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A Novel Receptor Based on a C_{3v}-Symmetrical PN_3-Calix[6]cryptand

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Abstract: A C_{3v}-symmetrical PN_3-calix[6]cryptand was prepared in six steps from the known 1,3,5-tris-methylated calix[6]arene through a remarkably efficient [1 + 1] macrocyclization reaction. A ^{1}H NMR study showed that the P,N-crypto cap rigidifies the whole edifice in a cone conformation ideal for molecular recognition applications. The ability of this new receptor to perform selective endo-complexation is illustrated with ammonium guests.

Readily available calix[6]arenes can be useful building blocks for the preparation of molecular receptors.[1] However, to obtain good hosts, it has been shown that the flexible calix[6]arenes have to be constrained in a cone conformation through their capping at one rim. A straightforward strategy consists of their grafting of nitrogenous arms at the narrow rim. Upon binding to a metal ion, the whole calixarene structure becomes rigidified and displays remarkable host properties. Hence, the resulting *funnel complexes* can coordinate a neutral guest inside a well-defined and selective hydrophobic cavity.[2] However, these edifices suffer from the weakness of the coordination links. To remedy this problem, we were interested in the synthesis of novel derivatives whose coordinating arms would be further connected by covalent bridges. Such cage-like calix[6]arenes are expected to possess reinforced complexation abilities toward metal ions or organic guests. Yet, the synthesis of such structures is far from straightforward. Indeed, if calix[6]arenes bearing dipodal subunits have been prepared,[3] there is only a few reports on tripodal calix[6]cryptands.[4] One way for the introduction of an aza-cap consists of the macrocyclization of a nitrogenous tripod with a calixarene prefunctionalized with three electrophilic arms. This approach led to the synthesis of calix[6]tren[5] as the first member of the so-called N_3-calix[6]cryptands. An alternative way consists of the establishment of covalent links between the nitrogenous arms pregrafted on the calixarene. Indeed, we recently showed that condensation of calix[6]triamine **1** with formaldehyde gives rise to a triazacyclohexane-capped calixarene, namely, calix[6]TAC.[6] This route has now been extended with a trisaldehyde. The key step is a remarkably efficient condensation of a triphenylphosphine derivative with **1** to give a calixtrisimine, which could be subsequently reduced into a trisamine. These two PN_3-calix[6]cryptands are the first of their kind.[7] Preliminary host−guest studies with the latter revealed very promising features.

The calixarene synthon **1** was obtained according to an efficient two-step sequence (77% overall yield)[6] from the symmetrically 1,3,5-tris-*O*-methylated calix[6]arene ($X_6H_3Me_3$).[8] A triphenylphosphine bearing aldehyde substituents in the *ortho* position of the phenyl rings (**2**)[9] was chosen as the P,N-capping unit. Macrocyclization of **1** with trisaldehyde **2** was performed in one pot by first mixing the reactants in dichloromethane for 16 h and then refluxing the reaction mixture in absolute ethanol for 2 h. Under these specific conditions, calix[6]trisimine **3** was isolated in high yield (91%). When carried out only in dichloromethane or ethanol, the reaction led to intermediate products or lower yields, respectively. It is noteworthy that among the many different tripodal aldehydes that we tested (mostly 1,3,5-sustituted benzenes bearing aldehydic arms), only **2** displayed such a remarkable reactivity with calix[6]triamine **1**. It shows

