Dioxabenzosapphyrin: a New Benzodifuran-derived Sapphyrin Analogue

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Supplementary Material

Contents

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General Procedures and Synthetic Experimental

Proton and ^{13}C-NMR spectra were measured at 25 ºC using Varian Unity Innova instruments at 400, 500, or 600 MHz. UV-vis spectra were recorded on a BECKMAN DU 640B spectrophotometer. High resolution CI mass spectra were obtained on a VG ZAB2-E mass spectrometer.

Diethyl 3,6-dimethylbenzofuran-2,7-dicarboxylate (5) Dicarboxylate **5** was obtained from the corresponding diethyl 2,2'-[1,2-phenylenebis(oxy)]bisacetoacetate in 5.7% yield according to the procedure of Nuth.[1] ^{1}H-NMR (400 MHz, $CDCl_3$) [ppm] 1.44 (t, J = 7.2 Hz, 6H), 2.63 (s, 6H), 4.45 (q, J = 7.2 Hz, 4H), 7.49 (s, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) [ppm] 9.5, 14.3, 61.03, 115.9, 126.5, 129.5, 139.1, 141.3, 159.9; HRMS (CI): m/z 331.1183 (M+H), calcd for $C_{18}H_{19}O_6$ 331.1182.

(3,6-Dimethylbenzofuran-2,7-yl)dimethanol (6) Diester **5** (140 mg, 0.423 mmol in 5mL THF) was added slowly to a suspension of $LiAlH_4$ (160 mg, 4.23 mmol in 20 mL anhydrous THF) under argon at 0 ^{o}C. After the addition was complete, the reaction was stirred for 1 h at 0 ^{o}C. The reaction was then stirred at room temperature overnight. Water was added carefully to quench the reaction. The resulting solution was filtered through a celite pad and washed with ethyl acetate. The filtrate and washings were washed with water and the organic layer was separated and dried over anhydrous Na_2SO_4 before the solvent was removed in vacuo. Compound **5** was isolated in this way without having to resort to column chromatography (70 mg, 70%). ^{1}H-NMR (500 MHz, DMSO-*d*$_6$) [ppm] 2.24(s, 6H), 4.57 (d, J = 6.0 Hz, 4H), 5.31 (t, J = 6.0 Hz, 2H). ^{13}C-NMR (125 MHz, DMSO-*d*$_6$) [ppm] 7.8, 53.8, 112.6, 114.7, 137.7, 152.4; HRMS (CI): m/z 229.0864 [M-H_2O]$^+$, calcd for $C_{18}H_{19}O_6$ 229.0865.

Diethyl 3,6-dimethylbenzofuran-2,7-dialdehyde (7) MnO_2 (42 mg, 0.483) was added to a suspension of diol **6** (70 mg, 4.83 mmol in 10 mL anhydrous CH_2Cl_2) under argon at room temperature. The reaction mixture was then stirred at room temperature overnight. The resulting solution was filtered through a celite pad and washed with CH_2Cl_2. The filtrate and washings were collected and solvent was removed in vacuo. Compound **7** could be isolated in this way without the need for column chromatography (52 mg, 75%). ^{1}H-NMR (500 MHz, DMSO-*d*$_6$) [ppm] 2.66 (s, 6H), 7.80 (s, 2H), 10.04 (s, 2H). ^{13}C-NMR (125 MHz, DMSO-*d*$_6$) [ppm] 8.1, 117.8, 130.06, 139.2, 148.8, 180.0; HRMS (CI): m/z 243.0660 [M+H]$^+$, calcd for $C_{14}H_{11}O_4$ 243.0657.

Dioxabenzosapphyrin (3) Tetramethyldiethyltripyrromethane dicarboxylic acid **8** (18.7 mg, 0.041 mmol) was stirred with TFA (1 mL) under argon at room temperature for 2 min, after which dichloromethane (83 mL) and dialdehyde **7** (10 mg, 0.041 mmol) were added. The resulting solution was stirred in the dark under argon for 12 h. DDQ (24 mg, 0.10 mmol) was added and the reaction mixture was stirred for 30 min. The solvents were then removed and the residue was purified directly by chromatography over silica gel, eluting with methanol-dichloromethane (0-5% MeOH in CH_2Cl_2). The green fraction was collected and the solvent was removed under reduced pressure. The resulting solid was further purified by recrystallizing from ethyl acetate, a purification procedure that

afforded dioxabenzosapphyrin **3** in the form of its bis-TFA salt (9.3 mg; 40%). ^{1}H-NMR (500 MHz, $CDCl_3$ + *p*-TsOH + MeOH-d_4) [ppm] -5.29 (bs, 2H), -2.56 (1.33 (bs, 1H), 2.26 (t, J = 7.5 Hz, 12H), 4.33 (s, 6H), 4.77 (m, 8H), 4.88 (s, 6H), 4.17 (m, 8H), 4.88 (s,6H), 10.08 (s, 2H), 11.81 (s, 2H), 12.08 (s, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$ + *p*-TsOH + MeOH-d_4) [ppm] 12.9, 13.2, 17.8, 18.4, 21.1, 101.3, 122.10, 124.56, 128.0, 129.2, 133.2, 136.6, 138.90, 140.9, 145.6, 146.5, 147.2. HRMS (ESI): m/z 570.3121 $[M+H]^+$, calcd for $C_{38}H_{40}N_3O_2$ 570.3121. UV-vis (**3**·$(TFA)_2$ in CH_2Cl_2) max [nm] (ε, M^{-1}•cm^{-1}) 455 (83,000), 673 (12,300), 681 (9,200). 827 (7,400). This compound was further characterized by X-ray diffraction analysis.

Benzosapphyrin (4) Tetramethyldiethyltripyrromethane dicarboxylic acid **8** (18.7 mg, 0.041 mmol) was stirred with TFA (1 mL) under argon at room temperature for 2 min, after which point dichloromethane (83 mL) and benzobipyrroledialdehyde (10 mg, 0.041 mmol) were added. The resulting solution was stirred in the dark under argon for 12 h. DDQ (10 mg, 0.044 mmol) was added and the reaction mixture was stirred for an additional 30 min. The solvents were then removed under reduced pressure and the residue was then directly purified by chromatography over neutral alumina, eluting with methanol-dichloromethane (0-10% acetone in EtOAc). The green fraction was collected and the solvent was removed under reduced pressure. The resulting mixture was further purified by preparative TLC, which consistently afforded pure benzosapphyrin **4.** The benzosapphyrin **4** obtained in this way was then dissolved in dichloromethane, washed with $NaHCO_3$ and further washed with HCl (1 N). The organic solution was treaded with anhydrous Na_2SO_4 After filtration, the solvents were removed under reduced pressure; this yield the bis-hydrochloride salt of benzosapphyrin (4.0 mg; 17%). ^{1}H-NMR (500 MHz, $CDCl_3$) [ppm] -4.40 (bs, 2H), -3.10 (bs, 1H), -2.36 (bs, 2H), 2.20 (t, J = 7.8 Hz, 4H), 2.29 (t, J = 7.8 Hz, 4H), 4.10 (s, 6H), 4.23 (s, 6H), 4.33 (q, J = 7.8 Hz, 8H), 8.68 (s, 2H), 11.39 (s, 2H), 11.48 (s, 2H). ^{13}C-NMR (150 MHz, $CDCl_3$) [ppm] 12.6, 12.7, 17.6, 18.4, 20.9, 92.8, 101.0, 121.5, 126.3, 130.1, 130.2, 134.4, 136.20, 136. 80, 138.1, 142.5, 143.5. HRMS (CI): m/z 568.3434 $[M+H]^+$, calcd for $C_{38}H_{42}N_5$ 568.3440.

UV-vis Spectra of 3

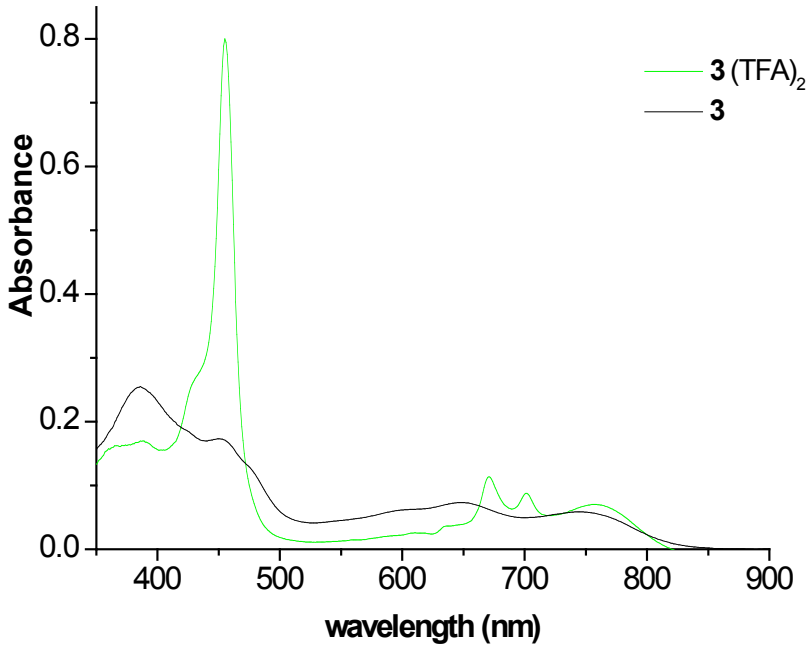

Figure S1. Uv-vis spectrum of dioxabenzosapphyrin **3** (black line) and **3**•$(TFA)_2$ (green line) in dichloromethane.([3] = [3•$(TFA)_2$] = 9.55×10^{-6} M)

