

Supplementary Information

Crystal Structure of Spherical Aromatic Amide: Pseudopolymorphs and Formation of Infinite Water Cluster in the Channel Structure

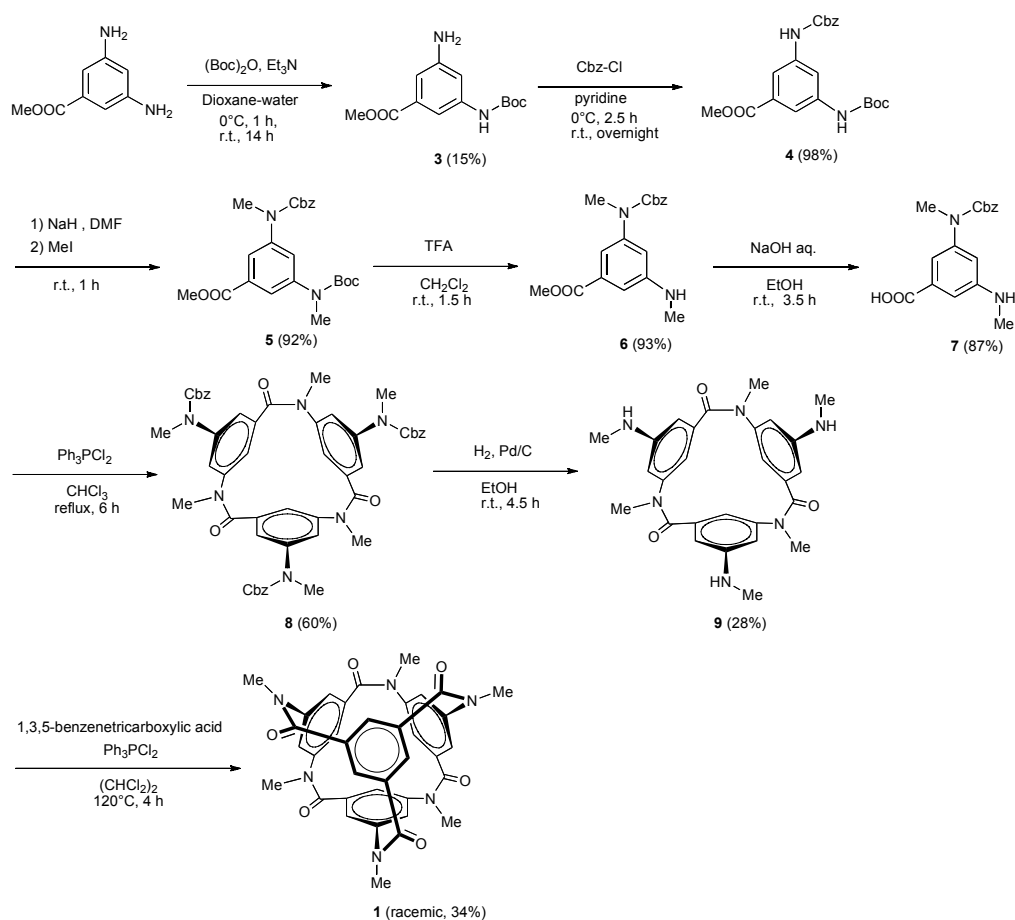
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Synthesis property.

Scheme S1. Synthesis of spherical aromatic amide **1**.



Synthesis of Methyl 3-amino-5-(*N*-*tert*-butyloxycarbonylamino) benzoate (**3**)

