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Synthesis and chemistry of new benzoporphyrins

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Abstract

Benzoporphyrins **5** and **6** are the major products obtained from the cycloaddition reactions of β-fused metallopyrroloporphyrins **1** and **2** with dimethyl acetylenedicarboxylate. In the presence of excess dienophile a bis-adduct is also obtained which undergoes retro-Diels–Alder reaction to produce **5**. Benzoporphyrin **5** was converted into the first reported β-fused benzochlorins **9–11**, and the free-base benzoporphyrin **12** was regioselectively brominated to afford **13**. Exhaustive bromination also yields hexabromobenzoporphyrin **14**. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: benzoporphyrins; chlorins; chlorin derivatives; cycloadditions; halogenation; porphyrins; porphyrin analogues.

Since the discovery of benzoporphyrins in some petroleum and related deposits,[1] several synthetic approaches to these compounds have been described[2–8] in order to explore their interesting chemical and physical properties. The extension of the macrocyclic π-system through a fused benzene ring typically causes significant red-shifts in the optical spectra, increased basicity, and decreases in the oxidation potentials of these compounds. Benzoporphyrins have been prepared from the oxidation (with DDQ) of dihydrobenzo-[2–4] and tetrahydrobenzoporphyrins,[5] from condensation of benzodipyrromethene hydrobromides,[6] from Diels–Alder type reactions involving β-vinylporphyrins and activated dienophiles,[7] and from retro-Diels–Alder reactions using bicyclic-ethanodihydrobenzoporphyrins.[8] We report herein a novel synthetic approach to monobenzoporphyrins via the [4+2] cycloaddition reaction of fused metallopyrroloporphyrins, and the reactivity of the product towards bromination and nitration reactions; nucleophilic addition of malononitrile to a β-nitrobenzoporphyrin in the presence of base also led to the formation of previously unreported β,β′-fused benzochlorins.

N-Protected pyrroles have been successfully used in a variety of [4+2] cycloaddition reactions with activated dienophiles.[9] We recently reported[10] the synthesis of β-fused pyrroloporphyrins (e.g. **1, 2**) from the Barton–Zard condensation[11] of metallo-2-nitro-*meso*-tetraphenylporphyrins with isocyanoacetates, and an *N*-Boc protected metallopyrroloporphyrin has been shown to undergo a Diels–Alder reaction

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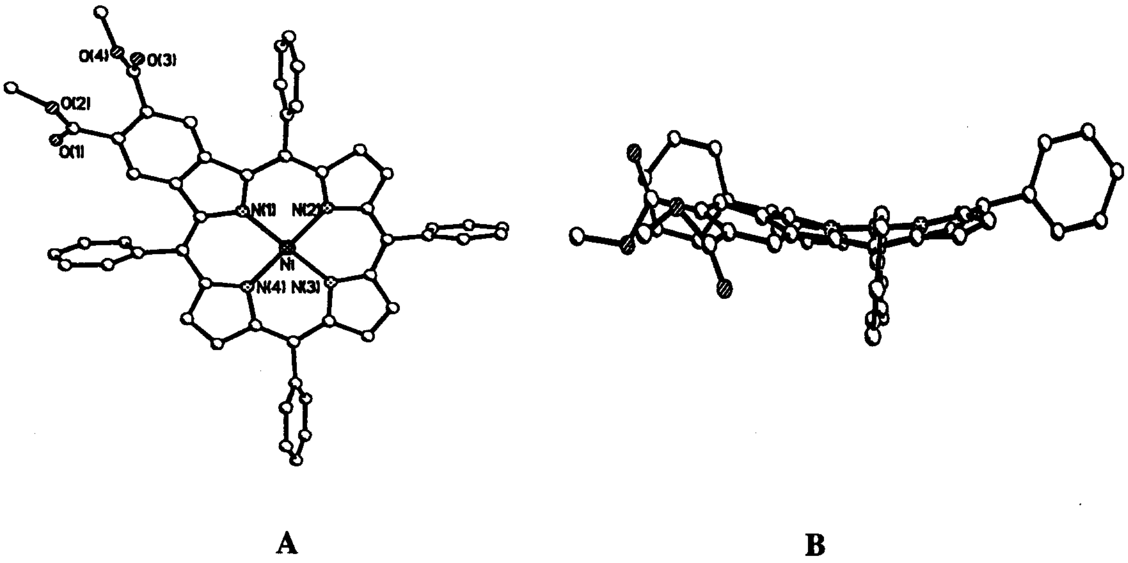
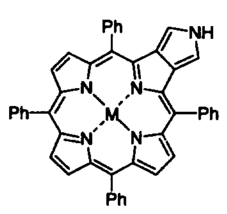


Figure 1. X-Ray structure of **6**. (A) top view, (B) side view. Hydrogens have been omitted for clarity[13,14]

in the presence of an activated dienophile.[12] Our own studies on the cycloaddition reactions of *N*-unprotected metallopyrroloporphyrins led to the discovery of a new synthetic route to benzoporphyrins.

