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Synthesis and Crystal Structure of a Calix[3]indole with Cone Conformation: A New Molecular Receptor

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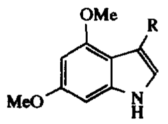
***Abstract*:** A calix[3]indole with 2,7-linkages has been synthesised from an indolylglyoxylamide and shown by X-ray crystallography to have a cone or cup shaped conformation and to contain a molecule of ethanol inside the cup.

We wish to report the first examples of the cone conformers of calix[3]indoles and describe some of the requirements for their formation. Previously, we have shown that the 7-hydroxymethyl-3-aryl-4,6-dimethoxyindoles **2** and the 2-hydroxymethyl-3-aryl-4,6-dimethoxylindoles **3**, derived from the indoles **1**, undergo acid-catalysed cyclo-oligomerisation to the calix[3]indoles **4** in good yield and under a variety of conditions[1]. These cyclo-trimers show a methylene singlet resonance in their ^{1}H n.m.r. spectra, consistent with a rapidly inverting cone conformer or fluxional flattened partial cone conformer. The latter is the more probable situation because (i) X-ray data for the related triaryl substituted cyclo-trimers **5** shows a flattened partial cone conformation[2,3] and (ii) no metal complexes of these compounds have been prepared, as would be expected for cone structures. In the case of the aryl-substituted calix[3]indoles **5**, ^{1}H n.m.r. spectroscopy shows that the indole rings are all in different environments, as are the three methine linker protons. Clearly the presence of substituents on the linking carbons stops the fluxional equilibration and produces rigid structures. In a cone conformation, the three substituents could be effectively axial or equatorial. We reasoned that one way of stabilising the cone conformation would be to achieve a situation in which three axial substituents were held together by some attractive force such as hydrogen bonding. We therefore decided to investigate acid catalysed reactions of the alcohols **8** and **9**, obtained by reduction of the 7- and 2-indolylglyoxylamides **6** and **7** respectively. Reactions of the indoles **1** with oxalyl chloride, followed by quenching with an amine, gave the 7- and 2-glyoxylic amides **6** and **7** in varying proportions depending on the reaction solvent.

Treatment of alcohols **8** and **9** under a variety of acidic conditions gave macrocyclic trimers **10** in good yield. These cyclo-trimers were predominantly in the flattened partial cone conformation, as shown by different ^{1}H n.m.r. signals for each indole ring and methine proton. In particular, the indole NH protons showed characteristically different chemical shifts, reflecting different degrees of hydrogen bonding. In all acid catalysed reactions, a symmetrical product was also obtained and was indicated by an additional set of ^{1}H n.m.r. signals. Significantly, the single indole NH resonance showed very substantial hydrogen bonding, presumably to the carbonyl oxygen atom of the neighbouring amide group. Thus the ^{1}H n.m.r. data were



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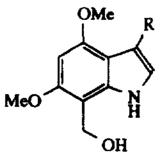

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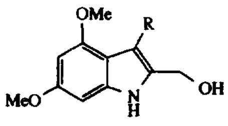
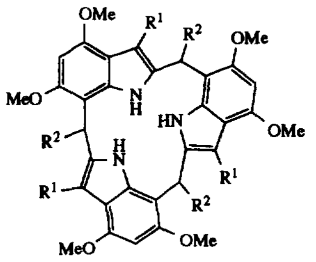


3

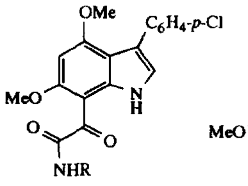
1-3 R = Ar



4 R^1=Ar, R^2=H

5 R^1=Me, R^2=Ar

consistent with a cone structure, in which the three amide substituents were in axial positions and hydrogen bonded to the indole NH protons. In the case of N-methyl amides, a greater proportion of cone conformer was obtained from the 7-alcohol **8a** rather than the 2-alcohol **9a**, whereas the situation was reversed for the N-t-butyl amides **8b** and **9b**: in other examples there appeared to be no preference. Traces of calix[4]- and calix[5]-indoles were also formed from the 7-alcohols **8**. Isolation of the symmetrical cone conformers of calix[3]indoles could not be achieved in all cases, because of strong interaction with chromatographic silica gel. The most successful system was that with t-butylamide substituents, as chromatography allowed isolation of compounds **10b(cone)** and **10b(f.p.cone)** in yields of 17% and 45% respectively[4].



