

Expanding Roles for Templates in Synthesis

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What Is a Template?

Watson and Crick discovered the DNA double helix in 1953 and realized immediately that its replication involved a templated synthesis.¹ Their work inspired Todd to suggest in 1956 that organic templates might one day be used to control laboratory syntheses in a similar way.² In retrospect, it is clear that metal ion templated syntheses of phthalocyanines had been observed as early as 1932,³ but it is only with Busch's pioneering and systematic work in the 1960s that different modes of templating were seriously studied and classified.^{4,5} The recent emergence of supramolecular chemistry has brought together the historically separate organic and inorganic strands of template chemistry so that metal-ligand binding, hydrogen bonding, and π - π interactions can now be exploited to allow the synthesis of ever-larger molecules with a remarkable degree of control. In this Account, we refine and expand the original template classifications proposed by Busch⁴ to embrace the many approaches that are now available; we illustrate these approaches with examples from the literature and with our own syntheses of porphyrin oligomers; and we attempt to elucidate the features that lead to efficient templating.

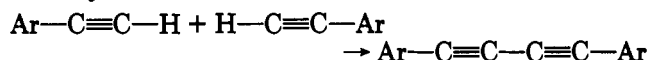
"A chemical template organizes an assembly of atoms, with respect to one or more geometric loci, in order to achieve a particular linking of atoms."⁶ The distinction between a template and a reagent is that a template intervenes in the macroscopic geometry of the reaction rather than in the intrinsic chemistry. The template provides instructions for the formation of a single product from a substrate or substrates which otherwise have the potential to assemble and react in a variety of ways. Changing the template should result in a different substrate assembly and consequently a different product. In general, after the template has directed the formation of the product, it is removed to yield the template-free product, although this feature is not found where the template is an integral part of the structure it helps to form.⁷⁻⁹

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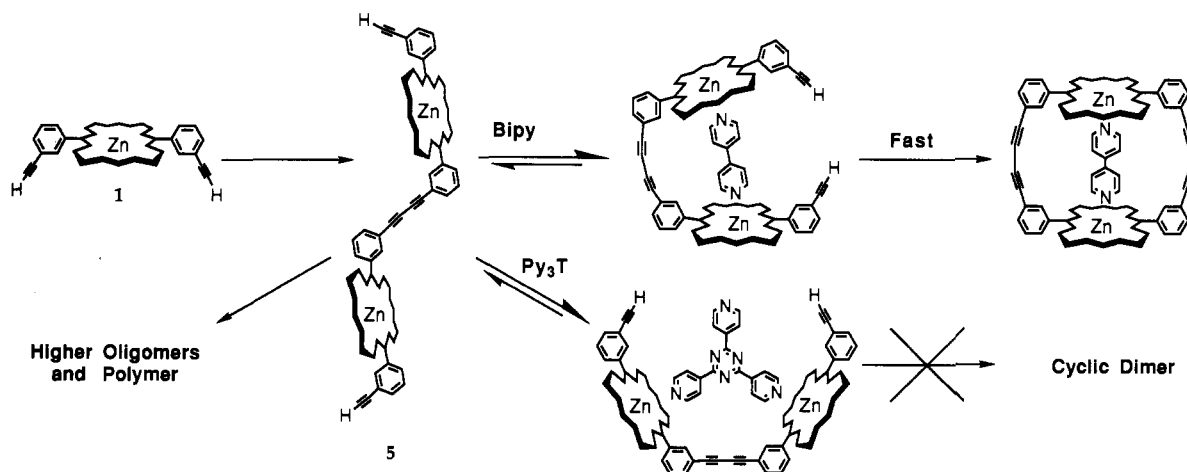
Our interest in building enzyme mimics based on porphyrins led us to synthesize cyclic porphyrin oligomers using Glaser coupling.¹⁰ This reaction oxidatively combines two terminal acetylenes to give a butadiyne link:



The linkage has the attractions of being linear and relatively rigid, and the reaction can be made essentially quantitative: under optimized conditions, there is little side reaction and no unreacted starting material remains. The nature and yields of the products are determined solely by geometrical considerations and by the kinetics of the encounter between reactive ends. Thus, reaction of the monomeric porphyrin **1** gives a complex mixture of cyclic oligomers. The dimer **2** and trimer **3** are relatively easy to isolate, but the tetramer **4** is very difficult to separate from the small quantities of even higher oligomers formed in the reaction. The separated oligomers proved to have very different ligand-binding characteristics,¹⁰ tempting us to try using these differences to influence the synthesis by templating. After much optimization of conditions, we arrived at a very successful cyclic dimer synthesis using 4,4'-bipyridyl (Bipy) as the template.¹¹

