Syntheses of 6-Amino-1,3-benzodioxin and Its *p*-Arylazo-Substituted Calix[4]arenes

Mei-ling Yeh, Fa-shin Tang, Shu-ling Chen, Wen-chin Liu, and Lee-gin Lin*

Institute of Applied Chemistry, Chinese Culture University, Taipei, Taiwan, 11114, R. O. C.

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The *p*-arylazo-substituted calix[4]arenes were synthesized by a diazo-coupling reaction between calix[4]arene and the diazonium salt of 6-amino-1,3-benzodioxin. The monoarylazo-, 1,2-diarylazo-, 1,3-diarylazo-, triarylazo-, and tetraarylazo-*para*-substituted calix[4]arenes were isolated and characterized by spectral methods. 6-Amino-1,3-benzodioxin was prepared by palladium metal reduction of 6-nitro-1,3-benzodioxin.

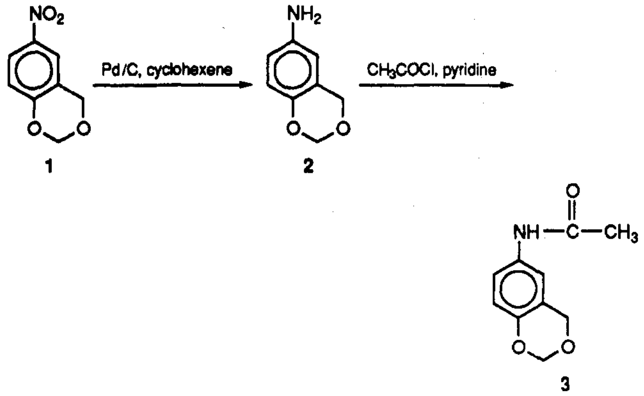
Introduction

Cyclic phenol–formaldehyde resins, known as calixarenes, contain a molecular cavity and are able to occlude a small organic molecule to form a host–guest complex.[1] This host–guest complexation phenomenon has attracted considerable attention in the context of enzyme mimic studies.[2]

The dimensions of the calixarene's cavity are governed by three factors. The diameter of the cavity is controlled by the number of units in the cyclic array. The depth of the cavity is controlled by the various substituents at the *para*-position, while the shape of the cavity is controlled by the conformational behavior of the calixarene itself. These factors play important roles in the host–guest complex interaction, and the methods of controlling these factors have been extensively studied.[3] However, reported studies have focused on the symmetrical calixarenes, and have rarely mentioned calixarenes with asymmetrical para-substitution. In this paper, we report the synthesis and the ^{1}H-NMR behavior of a complete set of *p*-(arylazo)-calix[4]arenes.

Results and Discussion

Synthesis of 6-Amino-1,3-benzodioxin (2). In our earlier studies of the condensation of para-substituted phenols with paraformaldehyde under acidic conditions, we observed that 6-amino-1,3-benzodioxin (2) was not produced by a direct condensation of *p*-aminophenol and paraformaldehyde.[4] Compound 2 was prepared by reducing the nitro group of the corresponding 6-nitro-1,3-benzodioxin (1). Palladium on charcoal and cyclohexene[5] gave 2 in quantitative yield. However, an orange color developed due to oxidation during the workup procedure and the final isolated yield was only 45%. When pure 2 was briefly exposed to air, a light orange color appeared on the crystal surfaces, and inconsistent elemental analysis data resulted. Acetylation of 2 was carried out to prevent the oxidation, and the elemental analysis of acetylated compound 3 showed acceptable values.



Synthesis of Tetrakis(arylazo)-Substituted Calix[4]arene 4 and Tris(arylazo)-Substituted Calix[4]arene 5. The diazo-coupling between *p*-carboxybenzenediazonium salt and calix[4]arene was reported to proceed in quantitative yield by Morita and Taniguchi *et al.*[6] The diazo-coupling reaction between the diazonium salt of 2 and calix[4]arene was attempted under modified conditions, and a large amount of brownish solid resulted. The ^{1}H-NMR spectrum indicated that the major component of this brownish solid was tetrakis(arylazo)-substituted compound 4. Purification of 4 was achieved by treating the product mixture with various organic solvents which left pure 4 as a bright yellow powder. The washing solution, which contained another compound, was concentrated and recrystallized from $CHCl_3$ and *n*-hexane to give a small amount of brown tris(arylazo)-substituted 5.

