The roles of templates in the syntheses of porphyrin oligomers

Sally Anderson, Harry L. Anderson and Jeremy K. M. Sanders*
Cambridge Centre for Molecular Recognition, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK

4,4′-Bipyridyl is an efficient template for the formation of cyclic porphyrin dimer from a diethynyl porphyrin monomer; *s*-tri(4-pyridyl)triazine promotes the formation of cyclic trimer from the same starting material to a lesser degree whereas *meso*-tetra(4-pyridyl)porphyrin is not a practical template for the preparation of cyclic porphyrin tetramer from monomer. The factors responsible for these differences in template efficiency were elucidated by analysing the product distributions from coupling linear porphyrin dimer and tetramer in the presence of these and other ligands. The 4,4′-bipyridyl template increases the kinetic effective molarity for the cyclisation of linear dimer by a factor of 20. *meso*-Tetra(4-pyridyl)porphyrin is a good template for the cyclisation of linear porphyrin tetramer; it is also a good template for the preparation of cyclic tetramer from linear dimer and this is the best preparative route to cyclic tetramer. There are three roles for the *meso*-tetra(4-pyridyl)porphyrin template in the latter case: (i) as a negative template it prevents linear dimer cyclising to cyclic dimer, (ii) as a linear template it promotes the formation of linear tetramer from two linear dimers, and (iii) as a cyclisation template it accelerates the closure of linear tetramer to cyclic tetramer. All three roles were detected under optimum conditions but the second role is not significant when TMEDA is present during coupling.

In this fourth paper we try to answer the question 'What features are required for a good cyclisation template?' In the preceding paper[1] we demonstrated the practical use of templates in the syntheses of a range of porphyrin oligomers, but did not discuss the role of the template in any mechanistic detail. The formation of cyclic oligomers from monomer units, and the demonstration that this coupling can be directed towards a particular size of oligomer by use of a template, implies the formation of linear intermediates, and raises questions about the binding of these putative intermediates to the templates. The binding properties of some of these cyclic and linear oligomers were discussed in the second paper[2] in this series and here we combine the two themes of templating and binding to elucidate the features required for a good template.

The earliest work described here has been reported in preliminary form elsewhere[3,4] and led (a) to the syntheses in the preceding paper and (b) to our classification of templates as *positive* or *negative*. However, most of the experiments reported here are new; they were designed to estimate relative rates of inter- and intra-molecular coupling for linear dimer and tetramer, and to explore how many of the steps in the one-pot synthesis of cyclic tetramer from linear dimer are subject to template control.

The efficiency of cyclisation and therefore templating, is easily expressed in terms of a kinetic effective molarity, EM_{kin};[5] this is closely related to the thermodynamic effective molarity discussed in paper II.[2] EM_{kin} is defined as the concentration at which the rate of intramolecular coupling equals that of intermolecular coupling; it is the effective molarity of one end of the linear oligomer experienced by the other during the reaction. It can be calculated from the product distribution, as shown in Fig. 1, where $[SM]_0$ is the initial concentration of starting material, which can be approximated as the average concentration of terminal acetylene groups [C≡CH] since $2[SM]_0$ is the initial [C≡CH] and k is a second-order rate constant, then

$$\frac{X\%}{Y\%} = \frac{\text{Rate of intramolecular reaction}}{\text{Rate of intermolecular reaction}} = \frac{kEM_{kin}}{k[SM]_0} = \frac{EM_{kin}}{[SM]_0}$$

and

$$EM_{kin} = \frac{X[SM]_0}{Y}$$

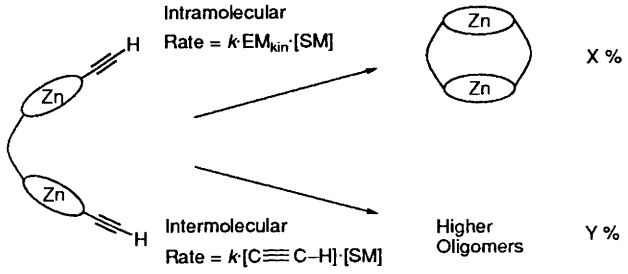


Fig. 1 Definition and calculation of EM_{kin} for linear dimer **Zn_2-l-Diml b** cyclisations

Results

Templated cyclisations of monomers

Coupling of **Zn-Monl b** under the CuCl-TMEDA conditions outlined in the preceding article[1] was always complete within 15 min; after a further 15 min the reaction was quenched with water, acidified to remove the zinc and the template and then washed with water. These crude acid-washed samples were analysed by ^{1}H NMR. The *meso* region in the ^{1}H NMR spectrum was found to be most eloquent (Fig. 2) since the *meso*-resonances of the cyclic oligomers are shifted to progressively lower chemical shift, relative to monomer, by the trans-cavity porphyrin ring-current.[6] The *meso* resonances for cyclic dimer, trimer and higher oligomers can be resolved and integrated to give the yields shown in Table 1. From this mixture cyclic trimer and dimer were isolated. Cyclic dimer was found to bind with high affinity to **BiPy** and cyclic trimer to **Py_3T**. When coupling of monomer was carried out in the presence of a six-fold excess of **BiPy** the yield of cyclic dimer was increased from 23 to 72%, whilst the yield of cyclic trimer was reduced to 4 from 34%. As would be expected, the yield of cyclic trimer was increased in the presence of **Py_3T**, the yield of trimer being increased to 55% and the yield of dimer being reduced to 6%.

The relationship between binding properties and template

* E-mail: jkms@cus.cam.ac.uk.

Table 1 Templating effects of various ligands on the TMEDA·CuCl mediated cyclisation of **ZnDim1b**. Yields are ± 5%

Template	Py	BiPy	Py_2Et	Py_2Pr	Py_2Py	Py_3T
Yield (%) of H_4-c-Dim1b	23	72	27	7	8	6
Yield (%) of H_6-c-Tri1b	34	4	34	43	44	52

Table 2 Yields for cyclic dimer H_4-c-Dim1b and other higher oligomers from the templated cyclisations of linear dimer Zn_2-l-Dim1b (2×10^{-4} mol dm^{-3}) in the presence of various amine ligands; yields are ± 5% and EM_{kin} is ± 15%

Template	% Cyclic dimer	% Higher cyclic oligomers	EM_{kin} (mmol dm^{-3}) for cyclisation	Rate factor[a]
None	21	79	0.05	(1)
BiPy	83	17	1.0	20
Py_2Py	12	88	0.03	0.6
H_2-Py_4P	14	86	0.03	0.6

[a] Rate of the templated intramolecular cyclisation of linear dimer to cyclic dimer compared with the rate of intramolecular cyclisation of linear dimer in the untemplated reaction.

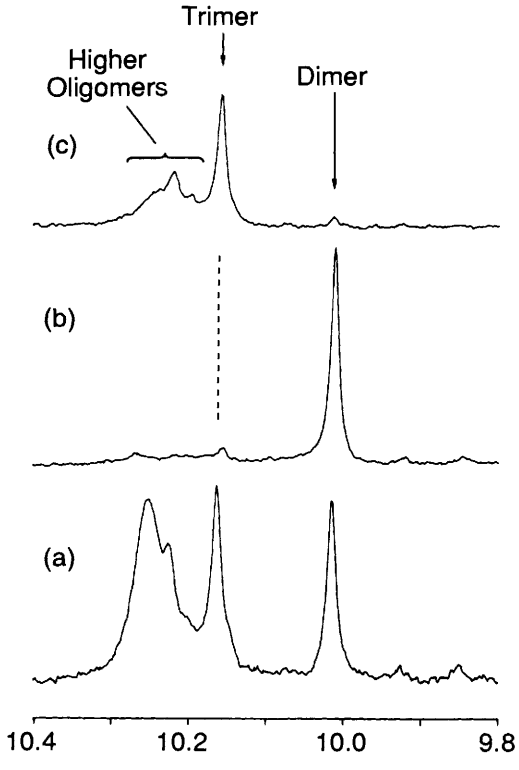


Fig. 2 *meso*-Region of ^{1}H NMR spectra of crude reaction mixtures from TMEDA Glaser–Hay coupling reactions of **ZnMon1b** using (*a*) no template, (*b*) **Bipy** and (*c*) Py_3T

behaviour was explored by determining the template effects for **Py**, **BiPy**, Py_2Et, Py_2Pr, Py_2Py and Py_3T under identical conditions (0.5 mmol dm^{-3} monomer, 3.0 mmol dm^{-3} template, 30 mmol dm^{-3} CuCl·TMEDA, dry dichloromethane, dry air, 25 °C, 1 h, stir). The origins of the template effect can be understood by considering the templated yields for the various ligands given in Table 1.

Py_3T enhances formation of Zn_3-c-Tri1b and inhibits formation of Zn_2-c-Dim1b whereas **BiPy** has the opposite effect, templating formation of Zn_2-c-Dim1b. The first step in either of these reactions must be the linking of two monomer units to yield a linear dimer (Fig. 3). Then the dimer can cyclise to yield cyclic dimer, react with a further monomer unit to yield linear trimer or react with a further linear dimer to give linear tetramer. It seems likely that the criterion for an efficient cyclic dimer-producing template is simply that the template should bind to the linear intermediate, hold it in the right conformation to accelerate intramolecular coupling and so increase the probability that linear dimer cyclises.

For an efficient trimer template the criteria are more complicated: the template must both bind to linear dimer in such a way as to reduce the dimer cyclisation probability and also bind to linear trimer so as to increase the probability of trimer cyclisation. Py_3T is the best template for the synthesis of trimer but achieves this mainly by preventing dimer cyclisation. Bifunctional templates are almost as effective as the trifunctional ligand Py_3T in directing trimer formation, implying that something more subtle is occurring than merely attaching three monomers to a central template core and then coupling the units together.† It is also unlikely that this would occur since an excess of the template is added to the reaction mixture favouring a 1:1 complex between template and monomer. Trimer cyclisation is apparently so well structure-directed that our current templates do little to improve on linear trimer's natural tendency to cyclise.

