Supporting Information for:

Bioconjugatable Porphyrins Bearing a Compact Swallowtail Motif for Water Solubility

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I. Zinc-facilitated hydrolysis of porphyrin-diphosphates. Although the isolated yields of **Zn12a** and **Zn12b** were reasonable, the spectroscopic yields were higher (30-45%). It is likely that some losses occur during the chromatographic purification. The elution mixture contains a protic solvent (methanol), which can result in the decomposition of the phosphate-functionalized swallowtail groups in the presence of a zinc central atom (*vide infra*). This is supported by the fact that during the elution a number of porphyrinic species were observed, none of which were observed upon LD-MS analysis of the crude sample. Performing most of the elution with a mixture of ethyl acetate/CH_2Cl_2, followed by MeOH/CH_2Cl_2 resulted in an increase in the yield to 22% for **Zn12a**.

Porphyrin **Zn12a** contains both the bioconjugatable site and the water-solubilizing groups, masked by *tert*-butyl and methyl esters, respectively. Attempts at the simultaneous removal of the *tert*-butyl and methyl ester protecting groups with TMS-Br were unsuccessful. A series of test reactions carried out on **Zn12b** revealed that the phosphate groups were susceptible to displacement by bromide, as indicated by LD-MS analysis of the crude reaction mixture, and LD-MS and ^{1}H NMR spectroscopic analysis of the pure porphyrin product. This compound is identical to **14b**. When the reactions were conducted at room temperature as opposed to refluxing chloroform, in the presence of only a slight excess of TMS-Br, the bromination was suppressed, but the isolation of the desired compound bearing unprotected phosphate groups proved challenging. The following observations were made:

(1) The crude porphyrin-diphosphates, while displaying excellent water-solubility initially, precipitated out of solution within minutes.

(2) Because TMS-Br removed some of the zinc, remetalation was attempted with zinc acetate. This resulted in the immediate and quantitative precipitation of the porphyrinic species from the solution. Most (but not all) of the precipitate could be redissolved in concentrated (15 wt%) aqueous NaOH.

(3) When **Zn12b** was treated with TMS-Br in the presence of TEA to suppress demetalation (*49,50*), the deprotected porphyrin-diol **Zn11b** was not formed until the addition of a protic solvent. During the workup, **Zn11b** formed in quantitative yield, as determined by ^{1}H NMR spectroscopy and LD-MS [obsd *m/z* 567, calcd 566 for demetalated $(M + H)^+$] of the purified sample.

(4) A sample of **Zn12b** in a mixture of $CDCl_3$/CD_3OD was monitored by ^{1}H NMR and LD-MS. Within 8 h the formation of porphyrin **11b** was almost quantitative (obsd *m/z* 566 (demetalated **11b**), disappearance of phosphate methyl ester singlets).

(5) Basic hydrolysis (H_2O/MeOH, NaOH, various concentrations) removed only two of the methyl esters, but none of **Zn11b** was formed (*S1*).

These observations suggested that the zinc atom plays a pivotal role in the displacement of the phosphate groups, both during purification of the crude porphyrin-forming reaction mixture and upon deprotection with TMS-Br. A proposed mechanism for zinc ion-mediated loss of phosphate is depicted in Figure S1. The coordination of one of the phosphate oxygens to the apical site of the zinc ion renders the phosphorous atom susceptible to attack by nucleophiles, resulting in the cleavage of the indicated O-P bond. Zinc ion is well known to promote phosphate hydrolysis in biological systems (*S2*). This geometry in unavailable if the fifth coordination site of the metal is occupied by a different electron pair donor, e. g. OH^-, which explains why **Zn11b** was not observed during basic hydrolysis. It is also possible that an additional coordination event takes place upon the addition of zinc to the sample (point 2 above). The zinc metal may coordinate the phosphate groups making them inaccessible for the solvent, which results in precipitation of the porphyrin. Addition of concentrated aqueous NaOH dissolves the precipitate because the large excess of hydroxide ions disrupts the zinc-O-phosphate complex.

