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Selectively formylated and bridged calix[6]arene derivatives at the upper rim

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Abstract—The strategy of bridging the anisole units at the upper rim of calix[6]arene has been applied to strain the conformations of calix[6]arene. Based on the selective formylation of the 1,3,5-tri-*p*-*tert*-butylcalix[6]arene, several new calix[6]arene derivatives with different 1,3-bridged chains or a 1,3,5-tripod bridge at the upper rim have been prepared with moderate yields. The ^{1}H NMR spectra indicate that these calix[6]arene derivatives adopt a cone conformation, which has also been confirmed by the theoretical calculation at AM1 level. X-ray crystal structure of 1,3,5-tripod bridged compound **5** discloses that the calix[6]arene host stands in a cone conformation with approximate C_{3v} symmetry, and that a methanol molecule is enclosed in its hydrophobic cavity and stabilized by multi hydrogen bonds.
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1. Introduction

Calixarenes have been widely investigated as artificial receptors for cations, anions, and neutral molecules, or as versatile platforms, which can be functionalized to provide a range of interesting molecular architectures for self-assembling, biomimic catalysis, and chemosensing.[1] Among the calix[*n*]arenes and other calix-aromatic molecules, calix[4]arene is the most attractive, because it can be easily transformed to various derivatives by simple, selective modifications at the upper or lower rim. In addition, by introduction of propyl or larger groups at the lower rim, the conformation of calix[4]arene can be immobilized,[2] which is important for construction of preorganized receptors. However, this can't be applied in bigger cyclic oligomers such as calix[6]arene even with cholesteryl at its lower rim, because calix[6]arene enjoys both '*oxygen-through-the-annulus rotation*' and '*para-substitutent-through-the-annulus rotation*'.[3] In order to complex organic molecule with its larger intracavity, calix[6]arene needs to be immobilized in a cone conformation.[1b,4] Moreover, synthesis of conformation-constrained calixarenes is a fundamental subject for construction of optically pure inherently chiral receptors.[5] To address this problem, several strategies have been developed, including introduction of intramolecular covalent bonds at either the upper or the lower rim of the calix[6]arene skeleton,[1b] or formation of stable complexes through noncovalent bonds.[6] Now doubly and multiply bridged calix[6]arenes at the lower or upper rim have been reported.[1b,7] The rotation freedom of the anisole units in these derivatives is indeed decreased. Some of them have been successfully applied for including larger substrates within their inner cavity.[8] However, these works mostly focus on the modification at the lower rim, while research on the immobilization of the calix[6]arene conformation by linking the *para* positions of the anisole units is rare.[9] In this paper, based on the selective formylation of the 1,3,5-tri-*p*-*tert*-butylcalix[6]arene, several novel conformation-frozen calix[6]arene derivatives with different 1,3-bridged chains and 1,3,5-tripod bridge at the upper rim are reported and their conformation characters have been investigated by ^{1}H NMR spectra, semi-empirical molecular modeling, and X-ray crystallography.

2. Results and discussion

2.1. Synthesis of upper-rim-bridged calix[6]arenes

The synthesis procedure of upper-rim-bridged calix[6]arenes is illustrated in Scheme 1. Although various substitutions or *ipso*-substitution of calix[4]arene have been described in the last decades, the modification of *para* position of calix[6]arene, especially selective reaction still needs more attention.[10] The common method usually starts with selective reaction of the hydroxyl groups at the lower rim. Then this selectivity can be transferred to the *para* positions, using the fact that phenol units are more reactive than phenol ether. Therefore,

Keywords: Calix[6]arene; Upper-rim-bridged; 1,3,5-Tripod-bridged; Supramolecular chemistry; Inclusion compounds.
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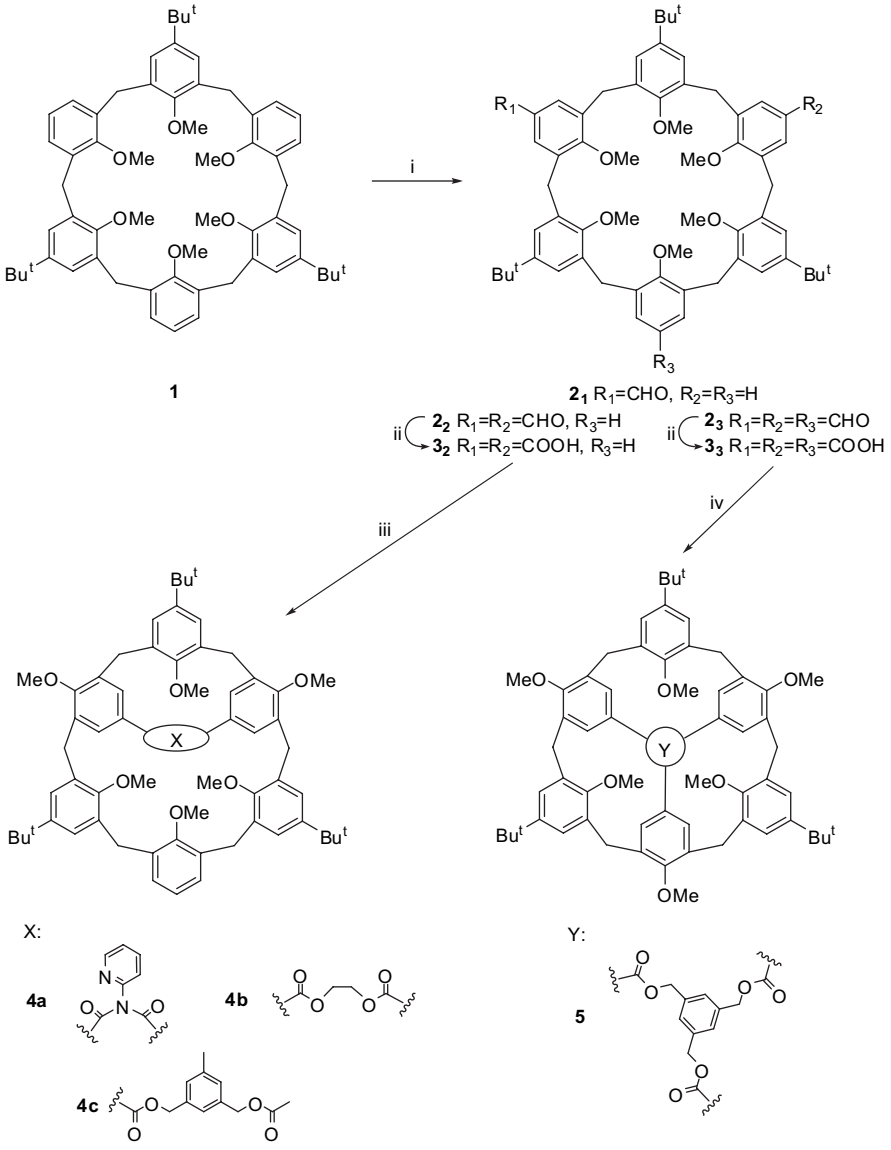

