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Lipophilic Technetium Complexes
VI. Neutral Oxotechnetium(V) Complexes with Monothiole/Tridentate Dithiole Coordination

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Abstract

Reaction of tridentate dithiole ligands HS–CH_2–CH_2–X–CH_2–CH_2–SH (HSXSH, X = O, S) and monothioles R–SH (thiophenoles, aliphatic thioles, mercaptoacetic acid ethylester) with Tc(V) gluconate (or other starting materials containing the oxotechnetium(V) core such as tetrachlorooxotechnetate) leads to a series of mononuclear, neutral complexes of the general formula TcO(SXS)(SR). In the absence of the monodentate thioles, dinuclear complexes of the general formula $(TcO)_2(SXS)_3$ are formed. Infrared, NMR, and UV–Vis data of the resulting compounds are reported. A concept for designing small-sized, neutral Tc complexes, involving the principle of common reaction of both a tridentate and a monodentate ligand with an appropriate Tc precursor, is proposed.

Introduction

Oxo complexes of Tc(V) have been under intensive study [1] in part with ligands containing sulphur donors. Most of the attention with regard to ligands has focussed on bidentate dithiole ligands which coordinate to the TcO^{3+} core by four donor atoms resulting in the well-known anionic oxotechnetium(V) complexes [2, 3]. Unlike this, tridentate thioles are not sufficient to stabilize the TcO^{3+} core to definite mononuclear species. Reaction of ligands of the general formula HSXSH (X = O, S) with the TcO^{3+} core should be of the form $TcO(SXS)^+$, leaving one open coordination site to potentially bind a monodentate ligand (Fig. 1). Alternatively, the available site could be involved in bridging to a second technetium in a dinuclear complex.

In this paper we report on the synthesis and characterization of dinuclear Tc(V) complexes of the tridentate ligands HS–CH_2–CH_2–X–CH_2–CH_2–SH (HSXSH, X = O or S) and a new class of mononuclear oxotechnetium(V) complexes in which the metal is coordinated to a tridentate dithiole ligand as well as to a monodentate thiole ligand. The synthesis and characterization of the first representative which contains 3-thiapentate-1,5-dithiole as tridentate ligand and thiophenole as co-ligand has been dealt with in a previous paper [4].

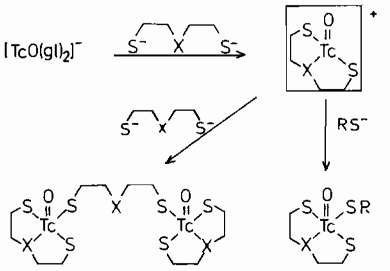

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Fig. 1. Formation of dinuclear complexes (**1a, b**) with tridentate ligands and mononuclear complexes (**2a–k**) with tridentate/monodentate thiole ligands.

Experimental

Methods

TLC was carried out on Silufol plates (Kavalier/CSSR) with acetone, acetone/methanol (1:4 vol./vol.), and water as eluent. The content of technetium was determined by liquid-scintillation counting.

Infrared spectra were recorded in KBr discs on a UR 20 spectrometer; UV–Vis spectra on a Specord M 40 of Carl-Zeiss Jena. ^1H NMR spectra were measured on a spectrometer WH 90 DS Bruker Spectrospin. All spectra were measured in $CDCl_3$.

Preparations

Tc(V) gluconate was prepared by stepwise addition of stannous chloride to an aqueous solution of pertechnetate in an excess of sodium gluconate as described in ref. 5.

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General procedure for the preparation of compounds in the carrier-added level

One ml Tc gluconate solution (0.6 μmol) is diluted with 0.5 ml of acetonitrile. A solution of 1 μmol HSXSH in 0.2 ml of acetonitrile (for preparation of **1a**, **1b**) or a solution of 0.6 μmol of HSXSH and 0.9 μmol of the thiophenole (or 1.5 μmol of the aliphatic thiole, respectively) in 0.1 ml of acetonitrile (for the preparation of **2a–k**) is added. The colour of the solution turns to red–brown. After stirring for 30 min, the mixture is extracted with 1 ml chloroform. The organic phase is washed twice with 1 ml water and dried over sodium sulphate.

