Sulfur Complexes

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# Metal and Ligand Control of Sulfenate Reactivity: Arene Ruthenium Thiolato-Mono-*S*-Oxides**

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Cationic organometallic ruthenium(II) arene complexes with pseudooctahedral "piano-stool" geometry (**M-L** in Figure 1) show activity towards cancer cells comparable to that of the clinically used drugs cisplatin and carboplatin.[1] The monodentate ligand **L** is a leaving group that provides a binding site for nucleotides (DNA). Complexes in which **L** is a thiolato group have attracted our interest recently as the thiolato adduct with the intracellular thiol of the tripeptide glutathione (γ-L-Glu-L-Cys-Gly, GSH) appears to undergo facile oxidation to a sulfenato complex (thiolato-mono-*S*-oxide).[2] Such ligand-centered oxidations of thiolato ligands to sulfenato ligands could possibly weaken the ruthenium–sulfur bond and so introduce a good leaving group, a reaction that might be important for biological activity.

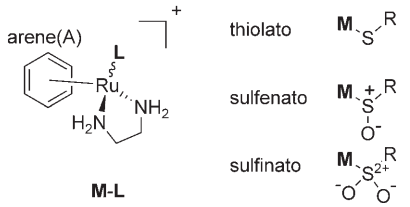
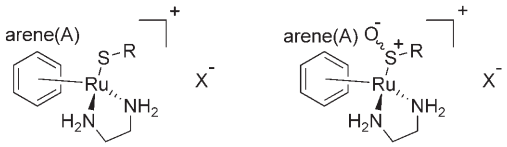



***Figure 1.*** General structure of ruthenium arene complexes with thiolato, sulfenato, and sulfinato ligands.

Some examples of the direct oxidation of metal-bound thiolato ligands are known,[3–9] but oxidation usually leads to sulfinato ligands rather then sulfenato ligands.[3,10] One important difference between thiolato, sulfenato, and sulfinato ligands is the ability of sulfenates to exert high *trans* effects.[11–13] Sulfenates can be either oxidized[14] or reduced.[6,15] Notably, the corresponding free ligands (sulfenic acids) are unstable and highly reactive,[16,17] and the sulfur–oxygen bond is longer[6,9,14,18] than those in sulfinates; sulfenates have a negatively charged oxygen atom that forms hydrogen bonds[4,19] and can be protonated.[5,6] Nevertheless, the oxygen atom in sulfenates can exchange with water oxygen atoms and provides some catalytic activity in nitrile hydrolysis.[3] With these properties, it is not surprising that sulfenato ligands (as cysteine sulfenates) are found in catalytic centers of enzymes, namely, in Fe and Co nitrile hydratase (NHase),[11] and are of much interest in biological signaling processes.[20]

Despite the importance of sulfenato complexes in biology and the large number of known thiolato complexes, there is still a lack of understanding of the chemistry of simple S-bound mononuclear sulfenato complexes. Herein we report the first direct oxidation of a nonchelated thiolato ligand to a sulfenato ligand, as well as the determination of its acidity, hydrolysis, and influence on ligand exchange rates at the metal center in complexes of pharmaceutical interest.

The thiolato complexes **1a** and **1b** (Figure 2) are soluble in water and stable in the presence of oxygen; no hydrolysis is observed. Reaction with hydrogen peroxide leads to bleaching of the aqueous solution within a few minutes. Monitoring of this reaction by NMR spectroscopy in $H_2O/D_2O$ revealed that addition of one molar equivalent of $H_2O_2$ yields almost exclusively the corresponding sulfenato complexes **2a** and **2b** (Figure 2). The sulfinato complexes are formed upon addition of excess $H_2O_2$. UV/Vis spectra show two isosbestic points, indicating that the first oxidation step is dominated by formation of the sulfenato complex rather than a sulfenato/sulfinato mixture (Figure 3). An increase in absorption at higher wavelength ($\lambda = 310$ nm) and a decrease at lower wavelength ($\lambda = 240$ nm) was observed for oxidation of **1a** to the sulfenato complex **2a** (Figure 3).[6,8]




**1a**) A = ($\eta^6$-hmb), R = *i*Pr, X = $PF_6$;
**1b**) A = ($\eta^6$-*p*-cymene), R = *i*Pr, X = I;
**1c**) A = ($\eta^6$-*p*-cymene), R = Ph, X = I;

**2a**) A = ($\eta^6$-hmb), R = *i*Pr, X = $PF_6$;
**2b**) A = ($\eta^6$-*p*-cymene), R = *i*Pr, X = I;

***Figure 2.*** Thiolato and sulfenato complexes studied herein.

Owing to the chirality of sulfur, four $^1$H NMR peaks (two AB spin systems) were observed for the aromatic protons of

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

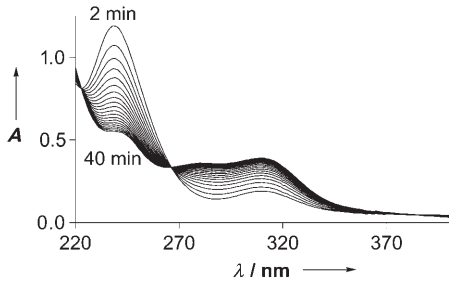



***Figure 3.*** UV/Vis spectra recorded at 298 K during the oxidation of thiolato complex **1a** (0.1 mM) to sulfenato complex **2a** by $H_2O_2$ (0.2 mM). Spectra were recorded 2 min after mixing, and then every 2 min.