Scheme 1. Reagents and conditions: (i) $(CH_2)_6N_4$, TFA, 78 °C ($\mathbf{2_1}$, $\mathbf{2_2}$) or 120 °C ($\mathbf{2_3}$); (ii) NH_2SO_2H, $NaClO_2$, $CHCl_3$/acetone, rt; (iii) **4a**: $SOCl_2$, reflux, then 2-aminopyridine, DMAP, THF, rt; **4b**: 1,2-dibromoethane, Na_2CO_3, DMF, 75 °C; **4c**: 3,5-dibromomethyltoluene, Na_2CO_3, DMF, 75 °C; (iv) 1,3,5-tribromomethylbenzene, Na_2CO_3, DMF, 75 °C.

1,3,5-trimethoxylcalix[6]arene, an easily prepared starting material with gram scale, could be selectively de-*p*-*tert*-butylated, then methylated in other three hydroxyl groups to form compound **1**.[11] Ungaro et al. have reported the full formylation of three de-*tert*-butylated anisole units of compound **1** using Duff-reaction (hexamethylenetetramine/trifluoroacetic acid), and the triformylation compound $\mathbf{2_3}$ could be obtained in a good yield.[11] Here by controlling the equivalents of the formylation reagents, reaction temperature and time, monoformylation compound $\mathbf{2_1}$ and diformylation compound $\mathbf{2_2}$ have been prepared with 64% and 52% yields, respectively. The formyl groups were then oxidized to carboxyl groups under the treatment of sodium chlorite and aminosulfonic acid according to the preceding report.[12] Starting from the dicarboxylic acid $\mathbf{3_2}$, we can conveniently bridge the 1,3-anisole units at the upper rim of calix[6]arene with common coupling conditions in a fairly good yield. Three atoms bridged **4a**, six atoms bridged **4b**, and nine atoms bridged **4c** have been prepared in this way.

2.2. Conformation of upper-rim-bridged calix[6]arenes

In order to study the conformation of calix[6]arene derivatives **4a–c**, their ^{1}H and 2D-COSY NMR studies at 25 °C in $CDCl_3$ were carried out, and the chemical shifts of bridge methylene and phenolic methyl protons are listed in Table 1.

Table 1. ^{1}H NMR chemical shifts of methylene bridge and aromatic methoxyl protons of calix[6]arenes (ppm)

	ArCH_2Ar[a] (ppm)	ArOCH_3 (ppm)
4a	4.41 and 3.51, 4.37 and 3.62, 4.26 and 3.60	3.86 (6H), 3.63 (3H), 3.22 (3H), 2.39 (6H)
4b	4.46 and 3.53, 4.42 and 3.54, 4.18 and 3.61	3.90 (6H), 3.66 (3H), 2.63 (6H), 2.42 (3H)
4c	4.50 and 3.37, 4.42 and 3.57, 4.20 and 3.70	3.82 (6H), 3.46 (3H), 2.74 (6H), 2.34 (3H)

[a] All of the peaks are doublets with coupling constants about 15 Hz, and each corresponding to two protons.

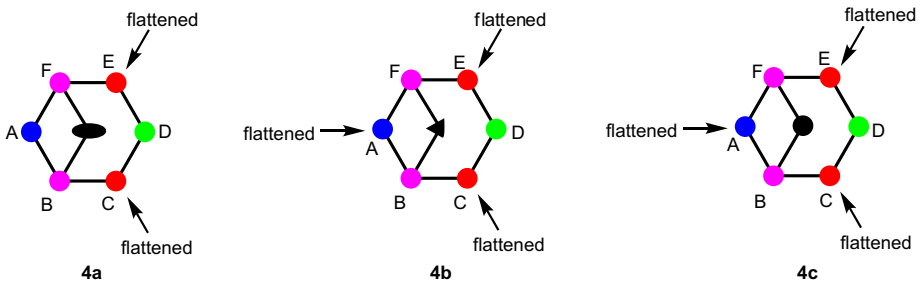

Chart 1. The symmetry topology of compounds **4a–c**.

