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Citation for published version:

Cowie, TY, Kennedy, L, Zurek, JM, Paterson, MJ & Bebbington, MWP 2015, 'Crossed McMurry coupling reactions for porphycenic macrocycles: Non-statistical selectivity and rationalisation', *European Journal of Organic Chemistry*, vol. 2015, no. 17, pp. 3818-3823. <https://doi.org/10.1002/ejoc.201500221>

Digital Object Identifier (DOI):

[10.1002/ejoc.201500221](https://doi.org/10.1002/ejoc.201500221)

Link:

[Link to publication record in Heriot-Watt Research Portal](#)

Document Version:

Peer reviewed version

Published In:

European Journal of Organic Chemistry

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Crossed McMurry Coupling Reactions for Porphycenic Macrocycles: Non-statistical Selectivity and Rationalisation

Thomas Y. Cowie, Lorna Kennedy, Justyna M. Żurek, Martin J. Paterson* and Magnus W. P. Bebbington^[a]

Abstract: Crossed McMurry reactions of bisfuran or bistiophene dialdehydes with bipyrrole dialdehydes have been studied for the first time. Only those porphycenic macrocycles derived from homocoupled McMurry products were formed. The results are explained using both density functional theory and electron propagator computations to model the electron affinity of the dialdehyde starting materials. It was predicted that bisfuran\bistiophene cross-coupling would indeed occur, and this was demonstrated via the first synthesis of a novel dioxo,dithio hetero-porphycenoid annulene. This approach will allow the prior identification of viable substrates for related crossed McMurry reactions.

Introduction

Porphycenes are structural isomers of porphyrins, consisting of a planar macrocyclic ring with an aromatic 18 π -electron configuration (Fig. 1). Their chemistry has been widely studied,¹ and they have attracted considerable interest for their potential applications in catalysis,² materials chemistry,³ non-linear optics,⁴ photo inactivation of bacteria⁵ and protein mimicry.⁶ In particular, they have recently become of interest as sensitisers for two-photon absorption (TPA) for use in photodynamic therapy (PDT).⁷ In PDT one needs to photosensitise in the tissue transparency window (600 – 1000 nm) and porphyrin chromophores have been the standard for linear absorption. However, their maximum absorption at 630 nm limits use due to e.g., tissue depth penetration. The idea of using two-photons, each of twice the excitation wavelength is a promising approach in modern PDT research. Unfortunately the TPA characteristics of porphyrins are not ideal (i.e., low TPA cross section at desired wavelengths). However, recent work has shown that their structural isomers, the porphycenes do have this desired property.^{8a,b} As part of an interdisciplinary research program aimed at the rational design of two-photon sensitisers, we have previously undertaken a computational study on the effect of heteroatom substitution on TPA properties.^{9a,b} It has been predicted that while one-photon absorption is insensitive to core aromatic substitution, and results in almost identical absorption spectra (i.e., Soret and Q bands) for such electronic isomers, that crucially the non-linear (two-photon) absorption is highly sensitive such

features. This fascinating aspect highlights the very subtle molecular tuning that is possible for non-linear optical applications. Here, incorporation of two oxygen atoms into the porphycene core (Fig. 1) was predicted to lead to resonance enhancement (in the Q-band region) that produced a remarkable improvement in the TPA cross-section. Only a single macrocycle containing two pyrrole and two furan units (of type **2**) has been reported, and no yield or characterisation data are disclosed.¹⁰