NMR Spectra

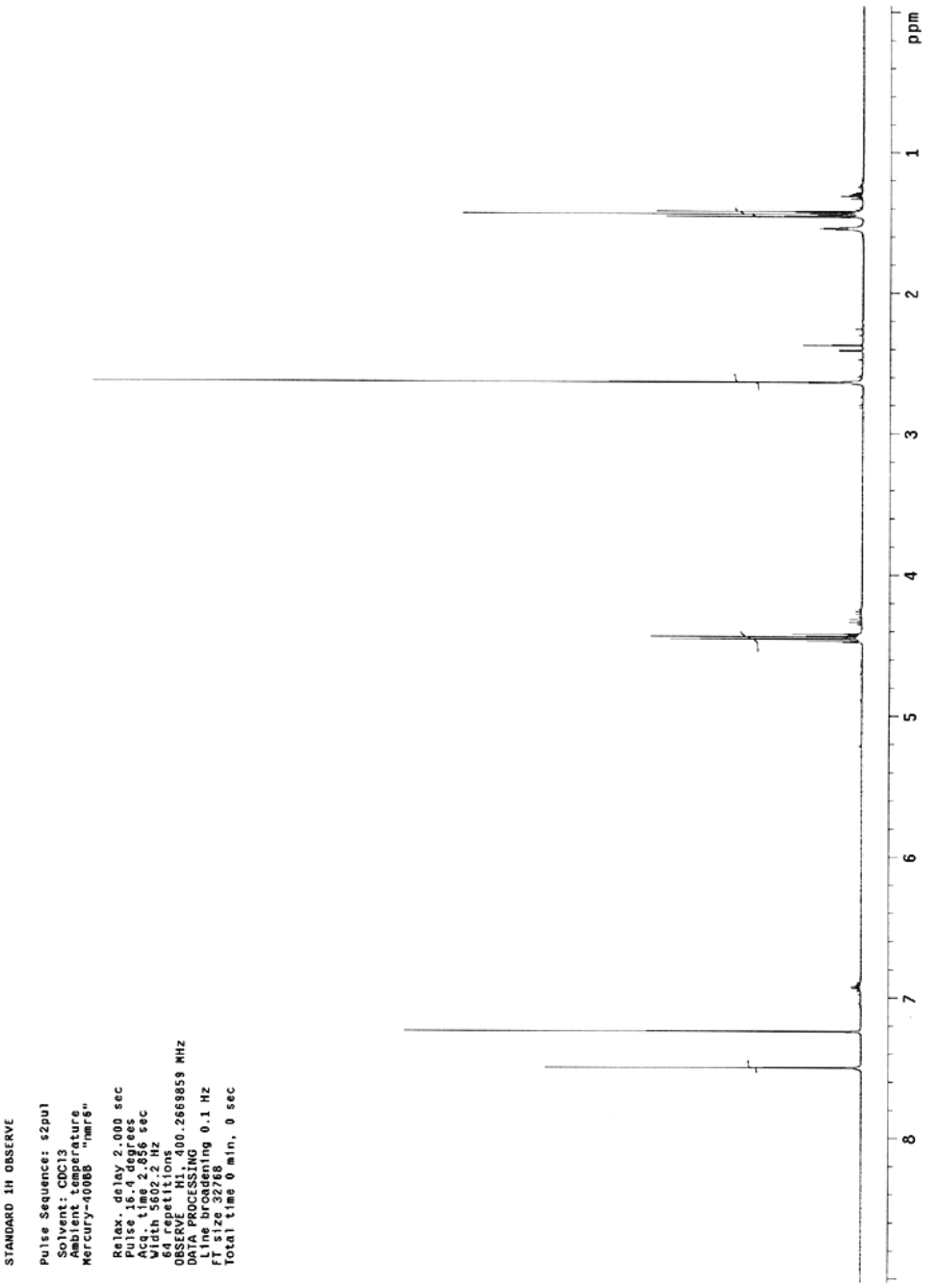

Figure S2. ^{1}H NMR spectrum of **5** recorded in $CDCl_3$

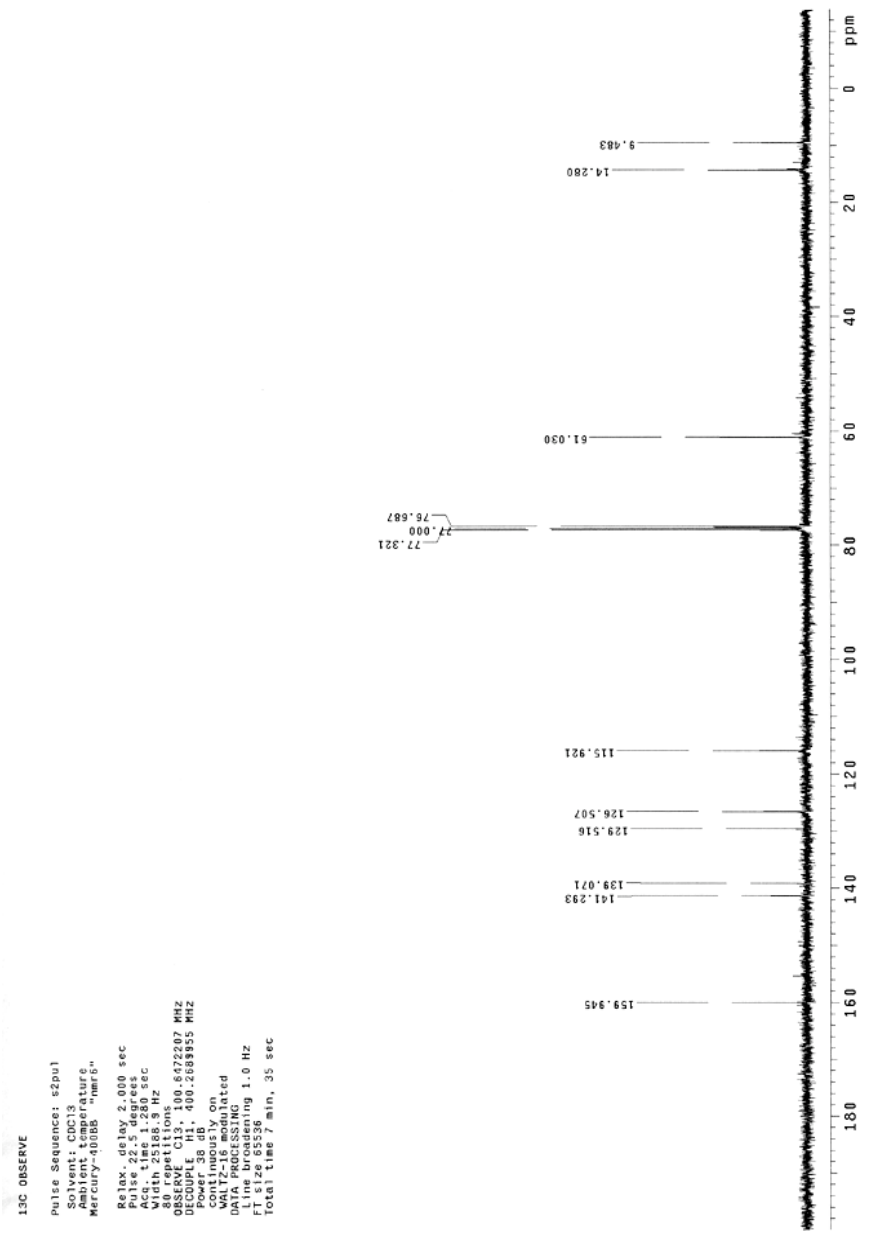

Figure S3. ^{13}C NMR spectrum of **5** recorded in $CDCl_3$

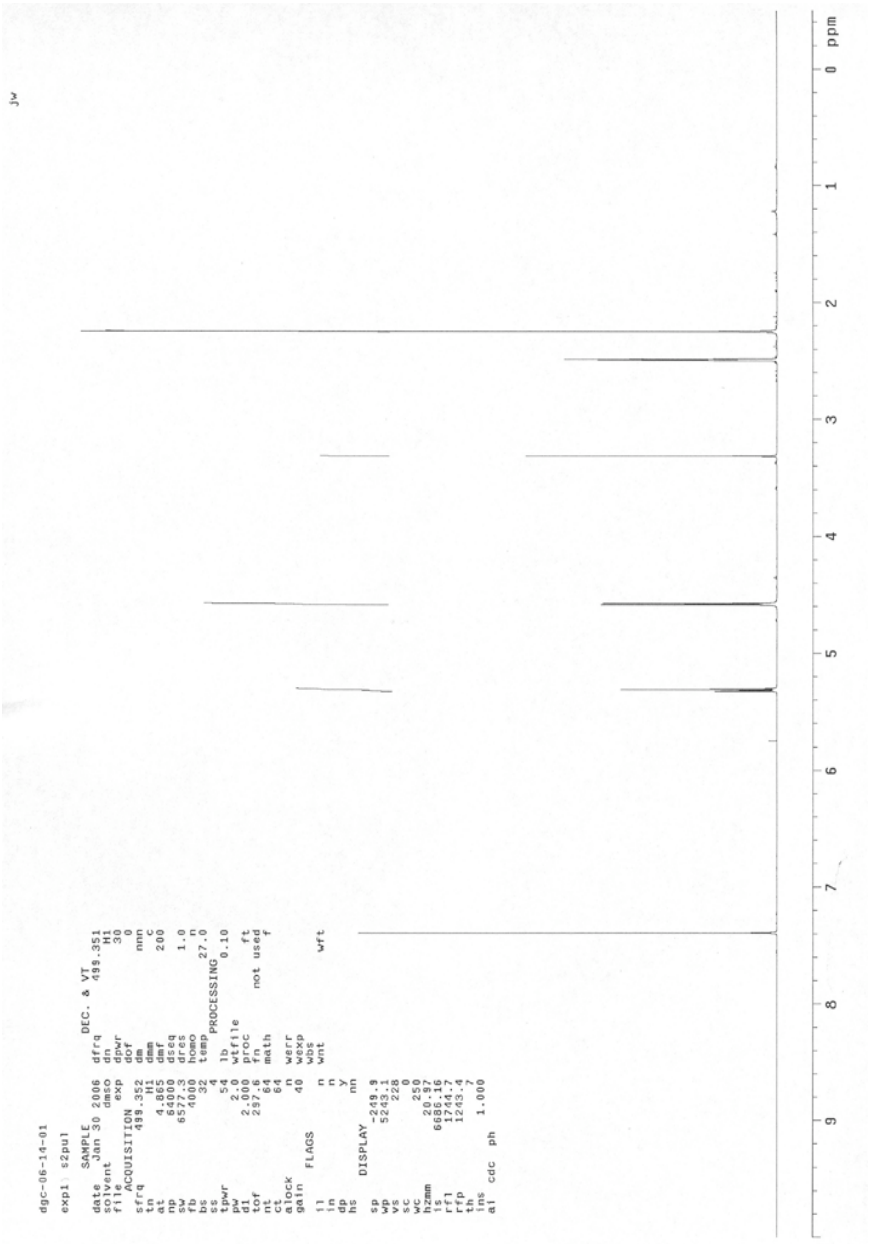

Figure S4. ^{1}H NMR spectrum of **6** recorded in $CDCl_3$

