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The selective preparation of partial cone *O*-aryl calix[4]arene ethers from 1,3-dimethoxycalix[4]arene: a new platform for the preparation of non-aggregated dyes☆

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Dedicated to Professor Clifford C. Leznoff on his retirement

Abstract—We report a new direct route for the selective preparation of novel partial cone *O*-aryl ether calix[4]arenes to be used as new platforms for the preparation of non-aggregated dyes. These partial cone conformers have the aromatic substituents lying within the calix[4]arene annulus via the upper rim.

Over the past 35 years, calixarenes have emerged as perhaps one of the most versatile macrocyclic systems in modern chemistry.[1] Much of this success lies in the unique bowl-like structure of the calix[4]arene, a structure which possesses a hydrophobic upper rim and a hydrophilic lower rim. Each rim can be selectively functionalised to yield structures with unique and selective host–guest properties.[2] The unique bowl-like structure of the calix[4]arene is also conformationally flexible and, as a result, can exist in four possible conformations: cone, partial cone, 1,3-alternate and 1,2-alternate. However, the cone is perhaps the most commonly studied of these four conformations, since the selective preparation and functionalisation of the other conformations is far more challenging and may require lengthy synthesis.

We are particularly interested in developing the partial cone conformation of calix[4]arenes as a new platform for the isolation of dye cores. Successful isolation of dye cores will allow for enhanced performance of dyes in many applications such as catalysis, oxygen sensing, haemoglobin mimetics, optical filters and improved photosensitisers for application in photodynamic therapies.[3] We envisaged placing an aromatic fragment of a dye into the upper rim of the calix[4]arene, which will result in placing two of the *t*-butyl groups of the calix[4]arene above and below the plane of the dye.

To achieve this goal an aromatic substituent containing the necessary functional groups required for dye preparation must be selectively introduced into the upper rim of the calix[4]arene. One of the most convenient methods of introducing an aryl substituent into a calix[4]arene is via an S_NAr reaction. A single report has shown that S_NAr reactions can be readily used to introduce O-aromatic groups into the calix[4]arene.[4] Unfortunately, the conformational outcome of these reactions could not be controlled since substitution on both the lower rim and upper rim are in competition with each other.

To achieve the selective preparation of the partial cone conformation it is necessary to eliminate the lower rim reaction from occurring. We found from molecular modelling that if the cone conformation of distal dimethoxy calix[4]arene (**1**) is to react with an aryl substrate possessing a substituent *ortho* to the leaving group, a strong steric interaction would occur between the methyl groups on the lower rim of **1** and the *ortho* substituent of the aryl substrate. As a result, substitution

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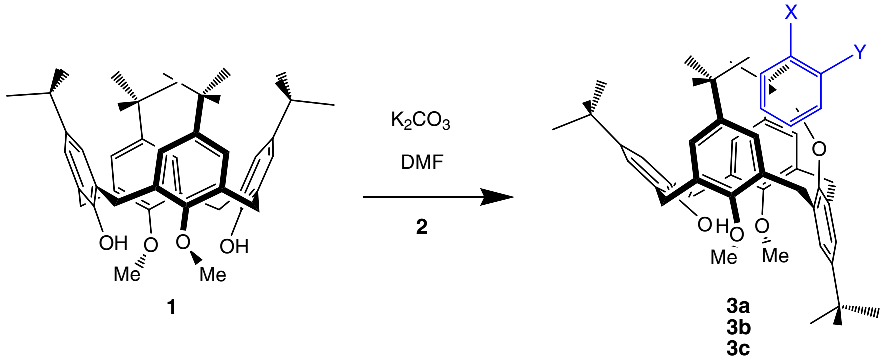


Scheme 1.

on the lower rim will be prevented, however, substitution onto the upper rim can still occur which will lead to the formation of a product in the partial cone conformation.

To prove this hypothesis we decided to attempt a series of S_NAr reactions using **1** as outlined in Scheme 1.

