Supplementary Material (ESI) for Chemical Communications

Supporting information for Chemical Communication

Dynamic synthesis of a macrocycle containing a porphyrin and an electron donor

Amy L. Kieran,[a] Sofia I. Pascu,[a] Thibaut Jarrosson,[a] Maxwell J. Gunter[b] and Jeremy K. M. Sanders*[a]

[a] *Department of Chemistry, University of Cambridge, Lensfield Rd., Cambridge CB2 1EW, UK, Fax: +44 1223 336017; Tel: +44 1223 336411; E-mail: jkms@cam.ac.uk*

[b] *School of Biological, Biomedical and Molecular Sciences, University of New England, Armidale, NSW 2351, Australia*

Instrumentation

^{1}H NMR spectra were recorded on Bruker DRX-500, DRX-400 or DPX-250 instruments or on a DRX instrument fitted with a cryoprobe.[†] ^{13}C NMR spectra were recorded on Bruker DPX-400 (100 MHz) or DRX-500 (125 MHz) instrument. Chemical shifts are quoted in parts per million with reference to residual protons of the deuterated solvent for the ^{1}H and the ^{13}C resonances of the solvent for ^{13}C NMR.

MALDI TOF mass spectra were recorded on a Kratos Kompact 4, and electrospray mass spectra were recorded on a Micromass Quattro-LC triple quadrupole apparatus (QUATTRO).

Solution state IR spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer at 4 cm^{-1} resolution or better.

Uv-vis absorption spectra were recorded on a Hewlett Packard 8452A diode array spectrometer.

HPLC analyses were carried out on a Hewlett Packard 1050 system coupled to a UV analyser and the data were processed using HP Chemstation software. Separations were achieved in the reverse phase using a Jupiter Phenomemex column (300 Å,

[†] A cryoprobe is a NMR probe, which is cooled to approximately 26 K. This gives a greatly improved signal to noise ratio, making it ideal for the measurement of NMR spectra of species at low concentration.

25.0 cm × 4.6 mm, 5 μm particle size), a C18 phase. All separations were achieved by the gradient elution of MeOH and THF mixtures tabulated below with a flow rate of 1 ml min^{-1} and an injection volume of 2 μl. Assignments were made in the first instance by isolation and mass spectrometric analysis, and then by comparison with known samples. The chromatography was carried out at 20 °C in a HP oven, to minimise temperature fluctuations which lead to variable retention times.

HPLC Gradients:

Time (min)	% MeOH	% THF
0	80	20
15	40	60
20	40	60

The isothermal calorimetry measurements (microcalorimetry) were conducted by using a thermostated and fully computer-operated MCS-ITC calorimeter from MicroCal, LLC, Northampton, MA, USA. Aliquots of 10 μl were titrated into the calorimetric cell every 3 mins over a one and a half hour period. Data analysis using the customised ITC module of the Origin 5.0 software package and a least squares fitting procedure to fit the data to the appropriate binding model. All measurements were carried out at 25 °C. For each system studied a blank run was carried out in which the titrant was titrated into the cell containing solvent only to allow corrections for the heat effects due to dilution to be made.

Thin Layer Chromatography was carried out on Kieselgel 60 F_{24} (Merck) 0.2 mm plates. Porphyrins were inspected initially by sight and then visualised by UV light. Other organic compounds were visualised by UV absorption, or developed with phosphomolybdic acid in 20 % aqueous ethanol or vanillin. Column chromatography was carried out using neutral alumina (Aldrich) or Kieselgel 60 (Merck) 230-400 mesh and using distilled solvents.

All chemicals were purchased from Acros, Aldrich, Avocado or Fluka in reagent grade quality or better and used without further purification. All solvents were distilled prior to use and dry solvents were freshly distilled from CaH_2 under argon. Ultrapure water was obtained from a Millipore water purification system. HPLC

grade $CHCl_3$ and MeOH (Aldrich) and THF (Fisher) were filtered with a 0.45 μm Millipore filter and used without further purification.

