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Cobaltoceniumselenolate Gold(I) Complexes: Synthesis, Spectroscopic, Structural and Anticancer Properties

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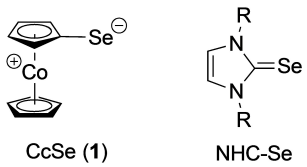
Cobaltoceniumselenolate is an unusual, highly air-sensitive, mesoionic compound containing a very soft anionic selenium donor atom. Here we explore its coordination chemistry with Au(I) metal centers and show that its hetero- and homoleptic gold complexes are highly colored, air-stable compounds, which were characterized by $^{1}H/^{13}C/^{31}P/^{77}Se$ NMR, IR, UV-Vis, HR-MS and single crystal XRD. Cytotoxicity of these polar, water-soluble complexes was studied against various standard cancer cell lines (A549MDA-MB-231, HT-29) revealing good anticancer activity of all three complexes.

The rich coordination chemistry of organic selenium ligands with soft d^{10} coinage metal centers [Cu(I), Ag(I), Au(I)] is largely dominated by air-sensitive anionic selenolates (R–Se^{-}, R = alkyl or aryl)[1] and air-stable neutral cyclic selenoureas.[2] The latter compounds are in great structural variety easily available by simple synthesis from their corresponding N-heterocyclic carbenes (NHCs) or NHC-precursors[3] via direct selenation or one-pot deprotonation-selenation, respectively.[2,3] The major interest in cyclic selenoureas is currently based on their widespread use as a convenient ^{77}Se NMR probe to quantify the π-acidity of their parent NHCs.[4]

Recently we reported on cobaltocenylidene (CcC), a mesoionic, very electron-rich metalloceno carbene, stabilized in a gold(III) complex, and on its cobaltoceniumselenolate derivative CcSe (**1**) (Scheme 1),[5] that was prepared to evaluate the σ-donor character and π-backbonding ability of this unusual redox-responsive organometallic carbene by its ^{77}Se NMR properties. Cobaltoceniumselenolate (**1**) is an extremely air-sensitive, dark purple compound with a zwitterionic structure composed of an undistorted cationic cobaltocenium moiety with an anionic selenido substituent, as shown by single crystal structure analysis (Scheme 1).[5] Compared to the air-stable selenium derivatives of standard NHCs, cyclic selenoureas,[2] which feature a selenium-carbon double bond, **1** is electronically clearly distinctly different and represents the unusual case of a neutral selenolate ligand. In addition, contrarious steric properties are evident for **1** (axial shielding by the cobaltocenium moiety) and cyclic selenoureas (peripheral shielding by the wingtip substituents). Hence we became interested to investigate Au(I) complexes of **1** in comparison to their cyclic selenourea complexes and for potential applications as new metallodrugs, inspired by current studies in anticancer research on redox-active metal complexes,[6] gold anticancer metallodrugs,[7] and organoselenium anticancer agents.[8]

Synthesis: Cobaltoceniumselenolate (**1**) is available from iodocobaltocenium hexafluoridophosphate[9] by a nucleophilic aromatic substitution with sodium selenide under strictly inert conditions as recently published.[5] In-situ synthesis of **1** followed by oxidation on air led to its dicationic diselenide bis (hexafluoridophosphate) **2a** [CcSeSeCc]$(PF_6)_2$ in a satisfying yield of 75% (Scheme 2). Because it proved quite difficult to obtain suitable single crystals for **2a**, we synthesized also its tetraphenylborate analog **2b** [CcSeSeCc]$[B(C_6H_5)_4]_2$ in a similar manner using sodium tetraphenylborate in the work-up procedure (see Supporting Information). As desired, good-quality single crystals of **2b** could be obtained for the XRD analysis discussed below. Reaction of the cobaltoceniumselenolate (**1**) with (triphenylphosphine)gold chloride afforded either hetero or homoleptic complexes, depending on stoichiometry



CcSe (**1**) NHC-Se

Scheme 1. Pertinent Lewis valence structures of cobaltoceniumselenolate (**1**, left) and standard NHC selenium derivatives, cyclic selenoureas (NHC–Se, right).

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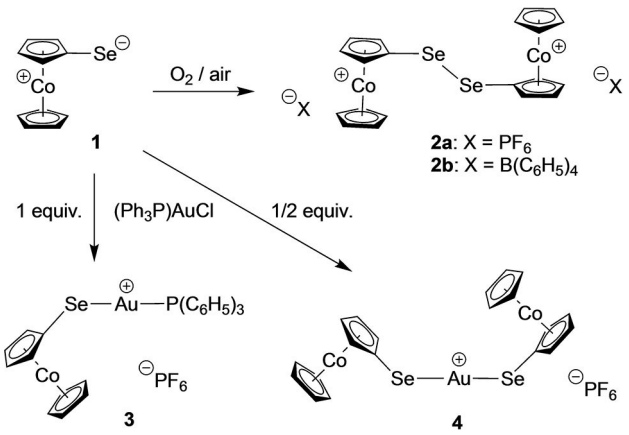

Scheme 2. Synthesis of compounds **2a**, **2b**, **3** and **4**.

