Calix[2]phenol[2]pyrrole and a fused pyrrolidine-containing derivative

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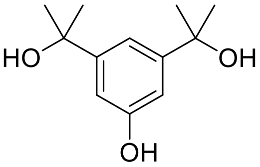
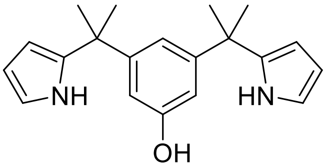
Contents

General and Synthetic details

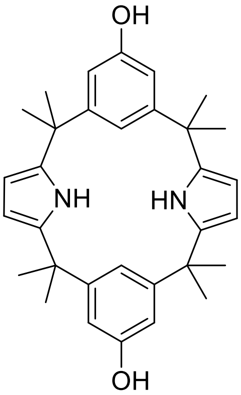
Proton and ^{13}C-NMR spectra were measured at 25 ºC using Varian Unity Innova 400 instruments at 400 MHz. Chemicals and solvents were purchased commercially and used without further purification.



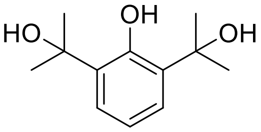
2,2'-(5-Hydroxy-1,3-phenylene)dipropan-2-ol (**2**). Dimethyl 5-hydroxyisophthalate (1.0 g, 4.75 mmol) were dissolved in 25 mL of dry THF under argon at 0 °C. MeMgBr (26.2 mL, 26.16 mmol in THF) was added and the reaction mixture was stirred at room tempearture overnight. After the reaction was carefully quenched with water, the solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and then washed with 1N aqueous HCl. The organic layer was separated, dried over Na_2SO_4, and subjected to filtration. After the organic solvent was removed under reduced pressure, the resulting residue was purified via column chromatography over silica gel (eluent: hexane/ethyl acetate 1:1). This yielded **2** as a white solid (0.73 g, 3.46 mmol, 73%).^{1}H-NMR (500 MHz, DMSO-d_6) [ppm] 1.35 (s, 12H), 4.83 (s, 2H), 6.67 (d, J = 2.0 Hz, 2H), 6.94 (d, J = 2.5 Hz, 1H), 9.01 (s, 1H), ^{13}C-NMR (125 MHz, DMSO-d_6) [ppm] 32.4, 71.1, 109.8, 112.0, 151.7, 156.8. HRMS–ESI: m/z [M + Na]$^+$ calcd for $C_{12}H_{18}O_3$: 233.1154; found: 233.1148.



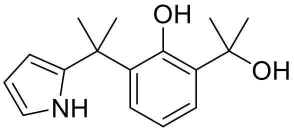
3,5-Bis(2-(1H-pyrrol-2-yl)propan-2-yl)phenol (**3**). Precursor **2** (1.0 g, 4.75 mmol) and pyrrole (1.59 g, 5 equiv.) were dissolved in (20 mL) under argon at room temperature. *p*-TsOH (20 mg, 0.017 mol) was added and the reaction mixture was stirred for 5 h. After the addition of triethylamine (1 mL) to neutralized the reaction mixture, the solvent was removed under reduced pressure. The crude product was purified via column chromatography over silica gel (eluent: hexane/ethyl acetate 4:1). This yielded **3** as a yellow foam (0.623 g, 2.02 mmol, 43%). ^{1}H-NMR (500 MHz, CD_3CN) [ppm] 1.58 (s, 12H), 5.95 (m, 2H), 6.00 (dd, J = 3.5, 3.5 Hz, 2H), 6.43 (dd, J = 3.5, 3.5 Hz, 2H), 6.59 (s, 1H), 6.62 (dd, J = 3.5, 3.5 Hz, 2H), 6.73 (t, J = 3.5, Hz, 2H), 8.69 (bs, 2H), ^{13}C-NMR (125 MHz, CD_3CN) [ppm] 29.4, 39.2, 104.2, 107.2, 111.1, 115.7, 116.8, 140.3, 151.2, 156.5. HRMS–ESI: m/z [M + Na]$^+$ calcd for $C_{20}H_{25}N_2O$: 309.1967; found: 309.1960.



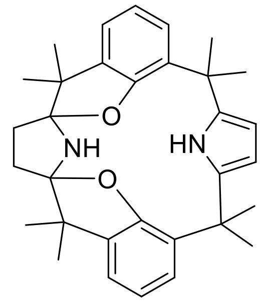
Calix[2]phenol[2]pyrrole (**4**). Precursors **1** (0.136 g, 0.65 mmol) and **3** (0.200 g, 0.65 mmol) were dissolved in DCM/acetonitrile (10/7, v/v; 17 mL). *p*-TsOH (40 mg, 0.023 mol) was added and the reaction mixture was stirred for 24 h. After the addition of triethylamine (0.5 mL) to neutralized the reaction mixture, the solvent was removed under reduced pressure. The crude product was purified via column chromatography over silica gel (eluent: petroleum ether/ethyl acetate 2:1). This gave **4** as a yellow foam (40 mg, 0.082 mmol, 13%). H-NMR (500 MHz, acetone-d_6) [ppm] 1.42 (s, 24H), 5.77 (d, J = 3.0 Hz, 4H), 6.27 (t, J = 1.5 Hz, 2H), 6.59 (d, J = 1.5 Hz, 4H), 7.85 (s, 2H), 8.09 (bs, 2H), ^{13}C-NMR (125 MHz, acetone-d_6) [ppm] 30.3, 38.5, 103.2, 109.7, 119.9, 140.3, 151.7, 157.2. HRMS–CI: m/z $[M + H]^+$ calcd for $C_{32}H_{39}N_2O_2$: 483.3012; found: 483.3009.



2,2'-(2-Hydroxy-1,3-phenylene)dipropan-2-ol (**6**). Dimethyl 2-hydroxyisophthalate (1.6 g, 6.72 mmol) was dissolved in 40 mL dry THF under an argon atmosphere at 0 °C. MeMgBr (37.0 mL, 37.0 mmol in THF) was added and the reaction mixture was stirred for 3 h. After the reaction was quenched via the careful addition of water, the solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and then washed with 1N aqueous HCl. The organic layer was separated off, dried over Na_2SO_4, and subject to filtration. After the organic solvent was removed under reduced pressure, the resulting residue was purified via column chromatography over silica gel (eluent: hexane/ethyl acetate 3:1), yielding **6** as a white solid (1.0 g, 4.74 mmol, 62%).^{1}H-NMR (400 MHz, CD_3CN) [ppm] 1.59 (s, 12H), 4.47 (s, 2H), 6.80 (t, J = 8.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 2H), 10.41 (s, 1H), ^{13}C-NMR (125 MHz, DMSO-d_6) [ppm] 30.7, 75.3, 120.4, 126.0, 135.1, 154.8. HRMS–ESI: m/z $[M + Na]^+$ calcd for $C_{12}H_{18}O_3$: 233.1154; found: 233.1150.



2-(2-(1H-Pyrrol-2-yl)propan-2-yl)-6-(2-hydroxypropan-2-yl)phenol diphenylsilane (**7**). Precursor **5** (1.0 g, 4.75 mmol) and pyrrole (1.59 g, 5 equiv.) were dissolved in acetonitrile (40 mL) under an argon atmosphere at room temperature. *p*-TsOH (110 mg, 0.64 mol) was added and the reaction mixture was stirred overnight. After triethylamine (1 mL) was added to neutralize the reaction mixture, the solvent was removed under reduced pressure. The crude product was purified via column chromatography over silica gel (eluent: hexane/ethyl acetate 4:1), yielding **7** as a yellow foam (0.84 g, 3.23 mmol, 68%). ^{1}H-NMR (500 MHz, CD_3CN) [ppm] 1.17 (s, 6H), 1.24 (s, 6H), 1.72 (s, 6H), 1.80 (s, 2H), 2.41 (d, J = 8.5 Hz, 2H), 2.66 (d, J = 7.5 Hz, 2H), 3.40 (bs, 1H), 5.75(s. 2H), 5.89 (m, 1H), 6,76 (t, J = 7.0 Hz, 2H), 6.88 (d, J = 7.5 Hz, 2H), 10.0 (bs, 1H), ^{13}C-NMR (125 MHz, CD_3CN) [ppm] 27.9, 29.9, 38.8, 54.6, 75.6, 103.6, 107.2, 116.4, 118.8, 124.4, 126.7, 132,4, 135.8, 140.7, 154.8. HRMS–ESI: m/z $[M + Na]^+$ calcd for $C_{16}H_{21}NO_2Na$:282.1470; found:282.1464.



Fused calix 9. Precursor **7** (0.800 g, 1.43 mmol, 2 equiv.) was dissolved in dry acetonitrile (50 mL) under an argon atmosphere. Methansulfonic acid (80 mg, 0.83 mmol) was added and the reaction mixture was stirred for 24 h. After the addition of triethylamine (1 mL) to neutralize the reaction mixture, the solvent was removed under reduced pressure. The crude product was purified via column chromatography over silica gel (eluent: hexanes/ethyl acetate 10:1). This yielded **9** as a white solid (74 mg, 0.15 mmol, 10%). ^{1}H-NMR (500 MHz, CD_2Cl_3 [ppm] 0.85 (t, *J* = 6.8 Hz, 3H), 1.17 (s, 9H), 1.28 (m, 6H), 1.51 (m, 2H), 3.21 (td, *J* = 7.2, 7.2 Hz, 2H), 4.53 (t, *J* = 4.8 Hz, 1H), 6.54 (d, *J* = 9.2 Hz, 1H), 6.94 (bs, 1H), 7.00 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.37 (m, 5H), 7.47 (m, 3H), 7.71 (m, 4H), 7.81 (dd, *J* = 8.8, 2.8 Hz, 1H), 8.20 (d, *J* = 8.8 Hz, 1H), 8.36 (d, *J* = 2.8 Hz, 1H), ^{13}C-NMR (125 MHz, CD_2Cl_3) [ppm] 21.1, 28.5, 28.6, 28.8, 29.7, 37.1, 45.1, 102.5, 112.2, 120.5, 120.9, 125.2, 131.1, 137.8, 139.8, 154.0, HRMS–CI: m/z $[M + H]^+$ calcd for $C_{32}H_{39}N_2O_2$: 483.3012; found: 483.3009.