Preparation of analytical libraries

All analytical scale reactions were carried out at RT on a 0.5 ml or 1 ml scale. The monomer(s) were dissolved to give a solution of 20 mM. The stock solution was then diluted to give the required concentration for cyclisation (5 mM unless otherwise stated) to give the correct volume. DBU was added to the reaction to initiate exchange at a concentration such that ca. 20 – 40 μl were added to give the required equivalents of DBU (0.1 equivalents with respect to thiol equivalents). HPLC or MS analysis was performed by removal of 10 – 50 μl aliquots from the reaction mixture. All templates were solids: for the higher MW templates, the required mass was simply weighed out and added. For the low MW templates, highly concentrated solutions of the template were made up, so that less than 10 μl of solution was added to give the correct equivalents. All cyclisations were stirred at RT and followed by HPLC analysis every 24 hours for up to seven days.

Large scale cyclisation under templating conditions

Large scale cyclisations were carried out at 5 mM concentration on the 50 – 100 mg scale. Stoichiometric addition of template, and 0.1 equivalents of DBU with respect to thiol equivalents were set up as described above. The reactions were stirred at RT until thermodynamic equilibrium was reached, as ascertained by HPLC analysis of 10 – 50 μl aliquots removed from the mixture. On equilibrium being reached, the solvent was removed by rotaevaporation, and the resulting residue dissolved in a 20 ml of CH_2Cl_2. This was washed with water 1 × 20 ml, dried over $MgSO_4$, and the solvent removed. The solid was then dissolved in $CHCl_3$, and subjected to flash filtration over alumina, eluting with $CHCl_3$.

Thioacetic acid-*S*-[2-(2-hydroxy-ethoxy)-ethyl] ester

2-(2-Chloroethoxy)ethanol (10.7 ml, 102 mmol) was stirred in acetonitrile (500 ml), and catalytic KI and potassium thioacetate (13 g, 113 mmol) were added. The mixture was then heated to reflux for 12 hours, until TLC indicated reaction was complete. The solution was allowed to cool to RT and diluted H_2O (750 ml). The aqueous

solution was then extracted with EtOAc (4 × 250 ml), and evaporated to dryness. Column chromatography (CH_2Cl_2:EtOAc 9:1) afforded the product as a brown oil. Yield: 15.2 g (92 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.72 (t, *J* = 5 Hz, 2H, $HOCH_2CH_2OC$), 3.62 (t, *J* = 6 Hz, 2H, CH_2OCH_2), 3.57 (t, *J* = 5 Hz, 2H, $HOCH_2$), 3.12 (t, *J* = 5 Hz, 2H, CH_2CH_2S), 2.34 (s, 3H, $SOCH_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 72.0, 69.6, 68.7, 61.6, 30.4, 28.67.

Thioacetic acid-*S*-{2-[2-(toluene-4-sulfonyloxy)-ethoxy]-ethyl} ester

Tosyl chloride (19 g, 100 mmol), NEt_3 (20.2 ml, 150 mmol) and a catalytic amount of dimethylaminopyridine (506 mg, 5 mmol) were added to a solution of thioacetic acid-*S*-[2-(2-hydroxy-ethoxy)-ethyl]ester (15 g, 91 mmol) in CH_2Cl_2 (500 ml) at 0 °C. The mixture was slowly raised to RT. After 10 hrs, the solution was washed with dilute HCl (750 ml, 3N), followed by aqueous Na_2CO_3 (2 × 350 ml). The organic layer was dried over Na_2SO_4, filtered over a plug of silica, and washed off with EtOAc. The solvent was removed, and the resulting brown oil used without further purification. Yield: 28.3 (98 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8 Hz, 2H, *m*-Ar*H*), 7.33 (d, *J* = 8 Hz, 2H, *o*-Ar*H*), 4.13 (t, *J* = 4.8 Hz, 2H, $HOCH_2$), 3.62 (t, *J* = 4.8 Hz, 2H, $HOCH_2CH_2OC$), 3.49 (t, *J* = 6.5 Hz, 2H, CH_2OCH_2), 2.98 (t, *J* = 6.5 Hz, 2H, CH_2CH_2S), 2.43 (s, 3H, CH_3), 2.32 (s, 3H, $SOCH_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 144.7, 132.9, 129.7, 127.8, 69.7, 69.0, 68.2, 30.4, 28.5, 21.5.

