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

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Crossed McMurry reactions of bifuran- or bithiophenedi-carbaldehydes with bipyrroledicarbaldehydes have been studied for the first time. Only those porphycenic macrocycles derived from homocoupled McMurry products were formed. The results are explained by using both density functional theory and electron propagator computations to model the electron affinity of the dialdehyde starting materials. It was predicted that bifuran/bithiophene cross-coupling would indeed occur, and this was demonstrated by the first synthesis of a novel dioxa,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 18π-electron configuration (Figure 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 bacteria[5] 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 the 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 porphycenes 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,8b] 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,9b] 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 – crucially the non-linear (two-photon) absorption is highly sensitive to 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 (Figure 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]

Figure 1. Structure of the parent porphycene 1 and dioxa-porphycene isomers 2–4.

Porphycenes are traditionally prepared by reductive McMurry coupling of two bipyrrroledicarbaldehyde units in...
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modest yield.[1,11] Very few other reliable methods exist for their preparation.[12a,12b] Examples of peripheral functionalisation and the inclusion of additional heteroatoms within the ring structure have emerged.[13–16] Cross-coupling of two different bipyroles 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 bipyrole and bipyrole 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.

![Scheme 1. Recent porphycene synthesis by crossed McMurry reaction.](image)

### Results and Discussion

Bipyrole[17i] 6 and bipyrole[19] 9 (Table 1) were prepared according to 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,[11] 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 bipyrole. Under these circumstances the bipyrole would be consumed much more rapidly than the bipyrole, leading to the observed selectivity. Use of diacetylbipyrole[21] 10 was attempted in order to

![Scheme 2. Retrosynthesis of dioxaporphycene 4.](image)

### Table 1. Crossed McMurry reactions between bipyrole subunits.

| Reaction | Isolated yield of macrocyclic product [%] |
|----------|-----------------------------------------|
| 6 + 9    | 11b: 12                                 |
| 6 + 10   | 11b: 12                                 |
| 6 + 8    | 11a: 7; 11b: 6; 11c: 6                  |
| 13a: not observed |

[a] Macrocycles 11a, 11b, 12a and 12b were prepared independently by homocoupling of the appropriate dialdehydes; see Experimental Section and Supporting Information. Diagnostic signals for macrocyclic products were found between δ = 6 and 9 ppm in the 1H NMR spectra.
reduce the rate of homodimerisation, 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. 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 biheterocycle system, in two complementary ways. Firstly, we used electron propagator theory (P3 propagator method) to calculate the 3rd-order correlated electron affinity (EA) for the LUMO (using the cc-pVTZ basis). 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.

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

| Dicarbonyl derivative | Orbital | 3rd-order P3 propagator | B3LYP relaxed EA [eV] |
|----------------------|---------|-------------------------|----------------------|
|                      | LUMO EA [eV] | PS |                         |                      |
| Diformylbifuran 9    | -0.506  | 0.882 | -1.47                   |
| Diacetyl bifuran 10  | -0.264  | 0.882 | -1.24                   |
| Diformylbipyrole 14  | -0.003  | 0.883 | -1.01                   |
| Diformylbithiophene 15 | -0.891  | 0.884 | -1.78                   |

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 bipyrole system 14, (used here without pendant groups for conformational simplicity) with a LUMO EA of −0.003 eV, is therefore significantly more difficult to reduce than the bifurans and bithiophenes under study, which have much more favorable LUMO EAs ranging from −0.26 to −0.89 eV. These results are consistent with SET to the bifurans 9 and 10 being therefore more rapid than for the bipyroles, 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 bifurand-carbaldehyde 9 and the bithiophenedicarbaldehyde[24] 15 were both significantly more negative than those for the bipyroles 6 and 8. Thus, they could be potential reaction partners in a crossed McMurry reaction, and we indeed found that a mixture of 9 and 15 gave some of the heterodimer-derived macrocycle 16 in addition to homodimerised product[25] (Scheme 3).

