Ethyne-Linked Cyclic Porphyrin Oligomers: Synthesis and Binding Properties

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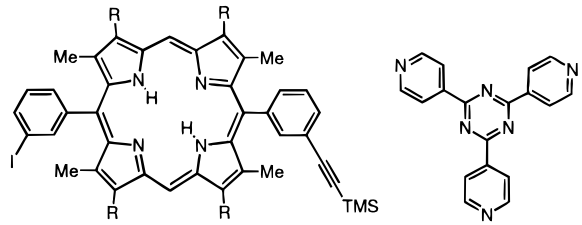
Received September 25, 1996

We report here a short new route to the ethyne-linked cyclic porphyrin dimer **$Zn_2$1** and trimer **$Zn_3$2**, which are of interest as part of our project to create receptors capable of binding, recognition, and catalysis.[1] The first milestone was controlled synthesis of the butadiyne-linked-2,2,2 trimer **$Zn_3$3** and related oligomers using templated Glaser−Hay coupling.[1,2] The 2,2,2-trimer has stereoselectively accelerated an *exo*-Diels−Alder reaction,[3] and catalyzed acyl transfers,[4] but synthesis of oligomers from monomers by the Glaser−Hay route limits the range of architectures and cavity size that can be prepared. An area of particular interest was the preparation of smaller, more rigid cavities with monoethyne units as the linkers.

We have previously reported a stepwise approach to asymmetric oligomers such as the 1,1,2-trimer using preformed porphyrins.[5] The obvious route to monoethyne-linked oligomers was Pd-catalyzed coupling of the monomer **$H_2$4**, but numerous attempts under a range of conditions failed to give significant amounts of the desired product. Templated coupling of **Zn4** in the presence of tripyridyltriazine **Py_3T** was also attempted without success; this is not surprising given the requirement of large amine concentrations for the coupling.



$H_2$4 R = CH_2CH_2COOMe

Py_3T

Topologically-linear porphyrin dimers have been synthesized previously by stepwise[6] or statistical[7] routes, and larger oligomers[8] have been derived from a combination of these methods, but we are not aware of any cyclic oligomers prepared from preformed linkers by the simultaneous construction of the porphyrin nucleus and the macrocycle that contains the porphyrin nuclei. Stepwise synthesis of a symmetrical species appeared conceptually unattractive, so we opted for the approach in Scheme 1, recognizing the low yield that inevitably results from a simultaneous multiple porphyrin synthesis.

Dialdehyde **5** was prepared by coupling of 3-ethynylbenzaldehyde and 3-bromobenzaldehyde, while the α-free dipyrromethane **6** was prepared by decarboxylation of the corresponding diacid using TFA. The porphyrin synthesis was carried out at high dilution conditions in dichloromethane using TFA as a catalyst (Scheme 1). Isolation of **$H_4$1** by column chromatography was relatively easy as it is the most mobile product. Trimer **$H_6$2** was more difficult to isolate and was never obtained completely free of higher oligomers. HPLC analysis indicated that the trimer was contaminated by approximately 3% of what we believe to be 1,1,1,1-tetramer and approximately 2% of another higher oligoporphyrin, but it was not possible to separate these on a preparative scale. 1,1-Cyclic dimer **$H_4$1** and 1,1,1-cyclic trimer **$H_6$2** were obtained in 3−4% and 1−2% yield, respectively, giving sufficient material to allow valuable binding studies to be carried out.

Comparison of the ^{1}H-NMR spectra of the free base 1,1-dimer **$H_4$1** and its 2,2-linked analogue **$H_4$7**[9] shows, as expected, larger transannular ring current effects in the smaller molecule: the NH signals are shifted upfield from −2.48 ppm in the monomer to −2.63 ppm in the 2,2-dimer to −2.88 ppm in the smaller dimer and the *meso* signals from 10.28 (monomer) to 10.01 (2,2-dimer) to 9.78 ppm. The geometry and small cavity size of the cyclic 1,1-system introduces a degree of strain that can be relieved by "doming" of the porphyrins. Consequently, the aromatic protons, H_2, directed into the cavity are shifted upfield from 8.20 ppm in the monomer to 7.08 ppm in the 2,2-dimer and to 6.76 ppm in the 1,1-dimer due to the enhanced shielding of the porphyrin ring currents.