It could be seen that 12 bridge methylene protons of all the 3 calix[6]arenes present 6 sharp and well-defined AX (or AB) doublets. These doublets belong to three spin–spin coupling systems, and all have coupling constants around 15 Hz. Three of them locate in the downfield with chemical shifts from 4.00 to 4.50 ppm, the other three in the upfield from 3.30 to 3.70 ppm. According to the 2D-COSY NMR, the difference of chemical shifts between axial and the equatorial hydrogens in the same carbon (or the same coupling system) is about 0.4 to 0.9 ppm. The above-mentioned facts confirmed that at room temperature these calix[6]arene derivatives adopted a distorted but fixed cone conformation with some anisole units in the flattened positions. Furthermore, because of only three sets of bridge methylene signals present, there should be a symmetrical plane in these molecules, and they have C_s-symmetry.

The approximately cone conformation of **4** was also supported by the upfield shift (δ<3 ppm) of some methoxy group protons at the lower rim of calix[6]arene. These protons have been shielded by the aromatic rings of calixarene, which indicates that they locate in the center of hydrophobic cavity and related anisole units take flattened arrangement. However, the different patterns of phenolic methyl signals indicate that there is minor deviation from their 'cone conformation'. Compound **4a**, with the shortest upper rim bridge chain, has two identical upfield shift methoxy proton signals. That the anisole units C and E (Chart 1) adopt

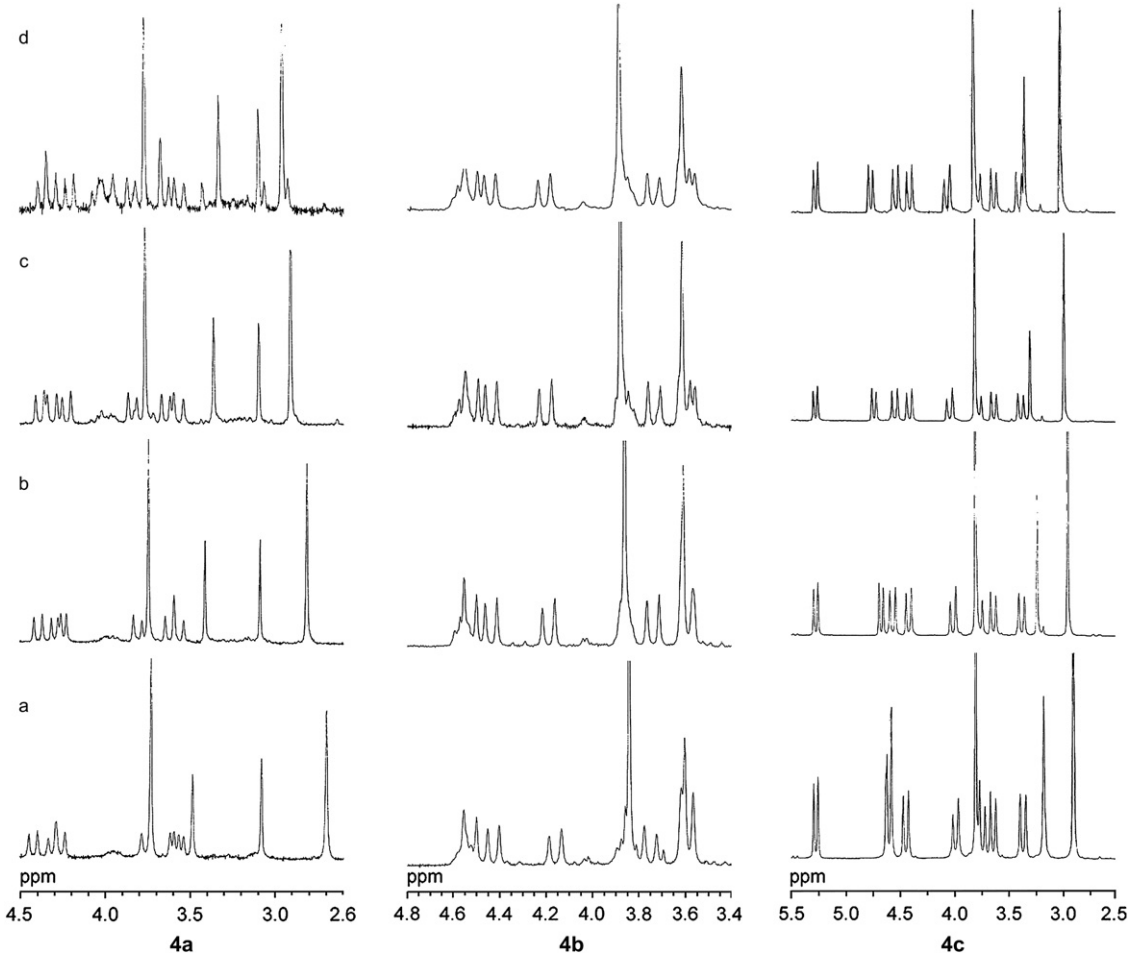

Figure 1. The partial ^{1}H NMR spectra of 1,3-bridged calix[6]arenes **4a–c** in $C_6D_4Cl_2$ at different temperatures: (a) 300 K; (b) 330 K; (c) 360 K; (d) 380 K.

