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SYNTHESIS, MOLECULAR STRUCTURE, AND OXIDATION BEHAVIOR OF EXHAUSTIVELY METHYLATED AZACALIX[6]ARENE

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Abstract – The molecular structure and oxidation behavior of an exhaustively methylated azacalix[6]arene have been investigated with the intention of developing high-spin materials. The azacalix[6]arene adopted a distorted 1,3-alternate conformation in the solid state, whereas the conformation was highly flexible in solution at ambient temperature. As a result of the flexible structure in solution, the decreased stability of the corresponding cation radicals was observed, as compared to that of the smaller inflexible homologue yielding stable cation radicals. Both the conformational inflexibility and the steric protection of reactive sites were found to be crucial for stabilizing the oxidized species of this molecular system.

INTRODUCTION

Azacalixarene is a macrocyclic *m*-phenylene oligomer connected with nitrogen atoms and has recently emerged as a new family of calixarene.[1] Azacalixarene has attracted considerable attention as a building block for supramolecules as well as electronic and/or magnetic materials because the nitrogen bridges can act as hydrogen-bonding, electron-donating, and spin-bearing sites. In the magnetic materials chemistry, *m*-phenylene moiety is a promising scaffold to construct an organic magnet on the basis of its π-topological symmetry.[2] Accordingly, azacalixarenes consisting of *m*-phenylene and nitrogen bridges are expected to give a high-spin ground state upon oxidation. In accordance with this expectation, we have very recently reported that the dication radical of azacalix[4]arene **1** exists in a triplet ground state.[3] This foregoing finding in **1** prompted us to study its homologue with larger ring size to develop organic magnetic materials in higher spin states. In this study, we have prepared exhaustively methylated

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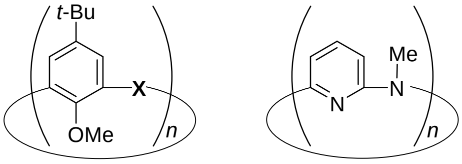
This paper is dedicated to Professor Dr. Ryoji Noyori on the occasion of his 70th birthday.

azacalix[6]arene **2**, which is anticipated to yield the oxidized species in the spin states of up to $S = 3$. Here we report the molecular structure and the oxidation behavior of **2**, as well as the structural requirements for constructing the stable radical species of azacalixarene.

