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Unprecedented Selective *ipso*-Nitration of Calixarenes Monitored by the *O*-Substituents

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The electrophilic *ipso*-reactions of a *t*Bu-calix[6]arene that presents alternate *O*-methyl and *O*-2-methylen-*N*-methyl-imidazolyl groups (**1**) at the small rim have been studied. Whereas **1** underwent *per*-sulfonation in sulfuric acid, it selectively reacted with nitric acid to yield a tris-nitro derivative. The *ipso*-nitration occurred regioselectively on the calixarene anisol units. The reaction has been studied with various *t*Bu-calixarenes (**2**−**11**) presenting alternate anisol and phenol ether units. The regioselectivity of the process appeared to be correlated to the presence of a protonable site on the *O*-substituent. It is proposed that the corresponding protonated heteroatom (N for the amines, O for the amides and the carboxylic acid), situated in the γ or ϵ position of the phenoxy moieties, deactivates the corresponding aromatic ring by removing electron density through intramolecular hydrogen bonding. The high control operated by the *O*-substituents at the small rim even allowed the selective *ipso*-nitration of partially detertiobutylated calixarene $\mathbf{1}^{H3}$. Hence, these findings open new routes to a wide range of nonsymmetrically substituted calixarenes at the large rim.

Introduction

Over the past few years, we have been developing a novel supramolecular coordination chemistry based on the assembly of a transition metal ion with a calix[6]-arene-based tris-imidazolyl ligand that acts as a funnel for a neutral guest molecule interacting with the metal center.[1−10] Recently, we have shown that these biomimetic organo-soluble systems could be transposed in water thanks to the selective replacement of three *t*Bu groups by three sulfonate groups at the large rim of the calixarene structure.[5] However, since sulfonation with H_2SO_4 is known to be a nonselective process,[11,12] the disymmetrization of the large rim required two preliminary steps. First, the selective removal with $AlCl_3$ of three *t*Bu groups needed to be carried out on a calixarene bearing mixed phenol/anisol units in alternate position, then the corresponding free positions had to be protected by bromine substituents. Here, we report the first example of a selective *ipso*-reaction that allows the *direct* disymmetrization of the large rim of a fully *O*-alkylated calix[6]arene. The methodology is of wide utility and opens the route for a new range of calixarene derivatives that are selectively functionalized at the large rim.

Results and Discussion

Since sulfuric and nitric acids are the only two reagents that are known to be efficient for the *ipso*-reaction on *t*Bu-calixarenes, we decided to test them on the tris-imidazole based ligand **1**. Indeed, when **1** was heated in concentrated H_2SO_4 at 60 °C, *ipso*-sulfonation took place on all phenolic units and the corresponding hexa-sulfonated product $\mathbf{1}^{(SO3Na)6}$ was isolated (Scheme 1).[13] Shortening the reaction time or lowering the temperature did not allow us to isolate any intermediate that would be only partially sulfonated. In strong contrast, reacting **1** with nitric acid in excess led to its partial *ipso*-nitration. When the reaction was initiated at 0 °C in a 1:1 (v/v) mixture of fuming HNO_3 and glacial AcOH in dry CH_2Cl_2, then continued at room temperature for 1 h, a tris-nitrated compound ($\mathbf{1}^{(NO2)3}$) was isolated in 80% yield (Scheme 1). On the other hand, increasing the reaction time, the temperature, or the concentration of the reagents did not yield the corresponding hexa-nitrated product. Such

