JOC Note

Chiral Spherical Molecule Constructed from Aromatic Amides: Facile Synthesis and Highly Ordered Network Structure in the Crystal

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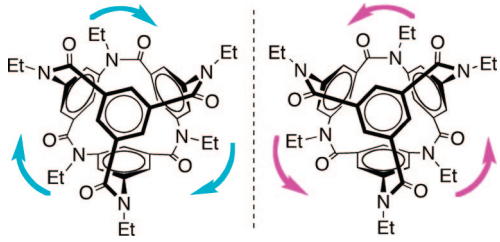

A novel chiral spherical molecule composed of aromatic amide was synthesized in short steps. The molecule is constructed from four benzene rings connected by six amide bonds and has multiple functionalizable points and an asymmetric structure. The racemic spherical molecule constructed channel network structures in the crystalline state.

Spherical molecules are of interest because of their high symmetry and associated customizable functionality.[1] For example, they are expected to be valuable scaffolds for stereoselective organic reactions[2] or dendrimer cores,[3] because they have mechanical rigidity and well-defined conformation. Moreover, bulky spherical molecules can generate interesting 3-D architecture in the crystalline state.[4] Consequently, extensive efforts have been devoted to obtaining functional spherical molecules,[5] and it is important to find new types of spherical molecules with pseudopolyhedral structure that can be synthesized and modified more easily than typical polyhedral.

For this purpose, we designed a new type of spherical molecule and developed an effective synthesis. The aromatic amide **1** is a simple spherical molecule constructed from four benzene rings connected by six amide bonds. It has pseudo-C_3 symmetry and is a chiral structure, as a result of the direction of its amide bonds,[6] with multiple functionalizable nitrogen atoms. Here, we report an effective construction and structural analysis of the novel chiral spherical molecule **1**. X-ray crystallographic analyses reveal attractive 3-D network structures of the racemic or enantiopure spherical molecules.

In the synthesis of the spherical molecule, preorganization of the small partial structures was used effectively.[7] Previously, we have succeeded in the synthesis of a cyclic aromatic amide trimer in high yield, by utilizing the stereochemistry of tertiary aromatic amide in the presence of dichlorotriphenylphosphorane as condensation reagent.[8] The cyclic amide trimer **3** was obtained in this manner.[9] Subsequently, direct conversion from nitro groups of **3** to ethylamino groups was successful by catalytic hydrogenation in the presence of acetonitrile (Scheme 1).[10] Direct condensation of alkylated triamine **4** with trimesic acid provided the spherical amide **1**. An overall yield of **1** from commercially available 3-amino-5-nitrobenzoic acid is 18% in only four steps.

Cyclic amide trimer **3** and **4** have two enantiomeric bowl-shaped conformations based on the direction of the amide bond.[9] These atropisomers are not separable because they are easily converted to each other by flipping of benzene rings in a solution at ambient temperature.[9] The addition of a trimesic acid as a capping group covalently captures this conformation and generates a fixed chiral structure. Therefore, **1** is obtained as a racemic mixture of both enantiomers. Chiral separation of racemic **1** was carried out by chiral HPLC. The enantiopure

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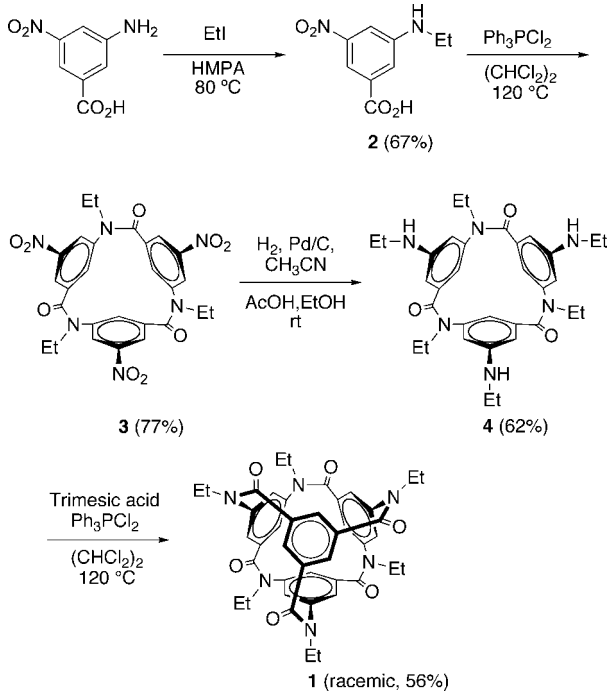
SCHEME 1. Synthesis of Spherical Molecules