To a solution of methyl 3,5-diamino benzoate (15.0 g, 90 mmol) in a 2:1 mixture of dioxane/water (540 mL) was added di-*tert* butyldicarbonate (18.0 mL, 79 mmol), and trimethylamine (27.0 mL, 27 mmol). The mixture was gently stirred at 0°C for 1 h and at room temperature for 14 h. The reaction mixture was evaporated, and the residue was triturated numerous times with ethanol to give product **3**: 3.56 g, 15% yield, brown crystal, mp 136°C . IR (KBr): 1713, 3285, 3383, 3478 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 1.51 (9H, s), 3.87 (3H, s), 6.51 (1H, br, s), 7.03 (1H, dd, $J = 1.5, 1.5\text{ Hz}$), 7.17 (1H, dd, $J = 1.5, 1.5\text{ Hz}$), 7.24 (1H, br, s). ^{13}C NMR (100 MHz, CDCl_3): δ 28.3, 52.1, 80.7, 109.0, 109.7, 110.6, 131.6, 139.5, 147.2, 152.6, 166.9. MS (DI-EI) $m/z = 266$ [M^+]. Anal. Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.59; H, 6.75; N, 10.46.

Synthesis of Methyl 3-(N-benzyloxycarbonylamino)-5-(N-tert-butyloxycarbonylamino) benzoate (4)

To a solution of **3** (1.39 g, 5.2 mmol) in pyridine (50 mL) at 0 °C was added Cbz-chloride (1.49 mL, 10 mmol). After stirring at room temperature over night, the mixture was poured into 2 M HCl (100 mL) with ice and filtered. The filtrate was recrystallized from AcOEt to give product **4**: 2.04 g, 98% yield, pale yellow powder, mp 165 °C. IR (KBr): $\nu = 1700, 3335 \text{ cm}^{-1}$. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 1.51 (9H, s), 3.87 (3H, s), 5.20 (2H, s), 6.64 (1H, br, s), 6.86 (1H, br, s), 7.69 (2H, d, $J = 2.0$ Hz), 7.91 (1H, br), 7.31–7.43 (5H, m). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 28.3, 52.3, 67.2, 81.0, 112.5, 114.0, 114.3, 128.3, 128.4, 128.6, 131.5, 135.9, 138.7, 139.4, 152.5, 153.1, 166.5. MS (DI-EI) $m/z = 400$ [M^+]. Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_6$: C, 62.99; H, 6.04; N, 7.00. Found: C, 62.82; H, 6.14; N, 6.93.

Synthesis of Methyl 3-(N-benzyloxycarbonyl-N-methylamino)-5-(N-tert-butyloxycarbonyl-N-methylamino)benzoate (5)

To a solution of **4** (2.32 g, 5.8 mmol) in DMF (60 mL) under argon was added sodium hydride (60% in oil) (0.210 g, 8.7 mmol). The solution was stirred at 0 °C for 5 minutes. Methyl iodide (0.56 mL, 17 mmol) was added, and the solution was stirred for 25 min at room temperature. Then, the solution was re-cooled to at 0 °C and sodium hydride (60% in oil) (0.210 g, 8.7 mmol) was added. After 5 minutes, methyl iodide (0.56 mL, 17 mmol) was added, and the solution was stirred for 25 minutes at room temperature. The solution was poured onto ice. After extraction with AcOEt, the organic layer was successively washed with 2 M HCl, brine, saturated NaHCO_3 , brine and dried over Na_2SO_4 . The organic layer was evaporated to give crude products. The crude was purified by chromatography on a silica gel column with AcOEt/hexane (1:4 v/v) as the eluent to give product **5**: 2.20 g, 92% yield, clear oil. IR (Nujol): 1713 cm^{-1} . $^1\text{H NMR}$ (400 MHz, CDCl_3): δ (9H, s), 3.24 (3H, s), 3.34 (3H, s), 3.91 (3H, s), 5.17 (2H, s), 7.27–7.37 (5H, m), 7.42 (1H, br, s), 7.72 (1H, dd, $J = 2.0, 2.0$ Hz), 7.77 (1H, dd, $J = 2.0, 2.0$ Hz). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 28.5, 37.3, 37.8, 52.6, 67.8, 81.2, 123.3, 123.9, 127.5, 128.1, 128.3, 128.7, 131.2, 136.5, 143.7, 144.5, 154.5, 155.4, 166.4. MS (EI-DI) $m/z = 428$ [M^+]. HRMS (FAB) Calcd for $\text{CH}_{32}\text{N}_2\text{O}_6$ [M^+]: 428.1947. Found 428.1947.