NMR spectroscopic studies

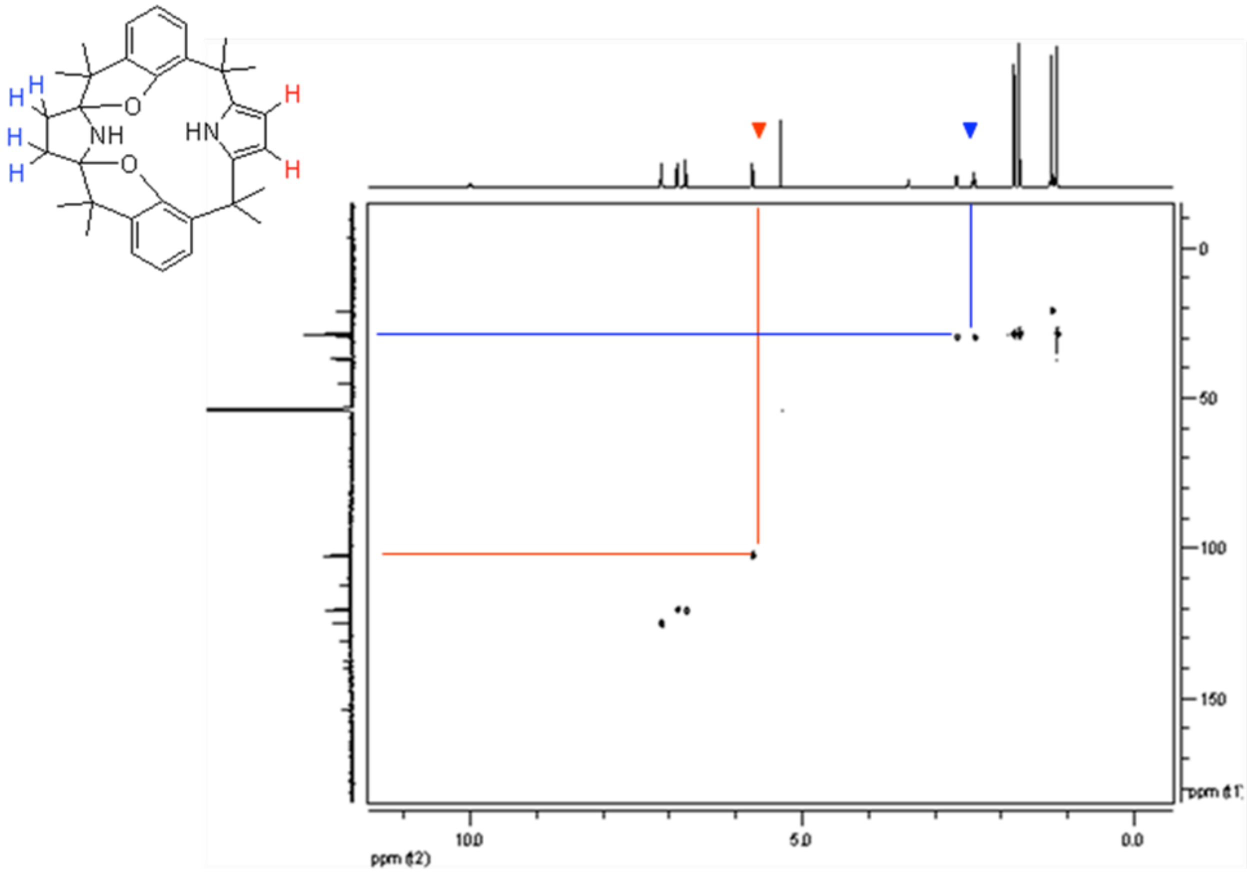


Figure S1. C-H Correlation Spectrum of **9** recorded in CD_2Cl_2 at 25°C

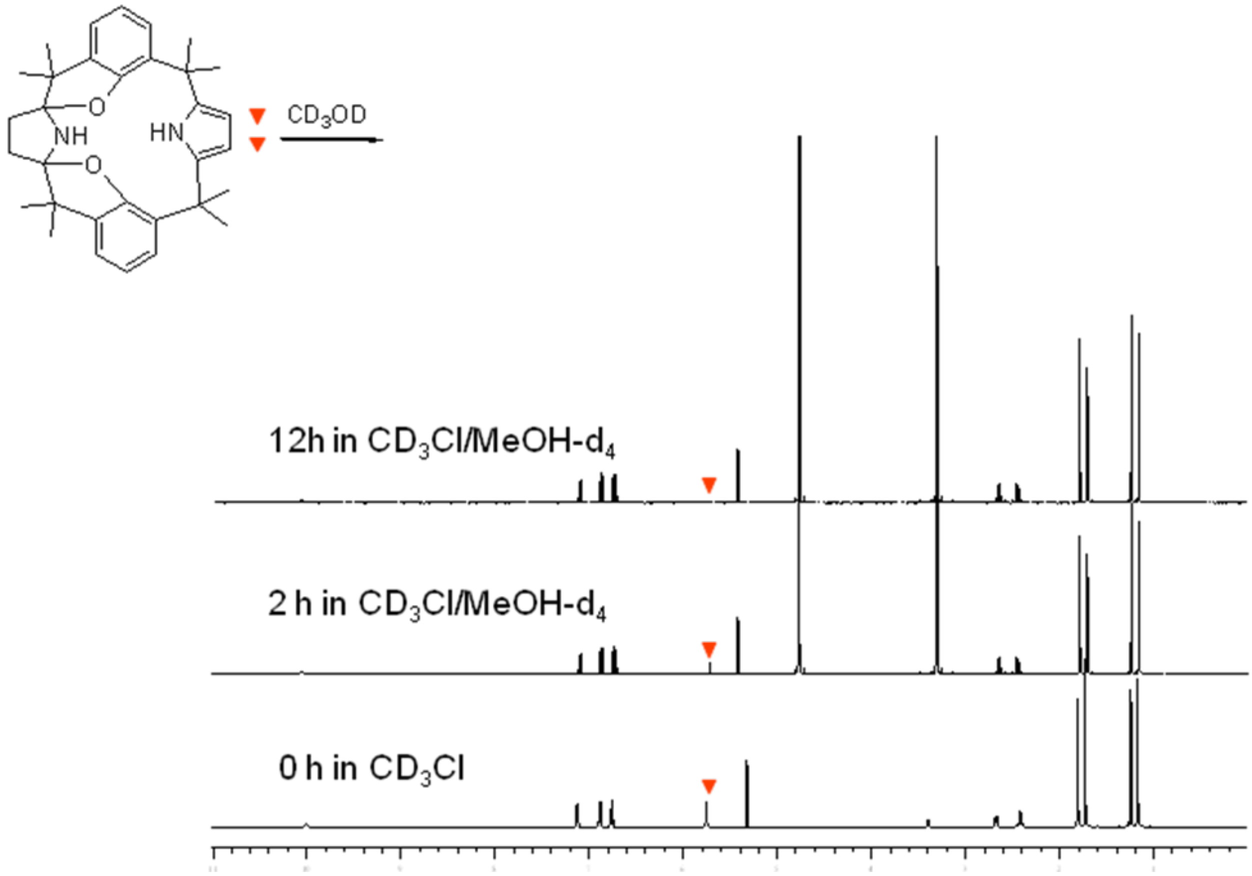


Figure S2. ^{1}H NMR spectra of **9** recorded in CD_2Cl_2 before and after the addition of MeOH-d_4

Experiments for anion binding

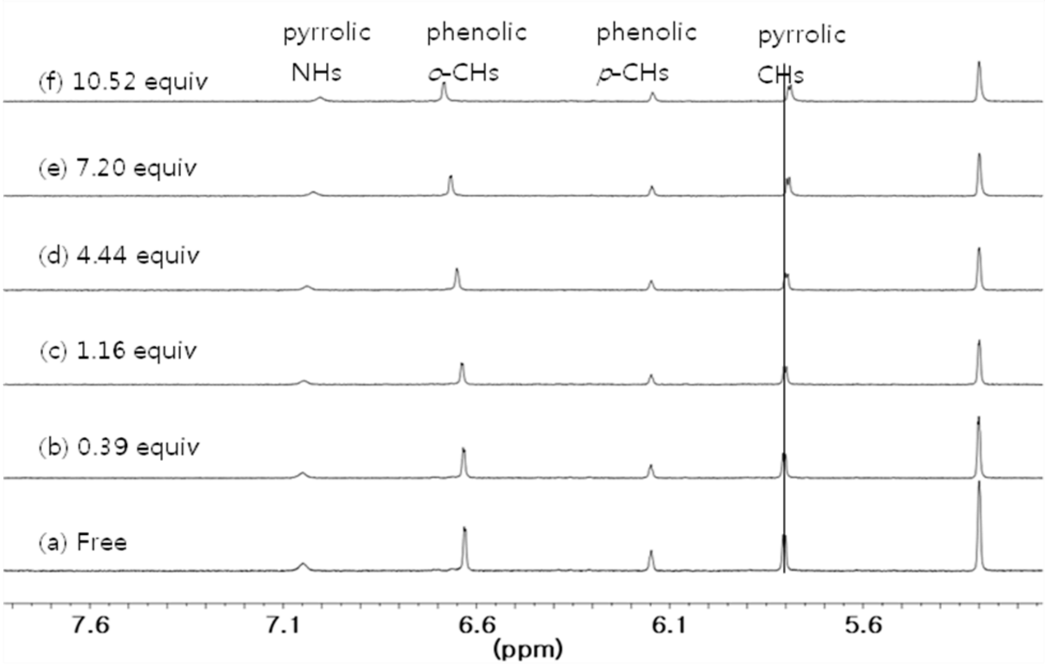


Figure S3. Proton NMR spectra of **4** recorded in CD_2Cl_2/DMSO-d_6 (20/1, v/v) upon the addition of TBACl (tetrabutylammonium chloride).

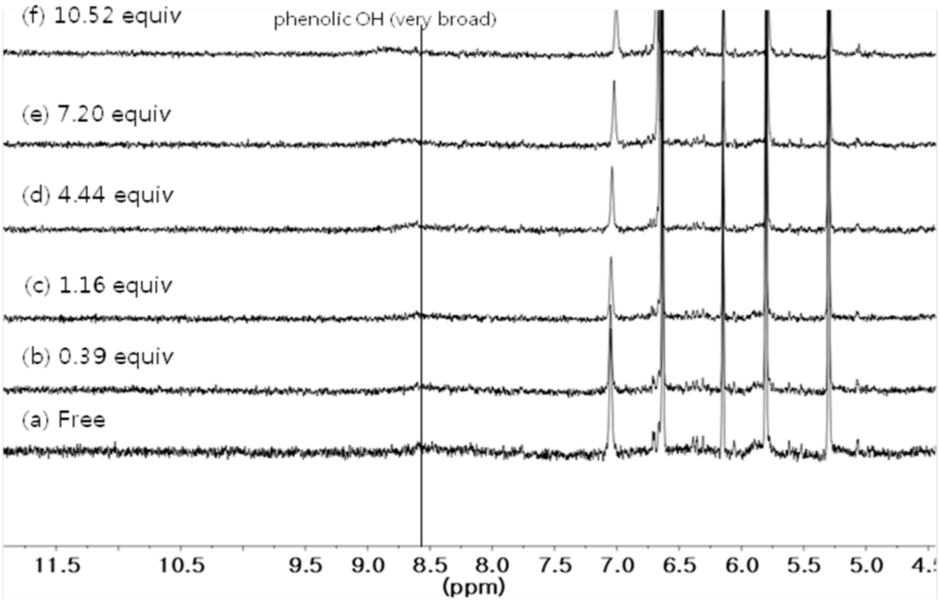


Figure S4. Proton NMR spectra of **4** recorded in CD_2Cl_2/DMSO-d_6 (20/1, v/v) before and after adding increasing quantities of TBACl (tetrabutylammonium chloride). The titration was ceased when no further spectral changes were observed.