The first step in this templated reaction must be the combination of two porphyrin units to yield linear dimer **5** (Scheme I). Then either an intramolecular cyclization occurs or a reaction with a further monomer porphyrin yields a linear porphyrin trimer. The latter process is prevented by the Bipy template, which induces the reactive ends of the linear dimer intermediate to come into close proximity and so increases the rate of intramolecular cyclization. This reaction therefore proceeds in the same way as classical metal cation templated macrocyclizations.^{4,12} The yield of the cyclic dimer was increased by a factor of 3 in the presence of Bipy.

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Scheme I. Templated Glaser Coupling of Bis-Alkynyl Porphyrin 1 in the Presence of BiPy and Py₃T

The templated synthesis of the cyclic trimer, using the complementary ligand tripyridyltriazine, Py₃T, was less successful, improving the yield from 34% to around 50%, while at the same time drastically reducing the yield of the dimer. Again, the first step must be the coupling of monomer units to yield the linear dimer, but the conformation adopted when this is bound to Py₃T has the reactive ends held apart (Scheme I); intramolecular cyclization is now disfavored, leaving the way open for intermolecular reaction to take place. However, the proportion of monomer in the reaction mixture will decline rapidly and therefore the probability of the linear dimer yielding the linear trimer will also be low toward the end of the reaction. The coupling of the monomer in the presence of 2,6-dipyridylpyridine, Py₂Py, which should bind to the linear dimer in a way similar to that of tripyridyltriazine but which lacks the third binding site, gives a similar product distribution. This confirms that the template in the synthesis of the cyclic trimer plays a mainly preventative role.

Our detailed analysis of these differences in the templating abilities of BiPy and Py₃T led to efficient syntheses of porphyrin tetramers and an octamer and the new—and generally applicable—understanding of template principles described below.

Classification of Templates

Busch classified templates as either thermodynamic or kinetic.⁴ Thermodynamic templating occurs in reversible reactions under thermodynamic control: the template, when added to a reaction mixture at equilibrium, binds to one of the products and shifts the equilibrium toward this species. Acetonitrile can be used as a template for the formation of a dodecavanadate basketlike cage; this reaction is thought to be under thermodynamic control and gives over 80% yield in the presence of the template.¹³ The synthesis of zeolites is another important example of thermodynamic templating,¹⁴ and an exciting recent development in this area has been the synthesis of mesoporous molecular sieves with pore sizes up to 200 Å, using liquid

crystals as templates.^{15,16} Thermodynamic templating can result in very high yields because the template only has to stabilize the product.

Kinetic templates operate on irreversible reactions so they have to stabilize all the transition states leading to the desired product. Kinetic templates almost invariably bind the product more strongly than the starting material, so they also favor formation of the product thermodynamically. Similarly thermodynamic templates are likely to accelerate formation of the product by transition-state stabilization, so the classification of the observed effect depends primarily on whether the reaction is under kinetic or thermodynamic control.

In this Account, we focus on kinetic templates, which are more difficult to design and understand, but are also ultimately more versatile. Kinetic templates recognize and bind a species during a reaction in such a way as to favor a particular geometry and orientation of reactive groups, so inducing the reaction to proceed toward a single product. In this they mimic one important feature of enzymic catalysis, that is, by binding substrates in close proximity they lower ΔS^* for a reaction. They increase the effective molarity of the reactive groups and the specificity of the reaction. Enzymes, of course, are also capable of catalytic turnover, a trick that is achieved by binding the transition state more strongly than the substrates or the products. An ideal template—like a catalytic antibody¹⁷—would also be catalytic by showing complementarity only to the transition state for a given reaction, but templates usually bind strongly to the product and so are inhibited from showing turnover.