We chose as our starting materials a range of nitro and fluoro aromatic aldehydes (**2a**,**b**), mononitriles (**2c**–**f**) and *ortho*-bis-nitriles (**2g**,**h**), all of which are commercially available and ideal starting materials for dye synthesis. Outlined in Table 1 are the results for these reactions. The reactions attempted with **2a** and **2b** with K_2CO_3 in DMF at room temperature failed to give products. Higher temperatures were employed, however, no desired substituted calix[4]arene was obtained. It would appear that the aromatic aldehydes were not reactive enough for the S_NAr displacement with **1**. Of the mononitrile series only **2f** gave a product, **3a**, in 24% yield. The bis-nitriles **2g** and **2h** both gave mono-substituted products **3b** and **3c** in 40% and 53% yields, respectively. We did find some undesired bis-substituted product in the reaction involving **2g** but found that by strictly controlling the stoichiometry of **2g** to **1** we could actually minimise the undesired bis-substitution of **1** to trace amounts.

Table 1. Series of nucleophilic substitution reactions of **1** with various aryl substrates

Substrate	Product(s)	Yield (%)
3-Nitrobenzaldehyde (**2a**)	No reaction	—
3-Fluorobenzaldehyde (**2b**)	No reaction	—
2-Fluorobenzonitrile (**2c**)	No reaction	—
2-Nitrobenzonitrile (**2d**)	No reaction	—
3-Nitrobenzonitrile (**2e**)	No reaction	—
2-Chloro-6-nitrobenzonitrile (**2f**)	**3a**	24
3-Nitrophthalonitrile (**2g**)	**3b**	40
4-Nitrophthalonitrile (**2h**)	**3c**	53

The ^1H NMR of **3b** (Fig. 1) revealed that the 4 and 5 protons of the phthalonitrile substituent are shifted upfield to 4.6 and 3.5 ppm, respectively. The observed upfield shift can only be caused by the anisotropic effect of the calixarene annulus on the phthalonitrile protons. X-ray crystal structure analysis of **3b** confirmed that the phthalonitrile substituent is tilting into the aromatic annulus of the calix[4]arene via the upper rim (Fig. 2). ^1H NMR also confirmed that **3a** exists in the partial cone conformation with a triplet at 3.1 ppm and a doublet at 3.9 ppm for the 4 and 5 protons of the aromatic substituent.

As expected, product **3c** was a mixture of two conformations, as confirmed by both ^1H NMR and X-ray crystal-

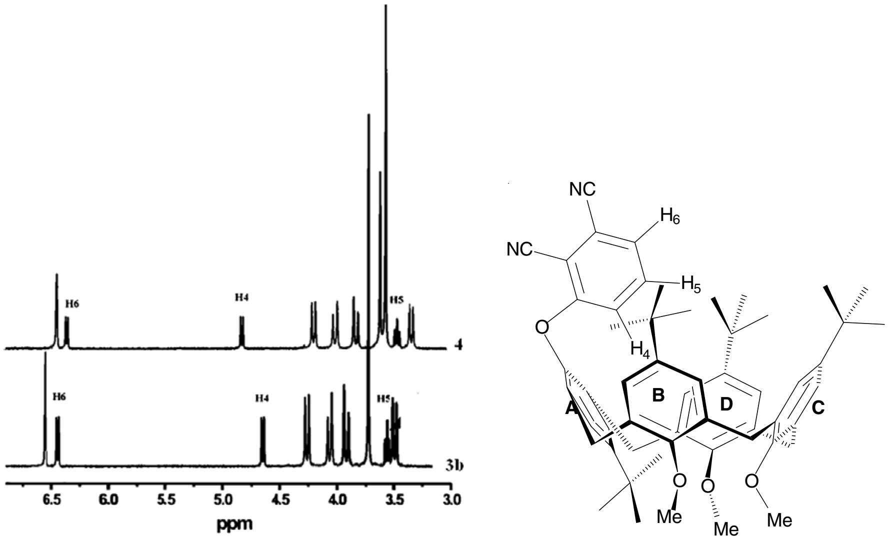


Figure 1. Room temperature ^1H NMR of **3b** and **4** in nitrobenzene-d_5.

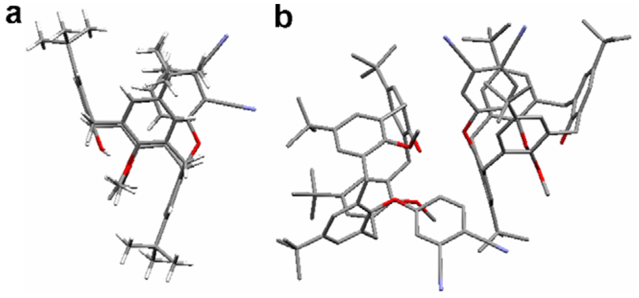


Figure 2. (a) The X-ray structure side view of **3b**. (b) The crystal structure of **3c** showing both cone and partial cone conformations.

lography (Fig. 2). Unfortunately, these conformations could not be separated.