Synthesis of

Methyl 3-(N-benzyloxycarbonyl-N-methylamino)-5-(N-methylamino) benzoate (6).

To a solution of **5** (1.28 g, 3.0 mmol) in dichloromethane (30 mL) at room temperature was added, with stirring, TFA (3.3 mL). After 10 minutes, TFA (3.0 mL)

was added to the solution, and stirred at room temperature for 1.5 h. The solution was poured onto ice and alkalized with saturated NaHCO₃, and extracted with AcOEt. The organic layer was successively washed with brine and dried over Na₂SO₄. The solvent was evaporated and the crude product was purified by chromatography on a silica gel column with AcOEt/hexane (1:2 v/v) as the eluent to give product **6**: 0.913 g, 93% yield, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 2.84 (3H, s), 3.31 (3H, s), 3.89 (3H, s), 5.16 (2H, s), 6.73 (1H, br, s), 7.17 (1H, dd, *J* = 2.5, 1.5 Hz), 7.27 (1H, dd, *J* = 1.5, 1.5 Hz), 7.28–7.39 (5H, m). ¹³C NMR (100 MHz, CDCl₃): δ 31.1, 37.7, 52.2, 67.4, 111.7, 115.0, 116.2, 127.8, 127.9, 128.4, 131.6, 136.5, 144.3, 148.8, 155.3, 166.8. MS (EI-DI) *m/z* = 328 [M⁺]. HRMS (FAB) Calcd for C₁₈H₂₀N₂O₄ [M+H]⁺: 329.1501. Found 329.1523.

Synthesis of 3-(N-benzyloxycarbonyl-N-methyl)-5-(N-methylamino)benzoic acid (7).

To a solution of **6** (0.0985 g, 0.3 mmol) in ethanol (1.2 mL) was added, with stirring, 4 M NaOH (0.6 mL). The mixture was stirred for 3.5 h at room temperature. The mixture was neutralized with 2 M HCl, and extracted with AcOEt. The organic layer was evaporated to give crude product. The crude was purified by chromatography on a silica gel column with CH₂Cl₂/MeOH (20:1 v/v) as the eluent to give product **6**: 0.0816 g, 87% yield, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 2.84 (3H, s), 3.33 (3H, s), 5.18 (2H, s), 6.73 (1H, br, s), 7.19 (1H, dd, *J* = 2.5, 1.5 Hz), 7.26–7.38 (5H, m). ¹³C NMR (100 MHz, CDCl₃): δ 30.6, 37.7, 67.4, 111.5, 115.0, 115.8, 127.8, 128.0, 128.4, 130.7, 136.5, 144.3, 149.8, 155.4, 171.5. MS (FAB) *m/z* = 315 [M+H]⁺. HRMS (FAB) Calcd for C₁₇H₁₈N₂O₄ [M⁺]: 314.1267. Found 314.1269.

Synthesis of Compound 8.

To a solution of **7** (0.212 g, 0.67 mmol) in dry chloroform (7 mL) was added, with stirring, dichlorotriphenylphosphorane (0.538 g, 1.6 mmol). The mixture was refluxed for 6 h with stirring, and the reaction was poured onto ice. The reaction mixture was extracted with AcOEt, and the organic layer was successively washed with brine and dried over Na₂SO₄ and evaporated to give crude product. The crude was purified by chromatography on a silica gel column with AcOEt/hexane (1:5 v/v) as the eluent and the products were purified again by chromatography on a silica gel column with AcOEt/CH₂Cl₂ (1:1 v/v) as the eluent to give product **8**: 0.139 g, 60% yield, pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 2.98–3.20 (9H, br), 3.24 (9H, s), 5.10 (6H, br, s), 7.27–7.39 (27H, m). MS (FAB) *m/z* = 889 [M+H]⁺

Synthesis of Compound 9.