Templates can also be classified according to the strength of interactions between the template and the substrates and the subsequent induced interaction between the bound substrates (Figure 1). Classical templates bind noncovalently to their substrates but assist in the formation of covalent bonds. A good example is the metal cation induced synthesis of crown

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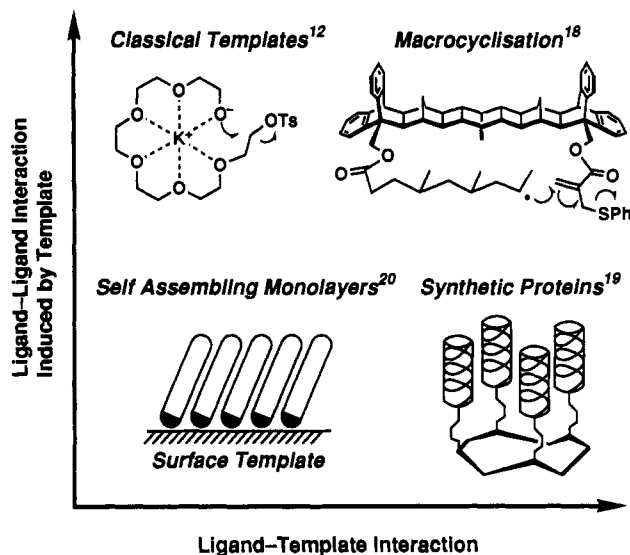


Figure 1. Templating and self-assembly: templating systems range from those where noncovalent substrate-template interactions induce noncovalent interactions between substrates (bottom left) to those where covalent interactions induce further covalent interactions (top right).

ethers.¹² A closely related class includes templates like Feldmann's,¹⁸ in which intermolecular steps are transformed to intramolecular ones; the only difference between this and the classical templates is the covalent nature of the bond between the template and substrates. The other examples shown in Figure 1 involve the template-induced formation of noncovalent interactions. They would commonly be referred to as self-assembly but could also be classified as aggregation templated systems. In the case of the synthetic protein,¹⁹ several amphiphilic helical building blocks are covalently attached to a template, so determining the folding topology of the final globular structure. The self-assembly of surface monolayers is another good example of aggregation templating: when aliphatic carboxylic acids form monolayers on a water surface, or long-chain thiols self-assemble into a monolayer on gold,²⁰ the surface holds the organic groups in the correct orientation for optimal van der Waals interaction between the hydrocarbon chains. In other words, a noncovalent interaction between the template and substrates induces a second noncovalent interaction. These final examples show the close relationship between templating and self-assembly.²¹ Finally, templates can be classified according to their topology, as shown in Figure 2. We now explore the features of cyclization, linear, and interweaving templates.

Cyclization Templates. The simplest type of template in this category, and perhaps the most widely exploited, is the metal cation which induces macrocyclization.^{22,23} As mentioned above, this same kind of effect is exhibited in our templated synthesis of the

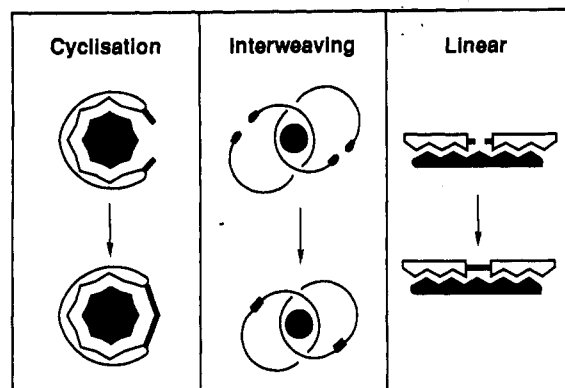


Figure 2. Three topological classes of templates.

cyclic porphyrin dimer from the monomer.¹¹ In these examples, the linear intermediate was produced in situ and not isolated. We synthesized the linear porphyrin dimer **5**²⁴ so that the templated cyclization step could be observed in isolation. The presence of Bipy increased the yield of the cyclic dimer by 4-fold, confirming that Bipy binding to the linear dimer enforces a conformation in which intramolecular cyclization occurs more rapidly than intermolecular coupling.

Similarly, tetrapyrrolylporphyrin, Py₄Porph, enhanced the cyclization of linear porphyrin tetramer **6** to such an extent that **4** was the only product detected (Scheme II; yield > 90%). The binding constant for the 4-Py₄Porph complex as measured by UV spectroscopy is $2 \times 10^{10} \text{ M}^{-1}$.²⁵ Bipy binds to **4** even more strongly, the binding constant for the 2:1 complex being $5 \times 10^{16} \text{ M}^{-2}$, but it is less effective as a cyclization template, the yield of **4** being only 70%. The implications of this observation are explored in the final section.