The isolated yields of compounds 4 and 5 varied in this diazo-coupling reaction, but 5 was always produced in some small amount. Attempts to prepare a substantial amount of 5 by modifying the reaction conditions resulted in complex product mixtures, and compound 5 never appeared as a major product.

Synthesis of Monoarylazo-Substituted Calix[4]arene 8. If the amount of diazonium salt 2 was reduced to one mol equiv and the addition of reactants was reversed in the diazo-coupling reaction, then compound 8 and three other minor products were produced. The TLC analysis

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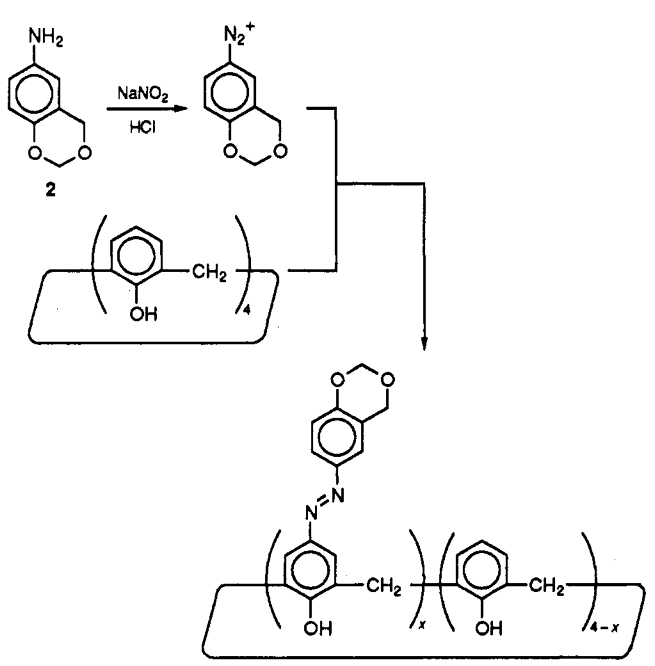

4: *x* = 4, tetrakis(arylazo)-
5: *x* = 3, tris(arylazo)-
6: *x* = 2, 1, 2-bis(arylazo)-
7: *x* = 2, 1, 3-bis(arylazo)-
8: *x* = 1, monoarylazo-

indicated that one of the minor products was tris(arylazo) compound **5**, while the other two components, discussed in the next section, were compounds **6** and **7**. Compound **8** was obtained in 40% yield by careful control of the reaction conditions; if the reaction conditions were altered, either a large amount of the starting material was recovered or the amount of the three other minor components was increased. Both situations increased the difficulty of separation and also reduced the final isolated yield of **8**.

Synthesis of 1,2-Bis(arylazo)-Substituted Calix[4]-arene 6 and 1,3-Bis(arylazo)-Substituted Calix[4]-arene 7. Compounds **6** and **7**, which had R_f values between those of compounds **5** and **8**, were both bis(arylazo)-substituted calix[4]arenes. Those compounds were prepared in a manner similar to compound **8**, the difference being the use of double the amount of diazonium salt **2**. Three major products, compounds **5–7**, were afforded and were separated by chromatography. Compound **5** was easy to isolate from the product mixtures, but the separation of compounds **6** and **7** was difficult, as their R_f values differed only slightly. Therefore, the isolated yields of compounds **6** and **7** were only 19 and 8%, respectively.

The final yields of **6** and **7** improved by replacing calix[4]arene with the monoarylazo-substituted compound **8**. Through such replacement, not only were the isolated yields of **6** and **7** increased to 32 and 16%, respectively, but the formation of compound **5** was reduced. The final yields of compounds **6** and **7** in both coupling reactions approximated a 2:1 ratio. This result suggested that the diazonium salt was an excellent electrophile and would attack any available position on the calix[4]arene to yield the corresponding arylazo-substituted products without being affected by steric hindrance.

NMR Behavior of Five Arylazo Compounds (4–8). Gutsche analyzed the four ideal conformations of *p-tert*-butylcalix[4]arene and suggested a distinctive ^{1}H-NMR spectral pattern for each conformer.[7] A distinctive ^{1}H-NMR spectral pattern was also expected for the five arylazo compounds when in a particular conformation. The five arylazo compounds all possess four free phenolic hydroxy groups and are expected to exist in the most-stable "cone" conformation. Additionally, the different numbers of *p*-substituents produce different magnetic environments in these compounds, and the methylene hydrogens are expected to display different ^{1}H-NMR spectral signal patterns for each arylazo compound.