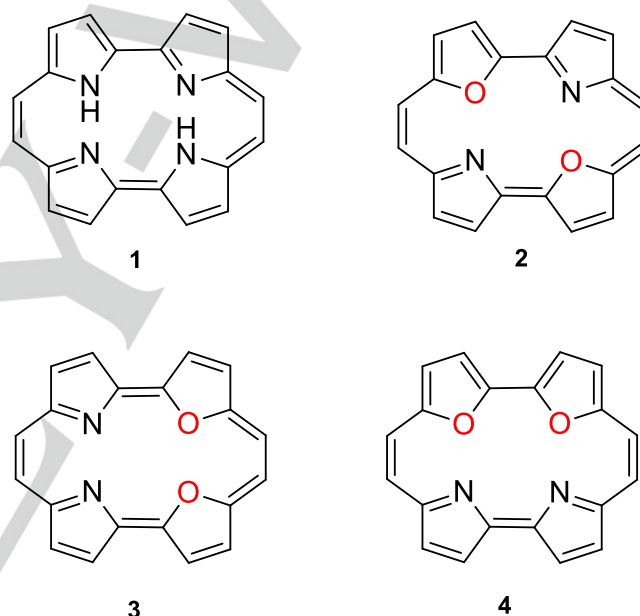


Fig. 1. Structure of the parent porphycene **1** and dioxaporphycene isomers **2-4**.

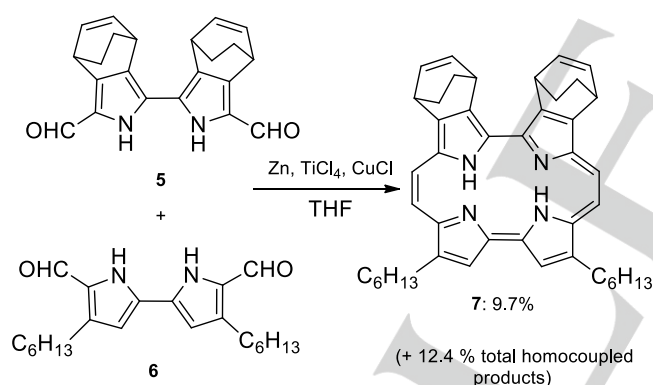
Porphycenes are traditionally prepared by reductive McMurry coupling of two bispyrrolyl dialdehyde units in modest yield.^{1,11} Very few other reliable methods exist for their preparation.^{12a,b} Examples of peripheral functionalisation and the inclusion of additional heteroatoms within the ring structure have emerged.¹³⁻¹⁶ Cross-coupling of two different bipyrroles has also been reported (Scheme 1).¹⁷ We reasoned that one of the most promising dioxaporphycene systems for TPA, namely **4**, might be accessed most directly through crossed McMurry coupling of bisfuran and bipyrrole subunits (Scheme 2). Typically statistical mixtures are obtained in crossed McMurry reactions.¹⁸ We therefore chose to carry out a systematic study of these processes using mixtures of furan, pyrrole and thiophene-derived dicarbonyl substrates relevant to our desired targets, which have until now been unexplored.

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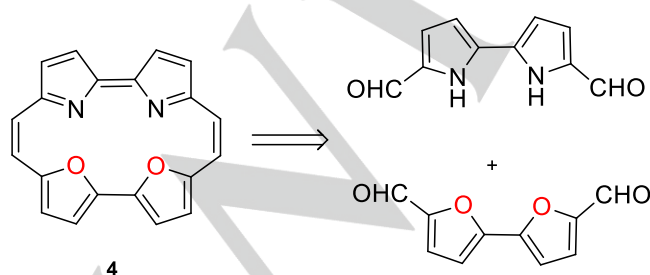
Results and Discussion

Bipyrrole¹⁷ⁱ **6** and bisfuran¹⁹ **9** (Table 1) were prepared by literature methods and an equimolar mixture of these dialdehydes was subjected to standard McMurry conditions for porphycene synthesis. Intriguingly, this reaction returned only macrocycles derived from homocoupled products **11b** and **12a** in a 1 : 3 ratio, with no signals in the crude NMR spectrum indicating the formation of any other macrocyclic products such as **13**.²⁰ The total yield of macrocyclic products was within the range of what would normally be expected for a porphycene synthesis,¹ suggesting that we had successfully isolated all the macrocycles present. Our initial, tentative explanation for this, based on the accepted mechanism for the McMurry reaction,¹⁸ was that the more electron-rich pyrrole was both more difficult to reduce *and* less reactive in the subsequent dimerisation of the radical anion species than the bisfuran. Under these circumstances the bisfuran would be consumed much more rapidly than the bipyrrole, leading to the observed selectivity. Use of diacetyl bisfuran²¹ **10** was attempted in order to reduce the rate of homo-dimerisation but once again only the homodimeric products **11b** and **12b** were obtained, albeit in a 2:3 ratio. To confirm that the pyrrole components we had used were compatible with the reaction conditions, we successfully prepared the mixed porphycene **11c** from **6** and **8**, obtained as part of what appears to be a statistical mixture including homocoupled products **11a** and **11b**.