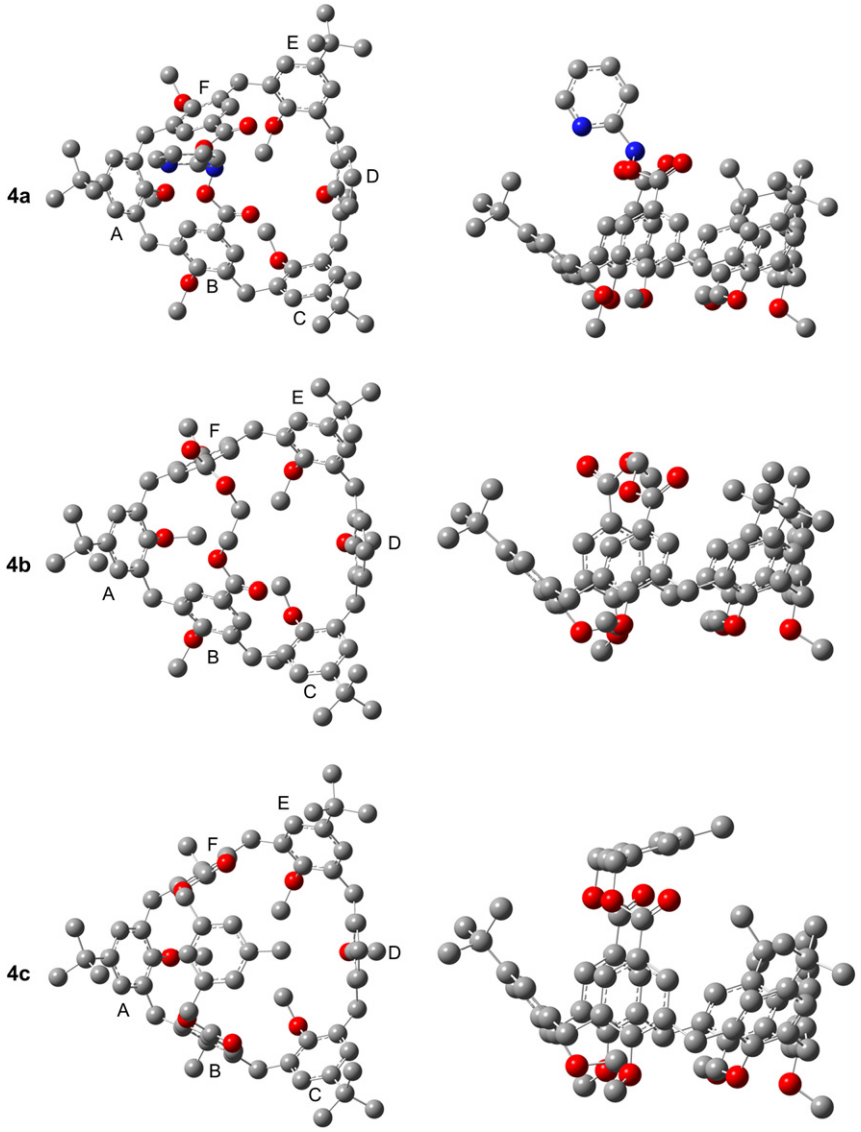

Figure 2. The optimized conformation of 1,3-bridged calix[6]arenes **4a–c** by AM1 level calculation. Left: top view; right: side view. Hydrogen atoms are omitted for clarity.

flattened position is the best explanation for this phenomenon. Both **4b** and **4c** have three upfield methoxyl, two identical and one different. Considering the structure and symmetry of these two molecules, the three anisole units adjacent to the bridged anisole units A, C, and E may adopt flattened positions. It is noteworthy that the proton NMR signal of the ethylene group in **4b** has split into two signals at 4.6 and 4.0 ppm. This indicates that the free rotation of the ethylene group is cumbered. The reason may be the rigidity of bridge chain or/and steric repulsion between the ethylene group and upper rim *tert*-butyl group. The same split was also observed in the benzyl methylene group of the upper rim bridge in **4c** and the AB doublets with coupling constant of 12 Hz confirm the rotation freezing of bridge chain.

The variable temperature NMR spectra of **4a–c** were recorded from 300 to 380 K in $C_6D_4Cl_2$, and the bridge methylene region is illustrated in Figure 1.

It could be seen that there are no obvious changes in the NMR spectra of **4b** and **4c** in experimental temperature region, which indicated that their conformation was unchanged even up to 100 °C. In the case of **4a**, the NMR spectra became more complex and some new signals appeared when the temperature rose, which may be due to decomposition or generation of new conformations.[9]

2.3. Molecular modeling of 4a–c

Despite experimental studies in solution NMR, the exact three-dimensional structures of these calix[6]arenes are not very clear yet. Today's molecular modeling can offer an important and precise prediction. We chose AM1 level in Gaussian 03 package[13] to optimize the conformations of these four bridged calix[6]arenes, which has shown reasonable results for predicting the lowest energy conformation of calix[6]arene compared to ab initio DFT method.[14] The starting models were referenced to the structure deduced from NMR spectra, and the optimized conformations are shown in Figure 2.

From Figure 2, we can see that the bridging of 1,3-anisole units of calix[6]arene forms a new smaller ring consisting

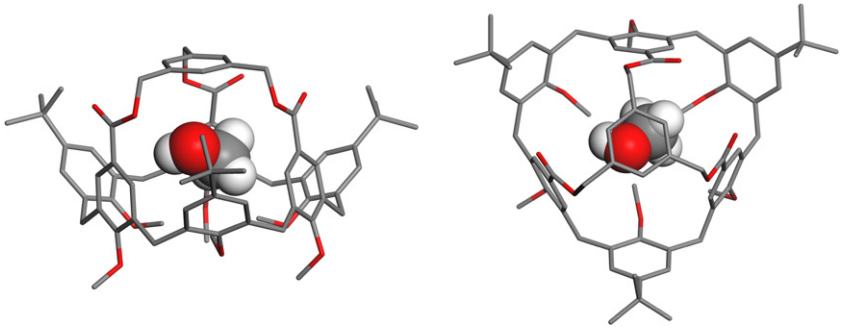

Figure 3. X-ray structure of tripod capped calix[6]arene **5**. Left and right: side and top views, respectively. Hydrogen atoms and solvents except in the cavity are omitted for clarity.

of A–B–bridge–F and a new bigger ring consisting of D–C–B–bridge–F–E. The rotation of the A unit is sterically impossible because either the methoxy group or the *tert*-butyl group inevitably hits the bridge chain when the A unit rotates. In the bigger D–C–B–bridge–F–E ring, although the D unit retains considerable conformational freedom, *oxygen-through-the-annulus rotation* and *para-substitutent-through-the-annulus rotation* of anisole units C and E are also difficult. The inward anisole units B, F, and the bridge chain cause a steric hindrance when C and/or E rotate. Therefore, all anisole units except D unit can only wobble in a small scale without changing the whole conformation of calix[6]arene skeleton, which is similar to the result from variable temperature ^{1}H NMR spectra.

