Synthesis and electrospray mass spectrometry study of Pd(II) complexes of low-rim amino acid substituted calix[4]arenes†

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The reactions between Pd(II) and low-rim amino acid substituted calix[4]arenes {$\mathbf{L}^a$ = 5,11,17,23-tetra-4-*tert*-butyl-25,27-di{[(2′-amino-4′-methylthio)-L-butyryl]aminoethoxy}-26,28-dihydroxycalix[4]arene, $\mathbf{L}^b$ = 5,11,17,23-tetra-4-*tert*-butyl-25,27-di({[(*N*-*tert*-butoxycarbonyl)-2′-amino-4′-methylthio]-L-butyryl}aminoethoxy)-26,28-dihydroxycalix[4]-arene (diN-BOC-$\mathbf{L}^a$) and $\mathbf{L}^c$ = 5,11,17,23-tetra-4-*tert*-butyl-25,27-di{[(*N*-*tert*-butoxycarbonyl)-2′-aminoacetyl]-aminoethoxy}-26,28-dihydroxycalix[4]arene} were studied by electrospray mass spectrometry. When $\mathbf{L}^a$ was refluxed with 2.2 equiv. of *trans*-$[Pd(Py)_2Cl_2]$ or 1.1 equiv. of $PdCl_2$, the mononuclear complex $Pd\mathbf{L}^aCl_2$ was formed. When refluxed with 2.2 equiv. of $PdCl_2$, the binuclear complex $Pd_2\mathbf{L}^aCl_4$ was obtained. The same binuclear complex $Pd_2\mathbf{L}^aCl_4$ was also obtained as the final adduct when $\mathbf{L}^b$ was refluxed with 3.5 equiv. of $PdCl_2$, during which two BOC groups are removed one-by-one after 6 and 16 h, respectively. However, when $\mathbf{L}^b$ was refluxed with *trans*-$[Pd(Py)_2Cl_2]$ in methanol, no reaction was observed. In order to understand whether the coordination to Pd(II) of the S atom in methionine is necessary for the removal of BOC groups, the reaction of $\mathbf{L}^c$ containing diN-BOC-glycine with $PdCl_2$ was also conducted. The result showed that the BOC groups can also be removed and the Pd(II) complex is not formed until both BOC groups are detached from $\mathbf{L}^c$. These data reveal that the detachment of BOC groups is likely induced by $PdCl_2$, which acts as a Lewis acid during the reaction. This method can be potentially applied to the preparation of analogs of Pd(II) and other metal complexes of calixarenes substituted at the lower rim by BOC-protected amino acids or peptides without prior treatment of the BOC groups.

Calixarenes are quantitatively available compounds possessing hydrophobic cavities.[1,2] They can be readily modified to give compounds with interesting properties such as the inclusion of neutral molecules and ions. For example, they can be functionalized as ionophores for metal ions,[3] as amphiphilic molecules[4–7] and as optical sensors for alkaline metal ions.[8–12] Recent work has demonstrated that the metal complexes of calixarene and its derivatives can be employed as functional materials or biomimetic model compounds.[13,14] Another important and unusual property of calixarene derivatives is their ability to form monolayers and LB films, which can be extended to the study of their interfacial properties.[4–7] To make films of practical use, the mechanical strength of the monolayer and LB films must be enhanced. We have shown recently that Pd(II) chloride complexes of calixarene derivatives form robust films at the air–water interface through a Cl^- bridge.[15] Electrospray mass spectrometry, a powerful technique to analyze large biomolecules,[16,17] has been recently applied to the study of metal complexes and organometallic compounds.[18–26] Due to its "soft ionization" technique, the integrity of the molecules is readily kept during the ionization process. A special benefit for the ionization for calixarenes comes from the extraordinary affinity of calixarenes for alkali metal ions, especially Na^+, because of the "π-cation" interaction.[27] Therefore, ESMS is a sensitive, reliable and convenient method for the study of calixarene systems.

In this paper, we have synthesized three amino acid substituted calix[4]arenes ($\mathbf{L}^a$, $\mathbf{L}^b$ and $\mathbf{L}^c$) and investigated their coordination reactions towards Pd(II) using ESMS. We find that an excess of $PdCl_2$ can act as a Lewis acid to cleave the BOC group, which is the amino acid protecting group in the calixarene ligands during the coordination reaction.

† Electronic supplementary information (ESI) available: 9 figures showing ESMS spectra and calculated IDPs. See http://www.rsc.org/suppdata/nj/b1/b103272k/

Experimental

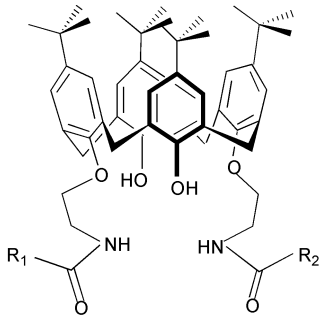
All chemicals were of reagent grade and were commercially available. The samples for elemental analysis were heated at 120 °C under reduced pressure (0.1 Torr) for 24 h.

ESMS determination

An LCQ electrospray mass spectrometer (ESMS, Finnigan) was employed to determine *m*/*z*. All samples were diluted with methanol to around 100 μM and 1.0 μL of the dilute solution was loaded into the injection valve. The mobile phase was CH_3OH, delivered at a rate of 200 μL min^{-1}. The voltage at the electrospray needles was 5 kV and the capillary was heated to 200 °C. Zoom scan was frequently used in the experiments for observation of isotopic distribution patterns (IDPs). Calculated IDPs were given by the IsoPro 3.0 program.[28]