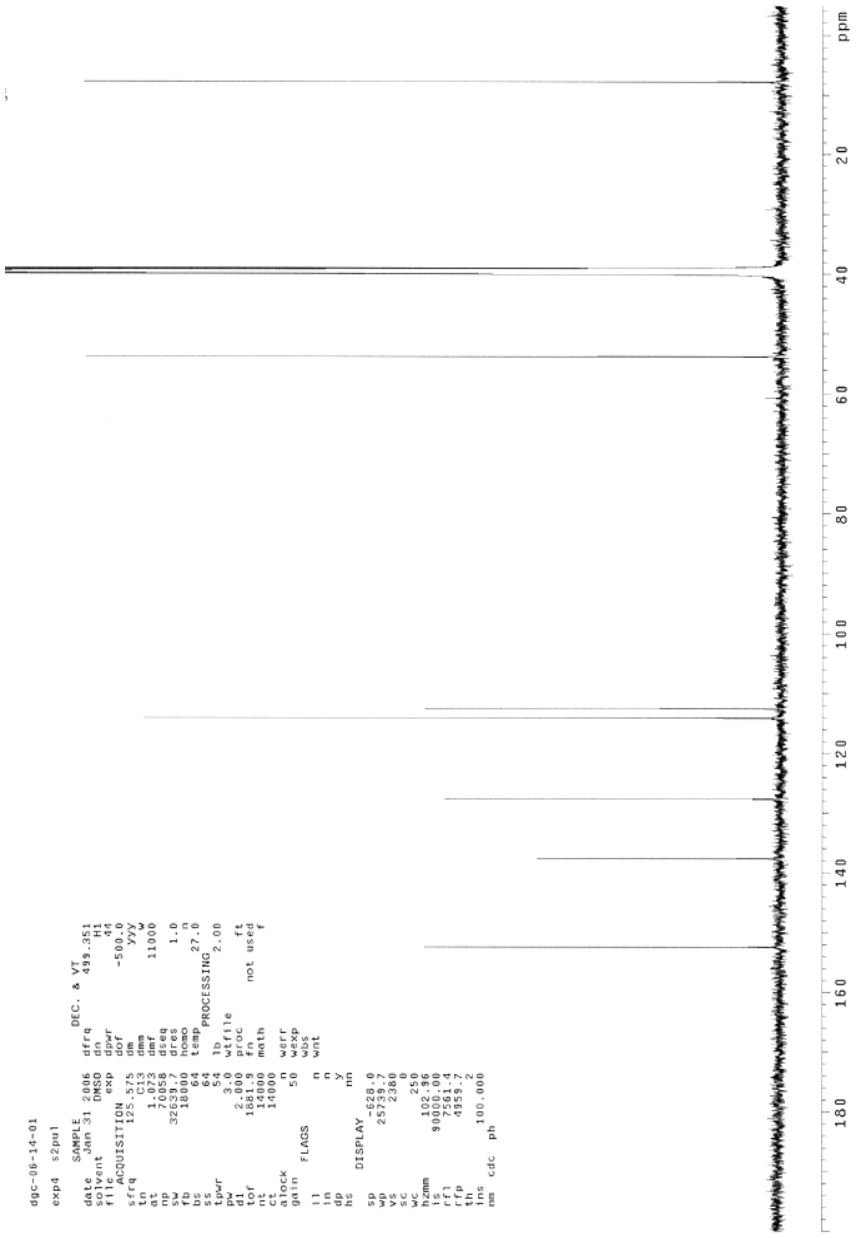

Figure S5. ^{13}C NMR spectrum of **6** recorded in $CDCl_3$

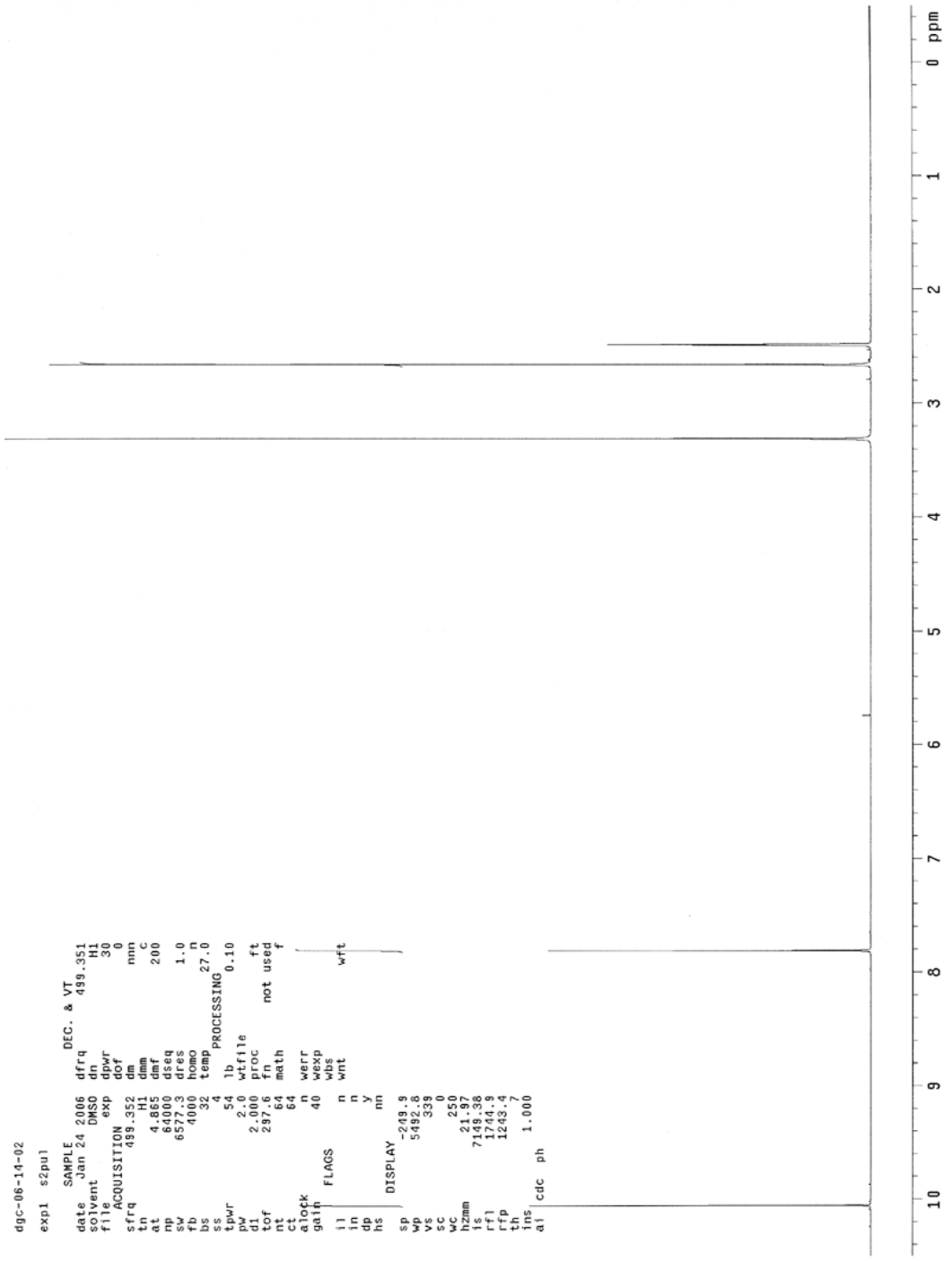

Figure S6. ^{1}H NMR spectrum of **7** recorded in DMSO

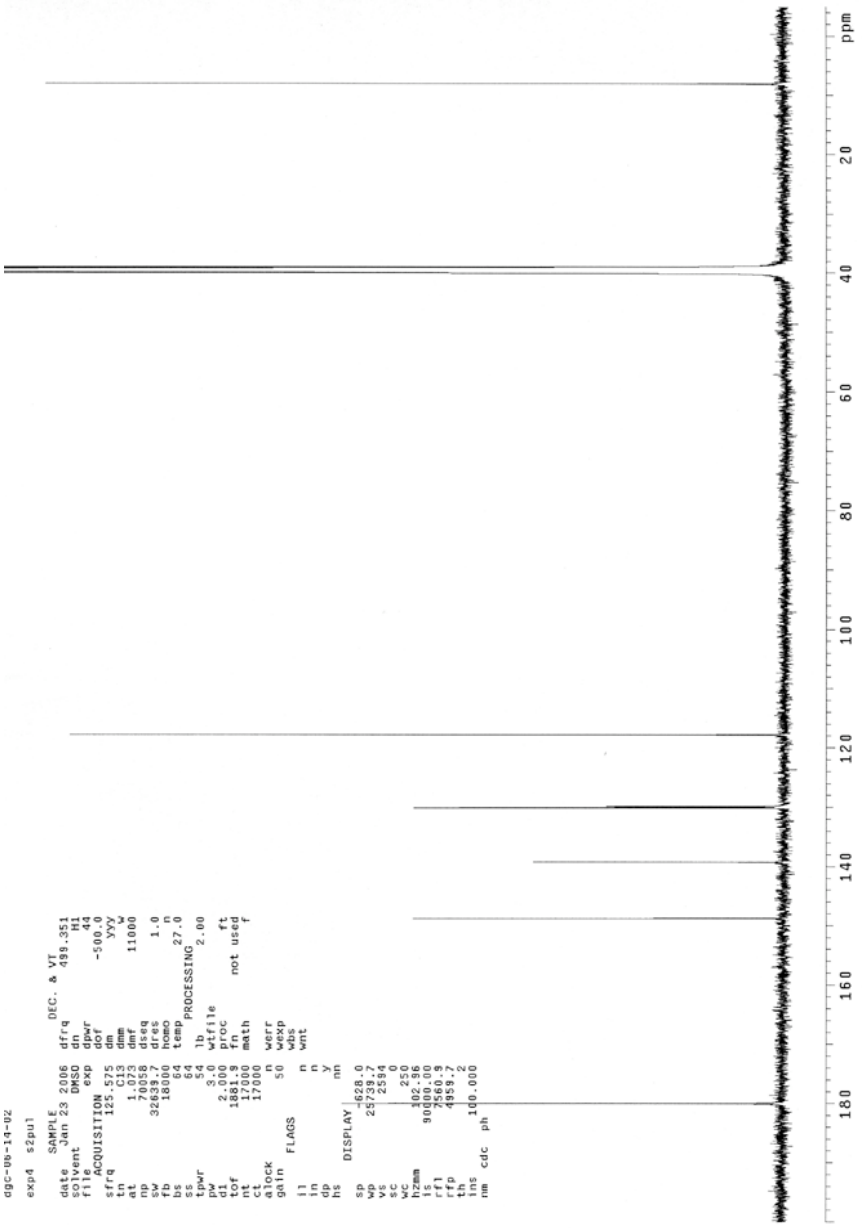

Figure S7. ^{13}C NMR spectrum of **8** recorded in DMSO

