

b-Bilene to *a,c*-biladiene transformation during syntheses of isoporphyrins and porphyrins†

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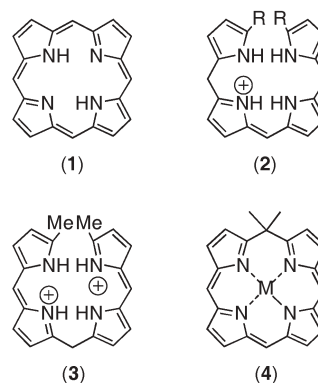
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Reaction of 1,19-di-unsubstituted *b*-bilene salts with α -ketoesters gives isoporphyrins, and eventually porphyrins, by way of an *a,c*-biladiene salt intermediate.

A multitude of different approaches for the synthesis of porphyrins (1) have been reported. The most popular include MacDonald '2 + 2' condensation of dipyrromethanes (either in the presence of a *meso*-carbon-linking unit, or with the linking carbons attached to the dipyrromethanes),¹ cyclizations of various *b*-bilenes (2),^{2–4} and oxidative cyclizations of 1,19-dimethyl-*a,c*-biladienes (3).^{5,6} On the other hand, stable isoporphyrins (4, M = H) have to date only been prepared from monopyrroles by MacDonald condensation of a 1,9-diformyldipyrromethane with a 5,5-disubstituted dipyrromethane.^{7,8} Relatively unstable metalloisoporphyrins were first reported in 1970.⁹ Metal-free isoporphyrins are tautomers of metalloporphyrins in which the central four-nitrogen core contains only one NH, and which have an sp³ hybridized carbon at a *meso*-position; they can be regarded as the equivalent of a benzenonium ion in the electrophilic substitution of a porphyrin at the *meso*-position. Such isoporphyrins are relatively unstable in the unmetalated form, and only the zinc(II) complexes (4, M = ZnCl) have, to date, been isolated. X-Ray structural data,¹⁰ and photophysical¹¹ and electrochemical properties¹² of stable zinc(II) isoporphyrins have also been reported. In the present paper we show that isoporphyrins can be prepared by reaction of *b*-bilene salts (2) with ketones (*e.g.*, acetone) and with α -ketoesters (*e.g.*, methyl pyruvate) or α -diketones, and that the isoporphyrins from the α -ketoesters can be transformed into the corresponding *meso*-substituted porphyrins. We also show that a novel *b*-bilene to *a,c*-biladiene transformation takes place during isoporphyrin formation using pyruvates, and this is confirmed by the X-ray crystal structure of a dimeric zinc(II) *a,c*-biladiene complex.

b-Bilene (5a) was synthesized by condensation of the dipyrromethane carboxylic acid (6) with 1-formyl dipyrromethane (7) in 80% yield.^{7,8} Fig. 1 shows its X-ray structure,[‡] and Fig. 2A the optical spectrum of 5a. *b*-Bilene 5a exists in the crystal as the hydrochloride, with all four N atoms protonated. It wraps with approximate twofold symmetry around the chloride ion and forms four hydrogen bonds to it, having N...Cl distances in the range 3.130(2)–3.404(2) Å. The two central pyrrole rings are approximately coplanar, forming a dihedral angle of 4.0(6)°, while the



distal pyrrole rings both form dihedral angles of 73.50(5)° with their nearest central pyrroles.

Treatment of 5a with TFA (to give 5b) followed by addition of α -ketoesters (typically methyl pyruvate, but other α -ketoesters and α -diketones also react well) as the carbon-linking unit, rapidly gave a trifluoroacetate salt intermediate (8) with an optical spectrum [447 nm (ϵ 2.46 \times 10⁵ dm³ mol⁻¹ cm⁻¹), 518 (1.15 \times 10⁵), Fig. 2B] closely resembling that of an *a,c*-biladiene bis-trifluoroacetate;§ proton-NMR signals were observed at 7.33, 7.27 and 4.36 ppm for protons *a*, *c* and *b*, respectively.§ Mechanistically (Scheme 1), the initially formed *b*-bilene 9 and *a,b*-biladiene dication 10 must have undergone acid–base equilibria to give the *a,c*-biladiene 8 in which the two cationic charges are separated (compared with 10). The process is presumably driven by the formation of the exocyclic double bond (*e.g.*, in compound 9) during the initial reaction with α -ketoester. Indeed, measurement of proton NMR spectra in

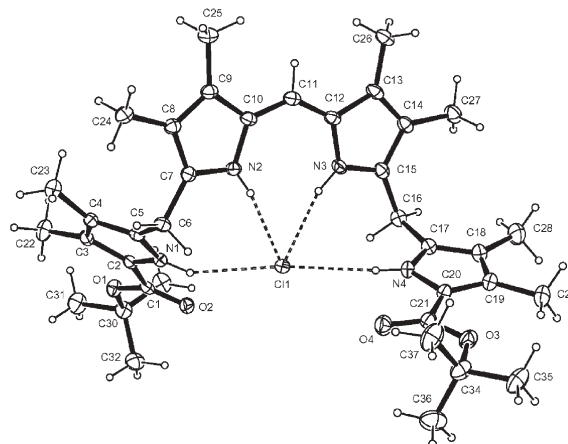


Fig. 1 X-Ray crystal structure of 5a; ellipsoids are drawn to show 50% probability.

