Calix[3]indoles, New Macrocyclic Tris(indolylmethylene) Compounds with 2,7-Linkages†

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A series of macrocyclic tris(indolylmethylene) compounds (calix[3]indoles] can be obtained from 7- or 2-hydroxymethylindoles or from the combination of either an indole with a bis(hydroxymethyl)-2,7′-diindolylmethane or a bis(hydroxymethyl)indole with a 2,7′-diindolylmethane; an isomeric series can be obtained from the combination of an indole with a bis(hydroxymethyl)-2,2′-diindolylmethane.

We report several methods for the synthesis of the tris(indolylmethylene) macrocycles **8**, in which three indole rings are linked by methylene groups between C-2 and C-7 in each case.‡ We have previously shown that 4,6-dimethoxy-3-methylindole[1] undergoes reaction with aryl aldehydes and phosphoryl chloride to give the related macrocycles with arylmethine links.[2] The same macrocycles can alternatively be produced from the presumed intermediate hydroxymethyl compound.

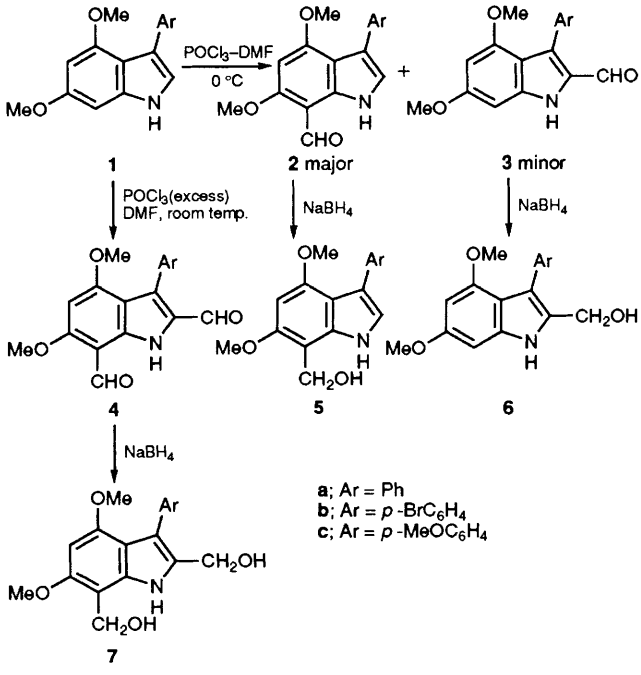
The same reactions occur when the 3-methylindole is replaced by several 3-aryl-4,6-dimethoxyindoles **1**[3–5] and therefore appear to be quite general. On the other hand, reaction of the 3-arylindoles **1** with formaldehyde and phosphoryl chloride yields a multitude of uncharacterised products. We have therefore investigated acid-catalysed reactions of various hydroxymethyl-substituted indoles, derived by reduction of the related aldehydes.[6]

Formylation of the 3-arylindoles **1** with one equivalent of the Vilsmeier reagent gives a strong predominance of the 7-carbaldehydes **2** over the 2-carbaldehydes **3**: two or more equivalents readily yield the 2,7-dicarbaldehydes **4**. All of these aldehydes can be easily reduced by sodium borohydride to give the respective alcohols **5**, **6** and **7** (Scheme 1).

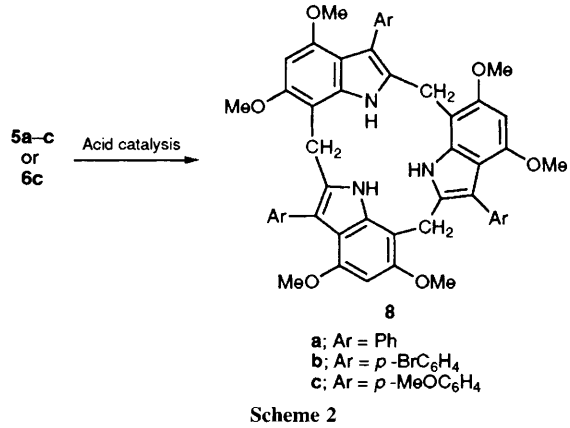
The 7-hydroxymethyl compounds **5** undergo rapid acid-catalysed reaction to generate the macrocycles **8** in approximately 60% yield. Compound **8c** can also be obtained by similar treatment of the 2-hydroxymethyl compound **6c** (Scheme 2). Appropriate conditions include toluene-*p*-sulfonic acid in glacial acetic acid for 2–5 min, toluene-*p*-sulfonic acid in dichloromethane, or boron trifluoride–ether in tetrahydrofuran.