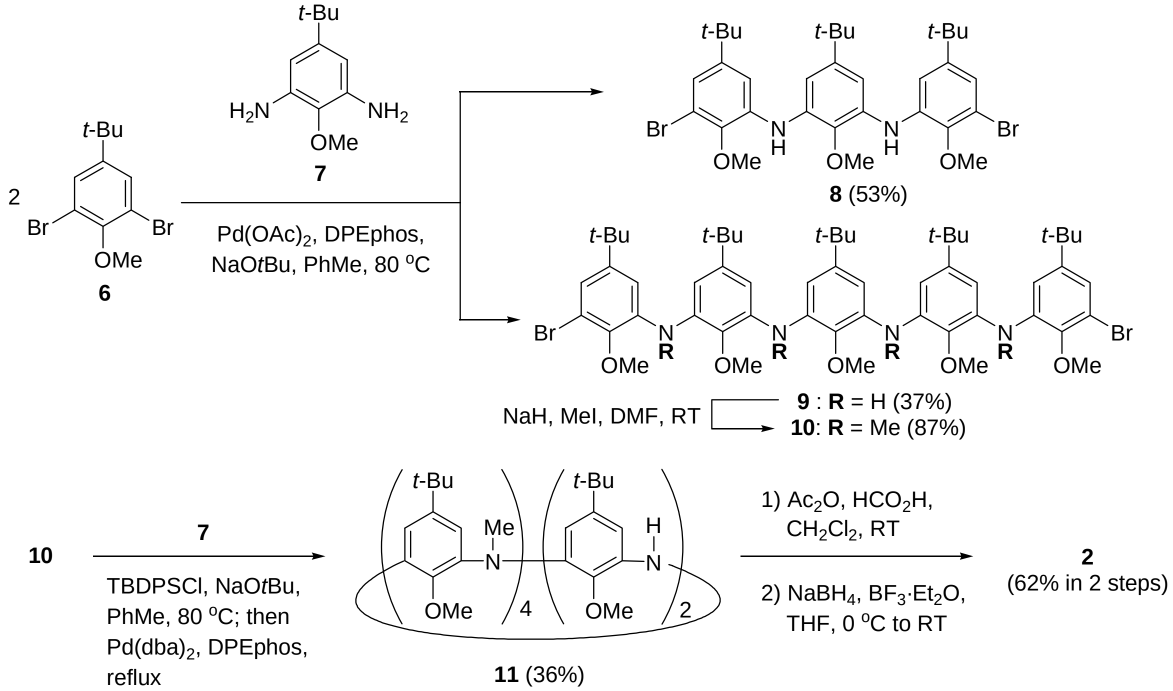


1: **X** = NMe, *n* = 4
2: **X** = NMe, *n* = 6
3: **X** = CH_2, *n* = 6

4: *n* = 5
5: *n* = 6

RESULTS AND DISCUSSION

Synthesis. Exhaustively methylated azacalix[6]arene **2** was synthesized by applying a fragment coupling approach shown in Scheme 1. Buchwald-Hartwig aryl amination[4] of dibromoanisole **6** with phenylenediamine **7** gave an easily separable mixture of trimer **8**[5] and pentamer **9**. *N*-Methylation of pentamer **9** proceeded smoothly with NaH/MeI to afford fully *N*-methylated pentamer **10**. To the ring-closing reaction of **10** with **7**, Buchwald-Hartwig cross-coupling reaction using the *in situ* temporal *N*-silylation of **7** was applied,[6] yielding regioselectively *N*-methylated azacalix[6]arene **11**. However, *N*-methylation of **11** with MeI in the presence of base failed to give exhaustively methylated azacalix[6]arene **2** as the final product. After our numerous attempts, azacalix[6]arene **2** was obtained by



Scheme 1. Synthesis of exhaustively methylated azacalix[6]arene **2**. DPEphos = Bis[2-(diphenylphosphino)phenyl] ether. TBDPSCl = *tert*-Butyldiphenylsilyl chloride.

formylation of **11** and the subsequent BH_3 reduction. It should be noted that this synthetic procedure in 5 steps is essential to improve the overall yield because the apparently effective Pd(0)-catalyzed cross-coupling reaction of *N*-methylated pentamer **10** and 5-*tert*-butyl-2-methoxy-*N,N'*-dimethyl-1,3-phenylenediamine leads to a poor yield of azacalix[6]arene **2** because of the occurrence of β-elimination reaction as an undesirable side-reaction.[6]

Molecular structure. A single crystal of azacalix[6]arene **2** was obtained by slow crystallization from a toluene/ethanol solution, and X-ray crystallographic analysis of **2** was carried out. Azacalix[6]arene **2** crystallizes with one molecule of toluene which is located outside the cavity (Figure 1). As compared with azacalix[6]pyridine **5**,[7] which adopts a roughly triangular shape with almost planarity, azacalix[6]arene **2** possesses a distorted 1,3-alternate conformation, where the two anisole rings (A and C) are oriented toward the same direction with respect to the mean plane defined by all the bridging nitrogen atoms. Five methyl groups on the bridging nitrogens point outward the cavity, and the remaining one (C67) inward. In other words, azacalix[6]arene **2** forms a closed cavity by the self-inclusion of one *N*-methyl group, which interacts with the anisole ring (E) via intramolecular CH/π interaction (C(67)…the centroid of ring E, 3.81 Å; C(67)-H…the centroid of ring E, 3.23 Å and 120°), as shown in Figure 1b. Similar self-inclusion of *N*-methyl group was reported in azacalix[5]pyridine **4**,[8] though its almost planar conformation was much different from **2**.

