# The First Lower-Rim *O*-Arylation of Calix[4]arenes

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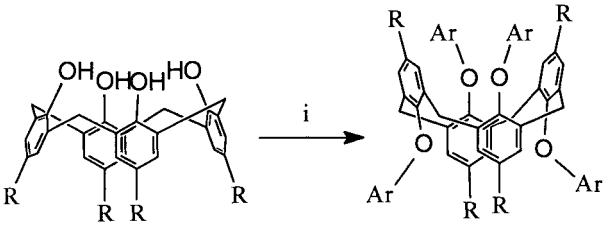
The first lower-rim full *O*-pyridyl and *O*-quinolyl ether derivatives of calix[4]arene and *p-tert*-butylcalix[4]arene in 1,3-alternate conformation have been synthesized using cesium carbonate as a promoter at high reaction temperature and their structures and conformations were characterized by $^1$H NMR spectra and X-ray crystallography.

Calix[4]arene are cyclic oligmers of *p-tert*-butylphenol and formaldehyde which posses rigid, cone-like, polyhydroxy structures and can be efficiently synthesized by Gutsche's method.[1] This cone conformation of calix[4]arenes is highly preorganized by the cyclic hydrogen bonds of the hydroxyl groups on the lower-rim.[2] With the introduction of alkyl groups on the lower-rim by Williamson etherification under different reaction conditions and in the presence of different bases, this preorganized cone conformation can be destroyed or fixed by larger alkyl groups than ethyl group. So, the reaction conditions and the acid binding reagents have been extensively investigated by Shinkai's and Reinhoudt's respective research groups.[3–5] In the light of these reaction conditions, compounds with different *O*-alkyl groups possessing cone, partial cone, 1,2-alternate and 1,3-alternate conformations have been synthesized and their guest-selectivities towards neutral molecules, cations and anions have also been evaluated.[2,6–10] But up to now, there is not any report touching upon the *O*-arylation of calixarenes. Furthermore, the lower-rim *O*-aryl calix[4]arene derivatives will form some new potential useful hydrophilic cavities for more guest molecules and ions. In this paper, we report here the lower-rim *O*-arylation of the four hydroxy groups of calix[4]arenes **1** and **2**.

Our aim is to obtain a series of hollow molecules possessing two same sized divergent cavities for further investigating their properties, such as metal cations coordinate behaviors, ion-selective performances and neutral molecules recognition. Therefore, we used $Cs_2CO_3$ as a template for the synthesis of 1,3-alternate conformer. Although traditional Ullmann ether synthesis usually added a copper salt as a catalyst, we considered that nitrogen atoms on the substrates and products are easily coordinate with copper salts, which may cause some template interference and purification problems. So, we give up to add any copper catalyst in this reaction.

The reaction condition of the *O*-arylation of calix[4]arenes **1** and **2** is shown in Scheme 1. Thus, treatment of calix[4]arene **1** with an excess of 2-bromopyridine in the presence of cesium carbonate (2.5 equiv per hydroxy) at the refluxed temperature of diphenyl ether afforded 25,26,27,28-tetrakis(pyridyl-2-oxy)-calix[4]arene **3** in 30% yield after purified by column chromatography ($CHCl_3$/petroleum ether, 50:50 v/v). Similarly, reaction of **1** with 2-bromo-4-methylquinoline or **2** with 2-bromo-4-methylquinoline gave the same 1,3-alternate conformers 25,26,27,28-tetrakis(4-methylquinolyl-2-oxy)calix[4]arene




**1, 2** **3–5**

**1**: R = H; **2**: R = *t*-Bu; **3**: R = H, Ar = pyridyl; **4**: R = H Ar = 4-methylquinolyl; **5**: R = *t*-Bu, Ar = 4-methylquinolyl.

**Scheme 1.** Reagent and condition: i, $Cs_2CO_3$, $Ph_2O$, 2-bromopyridine or 2-chloro-4-methylquinoline, refluxed for 4 h.

**4**[11] and 25,26,27,28-tetra-(4-methylquinol-2-oxyl)-5,11,17,23-tetra-*tert*-butylcalix[4]arene **5** in 30% and 75% yields, respectively. While treatment of **1** with 2-bromopyridine in the presence of potassium carbonate as a base under the refluxed temperature of DMF, the *O*-arylation reaction does not occur.

In the $^1$H NMR spectra of compound **3**, the singlet of the methylene bridge of calix[4]arene skeleton at 3.44 ppm suggest that **3** take a 1,3-alternate conformation in solution. But all of the signal of pyridyl groups are in broad singlets at 8.27, 7.84, 7.02 and 6.27 ppm, respectively, which revealed that the pyridyl groups rotate quickly in solution. Similarly, the singlet of the bridge methylene protons at 3.63 ppm of compound **4** implied that it also takes a 1,3-alternate conformation in solution. Contrary to **3**, the quinolyl groups give a set of good splitted signals in the $^1$H NMR spectra, so does compound **5**.