Templated cyclisations of linear dimer

In order to understand the role of **BiPy** in the templated conversion of monomer **Zn-Mon1b** into cyclic dimer Zn_2-c-Dim1b the linear dimer Zn_2-l-Dim1b intermediate was synthesised[1,4] and its cyclisation behaviour in the presence of the three templates **BiPy**, Py_2Py and H_2-Py_4P investigated. A reaction was also carried out in the absence of a template as a control. **BiPy** increased the yield of cyclic dimer from 21 to 83% with a corresponding drop in the yield of larger oligomers (Table 2). So, the *ratio* of cyclic dimer : other products increased 20-fold, corresponding to a 20-fold rate acceleration and an EM_{kin} of 1 mmol dm^{-3}. The untemplated cyclisation has an effective molarity because it is an intramolecular reaction. The added template can then either enhance cyclisation leading to an increase in EM_{kin} or promote intermolecular reaction, in which case EM_{kin} is reduced compared to the untemplated reaction; in other words the effective molarities shown in Table 2 should all be considered relative to the untemplated reaction. In a linear templated reaction the untemplated reaction is bimolecular and therefore cannot have an EM_{kin} and the template induced effective molarity is an absolute value. This increase in effective molarity can be attributed to the **BiPy** ligand's influence on the conformation of the linear dimer and **BiPy**'s ability to bind preferentially to the transition state for the intramolecular reaction. When bound to linear dimer **BiPy** forces the reactive acetylene ends of the dimer to be brought into close proximity, and intramolecular coupling to the cyclic dimer occurs more quickly than intermolecular coupling. The measured binding constants[2] show that the cyclisation reaction is driven by a progressive increase in binding energy as the

† This obvious pre-assembly mechanism of templating is also ruled out by simple calculations: with millimolar concentrations of porphyrin, and affinities of (at best) 10^3 under the reaction conditions, one would not expect significant concentrations of multiply bound complexes such as $(Zn\text{-}Mon1b)_2BiPy$ or $(Zn\text{-}Mon1b)_3{\cdot}Py_3T$. Pre-assembly does become a viable route when binding affinities are much greater.[7]

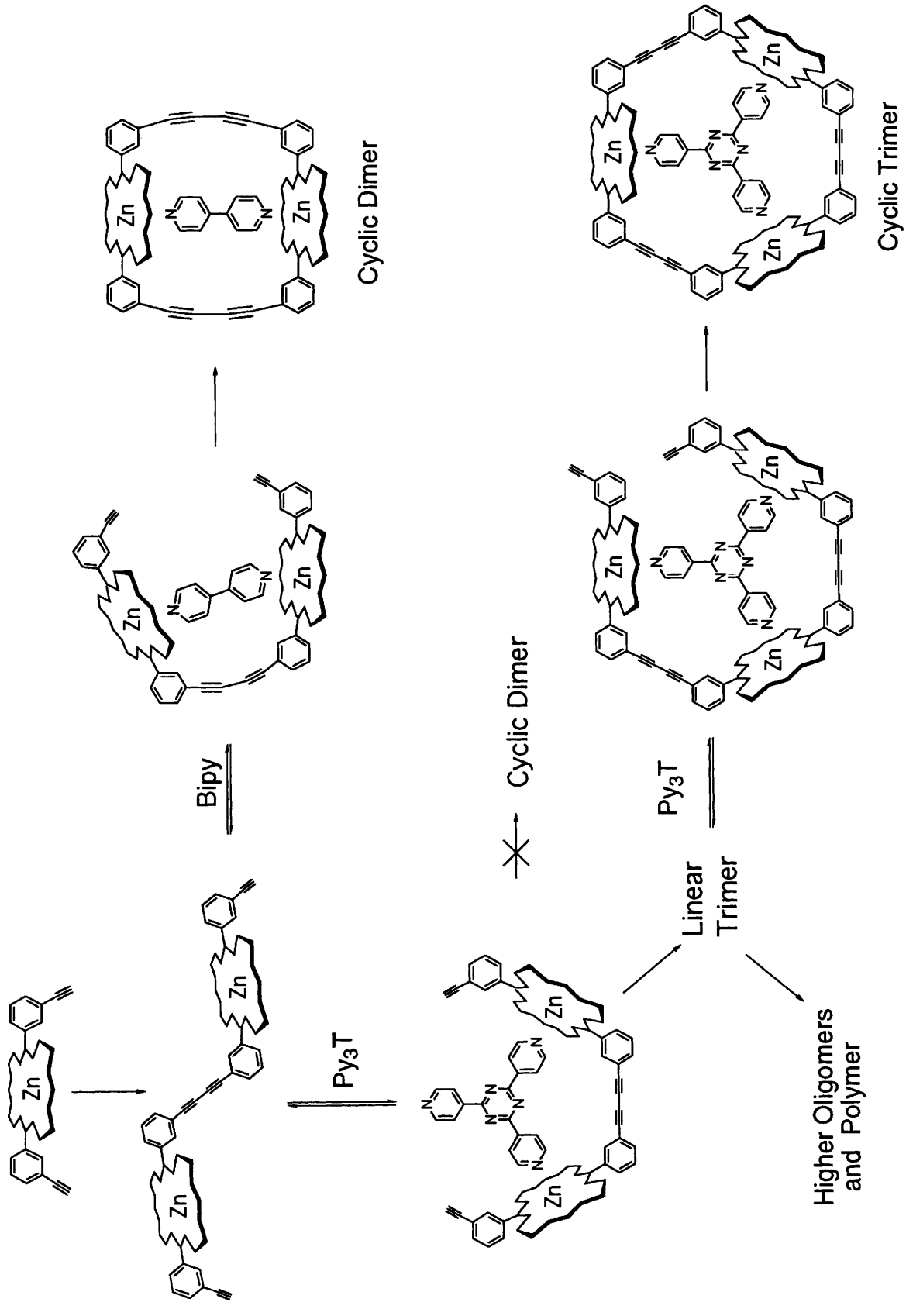


Fig. 3 Proposed mechanism for the template assisted synthesis of cyclic dimer and trimer

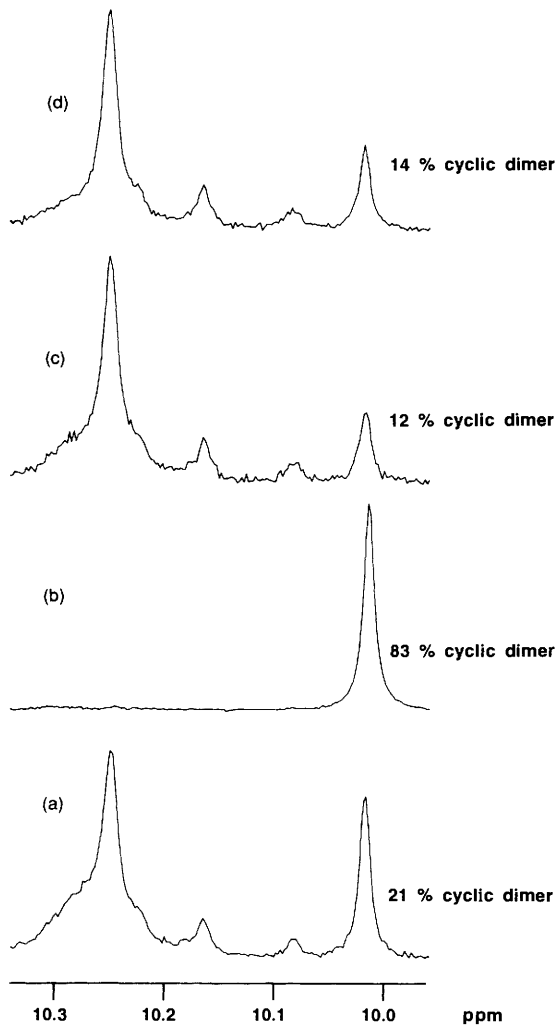


Fig. 4 ^{1}H NMR analysis of the *meso*-regions of reaction mixtures from TMEDA·CuCl Glaser–Hay coupling of **Zn_2-l-Diml b** using (*a*) no template, (*b*) **Bipy**, (*c*) **Py_2Py** and (*d*) **H_2-Py_4P**

Table 3 ^{1}H NMR yields (± 5%) for the cyclisation of linear dimer in the presence of **H_2-Py_4P** with 2,2′-**BiPy** as the CuCl chelator. [**Zn_2-l-Diml b**] = 1 mmol dm^{-3}. EM_{kin} ± 15%

Expt	Template **H_2-Py_4P**	% Cyclic dimer	EM_{kin} (mmol dm^{-3}) Linear dimer cyclisation	% Cyclic tetramer	% Higher oligomers
a	None	25	0.3	10	65
b	0.5 equiv.	9	0.1	78	13
c	6 equiv.	1.5	0.015	61	37

reaction proceeds from linear dimer ($K = 6 \times 10^6$ mol^{-1} dm^3) to cyclic dimer ($K = 1 \times 10^9$ mol^{-1} dm^3).

What happens when linear porphyrin dimer is coupled in the presence of **Py_2Py** or **H_2-Py_4P**? In these cases the yields of cyclic dimer are reduced to approximately two thirds of the untemplated values, corresponding to a reduction in EM_{kin} by over a factor of 2 and hence a reduction in the rate of cyclisation to 60% of its original value. When linear dimer is bound to either of these ligands, it adopts a conformation in which the reactive ends are held apart.[2] These templates therefore act as modest *negative* cyclisation templates for the formation of cyclic dimer from linear dimer. The results support the conformations of the template complexes deduced from binding experiments in pure CH_2Cl_2.

Surprisingly, even in the presence of **H_2-Py_4P**, 14% of the linear dimer underwent intramolecular cyclisation, indicating that under these Glaser–Hay coupling conditions not all the linear dimer is bound all the time. If the binding constant under the reaction conditions was the same as that in pure CH_2Cl_2 (3×10^6 mol dm^{-3}) then only 1% would be unbound. Hence, not surprisingly, the strength of pyridyl-porphyrin binding in 30 mmol dm^{-3} TMEDA·CuCl is lower than in CH_2Cl_2. The interesting question now arises, could the templating effect be enhanced by the use of a chelating ligand for CuCl with a lower binding affinity for zinc porphyrins?

