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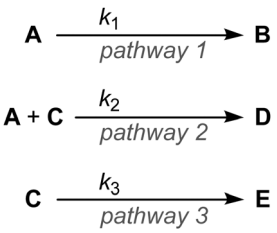
Scavenger templates: a systems chemistry approach to the synthesis of porphyrin-based molecular wires†

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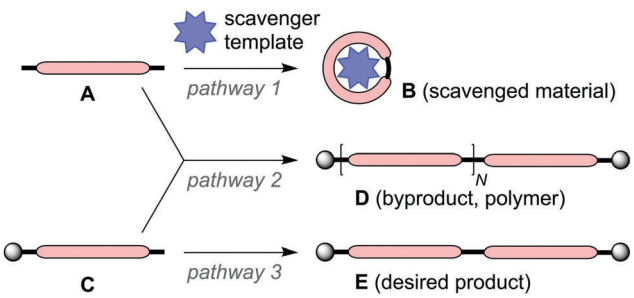
A hexa-pyridyl template can be used as a scavenger to facilitate the synthesis of a linear porphyrin dodecamer from a mixture of linear hexamers with one or two terminal reactive groups. The template suppresses polymer formation by rapidly cyclizing the fully deprotected hexamer, thus up-regulating formation of the linear dodecamer.

Complex networks of chemical reactions determine the behaviour of living cells.[1] Even simple networks of a few reactions can display surprising emergent behaviour such as bistability and temporal oscillations, and the study of these effects is known as 'systems chemistry'.[2–6] A key principle of systems chemistry is that in a network of reactions up-regulation of one reaction pathway can change the flux of material through another reaction pathway, even when, at first sight, the two reactions are unconnected. This idea is easily appreciated by considering the example of three irreversible reactions shown in Scheme 1. Increasing the rate constant k_1 (while keeping k_2 and k_3 constant) increases the fraction of **A** that is converted to **B** because rapid conversion of **A** to **B** reduces the concentration of **A**, suppressing formation of **D**. Increasing k_1 also increases the fraction of **C** that is converted to **E**, since the competing formation of **D** is suppressed. Up-regulating pathway 1 has the effect of up-regulating pathway 3; these two reactions are coupled because both **A** and **C** participate in pathway 2.

The approach to indirect up-regulation summarized in Scheme 1 was applied to template-directed synthesis by Sanders and co-workers in 1992, in a strategy called 'scavenger templating' (Scheme 2).[7] In this system, the desired reaction is dimerization of **C** to give **E** (pathway 3), but the monofunctional compound **C** is difficult to separate from a bifunctional analogue **A**, and in the absence of the template, **A** couples with **C** to form **D** (pathway 2), reducing the yield of **E**. In the presence of the template, **A** undergoes rapid cyclization to give **B** (pathway 1), indirectly



Scheme 1 In this general network of three reactions, up-regulation of pathway 1 causes up-regulation of pathway 3.



Scheme 2 Scavenger templating.

up-regulating the conversion of **C** into **E**, and increasing the yield of the desired product. Here we demonstrate the application of this approach to favor the formation of a butadiyne-linked π-conjugated porphyrin dodecamer $\mathbf{P12_{Si2}}$ (structure shown in Fig. 1).

Conjugated porphyrin oligomers such as $\mathbf{P12_{Si2}}$ have a variety of unusual optical properties,[8,9] and they are described as 'molecular wires' because of their ability to mediate long-range charge transport.[10–12] These mono-disperse oligomers are generally synthesized *via* an iterative process, using partial deprotection of bis-acetylenic building blocks, chromatographic isolation of the mono-deprotected compound and oxidative Glaser coupling.[9,13] The chromatographic separation of the mixture of protected and deprotected alkynes is the limiting step, and in principle this problem can be avoided by using a scavenger template.