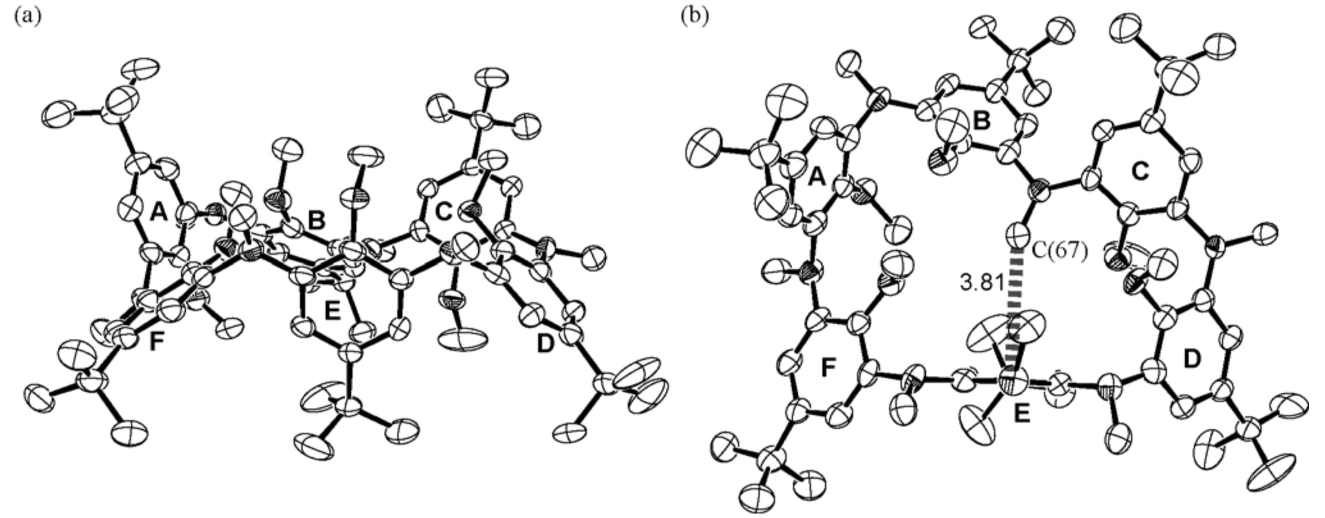


Figure 1. ORTEP[9] drawings of azacalix[6]arene **2**: side and top view (a and b, respectively). Hydrogen atoms and toluene are omitted for clarity. Number in panel (b) represents the distance (Å) of CH/π interaction between *N*-methyl group (C(67)) and the centroid of ring E.

To explore the conformation of **2** in solution, variable-temperature ^1H NMR was measured. Figure 2a shows the ^1H NMR spectrum of **2** in CD_2Cl_2 at room temperature, where four slightly broad singlet signals appear at δ 6.69, 3.19, 3.13, and 1.20 ppm for the aromatic, *N*-methyl, *O*-methyl, and *tert*-butyl