(Scheme 2). In a 1:1 CcSe:Au ratio, heteroleptic [(CcSe)(PPh_3)Au]PF_6 (**3**) was obtained (61% yield), whereas a 2:1 CcSe:Au ratio afforded homoleptic [$(CcSe)_2$Au]PF_6 (**4**) in 56% yield.

Physical, spectroscopic and structural properties (for details and spectra see Supporting Information): Complexes **2ab**, **3** and **4** are air-stable salts with melting points from 135–162 °C, soluble in polar solvents like acetonitrile, dimethylformamide, dimethylsulfoxide, acetone, nitromethane, methanol and to a lesser degree in dichloromethane and water. Whereas dicationic diselenides **2ab** are yellow compounds, monocationic gold(I) selenolate complexes **3** and **4** are highly colored dark-red materials, due to their strong selenium-gold charge-transfer absorptions (Figure 1). ^{1}H NMR spectra of **2ab**, **3** and **4** showed the typical pattern of monosubstituted metallocenes [s(5H), Cp and 2×pseudo-t(2H), substituted Cp] in the usual spectral region of cobaltocenium salts (5.3–6.0 ppm), in addition to phenyl-hydrogen signals in the aromatic region for tetraphenylborate salt **2a** and triphenylphosphine complex **3**. ^{13}C NMR spectra of **2a**, **3** and **4** displayed their cobaltocenium signals at 85–89 ppm (Cp and C–H carbons of substituted Cp) and those of the substituted carbon resonances at 96.2 (**2a**), 104 (**3**) and 88.6 (**4**), indicative of the difference in their structure [diselenide **2a** versus heteroleptic **3** and homoleptic **4** CcSe Au(I) complexes). For **3** the ^{31}P NMR signals were observed at 39.2 ppm [PPh_3 coordinated to Au(I)] and −143.3 ppm [PF_6^-, septet, $^{1}J(^{19}F–^{31}P) = 706$ Hz]. ^{77}Se NMR chemical shifts of **2a** and **3** were detected at 429 and 596 ppm versus dimethylselenide as reference. Unfortunately, no signal could be observed for complex **4**, even on very long data acquisition periods, probably due to poor relaxation properties. In comparison to the ^{77}Se signal of the free CcSe ligand [$\delta(^{77}Se) = 258$ ppm],[5] the Au(I)-coordinated CcSe ligand in complex **3** [$\delta(^{77}Se) = 596$ ppm] is highly deshielded by 338 ppm. IR spectra of **2a**, **3** and **4** are rather simple with the most prominent signals at approximately 810 and 550 cm^{-1} arising from the strong $\nu_{P\text{-}F}$ absorptions of the hexafluoridophosphate counterions. The identity of compounds **2a**, **3** and **4** is further corroborated by their high-resolution mass spectra with excellent agreement of experimental with calculated values.

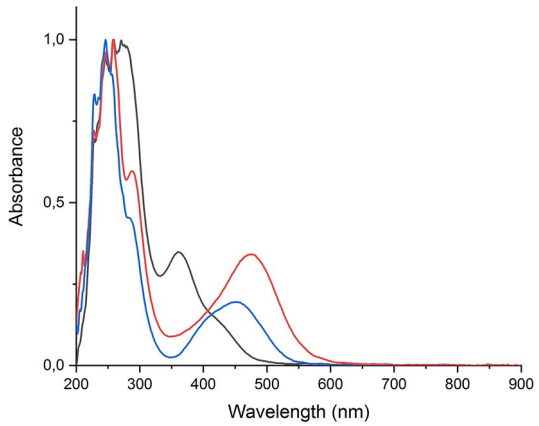

Figure 1. Overlay of UV-vis spectra of **2a** (black line), **3** (blue line) and **4** (red line).

Single crystal structure analyses are available for **2b**, **3** and **4** (Figure 2 and Supporting Information) with good R_1 values of 4.49, 4.61 and 4.86%, respectively. The cobaltocenium substituents of all three compounds are undistorted and bond distances at the selenium atoms (**2b**: Se–Se = 2.310 Å, **3**: Se–Au = 2.425 Å, **4**: Se–Au = 2.398 Å) are comparable to those of non-cobaltocenium dicationic diselenides[10] or NHC–Se-Au(I) complexes.[2d] Bond angles at the tetrahedral selenium atoms of