In summary, zinc porphyrins bearing phosphate-terminated swallowtail groups were not obtained for the pent-3-yl groups examined. Accordingly, we turned our attention to free base and copper analogues of the porphyrin-diphosphates.

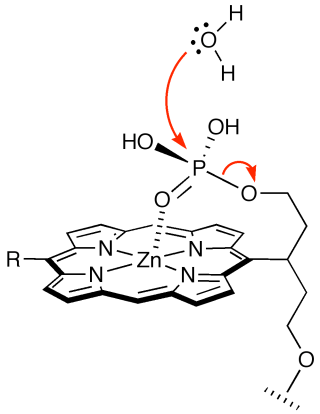

Figure S1. Possible geometry adopted by the zinc chelates **Zn12a** and **Zn12b** in solution. Coordination of the phosphate group to the apical zinc site renders the phosphate vulnerable to attack by nucleophiles.

II. VT-NMR Experiments.

Conditions. VT-NMR experiments were conducted in toluene-d_8. The probe temperature was increased in 10 °C-steps and the sample was allowed to equilibrate for 5 min. Temperature range: 20–90 °C.

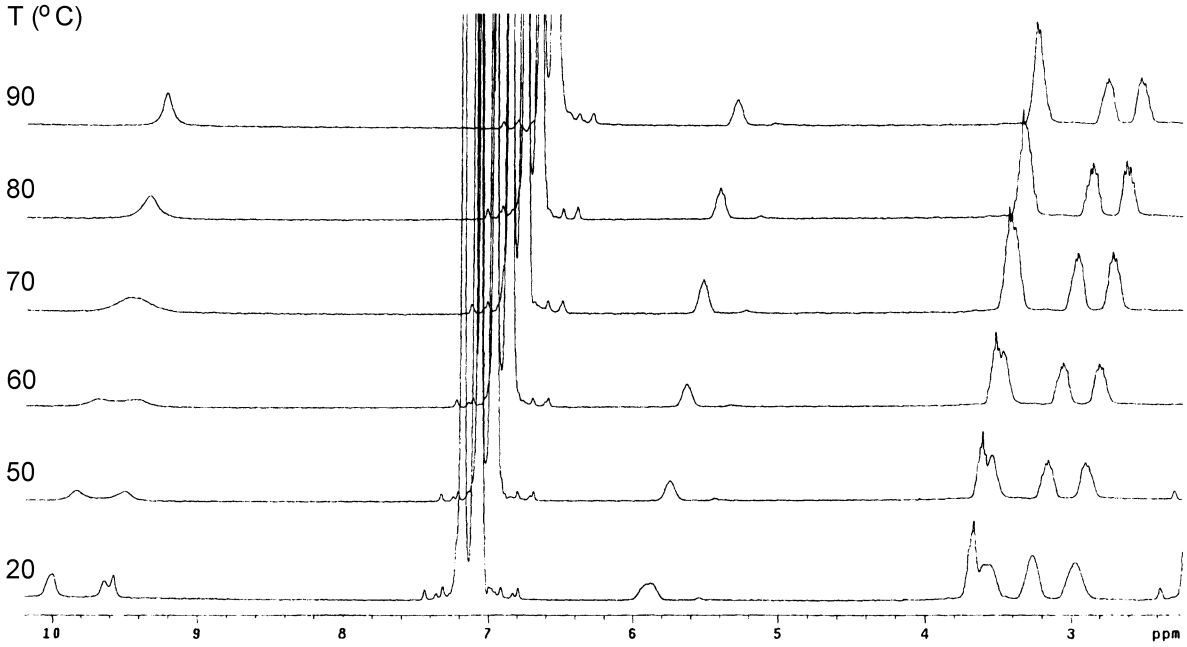

Figure S2: Stacked plot of VT-NMR spectra for porphyrin **17**.

