# Supporting Information

## General Details

NMR spectra were obtained using either a Brücker 400 or 500 DPX spectrometer. Stock solutions of porphyrin were prepared to a concentration of 0.1-0.9 mM in 5 mM phosphate buffer (50 mM NaCl where appropriate). Once the porphyrins had been dissolved, the pH was adjusted to 7.4 *via* addition of sodium hydroxide or HCl. Stock solutions of horse heart cytochrome c were prepared in 5 mM phosphate buffer and the pH adjusted to 7.4 as above. The concentration of horse heart cytochrome c (obtained from Sigma and used without further purification) was determined using the molar extinction coefficient at 550 nM of $2.95 \times 10^4$ after redcuction to Fe (III) using dithionite. Fluorescence spectra were measured on a Hitachi F-4500 instrument. The excitation wavelength was taken as the maximum of the soret band in the UV spectrum. UV spectra were measured using a Cary-3E spectrometer, an Agilent A453 spectrometer and a molecular devices spectra max 250 plate reader spectrometer. Where UV-difference titrations were carried out a quartz tandem mixing cell was used and the spectra of the porphyrin in the presences of protein subtracted from the additive spectra of porphyrin and protein. CD spectra were measured on an Aviv 62DS spectrapolarimeter. An averaging time of 10s per data point (each nM) was used and where appropriate, the spectra were corrected by subtraction of the contribution made by porphyrin but are otherwise unchanged.

## Tryptic Proteolysis Experiments

60 μL of cytochrome c (20 μM) and porphyrin (80 μM) were incubated for 10 min. (5 mM phosphate, 50 mM NaCl, pH 7.4). Trypsin (2 μg in 2 μL of 0.1 N HCl) was added to the reaction mixture and at appropriate intervals, 10 μL of the solution was removed from the reaction mixture and quenched by addition to 20 μL Tris Sample buffer (Biorad 2%) and heating at 95ºC for 5 minutes. At the end of the reaction, the samples were loaded onto 16.5% tris/tricine gels and constant voltage of 100 V was applied for 2 hrs (running buffer 10x SDS tris/tricine). The gels were washed with water (15 minutes) 10% acetic acid 0.025 % Commasie blue staining solution (2 hours) and water (2 hours). The gels were dried in the standard manner and imaged using a PC.

## *meso*-tetrakis-(4-carboxyphenyl tyrosylaspartic acid) porphyrin 1a

To a stirred solution of meso-tetrakis-(4-carboxyphenyl) porphyrin (0.10 mg, 0.126 mmol) in anhydrous dichloromethane (25 mL) was added oxaloyl chloride (0.79 g, 6.22 mmol) and a catalytic amount of DMF (1 μL). The reaction mixture was then stirred overnight under an inert atmosphere before being concentrated and dried for two hours under high vacuum. The resultant crude acid chloride was then dissolved in anhydrous tetrahydrofuran (5 mL), to which was added dropwise over thirty minutes a solution of tyr(OtBu)Asp(OtBu)OtBu (0.29 g, 0.632 mmol) and diisopropylethylamine (1.0 g, 1.4 mL, 8.06 mmol) in anhydrous dichloromethane (5 mL). The reaction mixture was allowed to stir under an inert atmosphere for two hours then diluted to ca. 60 mL with dichlormethane and washed with sodium hydroxide (1 N, 60 mL), citric acid (10%, 100 mL) and saturated sodium chloride before being dried over magnesium sulphate, filtered and concentrated. The resultant dark red solid was subjected to preparative TLC (50%

