromatography as a pale yellow gummy solid in 30% yield. The structure of **3Br_C3A** was absolutely supported by the HR ESI-MS measurement, in which the observed peak pattern agreed well with the simulated pattern (Fig. S5, ESI†). Again, in the ^{1}H-NMR spectrum of **3Br_C3A** (Fig. 4, top), methylene proton signals adjacent to the amide nitrogen were separately observed at 3.2 ppm and 4.2 ppm, which is ascribed to the diastereotopic environment originated from the chirality of **3Br_C3A**. The HSQC chart of the aromatic region suggested that there are four kinds of doublet (J = 1.8 Hz), double doublet (J = 1.8 Hz and 8.1 Hz), and doublet (J = 8.1 Hz) peaks (Fig. 4, bottom). These four kinds of signals were found to be derived from the stereoisomers (*syn* and *anti*) having the same molecular weight because the comparable diffusion constants ($D \sim 5 \times 10^{-10}$ m^2 s^{-1}) were obtained within the experimental error in the DOSY analysis of a set of aromatic protons at 7.64 (a), 7.61 (b), 7.47 (c), and 7.38 (d) ppm (Fig. 5).[25] All coupling patterns of aromatic proton signals could be resolved by the DQF-COSY measurement (Fig. S6, ESI†), and the *syn*/*anti* ratio was calculated as 25/75 from the integral ratio in the ^{1}H-NMR spectrum (Fig. 4, top inset and Fig. 6).[26]

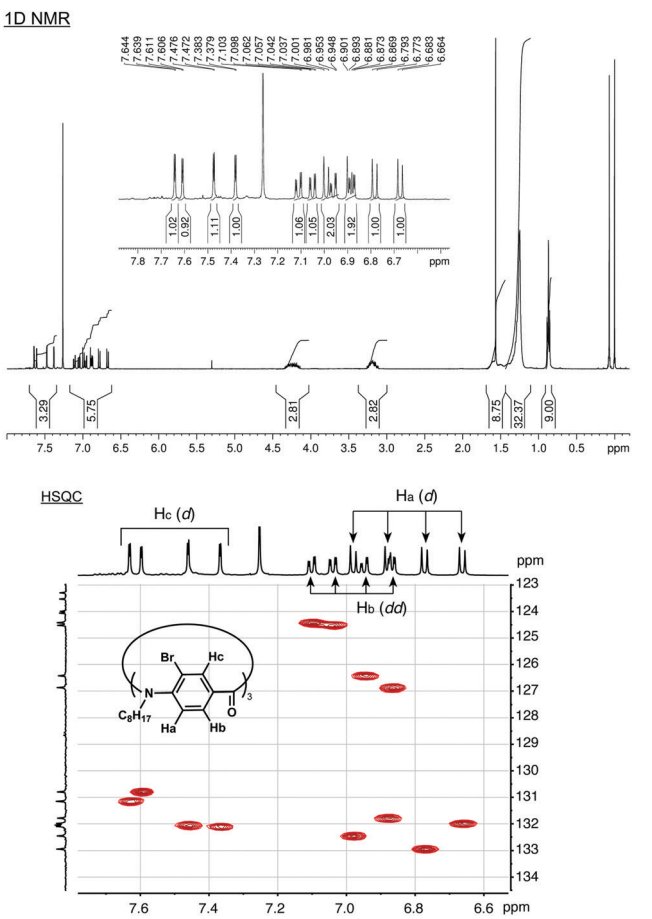


Fig. 4 (top) 1D NMR spectrum of **3Br_C3A** in $CDCl_3$. Inset shows the expanded spectrum of the aromatic region. (bottom) HSQC chart of **3Br_C3A** in $CDCl_3$.

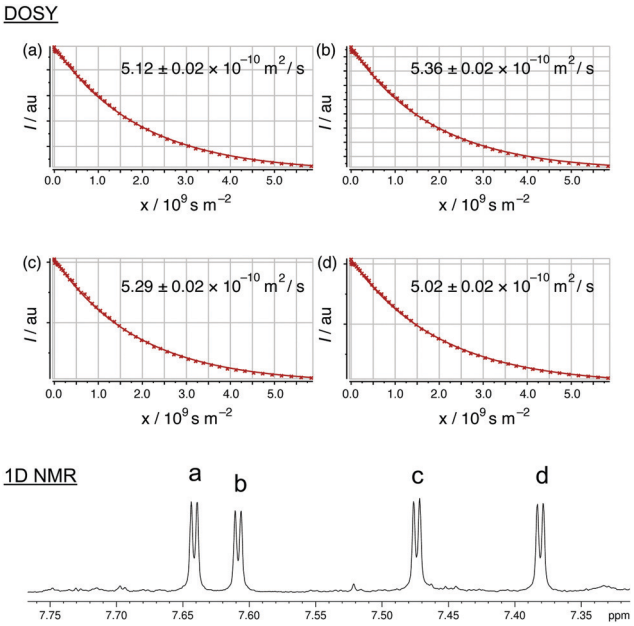


Fig. 5 Results of DOSY analysis for four aromatic protons (see the Experimental section for details).

