Calixarene Metalloreceptors. Synthesis and Molecular Recognition Properties of Upper-Rim Functionalized Calix[4]arenes Containing an Organopalladium Binding Site

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The compound 5,17-bis(2-chloroacetamido)-25,26,27,28-tetrapropoxycalix[4]arene, **4**, was prepared in the cone conformation by the published method. Compound **4** was reacted with α,α′-*m*-xylenedithiol and sodium ethoxide under high-dilution conditions in ethanol solution. The resulting macrobicyclic calix[4]arene, HL^1, **5**, contains a symmetrically disposed macrocyclic loop across the upper rim of the calix[4]arene. Palladation of **5** yielded $[Pd(L^1)(CH_3CN)][BF_4]$, **6**. Similarly 5,17-bis[2-(4-(chloromethyl)phenoxy)acetamido]-25,26,27,28-tetrapropoxycalix-[4]arene, **8**, was used to prepare HL^2, **9**. Compound **9** is similar to **5** but contains an aromatic spacer group separating the xylyl fragment from the calixarene unit. Palladation of **9** yielded $[Pd(L^2)(CH_3CN)][BF_4]$, **11**. All new compounds and complexes were characterized in solution by ^{1}H NMR spectroscopy, and the molecular structure of **5** was verified by a single-crystal X-ray diffraction study. Compound **5** crystallized in the space group $P2_1/c$ with $a = 23.5095(1)$ Å, $b = 9.9090(1)$ Å, $c = 23.3586(1)$ Å, $\beta = 91.53(1)°$, $V = 5439.59(8)$ Å^3, and $Z = 4$. The structure was refined to $R(F) = 10.13\%$ and $R_w(F^2) = 21.91\%$ for 5799 reflections with $F_o^2 > 2\sigma(F_o^2)$. Compounds **6** and **11** are calix[4]arene-based metalloreceptors containing an organopalladium binding site and a hydrophobic cavity provided by the calix[4]arene. Binding of a substrate through σ-bonding to the palladium center and interaction within the hydrophobic site were demonstrated in solution by ^{1}H NMR spectroscopy. These multiple receptor−substrate interactions are used by **11** for the molecular recognition of 4-phenylpyridine in the presence of 2-phenylpyridine or 3-phenylpyridine.

Introduction

Metal complexes which contain a ligand with additional sites for noncovalent binding have been employed as hosts for a variety of neutral, cationic, and anionic guests. These complexes are often referred to as metalloreceptors.[1,2] In previous reports, we have described a series of organopalladium-based metalloreceptors with peripheral sites capable of hydrogen-bonding and/or π-stacking interactions. These complexes have been successfully applied to the molecular recognition of aliphatic amines,[2] aromatic amines,[3] hydrazines,[4] and DNA nucleobases.[5]

In an effort to increase the scope of these metalloreceptors for a range of substrates, we designed a series of receptors in which the subunit for second-sphere, noncovalent interaction is a calix[4]arene unit.[6] Calix[4]arenes[7] are known to act as receptors for cationic,[7,8] anionic,[9−11] or neutral[12,13] substrates by providing a platform for the attachment of convergent binding groups, at the upper[15,12] or lower rim,[8,9,13] or by utilizing the bowl-shaped arrangement of the four aromatic groups as a hydrophobic cavity.[14] Our strategy was the construction of a "handle" on the top of the calixarene "basket". This would allow for the possibility that a peripherally coordinated metal center (handle) would have a binding site oriented toward the hydrophobic cavity of the calix[4]arene (basket). A substrate

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could potentially interact simultaneously with the metal center and the calixarene cavity. The synthesis of these new metalloreceptors is reported herein along with preliminary studies to demonstrate molecular recognition of bound substrate using phenyl-substituted aromatic amines.

Experimental Section

All starting materials were purchased from Aldrich and used without further purification, except acetonitrile, which was distilled from CaH_2 under N_2(g). All reactions were performed under an atmosphere of N_2(g). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC300 spectrometer locked to the deuterated solvent at 300.1 and 75.5 MHz, respectively. LSI-MS and EI-MS spectra were recorded on a Kratos Profile mass spectrometer Elemental analyses were performed by Canadian Microanalytical Service, Delta, British Columbia, Canada.

Preparation of 5,17-Bis(2-chloroacetamido)-25,26,27,28-tetrapropoxycalix[4]arene (4). This material was prepared from **3** by the method of Reinhoudt[15] and characterized as follows. ^{1}H NMR ($CDCl_3$): δ (ppm) 7.90 (s, NH, 2H), 6.78 (s, Ar H, 4H), 6.60 (m, Ar H, 6H), 4.43 (d, $ArCH_2$, 4H), 4.08 (s, CH_2Cl, 4H), 3.82 (m, $ArOCH_2$, 8H), 3.13 (d, $ArCH_2$, 4H), 1.90 (m, CH_2, 8H), 0.97 (m, CH_3, 12H).

Preparation of Macrobicyclic Ligand HL^1 (5). α,α'-*m*-Xylenedithiol (57.8 μL, 0.39 mmol) was dissolved in a freshly prepared ethanolic solution (100 mL) of sodium ethoxide (Na: 0.018 g, 0.78 mmol). **4** (0.303 g, 0.39 mmol) in ethanol (50 mL) was added dropwise over a 4 h period. The reaction mixture was stirred an additional 12 h at room temperature. The solvent was removed, and the residue was dissolved in CH_2Cl_2 and washed successively with 1.0 M HCl, H_2O, and $NaHCO_3$ solutions. The organic extracts were dried over anhydrous $MgSO_4$, and the solvent was removed. The crude product was recrystallized from CH_2Cl_2/CH_3CN. Yield: 0.336 g (86%). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.79 (s, NH, 2H), 7.28−7.11 (m, Ar H, 8H), 6.93 (t, Ar H, 2H), 5.96 (s, Ar H, 4H), 4.42 (d, $ArCH_2$, 4H), 4.03 (t, OCH_2, 4H), 3.68−3.59 (m, OCH_2 + SCH_2, 8H), 3.42 (s, 3H, CH_3OH), 3.14 (d, $ArCH_2$, 4H), 2.90 (s, CH_2S, 4H), 1.99−1.84 (m, CH_2, 8H), 1.09 (t, CH_3, 6H), 0.87 (t, CH_3, 6H). ^{13}C NMR ($CDCl_3$): δ (ppm) 167.00 (CO), 157.92, 153.78, 137.12, 136.72, 133.79, 130.36, 130.00, 129.58, 129.05, 128.26, 124.44, 122.33 (Ar C), 77.33, 76.58 (OCH_2), 47.54 (CH_3OH), 35.52, 34.03 (CH_2S), 31.12 ($ArCH_2$), 23.60, 22.98 (CH_2), 10.93, 9.87 (CH_3). LSI-MS: $[M + 1]^+$ *m*/*z* 873. Anal. Calcd for $C_{52}H_{60}N_2O_6S_2 \cdot CH_3OH$: C, 70.32; H, 7.13; N, 3.10. Found: C, 70.48; H, 6.75; N, 3.48.

