results demonstrate that it may be possible to modulate prototropic exchange by pendant arms in ligands such as **1** to design a series of contrast agents with differing pH sensitivities.

Experimental Section

Diethyl aminomethylphosphonate[14] was treated with bromoacetyl bromide to give diethyl bromoacetamidomethylphosphonate. The latter compound (2.88 g, 0.01 mol) was stirred with cyclen (0.43 g, 0.0025 mol) and potassium carbonate (1.5 g, 0.011 mol) in acetonitrile (10 mL) at 60–70 °C for 6 h. After removal of salts by filtration, the ester of **1** was isolated as a pale-yellow solid (2.48 g). The ethyl esters were deprotected in 30 % HBr in glacial acetic acid (8 mL) by stirring overnight at room temperature. Pure **1** was precipitated from methanol using diethyl ether to yield a white solid: 0.53 g, 85.5 %. ^{1}H NMR (D_2O): $\delta = 3.72$ (br., 8H; NCH_2CO), 3.52 (d, 8H; CH_2P), 3.25 (br., 16H; NCH_2CH_2N); ^{13}C NMR (D_2O): $\delta = 170.65$ (CO), 56.50 (NCH_2CO), 51.83 (NCH_2CH_2N), 38.24 (d, CH_2P). Satisfactory C, H, N analysis.

[Ln(**1**)] complexes were prepared in water by mixing a LnX_3 solution with ligand **1** at pH ~ 9. All NMR spectra were recorded at 11.7 T on a Varian INOVA 500 spectrometer using either a 5 mm inverse probe (^{1}H) or a 5 mm tunable broadband probe (^{17}O, ^{13}C and ^{31}P). *tert*-Butyl alcohol was used as an internal chemical shift reference for ^{1}H and ^{13}C while 85 % H_3PO_4 was used as an external reference for ^{31}P experiments. The sample of [Dy(**1**)] used for the ^{17}O experiments contained 5 % dioxane for purposes of correcting the observed water shifts for bulk susceptibility shifts. Water proton relaxation measurements were performed under temperature control using a MRS-6 NMR analyzer operating at 20 MHz (Institut Jozef Stefan, Ljubljana, Slovenija). ^{1}H images were collected using a GE (Bruker) Omega 4.7 T imaging system and a 20 mm Helmholtz coil. Potentiometric titrations were performed in 0.1 M NMe_4Cl at 25 °C under a N_2 atmosphere using an Accumet 925 pH meter, an Orion 8103 Ross combination electrode, and a Brinkmann/Metrohm 665 Dosimat titrator. The resulting activity versus volume titration curves were analyzed by using a spreadsheet program described previously.[15]

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Gold(I) and Gold(0) Complexes of Phosphinine-Based Macrocycles**

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In the vast majority of gold complexes (organometallic, coordination, and catalytic species) the metal center has an oxidation state from +1 to +3.[1] Indeed, monomeric zerovalent gold complexes, as their Group 11 congeners (complexes of Cu or Ag),[2] eluded isolation for a long time, and are still rare.[3] In any case, these gold(0) complexes appear thermodynamically too unstable to be used in chemical transformations. Carbonyl derivatives $[Au(CO)_n]$ ($n = 1-3$) were obtained by cryochemical methods and characterized in matrices at low temperatures; they decompose above 77 K.[4] In this context, the synthesis of new and more stable Au^0 species is a topical and challenging field of investigation.