ethyl acetate in dichloromethane, $SiO_2$) to give the fully protected product which, could be deprotected by stirring in 90% trifluoroacetic acid in water (10 mL) for a period of four hours and then isolated by removal of the solvent and re-dissolving in 40% acetonitrile in water followed by lyopholization to give the receptor as a green powder. Yield: 192 mg, 80%; mp >300 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ = -2.94 (bs, 2H), 2.70 (dd, 4H, *J* = 16.2, 6.3 Hz), 2.82 (dd, 4H, *J* = 16.2, 5.0 Hz), 2.98 (m, 4H), 3.13 (m, 4H), 4.67 (m, 4H), 4.85 (m, 4H), 5.65 (bs, 8H), 6.72 (d, 8H, *J* = 8.1 Hz), 7.28 (d, 8H, *J* = 8.1 Hz), 8.24 (d, 8H, *J* = 6.8 Hz), 8.31 (d, 8H, *J* = 6.8 Hz), 8.59 (d, 4H, *J* = 7.1 Hz), 8.84 (s, 8H), 8.91 (d, 4H, *J* = 6.8 Hz); MALDI-TOF-MS *m/e* 1903.6 $[M+H]^+$ calcd for $C_{100}H_{86}N_{12}O_{28}$(+H), found 1904.5. UV/vis ($H_2O$, 5 mM phosphate, pH = 7.4) λ 414, 518, 555, 580, 634 nm.

***meso*-tetrakis-(4-carboxyphenyl tyrosylaspartic acid) Zinc (II)porphyrin 1b**

To a stirred solution of free-base porphyrin (10 mg, 0.005 mmol) in spectrophotometric grade methanol (50 mL) was added solid zinc chloride (100 mg, 10 fold wt. excess). The reaction mixture was brought to reflux and stirred until complete as evidenced by UV spectroscopy. The reaction mixture was then concentrated to a volume of ca. 10 mL and neutral water was added to precipitate the metalloporphyrin. The reaction mixture was then filtered through a pad of celite from which the metalloporphyrin was recovered by washing with 40% acetonitrile in water followed by lyophilization to yield the product as a red powder. Yield: 9.5 mg, 92%; mp >300 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) δ = 2.45 (m, 4H), 2.60 (m, 4H), 2.91 (m, 4H), 3.10 (m, 4H), 4.47 (m, 4H), 4.74 (m, 4H), 6.64 (d, 8H, *J* = 8.2 Hz), 7.18 (d, 8H, *J* = 8.2 Hz), 8.11 (m, 8H), 8.17 (m, 8H), 8.68 (s, 8H), 8.76 (m, 2H), 8.81 (m, 2H), 9.11 (s, 4H); MALDI-TOF-MS *m/e* 1967 $[M+H]^+$ calcd for $C_{100}H_{84}N_{12}O_{28}Zn$(+H), found 1967.47. UV/vis ($H_2O$, 5 mM phosphate, pH = 7.4) λ 423, 556, 597 nm.

***meso*-tetrakis-(4-carboxyphenyl tyrosylaspartic acid) Copper (II)porphyrin 1c**

To a stirred solution of free base porphyrin (10 mg, 0.005 mmol) in spectophotometric grade methanol (50 mL) was added anhydrous copper chloride (100 mg, 10 fold wt. excess). The reaction mixture was brought to reflux and stirred until complete as evidenced by UV spectroscopy. The reaction mixture was then concentrated to a volume of ca. 10 mL and neutral water was added to precipitate the metalloporphyrin, which was then subjected to centrifuge and the supernatant decanted. 0.01 N HCl was added to the resultant "pellet" and the mixture again subjected to centrifuge and the supernatant decanted. After this step had been repeated several times the dark red "pellet" was dissolved in 40% acetonitrile in water and lyophollized to give a dark red powder. Yield: 6.2 mg, 60%; mp >300 °C; MALDI-TOF-MS *m/e* 1965 $[M+H]^+$ calcd for $C_{100}H_{84}N_{12}O_{28}Cu$(+H), found 1965. UV/vis ($H_2O$, 5 mM phosphate, pH = 7.4) λ 412, 542, 586 nm.

