Supplementary Material (ESI) for Chemical Communications

Supplementary information for:

A versatile building block for pyrazole-pyrrole hybrid macrocycles

Stamatia Katsiaouni,[a] Sebastian Dechert[a], Christian Brückner*[b] and Franc Meyer*[a]

[a]*Institut fuer Anorganische Chemie der George-August-Universitaet Goettingen, Tammannstrasse 4, 37077 Goettingen, Germany. Fax: (++49)-551-393063; Tel: (++49)-551-393012;*

E-mail: franc.meyer@chemie.uni-goettingen.de

[b]*University of Connecticut, Department of Chemistry, Unit 3060 Storrs, CT 06269-3060, USA.*

Email: c.bruckner@uconn.edu

SYNTHESIS

General

^{1}H, ^{19}F , and ^{13}C NMR spectra were measured on Bruker Avance spectrometers and are reported on the δ scale; ^{19}F NMR spectra were referenced against C_6F_6; the multiplicities are expressed like following: s = singlet, d = doublet, t = triplet, q = quartet; where necessary, assignment of the NMR signals was derived from 2D spectra; mass spectra were recorded using a Finnigan MAT 8200 mass spectrometer (EI), a Finnigan MAT LCQ (ESI), or a Finnigan MAT 95 (FAB); IR data were collected with a Digilab Excalibur spectrometer; the relative intensities of IR spectra are reported as follows: br = broad, s = strong, m = medium, w = weak; the UV-Vis spectra were recorded using a Analytik Jena Specord S 100 spectrometer in a 1 cm pathway cuvette; melting points were determined using a Büchi Melting point B-540 apparatus and are uncorrected; elemental analyses were measured by the Analytical Laboratory of the Institut für Anorganische Chemie der Universität Göttingen using a Heraeus CHN-O-RAPID instrument. Solvents were

dried (P_5O_{10} for CH_2Cl_2, Mg for MeOH and CaH_2 for DMF) and distilled prior to use. All other reagents were used as received. 3,5-Bis-chlormethyl-1*H*-pyrazole hydrochloride[1] and 3,4-diethylpyrrole[2] were prepared as described in the literature. Column chromatography was performed on MN (Macherey-Nagel AG) aluminium oxide (basic, Brockmann Activity 1) unless otherwise indicated. Analytic thin layer chromatography (TLC) was carry out using aluminium oxid (layer thickness 0.2 mm) alumninium-backed TLC-cards with fluorescent indicator (254 nm) purchased from Fluka.

3,5-Bis-chloromethyl-1*H*-pyrazole (2)[1, 3]

3,5-Bis-chloromethyl-1*H*-pyrazole hydrochloride was suspended in CH_2Cl_2 and over-laid with an aqueous $NaCO_3$ solution (0.1 M, excess). After stirring the reaction mixture overnight at room temperature, the mixture was extracted with CH_2Cl_2, the organic phase isolated, dried (Na_2SO_4 or $MgSO_4$), and evaporated to dryness *in vacuo* to obtain the target compound in near-quantitative yields. The compound was not further purified and used directly for the next step. m.p.: 71-75 °C; ^{1}H NMR (200 MHz, $CDCl_3$, 301 K): δ (ppm) = 4.62 (s, 4H; 2×C*H*$_2$), 6.38 (s, 1H; C*H*$^{pz\text{-}4}$), 10.14 (s, 1H; N*H*); ^{13}C-NMR (101 MHz, $CDCl_3$, 301 K): δ (ppm) = 36.5 (*C*H$_2$), 105.3 (*C*H$^{pz\text{-}4}$), 145.0 (*C*$^{pz/3,5}$); MS (EI): *m/z* (%): 164 (20) $[M]^+$, 129 (100) $[M\text{-}Cl]^+$, 94 (16) $[M\text{-}2\times Cl]^+$, 65 (22) $[(C_3HN_2)]^+$; IR (KBr): ν = 3192 (s), 3108 (s), 2994 (s), 2869 (s), 1458 (w), 1315 (w), 1264 (m), 1142 (w), 1006 (w), 730 (m) cm^{-1}; elemental analysis calcd (%) for $C_5H_6N_2Cl_2$: C: 36.39, H: 3.66, N: 16.98, Cl: 42.97; found: C: 36.74, H: 3.43, N: 16.98.

3,5-Bis(3,4-dimethyl-1*H*-pyrrole-2-yl-methyl)-1*H*-pyrazole (3):

3,4-Diethylpyrrole (3.5 g, 28.4 mmol) was, under anhydrous conditions (N_2), dissolved in dry CH_2Cl_2 (200 mL). The reaction mixture was cooled in an acetone-dry ice bath to -78 ºC and *n*-BuLi (2.5 M in hexan, 11.4 mL, 28.4 mmol) was added carefully in portions. After stirring for 1.5 h, 3,5-bis-chloromethyl-1*H*-pyrazole (**2**) (1.0 eq, 1.33 g, 8.10 mmol) dissolved in dry CH_2Cl_2 (50 mL) was added drop-wise. The reaction was stirred for 4 h at -78 °C. Subsequently, the

[1] T.G. Schenck, J. M. Downes, C. R. C. Milne, P. B. MacKenzie, H. Boucher, J. Whelan and B. Bosnich, *Inorg. Chem*. 1985, **24**, 2334.
[2] a) L. Sessler, A. Mozaffari and J. M. R. Johnson, *Org. Synth.* 1992, **70**, 68. b) D. Hartman and L. M. Weinstock, *Org. Synth., Coll. Vol VI* , 1988**,** 620.
[3] S. Katsiaouni, *Diplomarbeit*, 2004, Göttingen, Germany.

reaction was allowed to warm to room temperature overnight. A saturated aq. NH_4Cl solution (150 ml) was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over Mg_2SO_4, filtered, and the solvent removed by rotary evaporation to yield a brown oil that was purified by column chromatography (basic alumina, Brockmann activity I, CH_2Cl_2:MeOH 45:1). After the removal of the solvent, **3** was obtained as a hygroscopic light brown solid (2.49 g, 91 %). The product is susceptible to slow decomposition at room temperature in air and is best kept in the freezer under N_2. R_f = 0.50 (aluminium oxide, CH_2Cl_2:MeOH 1:20); m.p.: 36 – 45 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 301 K): δ (ppm) = 1.11-1.14 (t, ^3J (H,H) = 7.5 Hz, 6H; CH_3), 1.21-1.24 (t, ^3J (H,H) = 7.51 Hz, 6H; CH_3), 2.45-2.51 (m, ^3J (H,H) = 7.5 Hz, 8H; CH_2CH$_3$), 3.83 (s, 4H; py-CH_2-pz), 5.88 (s, 1H; CH^{pz}), 6.33-6.34 (m, 2H; CH^{py}), 8.19 (br s, 2H; NH), 8.69-10.19 (br s, NH); ^{13}C NMR (126 MHz, $CDCl_3$, 301 K): δ (ppm) = 14.6 (*C*H$_3$), 16.1 (*C*H$_3$), 17.4 (*C*H$_2$), 18.5 (*C*H$_2$), 23.8 (py-*C*H$_2$-pz), 103.5 (*C*H^{pz}), 112.8 (*C*H^{py}), 120.3 (C^q), 123.8 (C^q), 124.8 (C^q), 147.1 (C^{pz}); MS (EI): *m/z* (%): 338 (62) $[M]^+$, 323 (10) $[M-(CH_3)]^+$, 309 (7) $[M-(C_2H_5)]^+$, 217 (20) $[M-(C_8H_{11}N)]^+$, 200 (22) $[M-(C_9H_{16}N)]^+$, 186 (5) $[M-(C_{10}H_{18}N)]^+$, 154 (12) $[(C_9H_4N_3)]^+$, 122 (100) $[(C_8H_{12}N)]^+$. HRMS-(+)ESI (methanol/water): *m/z* calcd for $C_{21}H_{31}N_4$ $[M+H]^+$: 339.25432, found: 339.25433; IR (KBr): ν = 3356 (s), 2926 (m), 1674 (m), 1558 (m), 1443 (s), 298 (w), 1083 (w), 1002 (w), 779 (m), 532 (m) cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{30}N_4 \cdot (H_2O)_{0.25}$: C 73.52, H 8.97, N 16.34; found: C 73.59, H 8.67, N 16.45.

