Dynamic combinatorial olefin metathesis: templated synthesis of porphyrin boxes†‡

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A porphyrin macrocyclic square is efficiently prepared by a dynamic combinatorial approach to olefin metathesis and shown by scanning tunneling microscopy (STM) to self-assemble into highly ordered arrays on a graphite surface.

For decades, numerous chemists have devoted themselves to preparing a wide range of multiporphyrin assemblies for their diverse, often biologically inspired applications such as light-harvesting,[1] photodynamic therapy,[2] and catalysis.[3] Porphyrins and porphyrin assemblies are also promising constituents of functional surfaces.[4] Large cyclic structures containing porphyrin moieties, however, have received comparatively little attention.[5] To date, the most successful synthetic strategy for preparing cyclic arrays of porphyrins relies on coordination chemistry, as has been shown by Hupp and co-workers[6] and Stang *et al.*,[7] who prepared transition-metal containing macrocyclic arrays in virtually quantitative yields. Although materials and devices based on these complexes have been reported,[6b,8] the relative chemical and thermal instability of metal–ligand bonds exclude them from many applications that require conditions inherently incompatible with these bonds.

Covalent bonds are generally a far more robust way to interlink molecules, yet despite the impressive work of Sanders *et al.*[5a–c] and Lindsey *et al.*,[5d] the preparation of covalently linked cyclic porphyrin structures is limited by kinetically controlled conventional organic synthesis. In recent years, however, a strategy generally referred to as dynamic combinatorial chemistry (DCC) has emerged as a powerful tool to prepare covalent macrocycles and intertwined structures.[9] In DCC, bond formation is reversible, allowing for additional interactions to direct the thermodynamically controlled reaction towards a desired product.

Inspired by this approach, we set out to utilize the principles of DCC with our ongoing research program to prepare so-called processive enzyme mimics,[10] synthetic analogs of natural enzymes that form a pseudorotaxane topology in the processes of DNA maintenance, replication and degradation. For this goal, an efficient synthetic route to prepare robust, cavity-containing porphyrin architectures to thread onto DNA and DNA mimics is required. Here we report the novel preparation of such an architecture **Zn4.TPyP** (Scheme 1) as well as evidence of its self-assembly into highly ordered arrays on a graphite surface by means of STM.

Our synthetic strategy relies on olefin metathesis, employing olefin functionalized zinc porphyrins **Zn1**, a choice of Grubbs' first (**Ru2**) or second (**Ru3**) generation catalyst, and a tetrapyridylporphyrin (**TPyP**) template (Scheme 1). In our initial attempts, we treated a 4 : 1 mixture of **Zn1** and **TPyP** in dichloromethane with **Ru3** (route A). The choice for this catalyst was based on the fact that it is tolerant towards amines in contrast to **Ru2**.[11] The feasibility of this approach has been demonstrated,§ yet in our hands it failed to produce cyclic tetramer **Zn4.TPyP** in acceptable yield (<28%). Instead, a mixture of numerous oligomers, as revealed by MALDI mass spectrometry, was obtained. After varying several relevant reaction parameters and zinc porphyrins,¶ we eventually concluded that extremely high catalyst loading (up to 0.5 equivalents compared to the zinc porphyrin) and extensive chromatography is required to obtain at best moderate isolated yields of cyclic tetramer **Zn4.TPyP**. In addition, this tetramer proved to be a mixture of several compounds differing in size by one or more methylene groups as a result of isomerization reactions catalyzed by **Ru3** (Fig. 1a).[12] We tentatively attribute the disappointingly low yield to coordination of **TPyP** to **Ru3**, which results in deactivation of the catalyst and lowering of the effective template concentration.

In order to enhance the yield, we reasoned that it would be more efficient to first pre-equilibrate the zinc porphyrins into a 'library' of linear and cyclic porphyrin oligomers and subsequently utilize the template to direct the reaction towards the desired product **Zn4.TPyP**. Accordingly, we prepared a mixture of random linear and cyclic oligomers in the absence of a template from zinc porphyrin **Zn1** by treating it with **Ru2**, which does not display isomerization activity (Scheme 1, route B). Although we did not perform quantitative analysis of the library, MALDI mass spectrometry qualitatively confirmed our conjecture that the cyclic tetramer is only a minor component of the mixture. Subsequent treatment of the library, foregoing any workup, with 0.25 equivalents of template **TPyP** (with respect to the original **Zn1** concentration) and 0.1 equivalents of **Ru3**, yielded an easily

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† Electronic supplementary information (ESI) available: detailed synthetic procedure and characterization of **Zn4.TPyP** by means of NMR and UV-VIS spectroscopy, MALDI-TOF MS and GPC. See http://www.rsc.org/suppdata/cc/b5/b503619d/