Table 1. The ^{1}H-NMR Spectral Pattern for Calix[4]arenes' Methylene Hydrogens with Different Numbers of Para-Substituents

para-substitution	^{1}H-NMR spectral pattern for calix[4]arenes' methylene hydrogens
tetra	one pair of doublets
tri	two pairs of doublets (ratio 1:1)
1,2-di	three pairs of doublets (ratio 1:2:1)
1,3-di	one pair of doublets
mono	two pairs of doublets (ratio 1:1)

The structure of each arylazo compound was assigned based on the ^{1}H NMR spectral pattern in the aromatic region. The calix[4]arenes' methylene hydrogens, however, always appeared as two broad signals at room temperature. When the spectra were measured at −20 °C, the broad signals became sharper and a splitting pattern appeared. Arylazo compounds **4** and **7**, the symmetrical compounds, displayed one pair of doublets; compounds **5** and **8** displayed two pairs of doublets with a ratio of 1:1, while compound **6** displayed three pairs of doublets with a peak area ratio of 1:2:1. Pertinent regions of the low-temperature ^{1}H-NMR spectra are shown in Figure 1. Theoretically, the ^{1}H-NMR methylene spectral patterns of all *para*-substituted calix[4]arenes, in the ideal cone conformation, will be analogous to those of these five arylazo compounds, as shown in Table 1.

Experimental Section

All reagents were obtained from Merck Chemical Co. and used without further purification. Melting points were taken in capillary tubes on a Mel-Temp apparatus (Laboratory Devices Cambridge, MA) and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian Gemini 200 spectrometer. Chemical shifts are reported as δ values in ppm relative to TMS (δ 0.0) as an internal standard. FAB-MS spectra were taken on a JEOL JMS-HX 110 mass spectrometer, and EI-MS spectra were taken on a Finnigan MAT TSQ-46C GS/MS/MS/DS spectrometer. Elemental analyses were taken on a Perkin-Elmer 240C analyzer. Column chromatographic separations were performed with Merck Silica gel (230–400 mesh ASTM) on columns of 25 mm diameter filled to a height of 150 mm. TLC analyses were carried out on Merck aluminum-backed silica gel 60 F_{254} plates (absorbant thickness 0.2 mm).

6-Nitro-1,3-benzodioxin (1). A slurry of 1.39 g (10 mmol) of *p*-nitrophenol, 3.00 g (100 mmol) of formaldehyde, and 0.19 g (1.00 mmol) of *p*-toluenesulfonic acid in 50 mL of toluene was refluxed for 4 h. The toluene was removed by evaporation, and the residue was treated with CH_3OH to produce a pale yellow solid. Recrystallization from $CHCl_3$ and CH_3OH afforded 1.92 g (84%) of light yellow needle-like crystals: mp 146–147 °C; ^{1}H-NMR ($CDCl_3$) δ 8.03–8.07 (dd, 1H, Ar*H*), 7.90–7.91 (d, 1H, Ar*H*), 6.92–6.95 (d, 1H, Ar*H*), 5.30 (s, 2H, $ROCH_2OR$), 4.93 (s, 2H, $ArCH_2OR$); *m/e* 181 (M^+), 151 (M^+ − HCHO).

6-Amino-1,3-benzodioxin (2). A slurry of 3.70 g (20 mmol) of **1**, 0.90 g (0.85 mmol) of palladium on charcoal, and 8.00 g (100 mmol) of cyclohexene was refluxed in 200 mL of THF for 5 h under an argon atmosphere. The reaction mixture was filtered, and THF was removed to give an oily material. This oily material was dissolved in $CHCl_3$ and treated with *n*-hexane, and 1.35 g (45%) of colorless crystals was afforded after storage in the refrigerator for 4 h: mp 56–57 °C; IR ($CHCl_3$) 3300 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 6.66–6.70 (d, 1H, Ar*H*), 6.46–6.54 (dd, 1H, Ar*H*),

