Novel building blocks for crystal engineering: The first synthesis of oligo(imidazole)s

by

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General. ^{1}H NMR and NOESY spectra were recorded at 270 MHz and 600 MHz, respectively, with $CDCl_3$ or DMSO-d_6 as solvent and Me_4Si or residual solvent as an internal standard. Infrared spectra and electronic spectra were recorded using KBr plates. EI-MS spectra were recorded at 70 eV and 3-nitrobenzyl alcohol was used as matrix for FAB-MS spectra. Melting points were measured with a hot-stage apparatus and are uncorrected. Elemental analyses were performed at the Graduate School of Science, Osaka University. X-ray crystallographic measurement was made on a Rigaku AFC7R diffractometer with graphite monochromated Cu Kα radiation at room temperature. The structure was determined by direct method using SIR 92. R_f values on TLC were recorded on E. Merck precoated (0.25 mm) silica gel 60 F_{254} plates. The plates were sprayed with a solution of 10% phosphomolybdic acid in 95% EtOH and then heated until the spots became clearly visible. Silica gel 60 (100–200 mesh) was used for column chromatography. Recycle preparative gel permeation chromatography (GPC) was performed using tandemly connected two polystyrene gel columns (JAIGEL 1H, Japan Analytical Industry) with $CHCl_3$ as eluant. Solvents were dried (drying agent in parenthesis) and distilled under argon atmosphere prior to use: THF

(Na-benzophenone ketyl); DMF (CaH_2). 4-Iodoimidazole (**10**)[*1] and 1,1'-bis{[2''-(trimethylsilyl)ethoxy]methyl}-2,2'-biimidazole (**6**)[*2,3] were prepared by the literature procedures. Activated Zn[*4] and $Pd(PPh_3)_4$[*5] were also prepared and purified by the same procedure described in the literatures. All reactions requiring anhydrous conditions were conducted under argon atmosphere.

4-Bromo-1,1'-bis{[2''-(trimethylsilyl)ethoxy]methyl}-2,2'-biimidazole (7)[*3] **and 5-Bromo-1,1'-bis{[2''-(trimethylsilyl)ethoxy]methyl}-2,2'-biimidazole (8).**[*3] The SEM-protected biimidazole **6** (5.29 g, 13.4 mmol) and NBS (2.62 g, 14.7 mmol) were placed in a 500-mL Schlenk tube and dissolved in CCl_4 (200 mL). This mixture was refluxed for 2.5 h. After being cooled to room temperature, the reaction mixture was filtered through the celite column and rinsed with Et_2O (50 mL). The filtrates were concentrated under reduced pressure and the residual oil was subjected to silica gel column chromatography with a 100:1~8:1 mixture of hexane and ethyl acetate as eluant, to give **7** (1.34 g, 21%) as a red oil and **8** (1.75 g, 28%) as a red oil. **7**: TLC R_f 0.61 (1:3 hexane/ethyl acetate); ^{1}H NMR (270 MHz, $CDCl_3$) δ –0.04 (s, 9), 0.03 (s, 9), 0.8–0.9 (m, 4), 3.50–3.60 (m, 4), 5.88 (s, 2), 5.90 (s, 2), 7.12 (d, 1, J = 1.3 Hz), 7.14 (s, 1) , 7.17 (d, 1, J = 1.0 Hz). **8**: TLC R_f 0.33 (1:3 hexane/ethyl acetate); ^{1}H NMR (270 MHz, $CDCl_3$) δ –0.08 (s, 9), –0.04 (s, 9), 3.47–3.56 (m, 4), 5.83 (s, 2), 6.02 (s, 2), 7.10 (s, 1), 7.14 (d, 1, J = 1.3 Hz), 7.18 (d, 1, J = 1.3 Hz). The structure of **8** was confirmed by the measurement of the NOESY spectra on the basis of nuclear Overhauser effects (NOE).