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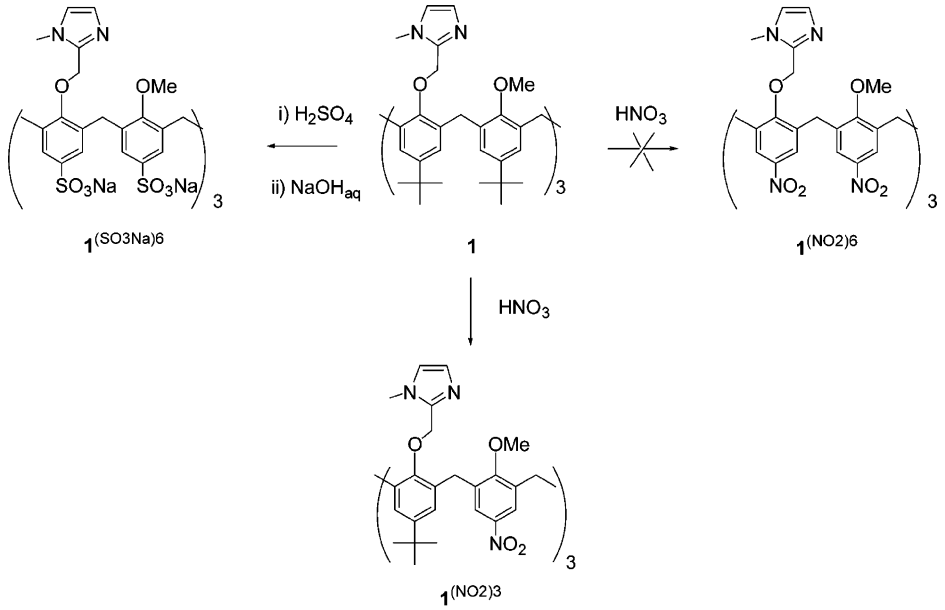
SCHEME 1. Comparative Functionalization of Calixarene 1 at the Large Rim by Sulfuric and Nitric Acids



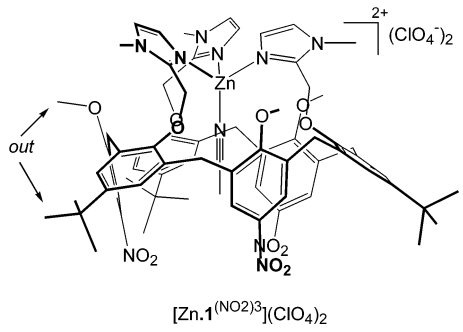
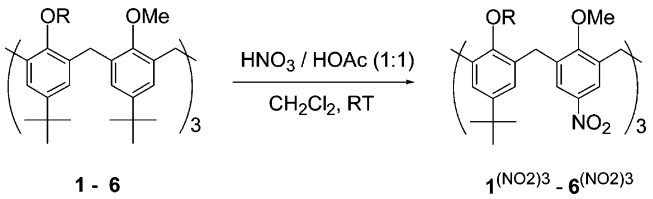


FIGURE 1. Schematic representation of the conformation adopted by the zinc complex obtained with ligand $\mathbf{1}^{(NO2)3}$ in acetonitrile.

harsher experimental conditions actually led to the decomposition of the compounds.

The ^{1}H NMR spectrum of $\mathbf{1}^{(NO2)3}$ in $CDCl_3$ displayed a very simple profile with a unique resonance for the *t*-Bu substituents that integrated for 27 protons. The formation of this C_{3v} symmetrical compound must thus result from the selective *ipso*-nitration on alternate positions at the lower rim of the calixarene. Due to the relative broadness of the peaks, probably related to some conformational fluxionality, we could not determine, by NMR C−H correlation experiments directly run on $\mathbf{1}^{(NO2)3}$, on which aromatic units the remaining *t*-Bu groups were situated. To rigidify the calixarene structure, we prepared the corresponding zinc complex $[Zn{\cdot}\mathbf{1}^{(NO2)3}](ClO_4)_2$ by reacting 1 equiv of $Zn(ClO_4)_2{\cdot}6H_2O$ with $\mathbf{1}^{(NO2)3}$ in THF. The ^{1}H NMR spectrum of the Zn complex, recorded in CD_3CN, displayed very well defined and narrow resonances, in accordance with the formation of a tetrahedral dicationic species with an average C_{3v} symmetry (Figure 1). We have previously shown[9] that in this family of complexes the phenolic units necessarily adopt an alternate *in* and *out* position, projecting their *O*-substituents in opposite directions. The normal chemical shifts for the *t*-Bu and methoxy groups (δ 1.43 and 3.78 ppm, respectively) observed for complex $[Zn{\cdot}\mathbf{1}^{(NO2)3}](ClO_4)_2$ indicates that they all are situated in out-position relative to the calixarene cavity. This suggests that the methoxy and *t*-Bu groups are not linked to the same phenol units (Figure 1). This was indeed confirmed by HMQC and HMBC NMR experiments, which allowed the assignment of each proton and carbon of the complex. Hence, we could deduce that nitration selectively proceeded at the para position of the three anisole units.

