ChemComm

Alphabet Soup within a Porphyrinoid Cavity: Synthesis of Heterocarbaporphyrins with CNNO, CNOO, CNSO and CNSeO Cores from an Oxacarbatripyrrin

Journal:	*ChemComm*
Manuscript ID	CC-COM-06-2018-004976.R1
Article Type:	Communication

Journal Name

COMMUNICATION

Alphabet Soup within a Porphyrinoid Cavity: Synthesis of Heterocarbaporphyrins with CNNO, CNOO, CNSO and CNSeO Cores from an Oxacarbatripyrrin

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

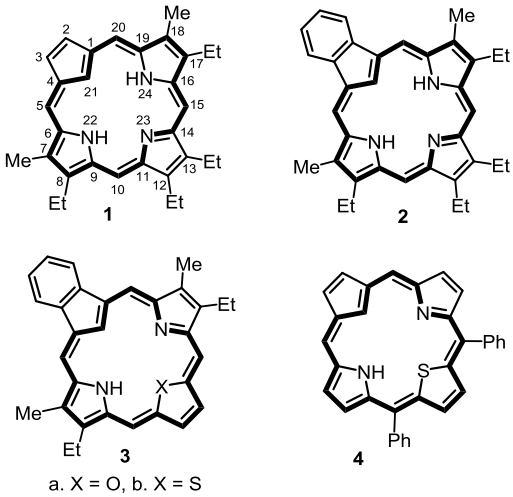
www.rsc.org/

Tyler J. Smolczyk[a] and Timothy D. Lash,*[a]

The first examples of porphyrin analogues with four different core atoms have been synthesized from an oxacarbatripyrrin intermediate. Acid-catalyzed condensation of the tripyrrin analogue with pyrrole or furan dialdehydes gave 22-oxa- and 22,23-dioxacarbaporphyrins, while reactions with furan, thiophene or selenophene dicarbinols afforded diphenyl dioxa-, oxathia- and oxaselenacarbaporphyrins.

Carbaporphyrins are porphyrin analogues where one or more of the core nitrogen atoms have been replaced with carbons.[1,2] Structures of this type have attracted a considerable amount of interest owing to their stability, aromatic properties, unusual reactivity and ability to generate organometallic derivatives.[3-5] Furthermore, carbaporphyrin derivatives have shown some promise in the treatment of leishmaniasis.[6] In addition, core modified porphyrins have found applications in the development of chemosensors[7] and have proven to be adept at stabilizing transition metal ions in unusual oxidation states.[3,8] True carbaporphyrins include the cyclopentadienyl analogue **1**[9] and benzo-fused structures such as **2**.[10] The latter system has been particularly well studied due in part to its relative ease of synthesis. Carbaporphyrins such as **2** act as trianionic ligands generating silver(III),[4] gold(III),[4] rhodium(III)[5] and iridium(III) complexes,[5] all of which retain highly diatropic characteristics. However, closely related 23-oxa- and 23-thiacarbaporphyrins **3a** and **3b** are dianionic ligands and form stable organometallic complexes with nickel(II), palladium(II) and platinum(II).[11] Thiacarbaporphyrin **4**[12] and a 22-oxacarbaporphyrin[13] have also been reported to give palladium(II) complexes. *N*- and *C*-Alkylcarbaporphyrins also afford palladium(II) and nickel(II) complexes.[14,15]