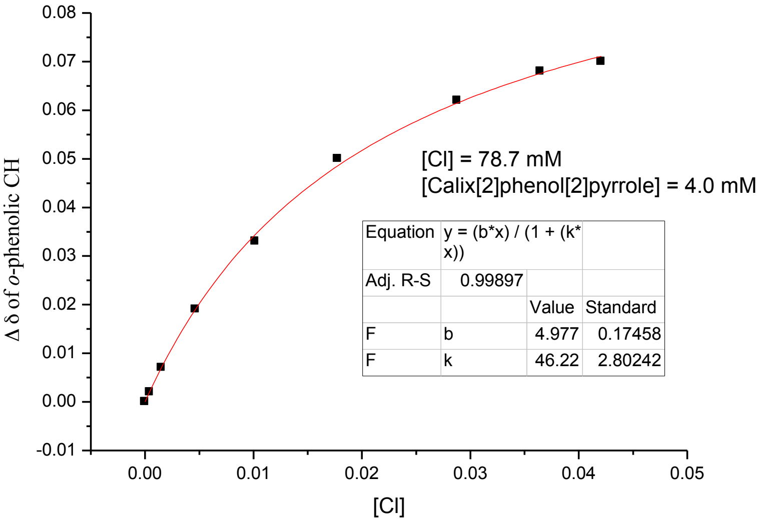


Figure S5. ^1H NMR spectroscopic titration curve for the addition of chloride anion (in the form of its tetrabutylammonium salt, TBACl) to compound **4** in CD_2Cl_2/DMSO-d_6 (20/1, v/v) at 25 °C. The curve shows the fit of the experimental data to a 1:1 binding profile.

X-ray data for macrocycles 4 and 9

Table 1. Crystal data and structure refinement for **9** (CCDC 858002).

Empirical formula	C66 H79N5 O4	
Formula weight	1005.61	
Temperature	153(2) K	
Wavelength	0.71075 Å	
Crystal system	Orthorhombic	
Space group	Pna21	
Unit cell dimensions	a = 24.3554(10) Å	α= 90°.
	b = 11.3368(3) Å	β= 90°.
	c = 20.2929(4) Å	γ = 90°.
Volume	5603.1(3) Å^3	
Z	4	
Density (calculated)	1.179 Mg/m^3	
Absorption coefficient	0.073 mm^{-1}	
F(000)	2120	
Crystal size	0.20 x 0.16 x 0.11 mm^3	
Theta range for data collection	3.35 to 27.48°.	
Index ranges	-31<=h<=31, -14<=k<=14, -26<=l<=26	
Reflections collected	12374	
Independent reflections	6597 [R(int) = 0.0527]	
Completeness to theta = 27.48°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.961	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6597 / 1872 / 849	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0519, wR2 = 0.1218	
R indices (all data)	R1 = 0.0972, wR2 = 0.1394	
Absolute structure parameter	-3.0(17)	
Extinction coefficient	0.0019(4)	
Largest diff. peak and hole	0.261 and -0.201 e.Å^{-3}	

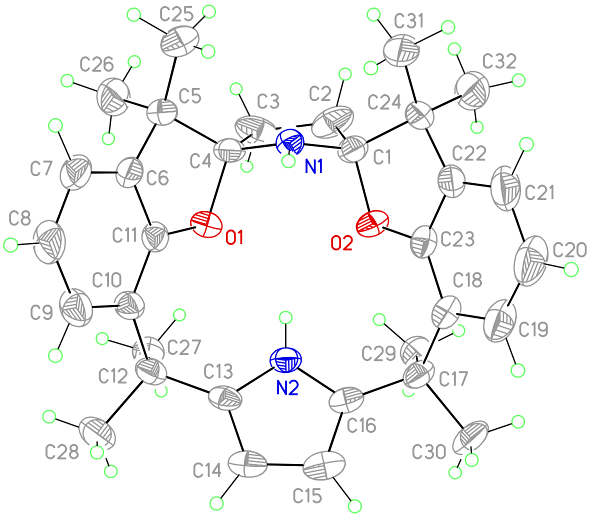


Figure S6. View of molecule 1 of **9** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

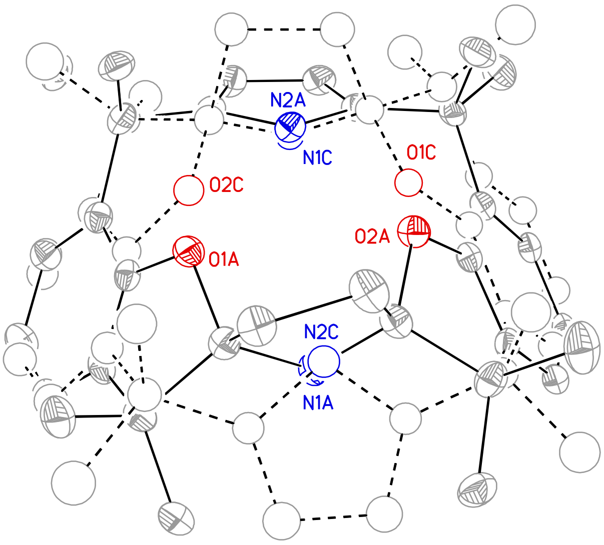


Figure S7. View of the disorder in molecule 2 of **9** showing a partial atom labeling scheme. Displacement ellipsoids are scaled to the 30% probability level.

Table 2. Crystal data and structure refinement for **4** (CCDC 858003)

Empirical formula	C32 H38 N2O2	
Formula weight	482.64	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/n	
Unit cell dimensions	a = 7.3075(2) Å	α= 90°.
	b = 17.5050(4) Å	β= 91.307(1)°.
	c = 9.9498(3) Å	γ = 90°.
Volume	1272.43(6) Å^3	
Z	2	
Density (calculated)	1.260 Mg/m^3	
Absorption coefficient	0.078 mm^{-1}	
F(000)	520	
Crystal size	0.30 x 0.20 x 0.18 mm^3	
Theta range for data collection	2.35 to 27.43°.	
Index ranges	-9<=h<=9, -22<=k<=22, -12<=l<=12	
Reflections collected	5334	
Independent reflections	2892 [R(int) = 0.0184]	
Completeness to theta = 27.43°	99.5 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2892 / 0 / 240	
Goodness-of-fit on F^2	0.986	
Final R indices [I>2sigma(I)]	R1 = 0.0417, wR2 = 0.1076	
R indices (all data)	R1 = 0.0555, wR2 = 0.1164	
Extinction coefficient	$1.3(3)\text{x}10^{-5}$	
Largest diff. peak and hole	0.253 and -0.211 e.Å^{-3}	

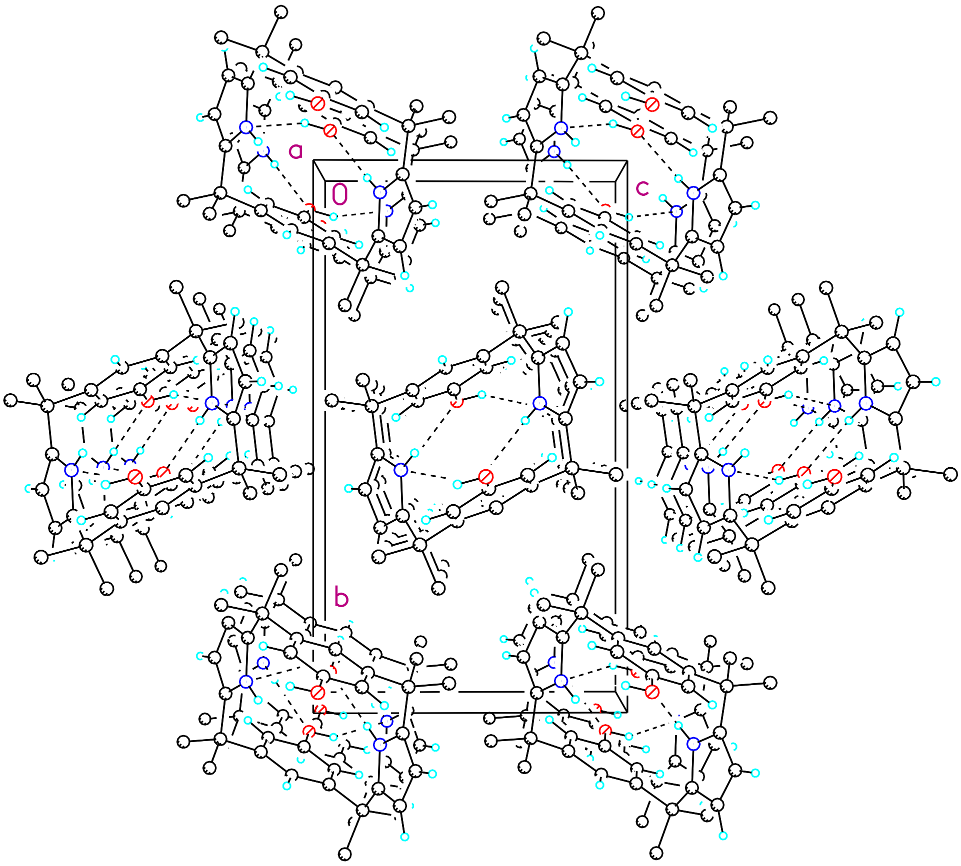


Figure S8. Unit cell packing diagram for **4**. The view is approximately down the **a** axis. The molecules stack in H-bound columns parallel to **a**. Dashed lines are indicative of H-bonding interactions. The geometry of these interactions is: N1-H12N···O1, N···O 3.276(2)Å, H···O 2.36(2)Å, N-H···O 165(1)°; O1-H1O···N1, O···N 3.326(2)Å, H···N 2.58(3)Å, O-H···N 144(2)°.