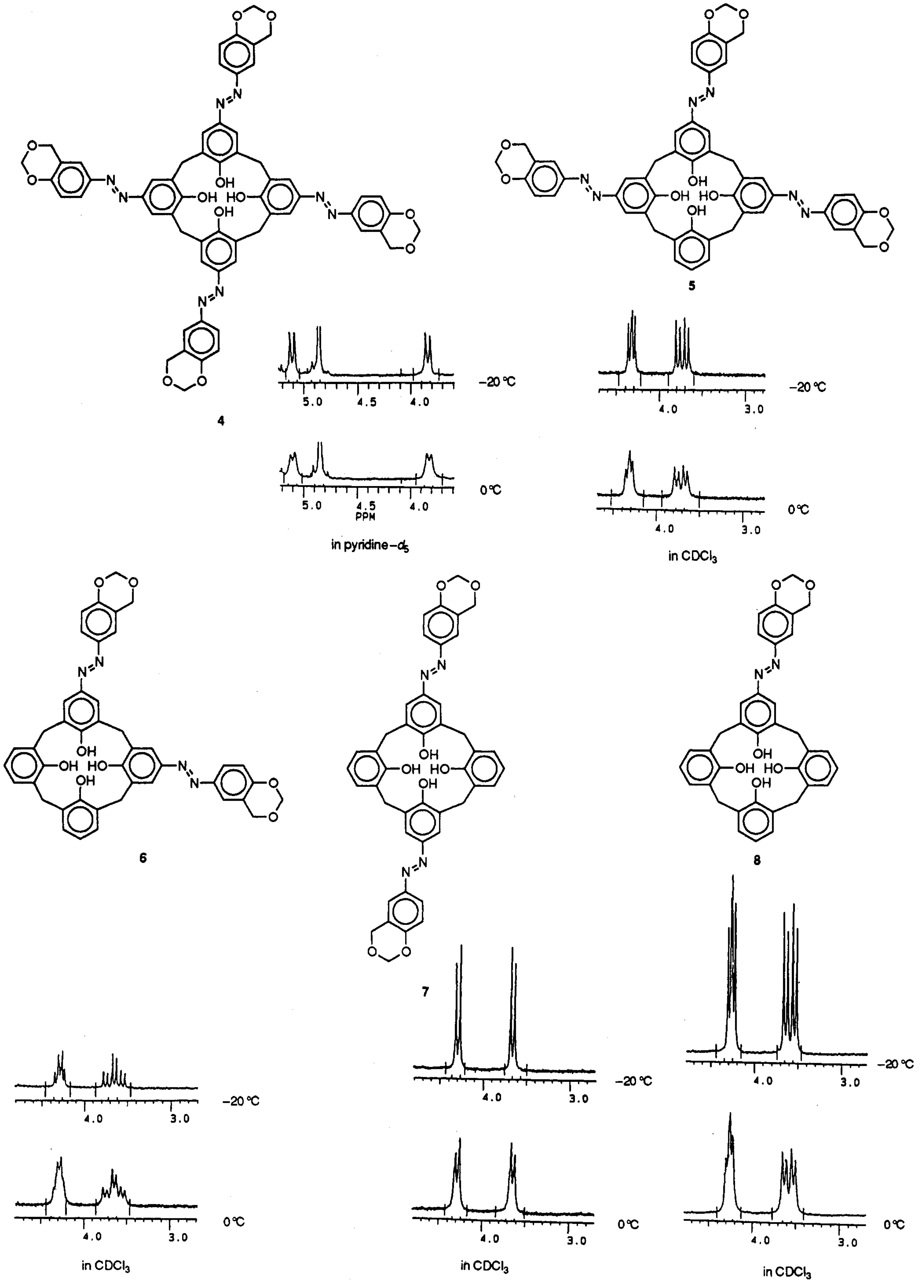

Figure 1. The low-temperature ^{1}H-NMR spectral signals of the calix[4]arenes' methylene hydrogens.

6.25–6.26 (d, 1H, Ar*H*), 5.15 (s, 2H, ROC*H*$_2$OR), 4.79 (s, 2H, ArC*H*$_2$OR); *m/e*: 151 (M$^+$), 121 (M$^+$ − HCHO). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 5.96; N, 9.27%. Found: C, 60.99; H, 5.72; N, 8.91%.