To maximise the template effects template-porphyrin binding during coupling should match that in pure CH_2Cl_2. Hence the chelating ligand for CuCl must not show appreciable binding to zinc porphyrins. 2,2′-Bipyridyl (2,2′-**BiPy**) binds less strongly than TMEDA to zinc porphyrins and facilitates coupling, so this was the chosen ligand. With CuCl·2,2′-**BiPy** Glaser–Hay coupling was achieved with better templating efficiency than with CuCl·TMEDA, but the coupling reaction was slower. Preparatively, this is a drawback because traces of starting material sometimes contaminated the product and because long reaction time can lead to appreciable copper metallation of the porphyrins, but it does facilitate following the kinetics of templated reactions directly. The slow reaction rate can be attributed to low solubility of the copper(I) 2,2′-**BiPy** complex and to the lower pK_b of this ligand, and thus the lack of a suitable base to assist in the formation of the copper acetylide intermediate. The reaction can be made faster by the addition of DBU as a base,[8] but this impairs the template effect. We did not explore further chelating ligands, although a set of conditions which would lead to both efficient coupling and to maximum template effects could probably be found. This illustrates the advantage of looking at template effects in coupling reactions which do not require reagents; the Diels–Alder reaction that is greatly accelerated by cyclic porphyrin trimer acting as a linear template is an example.[9]

The reactions summarised in Table 3 were carried out using 2,2′-**BiPy** as the chelator for copper to quantify the improvement observed in templating; experiment (a) was the control with no template, (b) had just enough **H_2-Py_4P** to bind all the linear dimer **Zn_2-l-Diml b** in a 1 : 2 complex and (c) had a six-fold excess of **H_2-Py_4P**. The concentration of linear porphyrin dimer was 1 mmol dm^{-3}, that is five times greater than that employed for the TMEDA·CuCl reaction but the same as that used in the competition coupling experiment described later. Under these conditions coupling was generally complete within 4 h. The higher the concentration of **H_2-Py_4P** the greater the negative templating effect and the smaller the proportion of cyclic dimer in the reaction mixture. These results confirm that TMEDA·CuCl weakens binding between linear porphyrin oligomers and the templates. The yield of cyclic dimer **Zn_2-c-Diml b** in the presence of a six-fold excess of **H_2-Py_4P** is reduced to approximately 1.5% of the total. From these results we suggest that if binding between template and porphyrin were unimpaired by the copper chelating ligand, then the yield of cyclic dimer after coupling would be insignificant.

Interestingly, the untemplated process with the 2,2′-**BiPy**·CuCl reagent showed a much higher effective molarity for cyclisation compared with the TMEDA coupling reaction even in the absence of a template. This can be attributed to TMEDA binding to linear dimer causing steric hindrance and slowing down the intramolecular cyclisation reaction. Presumably 2,2′-**BiPy** cannot bind as strongly and thus linear dimer cyclises more easily under these conditions.

Templated cyclisations of linear tetramer

Coupling of linear tetramer **Zn_4-l-Tet l b** under our standard

Table 4 Yields of cyclic tetramer **Zn_4-c-Tet1b** and higher cyclic oligomers from the templated cyclisations of linear tetramer **Zn_4-l-Tet1b** (1×10^{-4} mol dm^{-3}); yields ± 5%; EM_{kin} ± 15%

Template	% Cyclic tetramer	% Higher cyclic oligomers	EM_{kin} (mmol dm^{-3}) for cyclisation	Rate factor[a]
None	60	40	0.15	(1)
H_2-Py_4P	90	10	0.9	6
BiPy	75	25	0.3	2

[a] Rate enhancement for the intramolecular cyclisation of linear tetramer in the presence of various templates.

Table 5 ^{1}H NMR yields (± 5%) for the cyclisation of linear dimer **Zn_2-l-Dim1b** (2×10^{-4} mol dm^{-3}) in the presence or absence of **H_2-Py_4P** template

Template	% Yield of cyclic tetramer	% Yield of cyclic dimer	% Yield of other higher oligomers
H_2-Py_4P	77	14	9[a]
None	39	21	40[a]

[a] This final fraction was found by ES MS analysis to contain cyclic hexamer and octamer.

Glaser–Hay conditions (TMEDA·CuCl) in the presence of a six-fold excess of **H_2-Py_4P** yielded 90% cyclic tetramer **Zn_4-c-Tet1b** as measured by ^{1}H NMR and HPLC; 60% yield of cyclic tetramer was obtained even in the absence of template. The increased yield of cyclic tetramer in the presence of **H_2-Py_4P** corresponds to a six-fold increase in EM_{kin} (Table 4).

These results support the conclusions deduced about the structure of the 1 : 1 complex between cyclic tetramer and **H_2-Py_4P** from binding studies described in the second paper in this series:[2] when linear tetramer binds to **H_2-Py_4P** the reactive acetylenic groups are brought into close proximity. However, during coupling it may not be the case that the 1 : 1 complex is the only species present. The relative stabilities of the 1 : 1 and the 1 : 2 complexes between linear tetramer (1×10^{-4} mol dm^{-3}) and **H_2-Py_4P** (6×10^{-4} mol dm^{-3}) can be approximated from the experimentally measured values of the binding constants for linear tetramer **Zn_4-l-Tet1b(SiMe$_3$)$_2$** plus **H_2-Py_4P**, and linear dimer **Zn_2-l-Dim1b(SiMe$_3$)$_2$** plus **H_2-Py_4P**. The stability of the 1 : 1 complex may not influence the observed yields if exchange between the 2 : 1 and 1 : 1 complex is very rapid, and if the cyclisation is substantially accelerated in the 1 : 1 complex then the template will be effective even if the 2 : 1 complex predominates. We have not investigated the effect of varying **H_2-Py_4P** concentration on this reaction, but below we discuss the changes in product distribution with different concentrations of template for the **H_2-Py_4P** templated coupling of linear dimer to cyclic tetramer.

When **BiPy** was used as a template in the Glaser–Hay cyclisation of linear tetramer **Zn_4-l-Tet1b**, the yield of cyclic tetramer **Zn_4-c-Tet1b** was 75%, as compared to 60% for the untemplated reaction. This modest improvement in yield corresponds to an increase in effective molarity for cyclisation by a factor of about 2.

H_2-Py_4P Templated conversion of linear dimer into cyclic tetramer

On further analysis of the **H_2-Py_4P** templated linear dimer **Zn_2-l-Dim1b** cyclisation (Table 5) we found that the major product was cyclic tetramer **Zn_4-c-Tet1b**. When cyclisation of linear dimer is carried out in the presence of an excess of **H_2-Py_4P** there are essentially two products: cyclic dimer **Zn_2-c-Dim1b** and cyclic tetramer **Zn_4-c-Tet1b**. Cyclic tetramer is produced in 77% yield in the **H_2-Py_4P** templated reaction; this is the most efficient route for preparing large quantities of cyclic tetramer. Isolated recrystallised yields for cyclic tetramer in the range of 54% are achieved.

When 2,2′-**BiPy** was used to chelate to the copper a greater insight into the role of the template was obtained (Table 3). The yield was highest and the reaction cleanest when only half an equivalent of **H_2-Py_4P** was present during the reaction, suggesting that in the presence of an excess of **H_2-Py_4P** some aggregates other than the simple 1 : 1 complexes between linear dimer and **H_2-Py_4P** and that between linear tetramer and **H_2-Py_4P** are formed. The reaction with 6 equivalents of **H_2-Py_4P** was slower than that with half an equivalent of **H_2-Py_4P**, because intermolecular coupling between **H_2-Py_4P** bound dimers is probably slower. The TMEDA·CuCl coupling reaction is still the synthetically most viable due to the shorter reaction time required.

The template has two obvious roles in this reaction: firstly as a *negative* cyclisation template, preventing the formation of cyclic dimer, and secondly as a positive cyclisation template promoting the formation of cyclic tetramer from linear tetramer. These two template effects are easy to quantify from the ratio of products in the final reaction mixture (see Tables 3 and 5).

A possible mechanism for the **H_2-Py_4P** templated conversion of linear dimer into cyclic tetramer is outlined in Fig. 5. Here we suggest three roles for the template **H_2-Py_4P**, two of which have just been discussed. The third involves the coupling of two linear dimer units to yield linear tetramer. This last effect is unlikely to be significant in the presence of a large excess of **H_2-Py_4P**, since most of the linear dimer will be bound to **H_2-Py_4P** as the 1 : 1 complex and not the 2 : 1 complex required for potential linear templating.

Linear templating is the acceleration of a bimolecular reaction between two bound substrates and is observed in many natural enzyme systems. To test whether there is a linear templating effect only half an equivalent of **H_2-Py_4P** was used as template, so that the predominant species during coupling would be the 1 : 2 complex, where every **H_2-Py_4P** is bound to two linear dimers. The reaction under the TMEDA·CuCl conditions showed little or no templating, presumably because binding between **H_2-Py_4P** and linear dimer is too weak under these conditions.

Is H_2-Py_4P a linear template for coupling two linear dimers?

Most of our template effects have been investigated by product distribution analysis, but this approach cannot be used to probe the extent of linear templating in the reaction shown in Fig. 5 because a linear tetramer **Zn_4-l-Tet1b** intermediate is an inevitable first step of both the templated and untemplated reactions. There are two ways in which the extent of linear templating could be analysed: firstly we could follow the reaction so that the concentration of starting materials, intermediates and products would be evident at given time intervals and therefore the rate of linear tetramer formation could be calculated. Secondly, we could couple a mixture of free base and metallated linear dimers which are blocked at one end: in this experiment coupling is necessarily terminated at the linear tetramer stage, and the question becomes whether the distribution of metallated and free base sites in the coupling products is influenced by the presence of **H_2-Py_4P**. We pursued both approaches; initially we discuss the second, outlined schematically in Fig. 6.

