Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 5563–5568

TETRAHEDRON

Selective functionalization at the small rim of calix[6]arene. Synthesis of novel non-symmetrical N_3, N_4 and N_3Ar*O* biomimetic ligands

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Received 10 March 2003; accepted 20 May 2003

Abstract—Eight novel calix[6]arene-based biomimetic ligands for transition metal ions have been synthesized. They display a non-symmetrical N_3, N_4 or N_3Ar*O* binding core that mimics enzyme active sites presenting histidine and tyrosine residues. The key step for their synthesis is the mono-alkylation at the small rim of the C_{3v} symmetrical trimethyl ether derivative of *t*Bu-calix[6]arene with *N*-Boc-2-chloroethylamine to yield a novel calix[6]arene synthon. Its combined *O*-alkylation with a chloromethyl aromatic amine and *N*-deprotection or alkylation or reductive alkylation with a salicylaldehyde derivative yielded the calix[6]arene-based ligands with mixed *N*/*O* donors. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

We are involved in a research program devoted to the modeling of metallo-enzyme active sites with supramolecular systems. In the recent years, we have shown that calix[6]arenes can be used as a platform for the preorganization of a metal ion binding site in close proximity of a hydrophobic cavity. For that purpose, selective alternate alkylation of three out of the six phenolic units of the calix[6]arene was the key step for obtaining a variety of C_{3v} symmetrical N_3 ligands.[1,2] Because of the great diversity of metallo-enzyme active sites, we were interested in developing a novel synthetic strategy allowing the disymetrisation of the calix[6]arene-based system.[3] Therefore, we explored the selective functionalization of the C_{3v} tris(methylated)calixarene $X_6Me_3H_3$ and found a novel procedure giving rise to its monoalkylation with an amino-protected group. This key step allowed us to synthesize within 3 or 4 steps starting from $X_6Me_3H_3$ non-symmetrical N_3, N_4 and N_3Ar*O* ligands.

2. Results

2.1. Selective functionalization of calix[6]arene $X_6Me_3H_3$

The synthesis of C_{3v} symmetric N_3 calix[6]arene-based ligands were achieved by per-alkylation of the 1,3,5-trimethylether of *t*Bu-calix[6]arene $X_6Me_3H_3$ using various alkyl chloride (2-chloromethyl-*N*-methylimidazole, 2-chloromethyl-*N*-methylbezimidazole, *N*-chloromethyl-pyrazole, 2-chloromethylpyridine, *N*,*N*-dimethyl-2-chloro-ethylamine) in the presence of excess NaH[1,4] or K_2CO_3,[2] in THF/DMF or DMF, respectively. When the calixarene was reacted with only a stoichiometric amount of the above-mentioned alkylating agent and/or base, the tris(alkylated) compound $X_6Me_3N_3$ remained by far the major product and a sizeable part of $X_6Me_3H_3$ was recovered. The mono- and di-alkylated products were formed only in very small amounts.

In strong contrast with these results, when the Boc-protected chloroethylamine was used as an electrophilic agent, partially alkylated compounds were obtained as major products and peralkylation of $X_6Me_3H_3$ revealed itself to be a minor process. Thus, optimization of the reaction conditions, thanks to a careful control of both the reaction conditions and the relative stoichiometric quantities of each reagent, led to an efficient procedure for the preparation of a novel non-symmetrical calix[6]arene synthon. When $X_6Me_3H_3$ was reacted with $ClCH_2CH_2NHBoc$[5] (5 equiv.) and NaH (3.2 equiv.) in a THF/DMF 5:1 mixture, calix[6]arene $X_6Me_3H_2$(NHBoc) was obtained with a 75% yield based on converted $X_6Me_3H_3$ (Scheme 1). Column chromatography allowed its separation from the di-alkylated product $X_6Me_3H(NHBoc)_2$ and the tri-alkylated product $X_6Me_3H(NHBoc)_3$ (identified by ES-MS) that were formed in only small amounts. The ^{1}H NMR spectrum of $X_6Me_3H_2$(NHBoc) is characteristic of a C_s-symmetrical species with the methoxy groups rejected out of the calixarene cavity (δ_{OMe}=3.40 and 3.88 ppm) and the

Keywords: calix[6]arene; selective alkylation; biomimetic; mixed *N*/*O*-ligand.

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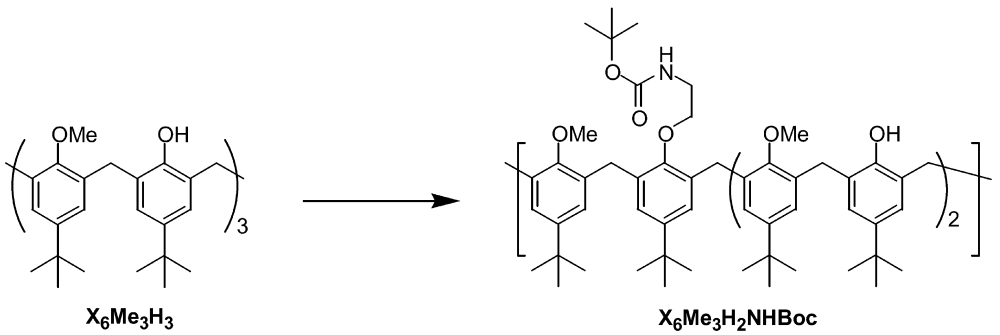
doi:10.1016/S0040-4020(03)00780-4