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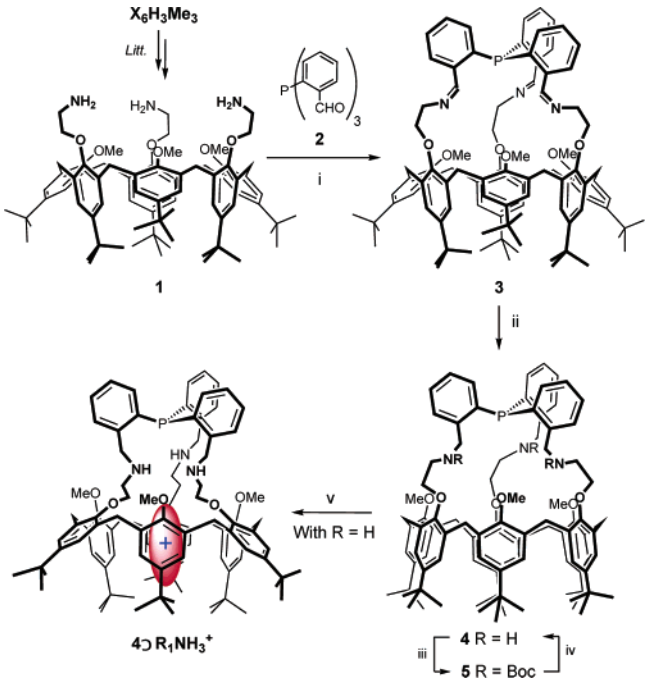
SCHEME 1. Synthesis of C_{3v}-symmetrical PN_3-calix[6]cryptands and endo-Complexation of Ammoniums by 4[a]



[a] (i) CH_2Cl_2, rt, 16 h then EtOH, reflux, 2 h, 91%. (ii) $NaBH_4$, EtOH, CH_2Cl_2, 0 °C then rt. (iii) $(Boc)_2O$, TEA, THF, 0 °C then rt, 16 h, 36% overall yield from 3. (iv) TFA, CH_2Cl_2, rt, 8 h, 93%. (v) $R_1NH_3^+ \cdot Pic^-$, $CDCl_3/CD_3OD$ (98:2).

that the P,N-cap perfectly fits from a geometrical point of view with the calixarene structure. Surprisingly, the reduction of trisimine **3** was difficult to manage. All of the reducing agents tested so far under various conditions[10] led to a mixture of unidentified compounds in addition to the awaited C_{3v}-symmetrical PN_3-calix[6]-cryptand **4**. The best result was finally obtained by adding, dropwise at low temperature, trisimine **3** to a large excess of $NaBH_4$ in ethanol. Last, to isolate the desired compound **4**, a two-step purification sequence was necessary (crystallization or chromatography remained, in our hands, unsuccessful). Thus, **4** was converted into its carbamate derivative **5**, which was purified by flash chromatography on silica gel (36% overall yield from **3**). Final deprotection (93% yield) of the amino groups with trifluoroacetic acid (TFA) led to compound **4**. Thus, the C_{3v}-symmetrical PN_3-calix[6]cryptands **3** and **4** were obtained in three and six steps from $X_6H_3Me_3$ with 70% and 23% overall yields, respectively (Scheme 1).

The conformations of the PN_3-calix[6]cryptands **3** and **4** were studied by ^1H NMR analysis. Their overall room temperature profiles ($CDCl_3$) were characteristic of a major C_{3v}-symmetrical cone conformation with the methoxy substituents pointing toward the inside of the cavity (see Figure 1a for compound **4**). Two sharp doublets for the $ArCH_2$ methylene protons attested to the rigidification of the edifices as a consequence of the capping by the PN_3 unit. A careful comparison of the spectra of cryptands **3** and **4** yet evidenced some noticeable differences:

(i) Their methoxy resonances are differently high-field shifted: $\delta_{OMe} = 2.42$ and 2.87, respectively.

(ii) The two *t*Bu signals of **4** display only a small difference in δ shifts ($\Delta\delta_{tBu} = 0.09$ ppm) compared to those of **3** ($\Delta\delta_{tBu} = 0.58$ ppm).

(iii) The same observation can be made for the aromatic protons of the calixarene walls ($\Delta\delta_{ArH} = 0.04$ ppm for **4** and $\Delta\delta_{ArH} = 0.54$ ppm for **3**).