**Di-*t*-butyl-N-(4-aminomethyl-benzoyl)-iminodiacetate**

To a vigorously stirred solution of 4-(aminomethyl)benzoic acid (1.0 g, 6.6 mmol) in 50 mL of water at 0 ºC was added, slowly, benzylchloroformate (1.1 mL, 7.3 mmol) and the solution was warmed to room temperature and stirred for 16 hours. The solution was acidified to pH 3 with 1 M HCl and the product filtered off as a pure white solid and

washed with 50 mL each of water, ethanol and diethyl ether yielding 1.8 g (95%). The Z-protected 4-(aminomethyl) benzoic acid (260 mg, 0.91 mmol), di-*t*-butyl-iminodiacetate (250 mg, 1.0 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) (190 mg, 0.98 mmol) were placed in 25 mL of dry dichloromethane and stirred at room temperature for 4 hours. The solution was extracted successively with 30 mL each of 1 M HCl, saturated sodium bicarbonate and brine, dried over sodium sulfate and evaporated to dryness. The product was purified on a silica column eluting with 2:1 hexanes/ethyl acetate yielding 375 mg (80%) of the Z-protected product as a white solid. The product (375 mg, 0.73 mmol) was deprotected by catalytic hydrogenation in 12 mL of vigorously stirred methanol with 10% Pd/C (42 mg, 0.04 mmol) catalyst under 1 atm of hydrogen for 4 hours. The solution was filtered through celite and the methanol evaporated. The final product was purified on a silica column eluting with dichloromethane with 0.5% triethylamine and an increasing fraction of methanol from 2.5% to 10% yielding the pure deprotected product as a colorless, sticky, solid (250 mg, 69% overall yield): $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, $J$ = 8.1 Hz, 2H), 7.34 (d, $J$ = 8.1 Hz, 2H), 4.16 (s, 2H), 3.95 (s, 2H), 3.90 (s, 2H), 1.47 (s, 9H), 1.44 (s, 9H).

**_meso_-tetrakis-(4-carboxyphenyl amidomethyl-benzoyl)-iminodiacetate) porphyrin 2a**

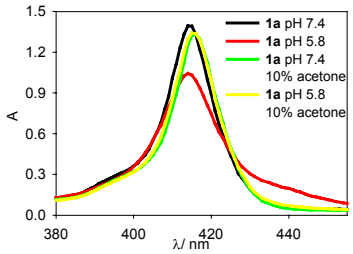
To a solution of *meso*-tetrakis-(4-carboxyphenyl) porphyrin (63 mg, 0.08 mmol) in 10 mL of dry dichloromethane was added di-*t*-butyl-N-(4-aminomethyl-benzoyl)-iminodiacetate (120 mg, 0.32 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) (86 mg, 0.35 mmol), and the mixture was stirred at room temperature under nitrogen overnight. The reaction mixture was extracted successively with saturated sodium bicarbonate, 1 M sodium hydroxide and brine, dried over sodium sulfate and evaporated to dryness. The *t*-butyl protected product was purified on a silica column eluting with dichloromethane with an increasing fraction of methanol from 0% to 5%. Treatment with 95% TFA/$H_2O$ (5 mL) at room temperature for 4h followed by evaporation afforded the triflate salt of the free acid product as a dark green solid (104 mg, 65%): $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.40 (t, $J$ = 5.0 Hz, 4H), 8.80 (s, 8H), 8.29 (d, $J$ = 8.5 Hz, 8H), 8.26 (d, $J$ = 8.5 Hz, 8H), 7.47 (d, $J$ = 8.1 Hz, 8H), 7.29 (d, $J$ = 8.1 Hz, 8H), 4.62 (d, $J$ = 4.7 Hz, 8H) 4.08 (s, 8H), 3.97 (s, 8H), -3.00 (s, b, 2H); MALDI-TOF MS *m/e* 1783.5 $[M+H]^+$ calcd for $C_{96}H_{78}N_{12}O_{24}$(+H), found 1783.4; UV/vis ($H_2O$, 5 mM phosphate, pH = 7.4) λ 416, 517, 554, 581, 635 nm.