Preparation of Metalloreceptor [Pd(L^1)(CH_3CN)][BF_4] (6). Calixarene **5** (0.1 g, 0.12 mmol) was suspended in acetonitrile (50 mL), and the suspension was heated to reflux. Once **5** had completely dissolved, a solution of $[Pd(CH_3CN)_4][BF_4]_2$ in acetonitrile was added dropwise over a period of 15 min. The reaction mixture was refluxed 2 h, and cooled to room temperature, and the solvent was removed. Yield: 0.12 g (93%). ^{1}H NMR (CD_3CN): δ (ppm) 8.29 (s, NH, 2H), 7.69 (br s, Ar H, 2H), 7.23 (d, Ar H, 4H) 7.05 (s, Ar H, 3H), 6.95 (t, Ar H, 2H), 6.54 (br s, Ar H, 2H), 4.48 (d, $ArCH_2$, 4H), 4.38 (br s, CH_2S, 4H), 4.07 (m, CH_2S + OCH_2, 8H), 3.69 (t, OCH_2, 4H), 3.29 (d, $ArCH_2$, 4H), 2.12 (m, CH_2, 4H), 1.95 (m, CH_2, 4H), 1.02 (t, CH_3, 6H), 0.94 (t, CH_3, 6H). ^{1}H NMR (CD_3NO_2): δ (ppm) 8.09 (s, NH, 2H), 7.72 (br s, Ar H, 2H), 7.28 (d, Ar H, 4H), 7.08 (m, Ar H, 3H), 7.00 (t, $ArCH_2$, 2H), 6.67 (br s, $ArCH_2$, 2H), 4.59 (d, $ArCH_2$, 4H), 4.45 (br s, CH_2S, 4H), 4.21 (s, CH_2S, 4H), 4.18 (t, OCH_2, 4H), 3.78 (t, OCH_2, 4H), 3.33 (d, $ArCH_2$, 4H), 2.21 (m, CH_2, 4H), 1.98 (m, CH_2, 4H), 1.09 (t, CH_3, 6H), 1.01 (t, CH_3, 6H), −1.80 (br s, MeCN, 3H). ^{13}C NMR (CD_3NO_2): δ (ppm) 164.90 (br), 158.58, 154.92, 148.93 (br), 137.44, 136.11, 134.16 (br), 130.95 (br), 127.76 (br), 124.58 (br), 121.48 (br), 79.82, 77.82, 45.91 (br), 45.25 (br), 31.96, 24.61, 24.28, 11.23, 10.27. LSI-MS: $[M - CH_3CN - BF_4]^+$ *m*/*z* 978. Anal. Calcd for $C_{54}H_{62}BF_4N_3O_6PdS_2 \cdot CHCl_3 \cdot CH_3OH$: C, 53.53; H, 5.44; N, 3.35. Found: C, 53.56; H, 5.49; N, 2.92.

Preparation of 5,17-Bis[2-(4-(hydroxymethyl)phenoxy)acetamido]-25,26,27,28-tetrapropoxycalix[4]arene (7). 4-Hydroxybenzyl alcohol (0.0384 g, 0.31 mmol) and K_2CO_3 (0.0257 g, 0.186 mmol) were refluxed in acetonitrile (10 mL) for 1 h. Compound **4** (0.120 g, 0.155 mmol) in acetonitrile (5 mL) was added, and the reaction mixture was refluxed 12 h. The solvent was removed under vacuum, and the residue was dissolved in CH_2Cl_2. This solution was washed with 0.1 M HCl (three times) and H_2O (once). The organic layer was dried over anhydrous $MgSO_4$ and filtered. The white solid product was isolated after removal of the solvent. Yield: 0.128 g (87%). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.94 (s, NH, 2H), 7.24 (d, Ar H, 4H), 6.84 (m, Ar H, 8H), 6.59 (m, Ar H, 6H), 4.60 (s, CH_2OH, 4H), 4.43 (d, $ArCH_2$, 4H), 4.36 (s, CH_2CO, 4H), 3.82 (m, $ArOCH_2$, 8H), 3.14 (d, $ArCH_2$, 4H), 1.89 (m, CH_2, 8H), 0.97 (m, CH_3, 12H). ^{13}C NMR ($CDCl_3$): δ (ppm) 165.64 (C═O), 156.51, 156.32, 154.09, 135.81, 134.84, 134.49, 130.41, 128.76, 128.18, 122.20, 120.80, 114.89 (Ar C), 76.79 (OCH_2), 67.56 (CH_2C═O), 64.70 (CH_2OH), 31.03 ($ArCH_2$), 23.21 (CH_2), 10.33 (CH_3). LSI-MS: [M+1] = 951. Anal. Calcd for $C_{58}H_{66}N_2O_{10}$: C, 73.23; H, 7.01; N, 2.95. Found: C, 73.36; H, 7.12; N, 2.92.

Preparation of 5,17-Bis[2-(4-(chloromethyl)phenoxy)acetamido]-25,26,27,28-tetrapropoxycalix[4]arene (8). Compound **7** (0.12 g, 0.127 mmol) was dissolved in CH_2Cl_2 (5 mL), and the solution was cooled in an ice bath to 0 °C. Thionyl chloride (100 μL) was added to the above solution, and stirring was continued for 1 h at room temperature. Solvent and excess thionyl chloride were removed under vacuum. The residue was dissolved in CH_2Cl_2 and washed with 1 M Na_2CO_3 (three times). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed to yield a white solid product. Yield: 0.11 g (90%). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.91 (s, NH, 2H), 7.31 (d, Ar H, 4H), 6.86 (m, Ar H, 8H), 6.56 (m, Ar H, 6H), 4.55 (s, CH_2Cl, 4H), 4.43 (m, $ArCH_2$ + CH_2CO, 8H), 3.81 (m, $ArOCH_2$, 8H), 3.14 (d, $ArCH_2$, 4H), 1.90 (m, CH_2, 8H), 0.98 (m, CH_3, 12H). ^{13}C NMR ($CDCl_3$): δ (ppm) 165.50 (CO), 157.30, 156.50, 154.20, 136.02, 134.53, 131.45, 130.46, 128.26, 122.31, 120.89, 115.16 (Ar C), 6.90 (OCH_2), 67.63 (CH_2CO), 45.92 (CH_2Cl), 31.14 ($ArCH_2$), 23.35, 23.26 (CH_2), 10.47, 10.37 (CH_3). LSI-MS: [M+1] = 988. Anal. Calcd for $C_{58}H_{64}Cl_2N_2O_8$: C, 70.49; H, 6.54; N, 2.84. Found: C, 70.66; H, 6.66; N, 2.91.