All of this indicates that, whereas the calix[6]arene structure of cryptand **3** adopts a classical alternate flattened cone conformation, cryptand **4** stands in a straight and regular cone conformation (Scheme 1). Such a differing behavior may be due to the presence of a hydrogen-bonding network between the amino groups, as was observed for other related calixarenes bearing protic arms.[5,6]

The ability of PN_3-calix[6]cryptand **4** to complex cationic ammonium guests, as does the closely related calix-[6]TAC receptor, was investigated by ^1H NMR. First, the study was conducted at 293 K by introducing progressively a CD_3OD solution of either ethyl- or propylammonium picrate salts ($R_1NH_3^+$, Pic^-) into a $CDCl_3$ solution of receptor **4** (Scheme 1). In both cases, the C_{3v} NMR signature of the receptor considerably broadened. However, the formation of endo-complexes $\mathbf{4}\supset R_1NH_3^+$ were evidenced thanks to the appearance of extra resonances in the high-field region. Indeed, broad signals corresponding to the alkyl groups of the ammonium guest were observed at $\delta_{Me} = -1.69$ ppm for R_1 = Et and at $\delta_{Me} = -1.91$ and $\delta_{CH2} = -1.20$ ppm for R_1 = Pr. It is noteworthy that the *in* and *out* exchange process of the guests was relatively slow at room temperature (vs the NMR time scale), which attests to their strong binding in the cavity. However, on one hand, increasing the amount of ammonium salt above the stoichiometry barely increased the quantity of endo-complexes $\mathbf{4}\supset R_1NH_3^+$. On the other hand, lowering the temperature led to the growth of the signals of the included guests and a splitting of the host resonances.[11] At 233 K, the major species presented a C_{3v}-symmetrical profile with 1 equiv of high-field shifted ammonium, which corresponds to the expected endo-complex $\mathbf{4}\supset R_1NH_3^+$. The minor species exhibited a contrasting dissymmetrical profile with differentiated aromatic and *t*Bu signals. A superimposable dissymmetrical NMR signature was actually obtained at 233 K upon the addition of picric acid (1 equiv) into a solution of free cryptand **4**.[12] Hence, this species was unambiguously identified as the monoprotonated host $\mathbf{4}\cdot H^+$ that is in equilibrium with the endo-complex according to equation: $\mathbf{4}\supset R_1NH_3^+ \rightleftarrows \mathbf{4}\cdot H^+ + R_1NH_2$. Indeed, a low temperature favors the enthalpy-driven binding of

(10) Reducing agent tested from a slight to a large excess and at different concentrations (in EtOH, THF, or CH_2Cl_2): $NaBH(OAc)_3$, $LiAlH_4$, $NaBH_4$, $NaBH_3CN$, BH_3, H_2/Pd^0. Moreover, the direct reaction of trisamine **1** and trisaldehyde **2** in the presence of either $NaBH(OAc)_3$ or $NaBH_3CN$ under various conditions (Brönsted or Lewis acid catalysis) did not improve the crude yield in **4** according to the ^1H NMR analyses of the reaction mixtures.

(11) The coalescence between the signals of the two species was observed between 253 and 278 K.

(12) A variable temperature ^1H NMR study has shown that $\mathbf{4}\cdot H^+$ displayed a C_{3v}-symmetrical signature at 330 K (see Supporting Information). Addition of an excess of picric acid (5 equiv) to a $CDCl_3$ solution of **4** led to a different species possessing a C_{3v} symmetry even at 233 K and identified as the fully protonated receptor $\mathbf{4}\cdot 3H^+$. This latter will be described elsewhere.

