

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, HL¹, **5**, contains a symmetrically disposed macrocyclic loop across the upper rim of the calix[4]arene. Palladation of **5** yielded [Pd(L¹)(CH₃CN)][BF₄], **6**. Similarly 5,17-bis[2-(4-(chloromethyl)phenoxy)acetamido]-25,26,27,28-tetrapropoxycalix[4]arene, **8**, was used to prepare HL², **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(L²)(CH₃CN)][BF₄], **11**. All new compounds and complexes were characterized in solution by ¹H 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 *P*2₁/*c* with *a* = 23.5095(1) Å, *b* = 9.9090(1) Å, *c* = 23.3586(1) Å, β = 91.53(1)°, *V* = 5439.59(8) Å³, and *Z* = 4. The structure was refined to *R*(*F*) = 10.13% and *R*_w(*F*²) = 21.91% for 5799 reflections with *F*_o² > 2σ(*F*_o²). 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 ¹H 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]arenes⁷ 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 metallo-receptors 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 CaH₂ under N₂(g). All reactions were performed under an atmosphere of N₂(g). ¹H NMR and ¹³C 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 Reinhoudt¹⁵ and characterized as follows. ¹H NMR (CDCl₃): δ (ppm) 7.90 (s, NH, 2H), 6.78 (s, Ar H, 4H), 6.60 (m, Ar H, 6H), 4.43 (d, ArCH₂, 4H), 4.08 (s, CH₂Cl, 4H), 3.82 (m, ArOCH₂, 8H), 3.13 (d, ArCH₂, 4H), 1.90 (m, CH₂, 8H), 0.97 (m, CH₃, 12H).

Preparation of Macrobicyclic Ligand HL¹ (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 CH₂Cl₂ and washed successively with 1.0 M HCl, H₂O, and NaHCO₃ solutions. The organic extracts were dried over anhydrous MgSO₄, and the solvent was removed. The crude product was recrystallized from CH₂Cl₂/CH₃CN. Yield: 0.336 g (86%). ¹H NMR (CDCl₃): 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, ArCH₂, 4H), 4.03 (t, OCH₂, 4H), 3.68–3.59 (m, OCH₂ + SCH₂, 8H), 3.42 (s, 3H, CH₃OH), 3.14 (d, ArCH₂, 4H), 2.90 (s, CH₂S, 4H), 1.99–1.84 (m, CH₂, 8H), 1.09 (t, CH₃, 6H), 0.87 (t, CH₃, 6H). ¹³C NMR (CDCl₃): 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 (OCH₂), 47.54 (CH₃OH), 35.52, 34.03 (CH₂S), 31.12 (ArCH₂), 23.60, 22.98 (CH₂), 10.93, 9.87 (CH₃). LSI-MS: [M + 1]⁺ m/z 873. Anal. Calcd for C₅₂H₆₀N₂O₆S₂·CH₃OH: C, 70.32; H, 7.13; N, 3.10. Found: C, 70.48; H, 6.75; N, 3.48.