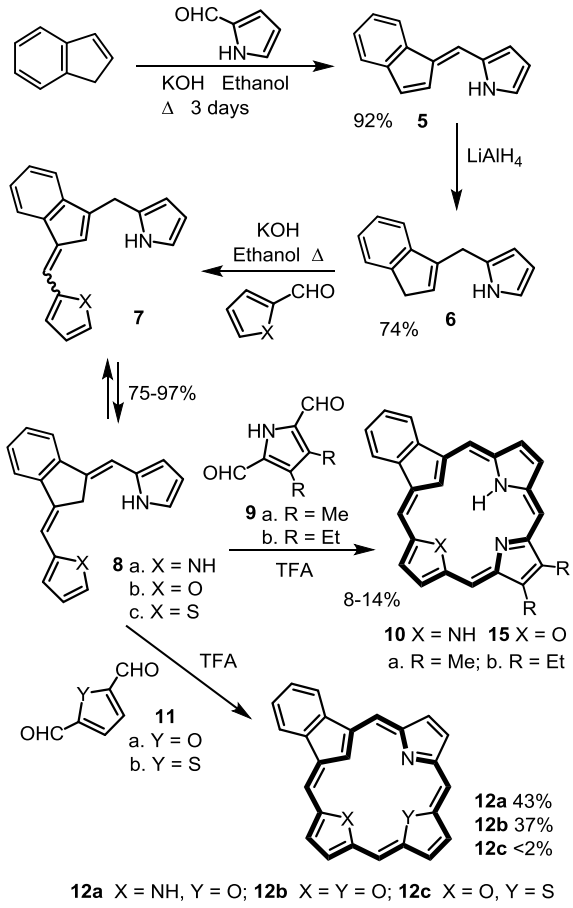
Recently, we reported a new route to carbaporphyrins using a novel carbatripyrrin intermediate.[16] Reaction of indene with pyrrole-2-carbaldehyde and potassium hydroxide in refluxing ethanol generated fulvene **5** and subsequent reduction with lithium aluminum hydride in refluxing THF afforded the related dihydrofulvene **6** (Scheme 1). When **6** was condensed with pyrrole-2-carbaldehyde in refluxing KOH/ethanol under dilute conditions, mixtures of carbatripyrrene products **7a** were formed. However, under more concentrated conditions, pure carbatripyrrin **8a** precipitated from solution. It was speculated that **8a** was present in equilibrium with intermediates such as **7** but under concentrated conditions precipitation of poorly soluble **8a** drove the equilibrium towards the formation of this species. Carbatripyrrin **8a** reacted with pyrrole dialdehydes **9** in the presence of trifluoroacetic acid to give carbaporphyrins **10**, while condensation with furan dialdehyde **11a** afforded oxacarbaporphyrin **12a** (Scheme 1). Furthermore, **8a** reacted with furan, thiophene and selenophene dialcohols **13a-c** to produce diphenylheterocarbaporphyrins **14** (Scheme 2). These diphenylporphyrinoids reacted with nickel(II) or palladium(II) acetate to give nickel(II) and palladium(II) complexes and also generated unique oxidation products. In total, this strategy provided access to porphyrin analogues with CNNN, CNON, CNSN and CNSeN coordination cores.[16]



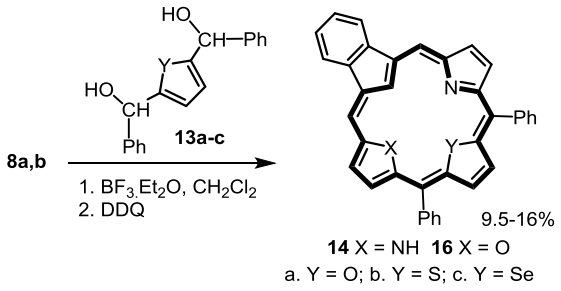
The generality of the carbatripyrrin strategy has not as yet been demonstrated as it relies on the poor solubility of carbatripyrrin **8a** to generate this key intermediate. Alteration of the core atoms within the porphyrin macrocycle allows the

[a] *Department of Chemistry, Illinois State University, Normal, Illinois 61790-4160. Email: tdlash@ilstu.edu*

Electronic Supplementary Information (ESI) available: Full experimental details and selected ^{1}H NMR, ^{1}H-^{1}H COSY, HSQC, DEPT-135, ^{13}C NMR, and UV-Vis spectra are provided.. See DOI: 10.1039/x0xx00000x



Scheme 1 Synthesis of heterocarbaporphyrins



Scheme 2 Synthesis of diphenyl heterocarbaporphyrins.