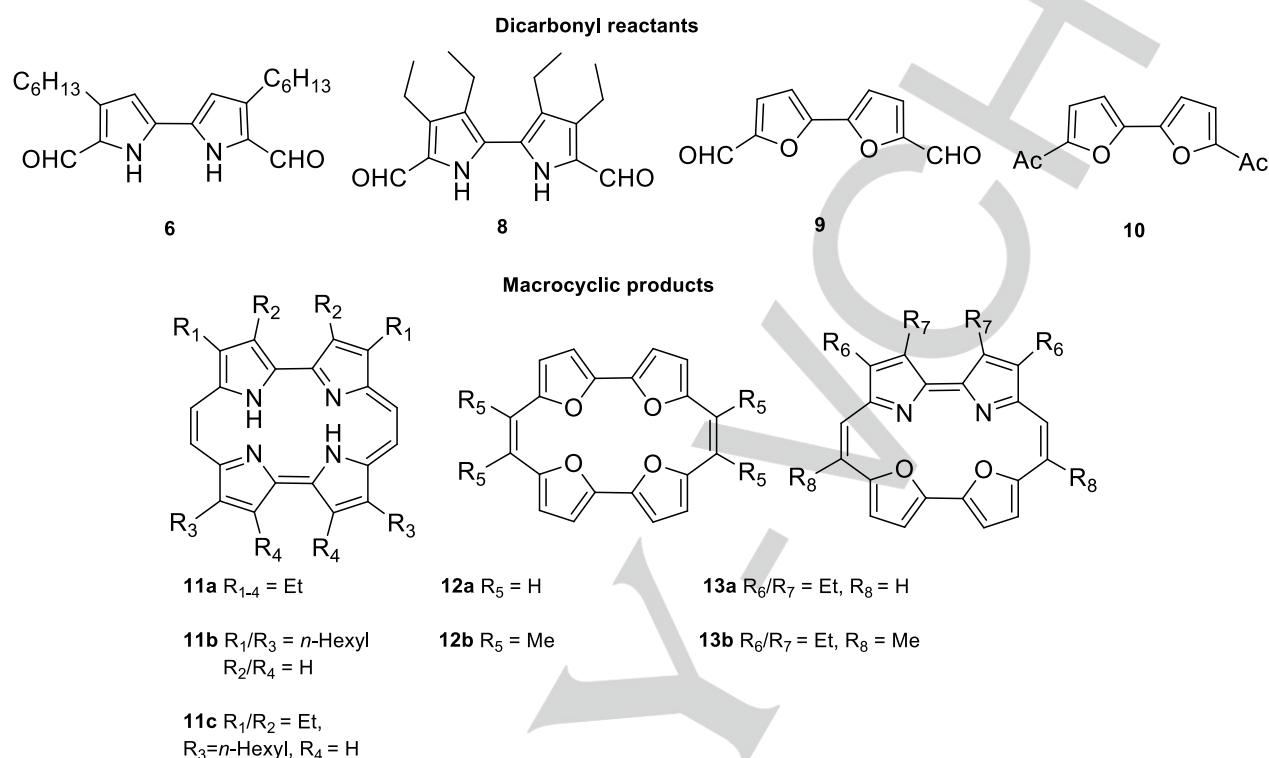
The success of crossed McMurry reactions is known to depend in part on the reducibility of the reactants.^{18,22} We postulated that for crossed McMurry reactions to be successful in macrocycle synthesis, each compatible coupling partner should have a similar rate of reduction, so that each reduced species can exist simultaneously at a significant concentration. It was supposed that single electron transfer (SET) from the reducing metal was likely to be the rate-determining step in the McMurry reaction. We therefore computed the electron affinity, and thus overall reducibility, of each bis-heterocyclic system, in two complementary ways. Firstly we used electron propagator theory (P3 propagator method) to calculate the 3rd-order correlated electron affinity for the LUMO (using the cc-pVTZ basis).^{23a-c} These EAs are given in table 2. Notably the pole strengths (PS) are all above 0.85, and thus the quasi-single particle picture is valid. Density functional theory (B3LYP functional and cc-pVTZ basis) was used to directly calculate relaxed electron affinities (difference between geometry optimised neutral and radical anions, i.e., opposite sign electron attachment energies). We omit the hexyl chains but note that calibration calculations with smaller basis sets show the effect of such pyrrole substituted alkyl chains to be small.