2.4. The structure and complexes of 1,3,5-tripod capped calix[6]arene

In order to investigate the more rigid conformation and the inclusion properties with the hydrophobic cavity of calix[6]-arene, 1,3,5-tripod capped calix[6]arene **5** has been prepared by the reaction of 1,3,5-tribromomethylbenzene and *p*-tricarboxylcalix[6]arene $\mathbf{3_3}$ in the presence of base. In its ^{1}H NMR spectrum, there are only two doublets from the methylene protons of calix[6]arene skeleton with 4.39 and 3.48 ppm of chemical shifts and 15.0 Hz of coupling constant. The six methoxy protons show two kinds of signals: one is at 3.85 ppm, another at 2.37 ppm. The latter belongs to those protons located in the shielding field of aromatics. Under variable temperature conditions, the doublets of the methylene proton signals between two aromatic units of calix[6]arene have no obvious change, which indicated that the conformation of this compound was also immobilized in *cone*.

X-ray quality crystals of **5** were grown from MeOH/$CHCl_3$ solution. The molecular structure is presented in Figure 3. The calix[6]arene host stands in a cone conformation with approximate C_{3v} symmetry. The three anisole units with *tert*-butyl groups are flattened, where *tert*-butyl groups are in the *out* position. Other three anisole units are almost upright. The capped 1,3,5-subsitituted benzene locates on the top of the cavity and closes the upper entrance. At the lower rim, six methoxy groups also show alternate arrangement. The three methoxy groups of upright anisole units are almost outward. Other three methoxy groups of anisole units with *tert*-butyl groups are oriented toward the hydrophobic cavity, which closes the lower entrance of the cavity. Similar to the most 1,3,5-trimethoxycalix[6]arenes with C_{3v} cone conformation, there are classical CH$\cdots\pi$ interactions between these inside three methoxy groups and their nearby aromatic walls [d($C_{methoxy}\cdots$Ar)=3.231 and 3.420, 3.222 and 3.480, and 3.376 and 3.305 Å].[15] Within the rigid hydrophobic cavity of **5**, a methanol molecule is enclosed in the crystalline state. This molecule is stabilized in the cavity by multi weak hydrogen bonds. There are two kinds of weak O–H$\cdots$Ar interactions between hydroxyl group and the nearest aromatic rings. One is with capped benzene [d(O$\cdots Ar_{top}$)=3.452 Å], another is with faced anisole unit [d(O$\cdots$Ar)=3.413 Å]. The methyl group interacts with the nearest two aromatic walls with C–H$\cdots$Ar force [d($C_{methanol}\cdots$Ar)=3.286 and 3.461 Å], which is stronger than the O–H$\cdots$Ar interactions.

3. Conclusion

We have prepared several new calix[6]arene derivatives with different 1,3-bridged chains and 1,3,5-tripod bridge at the upper rim in moderate yields from the selective formylation of the 1,3,5-tri-*p*-*tert*-butylcalix[6]arene. The ^{1}H NMR spectra indicate that these calix[6]arene derivatives adopted a cone conformation. The theoretical calculation at AM1 level has been used for optimizing the conformation of the three 1,3-bidged calix[6]arenes. X-ray crystal structure of 1,3,5-tripod bridged compound **5** discloses that the calix[6]-arene host stands in a cone conformation with approximate C_{3v} symmetry. A methanol molecule is enclosed in the hydrophobic cavity of **5** in the crystalline state, and stabilized in the cavity by multi weak hydrogen bonds. We believe that our research may be beneficial for the construction of more calix[6]arenes with frozen cone conformation and bigger intracavity for inclusion of diverse neutral organic molecules.

4. Experimental

4.1. General

Melting points were determined on an electrothermal melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained at 300.13 and 75 MHz on a Bruker DMX300 NMR spectrometer ($CDCl_3$ and TMS as internal

standard), respectively. MALDI-TOF MS were recorded with a Bruker BIFLEXIII spectrometer with CCA (2-cyano-4′-hydroxycinnamic acid) as the matrix. All chemicals were of reagent grade and were used without further purification. Petroleum ether used for column chromatography refers to the 60–90 °C fraction. Molecular modeling was realized in the workstation of the Institute of Chemistry, Chinese Academy of Sciences. Compounds $\mathbf{2_3}$ and $\mathbf{3_3}$ have been reported in the literature.[11,12]