reactivity and physical and spectroscopic properties to be modified,[1,2,17,18] but currently only a limited number of heterocarbaporphyrin systems have been reported. With this in mind, we set out to determine whether the carbatripyrrin strategy could be adapted to the synthesis of further modified heterocarbaporphyrins. Dihydrofulvene **6** was reacted with furfural in refluxing KOH-ethanol and oxacarbatripyrrin **8b** precipitated from the reaction solution in 78% yield (Scheme 1). Similarly, thiophene-2-carbaldehyde condensed with **6** under the same conditions to give thiacarbatripyrrin **8c** in 97% yield. Heterocarbatripyrrins **8b,c** exhibited similarly poor solubility characteristics to carbatripyrrin **8a** and this aided in the formation of these novel intermediates. However, it was not self-evident that **8b** and **8c** would be sufficiently reactive to form new classes of heterocarbaporphyrins. Furan is substantially less reactive than pyrrole towards electrophilic substitution and this factor could inhibit crucial carbon-carbon bond formation.[19] Thiophene is much less reactive again and this further decreases the chances that **8c** could be used to generate porphyrinoid macrocycles. As it turned out, **8c** failed to give porphyrin-like products under any of the reaction conditions that were explored. However, **8b** proved to be a versatile precursor to heterocarbaporphyrins with CNNO, CNOO, CNSO and CNSeO cores.

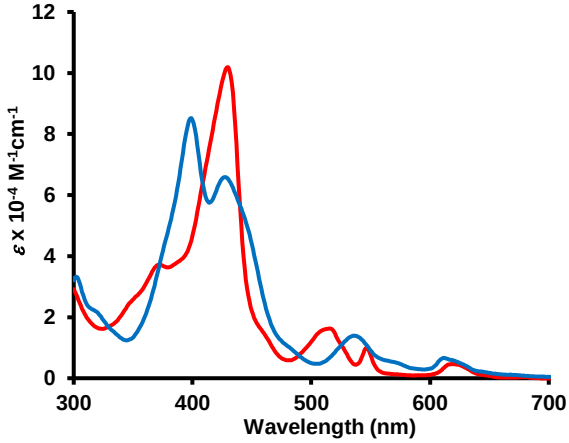


Figure 1 UV-vis spectrum of **15b** in 1% Et_3N-CH_2Cl_2 (red line, free base) and 1% TFA-CH_2Cl_2 (blue line, cation **15b**H^+)

Reaction of **8b** with pyrrole dialdehyde **9a** in the presence of TFA in dichloromethane afforded 22-oxacarbaporphyrin **15a** in 8% yield (Scheme 1). Similarly, **9b** reacted with **8b** to give the related diethylporphyrinoid **15b** in 14% yield. These porphyrin analogues retain strongly aromatic characteristics and the proton NMR spectra for **15a** and **15b** showed the *meso*-protons as four highly deshielded 1H singlets between 9.63 and 10.23 ppm. The pyrrolic and furan protons were similarly shifted downfield to give four 1H doublets between 9.10 and 9.55 ppm, while the internal CH appeared upfield between -5.4 and -5.8 ppm. The UV-vis spectra were also porphyrin-like and **15b** gave rise to a Soret band at 430 nm and Q bands at 515, 547, 618 and 679 nm (Figure 1). Addition of trace amounts of TFA to solutions of **15a,b** gave rise to the related monocations **15a**H^+ and **15b**H^+ (Scheme 3). The UV-vis spectra showed two Soret-like bands at 393 and 432 nm and two weaker absorptions at higher wavelengths. The UV-vis spectra were essentially unchanged in 50% TFA-CH_2Cl_2, indicating that the formation of diprotonated species such as