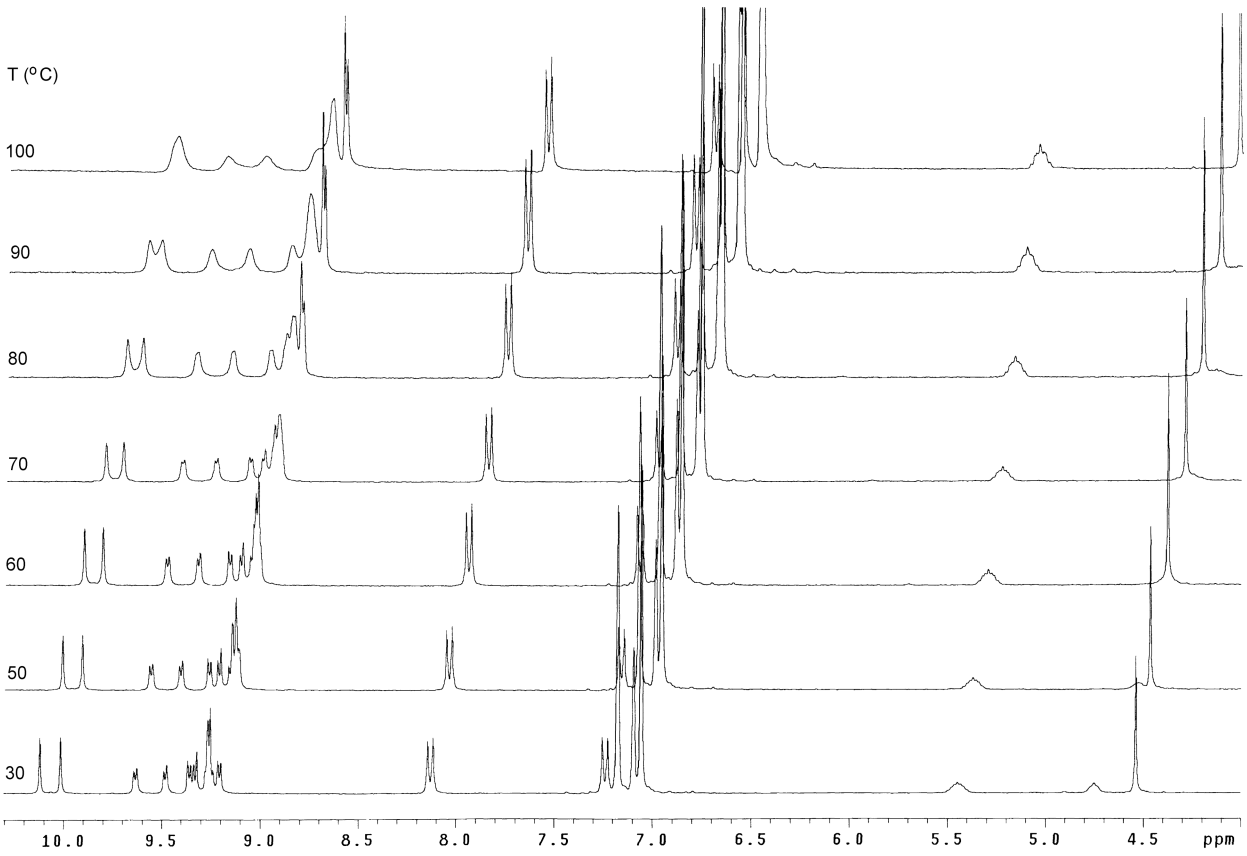

Figure S3: Stacked plot of VT-NMR spectra for porphyrin **Zn12b**.

III. NOESY Experiments.

Conditions. NOESY experiments were carried out in DMF-d_7 (**Zn12b**) or $CDCl_3$ (**17**) at room temperature. Parameters: relaxation delay: 1.000 s; mixing time: 0.200 s; acquisition time: 0.213 s.