3,5-Bis-(3,4-diethyl-1-formylpyrrol-2-ylmethyl)-1*H*-pyrazole (1):

A procedure for the diformylation of dipyrromethanes was adopted from the literature:[4] To a cooled (ice bath) solution of **3** (282 mg, 0.83 mmol) in dry DMF (608 mg, 8.33 mmol, 10 eq) was added benzoyl chloride (0.76 mL, 6.7 mmol, 8.0 eq) under a N_2 atmosphere. The reaction mixture was stirred at 0 °C for 2 h, followed by additional 4 h at room temperature. (For larger scale preparations we recommend to stir the reaction mixture several hours longer.) The dark brown mixture was cooled to 0°C and quenched by addition of a wet, ethanolic Na_2CO_3 solution (1.0 g Na_2CO_3 dissolved in 80 mL 1:1 H_2O:EtOH). The solution was extracted with CH_2Cl_2 (3 × 100 mL), the organic phase was dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The

[4] R. P. Briñas and C. Brückner, *Tetrahedron*, 2002, **58**, 4375.

resulting black oil was purified using column chromatography (basic alumina, Brockmann activity I, CH_2Cl_2:MeOH 20:1). The third, main fraction was collected and the solvent was evaporated under vacuum to afford **1** as a lightly brown solid. Subsequent recrystallization from EtOH gave **1** as a light ocher solid (288 mg, 88 %; the yields of large scale preparations were reduced to 40-70 %). R_f = 0.44 (aluminium oxide, CH_2Cl_2:MeOH 15:1); m.p.: 191 – 195 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 301 K): δ (ppm) = 0.89-0.92 (t, ^3J (H,H) = 7.5 Hz, 6H; CH_3), 1.09-1.12 (t, ^3J (H,H) = 7.5 Hz, 6H; CH_3), 2.29-2.33 (q, ^3J (H,H) = 7.5 Hz, 4H; CH_2CH$_3$), 2.60-2.65 (q, ^3J (H,H) = 7.5 Hz, 4H; CH_2CH$_3$), 3.80 (s, 4H; py-CH_2-pz), 5.74 (s, 1H; CH^{pz}), 9.45 (s, 2H; C*H*O), 11.40 (br s; N*H*), 12.28 (br s; N*H*). ^{13}C NMR (126 MHz, DMSO-d_6, 301 K): δ (ppm) = 15.8 (*C*H$_3$), 16.2 (*C*H$_2$CH$_3$), 16.6 (*C*H$_2$CH$_3$), 17.4 (*C*H$_3$), 23.4 (br, py-*C*H$_2$-pz), 102.7 (*C*H^{pz}), 122.9 (*C*^{q}), 127.0 (*C*^{py}CHO), 135.5(*C*^{q}), 136.4 (*C*^{q}), 144.6 (br, *C*^{q}), 176.3 (*C*HO). MS (EI): *m/z* (%): 394 (100) $[M]^+$, 365 (63) $[M-(C_2H_5)]^+$, 351 (5) $[M-(C_3H_7)]^+$, 337 (13) $[M-2\times(C_2H_5)+H]^+$, 323 (5) $[M-2\times(C_2H_5)-(CH_3)+2H]^+$, 243 (28) $[M-(C_9H_{12}NO)]^+$, 228 (16) $[C_{13}H_{16}N_4]^+$, 214 (18) $[C_{12}H_{14}N_4]^+$, 200 (12) $[C_{11}H_{12}N_4]^+$, 150 (30) $[C_9H_{12}NO]^+$, 122 (50) $[C_8H_{12}N]^+$, 94 (7) $[C_5N_2H_6]^+$; HRMS-(+)ESI (methanol/water): *m/z* calcd for $C_{23}H_{31}N_4O_2$ $[M+H]^+$: 395.24415; found: 395.24413; IR (KBr): ν = 3243 (s), 2929 (m), 1608 (vs), 1448 (m), 1350 (m), 1280 (w), 1134 (w), 1010 (m), 856 (w), 772 (s) cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{30}N_4O_2\cdot(H_2O)_{0.5}$: C 68.46, H 7.74, N 13.88, O 9.912, found: C 68.44, H 7.74, N 14.29.

Schiff base macrocycle (4):

Bisaldehyde **1** (200 mg, 0.51 mmol) was dissolved under N_2 in dry MeOH (250 mL) at 50 °C. To the stirred solution was added drop-wise 1,2-diaminobenzene (54.0 mg 0.51 mmol, 1.0 eq.) dissolved in dry MeOH (10 mL). After 15 min, TFA (1.54 mL, 20.0 mmol, 40 eq.) was added in small portions and the reaction mixture was heated to reflux under N_2 for 20 h. After this time, the solvent was removed on the rotary evaporator and the resulting brown-red solid was purified by column chromatography (basic alumina, Brockmann activity I, CH_2Cl_2:MeOH 30:1) to provide product **4** as a yellow-orange solid (213 mg, 90 %). Single crystals of **4** were grown at 5 °C from a saturated ethanolic solution of **4**. R_f = 0.79 (aluminium oxide, CH_2Cl_2:MeOH 30:1); m.p.: 241-244 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 301 K): δ (ppm) = 1.01-1.04 (t, ^3J (H,H) = 7.5 Hz, 6H; CH_3), 1.16-1.19 (t, ^3J (H,H) = 7.5 Hz, 6H; CH_3), 2.30-2.35 (m, 4H; CH_2CH$_3$), 2.53-2.57 (q, ^3J (H,H) = 7.4 Hz, 4H; CH_2CH$_3$), 3.88 (s, 4H; py-CH_2-pz), 5.67 (s, 1H; CH^{pz}), 7.17 (s,

4H; C*H*^{Ph}), 8.16 (s, 2 × *H*C=N), 10.50 (br s, N*H*); ^{13}C NMR (126 MHz, $CDCl_3$, 301 K): δ (ppm) = 16.0 (*C*H_3), 17.0 (*C*H_2CH$_3$), 17.3 (*C*H_2CH$_3$), 17.4 (*C*H_3), 24.0 (br, py-*C*H_2-pz), 103.9 (*C*H^{pz}), 117.2 (br, *C*^{Ph}), 122.6 (*C*^{tert}), 125.7 (*C*^{Ph}), 132.5 (br, *C*^{tert}), 146.1 (br, H*C*=N); MS (ESI in MeOH) *m/z* (%): 467 (100) $[M+H]^+$; MS (FAB in 4-NBA) *m/z* (%): 467 (100) $[M+H]^+$; HRMS-(+)ESI (MeOH/H_2O): *m/z* calcd for $C_{29}H_{35}N_6$ $[M+H]^+$: 467.29177; found $[M+H]^+$: 467.29177; IR (KBr): ν = 3428 (m), 3268 (w), 3061 (w), 2961 (m), 2926 (w), 2868 (w), 1614 (vs), 1569 (s), 1443 (s), 1383 (w), 1335 (w), 1264 (m), 1210 (m), 1101 (w), 1057 (w), 1010 (w), 963 (w), 894 (w), 807 (w), 745 (w) cm^{-1}; UV-vis ($CHCl_3$): λ_{max} [nm] (ε) = 332 (23670), 361 (17560); elemental analysis calcd (%) for $C_{29}H_{34}N_6(CH_3OH)_{1.5}$ (514.7): C 71.18, H 7.83, N 16.33, found: C 71.19, H 7.49, N 16.04.

Schiff base macrocycle (4·TFA):

The same preparation as described for **4**, however, the basic alumina-based deprotonation step is replaced by a recrystallization of the crude protonated material. Thus, after cooling the reaction mixture to ambient temperature, the solvent was removed on the rotary evaporator and the resulting brown-red solid was purified by crystallisation in MeOH/CH_2Cl_2 for one day at 5 °C. Red single crystals of the TFA-salt grew by slow evaporation of a saturated MeOH/CH_2Cl_2 solution of **4·TFA**. m.p.: 222-235 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 301 K): δ (ppm) = 1.13-1.16 (t, ^3J (H,H) = 7.5 Hz, 6H; C*H*$_3$), 1.17-1.20 (t, ^3J (H,H) = 7.5 Hz, 6H; C*H*$_3$), 2.50-2.54 (m, 4H; C*H*$_2$CH$_3$, DMSO-d_6), 2.73-2.78 (q, ^3J (H,H) = 7.5 Hz, 4H; C*H*$_2$CH$_3$), 3.42 (br, N*H*), 4.13 (s, 4H; py-C*H*$_2$-pz), 6.21 (s, 1H; C*H*^{pz}), 7.30-7.34 (dd, ^3J (H,H) = 3.3 Hz, 2H; C*H*^{Ph}), 7.80-7.82 (dd, ^3J (H,H) = 3.3 Hz, 2H; C*H*^{Ph}), 8.62 (s, 2H; 2 × *H*C=N), 11.15 (br s, N*H*); ^{13}C NMR (126 MHz, DMSO-d_6, 301 K): δ (ppm) =; 15.1 (*C*H_3), 16.2 (*C*H_2CH$_3$), 16.6 (*C*H_2CH$_3$), 17.0 (*C*H_3), 24.2 (br, py-*C*H_2-pz), 104.4 (*C*H^{pz}), 116.7 (*C*H^{Ph}), 123.1 (*C*^{q}), 125.2 (*C*^{q}), 126.6 (*C*H^{Ph}), 136.0 (*C*^{q}), 141.1 (br, *C*^{q}), 142.3 (br, H*C*=N), 157.5 (*C*^{q,pz}); ^{19}F NMR (188 MHz, DMSO-d_6, 301 K): 89.0 (s, C*F*$_3$COO); MS (ESI in MeOH) *m/z* (%): 467 (58) $[M+H]^+$, 933 (78) $[2 \times M+H]^+$, 1047 (100) $[2 \times M+(CF_3COOH)]^+$; IR (KBr): ν = 3430 (m), 3210 (w), 3178 (w), 2957 (m), 2947 (w), 1640 (vs), 1570 (s), 1552 (w), 1435 (w), 1304 (w), 1190 (m), 1180 (m), 1010 (w), 958 (w), 801 (m), 756 (w) cm^{-1}; UV-vis ($CHCl_3$): λ_{max} [nm] (ε) = 361 (35800), 448 (8070).

