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Carboranylcorroles

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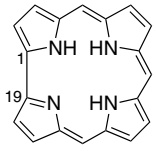
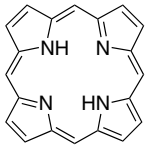
Abstract—The first syntheses of *closo*-carboranylcorroles (**3**, **4**, and **11**) have been achieved in a one-pot procedure from the condensation of pyrrole and carboranylbenzaldehydes, without the concomitant formation of the corresponding tetraarylporphyrins. The water-soluble *nido*-carboranylcorrole **9** was prepared from **7** in quantitative yield using tetrabutylammonium fluoride. The first X-ray molecular structure of a Cu(III) carboranylcorrole complex **7** is also presented. Carboranylcorroles absorb in the red region of the optical spectrum and should have potential application in both BNCT and PDT.

The history of corroles (**1**) dates back to 1960 as a result of Johnson and Price's attempt to synthesize the corrin nucleus of vitamin B_{12} by way of an aromatic corrole intermediate.[1] 8,12-Diethyl-2,3,7,13,17,18-hexamethylcorrole was prepared in 58% yield from photocyclization of a 1,19-dideoxy-*a*,*c*-biladiene.

The corrole ring possesses a porphyrin-like conjugated system, the structure of which was confirmed by Hodgkin et al. in 1971 with a crystal structure.[2] The corrole macrocycle was found to be slightly nonplanar, probably because of the short N–N bonds near the direct C(1)–C(19) link.



(**1**)



(**2**)

Recently the synthesis and chemistry of corroles and their core-modified derivatives have blossomed into a major area of tetrapyrrole science.[3–5] From 1999 onward, synthetic access to the corrole system was significantly improved; Gross and co-workers[6,7] and Paolesse and co-workers[8,9] almost simultaneously developed simple 'Rothemund-based' one-pot synthetic procedures for the preparation of corroles. Improved availability of these corroles led to the discovery, in recent years, of some interesting properties of the macrocycle, and prompted the yet more increased attention on corrole chemistry and applications.

Corroles (**1**) differ from porphyrins (**2**) in that they lack one of the porphyrin interpyrrolic carbon atoms and possess a smaller inner core, with three central 'pyrrole-type' and one 'pyrrolenine-type' nitrogen atoms; thus, the molecule functions as a trianionic ligand rather than dianionic as do the corresponding porphyrins. Consequently the chemistry of corroles is in many ways distinct from that of porphyrins. For example, corroles have the ability to stabilize metal atoms in higher oxidation states [e.g., nickel(III), copper(III), iron(IV), and cobalt(IV)] compared with porphyrins.[4,10] Furthermore, corroles are stronger acids but weaker bases than porphyrins. Two general methods for the synthesis of metallocorroles consist of either the cyclization of 1,19-dideoxy-*a*,*c*-biladienes in the presence of a metal ion template, or on insertion of the metal into a preformed free-base corrole.

The ability of corroles to stabilize unusually high metal oxidation states, as observed by Vogel et al.,[10] has led to their application as catalysts. In 1999, Gross et al. demonstrated that the iron(IV) complex of 5,10,15-tris-(pentafluorophenyl)corrole was an efficient catalyst in epoxidation, hydroxylation, and cyclopropanation reactions.[6] The Gross group also reported the use of corroles as molecular magnets[11] and as catalysts for aziridination.[12] The affinity of corroles for cancer cells

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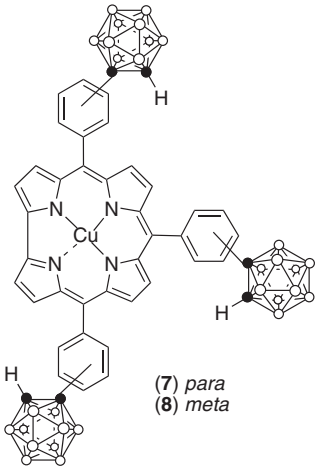
has also been investigated by Aviezer et al., who demonstrated that 5,10,15-tris[4-(2-pyridyl)tetrafluorophenyl]-corrole was efficient in blocking fibroblast growth factors and vascular endothelial growth factors, which play key roles in the multistep pathway of tumor progression, metastasis, and angiogenesis.[13] That study indicates that corroles are potential candidates for anticancer applications. In addition, corroles absorb long wavelength light (500–600 nm), are fluorescent, and can selectively accumulate in tumor cells. Similar to porphyrins, these properties can provide the basis for their application as phototherapeutic agents for the treatment of malignant tumors using PDT.[14] We reasoned that boron-containing corroles, that are water-soluble and amphiphilic, can be designed and synthesized to deliver a high amount of boron into tumor cells. Therefore, such photosensitizers could have *dual* application in both photodynamic therapy (PDT) and in boron neutron capture therapy (BNCT) for the treatment of cancer.[14]

