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Synthesis of New Rigid Dimeric Calix[4]arene

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A new Dimeric calixarene from the head to head linkage of two calix[4]arene units fixed in the cone conformation was synthesized via Sonogashira cross-coupling reaction. The structure of 10 was confirmed by NMR, MS and IR-spectroscopy.

Keywords: Double calix[4]arenes; Cross-coupling; Catalysis

INTRODUCTION

Calixarenes have attracted attention because of their potential for forming host–guest complexes and serving as useful building blocks in supramolecular chemistry. Generally, the parent calixarenes begin to act as synthetic receptors only after appropriate regio- and stereoselective functionalization of the phenolic oxygen at the lower rim or aromatic *para*-position on the phenyl ring at the upper rim [1]. Calixarenes with two binding sites are very useful models for molecular recognition studies and the synthesis of double calixarenes has been attempted by several research groups [2–7]. Different methods have been used for the synthesis of dimeric calix[4]arenes such as diazo addition reactions [8], quadruple cycloadditive macrocyclization [9], formation of amide bonds [10], and Sonogashira cross-coupling reaction [4]. Incorporation of linear and rigid ethynyl groups could increase the span betweem the two hemispheres which is the advantage of the latter method.

Generally, in all double calix[4]arenes, the two subunits are free to rotate about the bridge, allowing the two rigid caps to adapt in response to a potential guest and possibly co-operate in binding. *Shinkai* has shown that two cone-calix[4]arenes connected at the upper rim, has a strong inclusion ability for cationic guest molecules [11].

RESULTS AND DISCUSSION

Synthesis Path

Compound **1** was prepared according to the literature procedure [12]. For the stepwise O-alkylation of calix[4]arene, we have used the mixture of $Ba(OH)_2$. $8H_2O$ and BaO (vide post) and we have obtained **2** in cone conformation [13]. Introduction of a single functional group at the upper rim of the fully de-tertbutylated calix[4]arene has been performed by Gutsche *et al.* [14]. *Ipso*-Nitration of tetraalkylated *tert*-butylcalix[4]arene has been used to synthesis is the corresponding tetranitro compounds in 85% yield [15]. The presence of electron-donating groups (OH), at the lower rim, makes calix[4]arenes excellent substrates for ipso nitration [16,17]. Under less drastic conditions (treatment of a solution of **2** in CH_2Cl_2 with a mixture of concentrated nitric acid and glacial acetic acid at room temperature), the reaction can be restricted to one phenolic unit and mononitro compounds **3** are formed more or less exclusively. Subsequently, O-propylation of OH group in **3** yielded **4** in cone conformation (Scheme 1).

The reduction of nitrocalixarene derivatives using hydrazine and $FeCl_3$ [18] or $SnCl_2$ and EtOH [19] has been reported. We have used hydrazine and Raney Nickel as reduction agents. Under these conditions the treatment of **4** afforded the monoamino compound **5** in 85% yield.

For classical iodination of calixarenes, two strategies have been reported in the literature. The first method is direct iodination of tetraalkylatedcalix[4]arene

