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Synthesis of upper rim calix[4]arene carcerands

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Abstract

The synthesis of novel tetra-olefinic calix[4]arene carcerands is described using a synthetic strategy involving palladium catalysed Heck coupling followed by imine formation.

Keywords: Synthesis; Macrocycles; Carcerands; Palladium

Carcerands have been defined by Cram as molecules that form a closed, hollow shell derived from the Latin word for prison.[1,2] Carcerands are defined by the size of their inner cavity and form fascinating container molecules for application in supramolecular chemistry.

We recently reported on the synthesis of upper rim tetra-olefin substituted calix[4]arenes using the palladium catalysed Heck reaction.[3,4] In subsequent work, we demonstrated that tetra-acrylamido calix[4]arenes form dimeric molecular capsules through a series of eight hydrogen bonds between two preorganised macrocycles.[5,6] Following this observation it appeared evident that two such geometrically preorganised macrocycles might form a covalently linked capsule, or in other words a carcerand, through a series of covalent bonds between two appropriately functionalised macrocycles. In this Letter, we report on the synthesis of such carcerands.

To achieve the goal of carcerand synthesis we extended our recently developed Heck coupling methodology to prepare deep-cavity tetraformyl calix[4]arene acrylates **2a**,**b** and **3a**,**b** from tetraiodo calix[4]arenes **1a**,**b** and 3- or 4-formylphenyl acrylate using palladium acetate and 1,3-bis-(diphenylphosphino)propane as a co-ligand. The coupling proceeded as expected to give the deep cavity calix[4]-arenes **2** and **3** in good yields as the all-trans isomers. All spectroscopic data were in agreement with the structures. The chemical shifts of the calix[4]arene methylene protons provided evidence for the presence of a deep-cavity as discussed previously.[4–6] The four formyl groups at the upper rim were chosen to allow covalent linkage of two complementary calix[4]arene units (see Fig. 1).

With the tetra-formyl calix[4]arenes **2a** and **3a** in hand, we investigated their covalent linking. For linking two calix[4]arenes we chose imine formation[7] and reacted **2a** and **3a** with a selection of various diamines **4**–**7**. A 1:2 stoichiometry was used in all cases and the progress of the reactions was monitored by ^{1}H NMR and ESI-MS. Table 1 summarises the results.

Reaction of **2a** and **3a** with diamines **4**–**6** revealed no evidence of carcerand formation. The ESI mass spectra showed the presence of a complex mixture of products. Furthermore, the ^{1}H NMR spectra of the crude reaction mixtures showed a mixture of compounds with extremely broad lines indicative of oligomerisation and polymerisation processes. Reaction of **2a** and **3a** with 1,4-diaminobenzene **7**, however, revealed the formation of single carcerands **8a** and **9a** according to ^{1}H NMR spectroscopy and ESI mass spectroscopy. The predicted m/z of the above carcerands approaches the mass boundary for low

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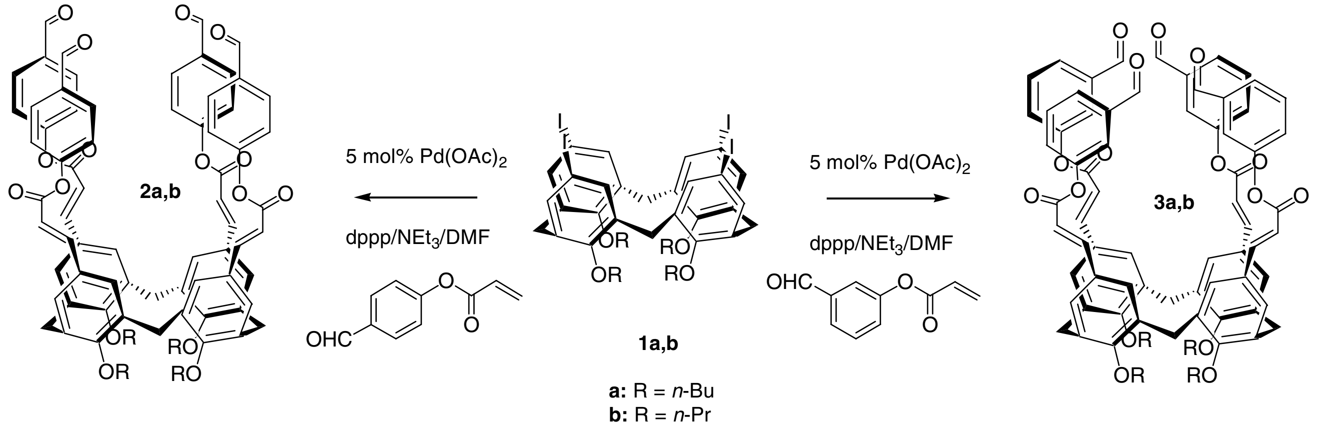


Fig. 1. Synthesis of calix[4]arenes **2a**,**b** and **3a**,**b**.