Preparation of Metalloreceptor [Pd(L¹)(CH₃CN)][BF₄] (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(CH₃CN)₄][BF₄]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%). ¹H NMR (CD₃CN): 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, ArCH₂, 4H), 4.38 (br s, CH₂S, 4H), 4.07 (m, CH₂S + OCH₂, 8H), 3.69 (t, OCH₂, 4H), 3.29 (d, ArCH₂, 4H), 2.12 (m, CH₂, 4H), 1.95 (m, CH₂, 4H), 1.02 (t, CH₃, 6H), 0.94 (t, CH₃, 6H). ¹H NMR (CD₃NO₂): 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, ArCH₂, 2H), 6.67 (br s, ArCH₂, 2H), 4.59 (d, ArCH₂, 4H), 4.45 (br s, CH₂S, 4H), 4.21 (s, CH₂S, 4H), 4.18 (t, OCH₂, 4H), 3.78 (t, OCH₂, 4H), 3.33 (d, ArCH₂, 4H), 2.21 (m, CH₂, 4H), 1.98 (m, CH₂, 4H), 1.09 (t, CH₃, 6H), 1.01 (t, CH₃, 6H), -1.80 (br s, MeCN, 3H). ¹³C NMR (CD₃NO₂): 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 - CH₃CN - BF₄]⁺ m/z 978. Anal. Calcd for C₅₄H₆₂BF₄N₃O₆PdS₂·CHCl₃·CH₃OH: 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 K₂CO₃ (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 CH₂Cl₂. This solution was washed with 0.1 M HCl (three times) and H₂O (once). The organic layer was dried over anhydrous MgSO₄ and filtered. The white solid product was isolated after removal of the solvent. Yield: 0.128 g (87%). ¹H NMR (CDCl₃): 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, CH₂OH, 4H), 4.43 (d, ArCH₂, 4H), 4.36 (s, CH₂CO, 4H), 3.82 (m, ArOCH₂, 8H), 3.14 (d, ArCH₂, 4H), 1.89 (m, CH₂, 8H), 0.97 (m, CH₃, 12H). ¹³C NMR (CDCl₃): 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 (OCH₂), 67.56 (CH₂C=O), 64.70 (CH₂OH), 31.03 (ArCH₂), 23.21 (CH₂), 10.33 (CH₃). LSI-MS: [M + 1] = 951. Anal. Calcd for C₅₈H₆₆N₂O₁₀: 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 CH₂Cl₂ (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 CH₂Cl₂ and washed with 1 M Na₂CO₃ (three times). The organic layer was dried over MgSO₄ and filtered, and the solvent was removed to yield a white solid product. Yield: 0.11 g (90%). ¹H NMR (CDCl₃): 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, CH₂Cl, 4H), 4.43 (m, ArCH₂ + CH₂CO, 8H), 3.81 (m, ArOCH₂, 8H), 3.14 (d, ArCH₂, 4H), 1.90 (m, CH₂, 8H), 0.98 (m, CH₃, 12H). ¹³C NMR (CDCl₃): 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 (OCH₂), 67.63 (CH₂CO), 45.92 (CH₂Cl), 31.14 (ArCH₂), 23.35, 23.26 (CH₂), 10.47, 10.37 (CH₃). LSI-MS: [M + 1] = 988. Anal. Calcd for C₅₈H₆₄Cl₂N₂O₈: C, 70.49; H, 6.54; N, 2.84. Found: C, 70.66; H, 6.66; N, 2.91.

Preparation of Macrobicyclic Ligand HL² (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 H₂O. The organic extracts were dried over anhydrous MgSO₄ and the solvent removed. The crude product was purified by chromatography (SiO₂; eluent 1% MeOH/CH₂Cl₂). Yield: 0.045 g (17%).

Method B. Diol **10** (0.53 g, 1.4 mmol) and NaH (2.8 mmol) were suspended in CH₃CN (500 mL), and the suspension was brought to reflux. A solution of **4** (1.08 g, 1.4 mmol) in CH₃CN (150 mL) and CH₂Cl₂ (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 CH₂Cl₂ and washed with 1.0 M HCl (twice) and H₂O (once). The organic extracts were dried over anhydrous MgSO₄, and the solvent was removed. The crude product was purified by chromatography (SiO₂; eluent 2% MeOH/CH₂Cl₂); R_f = 0.48. Yield: 0.38 g (25%). ¹H NMR (CDCl₃): 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, ArCH₂, 4H), 4.20 (s, CH₂CO, 4H), 4.08 (t, OCH₂, 4H), 3.80 (s, CH₃OH, 3H), 3.65 (t, OCH₂, 4H), 3.53 (s, CH₂S, 4H), 3.50 (s, CH₂S, 4H), 3.17 (d, ArCH₂, 4H), 2.00 (m, CH₂, 4H), 1.88 (m, CH₂, 4H), 1.09 (t, CH₃, 6H), 0.89 (t, CH₃, 6H). ¹³C NMR (CDCl₃): 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 (ArOCH₂), 67.07 (CH₂CO), 44.40 (CH₃OH), 35.02, 34.31 (CH₂S), 31.04 (ArCH₂),

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23.44, 22.85 (CH₂), 10.78, 9.75 (CH₃). LSI-MS: [M+1] = 1085. Anal. Calcd for C₆₆H₇₂N₂O₈S₂·CH₃OH: 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 CH₃CN for 24 h. The solvent was removed under vacuum, the residue dissolved in CH₂Cl₂, and the excess 4-hydroxybenzyl alcohol removed by filtration. The filtrate was dried over anhydrous MgSO₄ and the solvent removed. The crude product was triturated with anhydrous ethanol and purified by chromatography (SiO₂; eluent 10% MeOH/CH₂Cl₂). Yield: 0.61 g (54%) ¹H NMR (CD₃CN): 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, CH₂S, 8H). ¹³C NMR (CD₃CN): 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 C₂₂H₂₂O₂S₂, *m/z* 382.106 13. Found, *m/z* 382.105 26.