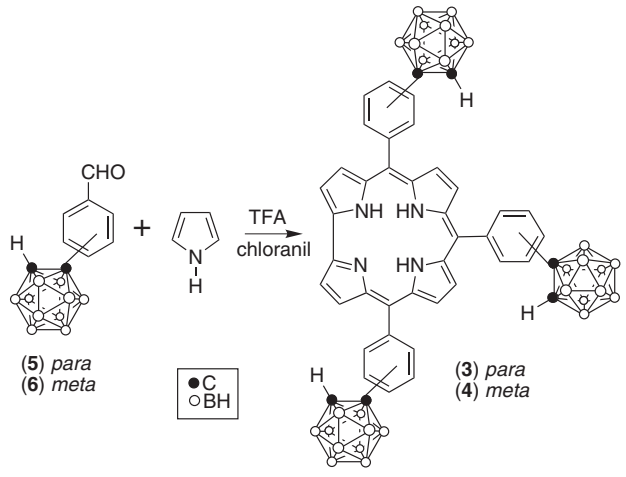
Our synthetic strategy toward carboranylcorroles resulted from our serendipitous observation that pyrrole and aldehydes bearing bulky electronegative groups react selectively to give the smaller corrole ring in preference to porphyrin. Presumably, steric congestion is avoided by formation of a smaller macrocyclic ring. Thus, we further investigated the approach employed by Paolesse and co-workers.[8,9,15] This simple one-step procedure allows the synthesis of the corrole ring without concomitant formation of the corresponding porphyrin.

Corroles (**3** and **4**) bearing the carborane cages on the *para*- and *meta*-position, respectively, were synthesized according to Scheme 1. These corroles feature three carborane cages directly linked to the *meso*-phenyl groups of the corrole macrocycle and contain 33% boron by weight. Benzaldehydes **5** and **6** were prepared from commercially available 4- and 3-bromobenzaldehyde, as previously described.[16,17] Condensation of **5** and **6** with pyrrole in the ratio of 1:10, followed by oxidation with *p*-chloranil yielded corroles **3** and **4** in 10% (*para*) and 9% (*meta*) yields. During chromatographic purification of both products, the corrole fraction was preceded by an olive green band, which was difficult to separate. This band has been previously observed by several authors and it is believed to be a linear oligopyrrole produced as a by-product during the condensation reaction.[15] There was no porphyrin observed by TLC or MS analysis, but a sapphyrin-like macrocycle was also formed as a by-product, in trace amounts. Since the ^{1}H NMR spectra of corroles **3** and **4** showed only broad peaks, we prepared their copper(III) complexes (**7**, **8**) in quantitative yield, using $Cu(OAc)_2$ in methanol at room temperature. Corroles **7** and **8** show well-resolved ^{1}H NMR spectra, with characteristic peaks for the *o*-carborane BH protons between 1.5 and 3.5 ppm, the CH-carborane proton as a broad singlet at 4.1 ppm and the β-pyrrolic and phenyl protons in the aromatic region between 7.1 and 8.0 ppm.[18]



The structure of corrole **7** was further confirmed by single crystal X-ray diffraction,† and is shown in Figure 1. The macrocycle exhibits a slight non-planar saddle distortion, with average out-of-plane deviation for the 23 atoms of the corrole core being 0.16 Å and maximum deviation 0.34(1) Å. The coordination geometry is square planar, with a slight tetrahedral distortion, the four N atoms lying alternately 0.16(1) Å above and below their best plane, and the Cu atom 0.053(2) Å out of that plane. Cu–N distances are in the range 1.827(15)–1.898(16) Å.

The preparation of amphiphilic water-soluble *nido*-carboranyl corroles **9** and **10** was attempted by basic degradation of the *o*-carboranyl cages using pyridine and piperidine in a 1:3 ratio, as previously reported for carboranylporphyrins.[17] However, quite unexpectedly this reaction was unsuccessful and neither ^{1}H NMR



Scheme 1. Syntheses of *closo*-carboranylcorroles (**3** and **4**).

