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Abstract: A new strategy of acid-catalysed reactions of indole methanols with a 3-aryl-4,6-dimethoxyindole-7-aldehyde leads to an efficient synthesis of a calix[3]indole with 2,2; 7,2; 7,7-links. A new calix[4]indole containing four indole units with 2,2; 7,2; 7,7; 2,7-links has also been prepared by this strategy.

Key words: indoles, diindolylmethanes, macrocyclic compounds, acid-catalysed reactions, ipso-substitution reactions, formaldehyde extrusion

Macrocycles containing pyrroles are well established in the field of supramolecular chemistry for the reason that the pyrrole NH groups readily form hydrogen bonds with guest molecules or on deprotonation the nitrogen atoms can bind to metal ions.1–3 Two well-known systems are calix[4]pyrroles and porphyrins.4,5 However macrocycles containing indoles have not been widely studied in this context, despite the similar acidity of an indole NH group to that of a pyrrole. The expansion of the five-membered pyrrole ring system to the larger and more highly conjugated indole system creates new synthetic and structural possibilities with great potential for supramolecular chemistry.

Figure 1 Possible structural frameworks of calix[3]indoles

The synthesis of 3-substituted 4,6-dimethoxyindoles has enabled their enhanced activity at C2 and C7 to be investigated in a variety of ways.6–11 Acid-catalysed reactions of these indoles with aryl aldehydes have led to the formation of calix[3]indoles, presumably via intermediate indole methanols.12

In principle, these calix[3]indoles can contain either three arylmethene linkages between C2 and C7, or one such linkage between C2 and C2, C2 and C7, and C7 and C7 (see Figure 1). Both types have already been synthesised.

Figure 2 Possible structural frameworks of calix[4]indoles

Both 3-substituted 4,6-dimethoxyindole-7-carbaldehydes and 4,6-dimethoxyindole-2-carbaldehydes can be prepared via the Vilsmeier–Haack formylation reaction.13 Subsequent reduction of the formyl groups with sodium borohydride affords the simple indole C7- and C2-methanols, which can also undergo acid-catalysed cyclisation to calix[3]indoles.14–17

However, in this process, calix[4]indoles can also be generated, and show four methylene linkages between C2 and C7. There are four possible ways of linking four indoles through the C2 and C7 positions with four methylene links. These basic structures are shown in Figure 2.

We now report new, highly effective stepwise sequences for the synthesis of a calix[3]indole and the first example of a calix[4]indole with a 2,2; 7,2; 7,7; 2,7 set of methylene linkages.

These stepwise sequences involve the monoindole 2,7-di- methanol 1 and the diindolyl 7,7’-dimethanol 2, which have been previously reported.14 Reaction of dimethanol

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1 with two equivalents of the indole-7-aldehyde 3 in isopropanol containing p-toluenesulfonic acid gave the triindolylmethane dialdehyde 4,18 which precipitated from the reaction mixture and was obtained in 90% yield. Reduction of the dialdehyde 4 with sodium borohydride in a mixture of ethanol and tetrahydrofuran gave the dimethanol 5 in 98% yield. Treatment of this dimethanol 5 with p-toluuenesulfonic acid in anhydrous dimethyl sulfoxide generated the calix[3]indole 619 in 89% yield (Scheme 1).

Compound 6 is a new example of this class of previously reported calixindoles. Its 1H NMR spectrum showed proton resonances for six different methoxy groups at $\delta = 3.61, 3.62, 3.63, 3.64, 3.73,$ and $3.76$ ppm, and three different methylene resonance singlets at $\delta = 3.93, 4.15,$ and $4.20$ ppm.

Similar treatment of the 7,7′-dimethanol 2 with two equivalents of the indole-7-carbaldehyde 3 in isopropanol containing p-toluuenesulfonic acid gave the tetraindole dialdehyde 720 in 68% yield (Scheme 2). Reduction of dialdehyde 4 with sodium borohydride in a mixture of ethanol and tetrahydrofuran gave the dimethanol 8 in 98% yield. The calix[4]indole 921 was formed in 69% yield when the dimethanol 8 was treated with p-toluuenesulfonic acid in anhydrous dimethyl sulfoxide briefly at room temperature.

The new calix[4]indole 9, and the first example of this type, was characterised fully and its NMR spectra were particularly revealing with regard to structural symmetry. Seven different methoxy proton resonances were observed at $\delta = 3.44, 3.53, 3.75, 3.80, 3.95, 3.99$ and $4.01$ ppm for the eight methoxy groups. There are three different methylene groups, the protons of which form AB doublets resonating at $\delta = 3.98, 3.99$ and $4.16$ ppm, and four different H5 protons at $\delta = 5.91, 6.26, 6.33$ and $6.48$ ppm. Furthermore an X-ray crystal structure was obtained (see Figure 3), and showed a rigid cube-like structure, similar to that of a calix[4]indole with four 2,7-methylene links.15

It is noteworthy that both types of calix[4]indoles pre-
pared so far show rigid structures leading to non-identical methylene protons, whereas the calix[3]indoles, such as compound 6 are quite flexible, allowing their methylene link protons to equilibrate on the NMR time scale and show singlet resonances.

The cyclisation reactions of compound 5 to 6 and of compound 8 to 9 are typical of 4,6-dimethoxyindoles that are substituted at both C2 and C3 and bear a hydroxymethyl group at C7. This process involves a mildly acid-catalysed ipso-substitution in which the restoration of the indole aromaticity requires the loss of formaldehyde. A postulated mechanism, exemplified for the conversion of compound 8 to macrocycle 9, is shown in Scheme 3. Although the indole C5 position is unsubstituted, it is protected against electrophilic substitution by the adjacent methoxy groups, which are in turn buttressed by the C3 and C7 substituents. We have observed many examples of this remarkably effective and irreversible formaldehyde extrusion process for the formation of 7,7′-diindolylmethanes. The formation of compounds 6 and 9 demonstrate the effectiveness of this synthetic strategy for macrocyclisation reactions.