Preparation of Metalloceptor [Pd(L²)(CH₃CN)](BF₄) (11). Calixarene **9** (0.100 g, 0.092 mmol) was suspended in CH₃CN (100 mL), and the suspension was refluxed until complete dissolution. A solution of [Pd(CH₃CN)₄](BF₄)₂ (0.041 g, 0.092 mmol) in CH₃CN was then added dropwise. The reaction mixture was refluxed for 6 h, after which the solvent was removed. Yield: 0.117 g (96%). ¹H NMR (CD₃CN): 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, ArCH₂, 4H), 4.37 (s, CH₂CO, 4H), 4.33 (br s, CH₂S, 4H), 4.28 (s, CH₂S, 4H), 4.08 (t, OCH₂, 4H), 3.66 (t, OCH₂, 4H), 3.20 (d, ArCH₂, 4H), 2.05 (m, CH₂, 4H), 1.90 (m, CH₂, 4H), 1.07 (t, CH₃, 6H), 0.91 (t, CH₃, 6H). ¹³C NMR (CD₃CN): 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 (ArOCH₂), 67.84 (CH₂CO), 45.14, 43.49 (CH₂S), 31.87 (ArCH₂), 24.24, 23.79 (CH₂), 11.14, 10.13 (CH₃). LSI-MS: [M - CH₃CN - BF₄ + H]⁺ *m/z* 1190. Anal. Calcd for C₆₈H₇₄BF₄N₃O₈PdS₂·CH₂Cl₂: C, 59.09; H, 5.47; N, 3.00. Found: C, 59.77, H, 5.51, N, 2.67.

Preparation of [Pd(L¹)(py)](BF₄) (12). Metalloceptor **6** (0.05g, 0.045 mmol) was dissolved in CH₃CN (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 CH₂Cl₂/Et₂O. Yield: 0.040 g (77%). ¹H NMR (CD₃NO₂): 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, CH₂Cl₂), 4.65 (d, ArCH₂, 4H), 4.52 (br s, CH₂S, 4H), 4.35 (br s, CH₂S, 4H), 3.93 (m, OCH₂, 4H), 3.72 (t, OCH₂, 4H), 3.32 (d, ArCH₂, 4H), 2.24 (m, CH₂, 4H), 1.99 (m, CH₂, 4H), 1.11 (t, CH₃, 6H), 0.99 (t, CH₃, 6H). ¹³C NMR (CD₃NO₂): 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 - BF₄]⁺ *m/z* 978. Anal. Calcd for C₅₇H₆₄N₃O₆S₂PdBF₄·CH₂Cl₂: C, 56.66; H, 5.41; N, 3.42. Found: C, 56.83; H, 5.47; N, 3.46.

Preparation of [Pd(L¹)Cl](13). Metalloceptor **6** (0.10 g, 0.09 mmol) was dissolved in CH₃CN (25 mL). This solution was warmed to 50 °C, and an excess of NH₄Cl (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 CHCl₃/Et₂O or chromatographed on SiO₂ (eluent 10% MeOH/CH₂Cl₂). Yield: 0.075 g (82%). ¹H NMR (CD₃NO₂): 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, ArCH₂, 4H), 4.47 (s, CH₂S, 4H), 4.22 (t, OCH₂, 4H), 3.89 (s, CH₂S, 4H), 3.77 (t, OCH₂, 4H), 3.22 (d, ArCH₂, 4H), 2.10 (m, CH₂, 4H), 1.96 (m, CH₂, 4H), 1.16 (t, CH₃, 6H), 0.99 (t, CH₃, 6H). ¹³C NMR (CD₂Cl₂): 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 C₅₂H₅₉ClN₃O₆PdS₂: C, 61.58; H, 5.88; N, 2.76. Found: C, 61.75; H, 5.98; N, 2.83.