4.2. Compound 2_1

Compound **1** (0.107 g, 0.12 mmol) and hexamethylenetetramine (0.336 g, 2.4 mmol) were dissolved in trifluoroacetic acid (1.5 mL), and the resulting reaction mixture was stirred at reflux for 2 h. After the reaction was cooled to room temperature, 1 M HCl (20 mL) was added to quench the reaction. The mixture was stirred for another 0.5 h and then extracted with dichloromethane (75 mL) three times. The combined organic phases were washed with saturated brine, and dried over Na_2SO_4. The crude product was purified by column chromatography on silica gel using petroleum ether/acetone (30:1 v/v) as eluent affording a white solid in 64% yield. Mp: 249–251 °C; ^{1}H NMR: δ 9.73 (s, 1H, ArCHO), 7.43 (s, 2H, ArH), 7.07 (s, 2H, ArH), 7.04 (s, 2H, ArH), 7.00 (s, 2H, ArH), 6.92–6.83 (m, 6H, ArH), 3.94 (br s, 12H, $ArCH_2Ar$), 3.30 (s, 6H, $ArOCH_3$), 3.22 (s, 3H, $ArOCH_3$), 3.08 (s, 6H, $ArOCH_3$), 2.94 (s, 3H, $ArOCH_3$), 1.18 (s, 27H, $C(CH_3)_3$); ^{13}C NMR: δ 191.6, 161.6, 155.9, 154.1, 146.2, 145.9, 135.7, 134.7, 134.3, 133.6, 133.5, 132.5, 131.8, 130.5, 128.5, 126.7, 126.3, 125.9, 123.4, 60.1, 60.0, 34.1, 31.4, 30.7, 30.5; IR (KBr): ν 2956, 1697, 1596, 1462 cm^{-1}; MALDI-TOF MS: *m/z* 939 ([M+Na]$^+$), 955 ([M+K]$^+$); elemental analysis calcd for $C_{61}H_{72}O_7$: C, 79.88; H, 7.91. Found: C, 79.49; H, 7.98.

4.3. Compound 2_2

Compound **1** (0.107 g, 0.12 mmol) and hexamethylenetetramine (0.497 g, 3.36 mmol) were dissolved in trifluoroacetic acid (2.1 mL), and the resulting reaction mixture was stirred at reflux for 3 h. After the reaction was cooled to room temperature, 1 M HCl (20 mL) was added to quench the reaction. The mixture was stirred for another 0.5 h and then extracted with dichloromethane (75 mL) three times. The combined organic phases were washed with saturated brine, and dried over Na_2SO_4. The crude product was purified by column chromatography on silica gel using petroleum ether/acetone (20:1 v/v) as eluent affording a white solid in 52% yield. Mp: 256–258 °C; ^{1}H NMR: δ 9.76 (s, 2H, ArCHO), 7.47 (s, 4H, ArH), 7.07 (s, 2H, ArH), 7.01 (s, 2H, ArH), 6.98 (s, 2H, ArH), 6.91–6.89 (m, 2H, ArH), 6.81–6.79 (m, 1H, ArH), 3.96 (br s, 12H, $ArCH_2Ar$), 3.37 (s, 3H, $ArOCH_3$), 3.25 (s, 6H, $ArOCH_3$), 3.17 (s, 3H, $ArOCH_3$), 3.05 (s, 6H, $ArOCH_3$), 1.19 (s, 27H, $C(CH_3)_3$); ^{13}C NMR: δ 192.5, 162.5, 156.8, 155.0, 154.9, 147.4, 147.1, 136.8, 136.4, 135.4, 134.6, 133.6, 133.5, 132.8, 131.5, 131.4, 129.4, 127.6, 127.2, 126.8, 124.4, 61.2, 61.1, 61.0, 35.0, 32.3, 31.6, 31.4; IR (KBr): ν 2956, 1696, 1593, 1475 cm^{-1}; MALDI-TOF MS: *m/z* 967 ([M+Na]$^+$), 983 ([M+K]$^+$); elemental analysis calcd for $C_{62}H_{72}O_8$: C, 78.78; H, 7.68. Found: C, 78.75; H, 7.62.

4.4. Compound 3_2

Compound $\mathbf{2_2}$ (0.142 g, 0.15 mmol) was dissolved in a mixed solvent of chloroform (7 mL) and acetone (7 mL), and then a solution of NH_2SO_2OH (0.262 g, 2.70 mmol) and $NaClO_2$ (0.204 g, 2.26 mmol) in water (2 mL) was added. After the mixture was stirred at room temperature for 5 h, the solvent was removed under reduced pressure and then 10% HCl (20 mL) was added. The precipitate was collected and dissolved in dichloromethane (20 mL), and dried over Na_2SO_4. The pure product was recrystallized from CH_2Cl_2/MeOH as a white solid, yield 95%. Mp: 255–257 °C; ^{1}H NMR: δ 7.65 (s, 4H, ArH), 7.24 (s, 2H, ArH), 7.21 (s, 2H, ArH), 7.07 (s, 2H, ArH), 6.71 (s, 3H, ArH), 3.94 (br s, 12H, $ArCH_2Ar$), 3.67 (s, 6H, $ArOCH_3$), 3.38 (s, 3H, $ArOCH_3$), 2.90 (s, 6H, $ArOCH_3$), 2.18 (s, 3H, $ArOCH_3$), 1.36 (s, 9H, $C(CH_3)_3$), 1.26 (s, 18H, $C(CH_3)_3$); ^{13}C NMR: δ 172.0, 160.7, 155.6, 154.2, 146.3, 146.1, 135.1, 134.7, 134.4, 133.5, 132.6, 132.4, 130.7, 130.6, 128.3, 127.0, 126.9, 126.7, 126.6, 126.4, 124.4, 123.6, 60.5, 60.3, 60.2, 60.1, 34.4, 34.2, 34.1, 31.5, 31.0, 30.9, 30.8, 30.6, 30.4, 30.2, 30.2, 30.1, 29.9, 29.7; IR (KBr): ν 3234, 2959, 2830, 1706, 1600, 1477, 1427 cm^{-1}; MALDI-TOF MS: *m/z* 999 ([M+Na]$^+$), 1015 ([M+K]$^+$); elemental analysis calcd for $C_{62}H_{72}O_{10}$: C, 76.20; H, 7.43. Found: C, 76.28; H, 7.20.