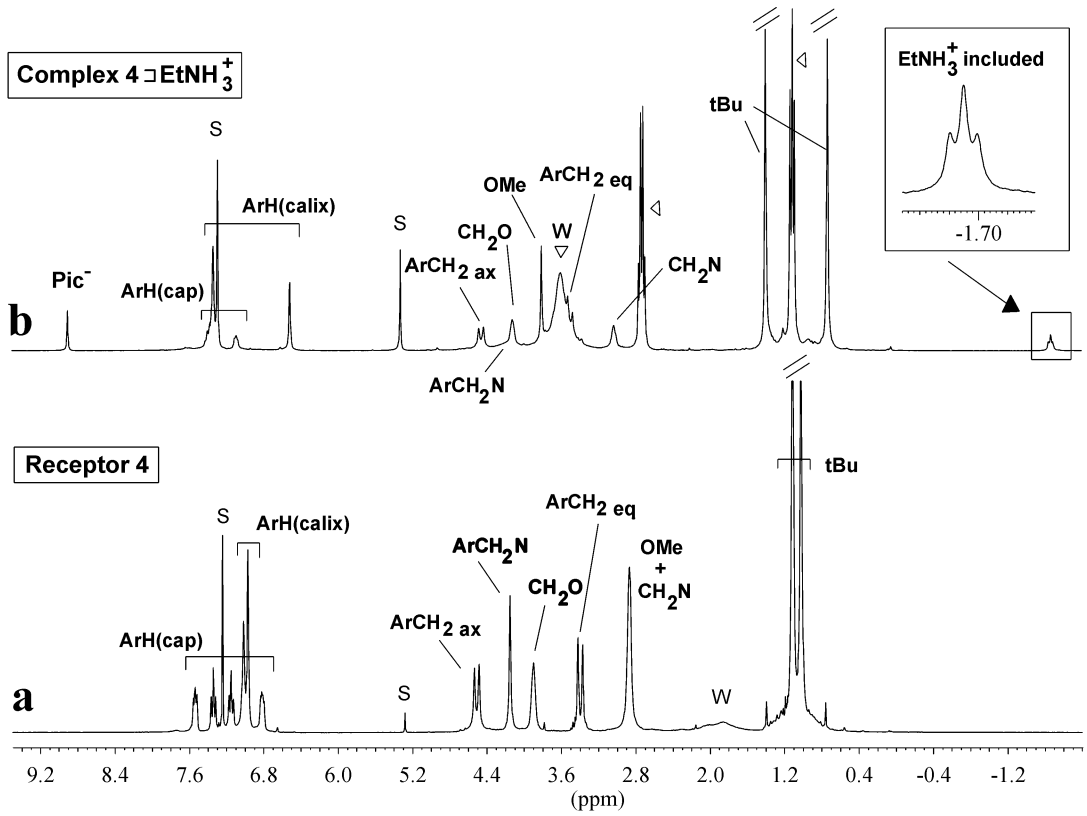


FIGURE 1. (a) ^{1}H NMR (300 MHz) spectra of receptor **4** at 298 K in $CDCl_3$. (b) ^{1}H NMR (300 MHz) spectra of the complex **4**⊃$EtNH_3^+$ at 233 K in $CDCl_3/CD_3OD$ (98:2). Residual solvent, water, and free guest are labeled S, W, and ▽, respectively.

the organic guest thanks to the establishment of cationic- and CH-π interactions within the calixarene cavity.[13] Also in agreement with the Le Châtelier principle, the equilibrium could be totally displaced toward the formation of the inclusion complex **4**⊃$R_1NH_3^+$ by further addition of an excess (ca. 15 equiv) of free amine R_1NH_2 (Figure 1b for R_1 = Et).

The NMR spectra of complexes **4**⊃$EtNH_3^+$[14] and **4**⊃$PrNH_3^+$ showed similarities in their structural features:

(i) Upon complexation the MeO groups are projected away from the cavity as shown by their normal resonance (δ_{OMe} = 3.80 ppm in both cases).

(ii) As a result, the calixarene *t*Bu substituents reverse their relative alternate *in* and *out* positions compared to free host **4** and the calixarene cone is flattened ($\Delta\delta_{tBu}$ = 0.66 and 0.64 ppm with R_1 = Et and Pr, respectively).