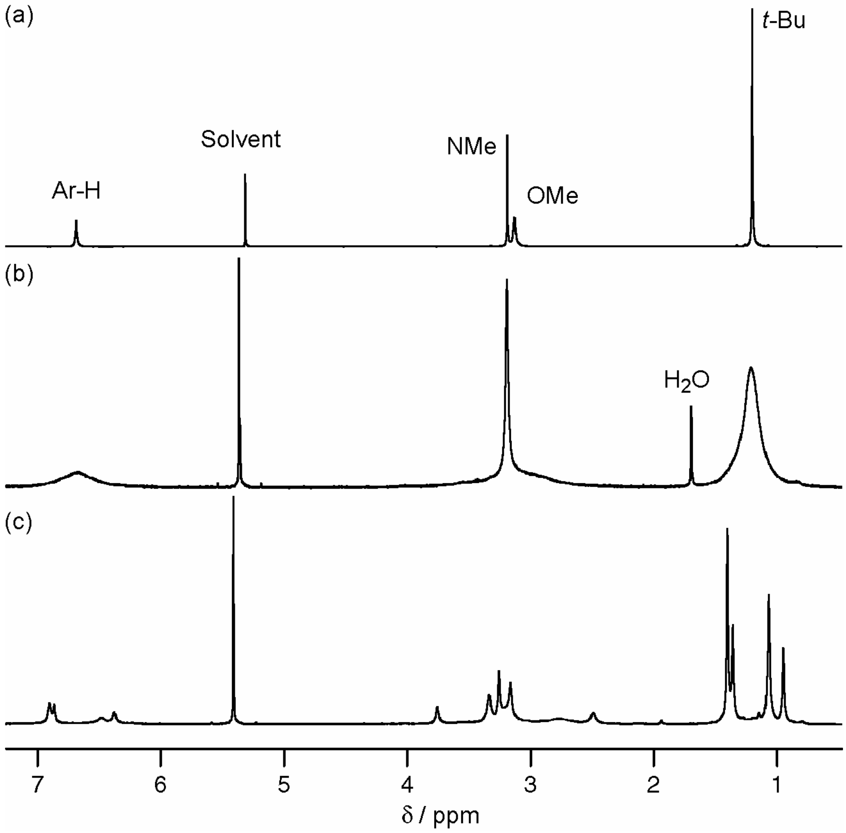


Figure 2. Variable-temperature ^{1}H NMR spectra of azacalix[6]arene **2** in CD_2Cl_2 at 25 °C (a), –35 °C (b), and –80 °C (c).

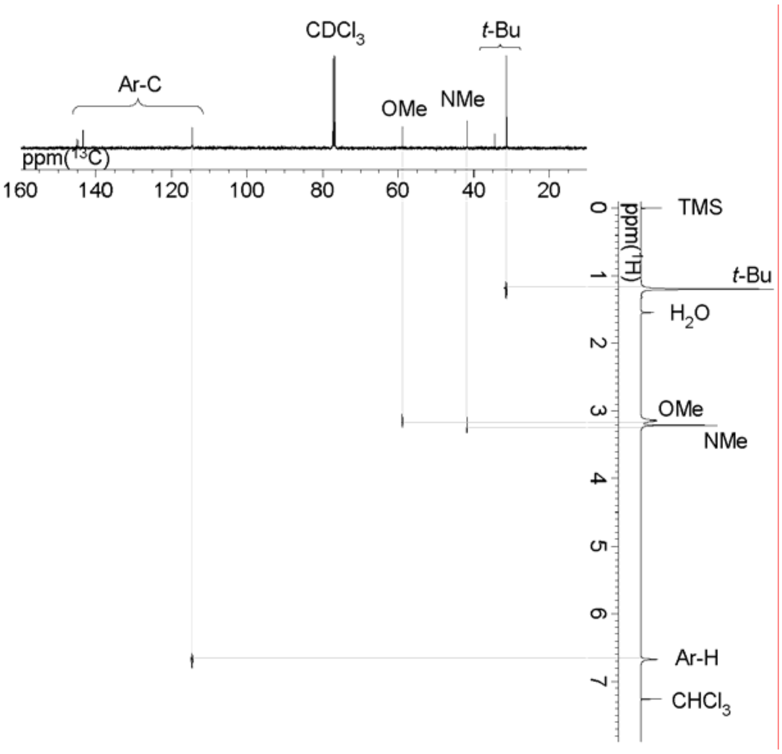


Figure 3. CH COSY spectrum of azacalix[6]arene **2** in $CDCl_3$ at room temperature.

hydrogens, respectively, as verified by the CH COSY spectrum (Figure 3). As the temperature was lowered, all the signals became further broadened and then split below –35 °C (Figures 2b and c). The observed changes in the spectra clearly indicates that azacalix[6]arene **2** is conformationally flexible at room temperature. However, the coalescence temperature of about –35 °C is higher than that of carbocyclic analogue **3**, which is reported to be too flexible to suppress the ring inversion even at –80 °C. Sluggish ring inversion of azacalix[6]arene **2** would be attributable to the steric hindrance and/or electronic effect arising from the bridging methylamino groups.

