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Stepwise π-extension of *meso*-alkylidenyl porphyrins through sequential 1,3-dipolar cycloaddition and redox reactions†

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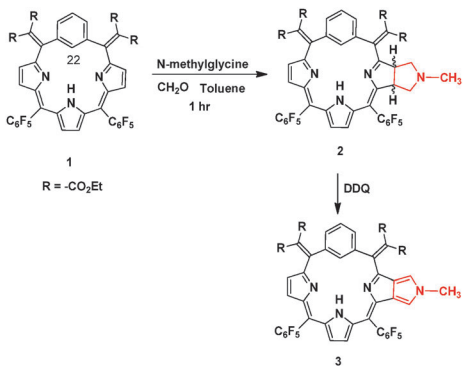
Several regioselectively π-extended, pyrrole fused porphyrinoids have been synthesized by the 1,3-dipolar cycloaddition of *meso*-alkylidene-(benzi)porphyrins. Pd(II) complexes gave oxidation resistant, bis-pyrrole fused adducts. The repeated 1,3-dipolar cycloaddition followed by oxidation–reduction of pentaphyrin analogs afforded π-extended porphyrin analogs.

The development of new synthetic methods for the construction of functionalized porphyrins has received considerable interest recently because of the potential application of porphyrin-based materials in various applications, including medicine and materials chemistry.[1] Modification of the β-pyrrolic positions is one of the most commonly used approaches for the functionalization and modification of porphyrins, and a large number of modified porphyrins have been constructed during the last few years using this strategy.[2] We recently became interested in the development of the rare class of modified porphyrinoids, which have not been studied previously in any great detail.[3–6] Among them, the *meso*-alkylidenyl porphyrins represent newly developed porphyrinoid frameworks, and compounds belonging to this class have been reported to show unique tautomerization properties.[5]

There is growing interest in the development of an in-depth understanding of the relationship between the electronic features of porphyrinoid macrocycles and their aromaticity. With this in mind, we have become particularly interested in the development of synthetic methods for the systematic extension and functionalization of the π-systems in porphyrinoids. Herein, we report the development of a cycloaddition reaction involving the reaction of the *meso*-diethyl malonylidene-*m*-benziporphyrin and the *meso*-diethyl malonylidene-*m*-benzipentaphyrin with azomethine ylides, which were generated *in situ* from the reaction of *N*-methylglycine with formaldehyde. This synthetic methodology has been well documented in the literature and has become an important alternative to the synthesis of π-extended porphyrin analogs. Cavaleiro *et al.* and Dolphin[7–9] have shown that the 1,3-dipolar cycloaddition reaction of porphyrins with 1,3-dipolarophiles could be used as an excellent tool for the preparation of π-extended porphyrins.

The versatility and synthetic utility associated with these reactions could be applied to the synthesis of the π-extended analogs of the *meso*-alkylidenyl porphyrinoids. To demonstrate the utility of this reaction, we herein report the 1,3-dipolar cycloaddition reactions (DCAR) of *meso*-alkylidenyl porphyrin analogs with *in situ* generated azomethine ylides.[10] As shown in Scheme 1, a typical reaction consisted of a mixture of paraformaldehyde, *N*-methylglycine (1.5 equiv.) and the porphyrin **1** being heated in toluene at 90 °C for 1 h under an atmosphere of nitrogen.[4,11] Upon completion of the reaction, as indicated by the disappearance of compound **1** by TLC, the reaction was stopped and subjected to a standard work-up procedure to afford adduct **2** in an isolated yield of 16%. Adduct **2** was the only isolated product and other regioisomers were not detected.

The amount of *N*-methylglycine added to the reaction appeared to be critical to the purity profile of the reaction. Subsequent *in situ* oxidation with DDQ afforded the oxidized product **3**.



Scheme 1 1,3-Dipolar cycloaddition of *meso*-alkylidenyl porphyrin **1** with *N*-methylglycine followed by oxidation.

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Only trace amounts of the bis- and tris-adducts were detected by MALDI-TOF MS analysis.

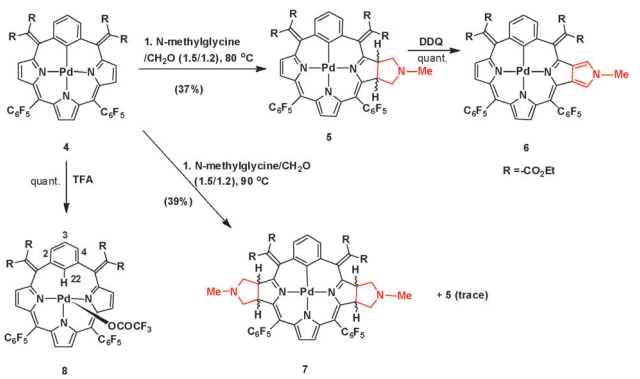
Attempts to react compound **1** with an excess of *N*-methylglycine to obtain multiply cyclized adducts were not successful, with prolonged reaction times and large excesses of *N*-methylglycine affording complex mixtures of products. Subsequent analysis of these compounds by proton NMR spectroscopy in $CDCl_3$ revealed that the N–H proton in **2** appeared as a sharp singlet at 11.67 ppm, while the same proton appeared at 11.97 ppm in the oxidized compound **3**.[12] This shift in the resonance signal to a lower field indicated the existence of an intramolecular hydrogen bonding interaction in both cases.

