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An efficient route to disymmetrically substituted calix[6]arenes. Synthesis of novel ligands presenting a N_2S or $N_3CO_2^-$ binding core

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Abstract—The C_{3v} tris-methoxy calix[6]arene was selectively mono-alkylated by dibromoethane yielding a key intermediate for the design of disymmetrically O-substituted calix[6]arenes. Indeed, subsequent reactions with various functional groups afforded novel calix[6]arene-based biomimetic ligands that present a mixed donor N_2S or $N_3CO_2^-$ environment in an efficient way.

In the past few years, we have developed a novel biomimetic system that is based on calixarene structures. Selectively functionalized on alternate positions by three nitrogenous arms, the calix-ligands were shown to provide good supramolecular mimics for the tris-histidine coordination core often encountered in metallo-proteins. Indeed, the calixarene cavity acts as a selective funnel for small molecules that interact with the metal center. The tris-imidazolyl derivatives are the most biomimetic ligands of the family, capable of reproducing some remarkable properties observed in Zn and Cu enzymes.[1–5] However, nature makes use of a variety of protein residues other than His to coordinate a metal ion in enzyme active sites. For example, Glu or Asp is found in most Fe-enzymes.[6] Cu-hydroxylases display two different copper sites: a $(His)_3Cu$ and a His_2MetCu.[7] These two sites play different roles although it is not yet clear, which roles they have or why they are different. Therefore, we were interested in developing calix-based models that present a mixed donor environment that includes a carboxylate or a thioether binding site.

While *per*-alkylation of the calixarene narrow rim has been widely described,[8] its selective functionalization remains a challenge. In spite of the reduced number of free phenolic positions left on the C_{3v} tris-methoxy-*t*-Bu-calix[6]arene, $X_6Me_3H_3$,[9] the procedures described so-far for its disymmetrization remain surprisingly scarce.[10,11] We have recently described a procedure that allows the selective introduction of an ethylamino Boc-protected group. The latter could be further functionalized with a variety of electrophiles such as aromatic aldehydes, allowing the synthesis of N_4 and N_3ArOH calixarene-based ligands.[11,12] We now describe a second method of disymmetrization that is complementary to the previous procedure since it allows the introduction of an electrophilic arm at the narrow rim of the calixarene. The corresponding new synthon was further derivatized into a thioether or *N*-methylglycine ester, opening a route toward calixarene-based ligands that present N_2S or $N_3CO_2^-$ donor groups, respectively.

The reaction of calix[6]arene derivatives with 1,2-dibromoethane has already been studied. On the one hand, a preparative procedure for the *per*-alkylation of $X_6Me_3H_3$ leading to the C_{3v} derivative $X_6Me_3(CH_2CH_2Br)_3$ has been described (72% yield).[13] No selective alkylation was mentioned in this case. On the other hand, it was recently reported that *t*-Bu-calix[6]arene itself (X_6H_6) could be selectively mono-alkylated in a moderate yield (35%).[14] We now report a modified procedure leading to the mono-alkylated derivative of $X_6Me_3H_3$ as a major product. Indeed, $X_6Me_3H_3$ was reacted with dibromoethane in excess (11 equiv) in the presence of NaH (4 equiv) in refluxing THF. A careful monitoring of the reaction showed that

