Cyclizations of 1',8'-Dimethyl-*a,c*-biladiene Salts to give Porphyrins: A Study With Various Oxidizing Agents

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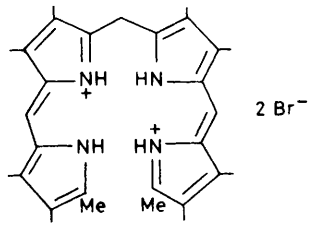
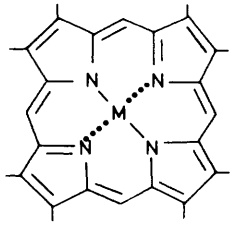
Cyclizations of the *a,c*-biladiene salts (**3**) and (**4**) to give the porphyrins (**5**) and (**6**), respectively, have been studied in the presence of a variety of chelating agents and oxidants. As a standard, the established procedure [copper(II) chloride–boiling dimethylformamide–6 min] gave compounds (**5**) and (**6**), in 37 and 20% yields respectively. Using zinc(II) acetate as a chelating agent for the *a,c*-biladienes, a large number of oxidants have been studied (in place of the copper chloride); best yields of porphyrin were obtained with potassium chromate [31% of (**5**); 22% of (**6**)] and silver iodate [35% of (**5**); 31% of (**6**)]. Other oxidants [PbO_2, $K_2Cr_2O_7$, KI, $Hg(OAc)_2$, Ag_2O, and AgOAc] gave moderate yields of porphyrin, and others (Table 1) gave either a trace of porphyrin, or none at all. In a useful modification of the copper(II) chloride cyclization, *a,c*-biladienes have been cyclized during 2 h at room temperature to give porphyrins in yields of 34—65% after removal of chelated copper.

1',8'-Dimethyl-*a,c*-biladiene salts (**1**) in refluxing dimethylformamide containing a copper(II) salt cyclize to give copper(II) porphyrins (**2a**).[1] Use of a base and nickel(II) or cobalt(II) salts converts 1',8'-dimethyl-*a,c*-biladienes into the corresponding tetradehydrocorrin salts.[2] However the harsh acidic conditions (H_2SO_4–CF_3CO_2H) required to remove the copper from the porphyrin product decrease the yields of the free base (**2b**) and in certain cases cause modification of acid labile substituents. In the present work a variety of oxidizing agents were used in the cyclization in order to produce the porphyrin free base or a labile metal complex [*e.g.* zinc(II)], rather than the usual copper(II) chelate. Two *a,c*-biladienes (**3**)[3] and (**4**)[4] were used in the study. The first, biladiene (**3**), is symmetrical along one axis and the second, biladiene (**4**), contains a free β-position adjacent to the terminal methyl group. These two *a,c*-biladienes were selected in order to show the generality of the newly developed methodology. As a standard for comparison with other oxidants, the two *a,c*-biladienes (**3**) and (**4**) were cyclized in the presence of copper(II) acetate to give porphyrins (**5**) and (**6**) in 37 and 20% yields, respectively, after removal of copper (entry 1 in Table 1).