To a solution of **8** (0.142 g, 0.16 mmol) in ethanol (5 mL) under hydrogen atmosphere was added, with stirring, Pd/C (5%, 40 mg) for 4.5 h at room temperature. The mixture was filtered and evaporated to give crude product, which was purified with recrystallized from CH₂Cl₂/MeOH (20:1 v/v) to give product **9**: 0.0217 g, 28% yield, white powder. ¹H NMR (400 MHz, CDCl₃): δ 2.65 (9H, s), 3.20–3.29 (9H, br), 5.76–6.78 (9H, br, m). MS (EI-DI) *m/z* = 487 [M+H]⁺. HRMS (FAB) Calcd for C₂₇H₃₁N₃O₆ [M+H]⁺: 487.2458. Found 487.2458.

Synthesis of Spherical Molecule 1.

To a solution of **9** (0.0175 g, 0.036 mmol) in 1,1,2,2-tetrachloroethane (0.36 mL) were added, with stirring, dichlorotriphenylphosphorane (0.0288 g, 0.086 mmol) and 1,3,5-benzenetricarboxylic acid (0.00761 g, 0.036 mmol) for 4 h at 120 °C. The solution was evaporated and the crude products were purified by gel filtration with MeOH to give product **1**: 0.00783 g, 34% yield, white powder. ¹H NMR (400 MHz, CD₃OD): δ 3.29 (9H, s), 3.30 (9H, s), 7.11–7.17 (9H, m), 7.22 (3H, dd, *J* = 2.0, 2.0 Hz). ¹³C NMR (100 MHz, CD₃OD): δ 38.6, 38.7, 127.2, 128.4, 128.6, 131.2, 139.6, 142.3, 146.9, 147.3. MS (FAB) *m/z* = 643 [M+H]⁺. Anal. Calcd for C₂₁H₂₄N₂O₆ · 1/3(H₂O): C, 66.66; H, 4.77; N, 12.96. Found: C, 66.63; H, 4.70; N, 12.82.

X-ray crystallography.

Details of measurement and analysis. Single crystal X-ray diffraction data of the crystals were collected on a CCD diffractometer with graphite monochromated MoK α ($\lambda = 0.71073 \text{ \AA}$) radiation. The crystal structure was solved by direct methods SHELXS-97 and refined by full-matrix least-squares SHELXL-97.^{*1} All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included as their calculated positions except for water molecules.

The positions of hydrogen atoms in water molecules in crystal **1a** were not determined based on the electron density.

The geometrical parameters for potential hydrogen bonds including CH/O and CH/N interactions (Table S1 and S2) are calculated by SHELXL program and PLATON program.^{*2}

