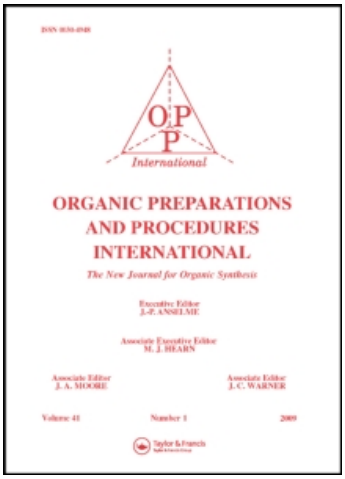

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ipso-NITRATION OF HEXAMETHOXY[(2.1)$_3$]METACYCLOPHANE, A CALIXARENE ANALOGOUS MACROCYCLIC METACYCLOPHANE

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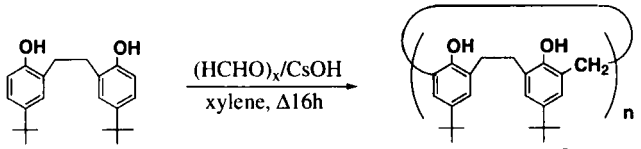
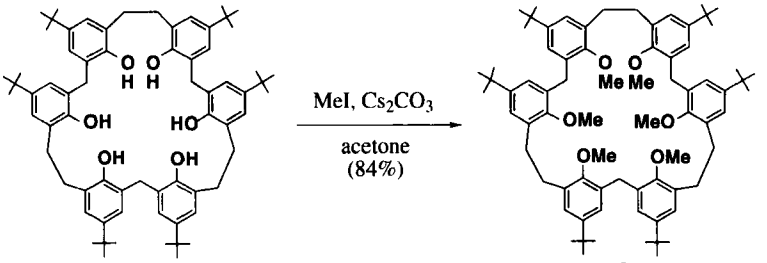
Calix[n]arenes[1] are easily available ditopic platforms extensively used in supramolecular chemistry to build up more complex synthetic receptors for ions and molecules.[2] The complexing ability of these hosts can be tuned by altering either the nature and the number of the building sites introduced at both upper and lower rims, or by controlling the conformational properties of calixarenes. For example, it was found that calix[n]arenes can be converted to neutral ligands by etherification of the OH groups with ethyl bromoacetate. Recently, Reinhoudt *et al.* reported[3] the synthesis of cone amino tetraalkoxy calix[4]arenes starting from the corresponding nitro derivatives which were used to obtain receptors having binding sites at the upper rim.[4] On the other hand, we have recently described[5] a convenient and selective synthesis of a series of hydroxy[(2.1)$_n$]MCPs (MCP = metacyclophane) with six or eight arene units (**2**) involving base-catalyzed condensation of 1,2-*bis*(5-*tert*-butyl-2-hydroxyphenyl)ethane (**1**) with formaldehyde under reflux in xylene and



1 **2** a; n = 3, b; n = 4

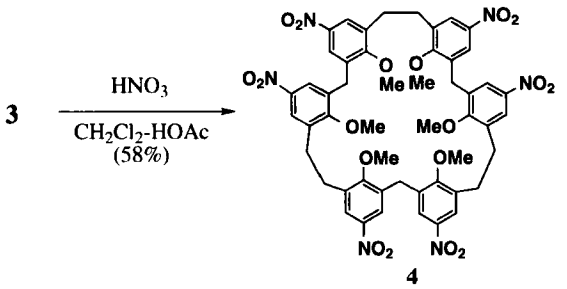
reported their unique properties. The ring size and flexibility are different between calix[n]arene and calixarene analogs [(2.1)$_n$]MCPs. It is thus interesting to assess what kind of ionophoric cavity the functionalized [(2.1)$_n$]MCPs **2** provides. However, to the best of our knowledge, except Vögtle's [2$_n$]MCPs[6] no precedent exists for molecular design of such unsymmetrical or incomplete "homocalixarene-based ionophores" bearing six or eight benzene rings This paper reports the direct introduction of substituents on the upper rim into [(2.1)$_3$]MCP **2a** by *ipso*-nitration.

An attempted alkylation of the flexible macrocycle **2a** with MeI in the presence of Cs_2CO_3 under acetone reflux led to complete *O*-methylation, affording the hexamethoxy derivative **3** in 84% yield.