Thioacetic acid *S*-[2-(2-{5-[2-(2-acetylsulfanyl-ethoxy)-ethoxy]-naphthalen-1-yloxy}-ethoxy)-ethyl] ester

Under Ar, a solution of thioacetic acid-*S*-{2-[2-(toluene-4-sulfonyloxy)ethoxy]-ethyl} ester (1.59 g, 5 mmol) in acetone (100 ml) was added dropwise to a refluxing suspension of naphthalene-1,5-diol (400 mg, 2.5 mmol) and K_2CO_3 (6.9 g, 50 mmol) in acetone (400 ml). The suspension was refluxed for 20 hours, and then allowed to cool to RT, filtered over celite, and the solvent was removed. The residual oil was re-dissolved in $CHCl_3$, washed with H_2O (100 ml), and 10 % NaOH (200 ml). The

solution was dried over $MgSO_4$, and the solvent removed. Purification was attempted by chromatography (EtOAc:hexane 1:5) repeatedly. Yield: < 50 mg.
(For detailed characterisation, see later).

2-(2-{5-[2-(2-Hydroxy-ethoxy)-ethoxy]-naphthalen-1-yloxy}-ethoxy)-ethanol

A solution of 2-(2-chloroethoxy)ethanol (10.1 ml, 110 mmol) in CH_3CN (100 ml) was added dropwise to a suspension of naphthalene-1,5-diol (8.01 g, 50 mmol) and K_2CO_3 (69 g, 0.5 mol) in CH_3CN (900 ml), and the resulting suspension refluxed overnight. After cooling to RT, the suspension was filtered over celite, concentrated and washed with H_2O (2 × 200 ml). The solvent was removed to yield a yellow solid, which was recrystallised from toluene to afford the desired product as pale yellow crystals. Yield: 16.6 g (99%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8 Hz, 2H, ArH_1), 7.25 (t, *J* = 8 Hz, 2H, ArH_2), 6.76 (d, *J* = 8 Hz, ArH_3), 4.18 (t, *J* = 4 Hz, 4H, CH_2O), 3.88 (t, *J* = 4 Hz, 4H, CH_2O), 3.62 (m, 4H, CH_2O);

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 126.7, 125.1, 114.5, 105.8, 72.7, 69.6, 67.8, 61.2.

2-(2-{5-[2-(2-Toluene-4-sulfonyloxy-ethoxy)-ethoxy]-naphthalen-1-yloxy}-ethoxy)-ethoxysulfonyl-4-toluene

Tosyl chloride (21 g, 110 mmol), NEt_3 (17.7 ml, 125 mmol) and a catalytic amount of dimethylaminopyridine (506 mg, 5 mmol) were added to a solution of 2-(2-{5-[2-(2-hydroxy-ethoxy)-ethoxy]-naphthalen-1-yloxy}-ethoxy)-ethanol (16.6 g, 50 mmol) in CH_2Cl_2 (250 ml) at 0 °C. The mixture was warmed to RT. After 10 hours, the solution was washed with dilute HCl (750 ml, 1N), aqueous Na_2CO_3 (2 × 350 ml) and H_2O (2 × 100 ml). The organic layer was dried over $MgSO_4$, filtered over a plug of silica, and washed off with CH_2Cl_2. The solvent was removed, and the resulting brown solid recrystallised from hexane to give the product as white crystals. Yield: 31.8 g (98 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8 Hz, ArH_1), 7.78 (d, *J* = 8 Hz, ArH_4), 7.35 (t, *J* = 8 Hz, ArH_2), 7.25 (d, *J* = 8 Hz, ArH_5), 6.83 (d, *J* = 8 Hz, ArH_3), 4.23 (m, 8H, OCH_2), 3.93 (t, *J* = 4 Hz, OCH_2), 3.84 (t, *J* = 4 Hz, OCH_2), 2.37 (s, 6H, CH_3);