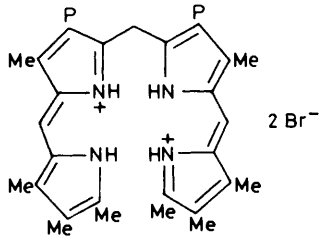
The sequence of reactions was first carried out only in the presence of the oxidizing agents listed in Table 1; results were unsatisfactory and only traces of the appropriate porphyrin were isolated. In case a chelating agent was necessary to bring the methyl groups in close proximity and promote the cyclization, anhydrous zinc(II) acetate was added to the cyclization mixture,[1,5] and this greatly enhanced the yields (Table 1). Use of PbO_2, $K_2Cr_2O_7$, KI, K_2CrO_4, and $Hg(OAc)_2$ with *a,c*-biladienes (**3**) and (**4**) gave the zinc porphyrins (**7**) and (**8**), respectively, in modest yields. However, cyclizations with Ag_2O, AgOAc, and $AgIO_3$ gave mixtures of the zinc complexes (**7**) and (**8**) and the free base porphyrins (**5**) and (**6**) in an approximately 3:1 ratio. Yields were optimal when potassium chromate and silver iodate were used, and porphyrin (**5**) was obtained in 31 and 35% yields, respectively, while porphyrin (**6**) was isolated in 22 and 31% yields respectively, after the removal of zinc. The use of a different solvent (*N*-methylformamide) did not increase the yields of the porphyrin as it had been shown to do in the copper(II) promoted cyclization.[4] In order to obtain the free-base porphyrin it was decided to use a metal oxidant which could be easily removed once the porphyrin was formed. Since magnesium porphyrins are very sensitive to acids and are easily cleaved, it was decided to use magnesium(II) acetate. This metal salt was added to the *a,c*-biladiene (**4**) and the red solution immediately turned green. After addition of the oxidizing agent ($AgIO_3$) or (K_2CrO_4) the free base porphyrin (**6**) was isolated in 14 and 3% yield. The remaining entries in Table 1 yielded only a trace of porphyrin, even in the presence of zinc(II) acetate. Use of I_2, $FeClO_4$, $Tl(NO_3)_3$, $Pb(OAc)_4$, and benzoyl peroxide gave no porphyrins.



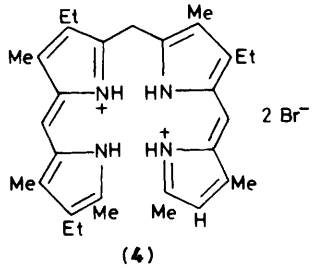
(**1**)



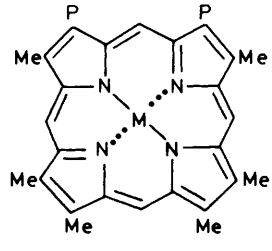
(**2**) **a**; M = Cu
b; M = 2H



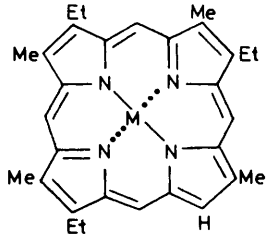
(**3**)



(**4**)



(**5**) M = 2H
(**7**) M = Zn



(**6**) M = 2H
(**8**) M = Zn
(**12**) M = Cu

P = $CH_2CH_2CO_2Me$

Table 1. Cyclizations of *a,c*-biladiene dihydrobromides (**3**) and (**4**) with various oxidizing and chelating salts.[a]

Oxidizing salt (15 equiv.)	Chelating salt (15 equiv.)	Porphyrin[b] (**6**) yield (%)	Porphyrin[c] (**5**) yield (%)	Product complex[d]
$Cu(OAc)_2$	$Zn(OAc)_2$	20	37	Cu
PbO_2	$Zn(OAc)_2$	7	31	Zn
$K_2Cr_2O_7$	$Zn(OAc)_2$	5	25	Zn
K_2CrO_4	$Zn(OAc)_2$	22	31	Zn
K_2CrO_4	$Mg(OAc)_2$	3		FB
K_2CrO_4	None	0	0	
K_2CrO_4	$Zn(OAc)_2$	10[e]		Zn
KI	$Zn(OAc)_2$	11	15	Zn
$Hg(OAc)_2$	$Zn(OAc)_2$	4	11	Zn
Ag_2O	$Zn(OAc)_2$	11	13	Zn and FB
AgOAc	$Zn(OAc)_2$	6	15	Zn and FB
$AgIO_3$	$Zn(OAc)_2$	31	35	Zn and FB
$AgIO_3$	$Mg(OAc)_2$	14		FB
$AgIO_3$	None	2	1	FB
$AgIO_3$	$Zn(OAc)_2$	28[e]		Zn
$AgIO_3$	$Hg(OAc)_2$	0		
$Na_2S_2O_3$	$Zn(OAc)_2$	Trace		Zn
$Co(OAc)_2 \cdot 4H_2O$	$Zn(OAc)_2$	Trace		Zn
$SnCl_2 \cdot 2H_2O$	$Zn(OAc)_2$	Trace		Zn
$LiClO_4$	$Zn(OAc)_2$	Trace		Zn
$Fe(NH_4)_2(SO_4)_2$	$Zn(OAc)_2$	Trace		Zn
$K_4Fe(CN)_6$	$Zn(OAc)_2$	Trace		Zn
$Zn(OAc)_2$	$Zn(OAc)_2$	Trace		Zn
I_2	$Zn(OAc)_2$	0		
$FeClO_4$	$Zn(OAc)_2$	0		
$Tl(NO_3)_3 \cdot 3\ H_2O$	$Zn(OAc)_2$	0		
$Pb(OAc)_4$	$Zn(OAc)_2$	0		
(Benzoyl peroxide)	$Zn(OAc)_2$	0		