Synthesis of the ligands

5,11,17,23-Tetra-4-*tert*-butyl-25,27-di({[(*N*-*tert*-butoxycarbonyl)-2′-amino-4′-methylthio]-L-butyryl}aminoethoxy)-26,28-dihydroxycalix[4]arene ($\mathbf{L}^b$). The low-rim calix[4]arene diamine 5,11,17,23-tetra-*tert*-butyl-25,27-diaminoethoxy-26,28-dihydroxycalix[4]arene was synthesized by a procedure similar to that of Zhang and Huang.[29] It was acylated by *N*-BOC-methionine using a procedure similar to those used in peptide synthesis.[30] *N*-BOC-Methionine (200 mg, 0.8 mmol) was dissolved in 5 ml $CHCl_3$ and cooled in an ice-water bath. *N*,*N*′-Dicyclohexylcarbodiimide (DCC; 165 mg, 0.8 mmol) was added to the flask over 0.5 h. Then, 294 mg (0.4 mmol) of



L[a]: $R_1 = R_2 =$ L–H_2N–C*H–CH_2CH_2–S–CH_3

L[b]: $R_1 = R_2 =$ L–BOC–NH–C*H–CH_2CH_2–S–CH_3

L[c]: $R_1 = R_2 =$ BOC–NH–CH_2–

A: $R_1 =$ L–BOC–NH–C*H–CH_2CH_2–S–CH_3

$R_2 =$ L–H_2N–C*H–CH_2CH_2–S–CH_3

B: $R_1 =$ BOC–NH–CH_2–

$R_2 = H_2N$–CH_2–

C: $R_1 = R_2 = H_2N$–CH_2–

calix[4]arene diamine in chloroform was added dropwise over 2 h at 0 °C. The reaction was finished in 3 days at room temperature. After the solid was filtered off, the filtrate was evaporated to dryness *in vacuo*. Then the residue was dissolved in a minimum of ethyl acetate and the solution was filtered again. After the solvent was removed *in vacuo* from the filtrate, 402 mg **L**[b] was obtained as a white solid. Yield 84%. M.p. 112–114 °C. $R_f = 0.3$ (silica gel, petroleum ether–ethyl acetate, 1 : 1). IR (KBr, cm^{-1}): 3334 (NH), 1715 [$OCOC(CH_3)_3$], 1671 (CONH). ^{1}H NMR ($CDCl_3$, 500 MHz, δ): 8.93 (s, 2H, OH), 7.01, 6.95 (2d, 8H, ArH), 5.22 (d, 2H, OCONH), 4.37 (m, 2H, CONH), 4.34 (d, 2H, *endo*-ArC*H*Ar, $J = 13.7$ Hz), 4.31, 4.17 (m, 4H, OCH_2), 4.27 (d, 2H, *endo*-ArC*H*Ar, $J = 12.5$ Hz), 4.01, 3.84 (2m, 4H, NCH_2), 3.54 (m, 2H, COCH), 3.45 (d, 2H, *exo*-ArC*H*Ar, $J = 13.7$ Hz), 3.30 (d, 2H, *exo*-ArC*H*Ar, $J = 12.5$ Hz), 2.30, 2.08 (2m, 4H, CH_2CH_2S), 1.89 (m, 4H, SCH_2), 1.76 (s, 6H, SCH_3), 1.35 [s, 18H, $C(CH_3)_3$], 1.16 [s, 18H, $C(CH_3)_3$], 1.09 [s, 18H, $C(CH_3)_3$]. Anal. calc. for $C_{68}H_{100}N_4O_{10}S_2$: C 68.20, H 8.42, N 4.68; found: C 68.30, H 8.69, N 4.55%. ESMS (*m*/*z*): 1219.6 $[M + Na]^+$, 1197.4 $[M + H]^+$; calc.: 1219.7, 1197.7.

5,11,17,23-Tetra-4-*tert*-butyl-25,27-di{[(2′-amino-4′-methylthio) butyryl]aminoethoxy}-26,28-dihydroxycalix[4]arene (L[a]). The residue first obtained in the synthesis of **L**[b] was treated with 120 ml CH_3OH containing 1.62 g $HClO_4$ (72%) at 45 °C for 9 h. After the solvent was removed, the gel-like residue was dissolved in water. NH_3 aqueous solution was added to adjust the pH of the solution to 9.0 at 0 °C. The solution was then extracted with $CHCl_3$ several times. The collected organic phase was evaporated to dryness. Recrystallization of the residue from methanol gave 207 mg of **L**[a]. Yield 52.0% (relative to calix[4]arene diamine). M.p. (uncorrected) 200–202 °C. $R_f = 0.75$ (silica gel, $CHCl_3$–CH_3OH, 8 : 1). IR (KBr, cm^{-1}): 3391 (NH_2), 1670 (CONH). ^{1}H NMR ($CDCl_3$, 500 MHz, δ): 8.37 (br, 2H, CONH), 7.78 (s, 2H, OH), 6.97, 6.80 (2s, 8H, ArH), 4.14 (d, 4H, *endo*-ArC*H*Ar, $J = 13.0$ Hz), 4.02 (m, 4H, OCH_2), 3.86, 3.81 (m, 4H, NCH_2), 3.54 (m, 2H, COCH), 3.28 (d, 4H, *exo*-ArC*H*Ar, $J = 13.0$ Hz), 2.52 (m, 4H, SCH_2), 2.07, 1.75 (2m, 4H, CH_2CH_2S), 1.92 (s, 6H, SCH_3), 1.80 (br, NH_2), 1.19 [s, 18H, $C(CH_3)_3$], 0.94 [s, 18H, $C(CH_3)_3$]. ^{13}C NMR ($CDCl_3$, 500 MHz, δ): 175.43 (CONH), 148.64, 148.61 (Ar*C*O), 147.45, 142.21 (*ortho*-C-Ar), 132.39, 127.53 (*para*-C-Ar), 125.61, 125.25 (*meta*-C-Ar), 74.79 (OCH_2), 54.68 (NH*C*HCO), 39.21 (CONHCH_2), 34.30 (SCH_3), 33.87, 33.71 [*C*$(CH_3)_3$], 31.50 (ArCH_2Ar), 30.85, 30.67 [*C*$(CH_3)_3$], 29.80 (SCH_2CH_2), 15.08 (SCH_2CH_2). Anal. calc. for $C_{58}H_{84}N_4O_6S_2$: C 69.84, H 8.49, N 5.62; found: C 69.58, H 8.62, N 5.93%. ESMS (*m*/*z*): 997.5 $[M + H]^+$, 499.4 $[M + 2H]^{2+}$; calc.: 997.6, 499.3.