Table 1
Yields of the reactions of calix[4]arenes **2a**,**b** and **3a**,**b** with diamines **4**–**7**

Calix[4]arene	Diamine	Yield (%)	Calix[4]arene	Diamine	Yield (%)
2a	**4**	0 (Polymer)	**3a**	**6**	0 (Polymer)
2a	**5**	0 (Polymer)	**3a**	**7**	86 (**9a**)
2a	**6**	0 (Polymer)	**2b**	**7**	85 (**8b**)
2a	**7**	84, (**8a**)	**3b**	**7**	85, (**9b**)

resolution LSIMS and ESI-MS (m/z ~3000) for the instrumentation available in our laboratory and hence no diagnostic molecular ion was observed (see Fig. 2).

As a direct consequence, calixarenes **2b** and **3b** were prepared possessing a calix[4]arene-*n*-propyl ether in good yields and reacted with diamine **7** to afford the carcerands **8b** and **9b** in good yields.

The ^{1}H NMR spectra of all four carcerands obtained showed broad lines as expected for compounds with molecular weights around 3000 g/mol. Surprisingly, all the carcerands showed two sets of signals in the ^{1}H NMR spectra for the four repeating units indicative of a reduced symmetry as opposed to the expected C_4 symmetry.[8,9] This evidence strongly suggests a pinched cone structure of reduced symmetry (structure **9a** in Fig. 3) in the form of two sets of doublet signals as opposed to one set of doublet signals for the narrow rim Ar–CH$_2$–Ar protons. The difference $\Delta\delta$ between the two diastereotopic Ar–CH$_2$–Ar calixarene protons was reported as a good measure for the overall geometry of the calix[4] basket.[8,9] ^{1}H–^{1}H COSY spectroscopy allowed unambiguous identification of the two non-equivalent individual CH$_2$ groups and revealed $\Delta\delta$ values of $\Delta\delta_1 = 0.4$ ppm and $\Delta\delta_2 = 1.4$ ppm. The existence of two sets of well-defined olefinic doublets suggests that two sides in the 1,3-position are pinched together causing those olefinic protons to be equivalent, with the remaining two sides in the 2,4-position pulled outwards leading to a different proton environment for the second set of four olefinic protons. Although it is very difficult to assign the individual aromatic protons, the number of non-equivalent aromatic protons again reinforce the idea of reduced molecular symmetry. The presence of two imine proton signals suggests two non-equivalent imine protons. The rudimentary geometry optimisation of **8b** also suggests the orientation may resemble a basic parallelogram (when viewed from above). This is further supported by observations of similar calixarene capsules, which are shown to possess this particular pinched cone structure.[10–12]