Consider the reaction between black and white boxes: black can react with black or with white and white can react with white or with black. After a statistical reaction the product mixture should contain white-white, white-black and black-black molecules in the ratio 1 : 2 : 1. If a template is added which can bind two white boxes in close proximity and in the correct

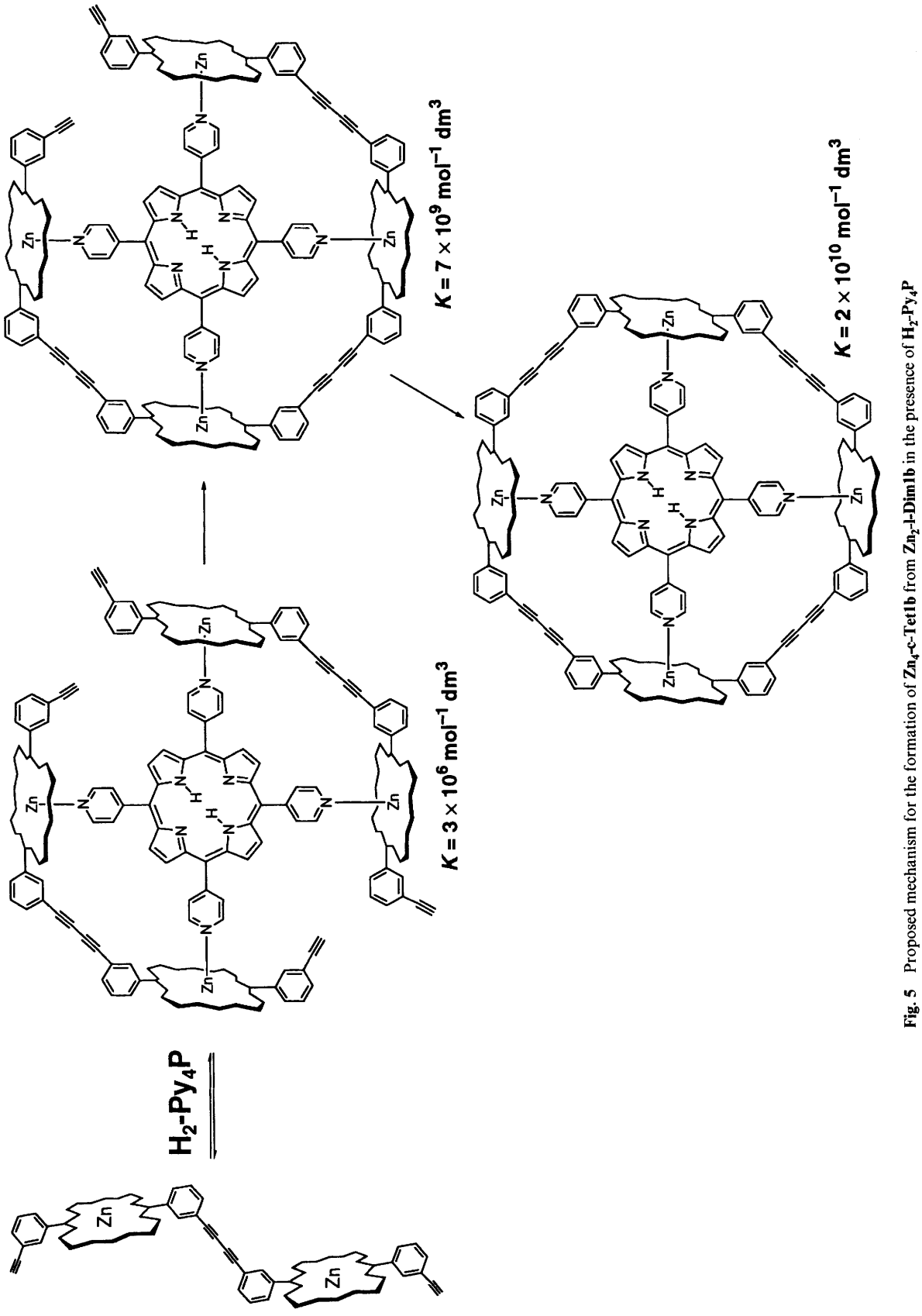


Fig. 5 Proposed mechanism for the formation of Zn_4-c-**Tet1b** from Zn_2-l-**Dim1b** in the presence of H_2-Py_4P

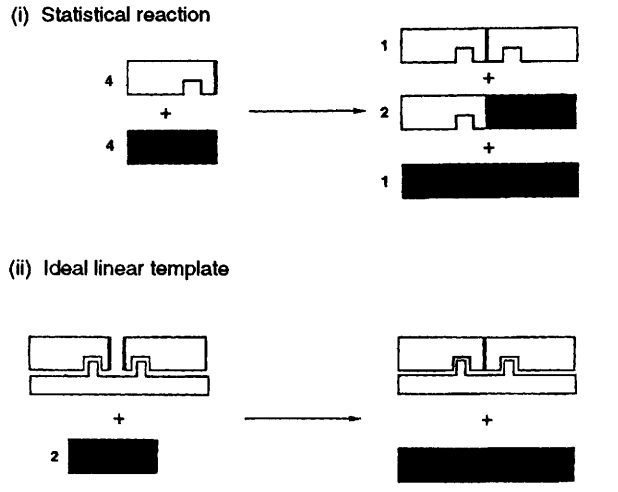


Fig. 6 (i) A statistical reaction; (ii) coupling in the presence of an ideal linear template

orientation for the formation of the white-white species, then the white boxes will react more quickly than the black ones and they will preferentially react to form the white-white product. The black ones are then left with no other choice than to form the black-black product. After coupling in the presence of an ideal linear template the product mixture would only contain black-black and white-white boxes in a 1 : 1 ratio. The following experiment was carried out to see whether coupling of linear dimers occurred more rapidly in the presence of **H_2-Py_4P**.

Does H_2-Py_4P promote the formation of fully metallated linear tetramer from a mixture of metallated and unmetallated linear dimers?

Linear dimers **H_4-** and **Zn_2-l-Dim1b,c(MHB)** are only reactive at one end. These were synthesised from linear dimer **Zn_2-l-Dim1b($SiMe_3$)$_2$**. Half of the TMS protecting groups were removed using 1 equivalent of tetrabutylammonium fluoride (TBAF) in chloroform, and the mixture of linear dimers was then coupled with an excess of 2-methylbut-4-yn-2-ol.

The required linear dimer **Zn_2-l-Dim1b(MHB)($SiMe_3$)** was isolated by flash column chromatography and the silicon protecting group was removed with TBAF. The linear dimer which would not bind to the template was prepared by converting **Zn_2-l-Dim1b(MHB)** into the free-base porphyrin **H_4-l-Dim1b(MHB)**. Experimentally it proved easiest to use a double-labelling strategy, the free base porphyrins carrying methyl ester side chains **H_4-l-Dim1b(MHB)** and the zinc porphyrins carrying isodecyl esters **Zn_2-l-Dim1c(MHB)**. The three coupling products are the linear porphyrin tetramers shown in Fig. 7.

A 2:2:1 mixture of **Zn_2-l-Dim1c(MHB) (A)**, **H_4-l-Dim1b-(MHB) (B)** and **H_2-Py_4P** was made up in CH_2Cl_2. When Glaser–Hay coupling was carried out using 30 mmol dm^{-3} TMEDA·CuCl, no significant template effect was observed as expected. The product distribution in the reaction mixtures was not statistical, even in the absence of **H_2-Py_4P** and the low yield (38%, a statistical reaction would yield 50%) of the mixed linear tetramer implies that one of the porphyrin dimers reacts more quickly under Glaser–Hay conditions than the other.

When 2,2′-**BiPy** was used as a chelating agent for the CuCl the reaction was much slower and even with a five-fold increase in concentration the reaction took about 4 h to reach completion. During this time slight copper metallation of the free base porphyrins was observed. The reactions were worked up in the usual way (washed with water, acidified and again washed with water). Acidification protonates the porphyrins, but only in the case of the zinc porphyrin is the metal lost. Copper binds to porphyrins much more strongly than zinc. HPLC of these mixtures showed three main peaks (Fig. 7). The slowest running component to the mixture which was derived from the coupling of **H_4-l-Dim1b(MHB)** appeared to consist of several closely running species; this was attributed to partial copper metallation of free base porphyrins during Glaser–Hay coupling. The sharpness of the first two peaks indicates that little or no copper metallation has taken place. Less copper metallation would be expected in these species since they are either wholly or partly protected with zinc.‡

In this reaction **H_2-Py_4P** acts as a linear template. It is clear that the template **H_2-Py_4P** makes a difference to the product distribution increasing the amount of **A_2** and **B_2** relative to **AB**, but it is not immediately clear what the effective molarity for the templated process is. Without an effective molarity for coupling of the mono-protected linear dimers we cannot quantify the effectiveness of **H_2-Py_4P** as a linear template.

Calculation of the effective molarity for linear templating from the product distributions

In order to calculate the effective molarity for the **H_2-Py_4P** templated reaction we need to know the proportion of the zinc metallated starting material **A** reacting intermolecularly and the proportion undergoing intramolecular reaction. The untemplated reaction of the zinc dimer, **A**, and the free-base dimer, **B**, does not lead to a statistical product distribution: **A_2** (1.0) + **AB** (1.2) + **B_2** (1.0) (Table 6). This indicates that either **A** or **B** reacts more quickly and TLC evidence suggests that the zinc porphyrins react faster; there is published evidence that electron-withdrawing groups enhance Glaser–Hay coupling reactivity.[10] The product distribution in the templated reaction is significantly different, the proportions being **A_2** (1.0):**AB** (0.7): **B_2** (1.0). Product **A_2** in the templated reaction can be divided into two parts: that derived from intermolecular reaction in free solution and that from intramolecular reaction when two **A** species are bound to the template. We assume that the rate of formation of **AB** is the same in the templated and untemplated reaction even though when **H_2-Py_4P** is present **B** may be reacting with bound **A** rather than **A** in free solution. When comparing the control with the templated process we must remember that some of **A** is reacting intramolecularly in the templated reaction whilst **B** can never undergo intramolecular reaction under the same conditions. This means that we need to calculate the initial ratio of **A**:**B** for the templated reaction which will subsequently undergo intermolecular reaction. Consider the three rate equations for the formation of **A_2**, **AB** and **B_2** (Table 7). k_{AB} Can be approximated to $\sqrt{k_A k_B}$ since the rate at which **A** and **B** react together must be proportional to the reactivity of **A** and the reactivity of **B**.§

The approach we have used has involved two sets of computer simulations. Firstly, relative values of k_A and k_B for the untemplated reaction were calculated by varying k_A and k_B until we obtained a product distribution which was the same as that observed experimentally for the untemplated process. This indicated that k_A is more than 10 times bigger than k_B. We then used these values to determine the proportions of **A_2**, **AB** and **B_2** expected for various initial ratios of **A**:**B**. We used trial and error to find the ratio of **A**:**B** which gave the same ratio for

‡ The UV detector of the HPLC analyser was set to 254 nm where there is little difference between the extinction coefficients of the copper and free base products, so slight copper metallation should not significantly alter the integrals of the three peaks. HPLC analysis was repeated on fully copper metallated product mixtures and gave the same results.