Since the double 1,3-dipolar cycloaddition of **1** with the azomethine ylide in a single step was unsuccessful, the metal-complex **4** was prepared separately before being subjected to the 1,3-dipolar cycloaddition reaction. The reaction of **1** with $PdCl_2$ proceeded smoothly to give the corresponding Pd(II)-complex **4** in high yield, which was reacted with the azomethine ylide (generated *in situ* from the reaction of *N*-methylglycine with paraformaldehyde) to afford a diastereomeric mixture of the bis-adduct **7** in 39% yield (Scheme 2).

Subsequent attempts to oxidize **7** with various oxidants, however, were unsuccessful, and resulted in extensive decomposition. The facile decomposition of **7** was attributed to the severe steric hindrance between the diethylmalonyl group and the annulated *N*-methylpyrrole ring when fully oxidized. Pleasingly, however, the reaction of compound **4** with the azomethine ylide to afford adduct **5** also afforded Pd(II)-complex **6** quantitatively by subsequent oxidation with DDQ.

Different products were formed depending on the reaction temperature, and it was therefore critically important to exercise strict control over the reaction temperature to obtain the desired product. As shown in Scheme 2, the mono-cyclized adduct **5** was formed as the major product when the reaction was conducted at 80 °C, whereas bis-adduct **7** was formed as the major product at elevated temperatures (>90 °C).

As shown in Fig. 1, the ^{1}H NMR spectrum of the free base porphyrin **1** displayed a broad singlet at 7.58 ppm, which was attributed to H(22). Interestingly, this resonance signal was not present in the ^{1}H NMR spectrum of the corresponding Pd(II)-complex **4**, indicating the Pd(II)–C(22) bond formation.



Scheme 2 Attempted cycloaddition reaction of **4**.

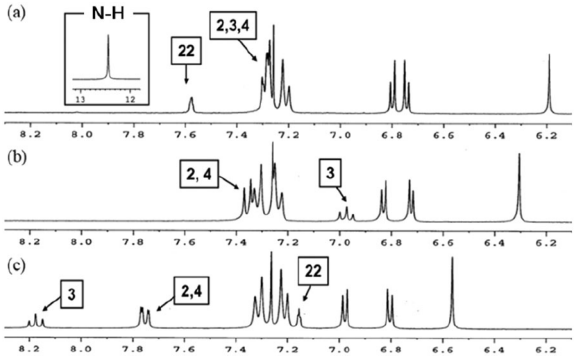


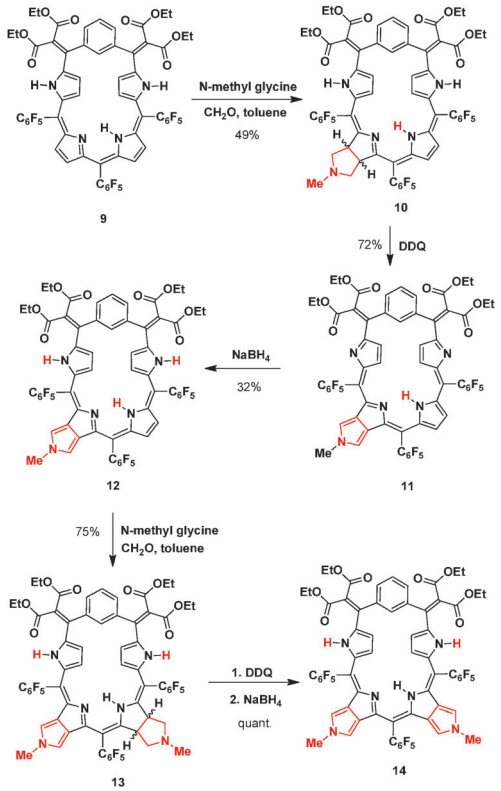
Fig. 1 ^{1}H NMR (400 MHz) spectral changes of (a) free base **1**, (b) Pd(II)-complex **4**, and (c) compound **4** following the addition of TFA ($CDCl_3$).

Upon treatment with excess trifluoroacetic acid, all three phenyl-Hs were clearly visible again. It was envisaged that the addition of excess acid to the Pd(II)-complex **4** would induce demetallation. However, in practice, this treatment resulted in the cleavage of the Pd(II)–C(Ph) bond only, and afforded compound **8** in quantitative yield.

The ^{1}H NMR spectrum of compound **8** in $CDCl_3$ revealed that there has been a significant down field shift of all the aryl protons (*i.e.*, 2, 3 and 4) while maintaining the normal coupling. This observation strongly suggested the existence of a d-π back bonding interaction between the phenyl group and Pd(II). It has been reported that the protonation can trigger the rehybridization of C(22) from trigonal to tetrahedral whereas the positive charge can readily disperse at the six-membered ring preserving still the Pd(II)–C(22) coordination.[13] But this is not the case with this heavily sterically hindered, conformationally locked porphyrinoid.

