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From thioether substituted porphyrins to sulfur linked porphyrin dimers: an unusual S_NAr *via* thiolate displacement?†

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Treatment of *meso* 2-ethylhexyl-3-mercaptopropionate substituted porphyrins with base at room temperature generated a porphyrin thiolate anion which *in situ* reacted in a nucleophilic aromatic substitution (S_NAr) reaction with remaining thioether derivative. This reaction yielded S-linked bisporphyrins in good yields, with mechanistic insight obtained *via* displacement reactions. Additionally, S_NAr of the thioether chain was achieved using S- and organolithium nucleophiles.

Owing to their biological and medical importance,[1] the synthesis of organosulfur compounds has been the focus of thorough investigations.[2] One important development is the nucleophilic aromatic substitution (S_NAr) with the thiolate anion.[3] Typically, thiolate S_NAr only occurs with activated aryls with leaving groups such as halides or tosylates,[4] requiring a very strong base, elevated temperature and/or the use of metal catalysts.[3c,5] Additionally, it is often hindered *via* competing oxidation reactions to form disulfide bonds (Fig. 1).[6] In a remarkable S_NAr, sulfur-linked porphyrin dimers were generated *via* a simple deprotection of a thioether appended porphyrin. While our initial goal was the synthesis of a free thiol group directly attached to the porphyrin macrocycle *via* base deprotection, bisporphyrin products were observed predominantly. Such sulfur linked bisporphyrins have not previously been reported and are easily produced, in contrast to other heteroatom linked porphyrin arrays which generally require many synthetic steps.[7]

These were generated *via* S_NAr by the thiolate at the *meso* position of the substituted porphyrin, with isooctyl-3-mercaptopropionate acting as an excellent leaving group. Substitution reactions on porphyrins are limited,[8] at best, and typically require highly specific activated systems and high temperatures. However, this room temperature *in situ* S_NAr of a seemingly unactivated porphyrin in such fashion represents, to the best of our knowledge, the first reaction of this type to be documented. This is somewhat reminiscent of previous work in our group, whereby using organolithium reagents a variety of substituents can be introduced to the porphyrin periphery *via* S_N type reactions.[9]

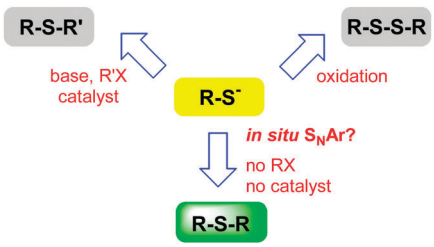

Fig. 1 Overview of thiolate reactivity.

Porphyrins bearing thiol and thioether substituents have a diverse range of optical applications due to their ability to form self-assembled monolayers (SAMs) on gold surfaces[10] and this attribute formed the basis for our interest in thioporphyrins. Adopting a versatile Pd-catalyzed porphyrin–sulfur bond forming reaction developed by Itoh and Mase,[11] a library of novel isooctyl-3-mercaptopropionate substituted porphyrins, so-called protected thiols, were synthesized.[12] This involved a Pd-catalyzed reaction of bromoporphyrins **1a–i** and the thiol 2-ethylhexyl-3-mercaptopropionate in good to excellent yields of 66–87%. These protected thiols have the potential to be used in Au–NP formulation or as a photosensitizer delivery system in PDT,[13] but our primary goal was for their use in deprotection reactions (Table 1). All protected thiols were subjected to base-mediated deprotection[14] in an effort to obtain a free thiol group directly attached to the porphyrin macrocycle. However, deprotection through β-elimination of the thioether chain of masked compounds **2a–g**, gave unusual results, with the S-linked bisporphyrins **3a–g** isolated as the major products (Table 2).

