Carbachlorins**

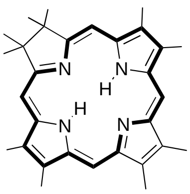
Michael J. Hayes and Timothy D. Lash*

Abstract: Acid-catalyzed 3+1 condensation of the aliphatic bicyclic dialdehyde **8**, or the related isolated alkene **7**, with tripyrrane **5** gave the first examples of carbachlorins (**9** and **11**) after oxidation with DDQ in refluxing toluene. These novel dihydroporphyrinoids exhibited strong Soret bands in their electronic absorption spectra at 404 nm, and a moderately strong band at 650 nm. The latter feature closely resembles the electronic spectra of true tetrapyrrolic chlorins. The ^{1}H NMR spectra for **9** and **11** showed a strong diamagnetic ring current consistent with 18-π-electron delocalization over the macrocycle. Addition of TFA gave rise to the related monocations **12**, and these species showed slightly enhanced diatropic ring currents, shown by significant upfield and downfield shifts for the internal and external protons, respectively. The UV/Vis spectra of **12** also had many similarities to those previously reported for tetrapyrrolic chlorin monocations, including the presence of a split Soret band. Carbachlorins **9** and **11**, however, differed from the related tetrapyrrolic structures by resisting oxidation to porphyrin.

Keywords: aromaticity • carbaporphyrins • chlorins • porphyrinoids • tripyrranes

Introduction

Chlorins (**1**) are an important group of dihydroporphyrins which provide the parent structure for many of the chlorophylls[1] and other biologically important pigments such as bonellin and heme d.[2] Chlorins display prominent absorptions in the long wavelength region of the visible spectrum,[3] typically near 650 nm, and this makes these pigments potential candidates as photosensitizers for photodynamic therapy.[4] Although many examples of highly conjugated macrocycles related to the porphyrins have been described,[5] little work has been carried out on the synthesis of chlorin analogues.[6, 7]



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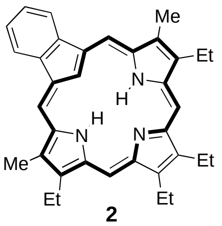

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The first syntheses of carbaporphyrins (e.g. benzocarbaporphyrin **2**)[8, 9] using the 3+1 approach[10–15] have been reported recently. These novel porphyrinoids display many unique chemical properties,[16] and we are presently investigating the possibility of reducing these structures to produce carbachlorins. However, we also speculated that it might be possible to synthesize carbachlorins directly by utilizing cyclopentanedialdehydes in the 3+1 methodology. In this paper we describe the successful application of this approach to the first syntheses of carbachlorins and the spectroscopic properties of these novel dihydroporphyrinoids.

Results and Discussion

The possibility that cyclopentanedialdehydes might be utilized in the 3+1 methodology to directly synthesize the carbachlorin system (Scheme 1) was appealing, but no comparable studies have been reported in the literature. Previous 3+1 syntheses[8–15] had made use of aromatic dialdehydes or highly conjugated dialdehydes where the formyl moieties are connected to sp^2 hybridized carbon atoms. The reactivities and geometries of aliphatic dialdehydes differ considerably from any of the dialdehydes utilized previously in this area, and this approach to carbachlorins by no means represents a simple extension of the previous protocols. In order to assess this synthetic route, *cis*-1,3-cyclopentanedicarboxaldehyde (**4**), which is readily available from the oxidative ring opening of norbornene with potassium permanganate under phase-transfer conditions,[17] was condensed with tripyrrane dicar-

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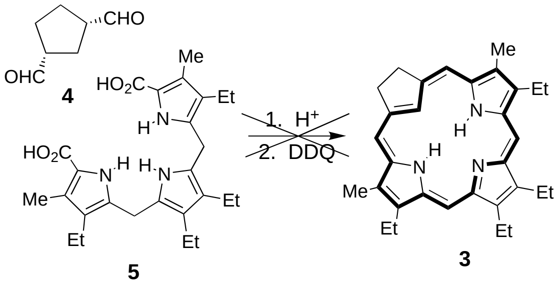
[*] Prof. Dr. T. D. Lash, M. J. Hayes
Department of Chemistry, Illinois State University
Normal, Illinois 61790-4160 (USA)
Fax: (+ 1) 309-438-5538
E-mail: tdlash@rs6000.cmp.ilstu.edu