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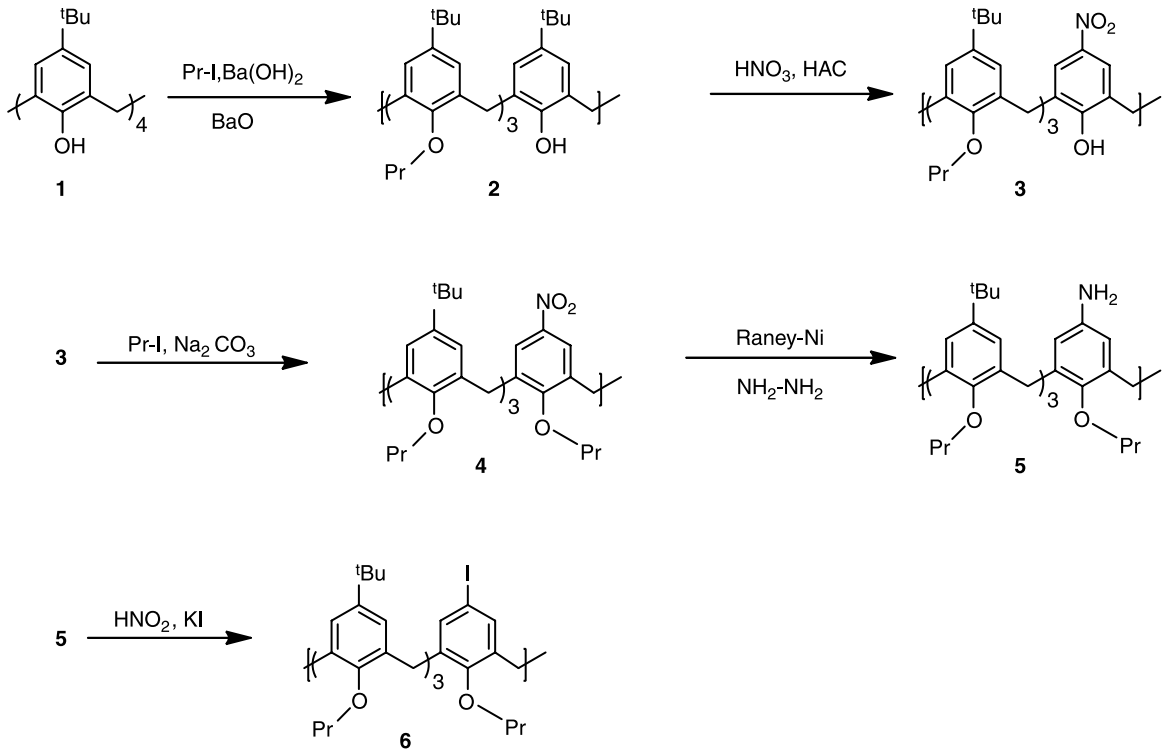


SCHEME 1 Synthesis of the Calixarene **6**.

by means of iodine–silver trifluoroacetate in refluxing chloroform, which is often used to prepare tetraiodocalix[4]arene [20]. The second method is bromide–lithium exchange of tetrabromophenylcalix[4]arene followed by subsequent quenching with iodine. In this work, we have used the Sandmeyer reaction to synthesise **6**.

Synthesis of Dimeric Calixarenes

Various reactions were previously used for synthesis of double calix[4]arene. These reactions are as follows, the reaction of monoiodo derivative with 3,3-dimethyl propargyl alcohol using palladium catalyst, and the reaction of alkylated calixarene with the *para*-formaldehyde in dichloromethane using trifluoroacetic acid as catalyst [4].

Another method was the reaction of various diacid with monoaminocalixarene [10]. In this paper, we have used the Sonogashira cross-coupling reaction, utilizing a planar spacer, 3,6-disubstituted-*9H*-fluorene-9-on **8** and **9** [21]. This spacer has the potential of directed tetramerization to obtain large and uniform molecular structure [22].

To synthesise dimeric calixarenes, we have used two methods (see Schemes 2 and 3). The conversion of **6** to **7**, because of the steric hindrance of the *tert*-butyl groups on **7**, has a very low yield (25%). However we have obtained the new calix[4]arene dimer **10** according to Schemes 2 and 3.

The structure of the double calix[4]arene incorporating a Flourenon-spacer **10** was confirmed by ^{1}H NMR, ^{13}C NMR, MALDI—TOF spectra and by elemental analysis.

Molecular Modeling

Force-field calculations were initially carried out as molecular mechanics calculations in water. To establish the minimum energy conformation of **10,** Monte-Carlo simulations were subsequently carried out in water (MacroModel 7.0, Schrödinger Inc., 2000. Force-field: Amber*). A 1000-step Monte-Carlo-simulation was performed (Fig. 1).

Molecular dynamics calculations confirmed the assumed high degree of preorganization within calixarene dimer **10** carrying the rigid aromatic spacer, whereas much more flexibility was found for the aliphatic bridge [7].

