COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Synthesis of mixed heterocalixarenes from benzofuranyl methanols and activated indoles

David StC Black,* Donald C. Craig and Robert Rezaie
School of Chemical Sciences, The University of New South Wales, UNSW, Sydney, NSW 2052, Australia. E-mail: d.black@unsw.edu.au; Fax: +61 2 9385 6141; Tel: +61 2 9385 4657

Received (in Cambridge, UK) 10th January 2002, Accepted 22nd February 2002
First published as an Advance Article on the web 14th March 2002

Mixed heterocalix[3]arenes and heterocalix[4]arenes containing indole and benzofuran rings can be synthesised *via* acid-catalysed reactions of benzofuranyl methanols and activated indoles: these new calixarene types are of interest as potential molecular receptors.

Reactions of indolyl methanols with activated indoles to give diindolylmethanes and calix[3]indoles, have been previously reported.[1,2] We now describe the reaction of benzofuranyl methanols with indoles to afford indolylmethyl benzofurans, which can be converted to mixed heterocalixarenes.

(Benzofuranyl)indolylmethane **3** was obtained in high yield when the 7-hydroxymethylbenzofuran **1**[3] was reacted with the indole-7-carbaldehyde **2**[2] in acetic acid at 55 °C (Scheme 1). When the corresponding alcohol reduction product of compound **3** was treated with a catalytic amount of Montmorillonite K10 clay or silica, the 7,7′-diindolylmethane **4** was obtained.[4] Overnight treatment with an excess of clay gave a 75% yield of the unexpected mixed heterocalix[3]arene **5**, whose structure (Fig. 1) was confirmed by X-ray crystallography.† The X-ray crystal was obtained from a mixture of DCM and ethyl acetate and was shown to be a 1 : 1 complex of the flattened partial cone heterocalix[3]arene molecule **5** with DCM. Compound **4** can also be converted to heterocalixarene **5** by further treatment with clay (Scheme 1). While the full mechanistic details for the formation of **5** have not been resolved, a plausible sequence involves conversion of aldehyde **3** to compound **4**, followed by the cleavage of methylene linkages in the presence of excess acid. The parent heterocyclic units resulting from this dissembling process could recombine to give the heterocalixarene **5**.[5] In this process it is significant that an internal indole fragment is lost from compound **4**, rather than a terminal benzofuran moiety. The proposed mechanism is further supported by

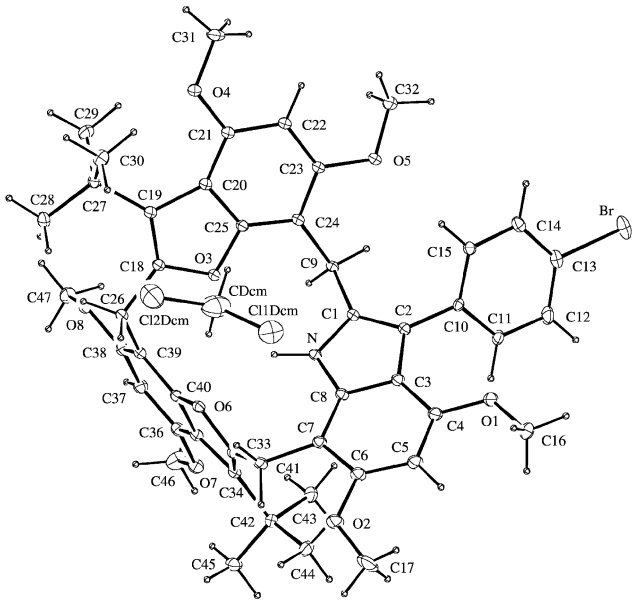
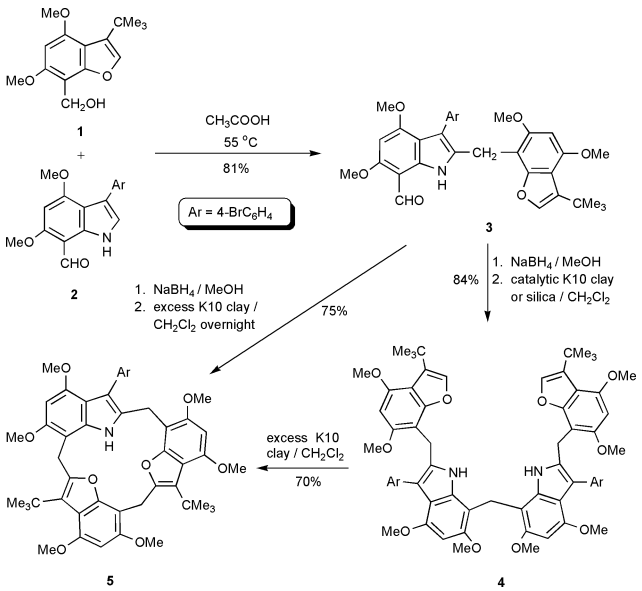


Fig. 1 X-Ray crystal structure of compound **5**.