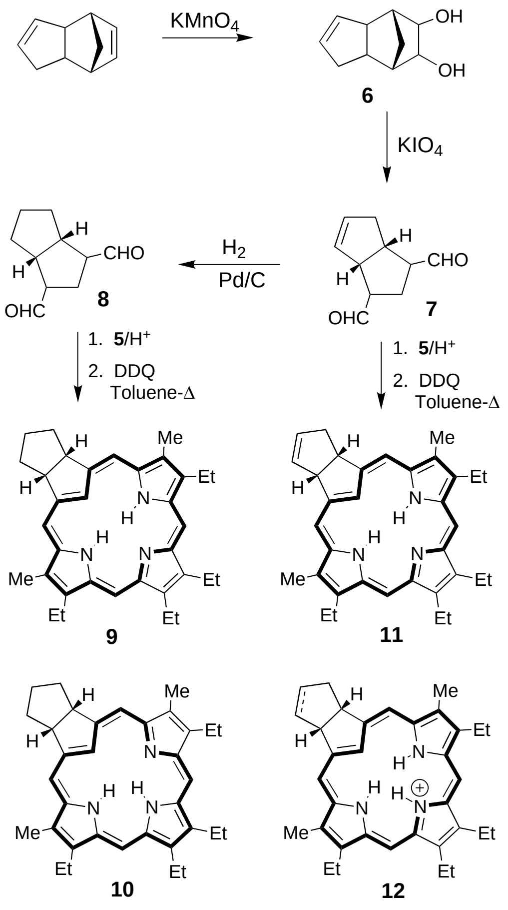
[**] Conjugated Macrocycles Related to the Porphyrins, Part 10; for Part 9, see ref. [8].



Scheme 1. Attempted synthesis of carbachlorin **3**.

boxylic acid **5**[11] in the presence of acid catalysts under a variety of reaction conditions and further oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), but no trace of the targeted carbachlorin **3**, or the related carbaporphyrin, could be identified in these studies.

The presence of β-pyrrolic substituents plays an important role in porphyrin formation, in part because these units induce the open-chain polypyrrolic intermediates to take on a helical geometry that facilitates cyclization. It seemed plausible that the absence of additional substituents on the cyclopentane ring in **4** might have impeded carbachlorin formation, and this prompted us to seek out suitably substituted cyclopentanedialdehydes for further studies. Regioselective reaction (Scheme 2) of dicyclopentadiene with potassium permanganate gave the diol **6**, and subsequent oxidative cleavage with potassium periodate gave the dialdehyde **7**.[18, 19] Hydrogenation of **7** over 10% palladium/charcoal in methanol gave the bicyclo[3.3.0]octanedialdehyde **8** in a quantitative yield. We condensed **8** with tripyrrane **5** under various conditions and in most cases noted the formation of a chlorin-like species. The best results were obtained when the acid-catalyzed condensation (1% trifluoroacetic acid (TFA)/CH_2Cl_2) was carried out under relatively dilute conditions, followed by extraction, neutralization, and oxidation with DDQ in refluxing toluene. After chromatography and recrystallization from chloroform/methanol, propanocarbachlorin **9** was isolated as moss-green crystals in a yield of 10–15%. Surprisingly, given the strongly oxidative conditions utilized in the final step for this synthetic procedure, no overoxidation to carbaporphyrin was noted in any of our experiments. This contrasts with tetrapyrrolic chlorins (**2**), which would be expected to oxidize to porphyrin under these reaction conditions.



Scheme 2. Synthesis of carbachlorins **9** and **11**.

Carbachlorin **9** gave bright green solutions in organic solvents such as chloroform and displayed a strong red-shifted absorption at 650 nm in its UV/Vis spectrum (Figure 1), in common with true chlorins (**2**). A strong Soret band was also noted at 404 nm. Interestingly, the Soret band was more porphyrin-like in this case than was observed for the electronic spectra of carbaporphyrins, for which this absorption is split and somewhat broadened. Under a long-wavelength ultraviolet lamp, solutions of **9** produced a deep red fluorescence that is also observed for true porphyrins and chlorins, but not for carbaporphyrins such as **2**. The ^{1}H NMR spectrum of **9** (Figure 2) showed the presence of a strong diamagnetic ring current, as would be expected for an aromatic species with 18-π-electron delocalization. Specifically, the *meso* protons were deshielded and appeared as two 2H singlets at $\delta = 9.15$ and 9.81, while the internal protons were strongly shielded with the CH appearing near $\delta = -7$ and the NH protons showing up as a very broad resonance at $\delta = -4$. The ^{13}C NMR spectrum of **9** confirmed the presence of a plane of symmetry in this structure, showing signals for 8 sp^3 and 10 sp^2 carbon atoms (the 2 *meso* carbons appear at $\delta = 96-98$, values that are reminiscent of true porphyrin structures[11]), and provided further evidence to demonstrate the isomeric purity of this product.[11] The structure of **9** was also confirmed by elemental analysis and by EIMS, which revealed minimal benzylic fragmentation and a strong molecular ion. It should be noted, however, that tautomers such as **10** may also be present, although these must rapidly interconvert with **9** on the NMR timescale.