6-(*N*-Acetylamino)-1,3-benzodioxin (3). A slurry of 0.60 g (3.30 mmol) of 1, 0.14 g (0.13 mmol) of palladium on charcoal, 1.39 g (17 mmol) of cyclohexene, and 40 mL of THF was refluxed under an argon atmosphere for 5 h. The reaction mixture was filtered, and solvent was removed to give an yellow oily material. This residue was dissolved in 10 mL of pyridine, and 3 mL of acetyl chloride was added dropwise at ice bath temperature. The reaction mixture was stirred for 1 h, and poured into a large amount of diluted HCl. The organic compound was extracted with $CHCl_3$ twice, the extraction was concentrated and recrystallized from $CHCl_3$ and *n*-hexane to give 0.35 g (55%) of pale yellow crystals: mp 129–130 °C; ^{1}H-NMR ($CDCl_3$) δ 7.33 (d, 1H, Ar*H*), 7.32 (bs, 1H, ArN*H*Ac), 7.00–7.03 (dd, 1H, Ar*H*), 6.78–6.81 (d, 1H, Ar*H*), 5.20 (s, 2H, ROC*H*$_2$OR), 4.86 (s, 2H, ArC*H*$_2$OR), 2.29 (s, 3H, COC*H*$_3$); *m/e*: 193 (M$^+$), 163 (M$^+$ − HCHO). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.70; N, 7.25%. Found: C, 62.12; H, 5.72; N, 7.26%.

5,11,17,23-Tetrakis[(1,3-benzodioxin-6-yl)azo]-25,26,27,28-tetrahydroxycalix[4]arene (4), 5,11,17-Tris[(1,3-benzodioxin-6-yl)azo]-25,26,27,28-tetrahydroxycalix[4]arene (5). A solution of 0.21 g (0.50 mmol) of calix[4]arene in 10 mL of pyridine and 20 mL of THF was added dropwise into a cold solution (ice bath temperature) of 0.38 g (1.25 mmol) of 2 and 0.22 g (3.00 mmol) of $NaNO_2$ in 40 mL of 2 N HCl to give a dark orange suspension. After being allowed to stir for 3 h, the reaction mixture was poured into water to precipitate a brown solid. The resulting brown precipitate was collected by filtration and washed with $CHCl_3$ and acetone to afford 0.38 g (71%) of bright yellow solid 4: mp 320 °C dec; ^{1}H-NMR (pyridine-d_5) δ 8.17 (s, 8H, Ar*H*), 7.70–7.74 (dd, 4H, Ar′*H*), 7.43–7.44 (d, 4H, Ar′*H*), 6.96–6.99 (d, 4H, Ar′*H*), 5.26 (s, 8H, ROC*H*$_2$OR), 5.08–5.12 (bd, 4H, ArC*H*$_2$Ar), 4.85 (s, 8H, ArC*H*$_2$OR), 3.81–3.84 (bd, 4H, ArC*H*$_2$Ar); FAB-MS *m/e* 1073 (M$^+$ + 1). Anal. Calcd for $C_{60}H_{46}N_8O_{12}$: C, 67.16; H, 4.29; N, 10.45. Found: C, 67.12; H, 4.66; N, 10.15%.

The washing solutions were collected, and the solvent was evaporated to leave a brown residue. Further recrystallization from $CHCl_3$ and *n*-hexane yielded 0.06 g (13%) of compound 5 as brown solid: mp 275 °C dec; ^{1}H-NMR ($CDCl_3$) δ 10.27 (bs, 4H, ArO*H*), 6.77–7.72 (m, 18H, Ar*H*), 5.26 (s, 6H, ROC*H*$_2$OR), 4.93 (s, 6H, ArC*H*$_2$OR), 4.28–4.36 (bd, 4H, ArC*H*$_2$Ar), 3.64–3.79 (bd, 4H, ArC*H*$_2$Ar); FAB-MS *m/e* 911 (M$^+$ + 1). Anal. Calcd for $C_{52}H_{42}N_6O_{10}$: C, 68.57; H, 4.62; N, 9.23%. Found: C, 68.51; H, 4.65; N, 8.94%.

