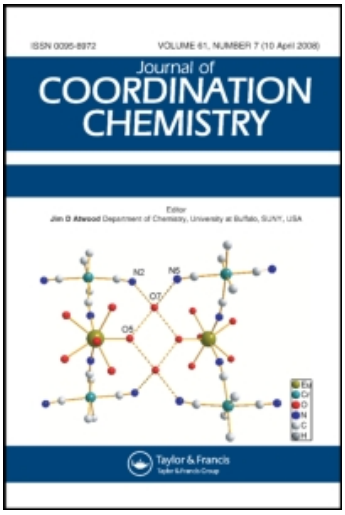

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THE CHEMISTRY OF RHENIUM AND TECHNETIUM. PART II. SCHIFF BASE COMPLEXES WITH POLYFUNCTIONAL AMINO ACIDS

Jan G. H. Du Preez[a]; Thomas I. A. Gerber[a]; Pieter J. Fourie[b]; André J. Van Wyk[b]
[a] Uranium Chemistry Research Unit, University of Port Elizabeth, Port Elizabeth, Republic of South Africa [b] Nuclear Development Corporation, Private Bag X256, Pretoria, Republic of South Africa

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THE CHEMISTRY OF RHENIUM AND TECHNETIUM. PART II.†. SCHIFF BASE COMPLEXES WITH POLYFUNCTIONAL AMINO ACIDS

JAN G.H. DU PREEZ, THOMAS I.A. GERBER,‡
Uranium Chemistry Research Unit, University of Port Elizabeth, P.O. Box 1600, Port Elizabeth, 6000, Republic of South Africa

and

PIETER J. FOURIE and ANDRÉ J. VAN WYK
Nuclear Development Corporation, Private Bag X256, Pretoria, 0001, Republic of South Africa
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Amino acid Schiff base technetium(V) complexes of salicylaldehyde with *l*-cysteine, *l*-serine, *l*-histidine, *l*-threonine, *l*-glutamic acid and *l*-tryptophan have been prepared by direct reaction and by constituent combination. The amino acid part of the ligands coordinates to the technetium through the carboxylate group, while the other available functional group of the amino acids plays a more minor role as a blocking group or in intramolecular bonding.

INTRODUCTION

In a previous report some uncommon properties of technetium(V) complexes of Schiff base type ligands have been described.[1] This work has now been extended to include Schiff bases containing amino acids as chelating agents for Tc(V), especially in the light of its possible nuclear medicinal application as mentioned before.[1]

This was done, first, by increasing the multidentate character of the Schiff base ligand and at the same time, increasing it from a potentially dianionic to a trianionic species, and secondly, by combining the Schiff base properties and amino acid properties in a single chelate, and thus possibly providing a system which could link the technetium to the required biological system in the body (heart muscle, brain tissue, *etc.*).

Previous studies of Schiff base amino acid complexes have been concerned mainly with bidentate amino acids,[2,3] or with complexes of transition metals other than technetium.[4-8] Schiff bases in which one of the coupling components of the base is an amino acid, readily form complexes with transition metals.[9] When an additional complexing group such as a phenol is present, it appears that the basic Schiff base arrangement remains unchanged and the additional group acts in various ways,[8] such as a blocking group, by coordination to the metal as an additional ligand, or by bridging two of the Schiff base entities by coordination to a second metal atom.

The characterisation of technetium Schiff base complexes with potentially terdentate amino acids would therefore extend the range of Schiff base complexes available and would be useful in defining the role of the additional potentially complexing groups. The isolation of this type of compound may also lead to the construction of technetium radiopharmaceuticals which could be used as radiotracers in nuclear medicine. The

†Part I in reference 1.
‡To whom correspondence should be directed.

preparation and characterisation of technetium(V) Schiff base complexes of a range of potentially tridentate amino acids with salicylaldehyde has, therefore, been undertaken.

EXPERIMENTAL

Technetium as $NH_4[TcO_4]$ was purchased from the Oak Ridge National Laboratory as the dry salt. ^{99}Tc is a weak β-emitter (0.292 keV); therefore, all manipulations were carried out in a radiation laboratory with a monitored fume hood. Personnel wore disposable laboratory coats and gloves at all times. Radioactive wastes, both liquid and solid, were disposed in special receptacles.