compounds ((+)-**1** and (−)-**1**) showed clear mirror-imaged CD spectra in acetonitrile (Figure 1).

X-ray crystallographic analysis was performed on a single crystal of racemic compound **1** that was obtained from a chloroform/methanol solution by slow evaporation of the solvent. Figure 2 shows that compound **1** has an expected spherical structure. The diameter of the circumscribed sphere of the four benzene rings is ∼9.5 Å and the longest diameter of a space-filling model (between the carbonyl carbon atoms facing each other) is ∼12 Å.

In the racemic crystal of **1**, the enantiomers are arranged alternately in a doughnut shape toward the *a* and *b* axes of the unit cell (Figures 3a and 3c). Furthermore, this network layer is laminated along the *c* axis, forming a channel network structure (Figure 3b). This circular shaped channel, which has a diameter of ∼4.0 Å (based on van der Waals radius) contains water molecules. It is known that bulky spherical molecule can

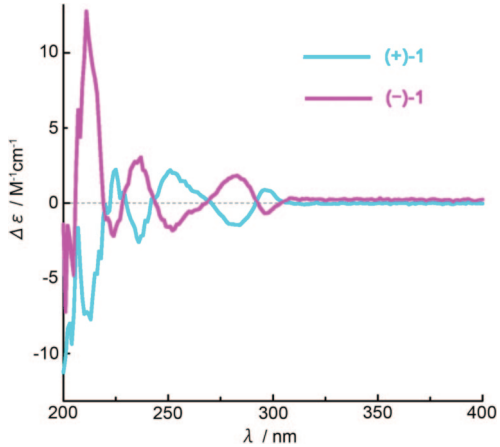


FIGURE 1. CD spectra of enantiopure (+)-**1** and (−)-**1** in acetonitrile.

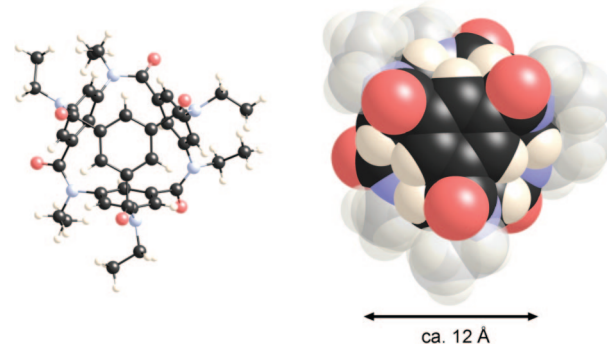


FIGURE 2. Structure of **1** in the crystal. Ball-and-stick model (left) and space-filling model (right). The ethyl groups are faded to make clear the shape of the spherical core.