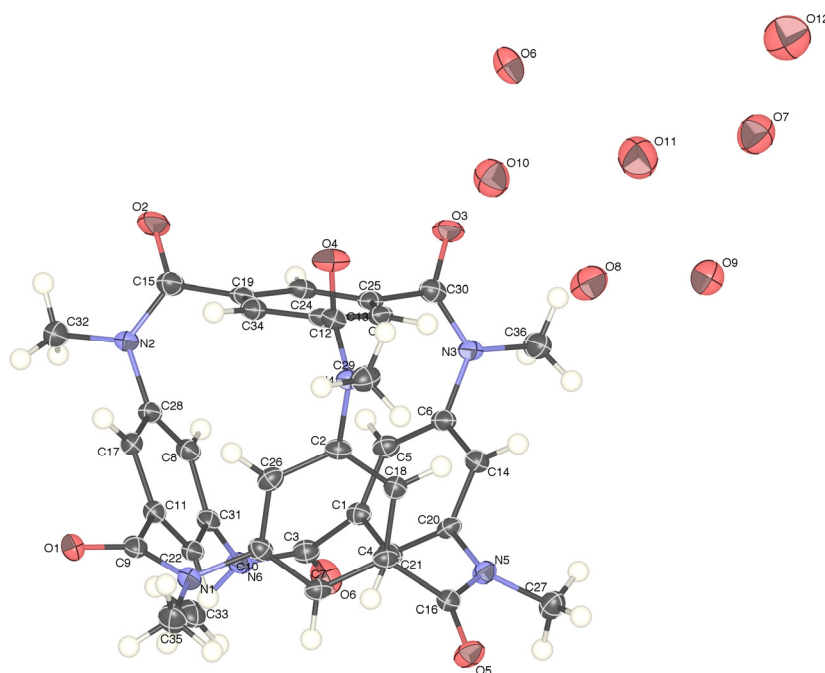


Fig. S1 Thermal ellipsoid diagram of crystal **1a**. Ellipsoids are drawn at the 50 % probability level while isotropic hydrogen atoms are represented by spheres of arbitrary size.

Table S1. Distances (d) and angles (\angle) of intermolecular hydrogen bonds and CH/O interactions in the crystal **1a**.

Classical hydrogen bonds		$d(\text{O}\dots\text{O})$	
$\text{O}(-\text{H})\dots\text{O}^{a, b}$		Å	
O(7)...O(9)#1		2.779	
O(7)...O(12)		2.725	
O(8)... <u>O(1)</u> #2		2.874	
O(8)... <u>O(5)</u> #3		2.791	
O(8)...O(9)#2		2.770	
O(9)...O(9)#4		2.790	
O(9)...O(11)		2.811	
O(10)... <u>O(3)</u> #5		2.861	
O(10)... <u>O(6)</u> #6		3.044	
O(10)...O(11)		2.775	
O(11)...O(12)		2.746	
O(12)...O(12)#7		2.732	
CH/O interactions	$d(\text{D}-\text{H})^c$	$d(\text{D}\dots\text{A})$	$\angle(\text{DHA})$
$\text{D}-\text{H}\dots\text{A}^{a, b}$	Å	Å	deg
C(8)-H(8)...O(6)#5	0.95	3.492	160
C(17)-H(17)...O(5)#8	0.95	3.323	160
C(18)-H(18)...O(1)#2	0.95	3.242	162
C(21)-H(21)...O(3)#1	0.95	3.104	134
C(24)-H(24)...O(6)#2	0.95	3.351	138
C(29)-H(29B)...O(2)#9	0.98	3.284	175
C(32)-H(32B)...O(4)#10	0.98	3.264	142
C(35)-H(35B)...O(4)#1	0.98	3.470	172

^a Symmetry transformations used to generate equivalent atoms:

#1 -1+x, y, z; #2 x, 1/2-y, -1/2+z; #3 1+x, y, z; #4 2-x, 1-y, 1-z;
 #5 2-x, -y, 1-z; #6 1-x, -y, 1-z; #7 1-x, 1-y, 1-z; #8 1+x, 1/2-y, 1/2+z;
 #9 -1+x, 1/2-y, -1/2+z; #10 x, 1/2-y, 1/2+z.

^b Underlined oxygen atoms are included in the amide group of the spherical amide **1**.

^c The positions of hydrogen atoms were calculated with constrains based on geometrical adequacy by "HFIX" of SHELXL program.