Preparation of [Pd(L²)(4-Phpy)](BF₄) (14). Compound **11** (0.085 g, 0.064 mmol) was dissolved in CHCl₃, 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.

Table 1. Crystallographic Data for 5·2CH₃CN

formula	C ₅₆ H ₆₆ N ₄ O ₆ S 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)		

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

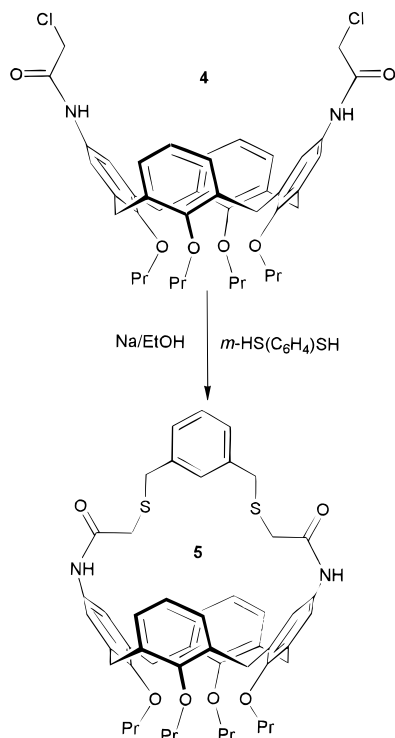
The isolated solid was recrystallized from CHCl₃/Et₂O. Yield: 0.091 g (99%). ¹H NMR (CD₃NO₂): δ (ppm) 7.49 (d, Ar H, 2H), 7.28 (d, Ar H, 4H), 7.11–6.96 (m, Ar H, 13H), 6.88 (d, Ar H, 2H), 6.37 (s, Ar H, 2H), 6.27 (d, Ar H, 4H), 4.73 (m, *m*-Phpy, 2H), 4.58 (d, ArCH₂, 4H), 4.36 (s, OCH₂CO, 4H), 4.24 (br s, CH₂S, 4H), 4.19 (t, OCH₂, 4H), 3.74 (s, CH₂S, 4H), 3.67 (t, OCH₂, 4H), 3.56 (t, *p*-Phpy, 1H), 3.26 (d, ArCH₂, 4H), 2.25 (m, CH₂, 4H), 1.92 (m, CH₂, 4H), 1.02 (t, CH₃, 6H), 0.99 (t, CH₃, 6H). ¹³C NMR (CD₃NO₂): 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 - BF₄]⁺ *m/z* 1345. Anal. Calcd for C₇₇H₈₀BF₄N₃O₈PdS₂·CH₂Cl₂: C, 61.67; H, 5.45; N, 2.78. Found: C, 61.49; H, 5.50; N, 2.94.

Preparation of Model Ligand HL³ (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%). ¹H NMR (CDCl₃): δ (ppm) 8.59 (s, NH, 2H), 7.42 (d, Ar H, 4H), 7.26–7.09 (m, Ar H, 10H), 3.68 (s, CH₂S, 4H), 3.20 (s, CH₂S, 4H). ¹³C NMR (CDCl₃): 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 C₂₄H₂₄N₂O₂S₂: C, 66.04; H, 5.55; N, 6.42. Found: C, 65.87; H, 5.55; N, 6.31.

Preparation of Model Metalloceptor [Pd(L³)(MeCN)](BF₄) (16). Compound **15** (0.98 g, 2.25 mmol) and [Pd(CH₃CN)₄](BF₄)₂ (1.0 g, 2.25 mmol) were gently refluxed in CH₃CN (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%). ¹H NMR (CD₃CN): 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, CH₂S, 4H), 4.01 (s, CH₂S, 4H), 2.25 (s, H₂O, 2H). ¹³C NMR (CDCl₃): δ (ppm) 164.06, 137.65, 129.07, 126.33, 124.90, 123.50, 120.02, 45.71 (br), 42.03. Anal. Calcd for C₂₆H₂₆BF₄N₃O₂PdS₂·H₂O: C, 45.40; H, 4.10; N, 6.11. Found: C, 45.70; H, 3.93; N, 6.51.