5,11,17,23-Tetra-4-*tert*-butyl-25,27-di{[(*N*-*tert*-butoxycarbonyl)-2′-aminoacetyl]aminoethoxy}-26,28-dihydroxycalix[4]arene (L[c]). Similar to the procedure for the synthesis of **L**[b], 153 mg (0.8 mmol) of *N*-BOC-glycine was dissolved in 5 ml $CHCl_3$ and cooled with an ice-water bath. After stirring with 165 mg (0.8 mmol) of DCC for 0.5 h, 294 mg (0.4 mmol) of calix[4]arene diamine in chloroform was added dropwise over 2 h at 0 °C. The reaction was finished in 30 h at room temperature. After the solid was filtered off, the filtrate was evaporated to dryness *in vacuo*. Then the residue was dissolved in a minimum of ethyl acetate and the solution was filtered again. After the solvent was removed *in vacuo* from the filtrate, 344 mg of **L**[c] was obtained as a white solid. Yield 82%. $R_f = 0.35$ (silica gel, petroleum ether–ethyl acetate, 1 : 1). M.p. 119–121 °C. IR (KBr, cm^{-1}): 3315 (NH), 1720 [$OCOC(CH_3)_3$], 1675 (CONH). ^{1}H NMR ($CDCl_3$, 500 MHz, δ): 8.43 (m, 2H, CONH), 8.32 (s, 2H, OH), 7.05, 6.98 (s, 8H, ArH), 5.52 (m, 2H, OCONH), 4.23 (d, 4H, *endo*-ArCH_2Ar, $J = 12.9$ Hz), 4.12–3.91, 3.47 (m, 12H, OCH_2CH_2N + NHCH_2CO), 3.40 (d, 4H, *exo*-ArCH_2Ar, $J = 12.9$ Hz), 1.41 [s, 18H, $OCOC(CH_3)_3$], 1.25, 1.09 [2s, 36H, $C(CH_3)_3$]. ^{13}C NMR ($CDCl_3$, 500 MHz, δ): 169.89 (CONH), 155.86 (BOC-*C*O), 149.19, 148.51 (Ar*C*O), 147.80, 142.68 (*ortho*-C-Ar), 132.78, 127.73 (*para*-C-Ar), 125.80, 125.41 (*meta*-C-Ar), 79.51 [BOC-*C*$(CH_3)_3$], 75.02 (OCH_2), 43.91 (NHCH_2CO), 39.31 (CONHCH_2), 33.95, 33.71 [*C*$(CH_3)_3$], 31.73 (ArCH_2Ar), 31.42, 30.89 [C(*C*$H_3)_3$], 28.18 (BOC-*C*H_3). Anal. calc. for $C_{62}H_{88}N_4O_{10}$: C 70.96; H 8.45; N 5.34; found: C 70.72; H 8.68; N 5.26%. ESMS (*m*/*z*): 1071.6 $[M + Na]^+$, 1049.4 $[M + H]^+$; calc.: 1071.6, 1049.6.

Synthesis of the Pd(II) complexes

PdL^aCl_2 and $Pd_2L^aCl_4$. **L**[a] was refluxed with 2.2 equiv. of *trans*-$[Pd(Py)_2Cl_2]$ or 1.1 equiv. of $PdCl_2$ in methanol for 2 days.[31,32] After cooling, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The product was purified by column chromatography (silica gel, $CHCl_3$–CH_3OH–H_2O, 60 : 35 : 9) and the mononuclear Pd(II) complex, PdL^aCl_2, was obtained as a yellow solid. Yields were 72 and 65%, respectively. M.p. decomposition at 190–198 °C. $R_f = 0.5$ (silica gel, $CHCl_3$–CH_3OH–H_2O, 60 : 35 : 9). Anal. calc. for $C_{58}H_{84}N_4O_6S_2Cl_2Pd$: C 59.30, H 7.21, N 4.77; found: C 59.08, H 7.56, N 5.05%. ESMS: see Fig. 1.

When 2.2 equiv. of $PdCl_2$ was used in the above experiment, a binuclear Pd(II) complex, $Pd_2L^aCl_4$, was obtained as a yellow solid upon purification through chromatography (silica gel, $CHCl_3$–CH_3OH, 15 : 1). Yield, 61%: m.p. decomposition at 230–235 °C. $R_f = 0.6$ (silica gel, $CHCl_3$–CH_3OH, 8 : 1). Anal. calc. for $C_{58}H_{84}N_4S_2O_6Cl_4Pd_2$: C 51.52, H 6.26, N 4.14; found: C 51.34, H 6.03, N 4.42%. ESMS: see Fig. 2.

The binuclear Pd(II) complex can also be synthesized by directly refluxing ligand **L**[b], the precursor of **L**[a], with 2.2 (or 3.5) equiv. of $PdCl_2$ in methanol for 45 h (36 h).