Other templated cyclization reactions include those described by Stoddart for the synthesis of catenanes and rotaxanes.⁷ In these examples, the π - π interactions between the substrate and the template induce the cyclization reactions. Metal cation templates can also be used to construct three-dimensional cages as in Raymond's iron-sequestering agent.²⁶ Sargeson's sepulchrates²⁷ are similar except that the template cannot be removed as it is entombed within the cage. Müller has also constructed polyoxovanadate cages around anion templates.²⁸

Scavenging. Cyclization templates can be used to scavenge cyclizable material in a reaction mixture and thus facilitate the formation of linear oligomers.²⁴ Consider the general strategy for synthesis of linear oligomers shown in Scheme III: oligomerization of the partially-protected material can only be carried out efficiently in the absence of fully-protected molecules because the latter can couple with monoprotected material to generate a new reactive oligomer and ultimately a complex mixture. Conventionally this problem is avoided by separation of the doubly-reactive

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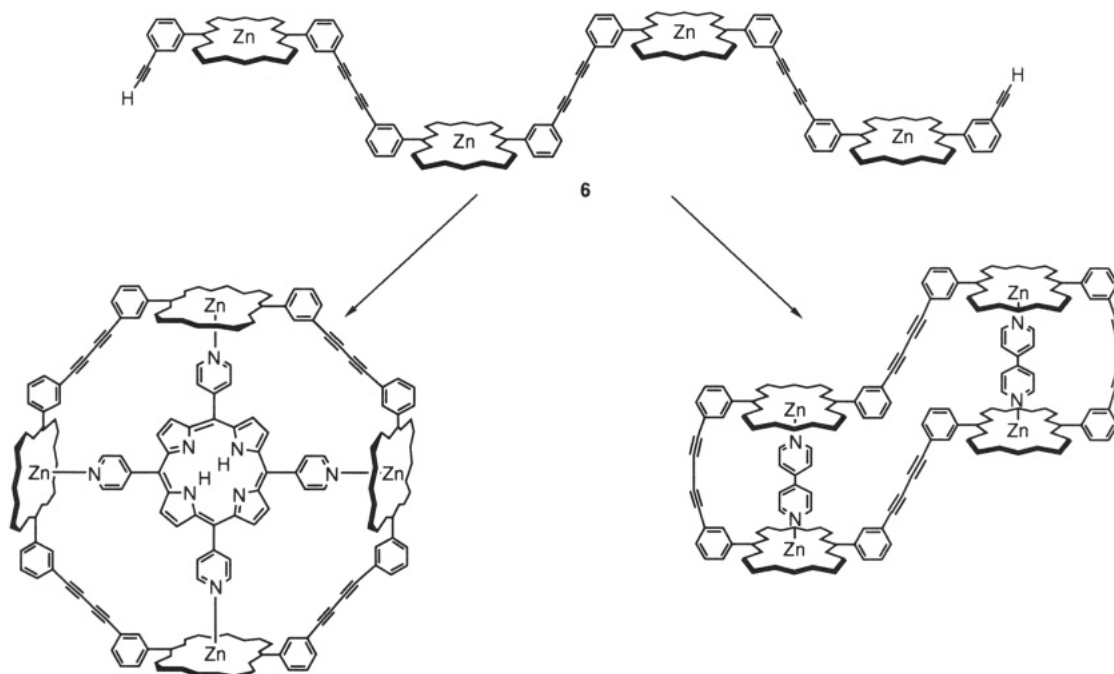
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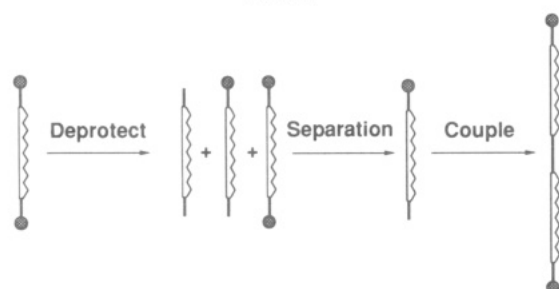
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Scheme II. Synthesis of Cyclic Porphyrin Tetramer 4 from Linear Tetramer 6 Using Py₄Porph and Bipy as Positive Cyclization Templates

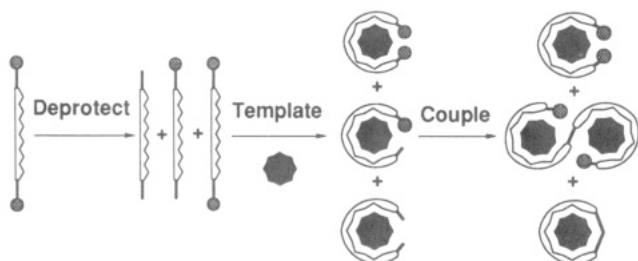


Scheme III. Strategy for the Synthesis of Linear Oligomers from a Symmetrically Protected Building Block^a



^a Hatched circles represent protecting groups.

