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A General Route for the Synthesis of Flexible Porphyrin Dimers

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Abstract: The synthesis of two cyclic porphyrin dimers is reported. In each case the porphyrins are connected by a rigid butadiyne link, and a flexible alkyl chain tether. The length of this tether controls both the porphyrin-porphyrin distance, and porphyrin-porphyrin geometry. It is hoped that the extra flexibility designed within these molecules will enable them to act as general catalytic hosts for future study.

We have recently designed and synthesised a number of cyclic porphyrin oligomers, whose internal cavities have ranged in diameter from 12 to 15Å.[1,2] These molecules demonstrated a unique ability to accelerate a variety of reactions between two bound species. By virtue of their size and shape these cavity-enhanced reactions can proceed with remarkable regio and stereoselectivities. For example, by careful choice of host we were able to stereoselectively accelerate a Diels-Alder reaction to give either the *exo* or the *endo* products.[3] These hosts were designed to recognise (and stabilise) the transition state of a specific reaction. However, if we are going to successfully catalyse other reactions, new hosts capable of binding, recognising and stabilising a variety of transition states would be required. However, it has proved very difficult to systematically vary and control both the flexibility [4] *and* the geometry of the porphyrin binding sites within our existing systems; additionally, the effort involved in designing and constructing a unique host for a specific reaction is enormous, and the results have often been disappointing. We therefore required a new general strategy for the construction of macrocyclic hosts possessing a pair of porphyrin binding sites whose geometry and flexibility could be systematically and easily varied. Such a system could then be utilised to catalyse many different bimolecular processes. In designing such a system we felt it important to include an element of *synthetic versatility*. That is, to develop a synthetic strategy, which could be easily modified so as to give macrocyclic hosts of different geometries, size and degrees of flexibility.

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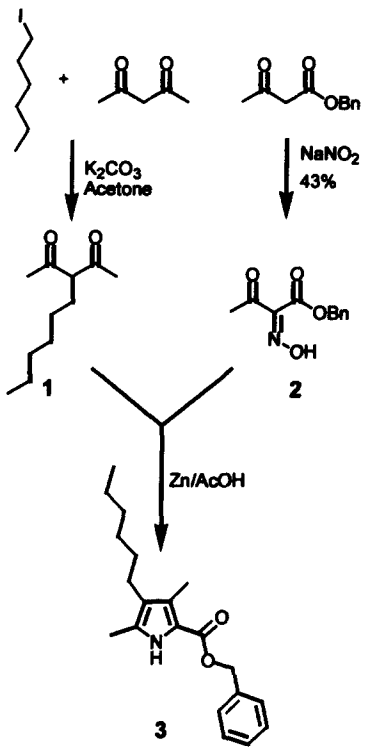
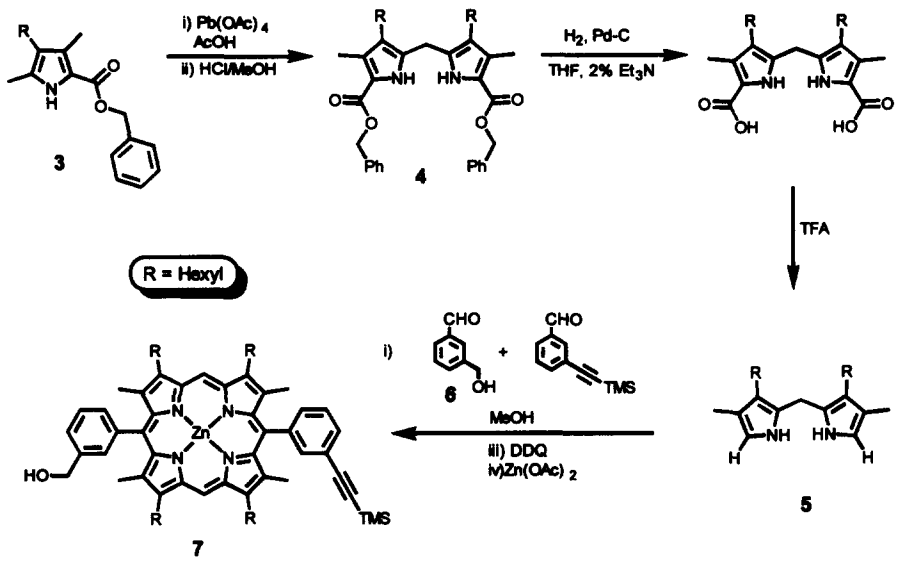