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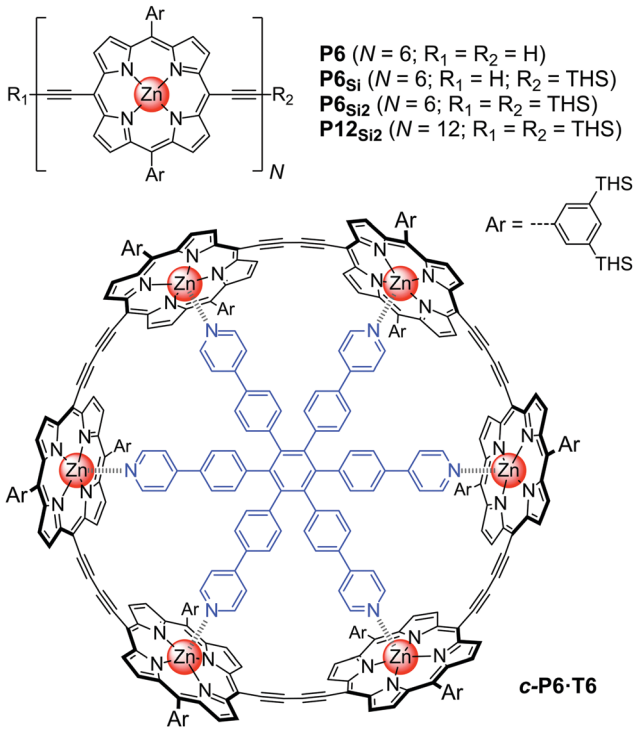
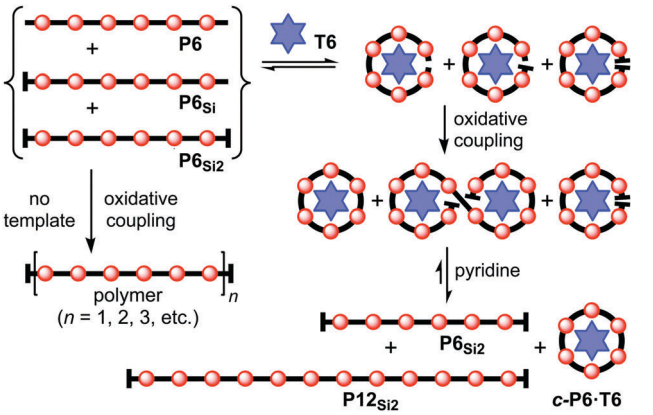


Fig. 1 Structures of the compounds used in this study. THS = tri-(*n*-hexyl)silyl.

Previous work has shown that the hexapyridyl template **T6** effectively directs the cyclization of the linear porphyrin hexamer **P6** to form the cyclic hexamer template complex ***c*-P6·T6** (Fig. 1).[14] Here we show that **T6** can be used as a scavenger template in the synthesis of $\mathbf{P12_{Si2}}$ and we analyze the factors determining the efficiency of this strategy.

This scavenger templating system is summarized in Scheme 3. When an inseparable mixture of the fully-deprotected, mono-protected, and fully-protected porphyrin hexamers (**P6**, $\mathbf{P6_{Si}}$ and $\mathbf{P6_{Si2}}$) is subjected to Glaser coupling, the product is a polydisperse mixture of linear oligomers, together with unreacted $\mathbf{P6_{Si2}}$ (Scheme 3, left). Addition of **T6** to the initial mixture of **P6**, $\mathbf{P6_{Si}}$ and $\mathbf{P6_{Si2}}$ leads to the formation of complexes in which the linear hexamers are forced into cyclic conformations. Under Glaser coupling conditions, the fully deprotected hexamer **P6** is rapidly cyclized to form ***c*-P6·T6.** This leaves mono-deprotected $\mathbf{P6_{Si}}$ to dimerize, yielding the desired dodecamer $\mathbf{P12_{Si2}}$ (Scheme 3, right).

Partial deprotection of hexamer $\mathbf{P6_{Si2}}$ was achieved by treatment with tetra-*n*-butylammonium fluoride (TBAF) while monitoring the reaction by ^{1}H NMR spectroscopy to give a mixture of $\mathbf{P6_{Si2}}:\mathbf{P6_{Si}}:\mathbf{P6}$ in the ratio of approximately 1 : 2 : 1. When the mixture was subjected to palladium-catalyzed Glaser coupling in the absence of template, the expected statistical mixture of oligomers was obtained, as determined by analytical gel permeation chromatography (GPC, Fig. 2a). We use palladium catalysis in these Glaser coupling reactions because these reaction conditions give essentially quantitative coupling at room temperature, even at low concentration.[15] In the presence of the template,



Scheme 3 Use of **T6** as a scavenger template in the synthesis of the porphyrin dodecamer $\mathbf{P12_{Si2}}$. Coupling conditions: benzoquinone, $Pd(PPh_3)_2Cl_2$, CuI, i-Pr_2NH, $CHCl_3$, 20 °C.