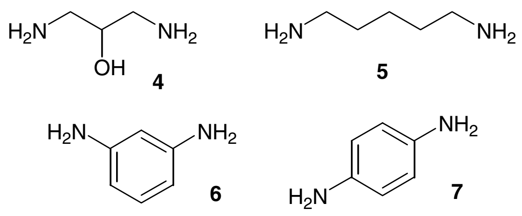
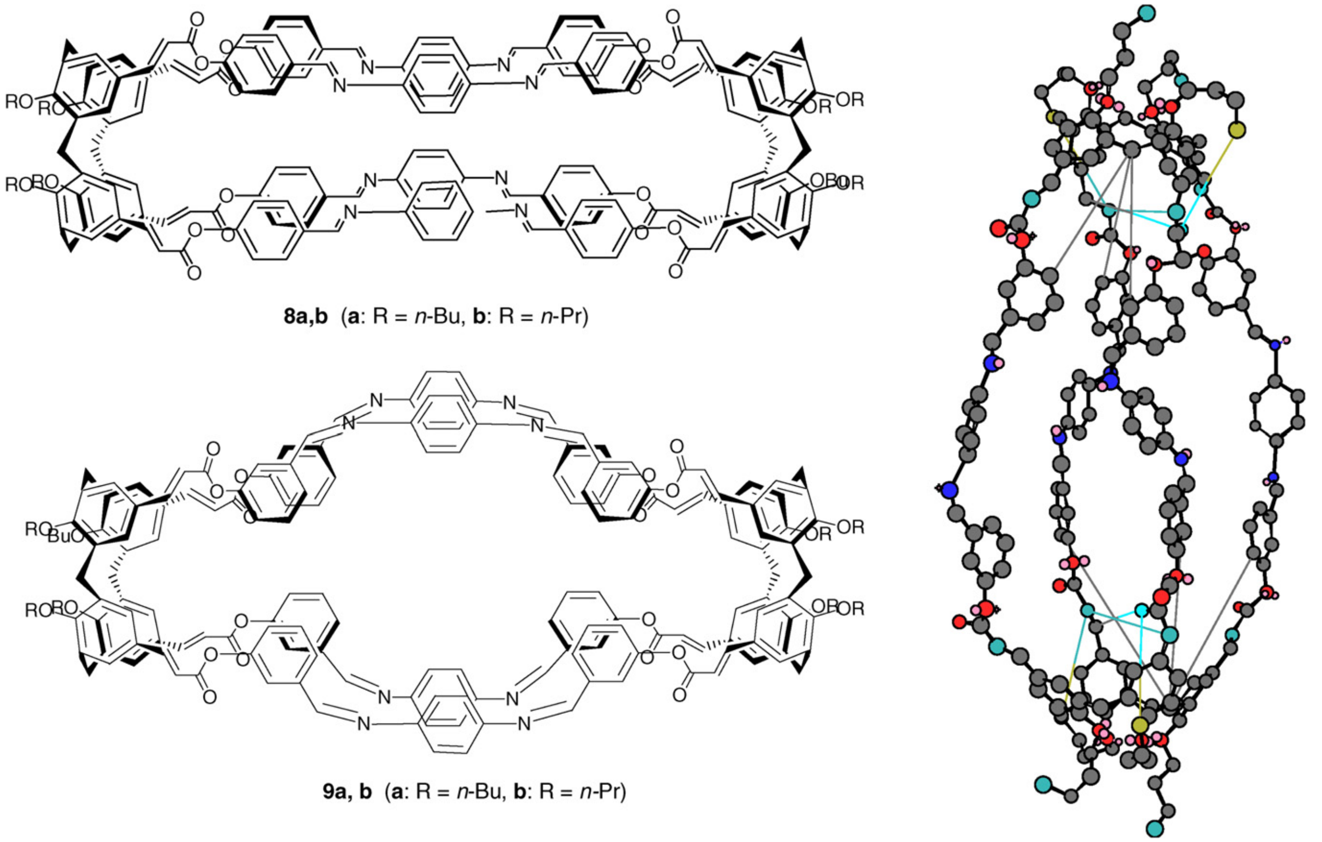


Fig. 2. Diamines used in carcerand formation.

ESI-MS in positive ion mode at 200 °C showed several peaks, which correlated to the carcerands **8b** and **9b** including molecular ions + Na at m/z 2887.[9] LSIMS gave a complex fragmentation pattern with a signal indicative of a molecular ion M+H+2H$_2$O at m/z 2901, which might occur through water inclusion in the carcerand cavity.

Molecular modelling allows an insight into the overall dimensions of the carcerands. For compounds **8a**,**b** the distance between the two calix[4]arenes (measured as the distance between C-5 and C-5′) was 270 pm. The diameter of the carcerand as measured by the distance between the two opposing aromatic rings furthest apart is 170 pm. The total volume of the carcerand **8a** can, therefore, be estimated to be 4.6 nm^3 making these compounds the largest carcerands synthesised to date, to the best of our knowledge.

Interestingly, the molecular model also showed the existence of a large cleft of around 700 pm between the



8a,b (**a**: R = *n*-Bu, **b**: R = *n*-Pr)

9a, b (**a**: R = *n*-Bu, **b**: R = *n*-Pr)

Fig. 3. Structures of carcerands **8a**,**b** and **9a**,**b** and the MM-2 minimised structure of **9a**.

aromatic rings of two proximal diamine linkers suggesting that small inclusion molecules could enter and leave the carcerand without difficulty.