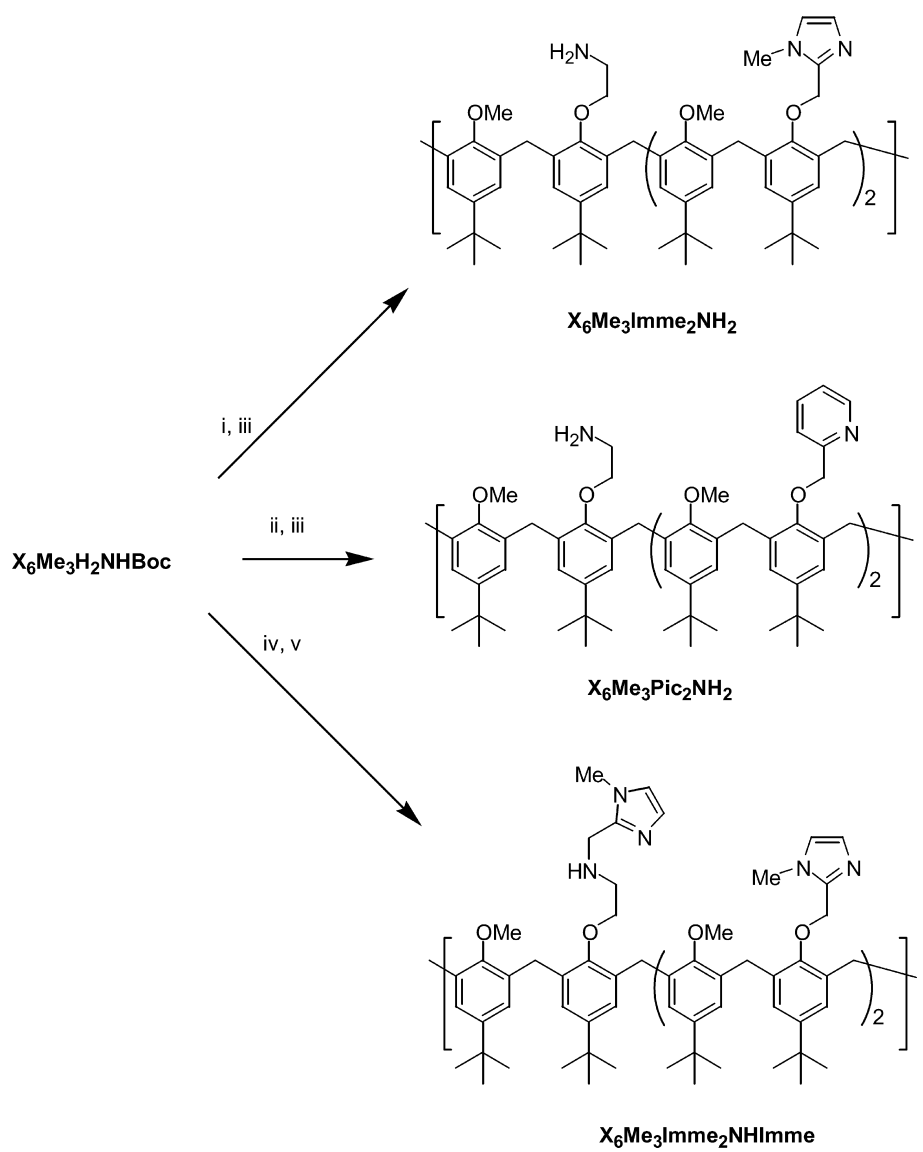


Scheme 1. Selective functionalization of $X_6Me_3H_3$. *Conditions*: NaH (3.2 equiv.), $ClCH_2CH_2NHBoc$ (5 equiv.), THF/DMF 4:1, reflux, 6 h.

OC_2H_4NHBoc arm partially included in the π-basic cavity (δ_{OCH_2}=2.55 ppm). The ^{13}C NMR resonances for the bridging methylene ($\delta_{ArCH2Ar}\approx 29-32$ ppm)[6] and a ROESY experiment confirmed that this new compound actually adopts a flattened cone conformation where the relative in and out positions of the phenolic units are the opposite of what was observed for the tri-alkylated N_3 products.[1]

2.2. Non-symmetrical N_3 and N_4 ligands

Preparation of the non-symmetrical N_3 ligand



Scheme 2. Synthesis of N_3 and N_4 ligands. *Conditions*: (i) NaH (4.55 equiv.), 2-chloromethyl-1-methylimidazole hydrochloride (2.5 equiv.), THF/DMF 5:1, reflux, 3 h; (ii) K_2CO_3 (16 equiv.), 2-chloromethylpyridine hydrochloride (6.3 equiv.), DMF, 150°C, 5 h; (iii) $CHCl_3/CF_3COOH$ 5:1, 25°C, 1 h; (iv) NaH (15 equiv.), 2-chloromethyl-1-methylimidazole hydrochloride (5 equiv.), THF/DMF 4:1, reflux, 5 h; (v) $CHCl_3/CF_3COOH$ 20:1, 25°C, 3 h.

$X_6Me_3Imme_2NH_2$, bearing one aliphatic primary amine and two imidazole moieties, was achieved by reacting $X_6Me_3H_2$(NHBoc) in a THF/DMF mixture with 2-chloromethyl-1-methylimidazole hydrochloride (2.5 equiv.) and NaH (4.55 equiv.).[7] The pyridine analog $X_6Me_3Pic_2NH_2$ was synthesized in DMF with 2-chloromethylpyridine hydrochloride and K_2CO_3 in excess as a base instead of NaH.[8] After treatment with trifluoroacetic acid, $X_6Me_3Imme_2NH_2$ and $X_6Me_3Pic_2NH_2$ were obtained in 83 and 63% yields, respectively (Scheme 2).