Oxidation behavior. Electrochemical response of azacalix[6]arene **2** was investigated by means of cyclic voltammetry. Figures 4a and b display the cyclic voltammograms of **2** in CH_2Cl_2 containing 0.1 M *n*-Bu_4NClO_4 as supporting electrolyte. Three irreversible oxidation waves were observed at 0.25, 0.38, and 0.45 V (vs. Fc/Fc^+), demonstrating that azacalix[6]arene **2** formed no stable oxidized species. This oxidation behavior is quite different from that of the smaller homologue **1** (Figure 4c),[3] which shows two reversible oxidation waves corresponding to the stepwise oxidations to mono- and dication radicals. The observed difference in the oxidation behaviors of **1** and **2** can be explained by considering two structural factors such as 1) steric protection and 2) conformational inflexibility.

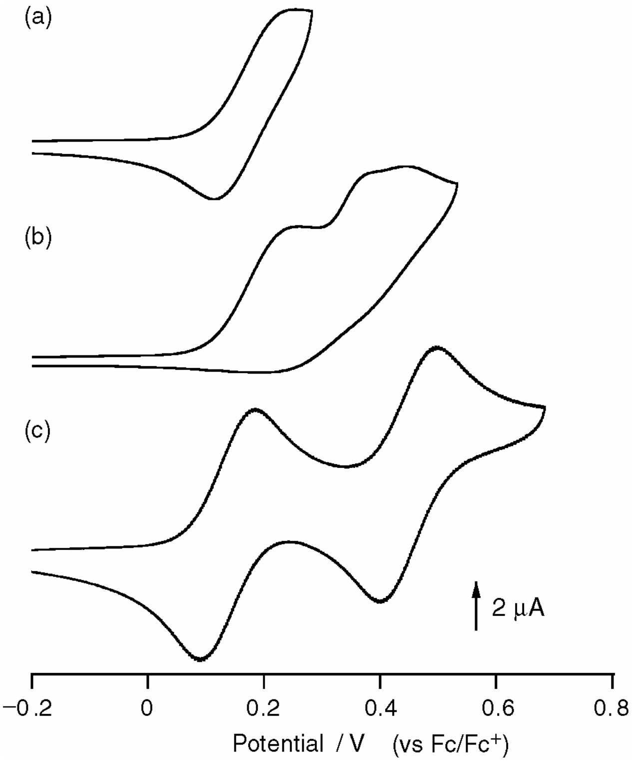


Figure 4. Cyclic voltammograms of azacalix[6]arene **2** (a and b) and azacalix[4]arene **1** (c) in CH_2Cl_2 containing 0.1 M *n*-Bu_4NClO_4 as supporting electrolyte. Scans were performed at room temperature and a rate of 100 mV sec^{-1}. Potentials were calibrated aganinst Fc/Fc^+.

Steric protection of reactive sites is significant for stabilizing organic radical molecules.[10] Our previous EPR study on azacalix[4]arene **1** demonstrated that the reactive sites with high spin densities were assigned to the bridging nitrogens and the aromatic carbons ortho to the nitrogen bridges.[3] As can be seen from the X-ray crystal structures of **1**[5] and **2** (Figure 1), their bridging nitrogen atoms are spatially shielded by the *N*-methyl groups and the adjacent aromatic rings. Besides, the reactive aromatic carbons are also protected by the *tert*-butyl groups located at the same aromatic rings. However, the steric protection in azacalix[6]arene **2** appears to be less effective than that of azacalix[4]arene **1** because of the lack of conforamational inflexibility, which is also crucial for retaining the steric protection and thus for stabilizing the oxidized species. As described above, azacalix[6]arene **2** is conformationally flexible at ambient temperature, whereas azacalix[4]arene **1** was reported to be inflexible even in solution.[11] Hence, the oxidized species of **1** are effectively stabilized by the steric protection of the reactive sites, but this is not the case for azacalix[6]arene **2**. Indeed, even monocation radical $\mathbf{2}^{\cdot+}$ was unstable in the electrochemical measurement. Free rotation around the C(sp^2)-N bond is ascribed to the observed difference in the stability of the cation radicals of **1** and **2**. This is consistent with our previous experimental fact that linear pentamer **10** with acyclic structure affords unstable dication radical.[3] Accordingly, it is reasonable to conclude that both steric protection and conformational inflexibility are essential for stabilizing the cation radicals of this molecular system.