§ In effect we assume the activation energy $\Delta G^{\ddagger}_{AB}$ to be *ca.* 0.5 ($\Delta G^{\ddagger}_{A}$ + $\Delta G^{\ddagger}_{B}$).

AB:$\mathbf{B_2}$ as we observed experimentally for the templated reaction, that is 0.7:1.

We found that for a 1:1 mixture of **A**:**B** the ratio k_B/k_A must be 0.083 in order to obtain the untemplated product distribution observed experimentally. We also found that for this ratio of k_B/k_A then a ratio of 0.7:1 (**AB**:$\mathbf{B_2}$) is observed when the initial starting material ratio **A**:**B** is 0.47:1, that is 32% **A** and 68% **B**. This implies that half of **A** reacts intermolecularly and half intramolecularly on the template. Since the reaction was carried out at an initial **A** concentration of 1 mmol dm^{-3} then the average concentration of **A** alkyne ends throughout the templated reaction will be 0.5 mmol dm^{-3} and so the effective molarity for the templated coupling is 0.5 mmol dm^{-3}. This is only a factor of 2 smaller than the estimate of the effective molarity for the **BiPy** templated cyclisation of linear dimer with TMEDA. Hence, a rather small difference in yields in this type of competition reaction may indicate a significant template effect.

Table 6 Results from the competition experiments between linear dimers, one of which can bind to the template and one which cannot

	Product distribution, templated[c]			Product distribution, untemplated[c]		
Chelator	$\mathbf{A_2}$	**AB**	$\mathbf{B_2}$	$\mathbf{A_2}$	**AB**	$\mathbf{B_2}$
TMEDA	1	0.5	1	1	0.5	1
2,2′-**BiPy**[a]	1	0.7	1	1	1.2	1
2,2′-**BiPy**[b]	1	0.55	1	1	1.1	1

[a] [Porphyrin dimer] = 2 mmol dm^{-3}. [b] [Porphyrin dimer] = 0.2 mmol dm^{-3}. [c] Proportions of $\mathbf{A_2}$, **AB** and $\mathbf{B_2}$ were calculated from HPLC analysis of crude reaction mixtures.

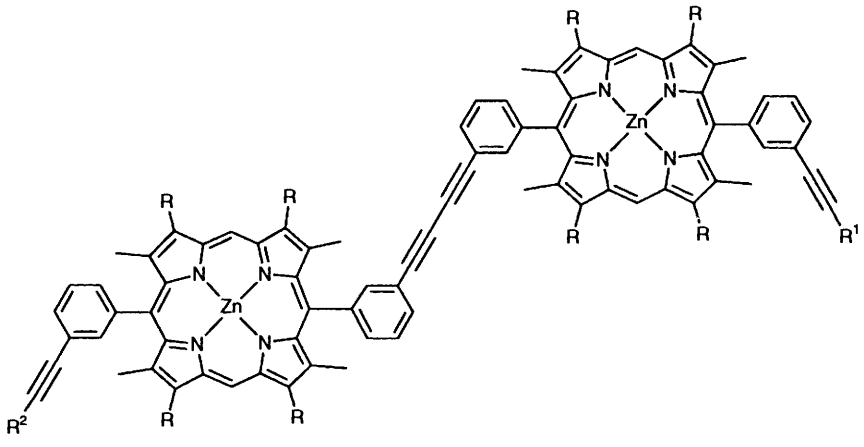
Any observed effect in the model system will be twice as large in the real system. In the model system where one end of the linear dimer has been blocked there are two possible binding orientations, one will be active for linear templating, the free acetylenes will be in close proximity and the blocking groups together and the other inactive with each blocking group being next to an acetylene. In the real system there is only one possible complex between linear dimer and $\mathbf{H_2}$-$\mathbf{Py_4P}$ under these conditions. When the templating effect is viewed in this light then it appears to be as significant as that observed for the **BiPy** templated closure of linear dimer to cyclic dimer.

Does $\mathbf{H_2}$-$\mathbf{Py_4P}$ exert a linear templating effect?: following the kinetics directly

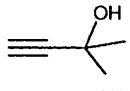
In this section we present experiments designed to investigate the $\mathbf{H_2}$-$\mathbf{Py_4P}$ templated coupling of linear dimer $\mathbf{Zn_2}$-**l-Dim1b** using 2,2′-**BiPy** Glaser–Hay coupling conditions, by following the kinetics of the reaction directly. We had been discouraged from following the TMEDA·CuCl mediated coupling of linear

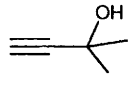
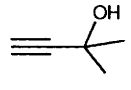
Table 7 Rate equations used to calculate the kinetic effective molarity for the $\mathbf{H_2}$-$\mathbf{Py_4P}$ templated coupling of **A** and **B**

Untemplated reactions	Templated reactions
$\frac{d[A_2]}{dt} = \frac{1}{2}k_A[A]^2$	$\frac{d[A_2]}{dt} = \frac{1}{2}k_A[A]^2 + EM_{kin}k_B[T\cdot A\cdot A]$
$\frac{d[AB]}{dt} = \sqrt{k_A k_B}[A][B]$	$\frac{d[AB]}{dt} = \sqrt{k_A k_B}[A][B]$
$\frac{d[B_2]}{dt} = \frac{1}{2}k_B[B]^2$	$\frac{d[B_2]}{dt} = \frac{1}{2}k_B[B]^2$



$\mathbf{Zn_2}$-l-Dim1b R^1 = H; R^2 = H

$\mathbf{Zn_2}$-l-Dim1b(MHB) R^1 =  ; R^2 = H

$\mathbf{Zn_2}$-l-Dim1b(MHB)$_2$ R^1 =  ; R^2 = 

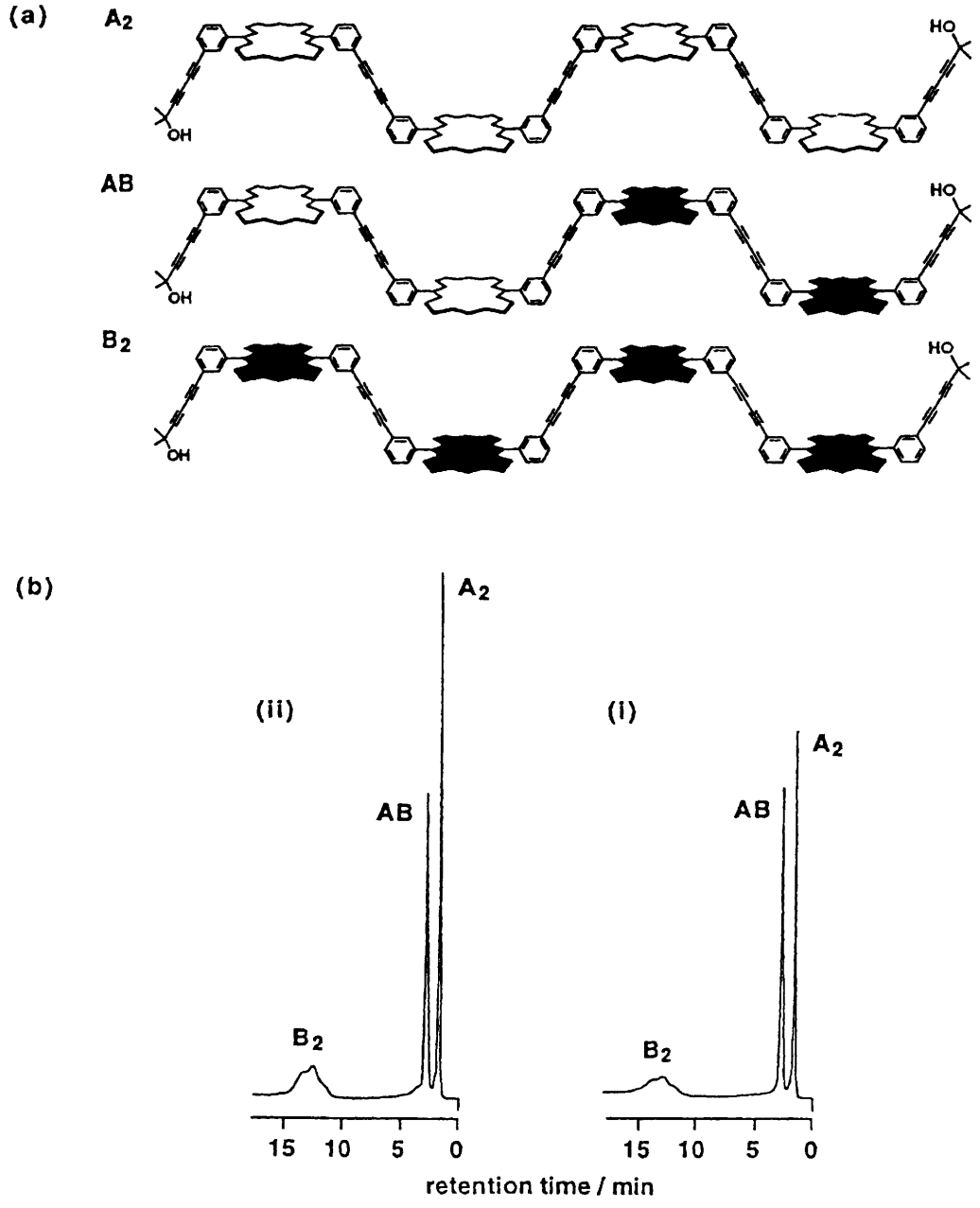


Fig. 7 (*a*) The three products from coupling of the mono-protected linear dimers **A** and **B**. Shaded porphyrins are free-base, methyl esters; unshaded porphyrins are zinc containing, isodecyl esters. (*b*) HPLC traces for (i) untemplated coupling of linear dimers **A** and **B** and (ii) H_2-Py_4**P** templated coupling.