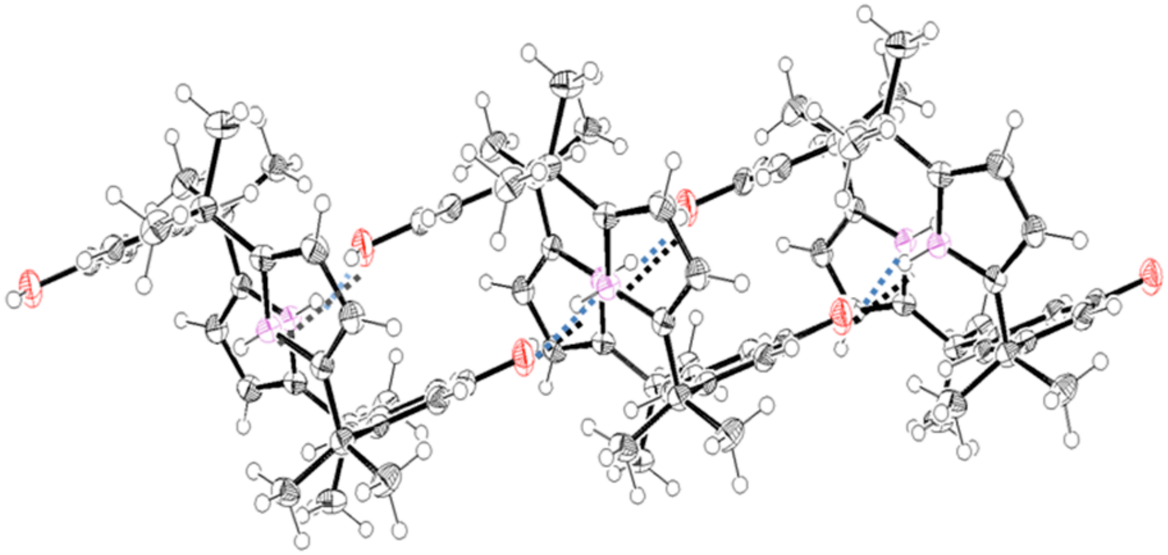


Figure S9. A molecular column of **4** in solid state. Thermal ellipsoids are scaled to the 50% probability level.

Table 3. Crystal data and structure refinement for **4**•TBAF (CCDC 858004)

Empirical formula	C99 H155 Cl6 F N6O5	
Formula weight	1740.99	
Temperature	153(2) K	
Wavelength	0.71075 Å	
Crystal system	Monoclinic	
Space group	I2/a	
Unit cell dimensions	a = 29.8044(8) Å	α= 90°.
	b = 10.3800(5) Å	β= 95.290(2)°.
	c = 31.855(2) Å	γ = 90°.
Volume	9813.1(8) Å^3	
Z	4	
Density (calculated)	1.178 Mg/m^3	
Absorption coefficient	0.230 mm^{-1}	
F(000)	3768	
Crystal size	0.38 x 0.24 x 0.02 mm	
Theta range for data collection	2.06 to 27.50°.	
Index ranges	-38<=h<=38, -12<=k<=13, -41<=l<=41	
Reflections collected	18633	
Independent reflections	10914 [R(int) = 0.0493]	
Completeness to theta = 27.50°	96.8 %	
Max. and min. transmission	0.9954 and 0.9178	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10914 / 68 / 562	
Goodness-of-fit on F^2	1.366	
Final R indices [I>2sigma(I)]	R1 = 0.0831, wR2 = 0.2221	
R indices (all data)	R1 = 0.1623, wR2 = 0.2553	
Largest diff. peak and hole	0.995 and -1.248 e.Å^{-3}	

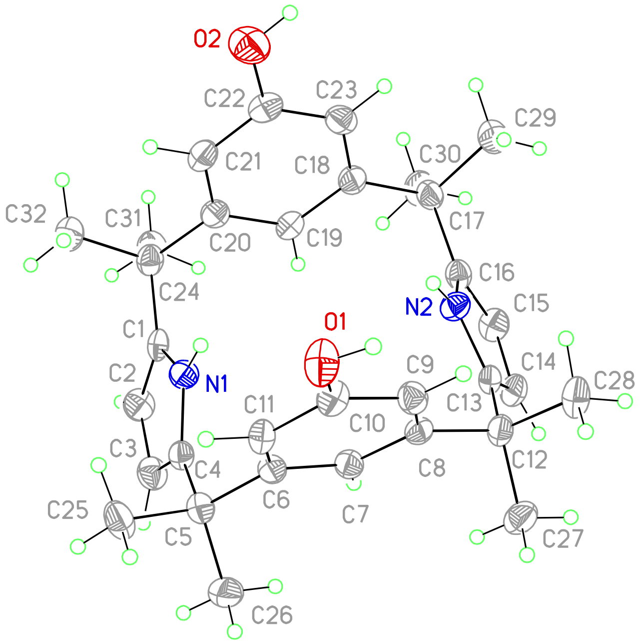
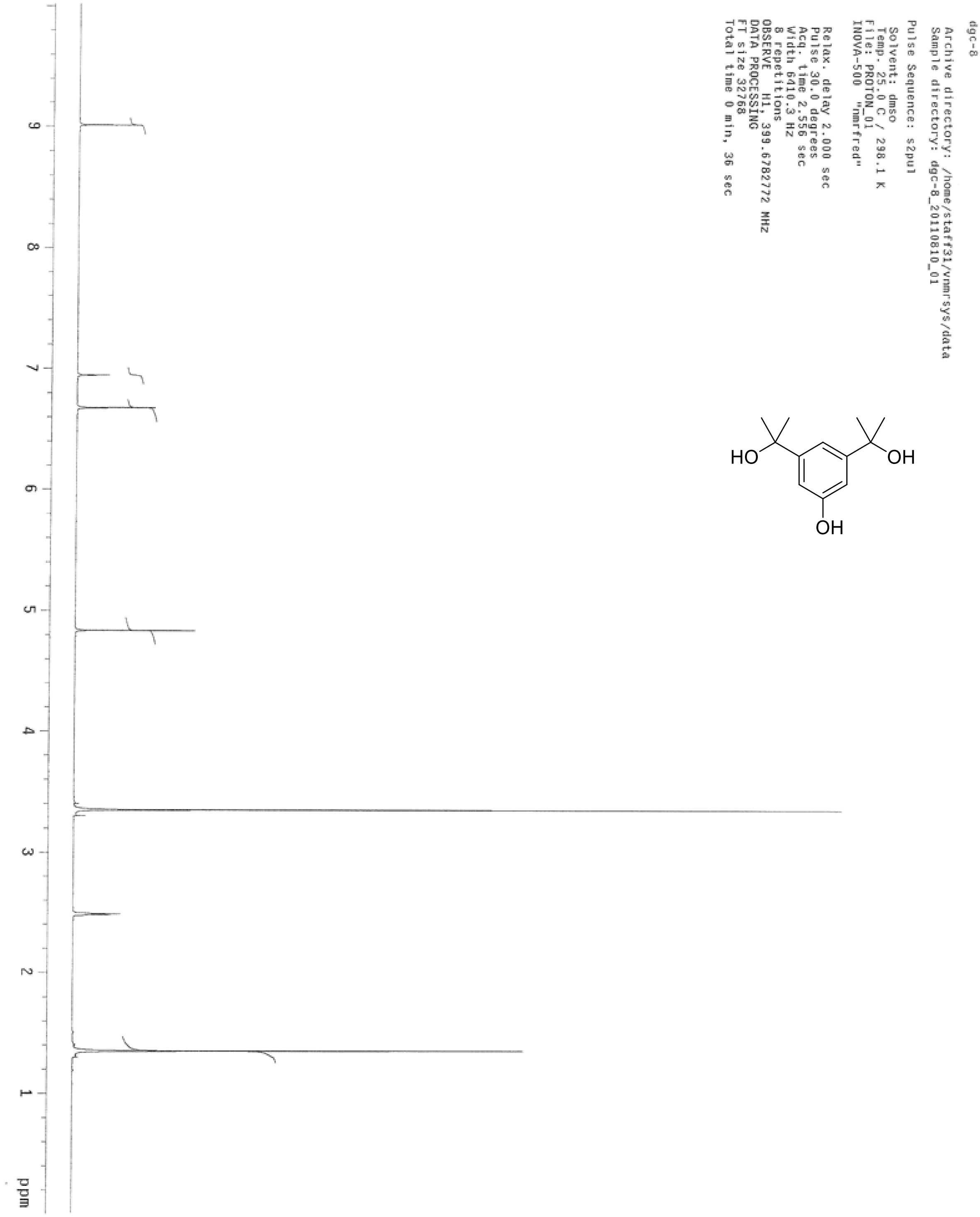
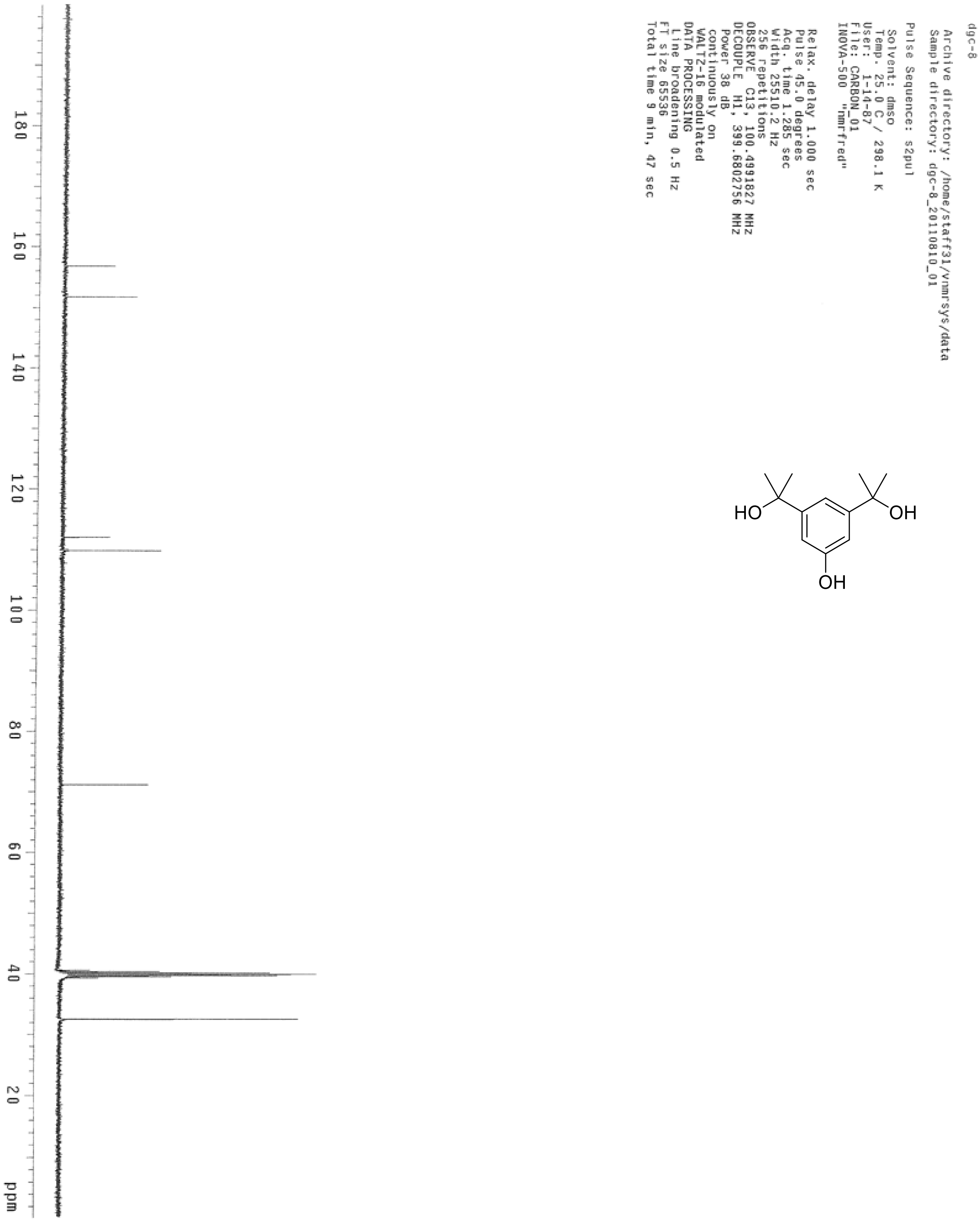