Preparation of Macrobicyclic Ligand HL^2 (9). Method A. Ethanol solutions (50 mL) of α,α'-*m*-xylenedithiol (0.0427 g, 0.25 mmol) and **7** (0.248 g, 0.25 mmol) were added dropwise to a solution of Na (0.0115 g, 0.5 mmol) in EtOH (100 mL) over a 12 h period at room temperature. The reaction mixture was stirred an additional 12 h, after which the solvent was removed and the residue was dissolved in ethyl acetate and washed with H_2O. The organic extracts were dried over anhydrous $MgSO_4$ and the solvent removed. The crude product was purified by chromatography (SiO_2; eluent 1% MeOH/CH_2Cl_2). Yield: 0.045 g (17%).

Method B. Diol **10** (0.53 g, 1.4 mmol) and NaH (2.8 mmol) were suspended in CH_3CN (500 mL), and the suspension was brought to reflux. A solution of **4** (1.08 g, 1.4 mmol) in CH_3CN (150 mL) and CH_2Cl_2 (minimum amount to dissolve **4**) was added dropwise over a period of 12 h. The resulting mixture was refluxed for an additional 48 h. After cooling to room temperature and removal of solvent, the residue was dissolved in CH_2Cl_2 and washed with 1.0 M HCl (twice) and H_2O (once). The organic extracts were dried over anhydrous $MgSO_4$, and the solvent was removed. The crude product was purified by chromatography (SiO_2; eluent 2% MeOH/CH_2Cl_2); R_f = 0.48. Yield: 0.38 g (25%). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.80 (s, NH, 2H), 7.28 (m, Ar H, 2H), 7.14 (m, Ar H, 8H), 7.00 (m, Ar H, 3H), 6.81 (s, Ar H, 1H), 6.64 (d, Ar H, 4H), 6.31 (s, Ar H, 4H), 4.47 (d, $ArCH_2$, 4H), 4.20 (s, CH_2CO, 4H), 4.08 (t, OCH_2, 4H), 3.80 (s, CH_3OH, 3H), 3.65 (t, OCH_2, 4H), 3.53 (s, CH_2S, 4H), 3.50 (s, CH_2S, 4H), 3.17 (d, $ArCH_2$, 4H), 2.00 (m, CH_2, 4H), 1.88 (m, CH_2, 4H), 1.09 (t, CH_3, 6H), 0.89 (t, CH_3, 6H). ^{13}C NMR ($CDCl_3$): δ (ppm) 165.22 (CO), 157.75, 155.71, 152.86, 137.48, 136.56, 133.55, 131.48, 130.68, 130.32, 130.15, 129.02, 127.57, 122.26, 121.55, 114.53 (Ar C), 77.18, 76.45 ($ArOCH_2$), 67.07 (CH_2CO), 44.40 (CH_3OH), 35.02, 34.31 (CH_2S), 31.04 ($ArCH_2$),

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23.44, 22.85 (CH_2), 10.78, 9.75 (CH_3). LSI-MS: [M+1] = 1085. Anal. Calcd for $C_{66}H_{72}N_2O_8S_2 \cdot CH_3OH$: C, 72.01; H, 6.86; N, 2.51. Found: C, 71.96; H, 6.54; N, 2.48.

Preparation of Dithioether Diol (10). 4-Hydroxybenzyl alcohol (1.46 g, 11.76 mmol), α,α′-*m*-xylenedithiol (0.5 g, 2.94 mmol), and a catalytic amount of *p*-toluenesulfonic acid were refluxed in CH_3CN for 24 h. The solvent was removed under vacuum, the residue dissolved in CH_2Cl_2, and the excess 4-hydroxybenzyl alcohol removed by filtration. The filtrate was dried over anhydrous $MgSO_4$ and the solvent removed. The crude product was triturated with anhydrous ethanol and purified by chromatography (SiO_2; eluent 10% MeOH/CH_2Cl_2). Yield: 0.61 g (54%) ^{1}H NMR (CD_3CN): δ (ppm) 7.14 (m, Ar H, 7H), 7.00 (Ar H, 1H), 6.72 (m, Ar H, 4H), 5.06 (s, OH, 2H), 3.54, 3.52 (s, s, CH_2S, 8H). ^{13}C NMR (CD_3CN): δ (ppm) 154.45, 138.37, 130.28, 129.69, 128.60, 127.60, 115.36, 35.37, 35.03. HR-EI-MS: calcd for $C_{22}H_{22}O_2S_2$, *m*/*z* 382.106 13. Found, *m*/*z* 382.105 26.

Preparation of Metalloreceptor [Pd(L^2)(CH$_3$CN)][BF$_4$] (11). Calixarene **9** (0.100 g, 0.092 mmol) was suspended in CH_3CN (100 mL), and the suspension was refluxed until complete dissolution. A solution of $[Pd(CH_3CN)_4][BF_4]_2$ (0.041 g, 0.092 mmol) in CH_3CN was then added dropwise. The reaction mixture was refluxed for 6 h, after which the solvent was removed. Yield: 0.117 g (96%). ^{1}H NMR (CD_3CN): δ (ppm) 8.19 (s, NH, 2H), 7.38 (d, Ar H, 4H), 7.15 (d, Ar H, 4H), 6.89 (m, Ar H, 9H), 6.61 (s, Ar H, 4H), 4.47 (d, $ArCH_2$, 4H), 4.37 (s, CH_2CO, 4H), 4.33 (br s, CH_2S, 4H), 4.28 (s, CH_2S, 4H), 4.08 (t, OCH_2, 4H), 3.66 (t, OCH_2, 4H), 3.20 (d, $ArCH_2$, 4H), 2.05 (m, CH_2, 4H), 1.90 (m, CH_2, 4H), 1.07 (t, CH_3, 6H), 0.91 (t, CH_3, 6H). ^{13}C NMR (CD_3CN): δ (ppm) 166.91 (CO), 158.43, 153.68, 151.38, 137.43, 134.88, 132.53, 130.05, 128.58, 123.66, 121.65, 115.93 (Ar C), 78.52, 77.31 ($ArOCH_2$), 67.84 (CH_2CO), 45.14, 43.49 (CH_2S), 31.87 ($ArCH_2$), 24.24, 23.79 (CH_2), 11.14, 10.13 (CH_3). LSI-MS: $[M - CH_3CN - BF_4 + H]^+$ *m*/*z* 1190. Anal. Calcd for $C_{68}H_{74}BF_4N_3O_8PdS_2 \cdot CH_2Cl_2$: C, 59.09; H, 5.47; N, 3.00. Found: C, 59.77, H, 5.51, N, 2.67.