4.5. Compound 4a

Compound $\mathbf{3_2}$ (0.134 g, 0.137 mmol) was dissolved in $SOCl_2$ (1 mL) and the reaction solution was stirred at reflux for 3 h. Then the excess $SOCl_2$ was evaporated. A solution of 2-aminopyridine (0.026 g, 0.274 mmol) and *N*,*N*-dimethyl-4-aminopyrridine (0.005 g, 0.40 mmol) in fresh distilled THF (10 mL) was added. The mixture was stirred for 3 h at room temperature. After the solvent was removed in vacuum, the residue was dissolved in CH_2Cl_2 and washed with water several times. The organic layer was separated and dried over anhydrous Na_2SO_4. The product was purified by column chromatography using petroleum ether/acetone (15:1 v/v) as eluent affording a white solid (69 mg, 50%). Mp: 180–182 °C; ^{1}H NMR: δ 8.16 (d, J=6.1 Hz, 1H, Py-H), 7.48 (t, J=8.02 Hz, 1H, Py-H), 7.25 (s, 1H, ArH), 7.17 (s, 2H, ArH), 7.12 (s, 2H, ArH), 7.05 (s, 2H, ArH), 6.96–6.90 (m, 3H, ArH, Py-H), 6.88 (s, 1H, ArH), 6.86–6.85 (m, 1H, ArH), 6.67 (d, 1H, Py-H), 6.40 (s, 2H, ArH), 4.41 (d, J=15.4 Hz, 2H, $ArCH_2Ar$), 4.37 (d, J=15.6 Hz, 2H, $ArCH_2Ar$), 4.26 (d, J=16.7 Hz, 2H, $ArCH_2Ar$), 3.86 (s, 6H, $ArOCH_3$), 3.63 (s, 3H, $ArOCH_3$), 3.60–3.51 (m, 6H, $ArCH_2Ar$), 3.22 (s, 3H, $ArOCH_3$), 2.39 (s, 6H, $ArOCH_3$), 1.37 (s, 18H, $C(CH_3)_3$), 1.33 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ 173.1, 158.9, 155.5, 155.1, 154.8, 153.6, 148.8, 147.5, 145.8, 137.7, 136.1, 134.1, 133.7, 132.9, 132.7, 132.5, 131.2, 128.9, 128.7, 127.9, 127.7, 127.3, 126.8, 124.2, 120.3, 118.5, 60.2, 60.2, 60.0, 59.7, 34.3, 34.2, 32.0, 31.7, 31.6, 31.5, 29.8; IR (KBr): ν 2956, 1708, 1589, 1468, 1432 cm^{-1}; MALDI-TOF MS: *m/z* 1035 ([M+H]$^+$), 1057 ([M+Na]$^+$), 1073 ([M+K]$^+$); elemental analysis calcd for $C_{67}H_{74}O_8N_2\cdot H_2O$: C, 76.40; H, 7.27; N, 2.66. Found: C, 76.54; H, 7.31; N, 2.64.

4.6. Compound 4b

Compound $\mathbf{3_2}$ (0.099 g, 0.102 mmol) and $BrCH_2CH_2Br$ (8.79 μL, 0.102 mmol) were dissolved in dry DMF

(30 mL), and Na_2CO_3 (0.270 g, 2.55 mmol) was added. The mixture was stirred overnight at 75 °C, and then the solvent was removed in vacuum. The residue was dissolved in CH_2Cl_2, washed with water several times, and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography using petroleum ether/acetone (20:1 v/v) as eluent affording a white solid (71 mg, 70%). Mp: 185–187 °C; ^{1}H NMR: δ 7.36 (s, 2H, ArH), 7.27 (s, 1H, ArH), 7.25 (s, 2H, ArH), 7.13 (s, 2H, ArH), 7.04 (s, 2H, ArH), 6.34–6.29 (m, 2H, ArH), 6.25 (s, 1H, ArH), 6.23–6.22 (m, 1H, ArH), 4.60–4.54 (m, 2H, $ArCO_2CH_2$), 4.46 (d, J=16.3 Hz, 2H, $ArCH_2Ar$), 4.42 (d, J=15.0 Hz, 2H, $ArCH_2Ar$), 4.18 (d, J=16.0 Hz, 2H, $ArCH_2Ar$), 4.00–3.95 (m, 2H, $ArCO_2CH_2$), 3.90 (s, 6H, $ArOCH_3$), 3.66 (s, 3H, $ArOCH_3$), 3.61–3.53 (m, 6H, $ArCH_2Ar$), 2.63 (s, 6H, $ArOCH_3$), 2.42 (s, 3H, $ArOCH_3$), 1.40 (s, 9H, $C(CH_3)_3$), 1.35 (s, 18H, $C(CH_3)_3$); ^{13}C NMR: δ 165.4, 159.8, 154.9, 154.8, 154.7, 154.6, 146.9, 146.4, 135.8, 135.5, 135.1, 133.8, 133.6, 133.3, 132.7, 132.2, 129.8, 128.4, 128.1, 127.9, 127.3, 127.1, 126.8, 124.5, 123.3, 61.6, 60.3, 60.2, 59.7, 59.6, 34.3, 34.2, 31.6, 31.5, 31.4, 30.8, 30.3; IR (KBr): ν 2956, 1721, 1600, 1482, 1465, 1433 cm^{-1}; MALDI-TOF MS: m/z 1025 ([M+Na]$^+$), 1041 ([M+K]$^+$); elemental analysis calcd for $C_{64}H_{74}O_{10}$: C, 76.62; H, 7.43. Found: C, 76.66; H, 7.14.