An alternative approach to the triindolyl macrocycles **8** involves the combination of a 2,7-diindolylmethane fragment with an indole. Suitable 2,7-diindolylmethanes **9** can be prepared by reaction of the 7-hydroxymethylindoles **5a**,**c** with indole **1c** in glacial acetic acid (Scheme 3). Formylation of diindolylmethanes **9** gave the dialdehydes **10**, which were reduced to the dialcohols **11**.

Combination of the dialcohol **11c** with indole **1c** in acetic acid gave the macrocycle **8c** in 30% yield together with polymeric material. More usefully, compound **8c** was similarly formed in 36% yield from the diindolylmethane **9c** and the dialcohol **7c** (Scheme 4). This synthetic route enables the incorporation of different indoles into the macrocycle. For example, the similar combination of diindolylmethane **9a** and dialcohol **7c** gives a macrocycle related to **8**, but in which the indole 3-substituents are one phenyl and two *p*-methoxyphenyl groups.



Scheme 1 DMF = dimethylformamide



Scheme 2

† These compounds can also be named using cyclophane nomenclature. Compounds **8** are [1.1.1](2,7)indolophanes and compounds **14** are [1.1.1](2,2)(7,2)(7,7)indolophanes.

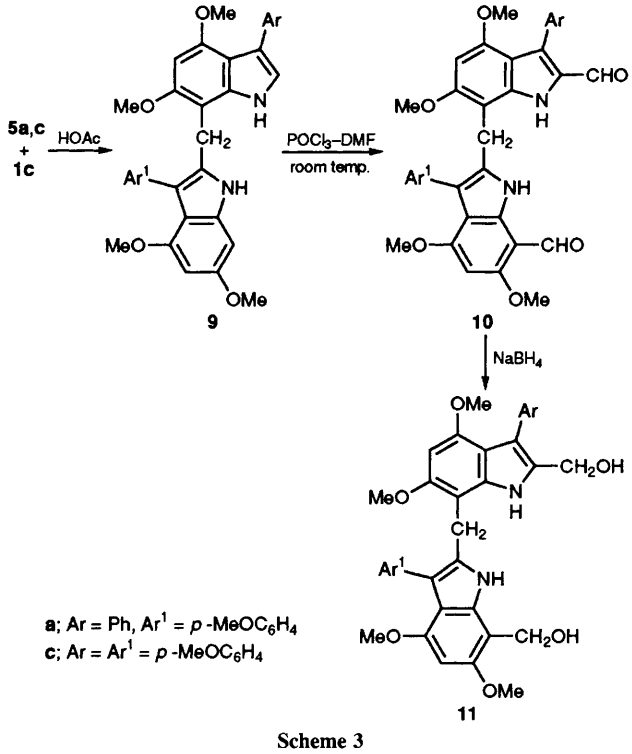
‡ All new compounds gave spectroscopic and microanalytical data in accord with assigned structures. Data are quoted for the dialcohols **11c** and **13c** and the macrocycles **8c** and **14c**.

8c: 57% yield; m.p. 220–222 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66, 3.68 and 3.85 (each s, 9H, OMe), 4.13 (6H, s, CH_2) 6.21 (3H, s, CH), 6.88 and 7.30 (each d, *J* 8.7 Hz, 6H, ArH), 7.82 (3H, br s, NH); MS *m/z* 885 (M^+, 100%).