Preparation of [Pd(L^1)(py)][BF$_4$] (12). Metalloreceptor **6** (0.05g, 0.045 mmol) was dissolved in CH_3CN (50 mL), and an excess of pyridine was added. The reaction mixture was warmed to 50 °C and stirred for 2 h. The solvent was reduced, and the product was precipitated with the addition of diethyl ether. The crude product was recrystallized from CH_2Cl_2/Et_2O. Yield: 0.040 g (77%). ^{1}H NMR (CD_3NO_2): δ (ppm) 8.86 (m, py, 1H), 8.75 (t, py, 1H), 8.17 (t, py, 1H), 7.52 (br s, NH + py, 4H), 7.37 (d, Ar H, 4H), 7.31 (br s, Ar H, 2H), 7.17 (t, Ar H, 2H), 7.07 (s, Ar H, 3H), 6.01 (br s, Ar H, 2H), 5.44 (s, 2H, CH_2Cl_2), 4.65 (d, $ArCH_2$, 4H), 4.52 (br s, CH_2S, 4H), 4.35 (br s, CH_2S, 4H), 3.93 (m, OCH_2, 4H), 3.72 (t, OCH_2, 4H), 3.32 (d, $ArCH_2$, 4H), 2.24 (m, CH_2, 4H), 1.99 (m, CH_2, 4H), 1.11 (t, CH_3, 6H), 0.99 (t, CH_3, 6H). ^{13}C NMR (CD_3NO_2): δ (ppm) 163.34, 159.44, 154.92, 150.27, 148.34, 138.98, 137.84, 134.67, 134.16, 131.83, 127.72, 124.81, 124.20, 121.38 (br), 79.62, 77.82, 52.02, 47.72, 44.66, 32.51 (br), 24.64, 24.14, 11.20, 10.22. LSI-MS: $[M - py - BF_4]^+$ *m*/*z* 978. Anal. Calcd for $C_{57}H_{64}N_3O_6S_2PdBF_4 \cdot CH_2Cl_2$: C, 56.66; H, 5.41; N, 3.42. Found: C, 56.83; H, 5.47; N, 3.46.

Preparation of [Pd(L^1)Cl] (13). Metalloreceptor **6** (0.10 g, 0.09 mmol) was dissolved in CH_3CN (25 mL). This solution was warmed to 50 °C, and an excess of NH_4Cl (0.05 g, 1.2 mmol) was added. The product precipitated from solution and was isolated by filtration. The crude product could be recrystallized from $CHCl_3/Et_2O$ or chromatographed on SiO_2 (eluent 10% MeOH/CH_2Cl_2). Yield: 0.075 g (82%). ^{1}H NMR (CD_3NO_2): δ (ppm) 8.15 (s, NH, 2H), 7.14 (d, Ar H, 4H), 7.06 (m, Ar H, 3H), 6.89 (t, Ar H, 2H), 6.37 (s, Ar H, 4H), 4.58 (d, $ArCH_2$, 4H), 4.47 (s, CH_2S, 4H), 4.22 (t, OCH_2, 4H), 3.89 (s, CH_2S, 4H), 3.77 (t, OCH_2, 4H), 3.22 (d, $ArCH_2$, 4H), 2.10 (m, CH_2, 4H), 1.96 (m, CH_2, 4H), 1.16 (t, CH_3, 6H), 0.99 (t, CH_3, 6H). ^{13}C NMR (CD_2Cl_2): δ (ppm) 164.52, 157.93, 153.66, 136.75, 133.84, 130.82, 129.26 (br), 125.95, 123.35 (br), 122.47 (br), 77.80, 76.90, 46.46, 40.05, 31.23, 23.88, 23.23, 11.01, 9.93. LSI-MS: $[M - Cl]^+$ *m*/*z* 978. Anal. Calcd for $C_{52}H_{59}ClN_2O_6PdS_2$: C, 61.58; H, 5.88; N, 2.76. Found: C, 61.75; H, 5.98; N, 2.83.

Preparation of [Pd(L^2)(4-Phpy)][BF$_4$] (14). Compound **11** (0.085 g, 0.064 mmol) was dissolved in $CHCl_3$, and the solution was warmed to 50 °C. 4-Phenylpyridine (0.01 g, 0.064 mmol) was added, and the reaction mixture was stirred an additional 2 h at 50 °C. The solvent was reduced, and product precipitated upon addition of diethyl ether. The isolated solid was recrystallized from $CHCl_3/Et_2O$. Yield: 0.091 g (99%). ^{1}H NMR (CD_3NO_2): δ (ppm) 7.49 (d, Ar H, 2H), 7.28 (d, Ar H, 4H), 7.11−6.96 (m, Ar H, 13H), 6.88 (d, Ar H, 2H), 6.37 (s, Ar H, 2H), 6.27 (d, Ar H, 4H), 4.73 (m, *m*-Phpy, 2H), 4.58 (d, $ArCH_2$, 4H), 4.36 (s, OCH_2CO, 4H), 4.24 (br s, CH_2S, 4H), 4.19 (t, OCH_2, 4H), 3.74 (s, CH_2S, 4H), 3.67 (t, OCH_2, 4H), 3.56 (t, *p*-Phpy, 1H), 3.26 (d, $ArCH_2$, 4H), 2.25 (m, CH_2, 4H), 1.92 (m, CH_2, 4H), 1.02 (t, CH_3, 6H), 0.99 (t, CH_3, 6H). ^{13}C NMR (CD_3NO_2): δ (ppm) 165.38, 158.88, 157.96, 153.90, 153.41, 153.20, 138.09, 134.78, 134.14, 133.51, 133.16, 132.26, 130.88, 127.37, 126.83, 124.88, 124.32, 124.02, 122.45, 122.28, 115.83, 79.51, 77.85, 67.04, 47.14, 46.02, 32.06, 24.69, 24.40, 11.29, 10.35. LSI-MS: $[M - BF_4]^+$ *m*/*z* 1345. Anal. Calcd for $C_{77}H_{80}BF_4N_3O_8PdS_2 \cdot CH_2Cl_2$: C, 61.67; H, 5.45; N, 2.78. Found: C, 61.49; H, 5.50; N, 2.94.