dimer Zn_2-**l-Diml b** directly because the reaction had usually reached completion within 10 min and the reaction time was found to be irreproducible and dependent on the stirring rate. With the use of 2,2′-**BiPy** the reaction is much slower and therefore slight differences in stirring rate have much less effect on the rate of reaction; the rate of oxygen-phase transfer is not rate limiting. Three starting material combinations were used: the first (**X**) contained a six-fold excess of H_2-Py_4**P**, the second (**Z**) half an equivalent and the third (**Y**) had no template and was the control. The concentration of linear dimer was 0.2 mmol dm^{-3} the same as that employed for the earlier TMEDA·CuCl mediated coupling experiments. Samples were withdrawn from the reaction mixtures at intervals in the course of the reaction, quenched with water, acidified and then washed a second time with water. These samples were analysed by HPLC. Fig. 8(i) shows the HPLC trace for a reconstituted 1:1:1:1 mixture of the porphyrins linear dimer H_4-**l-Diml b**, cyclic dimer H_4-**c-Diml b**, linear tetramer H_8-**l-Tetl b** and cyclic tetramer H_8-**c-Tetl b**. The four species are clearly resolved when eluted with 90% chloroform and 10% dichloromethane. Fig. 8(ii) shows HPLC traces for three sets of reaction mixtures.

After 20 min of reaction **Z** and **Y** had progressed furthest whilst **X** was still mainly starting material; at 90 min reaction **Z** had progressed slightly further than reaction **Y**, but reaction **X** was by far the slowest. After 160 min reactions **Z** and **Y** were nearing completion whilst **X** lagged behind. The rate of formation of cyclic dimer was slowest when a six-fold excess of template was used and fastest in the untemplated reaction. Since very little cyclic dimer was formed with half a equivalent of H_2-Py_4**P** and yet the rate at which linear dimer was lost was about the same as that observed in the absence of a template, then the rate at which linear dimer units couple to linear tetramer must be greater when 0.5 equivalent of H_2-Py_4**P** is present. This supports the view that H_2-Py_4**P** can act as a linear

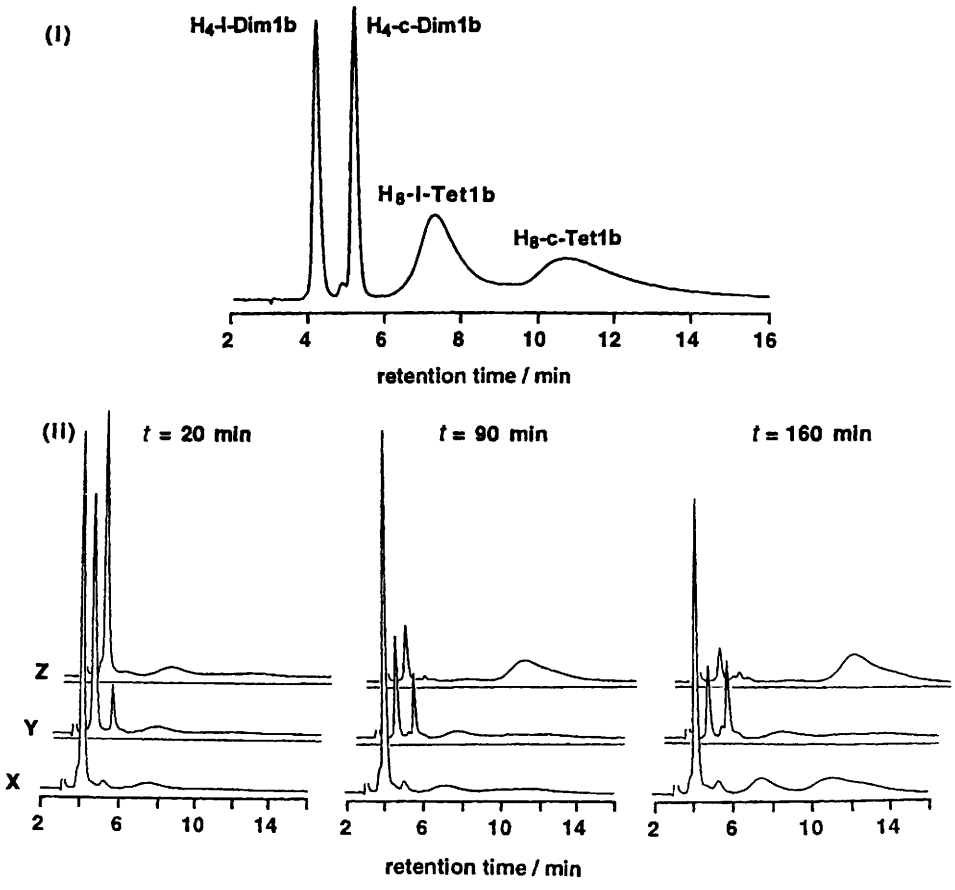


Fig. 8 (i) HPLC of a reconstituted mixture of **H_4-l-Dim1b**, **H_4-c-Dim1b**, **H_8-l-Tet1b** and **H_8-c-Tet1b** (1 : 1 : 1 : 1). (ii) HPLC of reaction mixtures from coupling of **Zn_2-l-Dim1b (X)** with 6 equivalents of **H_2-Py_4P (Y)** no template and (Z) 0.5 **H_2-Py_4P**.

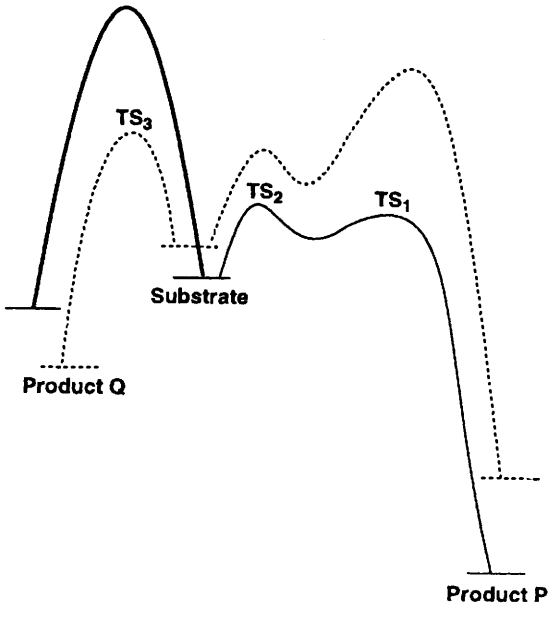


Fig. 9 Energy profiles for reactions which are untemplated (dashed line), positively templated (solid line) and negatively templated (bold line)

template under the right conditions. A further point of interest to be observed in these HPLC traces is that the rate of formation of cyclic tetramer is fastest where only 0.5 equivalent of **H_2-Py_4P** has been added, and seems to be very slow in the presence of a large excess of **H_2-Py_4P**. A large excess of **H_2-Py_4P** has two effects: it slows down coupling between linear dimer units, and it also prevents linear tetramer from undergoing cyclisation. The first of these effects can be explained by the formation of the 1 : 1 complex between linear dimer and **H_2-Py_4P**, and the second by the formation of high order aggregates between **H_2-Py_4P**, linear tetramer and linear dimer. In both cases the geometries are such that linear dimers do not react quickly to form linear tetramer and the rate at which linear tetramer is cyclised to cyclic tetramer is slow.

Discussion

Many of the ideas discussed above can be usefully summarised in energy profiles. Fig. 9 shows energy profiles for conversion of a substrate to two products **P** and **Q**. In order to encourage production of **P** by acting positively, the template must bind to the highest energy transition state (TS_1) and thereby lower $\Delta G^{\ddagger}$. But it must also enable the reaction to proceed along a well-defined channel in the reaction energy surface by binding to all the intermediates and transition states through which the reaction proceeds, lowering their energies. Alternatively, the template can act negatively by binding to the intermediates and transition states leading to the unwanted product **Q** in such a way as to increase their energies and so inhibit them. An ideal template of this sort has both a positive effect on the rate of the desired reaction and a negative effect on the rate of all the other reactions.

These ideas can be illustrated by considering the templated cyclisations of linear dimer **Zn_2-l-Dim1b** and tetramer **Zn_4-l-Tet1b**. For the dimer in the presence of **BiPy**, the strength of binding appears to increase continuously along the reaction pathway from linear **Zn_2-l-Dim1b(SiMe$_3$)$_2$** (6×10^6 mol^{-1} dm^3) to cyclic **Zn_2-c-Dim1b** (1×10^9 mol^{-1} dm^3), providing precisely the required positive guidance.

Returning to the templated formation of cyclic trimer in Fig. 3 we can now see that the template **Py_3T** must undertake a wide variety of roles if it is to be successful: complementarity to the trimer cyclisation transition state may be important, but unless the reaction is effectively guided to this transition state most of the substrate will have undergone irreversible side reactions before it is reached. It is pointless making a deep well in the reaction energy surface if a large proportion of the substrate never reaches it. What is required is a well defined channel along which the reaction can proceed.