CONCLUSION

In the present study, we have investigated the molecular structure and the oxidation behavior of azacalix[6]arene **2**, which is expected to exist in a high-spin ground state (up to $S = 3$) upon oxidation. Unlike our previously reported azacalix[4]arene **1**, the molecular structure of **2** was conformationally flexible in solution due to its larger annulated ring. As a result, the expected high spin states of the cation radicals of **2** could not be observed because of the instability of the oxidized species arising from the flexible molecular structure. However, it has been drawn from the present study that a synergetic effect of steric protection and conformational inflexibility is crucial for developing azacalixarene cation radicals in a high spin state.

EXPERIMENTAL

General. Melting points were determined on a Yanaco MP-J3 apparatus and are uncorrected. NMR spectra were recorded on a JEOL JNM-A500 instrument using tetramethylsilane (^{1}H NMR) and solvent resonance (^{13}C NMR) as internal standards. Electrochemical measurements were carried out on a BAS ALS600B using a platinum working electrode, a platinum counter electrode, and a silver reference electrode, and the potentials were calibrated against Fc/Fc$^+$. Infrared spectra were obtained on a Shimadzu

IRPrestige-21 spectrometer. Elemental analyses were conducted at the Microanalytical Centre, Kyoto University, Japan. Flash column chromatography were performed with Merck Kieselgel 60 or Kanto Chemical Silica gel 60N. Toluene and DMF were refluxed over and then distilled from CaH_2 under Ar before use. Compounds **6**[12] and **7**[13] were prepared according to the described procedure. Other chemicals were purchased from commercial suppliers and used as received.

***N,N'*-Bis[3-(3-bromo-5-*tert*-butyl-2-methoxyanilino)-5-*tert*-butyl-2-methoxyphenyl]-5-*tert*-butyl-2-methoxy-1,3-phenylenediamine (9)**. Compound **9** was obtained as a by-product when compound **8** was prepared by our described procedure.[5] A solution of **6** (6.57 g, 20.4 mmol), **7** (1.94 g, 9.97 mmol), $Pd(OAc)_2$ (119 mg, 0.53 mmol), bis[2-(diphenylphosphino)phenyl] ether (DPEphos) (403 mg, 0.748 mmol), and NaO*t*Bu (2.15 g, 22.3 mmol) in anhydrous toluene (60 mL) was stirred at 80 °C for 17 h under Ar. After cooling to rt, the reaction mixture was extracted with toluene and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over anhydrous K_2CO_3, filtered, and evaporated. Flash column chromatography on silica gel (hexane/CH_2Cl_2 = 2:1 then 1:2, v/v) gave **8** (3.58 g, 53%) and **9** (1.92 g, 37%). **9**: colorless solid, mp 234–235 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.48 (d, *J*=2.2 Hz, 2H, Ar-H), 7.19 (d, *J*=2.2 Hz, 2H, Ar-H), 7.15 (s, 2H, Ar-H), 7.07 (d, *J*=2.2 Hz, 2H, Ar-H), 7.04 (d, *J*=2.2 Hz, 2H, Ar-H), 6.56 (s, 2H, NH), 6.51 (s, 2H, NH), 3.87 (s, 6H, OMe), 3.82 (s, 3H, OMe), 3.80 (s, 6H, OMe), 1.34 (s, 9H, *tert*-Bu), 1.32 (s, 18H, *tert*-Bu), 1.31 (s, 18H, *tert*-Bu); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.8, 147.43, 147.36, 143.8, 137.0, 136.4, 136.2, 135.9, 135.6, 135.1, 120.8, 116.6, 112.6, 106.4, 106.0, 105.9, 60.2, 59.9, 59.8, 34.9, 34.8, 31.53, 31.51, 31.3; IR (KBr): 3405 ($\nu_{N\text{-}H}$) cm^{-1}; Anal. Calcd for $C_{55}H_{74}Br_2N_4O_5$: C, 64.07; H, 7.23; N, 5.43. Found: C, 64.29; H, 7.15; N, 5.39.