1,1',1'',1'''-Tetrakis{[2''''-(trimethylsilyl)ethoxy]methyl}-2,2':4',4'':2'',2'''-quaterimidazole (9). $NiCl_2(PPh_3)_2$ (251 mg, 0.38 mmol), PPh_3 (201 mg, 0.77 mmol) and activated Zn (25 mg, 0.38 mmol) was placed in a 15-mL thick-walled ampule tube and dissolved with DMF (2 mL). The reaction mixture was degassed by a repeated freeze-pump-thaw method and stirred at room temperature for 1 h. The SEM-protected 4-bromobiimidazole **7** (181 mg, 0.38 mmol) in DMF (1 mL) was degassed by a repeated freeze-pump-thaw method, and this solution was added to a DMF solution of the nickel complex prepared above method, then the tube was sealed. After being stirred at 100 °C for 46 h, the tube was opened at room

temperature and the reaction mixture was poured into a satd NaCl aqueous solution (30 mL). The resulting mixture was extracted with ethyl acetate (30 mL). The organic layer was washed with a satd NaCl aqueous solution (30 mL) and dried over Na_2SO_4, then filtered and concentrated under reduced pressure. The residual oil was subjected to silica gel column chromatography with a 3:1~1:3 mixture of hexane and ethyl acetate as eluant. The resulting mixture containing desired compound was subjected to GPC with $CHCl_3$ as eluant, to give **9** (60.2 mg, 40%) as a pale purplish pink powder. mp 76–77 °C; TLC R_f 0.52 (1:3 hexane/ethyl acetate); ^{1}H NMR (270 MHz, $CDCl_3$) δ –0.06 (s, 18), –0.05 (s, 18), 0.91 (t, 8, J = 8.1 Hz), 3.54–3.61 (m, 8), 5.95 (s, 4), 6.01 (s, 4), 7.16 (s, 2), 7.20 (s, 2), 7.53 (s, 2); IR (KBr) 3120, 2956, 1249, 1101, 856 cm^{-1}; FAB-MS, *m*/*z* 787 (M^+ + H); Anal. Calcd for $C_{36}H_{66}N_8O_4Si_4$: C, 54.92; H, 8.45; N, 14.23. Found: C, 54.53; H, 8.55; N, 14.08.

4-Iodo-1-{[2'-(trimethylsilyl)ethoxy]methyl}imidazole (11). NaH (60% oil suspension, 4.00 g, 100 mmol) was placed in a 250-mL Schlenk tube and washed with hexane (20 mL x 3) to remove the mineral oil, and then suspended with DMF (100 mL). 4-Iodoimidazole (**10**) (15.9 g, 81.9 mmol) was added to this suspension, and the mixture was stirred at room temperature for 1 h. SEMCl (16.0 mL, 90.4 mmol) was added to this suspension over 5 min. The reaction mixture was warmed up to 40 °C and stirred at this temperature for 3 h. The resulting mixture was poured into H_2O (150 mL) and extracted with ethyl acetate (150 mL). The organic extracts were washed with a satd NaCl aqueous solution (150 mL) and dried over Na_2SO_4, then filtered and concentrated under reduced pressure. The residual oil was subjected to silica gel column chromatography with a 3:1~1:3 mixture of hexane and ethyl acetate as eluant, to give **11** (13.5 g, 51%) as a yellow oil. The structure of **11** was confirmed by the measurement of the NOESY spectra on the basis of nuclear Overhauser effects (NOE). TLC R_f 0.53 (1:3 hexane/ethyl acetate); ^{1}H NMR (270 MHz, $CDCl_3$) δ –0.01 (s, 9), 0.90 (t, 2, J = 7.3 Hz), 3.49 (t, 2, J = 7.3 Hz), 5.25 (s, 2), 7.15 (s, 1), 7.50 (s, 1); IR (KBr) 3106, 2953, 1094, 837 cm^{-1}; EI-MS, *m/z* 324 (M^+, 13%); Anal. Calcd for $C_9H_{17}N_2OSiI$: C, 33.34; H, 5.28; N, 8.64. Found: C, 33.57; H, 5.22; N, 8.64.