Reaction of $X_6Me_3H_2$(NHBoc) with an excess of 2-chloromethyl-1-methylimidazole hydrochloride and NaH in a THF/DMF mixture led to the alkylation of both phenolic functions and the NHBoc moiety. After treatment with trifluoroacetic acid new compound $X_6Me_3Imme_2NHImme$ was obtained in 91% yield (Scheme 2).

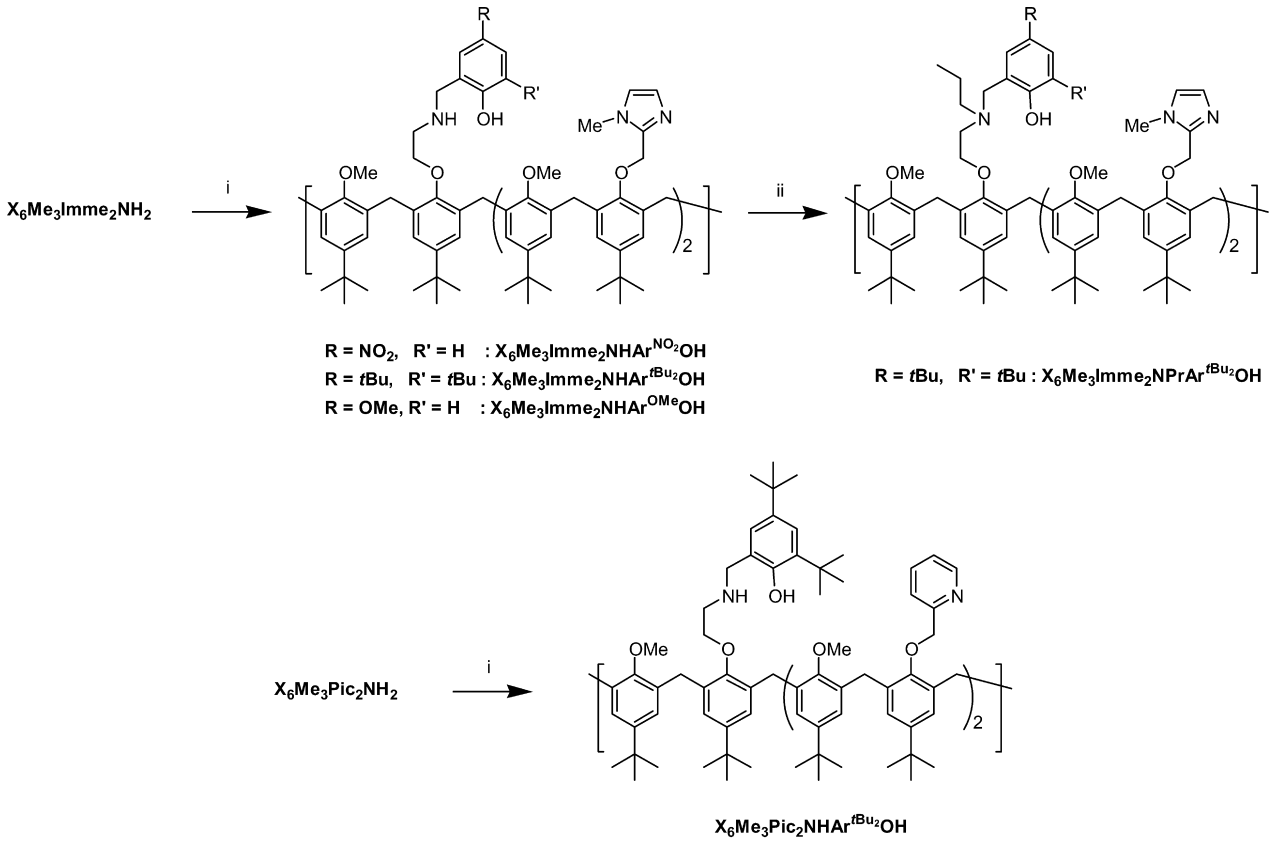
2.3. N_3Ar*O* ligands

A family of N_3Ar*O* ligands were prepared by reductive amination of $X_6Me_3Imme_2NH_2$ and $X_6Me_3Pic_2NH_2$ using various salicylaldehydes and $NaBH_4$ as the reducing agent in EtOH. Ligands $X_6Me_3Imme_2NHAr^{R,R'}OH$ and $X_6Me_3Pic_2NHAr^{tBu_2}OH$ were obtained in 50–76% yield according to Scheme 3. Finally, a ligand presenting a tertiary amine moiety in place of the secondary amine function was synthesized.[9] Indeed, $X_6Me_3Imme_2NHAr^{tBu_2}OH$ was quantitatively converted into $X_6Me_3Imme_2NPrAr^{tBu_2}OH$, bearing a *N*-propyl amino-phenol arm, by reductive amination using EtCHO and $NaBH_3CN$ in EtOH.

The ^1H NMR spectra of all these new ligands present a classical flattened C_s cone conformation with their methoxy groups folded into the π-basic cavity.