Spectra

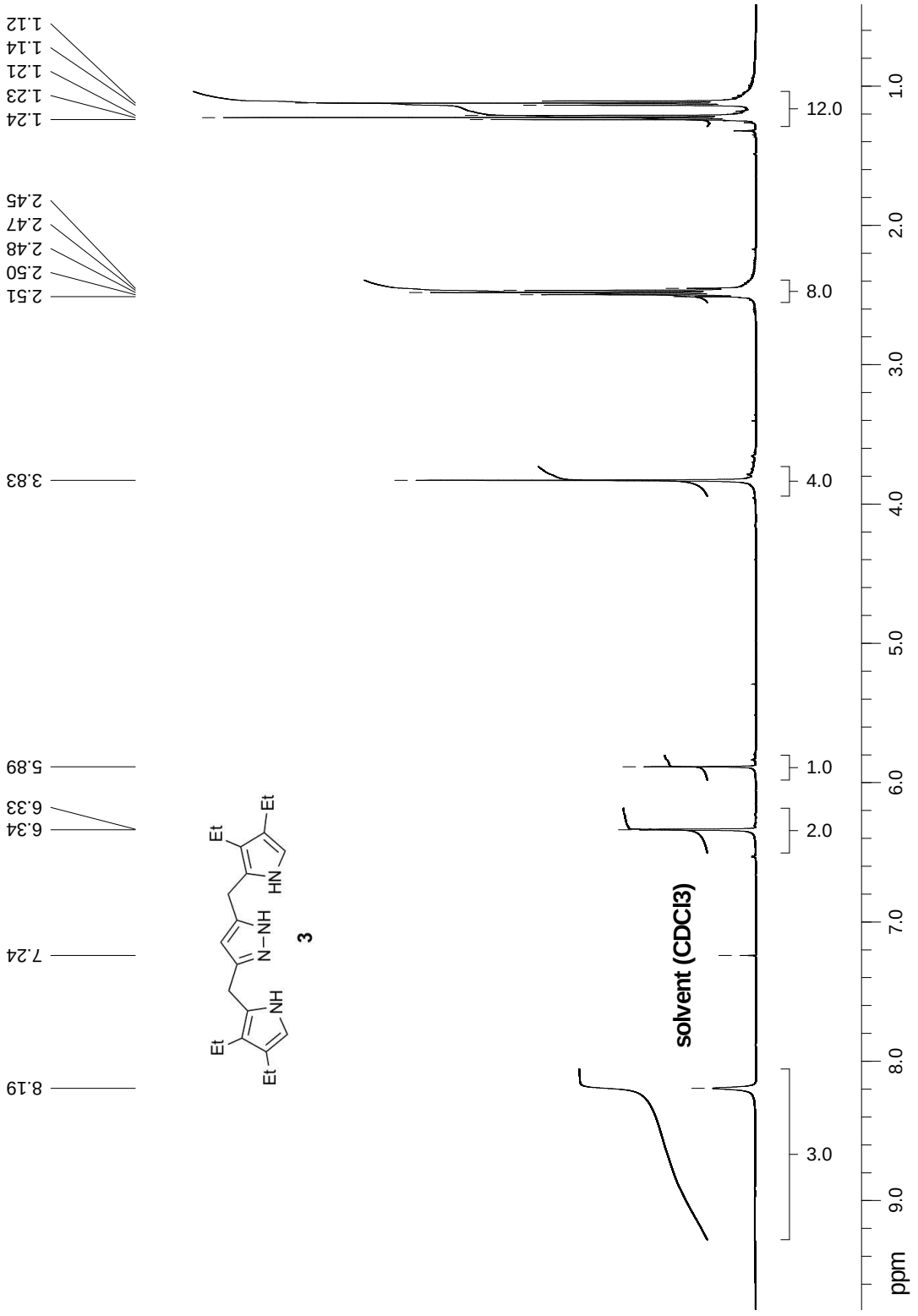

Figure S1: ^{1}H NMR spectrum of **3** in $CDCl_3$.

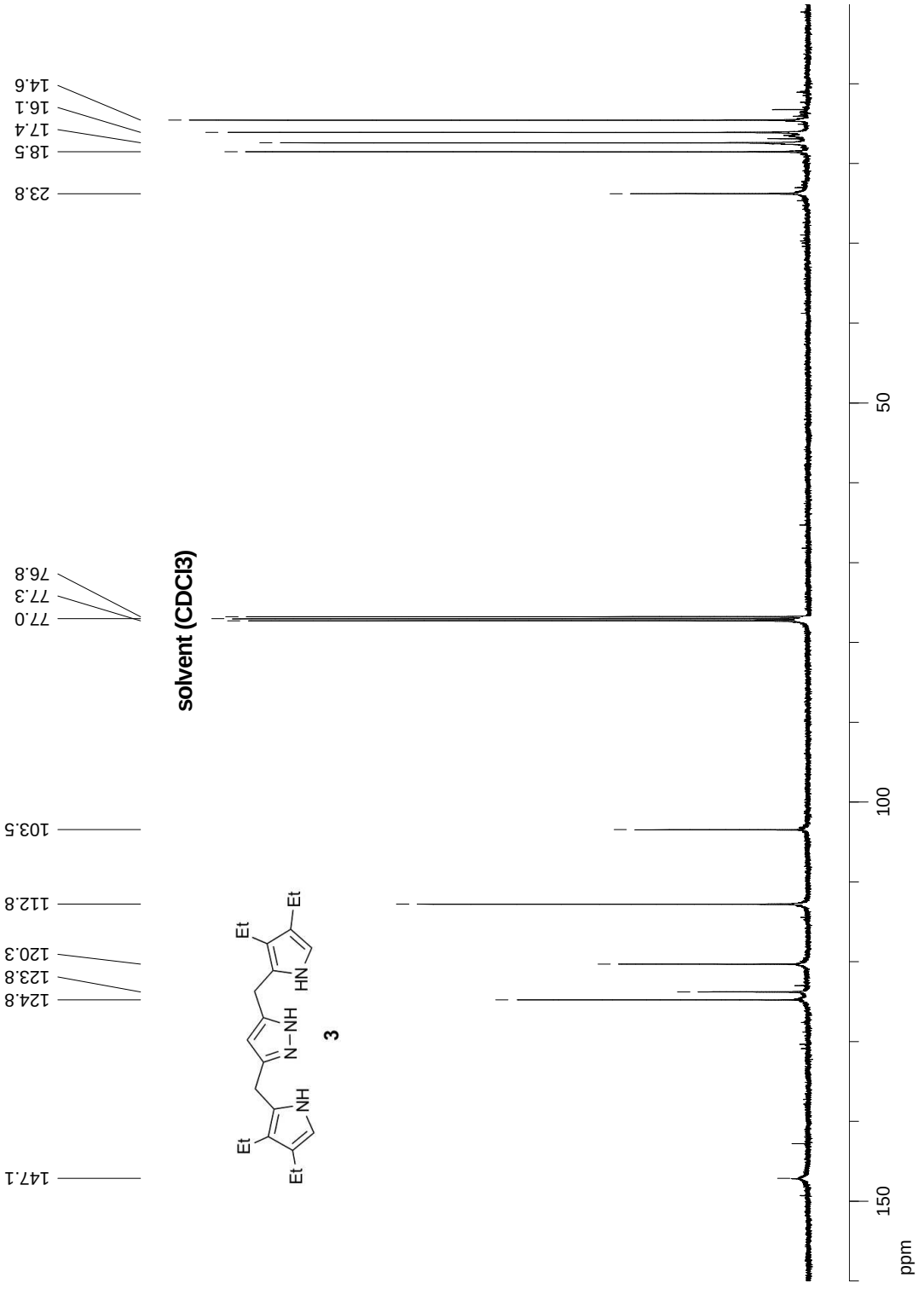

Figure S2: ^{13}C NMR spectrum of **3** in $CDCl_3$.