SCHEME 2. Selective Nitration of Calix[6]arenes Bearing Various R Substituents



As far as we know, such a selectivity for an *ipso*-substitution at the large rim of the calixarene has only scarcely been reported. Indeed, besides specific cases of mono- or di-nitration of C_{4v} symmetrical calix[4]arene tetraethers,[14−16] selective *ipso*-nitration (as the reaction with $AlCl_3$) was restricted to partially *O*-alkylated calixarenes that preferentially react at the para position of the phenol units.[17−19] To better understand why the electrophilic reagent is driven to attack the anisol groups in preference to the imidazolyl-substituted phenoxyl units, we tested the reaction of nitration on calix[6]arenes other than **1**, bearing various substituents instead of the

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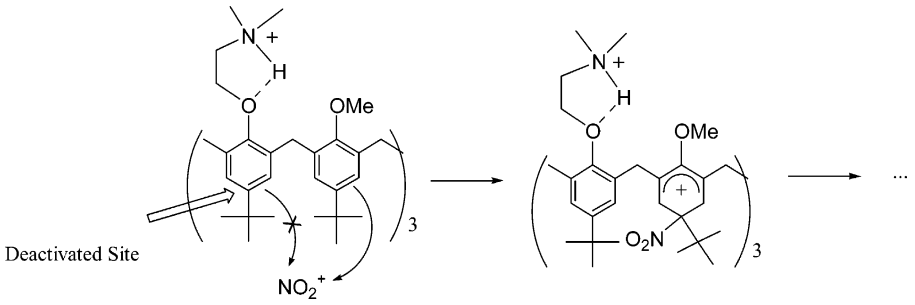
TABLE 1. Nitration of Calix[6]arenes 1−9 in CH_2Cl_2

starting material	R	product	yield	pK_a[a,20,21]
1	CH_2(Me-Im)	$\mathbf{1}^{(NO2)3}$	80	ImH^+/Im: 7
2	$CH_2CH_2NH_2$	$\mathbf{2}^{(NO2)3}$	55	$-NH_3^+/-NH_2$: 10−11
3	$CH_2CH_2NMe_2$	$\mathbf{3}^{(NO2)3}$	96	$-NMe_2H^+/-NMe_2$: 10−11
4	$CH_2CON[(CH_2)_4]$	$\mathbf{4}^{(NO2)3}$	56	$-C(OH^+)NR_2/-C(O)NR_2$: −0.5
5	CH_2CONH_2	$\mathbf{5}^{(NO2)3}$	62	$-C(OH^+)NH_2/-C(O)NH_2$: −0.5
6	CH_2CO_2H	$\mathbf{6}^{(NO2)3}$	82	$-C(OH^+)OH/-CO_2H$: −6
7	CH_2CO_2Et	$\mathbf{7}^{(NO2)3}$	63[b]	$-C(OH^+)OR/-CO_2R$: −6.5
8	CH_2CH_2OH	$\mathbf{8}^{(NO2)n}$	*c*	$-CH_2OH_2^+/-CH_2OH$: −2
9	$CH_2CH(CH_3)_2$	$\mathbf{9}^{(NO2)6}$	60	
10	$CH_2CH_2CH_2NMe_2$	$\mathbf{10}^{(NO2)3}$	75[b]	$-NMe_2H^+/-NMe_2$: 10−11

[a] For HNO_3/NO_3^-, p$K_a = -1.4$.[20] [b] The yield was estimated from ^{1}H NMR spectroscopy. [c] A complicated mixture of polynitrated products was observed by ^{1}H NMR spectroscopy.