Scheme 1. A recent porphycene synthesis through crossed McMurry reaction



Scheme 2. Retrosynthesis of dioxaporphycene **4**



Reaction	Isolated yield of macrocyclic product / %		
6 + 9	11b : 12	12a : 30	13a : not observed
6 + 10	11b : 12	12b : 23	13b : not observed
6 + 8	11a : 7 11b : 6, 11c 6	NA	NA

^a Macrocycles **11a**, **11b**, **12a** and **12b** were prepared independently by homocoupling of the appropriate dialdehydes, see experimental and supporting information. Diagnostic signals for macrocyclic products were found between 6-9 ppm in the ¹H NMR spectra.

Table 1. Crossed McMurry reactions between bisheterocyclic subunits

Thus, the 3rd order LUMO EA is a key parameter related to the kinetics of electron transfer from the metal, and thus the rate of formation of the key radical anion species, as it relates to the energetic requirements for the initial electron transfer. The relaxed EA from DFT relates to the stability of such radical anions once formed. We note that the same trend is seen for both approaches.

The parent bipyrrrole system **14**, (used here for without pendant groups for conformational simplicity) with a LUMO EA of -0.003 eV, is therefore significantly more difficult to reduce than the bisfuran and bisthiophenes under study, which have much more favorable LUMO EAs ranging from -0.26 to -0.89 eV. These results are consistent with SET into the bisfurans **9** and **10** being therefore more rapid than for the bipyrrroles, which could explain the complete selectivity for the formation of homodimerised products in their attempted crossed McMurry reactions.

We observed that the LUMO EAs for the bisfuran dialdehyde **9** and the bisthiophene dialdehyde²⁴ **15** were both significantly more negative than those for the bipyrrroles **6** and **8**. Thus they could be potential reaction partners in a crossed McMurry reaction, and indeed find that a mixture of **9** and **15** gave some of the heterodimer-derived macrocycle **16** in addition to homodimerised products.²⁵ (Scheme 3)

Careful chromatography allowed the isolation of the new macrocyclic system **16**, and crystals were obtained for an X-ray diffraction study to confirm the structure.²⁶ (Fig. 2) As expected, the macrocycle is not planar, as it cannot readily aromatise to an 18π system. The furan rings appear to be in conjugation with the