Figure S10. View of **4** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. Fluoride ions, TBA cations, and the disordered molecules have been omitted for clarity.

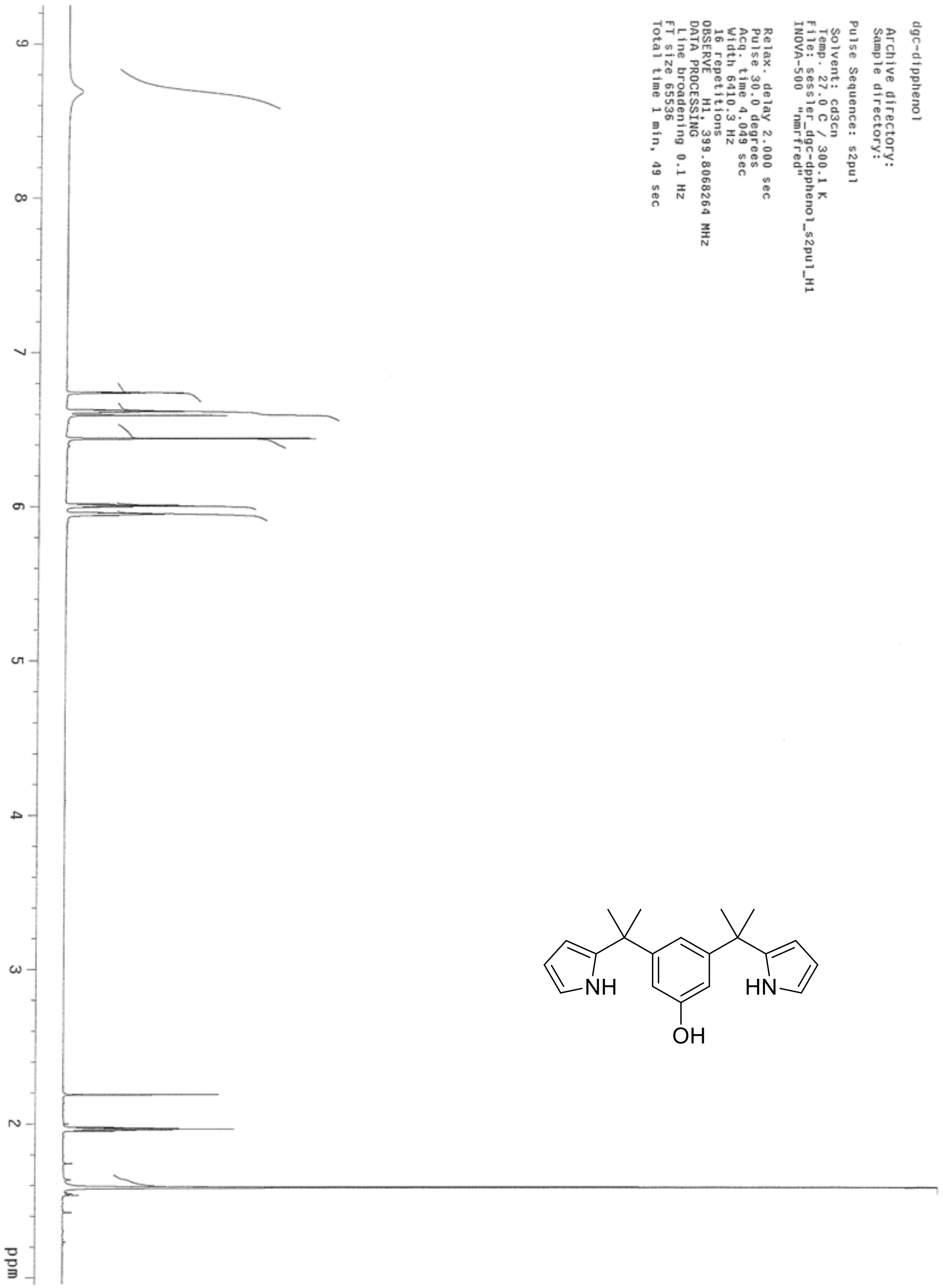
NMR Spectra



^{1}H NMR spectrum of **2** recorded in DMSO-d_6



^{13}C NMR spectrum of **2** recorded in DMSO-d_6



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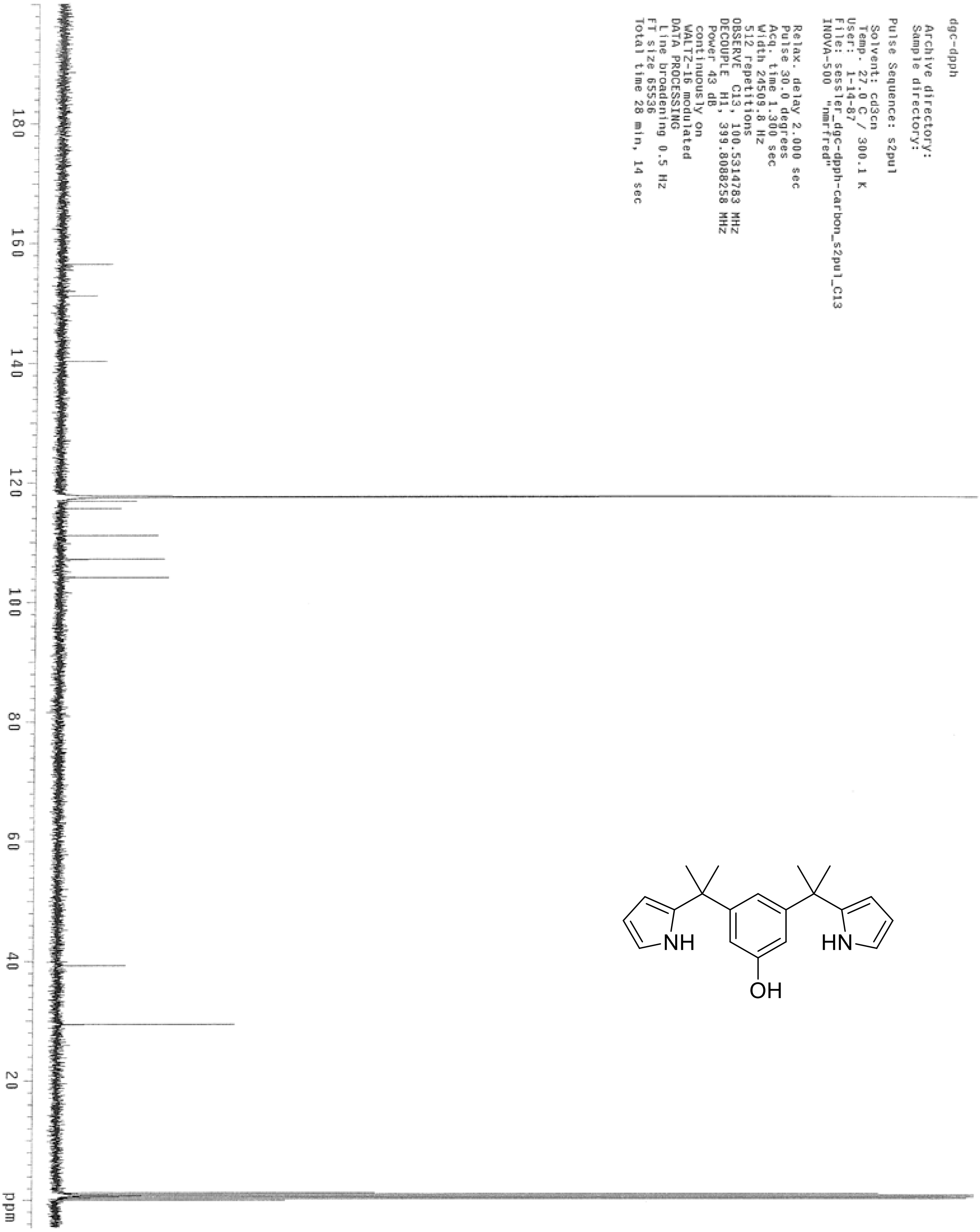