Recently, we reported on the synthesis of silacalix[*n*]phosphinines, a new class of macrocycles incorporating sp^2-hybridized phosphorus atoms.[5] In view of the adequate electronic balance between σ-donating and π-accepting properties in phosphinines, we proposed that these cavities

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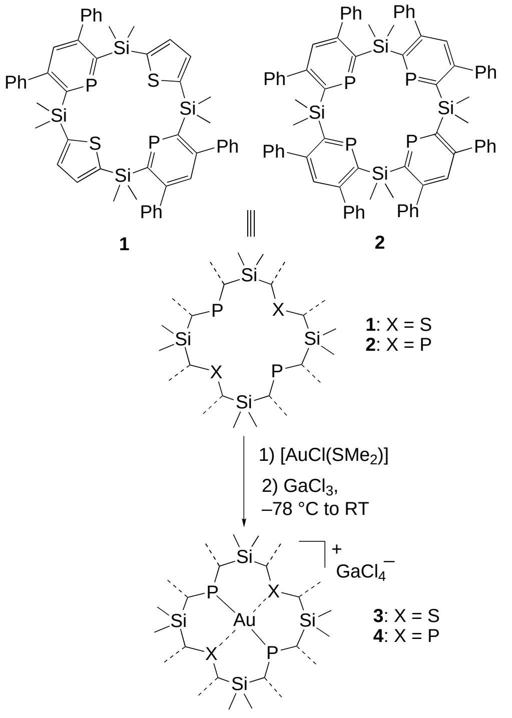
might work as a kind of "macrocyclic equivalent" of carbonyl groups and thus provide unusual reduced transition metal species of enhanced thermodynamic stability. To assess this proposal we focused our first studies on the synthesis and the reduction of gold(I) complexes. Here we report on results obtained with two of these macrocycles, namely, the silacalix[4]1,3-bis(phosphinine)-2,4-bis(thiophene) **1** and the silacalix[4]phosphinine **2** (see Scheme 1).[6]

Complexes **3** and **4** were prepared by allowing one equivalent of the macrocycle (**1** or **2**, respectively) to react with [AuCl(SMe$_2$)], followed by treatment with GaCl$_3$ as chloride abstractor, in dichloromethane at $-80\,^{\circ}$C (Scheme 1).[7] These two complexes were fully characterized and are, to the best of our knowledge, the first examples of macrocycles coordinated to a gold(I) center.



Scheme 1. Chemical structures of **1** and **2**, and their reaction with [AuCl(SMe$_2$)] to form Au$^{\mathrm{I}}$ cationic derivatives **3** and **4**.

In both cases, X-ray diffraction studies have been carried out. Only the structure of **4** is reported here (Figure 1).[8] The four phosphorus atoms lie in the same plane, but only two subunits (P1 and P3) are connected to the Au$^{\mathrm{I}}$ center, the two others (P2 and P4) only showing very weak interactions (P2–Au 2.974, P4–Au 2.905 Å). However, this geometry is not preserved in solution. The ^{31}P NMR spectrum of complex **4** consists of a sharp singlet (four magnetically equivalent P nuclei) down to $-80\,^{\circ}$C, indicating a fluxional behavior. Unfortunately, the complex precipitates out of solution below this temperature, precluding extraction of thermodynamic data. Apart from this feature and the fact that intramolecular phosphinine bond distances are slightly modified by complexation as previously noted,[9] the structure of **4** deserves no special comment.