2a **3**

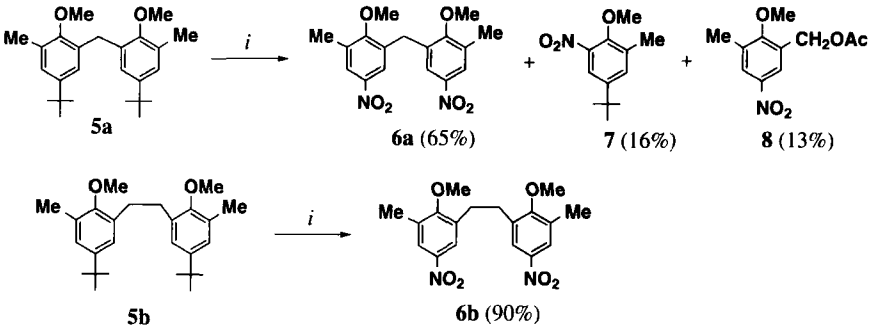
ipso-Nitration,[7] *i.e.* replacement of *tert*-butyl with nitro groups, is a particularly useful reaction in calixarene chemistry because it allows substitution of only the *tert*-butyl groups *para* to free phenolic OH or OMe groups. More recently, Reinhoudt *et al.*[3] described four-fold *ipso*-nitration of *tert*-butyltetramethoxycalix[4]arenes in high yield. We reported[8] that *ipso*-nitration of di-*tert*-butyldiphenylalkanes leads to the direct introduction of one or two nitro group(s) depending on the reaction conditions and investigated the mechanistic aspects of *ipso*-attack in electrophilic aromatic substitutions having more than two aromatic rings by consideration of the through-space electronic interactions among the other benzene rings. In fact, the exhaustive introduction of six nitro groups by direct replacement of *tert*-butyl groups by *ipso* aromatic nitration of hexa-*tert*-butylhexamethoxy-[(2.1)$_3$]MCP (**3**) has been shown to afford hexanitro[(2.1)$_3$]MCP (**4**) in 58% yield. Interestingly, only the *ipso*-attack at the *tert*-butyl groups to afford the hexanitro compound **4** occurred, no *ipso*-attack at the benzylic position to afford the cleavage products was observed.



4

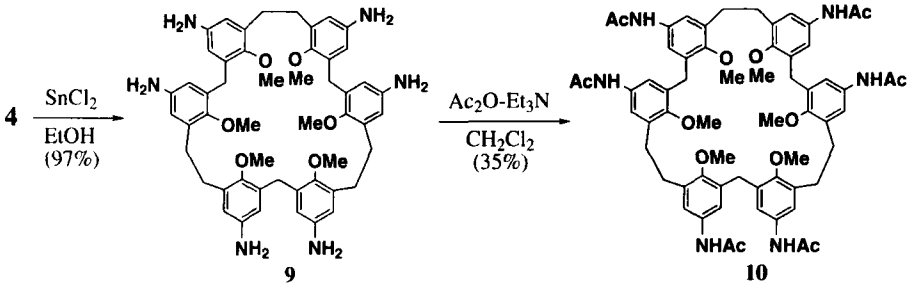
In the case of nitration of *bis*(5-*tert*-butyl-2-methoxy-3-methylphenyl)methane (**5a**), the *ipso*-attack at the *tert*-butyl groups to afford the dinitro compound **6a** in 65% yield was accompanied by a small amount of *ipso*-attack at the benzylic position to afford in low yields the cleavage products 4-*tert*-butyl-2-methyl-6-nitroanisole (**7**) and 2-acetoxymethyl-6-methyl-4-nitroanisole (**8**) in 16 and 13% yields, respectively. This is in contrast to the nitration of polymethyldiphenylmethanes which mainly affords products arising from cleavage at the diphenylmethane linkage.[9] Under similar reaction conditions, 1,2-*bis*(5-*tert*-butyl-2-methoxy-3-methylphenyl)ethane (**5b**) gave two-fold *ipso*-nitration product **6b** in 90% yield as the sole product.

Nitration of *p*-*tert*-butylcalix[6]arenes having the same number of benzene rings as **3** to obtain the six-fold *ipso*-nitration product has not been successful so far, affording only decomposition products. The synthesis of *p*-nitrocalix[6]arene has been achieved only by substitution of *p*-sulfonato



i) Fuming HNO_3,CH_2Cl_2-HOAc

groups.[10] Thus, introduction of three ethylene groups into the methylene bridges of calix[6]arenes might suppress *ipso*-attack at the benzylic position of the diphenylmethane linkage. The selective *ipso*-nitration of **3** is attributed to the highly activated character of the aryl ring and the increased stabilization of a σ-complex intermediate arising from the dienone-type σ-complex intermediate possible. Reduction of hexanitro[(2.1)$_3$]MCP (**4**) using $SnCl_2$ in refluxing EtOH gave in almost quantitative yield the corresponding hexaamino[(2.1)$_3$]MCP (**9**), which was converted to hexa(acetylamino) derivative **10** in 35% yield.