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.2, 144.7, 133.0, 129.8, 128.0, 126.8, 125.2, 114.7, 105.8, 70.0, 69.3, 69.0, 67.9, 21.6.

Thioacetic acid *S*-[2-(2-{5-[2-(2-acetylsulfanyl-ethoxy)-ethoxy]-naphthalen-1-yloxy}-ethoxy)-ethyl thioacetate

2-(2-{5-[2-(2-Tolyl-4-sulfonyloxy-ethoxy)-ethoxy]-naphthalen-1-yloxy}-ethoxy)-ethoxysulfonyl-4-toluene (11.9 g, 20 mmol) and potassium thioacetate (5.02 g, 44 mmol) were dissolved in acetone (200 ml), and refluxed for 8 hours. On cooling, H_2O (200 ml) was added and the aqueous layer extracted with EtOAc (5 × 100 ml). The combined organic extracts were dried over $MgSO_4$, and the solvent removed. Column chromatography (CH_2Cl_2) afforded the product as a yellow brown solid. Yield: 3.1 g (33 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, J = 8 Hz, 2H, ArH_1), 7.35 (t, J = 8 Hz, 2H, ArH_2), 6.84 (d, J = 8 Hz, ArH_3), 4.26 (t, J = 4.5 Hz, 4H, napth-OCH_2), 3.96 (t, J = 4.5 Hz, 4H, CH_2OCH$_2$), 3.75 (t, J = 6.3 Hz, 4H, OCH_2CH$_2$S), 3.62 (t, J = 6.3 Hz, 4H, CH$_2$CH_2S), 2.32 (s, 6H, SOCH_3);

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 154.2, 126.7, 125.0, 114.6, 105.7, 70.0, 70.4, 67.8, 30.5, 29.0.

2-(2-{5-[2-(2-Mercapto-ethoxy)-ethoxy]-naphthalen-1-yloxy}-ethoxy)-ethane thiol

The above thioacetate (0.5 g, 1.1 mmol) was dissolved in degassed CH_2Cl_2 (50 ml), and hydrazine monohydrate (0.55 ml, 11 mmol) was added, and the solution stirred. After 12 hours, the solvent was removed under reduced pressure, and degassed CH_2Cl_2 (100 ml) added. The solution was washed with degassed H_2O (2 × 100 ml), dried over $MgSO_4$ and evaporated. The dithiol was used without further purification.

^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.88 (d, J = 8 Hz, 2H, ArH_1), 7.39 (t, J = 8 Hz, 2H, ArH_2), 6.89 (d, J = 8 Hz, ArH_3), 4.30 (t, J = 4.6 Hz, 4H, napth-OCH_2), 3.95 (t, J = 4.5 Hz, 4H, CH_2OCH$_2$), 3.75 (t, J = 6.4 Hz, 4H, OCH_2CH$_2$S), 2.75 (q, J = 6.4, 8.3 Hz, 4H, CH$_2$CH_2SO), 1.67(t, 2H, J = 8.3 Hz, SH);

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 126.4, 125.1, 114.6, 105.9, 72.6, 69.6, 67.5, 30.3.