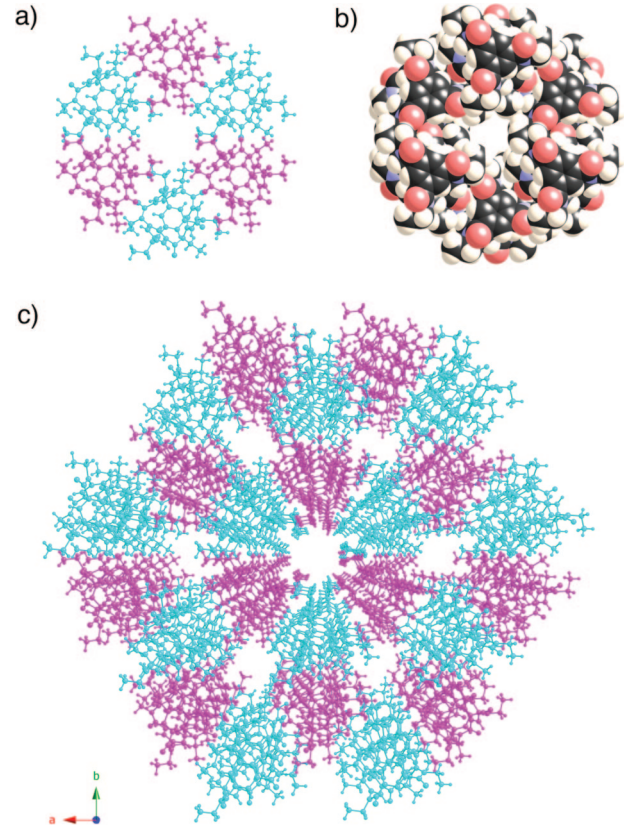


FIGURE 3. Packing structure in a racemic crystal of **1**. Ball-and-stick model (a), space-filling model (b), and channel network structure (c). Magenta- and cyan-colored molecules are enantiomers of each other. Water molecules are omitted for clarity.

construct a highly ordered aggregation in crystalline state.[11] In this case, the construction of highly ordered network structure is associated by weak intermolecular interactions (CH/O and CH/π interactions;[12] see Supporting Information).

In contrast, chiral separated enantiopure (+)-**1** did not form a channel-shaped network structure in the crystalline state (Figure 4). The chiral molecules built up as a 1-D columnar structure. This means that the difference of types of the weak

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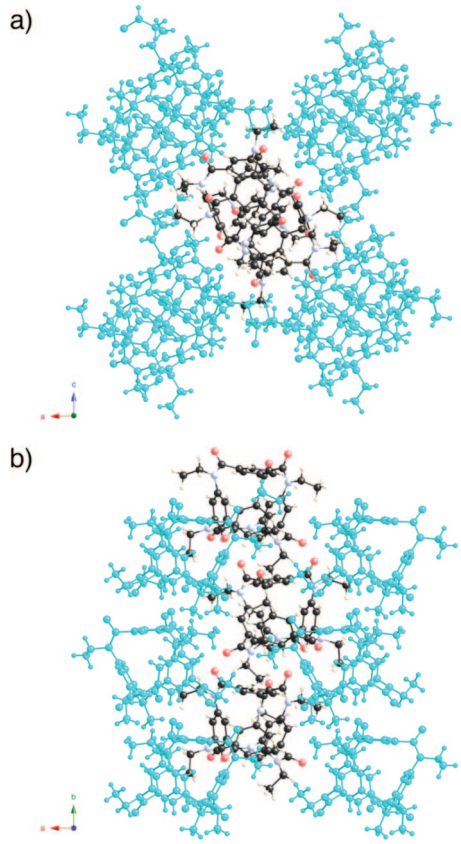

FIGURE 4. Packing structure in a chiral crystal of enantiopure (+)-**1**. Top view (a) and side view (b). The molecules except in the center column are colored in cyan, and water molecules are omitted to make the arrangement clear.

intermolecular interactions due to asymmetry of the spherical molecule brings about a change of the shape of network structure in the crystal (Figures S4 and S5 in Supporting Information).

In conclusion, we have designed a novel chiral spherical molecule and synthesized it in short steps by means of stereochemistry of the aromatic amide. It suggests that the preorganized aromatic amide component is useful for construction of various 3-D macromolecules.[13] In addition, the spherical molecule constructed a channel-shaped network by the multiple weak intermolecular interactions in the crystalline state. These features may be useful for the construction of functional molecular 3-D networks, such as molecular channels for clathration. Three stereoisomers of **1** (each consisting of two enantiomers) based on the directions of the amide bonds are also expected to exist. Differences in the direction of the functional groups in these spherical structures may result in unique organizational features, and we are currently attempting to synthesize the other isomers.