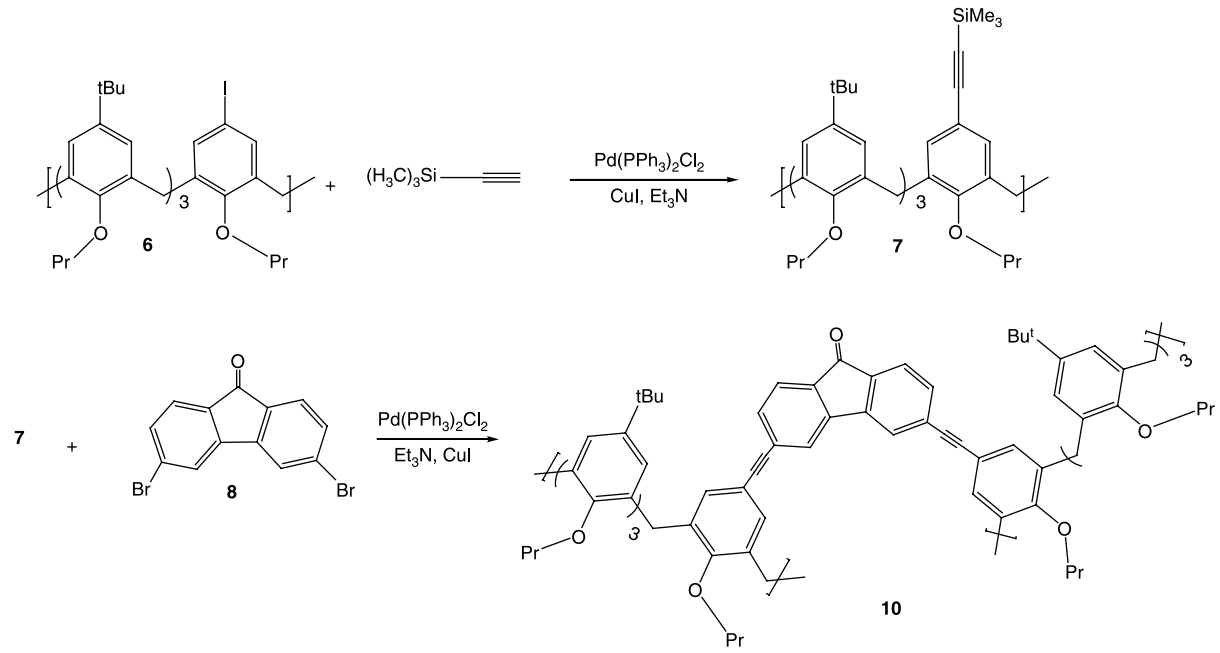
EXPERIMENTAL SECTION

Synthesis of Double Calix[4]arene 10

According to Scheme 2

5,11,17-Tri-tert.butyl-23-trimethylsilylethenyl-25-26,27,28-tetrapropoxycalix[4]arene **7**

A slurry of **6** (3.54 g, 4 mmol), trimethylsilylacethylene (1.7 mL, 12 mmol), $(Ph_3P)_2PdCl_2$ (0.040 g, 0.06 mmol), and Et_3N (75 ml), in dry DMF (50 ml) was stirred for 1 h at r.t. Then CuI (0.040 g, 0.21 mmol) was added and the mixture was stirred under N_2 for 48 h at 80°C. The reaction mixture was



SCHEME 2 Synthesis of the double calix[4]arene **10**.

diluted with water (500 ml), and then extracted with dichloromethane. The extract was washed with HCl (10%), saturated $NaHCO_3$ and brine. Then, it was evaporated and purified by column chromatography (silica gel/CH_2Cl_2: *n*-hexane 1:9) to give 2.57 g (82%) of **7**. Mp: 115–118°C.

^{1}H NMR (400 MHz; $CDCl_3$): δ 0.00 [9H, s, $Si(CH_3)_3$], 0.71 [9H, s, $C(CH_3)_3$], 0.81 [6H, t, CH_3], 0.98 [3H, t, CH_3], 1.25 [18H, s, $C(CH_3)_3$], 1.77 [4H, m, CH_2], 1.95 [4H, m, CH_2], 2.95, 4.28 [4H, 2d, $J = 12.8$ Hz, $ArCH_2Ar$], 3.53 [2H, t, OCH_2], 3.59 [2H, t, OCH_2], 3.88 [4H, m, OCH_2], 3.02, 4.32 [4H, 2d, $J = 13.0$ Hz, $ArCH_2Ar$], 6.16 [2H, s, ArH], 6.36 [2H, s, ArH], 6.94 [2H, d, $J = 2.1$ Hz, ArH], 7.00 [2H, d, $J = 2.1$ Hz, ArH].