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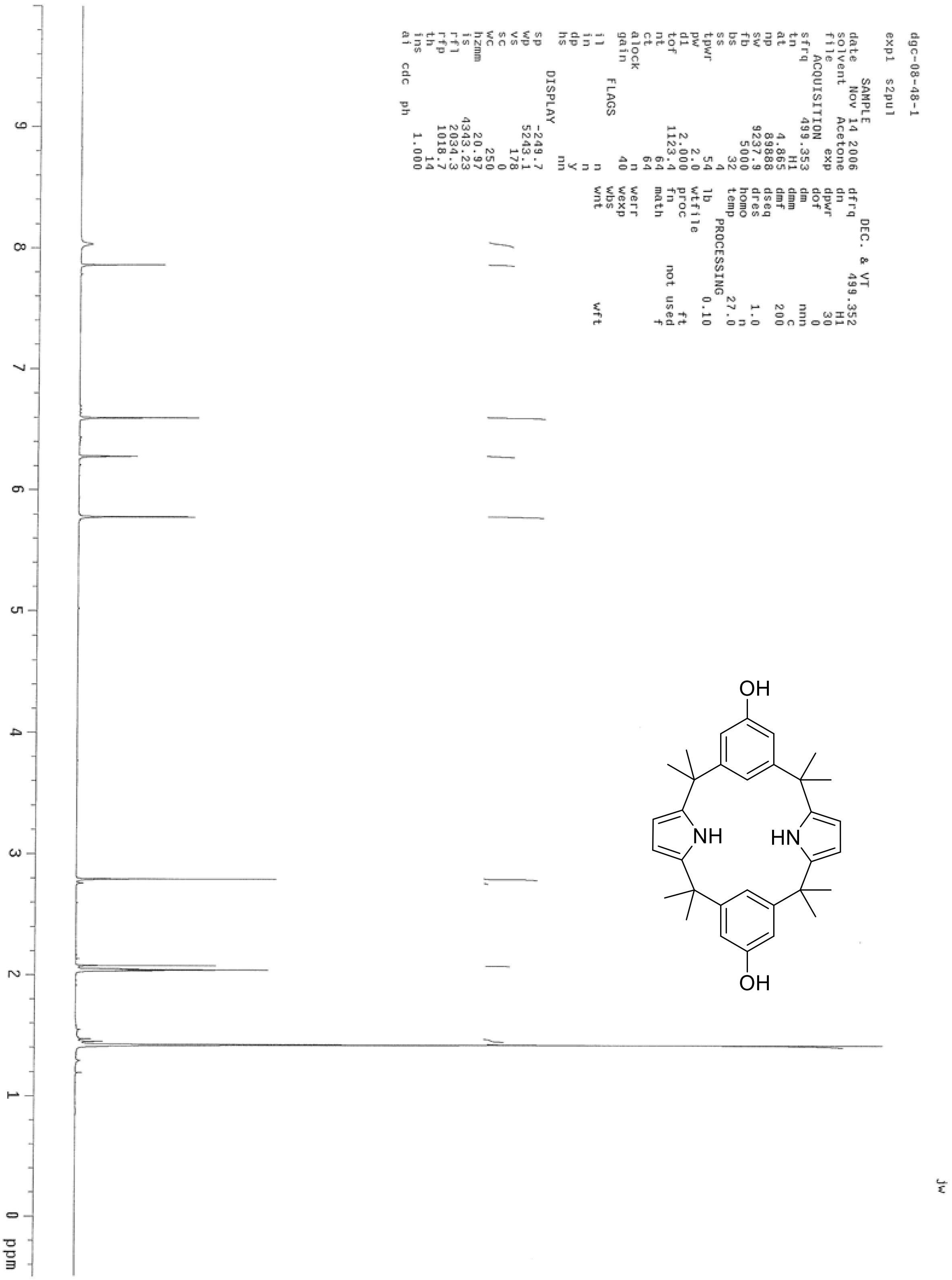

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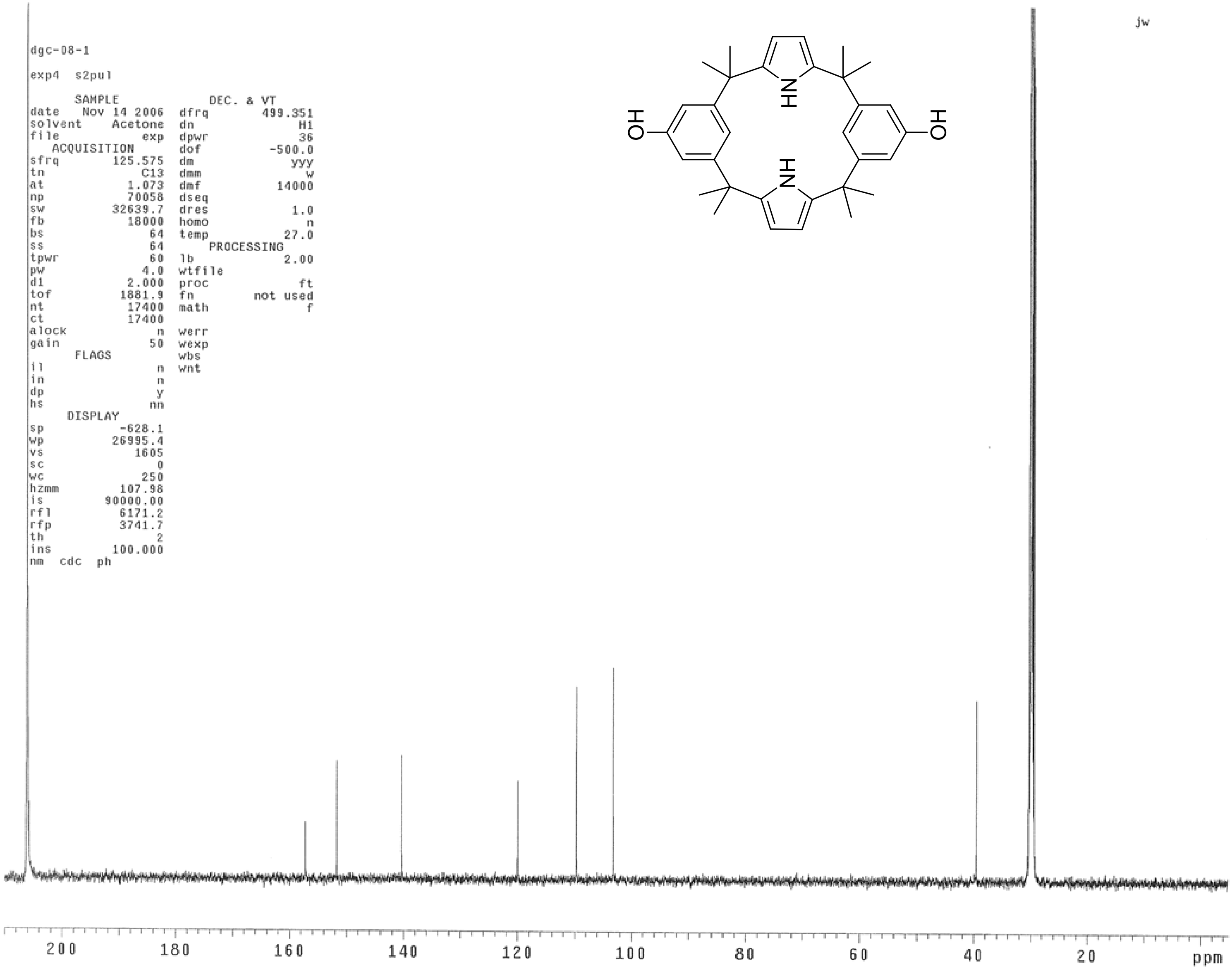

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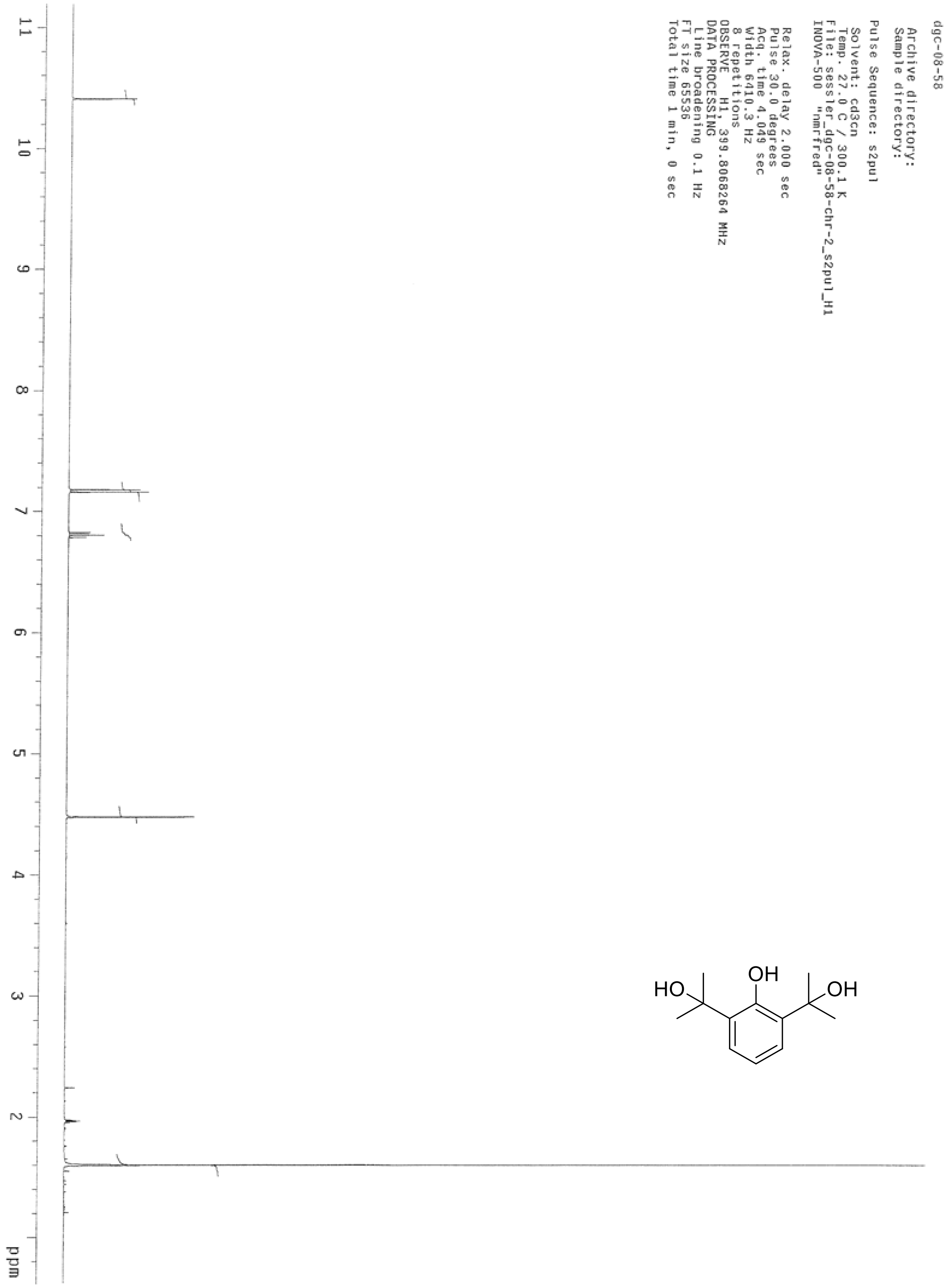
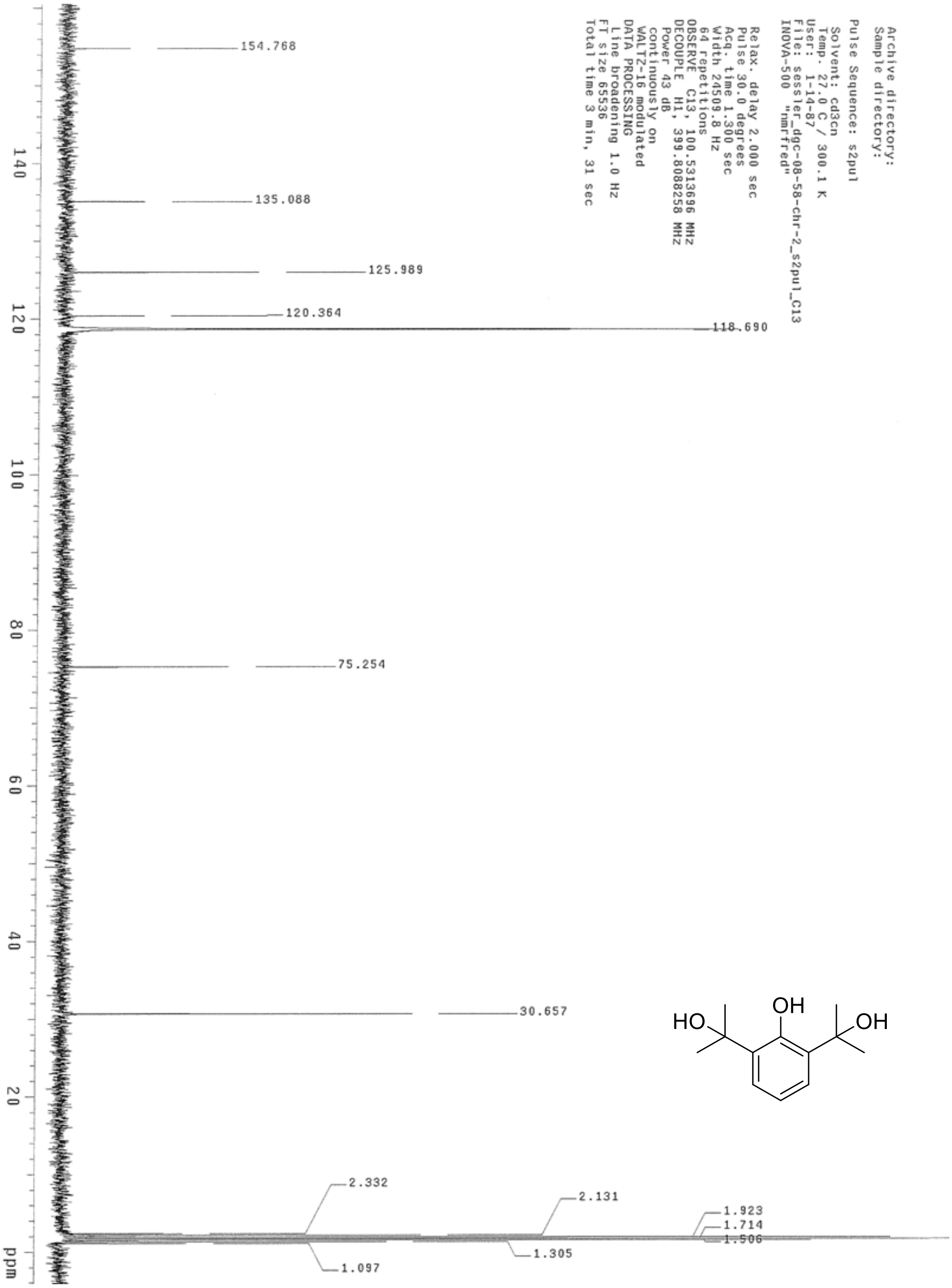
^{13}C NMR spectrum of **4** recorded in acetone-*d*$_6$