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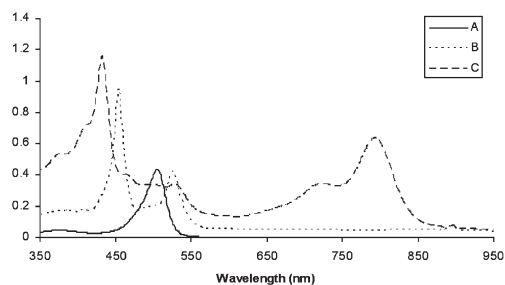
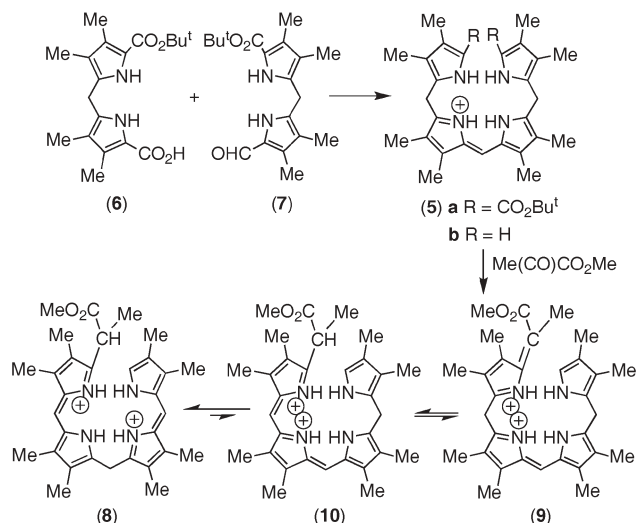


Fig. 2 Optical spectra, in CH_2Cl_2 , of A, *b*-bilene hydrochloride **5a**; B, *a,c*-biladiene bis-trifluoroacetate **8**; and C, compound **11**.



Scheme 1 Formation of *a,c*-biladiene **8** from *b*-bilene **5**.

$\text{CDCl}_3\text{-D}_2\text{O}$ show that the *b*- (δ 4.62 ppm) and *c*- (7.65 ppm) protons in **8** readily undergo exchange with deuterium during this process. So far as we are aware, this is the first example of a *b*-bilene-*a,b*-biladiene-*a,c*-biladiene transformation to be reported. Washing of a dichloromethane solution of **8** with aqueous sodium carbonate gave compound **11** with a long wavelength optical spectrum [ϵ $8.19 \times 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$], 774 (5.63×10^4), Fig. 2C] and characteristically, under neutral conditions, four downfield NH peaks at δ 11.95 (2), 11.34 and 11.15 ppm in its ^1H NMR spectrum.[¶]

Treatment of **8** or **10** with, for example, zinc(II) acetate gave a metal complex **12** with the optical spectrum shown in Fig. 3A. Treatment of this zinc(II) complex **12** with DDQ gave a high yield

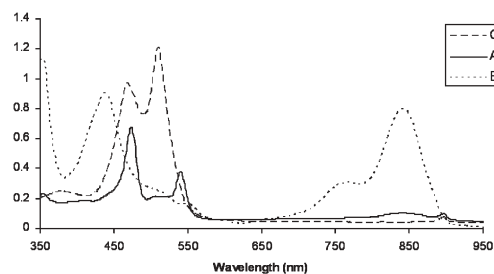
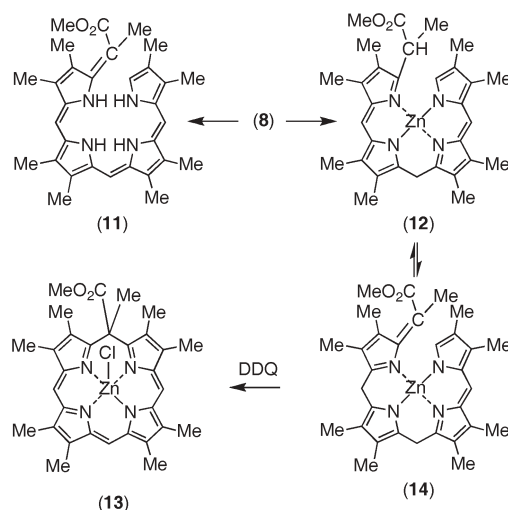


Fig. 3 Optical spectra, in CH_2Cl_2 , of A, zinc(II) *a,c*-biladiene complex **12**; B, zinc(II) isoporphyrin chloride **13**; and C, dimeric zinc(II) *a,c*-biladiene complex **15**.