[a] Conditions: heating at 160 °C for 6 min in dimethylformamide; [b] From *a,c*-biladiene (**4**); [c] From *a,c*-biladiene (**3**); [d] FB = Free base; [e] The solvent was diethylformamide.

The new methodology for cyclization of 1′,8′-dimethyl-*a,c*-biladienes gives comparable if not higher yields of porphyrin than the copper(II) promoted cyclization and has the advantage of providing the zinc(II) complex which can be easily demetallated. The free-base porphyrin can also be obtained; although the yields are not as high as the copper or zinc cyclizations, it has a great advantage over the previous methods if acid labile substituents are present.

It has been noted that zinc, nickel, and cobalt complexes of *b*-bilenes can be formed[1] with the corresponding acetate salt in refluxing methanol for 5 min. Further heating of the zinc and cobalt complexes for 48 h at 65 °C apparently gave no porphyrin and the nickel complex gave less than 1% of the desired product. However, similar treatment with copper acetate gave the copper porphyrin from the *b*-bilene. In view of these results it was felt pertinent to determine whether metal complexes of *a,c*-biladienes were formed in methanol and dimethylformamide. This qualitative analysis was accomplished using spectrophotometry, and in the absence of *X*-ray structural data, the interpretations are necessarily speculative. The *a,c*-biladiene solution in methanol was treated with acetate salts (Zn^{II}, Mg^{II}, Cu^{II}) to determine whether a stable chelated complex was formed and whether it plays a role in the cyclization process to give porphyrins. The *a,c*-biladiene salt (**4**) displayed a typical visible absorption pattern in methanol [λ (relative intensity) 444 nm (1.00) and 510 (1.80)] (Figure 1A). Addition of zinc acetate to the *a,c*-biladiene salt (**4**) caused bathochromic shifts with changes in intensities; [λ (relative intensity) 462 nm (3.22), 494 (1.00), and 528 (2.30)] (Figure 1B). The absorption did not

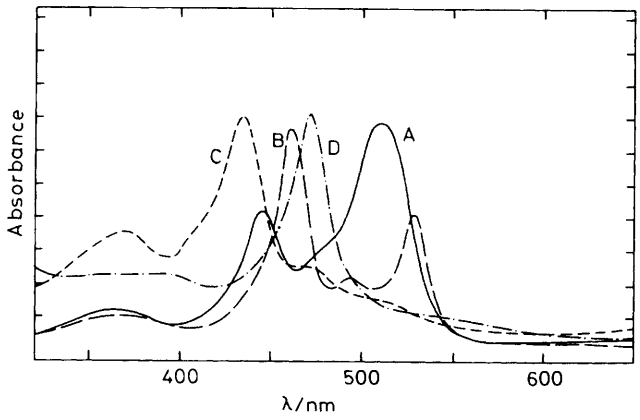
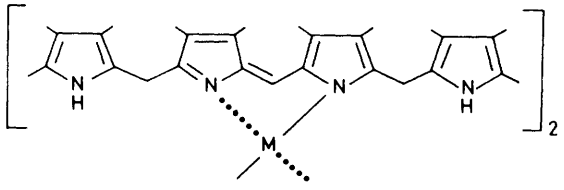


Figure 1. Electronic absorption spectra in methanol, of *a,c*-biladiene dihydrobromide (**4**); A, in absence of metal salts; B, in presence of zinc(II) acetate; C, in presence of magnesium(II) acetate; D, in presence of copper(II) acetate.

undergo any further change with time, but treatment with trifluoroacetic acid caused reversion to the original protonated form. It has been reported[1] that zinc complexes of *b*-bilenes form a dimer (**9**) which could also be formed with *a,c*-biladienes.