SCHEME 3. Proposed Mechanism for the Selective *ipso*-Nitration with 1−3[a]



[a] For **4**−**7**, a similar scheme can be drawn, where the protonated site is an oxygen atom.

imidazole groups (Scheme 2). Therefore, we synthesized calix[6]arenes functionalized in alternate positions by methoxy groups (as in **1**) and primary amines (**2**), tertiary amines (**3**, **10**), amides (**4** and **5**), acids(**6**), esters (**7**), alcohols (**8**), or alkyl groups of similar bulkiness (**9**). All these compounds were submitted to the exact same experimental procedure as that described for the selective nitration of **1** (Scheme 2, Table 1). The results are collected in Table 1.

For compounds **2**−**6** and **10**, selective tris-nitration proceeded as described above for **1**, and calixarenes $\mathbf{2}^{(NO2)3}$− $\mathbf{6}^{(NO2)3}$ and $\mathbf{10}^{(NO2)6}$ were obtained in 55−96% yield. The almost quantitative yield obtained with **3** attests to the high regioselectivity of the *ipso*-substitution. The relatively moderate yields for **2**, **4**, and **5** may be attributable to competitive degradation processes of the nitrogenous arms since no other product could be isolated. In strong contrast with these results, compound **9** yielded the hexa-nitrated calixarene $\mathbf{9}^{(NO2)6}$ as the sole isolable reaction product in 60% yield (Table 1). This last result is in accordance with those previously reported in the literature related to calixarenes.[19,22,23] Compounds **7** and **8** represent intermediate cases: a mixture of polynitrated products was obtained. Although for **7** the tris-nitrated product could clearly be identified by NMR and mass spectrometry out of the crude reaction mixture, it could not be isolated properly.

Obviously, the nature of the R groups plays a key role in directing the nitration positions. A possible explanation might well be related to the presence of a protonable site at the γ position of the phenolic oxygen atom. Indeed, for compounds **1**−**3**, due to their basic character, all nitrogenous arms must be protonated under the strongly acidic reaction conditions. This protonated nitrogen group is in an ideal position for hydrogen bonding to the phenolic oxygen atom, thereby deactivating the whole aromatic cycle toward electrophilic attack by removing the electron density (Scheme 3). Likewise, for compounds **4**−**8**, a protonable oxygen atom is situated at the γ position. According to their pK_a values relative to those of nitric acid (see Table 1), compounds **6**−**8** are not efficiently protonated by nitric acid, whereas the amides **4** and **5** are. Therefore, the latter two are cleanly and selectively tris-nitrated, which is not the case for ester **7**. The much higher acidity of the carboxylic proton in **6**, compared to that of the hydroxyl of alcohol **8**, can also explain the selectivity of the substitution for **6** and not for **8**.

Finally, when the protonable arm was lengthened by one methylene group such as in compound **10**, the nitration also occurred selectively. This is consistent with the formation of an efficient hydrogen bonding through a six-membered ring. In the case of **9**, such a deactivation process does not exist and the nitration proceeds on all phenol groups without discrimination. We tested the reaction on compound $\mathbf{1}^{H3}$ where the three *t*Bu groups in the para position of the amino arms have been removed (Scheme 4). In that case too, the nitration was selective and the tris-nitrated compound $\mathbf{1}^{H3(NO2)3}$ resulting from three *ipso*-reactions was isolated with a relatively good yield (66%). There is a precedent in calix[4]arene chemistry reporting that *ipso*-nitration is faster than classical

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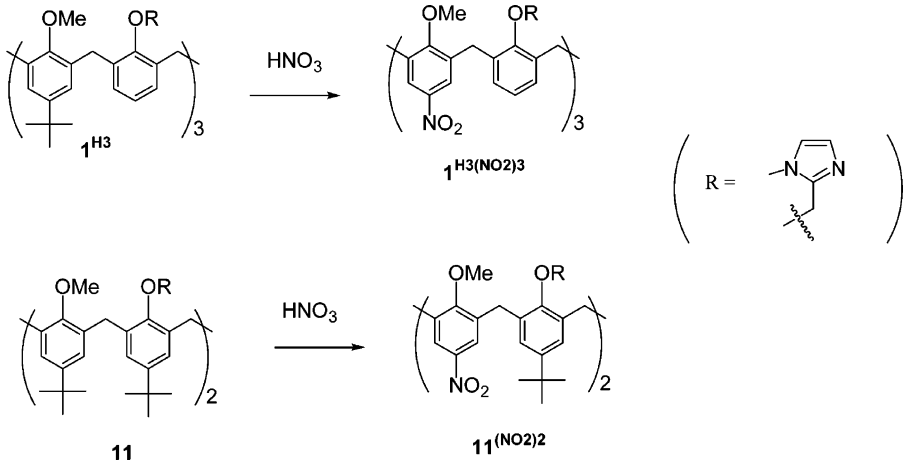
SCHEME 4. Selective *ipso*-Nitration of Calixarenes 1^{H3} and 11