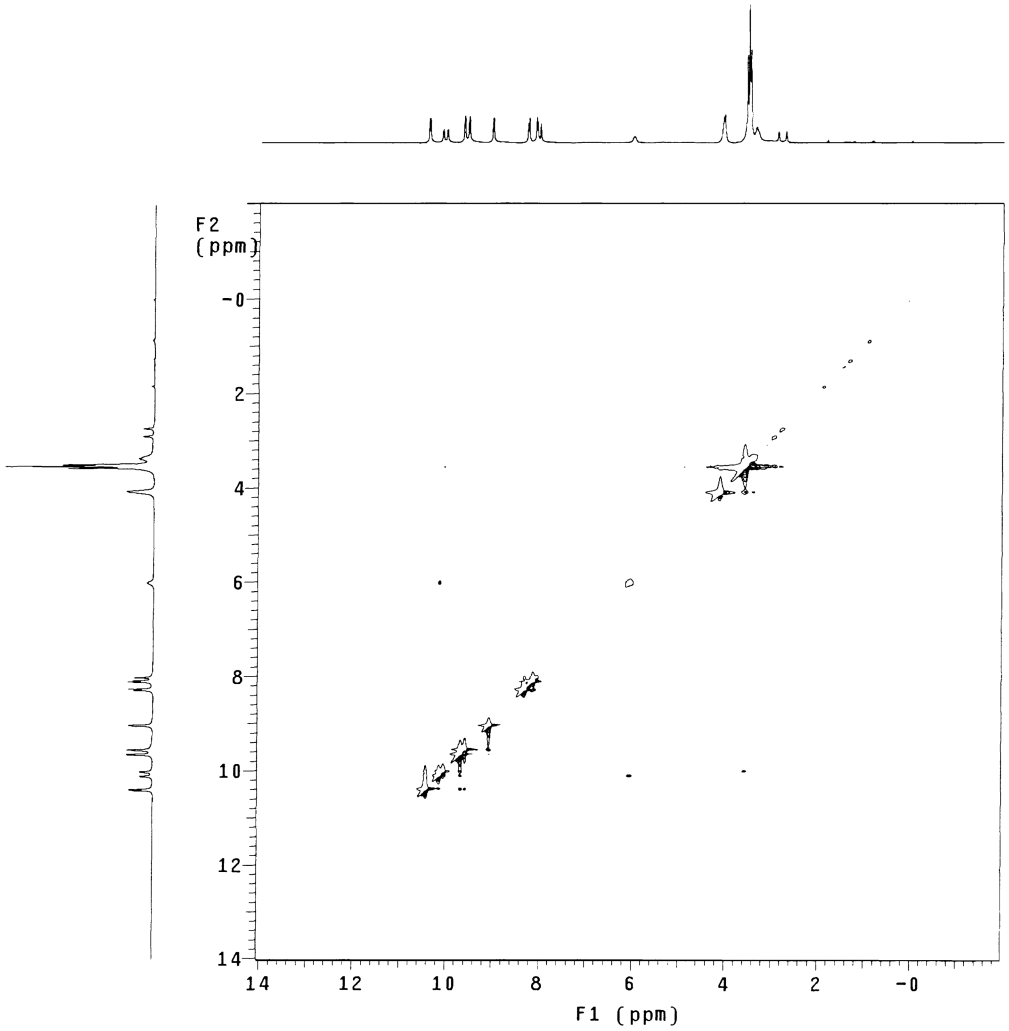

Figure S4: NOESY spectrum of porphyrin **Zn12b**.