5,15-Di(3-mercaptomethylphenyl)-2,8,12,18-tetra-n-hexyl-3,7,13,17-tetramethyl-porphyrin

5,15-Di(3-acetylthiomethylphenyl)-2,8,12,18-tetra-hexyl-3,7,13,17-tetramethyl-porphyrin (150 mg, 0.145 mmol) was dissolved in degassed CH_2Cl_2 (50 ml), and

hydrazine monohydrate (0.25 ml) was added. The solution was stirred under Ar for 12 hours, before the solvent was removed *in vacuo*. The residue was redissolved in degassed CH_2Cl_2 (50 ml) and washed with degassed H_2O (100ml) under Ar. The organic layer was dried over Na_2SO_4, and evaporated. The residue used without further purification. Yield: 134 mg (98 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.27 (s, 2H, *meso*), 8.15 (s, 2H, Ar-2), 7.98 (d, J = 7.5 Hz, 2H, Ar*H*-6), 7.75 (d, J = 7.5 Hz, 2H, Ar*H*-4), 7.72 (t, J = 7.5 Hz, 2H, Ar*H*-5), 4.03 (d, J = 7.3 Hz, 4H, CH_2SH), 4.01 (t, 8H, ^{1}CH_2), 2.54 (s, 12H, pyrrolic-CH_3), 2.22 (m, 8H, ^{2}CH_2), 1.99 (t, J = 7.3 Hz, 2H, S*H* (exchanges with D_2O)), 1.75 (m, 8H, ^{3}CH_2), 1.51 (m, 8H, ^{4}CH_2), 1.40 (m, 8H, ^{5}CH_2), 0.93 (t, J = 7 Hz, 12H, hex-^{6}CH_2), -2.36 (s, 2H, N*H*);

^{13}C NMR (125 MHz, $CDCl_3$): 146.9, 145.3, 144.1, 142.4, 137.8, 136.4, 133.5, 132.0, 128.3, 127.7, 118.9, 97.5, 53.4, 33.3, 31.8, 30.6, 26.5, 14.2;

UV-vis (CH_2Cl_2): λ 411, 508, 542, 574, 626 nm;

MS (MALDI): *m/z* 946.9 [M^+].

Naphthoxy bisdisulfide zinc porphyrin Zn·4

5,15-Di(3-mercaptomethylphenyl)-2,8,12,18-tetra-hexyl-3,7,13,17-tetramethyl-porphyrinato zinc(II) (100 mg, 0.1 mmol) was dissolved in a mixture of CH_2Cl_2 (24.5 ml) and MeOH (0.5 ml), containing 2-(2-{5-[2-(2-mercapto-ethoxy)-ethoxy]-naphthalen-1-yloxy}-ethoxy)-ethanethiol (36.8 mg, 0.1 mmol) and bis-*N*,*N*′-n-hexane substituted naphthalene diimide (43.4 mg, 0.1 mmol). LiBr (20 mg, 2.3 mmol) and DBU (6 μl, 0.04 mmol) were added and the solution stirred for 3 days under air. Column chromatography ($CHCl_3$) afforded the desired receptor as a pink-purple solid. Yield: 47 mg (34 %).

^{1}H NMR (500 MHz, CD_2Cl_2): δ 10.09 (s, 2H, meso H_1), 8.13 (t, br, 2H, H_4), 7.92 (s, 2H, H_2), 7.73 (m, 4H, H_3 and $_5$), 6.29 (d, J = 8.5 Hz, 2H, H_γ), 5.33 (t, J = 8 Hz, 2H, H_β), 4.24 (s, br, 6H, H_6 and H_α), 3.91 (t, J = 7.5 Hz, 8H, hex-^{1}CH_2), 3.62 (t, J = 6.3 Hz, 4H, H_{10}), 3.06 (t, br, H_8), 2.82 (t, J = 6.3 Hz, 4H, H_9), 2.48 (s, 12H, por-CH_3), 2.41 (s, br, 4H, H_7), 2.16 (m, 8H, hex-^{2}CH_2), 1.75 (m, 8H, hex-^{3}CH_2), 1.51 (m, 8H, hex-^{4}CH_2), 1.43 (m, 8H, hex-^{5}CH_2), 0.94 (t, J = 7 Hz, 12H, hex-^{6}CH_3);

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 147.7, 146.3, 143.4, 138.0, 136.5, 134.9, 132.3, 128.6, 127.8, 124.8, 123.3, 112.9, 104.2, 97.5, 69.6, 68.8, 68.2, 66.9, 44.1, 38.4, 33.4, 32.0, 30.1, 26.8, 22.8, 15.4, 14.1;

MS (MALDI): 1374.6 [M^+];

UV-vis (CH_2Cl_2): λ 414, 542, 576 nm.