† Carboranylcorrole (**7**) chloroform solvate, $C_{43}H_{53}B_{30}CuN_4{\cdot}CHCl_3$, triclinic space group *P*-1, $a = 12.097(2)$, $b = 14.148(2)$, $c = 17.305(3)$ Å, $\alpha = 97.327(5)$, $\beta = 105.708(5)$, $\gamma = 90.178(12)°$ $V = 2825.6(8)$ Å^3, $Z = 2$, $T = 100$ K, $R = 0.171$ for 7565 unique data with $\theta < 23.0°$ (Mo Kα). Except for the Cu atom, only isotropic refinement was possible. CCDC 271067.

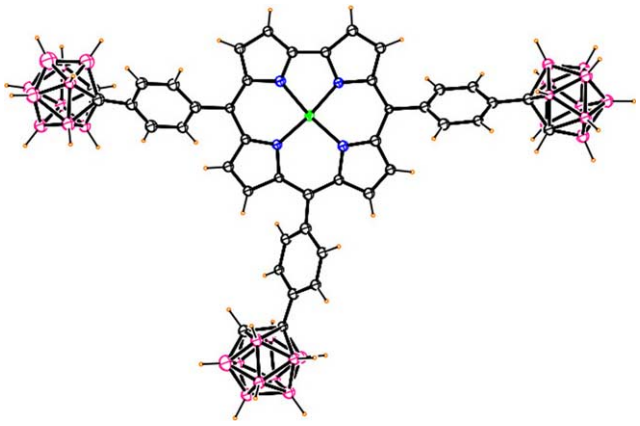
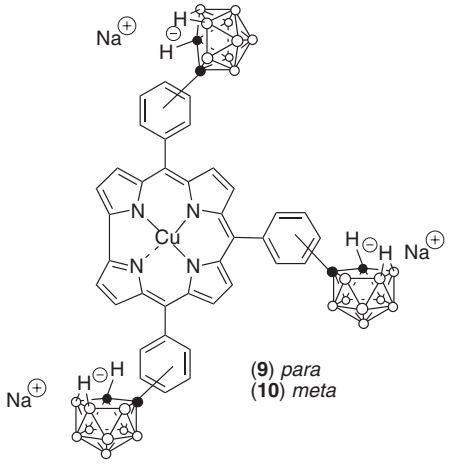


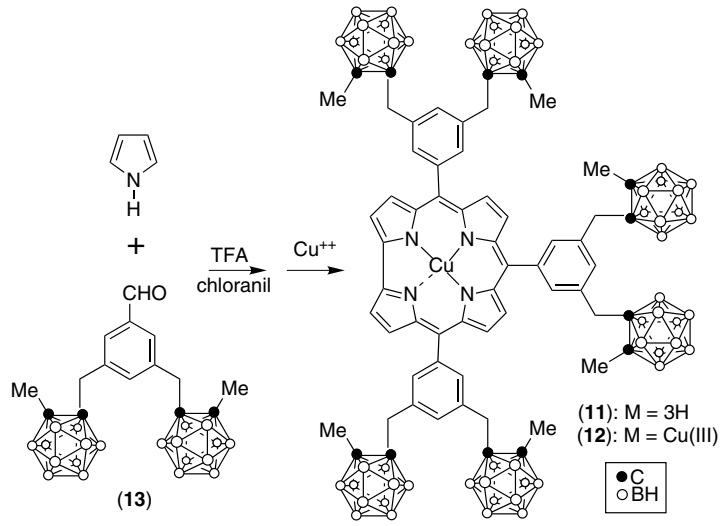
Figure 1. X-ray structure of copper(III) carboranylcorrole (**7**).

nor mass spectrometry indicated formation of the desired product. Corroles **9** and **10** were probably unstable to the basic reaction conditions and decomposed. This reaction was repeated with corrole **7** using tetrabutylammonium fluoride as the deboronating reagent,[19] followed by ion-exchange using a Dowex resin in the sodium form. The corresponding water-soluble *nido*-carboranyl corrole **9** was obtained in quantitative yield[20] and preliminary biological results of **9** show that it has very low cytotoxicity and is readily taken-up by human glioma T98G cells, localizing mainly within the cell lysosomes.