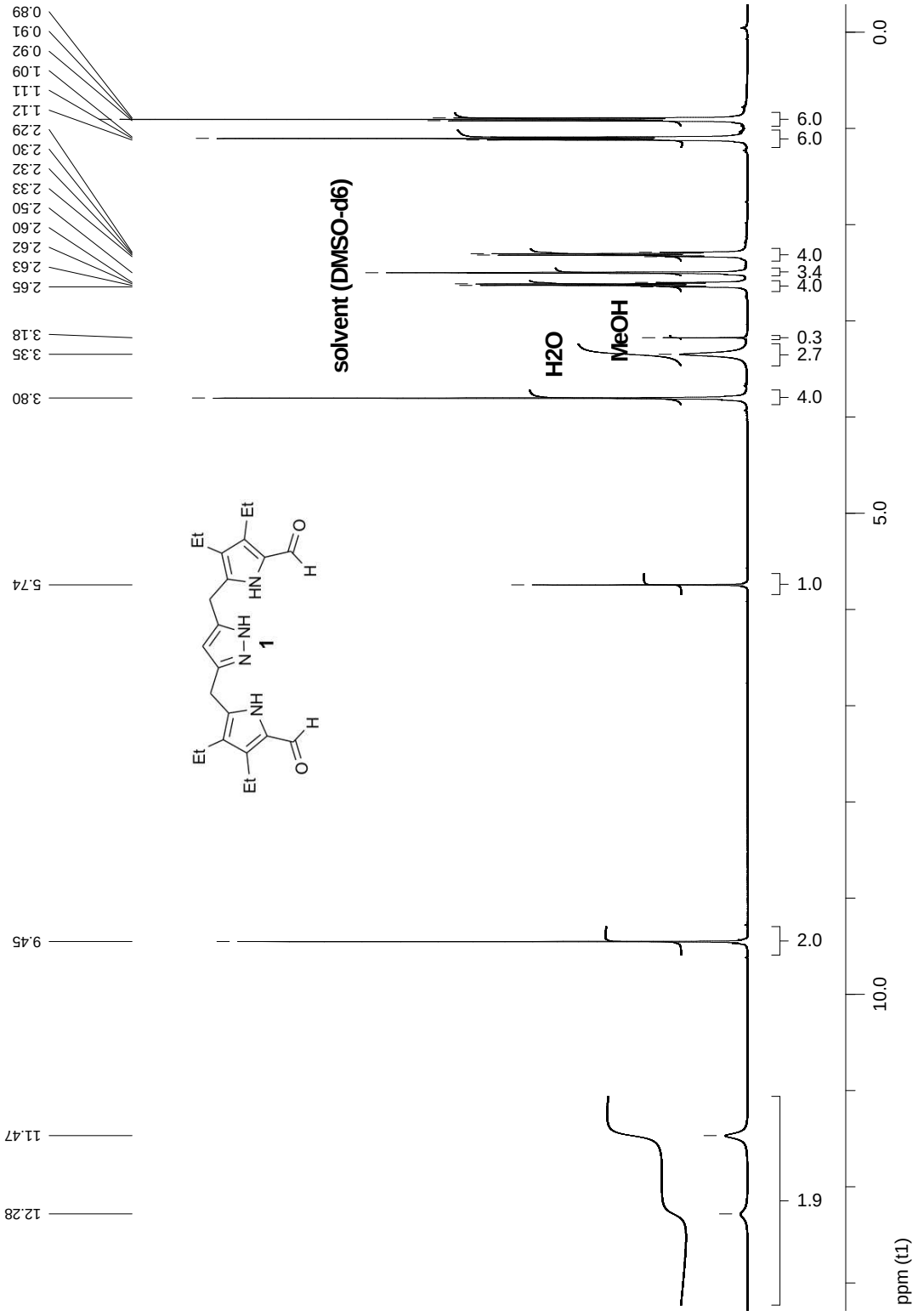

Figure S3: ^{1}H NMR spectrum of **1** in DMSO-d_6.

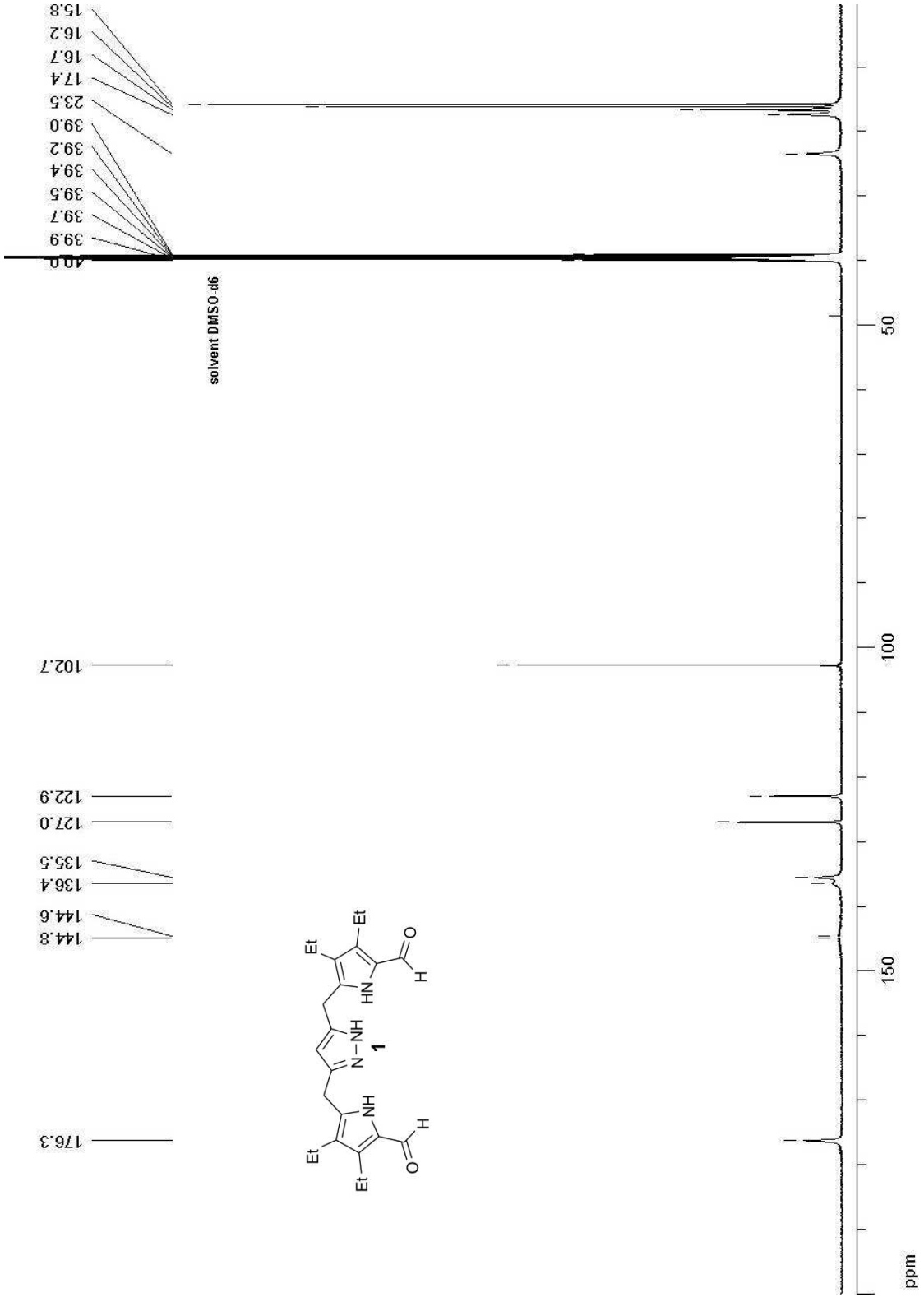

Figure S4: ^{13}C NMR spectrum of **1** in DMSO-d_6.