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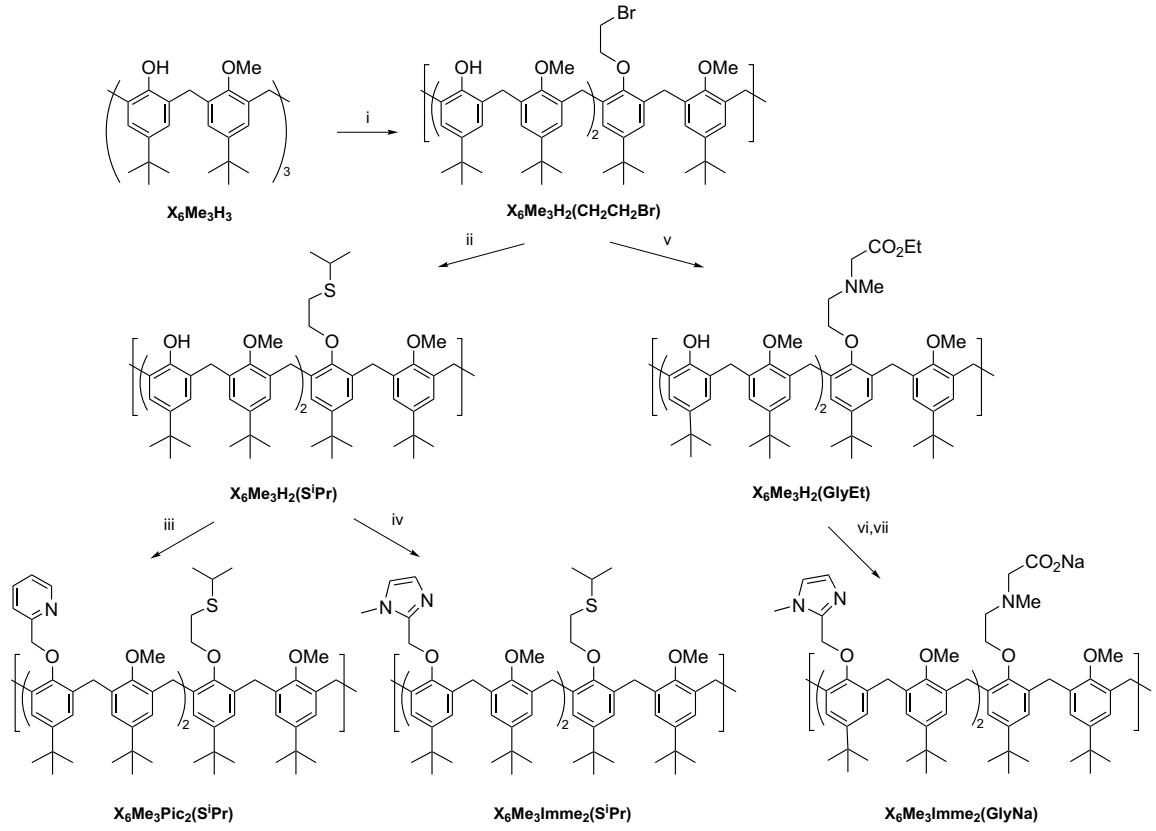

Scheme 1. Synthesis of calix[6]arene-based ligands presenting a N_2S and $N_3CO_2^-$ mixed coordination sphere. Reagents and conditions: (i) $BrCH_2CH_2Br$, NaH, THF, reflux (63%); (ii) *i*-PrSH, Cs_2CO_3, MeCN, rt (80%); (iii) PicCl·HCl, K_2CO_3, DMF, 150 °C (70%); (iv) ImmeCl·HCl, NaH, THF/DMF, reflux (94%); (v) $MeNHCH_2CO_2Et$·HCl, Et_3N, EtOAc, reflux (78%); (vi) ImmeCl·HCl, NaH, THF/DMF, reflux (80%); (vii) NaOH, $EtOH/H_2O$, rt (92%).

the formation of the desired mono-alkylated derivative $X_6Me_3H_2(CH_2CH_2Br)$ relative to the other products was optimum after 4 h of reflux. A two-step work-up of the reaction mixture allowed the isolation of the pure desired product without chromatography. It involved (i) recrystallization in acetone of the crude reaction product leading to a 'clean' mixture of $X_6Me_3H_2(CH_2CH_2Br)$ and starting material $X_6Me_3H_3$, (ii) their straightforward separation by solid–liquid extraction with cyclohexane. The isolated yield was 63% and the yield based on the consumed starting material was 79%.[15] This shows that the second alkylation was much slower than the first, as in the case of our previously reported reaction with the NBoc protected 2-chloroethylamine. This further substantiates our previous proposal, which claimed that the difficulties encountered in the selective introduction of a single nitrogenous arm was related to its basic character, which induced a cooperative effect in the alkylation process of the calixarene phenol units.[11]