3. Discussion–conclusion

Whereas the reaction of $X_6Me_3H_3$ with various alkyl chlorides bearing amino groups yielded the tris-alkylated compound as a major product, it was possible to implement selective mono-alkylation with an aminoethyl group protected as a carbamate. According to our experiments, it seems likely that per-alkylation of $X_6Me_3H_3$ undergoes a cooperative process, whereby the introduction of a second then a third basic group (i.e. an amine) on the calixarene skeleton is due to auto-catalysis. Masking the basicity of the amino arm with a sterically encumbered Boc protecting group may well be the key for the exceptional selectivity observed for the mono-alkylation with the chloroethylamine derivative. The mono-alkylated calix[6]arene $X_6Me_3H_2$-(NHBoc) revealed to be a key synthon. Indeed, it can be further functionalized on the phenol and/or the amino moieties. This allowed us to synthesize a new set of non-symmetrical N_3, N_4 and N_3Ar*O* calix[6]arene-based ligands, that can closely mimic the coordination sphere found in some enzymes. For example, the N_3Ar*O* ligands now present a phenol group that can model the tyrosine residue encountered in galactose oxidase.[10] The various donor strength and steric hindrance provided by this novel family of biomimetic ligands should also allow the tuning of the properties of the corresponding metal complexes.



Scheme 3. Synthesis of N_3O ligands. *Conditions*: (i) 2-hydroxy-3-*R'*-5-*R*-benzaldehyde (excess), EtOH, 25°C, 1 h, $NaBH_4$ (excess), 25°C, 1 h; (ii) EtCHO (6 equiv.), $NaBH_3CN$ (2 equiv.), EtOH, 25°C, 1 h.

Complexation studies with these ligands will be reported elsewhere.

4. Experimental

4.1. General

All solvents and reagents were obtained commercially. DMF was stored over 4 Å molecular sieves under argon. THF was distilled under argon over sodium/benzophenone. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 and Bruker ARX 250 spectrometers. ^{1}H and ^{13}C resonances corresponding to anisole moieties are noted 1 (e.g. tBu^1, ArH^1, C$^1_{Ar}$) and the others are noted 2. They were assigned with HMBC and HMQC experiments. IR spectra were recorded on a Perkin–Elmer 783 spectrometer. Elemental analyses were performed at the Institut de Chimie des Substances Naturelles, France.

4.1.1. 5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38-[2-[[(*tert*-butyloxy)carbonyl]-amino]-ethoxy]-calix[6]arene-40,42-diol [$X_6Me_3H_2$(NHBoc)]. Under an argon atmosphere, NaH (60% in oil, 252 mg, 6.3 mmol) and DMF (20 mL) were added to a solution of $X_6Me_3H_3$ (5,11,17,23,29,35-hexa-*tert*-butyl-37,39,41-trimethoxycalix[6]arene-38,40,42-triol)[11] (2.0 g, 1.97 mmol) in THF (80 mL). The reaction mixture was stirred for 30 min at room temperature and $ClCH_2CH_2NHBoc$[5] (1.77 g, 9.8 mmol) was introduced. After 6 h of refluxing, the solvent was concentrated under reduced pressure to a quarter of the volume and water (100 mL) was poured into the solution. The resulting precipitate was collected by filtration and dissolved in CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. Pentane was added to the yellow residue. A white precipitate of non converted $X_6Me_3H_3$ appeared and was filtered off. The filtrate was evaporated under reduced pressure. Column chromatography on silica gel using CH_2Cl_2/AcOEt 97:3 as the eluent yielded $X_6Me_3H_2$-(NHBoc) as a white powder (1.42 g). Yield: 75% (based on 82% converted $X_6Me_3H_3$). Mp: 165°C. IR (KBr): ν=1720 (C=O), 1535, 1515, 1488, 1440, 1420, 1398, 1365, 1295, 1250 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.57 (s, 9H, tBu^1), 1.02 (s, 18H, tBu^1), 1.25 (s, 18H, tBu^2), 1.38 (s, 9H, tBu^2), 1.47 (s, 9H, OtBu), 2.55 (s, 4H, OCH_2+NCH_2), 3.40 (s, 3H, OCH_3), 3.45 (d, J=14 Hz, 2H, Ar-αCH_{eq}), 3.55 (d, J=14 Hz, 2H, Ar-αCH_{eq}), 3.62 (d, J=14 Hz, 2H, Ar-αCH_{eq}), 3.88 (s, 3H, OCH_3), 4.22 (d, J=14 Hz, 2H, Ar-αCH_{ax}), 3.45 (d, J=14 Hz, 2H, Ar-αCH_{eq}), 4.28 (d, J=14 Hz, 2H, Ar-αCH_{ax}), 4.64 (d, J=14 Hz, 2H, Ar-αCH_{ax}), 5.53 (s, 1H, NH), 6.17 (s, 2H, ArH^1), 6.93 (d, J=2.0 Hz, 2H, ArH^1), 6.94 (d, J=2.3 Hz, 2H, ArH^2), 6.98 (d, J=2.0 Hz, 2H, ArH^1), 7.17 (d, J=2.3 Hz, 2H, ArH^2), 7.27 (s, 2H, ArH^2), 7.43 (s, 2H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.7 (OC(CH_3)$_3$), 29.0 (Ar-αCH_2), 30.7 (Ar-αCH_2), 31.2 (C(CH_3)$_3$), 31.6 (C(CH_3)$_3$), 32.0 (Ar-αCH_2), 33.7 (OC(CH_3)), 33.9 (C(CH_3)$_3$), 34.2 (C(CH_3)$_3$), 40.2 (NCH_2), 59.8 (OCH_3), 61.6 (OCH_3), 73.3 (OCH_2), 124.1 (C_{Ar}H), 124.2 (C_{Ar}H), 124.8 (C_{Ar}H), 125.5 (C_{Ar}H), 126.1 (C_{Ar}–CH_2), 126.2 (C_{Ar}–CH_2), 126.7 (C_{Ar}H), 127.8 (C_{Ar}H), 131.9 (C_{Ar}–CH_2), 132.2 (C_{Ar}–CH_2), 133.1 (C_{Ar}–CH_2), 133.3 (C_{Ar}–CH_2), 142.2 (C_{Ar}), 145.7 (C_{Ar}), 145.8 (C_{Ar}), 147.2 (C_{Ar}), 150.6 (C_{Ar}O), 151.3 (C_{Ar}O), 153.2 (C_{Ar}O), 153.3 (C_{Ar}O), 156.7 (C=O). Anal. calcd for $C_{76}H_{103}NO_8$: C 78.78, H 8.96, N 1.21; found C 78.74, H 9.01, N 1.18.