The **$Zn_2$1**−dimer is much less soluble in chloroform; its ^{1}H NMR signals are broad, particularly in the *meso* region. Addition of DABCO improves solubility, and subsequent characterization was carried out on the 1:1 DABCO−**$Zn_2$1** complex. Sharp resonances characteristic of a single product are observed in the ^{1}H NMR spectrum, with a diagnostic *meso* peak at 9.64 ppm and a sharp signal at −4.95 ppm corresponding to a DABCO bound between two porphyrin units.[10]

The ^{1}H NMR spectra of **$H_6$2** and **$Zn_3$2** exhibit only minor differences from their larger analogues **$H_6$3** and **$Zn_3$3**. The **Py_3T** complex of **$Zn_3$2** is, however, more revealing. The bound **Py_3T** appears as two doublets, at 1.72 (H_α) and 5.77 (H_β) ppm, shifted to higher field relative to the protons of the unbound ligand (9.00 and 8.56 ppm, respectively), due to the porphyrin ring currents. These changes in chemical shift ($\Delta\delta_H$ of −7.28 and −2.79 respectively) for the smaller trimer are greater than those observed in the corresponding complex of the

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(2) To aid discussion and comparison of these closely-related analogues we introduce a shorthand notation for the number of ethyne links between building blocks. Thus, the original butadiyne-linked trimer **Zn_3**3 is denoted 2,2,2, while **$H_4$1** is the 1,1-cyclic dimer and **$H_6$2** is the 1,1,1-cyclic trimer.

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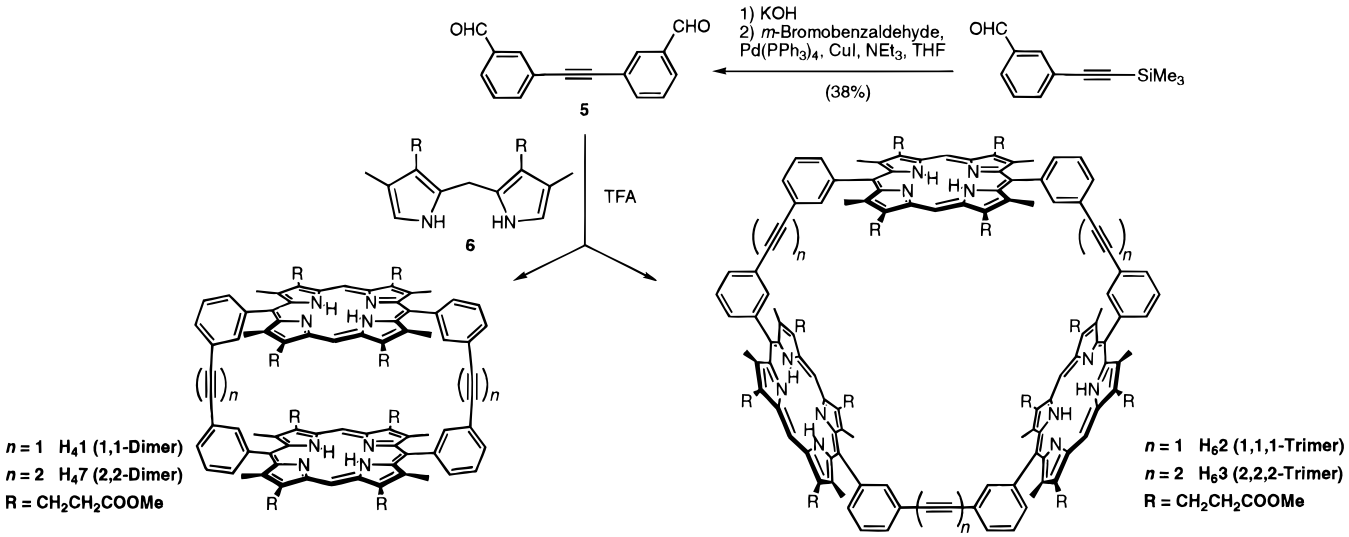
Scheme 1



