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Synthesis under reversible conditions of cyclic porphyrin dimers using palladium-catalysed allyl transesterification

Guido Kaiser and Jeremy K. M. Sanders*

Cambridge Centre for Molecular Recognition, University Chemical Laboratory, Lensfield Road, Cambridge, UK CB2 1EW. E-mail: jkms@cam.ac.uk

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Cyclic zinc-porphyrin dimers have been synthesised using reversible π-allyl palladium chemistry in the presence of bidentate pyridyl ligand templates.

Reversible covalent chemistry has the potential to be useful in the creation of diverse dynamic combinatorial libraries (DCLs)[1,2] and in the synthesis of specific supramolecular structures such as macrocycles and catenanes.[3] Examples of reversible reactions used to date include imine, hydrazone and disulfide exchange, olefin metathesis and metal–ligand interactions. However, there is always the need to expand the repertoire of available reactions and conditions. Here we report what we believe to be the first supramolecular application of π-allyl palladium-catalysed chemistry: furthermore, we demonstrate the use of a template to amplify an otherwise inaccessible synthetic target molecule from a complex mixture of interconverting oligomers.

We chose to apply π-allyl palladium chemistry to the synthesis of cyclic porphyrin dimers which might help our understanding of structure–activity relationships in the acceleration of a hetero Diels–Alder reaction.[4] Previously, such dimers have been prepared by intramolecular oxidative coupling of a linear porphyrin diester species (Fig. 1, route a)[4,5] since all attempts by our group to cyclise a linear dimer by irreversible esterification reactions (Fig. 1, route b) have failed; inevitably, these failures are unpublished. The attraction of route (b) using reversible π-allyl palladium chemistry is that, provided the product is thermodynamically accessible, its formation should be favoured by stabilisation through supramolecular complexation with an appropriate template. This is conceptually the inverse of the host-accelerated Diels–Alder reaction since the small guest is used to template the formation of the large host.

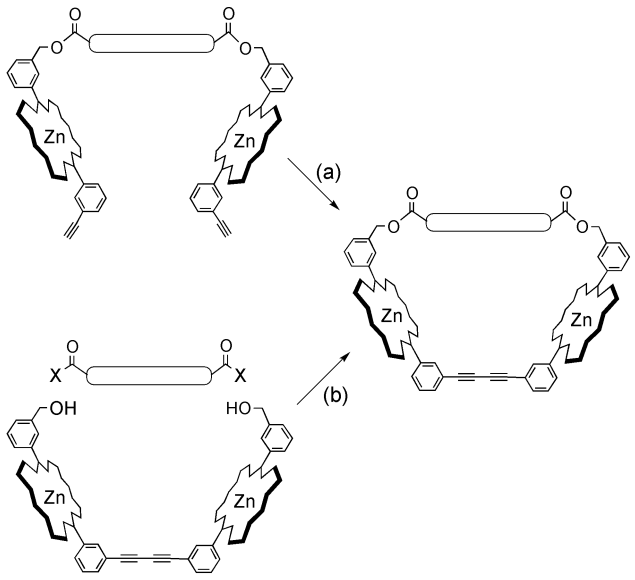
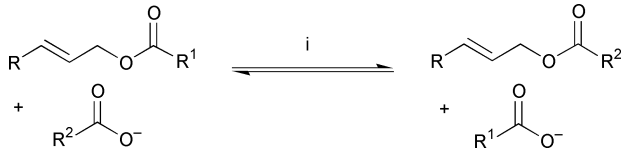


Fig. 1 Synthetic routes to capped porphyrin dimers.

It is well known that π-allyl palladium complexes generally undergo reversible reactions (Scheme 1),[6] and Amatore and Jutand *et al.* have recently confirmed the reversibility of the reaction between allyl esters and palladium(0).[7] Carboxylates and phenolates represent an ideal class of functional groups for isoenergetic exchange *via* reversible π-allyl palladium chemistry since they can act as both nucleophiles and leaving groups. In order to confirm the feasibility of using allyl esters as substrates, a simple model system based on cinnamyl esters was set up (Scheme 1, R = phenyl and *o*-tolyl; R^1 = CH_3, R^2 = Et). Complete exchange of the ester groups was observed after 6 h at 50 °C: all 4 possible permutations were present in equal amounts independently of which starting combination was employed. The reaction conditions appeared to be mild enough to be employed in the capping reaction of linear porphyrin dimers. The scientific challenge was therefore to devise a system where, for the first time, a linear porphyrin dimer would undergo a multi-step ring-closing transesterification reaction catalysed by palladium(0).