Here, both the isooctyl-3-mercaptopropionate group acts as an excellent leaving group and the porphyrin thiolate behaves as a very strong nucleophile. The reaction goes to completion in all

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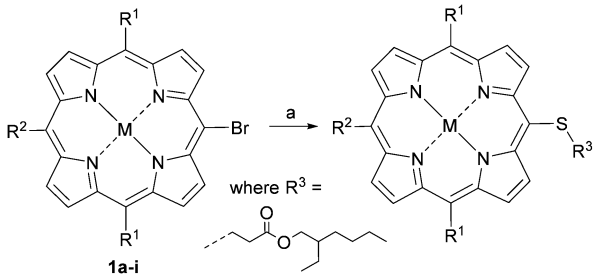
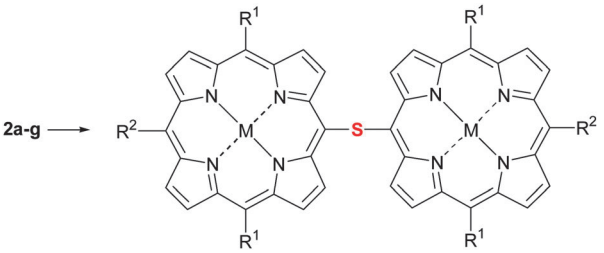
Table 1 Synthesis of porphyrin-thiol surrogates *via* Pd catalysis



Entry	R^1	R^2	M	Product	Yield
1	Tolyl	Ph	Zn^{II}	**2a**	85
2	Ph	Ph	Zn^{II}	**2b**	76
3	Ph	H	Zn^{II}	**2c**	76
4	Tolyl	Ph	2H	**2d**	70
4	Tolyl	H	2H	**2e**	68
5	Tolyl	H	Ni^{II}	**2f**	72
6	Tolyl	Ph	Ni^{II}	**2g**	63
7	Ph	Ph	Ni^{II}	**2h**	68
8	1-Ethylpropyl	*n*-Butyl	Ni^{II}	**2i**	65

[a] *Reagents and conditions*: $Pd_2(dba)_3$ (2.5 mol%), xantphos (5 mol%), iPr_2NEt, toluene, 80 °C, Ar, 16–24 h.

Table 2 Synthesis of S-linked dimers *via* base-mediated deprotection



Entry	R^1	R^2	M	Dimer[b]	Yield[a]
1	Tolyl	Ph	Zn^{II}	**3a**	63
2	Ph	Ph	Zn^{II}	**3b**	56
3	Ph	H	Zn^{II}	**3c**	55
4	Tolyl	Ph	2H	**3d**	n/d[c]
5	Tolyl	H	2H	**3e**	n/d[c]
6	Tolyl	H	Ni^{II}	**3f**	72
7	Tolyl	Ph	Ni^{II}	**3g**	68

[a] Yield of isolated product. [b] *Reagents and conditions*: NaOEt (2–5 eq.), toluene, Ar, 4–24 h. [c] Yield not determined due to inseparable mixture of S-linked and disulfide linked bisporphyrin.

cases, with yields only hindered by the competing free thiol and/or disulfide formation. These compounds are easily purified *via* extraction into dichloromethane, with the free-thiol and/or disulfide side products generally only solubilizing in more polar solvents such as ethyl acetate. The side products were confirmed *via* HRMS analysis and UV-vis absorption spectra (Fig. 3).[15] Zn(II) and Ni(II) dimers **3a–c** and **3f** and **3g** were isolated in good to excellent yields of 55–72%. However, free-base bisporphyrins **3d** and **3e** were more difficult to purify, with the S-linked dimers in most cases co-eluting with the disulfide derivative.