General procedure for the preparation of crystalline compounds

A solution of 100 μmol HSXSH in 0.5 ml acetone (for preparation of **1a**, **1b**) or of 50 μmol of HSXSH and 75 μmol of the appropriate thiophenole (or 125 μmol mercaptoacetic acid ethylester) in 0.5 ml acetone (for preparation of **2a–k**) is added, dropwise, to a stirred aqueous–acetonic solution (2:1 vol./vol.) of 50 μmol Tc gluconate. The reaction mixtures become orange–brown and brown solids precipitate. The solids are dissolved in 5 ml acetone, filtered and reduced in volume to 2 ml. After addition of 1 ml of methanol and further reduction of volume to 0.5 ml red–brown crystals precipitate.

Results and Discussion

Tridentate dithiole ligands $HS-CH_2-CH_2-X-CH_2-CH_2-SH$ (HSXSH) undergo ligand exchange reactions with Tc gluconate. However, they are not sufficient to stabilize the TcO^{3+} core to definite mononuclear units, and the reaction yields dinuclear products **1a** (X = S) or **1b** (X = O) respectively (see below). When a mixture containing HSXSH and an additional monodentate thiole is added to Tc gluconate in aqueous/acetonitrile solution, new compounds **2a–k** (Table 1) are formed (Fig. 1) and compounds **1a** (or **1b**, respectively) are found as the main impurities in reaction mixture. To minimize the formation of dinuclear species, tridentate/monodentate molar ratios of 1:1.5 for aryl thioles and 1:2.5 for aliphatic thioles are chosen. Under these conditions, the yields of compounds **2a–k** (in reaction mixture) are about 80%. The yields of crystalline compounds **1a**, **1b**, **2a**, **2d**, **2g**, **2h**, **2i** are about 50–65%. The latter have been fully characterized by chemical and spectroscopical methods.

Characterization

The red–brown compounds are lipophilic, as indicated by their solubility in organic solvents such as acetone, chloroform or methylene chloride. Accordingly, therefore, they migrate on TLC plates with acetone or acetone/methanol as eluents, but do not migrate in water (see Table 1).

The results of elemental analysis including that of Tc of isolated compounds (see Table 2) indicate that **1a** and **1b** have a Tc/SXS ratio of 2:3 and that compounds **2a–k** contain both types of ligands corresponding to the general formula TcO(SXS)(SR).

Infrared spectra of the compounds (Table 3) show bands in the region of 2860–2980 cm^{-1} corresponding to C–H vibrations due to the tridentate ligand framework. Vibrations assigned to the Tc=O group do not differ too much from each other and fall in the region of 930–940 cm^{-1} with the exception of **2h**, in which a three-band pattern (960, 950 and 930

TABLE 1. Tc complexes with tridentate dithioles HSXSH (1) and additional monothiole ligands RSH (2): characterization of complexes formed at the carrier-added level

Complex	HSXSH X =	R–SH R =	r.f. in TLC[a] acetone	ac/me	water	UV–Vis[b] max (nm)
1a	S		0.8	0.4	0	463
1b	O		0.8	0.5	0	423
2a	S	C_6H_5	0.9	0.6	0	474
2b	S	p-$Cl-C_6H_4$	0.9	0.6	0	472
2c	S	p-$NO_2-C_6H_4$	0.9	0.7	0	470
2d	S	p-$CH_3O-C_6H_4$	0.9	0.7	0	488
2e	S	p-$CH_3OOC-C_6H_4$	0.9	0.7	0	473
2f	S	n-C_4H_9	0.9	0.7	0	463
2g	S	$C_2H_5OOC-CH_2$	0.9	0.8	0.1	465
2h	O	C_6H_5	0.9	0.7	0	434
2i	O	p-$CH_3OOC-C_6H_4$	0.9	0.6	0	435
2j	O	n-C_4H_9	0.95	0.6	0	425
2k	O	$C_2H_5OOC-CH_2$	0.95	0.7	0.1	425

[a] TLC on Silufol, ac/me = acetone/methanol 1:4. [b] Compounds extracted from the reaction mixture with chloroform.