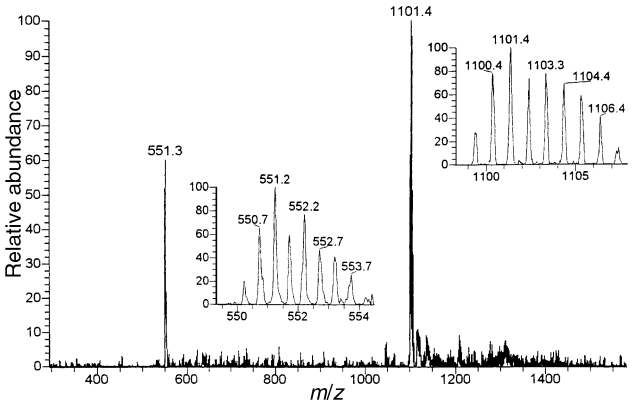


Fig. 1 The ESMS spectrum of complex $Pd\mathbf{L}^aCl_2$. The inserts are the measured IDPs (for the cluster around 1101, the peaks are separated by *m/z* 1 from each other, while for the cluster around *m/z* 551, by *m/z* 0.5) of $[Pd\mathbf{L}^a - H]^+$ and $[Pd\mathbf{L}^a]^{2+}$. The corresponding calculated IDPs are available in Fig. S4 (ESI). Measured *m/z* for $[Pd\mathbf{L}^a - H]^+$: 1099.4, 1100.4, 1101.4. 1102.4, 1103.4, 1104.4, 1105.4, 1106.4, 1107.4; calc. *m/z*: 1099.5, 1100.5. 1101.5, 1102.5, 1103.5, 1104.5, 1105.5, 1106.5, 1107.5. Measured *m/z* for $[Pd\mathbf{L}^a]^{2+}$: 550.2, 550.7, 551.2, 551.7, 552.2, 552.7, 553.2, 553.7, 554.3; calc. *m/z*: 550.2, 550.7, 551.2, 551.7, 552.2, 552.7, 553.2, 553.7, 554.2.

$Pd\mathbf{L}^bCl_2$. $\mathbf{L}^b$ was stirred with 3.5 equiv. $PdCl_2$ in methanol at room temperature for 6 h, and the residue obtained from the evaporation of solvent *in vacuo* was purified by column chromatography (silica gel, $CHCl_3$–CH_3OH 15 : 1), to give a pale yellow mononuclear complex, $Pd\mathbf{L}^bCl_2$. Yield 81%. M.p. decomposition at 189–195 °C. $R_f = 0.4$ (silica gel, $CHCl_3$–CH_3OH 15 : 1). Anal. calc. for $C_{68}H_{100}N_4O_{10}S_2Cl_2Pd$: C 59.40, H 7.33, N 4.07; found: C 59.28, H 7.61, N 3.81. ESMS (*m/z*): 1339.3 $[M - Cl]^+$, 1359.3 $[M + Na - H - Cl]^+$, 1377.4 $[M + K - H - Cl]^+$; calc. 1339.6, 1359.5, 1377.5%.

$PdCCl_2$ ($\mathbf{C} = \mathbf{H_2L^c} - 2$ BOC). $\mathbf{L}^c$ was refluxed with 2.2 equiv. of $PdCl_2$ in methanol for 18 h, and the residue obtained from the evaporation of the solvent *in vacuo* was purified by column chromatography (silica gel, $CHCl_3$–CH_3OH 10 : 1) to give a mononuclear Pd(II) complex, $Pd\mathbf{C}Cl_2$ ($\mathbf{C} = \mathbf{H_2L^c} - 2$ BOC), as a pale yellow solid. Yield 75%. M.p. decomposition at 223–227 °C. $R_f = 0.5$ (silica gel, $CHCl_3$–CH_3OH 10 : 1). Anal. calc. for $C_{52}H_{72}N_4O_6Cl_2Pd$: C 60.85, H 7.07, N 5.46; found: C 60.66, H 6.85, N 5.49%. ESMS: see Fig. 4.

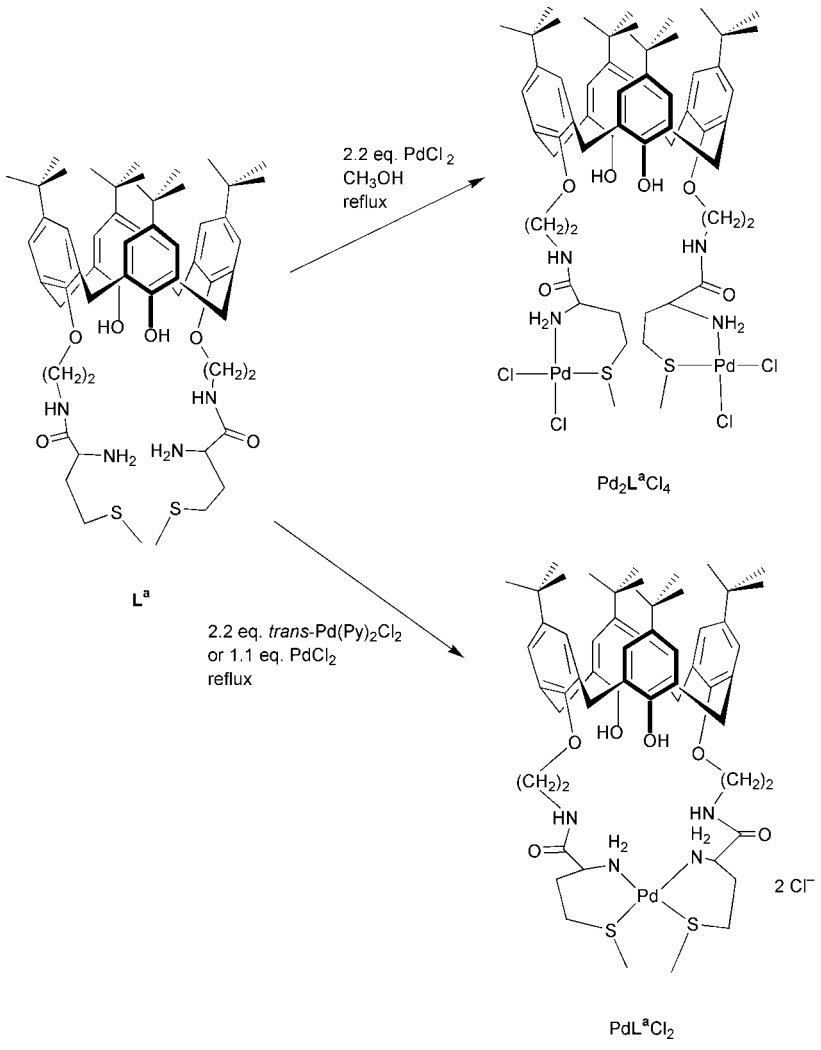
Coordination reaction followed by ESMS

The mixture of ligands with the corresponding Pd(II) compounds was first stirred at room temperature for 6 h and an aliquot of the mixture was then taken out for the ESMS determination. The mixture was then brought to reflux and aliquots for ESMS were taken out in 1 h intervals until the reaction was finished.