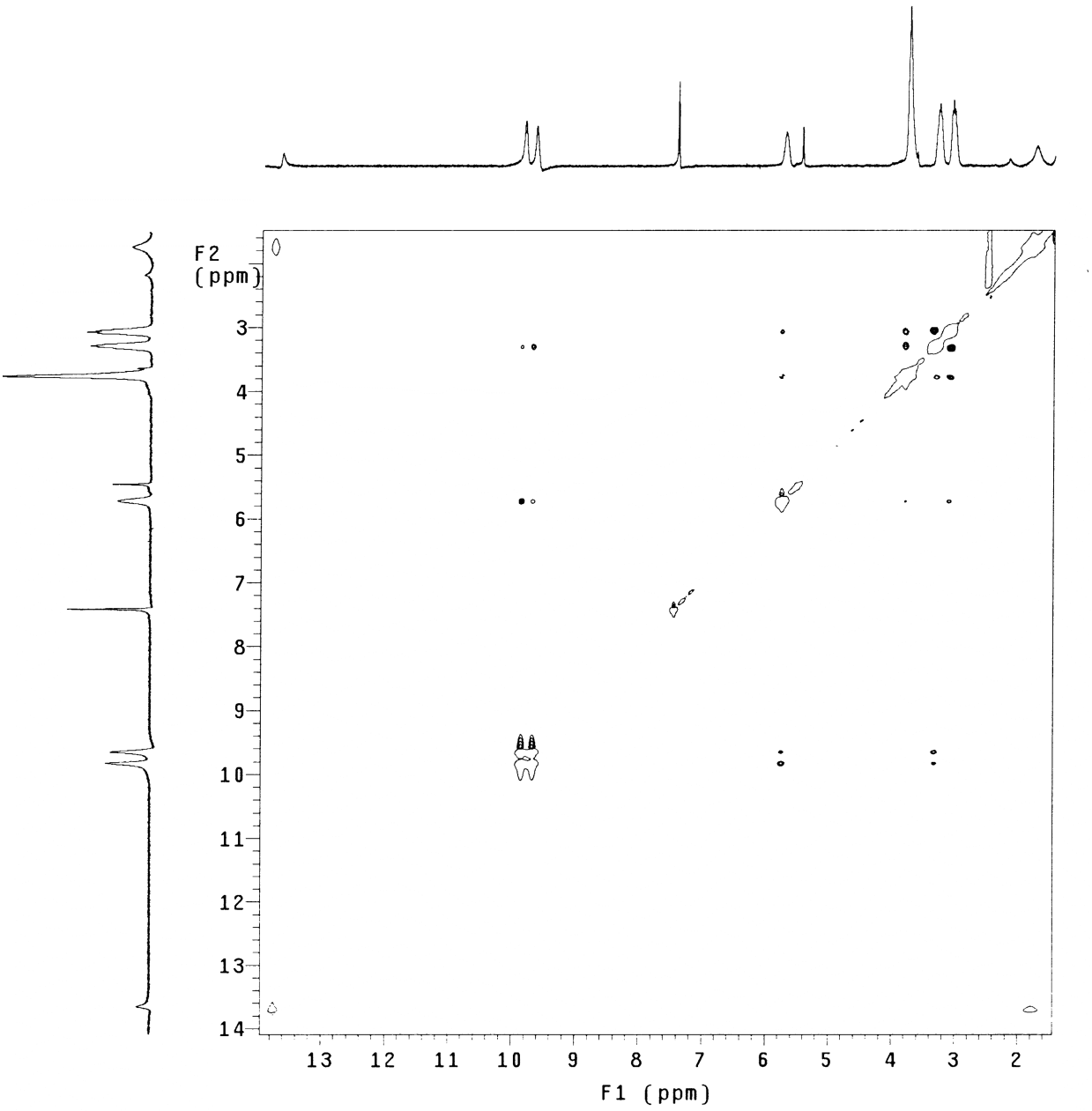

Figure S5: NOESY spectrum of porphyrin **17**.