*p*-cymene in **2b**. The methyl groups of the isopropyl sulfenato ligand in **2b** are also nonequivalent; peaks appear 0.29 ppm apart at $\delta = 1.50$ and 1.21 ppm. A similar splitting was observed for **2a**, which showed signals for the methyl groups at $\delta = 1.38$ and 0.91 ppm.

Pure samples of **2a** and **2b** were stable at pH 7 at ambient temperature in aqueous solution. Crystals of **2b** suitable for X-ray single-crystal analysis were obtained from a saturated solution in methanol/diethyl ether at 277 K overnight. The short intermolecular distance (O···O = 2.70 Å) between the sulfenato oxygen atom and the oxygen atom of the cocrystallized methanol is indicative of a hydrogen bond (Figure 4). A

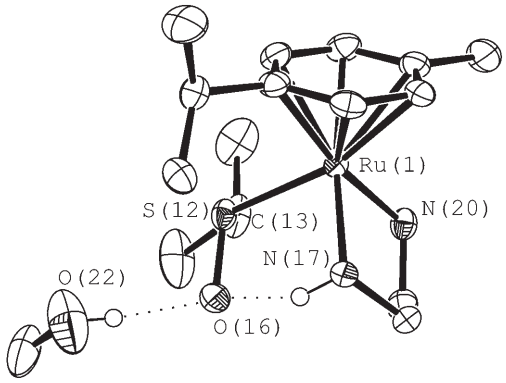



***Figure 4.*** ORTEP drawing (at 50% probability level) of the molecular structure of the sulfenato complex **2b**; hydrogen atoms (except those forming hydrogen bonds (D···A)) and the counter ion are omitted. Selected bond lengths [Å] and angles [°]: Ru(1)–S(13) 2.3790(8), Ru(1)–N(17) 2.122(3), Ru(1)–N(20) 2.142(3), S(12)–C(13) 1.823(4), S(12)–O(16) 1.552(2); N(17)···O(16) 2.74, O(22)···O(16) 2.70, N(17)-Ru(1)-N(20) 79.01(11), S(12)-Ru(1)-N(17) 83.65(7), S(12)-Ru(1)-N(20) 93.57(8).

second hydrogen bond is formed between N(17) (ethylenediamine NH) and the sulfenato oxygen atom O(16) (N···O = 2.74 Å), as indicated also by the small dihedral angle O(16)-S(12)-Ru(1)-N(17) of 7.8°. The sulfenato ligand is coordinated through the sulfur atom with a Ru–S bond length of 2.3790(8) Å, which is shorter than that in the related thiolato complex **1c** (Ru–S = 2.3936(6) Å, see the Supporting Information). In contrast, an elongation of the M–S(O) bond relative to M–S is observed for most sulfenato complexes.[9,21] The ability of the sulfenate ligand to form a strong hydrogen bond is in stark contrast to the behavior of thiolate ligands.

Interestingly, the only known Ru sulfenato complex is protonated on the oxygen atom, and the OH group is stabilized by strong hydrogen bonds.[5] In the case of the cationic complex **2b**, repulsion between the two positive charges should lead to a less basic sulfenate; consequently **2b** is not protonated, but is surprisingly basic ($pK_a = 3.37$, Figure 5 and the Supporting Information). This result is

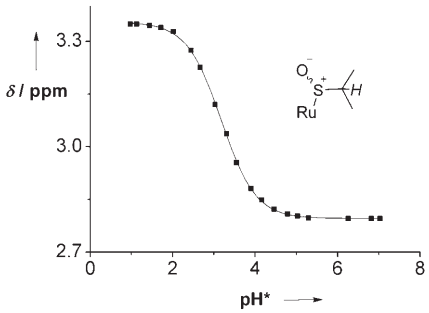



***Figure 5.*** Plot of chemical shift versus pH* (pH meter reading uncorrected for the effect of D on the glass electrode) for the Ru–S(O)C*H*Me$_2$ proton of complex **2b** (see the Supporting Information). The solid line corresponds to a computer best fit with a $pK_a$ value of 3.37 for protonation of the bound sulfenato ligand.