Infrared spectra were recorded on a Beckman IR 4250 grating spectrophotometer in the range 4000-250 cm^{-1} in KBr pellets. Optical spectra were obtained with a Perkin-Elmer 330 spectrophotometer. Melting points were measured on a Mettler FP1 apparatus. Conductivity measurements were performed in the appropriate solvents using a Metrohm E518 conductometer. Thermal studies were carried out using a Perkin-Elmer thermogravimetric balance and a System 4 Microprocessor Controller. Elemental analyses were performed using a Heraeus Rapid Analyser.

All solvents used were purified and dried by standard methods. Salicylaldehyde (Riedel-de-Haën) was vacuum distilled before use, and the amino acids were obtained from Merck and used without further purification.

The Schiff base amino acid ligands were prepared by the addition of equimolar quantities of the appropriate amino acid dissolved in a minimum quantity of distilled water to salicylaldehyde in ethanol. The product either precipitated almost immediately or crystallized on volume reduction.

Preparation of Complexes.

Oxo-(N-salicylidine-cysteine)technetium(V) dihydrate. 8.25×10^{-4} mol of salicylaldehyde (0.1007g) was dissolved in a 5 cm^3 ethanol, and mixed with 2.2 cm^3 of a 0.362 mol dm^{-3} aqueous $NH_4[TcO_4]$ solution. The slow addition of a freshly prepared solution of 0.555 g $Na_2S_2O_4$ (3.2×10^{-3} mol) in 10 cm^3 of a 0.6 mol dm^{-3} NaOH solution was followed by the addition of 0.0992 g (8.20×10^{-4} mol) *l*-cysteine in 15 cm^3 of a 0.6 mol dm^{-3} aqueous NaOH solution. Extraction of the solution with tetrahydrofuran and evaporation of the solvent under vacuum yielded a brown precipitate. The residue was recrystallized from water and methanol [Yield = 46%; m.p. $> 260^{\circ}C$].

Oxo-(N-salicylidine-histidine) technetium(V) dihydrate. 1.60×10^{-3} mol of *N*-salicylidine-histidine was dissolved in 50 cm^3 of methanol and to this was added 2.5 cm^3 of a 1 mol dm^{-3} $[CH_3O]Na$ solution (23 g sodium dissolved in 1000 cm^3 methanol). To this was added 2.2 cm^3 of a 0.362 mol dm^{-3} aqueous $NH_4[TcO_4]$ solution, followed by a freshly prepared aqueous solution of 0.555 g $Na_2S_2O_4$. Stirring this solution for 5 minutes gave rise to a brown precipitate, which was filtered and washed with methanol. The residue was recrystallized from water and methanol [Yield = 58%; m.p. $> 260^{\circ}C$].

The technetium complexes of *N*-salicylidine-threonine, *N*-salicylidine-glutamic acid, *N*-salicylidine-tryptophan and *N*-salicylidine-serine were prepared similarly, except that the tryptophone-containing complex was precipitated by addition of tetraphenylborate.

RESULTS AND DISCUSSION

Pertechnetate reacts with the potentially tetradentate amino acid Schiff bases in water or methanol, using sodium dithionite as reducing agent, to form complexes of the general formula $TcOL.nH_2O$, (where L = amino acid Schiff base). The properties and elemental

analyses of these complexes are given in Table I. The complexes were all soluble in water, and the electrical conductivities of 10^{-3} mol dm^{-3} aqueous solutions indicated that all the complexes, except [TcO(saltryp)] BPh_4, were undissociated. Magnetic studies indicated that all the complexes are diamagnetic.

Infrared data are given in Table II. All the complexes, except TcO(salcys).$2H_2O$, exhibit an intense infrared absorption in the range 965-975 cm^{-1}, which has been attributed to the Tc=0 group. This range differs appreciably from the 0=Tc=0 stretching frequencies observed in dioxotechnetium(V) complexes, which typically occur in the range 780-880 cm^{-1}.[10,11] Stretching frequencies in the range 920-1020 cm^{-1} have been observed[12,13] for a number of technetium(V) compounds containing the TcO^{3+} group and can be considered as useful evidence of the presence of this nucleus. The strong absorption in the infrared spectrum at 892 cm^{-1} for TcO(salcys).$2H_2O$, which we ascribe to the Tc=0 vibration, occurs at a lower wave-number than the general range for monooxotechnetium(V) complexes. This observation is of particular interest. Replacement of an oxygen atom (for example as in salser) with a sulphur donor atom (as in salcys) in distorted square pyramidal systems (an oxo group in axial position and four coordinating atoms in the square plane) leads, without exception, to a reduction of the Tc=0 stretching frequency in anionic (four monanionic donor atoms in the square plane) as well as neutral monooxotechnetium(V) complexes (three monanionic donor atoms in the plane).[1,14] The extent of the reduction of the technetium bond order (stretching frequency) could be expected to be somewhat lower in a neutral complex, although hardly as much as that found for TcO(salcys).$2H_2O$. This phenomenon should in our view be interpreted in terms of the fact that the thiolic sulphur donor atom in salcys can be regarded as part of a conjugated system, as shown in (*I*), which could increase the Tc-S bond order significantly, resulting in a large axial Tc=0 bond weakening. The nature of the planar donor atoms could also be expected to be a significant factor. In the case where an O_3N planar