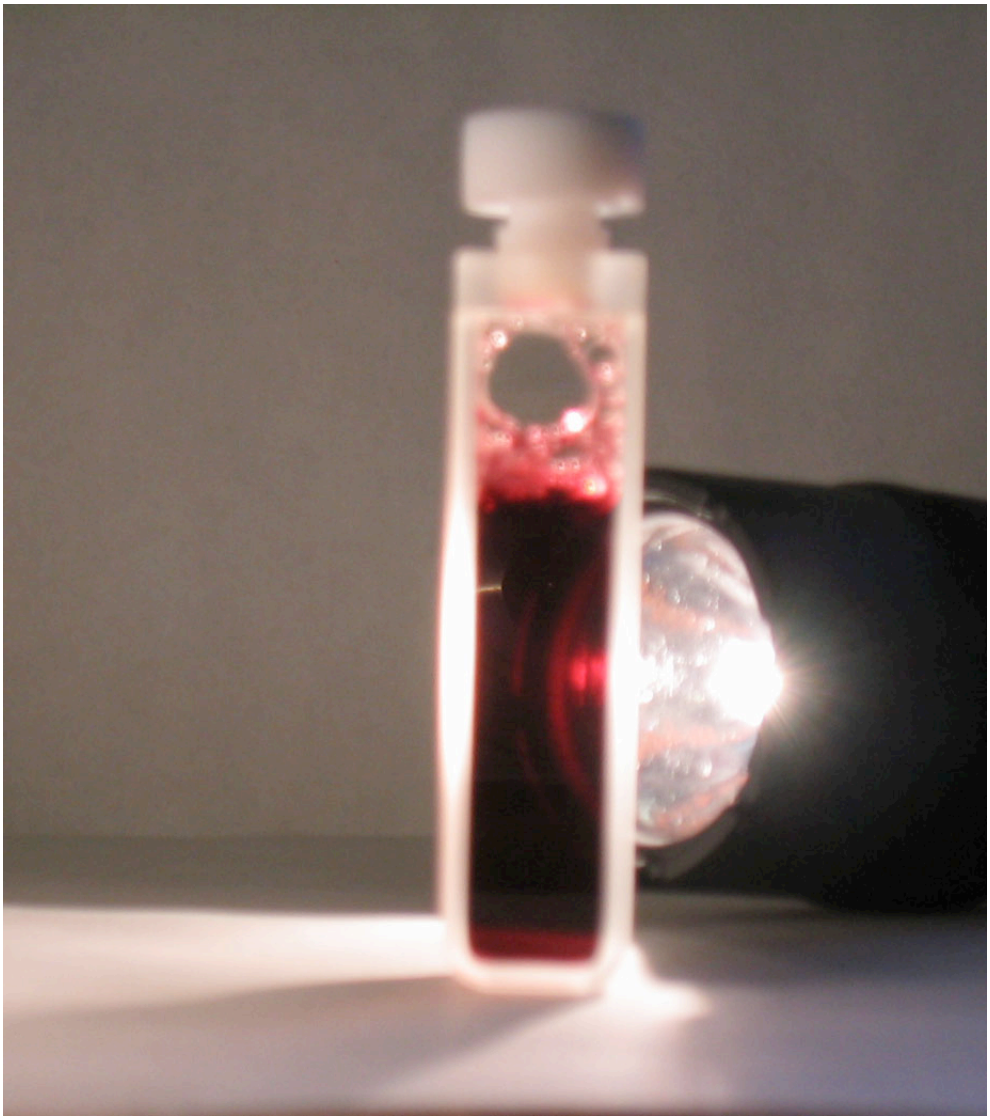

Figure S6. Photo of an aqueous solution of **Zn16b** at reasonable concentration (~5 mM, pH 7) in a 1-cm pathlength cuvette.

References:

(S1) Hirschbein, B. L., Mazenod, F. P., and Whitesides, G. M. (1982) Synthesis of phosphoenolpyruvate and its use in adenosine triphosphate cofactor regeneration. *J. Org. Chem. 47*, 3765-3766.

(S2) Feng, G., Mareque-Rivas, J. C., Torres Martin de Rosales, R., and Williams, N. H. (2005) A highly reactive mononuclear Zn(II) complex for phosphodiester cleavage. *J. Am. Chem. Soc*. *127*, 13470–13471.