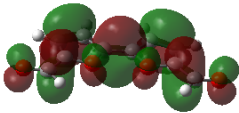
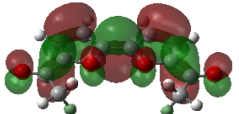
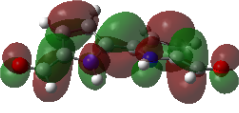
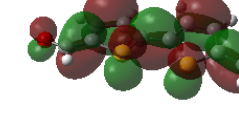
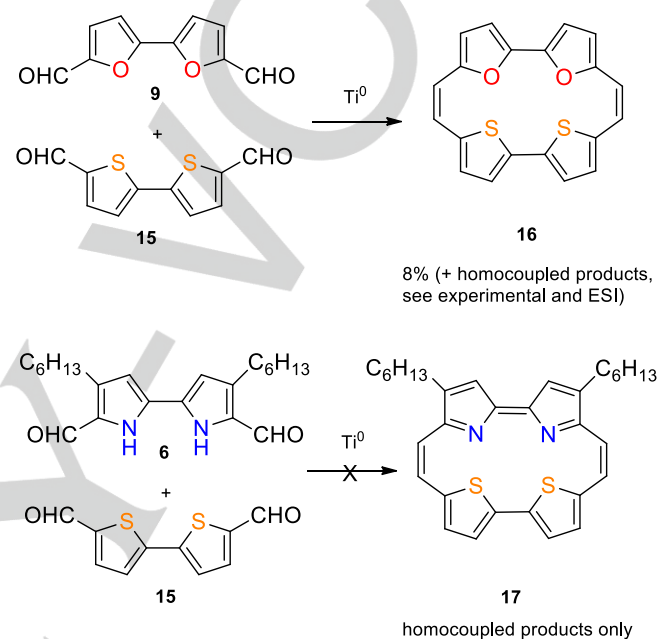
Dicarbonyl derivative	Orbital	3 rd order P3 propagator LUMO EA (eV)	B3LYP relaxed EA (eV)
 Diformyl-bisfuran 9	LUMO	-0.506	-1.47
	PS	0.882	
 Diacetyl-bisfuran 10	LUMO	-0.264	-1.24
	PS	0.882	
 Diformyl-bipyrrole 14	LUMO	-0.003	-1.01
	PS	0.883	
 Diformyl-bisthiophene 15	LUMO	-0.891	-1.78
	PS	0.884	

Table 2. McMurry reaction coupling partners, propagator derived LUMO electron affinity and B3LYP relaxed electron affinity. (PS = pole strength)

C=C double bonds (the O1-C11-C10-C9 dihedral angle is only 5.0°) but the more bulky thiophene rings are rotated out of the ring plane more significantly (S2-C8-C9-C10 dihedral angle is 24.9°). The solution phase NMR data also do not indicate the presence of any ring currents (see experimental).

As a further control experiment, we also subjected a mixture of bipyrrole and bisthiophene components **6** and **15** to the standard reaction conditions, and once again observed only products from homocoupling. It would appear that the reducibility of the dialdehyde components is not the only parameter affecting the relative rates of product formation from homo- and heterodimerisation, since the proportions of the products do not link in a simple way to the relative values for the LUMO EA. Steric effects are also likely to play a role in the C-C bond forming step

and thiophene is known to be significantly more bulky than furan or pyrrole.²⁷ However, given that the bisthiophene is known to homocouple,^{13b,28} and that formation of porphycenes **11a-c** involves more steric demand than dioxaporphycenes **13a-b**, it seems unlikely that a purely steric explanation accounts for the selectivity we have observed. Additionally, preliminary semi-empirical PM6 heats of formation calculations predict that **4** is more stable than **1**. It is therefore likely that the EA of the starting materials remains an important factor in governing the selectivity of these crossed McMurry reactions.



Scheme 3. Crossed McMurry reaction of bisthiophene **15**

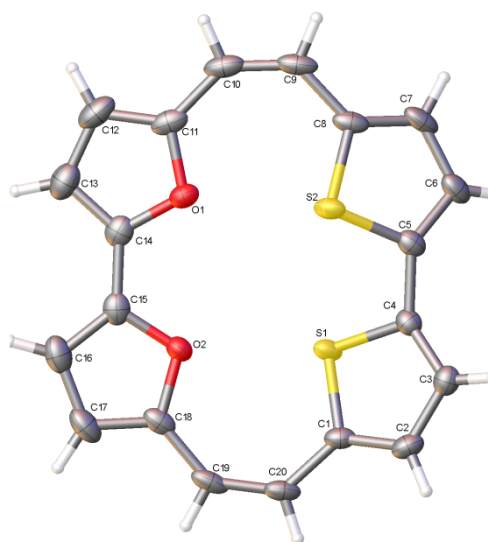


Fig. 2. X-ray structure of **16** (ellipsoids at the 50% level).