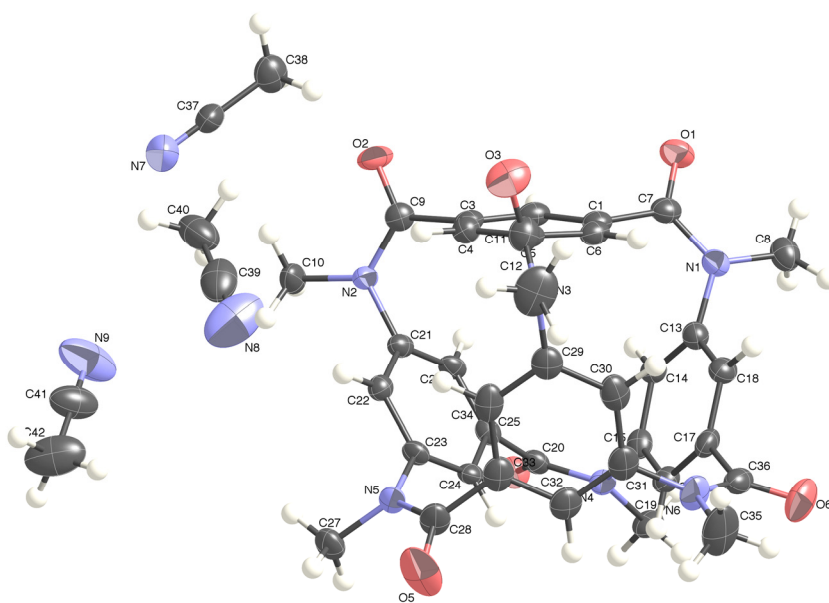


Fig. S2 ORTEP diagram of crystal **1b**. Ellipsoids are drawn at the 50 % probability level while isotropic hydrogen atoms are represented by spheres of arbitrary size.

Table S2. Distances (d) and angles (\angle) of intermolecular CH/O and CH/N interactions in the crystal **1b**.

CH/O interactions D-H...A ^{a, b}	$d(\text{D-H})^c$ Å	$d(\text{D...A})$ Å	$\angle(\text{DHA})$ deg
C(2)-H(2)...O(4)#1	0.95	3.287	142
C(10)-H(10B)...O(6)#2	0.98	3.532	171
C(24)-H(24)...O(2)#3	0.95	3.114	127
C(27)-H(27B)...O(6)#2	0.98	3.362	169
C(35)-H(35C)...O(3)#3	0.98	3.365	164
<u>C(38)</u> -H(38C)...O(1)#4	0.98	3.379	172
<u>C(38)</u> -H(38B)...O(2)#5	0.98	3.255	157
<u>C(40)</u> -H(40B)...O(1)#3	0.98	3.163	173
<u>C(42)</u> -H(42C)...O(5)#6	0.98	3.101	125
<u>C(40)</u> -H(40A)...O(6)	0.98	3.270	139
CH/N interactions D-H...A ^a	$d(\text{D-H})$ Å	$d(\text{D...A})$ Å	$\angle(\text{DHA})$ deg
C(4)-H(4)...N(9)#2	0.95	3.472	149
C(10)-H(10A)...N(8)#1	0.98	3.473	150
C(34)-H(34)...N(9)#2	0.95	3.517	163
C(35)-H(35B)...N(8)#4	0.98	3.592	170

^a Symmetry transformations used to generate equivalent atoms:

#1 1-x,1-y,1-z; #2 x,1/2-y,1/2+z; #3 1+x,y,z; #4 1-x,-1/2+y,1/2-z;

#5 1+x,1/2-y,-1/2+z; #6 -1+x,1/2-y,-1/2+z.

^b Underlined carbon atoms are included in the acetonitrile molecules.

^c The positions of hydrogen atoms were calculated with constrains based on geometrical adequacy by "HFIX" of SHELXL program.

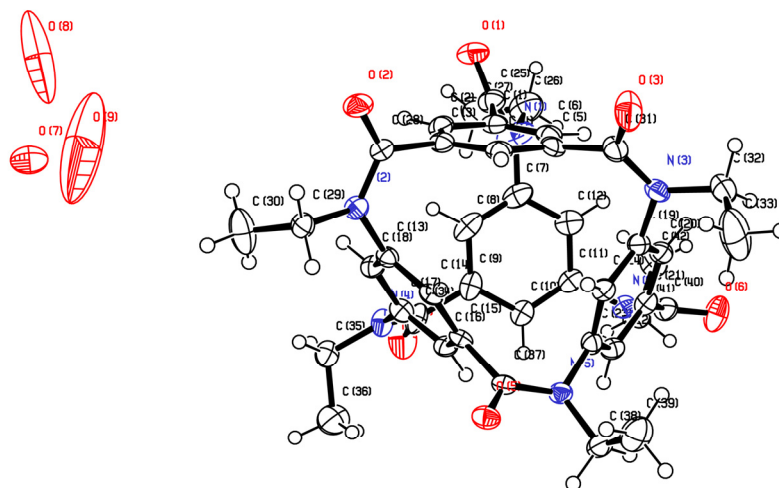


Fig. S3 Thermal ellipsoid diagram of crystal **2**.^{*3} Ellipsoids are drawn at the 50 % probability level while isotropic hydrogen atoms are represented by spheres of arbitrary size. The positions of hydrogen atoms included in the water molecules were not fixed.