11c: 86% yield; m.p. 164–166 °C; ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 3.61, 3.64, 3.65, 3.75, 3.76 and 3.79 (each s, 3H, OMe), 4.17 (2H, s, CH_2), 4.37 and 4.62 (each d, *J* 4.6 Hz, 2H, CH_2OH), 4.92 and 5.01 (each d, *J* 4.6 Hz, 1H, OH), 6.26 and 6.31 (each s, 1H, CH), 6.88, 6.94, 7.29 and 7.34 (each d, *J* 8.7 Hz, 2H, ArH), 9.76 and 10.14 (each s, 1H, NH).

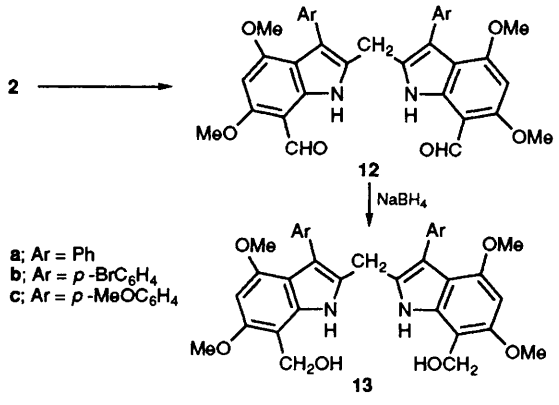
13c: 96% yield; m.p. 194–196 °C; ^{1}H NMR [300 MHz, $(CD_3)SO$], δ 3.62, 3.76 and 3.80 (each s, 6H, OMe), 3.98 (2H, br s, CH_2), 4.77 (4H, br s, CH_2OH), 6.29 (2H, s, CH), 6.72 and 7.03 (each d, *J* 8.7 Hz, 4H, ArH).

14c: 38% yield; m.p. 244–246 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59, 3.67, 3.68, 3.73, 3.79, 3.81, 3.85, 3.88 and 3.99 (each s, 3H, OMe), 3.71, 4.15 and 4.37 (each s, 2H, CH_2); 6.29, 6.30 and 6.34 (each s, 1H, CH), 6.67 and 6.75 (each d, *J* 8.7 Hz, 2H, ArH), 6.95 (4H, t, *J* 8.8 Hz, ArH), 7.05 and 7.44 (each d, *J* 8.7 Hz, 2H, ArH), 7.36, 7.69 and 8.39 (each br s, 1H, NH); MS *m/z* 885 (M^+, 100%).