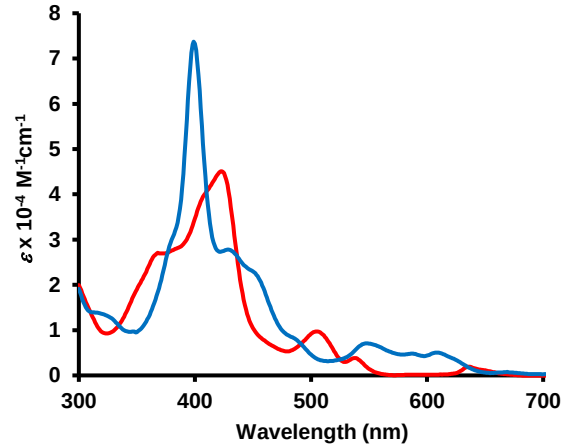


Figure 2 UV-vis spectrum of dioxacarbaporphyrin **12b** in 1% Et_3N-CH_2Cl_2 (red line, free base) and 1% TFA-CH_2Cl_2 (blue line, cation **12b**H^+)

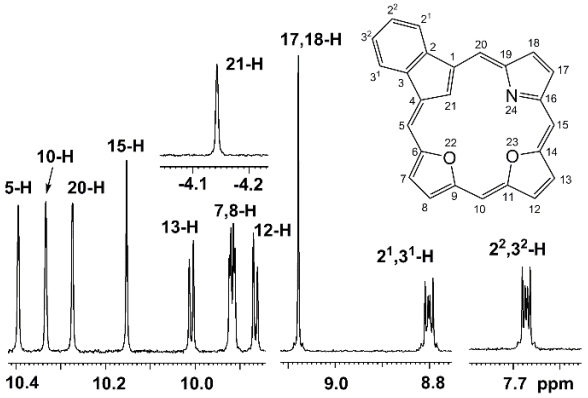
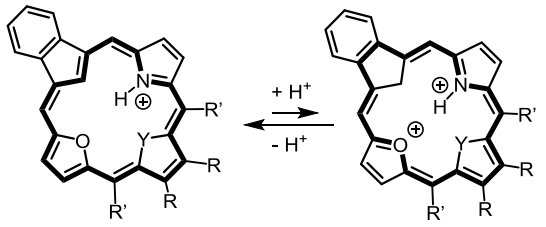


Figure 3 Proton NMR spectrum of **12b** in d_6-DMSO

15H_2^{2+} are not favoured for this system (Scheme 3). The proton NMR spectra for the monocations indicate that they have slightly enhanced diatropic properties and the *meso*-protons for **15b** in TFA-$CDCl_3$ gave rise to four 1H singlets at 10.33, 10.39, 10.43 and 10.47 ppm, while the internal CH showed up at -7.18 ppm. Hence the difference between the upfield and downfield resonances ($\Delta\delta$), which is a useful measure for magnitude of global diatropic character, is 17.65 ppm.

Reaction of **8b** with furan dialdehyde **11a** in the presence of TFA gave a dioxacarbaporphyrin **12b** in 37% yield. Even after prolonged vacuum drying, the sample retained one equivalent of chloroform and was therefore isolated as a chloroform solvate. The UV-vis spectrum for the free base form in 1% triethylamine-CH_2Cl_2 gave a broad Soret band at 427 nm and Q bands at 505, 538 and 636 nm (Figure 2). Addition of TFA led to the formation of a new species that was attributed to monocation **12b**H^+. The dioxacarbaporphyrin was poorly soluble in most organic solvents but gave high quality proton NMR spectra in d_6-DMSO at 70 °C. The proton NMR spectrum confirms the aromatic nature of this new porphyrinoid system, showing the inner CH at -4.24 ppm and four downfield 1H singlets at 10.15, 10.27, 10.33 and 10.39 ppm for the *meso*-protons (Figure 3). Tripyrrin analogue **8b** was also reacted with thiophene dialdehyde **11b** under the same conditions but gave only trace amounts (< 2%) of oxathiacarbaporphyrin **12c**.