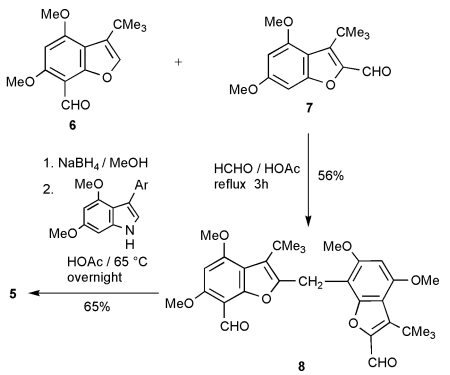
observation that the acid-catalysed reaction of benzofuran **1** with 3-(4′-bromophenyl)-7-hydroxymethyl-4,6-dimethoxyindole,[2] afforded a mixture of 3-*tert*-butyl-4,6-dimethoxycalix[3]benzofuran[3] and the heterocalix[3]arene **5**.

Additionally, the heterocalixarene **5** can be obtained from the reaction of the corresponding dialcohol reduction product of compound **8** with 3-(4′-bromophenyl)-4,6-dimethoxyindole[2] in acetic acid. Compound **8** can be formed by the combination of the two benzofuran aldehydes **6**[3] and **7**[3] with 37% aqueous formaldehyde in refluxing acetic acid (Scheme 2).

As part of a programme aimed at the preparation of larger heterocalixarenes, a benzofuran/indole-mixed heterocalix[4]arene **11**[6] was also synthesised. Benzofuran carbaldehyde **6** was heated in acetic acid at 70 °C for 40 h in the presence of formaldehyde solution. The resulting dibenzofuranylmethane **9** was reduced with sodium borohydride and the product reacted



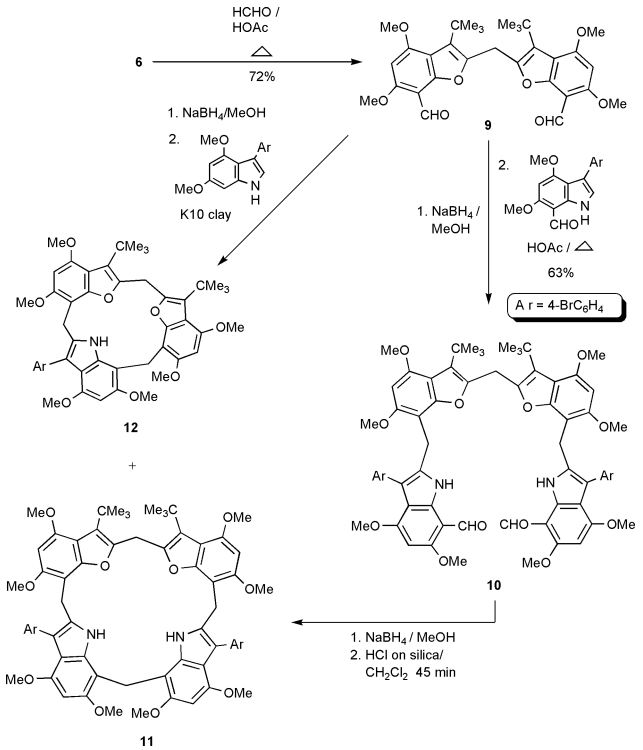
Scheme 1



Scheme 2

DOI: 10.1039/b200373b

with 4′-bromophenyl-4,6-dimethoxyindole-7-carbaldehyde in acetic acid at 65 °C overnight to give the dialdehyde **10**. The dialcohol reduction product of **10** in DCM (1.2 mM) was treated with dried HCl on silica at rt for 45 min to afford a new mixed heterocalix[4]arene **11** in 37% yield, together with the new unsymmetrically-linked heterocalix[3]arene **12**[7] obtained in 35% yield (Scheme 3). An excess of acid, higher concentration of the reaction mixture, the use of other sources of acid such as clay or *p*-toluenesulfonic acid, a longer reaction time, and a higher reaction temperature are all contributing factors which favour the formation of the calix[3]arene over the calix[4]arene. X-Ray crystallography confirmed the structure of compound **12** (Fig. 2) to exist in a flattened partial cone configuration.‡ Alternatively, the corresponding dialcohol reduction product of **9** undergoes reaction with 3-(4′-bromophenyl)-4,6-dimethoxyindole in the presence of clay in DCM overnight to give heterocalixarene **12** in 57% yield. Heterocalixarene **12** forms a stable copper(I) complex, as shown by NMR spectroscopy, but heterocalixarene **5** does not.