***N,N'*-Bis[3-(3-bromo-5-*tert*-butyl-2-methoxy-*N''*-methylanilino)-5-*tert*-butyl-2-methoxyphenyl]-5-*tert*-butyl-2-methoxy-*N,N'*-dimethyl-1,3-phenylenediamine (10)**. To a solution of **9** (516 mg, 0.500 mmol) in anhydrous DMF (5 mL) was added 60% NaH (206 mg, 5.15 mmol) at 0 °C under Ar. After stirring for 10 min, MeI (140 μL, 2.25 mmol) was added. Stirring was continued at rt overnight, and then Et_2O was added to the reaction mixture. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated. Flash column chromatography on silica gel (hexane/EtOAc = 19:1, v/v) gave **10** (472 mg, 87%) as colorless solid, mp 94–96 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.13 (d, *J*=2.3 Hz, 2H, Ar-H), 6.85 (d, *J*=2.3 Hz, 2H, Ar-H), 6.70 (d, *J*=2.4 Hz, 2H, Ar-H), 6.67 (s, 2H, Ar-H), 6.65 (d, *J*=2.4 Hz, 2H, Ar-H), 3.67 (s, 6H, OMe), 3.52 (s, 3H, OMe), 3.49 (s, 6H, OMe), 1.22 (s, 18H, *tert*-Bu), 1.20 (s, 9H, *tert*-Bu), 1.19 (s, 18H, *tert*-Bu); ^{13}C NMR: δ 147.8, 147.4, 145.9, 145.7, 144.8, 144.7, 144.4, 144.0, 143.7, 143.0, 122.9, 118.8, 117.8, 115.3, 115.1, 114.6, 59.8, 58.7, 58.6, 40.0, 39.6, 34.5, 31.4, 31.3, 31.2; Anal. Calcd for $C_{59}H_{82}Br_2N_4O_5$: C, 65.18; H, 7.60; N, 5.15. Found: C, 65.15; H, 7.70; N, 5.03.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-*N*,*N'*,*N''*,*N'''*-tetramethyl-2,8,14,20,26,32-hexaazacalix[6]arene (11). A solution of **7** (117 mg, 0.600 mmol), **10** (652 mg, 0.600 mmol), NaO*t*Bu (288 mg, 3.00 mmol), and *tert*-butyldiphenylsilyl chloride (TBDPSCl) (320 μL, 1.23 mmol) in anhydrous toluene (120 mL) was stirred at 80 °C under Ar. After stirring for 30 min, Pd(dba)$_2$ (172 mg, 0.3 mmol) and DPEphos (242 mg, 0.450 mmol) was added. The solution was heated under reflux for 9 h and then cooled to rt. The reaction mixture was passed through Celite and evaporated. Flash column chromatography on silica gel (hexane/CH_2Cl_2 = 1:1, v/v) and subsequent washing with Et_2O/MeOH gave **11** (239 mg, 36%) as colorless solid, mp > 300 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.11 (bs, 4H, Ar-H), 7.06 (d, *J*=2.1 Hz, 2H, Ar-H), 7.03 (bs, 2H, Ar-H), 6.82 (bs, 2H, Ar-H), 6.67 (bs, 2H, Ar-H), 6.12 (bs, 2H, NH), 3.48 (bs, 9H, OMe and NMe), 3.32 (bs, 6H, NMe), 3.27 (bs, 6H, OMe), 3.08 (bs, 6H, OMe), 2.27 (bs, 3H, OMe), 1.38 (bs, 27H, *tert*-Bu), 1.31 (s, 18H, *tert*-Bu), 1.10 (s, 9H, *tert*-Bu); ^{13}C NMR: δ 148.0, 146.6, 146.2, 146.1, 145.4, 145.1, 142.9, 142.2, 141.1, 138.4, 138.2, 136.5, 119.7, 115.8, 113.4, 110.4, 109.3, 101.4, 60.4, 60.0, 59.3, 58.8, 43.8, 42.9, 34.7, 34.6, 34.5, 31.5, 31.1; IR (KBr) 3362 ($\nu_{N\text{-}H}$) cm^{-1}; Anal. Calcd for $C_{70}H_{98}N_6O_6$: C, 75.10; H, 8.82; N, 7.51. Found: C, 74.89; H, 8.65; N, 7.51.