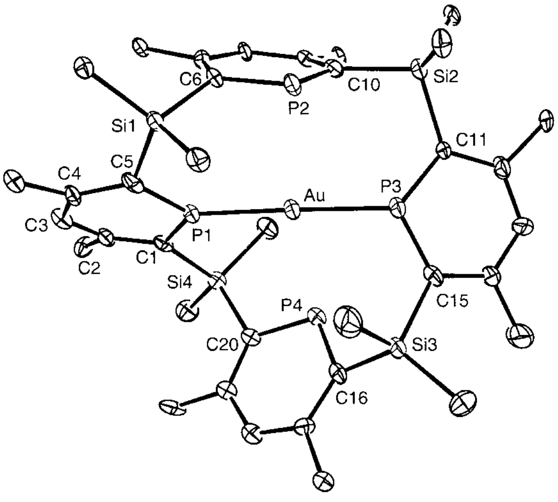


Figure 1. Structure of the cation of **4** in the crystal. Ellipsoids are scaled to enclose 50% of the electronic density. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Au–P1 2.307(2), Au–P2 2.974(2), Au–P3 2.331(2), Au–P4 2.905(3), P1–C1 1.730(8), C1–C2 1.39(1), C2–C3 1.40(1), C3–C4 1.39(1), C4–C5 1.40(1), C5–P1 1.732(8), C1–Si4 1.940(8), Si4–C20 1.892(9); P1-Au-P2 97.27(7), P1-Au-P3 176.48(9), P1-Au-P4 93.60(7), P2-Au-P3 85.49(7), P2-Au-P4 168.01(6), P3-Au-P4 83.46(8), Au-P1-C1 126.3(3), P1-C1-C2 117.1(6), C1-C2-C3 123.3(7), C2-C3-C4 126.8(7), C3-C4-C5 123.1(7), C4-C5-P1 117.0(6), C5-Si1-C6 100.6(3).

The electrochemical reduction of the two complexes was carried out in dichloromethane and reveals important information. First, complex **3** is irreversibly reduced at a peak potential of $E^{\circ} = -1.0$ V (versus saturated calomel electrode, SCE) at a scan rate of 0.05 V s^{-1}, which shows that the generated Au^0 species is not stable. Increasing the scan rate (up to 100 V s^{-1}) or decreasing the temperature (below 253 K) only led to a weak reversibility of the reduction. On the other hand, complex **4** undergoes a quasi-reversible process at $E^{\mathrm{p}} = -0.80$ V upon scanning at 0.1 V s^{-1} (263 K, Figure 2), indicating the formation of the Au^0 complex **5** (Scheme 2). This behavior markedly differs from that of the [Au(dppe)$_2$][GaCl$_4$] complex (dppe = diphenylphosphanylethane), which is irreversibly reduced at -2.0 V. The lower reduction potential recorded for complex **4** is in full agreement with the strong π-acceptor character of phosphinines, which increases the Lewis acidic character of the Au$^{\mathrm{I}}$ center. The chemical reduction of **4** was thus attempted in THF at $-78\,^{\circ}$C using sodium naphthalenide (NaNp) as reducing agent. The formation of complex **5** was evidenced by an immediate color change from red to deep purple. Unfortunately, **5** could not be isolated as it starts to decompose when the temperature reaches $-20\,^{\circ}$C, releasing the free ligand **2** and colloidal gold.

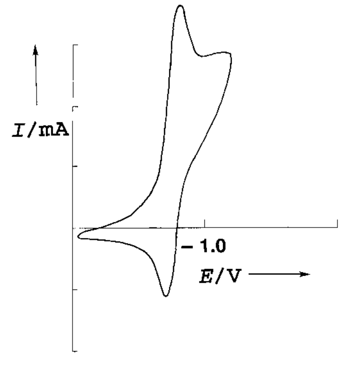
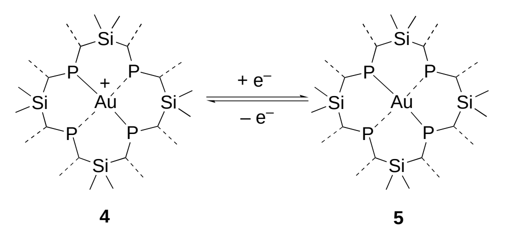


Figure 2. Cyclic voltammogram of complex **4** (2 mM in CH$_2$Cl$_2$, 0.3 M nBu$_4$NBF$_4$, 263 K) at a gold disk electrode (diameter 0.5 mm, scan rate 0.1 V s^{-1}). I = intensity, E = potential vs. SCE.



Scheme 2. Electrochemical reduction of complex **4** to form **5**.