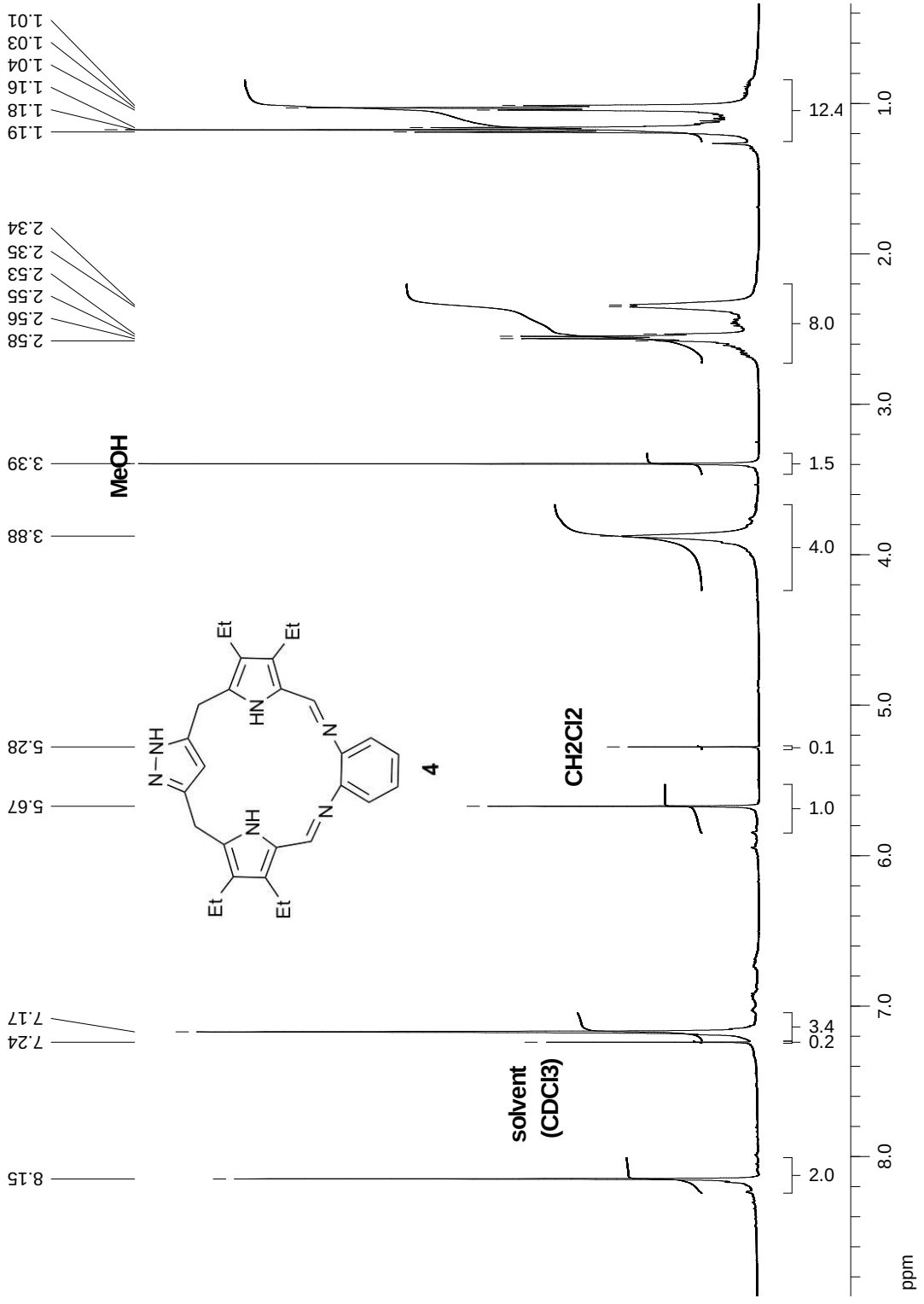

Figure S5: ^{1}H NMR spectrum of **4** in $CDCl_3$.

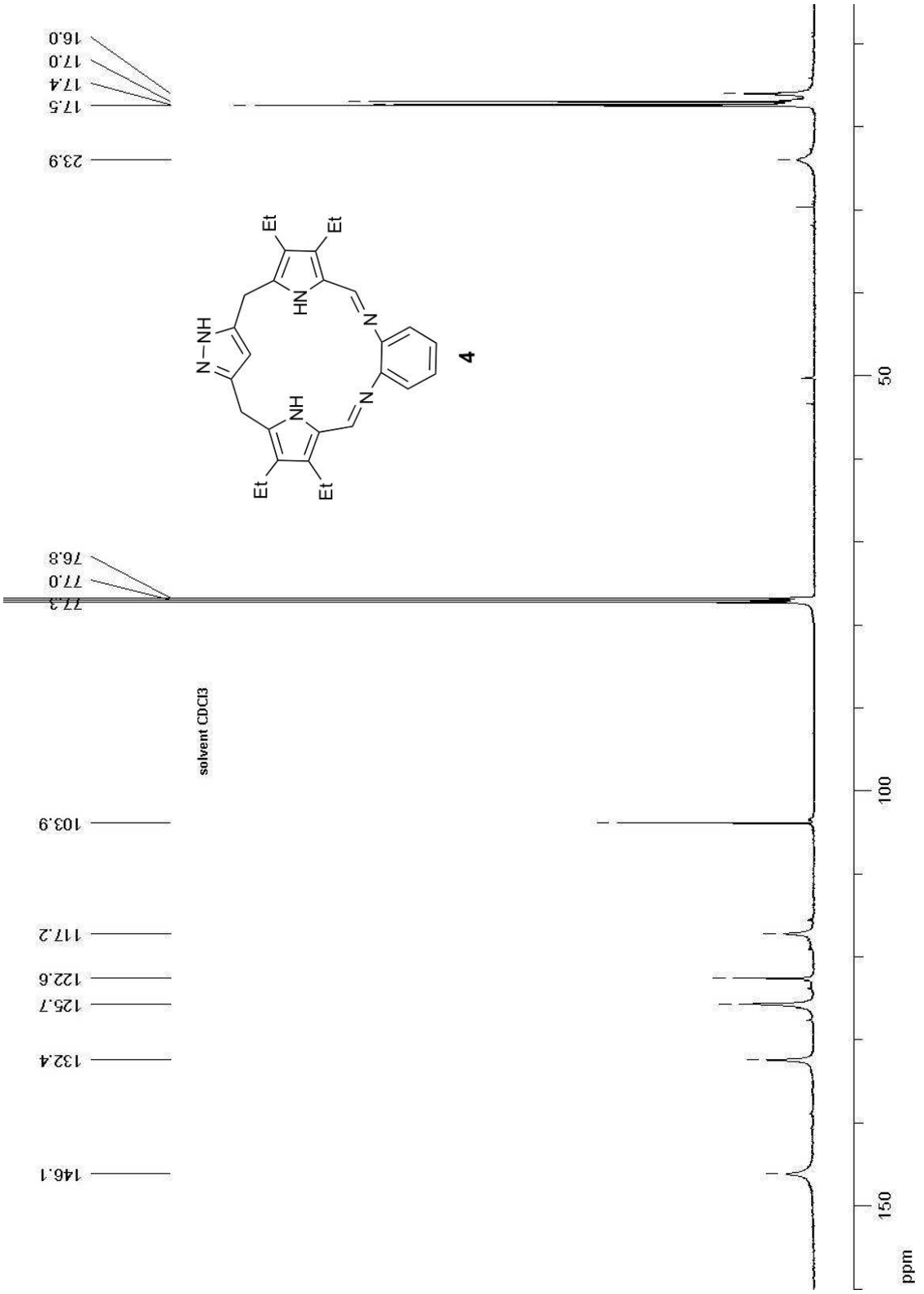

Figure S6: ^{13}C NMR spectrum of **4** in $CDCl_3$.