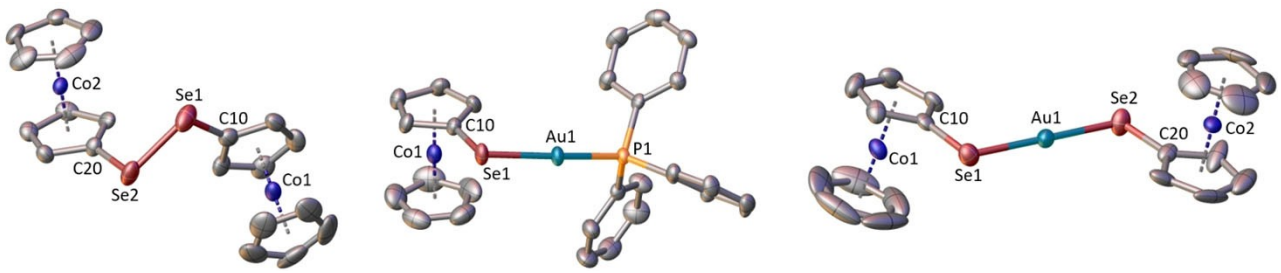

Figure 2. Molecular structures of **2b** (left), **3** (middle) and **4** (right). Counteranions tetraphenylborate (for **2b**) or hexafluoridophosphate (for **3** and **4**) omitted for clarity. Selected distances (Å) and angles (°) for **2b**: Se(1)–Se(2) = 2.3104(14), Se(1)–C(10) = 1.903(7), Se(2)–C(20) = 1.902(7); C(10)–Se(1)–Se(2) = 101.0(2), C(20)–Se(2)–Se(1) = 100.4(2). Selected distances (Å) and angles (°) for **3**: Au(1)–Se(1) = 2.4249(6), Au(1)-P(1) = 2.2673(13), Se(1)–C(10) = 1.891(5); C(10)–Se(1)–Au(1) = 99.01(16), P(1)–Au(1)–Se(1) = 170.37(4). Selected distances (Å) and angles (°) for **4**: Au(1)–Se(1) = 2.3979(7), Au(1)–Se(2) = 2.3912(8), Se(1)–C(10) = 1.872(6), Se(2)–C(20) = 1.870(6); Se(1)–Au(1)-Se(2) = 177.81(2), C(10)–Se(1)–Au(1) = 102.85(18), C(20)–Se(2)–Au(1) = 105.3(2).

Table 1. Cytotoxicity activity against 3 cancer cell lines expressed as IC_{50} values. Values were obtained in three independent experiments and are presented as mean values ± standard deviation.

	A549	HT-29	MDA-MB-231
2a	17.4 ± 0.1 μM	51.6 ± 2.2 μM	11.5 ± 1.6 μM
3	8.4 ± 0.9 μM	5.0 ± 0.2 μM	3.6 ± 0.3 μM
4	12.3 ± 1.5 μM	4.9 ± 0.3 μM	3.5 ± 0.4 μM

2b, **3** and **4** (99–105°) are slightly compressed in comparison to the standard value of 109.5°, as predicted by VSEPR theory by greater repulsion between electron lone pairs than between bonding pairs. The coordination geometry at the gold(I) centers of complexes **3** and **4** is more or less linear (**3**: 170.3°, **4**: 177.8°), as anticipated and similar as in NHC–Se-Au(I) complexes.[2d] One might expect either aurophilic[11] Au···Au or chalcogenophilic[12] Se···Se intermolecular bonding for these di/mono-cationic Se/Au species **2b**, **3** and **4**, however, no such intermolecular secondary bonds were observed (compare Supporting Information), most likely due to the position of the tetraphenylborate or hexafluoridophosphate counterions in the crystal lattice. In comparison, NHC–Se gold(I) complexes containing bulky wingtip substituents display dimeric solid state structures with weak Se···Se interactions.[10a]

Cytotoxicity studies: Three cancer cell lines (A549 lung carcinoma, HT-29 colon adenocarcocinoma, and MDA-MB-231 breast carcinoma), which represent very relevant human cancers were chosen to study to cytotoxic effects of the complexes **2a**, **3** and **4** (Table 1). Complexes **3** and **4** were more active than **2a** in all three cell lines. This cleary confirms that the cobaltoceniumselenolate partial structure causes a good to moderate cytotoxic effect, which can be significantly increased by introduction of a gold(I) center. The most sensitive cell line in the studied panel was MDA-MB-231. The assay with this cell line requires a 96 h incubation period instead of 72 h as for HT-29 and A549. The enhanced activity against MDA-MB-231 might therefore indicate that the biological activity of the complexes generally increases over time.

Summary: Starting from the zwitterionic cobaltoceniumselenolate ligand, CcSe, its diselenide oxidation product $[CcSeSeCc]^{2+}$ and monocationic hetero/homoleptic $[(CcSe)(PPh_3)Au]PF_6$/$[(CcSe)_2Au]PF_6$ gold(I) complexes were obtained. All three compounds are air-stable materials that were fully characterized by spectroscopic techniques (multinuclear NMR, IR, HR-MS, UV-Vis, XRD). Cytotoxic effects were observed with all three complexes against three selected cancer cell lines. Introduction of the gold(I) center significantly increased the cytotoxic activity of the cobaltoceniumselenolates.

Supporting Information (see footnote on the first page of this article): Experimental details, spectra, X-ray and crystallographic refinement details.

Deposition Numbers 2081773 (for **2b**), 2081774 (for **3**) and 2081775 (for **4**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Cobalt · Selenium · Gold · Sandwich complexes · Cytotoxicity

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