We proceeded to investigate the 1,3-dipolar cycloaddition reaction with the pentaphyrin analogue **9**. As shown in Scheme 3, the *meso*-diethylmalonylidene-(*m*-benzi)pentaphyrin **9** was reacted with the *in situ* generated azomethine ylide under similar conditions to those used for the cycloaddition of compound **4** to give the mono-cyclized adduct **10** in 49% yield. Subsequent oxidation with DDQ afforded the fully oxidized compound **11** in quantitative yield. Compound **11** was found to be unstable in solution and underwent a slow reduction process to give compound **12** during its purification by column chromatography over silica gel. The resulting mixture of **11** and **12** was treated with $NaBH_4$ to afford pure compound **12**. Given that our attempted one-pot double cycloaddition reaction for the conversion of **9** to **14** failed in the presence of an excess of the azomethine ylide, the cyclization was repeated following the isolation of compound **12**. In this particular case, the reaction proceeded smoothly to afford compound **13** in high yield, which was readily converted to compound **14** in quantitative yield by DDQ oxidation. All of the products and intermediates were characterized by ^{1}H NMR, UV-vis and high resolution mass spectrometry (ESI†).

The UV-vis absorption spectra of one pyrrole-extended compound **3** showed clear hypsochromic shifts. Notably, a red shift was observed in the Soret-like band (~30 nm) of the pyrrole-fused porphyrin (Fig. 2a). Fig. 2(b) shows the absorption spectra of the



Scheme 3 Sequential 1,3-dipolar cycloaddition reaction of pentaphyrin **9**.

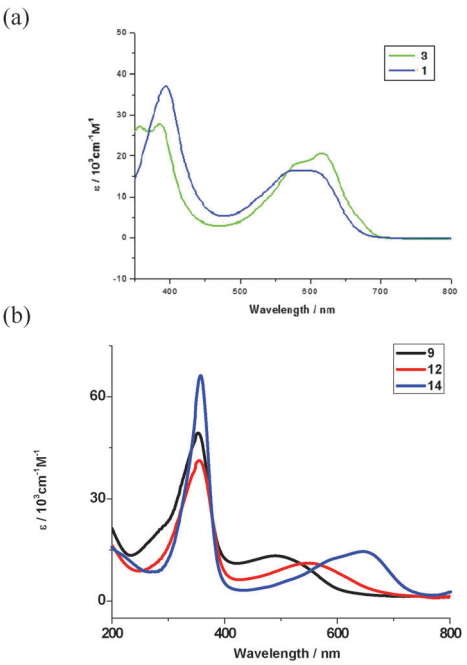


Fig. 2 UV-vis absorption spectra of (a) **1** (20.6 μM), **3** (19.6 μM), (b) **9** (16.4 μM), **12** (15.8 μM) and **14** (15.1 μM) in toluene.

pentaphyrin derivatives **9**, **12** and **14**. The Soret-like bands of these compounds remained almost unchanged following the introduction of the additional fused pyrrole ring, whereas large red-shifts were clearly observed in the Q-bands in the range of 600 to 652 nm.

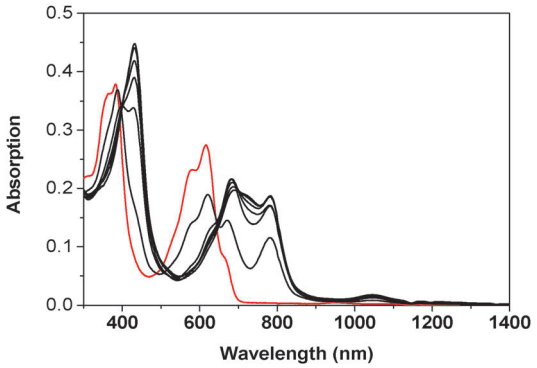


Fig. 3 Changes in the UV-VIS-NIR absorption spectra of porphyrin **1** following the gradual addition of TFA (1–20 equiv.) in toluene. Free (red trace), gradual addition of TFA (black).

Dramatic changes were observed in the UV-vis absorption spectra of **1** following titration with TFA in toluene, as shown in Fig. 3. The absorption signals of the free porphyrin shifted dramatically to longer wavelengths following the addition of TFA, and NIR bands emerged at around 1050 nm. The occurrence of this large red-shifted absorption was attributed to the extended conjugation resulting from the protonation-induced annular tautomerism.[8]

In summary, we have demonstrated that it is possible to systematically extend the π-system of *meso*-alkylidenyl porphyrins using successive 1,3-dipolar cycloaddition reactions with an azomethine ylide followed by oxidation. The newly synthesized π-extended analogues exhibit spectral features that could be used for chromogenic tuning. Studies directed towards developing a greater understanding of the protonation selectivity properties of these systems as well as identifying potential applications for their chromogenic properties are currently underway in our laboratory.

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