1,1'-Bis{[2''-(trimethylsilyl)ethoxy]methyl}-4,4'-biimidazole (12). The SEM-protected iodoimidazole **11** (12.01 g, 37.2 mmol), $Pd(PPh_3)_4$ (1.50 g, 1.30 mmol) and Et_3N (42.0 mL, 299 mmol) were placed in a 100-mL thick-walled ampule tube and dissolved with DMF (60 mL). The reaction mixture was degassed by a repeated freeze-pump-thaw method, then the tube was sealed. After being stirred at 100 °C for 72 h, the tube was opened at room temperature and the reaction mixture was poured into a satd $Na_2S_2O_3$ aqueous solution (150 mL). The resulting mixture was extracted with ethyl acetate (300 mL). The organic layer was washed with a satd NaCl aqueous solution (200 mL) and dried over Na_2SO_4, then filtered and concentrated under reduced pressure. The residual oil was subjected to silica gel column chromatography with ethyl acetate~5:1 mixture of ethyl acetate and MeOH as eluant, to give the coupling product **12** (6.80 g, 93%) as a soft yellow powder. mp 96–97 °C; TLC R_f 0.61 (3:1 ethyl acetate/MeOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ –0.15 (s, 18), 0.92 (t, 4, J = 8.3 Hz), 3.49 (t, 4, J = 8.3 Hz), 5.29 (s, 4), 7.40 (s, 2), 7.61 (s, 2); IR (KBr) 3109, 2953, 1250, 1098, 861, 831 cm^{-1}; EI-MS, *m/z* 394 (M^+, 42%), 278 ($M^+ - C_5H_{13}OSi + H^+$, 100%); Anal. Calcd for $C_{18}H_{34}N_4O_2Si_2$: C, 54,78; H, 8.64; N, 14.20. Found: C, 54,72; H, 8.74; N, 14.11.

1,1',1'',1'''-Tetrakis{[2''''-(trimethylsilyl)ethoxy]methyl}-4,4':2',2'':4'',4'''-quaterimidazole (13). The SEM-protected biimidazole **12** (500 mg, 1.20 mmol) was placed in a 100-mL Schlenk tube and dissolved with THF (5 mL). To this mixture was added *n*-BuLi (1.6 M hexane solution, 0.80 mL, 1.20 mmol) at –78 °C, and the reaction mixture was stirred at this temperature for 1 h. $CuBr{\cdot}SMe_2$ (246 mg, 1.20 mmol) was added to this mixture at one portion at –78 °C, and the reaction mixture was stirred under O_2-bubbling at this temperature for 2 h. After addition of a satd $Na_2S_2O_3$ aqueous solution (10 mL), the resulting mixture was extracted with ethyl acetate (10 mL). The organic layer was washed with a satd NaCl aqueous solution (100 mL x 3) and dried over Na_2SO_4, then filtered and concentrated under reduced pressure. The residual solid was subjected to GPC with $CHCl_3$ as eluant, to give the SEM-protected quaterimidazole **13** (196 mg, 41%) as a pale yellow powder. mp 145–146 °C; TLC R_f 0.57 (3:1 ethyl acetate/MeOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ –0.07 (s, 18), –0.01 (s,

18), 0.89–0.96 (m, 8), 3.40–3.60 (m, 8), 5.30 (s, 4), 6.01 (s, 4), 7.42 (s, 2), 7.56 (s, 2), 7.62 (s, 2); IR (KBr) 3077, 2954, 1257, 1090, 836 cm^{-1}; FAB-MS, *m/z* 787 (M^+ + H); Anal. Calcd for $C_{36}H_{66}N_8O_4Si_4$: C, 54.92; H, 8.45; N, 14.23. Found: C, 54.76; H, 8.40; N, 14.19.