4.1.2. 5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38-[2-(amino)ethoxy]-40,42-bis[(1-methyl-2-imidazolyl)methoxy]calix[6]arene ($X_6Me_3Imme_2NH_2$). Under an argon atmosphere, 2-chloromethyl-1-methylimidazole hydrochloride[12] (505 mg, 3.02 mmol) was introduced into a solution of $X_6Me_3H_2$(NHBoc) (1.40 g, 1.21 mmol) in THF (60 mL). NaH (60% in oil, 220 mg, 5.5 mmol) and DMF (12 mL) were added to the reaction mixture. After 3 h on refluxing, the solvent were concentrated under reduced pressure to a quarter of the volume and water (100 mL) was poured into the solution. The resulting precipitate was collected by filtration and dissolved in CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was dissolved in a $CHCl_3$/CF_3COOH 5:1 mixture (12 mL). The solution was stirred for 1.5 h and evaporated under reduced pressure. The oily residue was dissolved in CH_2Cl_2. The organic layer was washed with 1N NaOH, dried (Na_2SO_4) and evaporated under reduced pressure. Recrystallization in CH_2Cl_2/CH_3CN yielded $X_6Me_3Imme_2$-NH_2 as a white powder (1.1 g). Yield: 83%. Mp: 177°C. IR (KBr): ν=1500, 1481, 1479, 1468, 1465, 1454, 1414, 1392, 1362, 1292, 1285, 1245 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.82 (s, 27H, tBu), 1.34 (s, 18H, tBu), 1.37 (s, 9H, tBu), 2.14 (s, 3H, OCH_3), 2.31 (s, 6H, OCH_3), 2.99 (br t, 2H, NCH_2CH_2O), 3.23 (d, J=14.8 Hz, 2H, Ar-αCH_{eq}), 3.27 (d, J=14.8 Hz, 2H, Ar-αCH_{eq}), 3.50 (d, J=14.8 Hz, 2H, Ar-αCH_{eq}), 3.77 (br t, 2H, OCH_2CH_2N), 3.88 (s, 6H, NCH_3), 4.3–4.5 (m, 6H, Ar-αCH_{ax}), 5.02 (s, 4H, OCH_2Im), 6.66 (s, 2H, ArH), 6.68 (s, 4H, ArH), 6.91 (s, 2H, ImH), 6.99 (s, 2H, ImH), 7.20 (s, 2H, ArH), 7.23 (s, 2H, ArH). Anal. calcd for $C_{81}H_{111}N_5O_8{\cdot}2H_2O$ C 75.84, H 8.72, N 5.46; found C 75.74, H 8.74, N 5.54.

4.1.3. 5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38-[2-(amino)ethoxy]-40,42-bis[(2-pyridinyl)-methoxy]calix[6]arene ($X_6Me_3Pic_2NH_2$). Under an argon atmosphere, 2-chloromethylpyridine hydrochloride (1.05 g, 6.4 mmol) and K_2CO_3 (2.2 g, 16 mmol) were introduced into a solution of $X_6Me_3H_2$(NHBoc) (1.86 g, 1.6 mmol) in DMF (100 mL). The mixture was stirred for 3 h at 150°C. The solvent was evaporated under reduced pressure. The residue was dissolved in Et_2O. The organic solution was washed once with water, twice with brine and once with water, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was dissolved in a $CHCl_3$/CF_3COOH 5:1 mixture (48 mL). The solution was stirred for 1 h and evaporated under reduced pressure. The oily residue was dissolved in CH_2Cl_2. The organic solution was washed with 1N aq. NaOH, dried (Na_2SO_4) and evaporated under reduced pressure. Trituration in pentane yielded X_6Me_3-Pic_2NH_2 as a white powder (1.31 g). Yield: 67%. Mp: 234°C. IR (KBr): ν=1593, 1481, 1435, 1393, 1362, 1291, 1244 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.88 (s, 27H, tBu), 1.32 (s, 18H, tBu), 1.38 (s, 9H, tBu), 2.28 (s, 3H, OCH_3), 2.43 (s, 6H, OCH_3), 2.96 (br, 2H, NCH_2CH_2), 3.2–4.8 (br m, 14H, Ar-αCH_{eq}+Ar-αCH_{ax}+OCH_2CH_2), 5.10 (s, 4H, OCH_2Py), 6.74 (s, 4H, ArH), 6.80 (s, 2H, ArH), 7.1–7.4

(m, 7H, ArH+PyH), 7.76 (br t, 1H, PyH), 7.89 (br d, 1H, PyH), 8.57 (d, J=4.6 Hz, 1H, PyH). Anal. calcd for $C_{83}H_{105}N_3O_6$: C 80.35, H 8.53, N 3.39; found C 80.07, H 8.79, N 3.45.