15aH^+ Y = NH, R = Me, R' = H **15a**H_2^{2+} Y = NH, R = Me, R' = H
15bH^+ Y = NH, R = Et, R' = H **15b**H_2^{2+} Y = NH, R = Et, R' = H
12bH^+ Y = O, R = R' = H **12b**H_2^{2+} Y = O, R = R' = H
16H^+ Y = O, R = H, R' = Ph **16**H_2^{2+} Y = O, R = H, R' = Ph
16H^+ Y = S, R = H, R' = Ph **16**H_2^{2+} Y = S, R = H, R' = Ph
16H^+ Y = Se, R = H, R' = Ph **16**H_2^{2+} Y = Se, R = H, R' = Ph

Scheme 3. Protonation of heterocarbaporphyrins.

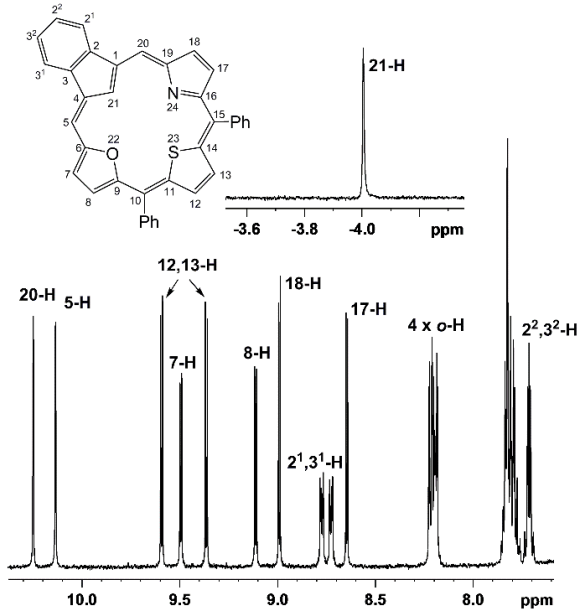


Figure 4. Proton NMR spectrum of porphyrin analogue **16b** in $CDCl_3$

In order to improve the solubility of the heterocarbaporphyrins, and provide access to additional core-modified structures, **8b** was reacted with furan, thiophene and selenophene dicarbinols **13a-c** in the presence of boron trifluoride etherate (Scheme 2). Following oxidation with DDQ, diphenyl dioxacarba-, oxathiacarba- and oxaselenacarbaporphyrins **16a-c** were isolated in 9.5%, 16% and 9.6% yield, respectively. All three compounds exhibited global aromatic properties, although the proton NMR spectra indicate that **16b** has the largest diamagnetic ring current while dioxacarbaporphyrin **16a** has the smallest (Table 1). The *meso*-protons for **16b** appeared as two 2H singlets 10.13 and 10.25 ppm, while the inner CH resonance showed up at -4.00 giving a $\Delta\delta$ value of 14.25. This compares to $\Delta\delta$ values of 13.91 and 14.10 for **16a** and **16c**, respectively. The presence of an electronegative oxygen in **16a** appears to slightly reduce the aromatic properties of these macrocycles compared to having a sulfur atom within the cavity, although the larger selenium atom present in **16c** may reduce the planarity of the system. Addition of TFA to solutions of **16a-c** afforded the corresponding monocations **16**H^+, all of which showed enhanced diatropic character compared to the free base forms. However, for the protonated species, **16a**H^+ showed the largest shifts ($\Delta\delta$ = 17.15 ppm), **16c**H^+ gave the smallest shifts ($\Delta\delta$ = 15.70 ppm), while **16b** had an intermediary $\Delta\delta$ value of 16.45 ppm (Table 1). Protonation increases the steric crowding within the porphyrinoid cavity and this issue is exacerbated by the presence of larger chalconide atoms leading to a further decrease in the planarity of the macrocycle. This explains why the aromatic ring current decreases as the atomic number for the heteroatom at position 23 increases going from O to S to Se. Addition of *d*-TFA to solutions of **16a-c** led to rapid deuterium exchange of the internal CH indicating that dications **16**H_2^{2+} (Scheme 3), or related C-protonated monocations, are in equibibrium with **16**H^+. However, even after several days at room temperature no exchange was observed with the *meso*-protons. Similar results were also obtained for oxacarbaporphyrins **15**. These results contrast with experiments reported for carbaporphyrin **2**, where slow deuterium exchange was noted at the *meso*-positions.[10b] The UV-vis spectra of **16a**, **16b** and **16c** were porphyrin-like with strong Soret bands at 429, 436 and 439 nm, respectively, and a series of Q bands between 500 and 720 nm. The corresponding