The linear porphyrin dimer **1** (Scheme 2) was synthesised according to previously published procedures:[5] the asymmetric porphyrin synthesis was carried out in 25% yield, followed by a Glaser–Hay coupling of the deprotected porphyrin monomers to give the linear dimer (60% yield). The simple dipyridyl **2** was chosen as the template, its role being kinetically to preorganise the linear porphyrin dimer by restricting rotation about the butadiyne axis, or thermodynamically to favour capped dimers over linears.

For the initial exchange experiments, alkyl diacids were expected to be sufficiently flexible and nucleophilic, in contrast to aryl acids which are more rigid and less nucleophilic. In the first instance, succinic acid was chosen. To aid structural analysis of the cyclic porphyrin dimer by NMR methods, labelled 1,4-^{13}C succinic acid was used.† In a typical experiment the linear porphyrin dimer **1** (20 mg, 1 eq.) and the template **2** (1 eq.) were dissolved in chloroform (2 ml), succinic acid (8 eq.), triethylamine (40 eq.) and tetrakis(triphenylphosphine)palladium(0) (0.1 eq.) were added and the solution was stirred at 55 °C under an inert atmosphere for 6 h. The mixture was demetallated using trifluoroacetic acid to remove the template and then remetallated using zinc acetate. The different porphyrin fractions were separated by preparative thin layer chromatography and dissolved in a fixed amount of solvent. Quantitative analysis of the product fractions was carried out by UV–Vis spectroscopy, based on the assumption that the molar extinction coefficients of the linear and cyclic dimers were similar. The relative absorbance of the products was measured and values are given in arbitrary absorbance units. Due to the



Scheme 1 *Reagents and conditions*: i, concentration of cinnamyl esters 10 mM, $Pd(PPh_3)_4$ (0.1 eq.), R^1CO_2H (< 0.1 eq.), Et_3N, $CHCl_3$, 50 °C, 6 h.

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small quantities of the fractions, accurate determination of the weights of the product was not possible.

In the absence of the template only traces of the capped dimer could be isolated (0.009 au—absorbance unit; less than 2% yield). However, in the templated experiments the isolated yield of pure **3** increased 6-fold to approximately 10% (0.055 au). The structure of the ring-closed dimer was confirmed by HMBC-NMR showing a cross-peak for the single enriched ^{13}C signal (δ = 172.4 ppm) with the allylic CH_2 protons (δ = 4.63 ppm). This significant and reproducible increase in the yield confirms the templating effect of the bidentate ligand and represents the first thermodynamic capping of a linear porphyrin dimer using reversible π-allyl palladium chemistry. To test the generality of the reaction, and to illustrate the feasibility of utilising libraries of capping groups at a later stage, cyclic dimers containing glutaric and 1,3-phenylenediacetic acid as capping groups were also prepared in comparable yields. In addition to NMR characterisation, MALDI-TOF mass spectrometry was used to distinguish between linear and cyclic species.

The control experiments without template and those in the presence of pyridine (2 eq.) gave the same results. Pyridine is a monodentate equivalent of the template **2**, *i.e.* the pyridine units are not covalently linked as for the bidentate template. This result confirms that the dipyridyl compound **2** templates the formation of the cyclic dimer by stabilising it and that the pyridyl functionality of the template does not influence the outcome of the transesterification. The large binding constants of template **2** to the linear and cyclic dimers, 3×10^6 and 2×10^7 M^{-1} respectively, are consistent with the observed templating effect.[8] However, the relatively small increase in the binding constant upon cyclization highlights the flexibility of the host and rationalises the low yield of **3**, *i.e.* the equilibrium is shifted only slightly from oligomeric species towards the formation of **3**.‡

It was possible to identify mono- and disubstituted linear dimers as intermediates of the reaction by MALDI-TOF and ^1H NMR. However, the relative quantities of all intermediates could not be estimated accurately due to the low solubility of oligomers and disubstituted linear dimers with two free carboxylic acid groups.§ It should be noted that the solubility of the mixture was not problematic during the reaction itself as the triethylamine salts of all intermediates are soluble in chloroform.