^{13}C-NMR: δ (100 MHz) 0.02, 9.86, 10.69, 10.84, 14.09, 22.65, 23.06, 23.38, 30.83, 31.22, 31.58, 31.67, 76.28, 77.00, 77.64, 106, 116.43, 124.56, 125.29, 126.06, 131.47, 131.95, 133.57, 134.88, 136.03, 144.14, 144.67, 149.73, 152.77, 154.89, 158.21.

M/Z (FD) 856 (M^+, 100%).

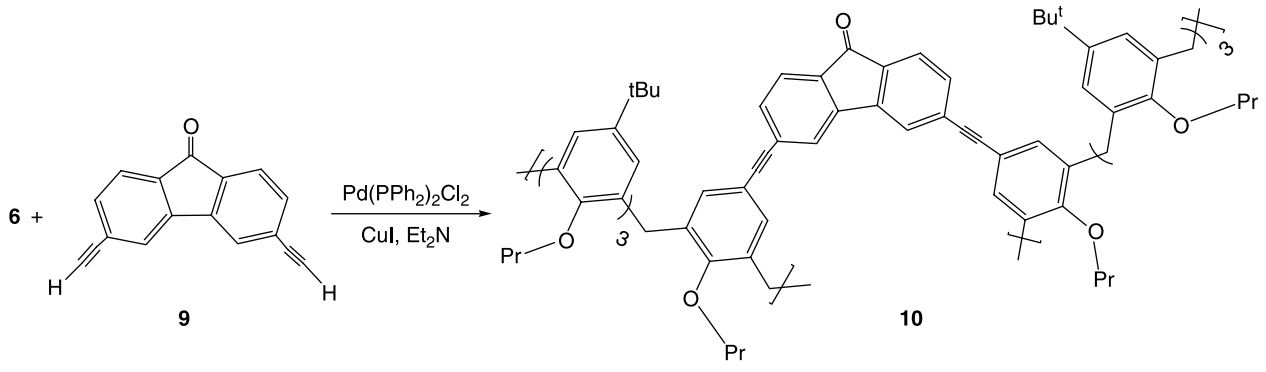
DOUBLE CALIX[4]ARENE **10**

A slurry of **7** (1.79 g, 2.1 mmol), 3,6-dibromo-*9H*-fluorene-9-on **8** (0.265 g, 1 mmol), $(Ph_3P)_2PdCl_2$ (0.028 g, 0.04 mmol), and Et_3N (50 ml), in dry DMF (50 ml) was stirred for 1 h at r.t. Then CuI (0.015 g, 0.08 mmol) was added and the mixture was stirred under N_2 for 24 h at 80°C. The reaction mixture was diluted with water (500 ml), and then extracted with dichloromethane. The extract was washed with HCl (10%), saturated $NaHCO_3$ and brine. Then, it was evaporated and purified by column chromatography (silica gel/ CH_2Cl_2: *n*-hexane 1:4) to give 0.99 g (25%) of **10**.

According to Scheme 3

DOUBLE CALIX[4]ARENE **10**

A slurry of **6** (1.86 g, 2.1 mmol), **9** (0.228 g, 1 mmol), $(Ph_3P)_2PdCl_2$ (0.028 g, 0.04 mmol), and Et_3N (50 ml), in dry DMF (50 ml) was stirred for 1 h at r.t. Then CuI (0.015 g, 0.08 mmol) was added and the mixture was



SCHEME 3 Synthesis of the double calix[4]arene **10**.