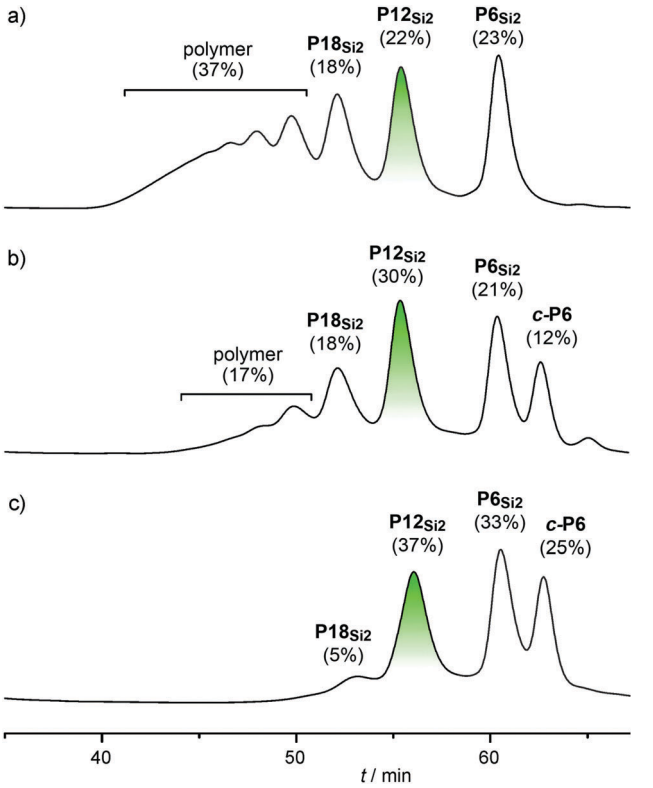


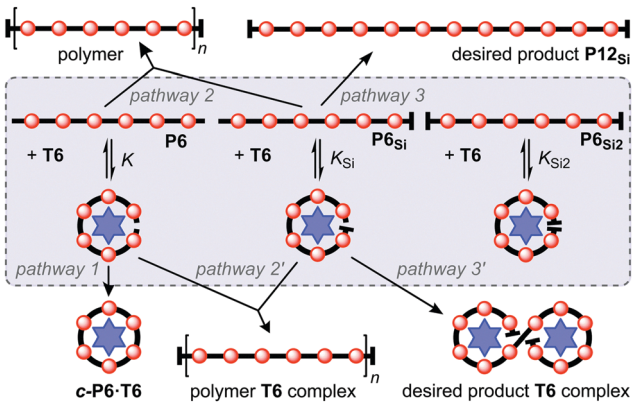
Fig. 2 Gel permeation chromatograms of the coupling reaction under different conditions. (a) Without template, hexamer concentration: 2 mM (b) with template, hexamer concentration: 2 mM (c) with template, hexamer concentration: 0.2 mM. The shaded peaks indicate the desired product $\mathbf{P12_{Si2}}$. Percentages are obtained by integration and are corrected for differences in molar absorption coefficient. Solvent: 1% pyridine in toluene; detector: absorption at 591 nm.

the yield of $\mathbf{P12_{Si2}}$ increases from 22% to 30%, with concomitant formation of cyclic hexamer ***c*-P6·T6** and a strong decrease in the amount of polymeric by-products (Fig. 2b). We used 2 equivalents of **T6**, relative to the total amount of hexamer ($\mathbf{P6_{Si2}}$ + $\mathbf{P6_{Si}}$ + **P6**), so that all the hexamer is bound to the template. During this reaction, there is a competition between

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intramolecular cyclization of **P6·T6**, to form ***c*-P6·T6**, and bimolecular coupling between **P6·T6** and $\mathbf{P6_{Si}}$**·T6**, which leads to the formation of polymer. Thus one would expect the effect of the scavenger template to be greater at lower concentrations, and this was confirmed experimentally: running the reaction at a lower concentration (0.2 mM rather than 2 mM) increases the yield of $\mathbf{P12_{Si2}}$ to 37%, while increasing the yield of ***c*-P6·T6** to 25% and totally suppressing polymer formation (Fig. 2c). Dilution has no detectable effect on the product distribution in the absence of **T6**, however the coupling reaction becomes slow under dilute conditions, necessitating the addition of several portions of catalyst over time.