A similar synthetic strategy was followed in the preparation of hexa-caboranylcorroles **11** and **12** containing 60 atoms of boron per macrocycle, approximating 40% boron by weight (Scheme 2). Condensation of di-carboranylaldehyde **13**[16,21] with pyrrole in a 1:10 ratio gave only an inseparable complex mixture of products. However, reducing the aldehyde/pyrrole ratio to 1:2 while still maintaining an excess of pyrrole afforded corrole **11** in 30% yield without formation of the corresponding porphyrin contaminant. Copper was inserted immediately, as described above, to aid in the purification process and to prevent decomposition. The ^{1}H NMR spectrum of **12** shows slightly upfield shifted resonances from those of **7** and **8**, with the *o*-carborane BH protons appearing between 1.6 and 3.4 ppm, the CH-carborane proton at 3.6 ppm and the β-pyrrolic and phenyl protons in the aromatic region between 7.2 and 8.0 ppm.[22]

The optical spectra of free-base corroles **3** and **4** in chloroform show a Soret band at ~420 nm and three Q-bands in the 500–600 nm region, typical for corroles. The Cu(III) corroles **7**, **8**, and **12** show blue-shifted Soret bands at ~410 nm and only two Q-bands. The fluorescence emission bands for corroles **3** and **4** were found to be similar, at λ_{max} 667 nm (excitation at 570 nm) and 664 nm (excitation at 567 nm), respectively, in chloroform. On the other hand, the fluorescence emission band for corrole **12** in the same solvent was found to be blue shifted at 516 nm upon excitation at 511 nm, possibly due to the more pronounced distortion of this macrocycle compared with **7** or **8**.



Scheme 2. Synthesis of hexa-carboranylcorroles.

In summary, we have synthesized new carboranylcorroles (**3**, **4**, **7**–**12**), via the condensation of pyrrole with carboranylbenzaldehydes. The highest yield obtained for this one-step condensation was 30% (for **11**), probably due to the bulkiness of the di-carboranylbenzaldehyde used, which might minimize the formation of additional polypyrrolic by-products. These compounds absorb 536–644 nm light, are fluorescent and contain 33–40% boron by weight, and thus have potential application as sensitizers in the PDT and in the BNCT treatment of cancer. The complete biological evaluation of corroles **9** and **10** is currently underway in our laboratories.