![Scheme 3. Crossed McMurry reaction of bithiophene 15.](image)

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] (Figure 2). As expected, the macrocycle is not planar, as it cannot readily aromatise to an 18π-electron system. The furan rings appear to be in conjugation with the 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 24.9°). The solution-phase NMR spectroscopic data also do not indicate the presence of any ring currents (see Experimental Section).

As a further control experiment, we also subjected a mixture of bipyrole and bithiophene 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. However, given that the bithiophene is known to be significantly more bulky than furan or pyrrole, it seems unlikely that a purely steric explanation accounts for the selectivity we have observed. Additionally, preliminary semiempirical 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.

Conclusions

We have examined the unusual product distributions in crossed McMurry reactions of biheterocycledicarbaldehydes and correlated the results with calculated electron affinities, as a measure of reducibility, of the starting materials. Work is currently underway to prepare bipyrrole and bifuran/bithiophene 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

General: Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks (CDCl3: δH = 7.26 ppm); J values are given in Hz, and s, br. s, d, dd, ddd, dt, t, br. t, td, q, quint, 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, respectively. IR spectra were obtained deposited neat or as a chloroform solution to a diamond/ZnSe plate. CCDC-1038696 (for 12b), -1038697 (for 11c), and -1038698 (for 16) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Typical Procedure for the Preparation of Porphycenic Macrocycles from Diformylibi-heterocycles: Under 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) dropwise. Upon completion of addition, the solution was stirred at reflux for 2 h. To the refluxing mixture a solution of 6 (185 mg, 0.52 mmol) and 8 (156 mg, 0.52 mmol) in THF (100 mL) was added dropwise over 1 h. The solution was stirred for an additional 1 h. The solution was cooled to 0 °C and quenched by the dropwise addition of ammonium hydroxide solution (6%, 100 mL) over 30 min. The solution was extracted with DCM (200 mL) and the organic layer separated and dried (Na2SO4). After removal of the solvent under reduced pressure, the residue was chromatographed, and the target compounds were isolated to yield 11a (10 mg, 7%), 11b (11 mg, 6%), 11c (17 mg, 6%).
(11 mg, 12%) and 12a as dark red crystals (14 mg, 31%); m.p. 270–271 °C. 1H NMR (400 MHz, CDCl3): δ = 4.95 (d, J = 3.2 Hz, 4 H), 4.85 (d, J = 3.2 Hz, 4 H), 4.19 (s, 4 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 155.5, 149.3, 116.3, 133.9, 109.2 ppm. IR: ν = 2927, 3078.