nitration.[23] Finally, the same experimental procedure applied to the calix[4]arene **11** analogue to **1** yielded the corresponding $\mathbf{11}^{(NO2)2}$ with an excellent yield (80%).

In conclusion, we have described new synthetic routes leading to the selective functionalization of the large rim of calix[6]arenes. These allowed the direct introduction of three nitro groups in alternate positions. Such a selectivity is unprecedented and is related to the nature of the substituents R beard by the phenolic units of the calixarene. Indeed, the presence of a protonable heteroatom in R deactivates the corresponding phenolic unit toward electrophilic substitution. These new routes are also remarkable because they open synthetic perspectives for selectively funtionalized calix[6]arenes. Indeed, the nitro groups can be easily reduced, leading to amino and amido derivatives.[18,19] Furthermore, the remaining *t*Bu substituents present on the large rim can be easily replaced by sulfonates. We are currently exploring these new routes to obtain water-soluble calixarenes designed for the coordination of a metal ion in aqueous media.[13,24]

Experimental Section

1,[6] **2**,[25] **3**,[9] **5**,[25] **6**,[26−28] **7**,[28] **8**,[29] and **11**[30] were prepared according to literature procedures.

5,17,29,11,23,35-Hexa-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tris[(1-pyrrolidinecarbonyl)methoxy]calix[6]-arene (4). $(COCl)_2$ (1 mL, 11.45 mmol, 27.2 equiv) was added to a solution of **6** (500 mg, 0.42 mmol) in anhydrous CH_2Cl_2 (40 mL) under argon. After 4 h at reflux, the mixture was evaporated under vacuum to dryness. The resulting crude product was dissolved in anhydrous benzene (40 mL), the mixture was cooled to 0 °C, and a solution of pyrrolidine (117 μL, 1.39 mmol, 3.3 equiv) and Et_3N (538 μL, 3.78 mmol, 9 equiv) in benzene (40 mL) was added dropwise. After 24 h at room temperature, the organic layer was washed with water (2 × 50 mL), dried ($MgSO_4$), and evaporated to dryness. The crude product was purified by crystallization ($CHCl_3$/MeOH) to yield **4** as a colorless solid (567.8 mg, 100%). Mp 257−259 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.21 (s, 6H), 6.61 (s, 6H), 4.55 (s, 6H), 4.46 (d, 6H, J = 8.9 Hz), 3.74 (m, 6H), 3.68 (m, 6H), 3.43 (d, 6H, J = 8.9 Hz), 2.19 (s, 9H), 1.91 (m, 6H), 1.87 (m, 6H), 1.37 (s, 27H), 0.76 (s, 27H). Anal. Calcd for **4**·2H_2O ($C_{87}H_{117}N_3O_9$·2H_2O, 1383.90): C 75.45, H 8.81, N 3.03. Found: C 75.54, H 8.31, N 2.78.

5,11,17,23,29,35-Hexa-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tris[(1-methyl)propyloxy]calix[6]arene (9). A solution of 1,3,5-trimethoxy-*p*-*tert*-butylcalix[6]arene[31] (155 mg, 0.15 mmol) in anhydrous THF (3 mL) was added under argon to a mixture of NaH (60%, 177 mg, 4.5 mmol, 30 equiv, washed with pentane prior to use) in THF (3 mL) and DMF (1.5 mL). After 15 min at room temperature, $(CH_3)_2CHCH_2I$ (170 μL, 1.48 mmol, 10 equiv) was added. After 7 days at reflux, the usual workup with CH_2Cl_2/H_2O gave the crude product that was filtered over silica gel with use of EtOAc/cyclohexane (3:7) to yield **9** as a colorless solid (152 mg, 92%). Mp 191−193 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.26 (s, 6H), 6.67 (s, 6H), 4.49 (br s, 6H), 3.62 (d, 6H, J = 6.4 Hz), 3.50 (br s, 6H), 2.27 (s, 9H), 2.18 (m, 3H), 1.37 (s, 27H), 1.09 (d, 18H, J = 6.7 Hz), 0.82 (s, 27H). Anal. Calcd for **5**·2H_2O ($C_{81}H_{114}O_6$·2H_2O, 1219.80): C 79.82, H 9.75. Found: C 79.79, H 9.75.