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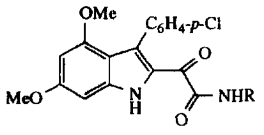

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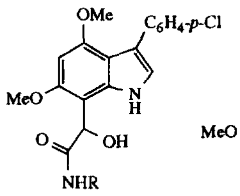

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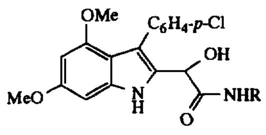
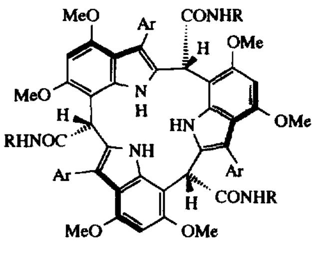


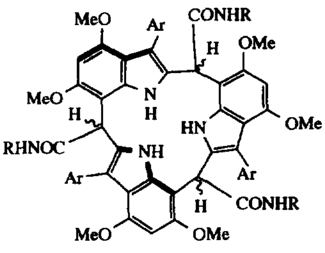
9

6-10	
a	R=Me
b	R=CMe_3



10 (cone)

Ar=C_6H_4-*p*-Cl



10 (f.p.cone)

Ar=C_6H_4-*p*-Cl

An X-ray crystal structure determination of compound **10b(cone)** confirmed the symmetrical cone conformation with three axial amide groups (Fig.1)[5]. However, the amide hydrogen bonding environment is slightly different in each case, and this structure is presumably 'frozen' in the solid state. The X-ray crystal was obtained from ethanol and was shown to be a 1:1 complex of the cone calix[3]indole molecule **10b(cone)** with ethanol: significantly the ethanol molecule is neatly positioned inside the cup. Molecular modelling calculations show that there is a small energetic preference for the flattened partial cone conformer over the cone conformer, but this preference decreases with increasing hydrogen bonding of the substituents. Therefore, just as calixarene conformations are controlled to a large extent by the generation of a phenolic hydrogen bonding network[6] so it appears that the shape of calixindoles might be controlled by rather different and unique hydrogen bonding networks involving substituents. This major new principle could not only enable predictable development in the calixindoles but be applied to other areas of molecular recognition as well.

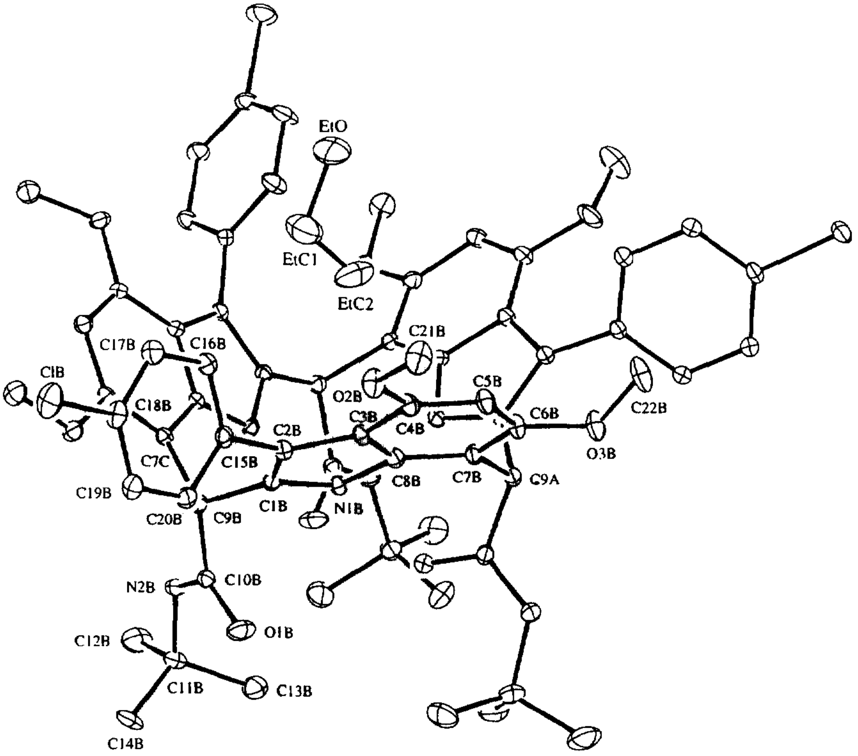


Fig.1. X-Ray crystal structure for calix[3]indole **10b(cone)**

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3. Black, D.StC.; Craig D.C.; Kumar, N. *Aust. J. Chem.*, in press.