In summary, this synthetic methodology has the capacity to generate calix[3]indoles containing one 2,2-, one 7,2- and one 7,7-link, and calix[4]indoles containing one 2,2-, one 7,7-, and two 7,2-links. Although all four substituents at C3 are the same in the case of compounds 6 and 9, there is the possibility to introduce two different substituents by this stepwise procedure. Furthermore, although the indole methanols 1 and 2 undergo ready reaction with 3-substituted 4,6-dimethoxyindoles,14 linkages occur at both C2 and C7 and product mixtures result. The use of the 7-aldehyde 3 provides much cleaner and regiospecific linkage formation.

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References and Notes

New Strategy for Calixindole Formation

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(17) Black, D. StC.; Rothnie, N. E.; Wong, L. C. H.


(18) Compound 4 was prepared from the indole-7-aldehyde 3 (0.900 g, 2.50 mmol), diindolyl dimethanol 1 (0.490 g, 1.25 mmol), p-toluene sulfonic acid monohydrate and isopropanol (100 mL). After stirring for 1 h, filtration and drying, the compound 7 (1.21 g, 90%) was obtained as a yellow solid; mp 256–257 °C (CH2Cl2–light petroleum). 1H NMR (300 MHz, CDCl3): δ = 3.66, 3.70, 3.82, 3.95, 3.99, 4.07 (6 × s, 18 H, OMe), 3.82 (s, 2 H, CH2, 2,2′-link), 4.18 (s, 2 H, CH2, 2,7′-link), 6.05, 6.15, 6.30 (3 × s, 3 H, indolyl H5), 6.91 (s, 1 H, NH), 6.96–7.32 (m, 12 H, ArH), 9.98, 10.59 (2 × s, 2 H, NH), 10.28, 10.32 (2 × s, 2 H, CHO). 13C NMR (75 MHz, CDCl3): δ = 20.9, 23.7 (CH2), 55.1, 55.2, 55.3, 56.3, 56.4, 56.7 (OMe), 86.6, 86.8, 89.1 (indolyl C5), 130.0, 130.3, 130.7, 131.2, 132.2, 132.4 (ArCH), 101.3, 104.2, 104.3, 110.9, 111.2, 111.9, 113.5, 114.6, 119.7, 119.9, 120.1, 129.1, 130.5, 130.7, 131.2 (2×), 133.6, 134.0, 134.8, 134.4, 136.3, 153.0, 153.3, 160.2, 160.5, 162.3, 162.4 (ArC), 187.8, 188.0 (CHO). IR (KBr): 3409, 3342, 2934, 2843, 1643, 1364 (CH3), 1303, 1363, 1621, 1878 cm–1. MS (ESI): m/z (%) = 1074 [M, 79/79/79Br] (10), 862 (15), 796 (20), 663 (80), 429 (60), 249 (420), 135 (100), 108, 70. Anal. Calcd for C22H23Br2N3O8: C, 55.7; H, 4.0; N, 3.7. Found: C, 57.9; H, 4.0; N, 3.7.

(19) Compound 6 was prepared by treatment of the triindolyl dimethanol 8 (0.300 g, 0.280 mmol) in anhyd dimethylsulfoxide (5 mL) with a catalytic amount of p-toluene sulfonic acid monohydrate and stirred at r.t. After 5 min, H2O was added and the resulting green precipitate was filtered off, washed with H2O, dried and recrystallised from EtOAc–hexane to yield the calixindole 9 (0.26 g, 89%) as a yellow-green solid; mp >300 °C. 1H NMR [300 MHz, CDCl3]: δ = 3.61, 3.62, 3.63, 3.64, 3.73, 3.76 (6 × s, 18 H, OMe), 3.93, 4.15, 4.20 (3 × s, 6 H, CH2), 6.33, 6.34 (2 × s, 3 H, indolyl H5), 7.10–7.15 (m, 4 H, ArH), 7.31–7.36 (m, 4 H, ArH), 7.45 (d, J = 8.3 Hz, 2 H, ArH), 7.54 (d, J = 8.3 Hz, 2 H, ArH), 9.49, 9.62, 9.95 (3 × s, 3 H, NH). 13C NMR [75 MHz, CDCl3]: δ = 21.2, 21.6, 23.3 (CH3), 55.3, 55.4, 55.5, 56.8, 57.4, (OMe), 89.7, 90.5, 90.8 (CS), 125.9,
128.4, 130.1, 132.9, 133.2, 133.5 (ArCH), 102.0, 104.3, 105.0, 111.4, 111.8 (2 ×), 114.0, 119.1, 131.4, 132.1, 132.3, 132.9, 134.8, 135.2, 135.4, 135.6, 136.1, 136.7, 137.0, 138.0, 152.0 (2 ×), 152.3, 152.5, 153.3, 154.1, 154.3 (ArC). IR (KBr): 3414, 2934, 2839, 1722, 1644, 1444, 1393, 1335, 1367, 1352, 1327, 1291, 1250, 1213, 1119, 1071, 993, 817, 794 cm⁻¹. UV–Vis (CHCl₃): λ_max = 233 (ε = 111,200 cm⁻¹M⁻¹), 289 (41,800) nm. MS (ESI): m/z (%) = 1036 [M + 1, 81/81/81/81Br] (20), 1030 [M + 1, 81/81/81Br] (40). Anal. Calcd for C₆₉H₅₆Br₄N₄O₁₀·H₂O: C, 57.6; H, 4.1; N, 4.1. Found: C, 59.6; H, 4.3; N, 4.0.

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