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References and notes

1. Cram, D. J.; Karbach, S.; Kim, Y. H.; Baczinsky, L.; Kalleymeyn, G.W. *J. Am. Chem. Soc.* **1985**, *107*, 2575.
2. Sherman, J. C.; Cram, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 4527.
3. Heck, F. *J. Am. Chem. Soc.* **1968**, *90*, 5535.
4. Kuhnert, N.; Le-Gresley, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3393.
5. Kuhnert, N.; Le-Gresley, A. *Chem. Commun.* **2003**, 2426.
6. Kuhnert, N.; Le-Gresley, A. *Tetrahedron Lett.* **2005**, *46*, 2059.
7. Kuhnert, N.; Le-Gresley, A. *Org. Biomol. Chem.* **2005**, *3*, 2175.
8. Analytical data for **8b**: light brown powder; mp 250 °C (dec); IR ν_{max} (Nujol) cm^{-1} 1748 (C=O), 1639 (C=N) 1615 (C=C); δ_H (500 MHz; $CDCl_3$) 8.49 (4H, s, CH=N), 8.38 (4H, s, CH=N), 8.00 (4H, d, *J* 16.2, Ar–CH=), 7.93 (4H, d, *J* 9.4, Ar–H), 7.67 (4H, d, *J* 8.3, Ar–H), 7.65 (4H, s, Ar–H), 7.48 (4H, d, *J* 9.4, Ar–H), 7.19 (4H, d, *J* 16.2, Ar–CH=), 7.16 (8H, d, *J* 8.3, Ar–H), 7.05 (4H, d, *J* 8.3, Ar–H), 7.04 (8H, s, Ar–H), 6.70 (8H, d, *J* 8.3, Ar–H), 6.67 (4H, d, *J* 16.2, CH–C=O), 6.57 (16H, s, Ar–H), 6.35 (4H, s, Ar–H), 6.01 (4H, d, *J* 16.2, CH–C=O), 4.49 (8H, d, *J* 12.9, C*H*$_A$H$_B$Ar), 4.18 (8H, m, O*CH*$_2$CH$_2$), 3.75 (8H, m, O*CH*$_2$CH$_2$), 3.25 (4H, d, *J* 12.9, CH$_A$*H*$_B$Ar), 1.90 (16H, m, C*H*$_2$CH$_2$O), 1.63–1.40 (8H, m, OCH$_2$CH$_2$C*H*$_2$), 1.00 (24H, t, *J* 8.3, C*H*$_3$CH$_2$); *m*/*z* (ESI, 0.1 mM in MeOH) 2887 (M+Na); CHN $C_{184}H_{160}N_8O_{24}\cdot 2CHCl_3$ requires: C, 71.9; H, 5.26; N, 3.61. Found: C, 71.1; H, 5.16; N, 3.66.
9. Analytical data for **9b**: light brown powder; mp above 250 °C (dec); IR ν_{max} (Nujol) cm^{-1} 1732 (C=O), 1640 (C=N), 1615 (C=C); δ_H (500 MHz; $CDCl_3$) 8.48 (4H, s, CH=N), 8.41 (4H, s, CH=N), 8.00 (4H, d, *J* 16.2, Ar–CH=), 7.82–7.64 (18H, m, Ar–H), 7.59–7.42 (20H, m, Ar–H & Ar–CH=), 7.24–6.96 (20H, m, Ar–H), 6.75–6.66 (8H, m, Ar–H & CH–C=O), 6.44–6.35 (6H, m, Ar–H), 6.06 (4H, d, *J* 16.2, CH–C=O), 4.49 (8H, m, CH$_A$H$_B$Ar) 4.16 (8H, m, OC*H*$_2$CH$_2$), 3.76 (8H, m, OC*H*$_2$CH$_2$), 3.29 (4H, d, *J* 12.8, CH$_A$*H*$_B$Ar), 1.90 (16H, m, C*H*$_2$CH$_2$O), 1.62–1.41 (8H, m, OCH$_2$CH$_2$C*H*$_2$), 1.03 (24H, t, *J* 8.3, C*H*$_3$CH$_2$); *m*/*z* (ESI, 0.1 mM in MeOH) 2887 (M+Na); CHN $C_{184}H_{160}N_8O_{24}\cdot 2CHCl_3$ requires: C, 71.4; H, 5.26; N, 3.61. Found: C, 71.0; H, 5.26; N, 3.98.
10. Gutsche, C. D. *Aldrichim. Acta* **1995**, *28*, 7.
11. Danil de Namor, A. F.; Hutcherson, R. G.; Sueros Velarde, F. J.; Alvarez-Larena, A.; Brisano, J. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2933.
12. Zhong, Z. L.; Ikeda, A.; Shinkai, S. *J. Am. Chem. Soc.* **1999**, *121*, 11906.