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Experimental Section

General. For ^{1}H and ^{13}C NMR, chemical shifts are reported in ppm on the δ scale relative to TMS or residual solvent. Coupling constants J are in hertz. Unless otherwise noted, NMR spectra were measured at room temperature. Reactions were carried out in dry solvents, unless otherwise mentioned.

Synthesis of 3-(Ethylamino)-5-nitrobenzoic Acid 2. Ethyl iodide (0.250 mL, 3.10 mmol) was added to 3-amino-5-nitrobenzoic acid (1.00 g, 5.49 mmol) in hexamethylphosphoric triamide (55 mL) under argon. After the solution was heated at 80 °C with stirring for 16 h, 100 mL of AcOEt was added. The mixture was washed with distilled water and brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The residues were purified by column chromatography with chloroform/methanol. 3-Amino-5-nitrobenzoic acid (0.317 g, 1.74 mmol) was recovered, and product **2** (0.525 g, 67%) was obtained as a yellow powder. Sufficient compound was obtained by repeat of similar method; mp 186−187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (1H, t, J = 1.4), 7.49−7.46 (2H, m), 4.39 (2H, q, J = 7.1), 3.25 (2H, q, J = 7.2), 1.41 (3H, t, J = 7.2), 1.30 (3H, t, J = 7.2); MS(FAB) m/z 210 (M^+). Anal. Calcd for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.49; H, 4.60; N, 13.36. Other spectral data is described in ref 9b.

Synthesis of Cyclic Trimer 3. Dichlorotriphenylphosphorane (6.02 g, 18.1 mmol) was added to **2** (1.96 g, 9.32 mmol) in 1,1,2,2-tetrachloroethane (22 mL) under argon. After heating at 140 °C with stirring for 7 h, the solution was evaporated. The residue was purified by column chromatography with chloroform/methanol. Preparative GPC with chloroform gave product **3** (1.38 g, 77%) as a white powder; mp 222−225 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.26 (s, 3H), 8.19 (S, 3H), 7.67 (S, 3H), 3.77 (6H, m), 1.09 (t, J = 7.0, 9H); ^{13}C NMR (100 MHz, DMSO) δ 167.0, 148.4, 143.0, 140.1, 134.0, 125.6, 122.0, 44.3, 12.8; MS(FAB) m/z 577 (MH^+). Anal. Calcd for $C_{27}H_{24}N_3O_6$: C, 56.25; H, 4.20. Found: C, 56.09; H, 3.78. Other spectral data is described in ref 9b.

Synthesis of Cyclic Trimer 4. After five vacuum/H_2 cycles to remove air from the reaction tube, the stirred mixture of the cyclic trimer **3** (0.865 g, 1.50 mmol), 10% Pd/C (0.260 g, 30 wt % of the substrate), acetonitrile (1.18 mL, 22.5 mmol), and acetic acid (0.520 mL, 9.08 mmol) in methanol (20 mL) and activated molecular sieves 3Å (5 g) was hydrogenated at ordinary pressure (balloon) at room temperature. After 5.5 days, acetic acid (0.520 mL, 9.08 mmol) and acetonitrile (0.590 mL, 11.3 mmol) were added. Then, the reaction mixture was stirred at room temperature for 3 days, filtered, and evaporated. The residue was purified by column chromatography with chloroform/methanol. And then, preparative GPC with chloroform gave product **4** (0.532 g, 62%) as a white powder; mp ≥ 300 °C; IR (KBr) 3352, 2970, 2932, 1637, 1588 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 393K) δ 6.34 (3H, s), 6.26 (3H, s), 6.01 (3H, m), 5.02 (3H, s), 3.66 (6H, q, J = 7.2), 2.96 (6H, m), 1.10 (9H, t, J = 6.8), 1.07 (9H, t, J = 7.2); ^{13}C NMR (100 MHz, DMSO, 393K) δ 149.1, 142.7, 139.0, 115.2, 112.7, 110.5, 43.8, 37.5, 14.1, 12.6; MS(FAB) m/z 571 (MH^+). Anal. Calcd for $C_{33}H_{42}N_6O_3 \cdot 1/3(CHCl_3)$: C, 65.73; H, 7.05; N, 13.66. Found: C, 65.60; H, 7.04; N, 13.62. ^{1}H and ^{13}C NMR spectra for **4** indicate many broad peaks at room temperature.[9b] VT-NMR spectra for **4** are shown in Supporting Information.