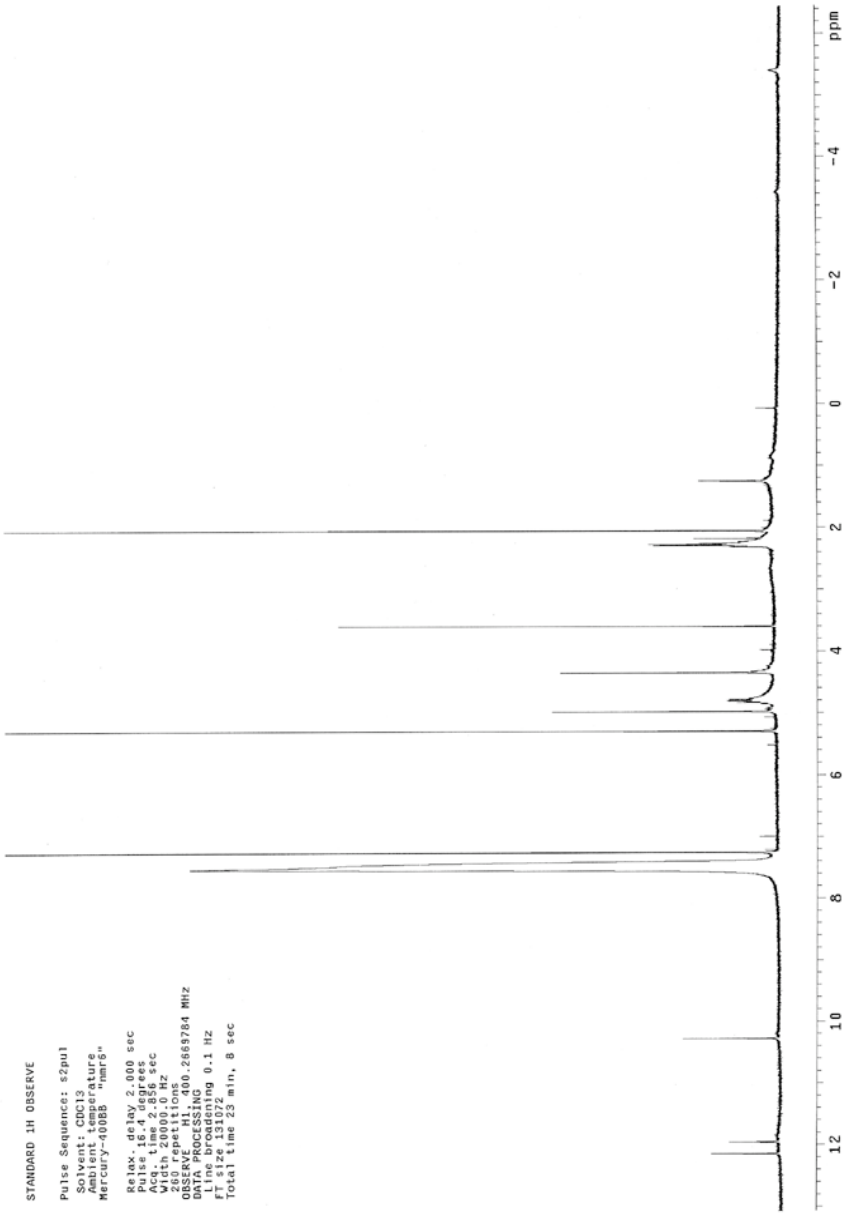

Figure S8. ^{1}H NMR spectrum of dioxabenzosapphyrin **3** recorded in TFA/$CDCl_3$

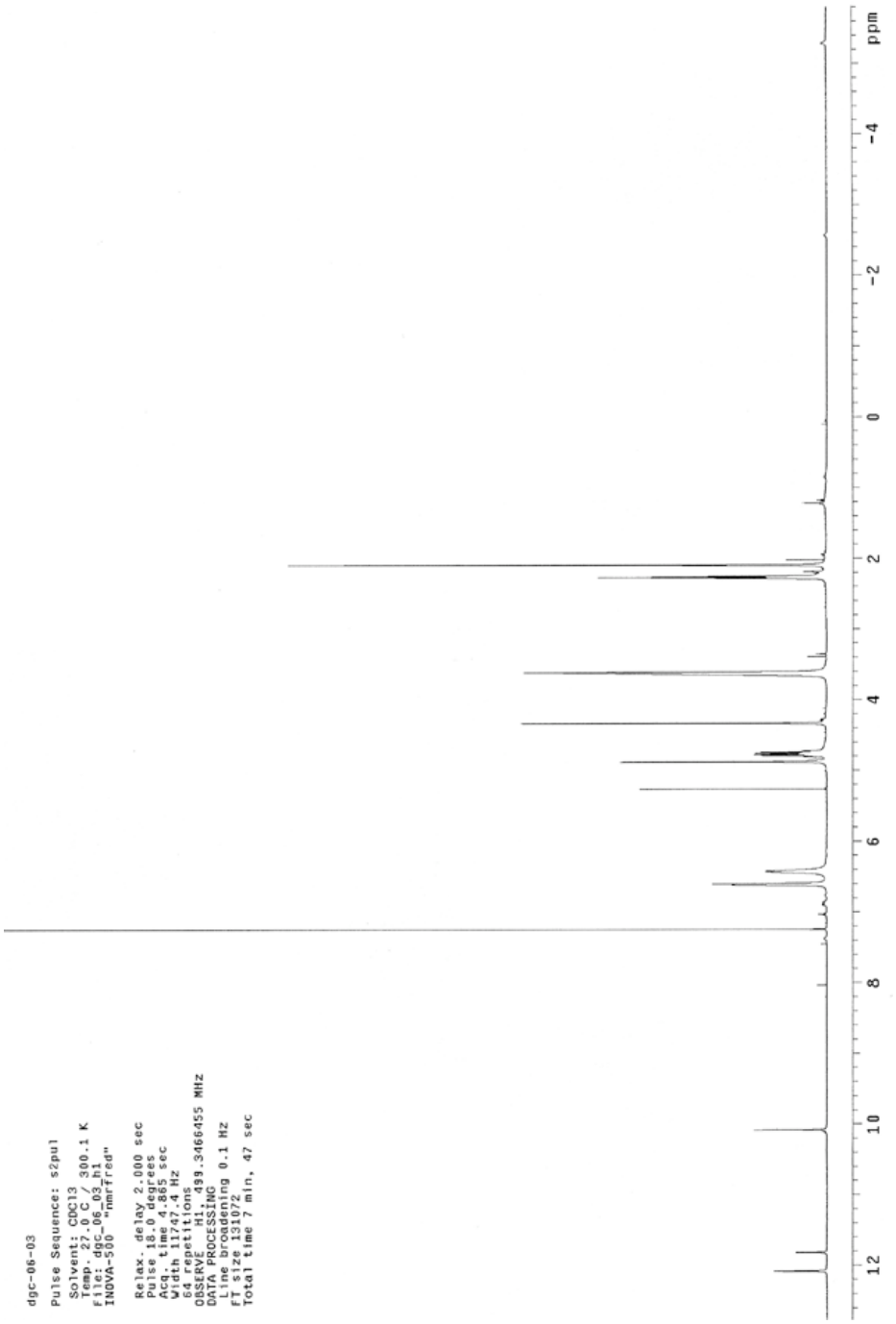

Figure S9. ^{1}H NMR spectrum of dioxabenzosapphyrin **3** recorded in MeOH-d_4/$CDCl_3$ (excess *p*-TsOH)**.**