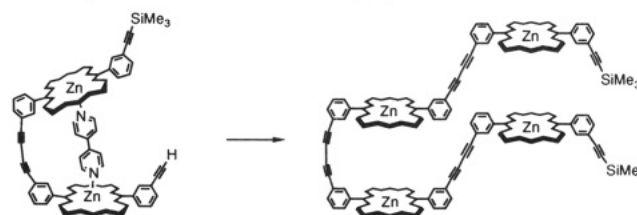
Scheme IV. Use of a Scavenger Template to Induce Molecules with Two Reactive Ends to Undergo Rapid Intramolecular Cyclization, So Allowing Efficient Coupling of Monoprotected Material^a



^a Hatched circles represent protecting groups.

material before coupling, but separation becomes ever more difficult with increasing chain length. Scavenger templates overcome this problem by enforcing intramolecular reaction of doubly-reactive molecules (Scheme IV); monoprotected molecules have no choice but to couple to each other. The separation can be postponed until after coupling, when it has become much easier because the desired linear compound is twice as massive as either the starting material or the cyclic byproduct.

Scheme V. Bipy as a Scavenger Template in the Synthesis of Linear Porphyrin Tetramer 6^a

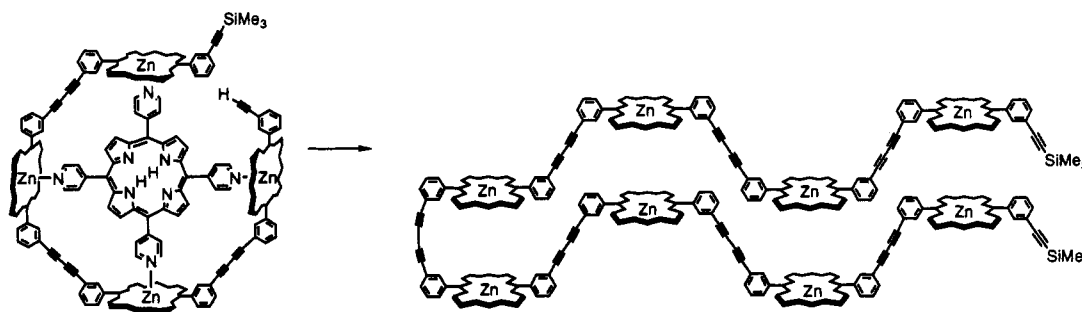


^a For clarity, only the coupling of the monoprotected linear dimer is shown.

We used this scavenging strategy to synthesize linear tetramer 6 from dimer 5 (Scheme V) and linear octamer 7 from tetramer 6 (Scheme VI), using Bipy and Py₄Porph, respectively, as templates. In both cases, the yields of the desired product are close to the theoretical maximum of 50%; the doubly-protected starting material can be recycled, and the cyclic byproduct is useful in its own right. In the absence of the template, both reactions do give significant amounts of the desired linear coupling product, but there are so many other coupling products that isolation of the pure material on a preparative scale is difficult and inefficient. In the presence of the scavenger template, only three products are formed, greatly easing the isolation process; this advantage is as important as the improvement in absolute yield.

Linear Templates. These template the reaction between two bound substrates rather than between two ends of the same substrate. The classic example of this type of templating is replication of DNA and RNA. In both cases, a single strand of DNA is used as a template, the base sequence on the template strand being complementary to the sequence produced on the new strand.