Scheme 2 Formation of zinc(II) isoporphyrin chloride **13** from *a,c*-biladiene **8**.

of the corresponding isoporphyrin chloride **13** (after anion exchange); this reaction possibly proceeds *via* the tautomer **14** of **12** (Scheme 2). Fig. 3B shows the optical spectrum of **13** and also indicates (small peak around 850 nm) that isoporphyrin formation was already in progress (presumably due to aerial oxidation) in the spectrum (Fig. 3A) of the zinc(II) *a,c*-biladiene **12**. A minor by-product **15** was also isolated from the complexation of zinc with the *a,c*-biladiene **8**, and it was obtained in higher yields when the reaction was performed under an argon atmosphere; its optical spectrum is shown in Fig. 3C and is clearly distinguished from that of **12** (Fig. 3A). X-Ray crystallography (Fig. 4) confirmed that this byproduct was the zinc(II) *a,c*-biladiene dimer **15**.[‡] In the Zn dimer complex **15** the two *a,c*-biladiene ligands wrap in helical fashion. The two Zn centers have distorted tetrahedral coordination, the N–Zn–N angles falling within a rather wide range 96.9(2)–133.5(2) $^\circ$, the smaller ones being in the chelate rings. Zn–N

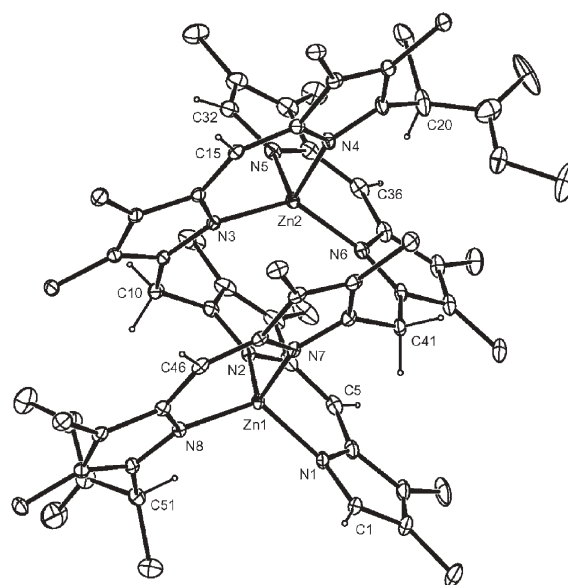
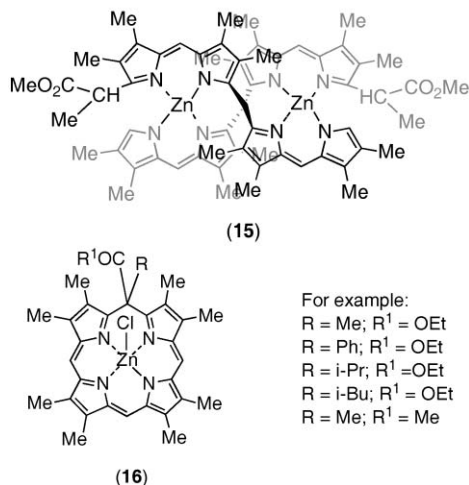


Fig. 4 X-Ray crystal structure of **15**; ellipsoids are drawn to show 20% probability.

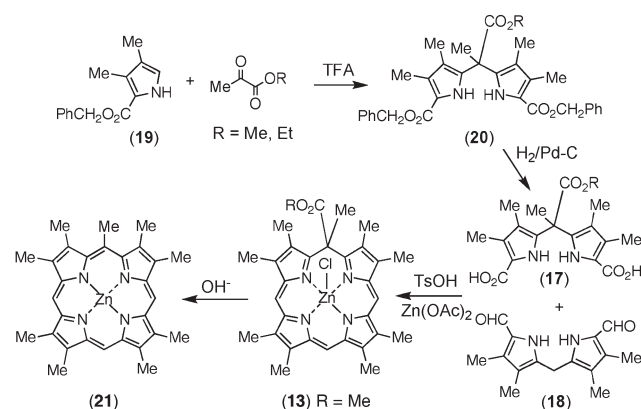
distances are in the range 1.975(5)–1.999(6) Å, and the Zn···Zn distance is 4.377(2) Å.