(iii) A slight downfield shift (+0.14 ppm with R_1 = Et and Pr) was observed for the signal corresponding to the OCH_2CH_2N arms, probably because of the establishment of hydrogen bonds between the nitrogen atoms of the cap and the guest.[13]

Finally, a ^{1}H NMR experiment was conducted in order to compare the affinity of ethyl- versus propylammonium guests toward receptor **4**. For this, picrate salts of $EtNH_3^+$ and $PrNH_3^+$ in solution in CD_3OD were added to the same solution of receptor **4** in $CDCl_3$. Subsequent addition of a large excess of $EtNH_2$ and $PrNH_2$ gave rise exclusively to the endo-complexes **4**⊃$EtNH_3^+$ and **4**⊃$PrNH_3^+$. Integration of the free and included guests allowed us to evaluate the relative affinities of the ammonium salts toward receptor **4**.[15] A ca. 16:1 ratio[16] in favor of $EtNH_3^+$ versus $PrNH_3^+$ was obtained. Considering that these two guests differ only by a methyl group, such a selectivity is quite remarkable, and in particular, it is much higher than that (6.4:1) measured with the closely related calix[6]TAC receptor.

In conclusion, the key step for the synthesis of the C_{3v}-symmetrical PN_3-calix[6]cryptands **3** and **4** was the condensation between calix[6]triamine **1** and trisaldehyde **2**. The exceptionally high yield of this macrocyclization may be attributed to a good geometrical fit between both synthons. The P,N-cap rigidifies the calixarene core in a cone conformation, thereby offering a well-defined hydrophobic cavity open at the large rim. As an illustration, host **4** was shown to strongly bind ammonium guests with a 16-fold selectivity in favor of ethylammonium over propylammonium. Further exploration of the host behavior of this new class of calix-cryptands toward various organic guests as well as their ability to act as strong chelators for metal ions is underway in our laboratories.

(13) Such interactions have been highlighted by the X-ray structure of the closely related endo-complex calix[6]TAC⊃$PrNH_3^+$. See ref 6.

(14) The complex **4**⊃$EtNH_3^+$ was also characterized by ^{31}P NMR analysis (121 MHz, $CDCl_3$): δ −45 (s).

(15) Integration of the methyl group of the free and included guests gave us the relative affinity defined as $[EtNH_3^+{}_{in}]/[PrNH_3^+{}_{in}] \times [PrNH_3^+{}_T]/[EtNH_3^+{}_T]$ where indexes "in" and "T" stand for "included" and "total amount", respectively (errors estimated ±10%).

(16) Given the large excess of free amines vs the added picrate salts and the calix-cryptand, this ratio was calculated considering that their slight difference of pK_a was neglectable.

Experimental Section

Calix[6]trisimine 3. Calix[6]triamine **1** (230 mg, 0.201 mmol) was dissolved in CH_2Cl_2 (400 mL). To this solution was added a solution of tris(2-carboxaldehyde)triphenylphosphine (70 mg, 0.202 mmol) in CH_2Cl_2 (100 mL). The resulting yellow solution was stirred overnight at room temperature. The solvent was removed under reduced pressure. The residue was dissolved in ethanol (500 mL) and refluxed for 2 h. The solvent was condensed to about 5 mL. The resulting white precipitate was collected by centrifugation and washed twice with ethanol (3 mL × 2). After drying on a vacuum pump, 262 mg (91%) of the desired product **3** was obtained as a white powder: mp 250 °C (decomp). IR (KBr): ν 1638, 1482, 1202, 758 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.77 (s, 27H, *t*Bu), 1.35 (s, 27H, *t*Bu), 2.42 (s, 9H, OCH_3), 3.30 (d, J = 15 Hz, 6H, Ar-αCH_{eq}), 3.92 (s_b, 6H, CH_2N), 4.21 (s_b, 6H, CH_2O), 4.45 (d, J = 15 Hz, 6H, Ar-αCH_{ax}), 6.68 (s, 6H, ArH_{calix}), 6.88 (dd, J_1 = 5 Hz, J_2 = 6 Hz, 3H, ArH_{cap}), 7.22 (s, 6H, ArH_{calix}), 7.29 (t, J = 8 Hz, 3H, ArH_{cap}), 7.43 (t, J = 7 Hz, 3H, ArH_{cap}), 8.19 (dd, J_1 = 5 Hz, J_2 = 8 Hz, 3H, ArH_{cap}), 8.86 (d, J = 5 Hz, 3H, CH=N). ^{31}P NMR (121 MHz, $CDCl_3$): δ −21 (s). Anal. Calcd for $C_{96}H_{114}N_3O_6P$, H_2O: C, 79.25; H, 8.04; N, 2.89. Found: C, 78.95; H, 8.01; N, 2.62.