1,1',1'',1''',1'''',1''''',1'''''-Hexakis{[2''''''-(trimethylsilyl)ethoxy]methyl}-4,4':2',2'':4'',4'':2''',2'''':4'''',4''''':sexiimidazole (14). The same experiment was conducted by using the SEM-protected biimidazole **12** (2.00 g, 5.06 mmol), *n*-BuLi (1.6 M hexane solution, 3.3 mL, 5.28 mmol), and $CuBr{\cdot}SMe_2$ (1.04 g, 5.06 mmol) with O_2-bubbling, which afford the SEM-protected quaterimidazole **13** (623 mg, 31%) as a pale yellow powder and sexiimidazole **14** (75 mg, 3%) as a pale yellow powder. **14**: mp 168–169 °C; TLC R_f 0.39 (10:1 ethyl acetate/MeOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ –0.06 (s, 36), 0.00 (s, 18), 0.91–0.97 (m, 12), 3.51–3.66 (m, 12), 5.30 (s, 4), 6.03 (s, 8), 7.41 (d, 2, *J* = 1.3 Hz), 7.55 (s, 2), 7.58 (s, 2), 7.60 (d, 2, *J* = 1.3 Hz); IR (KBr) 3075, 2954, 1251, 1090, 836 cm^{-1}; FAB-MS, *m/z* 1179 (M^+ + H); Anal. Calcd for $C_{54}H_{98}N_{12}O_6Si_6$: C, 54.97; H, 8.37; N, 14.24. Found: C, 54.67; H, 8.20; N, 14.06.

4,4'-Biimidazole (2). The SEM-protected biimidazole **12** (3.06 g, 7.75 mmol) was placed in a 50-mL round-bottomed flask and dissolved with EtOH (135 mL) and a 5 M HCl aqueous solution (230 mL). The reaction mixture was refluxed for 3 h. EtOH was removed by distillation under reduced pressure, and the residue was neutralized with a satd K_2CO_3 aqueous solution. The reaction mixture was concentrated under reduced pressure, and extracted with EtOH (50 mL). After the solution was concentrated under reduced pressure, the resulting powder was recrystallized from H_2O, to give **2** (565 mg, 54%) as a white powder. mp 280–282 °C; TLC R_f 0.24 (MeOH); ^{1}H NMR (270 MHz, DMSO-d_6) δ 7.19 (b, 2), 7.58 (s, 2); IR (KBr) 3600–2200, 1531, 754 cm^{-1}; EI-MS, *m/z* 134 (M^+, 100%); Anal. Calcd for $C_6H_6N_4$: C, 53.72; H, 4.51; N, 41.77. Found: C, 53.68; H, 4.40; N, 41.51.

2,2':4',4'':2'',2'''-Quaterimidazole (3). The SEM-protected quaterimidazole **9** (154 mg, 0.19 mmol) was placed in a 50-mL round-bottomed flask and dissolved in EtOH (2 mL) and a 5 M HCl aqueous solution (4 mL). The reaction mixture was refluxed for 3 h. EtOH was

removed by distillation under reduced pressure. The residue was neutralized with a satd K_2CO_3 aqueous solution. The resulting powder was collected by the filtration and washed with H_2O (2 mL), to give **3** (50 mg, 98%) as an olive gray powder. mp 298–300 °C; ^{1}H NMR (270 MHz, DMSO-d_6, 80 °C) δ 7.08 (s, 2), 7.37 (s, 1); IR (KBr) 3600–2400, 1530, 754 cm^{-1}; EI-MS, *m*/*z* 266 (M^+, 100%); Anal. Calcd for $C_{12}H_{10}N_8$: C, 54.13; H, 3.79; N, 42.08. Found: C, 46.16; H, 4.47; N, 34.96.

4,4':2',2'':4'',4'''-Quaterimidazole (4). The SEM-protected quaterimidazole **13** (533 mg, 0.68 mmol) was placed in a 50-mL round-bottomed flask and dissolved with EtOH (10 mL) and a 5 M HCl aqueous solution (20 mL). The reaction mixture was refluxed for 3 h. EtOH was removed by distillation under reduced pressure. The residue was neutralized with a 25% NH_3 aqueous solution, and left standing at 0 °C for 12 h. The resulting powder was collected by the filtration and washed with H_2O (5 mL), to give **4** (143 mg, 79%) as a yellowish gray powder. mp 280–282 °C; ^{1}H NMR (270 MHz, DMSO-d_6, 80 °C) δ 7.24 (s, 2), 7.32 (s, 2), 7.59 (s, 2); IR (KBr) 3600–2400, 1534, 758 cm^{-1}; EI-MS, *m*/*z* 266 (M^+, 64%), 133 (M^+ – $C_6H_5N_4$, 12%); Anal. Calcd for $(C_{12}H_{10}N_8)(H_2O)_4$: C, 42.60; H, 5.36; N, 33.12. Found: C, 42.72; H, 5.24; N, 32.76.