**_meso_-tetrakis-(4-carboxyphenyl amidomethyl-benzoyl)-iminodiacetate) copper (II) porphyrin 2b**

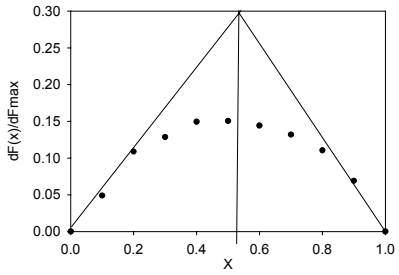
Compound 2a (15 mg, 0.0075 mmol) was dissolved in 5 mL of methanol and copper(II) chloride (2.5 mg, 0.019 mmol) was added. The solution was stirred for 3 hours at room temperature, after which time a red precipitate had formed and all green color had vanished from the solution. The red solid was filtered and washed with methanol, 0.01 M HCl, and water. The solid was dissolved off the filter with DMF and evaporated to dryness yielding 12 mg of product (90%); MALDI-TOF MS *m/e* 1844.5 $[M+H]^+$ calcd for $C_{96}H_{76}N_{12}O_{24}Cu$(+H), found 1844.4; UV/vis ($H_2O$, 5 mM phosphate, pH = 7.4) λ 416, 541, 576 nm.

**Analytical data:**

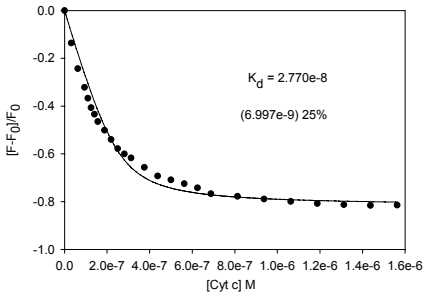
Job Plots binding constants and melts for **1a** were reported previously Jain, R. K.; Hamilton, A. D. *Org. Lett*. **2000**, *2*, 1721-1723 and Jain, R. K.; Hamilton, A. D. *Angew. Chem. Int. Ed*. **2002**, *41*, 641-643.



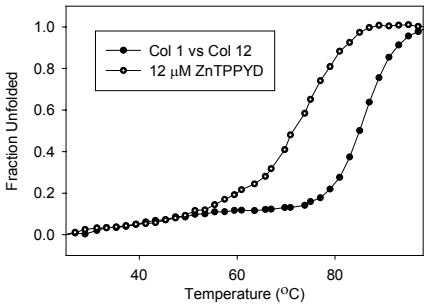

**Compound 1a** UV spectra, (5 μM, 5 mM phosphate) highlighting the differences in aggregation behaviour at different pH's with and without addition of organic solvent



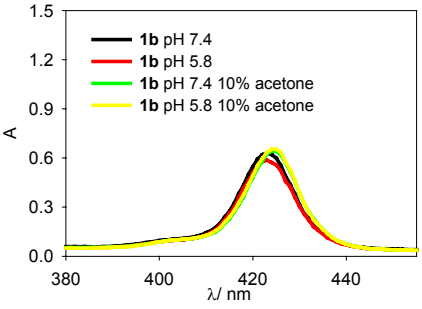

**Compound 1b**. Job plot for binding of zinc (II) porphyrin **1b** to Cytochrome *c*. Excitation wavelength was nm; fluorescence emission was monitored at 605 nm as a function of the mole fraction of Cytochrome c. The total concentration of the two species was held constant at 1 μM (298 K, pH 7.4 and 5 mM phosphate buffer).