Preparation of Model Ligand HL^3 (15). Na (0.20 g, 8.8 mmol) was dissolved in EtOH (80 mL). α,α′-*m*-Xylenedithiol (0.75 g, 4.4 mmol) was added to the NaOEt solution, and the mixture was stirred for 1 h at room temperature. Chloroacetanilide (1.5 g, 8.8 mmol) was added to the reaction mixture, and the solution was stirred for 12 h. Yield: 1.85 g (96%). ^{1}H NMR ($CDCl_3$): δ (ppm) 8.59 (s, NH, 2H), 7.42 (d, Ar H, 4H), 7.26−7.09 (m, Ar H, 10H), 3.68 (s, CH_2S, 4H), 3.20 (s, CH_2S, 4H). ^{13}C NMR ($CDCl_3$): δ (ppm) 167.14, 137.62, 137.40, 129.56, 128.92, 128.14, 124.59, 119.86, 36.80, 36.17. Anal. Calcd for $C_{24}H_{24}N_2O_2S_2$: C, 66.04; H, 5.55; N, 6.42. Found: C, 65.87; H, 5.55; N, 6.31.

Preparation of Model Metalloreceptor [Pd(L^3)(MeCN)][BF$_4$] (16). Compound **15** (0.98 g, 2.25 mmol) and $[Pd(CH_3CN)_4][BF_4]_2$ (1.0 g, 2.25 mmol) were gently refluxed in CH_3CN (50 mL) for 12 h. The solution was concentrated under vacuum, and pure product was obtained from crystallization at 4 °C. Yield: 1.37 g (91%). ^{1}H NMR (CD_3CN): δ (ppm) 8.74 (s, NH, 2H), 7.52 (d, Ar H, 4H), 7.33 (t, Ar H, 2H), 7.13 (t, Ar H, 1H), 6.98 (m, Ar H, 6H), 4.51 (br s, CH_2S, 4H), 4.01 (s, CH_2S, 4H), 2.25 (s, H_2O, 2H). ^{13}C NMR ($CDCl_3$): δ (ppm) 164.06, 137.65, 129.07, 126.33, 124.90, 123.50, 120.02, 45.71 (br), 42.03. Anal. Calcd for $C_{26}H_{26}BF_4N_3O_2PdS_2 \cdot H_2O$: C, 45.40; H, 4.10; N, 6.11. Found: C, 45.70; H, 3.93; N, 6.51.

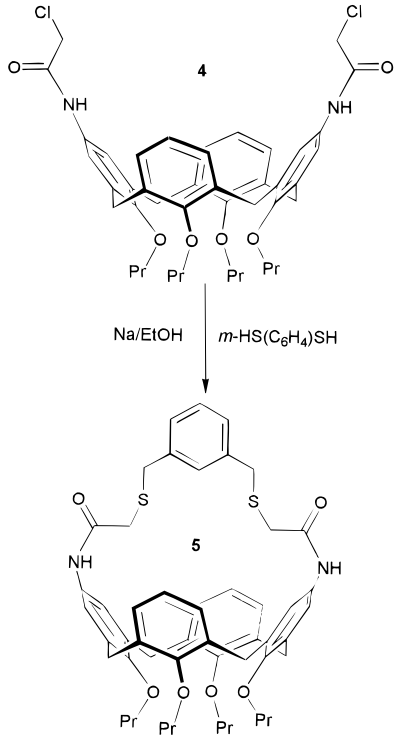
Table 1. Crystallographic Data for **5**·2CH_3CN

formula	$C_{56}H_{66}N_4O_6S_2$	ρ, g cm^{-3}	1.17
fw	955.25	*Z*	4
a, Å	23.5095(1)	μ, cm^{-1}	1.49
b, Å	9.9090(1)	*T*, °C	25
c, Å	23.3586(2)	goodness of fit	1.208
β, deg	91.53(1)	$R(F)$, %[a]	10.13
space group	$P2_1/c$ (No. 14)	$R_w(F^2)$, %[b]	21.91
V, Å^3	5439.59(8)		

[a] $R(F) = \sum\Delta/\sum(F_o)$; $\Delta = |F_o - F_c|$. [b] $R_w(F^2) = \sum[w(F_o^2 - F_c^2)^2]$.

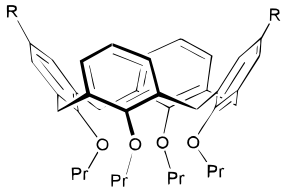
X-ray Diffraction Data Collection and Solution and Refinement of the Structure of 5. Crystallographic data and refinement parameters are summarized in Table 1. Crystals of **5** were obtained from slow evaporation of a saturated acetonitrile solution of the compound. Despite repeated attempts at recrystallization, all inspected crystals were twinned or had satellites. The data crystal was obtained by sectioning a larger multiple crystal. Approximately 10% of the observed reflections were rejected as diffraction contributions of a minor twin or satellite crystal. Unit-cell parameters were calculated from reflections obtained from 60 data frames collected at different sections of the Ewald sphere. The systematic absences in the diffraction data and the determined unit-cell parameters were uniquely consistent for the reported space group. A semiempirical absorption correction was applied on the basis of redundant data at varying effective azimuthal angles. Two acetonitrile solvent molecules were located in the asymmetric unit. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were treated as idealized contributions. The structure was solved by direct methods, completed by subsequent Fourier syntheses, and refined with full-matrix least-squares methods. All scattering factors and anomalous dispersion coefficients are contained in the SHELXTL 5.03 program library (G. Sheldrick, Siemens XRD, Madison, WI).