When copper(II) pyrroloporphyrin **1** (or its Ni complex **2**)[10] was refluxed in toluene under anhydrous conditions in the presence of excess dimethyl acetylenedicarboxylate, the Diels–Alder adduct **3** was produced in 60–80% yield; it was rapidly converted into benzoporphyrins **4** and **5** upon prolonged refluxing (overnight).



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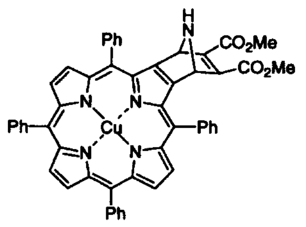
2: M = Ni



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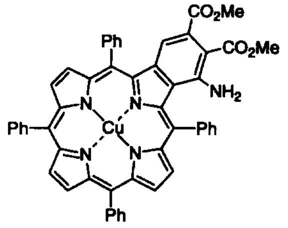

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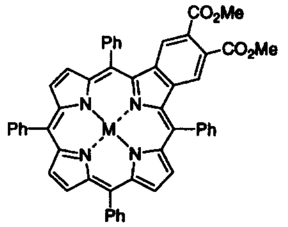
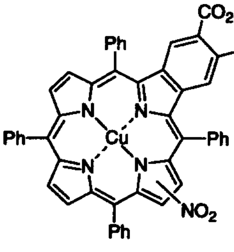


5: M = Cu
6: M = Ni

The reaction was easily followed by spectrophotometry since the starting material **1** displays a Soret absorption band at 430 nm; adduct **3** shows a Soret band at 420 nm, benzoporphyrin **4** at 436 nm, and compound **5** at 430 nm. Continuous heating led to formation and isolation of benzoporphyrin **5** as the sole product. The structure of benzoporphyrin **6** (obtained in a similar way from **2**) was further confirmed by X-ray crystallography (Fig. 1).[13,14] Benzoporphyrins **5** and **6** are probably formed by the dienophile-induced deamination of **3**.[15] Refluxing the reaction mixture in 1,2,4-trichlorobenzene (240°C) for 10–30 mins led to the formation of benzoporphyrin **5** (in 55–80% yield) and a bis-adduct (20–45% yield, Soret band at 440 nm) which showed multiple methoxy resonances in its proton NMR spectrum. The bis-adduct underwent a retro-Diels–Alder reaction upon prolonged refluxing (8–18 h) in 1,2,4-trichlorobenzene, producing benzoporphyrin **5**. The structure and mechanism of formation of the bis-adduct are being investigated.

The effect of the fused benzene ring on the chemistry and reactivity of benzoporphyrins was studied.

Mononitration of **5** using N_2O_4 in dichloromethane occurred in excellent yield with minimal formation of dinitro derivatives, giving products **7** and **8** as a regioisomeric mixture.



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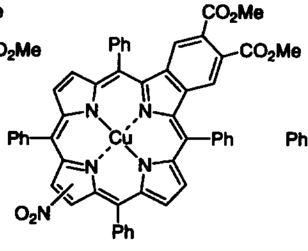

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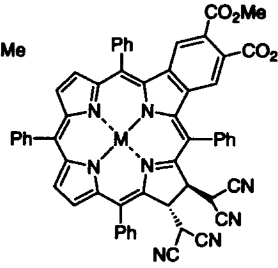
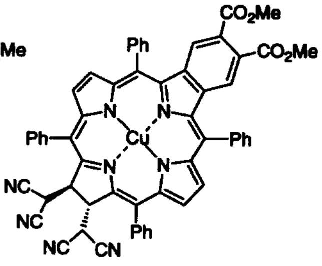