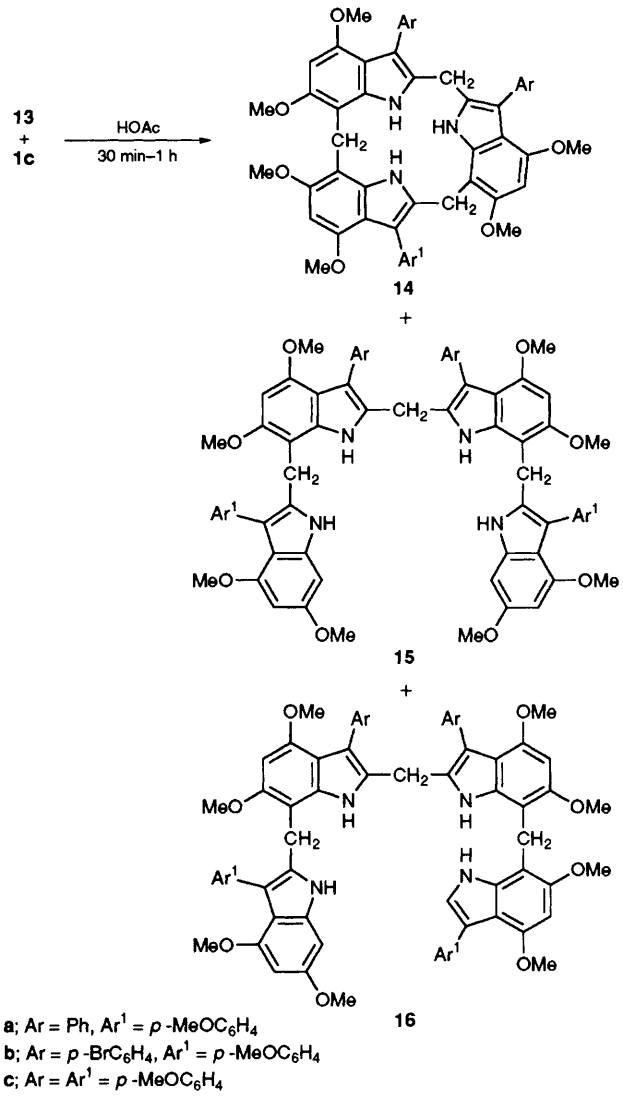


Scheme 3

Scheme 4



Scheme 5



Scheme 6

The regiochemistry of the above reactions is of considerable significance. Two orientations of addition are possible, one leading to the observed 2,7:2,7:2,7-linkages, the other to a 2,2:7,2:7,7-set of linkages. None of the latter products were observed. We have found that in general, the indoles **1** undergo acid-catalysed addition to benzylic alcohols preferentially at C-2 rather than C-7. Furthermore, the 7-hydroxymethyl compounds **5** are more reactive than the 2-hydroxymethyl compounds **6**. Consequently, in the reaction of **5** with **1**, the initial step would involve combination of the 7-hydroxymethyl group with an indole C-2 position, and this would be followed by a slower combination of a 2-hydroxymethyl group with an indole C-7 position to complete the macrocycle. The initial formation of a 2,7-link thus establishes the regiochemistry. Similar behaviour would occur in the reaction of **9** with **7**. The nature of the methylene linkages is clearly shown by NMR spectroscopy. For example, macrocycle **8c** shows three methoxy methyl proton signals, one methylene singlet and one indole 5-H singlet. When different C-3-aryl substituents are introduced, the ^{1}H NMR spectrum shows different methoxy, methylene and 5-H chemical shifts resulting from the removal of symmetry. The presence of singlet methylene proton resonances shows that these macrocycles are flexible and even at low temperature, no generation of AB systems can be seen. Reaction of **11c** with the *N*-methyl analogue of **1c** gives a macrocycle with an NMR spectrum showing three AB methylene patterns.

Compounds **8** are related to the calix[3]arenes,[7,8] but with the replacement of an ambident 4-substituted phenol by ambident indoles **1**.† Unlike the 4-substituted phenols, indoles **1** do not show orientational symmetry and two isomeric calix[3]indoles are possible.

We also report an efficient method for the synthesis of the isomeric [1.1.1](2,2)(7,2)(7,7)indolophane **14**. The indole-7-carbaldehydes **2** undergo reaction with formaldehyde in acetic acid to give the dialdehydes **12** in quantitative yield.[9,10] These can be reduced quantitatively with sodium borohydride to the corresponding dialcohols **13** (Scheme 5). Reaction of the dialcohols **13** with the indole **1c** in acetic acid gives the macrocycles **14** in 30–40% yields, together with the linear tetraindolyl oligomers **15** and **16** in yields of 20 and 5%, respectively (Scheme 6). The dialcohol **13c** can be combined

equally effectively with the *N*-methyl analogue of **1c** to give an *N*-methyl-substituted macrocycle in 40% yield.

The ^{1}H NMR spectrum of **14c** shows nine methoxy proton resonances, three 5-H singlets and three singlets at δ 3.7, 4.15 and 4.38 for the 2,2′-, 2″,7- and 7′,7″-linked methylene groups, respectively. This data clearly reflects the unsymmetrical arrangement of indole rings, but also shows that there is enough flexibility for inversion from one conformer to another. However, at lower temperature, the methylene signlets start to broaden, commencing with the 2″,7-linked methylene resonance.

The tetraindolyl oligomers **15** potentially provide excellent starting materials for higher indolylmethylene oligomers.

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