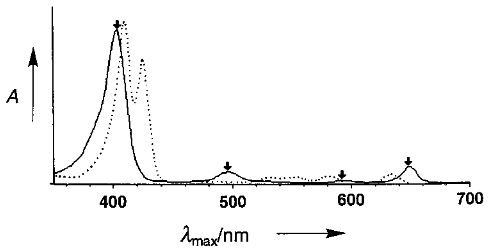


Figure 1. UV/Vis spectra of **9** in chloroform (free base; dotted line) and 1% TFA/chloroform (monocation **12**; solid line).

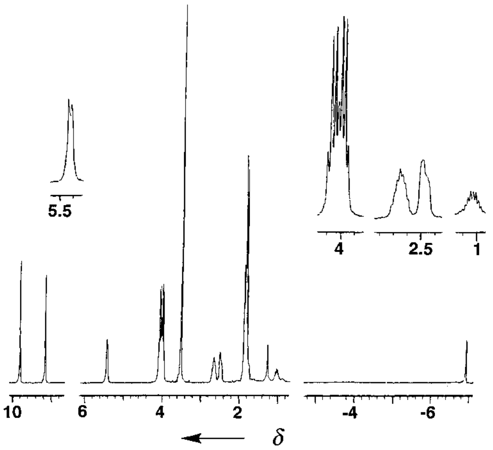


Figure 2. 300 MHz ^{1}H NMR spectrum of carbachlorin **9** in $CDCl_3$.

Tripyrrane (**5**) also condensed with the bicyclooctenedialdehyde **7** to give the related carbachlorin **11** in comparable yields (the isolated double bond does not appear to compromise this chemistry in any way); this further demonstrates the generality of the 3+1 methodology. The spectroscopic properties of **11** were similar to those observed for **9**. However, the loss of symmetry in this structure led to additional signals in its ^{1}H (Figure 3) and ^{13}C NMR spectra. The ^{1}H NMR spectrum showed four singlets between $\delta = 9$ and 10, corresponding to the *meso* protons, and the internal CH again appeared near $\delta = -7$ (Figure 3).

Both **9** and **11** generated the green monocations **12** in the presence of trace amounts of TFA. The monocations **12** retained the aromatic characteristics associated with the free bases **9** and **11** (strong diamagnetic ring currents in ^{1}H NMR spectroscopy, presence of strong Soret bands with $\varepsilon > 10^5$, etc.). However, in these species the Soret bands were split and shifted to longer wavelengths, while the first Q band underwent a hypsochromic shift to 634 nm (Figure 1). Interestingly, the electronic spectrum of the monocation for *trans*-octaethylchlorin shows many similarities to the spectral properties of **12**, exhibiting a split Soret band and a strong absorption near 620 nm.[20] In the ^{1}H NMR spectra, the *meso* protons of **12** were shifted slightly downfield compared to the free bases **9** and **11**, while the internal protons appeared at significantly upfield values. This indicates that the diatropic nature of the cations **12** is somewhat greater than for the free base carbachlorins, presumably because of the benefits of charge delocalization.

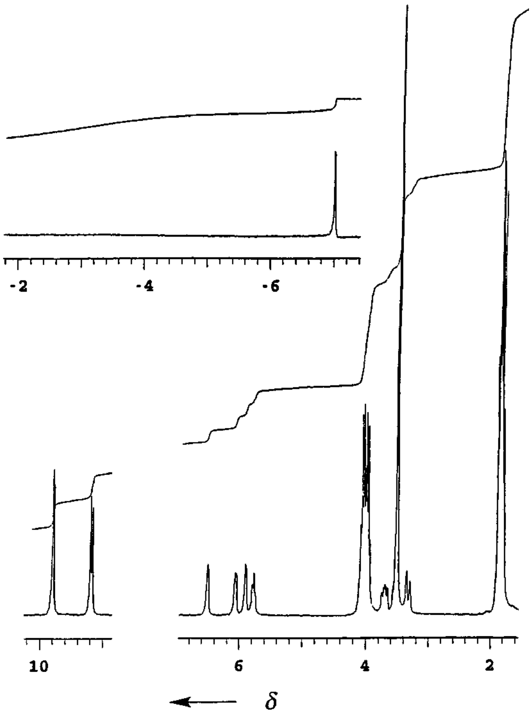


Figure 3. 300 MHz ^{1}H NMR spectrum of carbachlorin **11** in $CDCl_3$.