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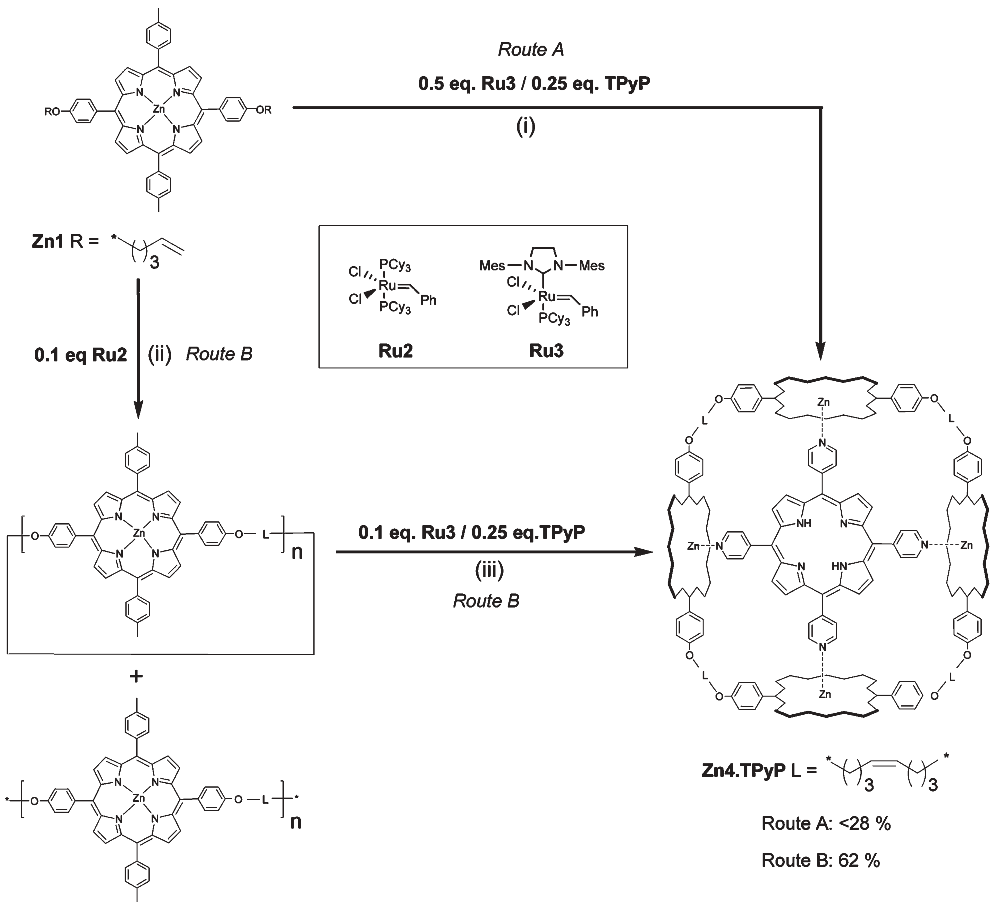

Scheme 1 Synthesis of **Zn4.TPyP** by templated olefin metathesis. **TPyP** = tetrapyridylporphyrin. (i) CH_2Cl_2, 12 h. (ii) CH_2Cl_2, 40 °C, 12 h. (iii) CH_2Cl_2, 6 h.

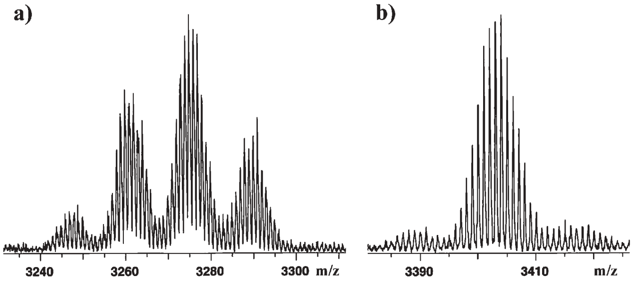

Fig. 1 MALDI MS spectra of cyclic tetramers prepared (a) according to route A and (b) according to route B. The supramolecular complex is not observed in these spectra; the template is observed at its expected mass (not shown).

separable mixture of mainly cyclic tetramer **Zn4.TPyP** (62%) and cyclic dimer (17%) among additional, uncharacterized by-products.

As expected, the decreased competition in binding of **TPyP** to **Ru3** and zinc porphyrins allows amplification of the thermodynamically most stable products from the library of oligomers.|| In addition, because of the reduced catalyst loading and diminished exposure of **Ru3** to terminal olefin bonds, isomerization activity is less pronounced and as a result a less polydisperse mixture of cyclic tetramers **Zn4.TPyP** is obtained (Fig. 1b).