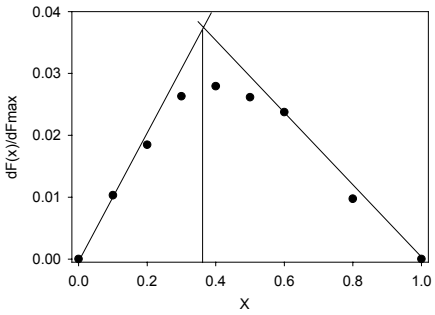

**Compound 1b.** Fluorescence titration of binding of zinc (II) porphyrin **1b** to Cytochrome *c*. Titrations were carried out with 0.5 μM porphyrin concentration in 5 mM sodium phosphate buffer, pH = 7.4, at 298K. Excitation wavelength was 415 nm; fluorescence was monitored at 605 nm. Fit as a 1:1 complex.



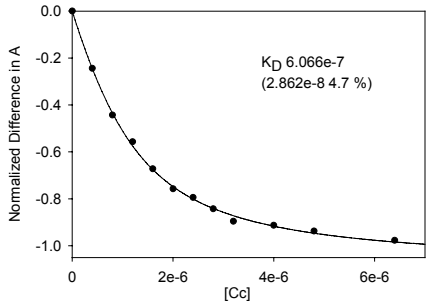

**Compound 1b.** Melt of Cyt. C (10 μM) with variable equivalents of zinc (II) porphyrin **1b**. Monitored by CD at 222 nm in 5 mM sodium phosphate, pH 7.4.



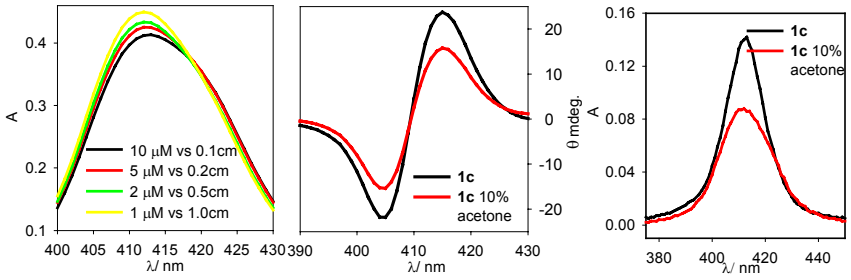

**Compound 1b** UV spectra (5 μM, 5 mM phosphate) highlighting the differences in aggregation behaviour at different pH's with and without addition of organic solvent



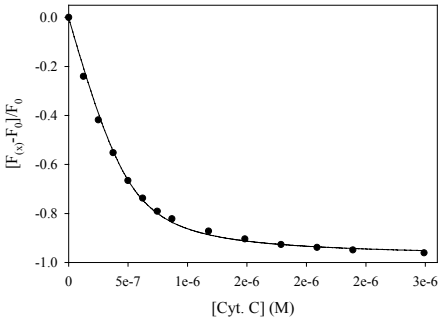

**Compound 1c.** Job plot by UV difference spectroscopy of the binding of copper(II) porphyrin **1c** in tandem cells monitored at 412 nm as a function of the mole fraction of Cytochrome *c*. The total concentration of the two species was held constant at 2 μM in 5 mM phosphate buffer 50 mM NaCl, pH 7.4 at 298 K.



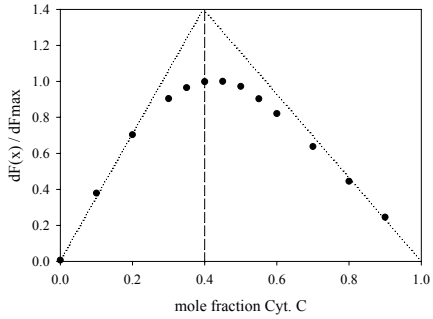

**Compound 1c.** UV difference titration of binding of copper (II) porphyrin **1c** to Cytochrome *c*. Titrations were carried out in tandem UV cells with 2.0 μM porphyrin concentration in 5 mM sodium phosphate buffer, 50 mM NaCl, pH = 7.4, at 298 K. UV difference was monitored at 412 nm. For the purpose of fitting the curve, **1c** was assumed to exist as a covalently linked dimer with a single $K_d$ value.