Calix[6]triscarbamate 5. To a 100-mL round-bottomed flask was added ethanol (25 mL) and $NaBH_4$ (204 mg, 5.4 mmol). The suspension was cooled to 0 °C, and a solution of calix[6]trisimine **3** (143 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The water−ice bath was removed, and the reaction mixture was stirred for 4 h at room temperature. The solvent was removed under reduced pressure. The resulting residue was dissolved with CH_2Cl_2 (40 mL) and HCl (1 N, 40 mL) and stirred for 1 h. The organic phase was separated, and the water phase was extracted with CH_2Cl_2 (30 mL × 2). The organic phases were combined and washed with NaOH (1 N, 50 mL) and then water (100 mL). The organic phase was condensed to dryness, and the crude residue corresponding to a mixture of compound **4** (144 mg) and calixarene-type byproducts was used directly for the next step without further treatment. To a 250-mL reactor was added the latter crude compound **4** (144 mg), THF (30 mL) and triethylamine (81 mg, 0.80 mmol). The solution was cooled to 0 °C, and a solution of di-*tert*-butyl dicarbonate (131 mg, 0.60 mmol) in THF (5 mL) was added dropwise. After the addition, the solution was stirred overnight at room temperature. After removal of the solvent, the resulting residue was dissolved in CH_2Cl_2 (50 mL) and washed with water (30 mL). The organic phase was separated and condensed to dryness. The residue was purified by column chromatography (CH_2Cl_2/AcOEt, 20/1 v/v). The product was collected as a white foam, which was triturated with ether to give 63 mg (36% overall yield from **3**) of pure **5** as a white powder: mp 250 °C (decomp). IR (KBr): ν 1690, 1483, 751 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 330 K): δ 0.80 (s, 27H, *t*BuAr), 1.07 (s, 18H, *t*BuO), 1.36 (s, 27H, *t*BuAr), 1.46 (s, 9H, *t*BuO), 2.57 (s, 9H, OCH_3), 3.31 (d, J = 15 Hz, 6H, Ar-αCH_{eq}), 3.40−5.20 (m, 18H, CH_2N + CH_2O), 4.59 (d, J = 14 Hz, 6H, Ar-αCH_{ax}), 6.49 (s_b, 3H, ArH_{cap}), 6.70 (s_b, 3H, ArH_{cap}), 6.72 (s, 6H, ArH_{calix}), 7.10 (t, J = 6 Hz, 3H, ArH_{cap}), 7.21 (s, 6H, ArH_{calix}), 7.34 (t, J = 7 Hz, 3H, ArH_{cap}). ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ 27.9 (C(*C*H_3)$_3$), 28.6, 28.9 (Ar-*C*H_2), 31.0, 31.6 (C(*C*H_3)$_3$), 34.0, 34.2 (Ar*C*(*C*H_3)$_3$), 49.3 (*C*H_2*C*H_2N), 51.4 + 51.7 (Ar*C*H_2N), 59.6 (OCH_3), 70.8 (O*C*H_2), 80.0 (O*C*(*C*H_3)$_3$), 123.4, 124.5, 125.0, 127.3, 127.6, 129.4, 132.2, 132.4, 133.1, 133.3, 133.5, 133.6, 145.5, 145.8 ($C_{Ar}H$ + C_{Ar}), 150.6, 154.0, 154.2, 155.9 ($C_{Ar}O$ + C=O). Anal. Calcd for $C_{111}H_{144}N_3O_{12}P\cdot 2H_2O$: C, 74.93; H, 8.38; N, 2.36. Found: C, 74.91; H, 8.26; N, 2.24. The presence of two signals for the $t\mathrm{Bu}_{Boc}$ groups in a 1:2 ratio may be ascribed to a different *Z*/*E* stereochemistry adopted by one of these groups compared to the other two. Also, the room temperature NMR spectrum of **5** attested to a loss of symmetry in the calixarene structure. All this may be related to the high sterical crowding at the level of the cap due to the bulkiness of the carbamate moieties.