Scheme 1



Results

Synthesis and Characterization of Calix[4]arene Ligands 5 and 9. The calix[4]arene-based ligands **5** and **9** were synthesized by building upon an existing calix[4]arene platform. Literature preparations were used to obtain the required 1,3-substitution pattern by nitration[16] of **1** to give **2** and reduction to yield **3**.[15] Reaction of **3** with 2 equiv of chloroacetyl chloride, according to the method of Reinhoudt et al., gave the diamide **4** in 65% yield.[15]

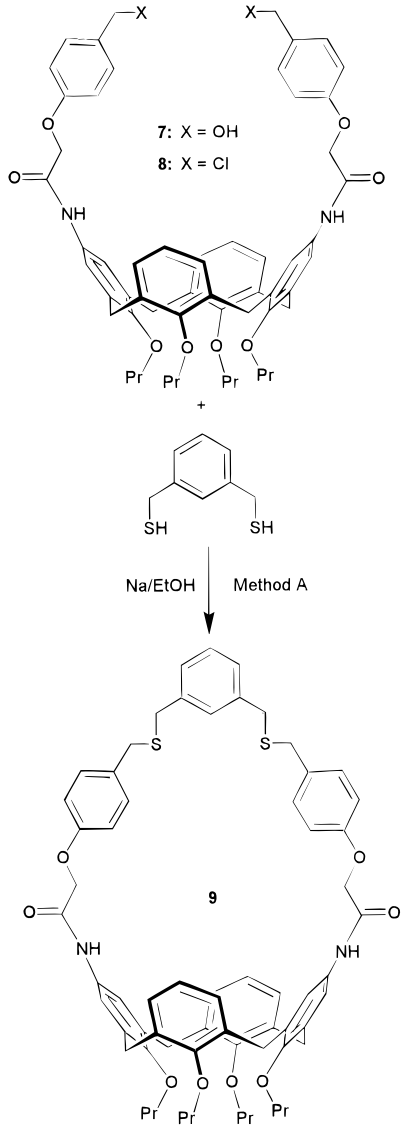


1: R = H
2: R = NO_2
3: R = NH_2
4: R = $NH(CO)CH_2Cl$

The substituted calix[4]arene, **4**, was converted directly to the macrobicycle **5**, in 86% yield, by treatment with α,α′-*m*-xylenedithiol in Na/ethanol under high-dilution conditions (Scheme 1).

Ligand **9** could be prepared by two methods. In method A, similar to that used for the preparation of **5**, the dibenzyl chloride **8** was reacted with α,α′-*m*-xylenedithiol in Na/ethanol under high-dilution conditions to give the macrobicycle in 17% yield (Scheme 2). Alternately, in method B, the α-chloroamide **4** was reacted with dithiaether **10** and NaH in acetonitrile under high-dilution conditions (Scheme 3). The yield of **9** from this

Scheme 2



cyclization reaction was 25%. Method B, therefore, proved to be a more efficient synthesis with higher yield and fewer steps.

The calix[4]arene molecules in this study have the lower rim substituted with *n*-propoxy groups in order to inhibit interconversion between the four possible conformations (cone, partial cone, 1,3-alternate, and 1,2-alternate). Once the cone conformation is isolated, the bulky nature of the propoxy groups ensures retention of this conformation throughout the synthetic sequence.[17] The ^{1}H NMR spectra of **5** and **9** show an AB quartet for the methylene Ar*CH*$_2$Ar protons, typical for calix[4]arenes in the cone conformation.[7] In addition, the Ar*CH*$_2$Ar peak at ∼δ 31 ppm in the ^{13}C NMR spectrum is indicative of the cone conformation.[18]

X-ray Structure of 5. A perspective ORTEP drawing of **5** with an atom numbering scheme is shown in Figure 1. The calix[4]arene portion of the molecule is in a *pinched-cone* conformation in which the substituted aromatic groups of the calix[4]arene are almost parallel; dihedral angle 19.5°. The loop containing the xylyl unit is bent at the sulfur atoms with C−S−C bond angles of 100.1(4) and 100.6(4)°, and the amido groups

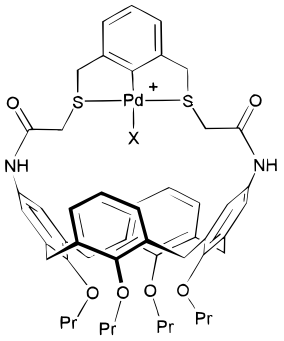
(16) Kelderman, E.; Derhaeg, L.; Heesink, G. J. T.; Verboom, W.; Engbersen, J. F. J.; van Hulst, N. F.; Persoons, A.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1075.

(17) Arduini, A.; Fabbi, M.; Mantovani, M.; Mirone, L.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Org. Chem.* **1995**, *60*, 1454 and references therein.

(18) Jaime, C.; de Mendoza, J.; Prados, P.; Neito, P. M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372.

are in a *syn* orientation. There are two molecules of acetonitrile in the asymmetric unit, but neither interacts with **5**; they simply appear to fill void space in the lattice.

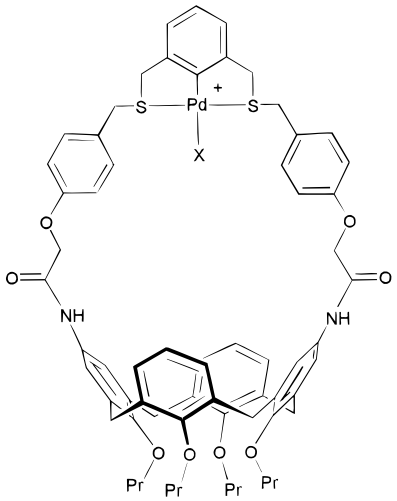
Synthesis and Characterization of Metalloreceptors 6 and 11. Palladation of **5** employing $[Pd(CH_3CN)_4][BF_4]_2$ in acetonitrile solution yielded the metalloreceptor **6** in 93% yield. Similarly, palladation of **9** produced the metalloreceptor **11** in 96% yield.



6: X = MeCN

12: X = py

13: X = Cl



11: X = MeCN

14: X =4-Phpy

The metalloreceptors **6** and **11** were isolated as pale yellow solids and could be recrystallized from CH_3CN/diethyl ether solutions. All spectroscopic and analytical data are consistent with palladation and the formula $[Pd(L)(CH_3CN)][BF_4]$. In general, resonances for the benzylic CH_2S protons are shifted downfield and are broad in the ^1H NMR spectrum compared to those of the free ligand HL. The effect of palladation is also evident in the ^{13}C NMR spectrum, with the resonance for benzylic carbon atoms shifted downfield by *ca.* 10 ppm. A strong ion peak for $[Pd(L)]^+$ was observed in the LSI mass spectrum for both compounds.