Scheme 3

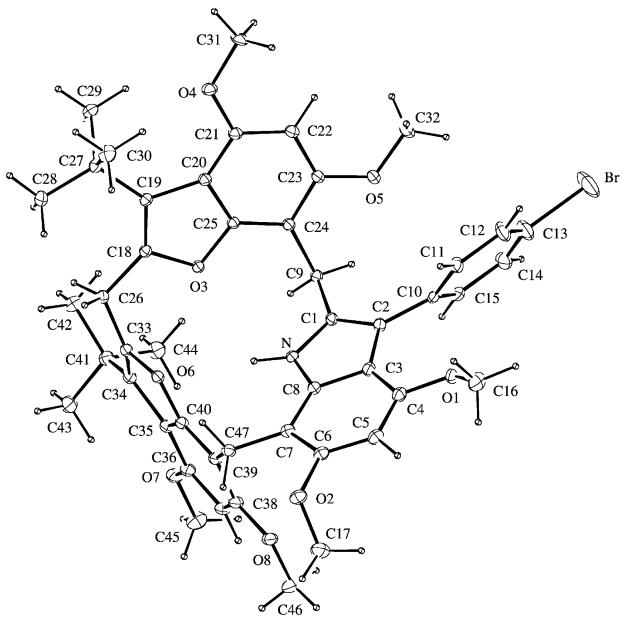


Fig. 2 X-Ray crystal structure of compound **12**.

The mixed heterocalixarenes such as compounds **5**, **11** and **12** are quite unprecedented. The fact that they can be synthesised by rational and high-yielding routes make them very suitable for the development of new and exciting molecular receptors.

Financial support from the Australian Research Council is gratefully acknowledged.

Notes and references

† *Crystal data* for **5**: $C_{47}H_{50}BrNO_8{\cdot}CH_2Cl_2$, M = 921.8, orthorhombic, space group *Pbcn*, a = 31.590(5), b = 14.915(4), c = 19.093(2) Å, V = 8996(3) Å^3, D_c = 1.36 g cm^{-3}, Z = 8, μCu = 27.94 cm^{-1}. Crystal size 0.15 × 0.19 × 0.21 mm, $2\theta_{max}$ = 100°, min. and max. transmission factors 0.57 and 0.70. The number of reflections was 2896 considered observed out of 4630 unique data. Final residuals R, R_w were 0.070, 0.097 for the observed data. CCDC 177625. See http://www.rsc.org/suppdata/cc/b2/b200373b/ for crystallographic data in .cif or other electronic format.

‡ *Crystal data* for **12**: $C_{47}H_{50}BrNO_8$, M = 836.8, monoclinic, space group $P2_1/c$, a = 14.222(4), b = 23.339(4), c = 13.043(4) Å, β = 106.52(1)°, V = 4151(3) Å^3, Dc = 1.34 g cm^{-3}, Z = 4, μCu = 17.80 cm^{-1}. Crystal size 0.10 × 0.13 × 0.14 mm, $2\theta_{max}$ = 100°, min. and max. transmission factors 0.71 and 0.85. The number of reflections was 2746 considered observed out of 4255 unique data, with *R*merge 0.037 for equivalent reflections. Final residuals R, R_w were 0.066, 0.084 for the observed data. CCDC 177626. See http://www.rsc.org/suppdata/cc/b2/b200373b/ for crystallographic data in .cif or other electronic format.

1 D. StC. Black, D. C. Craig and N. Kumar, *Tetrahedron Lett.*, 1995, **36**, 8075.

2 D. StC. Black, M. C. Bowyer, N. Kumar and P. S. R. Mitchell, *J. Chem. Soc., Chem. Commun.*, 1993, **10**, 819.

3 D. StC. Black, D. C. Craig, N. Kumar and R. Rezaie, *Tetrahedron*, 2002, in press.

4 This is a reaction typical of highly substituted and activated 7-hydroxymethylindoles and involves an *ipso* substitution with loss of formaldehyde and water.