4,4':2',2'':4",4''':2''',2'''':4'''',4''''':-Sexiimidazole (5). The SEM-protected sexiimidazole **14** (29 mg, 0.026 mmol) was placed in a 100-mL round-bottomed flask and dissolved with EtOH (2 mL) and a 5 M HCl aqueous solution (3 mL). The reaction mixture was refluxed for 3 h. EtOH was removed by distillation under reduced pressure. The residue was neutralized with a satd K_2CO_3 aqueous solution. The resulting powder was collected by the filtration, and washed with EtOH (2 mL) and Et_2O (2 mL), and dried at 60 °C under reduced pressure for 2 h, to give **5** (8 mg, 80%) as a dark brownish gray. mp > 300 °C; TLC R_f 0.31 (1:1:1 BuOH/H_2O/formic acid); ^{1}H NMR (270 MHz, DMSO-d_6□80 °C) δ 7.27 (s, 2), 7.35 (bs, 2), 7.41 (bs, 2), 7.61 (s, 2); FAB-MS, *m/z* 399 (M^+ + H); IR (KBr) 3500–2200, 1526 cm^{-1}, Anal, Calcd for $C_{18}H_{14}N_{12}$: C, 54.27; H, 3.54; N, 42.19. Found: C, 44.11; H, 3.94; N, 33.12.

4,4'-Biimidazolium dichloride {2·(HCl)$_2$}. Biimidazole **2** (329 mg, 2.45 mmol) was placed in a 50-mL round-bottomed flask and dissolved with EtOH (50 mL). A 12 M HCl aqueous solution (0.61 mL, 7.35 mmol) was added to this mixture at room temperature. The reaction mixture was refluxed for 3 h, and then cooled to room temperature. The resulting powder was collected by filtration, to give the salt (330 mg, 65%) as a white powder. mp 274–276 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ 8.22 (s, 2), 9.14 (s, 2); IR (KBr) 3200–2500, 1574 cm^{-1}; Anal. Calcd for $C_6H_8Cl_2N_4$: C, 34.80; H, 3.89; N, 27.06. Found: C, 34.82; H, 3.74; N, 26.90.

2,2':4',4'':2'',2'''-Quaterimidazolium tetrachloride {3·(HCl)$_4$}. Quaterimidazole **3** (30 mg, 0.11 mmol) was placed in a 30-mL round-bottomed flask and dissolved with EtOH (6 mL). 12 M HCl aqueous solution (0.060 mL, 0.72 mmol) was added to this mixture at room temperature. The reaction mixture was refluxed for 3 h, and then left standing at 0 °C for 24 h. The resulting powder was collected by filtration and washed with EtOH (5 mL) and Et_2O (5 mL), to give the salt (34 mg, 74%) as a soft yellow powder. mp >300 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ 7.79 (s, 4), 7.83 (s, 2); IR (KBr) 3600–2200, 1578, 894 cm^{-1}; Anal. Calcd for $(C_{12}H_{10}N_8)(HCl)_4(H_2O)_{0.25}$: C, 34.60; H, 3.51; N, 26.90. Found: C, 34.92; H, 3.48; N, 26.61.