TABLE 2. Melting points and analytical data of complexes **1** and **2**

Complex	Melting point (°C)	Analytical data found/calc. (%)			
		C	H	S	Tc
1a	decomp.	23.8/21.0	4.3/3.5	43.2/42.0	27.2/28.9
1b	148–149	23.7/22.6	3.9/3.8	30.2/30.1	30.8/31.0
2a	decomp.	see ref. 4			
2d	239–241	32.7/32.5	3.7/4.4	31.9/31.5	24.7/24.4
2g	111–112	24.7/24.8	3.5/3.9	33.2/33.3	26.1/25.7
2h	173–174	32.5/33.3	3.7/3.6	26.7/26.5	27.8/27.5
2i	190–191	34.8/34.5	3.6/4.3	22.9/25.0	22.2/23.7

TABLE 3. Infrared and electronic spectra of complexes **1** and **2**

Complex	Infrared (cm^{-1})			First intensive band in UV–Vis spectra[a]
	Tc=O	C=O	arom. C–H	
1a	930(sh)			463 (3.5)
1b	940(sh)			423 (3.4)
2a	935		760	474 (3.9)
2d	940		830	488 (3.2)
2g	940	1730		457 (3.6)
2h	[b]		750	434 (3.5)
2i	940	1720	820	441 (3.7)

[a] Peak positions in nm with lg molar absorptivities in parenthesis, compounds dissolved in chloroform. [b] Three bands at 930, 950, and 960 cm^{-1}.

TABLE 4. ^{1}H NMR data of complexes **2**

Complex	^{1}H NMR ($CDCl_3$) (ppm)				
	Signals of –SXS–		Signals of –SR		
2a	4.2m	8 H	7.2m	5 H	
2d	1.86–2.28m	4 H	7.61, 6.92	4 H	arom. H
	3.11–3.50m	2 H	3.84s	3 H	CH_3
	3.90–4.21m	2 H			
2g	2.09m	2 H	4.53s	2 H	S–CH_2
	3.36m	2 H	4.20q	2 H	–CH_2–CH_3
	3.86–4.25m	4 H	1.27t	3 H	–CH_2–CH_3
2i	3.22–3.66m	6 H	7.67, 8.03	4 H	arom. H
	4.82d	2 H	3.91s	3 H	CH_3

cm^{-1}) is observed. Shoulders in the Tc=O band of the dinuclear species **1a** and **1b** are due to the existence of two Tc=O groups. The presence of the monodentate co-ligand in the complex is indicated by additional peaks corresponding to ester group (**2g**, **2i**) or aromatic C–H bonds (**2a**, **2d**, **2h**), respectively.

The ^{1}H NMR data of the compounds are listed in Table 4. In general they confirm the presence of both types of ligands in the complex. The signals of the tridentate ligands fall in the region of about 1.8–4.2 ppm with the exception of **2i** with X = O, in which a signal (2 H) is shifted to low fields. As can further be seen, changes of the monodentate ligand are sensitively reflected by the SXS ligand pattern. The co-ligands show the expected signals which can be unambiguously assigned.

The UV–Vis spectra of all complexes are characterized by an intensive band in the 420–480 nm region (see Table 1) and additional absorptions at shorter wavelengths. The first intensive band is found to absorb in the 460–480 nm region for S_4 coordinated compounds, whereas compounds with oxygen containing ligands (X = O) are shifted to lower wavelengths (420–435 nm). The spectra of compounds prepared in the carrier-added level correspond to those of the isolated compounds (compare values in Table 1 and Table 3), which confirms the identity of the species formed at both concentration levels. Compared to the bis(dithiolato)oxotechnetium(V) complexes [2], the absorption of the S_4-coordinated complexes described here are at higher wavelengths (40 to 60 nm). The substituent R in the monodentate ligand has no significant influence: aryl-substituted compounds absorb only some nm longer than the corresponding alkyl compounds.