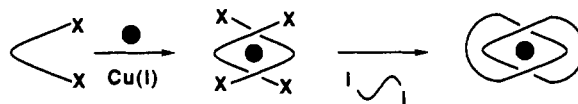
Kelly²⁹ has developed a linear template which binds two substrate molecules next to each other so as to enhance the bimolecular reaction between them. Sim-

Scheme VI. Py₄Porph as a Scavenger Template in the Synthesis of Linear Octamer 7

ilarly Lynn *et al.*³⁰ have looked at the reversible formation of an imine between two trinucleotides on a hexanucleotide template. Linear templates are not restricted to the formation of a single bond: a Diels-Alder reaction³¹ has been effectively templated by connecting a diene and a dienophile covalently through a phenylboronic acid, so transforming the reaction from intermolecular to intramolecular. This is a templated reaction in the sense that the phenylboronate linker is readily removed at the end of the reaction. A second Diels-Alder reaction is accelerated some 200-fold by binding of a diene and a dienophile in the cavity of cyclic porphyrin trimer 3,³² while Mock³³ has developed a cucurbituril-catalyzed 4 + 2 cycloaddition, and Feldmann¹⁸ has also described a system in which several bonds are formed in series. These examples all fall within our definition of linear templates.

Linear templates have the potential for self-replication³⁴ since the product can in principle be identical to the template. There are a growing number of examples of synthetic self-replicators which use the complementarity and hydrogen bonding observed between pyrimidine and purine bases³⁵⁻³⁷ or between the carboxylate anion and amidinium cation.³⁸ Some of these self-replicating systems also template the formation of other nonidentical systems.^{38,39}

Interweaving Templates. Sauvage's synthesis of catenanes uses copper(I) as a template to induce two phenanthroline ligands to adopt a tetrahedral conformation around the metal (Scheme VII). The template forces the ligands to remain interwoven while coupling with the linking group takes place. Removal of the metal yields the catenane. In this synthesis, the template does not increase the efficiency of cyclization of any individual ring so it is not a cyclization template, but it does increase the probability of the product having

Scheme VII. Copper(I) as an Interweaving Template in the Synthesis of a Catenane^a

^a The copper(I) binds two phenanthroline units to give a tetrahedral geometry; ring closure then yields the catenane efficiently.

an interesting topology. This strategy has been extended to the synthesis of a trefoil knot.⁴⁰

The templates used by Stoddart in the syntheses of catenanes and rotaxanes⁷ use π - π interactions to enhance both cyclization and interweaving, leaving the template as an integral part of the final product. Further examples of interweaving templating have been observed recently by Hunter⁸, Gunter,⁹ and Seeman.⁴¹ In the latter case, $\text{Co}(\text{NH}_6)^{3+}$ is used to change the topology of a DNA knot from 3_1 to 4_1 , although the precise role of the cobalt cation is not yet clear.

Negative Templates

The templates discussed so far favor reaction between bound substrates; they are positive templates. It is also possible for a template to disfavor reaction between bound substrates; they are then negative templates. A negative template disfavors the formation of a given product not by accelerating a competitive reaction but by specifically disfavoring the formation of that product. In some cases, the negative template may have a second function as a positive template during a subsequent step.²⁵ In principle, any system which can be induced to adopt a particular molecular architecture by a positive template can be prevented from doing so by a negative template. For example, the Glaser cyclization of linear dimer 5 can be inhibited by the negative cyclization template Py₂Py, the yield of the cyclic dimer being halved. Clearly the ligand binds so that the linear dimer adopts a conformation in which the reactive groups are held apart so as to discourage intramolecular cyclization to the cyclic dimer. This same effect was observed in the Py₃T-templated reaction of monomer 1 (Scheme I). To summarize the results described earlier, the template binds to the linear dimer intermediate, preventing it from cyclizing, and then acts as a modest cyclization template, improving the yield of the cyclic trimer. The major contribution to this increase is derived from the suppression of the cyclic dimer.