5,11,17,23,29,35-Hexa-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tris[(*N*,*N*-dimethylamino)propyloxy]calix[6]-arene (10). NaH (60% in oil, 118 mg, 2.95 mmol, 30 equiv, washed with pentane prior to use) was added under argon to a solution of 1,3,5-trimethoxy-*p*-*tert*-butylcalix[6]arene[31] (100 mg, 0.1 mmol) in THF (4 mL) and DMF (1 mL). After 30 min at room temperature, 3-(*N*,*N*-dimethylamino)propyl chloride hydrochloride (155 mg, 1 mmol, 10 equiv) was added. After 16 h at reflux, the usual workup with CH_2Cl_2/H_2O gave the crude product that was recristallized (CH_2Cl_2/CH_3CN) to give **10** as colorless crystals (95 mg, 76%). Mp (CH_2Cl_2/CH_3CN): 193 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.26 (s, 6H), 6.64 (s, 6H), 4.55 (d, 6H, J_{AB} = 14.8 Hz), 3.92 (m, 6H), 3.40 (d, 6H, J_{AB} = 14.8 Hz), 2.53 (m, 6H), 2.26 (s, 18H), 2.21 (s, 9H), 2.03 (m, 6H), 1.38 (s, 27H), 0.78 (s, 27H). ^{13}C NMR (125 MHz, $CDCl_3$): 154.39, 151.80, 145.61, 145.41, 133.48, 133.13, 127.85, 123.36, 71.03, 60.07, 56.55, 45.36, 34.13, 33.85, 31.54, 31.07, 29.56, 28.46. Anal. Calcd for **10**·0.5CH_2Cl_2 ($C_{84}H_{123}N_3O_6$·0.5CH_2Cl_2, 1313.36): C 77.28, H 9.52, N 3.20. Found: C 77.44, H 9.47, N 3.09.

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(32) Its ^{1}H NMR spectrum reflects a nonsymmetrical conformation. Its detailed interpretation is under current investigation.

5,17,29-Tri-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tris-[(1-methyl-2-imidazolyl)methoxy]calix[6]arene (1^{H3}). A solution of 5,17,29-tri-*tert*-butyl-37,39,41-trihydroxy-38,40,42-trimethoxycalix[6]arene[27] (300 mg, 0.35 mmol) was added under argon to a mixture of NaH (60% in oil, 420 mg, 10 mmol, 30 equiv, washed with pentane prior to use) in THF (12 mL) and DMF (3 mL). After 15 min at room temperature, 2-chloromethyl-1-methyl-1*H*-imidazole hydrochloride (360 mg, 2.1 mol, 6 equiv) was added. After 16 h at reflux, the usual workup with CH_2Cl_2/H_2O gave the crude product that was filtered over silica gel with use of CH_2Cl_2/MeOH (9:1) to give $\mathbf{1}^{H3}$ as a colorless solid (347 mg, 88%). For elemental analysis purposes, further purification was achieved by recristallization from acetonitrile. Mp (CH_3CN) 169 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.11 (s, 6H), 7.00 (s, 3H), 6.87 (s, 3H), 6.68 (br s, 9H), 4.90 (br s, 6H), 3.84 (br s, 12H), 3.61 (br s, 9H), 2.69 (s, 9H), 1.27 (s, 27H). Anal. Calcd for $\mathbf{1}^{H3}\cdot H_2O$ ($C_{72}H_{84}N_6O_6\cdot H_2O$, 1146.66): C 75.36, H 7.55, N 7.32. Found: C 75.26, H, 7.46, N, 7.37.

