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EDGE ARTICLE

 β -Oligofurans†Thomas Fallon,^a Anthony C. Willis,^{‡a} A. David Rae,^{‡a} Michael N. Paddon-Row^{*b} and Michael S. Sherburn^{*a}

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An iterative cross-coupling strategy has led to the first synthesis of the β -oligofuran family. Every member of the series of dibrominated analogues has been accessed from the bifuran to the octafuran, along with representative diiodides, non-halogenated congeners and cyclic analogues. Solution phase spectra indicate rapid conformational interchange at ambient temperature. Whereas DFT calculations reveal the existence of several similar energy conformations, molecular structures from single crystal X-ray analyses exhibit common conformational motifs throughout the oligomeric series.

Oligoarylenes exhibit a wide range of important properties that stem from their conformational preferences. For example, electron transport is displayed by those that exhibit planar, conjugated π -systems¹ and guest binding is seen in structures that adopt chiral helical conformations.² α -Oligothiophenes³ belong to the former category and are of enormous importance. Within the carbocyclic aromatic domain, *ortho*-⁴ and *meta*-phenylenes⁵ have been studied most, with analogues carrying alkene- and acetylene-spacers between phenylene groups enjoying particularly strong attention.⁶ With the exception of the oligothiophenes, heteroaromatic analogues are much less well studied.^{7,8} Nevertheless, interest is growing, with the synthesis and properties of the α -oligofurans **1** (see Fig. 1) recently reported.⁹ In contrast, few members of the family of β -oligofurans **2**—which can be seen as cyclised and oxygenated analogues of cross-conjugated hydrocarbons known as dendralenes **3**—have been reported¹⁰ and, perhaps surprisingly, no structural information has appeared in the literature.⁸ Herein we disclose an iterative synthesis of all members of the β -oligofuran family from the bifuran through to the octafuran. We also discuss the conformational preferences of these compounds, through reference to extensive X-ray crystal structure and computational analyses.

Initially, we investigated the extension of Iyoda's bifuran synthesis¹¹ (*i.e.* **4** $\rightarrow$ **6**, Scheme 1) to the higher *even* oligomers. Iyoda's reaction involves the selective single Li/Br exchange of 3,4-dibromofuran **4** and a Cu(II)-promoted oxidative homocoupling of the presumed organolithium species **5** to form the dibromobifuran **6**. Whereas extension to the dibromotetrafuran **8**—by way of lithiobifuran **7**—proceeded well, attempts to further extend the protocol to the octafuran **8** produced complex mixtures. The origin of the problem was traced to the lack of selectivity in Li/Br exchange with dibromides higher than bifuran **6**.¹²

After considerable experimentation, we developed a successful approach to the β -oligofuran family that takes advantage of the marked difference in reactivity between 3-bromo- and 3-iodofurans in cross-coupling reactions. Intriguingly, whereas the latter are reactive partners,¹³ the former are sluggish under standard cross-coupling conditions.¹⁴ The identification of this reactivity pattern prompted us to introduce a new 3,4-disubstituted furan, **11**, carrying both active nucleophilic (–*Bpin*) and latent electrophilic (–Br) functionalities. The general synthetic approach is depicted in Scheme 2. It involves Suzuki–Miyaura coupling of **11** with diiodides **10**. This transformation gives

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† Electronic supplementary information (ESI) available: experimental procedures, characterisation data of all new compounds, X-ray crystal structures, ¹H and ¹³C NMR spectra and computational details. CCDC reference numbers 860334–860345 contain the supplementary crystallographic data for compounds **6**, **8**, **9**, **17**, **18**, **20**, **22**, and **24–28**, respectively. These data can be obtained free-of-charge from the Cambridge Crystallographic Data Centre 12 Union Road, Cambridge CB2 1EZ, UK via www.ccdc.cam.ac.uk/data_request/cif. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2sc20130e

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Fig. 1 The structures under scrutiny, β -oligofurans (shaded), and related structures.

Scheme 1 Oxidative homo-coupling reactions. Reagents and conditions: (a) *n*-BuLi (1.0 mol equiv.), CuCl₂ (1.1 mol equiv.), Et₂O, −78 °C to rt.

Scheme 2 Summary of the successful synthesis of β -oligofurans. The common section of each structure is shaded.

dibromo- β -oligofuran **12**, with the chain extended by two furan units. Dibromide **12** is readily converted into the diiodide **13**, which is now primed for a further two-furan chain extension to give **14**.

The new building block, 3-bromo-4-pinacolboron furan **11**, was made from 3,4-dibromofuran **4** via selective single lithium/bromine exchange and electrophile trapping (Scheme 3). The twofold cross-coupling between **11** and 3,4-diiodofuran **15**¹⁵ proceeded well with Pd(PPh₃)₄ as catalyst to give dibromotrifuran **16**. Double Li/Br exchange, followed by trapping of the presumed dilithiotrifuran intermediate with elemental iodine, gave the diiodide **17**. From diiodotrifuran **17**, double Suzuki–Miyaura cross-coupling gave dibromopentafuran **18**, which underwent clean conversion to the corresponding diiodide **19**. A third iteration of the double cross-coupling gave dibromoheptafuran **20**. In the same way, the dibromotetrafuran **8** (prepared as outlined in Scheme 1) was converted into hexafuran **22** then octafuran **9**, by way of diiodide coupling partners **21** and **23**.