4,4':2',2'':4'',4'''-Quaterimidazolium tetrachloride {4·(HCl)$_4$}. Quaterimidazole **4** (30 mg, 0.11 mmol) was placed in a 30-mL round-bottomed flask and dissolved with EtOH (6 mL). A 12 M HCl aqueous solution (0.060 mL, 0.72 mmol) was added to this mixture at room temperature. The reaction mixture was refluxed for 3 h, and then left standing at 0 °C for 24 h. The resulting powder was collected by filtration and washed with EtOH (5 mL) and Et_2O (5 mL), to give the salt (40 mg, 86%) as a soft yellow powder. mp 277–279 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ 7.79 (s, 2), 7.97 (s, 2), 9.19 (s, 2); IR (KBr) 3600–2200, 1512, 838 cm^{-1}; Anal. Calcd for $(C_{12}H_{10}N_8)(HCl)_4(H_2O)_{0.25}$: C, 34.60; H, 3.51; N, 26.90. Found: C, 34.55; H, 3.38; N, 26.68.

4,4':2',2'':4",4''':2''',2'''':4'''',4''''':-Sexiimidazolium hexachloride {5·(HCl)$_6$}. Sexiimidazole **5** (19.4 mg, 0.049 mmol) was placed in a 30-mL round-bottomed flask and

dissolved with EtOH (2.0 mL). A 12 M HCl aqueous solution (2.0 mL, 24.0 mmol) was added to this mixture at room temperature. The reaction mixture was refluxed for 3 h, and then cooled to room temperature. The resulting powder was collected by filtration and washed with Et_2O (5 mL), to give the salt (16.6 mg, 55%) as a soft green powder. mp >300 °C; ^{1}H NMR (270 MHz, DMSO-d_6, 80 °C) δ 7.76 (s, 4), 7.95 (s, 2), 9.04 (s, 2); IR (KBr) 3600–2000, 1568, 893 cm^{-1}; Anal. Calcd for $(C_{18}H_{14}N_{12})(HCl)_6(H_2O)_3$: C, 32.21; H, 3.90; N, 25.04. Found: C, 32.17; H, 3.82; N, 24.52.

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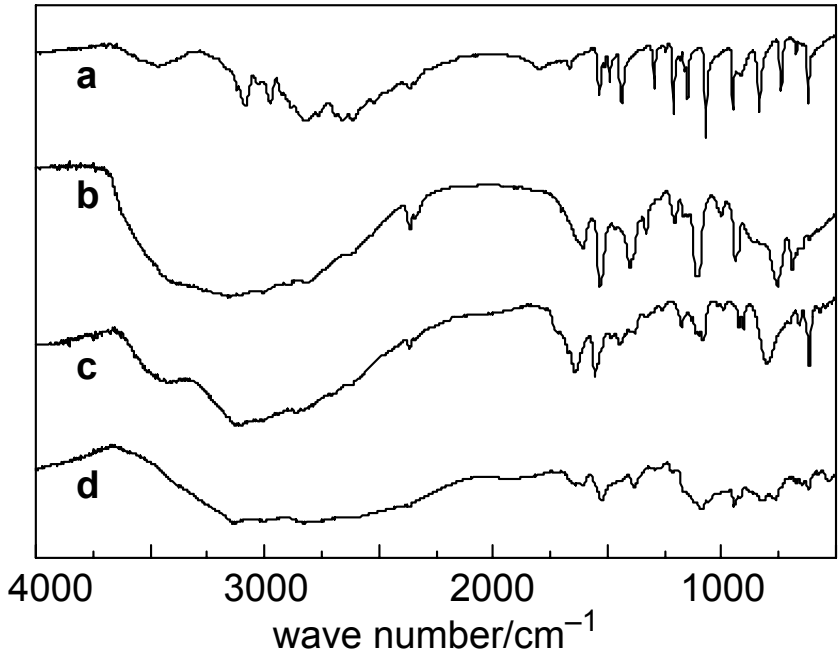

Figure S1. IR spectra measured by KBr pellet at room temperature. 4,4'-biimidazole (**2**, **a**), 2,2':4',4'':2'',2'''-quaterimidazole (**3**, **b**), 4,4':2',2'':4'',4'''-quaterimidazole (**4**, **c**) and 4,4':2',2'':4",4''':2''',2'''':4'''',4'''''-sexiimidazole (**5**, **d**).