5,11-Bis[(1,3-benzodioxin-6-yl)azo]-25,26,27,28-tetrahydroxycalix[4]arene (6), 5,17-Bis[(1,3-benzodioxin-6-yl)azo]-25,26,27,28-tetrahydroxycalix[4]arene (7). Method A: A solution of 0.15 g (1.00 mmol) of 2 in 30 mL of 2 N HCl was chilled in an ice bath, and 2 mL of $NaNO_2$ (0.11 g, 1.50 mmol) was added to produce a diazonium salt. To this solution were added 0.21 g (0.50 mmol) of calix[4]arene in 10 mL of pyridine and 20 mL of THF in one portion to give an orange-colored suspension. The whole reaction mixture was allowed to stir for 10 min, and the orange-colored solid was collected by filtration. The TLC analysis indicated three major components were present in the product mixtures. Further separation by column chromatography ($CHCl_3$/*n*-hexane: 1/3) yielded the first eluted compound 6 as an orange solid, weight 0.07 g (19%): mp 239–241 °C; ^{1}H-NMR ($CDCl_3$) δ 10.24 (bs, 4H, ArO*H*), 6.72–7.72 (m, 16H, Ar*H*), 5.27 (s, 4H, ROC*H*$_2$OR), 4.95 (s, 4H, ArC*H*$_2$OR), 4.23–4.35 (bd, 4H, ArC*H*$_2$Ar), 3.53–3.78 (bd, 4H, ArC*H*$_2$Ar); FAB-MS *m/e* 749 (M$^+$ + 1). Anal. Calcd for $C_{44}H_{36}N_4O_8$: C, 70.59; H, 4.81; N, 7.49%. Found: C, 70.12; H, 5.01; N, 7.35%.

The second eluted product 7 was a light orange solid, weight 0.03 g (8%): mp 268–269 °C dec; ^{1}H-NMR ($CDCl_3$) δ 10.22 (bs, 4H, ArO*H*), 6.75–7.63 (m, 16H, Ar*H*), 5.26 (s, 4H, ROC*H*$_2$OR), 4.93 (s, 4H, ArC*H*$_2$OR), 4.26–4.31 (bd, 4H, ArC*H*$_2$Ar), 3.63–3.67 (bd, 4H, ArC*H*$_2$Ar); FAB-MS *m/e* 749 (M$^+$ + 1). Anal. Calcd for $C_{44}H_{36}N_4O_8$: C, 70.59; H, 4.81; N, 7.49%. Calcd for $C_{44}H_{36}N_4O_8 \cdot CHCl_3$: C, 62.25; H, 4.27; N, 6.46%. Found: C, 62.55; H, 4.42; N, 6.81%.

The third component weighing 0.09 g (20%) was the orange compound 5.

Method B: A solution of 0.04 g (0.25 mmol) of 2 in 10 mL of 2 N HCl was chilled in an ice bath, and 2 mL of $NaNO_2$ (0.05 g, 0.70 mmol) was added to produce a diazonium salt solution. To this solution were added 0.15 g (0.25 mmol) of 8 in 5 mL of pyridine and 10 mL of THF to produce a deep orange suspension. The reaction mixture was stirred for 1 min, and water was added to precipitate an orange solid. The solid was collected and separated by column chromatography ($CHCl_3$/*n*-hexane: 1/3) to afford 0.06 g (32%) of compound 6, 0.03 g (16%) of compound 7, and 0.04 g (18%) of compound 5.

5-[(1,3-Benzodioxin-6-yl)azo]-25,26,27,28-tetrahydroxycalix[4]arene (8). A solution of 0.08 g (0.5 mmol) of 2 in 20 mL of 2 N HCl was chilled in an ice bath, and 2 mL of $NaNO_3$ (0.11 g, 1.5 mmol) was added to produce a diazonium salt. To this diazonium solution were added 0.21 g (0.5 mmol) of calix[4]arene in 10 mL of pyridine and 20 mL of THF in one portion to give an orange suspension. The reaction mixture was allowed to stir for 1 min, and solid was collected by filtration. Further separation by column chromatography ($CHCl_3$/*n*-hexane: 4/1) afforded 0.13 g (44%) of an orange solid: mp 251–253 °C; ^{1}H-NMR ($CDCl_3$) δ 10.21 (bs, 4H, ArO*H*), 6.69–7.71 (m, 14H, Ar*H*), 5.28 (s, 2H, ROC*H*$_2$OR), 4.95 (s, 2H, ArC*H*$_2$OR), 4.23–4.31 (bd, 4H, ArC*H*$_2$Ar), 3.52–3.67 (bd, 4H, ArC*H*$_2$Ar); FAB-MS *m/e* 587 (M$^+$ + 1). Anal. Calcd for $C_{36}H_{30}N_2O_6$: C, 73.72; H, 5.12; N, 4.78%. Calcd for $C_{36}H_{30}N_2O_6 \cdot H_2O$: C, 71.52; H, 5.29; N, 4.63%. Found: C, 72.20; H, 5.14; N, 4.59%.

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