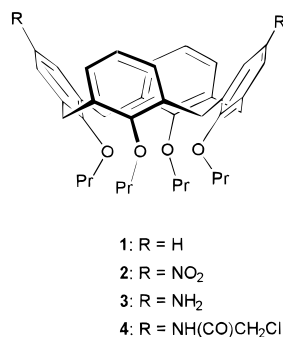
X-ray Diffraction Data Collection and Solution and Refinement of the Structure of 5. Crystallographic data and refinement parameters are summarized in Table 1. Crystals of **5** were obtained from slow evaporation of a saturated acetonitrile solution of the compound. Despite repeated attempts at recrystallization, 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

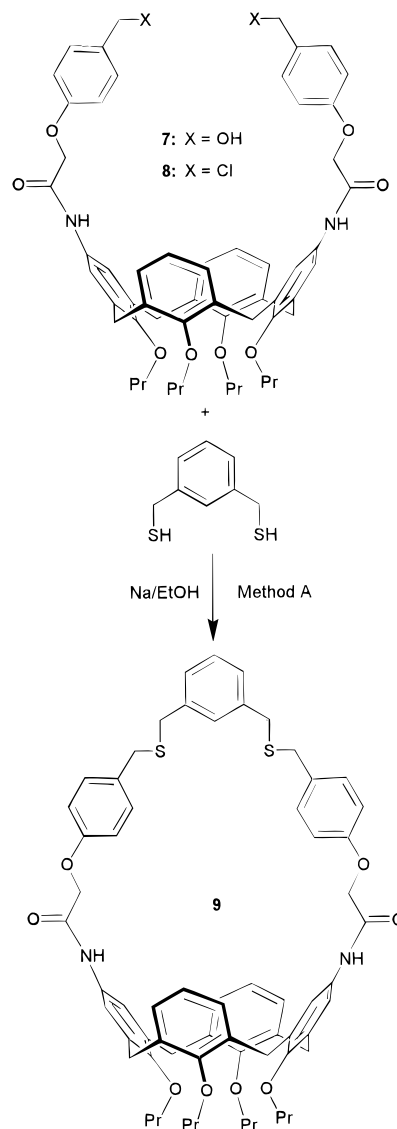
Synthesis and Characterization of Calix[4]arene Ligands 5 and 9. The calix[4]arene-based ligands 5 and 9 were synthesized by building upon an existing calix[4]arene platform. Literature preparations were used to obtain the required 1,3-substitution pattern by nitration¹⁶ of 1 to give 2 and reduction 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



The substituted calix[4]arene, 4, was converted directly to the macrobicyclic 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 macrobicyclic 9 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 inter-conversion 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 ¹H NMR spectra of 5 and 9 show an AB quartet for the methylene ArCH₂Ar protons, typical for calix[4]arenes in the cone conformation.⁷ In addition, the ArCH₂Ar peak at $\sim\delta$ 31 ppm in the ¹³C NMR spectrum is indicative of the cone conformation.¹⁸

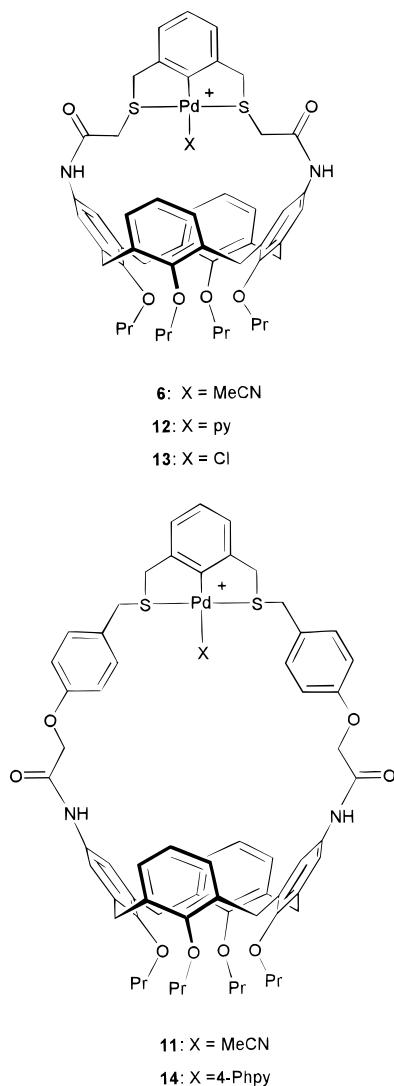
X-ray Structure of 5. A perspective ORTEP drawing of 5 with an atom numbering scheme is shown in Figure 1. The calix[4]arene portion of the molecule is in a *pinched-cone* conformation in which the substituted aromatic groups of the calix[4]arene are almost parallel; dihedral angle 19.5°. The loop containing 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.; Fabbri, 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 $[\text{Pd}(\text{CH}_3\text{CN})_4][\text{BF}_4]_2$ in acetonitrile solution yielded the metalloreceptor **6** in 93% yield. Similarly, palladation of **9** produced the metalloreceptor **11** in 96% yield.