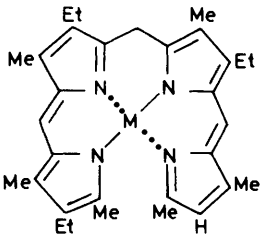


(**9**)

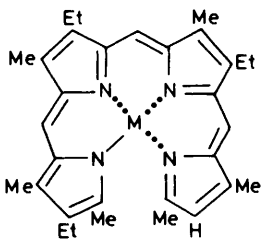
M = Zn

Addition of magnesium acetate transformed the two-peak spectrum to a single peak at 430 nm; this is presumably the metal chelate of structure (**10**) (Figure 1C). Treatment with trifluoroacetic acid did not alter the spectrum. Addition of copper(II) acetate in methanol converted the two absorptions into a single peak at 472 nm which in time (*ca.* 3 min) reverted to two peaks at 430 and 490 nm (Figure 1D). This species is believed to be the chelated *a,c*-biladiene (**11**). Addition of trifluoroacetic acid had no effect on the absorption spectra. All attempts to isolate the pure metal complexes failed. The *a,c*-biladiene (**4**) was refluxed in methanol containing an excess of magnesium acetate for 10 min to give a green solution which could not be purified by chromatography or crystallization. The zinc complex behaved similarly to give a mixture of products which could not be purified. However, the copper complex in refluxing methanol gave the porphyrin (**12**) in 13% yield. In an attempt to isolate the copper complex of the *a,c*-biladiene, the reaction was repeated at room temperature, but again only the copper porphyrin (**12**) (21%) was obtained.

The same sequence of reactions was repeated in dimethylformamide (the solvent used in the cyclization) in order to determine whether the *a,c*-biladiene behaves in a similar manner to form the metal chelate. Addition of the *a,c*-biladiene salt to dimethylformamide gave an absorption spectrum containing one major peak with several weaker absorptions [λ (relative intensity) 373 nm (1.90), 434 (4.70), 476 (1.20), and 512 (1.00)]. Since dimethylformamide is somewhat more basic than



(10) M = Mg
(11) M = Cu



(13) M = H
(14) M = Mg^+
(15) M = Cu^+

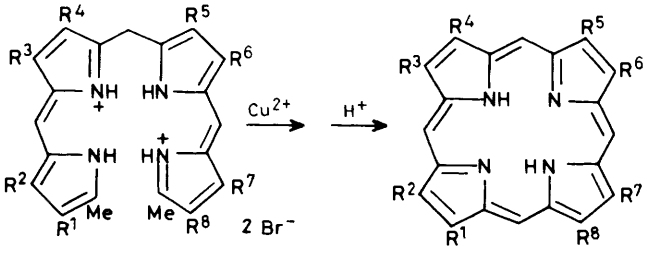
methanol, deprotonation rapidly gave the *a,b,c*-bilatriene (**13**) which characteristically possesses one major peak.[6] The addition of an excess of trifluoroacetic acid produced two peaks, at 446 and 512 nm, this spectrum being identical with the one in methanol. Addition of zinc acetate again gave three absorptions (at 468, 494, and 530 nm), with relative intensities of 1.25, 1.00, and 2.00, respectively; this compound is believed to be the dimer. Magnesium acetate instantaneously gave one broad band at 410 nm, representative of the complexed *a,b,c*-bilatriene species (**14**). Similarly, addition of copper(II) acetate initially gave two broad absorptions at 430 and 472 nm, again indicative of the chelated copper *a,b,c*-bilatriene complex (**15**). However, with time (*ca.* 10 min) it was observed that these broad absorptions slowly decreased and a sharp peak at 400 nm developed. The procedure was repeated with copper(II) chloride and the same effect was observed. The major product was shown to be the copper complex (**12**). In a spectrophotometric time dependence study, the formation of the porphyrin (**12**) from the copper(II) chelated *a,c*-biladiene (**4**) was monitored. Isosbestic points were observed at 340, 365, and 453 nm. If the reaction was allowed to proceed for 2 h, all the *a,c*-biladiene was converted into porphyrin, along with some baseline material. These findings prompted a further study of the cyclization of porphyrins *at room temperature* rather than under the typical harsh conditions involving boiling dimethylformamide.