These results confirmed our initial hypothesis that aryl substrates possessing substituents *ortho* to the leaving group will lead solely to a product in the partial cone conformation.

We discovered from ^{1}H NMR temperature studies (Fig. 3) that the partial cone conformation of **3b** is thermally stable up to temperatures of 125 °C. The only significant change observed in the spectrum was a slight upfield shift of the phthalonitrile triplet (H5). Upon cooling of the sample, the triplet reverts to its original chemical shift at 3.5 ppm.

We wished to convert **3b** to a phthalocyanine. To achieve this the remaining hyroxyl group of **3b** was alkylated using methyl iodide and NaH to give **4** in 90% yield after chromatography. Both ^{1}H NMR (Fig. 1) and the X-ray crystal structure of **4** confirmed that it remains in the partial cone conformation (Supplementary data).[5]

We chose to prepare the unsymmetrical phthalocyanine **5** since as it is a single isomer ^{1}HNMR can be used to determine if the partial cone conformation of the calix[4]arene is conserved in the final product. Preparation of **5** was achieved by condensing **4** with phthalonitrile (Scheme 2) in lithium/pentanol at 110 °C.

The isolated phthalocyanine mixture was purified by silica gel chromatography using chloroform as eluent. A single soluble band was isolated and was further purified by size exclusion chromatography (only a single

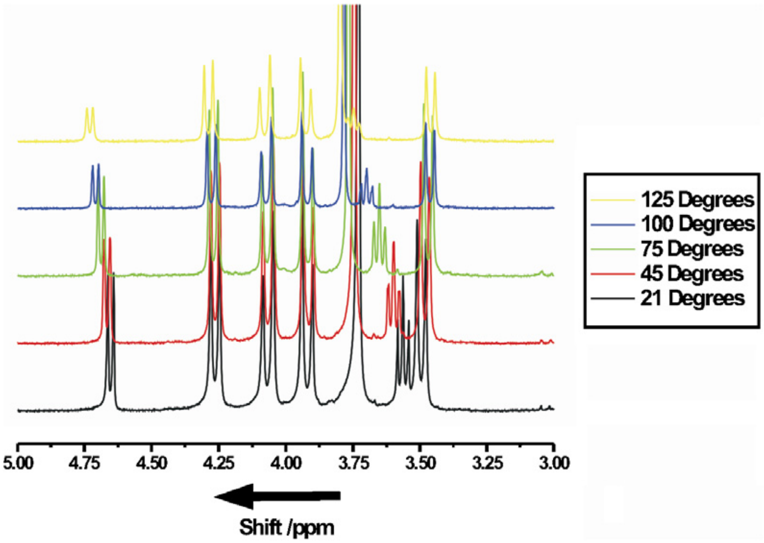
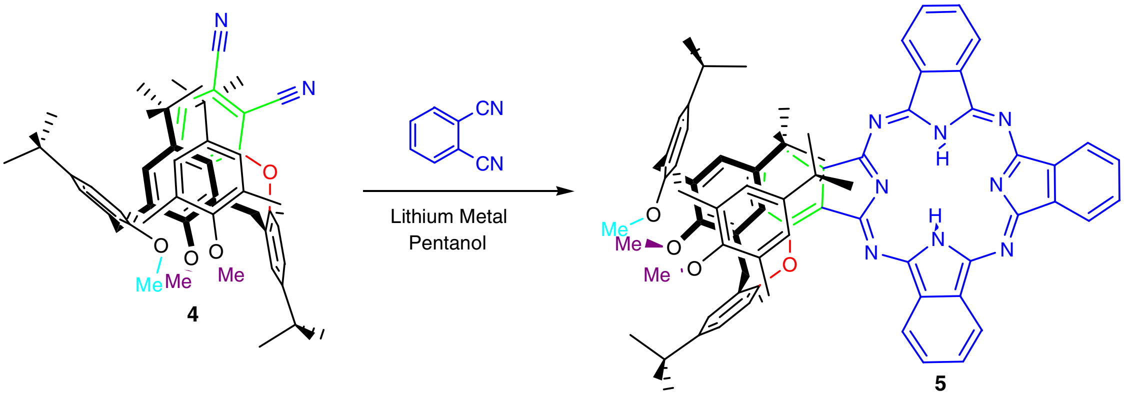


Figure 3. Temperature ^{1}H NMR studies of **3b** in nitrobenzene-d_5.