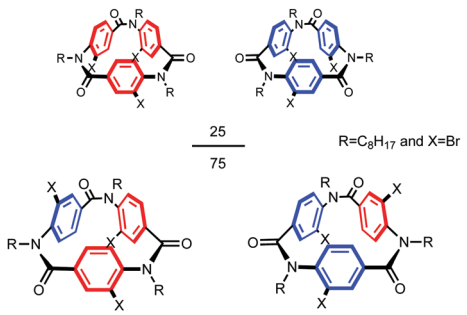
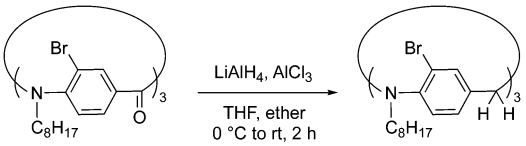


Fig. 6 Population of *syn*/*anti* stereoisomers in **3Br_C3A**.

Even when the dehydrative cyclic trimerization of **6** using PPh_3/Cl_3CCCl_3 was carried out at lower temperature (100 °C), an almost similar *syn*/*anti* ratio was observed (*syn*/*anti* = 27/73, Fig. S7, ESI†). **3Br_C3A** obtained using $SiCl_4$ also exhibited the same *syn*/*anti* ratio (25/75, not shown here). Namely, as for **3Br_C3A**, the *anti*-stereoisomer was the major product unlike in the case of **DiBr_C3A**. This *anti* preference characteristic of **3Br_C3A** was qualitatively supported by the DFT calculations because the *anti*-stereoisomer has a lower energy than the *syn*-stereoisomer (Fig. S8, ESI†). This result can be easily rationalized by the steric hindrance between bromo groups. Azumaya and co-workers have previously reported that the similar dehydrative cyclic condensation of 3-decyloxy-4-(4′-methoxybenzyl)aminobenzoic acid using Ph_3PCl_2 in 1,1,2,2,-tetrachloroethane at 120 °C gave a cyclic trimer with a *syn*/*anti* ratio of 33/66.[27] Accordingly, the population of *syn*/*anti* stereoisomers is supposed to be determined by the existence of substituents at the *ortho*-position relative to the amide nitrogen and less influenced by the character of the substituent.



3Br_C3A 3Br_C3Ared

Scheme 3 Reduction of the amide carbonyl group in **3Br_C3A**.

The population of stereoisomers was almost irrespective of the solvent character used in the NMR measurement. For example, the *syn*/*anti* ratio in DMSO-d_6 was calculated as 30/70 although the complete signal assignment was difficult (Fig. S9, ESI†). Therefore the interconversion between *syn*- and *anti*-conformers of **3Br_C3A** is not allowed due to the steric hindrance of the substituent on the benzene ring and the rigid amide linker (Fig. S10, ESI†), which was further demonstrated by the VT-NMR measurement. As indicated in the top view of Fig. S11 (ESI†), no peak coalescence was observed although the apparent down-field shifts were seen for some aromatic proton signals upon heating the 1,1,2,2-tetrachloroethane-d_2 solution of **3Br_C3A**. These peak shifts might be stemmed from the interaction between **3Br_C3A** and the solvent although further experiments are required. The integral ratio did not change by varying the temperature. As for methylene proton signals adjacent to the amide nitrogen (Fig. S11, ESI,† bottom), a peak only at around 3 ppm exhibited a down-field shift, but two peaks were separately observed even at 100 °C. We finally carried out the reduction of the amide carbonyl group[28] for obtaining the cyclic trimer **3Br_C3Ared**, which has a methylene group between the benzene ring and nitrogen atom (Scheme 3). Although the reduction by using $LiAlH_4$ unexpectedly resulted in the production of uncharacterizable compounds, the combination of $LiAlH_4$ with $AlCl_3$ succeeded in obtaining the target compound. Because the *anti*-stereoisomer should have three sets of doublet proton signals with J = 1.8 Hz in the equal integral ratio, the proton signal at 7.57 ppm can be assigned to the *syn*-stereoisomer (Fig. S12, ESI†).

Thus, from the integral ratio, the *syn*/*anti* ratio of **3Br_C3Ared** was calculated as 15/85. Even though the skeletal rigidity is relaxed after reducing the amide carbonyl group, the interconversion between *syn*- and *anti*-conformers is difficult due to the steric hindrance of the substituent on the benzene ring (*vide supra*). It can be speculated that the sterically crowded *syn*-stereoisomer of **3Br_C3Ared** partially decomposes as deduced from the presence of a peak at m/z = 296.1009 in the HR ESI-MS (Fig. S13, ESI†).

Conclusions

The design and synthesis of cyclic oligomers with well-defined conformations and functional groups are of much importance not only in pursuing the host–guest chemistry but also for developing supramolecular and polymer materials with smart functions. In this work, we have investigated the stereoselectivity in the dehydrative cyclic trimerization of 4-alkylaminobenzoic acids having two methoxy groups and one bromo group. The population of stereoisomers of the cyclic trimer, for example the *syn*/*anti* ratio, was influenced by the substituent on the benzene ring as evidenced by the comprehensive NMR analyses and preliminary theoretical calculations. We believe that our present findings have a great value for constructing supramolecular and polymer systems by using obtained compounds as new building blocks.

Conflicts of interest

There are no conflicts to declare.

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