The β-free *a,c*-biladiene (**4**) was dissolved in dimethylformamide containing copper(II) chloride (20 equiv.) The solution was stirred at room temperature for 2 h after which time the desired copper porphyrin (**12**) was recovered in 45% yield (Table 2). The reaction was repeated at lower temperatures; there were no porphyrin products observed at −10 °C. However, warming the mixture to 10 °C gave 27% of the desired copper porphyrin (**12**). Use of zinc acetate and silver iodate at room temperature also gave no porphyrin products until the addition of copper(II) salts, which, within 30 min, gave the copper porphyrin (**12**) in 12% yield. In order to further show the utility of the novel procedure, *a,c*-biladienes (**3**),[3] (**16**),[3] (**17**),[7] (**18**),[8] and (**19**)[8] were cyclized at room temperature with copper(II) acetate to give the porphyrins (**5**), (**20**), (**21**), (**22**), and (**23**) in 45, 47, 34, 65, and 57% yields, respectively, after the removal of copper (Table 2).

These results give some insight into the type of metal complexes formed during the cyclization process. It is interesting to note that the zinc and magnesium complexes do not give any porphyrin but the copper chelate smoothly oxidizes the *a,c*-biladiene to the porphyrin. This could be affected by two factors: the oxidizing capabilities of the metal used and the type of geometry the metal complex possesses. The zinc, cobalt, and nickel chelates are normally tetrahedral and are appreciably distorted in the square planar state. Therefore, addition of the metal salts to the *a,c*-biladiene presumably favours formation of a dimer similar to that of *b*-bilenes.[1] Once the dimers are formed a greater amount of energy is needed to disrupt this and form the cyclized adduct. However, copper readily forms a stable square planar chelate with the *a,c*-biladiene and this is easily oxidized to the planar porphyrin. The energy barrier in going from the tetrahedral zinc dimer to the square planar porphyrin may be sufficient to slow the reaction at room temperature in the presence of an oxidizing agent (silver iodate), whereas at elevated temperature the desired porphyrin is observed in modest yields.

Cyclizations of *a,c*-biladienes are still of interest and further research in isolating the intermediate metal chelates may be fruitful in defining the sequence of steps which promote the formation of porphyrins from them.

Table 2 Copper chloride promoted cyclizations of *a,c*-biladiene dihydrobromides at room temperature in dimethylformamide[a]



Biladiene No.	Substituents[d] R¹	R²	R³	R⁴	R⁵	R⁶	R⁷	R⁸	Porphyrin No.	Yield[b] (%)	Lit.[c] Yield[b] (%)	Ref.[c]
(3)	Me	Me	Me	P	P	Me	Me	Me	(5)	45	36	3
(4)	Et	Me	Me	Et	Me	Et	Me	H	(6)	45[e]	24	4
(18)	P	Me	Me	CE	Me	CE	P	Me	(22)	65	51	8
(19)	Me	P	Me	CE	Me	CE	Me	P	(23)	57	58	8
(17)	Me	CE	Me	P	P	Me	CE	Me	(21)	34	57	7
(16)	P	Me	Me	Me	Me	CE	Me	P	(20)	47	60	3

[a] Cyclizations at −10 and 0 °C gave no porphyrin after 2 h. [b] Yields are of metal-free porphyrin. [c] Using copper(II) chloride for 4—6 min in boiling dimethylformamide. [d] CE = CH_2CH_2Cl, P = $CH_2CH_2CO_2Me$. [e] Yield at 10 °C was 27%.

Experimental

Melting points were measured on a hot-stage apparatus, and are uncorrected. Silica gel 60 (Merck, 70—230 mesh) or alumina (Merck) were used for column chromatography, and preparative t.l.c. was carried out on 20 × 20 cm glass plates coated with Merck GF 254 silica gel (1 mm thick). Analytical t.l.c. was performed using Merck silica gel 60 F 254 precoated sheets (0.2 mm). Proton n.m.r. spectra were measured in $CDCl_3$ solution at 360 MHz using a Nicolet NT-360 spectrometer or at 90 MHz with a Varian EM-390 spectrometer with Me_4Si as internal standard. Electronic absorption spectra were measured, in CH_2Cl_2 solution, using a Hewlett-Packard 8450A spectrophotometer. Organic solutions were dried over anhydrous sodium sulphate. Elemental analyses were performed at the Berkeley Microchemical Analysis Laboratory, UC Berkeley.