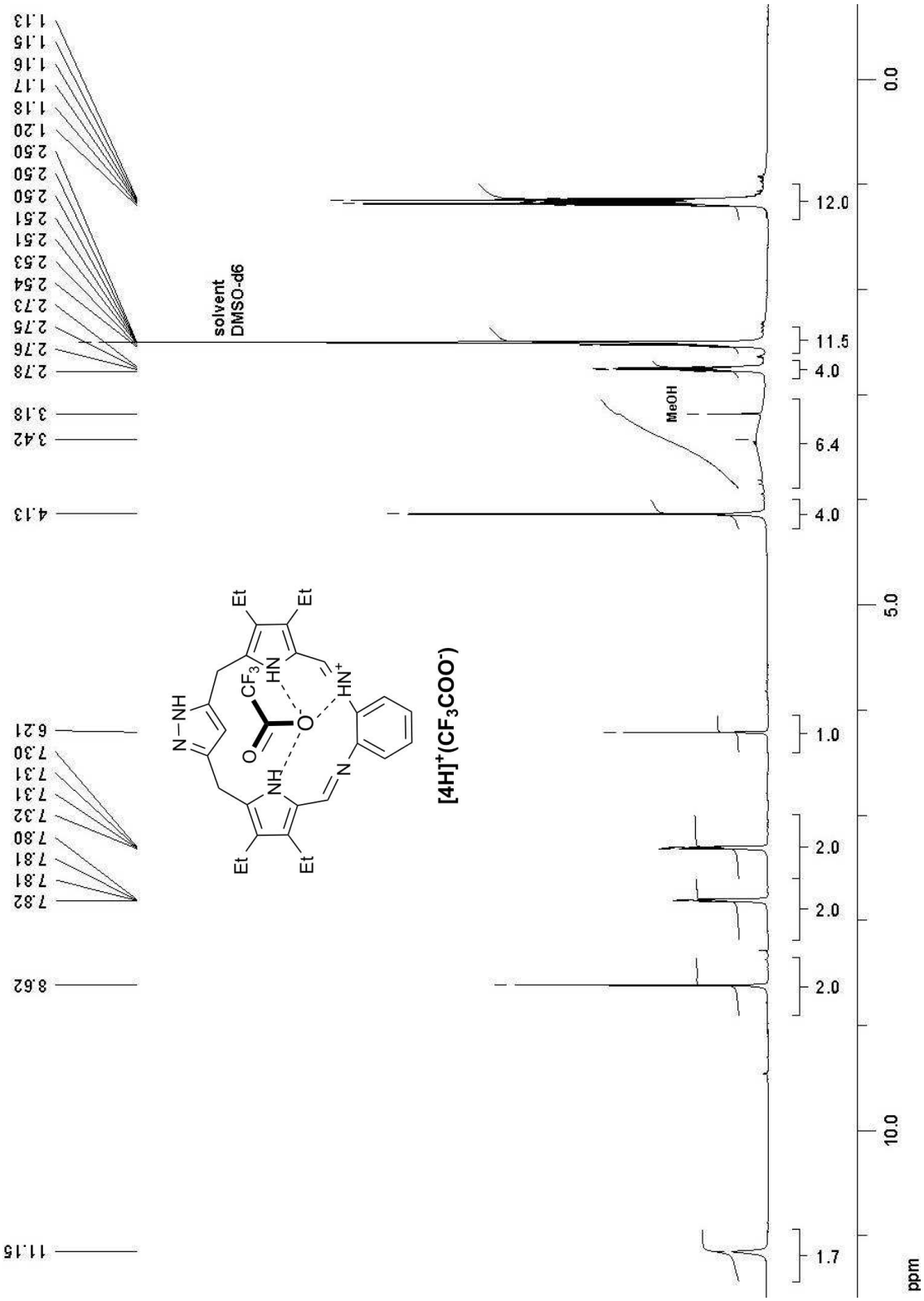

Figure S7: ^{1}H NMR spectrum of [**4**H]$^{+}$(CF_3COO^{-}) in DMSO-d_6.

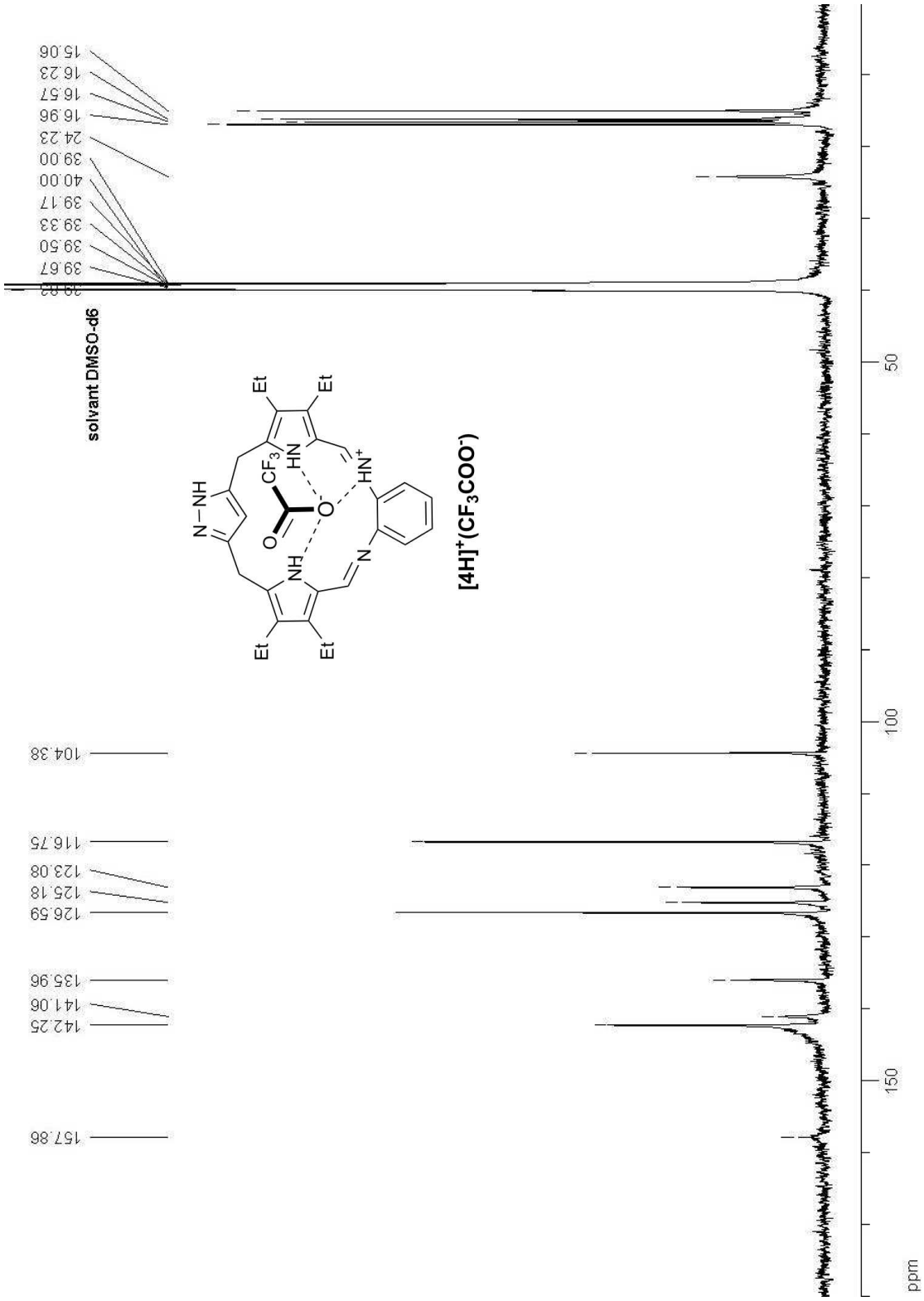

Figure S8: ^{13}C NMR spectrum of [**4**H]$^{+}$(CF_3COO^{-}) in DMSO-d_6.

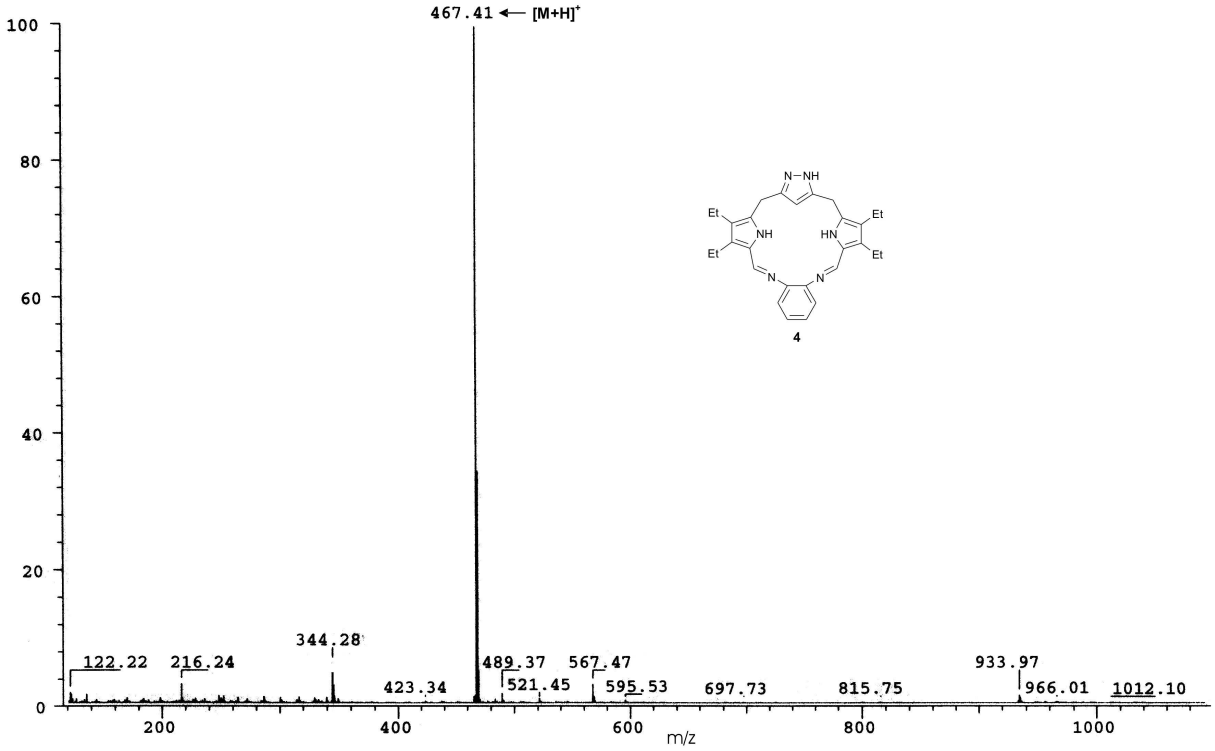

Figure S9: ESI-MS spectrum of **4** in methanol.