^{1}H NMR spectrum of **6** recorded in CD_3CN

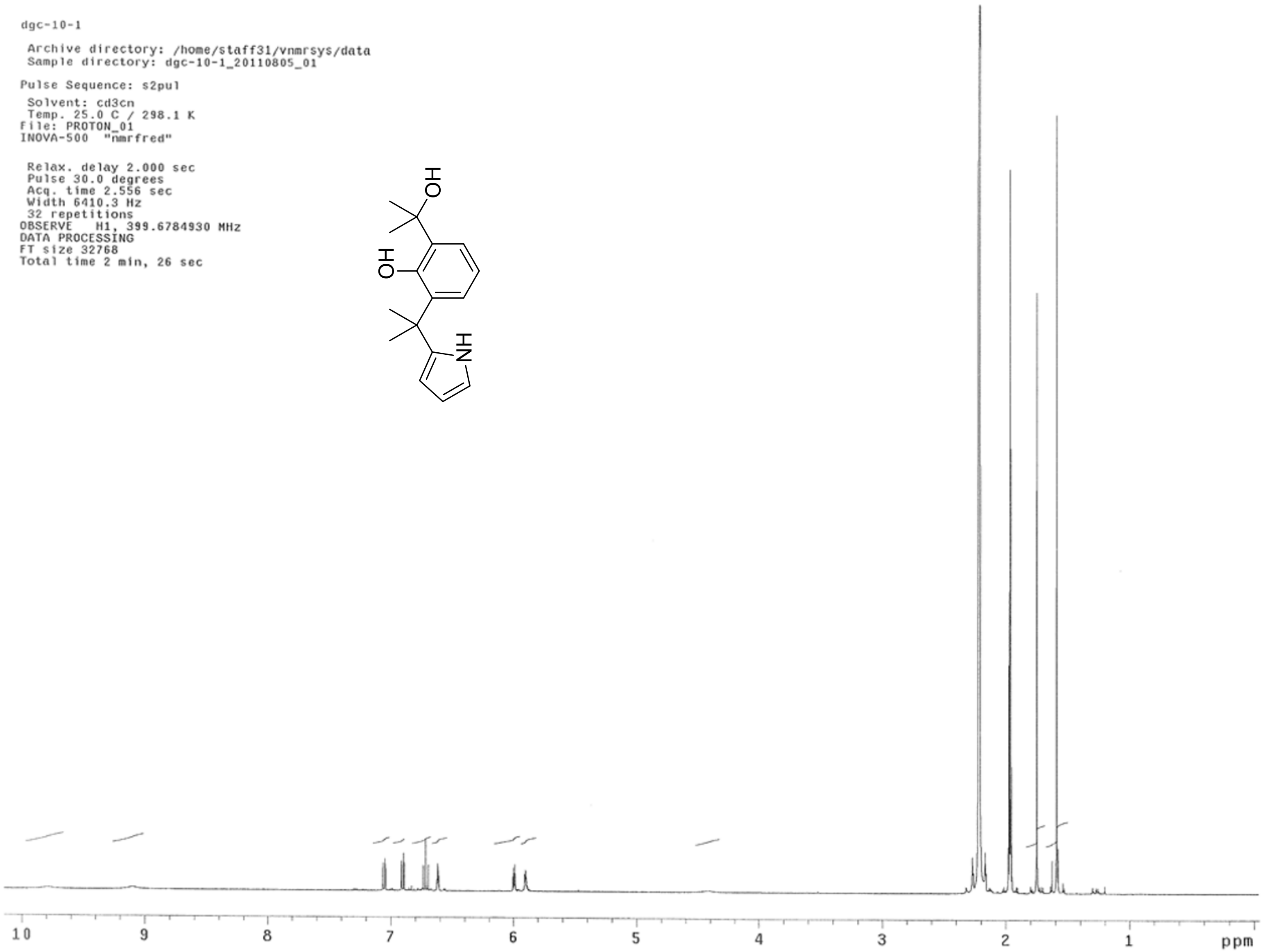


```
Archive directory:
Sample directory:

Pulse Sequence: s2pul
 Solvent: cd3cn
 Temp. 27.0 C / 300.1 K
User: 1-14-87
File: sessler_dgc-08-58-chr-2_s2pul_C13
INOVA-500  "nmrfred"

 Relax. delay 2.000 sec
 Pulse 30.0 degrees
 Acq. time 1.300 sec
 Width 24509.8 Hz
 64 repetitions
OBSERVE  C13, 100.5313696 MHz
DECOUPLE  H1, 399.8088258 MHz
 Power 43 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
Total time 3 min, 31 sec
```

^{13}C NMR spectrum of **6** recorded in CD_3CN



```
dgc-10-1

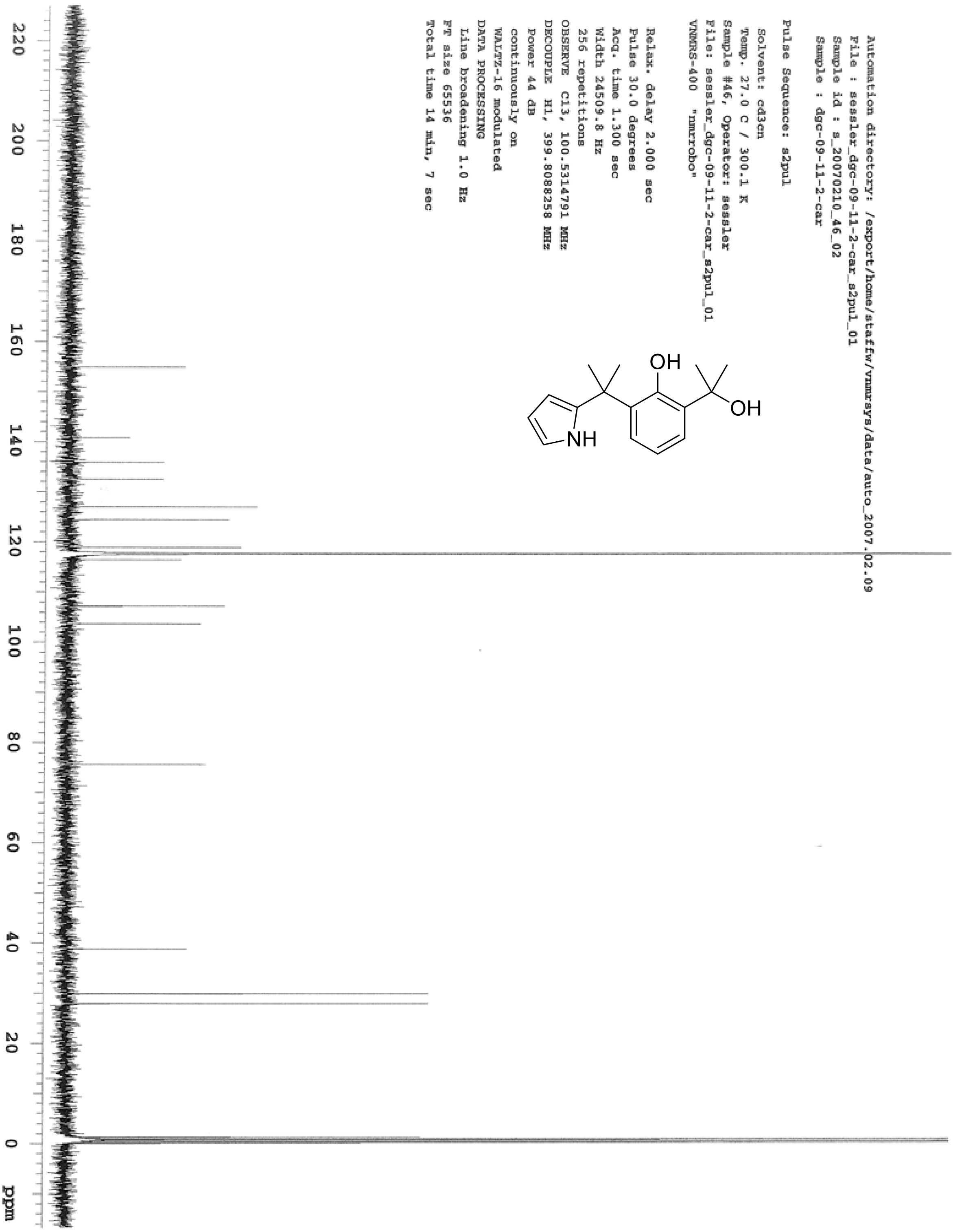
 Archive directory: /home/staff31/vnmrsys/data
 Sample directory: dgc-10-1_20110805_01

Pulse Sequence: s2pul

 Solvent: cd3cn
 Temp. 25.0 C / 298.1 K
File: PROTON_01
INOVA-500  "nmrfred"

 Relax. delay 2.000 sec
 Pulse 30.0 degrees
 Acq. time 2.556 sec
 Width 6410.3 Hz
 32 repetitions
OBSERVE   H1, 399.6784930 MHz
DATA PROCESSING
FT size 32768
Total time 2 min, 26 sec
```