We propose that upon thiolate generation, this nucleophile reacts immediately with any remaining starting material present forming the bisporphyrins *via* S_NAr.[16] Any remaining thiolate either precipitates out of solution or is oxidized to the disulfide linked dimer.[15] Attempts to hinder thiolate S_NAr generation of **3a** *via* the use of the more non-polar solvent *n*-hexane, in which the free thiol was likely to be insoluble and precipitate out of solution, were unsuccessful, with only starting material **2a** isolated. The X-ray structural analysis of **3b** clearly shows the thioether structure (Fig. 2). The compound crystallized as the axial methanol adduct and exhibits a skewed co-facial structure. The least-squares-planes of the two 24-atom macrocycles form an angle of 58.4(1)°.[17,18] The UV-vis absorption profiles of **3b** and **3d** are shown in Fig. 3. The S-linked bisporphyrins **3b** and **3d** display broad Soret band absorption with respect to their thiol surrogates **2b** and **2d**. In addition to this, the absorption profiles of side products of **3b** and **3d** from the reaction are shown in green and red respectively. We speculate that these are phlorin species as the profile shown is similar to those in the literature.[9c] They were most likely generated *via* tautomerization to the thione form of the free thiol (phlorin).[19]

To further elucidate both the strength of the porphyrin thiolate as a nucleophile and the susceptibility of the isooctyl-3-mercaptopropionate to act as a leaving group, some displacement (S_NAr) reactions were executed with similar aryl and aliphatic halides (Table 3, entries 1–4 and ESI†). The first reactions screened were the deprotections in the presence of aliphatic electrophiles. As expected, methyliodide **6** worked well for Zn(II) and Ni(II) porphyrins **2a** and **2i**, with easy displacement by the porphyrin thiolate and no dimer formation. Here, the thiolate generated immediately reacts with the electrophile, forming methylthio-porphyrin compounds **4a** and **4c** in yields of 71 and 95%, respectively. In the presence of other electrophiles, however, a marked difference in reactivity of Ni(II) and Zn(II) porphyrins was observed. For Ni(II) porphyrin **2g**, the reaction with 1-bromohexane **7** was slower than with electrophile **6**. With ten equivalents of the electrophile the desired

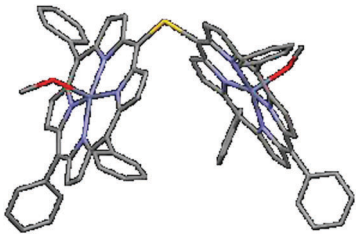


Fig. 2 View of the molecular structure of **3b** in the crystal. Hydrogen atoms and disordered positions have been omitted for clarity. Selected bond lengths and angles: C5–S1 = 1.826(6) Å, C25–S1 = 1.856(7) Å, C5–S1–C25 = 104.8(3)°.

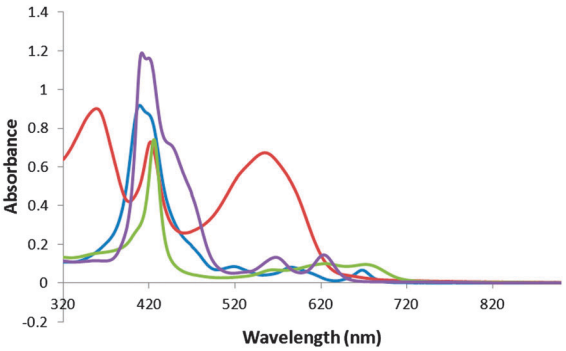
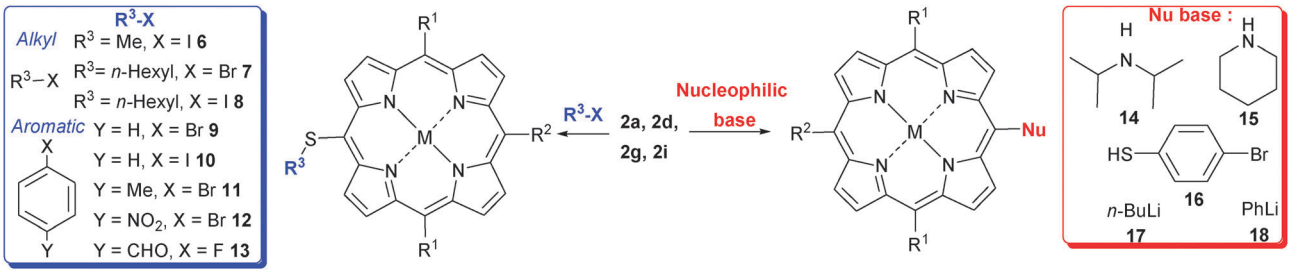


Fig. 3 UV-vis absorption spectra of **3b** (blue), **3d** (purple) and respective phlorin side products (**3b**-green and **3d**-red) in CH_2Cl_2.