The ^1H NMR spectrum of $X_6Me_3H_2(CH_2CH_2Br)$ in chloroform displayed peaks at 2.87 (OCH_2) and 2.34 (CH_2Br) ppm for the bromoethyl substituent. These unusually high-field shifted resonances indicated that the corresponding alkyl arm was partially included in the aromatic cavity, whereas the methoxy groups (3.46 ppm) were rejected out of the cavity.[16] Hence, the calixarene adopted a flattened cone conformation that is opposite to that observed for the precursor $X_6Me_3H_3$. For the purpose of a good ligand design (vide supra), we chose to functionalize further this electrophilic synthon with relatively bulky groups in order to discourage this self-inclusion process. $X_6Me_3H_2(CH_2CH_2Br)$ was subsequently reacted with 2-propanethiol in the presence of cesium carbonate to provide the thioether derivative $X_6Me_3H_2(S^iPr)$ in 90% yield.[17] The resonances displayed by the bulkier thioether arm are all normally shifted, in contrast to the protons belonging to the methoxy groups (2.12 ppm) that are again pointing toward the center of the hydrophobic calixarene cavity. Final reaction of the remaining two phenol units with 2-chloromethyl-1-methylimidazole (ImmeCl)[18] or 2-picolylchloride (PicCl) in excess in the presence of a base led to the isolation of two novel disymmetrically substituted calix[6]arenes, $X_6Me_3Imme_2(S^iPr)$[19] and $X_6Me_3Pic_2(S^iPr)$,[20] respectively (Scheme 1).

Following the same synthetic strategy, the electrophilic synthon $X_6Me_3H_2(CH_2CH_2Br)$ was reacted with *N*-methylglycine ethyl ester ($MeNHCH_2CO_2Et$) in the presence of triethylamine to yield $X_6Me_3H_2(GlyEt)$.[21] This step required careful experimental control. The best results were obtained using an excess of $MeNHCH_2CO_2Et$ and 16 h of heating at high temperature (90 °C). Although the starting material $X_6Me_3H_2(CH_2CH_2Br)$ was not totally consumed under these

conditions (15% recovered), it was easily separated from the product $X_6Me_3H_2$(GlyEt). Increasing the reaction time or the temperature decomposed the product. $X_6Me_3H_2$(GlyEt) was then *per*-alkylated with ImmeCl in excess.[22] Final hydrolysis of the ester function led to the sodium salt of the glycinate derivative, $X_6Me_3Imme_2$(GlyNa),[23] with a 67% overall yield (Scheme 1).

The ^{1}H NMR profiles of these three new 3- and 4-dentate ligands highly resembled those of their symmetrical analog $X_6Me_3Imme_3$ or $X_6Me_3Pic_3$. They display the same resonances with correct integration for the common part. In each case, the OCH_2CH_2X motif (X = S or N) is well defined with two triplets at normal δ-shifts. This shows that the same major flattened cone conformation is maintained. Complexation of metal ions with these mixed-donor calix-ligands is under current investigation.

