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

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Cobaltoceniumselenolate is an unusual, highly air-sensitive, mesionic 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, HRMS and single crystal XRD. Cytotoxicity of these polar, water-soluble complexes was studied against various standard cancer cell lines (A549/MDA-MB-231, HT-29) revealing good anticancer activity of all three complexes.

The rich coordination chemistry of organic selenium ligands with soft $^{19}$F-containing 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 carbene (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 $\pi$-acidity of their parent NHCs.[4]

Recently we reported on cobaltocenylidene (CC), a mesionic, very electron-rich metalallocene carbene, stabilized in a gold(III) complex, and on its cobaltoceniumselenolate derivative CoSe (1) (Scheme 1)[5] that was prepared to evaluate the $\sigma$-donor character and $\pi$-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 cobaltooceneium 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.[9] In-situ synthesis of 1 followed by oxidation on air led to its dicatonic diselenide bis(hexafluoridophosphate) 2a [CoSeSeCCl(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 [CoSeSeCCl(B(C$_6$H$_5$)$_4$)$_2$] 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.

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

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soluble in polar solvents like acetonitrile, dimethylformamide, dimethylsulfoxide, acetone, nitromethane, methanol and to a lesser degree in dichloromethane and water. Whereas dicatonic 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). 1H NMR spectra of 2ab, 3 and 4 showed the typical pattern of monosubstituted metallocenes [s(4H), Cp and 2×pseudot(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 tetrphenylborate salt 2a and triphenylphosphine complex 3. 13C 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 31P NMR signals were observed at 39.2 ppm [PPPh3 coordinated to Au(I)] and −143.3 ppm [PF6−, septet, 1J(19F−31P) = 706 Hz]. 77Se 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 77Se signal of the free CcSe ligand [δ(77Se) = 258 ppm],[5] the Au(I)-coordinated CcSe ligand in complex 3 [δ(77Se) = 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 νP–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.

Single crystal structure analyses are available for 2b, 3 and 4 (Figure 2 and Supporting Information) with good R 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 dicatonic diselenides[10] or NHC–Se–Au(I) complexes.[10] Bond angles at the tetrahedral selenium atoms of

![Scheme 2. Synthesis of compounds 2a, 2b, 3 and 4.](image)

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

![Figure 2. Molecular structures of 2b (left), 3 (middle) and 4 (right). Counteranions tetrphenylborate (for 2b) or hexafluoridophosphate (for 3 and 4) omitted for clarity. Selected distances (Å) and angles (°) for 2b: Se(1)–Se(2) = 2.310(14), Se(1)–C(10) = 1.903(7), Se(2)–C(20) = 1.902(7); C(10)–Se(1)–Se(2) = 101.2(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) = 99.0(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)–Se(2) = 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).](image)
Bonds were observed (compare Supporting Information), most therefore indicate that the biological activity of the complexes requires a 96 h incubation period instead of 72 h as for HT-

The assay with this cell line showed a moderate cytotoxic effect, which can be significantly increased if the cobaltoceniumselenolate partial structure causes a good to active than

Cytotoxicity studies: Three cancer cell lines (A549 lung carcinoma, HT-29 colon adenocarcinoma, 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 2a, 3 and 4 are more active than 2a in all three cell lines. This cleary confirms that the cobaltalciumselenolatesenal partially 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 cobaltoceniumselenolenate ligand, CcSe, its diselidene oxidation product [CcSeSeCc]^{2+} and monocationic hetero/homoleptic [(CcSe)(Ph)]Au(PF)

|       | 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   |

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

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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.

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