TABLE I
Compounds Prepared and Analyses.[a]

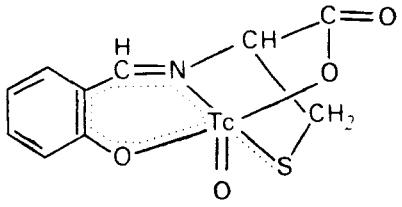
Compound	% Found			% Calculated		
	C	H	N	C	H	N
TcO(salcys).$2H_2O$	32.1	3.4	3.5	32.2	3.2	3.8
TcO(salser).$2H_2O$	33.4	3.4	3.7	33.6	3.4	3.9
TcO(salhis).$2H_2O$	38.0	3.7	10.5	38.3	3.5	10.3
TcO(salthr).$2H_2O$	35.5	3.8	3.7	35.6	3.8	3.8
TcO(salglut).1.$5H_2O$	37.1	3.5	3.4	36.9	3.4	3.6
[TcO(saltryp) (H_2O)]BPh_4.$2H_2O$	62.4	4.7	5.0	62.3	5.1	5.2

[a]Sal = salicylaldehyde; Cys = cysteine; Ser = serine, His = histidine; Thr = threonine, Glut = glutamic acid, Tryp = tryptophan.

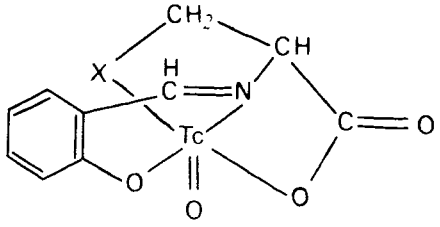
TABLE II
Selected Spectral Data (cm^{-1}) for the Complexes.

	νTc=0	νC=N	νaCOO	νsCOO	νOH
TcO(salcys).$2H_2O$	892	1638	1603	1422	3465
TcO(salser).$2H_2O$	972	1635	1615	1418	3430
TcO(salhis).$2H_2O$	970	1640	1606	1441	3385
TcO(salthr).$2H_2O$	967	1640	1614	1426	3400
TcO(salglut).1.$5H_2O$	965	1639	1621 1592	1431	3380
[TcO(saltryp) (H_2O)]$^+BPh_4^-$.$2H_2O$	973	1636	1607	1406	3410

chromophore, as in TcO(salser).$2H_2O$, is replaced by an O_2NS chromophore (in TcO salcys.$2H_2O$), the influence of the anionic sulphur donor atom and resultant significant increase in covalence of the Tc-S bond (and resultant weakening of the axial Tc=O bond) is underlined by the presence of the two or three electronegative oxygen atoms which will have much higher ionic interactions with the technetium(V) in these systems.



(I)



(II)

The infrared spectrum of TcO(salcys).$2H_2O$ indicates a coordinated azomethine group ($\nu_{C=N}$ at 1638 cm^{-1}) and a coordinated carboxylate (ν_{COO^-} at 1603 cm^{-1}). The ν_{O-H} band observed in the free ligand disappears upon coordination, and the ν_{C-O} phenolic stretch shifts to higher energy at 1526 cm^{-1} in the complex, indicating deprotonation and coordination of the phenolic oxygen atom. In the solid state the S-H stretching vibration at 2520 cm^{-1} in free salcys is absent in the complex, and a band at 568 cm^{-1} in the complex is likely to be that of the ν_{C-S} vibration (535 cm^{-1} in the ligand salcys). This suggests that the sulphur atom is coordinated to the technetium(V) ion. Elemental and thermal analyses suggest a dihydrate. It seems unlikely that these water molecules will be bonded in a sixth coordination position due to the large *trans* effect of the oxo group which leads to a vacant *trans* coordination site,[15] although in solution this site presumably contains a loosely bonded solvent molecule. There is thus sufficient evidence to suggest a distorted square pyramidal configuration around Tc(V) with the oxo group occupying the apical coordination site. For the serine complex a coordinated azomethine group ($\nu_{C=N}$ at 1635 cm^{-1}) and a coordinated carboxylate (ν_{COO}-at 1615 cm^{-1}) are indicated in the infrared spectrum. Elemental and thermal analyses suggest a dihydrate.