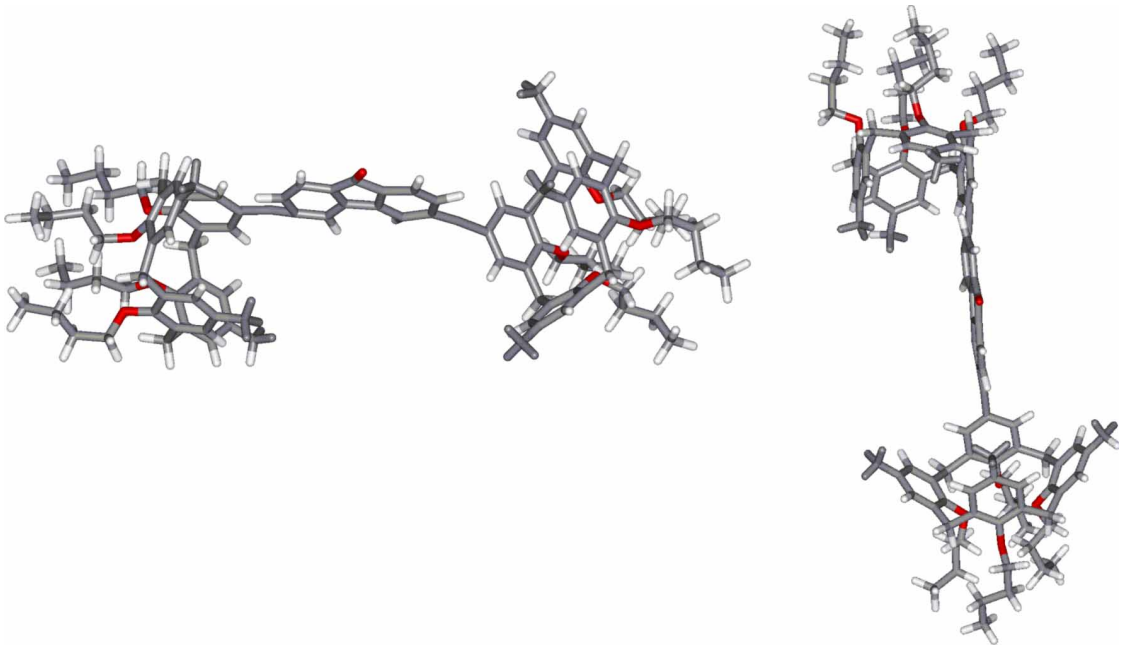


FIGURE 1 The structure of double calix[4]arene **10** (side view and top view) (MacroModel 7.0, Amber*, water, 1000 steps).

stirred under N_2 for 48 h at 80°C. The reaction mixture was diluted with water (500 ml), and then extracted with dichloromethane. The extract was washed with HCl (10%), saturated $NaHCO_3$ and brine. Then, it was evaporated and purified by column chromatography (silica gel/CH_2Cl_2: *n*-hexane 1:4) to give 1.34 g (38%) of **10**. Mp: 160–165°C.

^{1}H-NMR ($CDCl_3$): δ 0.78 [18H, t, $(CH_3)_3$], 0.86 [6H, t, CH_3], 0.93 [12H, t, CH_3], 1.09 [6H, s, CH_3], 1.37 [36H, s, $C(CH_3)_3$], 1.88–1.94 [8H, m, CH_2], 2.05 [8H, m, CH_2], 3.12, 4.43 [8H, 2d, $J = 13.0$ Hz, $ArCH_2Ar$], 3.13, 4.44 [8H, 2d, $J = 12$ Hz, $ArCH_2Ar$], 6.58 [4H, s, ArH], 7.07 [4H, d, $J = 2.2$ Hz, ArH], 7.11 [4H, d, $J = 2.2$ Hz, ArH], 7.20 [2H, d, $J = 7.7$ Hz, ArH], 7.40 [2H, s, ArH], 7.56 [2H, d, $J = 7.7$ Hz, ArH].

^{13}C-NMR (100 MHz): δ 9.64, 10.68, 10.80, 23.12, 23.43, 23.60, 31.05, 31.34, 31.77, 33.56, 34.13, 76.38, 77.00, 77.64, 87.23, 25.21, 115.84, 122.74, 124.09, 124.62, 125.26, 126.20, 130.76, 131.49, 132.17, 133.21, 134.26, 134.72, 136.03, 143.79, 144.35, 144.76, 152.99, 154.91, 156.19, 192.13.

MS (MALDI—TOF): M/Z: 1746.512. Anal. Calcd for $C_{121}H_{148}O_9$: C, 83.21%; H, 8.54%, Found C, 83.63%, H, 8.79%.

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