In conclusion, the stability of ethylene bridged multi-membered carbon skeletons was found to be advantageous for *ipso*-attack nitration, permitting the direct removal of *tert*-butyl groups without ring-opening side reactions. The results suggest that hexahydroxy[(2.1)$_3$]MCP **2** is a useful basic skeleton for the design of artificial receptors.

EXPERIMENTAL SECTION

All melting points are uncorrected. ^{1}H NMR spectra were recorded on a Nippon Denshi JEOL FT-270 NMR spectrometer in $CDCl_3$ with TMS as an internal reference. IR spectra were measured as KBr pellets or as liquid films on NaCl plates in a Nippon Denshi JIR-AQ2OM spectrometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct inlet system.
The preparation of 5,12,20,27,35,42-hexa-*tert*-butyl-8,15,23,30,38,45-hexahydroxy[(2.1)$_3$]MCP (**2a**),[5] *bis*(5-*tert*-butyl-2-methoxy-3-methylphenyl)methane (**5a**)[8b] and 1,2-*bis*(5-*tert*-butyl-2-methoxy-3-methylphenyl)ethane (**5b**)[8b] were described previously.

Alkylation of 2a with Methyl Iodide in the Presence of Cs_2CO_3.- A mixture of **2a** (1.0 g, 0.986 mmol) and cesium carbonate (3.20 g, 9.8 mmol) in dry acetone (30 mL) was heated at reflux for 1 h under nitrogen. Methyl iodide (0.62 mL, 9.8 mmol) was then added and the mixture heated at reflux for an additional 3 h. After cooling to room temperature, the reaction mixture was filtered. The filtrate was concentrated *in vacuo*. The residue was collected and washed with hexane to give 5,12,20,27,35,42-*hexa-tert-butyl*-8,15,23,30,38,45-*hexamethoxy*[2.1.2.1.2.1]*metacyclophane* (**3**) (920 mg, 84%) as a colorless solid. Recrystallization from $CHCl_3$-MeOH, 1:1 afforded **3** as colorless prisms, mp. 205-207°. NMR ($CDCl_3$): δ 1.15 (54 H, s), 2.92 (12 H, s), 3.33 (18 H, s), 3.81 (6 H, s), 6.83 (6 H, d, *J* 2.4), 6.91 (6 H, d, *J* 2.4).

Anal. Calcd. for $C_{75}H_{102}O_6$: C, 81.92; H, 9.35. Found: C, 81.79; H, 9.48

Nitration of 3 with Fuming Nitric Acid.- To a solution of **3** (500 mg, 0.45 mmol) in a mixture of CH_2Cl_2 (5.0 mL) and glacial acetic acid (5.0 mL) fuming HNO_3 (3.0 mL) was added at 0°. The mixture was stirred at room temperature. After 30 min., the mixture was poured into ice-water, extracted with CH_2Cl_2 and washed with water and 10% aqueous sodium bicarbonate. The combined extracts were washed with water and dried (Na_2SO_4), the solvent was evaporated *in vacuo* to leave a residue. Chromatography on silica gel (Wako, C-300) with benzene-$CHCl_3$, 1:1 as eluent, afforded crude **4** (274 mg, 58%) as a pale yellow solid. Recrystallization from $CHCl_3$-MeOH, 1:1 afforded 8,15,23,30,38,45-*hexamethoxy*-5,12,20,27,35,42-*hexanitro*[2.1.2.1.2.1]*metacyclophane* (**4**) as pale yellow prisms, mp. 176-178°. NMR ($CDCl_3$): δ 3.04 (12 H, s), 3.61 (18 H, s), 4.01 (6 H, s), 7.77 (6 H, d, *J* 2.9), 7.92 (6 H, d, *J* 2.9).

Anal. Calcd. for $C_{51}H_{48}N_6O_{18}$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.55; H, 4.97; N, 7.79

Nitration of 5a with Fuming Nitric Acid.- To a solution of *bis*(5-*tert*-butyl-2-methoxy-3-methylphenyl)methane (**5a**) (106.5 mg, 0.289 mmol) in a mixture of CH_2Cl_2 (2.5 mL) and glacial acetic acid (2.5 mL) was added fuming HNO_3 (0.83 mL) at 0°. After the mixture had been stirred at room temperature for 30 min., it was poured into ice-water, extracted with CH_2Cl_2, washed with water and 10% aqueous sodium hydrogen carbonate. The extract was dried over anhydrous sodium sulfate and concentrated. The residue was subjected to silica-gel (Wako, C-300; 100 g) column chromatography using hexane-benzene (1:1) and benzene as eluents to give 4-*tert-butyl*-2-*methyl*-6-*nitroanisole* (**7**) (10 mg, 16%), *bis*(2-*methoxy*-3-*methyl*-5-*nitrophenyl*)*methane* (**6a**) (65 mg, 65%) and 2-*acetoxymethyl*-6-*methyl*-4-*nitroanisole* (**8**) (9 mg, 13%), respectively.

bis(2-*Methoxy*-3-*methyl*-5-*nitrophenyl*)*methane* (**6a**) was obtained as pale yellow prisms, mp. 138-139° [hexane-benzene (4:1)]. NMR ($CDCl_3$): δ 2.41 (6 H, s), 3.78 (6 H, s), 4.11 (2 H, s), 7.81 (2 H, d, *J* 2.4), 7.99 (2 H, d, *J* 2.4); ms: *m/e* 346 (M^+).