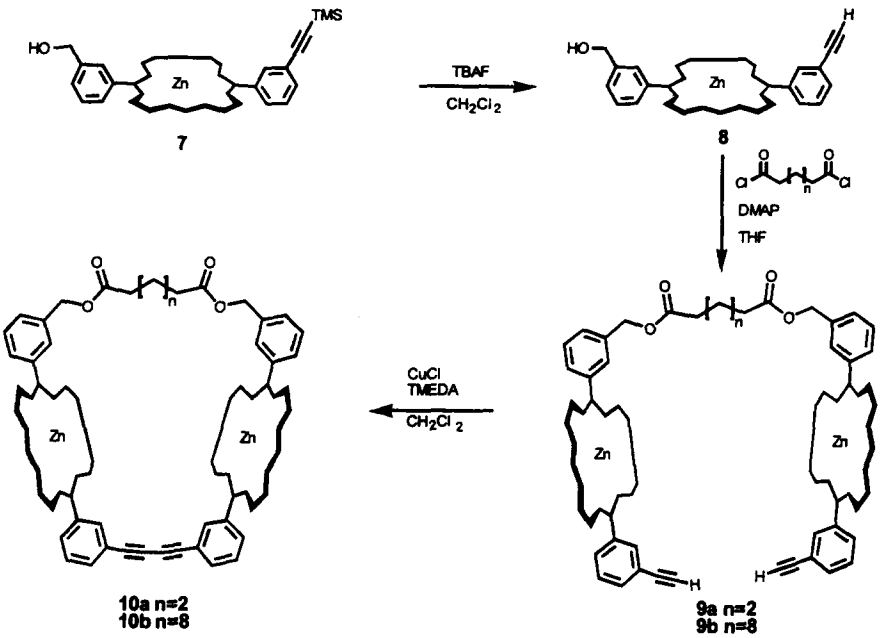
Scheme 1

This paper describes a versatile new approach to macrocyclic synthesis illustrated by two *flexible* porphyrin dimers, and is based on our previously reported stepwise approach.[2] To overcome solubility and reproducibility, we chose to construct our dimers using porphyrins with hexyl side chains. These porphyrins were synthesised from the corresponding hexyl-derived pyrrole, whose synthesis is shown in Scheme 1. 1-Iodohexane and 2,4-pentanedione were treated with potassium carbonate in acetone, to give the 3-hexyl-2,4-diketone **1**, which could be isolated in a 66% yield after distillation. 3-Hexyl-2,4-diketone **1** was then reacted with oxime **2** under reducing conditions to give the hexyl derived pyrrole **3** in 43 % yield.[5] The oxime **2** was readily synthesised from benzyl acetoacetate by treatment with sodium nitrite in water, Scheme 1. The porphyrin building block was efficiently synthesised, as shown below in Scheme 2, using a similar procedure to that reported earlier.[6] α-Acetylation of the hexyl-derived pyrrole **3** was accomplished by treatment with lead tetraacetate in acetic acid. Dimerization of this acetylated pyrrole was then achieved in refluxing methanolic HCl, yielding the dipyrrole **4** in 82%. Removal of the benzyl protecting groups from dipyrrole **4** by hydrogenolysis gave the bis α-acid quantitatively. Subsequent decarboxylation of the dipyrrole was carried out *via* treatment with concentrated TFA, giving the α-free dipyrrole **5** as an unstable oil, which was normally used immediately. The unsymmetrical porphyrin **7** was one of three possible products and was synthesised *via* a statistical procedure (the other two products being the *symmetrical* di-benzyl alcohol and the symmetrical di-TMS protected ethynyl porphyrins). The reaction sequence began with an acid catalysed condensation of *two* equivalents of the α-free dipyrrole **5**, with *one* equivalent of the TMS protected 3-ethynyl-benzaldehyde,[7] and *one* equivalent of 3-(hydroxy-methyl) benzaldehyde **6**.[8] Subsequent DDQ oxidation of the ensuing porphyrinogen, and finally metalation using zinc acetate, yielded a statistical mixture of symmetrical and unsymmetrical porphyrins. The desired porphyrin **7** could then be isolated, after careful chromatography, in an isolated yield of 24%. The symmetrical porphyrin products can be used for the preparation of other multi-porphyrin systems, greatly improving the overall efficiency of the synthesis.