PN_3-Calix[6]cryptand 4. Compound **5** (145 mg, 0.083 mmol), CH_2Cl_2 (4 mL), and TFA (400 μL) were stirred at room temperature for 8 h, and then the solvent was removed under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (10 mL) and washed with an aqueous NaOH solution (1 N, 10 mL). The organic phase was separated, washed with water (30 mL), and condensed to dryness. The crude residue was triturated with ether, and the resulting white precipitate was collected by centrifugation. The obtained solid was triturated twice with ether and dried under vacuum to give 112 mg (93%) of pure **4**: mp 245 °C (decomp). IR (KBr): ν 1638, 1482, 1202, 754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.03 (s, 27H, *t*Bu), 1.12 (s, 27H, *t*Bu), 2.87 (s_b, 15H, OCH_3 + CH_2CH_2N), 3.40 (d, J = 15 Hz, 6H, Ar-αCH_{eq}), 3.90 (s_b, 6H, OCH_2), 4.15 (s, 6H, Ar*C*H_2N), 4.51 (d, J = 15 Hz, 6H, Ar-αCH_{ax}), 6.82 (dd, J_1 = 4 Hz, J_2 = 4 Hz, 3H, ArH_{cap}), 6.97 (s, 6H, ArH_{calix}), 7.01 (s, 6H, ArH_{calix}), 7.15 (t, J = 7 Hz, 3H, ArH_{cap}), 7.34 (t, J = 7 Hz, 3H, ArH_{cap}), 7.53 (dd, J_1 = 4 Hz, J_2 = 4 Hz, 3H, ArH_{cap}). ^{13} C NMR (75 MHz, $CDCl_3$): δ 29.8 (Ar-*C*H_2), 31.3, 31.4 (C(*C*H_3)$_3$), 34.1 (Ar*C*(*C*H_3)$_3$), 49.6 (*C*H_2*C*H_2N), 52.6 + 52.8 (Ar*C*H_2N), 60.6 (OCH_3), 72.8 (O*C*H_2), 80.0 (O*C*(*C*H_3)$_3$), 125.1, 126.4, 127.3, 129.0, 129.9, 133.1, 133.5, 133.8, 145.6(6), 145.7(2) ($C_{Ar}H$ + C_{Ar}), 152.0, 153.9 ($C_{Ar}O$). ^{31}P NMR (121 MHz, $CDCl_3$): δ −35 (s). Anal. Calcd for $C_{96}H_{120}N_3O_6P$, $2.5H_2O$: C, 77.49; H, 8.47; N, 2.82. Found: C, 77.26; H, 8.29; N, 2.65.

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Supporting Information Available: General experimental methods; ^1H NMR spectra of **3** and **5** (at room temperature and 330 K); ^{13}C NMR specta of **4** and **5**; HMQC spectrum of **4**; ^1H spectrum of the mixture of complex **4**⊃$EtNH_3^+$ and **4**·H^+ at 233 K; ^1H NMR spectra of **4**·H^+ from 330 to 233 K; ^1H spectrum of the complex **4**⊃$PrNH_3^+$ at 233 K; ^{31}P NMR spectra of **3**, **4**,and **4**⊃$EtNH_3^+$. This material is available free of charge via the Internet at http://pubs.acs.org.

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