The ^1H NMR spectrum of **6** in CD_3NO_2 shows the coordinated CH_3CN group shifted significantly *upfield* at a chemical shift of δ −1.80 ppm. This suggests that in solution the CH_3 group is ensconced in the calix[4]arene cavity. There is also an inequivalence of the aromatic protons on the substituted rings of the calix[4]arene, suggesting some restricted rotation at room temperature. When the sample is heated, this inequivalence disappears. Also, the complex $[Pd(L^1)(Cl)]$, **13**, with a smaller Cl^-, substrate does not exhibit this feature at any temperature.

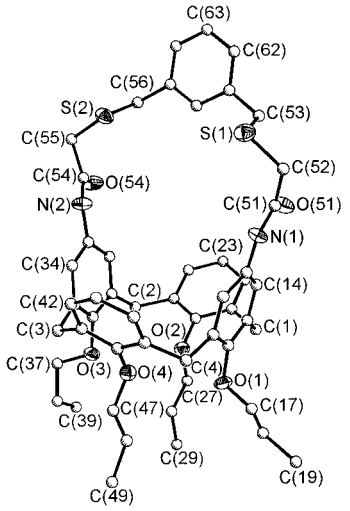
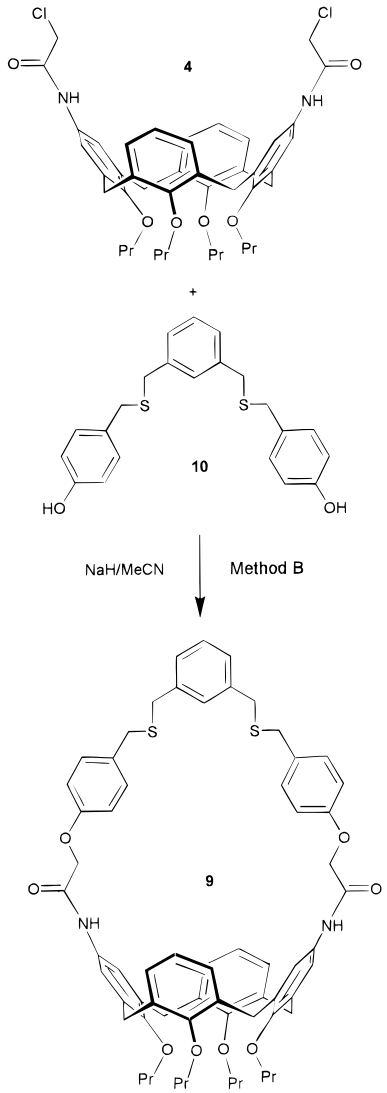


Figure 1. Perspective ORTEP drawing of **5** showing the atom-numbering scheme. 30% thermal ellipsoids are shown for the non-carbon atoms. All other atoms are shown as ideal spheres for clarity.

Scheme 3



Synthesis and Characterization of [Pd(L)(Y)][BF$_4$] (12: L^1, Y = py) (14: L^2, Y = 4-Phpy). Examination of CPK

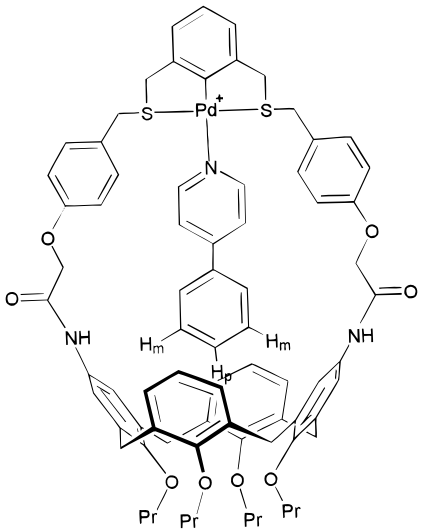


Figure 2. Drawing of **14** illustrating the positioning of the 4-Phpy substrate *inside* the calix[4]arene cavity.

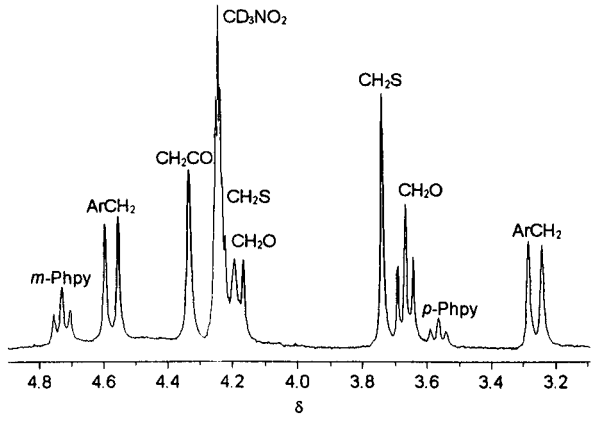


Figure 3. ^{1}H NMR spectrum of **14** (300 MHz, CD_2Cl_2/CD_3NO_2 (3:1)), in the region δ 3.2−4.8 ppm, identifying the upfield shifted resonances, *m*-Phpy and *p*-Phpy, indicative of binding 4-Phpy *inside* the calix[4]arene cavity.

models suggested that pyridine (py) would be a suitable substrate for **6**, since formation of a Pd−N bond would orient the aromatic moiety *into* the hydrophobic cavity provided by the calix[4]-arene. Similarly, since the metalloreceptor **11** contains a much larger overall cavity, 4-phenylpyridine (4-Phpy) was investigated as a suitable substrate. Additional $\pi-\pi$ stacking interactions could occur between the pyridine ring and the aromatic spacer of the metalloreceptor with the phenyl substituent oriented into the calixarene cavity.

Both **12** and **14** were easily prepared in quantitative yield by displacing the labile acetonitrile ligand with 1 equiv of the substrate molecule. For both receptors, ^{1}H NMR spectral data exhibited (i) complexation shifts for the pyridine protons consistent with binding to the palladium center via σ-donation and (ii) distinct features indicative of substrate interaction with the calix[4]arene moiety.