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-*N*,*N'*,*N''*,*N'''*,*N''''*,*N'''''*-hexamethyl-2,8,14,20,26,32-hexaazacalix[6]arene (2). A solution of **11** (112 mg, 0.100 mmol), formic acid (1.0 mL), and acetic anhydride (2.5 mL) in CH_2Cl_2 (10 mL) was stirred at rt under Ar. After stirring for 24 h, the reaction mixture was poured into crashed ice. The mixture was basified to pH ~ 9 by $NaHCO_3$ powder, extracted with CH_2Cl_2, dried over $MgSO_4$, and evaporated. The crude formylated product was immediately used for the subsequent BH_3 reduction. To a suspension of sodium borohydride (15 mg, 0.40 mmol) in THF (10 mL) was added boron trifluoride diethyl etherate (65 μL, 0.53 mmol). The mixture was cooled to 0 °C, and a solution of the crude formylated product in THF (6 mL) was added. After stirring for 16 h at rt, crashed ice was added, extracted with Et_2O, washed with brine twice, dried over $MgSO_4$, and evaporated. Flash column chromatography on silica gel (hexane/CH_2Cl_2 = 2:1 to 1:1, v/v) gave **2** (71 mg, 62%) as colorless solid, mp 271−272 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.68 (bs, 12H, Ar-H), 3.21 (s, 18H, NMe), 3.14 (bs, 18H, OMe), 1.20 (s, 54H, *tert*-Bu); ^{13}C NMR: δ 145.2, 144.7, 143.5, 114.4, 58.8, 41.7, 34.4, 31.4; Anal. Calcd for $C_{72}H_{102}N_6O_6$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.06; H, 8.99; N, 7.29.

Crystallography. The X-ray crystallographic data was collected on a Rigaku RAXIS RAPID imaging plate. The crystal structure was solved by direct methods and refined by full-matrix least squares. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using the riding model. All calculations were performed using a crystallographic software package, CrystalStructure version 3.8.0. Crystal data for **2**•toluene ($C_{79}H_{110}N_6O_6$): M_r = 1239.77, triclinic, space group P-1, a = 9.7866(8) Å, b = 16.042(1) Å, c = 23.963(2) Å, α = 77.714(2)^o, β = 84.139(2)^o, γ = 84.954(2)^o, V = 3648.4(5) Å^3, Z = 2, ρ_{calc} = 1.128 g/cm^3, $2\theta_{max}$ = 55.0, Mo Kα (λ = 0.71075 Å), μ = 0.706 cm^{-1}, T = 123 K, 16278 unique reflections, 821 variables, $R1$ = 0.1268 ($I > 2\sigma(I)$), $wR2$ = 0.4205, S = 0.994. CCDC-679238 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk).

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