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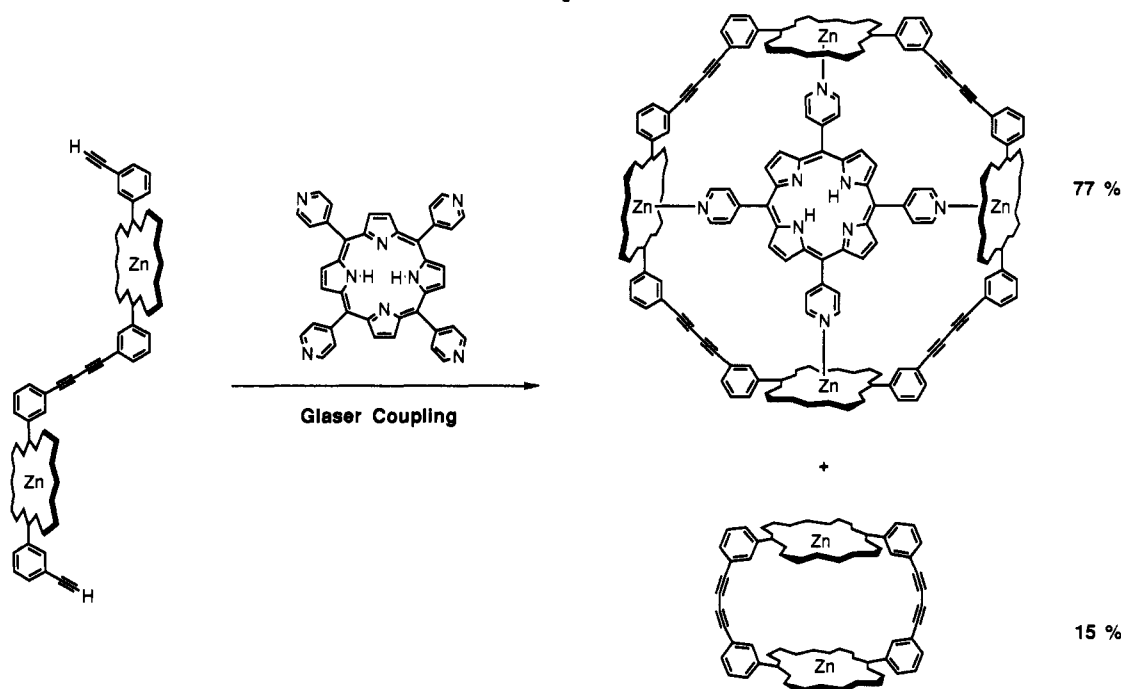
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Scheme VIII. Synthesis of Cyclic Porphyrin Tetramer 4 from Linear Dimer 5 Using Py₄Porph as the Template



A more satisfying example of negative templating is the efficient one-step synthesis (77% yield) of cyclic tetramer 4 from linear dimer 5 templated by Py₄Porph (Scheme VIII).²⁵ This is currently our best route for production of the cyclic tetramer. Here the template inhibits cyclic dimer formation by acting negatively and positively accelerates cyclization of the intermediate linear tetramer 6. Under some conditions, the coupling of two dimer units to yield a linear tetramer is also accelerated by the Py₄Porph template.²⁵

Discussion and Prospects

We indicated above that all templates can be categorized as thermodynamic or kinetic. If the reaction is under thermodynamic control, the only requirement for the template is that it should bind the desired product more strongly than all other species present in the equilibrium. Complementarity to the product is relatively easy to achieve since its binding properties can be determined independently.

For an efficient template in a system under kinetic control, the criteria are more complex. Figure 3 shows energy profiles for conversion of a substrate S to two products. In order to encourage production of product 1 by acting positively, the template must bind to the highest energy transition state (TS₁) and thereby lower ΔG^\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 (Figure 3(a)). Alternatively, the template can act negatively by binding to the intermediates and transition states of the unwanted side reactions in such a way as to increase their energies and so inhibit them (Figure 3(b)). 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 cyclizations of our linear dimer and tetramer. For the dimer in the presence of Bipy, the strength of binding appears to increase continuously along the reaction pathway from linear 5 ($6 \times 10^6 \text{ M}^{-1}$) to cyclic 2 ($6 \times 10^8 \text{ M}^{-1}$), providing precisely the required guidance.

The picture is more complex for linear tetramer 6; both Bipy and Py₄Porph act as positive cyclization templates, but Py₄Porph is more efficient even though Bipy binds to the product cyclic tetramer an order of magnitude more strongly. In both templated reactions, the transition state for ring closure must closely resemble the structure of the final complex so if this were the only step that mattered then Bipy would probably be a better template than Py₄Porph. However, the template must lead the initial substrate through a maze of alternative reaction pathways to reach the final transition state; its efficiency depends both on its ability to prevent the linear tetramer from undergoing intermolecular reaction and on its ability to bring the two reactive ends together. It appears that Bipy is less efficient than Py₄Porph at preventing the linear tetramer from undergoing intermolecular reaction early in the reaction pathway.

Returning to the templated formation of the cyclic trimer in Scheme I, we can now see that the template Py₃T must undertake a wide variety of roles if it is to be successful: complementarity to the trimer cyclization 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 to make 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.