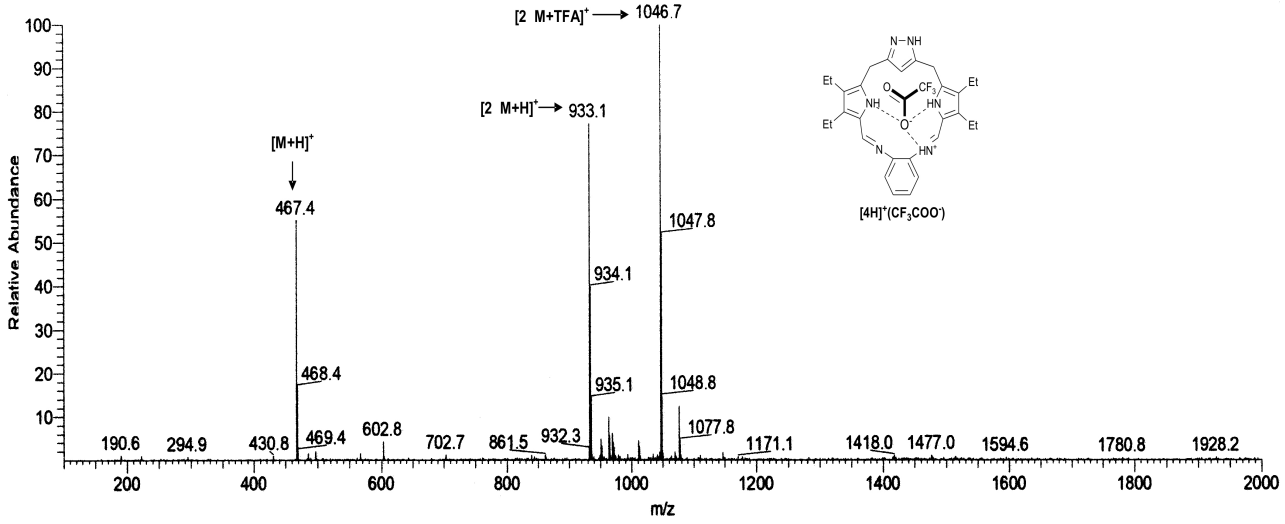

Figure S10: ESI-MS spectrum of [**4**H]$^+$(CF_3COO^-) in methanol.

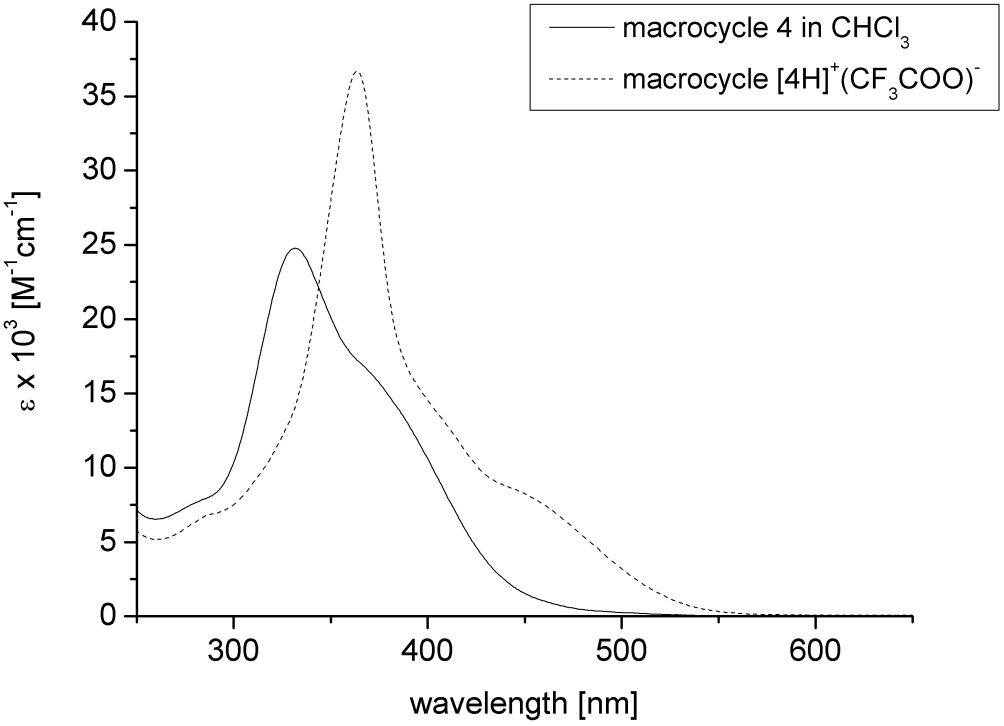

Figure S11: UV-vis spectrum of **4** and [**4**H]$^+$(CF_3COO^-) in $CHCl_3$.

X-ray Crystallography Data

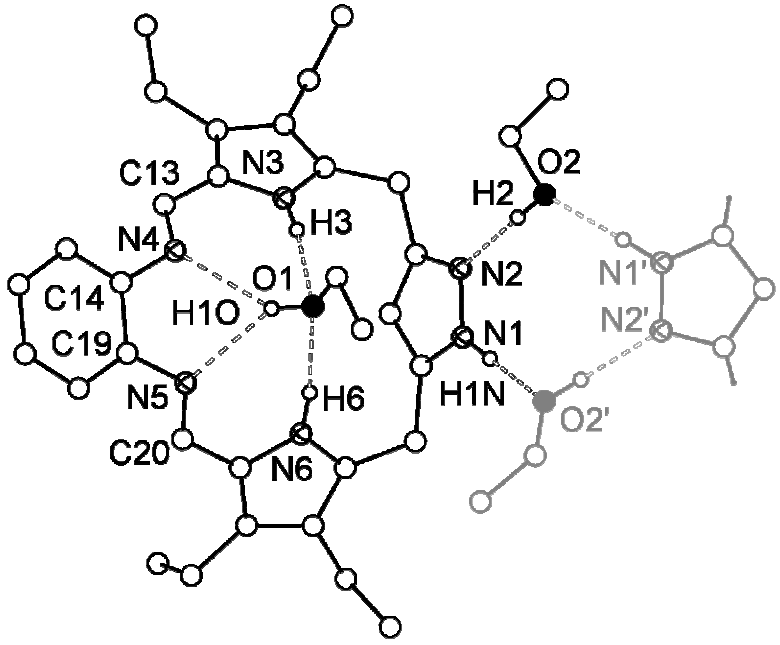

Figure S12: View of the molecular structure of **4**·2EtOH In the interests of clarity all hydrogen atoms not involved in hydrogen bonding and the disorder of the C_2H_5-group have been omitted. Selected atom distances (Å) and angles (°): N3···O1 2.906(2), N3–H3 0.92(3), O1···N4 2.962(2), O1···N5 2.934(2), O1–H1O 0.82(3), N6···O1 2.920(2), N6–H6 0.94(3), N1···O2' 2.783(2), N1–H1N 0.92(3), O2···N2 2.778(2), O2–H2 0.87(3), N4–C13 1.283(3), N4–C14 1.407(3), N5–C20 1.278(3), N5–C19 1.416(3); N3–H3···O1 172(3), O1–H1O··N4 143(3), O1–H1O··N5 141(3), N6–H6···O1 171(2), N1–H1N···O2' 179(2), O2–H2···N2 179(3), C13–N4–C14 121.3(2), C20–N5–C19 120.8(2). Symmetry transformation used to generate equivalent atoms ('): *–x*, *y*, 0.5–*z*.

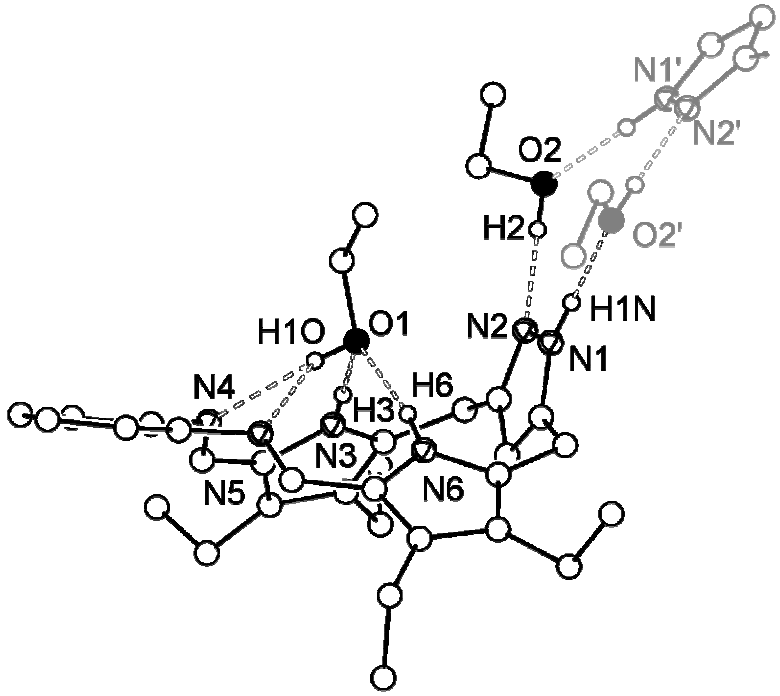

Figure S13: View of the molecular structure of **4**·2EtOH. In the interests of clarity all hydrogen atoms not involved in hydrogen bonding have been omitted. Symmetry transformation used to generate equivalent atoms (’): *–x*, *y*, 0.5–*z*.