4.1.4. 5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38-[2-[[(1-methyl-2-imidazolyl)methyl]amino]-ethoxy]-40,42-bis[(1-methyl-2-imidazolyl)methoxy]-calix[6]arene ($X_6Me_3Imme_2NHImme$). Under an argon atmosphere, $X_6Me_3H_2$(NHBoc) (400 mg, 0.345 mmol) was added to a suspension of NaH (60% in oil, 5,18 mmol) in THF (20 mL). After 15 min on stirring, DMF (5 mL) was added, followed 15 min later by 2-chloromethyl-1-methyl-imidazole hydrochloride[12] (346 mg, 2,07 mmol). After 5 h on refluxing, the solvent were concentrated under reduced pressure to a quarter of the volume and water (50 mL) was poured into the solution. The resulting precipitate was collected by filtration and dissolved in CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was dissolved in a CH_2Cl_2/CF_3COOH 20:1 mixture (10.5 mL). The solution was stirred for 3 h and evaporated under reduced pressure. The oily residue was dissolved in CH_2Cl_2. The organic layer was washed once with 1N NaOH and twice with H_2O, dried over (Na_2SO_4) and evaporated under reduced pressure. Trituration in pentane yielded $X_6Me_3Imme_2NHImme$ as a white powder (435 mg). Yield: 91%. Mp: 173°C (dec.). IR (KBr): ν=1505, 1488, 1470, 1462, 1420, 1399, 1365, 1290 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=0.76 (s, 9H, *t*Bu), 0.78 (s, 18H, *t*Bu), 1.37 (s, 27H, *t*Bu), 2.16 (s, 9H, OCH_3), 3.08 (br t, 2H, NCH_2CH_2O), 3.21 (d, J=15 Hz, 4H, Ar-αCH_{eq}), 3.38 (d, J=15 Hz, 2H, Ar-αCH_{eq}), 3.69 (s, 3H, NCH_3), 3.89 (s, 6H, NCH_3), 3.99 (br t, 2H, OCH_2CH_2N), 4.01 (s, 2H, NCH_2Im), 4.46 (d, J=15 Hz, 4H, Ar-αCH_{ax}), 4.54 (d, J=15 Hz, 2H, Ar-αCH_{ax}), 5.02 (s, 4H, OCH_2Im), 6.60 (s, 2H, ArH), 6.64 (s, 4H, ArH), 6.82 (s, 1H, ImH), 6.92 (s, 3H, ImH), 6.98 (s, 2H, ImH), 7.23 (s, 6H, ArH). Anal. calcd for $C_{86}H_{113}N_7O_6{\cdot}0.5H_2O$: C 76.52, H 8.51, N 7.26; found C 76.78, H 8.56, N 6.74.

4.1.5. 5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38-[2-[[(5-nitro-2-hydroxy)benzyl]amino]-ethoxy]-40,42-bis[(1-methyl-2-imidazolyl)methoxy]-calix[6]arene ($X_6Me_3Imme_2NHAr^{NO2}OH$). 2-Hydroxy-5-nitro-benzaldehyde (100.5 mg, 0.60 mmol) was introduced into a solution of $X_6Me_3Imme_2NH_2$ (500 mg, 0.40 mmol) in EtOH (50 mL). The yellow mixture was stirred for 1 h at room temperature. $NaBH_4$ (30.3 mg, 0.80 mmol) was added at 0°C. The solution was stirred for 1 h at room temperature. 1N aq. HCl was added until a white precipitate was formed. The suspension was stirred for 5 min and 1N aq. NaOH was added (pH ≈11–12). The suspension was extracted with AcOEt. The organic layer was washed with H_2O, dried (Na_2SO_4) and evaporated under reduced pressure. Recrystallization in CH_2Cl_2/pentane yielded $X_6Me_3Imme_2NHAr^{NO2}OH$ as a yellow powder (384 mg). Yield: 73%. Mp: 184°C. IR (KBr): ν=1589 (NO_2), 1499, 1492, 1480, 1450, 1414, 1392, 1362, 1285, 1235 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ=0.79 (s, 27H, *t*Bu), 1.36 (s, 27H, *t*Bu), 2.19 (s, 9H, OCH_3), 3.07 (br t, 2H, NCH_2CH_2), 3.23 (d, J=15.5 Hz, 4H, Ar-αCH_{eq}), 3.40 (d, J=15.5 Hz, 2H, Ar-αCH_{eq}), 3.88 (s, 6H, NCH_3), 4.00 (br t, 2H, OCH_2CH_2), 4.23 (s, 2H, NCH_2), 4.45 (d, J=15.5 Hz, 4H, Ar-αCH_{ax}), 4.50 (d, J=15.5 Hz, 4H, Ar-αCH_{ax}), 5.03 (s, 4H, OCH_2Im), 6.64 (s, 4H, ArH), 6.67 (s, 2H, ArH), 6.84 (d, J=8.8 Hz, 1H, Ar^{OH}-*o*-H), 6.92 (s, 2H, ImH), 6.98 (s, 2H, ImH), 7.24 (s, 6H, ArH), 8.01 (d, J=2.8 Hz, 1H, Ar^{OH}-*m*′-H), 8.06 (dd, ^3J=8.8 Hz, ^4J=2.8 Hz, 1H, Ar^{OH}-*m*-H). Anal. calcd for $C_{88}H_{112}N_6O_9{\cdot}H_2O$: C 74.65, H 8.12, N 5.94; found C 74.78, H 7.97, N 5.76.