monocations **16**H$^+$ in 1% TFA-CH_2Cl_2 gave broadened Soret bands, and both the Soret and Q bands underwent substantial bathochromic shifts with increasing atomic number for the heteroatoms at position 23 (Figure 5).

Table 1 Selected proton NMR chemical shifts for hetero-carbaporphyrins **16a-c** and the related monocations

	21	5	20	7	8	17	18
16a	-3.75	10.00	10.16	9.41	8.85	8.47	8.92
16b	-4.00	10.13	10.25	9.49	9.11	8.65	8.99
16c	-3.86	10.15	10.24	9.44	9.09	8.67	9.01
16aH$^+$	-6.51	10.58	10.64	10.04	9.50	9.17	9.67
16bH$^+$	-5.90	10.50	10.55	10.01	9.68	9.10	9.41
16cH$^+$	-5.23	10.39	10.47	9.97	9.66	9.07	9.33

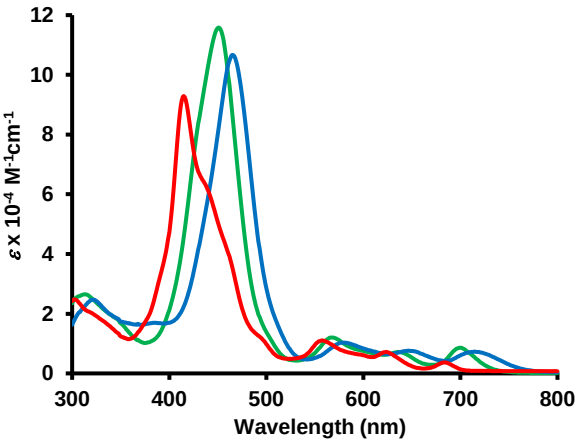


Figure 5 UV-vis spectra of heterocarbaporphyrin monocations **16**H+ in 1% TFA-CH_2Cl_2: **16**H$^+$ (red), **16b**H$^+$ (green), **16c**H$^+$ (blue)

In conclusion, syntheses of 22-oxa-, 22,23-dioxa-, 22-oxa-23-thia- and 22-oxa-23-selenacarbaporphyrins have been accomplished using an oxacarbatripyrrin as a key intermediate. Modification of the core atoms allows the spectroscopic properties of these porphyrin analogues to be fine-tuned. In addition, this strategy has allowed the first examples of porphyrin analogues with four different types of atoms within the macrocyclic core to be isolated and characterized. These modified porphyrinoids also have the potential to exhibit novel coordination chemistry complementing the results obtained for previously described carbaporphyrinoid ligands.[20]

This work was supported by the National Science Foundation under grants CHE-1212691 and CHE-1465049, and the Petroleum Research Fund, administered by the American Chemical Society.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 T. D. Lash In *Handbook of Porphyrin Science – With Applications to Chemistry, Physics, Material Science, Engineering, Biology and Medicine*, Vol. 16, K. M. Kadish, K. M. Smith and R. Guilard, eds.; World Scientific Publishing: Singapore, 2012, pp 1-329.

2 T. D. Lash, *Chem. Rev.*, 2017, **117**, 2313-2446.

3. T. D. Lash, *Chem. Asian J.*, 2014, **9**, 682-705.

4. (a) M. A. Muckey, L. F. Szczepura, G. M. Ferrence and T. D. Lash, *Inorg. Chem.*, 2002, **41**, 4840-4842. (b) T. D. Lash, D. A. Colby and L. F. Szczepura, *Inorg. Chem.*, 2004, **43**, 5258-5267. (c) B. Szyszko, K. Kupietz, L. Szterenberg and L. Latos-Grazynski, *Chem. Eur. J.* 2014, **20**, 1376-1382.