Studies with Various Oxidants (*Table 1*).—All the cyclizations of *a,c*-biladienes (**3**) and (**4**) followed the procedures outlined below on the same scale, utilizing 15 equiv. of the appropriate oxidizing agent and 15 equiv. of the chelating salt (zinc or magnesium acetate). Reaction time in each case was 6 min at 160 °C and the yields are recorded in Table 1.

6,7-*Bis*(2-*methoxycarbonylethyl*)-1,2,3,4,5,8-*hexamethylporphyrin* (**5**).—The *a,c*-biladiene dihydrobromide (**3**)[3] (60 mg) was dissolved in dimethylformamide (20 ml) containing zinc acetate (265 mg, 15 equiv.) and silver iodate (341 mg, 15 equiv.) and heated to 160 °C for 6 min. After cooling to room temperature the mixture was diluted with chloroform and filtered through a 3 cm pad of Celite. The filtrate was washed with water (3 × 100 ml), dried (Na_2SO_4), and the solvent removed. The residue was chromatographed on silica (elution with 2% methanol in dichloromethane). The major red band was collected and the solvent was removed. The porphyrin was dissolved in trifluoroacetic acid, diluted with chloroform, and then washed with aqueous sodium hydrogen carbonate and water. After drying (Na_2SO_4), the solvent was removed and the residue chromatographed on silica (elution with 2% methanol in dichloromethane) to give the title compound (16 mg, 35%), m.p. 317—319 °C (lit.,[9] 318—320 °C); δ($CDCl_3$) 3.76 (br s, 2 H, 2 × NH), 3.29 (t, 4 H, 2 × $CH_2CH_2CO_2Me$), 3.61, 3.65, and 3.66 (s, 9 H, 6 H, 9 H, 8 × Me), 4.43 (t, 4 H, 2 × $CH_2CH_2CO_2$-Me), and 10.05, 10.08, and 10.09 (each s, 1 H, 2 H, 1 H, *meso*-H).

2,4,7-*Triethyl*-1,3,5,8-*tetramethylporphyrin*, '*Pyrroetioporphyrin-XV*' (**6**).—The *a,c*-biladiene dihydrobromide (**4**)[4] (70 mg) was cyclized in dimethylformamide as described above in the presence of silver iodate (472 mg, 15 equiv.) and zinc acetate (365.5 mg, 15 equiv.) to give the title compound (16 mg, 32%), m.p. 268—269 °C (lit.,[4] 269—270 °C); δ($CDCl_3$) −3.80 (br s, 2 H, 2 × NH), 1.86 and 1.88 (each t, 6 H, 3 H, 3 × CH_2Me), 3.62, 3.64, 3.66, and 3.75 (each s, 3 H, Me), 4.09 (q, 6 H, CH_2Me), 9.08 (s, 1 H, 6-H), and 10.03, 10.09, and 10.13 (each s, 1 H, 2 H, 1 H).

Studies with Copper(II) *Chloride at Room Temperature*: (*Table 2*).—In a typical cyclization, the *a,c*-biladiene salt (40 mg) was dissolved in dimethylformamide (20 ml) containing dry copper(II) chloride (120 mg) and stirred at room temperature for 2 h. The mixture was diluted with chloroform (50 ml) and then washed with water (3 × 100 ml). The organic layer was dried (Na_2SO_4), evaporated to dryness, and the residue was taken up in 15% sulphuric acid in trifluoroacetic acid (5 ml) and stirred for 45 min. The solution was then diluted with chloroform (25 ml), washed with water (3 × 50 ml), dried (Na_2SO_4), and evaporated to dryness. The residue was chromatographed on silica gel (elution with dichloromethane) and evaporation of the red eluates gave the required porphyrin (yields in Table 2) which was crystallized from dichloromethane–hexane. In all cases, physical and spectroscopic properties were identical with those reported in the literature.

Acknowledgements

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