Conclusions

In summary, we have examined the unusual product distributions in crossed McMurry reactions of bisheterocyclic dialdehydes and correlated the results with calculated electron affinities, as a measure of reducibility, of the starting materials. Work is currently underway to prepare bipyrrrole and bisfuran/thiophene partners with more closely matched electron affinities, to test further the hypothesis presented herein. This approach will result in the rational design of suitable components for crossed McMurry reactions, ultimately allowing access to unsymmetrical porphycenes for further study.

Experimental Section

Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks (CDCl_3 at δ H 7.26). J values are given in Hz and s, bs, d, dd, ddd, dt, t, br t, td, q, qt, qn, sext and m abbreviations correspond to singlet, broad singlet, doublet, doublet of doublet, doublet of doublet of doublets, doublet of triplets, triplet, broad triplet, triplet of doublets, quartet, quartet of triplets, quintet, sextet and multiplet. Infrared spectra were obtained deposited neat or as a chloroform solution to a diamond/ZnSe plate.

Typical Procedure for the Preparation of Porphycenic Macrocycles from Diformyl Bisheterocycles. Under an atmosphere of nitrogen, a suspension of activated zinc (3.7 g) and copper (I) chloride (222 mg, 2.22 mmol) in THF (100 ml), was added titanium tetrachloride (3.11 ml, 28.8 mmol) drop wise. Upon completion of addition the solution was stirred at reflux for 2 hours. To the reflux solution of **6** (185 mg, 0.52 mmol) and **8** (156 mg, 0.52 mmol) in THF (100 ml) was added drop wise over 1 hour. The solution was stirred for an additional hour. The solution was cooled to 0 °C and quenched with the addition of ammonium hydroxide solution (6 %, 100 ml) was added drop wise over 30 mins. The solution was filtered and washed with DCM (200 ml). The combined organic layers were separated and dried over Na_2SO_4 . After removal of the solvent under reduced pressure the residue was chromatographed and target compounds were isolated to yield: **11a** (10 mg, 7%), **11b** (11 mg, 6%), **11c** (17 mg, 6%).

[2,3,6,7,12,13,16,17]-Octaethylporphycene (11a):²⁸ Blue crystals (10 mg, 7%); mp 212–214 °C; ^1H NMR (400 MHz, CDCl_3) δ 9.49 (s, 1H), 4.03 (q, $J = 7.5$ Hz, 2H), 3.88 (q, $J = 7.6$ Hz, 2H), 1.66 (t, $J = 7.6$ Hz, 3H), 1.59 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 143.4, 142.2, 137.4, 136.9, 110.0, 29.9, 21.6, 20.1, 18.2; IR (cm^{-1}) ν 2961, 2920, 2867, 1534, 1518, 1449, 1371, 1301, 1192, 1029.

[2,7,12,17]-Tetrahexylporphycene (11b):¹⁷ Violet crystals (11 mg, 6%); mp 120–122 °C; ^1H NMR (400 MHz, CDCl_3) δ 9.79 (s, 4H), 9.36 (s, 4H), 4.10 (t, $J = 7.6$ Hz, 8H), 3.29 (s, 2H), 2.44 (m, 8H), 1.82 (m, 8H), 1.59 (m, 8H), 1.48 (m, 8H), 1.00 (t, $J = 7.3$ Hz, 12H); ^{13}C NMR (101 MHz, CDCl_3) δ 145.1, 143.6, 134.2, 122.6, 110.5, 32.1, 29.7, 28.5, 22.8, 14.2; IR (cm^{-1}) ν 2950, 2923, 2852, 1697, 1558, 1454, 1367, 1298, 1259, 1233, 1206, 1090, 1033, 1009.