5. V. A. K. Adiraju, G. M. Ferrence and T. D. Lash, *Dalton Trans.*, 2016, **45**, 13691-13694.

6. V. M. Taylor, D. L. Cedeño, D. L. Muñoz, M. A. Jones, T. D. Lash, A. M. Young, M. H. Constantino, N. Esposito, I. D. Vélez and S. M. Robledo, *Antimicr. Agents Chemoth.*, 2011, **55**, 4755-4764.

7. (a) Y. Ding, W.-H. Zhu and Y. Xie, *Chem. Rev.*, 2017, **117**, 2203-2256. (b) R. Paolesse, S. Nardis, D. Monti, M. Stefanelli and C. Di Natale, *Chem. Rev.*, 2017, **117**, 2517-2583.

8. (a) I. Gupta and M. Ravikanth, *Coord. Chem. Rev.*, 2006, **250**, 468-518. (b) P. J. Chmielewski and L. Latos-Grazynski, *Coord. Chem. Rev.*, 2005, **249**, 2510-2533.

9. D. Li and T. D. Lash, *J. Org. Chem.*, 2014, **79**, 7112-7121.

10 (a) T. D. Lash and M. J. Hayes, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 840-842. (b) T. D. Lash, M. J. Hayes, J. D. Spence, M. A. Muckey, G. M. Ferrence and L. F. Szczepura, *J. Org. Chem.*, 2002, **67**, 4860-4874.

11. (a) D. Liu and T. D. Lash, *Chem. Commun.*, 2002, 2426-2427. (b) D. Liu, G. M. Ferrence and T. D. Lash, *J. Org. Chem.*, 2004, **69**, 6079-6093. (c) S. C. Fosu, G. M. Ferrence and T. D. Lash, *J. Org. Chem.*, 2014, **79**, 11061-11074.

12. A. Berlicka, P. Dutka, L. Szterenberg and L. Latos-Grazynski, *Angew. Chem. Int. Ed.*, 2014, **53**, 4885-4889.

13. P. Jain, G. M. Ferrence and T. D. Lash, *J. Org. Chem.*, 2010, **75**, 6563-6573.

14. T. D. Lash, *Org. Lett.*, 2011, **13**, 4632-4635. See also B. Szyszko, L. Latos-Grazynski and L. Szterenberg, *Angew. Chem. Int. Ed.*, 2011, **50**, 6587–6591.

15. N. Sahota, G. M. Ferrence and T. D. Lash, *J. Org. Chem.*, 2017, **82**, 9715-9730.

16. L. M. Stateman and T. D. Lash, *Org. Lett.*, 2015, **17**, 4530-4533.

17. T. Chatterjee, V. S. Shetti, R. Sharma and M. Ravikanth, *Chem. Rev.*, 2017, **117**, 3254-3328.

18. C. Brückner, J. Akhigbe and L. P. Samankumara In *Handbook of Porphyrin Science – With Applications to Chemistry, Physics, Material Science, Engineering, Biology and Medicine*, Vol. 31, K. M. Kadish, K. M. Smith and R. Guilard, eds.; World Scientific Publishing: Singapore, 2014, pp 1-275.

19. T. L. Gilchrist, *Heterocyclic Chemistry*, 3rd edition, Longman, 1997, pp 212 and 223.

20. T. D. Lash and G. M. Ferrence, *Inorg. Chem.*, 2017, **56**, 11426-11434.

Alphabet Soup within a Porphyrinoid Cavity: Synthesis of Heterocarbaporphyrins with CNNO, CNOO, CNSO and CNSeO Cores from an Oxacarbatripyrrin

Tyler J. Smolczyk and Timothy D. Lash*

The first examples of porphyrin analogues with four different core atoms have been synthesized from an oxacarbatripyrrin intermediate.