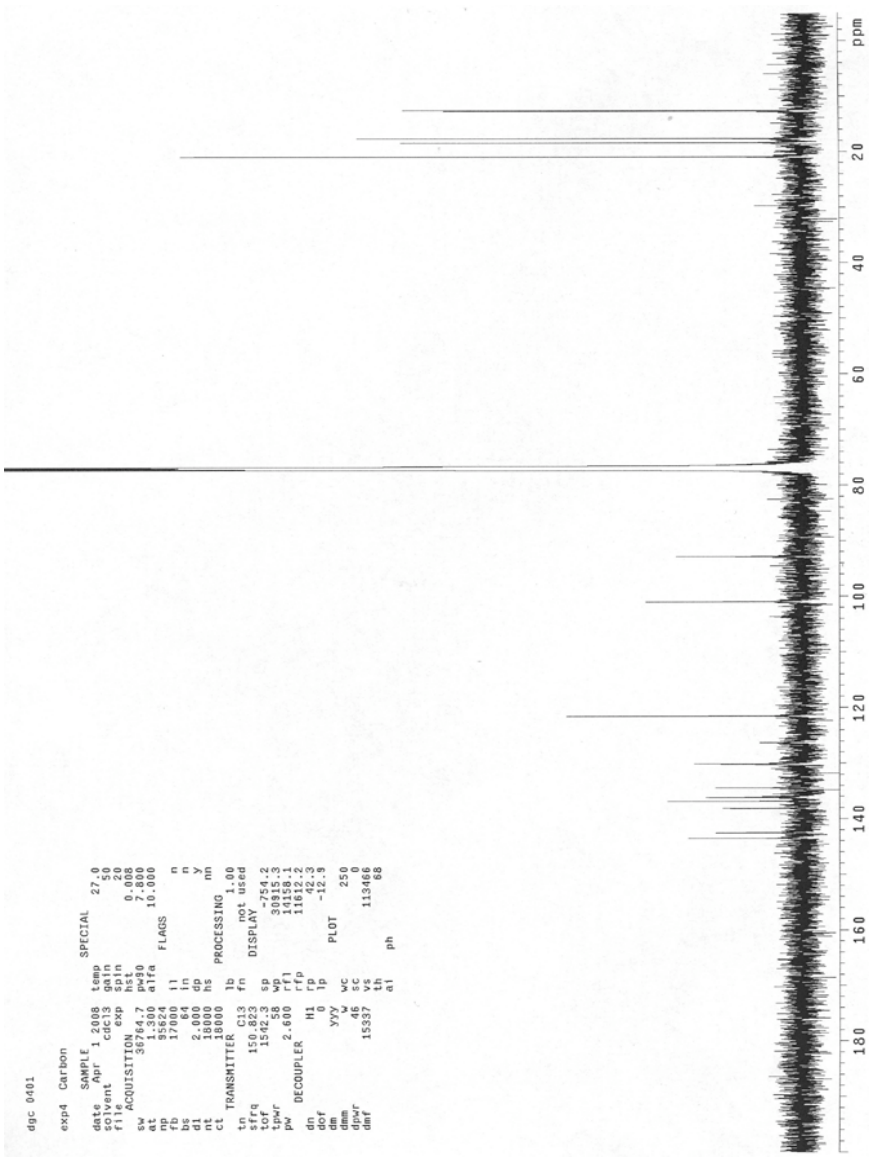

Figure S10. ^{13}C NMR spectrum of dioxabenzosapphyrin **3** recorded in MeOH-d_4/$CDCl_3$ (excess *p*-TsOH)

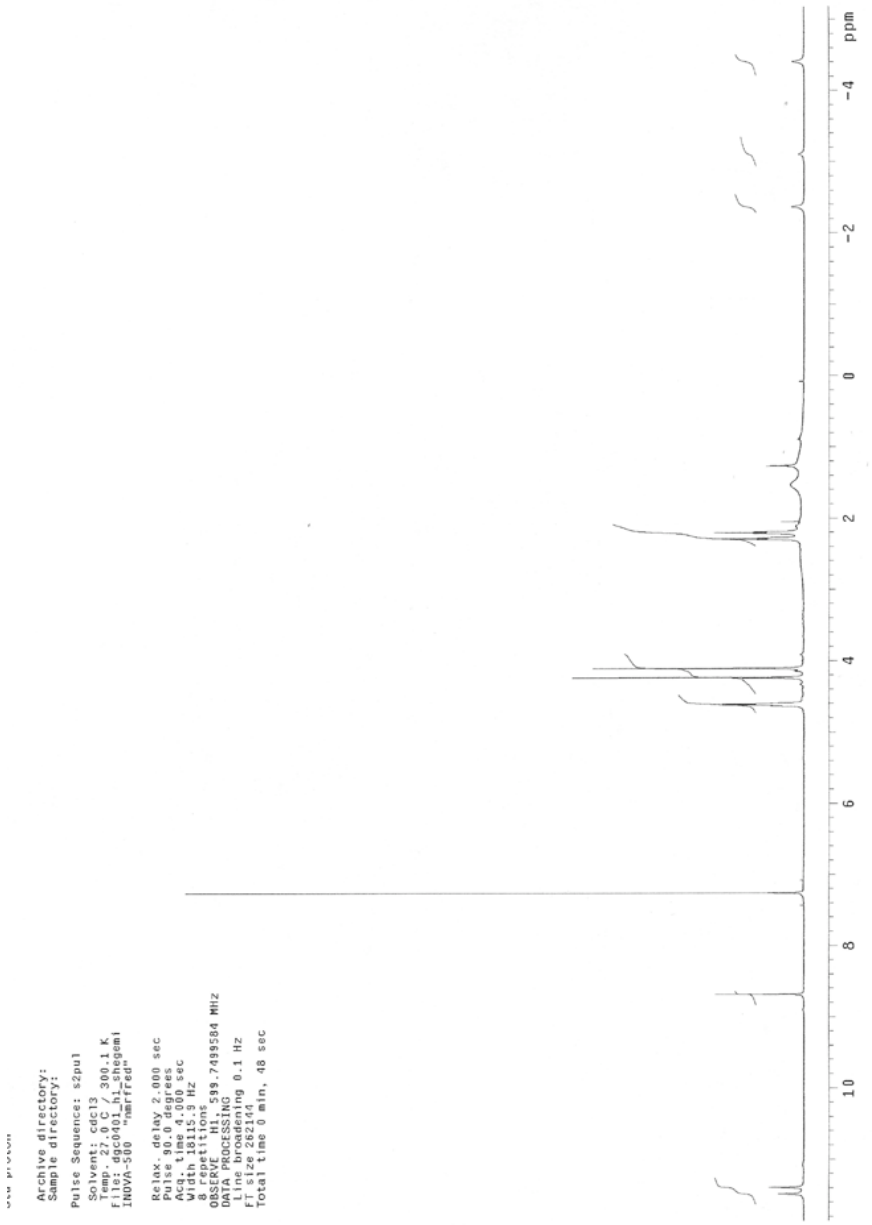

Figure S11. ^{1}H NMR spectrum of **4** recorded in $CDCl_3$

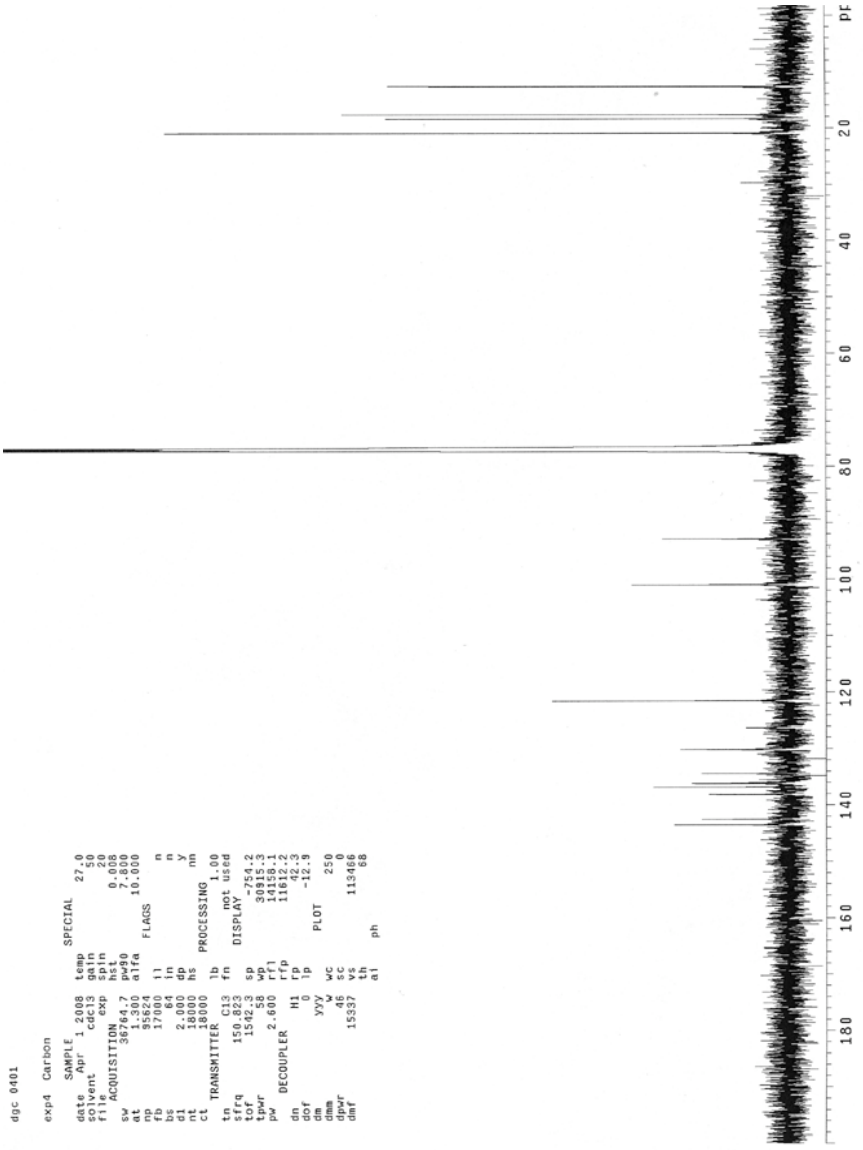

Figure S12. ^{13}H NMR spectrum of **4** recorded in $CDCl_3$

HPLC analysis of 3 and 4

Shimadzu HPLC
Sessler Lab
l Settings\User\Desktop\Group Files\DongGyu\obs-TFA and clo4\obs.lcd