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15. Preparation of $X_6Me_3H_2(CH_2CH_2Br)$: A mixture of $X_6Me_3H_3$ (2 g, 1.97 mmol), NaH (60% in mineral oil, 320 mg, 8 mmol, washed with pentane prior to use), and $BrCH_2CH_2Br$ (2 mL, 23 mmol) in anhydrous THF (40 mL) was refluxed for 4 h (85 °C for bath). After addition of H_2O (0.5 mL), the mixture was evaporated to dryness, extracted with CH_2Cl_2 and filtered over Celite. After removal of the solvent under vacuum, acetone (15 mL) was added to the crude product and the mixture was kept at 4 °C for 1 night. The colorless solid (1.80 g) isolated by filtration was a mixture of $X_6Me_3H_3$ and $X_6Me_3H_2(CH_2CH_2Br)$. Cyclohexane (60 mL) was added to this solid, heated at 60 °C (bath) for 0.5 h, cooled to rt, and filtered. The solid was the unreacted $X_6Me_3H_3$ (403 mg, 20%). The mother liquor was evaporated to dryness to give $X_6Me_3H_2(CH_2CH_2Br)$ as a colorless, NMR pure solid (1.396 g, 63%). For microanalysis purpose, the product was recrystallized in acetone. Mp: 287–289 °C; ESMS: $m/z = 1146$ ($M+Na^+$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.33 (s, 2H, Ar), 7.22 (s, 2H, Ar), 7.11 (d, 2H, $J = 2.4$ Hz, Ar), 7.01 (d, 2H, $J = 2.4$ Hz, Ar), 6.95 (d, 2H, $J = 2.4$ Hz, Ar), 6.78 (d, 2H, $J = 2.4$ Hz, Ar), 6.49 (s, 2H, D_2O exchangeable, OH), 4.01 (s, 4H, $ArCH_2Ar$), 3.88 (br s, 14H, 6H OMe+8H $ArCH_2Ar$), 3.46 (s, 3H, OMe), 2.87 (t, 2H, $J = 6.0$ Hz, OCH_2), 2.34 (t, 2H, $J = 6.0$ Hz, CH_2Br), 1.35 (s, 9H, *t*-Bu), 1.20 (s, 18H, *t*-Bu), 1.00 (s, 18H, *t*-Bu), 0.75 (s, 9H, *t*-Bu). Anal. Calcd for $X_6Me_3H_2(CH_2CH_2Br)\cdot Me_2CO$ ($C_{71}H_{93}O_6Br\cdot C_3H_6O$, 1180.48): C, 75.29; H, 8.45; Br, 6.77. Found: C, 75.28; H, 8.52; Br, 6.75.
16. This is not the case of the tris-bromoethyl derivative, $X_6Me_3H_2(CH_2CH_2Br)_3$, which presents resonances at 3.99 and 3.52 ppm for the same groups of protons, OCH_2 and CH_2Br, respectively (Ref. 13).
17. Preparation of $X_6Me_3H_2(S^iPr)$: ^{i}PrSH (105 μL, 1.13 mmol) and Cs_2CO_3 (316 mg, 0.97 mmol) were added to a suspension of $X_6Me_3H_2(CH_2CH_2Br)$ (500 mg, 0.45 mmol) in anhydrous CH_3CN (35 mL) under argon. The mixture was kept at 80 °C in a closed flask for 24 h. After evaporation to dryness, pentane was added to the solid, filtered over Celite, and evaporated to dryness to give the crude product, which was triturated in CH_3CN (450 mg, 90%). Mp 211 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.32 (s, 2H, D_2O exchangeable, OH), 7.19 (s, 2H, Ar), 7.11 (d, 2H, $J = 2.4$ Hz, Ar), 6.97 (d, 2H, $J = 2.2$ Hz, Ar), 6.89 (m, 4H, Ar), 6.84 (s, 2H, Ar), 3.84 (br s, 18H, two OCH_3 and $ArCH_2Ar$), 3.60 (t, 2H, OCH_2), 3.03 (m, 1H, SCH), 2.78 (s, 3H, OCH_3), 2.67 (t, 2H, SCH_2), 1.31 (m,15H, *t*-Bu and $CH(CH_3)_2$), 1.22 (s, 18H, *t*-Bu), 1.10 (s, 9H, *t*-Bu), 0.99 (s, 18H, *t*-Bu). Anal. Calcd for $C_{74}H_{100}O_6S\cdot H_2O$ (1134.73): C, 78.26; H, 9.05; S, 2.82. Found: C, 78.38; H, 8.98; S, 2.66.
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19. Preparation of $X_6Me_3Imme_2(S^iPr)$: NaH (60% in mineral oil, 700 mg, 17.5 mmol) was added under Ar to a solution of $X_6Me_3H_2(S^iPr)$ (800 mg, 0.72 mmol) in anhydrous THF (50 mL) and DMF (7.5 mL). After 0.5 h at rt, ImmeCl·HCl (1.05 g, 6.3 mmol) was added and the mixture was heated under reflux for 16 h. THF was evaporated under reduced pressure and water (150 mL) was added to the mixture. The solid was separated, washed with water (2 × 50 mL), and dissolved in CH_2Cl_2 (100 mL). The organic layer was washed with water (30 mL), dried (Na_2SO_4), and evaporated. The crude product was purified by recrystallization in CH_2Cl_2/pentane to give $X_6Me_3Imme_2(S^iPr)$ as a colorless solid (883 mg, 94%). Mp 155 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.21 (s, 6H, Ar), 6.96 (s, 2H, Im), 6.90 (s, 2H, Im), 6.62 (s, 6H, Ar), 5.01 (s, 4H, CH_2Im), 4.56 (d, 2H, $J_{AB} = 15.1$ Hz, $ArCH_2Ar$), 4.44 (d, 4H, $J_{AB} = 14.9$ Hz, $ArCH_2Ar$), 3.99 (t, 2H, $J = 3.8$ Hz, OCH_2), 3.88 (s, 6H, NCH_3), 3.38 (d, 2H, $ArCH_2Ar$), 3.19 (d, 4H, $ArCH_2Ar$), 2.99 (m, 3H, SCH and SCH_2), 2.17 (s, 6H, OCH_3), 2.11 (s, 3H, OCH_3), 1.36 (s, 18H, *t*-Bu), 1.24 (m, 15H, *t*-Bu and $CH(CH_3)_2$), 0.77 (s, 27H, *t*-Bu). Anal. Calcd for $C_{85}H_{116}N_4O_6S\cdot C_5H_{12}$ (1406.97): C, 77.62; H, 9.31; N, 3.98. Found: C, 77.63; H, 9.33; N, 3.59.
20. Preparation of $X_6Me_3Pic_2(S^iPr)$: A suspension of $X_6Me_3H_2(S^iPr)$ (150 mg, 0.13 mmol), K_2CO_3 (220 mg, 1.6 mmol), and PicCl·HCl (120 mg, 0.73 mmol) in anhydrous DMF (7 mL) was heated under Ar at 150 °C for 3 h.