9: M = Cu
11: M = 2H



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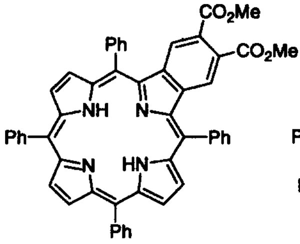
Control of the reactivity site through core metalation led preferentially to the adj-functionalized β-nitrobenzoporphyrins **7**. Indeed, after conjugate addition of malononitrile to the nitroalkene subunit in the presence of NaH and in refluxing tetrahydrofuran,[16] the blue-green β-fused-benzochlorin **9** was the major product isolated. Chlorin **9** and its opp-isomer **10** displayed long-wavelength absorption Q bands at 628 and 646 nm, respectively. Brief treatment with 33% HBr in acetic acid was found most efficient to demetalate **9**, albeit in low yield. The resulting metal-free derivative **11** displayed two sets of reduced pyrrolic protons in its proton NMR spectrum, confirming the proposed subunit regiochemistry of **9**.

Demetalation of **5** with 0.5% H_2SO_4 in trifluoroacetic acid quantitatively afforded the free-base benzoporphyrin **12**.



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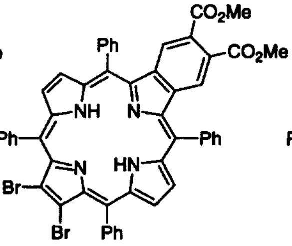

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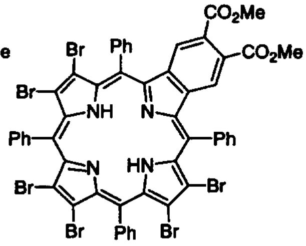

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Bromination of **12** (with excess NBS in refluxing $CHCl_3$) occurred at the pyrrole subunit opposite to the benzene ring to afford **13**, which reveals that such a fused ring acts as a 'bond-fixing'[17] entity leading (via a favored NH-tautomeric 18 π-electron pathway) to regioselective electrophilic substitution. Surprisingly, hexabromoporphyrin **14** (exclusive of any other partially brominated porphyrins) was also identified by mass spectrometry of the crude mixture (amounting to about 10% of **13**). Formation of **14** requires that the halogenation first takes place on a pyrrole unit adjacent to the fused benzene ring; this has the effect of eliminating the directing/blocking effect of the fused benzene ring. In other words, adjacent bromination of **12** induces the loss of a favored 18 π-system and results in an unprecedented perbromination of the porphyrin macrocycle without requiring core metalation. Compound **13** did not react upon reflux in $CHCl_3$ in the presence of a large excess of NBS, indicating synergistic control of the π-system by the bromo substituents and the antipodal fused benzene ring, thus preventing further bromination.

In conclusion, benzoporphyrins were the products obtained from the cycloaddition reactions of metallo[3,4-*b*]pyrroloporphyrins with dimethyl acetylenedicarboxylate; the β-fused benzene ring was found to direct electrophilic substitution to the opposite pyrrole unit, by way of a favored 18 π-electron delocalization pathway which excludes the benzene ring.[17]

Acknowledgements

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13. Crystal data for **6**: $C_{52}H_{34}N_4NiO_4$: X-ray diffraction data were collected on a Siemens P4/R4 rotating anode diffractometer with a nickel filter monochromator [λ(Cu Kα)=1.54178 Å] at 130(2) K in $\theta/2\theta$ scan mode to $2\theta_{max}=113°$. Crystals were grown from slow diffusion of cyclohexane into chloroform. A single parallelepiped crystal was selected with dimensions 0.16×0.1×0.05 mm. The crystal lattice was monoclinic with a space group of C2/c. Cell dimensions were a=20.496(4), b=15.114(3), c=26.105(4) Å, α,γ=90, β=104.391(14)°, V=7833(2) Å^3, and Z=4 (FW =837.54, ρ_{calc}=0.71 g cm^{-3}, μ=5.8 mm^{-1}). Of 5617 reflections measured, 5183 were independent and 3004 had $I>2\sigma$ (R_{int}=0.08); number of parameters=551. Final R factors were $R1$=0.070 (based on observed data) and $wR2$=0.197 (based on all data). The structure was solved by direct methods and refined (based on F^2 using all independent data) by full matrix least-squares methods (Siemens SHELXTL V. 5.03). Hydrogen atom positions were located by their idealized geometry and refined using a riding model. An absorption correction was applied using XABS2 (see Ref. 14). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC) (reference number CCDC/127788).
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