Sample Information

Acquired by	: Admin
Sample Name	: obs
Sample ID	: 2
Tray#	: 1
Vail#	: 2
Injection Volume	: 10 uL
Data Filename	: obs.lcd
Method Filename	: ACN 25 pct MGdPt Base Method no frc.lcm
Batch Filename	: dgc batch file.lcb
Report Filename	: Base General report2.lcr
Date Acquired	: 5/27/2008 5:57:06 PM
Data Processed	: 5/27/2008 6:22:09 PM

Chromatogram

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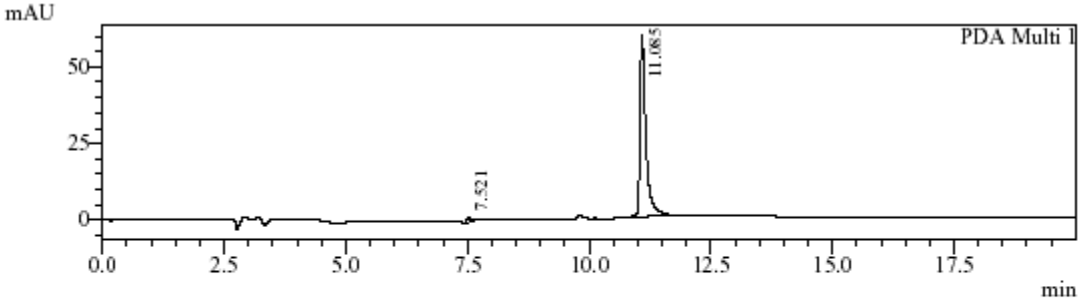


1 PDA Multi 1 / 451nm 4nm

PeakTable

PDA Ch1 451nm 4nm

Peak#	Ret. Time	Area	Area %
1	7.521	11810	2.337
2	11.085	493562	97.663
Total		505372	100.000

<<LC Program>>

Time	Unit	Command	Value
2.00	Pumps	B.Conc	25
10.00	Pumps	B.Conc	99
17.99	Pumps	B.Conc	99
18.00	Pumps	B.Conc	25
25.00	Controller	Stop	

Figure S13. HPLC analysis of **3** using 0.1% TFA in water and acetonitrile as the eluent

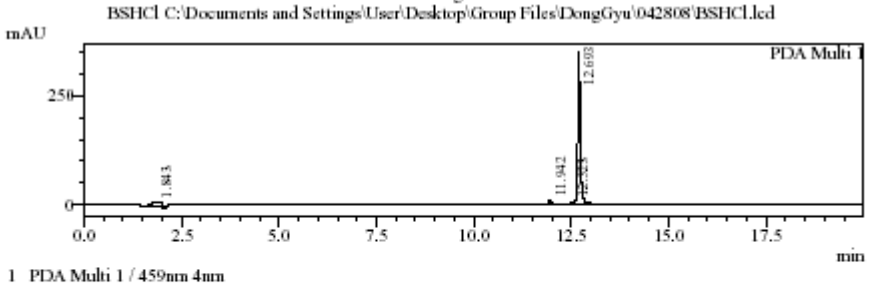
Shimadzu HPLC
Sessler Lab
cuments and Settings\User\Desktop\Group Files\DongGyu\042808\BSHCl.lcd BS

Sample Information

Acquired by	: Admin
Sample Name	: BSHCl
Sample ID	: dgc002
Tray#	: 1
Vail#	: 41
Injection Volume	: 20 uL
Data Filename	: BSHCl.lcd
Method Filename	: ACN 25 pct MGdPt Base Method no frc.lcm
Batch Filename	: dgc batch file.lcb
Report Filename	: Base General report2.lcr
Date Acquired	: 4/28/2008 3:56:50 PM
Data Processed	: 4/28/2008 4:21:51 PM

Chromatogram

BSHCl C:\Documents and Settings\User\Desktop\Group Files\DongGyu\042808\BSHCl.lcd



1 PDA Multi 1 / 459nm 4nm

PeakTable

PDA Ch1 459nm 4nm

Peak#	Ret. Time	Area	Area %	
1	1.843	187173	10.132	(solvent)
2	11.942	52545	2.844	
3	12.523	26215	1.419	
4	12.693	1581428	85.605	
Total		1847361	100.000	

<<LC Program>>

Time	Unit	Command	Value
2.00	Pumps	B.Conc	25
10.00	Pumps	B.Conc	99
17.99	Pumps	B.Conc	99
18.00	Pumps	B.Conc	25
25.00	Controller	Stop	

Figure S14. HPLC analysis of **4** using 0.1% TFA in water and acetonitrile as the eluent.

Anion Binding Studies

UV-Vis Anion Recognition Study:

Stock solutions of the host molecule being studied were made up in dichloroethane or methanol with the final concentrations being between 4.34×10^{-5} M and 3.99×10^{-5} M. Stock solutions of the guest in question were prepared by dissolving 10 - 500 equivalents of the corresponding tetrabutylammonium salts in 5 mL of a stock solution of the host in question. Making up the anion source solutions in this way allowed the binding studies to be carried out without having to make mathematical corrections to account for changes in host concentration as the result of dilution effects.

The general procedure for the UV-Vis binding studies involved making sequential additions of titrant (anionic guest) using Hamilton pipettes to a 2 mL aliquot of the host stock solution in the spectrometric cell. The data was then collated and combined to produce plots that showed the changes in host spectral features as a function of changes in the concentration of the guest.

Calculations of Equilibrium Constants, K_a

Equilibrium constants were calculated using equation 4.5 of Connors[2] where [L] = [anion]. The resulting equation, of the form, $y = B \times x / (1 + K_a \times x)$ or $y = (B \times x /(K_a \times x + 1)) + y_o$, was computer fit using Origin version 7.0, where x = [anion], y = ΔA, B = $\Delta\varepsilon \times b$, K_a = the equilibrium constant. The change in absorbance, ΔA, was calculated at a λ value where the spectral change was maximal.

Data Plots:

Representative binding isotherms and calculated curve fits are shown below.

Binding Studies of dioxabenzosapphyrin 3

For F^-

(a) (b)

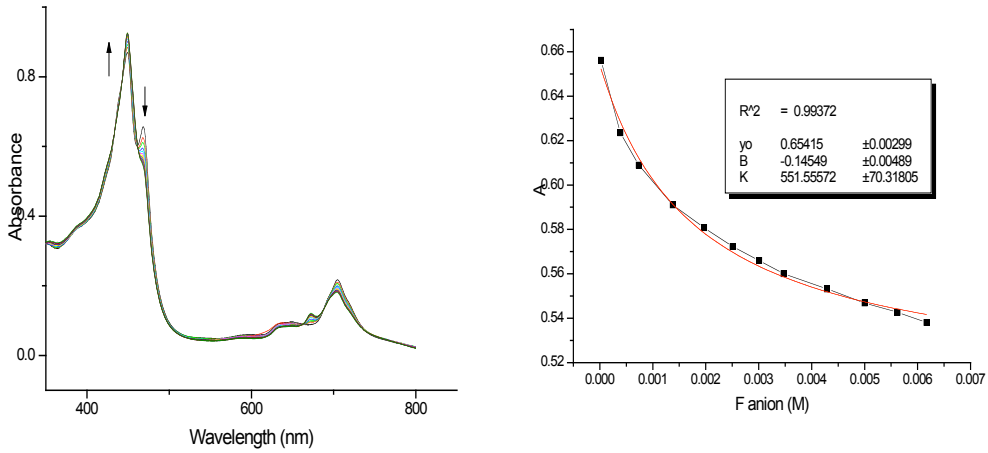


Figure S15. (a) Effect of the addition of TBAF on the absorption spectrum of dioxabenzosapphyrin in MeOH. The concentration of the dioxabenzosapphyrin used was 1.21 x 10^{-5} M, and the concetration range of anion was 2.43 x 10^{-5} to 6.17 x 10^{-3} M. (b) Plot of the absorption change of **3**•$(HF)_2$ at 469 nm vs. the concentration of TBAF, overlaid by the calculated 1:1 binding profile (derived for a UV-vis titration).

For Cl^-

(a) (b)

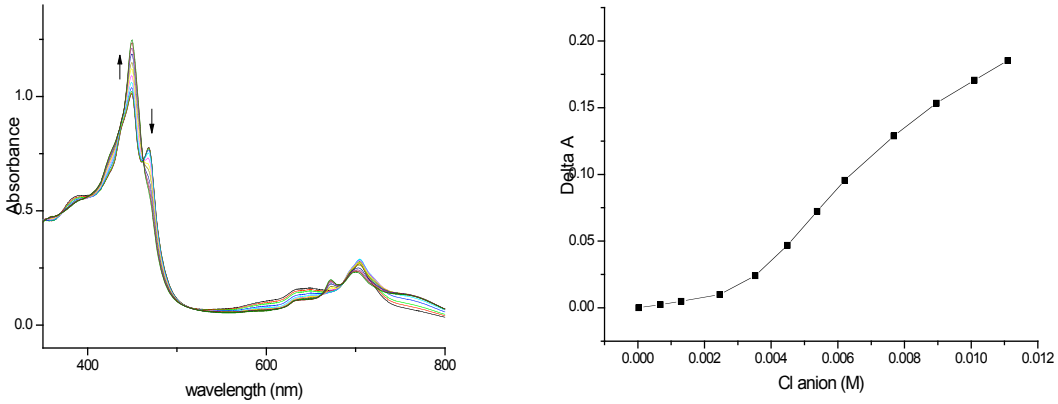


Figure S16. (a)Effect of Cl anion (as TBACl) titration on absorption spectra of **3**•$(HCl)_2$ in MeOH. The concentration of the dioxabenzosapphyrin used was 4.11 x 10^{-5} M and the concentration range of anion was 6.54 x 10^{-4} to 1.10 x 10^{-2} M. (b) Abnormal looking chloride titration curve obtained from a titration in MeOH. Plot of the absorption change of **3**•$(HClO_4)_2$ at 469 nm vs. the concenturation of TBACl.