Consequently, we attempted to detect the reduction product of **4** by EPR spectroscopy. Solutions of **4** in THF were reduced under vacuum (10–5 Torr) on a mirror of alkali metal (K or Na) in a sealed tube at $-80\,^{\circ}\mathrm{C}$. When the experiments were performed with a perfectly degassed solvent, the resulting signal ($g = 2.001$) was composed of 20 lines in accordance with a 700-MHz coupling with a nucleus of spin 3/2 (^{197}Au, natural abundance 100 %) and with a 160-MHz coupling with four equivalent nuclei of spin 1/2 (^{31}P, Figure 3). The same observations were made when **4** (largely in excess) was allowed to react with NaNp at $-80\,^{\circ}\mathrm{C}$ in the absence of contact with air (cryopumping). At 200 K the signal begins to decrease in intensity after 1 h, whereas it rapidly disappears at 230 K.

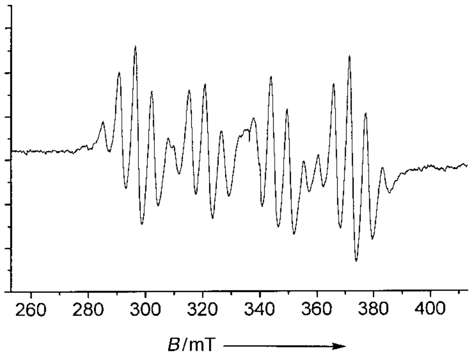


Figure 3. EPR spectrum obtained at 190 K after reaction of **4** in THF with a potassium mirror.

Comparison of the ^{197}Au and ^{31}P isotropic coupling constants with the corresponding atomic parameters (2876 MHz for ^{197}Au, 13306 MHz for ^{31}P) indicates that 24 % of the spin is confined in a gold s orbital and 1 % in an s orbital of each phosphorus atom.[10] The Au s-spin density is considerably smaller that the value reported for Ag^0 solvated by four acetonitrile molecules ($\rho_s = 0.70$)[11] or for the [Au(C$_6$H$_6$)] complex ($\rho_s = 0.90$).[12] Recording the spectrum at 77 K does not considerably modify the position of the lines, but affects their intensity distribution. Under these conditions, simulation could hardly determine to what extent the slight anisotropy of the signal is due to the g value or ^{197}Au hyperfine tensors. However, it shows that the ^{31}P hyperfine anisotropy is small and that the observed isotropic coupling is too large to result from inner shell polarization only. Experiments are planned to study the temperature dependence of the signal between 4 and 77 K and to check if the equivalence of the four phosphorus atoms does not result from a dynamic process which would subsist even at liquid nitrogen temperature.

In conclusion, we have shown that silacalix[4]phosphinine macrocycles may serve, at least in the case of Au^0, as a kind of "CO-like matrix". Studies aimed at determining whether this property can be extended to other reduced metallic centers are currently underway.

Experimental Section

3: A solution of GaCl$_3$ (0.022 g, 0.12 mmol) in CH$_2$Cl$_2$ (2 mL) was added to a solution of **1** (0.09 g, 0.10 mmol) and [AuCl(SMe$_2$)] (0.03 g, 0.10 mmol) in CH$_2$Cl$_2$ (3 mL) at $-80\,^{\circ}\mathrm{C}$. The reaction mixture was then slowly warmed to room temperature. After evaporation of Me$_2$S and a part of the solvent, **3** was precipitated with hexanes (10 mL). After filtration and drying, **3** was isolated as a pale yellow solid (0.12 g, 91 %). Crystals suitable for X-ray analysis were obtained at room temperature from slow diffusion of hexanes in a solution of **3** in chloroform. Elemental analysis calcd for C$_{50}$H$_{50}$AuCl$_4$GaP$_2$S$_2$Si$_4$: C 46.27, H 3.88; found: C 46.65, H 3.92; ^{31}P NMR (200 MHz, CD$_2$Cl$_2$, 25 °C): $\delta = 234.50$ (s); ^{1}H NMR (CD$_2$Cl$_2$, 25 °C): $\delta = 0.30$ (br s, 24 H; SiMe$_2$), 7.45–7.62 (m, 26 H; Ph, CH of thiophene rings, and H4 of phosphinines); ^{13}C NMR (200 MHz, CD$_2$Cl$_2$, 25 °C): $\delta = 3.8$ (br s; SiMe$_2$), 130.3–131.6 (m; Ph and C4 of phosphinines), 135.1 (virtual t, ΣJ(C,P) = 36.4 Hz; C3, C3′ of thiophene rings), 140.6 (s; C2, C2′ of thiophene rings), 142.0 (br s; C3, C3′ of Ph), 146.0 (virtual t, ΣJ(C,P) = 12.1 Hz; C3, C3′ of phosphinines), 161.4 (virtual t, ΣJ(C,P) = 13.9 Hz; C2, C2′ of phosphinines).