4. All new compounds gave spectroscopic and microanalytical data in accord with the assigned structures. Data are quoted for the alcohols **8b** and **9b**, and for the macrocycles **10b(cone)** and **10b(f.p.cone)**.
   8b: m.p. 186°C. υ_{max} 3530br, 3400br, 3180br, 1660m, 1620m, 1525m, 1210m cm^{-1}. λ_{max} 230 (e28,000), 285 (13,200), 302nm (11,500). ^{1}H n.m.r. ($CDCl_3$): δ 1.35, s, CMe_3; 3.88, 4.02, 2s, OMe; 5.65, s, CH; 6.37, s, H5'; 6.39, br, CONH; 7.06, d, *J* 2.6 Hz, H2'; 7.35, 7.54, 2d, *J* 8.7 Hz, aryl; 9.37, br, NH. ^{13}C n.m.r. ($CDCl_3$): δ 29.3, $\mathrm{C\underline{Me}_3}$; 52.17, $\mathrm{\underline{C}Me_3}$; 55.9, 57.9, OMe; 68.4, CH; 89.3, C5'; 122.7, C2'; 128.3, 131.4, aryl CH; 103.7, 112.4, 117.4, 132.1, 135.2, 137.2, 153.6, 155.1, aryl C; 173.2, carbonyl C. *m/z* 418 ($M^{37}Cl$, 5%), 416 ($M^{35}Cl$, 20%), 318 (70), 316 (100), 251 (50), 121 (70).
   9b: m.p. 109-110°C. υ_{max} 3350br, 1655m, 1625m, 1210m, 1150m cm^{-1}. λ_{max} 224 (e28,200), 242 (19,200), 275 (11,400), 300nm (7,600). ^{1}H n.m.r. ($CDCl_3$): δ 1.22, s, CMe_3; 3.74, 3.87, 2s, OMe; 4.18, br, OH; 5.17, s, CH; 5.39, br, CONH; 6.25, 6.50, 2d, *J* 1.6 Hz, H5', H7'; 7.42, 7.51, 2d, *J* 8.4 Hz, aryl; 8.55, br, NH. ^{13}C n.m.r. ($CDCl_3$): δ 29.1, $\mathrm{C\underline{Me}_3}$; 52.6, $\mathrm{\underline{C}Me_3}$; 55.7, 56.2, OMe; 67.1, CH; 87.4, C5'; 93.0, C7'; 128.8, 132.8, aryl CH; 112.1, 115.5, 130.1, 133.2, 134.0, 137.9, 155.4, 158.7, aryl C; 170.9, carbonyl C. *m/z* 418 ($M\ ^{37}Cl$, 5%), 416 ($M\ ^{35}Cl$, 10%), 318 (30), 316 (100).
   10b(cone): m.p. 215°C. υ_{max} 3420br, 3320br, 1670m, 1615m, 1595m, 1510m, 1210m cm^{-1}. λ_{max} 229 (e99,500), 277 (44,400), 309nm (28,300). ^{1}H n.m.r. ($CDCl_3$): δ 1.14, s, Me; 3.35, 3.56, 2s, OMe; 5.71, s, CONH; 5.77, s, CH; 6.03, s, H5; 7.00-7.40, br, aryl; 11.38, s, NH. ^{13}C n.m.r. ($CDCl_3$): δ 29.4, $\mathrm{C\underline{Me}_3}$; 40.2, alkyl CH; 52.5, $\mathrm{\underline{C}Me_3}$; 56.0, 56.4, OMe; 88.5, C5; 127.6, 133.2, aryl CH; 103.5, 114.1, 114.8, 132.0, 132.8, 136.0, 136.7, 152.7, 153.9, aryl C; 172.0, carbonyl C. *m/z* 1195 (M+1, 70%), 1126 (30), 1095 (40).
   10b(f.p.cone): m.p. 220-221°C. υ_{max} 3400br, 1670m, 1590m, 1205m, 1145m cm^{-1}. λ_{max} 228 (e90,000), 289nm (33,600). ^{1}H n.m.r. ($CDCl_3$): δ 0.99, 1.07, 1.23, 3s, Me; 3.50, 3.67, 3.70, 3.71, 3.77, 3.89, 6s, OMe; 5.29, 5.48, 6.10, 3s, CH; 5.26, 5.77, 6.12, 3s, CONH; 6.14, 6.17, 6.42, 3s, H5; 7.04-7.61, m, aryl; 8.84, 10.03, 11.30, 3s, NH. ^{13}C n.m.r. ($CDCl_3$): δ 28.6, 28.8, 29.4, $\mathrm{C\underline{Me}_3}$; 40.2, 42.9, 43.2, $\mathrm{\underline{C}Me_3}$; 51.8, 52.1, 52.1, 55.9, 55.9, 55.9, 56.9, 57.2, 58.5, OMe; 89.1, 89.1, 90.9, C5; 127.4, 127.8, 128.4, 132.5, 132.8, 132.8, aryl CH; 101.7, 101.9, 104.3, 113.2, 113.5, 113.8, 114.6, 115.3, 116.7, 131.4, 131.5, 131.8, 133.2, 133.2, 135.2, 135.5, 135.7, 136.0, 136.3, 137.1, 153.2, 153.5, 154.2, 154.3, 155.0, 155.2, aryl C; 169.9, 171.5, 171.8, carbonyl C. *m/z* 1195 (M+1, 80%).
5. *Crystal data* for **10b(cone)**:$(C_{22}H_{23}ClN_2O_3)_3.C_2H_5OH$, M 1242.7, monoclinic, space group $P2_1/c$, a 18.715(6), b 18.621(2), c 23.885(8)Å, β 126.69(1)°, V 6675(3)Å^3, D_c 1.24 g cm^{-3}, Z 4, μ_{Cu} 17.37 cm^{-1}. Crystal size 0.17 by 0.25 by 0.27 mm, $2\theta_{max}$ 100°, min. and max.transmission factors 0.67 and 0.80. The number of reflexions was 4688 considered observed out of 9747 unique data, with R_{merge} 0.022 for 161 pairs of equivalent 0kl reflexions. Final residuals R, R_w were 0.059, 0.076 for the observed data.
6. Gutsche, C.D. *Calixarenes*, RSC: Cambridge, 1989.

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