For MeOH

(a) (b)

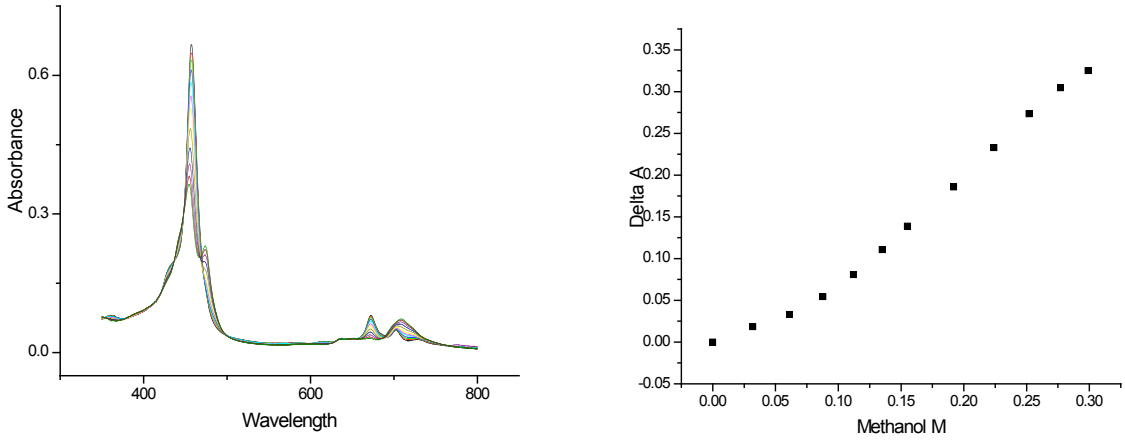


Figure S17. (a) Effect of the addition of MeOH on the absorption spectrum of dioxabenzosapphyrin $(HClO_4)_2$ in MeOH. The concentration of the dioxabenzosapphyrin used was 2.98 x 10^{-6} M, and the concentration range of the anion was 3.20 x 10^{-2} to 2.99 x 10^{-1} M. (b) Plot of the absorption change of **3**•$(HClO_4)_2$ at 457 nm vs. the concentration of MeOH.

For Phenol and 4-nitrophenol

(a) (b)

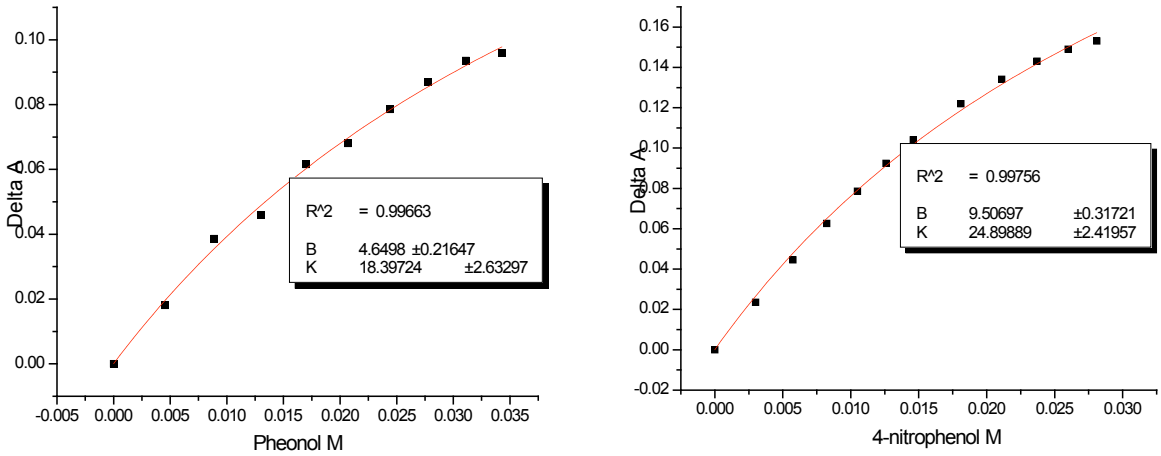
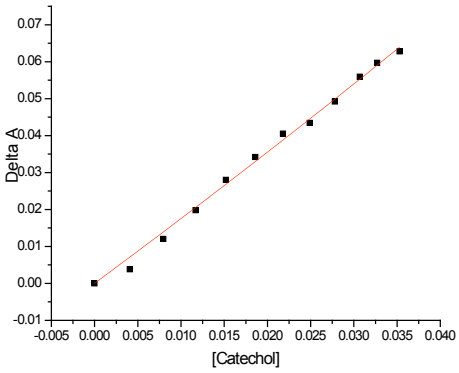


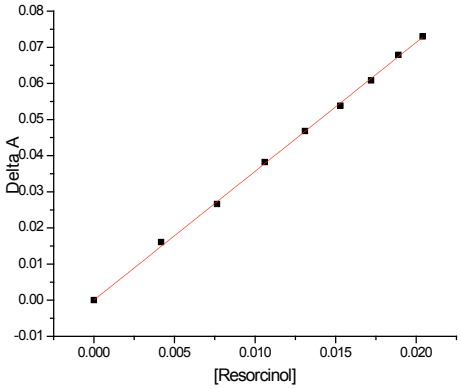
Figure S18. (a) Plot of the absorption change of **3**•$(HClO_4)_2$ at 466 nm vs. the concentration of phenol in dichloroethane (3.24 x 10^{-6} M), overlaid by the calculated 1 to 1 binding profile (b) Plot of the absorption change of **3**•$(HClO_4)_2$ at 455 nm vs. the concentration of 4-nitrophenol (4.86 x 10^{-6} M), overlaid by the calculated 1:1 binding profile (as derived for use with a UV-vis titration).

For phenol derivatives

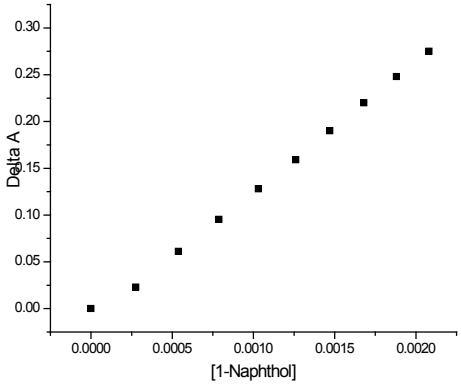
(a)



(b)



(c)



(d)

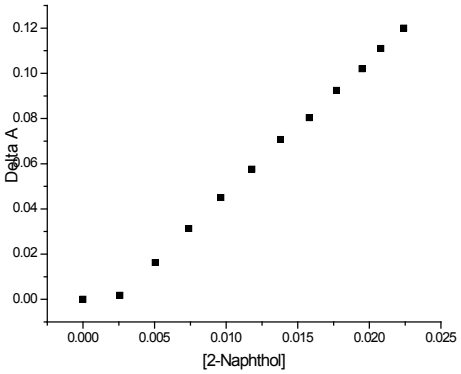


Figure S19. (a) Plot of the absorption change of **3**•$(HClO_4)_2$ at 455 nm vs. the concentration of catechol in dichloroethane (4.62 x 10^{-6} M). (b) Plot of the absorption change of **3**•$(HClO_4)_2$ at 455 nm vs. the concentration of resorcinol in dichloroethane (4.62 x 10^{-6} M). (c) Plot of the absorption change of **3**•$(HClO_4)_2$ at 459 nm vs. the concentration of 1-naphthol in dichloroethane (4.62 x 10^{-6} M). (d) Plot of the absorption change of **3**•$(HClO_4)_2$ at 455 nm vs. the concentration of 2-naphthol in dichloroethane (4.62 x 10^{-6} M).

Binding Studies of Benzosapphyrin 4
For F^-

(a) (b)

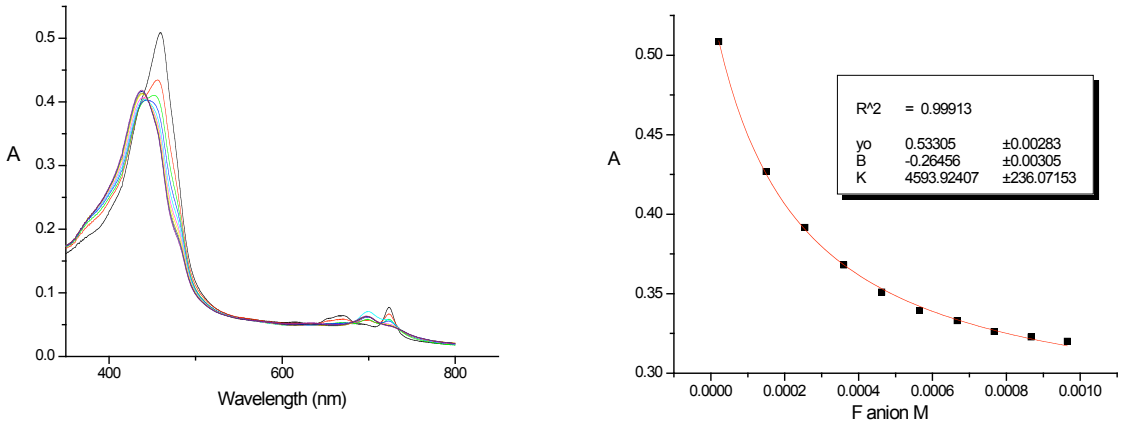


Figure S20. Effect of the addition of TBAF on the absorption spectrum of benzosapphyrin **4** in MeOH. The concentration of **4**•$(HF)_2$ used was 1.09 x 10^{-5} M, and the concentration range of the anionic substrate was between 2.17 x 10^{-5} to 9.65 x 10^{-4} M. (b) Plot of the absorption change of 3•$(HF)_2$ at 460 nm vs. the concentration of TBAF, overlaid by the calculated 1 to 1 binding profile (derived for a UV-vis titration). A deviation from 1:1 binding was seen at markedly higher fluoride anion concentrations.