5 Data for **5**: mp 180–182 °C (from ethyl acetate–petroleum ether)(Found C, 67.2; H, 6.1, N, 1.5. $C_{47}H_5BrNO_8$ requires C, 67.5; H, 6.0; N, 1.7%). ^{1}H NMR spectrum ($CDCl_3$): δ 1.28, 1.57 (18H, 2s, CMe_3); 3.33, 3.64, 3.85, 3.86, 3.96 (18H, 5s, 6 × OMe); 3.69, 4.37, 4.59 (6H, 3s br, CH_2); 6.12, 6.23, 6.42 (3H, 3s, benzofuran H5, indole H5); 7.26, 7.45 (4H, 2d, J 8.2 Hz, 4 × aryl); 8.14 (1H, s, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 19.1, 23.3, 25.3 (CH_2); 30.8, 32.0 (CMe_3); 31.3, 31.7 (CMe_3); 55.0, 55.2, 55.7, 57.1, 57.6 (6 × OMe); 89.6, 90.3, 91.3 (benzofuran C5, indole C5); 129.6, 133.1 (4 × aryl CH); 102.1, 103.5, 104.0, 110.0, 111.6, 112.7, 112.8, 113.0, 118.9, 122.5, 126.0, 133.5, 135.7, 136.2, 146.5, 148.0, 151.3, 151.7, 152.0, 152.3, 153.9, 155.0, 155.1 (arylC). Mass spectrum: *m*/*z* 837 (*M* ^{81}Br, 53%), 835 (*M* ^{79}Br, 53%), 607 (25), 480 (44).

6 Data for **11**: mp 287–290 °C (from ethyl acetate–petroleum ether)(Found: C, 65.3; H, 5.7; N, 2.2. $C_{64}H_{64}Br_2N_2O_{10}$ requires C, 65.2, H 5.5, N 2.4%). ^{1}H NMR ($CDCl_3$): δ 1.41 (s, CMe_3); 3.63, 3.67, 3.81, 3.92, 4.08, 4.36 (32H, 6s, 8 × OMe, 4 × CH_2); 6.23, 6.24 (4H, 2s, 2 × benzofuran H5, 2 × indole H5); 7.26, 7.40 (8H, 2d, J 9.3 Hz, 8 × aryl); 8.22 (2H, s, 2 × NH). ^{13}C NMR ($CDCl_3$): δ 20.4, 27.2, 28.8 (CH_2); 31.7 (CMe_3); 31.8 (CMe_3); 55.0, 55.2, 56.5, 57.8 (8 × OMe); 90.6, 90.7 (2 × benzofuran C5, 2 × indole C5); 129.8, 132.7 (8 × arylCH); 103.1, 103.6, 112.3, 112.6, 119.1, 124.2, 133.3, 135.3, 136.0, 145.4, 151.8, 152.2, 153.5, 154.4, 154.8 (aryl C). Mass spectrum: *m*/*z* (MALDI) 1179 (*M* + 1). IR (KBr) υ_{max} 3430, 2950, 1621, 1591, 1350, 1220, 1160, 1130 cm^{-1}.

7 Data for **12**: mp > 290 °C (from ethyl acetate–petroleum ether)(Found: C, 67.2; H, 6.0; N, 1.6. $C_{47}H_{50}BrNO_8$ requires C, 67.5; H, 6.0; N, 1.7%). ^{1}H NMR spectrum ($CDCl_3$): δ 1.51, 1.54 (18H, 2s, CMe_3); 3.36, 3.61, 3.64, 3.87, 3.92, 3.97 (18H, 6s, OMe); 4.55 (6H, sbroad, CH_2); 6.16, 6.28, 6.32 (3H, 3s, benzofuran H5, indole H5); 7.26, 7.46 (4H, 2d, J 8.2 Hz, 4 × aryl); 8.35 (1H, s, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 17.7, 19.1, 30.0 (CH_2); 31.7, 31.8 (CMe_3); 31.9, 32.1 (CMe_3); 55.0, 55.1, 55.4, 55.7, 57.0, 58.6 (OMe); 90.5, 90.9, 92.5 (benzofuran C5, indole C5); 129.6, 133.1 (4 × aryl CH); 103.6, 105.2, 105.4, 111.6, 112.4, 112.6, 119.0, 123.6, 126.1, 136.0, 136.3, 144.3, 144.5, 151.3, 151.4, 152.1, 153.2, 154.1, 154.2, 154.5, 156.1 (aryl C). Mass spectrum: *m*/*z* (MALDI) 836 (*M* + 1). IR (KBr) υ_{max} 3439, 2957, 1625, 1592, 1506, 1340, 1220, 1150, 1115.