^{1}H NMR spectrum of **7** recorded in CD_3CN



```
Automation directory: /export/home/staffw/vnmrsys/data/auto_2007.02.09
File : sessler_dgc-09-11-2-car_s2pul_01
Sample id : s_20070210_46_02
Sample : dgc-09-11-2-car

Pulse Sequence: s2pul

 Solvent: cd3cn
 Temp. 27.0 C / 300.1 K
 Sample #46, Operator: sessler
 File: sessler_dgc-09-11-2-car_s2pul_01
 VNMRS-400  "nmrobo"

 Relax. delay 2.000 sec
 Pulse 30.0 degrees
 Acq. time 1.300 sec
 Width 24509.8 Hz
  256 repetitions
 OBSERVE  C13, 100.5314791 MHz
 DECOUPLE  H1, 399.8088258 MHz
 Power 44 dB
  continuously on
 WALTZ-16 modulated
 DATA PROCESSING
  Line broadening 1.0 Hz
 FT size 65536
 Total time 14 min, 7 sec
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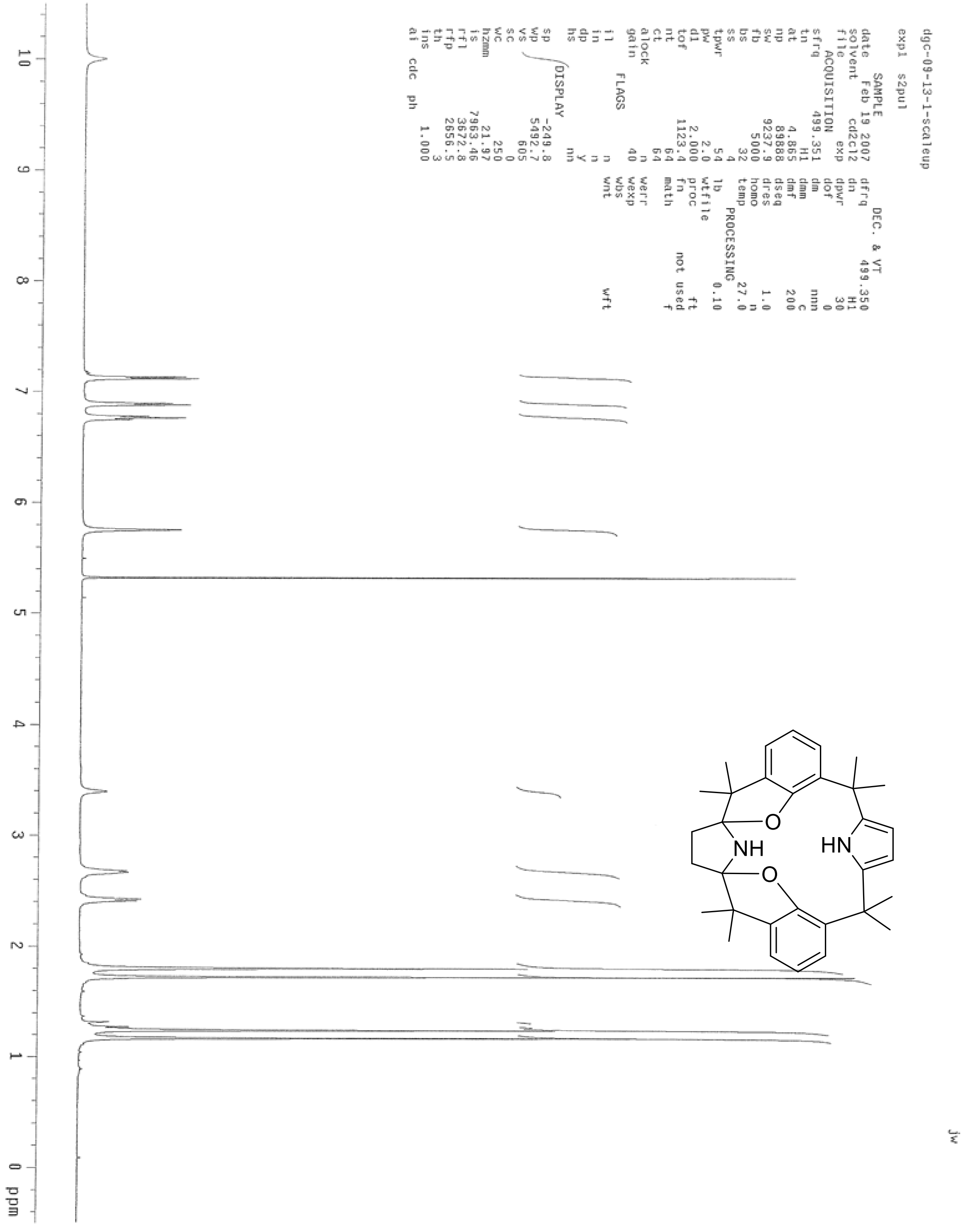
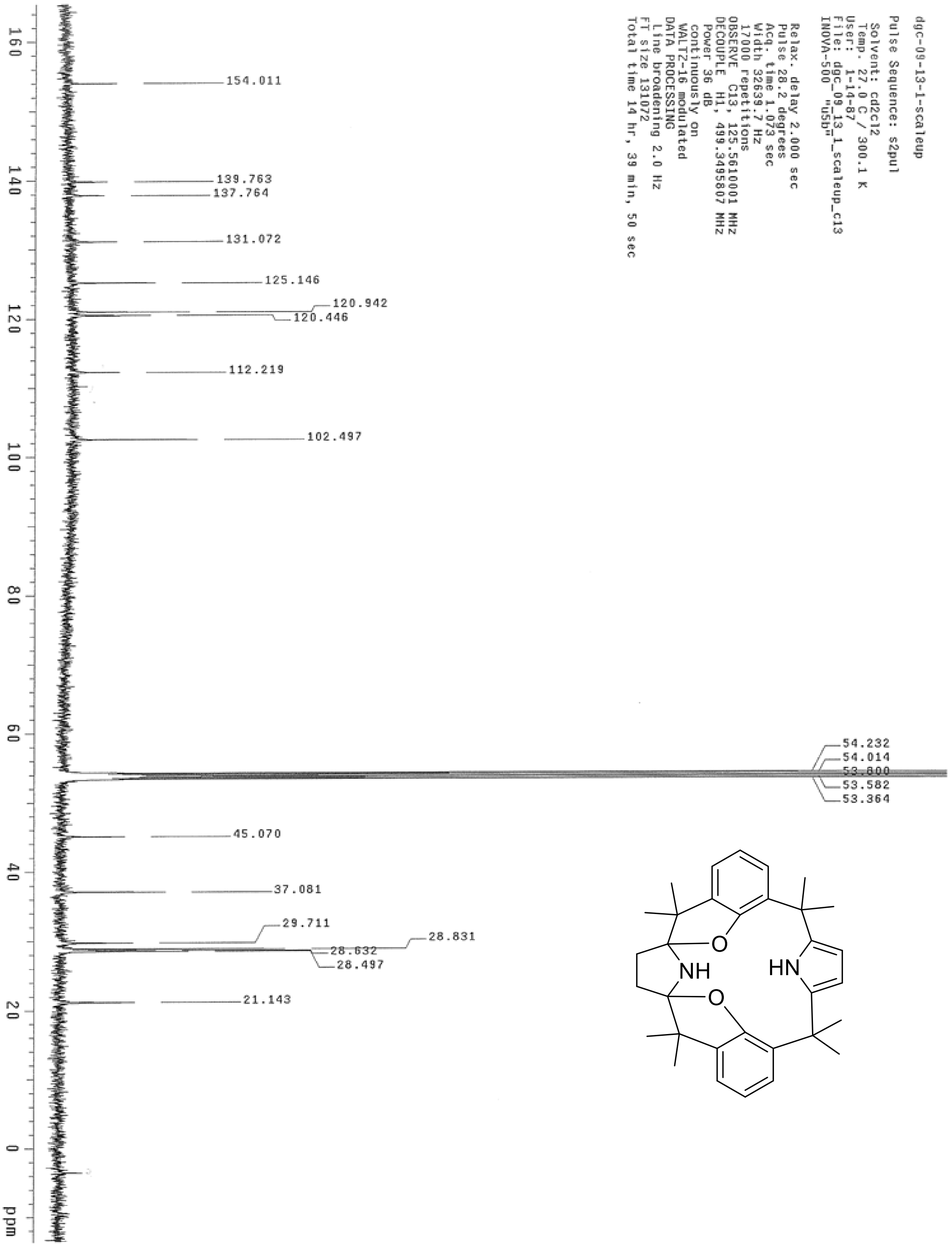
^{13}C NMR spectrum of **7** recorded in CD$_3$CN



^{1}H NMR spectrum of **9** recorded in CD_2Cl_2



^{13}C NMR spectrum of **9** recorded in CD_2Cl_2