Results and discussion

ESMS spectra of $\mathbf{L}^a$, $\mathbf{L}^b$ and $\mathbf{L}^c$

In the ESMS spectra of $\mathbf{L}^a$, $\mathbf{L}^b$ and $\mathbf{L}^c$, the isotopic distribution patterns (IDPs) of the main groups of peaks are almost



Scheme 1

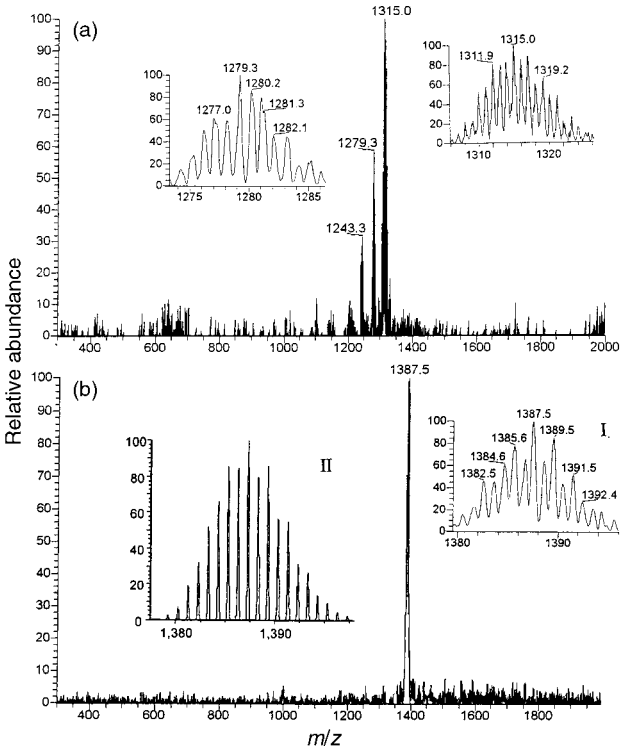


Fig. 2 (a) The ESMS spectrum of complex $Pd_2\mathbf{L}^aCl_4$ obtained in positive mode. The inserts are the measured IDPs of the two clusters of peaks with *m/z* around 1279 ($[Pd_2\mathbf{L}^aCl_2 - H]^+$) and 1315 ($[Pd_2\mathbf{L}^aCl_3]^+$), respectively. The corresponding calculated IDPs are available in Fig. S5 (ESI). Measured *m/z* values for $[Pd_2\mathbf{L}^aCl_2 - H]^+$: 1275.3, 1276.2, 1277.0, 1278.2, 1279.3, 1280.2, 1281.3, 1282.1, 1283.2, 1284.2, 1285.2; calc. *m/z*: 1275.3, 1276.3, 1277.3, 1278.3, 1279.3, 1280.3, 1281.3, 1282.3, 1283.3, 1284.3, 1285.3. Measured *m/z* for $[Pd_2\mathbf{L}^aCl_3]^+$: 1311.0, 1311.9, 1313.0, 1313.9, 1315.0, 1316.1, 1317.0, 1318.1, 1319.2, 1320.2, 1321.2; calc. *m/z*: 1311.3, 1312.3, 1313.3, 1314.3, 1315.3, 1316.3, 1317.3, 1318.3, 1319.3, 1320.3, 1321.3. (b) The ESMS spectrum of complex $Pd_2\mathbf{L}^aCl_4$ obtained in negative mode. The inserts are the measured IDP of the cluster of peaks with *m/z* around 1387 (I) and the calculated IDP of $[Pd_2\mathbf{L}^aCl_5]^-$ (II). Measured *m/z* values: 1382.5, 1383.5, 1384.6, 1385.6, 1386.5, 1387.5, 1388.5 1389.5, 1390.5, 1391.5, 1392.4; calc. *m/z*: 1382.2, 1383.3, 1384.3, 1385.3, 1386.3, 1387.3, 1388.3, 1389.3, 1390.3, 1391.3, 1392.3.

identical to the corresponding IDPs given by IsoPro 3.0 [see Fig. S1, S2 and S3 (ESI)]. In the ESMS spectrum of $\mathbf{L}^b$, there is only one main group of peaks around *m/z* 1219, which can be assigned to $[\mathbf{L}^b + Na]^+$, accompanied by two minor groups of peaks around *m/z* 1197 and 1235, which are attributable to $[\mathbf{L}^b + H]^+$ and $[\mathbf{L}^b + K]^+$, respectively. The strong "π-cation interaction" between the bridged phenolic ring and alkali metal cations is normally observed in the ESMS of other calixarenes.[27] It is interesting to note that $\mathbf{L}^b$ prefers sodium cations to potassium cations. In the case of $\mathbf{L}^a$, there are two main groups of peaks with *m/z* around 499 and 997, which are assigned as $[\mathbf{L}^a + 2H]^{2+}$ and $[\mathbf{L}^a + H]^+$. There is a minor group of peaks around *m/z* 1019, which is assigned to $[\mathbf{L}^a + Na]^+$. According to the abundance of the three groups of peaks, the "π-cation interaction" between the phenolic ring and sodium ion in this case is quite weak. For $\mathbf{L}^c$, the ESMS spectrum is similar to that of $\mathbf{L}^b$, there are three clusters of peaks with *m/z* around 1049, 1071 and 1087, which are assigned to $[\mathbf{L}^c + H]^+$, $[\mathbf{L}^c + Na]^+$ and $[\mathbf{L}^c + K]^+$, respectively.