4: A solution of GaCl$_3$ (0.017 g, 0.10 mmol) in CH$_2$Cl$_2$ (2 mL) was added to a solution of **2** (0.10 g, 0.082 mmol) and [AuCl(SMe$_2$)] (0.024 g, 0.082 mmol) in CH$_2$Cl$_2$ (4 mL) at $-80\,^{\circ}\mathrm{C}$. The reaction mixture was then slowly warmed to room temperature. After evaporation of Me$_2$S and a part of the solvent, **4** was precipitated with hexanes (10 mL). After filtration and drying, **4** was isolated as a red solid (0.12 g, 90 %). Crystals suitable for X-ray analysis were obtained at room temperature from slow diffusion of hexanes in a solution of **4** in CH$_2$Cl$_2$. Elemental analysis calcd for [C$_{76}$H$_{68}$AuCl$_4$GaP$_4$Si$_4$]: C 56.14, H 4.21; found: C 56.45, H 4.18; ^{31}P NMR (200 MHz, CD$_2$Cl$_2$, 25 °C): $\delta = 241.45$ (s); ^{1}H NMR (CD$_2$Cl$_2$, 25 °C): $\delta = 0.05$ (br s, 24 H; SiMe$_2$), 7.10–7.41 (m, 44 H; Ph and H4 of phosphinines); ^{13}C NMR (200 MHz, CD$_2$Cl$_2$, 25 °C): $\delta = 4.0$ (s; SiMe$_2$), 127.3–129.0 (m; Ph), 134.3–134.9 (virtual t, ΣJ(C,P) = 28.6; C4 of phosphinines), 143.8 (s; C3, C3′ of Ph), 157.0 (s; C3, C3′ of phosphinines), 158.2–159.0 (m, ΣJ(C,P) = 40.7; C2, C2′ of phosphinines).

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Keywords: gold · heterocycles · macrocyclic ligands · phosphinines · P ligands

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[8] X-ray structure determination for **4** ($C_{77}H_{70}AuCl_6GaSi_4P_4$): Crystals of **4** were grown from a solution in CH_2Cl_2; crystal size: 0.28 × 0.24 × 0.15 mm. Data were collected at 123 ± 0.5 K on an Enraf Nonius CAD4 diffractometer using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). The crystal structure was solved and refined using the Enraf Nonius MOLEN package. Monoclinic, space group $P21/c$ (no. 14), $a = 12.256(1)$, $b = 23.895(2)$, $c = 26.056(3)$ Å, $\beta = 95.76(2)^\circ$; $V = 7592.1(2.6)$ Å^3; $Z = 4$; $\rho_{calcd} = 1.497$ g cm^{-3}; $\mu = 26.8$ cm^{-1}; $F(000) = 3440$. A total of 15785 unique reflections were recorded in the range $2 \leq 2\theta \leq 51.8^\circ$, of which 7450 were considered as unobserved ($F^2 < 2\sigma(F^2)$), leaving 8335 for solution and refinement. A non-Poisson weighting scheme was applied with a p factor equal to 0.08. The final agreement factors were $R = 0.049$, $R_\omega = 0.069$, GOF = 1.35; max./min. residual electron density 2.10(13)/ – 0.19(13) e Å^{-3}. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-119267 (**3**) and CCDC-119268 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Discovery Through Total Synthesis—Epimerization at C7 in the CP Compounds: Is (7*S*)-CP-263,114 a Fermentation Product?**