[2,7]-Dihexyl-[12,13,16,17]tetraethylporphycene (11c): Deep blue crystals (17 mg, 6%); mp 133–135 °C; ^1H NMR (400 MHz, CDCl_3) δ 9.69 (d, $J = 11.2$ Hz, 1H), 9.62 (d, $J = 11.2$ Hz, 1H), 9.26 (s, 2H), 4.10 (q, $J = 7.5$ Hz, 4H), 4.03 (t, $J = 7.5$ Hz, 4H), 3.95 (q, $J = 7.6$ Hz, 4H), 2.37 (m, 4H), 1.75 (m, 4H), 1.73 (t, $J = 7.6$ Hz, 6H), 1.64 (t, $J = 7.5$ Hz, 6H), 1.43 (m, 4H), 1.26 (bs, 2H), 0.96 (t, $J = 7.3$ Hz, 6H), 0.86 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 145.0, 144.1, 143.3, 141.7, 137.3, 136.0, 135.0, 122.5, 110.6, 110.1, 32.0, 29.7, 28.4, 22.8, 22.6, 21.5, 20.1, 18.2, 18.1, 14.2; IR (cm^{-1}) ν 2961, 2922, 2853, 1504, 1467, 1449, 1370, 1292; MS (FTMS + p NSI Full MS) $\text{C}_{40}\text{H}_{54}\text{N}_4$: Theoretical mass $[\text{M}+\text{H}]^+$ 590.4421, found m/z : 591.4413.

(3Z,7Z)-1,2,5,6(2,5)-tetrauranacyclooctaphane-3,7-diene (12a): **12a** was obtained from the crossed McMurry reaction between **6** (100 mg,

0.28 mmol) and **9** (53 mg, 0.28 mmol). The crude oil was chromatographed on silica gel (CH_2Cl_2) to yield **11b** (11 mg, 12%) and **12a** as dark red crystals (14 mg, 31%); mp 270–271 °C; ^1H NMR (400 MHz, C_6D_6) δ 4.95 (d, $J = 3.2$ Hz, 4H), 4.85 (d, $J = 3.2$ Hz, 4H), 4.19 (s, 4H); ^{13}C NMR (100 MHz, C_6D_6) δ 155.5, 149.3, 116.3, 133.9, 109.2; IR (cm^{-1}) ν 3126, 1977, 1682, 1614, 1531, 1436, 1389, 1346, 1276, 1201, 1024.

(3Z,7Z)-3,4,7,8-tetramethyl-1,2,5,6(2,5)-tetrauranacyclooctaphane-3,7-diene (12b): **12b** was obtained from the crossed McMurry reaction between **6** (100 mg, 0.28 mmol) and **10** (61 mg, 0.28 mmol). The crude oil was chromatographed on silica gel (Pet. Ether 40 – 60 °C/ EtOAc ~20%) to yield **11b** (11 mg, 12%) and **12b** as brown/orange crystals (12 mg, 23%); mp 205–206 °C (dec.); ^1H NMR (300 MHz, CDCl_3) δ 6.30 (d, $J = 3.4$ Hz, 4H), 6.20 (d, $J = 3.4$ Hz, 4H), 2.04 (s, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 155.8, 144.1, 122.9, 111.0, 109.5, 45.0, 29.6, 19.9; IR (cm^{-1}) ν 2942, 2864, 1444, 1376, 1280, 1113; MS (FTMS + p NSI Full MS) $\text{C}_{24}\text{H}_{20}\text{O}_4$: Theoretical mass $[\text{M}+\text{H}]^+$ 373.1434, found m/z : 373.1433.