After cooling to rt, H_2O (50 mL) was added to the mixture. The solid formed was filtered, vacuum dried, and dissolved in pentane (50 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated to give $X_6Me_3Pic_2(S^iPr)$ as a pale-yellow solid (120 mg, 70%). Mp 124 °C; ^1H NMR (250 MHz, $CDCl_3$): δ 8.55 (br, 2H, Py), 7.88 (br, 2H, Py), 7.76 (br, 2H, Py), 7.25 (br, 6H+2H, Ar+Py), 6.68 (br, 6H, Ar), 5.14 (s, 4H, CH_2Py), 4.58 (br d, 4H, ArCH_2Ar), 4.02 (m, 2H, OCH_2), 3.5–4.5 (br, 4H, ArCH_2Ar), 3.40 (br d, 4H, ArCH_2Ar), 2.98 (m, 3H, SCH+SCH_2), 2.29 (br s, 9H, OCH_3), 1.30 (m, 33H, *t*-Bu+CH(CH_3)$_2$), 0.81 (s, 27H, *t*-Bu). Anal. Calcd for $C_{86}H_{110}N_2O_6S$ (1299.87): C, 79.46; H, 8.53; N, 2.20. Found: C, 79.17; H, 8.69; N, 2.01.

21. Preparation of $X_6Me_3H_2$(GlyEt): $MeNHCH_2CO_2Et$·HCl (720 mg, 4.7 mmol) and Et_3N (1.4 mL, 10 mmol) were added to a solution of $X_6Me_3H_2(CH_2CH_2Br)$ (720 mg, 0.64 mmol) in EtOAc (20 mL). The reaction was kept at 90 °C in a closed flask for 16 h. After cooling to rt, the mixture was filtered over Celite, rinsed with EtOAc (3×50 mL), and the solution was evaporated to dryness. The crude product was then filtered over silica gel, first using EtOAc–CH_2Cl_2 (1:99) as an eluant to recover the unreacted $X_6Me_3H_2(CH_2CH_2Br)$ (110 mg, 15%); then using MeOH–CH_2Cl_2–concd aq NH_3 (3:97:0.25) as an eluant to give $X_6Me_3H_2$(GlyEt) as a colorless solid (580 mg, 78%). For microanalysis purpose, the product was triturated in CH_3CN. Mp 157–159 °C; ^1H NMR (250 MHz, DMSO-d_6): δ 8.28 (s, 2H, D_2O exchangeable, OH), 7.28 (m, 6H, Ar), 6.89 (s, 2H, Ar), 6.64 (s, 2H, Ar), 6.61 (s, 2H, Ar), 4.43 (d, 2H, J_{AB} = 14.9 Hz, ArCH_2Ar), 4.32 (d, 4H, J_{AB} = 15.1 Hz, ArCH_2Ar), 4.14 (q, 2H, J = 5.8 Hz, OC$H_2$$CH_3$), 3.93 (m, 2H, OC$H_2$$CH_2$N), 3.55–3.43 (m, 6H, ArCH_2Ar), 3.37 (s, 2H, NCH_2CO), 3.00 (m, 2H, OCH_2CH_2N), 2.44 (s, 3H, OCH_3), 2.38 (s, 6H, OCH_3), 2.13 (s, 3H, NCH_3), 1.34 (s, 27H, *t*-Bu), 1.22 (t, 3H, OCH_2CH_3), 0.99 (s, 9H, *t*-Bu), 0.87 (s, 18H, *t*-Bu). Anal. Calcd for $C_{76}H_{103}NO_8$ (1158.63): C, 78.78; H, 8.96; N, 1.21. Found: C, 78.71; H, 9.04; N, 1.09.