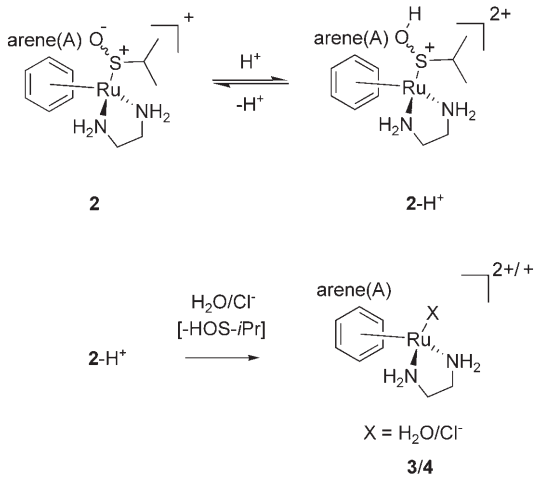
quite surprising, as the oxygen atom in complex **2b** is hydrogen-bonded to the nitrogen atom of the ethylenediamine (en) ligand, which should lower the electron density on the oxygen atom further.

To test stability under acidic conditions, a 3 mM solution of complex **2b** in water (pH 2.3, 310 K) was monitored by $^1$H NMR spectroscopy. After 24 hours, 40% of **2b** remained. When the *p*-cymene ligand was changed to hexamethylbenzene (hmb) the $pK_a$ value increased to 3.61, mainly as a result of the increased electron-donating ability of the arene (hmb). With this change in arene, the complex becomes more unstable towards acids. After 16 hours at pH 2.11 and 310 K, most of complex **2a** had reacted to give a mixture of two products.

To investigate the hydrolysis further, $^{15}$N-labeled complex **2a** was monitored by 2D [$^1$H,$^{15}$N]-HSQC NMR spectroscopy (see the Supporting Information). The cross-peaks were identical to those observed for a sample of the $^{15}$N-labeled chlorido complex **4a** dissolved in aqueous HCl (pH = 2.11), which partially hydrolyzes to **3a**. These data and the MS peaks indicate that indeed the hydrolysis of the sulfenato complex yields the reactive aqua adduct [($\eta^6$-hmb)Ru([$^{15}$N]en)($H_2O$)]$^{2+}$ (**3a**) as well as the chlorido complex [($\eta^6$-hmb)Ru([$^{15}$N]en)(Cl)]$^+$ (**4a**) (owing to the use of hydrochloric acid; Scheme 1).

Hence ruthenium sulfenato complexes appear to have a highly dipolar S=O bond with a relatively basic oxygen atom. In general, we can expect the oxygen atom of ruthenium sulfenato complexes to become more basic in uncharged or negatively charged complexes. Protonated complexes might

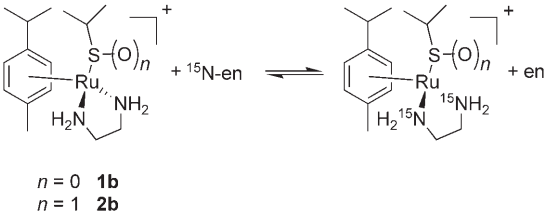
  




***Scheme 1.*** Hydrolysis of sulfenato complexes at low pH (HCl) through protonation of the sulfenato ligand.

be highly reactive and promote binding to DNA and other biological targets directly or through hydrolysis. Hydrolysis might be catalyzed by other Lewis acids, especially metal ions. For example, the binding of $Na^{+}$ [4] and $Zn^{2+}$ [6] as well as $Pt^{2+}$ [22] to the oxygen atom of sulfenates has been described in the literature.

Moreover ligand-centered oxidation of thiolates to sulfenato ligands also has a major influence on the stability of the whole complex. Strong cross-peaks assignable to $^{15}$N-labeled **1b** were found in the 2D [$^{1}$H,$^{15}$N] HSQC NMR spectrum of a mixture of [$^{15}$N]en and unlabeled **1b** after a few hours at ambient temperature. After 3 days at ambient temperature, the NH signals of **1b** had stronger clearly visible $^{15}$N satellites with a typical $^{1}J(^{15}N,^{1}H)$ coupling constant of approximately 75 Hz. This result indicates a relatively fast partial exchange of the en ligand in **1b** with $^{15}$N-labeled ethylenediamine in aqueous solution, whereas the same reaction occurs very slowly in case of the sulfenato complex **2b**. For **2b**, only weak signals were found in the 2D [$^{1}$H,$^{15}$N] HMQC NMR spectrum, and no NH $^{15}$N satellites were visible because of the very low natural abundance of the $^{15}$N isotope, indicating that the exchange of en ligand is very slow (Scheme 2).




***Scheme 2.*** Exchange of ethylenediamine is much faster for the thiolato complex **1b** ($n=0$) than for the sulfenato complex **2b** ($n=1$).

In conclusion, for first time we have succeeded in directly oxidizing a monodentate thiolato ligand to an S-bound sulfenato ligand. The π-bonded arene ligand and hydrogen-bond donor diamine ligand in the complex play significant roles in controlling the stability and reactivity of the $Ru^{II}$-bound sulfenate. Moreover, the sulfenato complexes **2a** and **2b** are readily protonated with $pK_a$ values of 3.37 and 3.61, respectively, and the protonated complexes can hydrolyze to form the corresponding chlorido and aqua complexes in which the organometallic metal–arene fragment remains intact. This provides a novel activation pathway of potential importance in the biological mechanism of action of ruthenium arene complexes.

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