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 $[\text{Pd}(\text{L})(\text{CH}_3\text{CN})][\text{BF}_4]$. 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 $[\text{Pd}(\text{L})]^+$ 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 $\delta -1.80$ 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

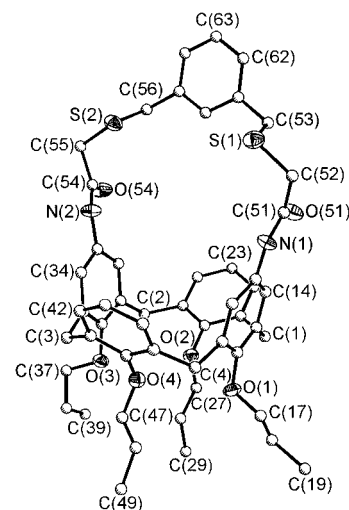
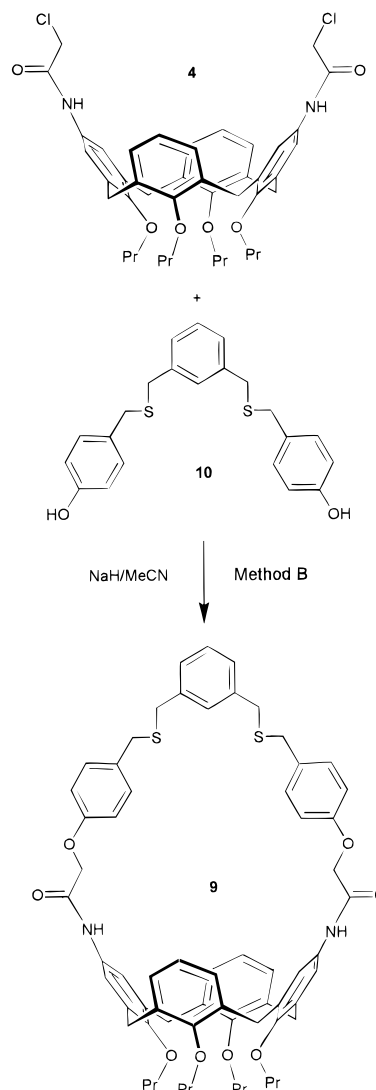


Figure 1. Perspective ORTEP drawing of **5** showing the atom-numbering scheme. 30% thermal ellipsoids are shown for the non-carbon atoms. All other atoms are shown as ideal spheres for clarity.

Scheme 3



disappears. Also, the complex $[\text{Pd}(\text{L}^1)(\text{Cl})]$, **13**, with a smaller Cl^- substrate does not exhibit this feature at any temperature.

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

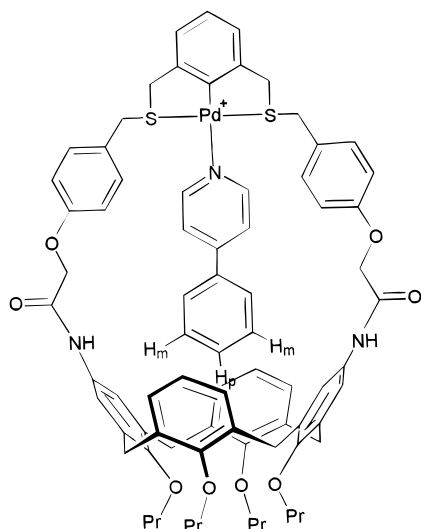


Figure 2. Drawing of **14** illustrating the positioning of the 4-Phpy substrate *inside* the calix[4]arene cavity.