Ideally one would like templates to be catalytic rather than stoichiometric, especially as they become more elaborate and sophisticated. Catalytic templates also

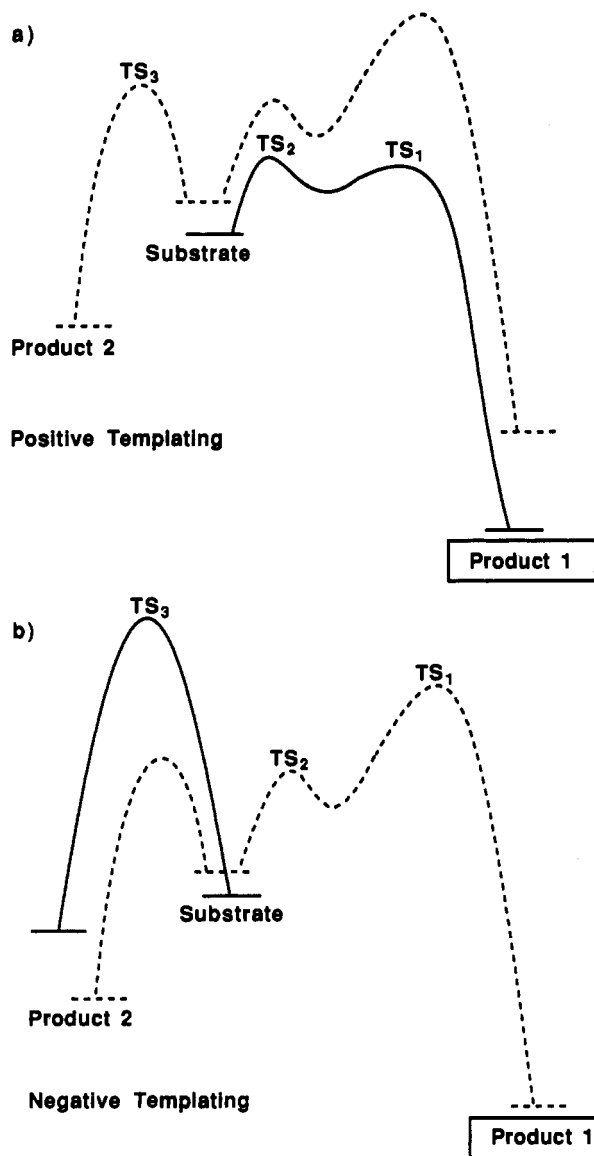


Figure 3. Energy profiles for untemplated (dashed line) and templated (solid line) reactions. (a) A positive template reduces the energies of intermediates and the transition states leading to product 1. (b) A negative template increases the energy of TS₂ thus disfavoring the formation of product 2.

have an intellectual appeal as enzyme mimics. Templates normally bind too strongly to their products to

operate catalytically, product inhibition severely limiting 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. In nearly all cases published so far, there are insufficient kinetic and thermodynamic data available to assess whether the transition state is bound more or less strongly than the product.⁴² Kirby has compared kinetic and thermodynamic effective molarities for a range of intramolecular reactions and found that they are generally of the same order of magnitude.⁴³ This implies that the templates will generally stabilize products and transition states by the same amount. However Rebek has found that some templates have a higher effective molarity for self-replication than for aggregation when there is some steric hindrance to dimerization,³⁷ but the only reliable way of designing a template to behave catalytically is to apply it in a situation where the product can be removed from equilibrium by a second process such as precipitation²⁸ or a subsequent, irreversible, reaction.⁴⁴

We have prepared an array of linear and cyclic porphyrin oligomers using the Glaser coupling as the only carbon-carbon bond-forming reaction and have achieved control through templating. Relatively small templates have been used to construct complex molecular architectures around them. Similarly these complex systems can be used as templates for reactions carried out within their spacious cavities.³² In principle, it appears that all bimolecular reactions and cyclization reactions should be amenable to acceleration and control by templates. It will be fascinating to see whether it is possible to make templates which bind transition states sufficiently selectively to operate efficiently as catalysts, capable of rivalling nature's enzymes. The application of templates appears limited only by our imagination and ingenuity—their role is, in every sense, expanding.

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(42) For an important exception, see: Ercolani, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* 1983, 105, 6146-6149.

(43) Kirby, A. J. *Adv. Phys. Org. Chem.* 1980, 17, 183-278.

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