Coordination reactions followed by ESMS

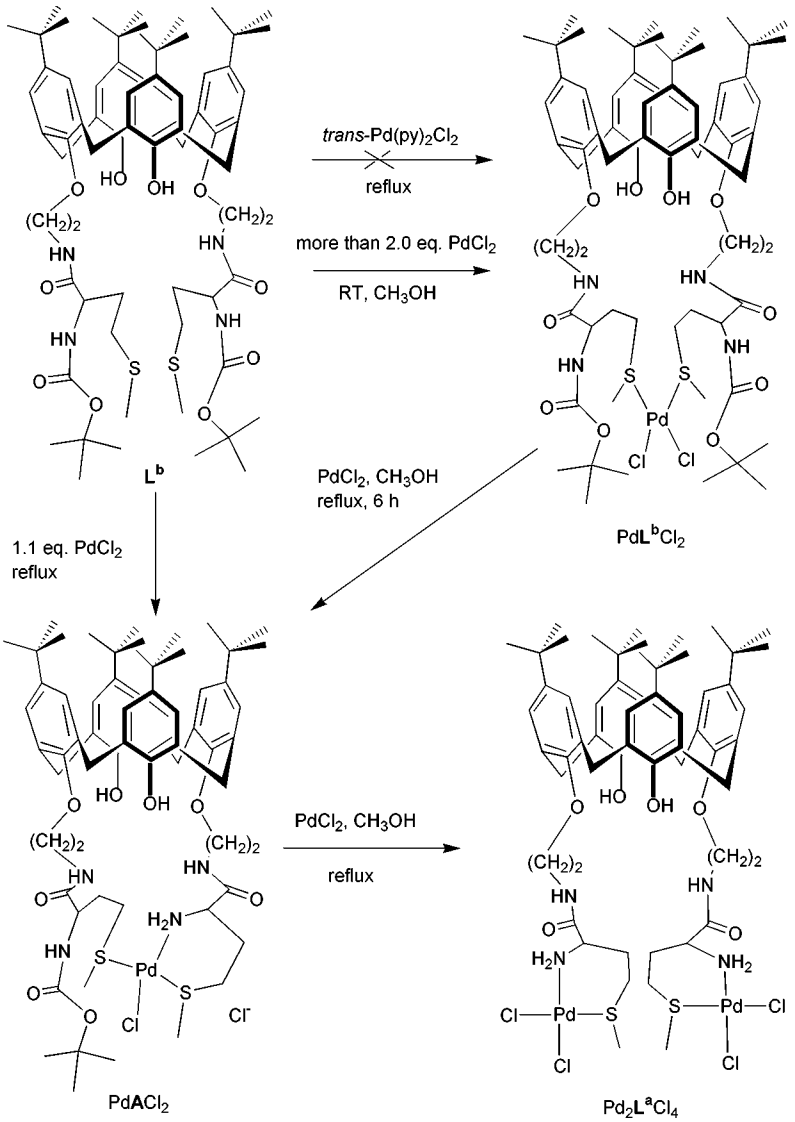
Reaction of *trans*-$[Pd(Py)_2Cl_2]$ with $\mathbf{L}^a$ and $\mathbf{L}^b$. When $\mathbf{L}^a$ is refluxed with *trans*-$[Pd(Py)_2Cl_2]$ in a molar ratio of 1 : 2.2 in methanol for 48 h, two main clusters of peaks with *m/z* around 551 and 1101 are observed in the ESMS spectrum. The IDPs of the two clusters of peaks are respectively identical to the IDPs of $[Pd\mathbf{L}^a]^{2+}$ and $[Pd\mathbf{L}^a - H]^+$ calculated by IsoPro 3.0 [Fig. 1 and Fig. S4 (ESI)], indicating the formation of the mononuclear complex $Pd\mathbf{L}^aCl_2$ (Scheme 1). The Pd(II) may be coordinated by two N atoms and two S atoms in the molecule, similar to that observed for Pd(II) amino acid complexes.[33–36] However, both ESMS and thin layer chromatography show that no reaction occurs between *trans*-$[Pd(Py)_2Cl_2]$ and $\mathbf{L}^b$, even after five days of refluxing. Compared with $\mathbf{L}^a$, $\mathbf{L}^b$ cannot gain from the chelate effect in the possible coordination between $\mathbf{L}^b$ and *trans*-$[Pd(Py)_2Cl_2]$, due to the absence of free amino group in the same methionine moiety. Moreover, the sites for donor atoms in *trans*-$[Pd(Py)_2Cl_2]$ are occupied by pyridine. The two factors together may be the origin for why $\mathbf{L}^b$ does not react with *trans*-$[Pd(Py)_2Cl_2]$.

Reaction of $\mathbf{L}^a$ with $PdCl_2$. When $\mathbf{L}^a$ is refluxed with $PdCl_2$ in a molar ratio of 1 : 1.1 or 1 : 2.2 in methanol for 2 days, the ESMS spectrum for the 1 : 1.1 molar ratio mixture is the same as that of $Pd\mathbf{L}^aCl_2$ (Fig. 1), while a binuclear palladium(II) complex is the main product for the solution with a molar ratio of 1 : 2.2. The observed IDPs of the main groups of peaks with *m/z* around 1279 and 1315 [Fig. 2(a)] are similar to the calculated IDPs of $[Pd_2\mathbf{L}^aCl_2 - H]^+$ and $[Pd_2\mathbf{L}^aCl_3]^+$ [Fig. S5 (ESI)]. When ESMS is used in the negative mode, only one cluster of peaks with *m/z* around 1387 is found, whose IDP is identical to that of $[Pd_2\mathbf{L}^aCl_5]^-$ given by IsoPro [Fig. 2(b)]. All these results indicate the formation of $Pd_2\mathbf{L}^aCl_4$. Elemental analysis of the purified product (see Experimental) also supports this conclusion. Therefore, the formation of either $Pd\mathbf{L}^aCl_2$ or $Pd_2\mathbf{L}^aCl_4$ is dependent on the molar ratio used in the experiments. The composition and possible coordination of the two complexes are shown in Scheme 1.