Scheme 2

The synthesis of the two cyclic dimers was concluded as shown in Scheme 3. The TMS group was first removed from porphyrin **7** using TBAF in CH_2Cl_2, to give the free acetylenic porphyrin **8** quantitatively. Two equivalents of this porphyrin **8** were then reacted with one equivalent of a *bis*-acid chloride giving the linear porphyrin dimers **9a** and **9b** in 72 and 85% yields respectively. Finally, cyclisation, using a standard Glaser-Hay coupling procedure, and purification *via* preparative TLC, gives the cyclic dimers **10a** and **10b** in 67 and 56% yields respectively. Mass spectrometry and NMR confirmed successful cyclisation.[9] The choice of *bis*-acid chloride dramatically affects the dimers final geometric properties. For example, molecular modelling revealed that a *bis* acid chloride with a four-carbon spacer would give the *tightly tethered* dimer **10a**, with a zinc to zinc distance of around 11Å and a relative porphyrin to porphyrin angle close to 20°. On the other hand, dimer **10b** has a 10-carbon spacer; this leads to a relatively *strain free* system with a zinc to zinc distance of around 15Å and a relative porphyrin to porphyrin angle of 60°. Although tethered, both dimers would be capable of considerable motional freedom, and therefore able to bind and stabilise a range of transition states with a variety of different geometries. In conclusion therefore, we have designed a novel and general procedure for the synthesis of macrocyclic hosts possessing a pair of porphyrin binding sites whose geometry and flexibility can be systematically and easily varied. By varying the number of carbons in the ester tether, or the number of ethyne links, we can easily control the size, geometry and flexibility of the internal cavities on a sub-Ångstrom scale. The catalytic and rate enhancing properties of these hosts are currently being investigated.[11] This research was supported by the EPSRC and is gratefully acknowledged.



Scheme 3

References.

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8. 3-(hydroxy-methyl) benzaldehyde **6** was synthesised by careful reduction of isophthalaldehyde using 1 equivalent of $NaBH_4$ (EtOH, 0°C, 10 mins) and working up in the normal way.
9. *Experimental for porphyrin 7.* Palladium on carbon (10% 200mg) was added to a solution of 5,5'-dibenzyloxycarbonyl-3,3'-hexyl-4,4'-dimethyl-2,2'-dihydrodipyrrin **4** (2.0g, 4.65mmole) in THF containing 2% triethylamine (100ml) and the mixture stirred under hydrogen for 2hrs. The catalyst was filtered off and the solvent removed. Degassed TFA (25ml) was added under argon at 0°C giving a solution of **5**. After 30 min a solution of 3-ethynylbenzaldehyde (0.633g, 4.65mmole) and 3-(hydroxy-methyl)benzaldehyde (939mg, 4.65mmole) in methanol (degassed) was cannulated into the mixture at -25°C. The reaction was allowed to warm up with stirring over 2 hours, DDQ (2.24g, 99mmole) was then added and stirring continued for a further 15 mins. Triethylamine (30 ml) was added and the solvent removed by evaporation. The crude residue was taken up in CH_2Cl_2 (50ml) and zinc acetate (4.58g, 25.0mmole) added, this solution was stirred for 30 mins with occasionally refluxing, on cooling more CH_2Cl_2 (50ml) and a saturated solution of $NaHCO_3$ was added (100ml). The CH_2Cl_2 layer was collected and washed with sat $NaHCO_3$ solution (100ml) and water (2x100ml), before being dried and concentrated under vacuum. Flash Chromatography (eluting with 3:1, hexane:ethylacetate), followed by recrystallisation from methanol and CH_2Cl_2, yielded the desired porphyrin **7** in 24%. δ_H($CDCl_3$ 250MHz); 0.28(9H,s), 0.89(12H,t, *J*=7.5Hz),1.48(17H,m),1.70(8H,p, *J*=7.5Hz), 2.17(8H,p, *J*=7.5Hz), 2.52(6H,s), 3.96(8H,t, *J*=7.5Hz), 4.3(6H,s), 4.95(2H,m), 7.75(3H,m), 7.91(1H,d, *J*=8.0Hz), 8.03(3H,m), 8.18(1H,s), 10.15(2H,s).λ_{max}/nm (CH_2Cl_2), 411, 539, and 575. *m/z* (MALDI) 1046, ($C_{66}H_{86}N_4OSiZn$ requires 1043).
10. Slow rotation around the aromatic groups of pre-cyclised dimers **9a** and **9b** leads to complicated ^1H NMR spectra for **9a** and **9b**. However, after cyclisation only one average conformation is possible and the H^1 NMR spectra of **10a** and **10b** are dramatically simplified.
11. *To be submitted.*