The most dramatic effects were observed for **14**. The protons of the aromatic spacer on the metalloreceptor are shifted *upfield* approximately 0.8 ppm, indicative of a π-stacking interaction,[19] while a dramatic change is observed for the *meta* and *para* protons on the phenyl ring of the 4-Phpy substrate. A ^{1}H−^{13}C HETCOR NMR experiment identified proton resonances at 3.59

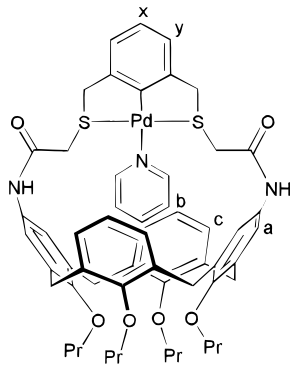


Figure 4. Drawing of **12** showing the labeling scheme for Figure 5 and illustrating the possible positioning of the py substrate inside the calix[4]arene cavity.

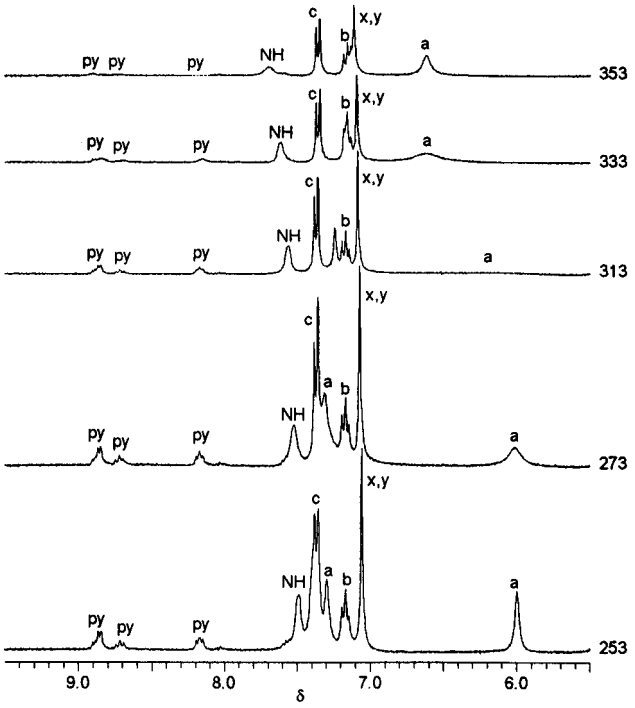


Figure 5. Variable-temperature NMR spectra of **12**.

and 4.71 ppm as belonging to the aromatic protons of the phenyl group of 4-Phpy. These protons are shifted *upfield* by 3.90 and 2.78 ppm relative to those of the free substrate. This almost certainly arises from inclusion of the phenyl ring *inside* the calix-[4]arene cavity.[20] (See Figures 2 and 3.)

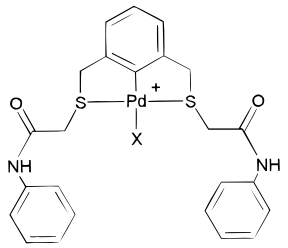
For **12**, the pyridine protons are shifted downfield as a result of coordination, but the only change to the calixarene portion of the molecule is a splitting of the calixarene aromatic protons on the substituted rings (labeled "*a*" in Figure 4). This splitting is consistent with an asymmetric coordination of the pyridine unit and suggests that py is too large for the receptor cavity. That is, in solution a conformation is adopted which coordinates py to the Pd center but *not* inside the calixarene cavity. A variable-temperature ^{1}H NMR study on this compound shows that the asymmetry observed at room temperature disappears with increasing temperature until a symmetrical spectrum is observed. (See Figure 5.) This may indicate a fluxional process occurs in which the pyridine moves "in and out of" or "through" the cavity. The symmetrical high-temperature structure observed would simply be an average of the two conformations in which the pyridine is coordinated to Pd but oriented outside

(19) (a) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525. (b) Burley, S. K.; Petsko, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 7995.

(20) Komoto, T.; Ando, I.; Nakamoto, Y.; Ishida, S.-I. *J. Chem. Soc., Chem. Commun*. **1988**, 135.

the cavity. The lack of upfield shifts similar to that observed for **14** is also evidence for this scenario.

Molecular Recognition of Phenyl-Substituted Pyridines. Since solution and modeling studies show that 4-Phpy is an excellent fit for receptor **11**, it was reasoned that this complementarity could be used to effect molecular recognition of this species over related Phpy compounds. Accordingly, competition studies were performed between 4-Phpy and 2-Phpy or 3-Phpy. In separate reactions, 1 equiv of **11** was mixed with 1 equiv of 4-Phpy and 1 equiv of either 2-Phpy or 3-Phpy. The ^{1}H NMR spectra were recorded, and the ratio of complexed to free 4-Phpy was determined by integration of the *p*-Ph proton. As a comparison, the same competition experiments were carried out using **16**, as a model receptor containing no calixarene unit.



16: X = MeCN

The results are summarized in Table 2. A comparison of the results for model receptor **16** with those for metalloreceptor **11** gave a measure of the ability of **11** to selectively recognize 4-Phpy. Thus, **11** exhibited a selectivity of 4 for 4-Phpy over 2-Phpy and a remarkable selectivity of 38 for 4-phenylpyridine over 3-phenylpyridine.

Discussion

The nature of the binding site in these new metalloreceptors was investigated by ^{1}H NMR spectroscopy and CPK models.

Table 2. Competition Reactions Showing Molecular Recognition of 4-Phpy

substrate pair	**16**	**11**	selectivity[b]
4-Phpy/2-Phpy	50/50[a]	80/20	4
4-Phpy/3-Phpy	4/96	60/40	38

[a] Ratio of receptor-bound substrates in a 1/1/1 mixture of the two competing substrates and the receptor. [b] The ratio for metalloreceptor **11** over the ratio for model receptor **16**.

For **14**, the marked upfield shifts of the phenyl protons must surely result from shielding of these hydrogens by an aromatic group *inside* the calixarene cavity.[20] Figure 3 shows a representation illustrating how this type of noncovalent interaction occurs as a result of the strong, oriented binding provided by the organopalladium center. In these new metalloreceptors, the Pd atom provides two important attributes: (1) it acts as a binding site for coordination of the substrate and (2) it directs the substrate into the hydrophobic cavity of the calix[4]arene. The first-sphere coordination via σ-donation to the organopalladium center anchors the substrate in place. Depending on the size and shape of the substrate, this may position the substrate inside the cavity, resulting in a second-sphere interaction. As demonstrated herein, a complementary set of substrate−receptor interactions has the potential to simultaneously provide functional group, size, and shape selectivity in a molecular recognition event.

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Supporting Information Available: An X-ray crystallographic file, in CIF format, for compound **5** is available on the Internet only. Access information is given on any current masthead page.

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