Reaction of $\mathbf{L}^b$ with $PdCl_2$. When $\mathbf{L}^b$ is reacted with $PdCl_2$ in a molar ratio of 1 : 3.5 at room temperature for 6 h, the main clusters of peaks in its ESMS spectrum are found with *m/z* around 1339, 1359, 1377 [Fig. S6(a) (ESI)]. Their IDPs obtained by zoom scan are identical to the calculated IDPs of $[Pd\mathbf{L}^bCl]^+$, $[Pd\mathbf{L}^bCl + Na - H]^+$ and $[Pd\mathbf{L}^bCl + K - H]^+$, respectively [Fig. S6(b) (ESI)], implying the formation of $Pd\mathbf{L}^bCl_2$. As shown in Scheme 2, the Pd(II) may be coordinated by two S and two Cl anions. In the spectrum, no peaks are observed for $\mathbf{L}^b$, indicating that all $\mathbf{L}^b$ is bound to Pd(II) in the solution. Compared with *trans*-$[Pd(Py)_2Cl_2]$, $PdCl_2$ is still not fully coordinated and its sites for donor atoms can be readily occupied by S.

When the mixture of $\mathbf{L}^b$ and $PdCl_2$ is refluxed, no further change is observed after the initial 2 h, compared with the reaction at room temperature. However, after 6 h, the two clusters of peaks for $[Pd\mathbf{L}^bCl + Na - H]^+$ and $[Pd\mathbf{L}^bCl + K - H]^+$ decreased in intensity, and two new clusters of peaks with *m/z* around 1200 and 1239 appeared (Fig. 3). Their IDPs are identical to those of $[Pd\mathbf{L}^b - BOC - H]^+$ and $[Pd\mathbf{L}^b - BOC + K - H]^+$ given by IsoPro 3.0, respectively [Fig. S7 (ESI)]. Therefore, a new complex $Pd\mathbf{A}Cl_2$ is formed in which **A** is $\mathbf{L}^b$ with one BOC group being removed. The $PdCl_2$, as Lewis acid, promotes the detachment of the *N-tert*-BOC groups of $\mathbf{L}^b$.[37,38] But when the mixture is kept at room temperature, neither **A** nor complex $Pd\mathbf{A}Cl_2$ are found (Scheme 2). Therefore, higher temperature is necessary for the removal of the BOC group.

When the mixture is refluxed for 16 h, the two clusters of peaks with *m/z* around 1359 and 1377 disappeared entirely and the relative intensity of the peaks with *m/z* around 1200 and 1239 decreased. New clusters of peaks with *m/z* 1279 and 1315 appeared, which are identical with those in Fig. 2(a), indicating the formation of $Pd_2\mathbf{L}^aCl_4$.



Scheme 2

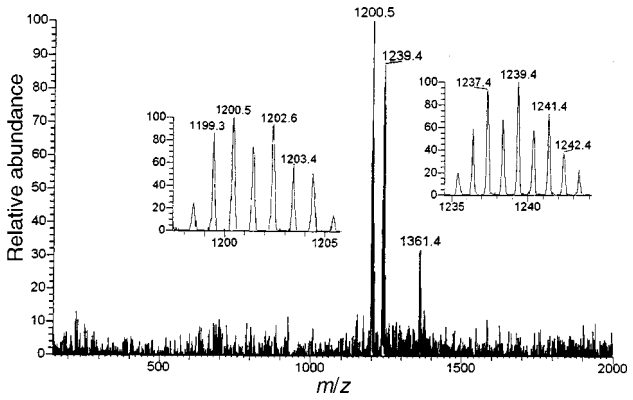
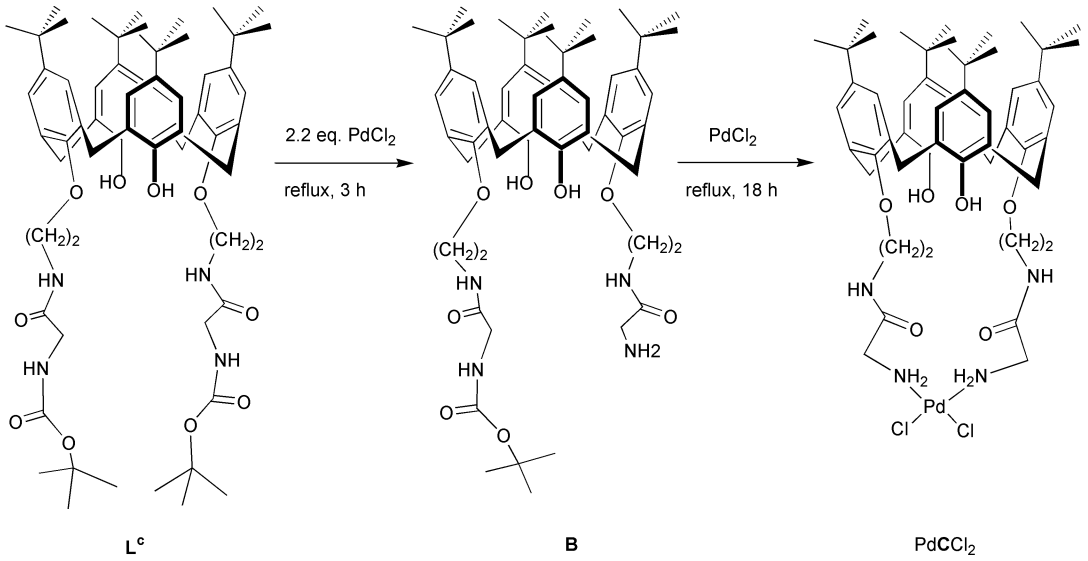


Fig. 3 The ESMS spectrum of complex $PdACl_2$ (refluxed for 6 h). Besides the clusters of peaks of $[PdL^bCl + Na - H]^+$ and $[PdL^bCl + K - H]^+$, there are two new clusters of peaks with *m/z* around 1200 and 1239. The inserts are the measured IDPs of 1200 ($[PdL^b - BOC - H]^+$) and 1239 ($[PdL^b - BOC + K - H]^+$). The peaks are all separated by *m/z* 1. The corresponding calculated IDPs are shown in Fig. S7 (ESI). *m/z* Values found: 1198.3, 1199.3, 1200.5, 1201.5, 1202.6, 1203.4, 1204.4, 1205.5 $[PdL^b - BOC - H]^+$, 1235.4, 1236.4, 1237.4, 1238.4, 1239.4, 1240.4, 1241.4, 1242.4, 1243.4 $[PdL^b - BOC + K - H]^+$; calc. *m/z* values: 1198.5, 1199.5, 1200.5, 1201.5, 1202.5, 1203.5, 1204.5 1205.5 $[PdL^b - BOC - H]^+$; 1235.5, 1236.5, 1237.5, 1238.5, 1239.5, 1240.5, 1241.5, 1242.5, 1243.5 $[PdL^b - BOC + K - H]^+$.