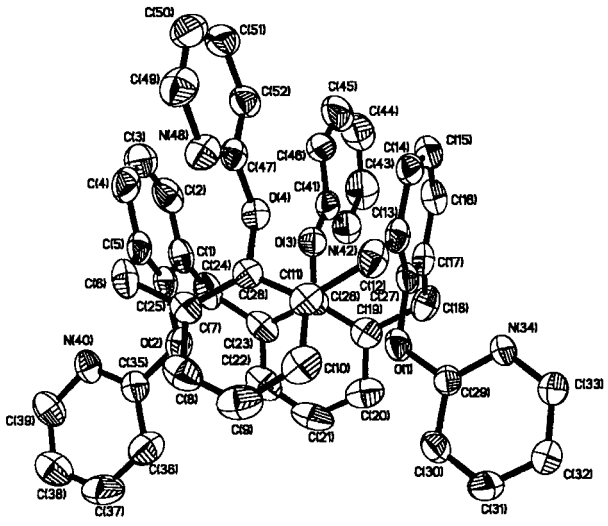


**Figure 1**. Structure of compound **3**.

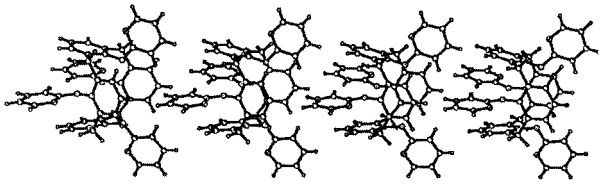


**Figure 2**. Infinite linear aggregate of **3** via self-inclusion.

The 1,3-alternate conformation of **3** was further proven by X-ray crystallography[12] as shown in Figure 1. The angles between the planes of the adjacent four arenes are 85.7, 90.7, 87.2 and 94.5°, respectively. The interplannar angles of the two pair of distal arenes are 19.9 and 36.3°, respectively, which implied that the two divergent cavities are not in equivalent size in solid state. The O···O separations are 4.773 Å between O(1) and O(2), and 4.034 Å between O(3) and O(4). The distance between C(36) and C(44A), and C(30) are 3.634 and 3.677 Å, respectively, which indicated that weak aromatic CH/π existed among molecules. It is worth note that compound **3** takes an infinite linear aggregate via self-inclusion, namely, the O(4) connected pyridyl was partially encompassed by the larger one of the two hydrophilic cavities as shown in Figure 2.

The preliminary ion-selectivities of **3** and **4** were investigated by an ion-selective electrode. Compounds **3** and **4** exhibited a good $Ag^+$-selectivity. Their coordinate properties together with their ion-selectivities will be reported in due course.

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**References and Notes**

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11 All compounds giving satisfactory analytical data. Selected data for compounds **4**: mp > 360 °C, $^1$H NMR (200 MHz, $CDCl_3$):δ 7.96(d, $J$ = 7.8 Hz, 4H), 7.72(d, $J$ = 7.6 Hz, 4H), 7.56(t, $J$ = 7.6 Hz, 4H), 7.48(t, $J$ = 7.8 Hz, 4H), 7.19(m, 4H), 6.87(t, $J$ = 7.3 Hz, 4H), 6.51(d, $J$ = 7.3 Hz, 4H), 3.63(s, 8H), 2.77(s, 12H). Calcd for $C_{68}H_{52}N_4O_4 \cdot 1.25CH_2Cl_2 \cdot CH_3OH$: C, 74.84; H, 5.22; N, 4.97%. Found: C, 75.13; H, 5.22; N, 4.78%.
12 Single-crystal diffraction measurements of crystals **3** and **4** on a Bruker Smart 1000 diffractometer with Mo Kα (λ = 0.71073 Å) at 293 K. Data for **3**: $C_{48}H_{36}N_4O_4$, $M_r$ = 732.81, crystal in monoclinic, space group $P2_1/n$, $Z$ = 8, $a$ = 18.939(15), $b$ = 10.298(8), $c$ = 39.34(3) Å, $\beta$ = 101.616(17)°, $V$ = 7509(11) Å$^3$, $D_c$ = 1.296 mg/mm$^3$, $\mu$ = 0.083 mm$^{-1}$, $F$(000) = 3072. A total of 26256 reflections were measured, 13246 unique. The structure was solved by direct method and refined on $F^2$ using SHELXTL software (G. M. Sheldrick, Göttingen, Germany). Final $wR_2$ = 0.1677, with a conventional $R_1$ = 0.0719 (reflections with I>2σ (I)) and a GOOF = 0.991 for 1009 refined parameters. **4**: $C_{68}H_{52}N_4O_4$, $M_r$ = 989.14, crystal in monoclinic, space group $C2/c$, $Z$ = 4, $a$ = 25.700(2), $b$ = 12.9650(10), $c$ = 17.1598(13) Å, $\beta$= 107.843(2)°, $V$ = 5442.7(7) Å$^3$, $D_c$ = 1.207 mg/mm$^3$, $\mu$ = 0.075 mm$^{-1}$, $F$(000) = 2080. $wR_2$ = 0.1270, $R_1$ = 0.0503.