Scheme 2.

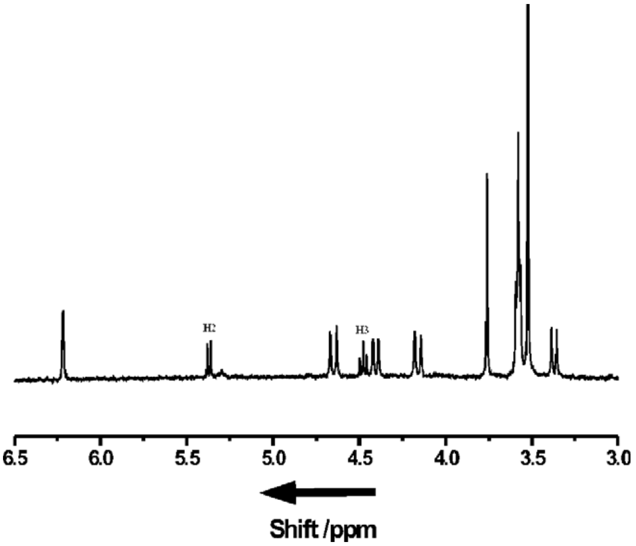


Figure 4. ^{1}H NMR of **5** showing the calix[4]arene bridging protons and the shielded aromatic protons of the phthalocyanine ring (toluene-d_8 10^{-4} M).

band was present) followed by a second silica gel column to give **5** in 30% yield. MALDI MS revealed the presence of a single cluster at 1202 which corresponded to **5**, no other calix[4]arene substituted phthalocyanine was present in the reaction mixture. The UV–vis spectrum of **5** ($CHCl_3$) showed that the outer Q-band red-shifted to 708 nm which is expected for a single alkyloxy substituent in the 1-position of the phthalocyanine.[3] Furthermore, **5** is highly soluble in organic solvents.

The ^{1}H NMR of **5** in toluene-d_8 (Fig. 4) revealed that the calix[4]arene substituent had remained in a partial cone conformation, with two of the *t*-butyl groups of the calixarene lying above and below the phthalocyanine ring.

This conclusion is supported by the presence of a doublet at 5.5 ppm and a triplet at 4.55 ppm (Fig. 4), these resonances can be assigned to the H2 and H3 protons of the phthalocyanine. The conformation of the calixarene has slightly changed, the AB spectrum of the bridging protons have reverted to an AX system indicating that all the rings of the calixarene are now parallel.

We also found that the internal protons of **5** were found at -0.3 ppm (concentration 2×10^{-4} M) in toluene-d_8 and at -0.28 ppm (2×10^{-4} M) in nitrobenzene-d_5 thereby demonstrating lower aggregation behaviour.[6]

UV–vis analysis of **5** showed no evidence of aggregation in solutions of 90% ethanol/$CHCl_3$. On comparison with other phthalocyanines, **5** outperformed the previously described dendritic phthalocyanines under the same polar solvent conditions.[7,8]

Fluorescence studies were also carried out to determine if the inclusion of the peripheral benzo group of the phthalocyanine into the calix[4]arene annulus would affect the optical properties of **5**. Excitation of **5** at 650 nm yielded a strong emission maxima at 715 nm showing a small Stokes shift of 7 nm which is typical for phthalocyanines. Excitation of **5** at 614 nm yielded the same emission spectrum. Thus the optical properties of the phthalocyanine were unaffected.

In summary, we have developed an efficient and selective method for the preparation of single *O*-aryl ether calix[4]arenes in the partial cone conformation. We have also found the partial cone conformation of these compounds to be highly stable, and in the case of **3b** can be converted to a phthalocyanine under harsh reaction conditions conformationally intact.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.095.

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8. It should be noted that **5** decomposes in $CDCl_3$ and CD_2Cl_2, yet is stable in bench grade $CHCl_3$ and CH_2Cl_2.