The infrared spectrum of the dihydrate salicylidine-histidine Schiff base complex TcO(salhis).$2H_2O$ again suggests a coordinated azomethine ($\nu_{C=N}$ at 1640 cm^{-1}) and coordinated carboxylate (ν_{COO^-} at 1606 cm^{-1}). The i.r. spectrum of the imidazole group was too complex to help in assessing its role in bonding, but it is assumed that it is the imidazole nitrogen which occupies the fifth bonding position as is the case in other

related complexes of biological importance. Thermal analysis of this complex indicates a dihydrate, with two water molecules (9.25% of molecular mass) being removed at 90°C (9.40% experimentally). The threonine-containing complex exhibits an infrared vibration at 1640 cm^{-1} (coordinated azomethine) and a peak at 1614 cm^{-1} (coordinated carboxylate). Elemental analysis and thermal balance results suggest a dihydrate.

For the hydrated glutamic acid Schiff base complex, the infrared spectrum again suggests a coordinated azomethine at 1639 cm^{-1}, and two coordinated carboxylate groups at 1621 cm^{-1} and 1592 cm^{-1}. Thermogravimetric studies indicate a loss of one water molecule (4.71% experimentally against 4.61% theoretically) at 70°C and half a water molecule at 94°C (2.22% exp.; 2.31% theor.)

The tryptophan Schiff base complex prepared is isolated as a trihydrate. There is a loss of two water molecules at 70°C and another at 230°C. This complex is a 1:1 electrolyte in aqueous solution, and the i.r. spectrum indicates a coordinated azomethine and a coordinated carboxylate. There is little evidence that the indole ring is complexed to the metal. It would, however, be expected to play a part as a blocking group in the crystal packing and there is an additional indole ring vibration at 3540-3600 cm^{-1}, possibly due to an interaction between the indole and an adjacent molecule. Based on this evidence one can thus assume a cationic five-coordinate technetium(V) complex, with one water molecule (that is lost at 230°C) coordinated to the metal. On the basis of all the available evidence, the most likely structure for these technetium(V) complexes, except $[TcO(saltryp)(H_2O)]^+$, is five-coordinate as shown in (*II*).

Electronic absorption spectral data for the complexes in aqueous solution are listed in Table III. The spectra of the complexes are characterised by a well defined band in the UV region, and at least one moderately intense band in the visible region. In all the complexes there is an intense band in the region 260-295 nm despite the different nature of the chromophoric system of the ligands. The weaker bands in the visible region by virtue of position and intensity may be due to d-d transitions.

In conclusion, if a comparison is now made between the action of the dianionic potentially terdentate Schiff base type chelates (L_1) studied previously[1] and the trianionic ligands obtained by combining the Schiff type with an amino acid (L_2), it becomes clear that the greater overall denticity of the latter coordinatively saturates the Tc(V) already as a pentacoordinate complex (monooxo TcL_2) in which the Tc=0 stretching frequency in the case of oxygen donor ligands are in the commonly experienced region (920-1020 cm^{-1}). By replacing an anionic oxygen atom, however, by an anionic sulphur atom in the chelate, the covalent interaction and electron transfer to the metal in the planar region is greatly increased, leading to a unusually large weakening of the Tc=0 bond (uncommonly low Tc=0 stretching frequency) for monooxo Tc(V) species. A similar treatment of the dianionic chelate ligands L_1 in the previous report[1] gives rise to significant bond weakening in the dioxo-Tc(V) interaction, rather than a lowering of the coordination number.

TABLE III
Electronic Spectral Data for the Amino Acid Schiff Base Technetium(V) Complexes in Water at 20°C

$TcO(salcys).2H_2O$	377(7900),	347sh,	263(9200)
$TcO(salser).2H_2O$	499(600),	290(1370)	
$TcO(salhis).2H_2O$	508(950),	434(710),	294(1920)
$TcO(salthr).2H_2O$	490(150),	317(530),	285(590)
$TcO(salglut).1.5H_2O$	425(610),	287(940)	
$[TcO(saltryp)(H_2O)]^+.BPh_4^-.2H_2O$	425(1200),	364(1500),	267(6800)

[a]Wavelengths of maxima given with extinction coefficients (M^{-1} cm^{-1}) in parentheses.

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