Conclusions

The first syntheses of carbachlorins have been accomplished in moderate yields by the 3+1 condensation of bicyclooctanedialdehydes with tripyrrane dicarboxylic acid **5** in the presence of 1% TFA/CH_2Cl_2. It is particularly notable that our best yields of carbachlorins were obtained under strongly oxidative conditions (2–3 equiv DDQ in refluxing toluene), but no indications of carbaporphyrin formation were observed. This contrasts with the tetrapyrrolic systems, where chlorins **2** readily oxidize to form porphyrins. The presence of an additional fused five-membered ring in **9** and **11** may be a factor, but our results suggest that carbachlorins are far more stable towards oxidants than the natural systems. This remarkable contrast, alongside the spectroscopic similarities noted above, suggests that these new dihydroporphyrinoids will reward further study and underscores the importance of the rapidly evolving new field of carbaporphyrinoid chemistry.

Experimental Section

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. UV spectra were obtained on a Beckmann DU-40 or a Hewlett Packard 8452A Diode Array spectrophotometer. NMR spectra were recorded on a Varian Gemini 300 NMR spectrometer. Mass spectral data were obtained from the Mass Spectral Laboratory, School of Chemical Sciences, University of Illinois at Urbana-Champaign, supported in part by a grant from the National Institute of General Medical Sciences (GM 27029). Elemental analyses were carried out by the School of Chemical Sciences Microanalysis Laboratory at the University of Illinois.

Propanocarbachlorin (9): Tripyrranedicarboxylic acid **5**[11] (100 mg) was stirred with TFA (1 mL) under an atmosphere of nitrogen for 10 min. Dichloromethane (99 mL) was added, followed immediately by dialdehyde **8** (36 mg), and the mixture was stirred under nitrogen for 16 h. The mixture was neutralized by the dropwise addition of triethylamine and the solvent removed under reduced pressure. The residue was taken up in toluene (50 mL), DDQ (100 mg) was added, and the resulting mixture was stirred under reflux for 1 h. The solvent was removed under reduced pressure, then the residue was dissolved in dichloromethane and washed with water. The solution was concentrated under reduced pressure and chromatographed on a Grade 3 alumina column eluted with chloroform. The colored fractions were rechromatographed on silica eluted initially with toluene and then 1% ethyl acetate/toluene. The product was collected as a green fraction. Recrystallization from chloroform/methanol gave the propanocarbachlorin (16 mg; 15%) as moss-green crystals, m.p. 236 °C; UV/Vis

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(1% $\mathrm{Et_3N/CH_2Cl_2}$): $\lambda_{\max}$ ($\log_{10}\varepsilon$) = 404 (5.32), 496 (4.22), 592 (3.69), 650 nm (4.36); UV/Vis (1% $\mathrm{TFA/CHCl_3}$): $\lambda_{\max}$ ($\log_{10}\varepsilon$) = 410 (5.35), 424 (5.24), 534 (3.93), 546 (3.99), 580 (4.04), 634 nm (4.18); ^{1}H NMR ($\mathrm{CDCl_3}$): $\delta = -6.93$ (s, 1H, 21-H), −4.0 (br s, 2H, 2 × NH), 1.03 (m, 1H), 1.75 (m, 1H, $\mathrm{CH_2}$-$\mathrm{C}\mathit{H}_2$-$\mathrm{CH_2}$), 1.83 (m, 12H, 4 × $\mathrm{CH_2C}\mathit{H}_3$), 2.50 (m, 2H), 2.65 (m, 2H, $\mathrm{C}\mathit{H}_2$-$\mathrm{CH_2}$-$\mathrm{C}\mathit{H}_2$), 3.51 (s, 6H, 2 × chlorin $\mathrm{CH_3}$), 3.94–4.08 (m, 8H, 4 × $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$), 5.42 (m, 2H, 2 × bridgehead H), 9.15 (s, 2H), 9.81 (s, 2H, 4 × *meso*-H); ^{1}H NMR ($\mathrm{TFA/CDCl_3}$): $\delta = -7.06$ (s, 1H, 21-H), −5.57 (br s, 1H), −4.2 (br s, 2H, 3 × NH), 1.02 (m, 1H), 1.8 (m, 1H, $\mathrm{CH_2}$-$\mathrm{C}\mathit{H}_2$-$\mathrm{CH_2}$), 1.67 (t, 6H), 1.85 (t, 6H, 4 × $\mathrm{CH_2C}\mathit{H}_3$), 2.50 (m, 2H), 2.67 (m, 2H, $\mathrm{C}\mathit{H}_2$-$\mathrm{CH_2}$-$\mathrm{C}\mathit{H}_2$), 3.47 (s, 6H, 2 × chlorin-$\mathrm{CH_3}$), 4.02–4.14 (m, 8H, 4 × $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$), 5.50 (m, 2H, 2 × bridgehead H), 9.58 (s, 2H), 10.09 (s, 2H, 4 × *meso* H); ^{13}C NMR (75.46 MHz, $\mathrm{CDCl_3}$): δ = 11.35, 17.46, 18.73, 19.71, 20.09, 24.78, 36.54, 53.13, 96.07, 97.61, 121.94, 128.92, 132.51, 136.53, 137.76, 142.93, 149.80, 151.23; MS (70 eV): m/z (%) = 491 (100) [M^+], 476 (8.4) [$M^+ - \mathrm{CH_3}$], 246 (16) [M^{2+}]; HRMS (EI): calcd for $\mathrm{C_{34}H_{41}N_3}$: m/z 491.33005; found: 491.33014; elemental analysis for $\mathrm{C_{34}H_{41}N_3}$: calcd C 83.05, H 8.40, N 8.54; found C 82.83, H 8.47, N 8.47.