Zn_3−2,2,2-trimer ($\Delta\delta_H = -6.61$ and -2.73 ppm).[11] Significant NOEs are observed between both side chain CH_2 groups and the *meso* proton, while a weak interaction between H_2 pointing into the cavity and the **Py$_3$T**-H_α confirms complexation of the ligand inside the cavity. Molecular modeling suggests that the Zn_3−1,1,1-trimer cavity is an ideal size to accommodate **Py$_3$T**, and a competitive binding experiment confirms this prediction. Addition of 1 equiv of Zn_3−1,1,1-trimer to a solution of the 1:1 Zn_3−2,2,2-trimer−**Py$_3$T** complex (∼2 mmol, $CDCl_3$) results in complete and rapid transfer of the **Py$_3$T** ligand to the smaller cavity. In the reverse experiment, addition of 1 equiv of Zn_3−2,2,2-trimer to a solution of the 1:1 Py$_3$T−**Zn$_3$2** complex, no net transfer of the ligand is observed. An accurate value for the ratio of the binding constants cannot be derived from these experiments, but it is safe to predict that the binding constant of **Py$_3$T** to the smaller Zn_3−1,1,1-trimer is at least 1 order of magnitude greater than that to the Zn_3−2,2,2-trimer; i.e., K must be greater than 10^{10} M^{-1}. This stability is reflected in the presence of a FAB MS peak at m/z 3159 corresponding to the molecular ion for the 1:1 complex. Such complexes are observed in the FAB mass spectra of nitro and dioxo porphyrins but not in the unsubstituted 2,2,2 series.[12]

Molecular modeling predicts an ideal fit for the DABCO ligand in the Zn_2−1,1-dimer cavity, and a competitive binding experiment between this compound and Zn_2−2,2-dimer confirms the preference for binding of DABCO inside the 1,1-cavity. Addition of 1 equiv of DABCO to Zn_2−2,2-dimer gives broad signals in the ^{1}H-NMR spectrum. The DABCO signal at −5.2 ppm is diagnostic of DABCO binding to two porphyrin units rather than one (for which it would appear at −3.0 ppm[10]). The broadening may be attributed to the formation of rapidly breaking and reforming DABCO−porphyrin polymers. For the 2,2-dimer, where the DABCO is a poor size match for the cavity, the ligand shows a preference for extracavity intermolecular binding, each DABCO experiencing the ring currents from the porphyrins directly bonded to it and also a weaker effect from the more distant porphyrins.[10] On addition of 1 equiv of Zn_2−1,1-dimer the DABCO is transferred almost exclusively into the smaller cavity, binding as a bidentate ligand. A sharp DABCO resonance is observed at −4.96 ppm, and this peak remains unchanged on addition of a large excess of DABCO. This indicates that the DABCO is in slow exchange with excess ligand as a result of strong binding: K must be greater than 10^8 M^{-1}. With excess DABCO, two sharp *meso* signals are observed at 9.64 and 9.79 ppm corresponding to the 1:1 complex and a 2:1 DABCO:Zn_2−2,2-dimer complex, respectively. In contrast, the corresponding competitive binding experiment using the larger bidentate ligand 4,4′-BiPy shows no ligand transfer into the smaller cavity, as predicted by molecular modeling.

In conclusion, this is a short, viable route to multimilligram quantities of pure 1,1-dimer because isolation by chromatography is relatively easy. However, our main target in view of its catalytic potential was trimer **Zn$_3$2**, but the low yield and difficulty in separation from higher oligomers render this route less effective in providing large quantities of this material. Why is this trimer so elusive? If the porphyrin moieties are assumed to be planar, then the trimer would appear to have a strain-free geometry. Crystallographic evidence[13] shows that the bis-aryl porphyrins are distorted in the 2,2,2-series, so it may be that the 1,1,1-trimer is rather strained. Furthermore, the synthetic approach of Scheme 1 probably leads to thermodynamic equilibration at the porphyrinogen level so strain at that stage would lead to a small yield.[14] The catalytic properties of the 1,1,1-trimer therefore remain tantalizingly out of reach. A single experiment shows that it accelerates our Diels−Alder reaction effectively and with considerable *endo*-selectivity as might be expected from the smaller cavity size.

Acknowledgment. We thank the European Community Human Capital and Mobility Program and the EPSRC for financial support.

Supporting Information Available: Experimental details of syntheses and spectroscopic characterization (5 pages).

JO961814U

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