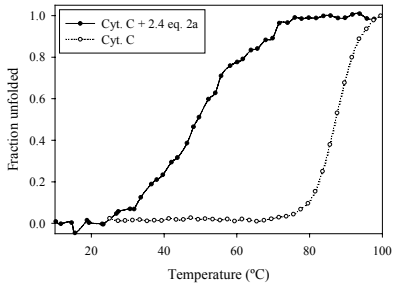

**Compound 1c,** (a) UV spectra (5 mM phophate, 50 mM NaCl, pH 7.4) (b) CD spectrum (10 μM, 5 mM phosphate, 50 mM NaCl, pH 7.4) (c) UV spectra (0.25 μM 5 mM phosphate, 50 mM NaCl) demonstartiung dimerisation.



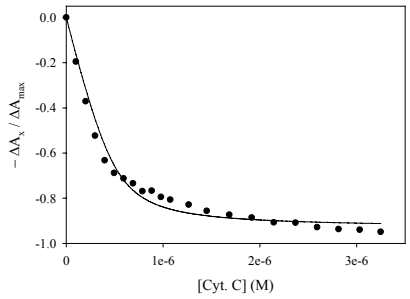

**Compound 2a.** Fluorescence titration of binding of free base porphyrin **2a** to Cytochrome *c*. Titrations were carried out with 0.5 μM porphyrin concentration in 5 mM sodium phosphate buffer, pH = 7.4, at 298K. Excitation wavelength was 416 nm; fluorescence was monitored at 643 nm. Fit as a 1:1 complex.



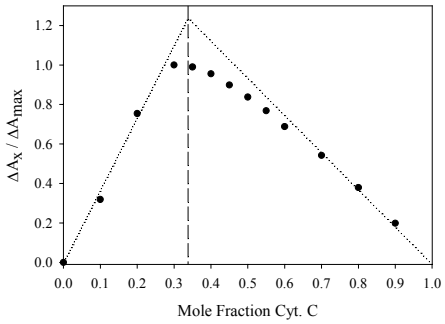

**Compound 2a.** Job plot for binding of free base porphyrin **2a** to Cytochrome *c*. Excitation wavelength was 416 nm; fluorescence emission was monitored at 643 nm as a function of the mole fraction of Cytochrome c. The total concentration of the two species was held constant at 4 uM (298 K, pH 7.4 and 5 mM phosphate buffer).



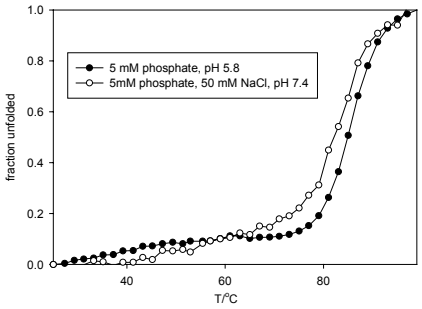

**Compound 2a.** Melt of Cyt. C (5 μM) with 0 and 2.4 equivalents of free base porphyrin **2a**. Monitored by CD at 222 nm in 5 mM sodium phosphate, pH 7.4.




**Compound 2b.** UV difference titration of binding of copper (II) porphyrin **2b** to Cytochrome *c*. Titrations were carried out in tandem UV cells with 1.0 μM porphyrin concentration in 5 mM sodium phosphate buffer, pH = 7.4, at 298 K. UV difference was monitored at 412 nm. For the purpose of fitting the curve, **2b** was assumed to exist in dimeric form in solution forming a 2:1 complex with a single $K_d$ value. Isosbestic points in the UV-difference spectra support the formation a single complex involving only protein and metalloporphyrin dimer.




**Compound 2b.** Job plot by UV difference spectroscopy of the binding of copper(II) porphyrin **2b** in tandem cells monitored from 405 to 425 nm as a function of the mole fraction of Cytochrome c. The total concentration of the two species was held constant at 10 μM in 5 mM phosphate buffer, pH 7.4 at 298 K.




Control melts of Cyt. C (10 μM) monitored by CD at 222 nm.