Single crystal X-ray analyses were carried out on samples of the dibromobifuran **6**, dibromotetrafuran **8**, dibromopentafuran **18**, dibromohexafuran **22**, dibromoheptafuran **20** and dibromo-octafuran **9**. Crystals of dibromotrifuran **16** suitable for X-ray analysis could not be obtained. Nevertheless, the corresponding diiodide **17** gave X-ray quality crystals, thus completing the set of dihalogenated β -oligofuran crystal structures from the dimer to the octamer. Samples of unsubstituted β -bifuran **25**, β -trifuran **26** and β -hexafuran **24** were also prepared¹² and subjected to single crystal X-ray analyses in order to ascertain the influence of substitution upon conformation. The crystal structures of the di-, tri-, tetra- and pentafurans are shown in Fig. 2.

β -Bifuran **25** is the only member of the series exhibiting a planar conformation in the crystal lattice, with an *s-trans* orientation being adopted. The dibromo-analogue **6** also exhibits a *transoid* conformation, albeit one that is twisted some 45° from planarity. In unsubstituted trifuran **26**, *cisoid* conformations are seen about the two furan–furan linking bonds, whereas the diiodo-analogue **17** exhibits a structure carrying one *cisoid* and one *transoid* conformation about the inter-furan bonds. The dibromotetrafuran **8** shows the beginnings of a helical turn and the dibromopentafuran **18** exhibits a compact helical conformation.¹⁶ The most striking feature of the last three structures is their similarity: the trifuran portion of **17** maps well onto both tetra- and pentafuran **8** and **18** (Fig. 2, blue shading).

The crystal structures of the higher oligomers, namely hexamers **22** and **24**, heptamer **20** and octamer **9** are shown in Fig. 3. These structures exhibit conformations that are conspicuously similar, with the hexafuran units of **22** and **24** mapping well onto the structures of the heptamer and octamer. The β -hexafuran **24** and its dibrominated analogue **22** are almost identical and adopt an arrangement of three essentially planar *transoid* furan pairings that are roughly orthogonal to one another. The structures of heptamer **20** and octamer **9** are akin to the hexafuran, with additional furan and bifuran units appended, respectively.

The gas phase lowest energy structures of the β -oligofurans were calculated using B3LYP/6-31G(d) theory¹⁷ in order to confirm that the single crystal X-ray analyses contain the lowest energy molecular structures. Our calculations on bifurans **6** and **25** successfully predict the preferred conformation. Nevertheless, in both cases, alternative conformations lie only slightly higher in

Scheme 3 Reagents and conditions: (a) *n*-BuLi (1.1 mol equiv.), (*i*-PrO)₃B (1.5 mol equiv.), THF, -78°C to rt, then pinacol (1.0 mol equiv.), MgSO₄, CH₂Cl₂, rt; (b) **11** (2.2 mol equiv.), Ag₂CO₃ (4.4 mol equiv.), Pd(PPh₃)₄ (0.05 mol equiv.), THF, reflux, 15 min; (c) *n*-BuLi (2.1 mol equiv.), Et₂O, -78°C , then I₂ (2.2 mol equiv.); (d) *n*-BuLi (2.2 mol equiv.), THF, -78°C , then MeOH.

free energy, at 7.3 and 4.3 kJ mol⁻¹, respectively.¹² With trifuran **26**, four conformations were located that differ in free energy by only 5.5 kJ mol⁻¹, giving rise to predicted conformer populations of 40 : 28 : 27 : 5. This pattern was consistent throughout the series of oligofurans, with the number of similar energy conformations increasing with increasing molecular size (tetrafurans **8**: 6 conformations located; pentafurans **18**: 10; hexafurans **22** and **24**: 28). We conclude, therefore, that the conformations witnessed in this series of X-ray crystal structures are the result of packing forces.

The solution phase conformational behaviour of the β -oligofurans is presumably complex, with a dynamic equilibrium existing between the calculated conformers. ¹H and ¹³C NMR spectra are relatively simple,¹² with only one set of signals being witnessed and the number of resonances corresponding to half the number of ¹H or ¹³C nuclei present in the structure. Evidently, conformational interchange in the β -oligofurans is rapid on the NMR timescale. Our DFT studies are consistent with these experimental findings, with calculated rotational barriers of only 10.2 kJ mol⁻¹ (for bifuran **25**) and 11.7 kJ mol⁻¹ (for 4-bromo-3,3'-bifuran).^{18–20}

3,4-Dibromofuran **4** and dibromobifuran **6** are convenient precursors to cyclotrimer **27** and cyclotetramer **28**, by way of efficient Ni(0)-mediated debrominative couplings (Scheme 4). Thus, the established^{21,22} *ortho*-dihaloarene cyclotrimerisation method works well when applied to 3,4-dibromofuran **4** to furnish cyclo- β -trifuran **27** in high (89%) yield. Bendikov and coworkers report lower selectivity for the cyclotrimer in their recent synthesis of the corresponding thiophene and selenophene

analogues.²² Presumably, the shorter C–O vs. C–S/C–Se bond length favours the cyclotrimerisation of the furan. Using dibromobifuran **6** as the substrate gives cyclotetrafurans **28** in 51% yield as the only isolable product.