4.1.6. 5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38-[2-[[(3,5-di-*tert*-butyl-2-hydroxy)benzyl]-amino]-ethoxy]-40,42-bis[(1-methyl-2-imidazolyl)-methoxy]calix[6]arene ($X_6Me_3Imme_2NHAr^{tBu_2}OH$). The title compound was synthesized from $X_6Me_3Imme_2NH_2$ (890 mg, 0.71 mmol) following the procedure described for $X_6Me_3Imme_2NHAr^{NO2}OH$ with EtOH (50 mL), 2-hydroxy-3,5-di-*tert*-butyl-benzaldehyde (251 mg, 1.07 mmol) and $NaBH_4$ (54 mg, 1.42 mmol). Work-up with CH_2Cl_2 and recrystallization in acetonitrile yielded $X_6Me_3Imme_2NHAr^{tBu_2}OH$ as a white powder (810 mg). Yield: 76%. Mp: 239°C. IR (KBr): ν=1500, 1492, 1480, 1452, 1414, 1414, 1392, 1362, 1287, 1245 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ=0.76 (s, 9H, *t*Bu), 0.79 (s, 18H, *t*Bu), 1.27 (s, 9H, *t*Bu), 1.37 (s, 27H, *t*Bu), 1.39 (s, 9H, *t*Bu), 2.15 (s, 3H, OCH_3), 2.17 (s, 6H, OCH_3), 3.10 (br t, 2H, NCH_2CH_2), 3.21 (d, J=14.6 Hz, 4H, Ar-αCH_{eq}), 3.41 (d, J=14.7 Hz, 2H, Ar-αCH_{eq}), 3.89 (s, 6H, NCH_3), 4.03 (br t, 2H, OCH_2CH_2), 4.10 (s, 2H, NCH_2Im), 4.45 (d, J=14.6 Hz, 4H, Ar-αCH_{ax}), 4.52 (d, J=14.7 Hz, 2H, Ar-αCH_{ax}), 5.01 (s, 4H, OCH_2Im), 6.61 (s, 2H, ArH), 6.65 (s, 4H, ArH), 6.89 (d, J=2 Hz, 1H, Ar^{OH}H), 6.91 (s, 2H, ImH), 6.97 (d, J=1.2 Hz, 2H, ImH), 7.21 (d, J=2 Hz, 1H, Ar^{OH}H), 7.23 (s, 2H, ArH), 7.24 (s, 4H, ArH). Anal. calcd for $C_{96}H_{131}N_5O_8{\cdot}H_2O$: C 77.74, H 8.90, N 4.72; found C 77.48, H 9.02, N 4.74.

4.1.7. 5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38-[2-[[(5-methoxy-2-hydroxy)benzyl]amino]-ethoxy]-40,42-bis[(1-methyl-2-imidazolyl)methoxy]-calix[6]arene ($X_6Me_3Imme_2NHAr^{OMe}OH$). The title compound was synthesized from $X_6Me_3Imme_2NH_2$ (500 mg, 0.40 mmol) following the procedure described for $X_6Me_3Imme_2NHAr^{NO2}OH$ with EtOH (50 mL), 2-hydroxy-5-methoxy-benzaldehyde (0.10 mL, 0.80 mmol) and $NaBH_4$ (45.4 mg, 1.2 mmol). Work-up with CH_2Cl_2 and recrystallization in CH_2Cl_2/pentane yielded $X_6Me_3Imme_2NHAr^{OMe}OH$ as a white powder (384 mg). Yield: 69%. Mp: 180°C. IR (KBr): ν=1500, 1492, 1480, 1452, 1414, 1392, 1362, 1287, 1245 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ=0.78 (s, 27H, *t*Bu), 1.37 (s, 27H, *t*Bu), 2.17 (s, 9H, OCH_3), 3.07 (br t, 2H, NCH_2CH_2), 3.22 (d, J=15.4 Hz, 4H, Ar-αCH_{eq}), 3.40 (d, J=14.8 Hz, 2H, Ar-αCH_{eq}), 3.73 (s, 3H, *p*-OCH_3-Ar^{OH}), 3.89 (s, 6H, NCH_3), 4.01 (br t, 2H, OCH_2CH_2), 4.11 (s, 2H, NCH_2), 4.45 (d, J=15.5 Hz, 4H, Ar-αCH_{ax}), 4.51 (d, J=15.5 Hz, 2H, Ar-αCH_{ax}), 5.02 (s, 4H, OCH_2Im), 6.64 (s, 7H, ArH+Ar^{OH}H), 6.74 (m, 2H, Ar^{OH}H), 6.92 (s, 2H, ImH), 6.98 (s, 2H, ImH), 7.23 (s, 2H, ArH), 7.24 (s, 4H, ArH). Anal. calcd for $C_{89}H_{115}N_5O_8{\cdot}H_2O$: C 76.30, H 8.42, N 5.00; found C 76.59, H 8.46, N 4.84.