Acknowledgements

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References and notes

1. Johnson, A. W.; Price, R. *J. Chem. Soc.* **1960**, 1649.
2. Hodgkin, D. C.; Harrison, H. R.; Hodder, O. J. R. *J. Chem. Soc. B* **1971**, 640.
3. Paolesse, R. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; Vol. 2, pp 201–232.
4. Erben, C.; Will, S.; Kadish, K. M. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; Vol. 2, pp 233–300.
5. Gryko, D. T.; Fox, J. P.; Goldberg, D. P. *J. Porphyrins Phthalocyanines* **2004**, *8*, 1091.
6. Gross, Z.; Galili, N.; Simkhovich, L.; Saltsman, I.; Botoshansky, M.; Bläser, D.; Goldberg, I. *Org. Lett.* **1999**, *1*, 599.
7. Gross, Z.; Galili, N.; Saltsman, I. *Angew. Chem., Int. Ed.* **1999**, *38*, 1427.
8. Paolesse, R.; Jaquinod, L.; Nurco, D. J.; Mini, S.; Sagone, F.; Boschi, T.; Smith, K. M. *Chem. Commun.* **1999**, 1307.
9. Paolesse, R.; Sagone, F.; Khoury, R. G. *J. Org. Chem.* **2001**, *66*, 550.
10. Vogel, E.; Will, S.; Shulze-Tilling, A.; Neumann, L.; Lex, J.; Bill, E.; Trautwein, A. X.; Wieghardt, A. *Angew. Chem., Int. Ed.* **1994**, *33*, 731.
11. Bendix, J.; Dmochowski, I. J.; Gray, H. B.; Mahammed, A.; Simkhovich, L.; Gross, Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 4048.
12. Simkhovich, L.; Gross, Z. *Tetrahedron Lett.* **2001**, *42*, 8089.
13. Aviezer, D.; Cotton, S.; David, M.; Segev, A.; Khaselev, N.; Galili, N.; Gross, Z.; Yayon, A. *Cancer Res.* **2000**, *60*, 2973.
14. Vicente, M. G. H. *Curr. Med. Chem. Anti-Cancer Agents* **2001**, *1*, 175.
15. Paolesse, R.; Marini, A.; Nardis, S.; Froiio, A.; Mandoj, F.; Nurco, D. J.; Prodi, L.; Montalti, M.; Smith, K. M. *J. Porphyrins Phthalocyanines* **2003**, *7*, 25.
16. Vicente, M. G. H.; Shetty, S. J.; Wickramasinghe, A.; Smith, K. M. *Tetrahedron Lett.* **2000**, *41*, 7623.
17. Vicente, M. G. H.; Nurco, D. J.; Shetty, S. J.; Osterloh, J.; Ventre, E.; Hedge, V.; Deutsch, W. A. *J. Photochem. Photobiol. B: Biol.* **2002**, *68*, 123.
18. *Selected data for* **3**: HRMS (MALDI-QTOF): Calcd for $C_{43}H_{56}B_{30}N_4$+H = 954.7584, found *m/z* 954.7581. UV–vis λ_{max} ($CHCl_3$) 420 nm (ε 125,000), 580 (19,500), 617 (14,700), 626 (8900). *Selected data for* **4**: HRMS (MALDI-QTOF) Calcd for $C_{43}H_{56}B_{30}N_4$+H = 954.7584, found *m/z* 954.7496. UV–vis λ_{max} ($CHCl_3$) 417 nm (ε 109,000), 578 (19,000), 615 (13,600), 644 (9100). *Selected data for* **7**: HRMS (MALDI-QTOF) Calcd for $C_{43}H_{53}B_{30}CuN_4$+H = 1014.6656, found *m/z* 1014.6606. UV–vis λ_{max} ($CHCl_3$) 412 nm (ε 124,000), 536 (9000), 615 (6400). ^{1}H NMR ($CDCl_3$) δ ppm: 1.6–3.4 (br, 30H), 4.09 (br, 3H), 7.18 (d, *J* = 4.5, 2H), 7.28 (d, *J* = 4.5, 2H), 7.61 (m, 10H), 7.71 (d, *J* = 8.4, 4H), 7.90 (d, *J* = 3.8, 2H). *Selected data for* **8**: HRMS (MALDI-QTOF) Calcd for $C_{43}H_{53}B_{30}CuN_4$+H = 1014.6656, found *m/z* 1014.6656. UV–vis λ_{max} ($CHCl_3$) 409 nm (ε 85,000), 535 (7000), 613 (5100). ^{1}H NMR ($CDCl_3$) δ ppm: 1.6–3.4 (br, 30H), 4.07 (br, 3H), 7.18 (br, 2H), 7.29 (br, 2H), 7.53 (br, 6H), 7.73 (br, 6H), 7.87 (br, 2H), 7.99 (br, 2H).
19. Fox, M. A.; Gill, W. R.; Herbertson, P. L.; MacBride, J. A. H.; Wade, K.; Colquhoun, H. M. *Polyhedron* **1996**, *15*, 565.
20. *Selected data for* **9**: MS (MALDI) *m/z* 306.94. UV–vis λ_{max} (ethanol) 424 nm (ε 404,500), 579 (7600). ^{1}H NMR (acetone-d_6) δ ppm: −2.38 (br, 3H), 1.5–3.5 (br, 27H), 4.10 (br, 3H), 7.35 (br, 2H), 7.68 (br, 2H), 8.11 (br, 10H), 8.47 (br, 4H), 8.93 (br, 2H).
21. Gottumukkala, V.; Luguya, R.; Fronczek, F. R.; Vicente, M. G. H. *Bioorg. Med. Chem.* **2005**, *13*, 1633.
22. *Selected data for* **12**: HRMS (MALDI-QTOF) Calcd for $C_{61}H_{107}B_{60}CuN_4$+H = 1632.3701, found *m/z* 1632.3721. UV–vis λ_{max} ($CHCl_3$) 412 nm (ε 115,000), 536 (8700), 609 (5400). ^{1}H NMR ($CDCl_3$) δ ppm: 1.6–3.4 (br, 60H), 2.19 (m, 18H), 3.59 (s, 12H), 7.20 (d, *J* = 4.5, 2H), 7.34 (d, *J* = 4.1, 2H), 7.44 (s, 3H), 7.55 (s, 6H), 7.61 (d, *J* = 4.1, 2H), 8.03 (br, 2H).