Naphthoxy bisdisulfide free base porphyrin 2H·4

5,15-Di(3-mercaptomethylphenyl)-2,8,12,18-tetra-hexyl-3,7,13,17-tetramethyl-porphyrin (100 mg, 0.1 mmol) was dissolved in a mixture of CH_2Cl_2 (24.5 ml) and MeOH (0.5 ml) with 2-(2-{5-[2-(2-mercapto-ethoxy)-ethoxy]-naphthalen-1-yloxy}ethoxy)-ethanethiol (36.8 mg, 0.1 mmol) and bis-*N*,*N*′-n-hexane substituted naphthalene diimide (43.4 mg, 0.1 mmol). LiBr (20 mg, 2.3 mmol) and DBU (6 μl, 0.04 mmol) were added and the solution stirred for 3 days under air. The mixture was then zinc metallated according to the general procedure (described below). Column chromatography ($CHCl_3$) yielded the desired receptor as the Zn analogue. Treatment with dilute HCl (100 ml), followed by washing with water (2 × 100 ml), drying over Na_2SO_4 and removal of solvent *in vacuo* gave the free base receptor. Yield: 46 mg (35%).

^{1}H NMR (500 MHz, CD_2Cl_2): δ 10.24 (s, 2H, meso H_1), 8.19 (d, 2H, H_3), 7.81 (s, 2H, H_2), 7.75 (m, 4H, H_4 and $_5$), 6.73 (d, J = 8.6 Hz, 2H, H_γ), 5.09 (t, J = 8 Hz, 2H, H_β), 4.22 (s, 4H, H_6), 3.97 (t, J = 7.8 Hz, 8H, hex-^{1}CH_2), 3.80 (d, br, 2H, H_α), 3.73 (t, J = 6 Hz, 4H, H_{10}), 3.16 (s, br, H_8), 2.90 (t, J = 6 Hz, 4H, H_9), 2.58 (s, 12H, por-CH_3), 2.20 (s, br, 4H, H_7), 2.16 (m, 8H, hex-^{2}CH_2), 1.75 (m, 8H, hex-^{3}CH_2), 1.47 (m, 8H, hex-^{4}CH_2), 1.36 (m, 8H, hex-^{5}CH_2), 0.92 (t, J = 7 Hz, 12H, hex-^{6}CH_3), -2.27 (s, 2H, N*H*);

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 147.7, 146.3, 143.4, 138.0, 136.5, 134.9, 132.3, 128.6, 127.8, 124.8, 123.3, 112.9, 104.2, 97.5, 69.6, 68.8, 68.2, 66.9, 44.1, 38.4, 33.4, 32.0, 30.1, 26.8, 22.8, 15.4, 14.1;

MS (MALDI): 1311.64 [M^+].

Zinc metallation

Free base **2H·4** can be converted to zinc complexes in essentially quantitative yield by treatment with excess $Zn(OAc)_2$ in $CHCl_3$ at RT, with gentle heating and agitation for 2-3 mins. After 30 mins, the solution was evaporated to dryness, and the residue taken

up in CH_2Cl_2. This was then filtered through a sintered glass funnel to remove the excess $Zn(OAc)_2.2H_2O$, the filtrate was washed with water, dried over Na_2SO_4, evaporated to dryness and recrystallised by addition of either MeOH or hexane to a saturated $CHCl_3$ or CH_2Cl_2 solution of the porphyrin.