Propenocarbachlorin (**11**): Small purple crystals[21] (11%) from chloroform/methanol, m.p. 226–227 °C; UV/Vis (1% $\mathrm{Et_3N/CHCl_3}$): $\lambda_{\max}$ ($\log_{10}\varepsilon$) = 404 (5.30), 496 (4.15), 594 (3.45), 650 nm (4.30); UV/Vis (1% $\mathrm{TFA/CHCl_3}$): $\lambda_{\max}$ ($\log_{10}\varepsilon$) = 410 (5.32), 426 (5.20), 532 (3.95), 546 (3.99), 582 (4.02), 634 nm (4.16); ^{1}H NMR ($\mathrm{CDCl_3}$): $\delta = -7.03$ (s, 1H, 21-H), −4.0 (br s, 2H, 2 × NH), 1.83 (m, 12H, 4 × $\mathrm{CH_2C}\mathit{H}_3$), 3.32 (m, 1H), 3.70 (m, 1H, $\mathrm{C}\mathit{H}_2$-CH=), 3.50 (s, 6H, 2 × chlorin-$\mathrm{CH_3}$), 3.94–4.09 (m, 8H, 4 × $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$), 5.77 (m, 1H), 5.90 (m, 1H), 6.07 (m, 1H), 6.51 (m, 1H, 2 × bridgehead CH and 2=CH), 9.16 (s, 1H), 9.19 (s, 1H), 9.78 (s, 1H), 9.80 (s, 1H, 4 × *meso* H); ^{1}H NMR ($\mathrm{TFA/CDCl_3}$): $\delta = -7.17$ (s, 1H, 21-H), −5.54 (br s, 1H), −4.17 (br s, 2H, 3 × NH), 1.67 (t, 6H), 1.85 (t, 6H, 4 × $\mathrm{CH_2C}\mathit{H}_3$), 3.32 (m, 1H), 3.71 (m, 1H, $\mathrm{C}\mathit{H}_2$-CH=), 3.47 (s, 6H, 2 × chlorin $\mathrm{CH_3}$), 4.02–4.16 (m, 8H, 4 × $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$), 5.81 (m, 1H), 5.90 (m, 1H), 6.13 (m, 1H), 6.49 (m, 1H, 2 × bridgehead CH and 2=CH), 9.62 (s, 2H), 10.08 (s, 1H), 10.10 (s, 1H, 4 × *meso* H); ^{13}C NMR ($\mathrm{CDCl_3}$): δ = 11.34, 17.47, 18.72, 19.69, 20.07, 41.94, 50.54, 61.25, 96.03, 96.41, 97.38, 97.72, 120.13, 128.87, 129.09, 130.93, 132.39, 132.79, 134.88, 136.32, 136.66, 137.82, 142.93, 143.08, 149.29, 150.06, 151.59; MS (70 eV): m/z (%) = 489 (100) [M^+], 474 (7.3) [$M^+ - \mathrm{CH_3}$], 245 (12) [M^{2+}]; HRMS (EI): calcd for $\mathrm{C_{34}H_{39}N_3}$: m/z 489.31440; found: 489.31422.

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