These new synthetic approaches to cyclotrimer **27** and cyclotetramer **28** compare favourably with earlier syntheses.^{11,23} Molecular structures from the first single crystal X-ray analyses of these compounds are depicted in Scheme 4. These experimental structures are consistent with gas phase, lowest energy conformations calculated using DFT theory. Cyclotrimer **27** shows a strong preference for a planar structure, with 1.45 Å C–C distances around the central six membered carbocycle. These distances are in line with the other oligofurans reported herein, and are in the range expected for single bonds between sp² carbons. They are also consistent with X-ray structural data obtained previously on related structures^{22,24} and calculated cyclopentadiene analogues.¹² Thus, the six membered carbocycle of cyclotrifuran **27** should be thought of as a substituted [6]radialene and not as a benzene ring. The eight membered carbocyclic ring of cyclotetrafurans **28** adopts a tub conformation, akin to that seen in cyclooctatetraene.²⁵

Conclusions

The first synthesis of the β -oligofuran family has been achieved through the introduction of a new 3,4-disubstituted furan building block. Experimental molecular structures from single crystal X-ray analyses show repeating conformational motifs, both in the series trimer $\rightarrow$ tetramer $\rightarrow$ pentamer (Fig. 2) and

Fig. 2 Molecular structures of the bifuran to the pentafulan from single crystal X-ray analyses. The common section of structures **17**, **8** and **18** is shaded in blue. Descriptors *t* and *c* refer to transoid and cisoid conformations about the inter-furan linkages, respectively.

separately, in the series hexamer $\rightarrow$ heptamer $\rightarrow$ octamer (Fig. 3). These intriguing solid-state conformations are likely governed by packing forces, since calculations indicate the existence of several similar energy conformations and conformational interchange is rapid in the solution phase at ambient temperature.

Experimental section

Representative twofold cross coupling procedure

A flask was charged with diiodotrifuran **17** (300 mg, 0.664 mmol), bifunctional furan **11** (399 mg, 1.46 mmol, 2.2 mol equiv.), silver carbonate (805 mg, 2.92 mmol, 4.4 mol equiv.) and $\text{Pd}(\text{PPh}_3)_4$ (38 mg, 0.033 mmol, 0.05 mol equiv.). The vessel was fitted with a septum cap and evacuated (*ca.* 1 mmHg) then placed under an atmosphere of argon for a total of 3 cycles. Dry, degassed THF (2.4 mL) was added and the stirred solution heated to reflux for 15 min. The reaction mixture was cooled then passed through a short plug of flash silica, washing with diethyl ether. The solvent was removed

Fig. 3 Molecular structures of hexafulans **22** and **24**, heptafulan **20** and octafulan **9** from single crystal X-ray analyses. The common section of these structures is shaded in blue.

from filtrate under reduced pressure and the residue was subjected to flash chromatography on silica gel, eluting with 15% toluene in hexane, to give dibromopentafulan **18** as a white solid (173 mg, 53%). Recrystallisation from dichloromethane/hexane gave crystals suitable for single crystal X-ray analysis. Mp: 67–70 °C; R_f 0.27 (15% toluene/hexane); ν_{max} (KBr)/ cm^{-1} 3150, 1765, 1493, 1337 and 1216; δ_{H} (300 MHz, CDCl_3) 7.68 (2H, d, J 1.8), 7.42 (2H, d, J 1.8), 7.35 (2H, s), 7.22 (2H, d, J 1.2), 7.15 (2H, d, J 1.5) ppm; δ_{C} (75 MHz, CDCl_3) 141.6 (CH), 141.3 (CH), 141.1 (CH), 140.8 (CH), 140.7 (CH), 117.5 (C), 116.4 (C), 116.1 (C), 114.8 (C), 101.6 (C) ppm; MS (70eV, EI): m/z (%): 489.9 (20, $[\text{M} (^{81}\text{Br}^{79}\text{Br})]^+$), 460.9 (54), 409.0 (100), 189.1 (74); HRMS: calcd for $\text{C}_{20}\text{H}_{10}^{81}\text{Br}^{79}\text{BrO}_5$ $[\text{M}]^+$: 489.8874; found 489.8862.

Scheme 4 Reagents and conditions: (a) $\text{Ni}(\text{cod})_2$ (1.1 mol equiv.), PPh_3 (1.1 mol equiv.), DMF, 70 °C, 24 h, 89%; (b) $\text{Ni}(\text{cod})_2$ (1.1 mol equiv.), 2,2'-bipyridine (1.1 mol equiv.), DMF, 70 °C, 24 h, 51%.

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