Dongfang Meng, Qiang Tan, and
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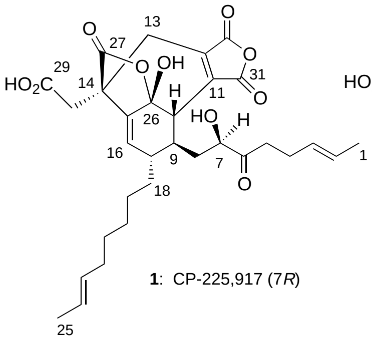
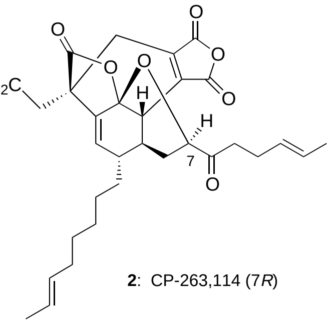
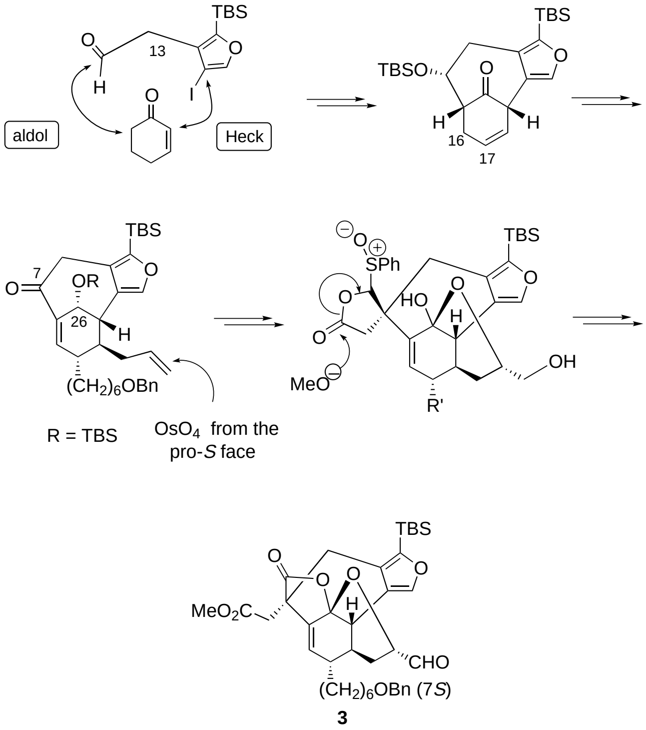


1: CP-225,917 (7*R*)



2: CP-263,114 (7*R*)

The goal of accomplishing the total syntheses of CP-225,917 (**1**) and CP-263,114 (**2**) has attracted the active participation of a variety of research groups.[1–3] These substances inhibit farnesyltransferase and squalene synthase activity. While the biological potential, if any, of agents that combine both activities is far from demonstrated, chemists have been attracted to this challenge by the novel molecular architecture of these target compounds. Elsewhere, we have described an approach to the synthesis of the CP series that delivered compound **3**, with the full framework to reach the target structure (Scheme 1).[3c]



Scheme 1. Synthesis of **3**.[3c]

We noted that the stereochemistry we were assigning at C7 (*S*)[4] of our synthetic structure was not the same as that assigned by the Pfizer discovery group to CP-263,114 (7*R*).[5, 6] However, one could not then be sure that the assignment to the natural product was necessarily correct. Some preliminary attempts on our part to epimerize aldehyde **3** were not successful and were attended by extensive decomposition. Accordingly, we undertook the installation of the remaining functionality required to go from **3** to the CP compounds (neglecting the issue of the C7 stereochemistry) in the hope of settling this question. Pentenylation of **3** followed by the oxidation of the resultant carbinol afforded **4** (Scheme 2).

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