We have observed kinetic effective molarities over the range 0.1–1 mmol dm^{-3}, implying that no template effects would have been observed if our syntheses had been carried out at higher concentrations. Why are these templating processes relatively inefficient whereas the templated Diels–Alder[9] reaction carried out inside the trimer cavity is about 1000 times more effective? One reason appears to be that Glaser–Hay coupling requires reagents which reduce the strength of the pyridyl-zinc porphyrin interaction whereas the Diels–Alder does not. A second reason which would lower the effective molarities is that the templated cyclisation requires the porphyrin aryl groups to be *cis* to each other, while at any moment half are likely to be *trans*. We could have tried to incorporate these factors into the kinetic effective molarity calculation by predicting the average amount of complex in the active conformation if we had had better information about the template binding equilibria in the presence of the coupling reagent.[11] All the values quoted in this paper reflect the overall rates of reaction and do not take into account the proportion of reactive species in the reaction mixture. The size of the molecules involved appears not to be a limitation and in principle it appears that all bimolecular reactions and cyclisation reactions should be amenable to acceleration and control by templates. This view is reinforced by the recent demonstration in this laboratory that one can pre-assemble four high-affinity dioxoporphyrins onto a **H_2-Py_4P** template and then achieve virtually quantitative coupling to the cyclic tetramer.[7]

Conclusions

BiPy is an efficient template for the TMEDA·CuCl promoted cyclisation of linear dimer, supporting the mechanism originally proposed in the synthesis of cyclic dimer from monomer. The template binds the linear dimer in an eclipsed gable conformation rather than extended and therefore acts as a good cyclisation template for the formation of cyclic dimer from linear dimer. The EM_{kin} for cyclisation is increased by a factor of 20 by the presence of the template. In contrast, the templates **Py_2Py** and **H_2-Py_4P** promote more extended conformations of linear dimer in which the reactive acetylene ends are held apart. These templates act as negative cyclisation templates for the formation of cyclic dimer from linear dimer. When the chelating ligand for copper was changed for 2,2′-bipyridyl (2,2′-**BiPy**) larger templating effects were observed, since 2,2′-**BiPy** binds less strongly to zinc porphyrins than TMEDA.

As well as preventing linear dimer from cyclising **H_2-Py_4P** promotes the formation of cyclic tetramer. Under the standard TMEDA·CuCl coupling conditions isolated yields of 50–60% of cyclic tetramer can be obtained directly from linear dimer. A detailed examination of the **H_2-Py_4P** templated 2,2′-**BiPy** promoted coupling of linear dimer revealed that a large excess of **H_2-Py_4P** slows the rate of coupling down, the starting material and linear intermediates forming complexes with the template which inhibit rather than promote coupling. With only 0.5 equivalent of **H_2-Py_4P** the reaction is much faster and both coupling of two linear dimers to linear tetramer and the cyclisation of linear tetramer to cyclic tetramer are efficiently templated. Both **H_2-Py_4P** and **BiPy** template the cyclisation of linear tetramer to cyclic tetramer. **H_2-Py_4P** is the more efficient template and leads to a 6-fold increase in the effective molarity for the cyclisation of linear tetramer. We have prepared an array of linear and cyclic porphyrin oligomers using Glaser–Hay coupling as the only carbon-carbon bond-forming reaction, and have achieved control through templating. Relatively small templates have been used to construct remarkably extended molecular architectures. It is perhaps worth noting that these syntheses all rely on pre-formed templates whose role is to trap or influence reactive intermediates. In many other templated syntheses, for example those of catenanes and rotaxanes, the template is itself often generated as a reactive intermediate.[12–14]

Templates normally bind too strongly to their products to operate catalytically: product inhibition severely limits turnover. If a template bound the product less strongly than either the transition state or the starting material, it would be less susceptible to product inhibition. It will be fascinating to see whether it is possible to make templates which bind transition states sufficiently selectively to operate efficiently as enzymes, capable of rivalling natural enzymes.

Experimental

Cyclisation of Zn_2-l-Diml b using a range of amine ligands as templates and TMEDA as the chelating agent for copper

Estimation of template effects by ^{1}H NMR of crude material. TMEDA (54 mm^3, 0.36 mmol) was added to a solution of **Zn_2-l-Diml b** (5 mg, 2.57 μmol), copper(I) chloride (35 mg, 0.36 mmol) and template (15 μmol) in CH_2Cl_2 (12.8 cm^3, freshly distilled ex CaH_2) and stirred under dry air for 30 min. The disappearance of starting material was followed by TLC. Each reaction mixture was washed with water (3 × 100 cm^3), treated with methanolic TFA (10%, 10 cm^3)¶ and then washed again with water (4 × 100 cm^3). The solvent was evaporated and the crude product dissolved in $CDCl_3$ and its ^{1}H NMR spectrum recorded. The *meso*-resonances were analysed to estimate the proportions of the total material corresponding to **H_4-c-Diml b** and **H_8-c-Tet1b**. IR spectra were also recorded to confirm that coupling had gone to completion. TLC (in $CHCl_3$) was used to check the product distribution and the absence of copper insertion.

Cyclisation of Zn_2-l-Diml b using H_2-Py_4P as a template and 2,2′-bipyridyl as the chelating agent for copper

2,2′-**BiPy** (14.5 mg, 93 μmol) was added to a solution of **Zn_2-l-Diml b** (6.4 mg, 3.3 μmol), CuCl (9.25 mg, 93 μmol) and **H_2-Py_4P** template in CH_2Cl_2(3.3 cm^3). Three reactions were carried out simultaneously under identical conditions except that the first contained no template, the second 0.5 equivalent **H_2-Py_4P** with respect to **Zn_2-l-Diml b** and the third a six-fold excess of **H_2-Py_4P**. The reactions were followed by TLC and seemed to be essentially complete after 5 h. The reactions were worked up as described above for the templating experiments with TMEDA. Each reaction mixture was analysed by ^{1}H NMR.

Templated cyclisations of Zn_4-l-Tet1b. TMEDA (52.5 mm^3, 0.35 mmol) was added to a solution of **Zn_4-l-Tet1b** (5 mg, 1.3 μmol), CuCl (35 mg, 0.35 mmol) and template (7.7 μmol) in CH_2Cl_2 (12.5 cm^3; freshly distilled ex CaH_2). The reaction was followed by TLC and work up carried out as described above.

Investigation into the ability of H_2-Py_4P to act as a linear template

Synthesis of H_4-l-Diml b(MHB). Zn_2-l-Diml b(SiMe$_3$)$_2$ (300 mg, 1.4 × 10^{-4} mol) was dissolved in $CHCl_3$ (300 cm^3),

¶ 10% TFA in MeOH needs to be freshly prepared to avoid MeO_2CCF_3.

degassed and saturated with argon. Tetrabutylammonium fluoride (TBAF) (160 mm^3, 1 mol dm^{-3} in THF; Aldrich) was then added to the solution in four 40 mm^3 portions at 30 min intervals. After each addition the $CHCl_3$ was brought to reflux and then a sample withdrawn for TLC. A second sample was taken after 15 min to see whether reaction was complete. After four additions approximately half of the silicon protecting groups had been removed from **Zn_2-l-Dim1b($SiMe_3$)$_2$**. A few grains of $CaCl_2$ were added to the mixture of dimers to remove the excess of fluoride before washing with water. The solvent was evaporated and the residue dried *in vacuo* for 1 h to remove all traces of $CHCl_3$. The partially deprotected dimer was then divided into two equal portions for coupling. Each portion was dissolved in CH_2Cl_2 (500 cm^3; freshly distilled ex CaH_2) to which CuCl (1.4 g, 14 mmol) and 2-methylbut-3-yn-2-ol (180 mm^3, 1.85 mmol) were added. When all the porphyrin was dissolved, TMEDA (2.1 cm^3, 14 mmol) was added and the mixture turned from bright pink to a dark brown. Coupling was followed by TLC and was complete after 10 min. The final mixture was washed with water (3 × 500 cm^3) to remove the copper and evaporated. The product was purified by flash column chromatography. The first fraction **Zn_2-l-Dim1b($SiMe_3$)$_2$** was removed with $CHCl_3$–CH_2Cl_2 (1:1.9), the second, **Zn_2-l-Dim1b($SiMe_3$)(MHB)**, with $CHCl_3$–CH_2Cl_2 (1:0.67) and the third, **Zn_2-l-Dim1b(MHB)$_2$** with $CHCl_3$–CH_2Cl_2 (19:1). Yield of **Zn_2-l-Dim1b($SiMe_3$)(MHB)** after recrystallisation from $CHCl_3$–MeOH 95 mg (32%); λ_{max}(CH_2Cl_2)/nm 334, 412, 538 and 574; δ_H(250 MHz; $CDCl_3$/[$^2H_5$]Pyridine) 0.23 (9 H, s), 1.54 (6 H, s), 2.16 (1 **H**, br s), 2.41 (6 H, s), 2.43 (18 H, s), 3.07 (16 H, t), 3.58 (12 H, s), 3.59 (6 H, s), 3.60 (6 H, s), 4.27 (16 H, t), 7.63–8.20 (16 H, m) and 10.03 (4 H, s); δ_C(100 MHz; $CDCl_3$–pyridine) 0.0, 16.6, 22.0, 31.1, 37.1, 51.6, 65.4, 66.8, 73.6, 74.2, 78.8, 82.0, 87.3, 94.3, 96.7, 96.9, 105.3, 117.6, 117.7, 118.2, 120.8, 120.9, 127.4, 127.6, 131.7, 132.1, 134.0, 136.9, 138.2, 138.5, 141.0, 141.1, 144.1, 144.4, 145.9, 147.3, 147.5 and 173.6; *m/z* (+ve FAB NOBA) 2100 (M^+) and 1050 (M^{2+}) ($C_{120}H_{116}N_8O_{17}SiZn_2$ requires 2101.31).

Zn_2-l-Dim1b($SiMe_3$)(MHB) (95 mg, 45 μmol) was dissolved in CH_2Cl_2 (50 cm^3, freshly distilled ex CaH_2) and the solution degassed and saturated with argon. TBAF (1 mol dm^{-3} solution in THF; Aldrich; 60 mm^3) was then added to the solution; the removal of the silicon protecting group was monitored by TLC. When no starting material remained a few grains of $CaCl_2$ were added to the reaction mixture to remove any excess of fluoride. The porphyrin was then passed down a short silica column eluting with $CHCl_3$ to give **Zn_2-l-Dim1b(MHB)**; λ_{max}(CH_2Cl_2)/nm 334, 412, 538 and 574; δ_H(250 MHz; $CDCl_3$) 1.50 (6 H, br s), 1.90 (1 H, br s), 2.44 (6 H, s), 2.47 (18 H, s), 3.12 (16 H, br t), 3.15 (1 H, s), 3.6 (24 **H**, m), 4.31 (16 H, br s), 7.67–8.24 (16 H, m) and 10.20 (4 H, br s); δ_C(100 MHz; $CDCl_3$/[$^2H_5$]pyridine) 15.5, 21.9, 31.1, 37.0, 51.5, 64.8, 66.2, 73.7, 74.1, 78.4, 81.9, 88.0, 96.9, 117.6, 120.8, 127.5, 132.0, 133.8, 136.8, 138.2, 141.0, 144.27, 144.33, 145.8, 147.3 and 173.5; *m/z* 2030 (M^+) and 1015 (M^{2+}) ($C_{117}H_{108}N_8O_{17}Zn_2$ requires 2029.11).