Typical Procedure for Selective Nitration. A mixture of fuming nitric acid (4.7 mL, 117 mmol) and glacial acetic acid (4.7 mL) was added dropwise under argon to a solution of hexa-*tert*-butylcalix[6]arene derivative (0.77 mmol) in anhydrous CH_2Cl_2 (78 mL) cooled to 0 °C. The temperature was then allowed to raise to 25 °C and the color of the solution quickly changed from violet to orange-yellow. After 1 h at room temperature, the mixture was carefully poured into aq 2.5% ammonia (200 mL) and the organic layer was washed with water (2 × 80 mL), dried (Na_2SO_4), and evaporated to dryness. Compounds $\mathbf{1}^{(NO2)3}$–$\mathbf{7}^{(NO2)3}$, $\mathbf{9}^{(NO2)6}$, $\mathbf{10}^{(NO2)3}$, $\mathbf{11}^{(NO2)2}$, and $\mathbf{1}^{H3(NO2)3}$ were prepared according to this procedure.

5,17,29-Trinitro-11,23,35-tri-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tris[(1-methyl-2-imidazolyl)methoxy]-calix[6]arene [$\mathbf{1}^{(NO2)3}$]. $\mathbf{1}^{(NO2)3}$ was obtained from **1** (1 g, 0.77 mmol); the crude product was filtered over silica gel with us eof MeOH/CH_2Cl_2/conc aq NH_3 (5:95:0.25) as eluant to give $\mathbf{1}^{(NO2)3}$ as a pale-yellow solid (779 mg, 80%). IR $\nu(NO_2)$ 1518 cm^{-1}.Mp (EtOAc/C_5H_{12}) 273−274 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 330 K) δ 7.72 (s, 6H), 6.95 (s, 6H), 6.87 (s, 3H), 6.70 (s, 3H), 4.71 (s, 6H), 3.79 (s, 12H), 3.23 (s, 9H), 3.16 (s, 9H), 1.13 (s, 27H). ^{13}C NMR (125 MHz, $CDCl_3$) 161.18, 152.75, 147.21, 143.41, 135.47, 134.97, 126.84, 126.51, 123.89, 122.39, 66.46, 60.03, 33.99, 32.53, 31.11, 29.81. Anal. Calcd for $\mathbf{6}\cdot H_2O$ ($C_{72}H_{81}N_9O_{12}\cdot H_2O$, 1281.61): C 67.43, H 6.52, N 9.83. Found: C 67.46, H 6.39, N 9.32.

[$\mathbf{1}^{(NO2)3}$·Zn](ClO_4)$_2$. $Zn(ClO_4)_2\cdot 6H_2O$ (28 mg, 0.075 mmol) was added to a solution of $\mathbf{1}^{(NO2)3}$ (100 mg, 0.078 mmol) in THF (2 mL) under Ar. After 10 min, pentane was added, and the precipitate was filtered off and dried under vacuum (104 mg, 90%). IR $\nu(NO_2)$ 1527 cm^{-1}. ^{1}H NMR (250 MHz, CD_3CN) δ 7.50 (s, 6H), 7.46 (s, 3H), 7.09 (s, 6H), 6.96 (s, 3H), 5.04 (s, 6H), 4.05 (d, 6H, J_{AB} = 16.1 Hz), 3.78 (s, 9H), 3.67 (d, 6H), 3.62 (s, 9H), 1.43 (s, 27H). Anal. Calcd for [$\mathbf{1}^{(NO2)3}$·Zn](ClO_4)$_2\cdot 4H_2O$ ($C_{72}H_{81}Cl_2N_9O_{20}Zn\cdot 4H_2O$, 1597.47): C 54.02, H 5.60, N 7.87. Found: C 53.63, H 5.33, N 7.61.

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Supporting Information Available: General experimental, procedures of purification and product data of nitrated compounds other than $\mathbf{1}^{(NO2)3}$ (S1−S4); ^{13}C and ^{1}H spectra of compounds $\mathbf{7}^{(NO2)3}$ and $\mathbf{10}^{(NO2)3}$ (S5−S7: Figure S1−S6). This material is available free of charge via the Internet at http://pubs.acs.org.

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