(3Z,7Z)-1,2(2,5)-difurana-5,6(2,5)-dithiophenacyclooctaphane-3,7-diene (16): **16** was obtained from the crossed McMurry reaction between **9** (128 mg, 0.68 mmol) and **15** (150 mg, 0.68 mmol). The crude oil was chromatographed on silica gel (Pet. Ether 40 – 60 °C/ EtOAc ~5%) to yield the expected dimeric (DI) and trimeric sulfur macrocycles (TRI)²⁵ (19 mg, 14%) and (22 mg, 12%), respectively, **12a** (17 mg, 16%) and **16** as brown crystals (9 mg, 8%); mp 146–148 °C; ^1H NMR (400 MHz, CDCl_3) δ 6.70 (d, $J = 3.6$ Hz, 1H), 6.61 (ddd, $J = 3.6, 0.9, 0.3$ Hz, 1H), 6.10 (d, $J = 3.5$ Hz, 1H), 5.98 (dt, $J = 3.4, 0.5$ Hz, 1H), 5.94 (ddd, $J = 12.5, 0.9, 0.5$ Hz, 1H), 5.63 (d, $J = 12.5$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.2, 146.5, 142.5, 139.0, 128.4, 124.8, 118.7, 118.5, 117.0, 111.6; IR (cm^{-1}) ν 2927, 1651, 1603, 1537, 1452, 1391, 1260, 1017, 906, 795, 744; MS (FTMS + p NSI Full MS) $\text{C}_{20}\text{H}_{12}\text{O}_2\text{S}_2$: Theoretical mass $[\text{M}+\text{H}]^+$ 349.0351, found m/z : 349.0349.

Attempted formation of (9Z,19Z)-12,17-dihexyl-21,22-dithiaporphyrin-9,19-diene (17): **17** was not obtained from the crossed McMurry reaction between **6** (100 mg, 0.28 mmol) and **15** (62 mg, 0.28 mmol). The crude oil was chromatographed on silica gel (Pet. Ether 40 – 60 °C/ EtOAc ~20%) to yield **11b** (7.1 mg, 8%), the expected dimeric and trimeric sulfur macrocycles²⁵ (2.1 mg, 4%) and (5.8 mg, 11%), respectively.

Supporting information available: ^1H and ^{13}C NMR spectra for all macrocycles, including annotated crude spectra of crossed reactions. X-Ray crystallographic data for compounds **11c**, **12b** and **16**. The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC numbers 1038697, 1038696 and 1038698 respectively) and are available free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-(0)1223-336033 or email: deposit@ccdc.cam.ac.uk).

Acknowledgements

We would like to thank HWU (for funding to T. Y. C.); the EPSRC for funding to L. K. and J. M. Z. (Grant no, EP/J006602/01) and for use of the National Mass Spectrometry Facility. MJP thanks the European Research Council (ERC) for funding under the European Union's Seventh Framework Programme (FP7/2007-2013)/ERC Grant No. 258990. We also thank Dr G. M. Rosair for assistance with X-ray crystallography.

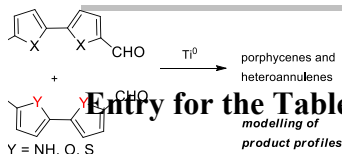
Keywords: porphycenes • macrocycles • McMurry coupling • heterocyclic chemistry

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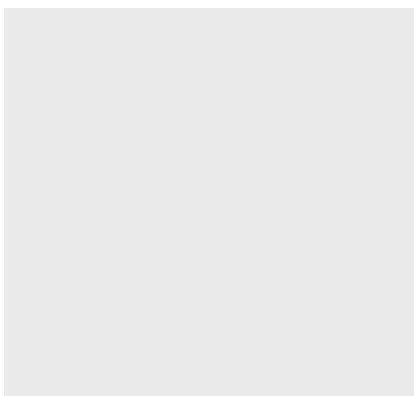


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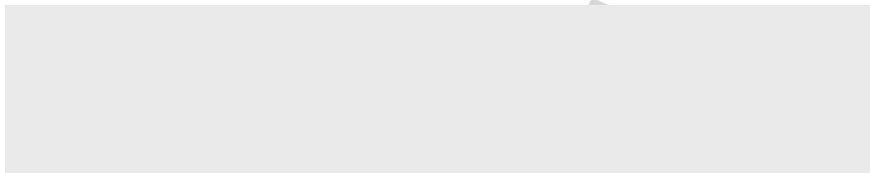
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