Supporting Information see the Supporting Information) and trimeric macrocycle was obtained from the crossed McMurry reaction between 6 (100 mg, 0.28 mmol) and 0.68 mmol). The crude oil was chromatographed on silica gel [petroleum ether (40–60 °C)/EtOAc ca. 5 %] to yield the expected[25] dimeric macrocycle (10 mg, 8 %; see the Supporting Information) and trimeric macrocycle was obtained from the crossed McMurry reaction between 6 (100 mg, 0.28 mmol) and 0.68 mmol). The crude oil was chromatographed on silica gel [petroleum ether (40–60 °C)/EtOAc ca. 5 %] to yield the expected[25] dimeric macrocycle (10 mg, 8 %; see the Supporting Information) and trimeric macrocycle was obtained from the crossed McMurry reaction between 6 (100 mg, 0.28 mmol) and 0.68 mmol). The crude oil was chromatographed on silica gel [petroleum ether (40–60 °C)/EtOAc ca. 5 %] to yield the expected[25] dimeric macrocycle (10 mg, 8 %; see the Supporting Information) and trimeric macrocycle was obtained from the crossed McMurry reaction between 6 (100 mg, 0.28 mmol) and 0.68 mmol). The crude oil was chromatographed on silica gel [petroleum ether (40–60 °C)/EtOAc ca. 5 %] to yield the expected[25] dimeric macrocycle (10 mg, 8 %; see the Supporting Information) and trimeric macrocycle was obtained from the crossed McMurry reaction between 6 (100 mg, 0.28 mmol) and 0.68 mmol). The crude oil was chromatographed on silica gel [petroleum ether (40–60 °C)/EtOAc ca. 5 %] to yield the expected[25] dimeric macrocycle (10 mg, 8 %; see the Supporting Information) and trimeric macrocycle was obtained from the crossed McMurry reaction between 6 (100 mg, 0.28 mmol) and 0.68 mmol). The crude oil was chromatographed on silica gel [petroleum ether (40–60 °C)/EtOAc ca. 5 %] to yield the expected[25] dimeric macrocycle (10 mg, 8 %; see the Supporting Information) and trimeric macrocycle was obtained from the crossed McMurry reaction between 6 (100 mg, 0.28 mmol) and 0.68 mmol). The crude oil was chromatographed on silica gel [petroleum ether (40–60 °C)/EtOAc ca. 5 %] to yield the expected[25] dimeric macrocycle (10 mg, 8 %; see the Supporting Information) and trimeric macrocycle was obtained from the crossed McMurry reaction between 6 (100 mg, 0.28 mmol) and 0.68 mmol). The crude oil was chromatographed on silica gel [petroleum ether (40–60 °C)/EtOAc ca. 5 %] to yield the expected[25] dimeric macrocycle (10 mg, 8 %; see the Supporting Information) and trimeric macrocycle was obtained from the crossed McMurry reaction between 6 (100 mg, 0.28 mmol) and 0.68 mmol). The crude oil was chromatographed on silica gel [petroleum ether (40–60 °C)/EtOAc ca. 5 %] to yield the expected[25] dimeric macrocycle (10 mg, 8 %; see the Supporting Information) and trimeric macrocycle was obtained from the crossed McMurry reaction between 6 (100 mg, 0.28 mmol) and 0.68 mmol). The crude oil was chromatographed on silica gel [petroleum ether (40–60 °C)/EtOAc ca. 5 %] to yield the expected[25] dimeric macrocycle (10 mg, 8 %; see the Supporting Information) and trimeric macrocycle was obtained from the crossed McMurry reaction between 6 (100 mg, 0.28 mmol) and 0.68 mmol). The crude oil was chromatographed on silica gel [petroleum ether (40–60 °C)/EtOAc ca. 5 %] to yield the expected[25] dimeric macrocycle (10 mg, 8 %; see the Supporting Information) and trimeric macrocycle was obtained from the crossed McMurry reaction between 6 (100 mg, 0.28 mmol) and 0.68 mmol). The crude oil was chromatographed on silica gel [petroleum ether (40–60 °C)/EtOAc ca. 5 %] to yield the expected[25] dimeric macrocycle (10 mg, 8 %; see the Supporting Information) and trimeric macrocycle was obtained from the crossed McMurry reaction between 6 (100 mg, 0.28 mmol) and 0.68 mmol). The crude oil was chromatographed on silica gel [petroleum ether (40–60 °C)/EtOAc ca. 5 %] to yield the expected[25] dimeric macrocycle (10 mg, 8 %; see the Supporting Information) and trimeric macrocycle was obtained from the crossed McMurry reaction between 6 (100 mg, 0.28 mmol) and 0.68 mmol) as a red solid (25 mg, 8 %). The crude oil was chromatographed on silica gel [petroleum ether (40–60 °C)/EtOAc = 20 %] to yield 11b (11 mg, 12%) and 12b as brown/orange crystals (12 mg, 23%); m.p. 205–206 °C (dec.). 1H NMR (300 MHz, CDCl3): δ = 6.30 (d, J = 3.4 Hz, 4 H), 6.20 (d, J = 3.4 Hz, 4 H), 2.04 (s, 12 H) ppm. 13C NMR (75 MHz, CDCl3): δ = 155.8, 144.1, 122.9, 111.0, 109.5, 45.0, 29.6, 19.9 ppm. IR: ν = 2942, 2864, 1444, 1376, 1136 cm⁻¹. MS (FTMS + p NSI Full MS): calcd. for C24H20O4 [M + H]+: 373.1434; found: 373.1433.

Full paper

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