4.1.8. 5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38-[2-[[(3,5-di-*tert*-butyl-2-hydroxy)benzyl]-amino]-ethoxy]-40,42-bis[(2-pyridinyl)methoxy]calix[6]-arene ($X_6Me_3Pic_2NHAr^{tBu_2}OH$). The title compound was synthesized from $X_6Me_3Pic_2NH_2$ (336 mg, 0.27 mmol)

following the procedure described for $X_6Me_3Pic_2NHAr^{NO2}OH$ with EtOH (20 mL), 2-hydroxy-3,5-di-*tert*-butyl-benzaldehyde (76 mg, 0.32 mmol) and $NaBH_4$ (20 mg, 540 mmol). Work-up with CH_2Cl_2 and purification by column chromatography on silica gel using C_6H_{12}/AcOEt 85:15 as the eluent yielded $X_6Me_3Pic_2NHAr^{tBu2}OH$ as a white powder (200 mg). Yield: 50%. Mp: 144°C. IR (KBr): ν=1594, 1482, 1435, 1392, 1362, 1291, 1291, 1238 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ=0.79 (s, 9H, *t*Bu), 0.83 (s, 18H, *t*Bu), 1.25 (s, 9H, *t*Bu), 1.37 (s, 36H, *t*Bu), 2.15 (s, 3H, OCH_3), 2.17 (s, 6H, OCH_3), 3.10 (br m, 1H, $NCHH'CH_2O$), 3.42 (d, J=15 Hz, 6H, Ar-αCH_{eq}), 4.05 (br m, 2H, $NCHH'CH_2O$+$NCH_2CHH'O$), 4.10 (s, 2H, NCH_2ArOH), 4.22 (br m, 1H, $NCH_2CHH'O$), 4.53 (d, J=15 Hz, 2H, Ar-αCH_{ax}), 4.60 (d, J=15 Hz, 4H, Ar-αCH_{ax}), 5.10 (s, 4H, OCH_2Py), 6.67 (s, 2H, ArH), 6.72 (s, 4H, ArH), 6.88 (d, J=2.5 Hz, 1H, $Ar^{OH}H$), 7.20 (d, J=2.5 Hz, 1H, $Ar^{OH}H$), 7.22–7.29 (m, 8H, ArH+PyH), 7.80 (br t, 2H, PyH), 7.92 (br d, 2H, PyH), 8.56 (d, J=4.6 Hz, 2H, PyH). Anal. calcd for $C_{98}H_{127}N_3O_7$: C 80.67, H 8.77, N 2.88; found C 80.87, H 9.07, N 2.83.

4.1.9. 5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38-[2-[*N*-[(3,5-di-*tert*-butyl-2-hydroxy)-benzyl],*N*-propylamino]-ethoxy]-40,42-bis[(1-methyl-2-imidazolyl)methoxy]calix[6]arene ($X_6Me_3Imme_2NPrAr^{tBu2}OH$). Propionaldehyde (0.12 mL, 1.78 mmol) was introduced into a solution of $X_6Me_3Imme_2NHAr^{tBu2}OH$ (435 mg, 0.30 mmol) in EtOH (20 mL).After 1 h on stirring at room temperature, $NaBH_3CN$ (37.3 mg, 0.60 mmol) was added and the reaction mixture was stirred for an additional hour. 10 drop of conc. HCl was added and the suspension was stirred for 1 h. 1N aq. NaOH was added (pH ≈11–12). The suspension was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4) and evaporated under reduced pressure. Recrystallization in acetonitrile yielded $X_6Me_3Imme_2NPrAr^{tBu2}OH$ as a white powder (450 mg). Yield: 100%. Mp: 149°C. IR (KBr): ν=1500, 1482, 1462, 1412, 1390, 1362, 1286, 1239 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ=0.76 (s, 9H, *t*Bu), 0.77 (s, 18H, *t*Bu), 0.92 (t, J=7.3 Hz, 3H, $NCH_2CH_2CH_3$), 1.25 (s, 9H, *t*Bu), 1.38 (s, 36H, *t*Bu), 1.62 (m, 2H, $NCH_2CH_2CH_3$), 2.12 (s, 3H, OCH_3), 2.16 (s, 6H, OCH_3), 2.68 (t, J=7.3 Hz, 3H, $NCH_2CH_2CH_3$), 3.06 (t, J=6.5 Hz, 2H, NCH_2CH_2O), 3.21 (d, J=15.0 Hz, 4H, Ar-αCH_{eq}), 3.33 (d, J=15.4 Hz, 2H, Ar-αCH_{eq}), 3.87 (s, 2H, NCH_2Im), 3.89 (s, 6H, NCH_3), 4.00 (t, J=6.5 Hz, 2H, OCH_2CH_2N), 4.45 (d, J=15.0 Hz, 4H, Ar-αCH_{ax}), 4.50 (d, J=15.4 Hz, 2H, Ar-αCH_{ax}), 5.02 (s, 4H, OCH_2Im), 6.60 (s, 2H, ArH), 6.62 (s, 4H, ArH), 6.83 (d, J=2.5 Hz, 1H, $Ar^{OH}H$), 6.91 (s, 2H, ImH), 6.97 (d, J=1.2 Hz, 2H, ImH), 7.17 (d, J=2.5 Hz, 1H, $Ar^{OH}H$), 7.23 (s, 2H, ArH), 7.24 (s, 4H, ArH). Anal. calcd for $C_{99}H_{137}N_5O_8{\cdot}H_2O$: C 77.96, H 9.05, N 4.59; found C 77.93, H 9.23, N 4.52.

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8. With NaH, no alkylated product was formed, which may well be due to degradation of 2-chloromethylpyridine.
9. It is known that complexes of some transition metal with secondary amine-based ligands may not be stable toward O_2 and may decompose into complexes where the secondary amine function of the ligand is oxidized into an imine. To avoid this problem, we checked that the N_3ArO ligands could be transformed into ligands with a tertiary amine arm.
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