Cyclic tetramer **Zn4.TPyP** was isolated by size exclusion chromatography in CH_2Cl_2 as its supramolecular complex, as concluded from ^1H and 2D NMR spectroscopy of the product in $CDCl_3$. The signals of **TPyP** are shifted upfield dramatically compared to free **TPyP**, indicating its binding inside the cavity of the tetramer. Specifically, the chemical shifts of the **TPyP** pyridine H_α, pyridine H_β, β-pyrrolic H and inner NH protons are 2.63 ($\Delta\delta = -6.44$), 5.80 ($\Delta\delta = -2.36$), 6.88 ($\Delta\delta = -1.99$) and −4.71 ($\Delta\delta = -1.79$) ppm, respectively. As a result, **Zn4.TPyP** necessarily adopts, on average, a box- or cup-shaped structure filled with the template.[5b]

In order to construct functional arrays and surfaces, we investigated the self-assembly of a template filled tetramer by STM. Imaging of **Zn5.TPyP**, prepared by reacting the hexenyloxyphenyl substituted analog of **Zn1** according to route A, at the interface of highly oriented pyrolytic graphite (HOPG) and a mixture of 1-phenyloctane and chloroform clearly revealed the presence of highly ordered domains, extending over more than 75 × 75 nm^2 (Fig. 2a). To date, only two STM investigations of large cyclic porphyrin architectures have appeared,[13] and neither of them have produced evidence for the presence of such highly ordered arrays as presented here.

Two orientations of the **Zn5.TPyP** complex at the interface are possible (Fig. 2b, orientations A and B). In orientation A, one of the zinc porphyrins of **Zn5.TPyP** is physisorbed on the HOPG

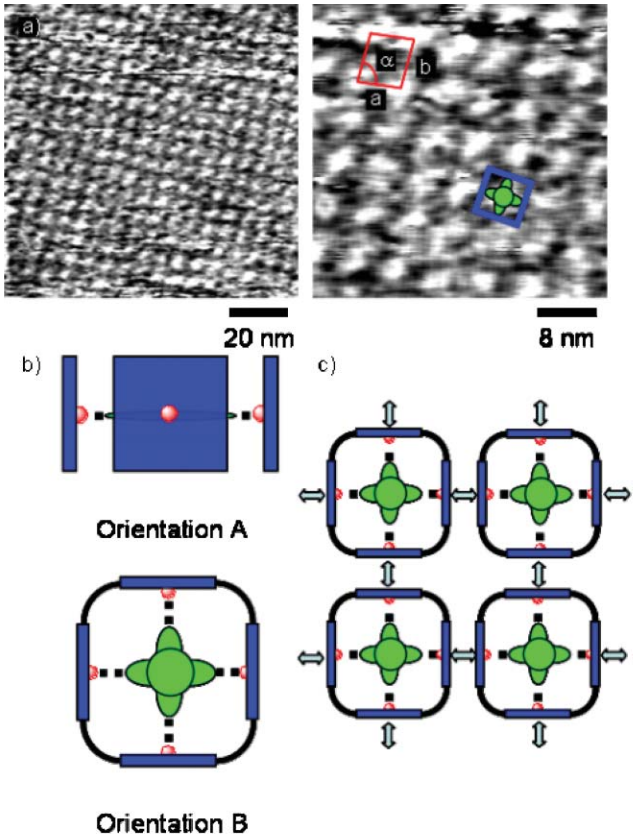

Fig. 2 (a) STM topography of self-assembled **Zn5.TPyP** at the interface of phenyloctane–$CHCl_3$ and a highly oriented pyrolytic graphite surface ($V_{bias} = -250$ mV, $I = 5$ pA). The unit cell ($a = 37 \pm 2$ Å, $b = 38 \pm 2$ Å, $\alpha = 84 \pm 2°$) is indicated by the red square and the proposed orientation is schematically illustrated by the blue square (**Zn5**) and the green guest (**TPyP**). (b) Top view of the two possible orientations of **Zn5.TPyP** with respect to the surface. (c) Schematic illustration of the proposed topology of **Zn5.TPyP** (top view), illustrating possible intermolecular π–π interactions (light blue arrows).

surface, which is the most commonly observed orientation of porphyrins on graphite.[14] This orientation however is not consistent with the observed square lattice and the topological periodicity of 3.7 ± 0.1 nm. We therefore propose that the zinc porphyrins of **Zn5.TPyP** are oriented 'edge-on' with respect to the surface (Fig. 2b, orientation B), leaving the **TPyP** template essentially parallel to the surface. This topology maximizes the number of stabilizing π–π interactions between neighboring zinc porphyrins (Fig. 2c).[15]

In summary, we have presented an efficient one-pot route to prepare a covalent porphyrin box by exploiting the dynamic covalent chemistry of olefin metathesis. The cyclic tetramers were shown to self-assemble on a surface into highly ordered arrays. We are currently exploring the potential of these and related macrocycles as components of (poly)rotaxane assemblies as well as building blocks for functional surfaces.

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Notes and references

§ In a similar approach, Inomata and Konishi prepared a six-membered zinc porphyrin cage around a pyridine appended gold nanocluster in 50% yield using a 70% catalyst loading, see ref. 16.

¶ Concentration (10^{-4} to 10^{-2} M), reaction time (up to 48 h), solvent (chlorinated hydrocarbons or toluene) or temperature (25 to 50 °C) did not have a significant effect, nor did employing other olefin chains (4 to 8 carbon atoms) or *meta*-substituted alkenyloxyphenyl porphyrins. The isolated yield never exceeded 30%.

‖ One might argue that the described system is not a genuine DCC synthesis, since equilibrium is reached only when ethene evolution is complete.

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