The network of reversible and irreversible reactions involved in this system is shown in Scheme 4. The main role of the **T6** template is to open a new reaction channel (pathway 1) to scavenge **P6** from the system. The template may also reduce the rates of pathways 2′ and 3′ (compared with 2 and 3), by steric hindrance of coupling of template-bound oligomers. This steric effect may be beneficial, by making pathway 1 compete more effectively with pathway 2′, but it could also become a problem, if it makes pathway 3′ so slow that formation of the desired product does not reach completion. We were interested to test the relative values of the binding constants K, K_{Si} and K_{Si2}, because the bulky terminal THS groups might be expected to hinder template binding in $\mathbf{P6_{Si}}$ and $\mathbf{P6_{Si2}}$. These binding constants are too high to measure by direct titration, but they can be determined by denaturing the complexes with pyridine.[16] UV-vis-NIR titrations of **P6·T6** and $\mathbf{P6_{Si2}}$**·T6** with pyridine gave $\log(K) = 18.49 \pm 0.21$ and $\log(K_{Si2}) = 18.08 \pm 0.27$ (see ESI† for details). Thus K appears to be slightly larger than K_{Si2}, as expected, but the difference is comparable to the experimental uncertainty. We also measured the relative affinities of **P6** and $\mathbf{P6_{Si2}}$ for **T6** by carrying out a ^{1}H NMR competition experiment in which **T6** was titrated into a solution of a 1 : 1 mixture of **P6** and $\mathbf{P6_{Si2}}$ in $CDCl_3$. The mixture of **P6**, $\mathbf{P6_{Si2}}$, **P6·T6** and $\mathbf{P6_{Si2}}$**·T6** is in slow exchange on the NMR timescale and the signals from the terminal β-pyrrole protons of the four species can be resolved; integration of these signals indicates that the ratio of the binding constants is $K/K_{Si2} = 1.95 \pm 0.13$ (see ESI† for details). This experiment confirmed that the deprotected hexamer binds the template more strongly than the protected hexamer, although the effect is surprisingly subtle.



Scheme 4 The reaction pathways involved in scavenger templating.

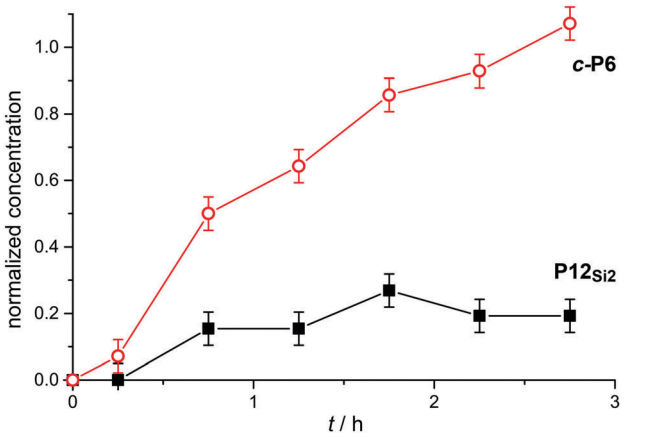


Fig. 3 The rates of formation of ***c*-P6·T6** and $\mathbf{P12_{Si2}}$ from coupling a mixture of **P6**, $\mathbf{P6_{Si}}$ and $\mathbf{P6_{Si2}}$ and **T6** (from GPC analysis) during the first 3 hours of reaction. Normalized concentrations are calculated by dividing the concentration at each time point by the final concentration at completion of the reaction.

We attempted to carry out kinetic experiments to test whether pathway 1 is actually faster than pathways 2′ and 3′ (Scheme 4). It is difficult to follow the kinetics of these reactions because fresh aliquots of catalyst need to be added over time to take the reaction to completion, however we were able to follow the initial stage of the reaction using analytical GPC. The results of this experiment (Fig. 3) confirm that formation of ***c*-P6·T6** is faster than formation of $\mathbf{P12_{Si2}}$, as expected for scavenger templating.