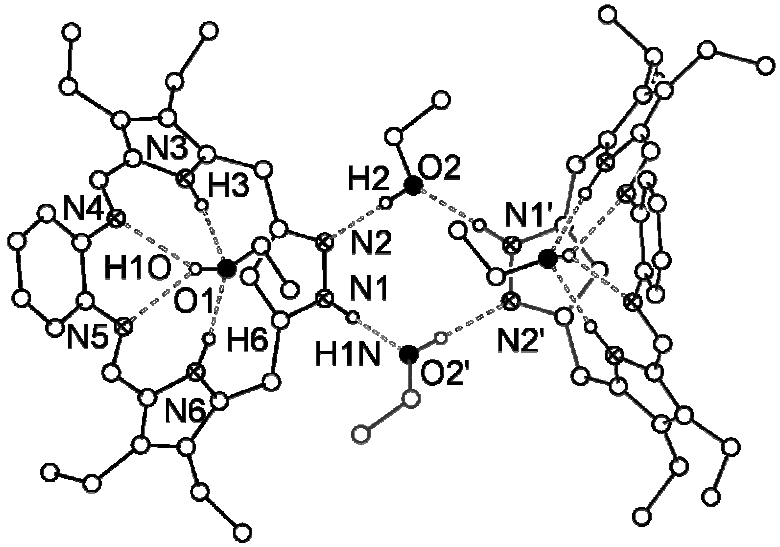

Figure S14: View of the hydrogen bonding interactions of **4**·2EtOH. In the interests of clarity all hydrogen atoms not involved in hydrogen bonding have been omitted. Symmetry transformation used to generate equivalent atoms (’): *–x*, *y*, 0.5–*z*.

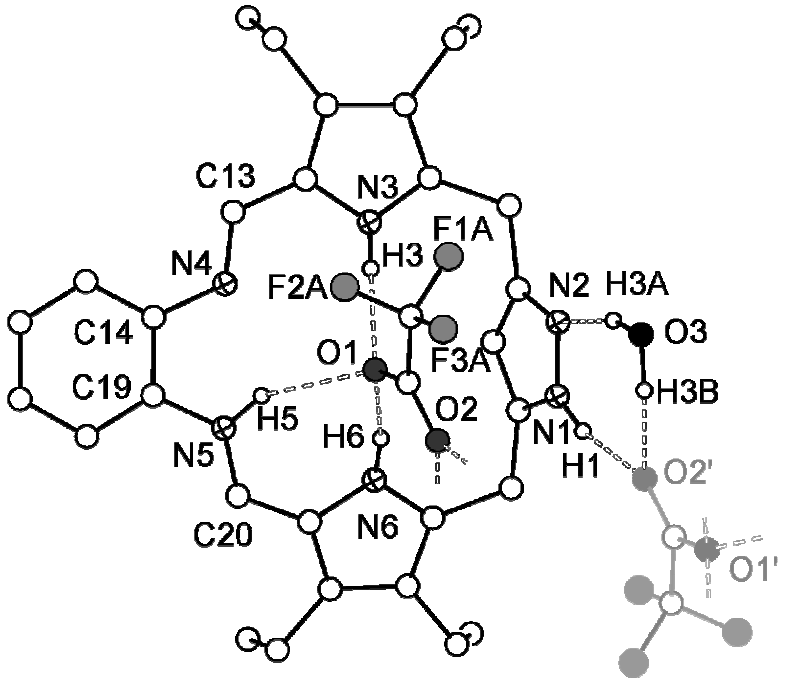

Figure S15: View of the molecular structure of $[\mathbf{4}H]^{+}\cdot(CF_3COO^{-})\cdot(H_2O)$. In the interests of clarity all hydrogen atoms not involved in hydrogen bonding and the disorder of the CF_3-group have been omitted. Selected atom distances (Å) and angles (°): N3···O1 2.931(3), N3–H3 0.87(3), N5···O1 3.242(3), N5–H5 0.90(3), N6···O1 2.824(3), N6–H6 0.96(4), N1···O2' 2.838(3), N1–H1 0.94(4), O3···N2 2.912(3), O3···O2' 2.749(3), O3–H3A 0.95(5), O3–H3B 1.01(5), N4–C13 1.290(3), N4–C14 1.412(3), N5–C20 1.319(3), N5–C19 1.416(3); N3–H3···O1 170(3), N5–H5···O1 145(2), N6–H6··O1 166(3), N1–H1···O2' 164(3), O3–H3A···N2 164(4), O3–H3B···O2' 161(4), C13–N4–C14 121.6(2), C20–N5–C19 127.8(2). Symmetry transformation used to generate equivalent atoms ('): 1–*x*, 2–*y*, 2–*z*.

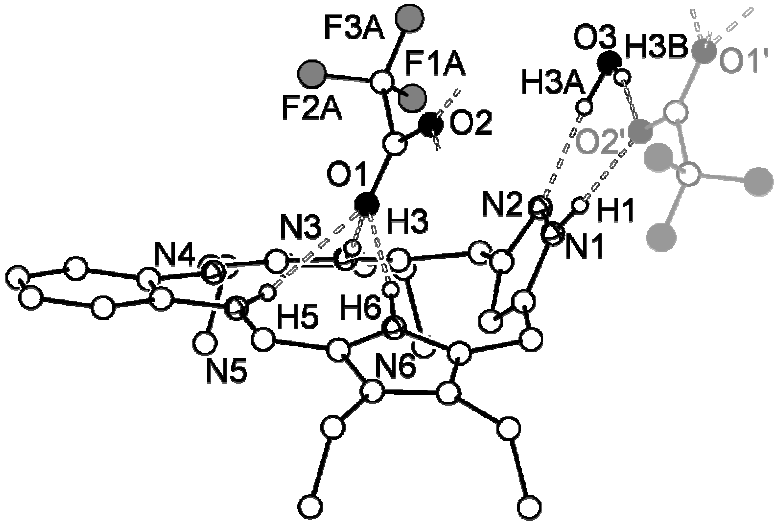

Figure S16: View of the molecular structure of $[\mathbf{4}H]^{+}\cdot(CF_3COO^{-})\cdot(H_2O)$. In the interests of clarity all hydrogen atoms not involved in hydrogen bonding have been omitted. Symmetry transformation used to generate equivalent atoms (’): 1–*x*, 2–*y*, 2–*z*.

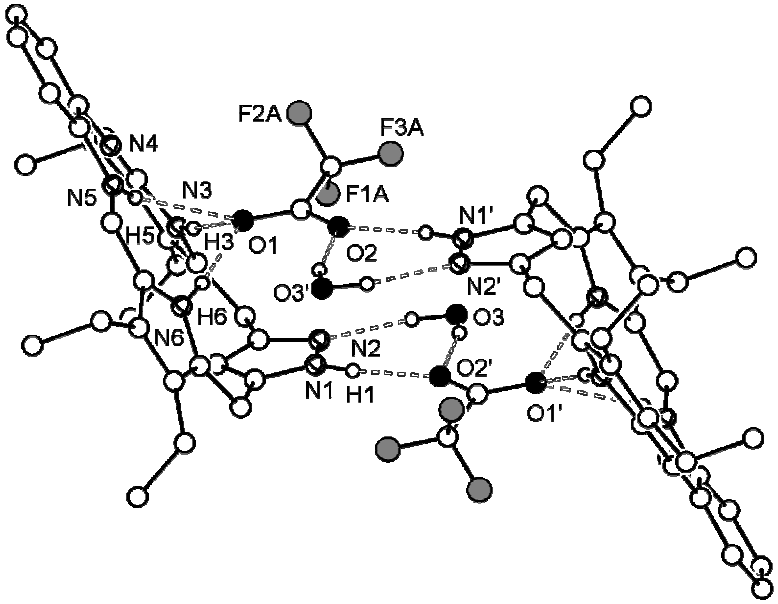

Figure S17: View of the hydrogen bonding interactions of $[\mathbf{4}H]^{+}\cdot(CF_3COO^{-})\cdot(H_2O)$. In the interests of clarity all hydrogen atoms not involved in hydrogen bonding have been omitted. Symmetry transformation used to generate equivalent atoms (’): 1–*x*, 2–*y*, 2–*z*.