In summary, we have shown the synthesis under reversible conditions of three cyclic porphyrin dimers using palladium-catalysed transesterification. The reaction was templated by a bidentate pyridyl ligand which improved the yield of the cyclic product 6-fold. To our best knowledge, this is the first supramolecular application of reversible π-allyl palladium chemistry; it is also one of the most effective examples yet reported of amplification of a specific product from an exchanging library of components.

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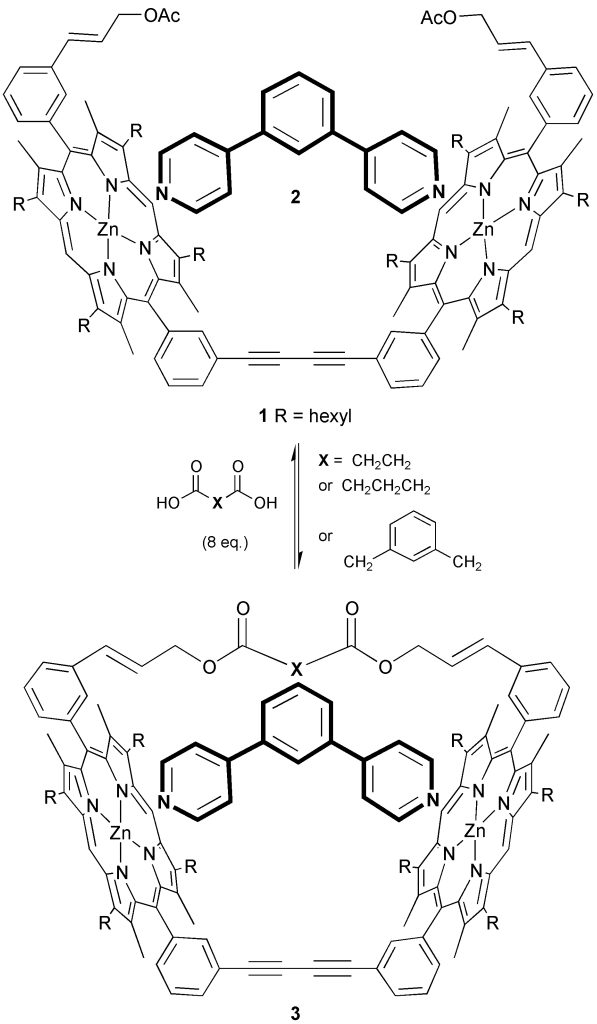

Scheme 2 *Reagents and conditions*: concentration of porphyrin dimer 5 mM, $Pd(PPh_3)_4$ (0.1 eq.), Et_3N, $CHCl_3$, 55 °C, 6 h.

Notes and references

† The molecular weights of linear dimer and unlabelled succinic capped dimer differ by only 2 a.m.u., precluding the use of MALDI-TOF mass spectrometry.

‡ This point is also apparent in the uniformity of yield from the three different capping acids of very different geometry.

§ The overall amount of isolated porphyrinic material was measured by UV–Vis spectroscopy and marked differences between the templated and non-templated reactions were observed. The overall recovery of soluble porphyrinic material was considerably lower for the non-templated reaction (0.1 au compared with 0.2 au for the templated reaction). This result implies that the template suppresses the formation of insoluble oligomers in addition to promoting the formation of cyclic product. The decrease in total oligomer formation is greater than the increase in cyclic dimer formation, suggesting that these are two separate effects, *i.e.* the dipyridyl compound **2** is a positive template for the cyclic dimer formation and a negative template for the oligomer formation.

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8 The binding constants were measured in dry $CHCl_3$ at 25 °C with host and guest concentrations of 10^{-5} M and 10^{-4} M respectively. The data were analysed using the commercial program Specfit.