Anal. Calcd. for $C_{17}H_{18}N_2O_6$: C, 58.95; H, 5.24; N, 8.09. Found: C, 58.65; H, 5.16; N, 7.92

4-*tert-Butyl*-2-*methyl*-6-*nitroanisole* (**7**) was obtained as pale yellow oil. NMR ($CDCl_3$): δ 1.32 (9 H, s), 2.36 (3 H, s), 2.87 (3 H, s), 7.42 (1 H, d, *J* 2.4), 7.62 (1 H, d, *J* 2.4); ms: *m/e* 223 (M^+).

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.68; H, 7.38; N, 6.09

2-*Acetoxymethyl*-6-*methyl*-4-*nitroanisole* (**8**) was obtained as pale yellow prisms, mp. 112-

114° [hexane-benzene (4:1)]. IR (KBr): 1744 (C=O) cm^{-1}; NMR ($CDCl_3$): δ 2.16 (3 H, s), 2.40 (3 H, s), 3.85 (3 H, s), 5.20 (2 H, s), 8.07 (1 H, d, *J* 2.4), 8.11 (1 H, d, *J* 2.4); ms: *m/e* 239 (M^+).

Anal. Calcd. for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.85. Found: C, 55.48; H, 5.30; N, 5.97

Compound **6b** was prepared in 90% yield as for **6a**.

1,2-*bis*(2-*Methoxy*-3-*methyl*-5-*nitrophenyl*)*ethane* (**6b**) as pale yellow prisms, mp. 159-161° [from hexane-benzene (1:1)]. NMR ($CDCl_3$): δ 2.39 (6 H, s), 2.99 (4 H, s), 3.84 (6 H, s), 7.94 (2 H, d, *J* 2.9), 7.97 (2 H, d, *J* 2.4); ms:*m/e* 360 (M^+).

Anal. Calcd. for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.88; H, 5.62; N, 7.87

Reduction of 4 with $SnCl_2$.- To a solution of **4** (100 mg, 0.097 mmol) in EtOH (8.0 mL) $SnCl_2 \cdot 2H_2O$ (1.19 g, 0.53 mol) was added. The mixture was stirred at 50°. After 18 h, the mixture was poured into ice-water, extracted with CH_2Cl_2 and washed with water and 10% aqueous sodium bicarbonate. The combined extracts were washed with water and dried (Na_2SO_4), the solvent was evaporated *in vacuo* to leave a residue. Column chromatography on silica gel (Wako, C-300) with $CHCl_3$ as eluent afforded the 8,15,23,30,38,45-*hexamethoxy*-5,12,20,27,35,42-*hexaamino*[2.1.2.1.2.1]*metacyclophane* (**9**) (80 mg, 97%) as a pale orange solid, mp. 202-205°. NMR ($CDCl_3$): δ 2.46 (12 H, broad s), 2.96 (12 H, s), 3.67 (18 H, s), 3.80 (6 H, s), 5.99 (6 H, d, *J* 2.93), 6.02 (6 H, d, *J* 2.93). Compound **9** was used for the next reaction without further purification.

Acetylation of 9 with Acetic Anhydride.- To a solution of **9** (80 mg, 0.094 mmol) and triethylamine (0.061 mL, 0.44 mmol) in CH_2Cl_2 (8.0 mL) was added acetic anhydride (0.038 mL, 0.405 mol). The mixture was stirred at room temperature. After 12 h, the mixture was poured into ice-water, extracted with ethyl acetate and washed with water. The combined extracts were washed with water and dried (Na_2SO_4), the solvent was evaporated *in vacuo* to leave a residue which was washed with hexane to afford 8,15,23,30,38,45-*hexamethoxy*-5,12,20,27,35,42-*hexa(acetylamino)*[2.1.2.1.2.1]*metacyclophane* (**10**) (36 mg, 35%) as a pale orange solid; mp. 221-223°. NMR (CD_3OD): δ 2.02 (18 H, s), 2.87 (12 H, s), 3.38 (18 H, s), 3.86 (6 H, s), 7.01 (6 H, d, *J* 2.44), 7.23 (6 H, d, *J* 2.44).

Anal. Calcd. for $C_{63}H_{72}N_6O_{12}$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.75; H, 6.42; N, 7.39

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