For Cl^-
(a) **(b)**

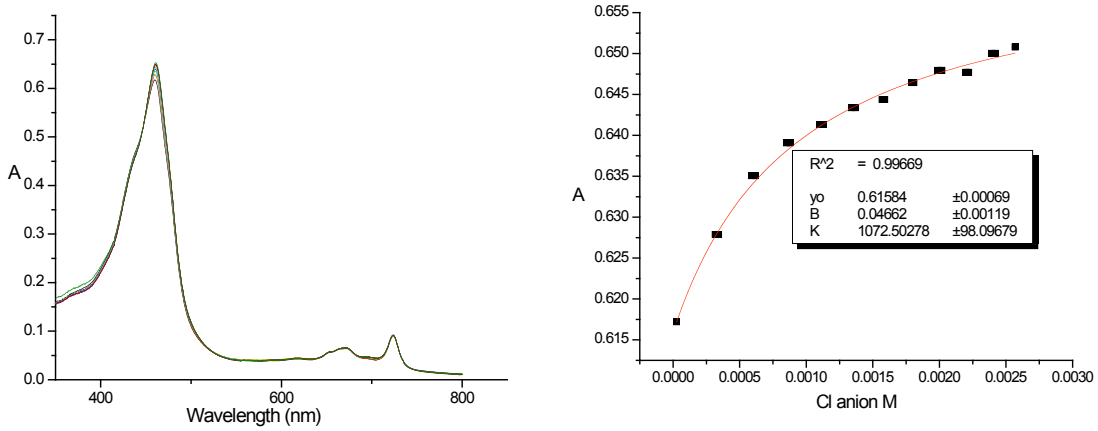


Figure S21. (a) Effect of the addition of TBACl on the absorption spectrum of benzosapphyrin **4** in MeOH. The concentration of the **4**•$(HCl)_2$ used was 1.74 x 10^{-5} M, and the concretion range of the anionic substrate was 3.48 x 10^{-5} to 3.68 x 10^{-3} M. (b) Plot of the absorption change of **4**•$(HCl)_2$ at 461 nm vs. the concentration of TBACl, overlaid by the calculated 1 to 1 binding profile (derived for a UV-vis titration).

For Phenol and 4-Nitrophenol:

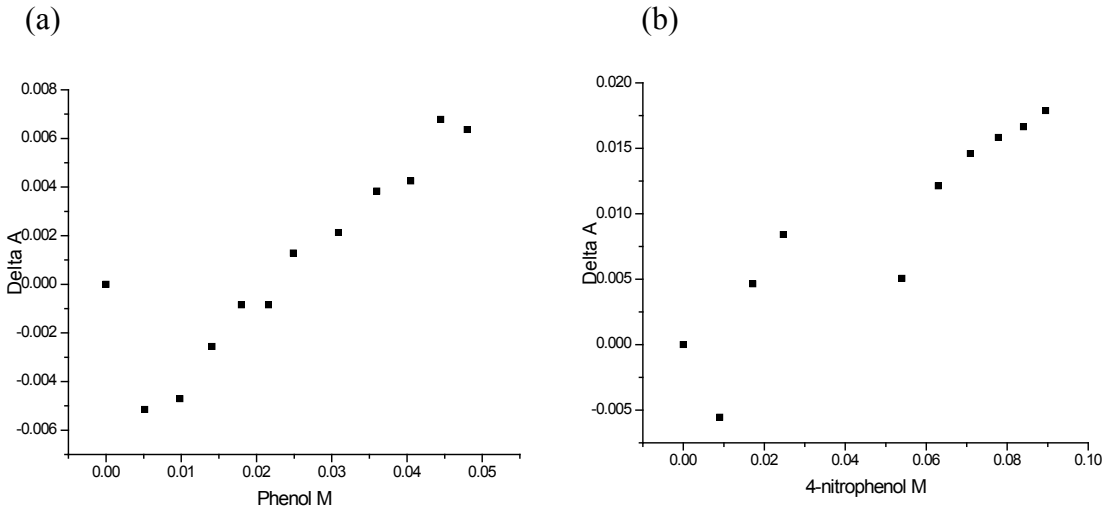


Figure S22. (a) Plot of the absorption change of **4**•$(HClO_4)_2$ (8.15 x 10^{-6} M in dichloroethane) at 463 nm vs the concentration of phenol in dichloroethane. (b) Plot of the absorption change of **4**•$(HClO_4)_2$ (8.15 x 10^{-6} M in dichloroethane) at 463 nm vs. the concentration of 4-nitrophenol.

X-ray Structure of 3 and Experimental

X-ray crystal structure of 3·(*p*-TsOH)$_2$

(a)

(b)

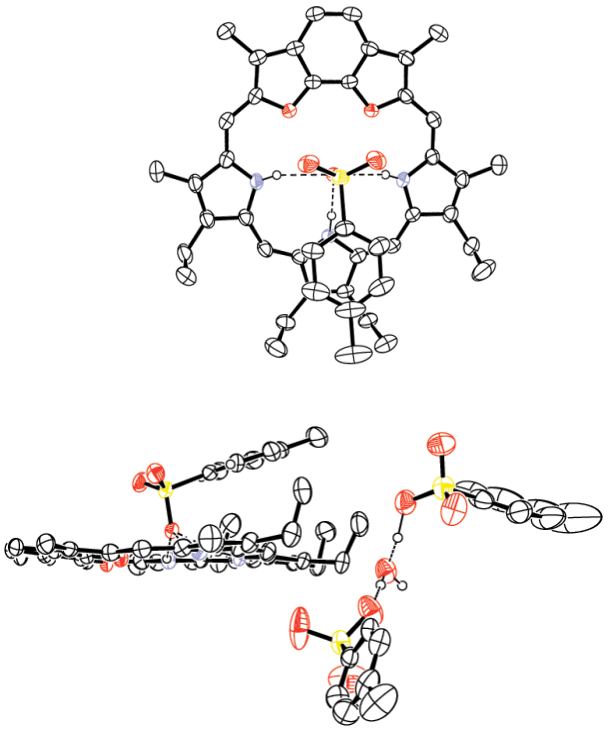


Figure 23. X-ray crystal structure of **3**·(*p*-TsOH)$_2$. (a) Top view; (b) Side view. Thermal ellipsoids are scaled to the 50% probability level. Most hydrogen atoms have been omitted for clarity.

X-ray Experimental for $(C_{38}H_{41}N_3O_2)^{2+}$ $2(C_7H_7SO_3)^-$ $(C_7H_8SO_3)^{1-}$ - H_3O^+ – $CHCl_3$ - CH_2Cl_2

Crystals grew as very dark blue plates by slow vapor diffusion of hexane in a solution of $CHCl_3$, CH_2Cl_2, MeOH, *p*-TsOH. The data crystal was plate that had approximate dimensions; 0.22 x 0.18 x 0.06 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 282 frames of data were collected using ω-scans with a scan range of 2° and a counting time of 266 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table S1. Data reduction were performed using DENZO-SMN.[3] The structure was solved by direct methods using SIR97[4] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[5] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The hydrogen atoms on nitrogen and the water molecule were observed in a ΔF map and refined with isotropic displacement parameters. One hydrogen atom near O1W was found halfway between the water molecule, O1W, and one of the oxygen atoms of a tosyl group, O1C. The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.045*P)^2 + (5.4073*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.189, with R(F) equal to 0.0773 and a goodness of fit, S, = 1.03. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[6] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[7] All figures were generated using SHELXTL/PC.[8]

Table S1. Crystal data and structure refinement for **3**

Empirical formula	C61 H68 Cl5 N3 O12 S3	
Formula weight	1308.61	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 12.1159(2) Å	α = 89.461(1)°.
	b = 16.7643(3) Å	β = 72.917(1)°.
	c = 17.1620(4) Å	γ = 71.945(1)°.
Volume	3155.18(11) $Å^3$	
Z	2	
Density (calculated)	1.377 Mg/m^3	
Absorption coefficient	0.392 mm^{-1}	
F(000)	1368	
Crystal size	0.22 x 0.18 x 0.06 mm	
Theta range for data collection	1.87 to 27.40°.	
Index ranges	-15<=h<=15, -21<=k<=19, -22<=l<=20	
Reflections collected	23069	
Independent reflections	14287 [R(int) = 0.0473]	
Completeness to theta = 27.40°	99.5 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	14287 / 0 / 781	
Goodness-of-fit on F^2	1.034	
Final R indices [I>2sigma(I)]	R1 = 0.0773, wR2 = 0.1503	
R indices (all data)	R1 = 0.1761, wR2 = 0.1890	
Largest diff. peak and hole	0.639 and -0.676 $e.Å^{-3}$	

References

1. Nuth, G. *Chem. Ber*, **1887**, 1337-1338.

2. Connors, K.A., *Binding Constants*; John Wiley & Sons: New York, **1987,** p. 148.

3. Otwinowski, Z.; Minor, W. *Methods Enzymol.,* **1997**, *276***,** 307 – 326.

4. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G., Polidori, G.; Spagna, R. *J. Appl. Cryst*. **1999**, *32*, 115-119.

5. Sheldrick, G. M. (1994). SHELXL97. Program for the Refinement of Crystal Structures. University of Gottingen, Germany.

6. $R_w(F^2) = \{\Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w(|F_o|)^4\}^{1/2}$ where w is the weight given each reflection.
   $R(F) = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|\}$ for reflections with $F_o > 4(\sigma(F_o))$.
   $S = [\Sigma w(|F_o|^2 - |F_c|^2)^2/(n - p)]^{1/2}$, where n is the number of reflections and p is the number of refined parameters.

7. Wilson, A. J. C. *International Tables for X-ray Crystallography, Volume. C*.; Kluwer Academic Press: Boston, **1992**, Tables 4.2.6.8 and 6.1.1.4.

8. Sheldrick, G. M. (1994). SHELXTL/PC (Version 5.03). Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, USA.