When L^b was refluxed with 1.1 equiv. $PdCl_2$ for 36 h, only $PdACl_2$ was formed. The ESMS spectrum is exactly identical to that obtained with a 1 : 3.5 ratio at room temperature. This result indicates that an excess of $PdCl_2$ is needed to remove both BOC groups. Due to the presence of the methionine moieties, the L^b coordinates to $PdCl_2$ readily and the excess of $PdCl_2$ may act as a Lewis acid to promote the removal of the BOC groups (Scheme 2). If L^b is refluxed with 2.2 equiv. $PdCl_2$, the two BOCs also can be removed. But the reflux time must be extended to 45 h.

Interaction between L^c and $PdCl_2$. Since a Pd(II) anchored to the side chain of a methionine residue in peptides can accelerate the cleavage of the neighboring peptide bond,[25,39,40] one may wonder whether the coordination of the S atom of methionine to Pd(II) is necessary for the removal of the BOC groups. To gain insight into the mechanism of the cleavage, the reaction of $PdCl_2$ with L^c in which BOC-met of L^b is replaced by BOC-gly, was also carried out. When 2.2 equiv. of $PdCl_2$ was stirred with L^c in methanol at room temperature for 6 h, no reaction took place. However, again, when the mixture was refluxed for 3 h, besides the clusters of peaks for L^c, a new cluster of peaks around *m/z* 949 was observed [Fig. S8 (ESI)]. Its IDP is in accord with that of $[L^c - BOC + 2H]^+$ given by IsoPro, suggesting that only one BOC group of L^c is removed and compound **B** is formed.



L^c B $PdCCl_2$

Scheme 3

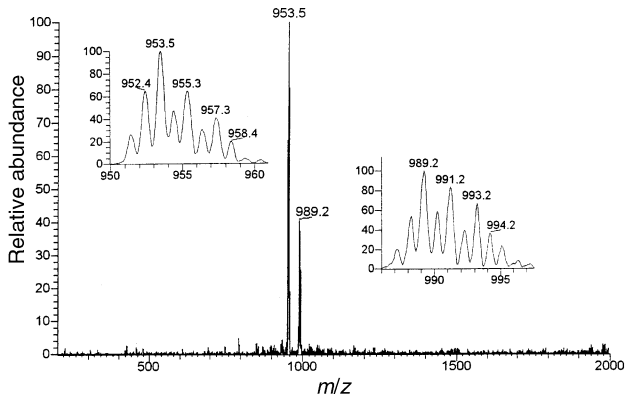


Fig. 4 The ESMS spectrum of complex $PdCCl_2$ (refluxed for 18 h). The inserts are the measured IDPs of the clusters of peaks with *m*/z around 953 ($[PdC - H]^+$) and 989 ($[PdCCl]^+$), respectively. The corresponding calculated IDPs are available in Fig. S9 (ESI). *m*/*z* Values found: 951.4, 952.4, 953.5, 954.4, 955.3, 956.3, 957.3, 958.4 $[M - 2Cl - H]^+$; 987.2, 988.2, 989.2, 990.2, 991.2, 992.2, 993.2, 994.2, 995.2 $[M - Cl]^+$; calc. *m*/*z* values: 951.4, 952.4, 953.4, 954.4, 955.4, 956.4, 957.4, 958.4 $[M - 2Cl - H]^+$; 987.4, 988.4, 989.4, 990.4, 991.4, 992.4, 993.4, 994.4, 995.4 $[M - Cl]^+$.

The ESMS spectrum shows that no complex of **B** is formed.

After refluxing for 18 h, only two clusters of peaks with *m*/*z* around 953 and 993 were observed in the ESMS spectrum (Fig. 4). Their IDPs are identical to those of $[PdC - H]^+$ and $[PdCCl]^+$ as predicted by IsoPro [Fig. S9 (ESI)], where **C** is formed by removing two BOC groups from L^c. No peaks for $[L^c + H]^+$, $[L^c + Na]^+$, $[L^c + K]^+$ and $[L^c - BOC + 2H]^+$ were observable. Therefore, both BOC groups can be removed when a longer refluxing time is used, resulting in a mononuclear $PdCCl_2$ complex (Scheme 3).

These results further illustrate that the removal of BOC groups from the ligands requires higher temperatures and proceeds through sequential steps.

Conclusion

The coordination reaction between *trans*-$[Pd(Py)_2Cl_2]$ or $PdCl_2$ and newly designed calixarene derivatives L^a, L^b and L^c were investigated by ESMS. The *trans*-$[Pd(Py)_2Cl_2]$ only reacts with L^a to form mononuclear PdL^aCl_2, while $PdCl_2$ reacts with all the ligands to give the mononuclear complexes PdL^aCl_2, PdL^bCl_2, $PdACl_2$, $PdCCl_2$ and the binuclear complex $Pd_2L^aCl_4$, depending on the ligands, molar ratio, reaction temperature and time. The BOC groups in L^b and L^c can be cleaved sequentially during their reaction with an excess of $PdCl_2$. These findings may be useful for the modification of two identical amino groups in the same molecule with different functional groups and for the direct synthesis of some Pd(II) complexes of amino acid substituted calixarenes from the corresponding *N*-BOC-protected derivatives without pre-treatment. This new method is likely applicable to the synthesis of other metal compounds.

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