22. Preparation of $X_6Me_3Imme_2$(GlyEt): NaH (60% in mineral oil, 36 mg, 0.9 mmol) was added under Ar to a solution of $X_6Me_3H_2$(GlyEt) (175 mg, 0.15 mmol) in anhydrous THF (10 mL) and DMF (1.5 mL). After 0.5 h at rt, ImmeCl·HCl (76 mg, 0.46 mmol) was added and the mixture was heated under reflux for 16 h (85 °C for bath). THF was evaporated under reduced pressure and water (30 mL) was added to the mixture. The solid formed was filtered, washed with water (2×30 mL), and dissolved in CH_2Cl_2 (30 mL). The organic layer was washed with water (10 mL), dried (Na_2SO_4), and evaporated. The crude product was purified by chromatography on silica gel (MeOH–CH_2Cl_2–concd aq NH_3 = 4:96:0.25) to yield $X_6Me_3Imme_2$(GlyEt) as a colorless solid (163 mg, 80%). Mp 160–162 °C; ^1H NMR (250 MHz, $CDCl_3$): δ 7.22 (s, 6H, Ar), 7.00 (s, 2H, Im), 6.91 (s, 2H, Im), 6.60 (s, 6H, Ar), 5.01 (s, 4H, CH_2Im), 4.53 (d, 2H, J_{AB} = 15.3 Hz, ArCH_2-Ar), 4.44 (d, 4H, J_{AB} = 14.9 Hz, ArCH_2Ar), 4.15 (q, 2H, J = 7.0 Hz, OC$H_2$$CH_3$), 4.02 (m, 2H, OC$H_2$$CH_2$N), 3.89 (s, 6H, C$H_3$Im), 3.45 (s, 2H, NC$H_2$$CO_2$Et), 3.38 (d, 2H, ArC$H_2$Ar), 3.19 (d, 4H, ArC$H_2$Ar), 3.05 (m, 2H, OCH_2CH_2N), 2.51 (s, 3H, NCH_3), 2.15 (s, 6H, OCH_3), 2.11 (s, 3H, OCH_3), 1.36 (s, 27H, *t*-Bu), 1.21 (t, 3H, OCH_2CH_3), 0.76 (s, 27H, *t*-Bu). Anal. Calcd for $X_6Me_3Imme_2$(GlyEt)·H_2O ($C_{87}H_{119}N_5O_8$·H_2O, 1380.92): C, 75.67; H, 8.83; N, 5.07. Found: C, 75.32; H, 8.41; N, 4.94.

23. Preparation of $X_6Me_3Imme_2$(GlyNa): A mixture of $X_6Me_3Imme_2$(GlyEt) (55 mg, 0.04 mmol) and aq 1 M NaOH (125 μL, 0.125 mmol) in 95° EtOH (1.5 mL) was kept at rt for 24 h. After evaporation of the solvents under reduced pressure, the mixture was added CH_2Cl_2 (10 mL), dried (Na_2SO_4), filtered over Celite, and evaporated. The crude product was purified by trituration in CH_3CN to give $X_6Me_3Imme_2$(GlyNa) as a colorless solid (50 mg, 92%). Mp 220–222 °C; ^1H NMR (250 MHz, CH_3OH-d_4): δ 7.31 (s, 2H, Ar), 7.25 (s, 4H, Ar), 7.18 (s, 2H, Im), 6.95 (s, 2H, Im), 6.73 (s, 4H, Ar), 6.65 (s, 2H, Ar), 5.07 (s, 4H, CH_2 Im), 4.52 (d, 2H, J_{AB} = 15.0 Hz, ArCH_2Ar), 4.40 (d, 4H, J_{AB} = 14.6 Hz, ArCH_2Ar), 4.09 (t, 2H, J = 6.5 Hz, OC$H_2$$CH_2$N), 3.89 (s, 6H, C$H_3$Im), 3.42 (d, 2H, ArC$H_2$-Ar), 3.20 (s, 2H, NCH_2CO), 3.16 (d, 4H, ArCH_2Ar), 3.09 (t, 2H, OCH_2CH_2N), 2.53 (s, 3H, NCH_3), 2.23 (s, 9H, OCH_3), 1.39 (s, 27H, *t*-Bu), 0.82 (s, 18H, *t*-Bu), 0.78 (s, 9H, *t*-Bu). Anal. Calcd for $X_6Me_3Imme_2$(GlyNa)·$3H_2O$ ($C_{85}H_{114}N_5NaO_8$·$3H_2O$, 1409.89): C, 72.36; H, 8.57; N, 4.96. Found: C, 72.39; H, 8.25; N, 4.99.