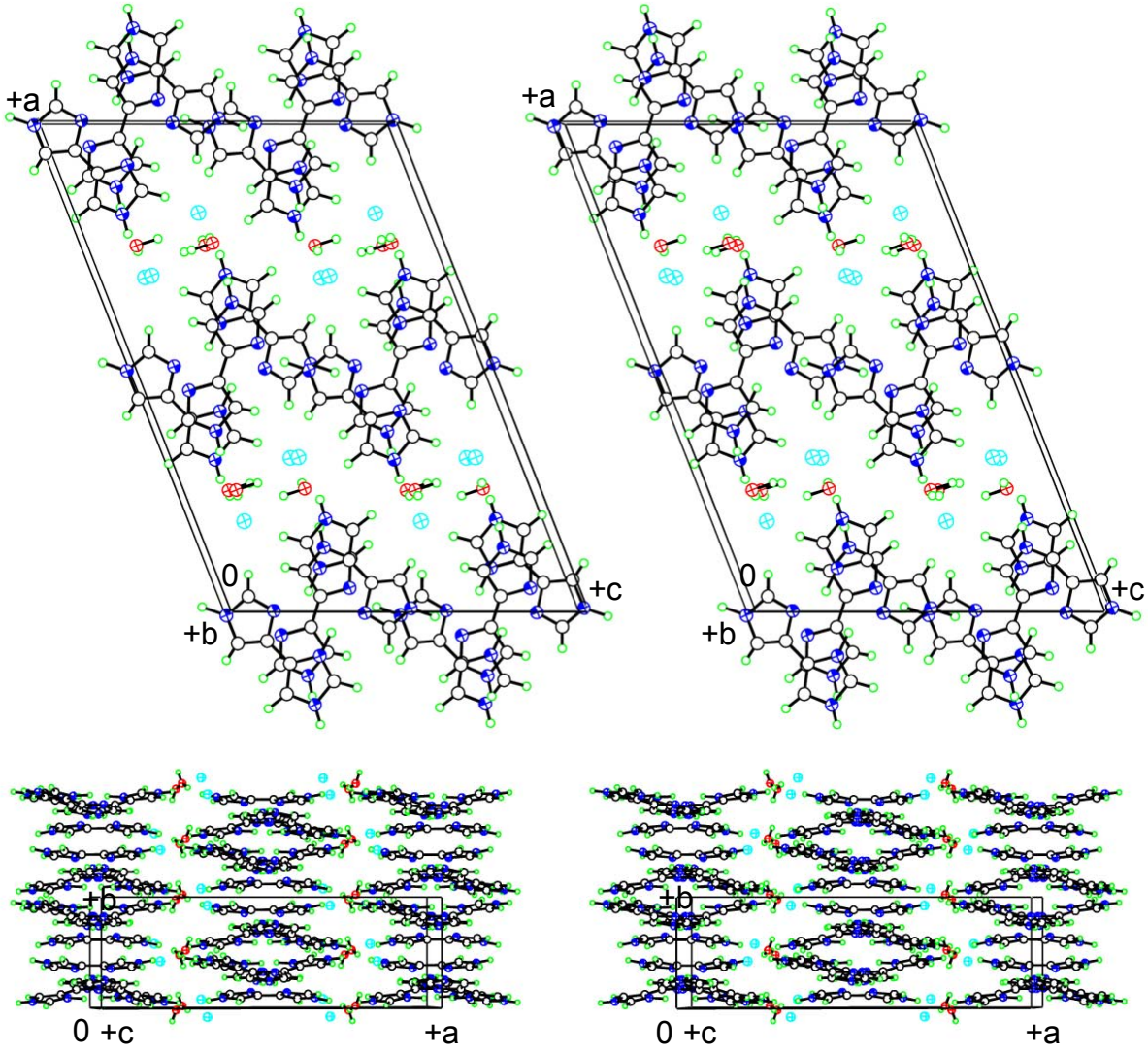

Figure S2. Stereoviews of the crystal packing for **2**·(**2**·HCl)$_2$(H$_2$O)$_2$. One-dimensional H-bonded structure (upper) and stacking of the neutral monomer with the monocation dimer (lower).