In summary, we have demonstrated that a hexapyridyl ligand **T6** acts as a scavenger template to promote the synthesis of a monodisperse π-conjugated linear porphyrin dodecamer $\mathbf{P12_{Si2}}$. The template prevents polymerization, thereby increasing the yield of the desired product from 22% to 37% (analytical GPC yields). The conventional alternative to using a scavenger template is to separate the mixture of linear hexamers (**P6**, $\mathbf{P6_{Si}}$ and $\mathbf{P6_{Si2}}$) or to carry out the coupling on the mixture of hexamers and to separate all the linear oligomeric products.[17] Recent advances in recycling HPLC and the development of polar protecting groups for alkynes[17–19] facilitate these separation strategies, but the use of a scavenger template is more biomimetic: nature does not create a required molecular structure by synthesizing complex mixtures of products then using the equivalent of HPLC to separate and discard unwanted species. This work illustrates the scope for creating artificial systems that control the outcome of complex networks of reactions by indirectly up-regulating specific pathways.

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Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 R. Albert, *J. Cell Sci.*, 2005, **118**, 4947–4957.
2 J. R. Nitschke, *Nature*, 2009, **462**, 736–738.
3 R. F. Ludlow and S. Otto, *Chem. Soc. Rev.*, 2008, **37**, 101–108.
4 G. Ashkenasy, T. M. Hermans, S. Otto and A. F. Taylor, *Chem. Soc. Rev.*, 2017, **46**, 2543–2554.
5 S. N. Semenov, L. J. Kraft, A. Ainla, M. Zhao, M. Baghbanzadeh, V. E. Campbell, K. Kang, J. M. Fox and G. M. Whitesides, *Nature*, 2016, **537**, 656–660.
6 V. del Amo and D. Philp, *Chem. – Eur. J.*, 2010, **16**, 13304–13318.
7 S. Anderson, H. L. Anderson and J. K. M. Sanders, *Angew. Chem., Int. Ed.*, 1992, **31**, 907–910.
8 M. Drobizhev, Y. Stepanenko, A. Rebane, C. J. Wilson, T. E. O. Screen and H. L. Anderson, *J. Am. Chem. Soc.*, 2006, **128**, 12432–12433.
9 P. Parkinson, D. V. Kondratuk, C. Menelaou, J. Q. Gong, H. L. Anderson and L. M. Herz, *J. Phys. Chem. Lett.*, 2014, **5**, 4356–4361.
10 M. U. Winters, E. Dahlstedt, H. E. Blades, C. J. Wilson, M. J. Frampton, H. L. Anderson and B. Albinsson, *J. Am. Chem. Soc.*, 2007, **129**, 4291–4297.
11 G. Sedghi, V. M. García-Suárez, L. J. Esdaile, H. L. Anderson, C. J. Lambert, S. Martin, D. Bethell, S. J. Higgins, M. Elliott, N. Bennett, J. E. Macdonald and R. J. Nichols, *Nat. Nanotechnol.*, 2011, **6**, 517–523.
12 R. C. Bruce, R. Wang, J. Rawson, M. J. Therien and W. You, *J. Am. Chem. Soc.*, 2016, **138**, 2078–2081.
13 P. N. Taylor, J. Huuskonen, G. Rumbles, R. T. Aplin, E. Williams and H. L. Anderson, *Chem. Commun.*, 1998, 909–910.
14 M. Hoffmann, J. Kärnbratt, M. H. Chang, L. M. Herz, B. Albinsson and H. L. Anderson, *Angew. Chem., Int. Ed.*, 2008, **47**, 4993–4996.
15 V. E. Williams and T. M. Swager, *J. Polym. Sci., Part A: Polym. Chem.*, 2000, **38**, 4669–4676.
16 H. J. Hogben, J. K. Sprafke, M. Hoffmann, M. Pawlicki and H. L. Anderson, *J. Am. Chem. Soc.*, 2011, **133**, 20962–20969.
17 N. Kamonsutthipaijit and H. L. Anderson, *Chem. Sci.*, 2017, **8**, 2729–2740.
18 S. Höger and K. Bonrad, *J. Org. Chem.*, 2000, **65**, 2243–2245.
19 G. Gaefke and S. Höger, *Synthesis*, 2008, 2155–2157.