Compounds **2a–k** do not undergo exchange reaction, e.g. with dithioles. Furthermore, their stability is underlined by the fact that ester hydrolysis is the dominating reaction when **2g** is dissolved in methanolic potassium hydroxide. It would seem that the complex core was not attacked under these conditions. Tertiary phosphines reduce Tc under abstraction of oxygen from the Tc=O group and formation of compounds which contain both sulphur and phosphine ligands [6].

These observations show that compounds **1a** and **1b** are dinuclear species of the general formula $(TcO)_2(SXS)_3$, in which two mononuclear $[TcO(SXS)]^+$ units are bridged by the dithiole ligand (Fig. 1). The synthesis of the dinuclear compounds is in accordance with results reported by Ravert *et al.* [7], who also found dinuclear oxotechnetium(V) complexes of tridentate SNS donor ligands HS–

$CH_2-CH_2-NR-CH_2-CH_2-SH$ with R = ethyl or butyl.

Compounds **2a–k** belong to a new type of Tc complexes containing two different sulphur donor ligands and have the general formula TcO(SXS)(SR). The dominant feature is that the combination of a tridentate ligand involving an ether or thioether group with a variable monodentate thiole leads to neutral species. Up to now there have been few complex compounds containing thioether groups [8, 9] and, as far as we know, the oxygen containing species **1b** and **2h–k** (X = O) are the first representatives of Tc complexes in which ether groups are involved in a definite coordination sphere.

Furthermore, because these lipophilic complexes have low molecular weights and are able to be modified in their molecular periphery either by changing the tridentate or the monodentate ligand, the compounds are favoured as potential agents for brain studies. Investigations on the *in vivo* behaviour of these and similar compounds will be published.

The 3 + 1 Principle

The synthesis described here is a special example of a more general reaction principle [10] (Fig. 2). Unlike to bidentate O- or S-donor ligands HXXH (X = O, S), which coordinate to the TcO^{3+} core via a four (2 + 2) donor atom set resulting in well-known anionic oxotechnetium complexes $[TcO(XX)_2]^-$ [2, 3, 11] tridentate ligands HXZXH require additional monodentate ligands in order to stabilize the TcO^{3+} core by a (3 + 1) donor atom set. Otherwise, the intermediate, resulting from the reaction of HXZXH with TcO^{3+} and having the form $[TcO(XZX)]^+$, is stabilized by the tridentate ligand itself to give dinuclear species.

There are some advantages in the fact that two different kinds of ligands are present in the molecule. The most important advantage from the radiopharmaceutical design point of view is the high degree of variability achieved either by modifying the tridentate or the monodentate ligand, which allows a fine-tuning of molecular properties. Variation of RSH is demonstrated in this article. Investigations of complexes derived from tridentate Schiff bases/monothioles will be published [12].

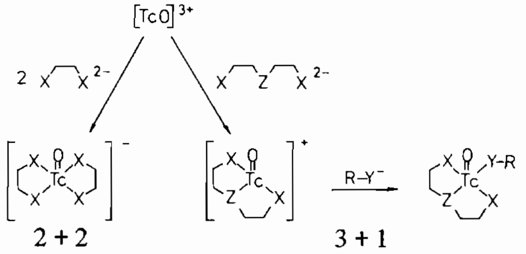

Fig. 2. Reaction scheme of formation of neutral oxotechnetium(V) complexes according to the (3 + 1) principle (X = O, S; Z = NR, O, S, C=N; Y = O, S, NR).

Furthermore, this reaction principle is not necessarily limited to ligands with sulphur donor atoms. It should also be possible to expand it to O and N donor ligands as well as to neutral ligands. A limiting factor is the competition between both types of ligands which occurs during the initial reaction towards Tc. Thus, comparable reactivity of both types of ligands is required in order to obtain mixed-ligand compounds. Otherwise formation of complexes derived from the individual tridentate or monodentate ligands may be preferred.

In general, the concept gives a new and fruitful approach to the designing of Tc compounds preferably used for radiopharmaceutical studies.

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