Treatment of compound **15** with TFA gave **8**, which, upon treatment with zinc(II) acetate gave the zinc(II) complex **12** as the major product; this clearly established interconvertibility between the two *a,c*-biladiene complexes **12** and **15**.



A number of new zinc(II) isoporphyrins (**16**) were prepared using the α -ketoester-*b*-bilene cyclizations; porphyrins with one bulky *meso*-substituent (e.g., isopropyl, isobutyl) are not easy to prepare by normal methods. α -Diketones also efficiently provided the bridging carbon. The high electrophilicity of the keto-carbonyl in α -ketoesters or α -dicarbonyl substrates compared with that of simple ketones (such as acetone) facilitated the rate of the reaction such that yields are much higher (33–56%) than previously reported using the MacDonald approach.³

For comparison purposes, the synthesis of the isoporphyrin **13** was also attempted using the conventional MacDonald^{1,7} ‘2 + 2’ pathway involving the condensation using the two dipyrromethanes **17** and **18** in the presence of zinc(II) acetate (Scheme 3). The 5,5-disubstituted dipyrromethane was synthesized by condensation of 2 equiv. of benzyl 3,4-dimethylpyrrole-2-carboxylate (**19**) with methyl or ethyl pyruvate under acidic conditions,



Scheme 3 Synthesis of zinc(II) isoporphyrin chloride **13** and zinc(II) *meso*-methylporphyrin **21** using the MacDonald protocol.

followed by catalytic hydrogenation of the resulting 5,5-disubstituted dipyrromethane **20** to yield the dicarboxylic acid dipyrromethane **17**. Condensation with the 1,9-diformyldipyrromethane **18** gave a typically low^{7,8} (14%) yield of zinc(II) isoporphyrin (**13**, R = Me or Et).

Saponification of the zinc(II) isoporphyrin (e.g., **13**) ester substituent to give carboxylic acid followed by spontaneous decarboxylation upon work-up led to the rapid formation of corresponding zinc(II) porphyrin (**21**). The reaction occurred at room temperature and formation of the product was monitored spectrophotometrically by observation of the increase in the extinction of the Soret band. TFA demetallation of **21** afforded a porphyrin with a characteristic ‘‘phyllo-type’’ electronic absorption spectrum.¹³ This overall process represents a completely new approach for mono-*meso*-substituted porphyrin synthesis. The availability of various new isoporphyrins **16** suggests that new 5-*meso*-substituted porphyrins, similar to **21**, will be equally accessible.

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Notes and references

‡ *Crystal data*: for **5a** at 110 K: [C₃₇H₅₁N₄O₄]Cl·2 CH₂Cl₂, monoclinic, space group *P2₁/c*, *a* = 18.373(3), *b* = 14.349(3), *c* = 19.252(4) Å, β = 116.763(11)°, *V* = 4531.8(15) Å³, *Z* = 4, 38 008 reflections collected with $\theta < 28.7^\circ$ (MoK α), 11 512 unique; *R*₁ = 0.052, *wR*₂ = 0.143 refined on *F*². Electron density corresponding to one disordered solvent removed using SQUEEZE, CCDC 642291.

For Zn complex **15** at 90 K: C₆₂H₇₂N₈O₄Zn₂, triclinic, space group *P* $\bar{1}$, *a* = 12.393(3), *b* = 14.837(3), *c* = 16.417(4) Å, α = 79.587(8), β = 75.834(8), γ = 76.550(9)°, *V* = 2822.0(11) Å³, *Z* = 2, 33 894 reflections collected with $\theta < 25.3^\circ$ (MoK α), 10228 unique; *R*₁ = 0.087, *wR*₂ = 0.217 refined on *F*², CCDC 642292. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b705182d

§ A typical 1,19-dimethyl-*a,c*-biladiene [8,12-bis(2-methoxycarbonyl-ethyl)-1,3,7,13,17,19-hexamethyl-*a,c*-biladiene dihydrobromide] has UV-Vis absorptions at 440 nm (ϵ 2.45 × 10⁵ dm³ mol⁻¹ cm⁻¹) and 508 (0.81 × 10⁵), and proton resonances at 7.22 ppm (*a,c*-protons) and 5.04 (*b* proton).

¶ Comparable data for 8,12-bis(2-methoxycarbonyl-ethyl)-1,3,7,13,17,19-hexamethyl-*a,c*-biladiene dihydrobromide are 426 nm (ϵ 4.47 × 10⁴ dm³ mol⁻¹ cm⁻¹) and 789 (2.02 × 10⁴); in the ¹H NMR spectrum, NH peaks appear at 14.23 and 13.99 ppm (each 2H).

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