4.7. Compound 4c

The reaction of **3$_2$** (0.099 g, 0.102 mmol), α,α′-dibromo-1,3,5-trimethylbenzene (0.028 g, 0.102 mmol), and Na_2CO_3 (0.270 g, 2.55 mmol) in dry DMF (30 mL) was carried out using the same procedure described in the synthesis of **4b**. After purification by column chromatography using petroleum ether/acetone (15:1 v/v) as eluent, the product was obtained as a white solid (71 mg, 70%). Mp: 261–263 °C; ^{1}H NMR: δ 7.66 (s, 2H, ArH), 7.33 (s, 2H, ArH), 7.31 (s, 2H, ArH), 7.19 (s, 2H, ArH), 7.13 (s, 2H, ArH), 7.06 (s, 2H, ArH), 6.98 (s, 1H, ArH), 6.78–6.70 (m, 3H, ArH), 5.51 (d, J=11.9 Hz, 2H, $ArCO_2CH_2Ar$), 4.63 (d, J=11.9 Hz, 2H, $ArCO_2CH_2Ar$), 4.50 (d, J=15.4 Hz, 2H, $ArCH_2Ar$), 4.42 (d, J=14.7 Hz, 2H, $ArCH_2Ar$), 4.20 (d, J=15.4 Hz, 2H, $ArCH_2Ar$), 3.82 (s, 6H, $ArOCH_3$), 3.70 (d, J=15.3 Hz, 2H, $ArCH_2Ar$), 3.57 (d, J=14.6 Hz, 2H, $ArCH_2Ar$), 3.46 (s, 3H, $ArOCH_3$), 3.37 (d, J=15.5 Hz, 2H, $ArCH_2Ar$), 2.74 (s, 6H, $ArOCH_3$), 2.34 (s, 3H, $ArOCH_3$), 2.31 (s, 3H, $ArCH_3$), 1.33 (s, 18H, $C(CH_3)_3$), 1.21 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ 166.0, 159.4, 155.4, 154.6, 154.3, 146.2, 146.0, 138.0, 136.3, 135.0, 134.5, 134.2, 132.9, 132.7, 131.9, 130.1, 129.6, 128.2, 128.0, 127.7, 127.6, 127.5, 126.4, 125.3, 123.5, 66.2, 60.5, 60.4, 60.3, 60.0, 34.2, 34.0, 31.6, 31.2, 30.9, 29.7, 29.2, 21.1; IR (KBr): ν 2957, 1741, 1468, 1280 cm^{-1}; MALDI-TOF MS: m/z 1115 ([M+Na]$^+$), 1131 ([M+K]$^+$); elemental analysis calcd for $C_{71}H_{80}O_{10}$: C, 77.99; H, 7.37. Found: C, 77.65; H, 7.21.

4.8. Compound 5

Compound **3$_3$** (0.102 g, 0.10 mmol) and 1,3,5-tribromomethylbenzene (0.036 g, 0.10 mmol) were dissolved in dry DMF (30 mL). After potassium carbonate (0.314 g, 3 mmol) was added, the reaction mixture was stirred overnight at 75 °C. Then the solvent was evaporated under vacuum, and dichloromethane (20 mL) was added. The solution was washed with water several times, and dried over anhydrous Na_2SO_4. After purification on column chromatography using petroleum ether/acetone (15:1 v/v) as eluent, the product was obtained as a white solid (74 mg, 65%). Mp: >300 °C; ^{1}H NMR: δ 7.42 (s, 3H, ArH), 7.34 (s, 6H, ArH), 7.31 (s, 6H, Ar*H*), 5.10 (s, 6H, $ArCO_2CH_2Ar$), 4.39 (d, J=15.1 Hz, 6H, $ArCH_2Ar$), 3.85 (s, 9H, $ArOCH_3$), 3.48 (d, J=15.0 Hz, 6H, $ArCH_2Ar$), 2.37 (s, 9H, $ArOCH_3$), 1.44 (s, 27H, $C(CH_3)_3$); ^{13}C NMR: δ 163.4, 157.6, 152.9, 144.9, 135.3, 133.1, 132.1, 131.0, 127.3, 126.6, 124.0, 64.0, 59.0, 58.6, 32.9, 30.1, 28.3; IR (KBr): ν 2959, 1721, 1600, 1482, 1466 cm^{-1}; MALDI-TOF MS: m/z 1157 ([M+Na]$^+$), 1174 ([M+K]$^+$); elemental analysis calcd for $C_{72}H_{78}O_{12}$: C, 76.17; H, 6.92. Found: C, 75.73; H, 7.06.

4.9. X-ray structure determination of 5

Crystal data: Mw=2660.83, monoclinic, colorless crystal (0.28×0.20×0.18 mm^3), a=18.247(6) Å, b=31.742(10) Å, c=24.834(8) Å, β=96.470(7)°, V=14,292(8) Å^3, space group $P2_1/n$, Z=4, ρ=1.237 g cm^{-3}, μ(Mo Kα)=2.44 cm^{-1}, 69,776 reflections measured at 293 K (Bruker SMART 1000 diffractometer) in the 1.05–25.00° θ range, 24,878 unique, 1725 parameters refined on F^2 [SHELXL][16] to final indices $R[F^2>4\sigma F^2]$=0.1028, wR=0.2454 [$w=1/[\sigma^2(F_0^2)+(0.1243P)^2+29.0749P]$ where $P=(F_0^2+2F_c^2)/3$]. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication CCDC 645482. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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