Table 3 Displacement reactions: (a) porphyrin thiol surrogate with alkyl/aromatic halides and (b) displacement of thioether chain by nucleophile



Entry	R^3–X[g]	R^1	R^2	M	Product	Yield[a]	Entry	Nucleophile[g]	R^1	R^2	M	Product	Yield[a]
1	**6**	Tolyl	Ph	Zn^{II}	**4a**[b]	71	5	**16**	Tolyl	Ph	2H	**5a**	48[d]
2	**7**	Tolyl	Ph	Zn^{II}	**4b**[b]	Trace[c]	6	**17**	Tolyl	Ph	2H	**5b**	<10[e,f]
3	**6**	1-Ethylpropyl	*n*-Butyl	Ni^{II}	**4c**[b]	95	8	**17**	Tolyl	Ph	Ni^{II}	**5c**	<10[e,f]
4	**7**	Tolyl	Ph	Ni^{II}	**4d**[b]	95							

[a] Isolated yield. [b] *Reagents and conditions*: R^3–X (5–10 eq.), NaOEt (21% in EtOH), toluene, rt, Ar, 3–18 h. [c] S-linked dimer predominant product. [d] *Reagents and conditions*: (i) S-nucleophile (3 eq.), K_2CO_3 (11 eq.), DMF, 110 °C, 2 h (ii) porphyrin (1 eq.), 110 °C, 2–16 h. [e] *Reagents and conditions*: (i) porphyrin, THF, −78 °C (ii) *n*-BuLi (6 eq.), −78 °C – rt, 2 h. [f] Predominant product was unreacted starting material. [g] For R^3–X **8–13** and nucleophiles **14, 15, 18** see page 11 of ESI.

product **4c** was obtained in almost quantitative yield of 95%. For Zn(II) compound **2a**, the hexyl substituted product **4b** was only obtained in <10% yield, suggesting that the Zn(II) thiolate is not as strong a nucleophile as its Ni(II) counterpart. For the aromatic displacements with aryl halides **9–11**, no substitution product was detected, only the sulfur linked porphyrin dimer. In both cases the dominant product was the disulfide-linked bisporphyrin. Additionally, the use of more activated aromatic halides such as **12** and **13**, did not see an improvement in reactivity, with only S-linked bisporphyrin **3a** being detected. Employing a variety of nucleophiles, the displacement of the thioether was investigated (Table 3, entries 5–7 and ESI† page 11). For N-nucleophiles, only S-linked dimers **3a** and **3g** were detected, indicating that the porphyrin thiolate is a much stronger nucleophile than these. Best results were observed using a soft S-nucleophile **16**. The thiolate generated from **16** displaced the thioether chain on the porphyrin forming **5a** in a yield of 48%, with some formation of dimer **3d**. Using organolithium reagents **17** and **18**, *n*-BuLi gave the most promising results where butylated products **5b** and **5c** were isolated in 10% yield but with concomitant degradation of the porphyrin macrocycle.

In conclusion, a library of thioether appended porphyrins was synthesized in excellent yields. The simple reaction sequence involves S_NAr of bromoporphyrins to yield porphyrin-alkyl thioethers, followed by base deprotection to generate porphyrin thiolate anions. In a final S_NAr these yield sulfur-linked porphyrin dimers in good to excellent yields. Mechanistic insight was gained *via* displacement chemistry, with the isooctyl-3-mercaptopropionate group acting as an excellent leaving group and the thiolate porphyrin as a strong nucleophile and proceeds *via* an addition–elimination mechanism.

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