Synthesis of Spherical Molecule 1. Dichlorotriphenylphosphorane (0.666 g, 2.00 mmol) was added to mixture of **4** (0.114 g, 0.200 mmol) and 1,3,5-benzenetricarboxylic acid (0.0462 g, 0.220 mmol) in 1,1,2,2-tetrachloroethane (10 mL) under argon. After heating at 120 °C with stirring for 5 h, the solution was evaporated. The residue was purified by column chromatography with chloroform/methanol. Preparative GPC with chloroform gave product **1** (0.809 g, 56%) as a white powder; mp ≥ 300 °C; IR (KBr) 3445, 3074, 2967, 2933, 1654, 1590 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (3H, s), 6.81 (3H, t, J = 1.6), 6.79 (3H, t, J = 1.6), 6.67 (3H, t, J = 1.8), 3.89−3.78 (6H, m), 3.75−3.64 (6H, m), 1.17 (9H, t, J =

7.2), 1.16 (9H, t, $J = 7.2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 168.5, 144.2, 143.2, 140.6, 137.8, 131.0, 127.5, 126.9, 126.2, 45.2, 45.0, 12.9, 12.7; MS(FAB) *m/z* 727 (MH^+). Anal. Calcd for $C_{42}H_{42}N_6O_6 \cdot 1/2(H_2O)$: C, 68.56; H, 5.89; N, 11.42. Found: C, 68.67; H, 5.67; N, 11.53.

X-ray Crystallographic Data for Racemic 1. $C_{42}H_{42}N_6O_6$, $1.5(H_2O)$, $M_r = 753.84$ g mol^{-1}, monoclinic, *Cc*, $a = 15.580(2)$, $b = 27.514(3)$, $c = 9.2074(9)$ Å, $\beta = 92.224(2)°$, $V = 3943.9(7)$ Å^3, $Z = 4$, $D_{calcd} = 1.270$ Mg m^{-3}, $\mu = 0.088$ mm^{-1}, $T = 150$ K, $2\theta_{max} = 56.50°$, 11003 reflections, 4466 unique ($R_{int} = 0.0460$), $R_1 = 0.0604$, $wR_2 = 0.1464$ ($I > 2\sigma(I)$), CCDC-650286. Other details are described in Supporting Information, including a CIF file.

X-ray Crystallographic Data for Enantiopure (+)-1. $C_{42}H_{42}N_6O_6$, $1.5(H_2O)$, $M_r = 753.84$ g mol^{-1}, monoclinic, $P2_1$, $a = 14.597(1)$, $b = 17.366(2)$, $c = 15.335(1)$ Å, $\beta = 91.590(1)°$, $V = 3885.7(6)$ Å^3, $Z = 4$, $D_{calcd} = 1.289$ Mg m^{-3}, $\mu = 0.090$ mm^{-1}, $T = 120$ K, $2\theta_{max} = 54.20°$ 19063 reflections, 8129 unique ($R_{int} = 0.0376$), $R_1 = 0.0501$, $wR_2 = 0.1151$ ($I > 2\sigma(I)$), CCDC-680551. Absolute structure of (+)-**1** is not clarified. Other details are described in Supporting Information, including a CIF file.

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Supporting Information Available: Copies of spectra and chromatograms, expanded structural data and crystallographic information files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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