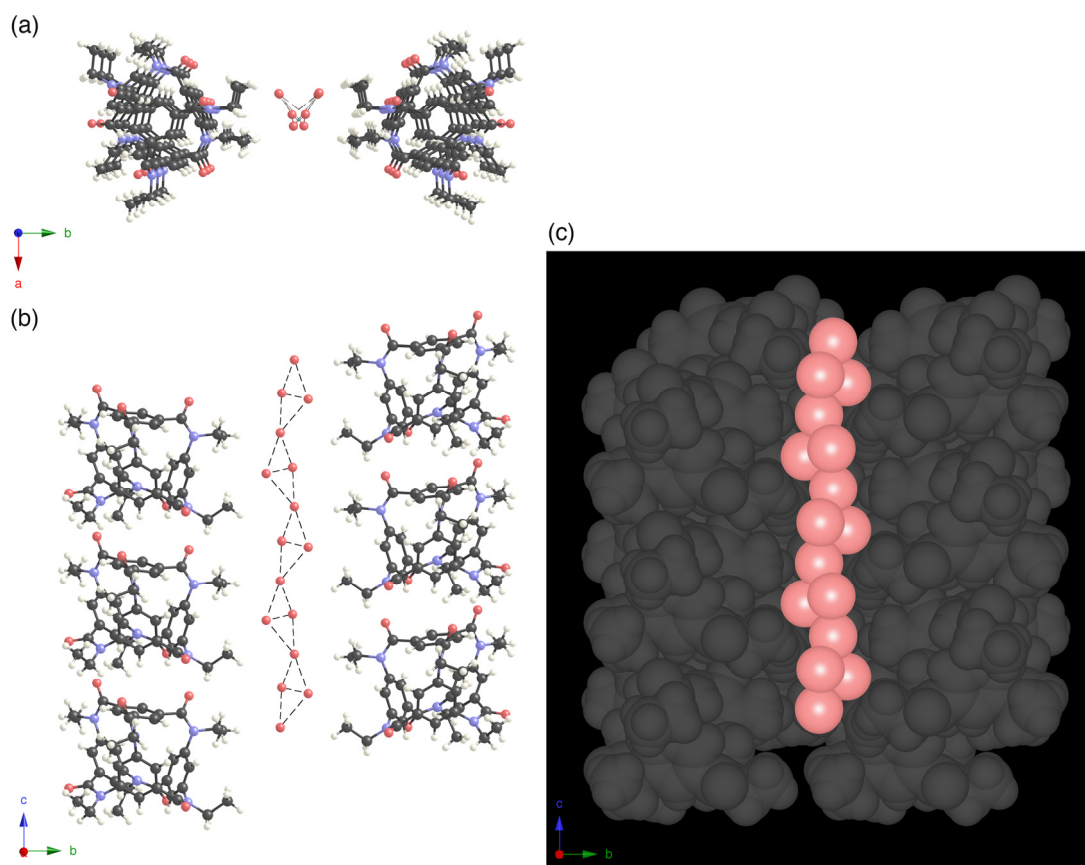


Fig. S4 1D network structure of water molecules in the crystal of **2**. (a) Top view. (b) Side view. H-bonds between water molecules are shown in dotted lines. (c) the channel (surface model) with incorporated water molecules (space-filling model).

References.

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- *3 H. Masu, K. Katagiri, T. Kato, H. Kagechika, M. Tominaga and I. Azumaya, *J. Org. Chem.*, 2008, **73**, 5143-5146.