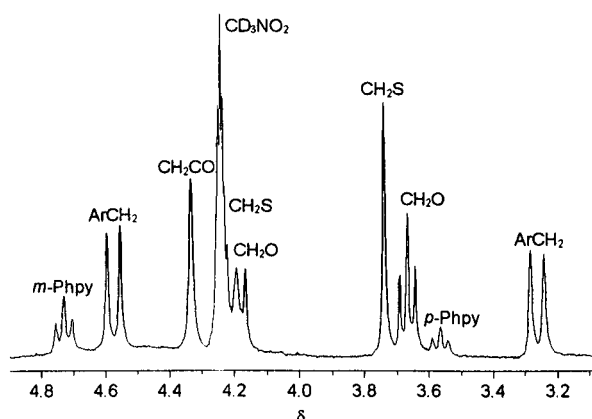


Figure 3. ^1H NMR spectrum of **14** (300 MHz, $\text{CD}_2\text{Cl}_2/\text{CD}_3\text{NO}_2$ (3:1)), in the region δ 3.2–4.8 ppm, identifying the upfield shifted resonances, *m*-Phpy and *p*-Phpy, indicative of binding 4-Phpy *inside* the calix[4]arene cavity.

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 π – π 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, ^1H 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 ^1H – ^{13}C HETCOR NMR experiment identified proton resonances at 3.59

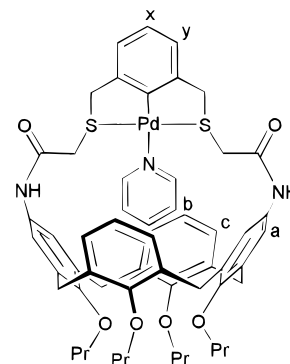


Figure 4. Drawing of **12** showing the labeling scheme for Figure 5 and illustrating the possible positioning of the py substrate *inside* the calix[4]arene cavity.

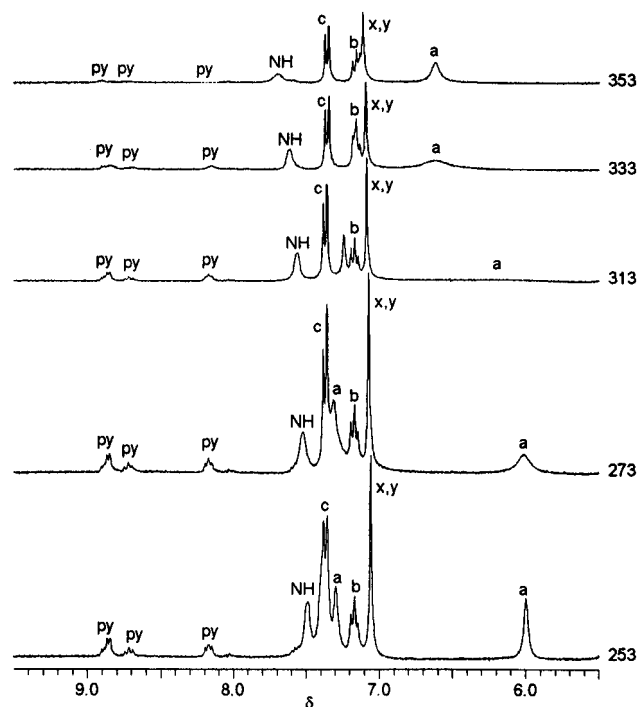


Figure 5. Variable-temperature NMR spectra of **12**.

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.)

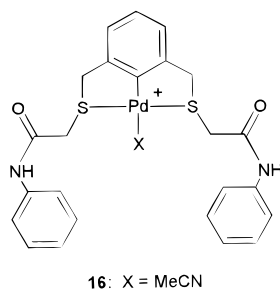
For **12**, the pyridine protons are shifted downfield as a result of coordination, but the only change to the calixarene portion of the molecule is a splitting of the calixarene aromatic protons on the substituted rings (labeled “a” in Figure 4). This splitting is consistent with an asymmetric coordination 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 ^1H 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 ^1H 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.



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 ^1H 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.

Acknowledgment. We thank the Natural Sciences and Engineering Council of Canada and the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this research.

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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