Zn_2-l-Dim1b(MHB) was demetallated with TFA (10% TFA in MeOH; 100 cm^3) and the product washed with water (4 × 100 cm^3); yield of **H_4-l-Dim1b(MHB)** 88 mg [33% from **Zn_2-l-Dim1b($SiMe_3$)$_2$**]; λ_{max}(CH_2Cl_2)/nm 333, 411, 506, 539, 574 and 630; δ_H(250 MHz; $CDCl_3$) −2.50 (4 H, s), 1.55 (6 H, s), 1.90 (1 H, s), 2.50 (6 H, s), 2.48 (18 H, s), 3.13 (16 H, s), 3.16 (1 H, s), 3.63 (12 H, s), 3.62 (12 H, s), 4.34 (16 H, t), 7.67–8.24 (16 H, m) and 10.2 (4 H, s); *m/z* 1901 (M^+), 951 (M^{2+}) and 3804 ($2M^+$) ($C_{117}H_{112}N_8O_{17}$ requires 1902.37).

Zn_2-l-Dim1c(MHB). **H_4-l-Dim1b(MHB)** (48 mg, 25 μmol) was mixed with 3,7-dimethyloctan-l-ol (30 cm^3) and titanium(IV) tetraisopropoxide (300 mm^3), and heated to 120 °C at 13 mmHg. After 4 h the solvent was removed under reduced pressure and the porphyrin dissolved in $CHCl_3$ and passed down a short silica column before recrystallisation from $CHCl_3$–MeOH to yield **H_4-l-Dim1c(MHB)**; λ_{max}(CH_2Cl_2)/nm 272, 291, 333, 411, 506, 539, 574 and 625; δ_H(250 MHz; $CDCl_3$) −2.50 (4 H, s), 0.67–1.60 (158 H, m), 1.95 (1 H, s), 2.52 (24 H, m), 3.11 (16 H, t), 3.16 (1 H, s), 4.06 (16 H, t), 4.33 (16 **H**, t), 7.69–8.23 (16 H, m) and 10.26 (4 H, s).

H_4-l-Dim1c(MHB) was metallated with zinc according to the standard procedure to yield **Zn_2-l-Dim1c(MHB)** (76 mg, 99%); λ_{max}(CH_2Cl_2)/nm 272, 293, 334, 412, 538 and 574; δ_H(250 MHz; $CDCl_3$) 0.68–1.55 (158 **H**, m), 1.92 (1 H, s), 2.46–2.48 (24 **H**, m), 3.11 (16 H, br t), 3.15 (1 **H**, s), 4.08 (16 H, br t), 4.32 (16 H, br t), 7.69–8.24 (16 H, m) and 10.22 (4 H, s); *m/z* (+ve FAB) 3039 (M^+) ($C_{189}H_{252}N_8O_{17}Zn_2$ requires 3039.27).

Estimation of the template effect

2,2′-**BiPy** (29 mg, 186 μmol) was added to a solution containing **H_4-l-Dim1b(MHB)** (1.25 mg, 0.66 μmol), **Zn_2-l-Dim1c(MHB)** (2.0 mg, 0.66 μmol), CuCl (18.5 mg, 187 μmol) and template **H_2-Py_4P** (0.2 mg, 0.33 μmol) in CH_2Cl_2 (6.65 cm^3). A second reaction was set up, similar with respect to the above, but in the absence of **H_2-Py_4P**. The reactions were followed carefully by TLC, and after 4 h had gone to completion. TLC indicated that each mixture contained three components. The mixtures were washed with water (3 × 25 cm^3), treated with methanolic TFA (10%, 5 cm^3) and then washed again with water (4 × 25 cm^3). After solvent had been removed by evaporation under reduced pressure the crude product was dissolved in $CHCl_3$ and the solution filtered through a 0.45 μm micropore filter. Partial copper metallation of free base porphyrins took place during coupling. This affected the slowest running product most, that is the linear tetramer with methyl esters which was derived from two free-base porphyrin dimers. Little or no copper metallation was visible in the two faster products. To be sure of this, half of each mixture was metallated with copper using an excess of copper(II) acetate, following the same procedure as outlined for zinc insertion. This worked well for the faster two species, since the presence of at least eight isodecyl esters made these compounds soluble even when metallated with copper. Unfortunately, **Cu_4-l-Tet1b(MHB)$_2$** is fairly insoluble in $CHCl_3$ and was mostly lost during filtration of the samples ready for HPLC.

HPLC analysis

HPLC was carried out using a Gilson Model 303 pump with a Hichrom 25 cm analytical column internal diameter 4.6 mm, containing Spherisorb S5W silica. The best separation of the components of the above mixtures was achieved eluting with $CHCl_3$ at a flow rate of 1 cm^3 min^{-1} (pressure of 0.6 kpsi). For the HPLC traces shown in Fig. 7(*b*) elution was carried out at a flow rate of 2 cm^3 min^{-1} (pressure 1.17 kpsi). HPLC with the UV detector set at 254 nm of the reaction mixtures both before and after the addition of copper gave the same ratio for the first two products; the ratios were calculated by weighing the relevant peaks and comparing their weights. For the copper metallated reaction mixtures the proportion of the slowest product was assumed to be the same as the fastest. The extinction coefficients for porphyrins with isodecyl side chains and methyl esters were found to be essentially the same. A calibration with **Cu_4-l-Tet1c(MHB)$_2$** was carried out and in the concentration regime employed peak mass is directly proportional to linear tetramer concentration. The estimation of the linear template effect was repeated: firstly increasing the concentration of porphyrin by a factor of 10 and secondly using TMEDA as the chelating agent for copper. HPLC analysis was carried out on all mixtures before and after the addition of copper.

Attempt to follow the coupling of Zn_2-l-Dim1b both in the presence and absence of the template H_2-Py_4P

Zn_2-l-Dim1b (60 mg, 31 μmol) and **Zn-Mon1b($SiMe_3$)$_2$** (2.7 mg, 2.4 μmol) were dissolved in a minimum volume of $CHCl_3$ and the resulting solution was divided into three equal portions from each of which the solvent was evaporated. Three different starting material mixtures were prepared.

(i) **Zn_2-l-Dim1b** (20 mg, 10 μmol), CuCl (142 mg, 1.42 mmol), **H_2-Py_4P** (38 mg, 61 μmol) and CH_2Cl_2 (50 cm^3). (ii) **Zn_2-l-Dim1b** (20 mg, 10 μmol), CuCl (142 mg, 1.42 mmol) and CH_2Cl_2 (50 cm^3). (iii) **Zn_2-l-Dim1b** (20 mg, 10 μmol), CuCl (142 mg, 1.42 mmol), **H_2-Py_4P** (3.2 mg, 5 μmol) and CH_2Cl_2 (50 cm^3). To each of these 2,2′-**BiPy** (223 mg, 1.42 mmol) was added. Samples (0.5 cm^3) were taken from each reaction mixture at intervals along the time course of the coupling. Each sample was collected in a small screw cap vial, quenched with water (2 cm^3), washed with water, treated with methanolic TFA (100 mm^3, 10% TFA in MeOH) and further washed with water. The solvent was evaporated. Each sample was examined by HPLC eluting with CH_2Cl_2–$CHCl_3$ (1:9) with a flow rate of 1 cm^3 min^{-1} and a pressure of 0.6 kpsi.

Acknowledgements

We thank the SERC, Rhône-Poulenc-Rorer, Magdalene and Trinity Colleges Cambridge for financial support, the SERC mass spectrometry service (Swansea) for FAB spectra and Prof François Diederich for generously providing facilities at the ETH, Zürich, Switzerland, where parts of the first four papers in this series were written.

References

1 S. Anderson, H. L. Anderson and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1995, preceding paper.
2 H. L. Anderson, S. Anderson and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1995, **18**, 2231.
3 H. L. Anderson and J. K. M. Sanders, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1400; S. Anderson, H. L. Anderson and J. K. M. Sanders, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 907.
4 S. Anderson, H. L. Anderson and J. K. M. Sanders, *Acc. Chem. Res.*, 1993, **26**, 469.
5 L. Mandolini, *Adv. Phys. Org. Chem.*, 1986, **22**, 1; A. J. Kirby, *Adv. Phys. Org. Chem.*, 1980, **17**, 183.
6 H. L. Anderson and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1995, **18**, 2223.
7 D. W. J. McCallien and J. K. M. Sanders, *J. Am. Chem. Soc.*, 1995, **117**, 6611.
8 S. F. Vasilevsky, H. D. Verkuijsse, L. Brandsma, *Rec. Trav. Chim. Pays-Bas*, 1992, **111**, 529.
9 C. J. Walter, H. L. Anderson and J. K. M. Sanders, *J. Chem. Soc., Chem. Commun.*, 1993, 458; C. J. Walter and J. K. M. Sanders, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 217.
10 F. Bohlmann, H. Schönowsky, E. Inhoffen and G. Grau, *Chem. Ber.*, 1964, **97**, 794.
11 I. Huc, R. J. Pieters and J. Rebek Jr., *J. Am. Chem. Soc.*, 1994, **116**, 10296.
12 D. B. Amabalino and J. F. Stoddart, *Pure Appl. Chem.*, 1993, **65**, 2351.
13 C. A. Hunter, *J. Am. Chem. Soc.*, 1992, **114**, 5303.
14 F. Vögtle, S. Meier and R. Hoss, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 1619.

Paper 5/01074H
Received 22*nd February* 1995
Accepted 1*st June* 1995