DALTON

Complexes of rhodium with thiobis(ethylenenitrilo)tetraacetic acid; a potential bifunctional chelate for use in radiotherapy ‡

Nigel A. Powell,*,†,[a] Angela M. Hill,[b] William Levason[b] and Michael Webster[b]

[a] *Johnson Matthey Technology Centre, Blount's Court, Sonning Common, Reading RG4 9NH, UK*
[b] *Department of Chemistry, University of Southampton, Southampton SO17 1BJ, UK*

Reaction of rhodium trichloride with the potential bifunctional chelating agent thiobis(ethylenenitrilo)tetraacetic acid (H_4tedta) gave the complex $[Rh(H_3tedta)Cl_2]\cdot H_2O$. Both chloride ligands are readily lost on refluxing in water, to give $[Rh(Htedta)]\cdot 3H_2O$ which has been characterised by an X-ray study. Further reaction with dilute HX (X = Cl, Br or I) led to the monohalides $[Rh(H_2tedta)X]\cdot nH_2O$ shown by $^{13}C\text{-}\{^1H\}$ NMR spectroscopy to have halide *trans* to sulfur. In contrast, thiocyanate is shown to bind *trans* to nitrogen. The complexes represent the first isolated mononuclear compounds of this thioether-containing analogue of ethylenediaminetetraacetate.

The nuclide ^{105}Rh has been proposed as being suitable for radiotherapy in cancer treatment.[1] It emits moderate-energy β particles (560 keV, ≈70%; 250 keV, ≈30%) and a γ ray suitable for imaging (319 keV, 19%) and has a half-life of 35.5 h. These favourable nuclear properties are complemented by the kinetic inertness of rhodium complexes which should minimise loss of the radionuclide from its carrier molecule *in vivo*, a distinct advantage over other radiotherapy candidates such as ^{90}Y and ^{131}I.[2,3]

An important aspect in the implementation of a metallic radiotherapeutic isotope is the development of a suitable bifunctional chelate, *i.e.* a molecule which will act both as a ligand to the radionuclide and as a linker to the desired carrier molecule. Typical examples of bifunctional chelates include diethylenetriaminepentaacetic acid (H_5dtpa)[4] and its macrocyclic analogues.[5] Previous studies with rhodium have described several such ligands, examples being oximes[6] and linear[7] and macrocyclic[8] amines. These reports demonstrate the drawback of the kinetic inertness of rhodium in that hot (90 °C) or refluxing conditions are required to cause reaction. Consequently, if the carrier moiety is heat-sensitive such as an antibody fragment or peptide, a two-step reaction sequence has to be utilised in which the initially formed complex is then linked to the carrier. This is inconvenient for use in a radiopharmacy where a single-step reaction is needed.

We were interested in developing ^{105}Rh as a radiopharmaceutical by designing bifunctional ligands with greater affinity for the metal, thus allowing the use of lower reaction temperatures. The approach adopted was to incorporate 'soft' thioether donors into ligand systems which are already utilised.[9] One compound selected for investigation was thiobis(ethylenenitrilo)tetraacetic acid (H_4tedta), a thioether-containing analogue of ethylenediaminetetraacetic acid (H_4edta) and H_5dtpa. Previous studies with it have mainly concerned the solution stability with such metals as calcium, cadmium and mercury,[10] lanthanides[11] and chromium,[12] and the crystal structure of a dicopper complex has been published.[13] As, to our knowledge, there are no previous reports of complexes of H_4tedta with rhodium, we undertook to examine the coordination chemistry of this system.

† *Present address:* Amersham International plc, Amersham Laboratories, White Lion Road, Amersham, Bucks. HP7 9LL, UK.
‡ *Non-SI unit employed:* eV ≈ 1.60 × 10^{-19} J.

Experimental

The $^{13}C\text{-}\{^1H\}$ NMR spectra were recorded on Bruker AM360 or JEOL GSX270 spectrometers with chemical shifts reported relative to $SiMe_4$, and ^{103}Rh NMR spectra on a Bruker AM360 instrument using Ξ = 3.16 MHz as zero reference. All solution measurements (NMR and UV/VIS) were made in aqueous solutions containing potassium phosphate buffer. Other physical measurements were made as described previously.[14] Microanalyses were obtained from the microanalytical laboratories of Imperial College or Strathclyde University.

Preparations

H_4tedta·H_2O. Solutions of sodium chloroacetate (77.8 g, 0.67 mol) in water (125 cm^3) and sodium hydroxide (26.7 g, 0.67 mol) in water (75 cm^3) were simultaneously added dropwise over 30 min to a refluxing solution of bis(2-aminoethyl) sulfide (20 g, 0.17 mol) in water (100 cm^3). After the addition was complete, refluxing was continued for 60 min. Ethanol (750 cm^3) was added to the cooled solution yielding an orange oil which was separated and acidified with concentrated hydrochloric acid to pH < 1. Sodium chloride immediately precipitated and was filtered off. The filtrate was set aside for 3 d to yield a white mass. The supernatant was decanted off and the solid washed well with water, filtered off, rinsed with ethanol and diethyl ether and dried *in vacuo* (17.22 g, 27%) (Found: C, 39.60; H, 6.15; N, 7.75. $C_{12}H_{22}N_2O_9S$ requires C, 38.90; H, 5.95; N, 7.55%). ^1H NMR (D_2O–NaOD): δ 2.66 (m, 4 H), 2.75 (m, 4 H) and 3.20 (s, 8 H). IR (KBr disc): 3428m, 3093m, 3010m, 1730 (sh), 1687s, 1639s, 1462m, 1380s, 1225w (br), 1013w (br), 840m (br) and 551 m cm^{-1}. Further quantities of the product precipitated from the supernatant over several days.

$[Rh(H_3tedta)Cl_2]\cdot H_2O$. Rhodium trichloride trihydrate (0.5 g, 2.0 mmol) and H_4tedta (0.74 g, 2.0 mmol) were refluxed together in water (30 cm^3) for 30 min. The solution was concentrated to *ca.* 10 cm^3 and on cooling an orange-yellow precipitate formed. This was filtered off, rinsed with water (5 cm^3), ethanol (10 cm^3) and diethyl ether (20 cm^3) and dried *in vacuo* (0.7 g, 65%) (Found: C, 26.35; H, 4.05; Cl, 12.80; N, 5.05. $C_{12}H_{21}Cl_2N_2O_9RhS$ requires C, 26.5; H, 3.9; Cl, 13.05; N, 5.2%). IR: 3598w, 3497m, 3424w, 2996m, 2501m (br), 1916m (br), 1747s, 1618s, 1559s (br), 1387s, 1255s, 1075w, 1042w, 978w, 898m, 838m, 493w and 385w cm^{-1}. UV/VIS (H_2O): 26 200 cm^{-1} (ε/dm^3 mol^{-1} cm^{-1} 98).

[Rh(Htedta)]·2H$_2$O. The complex [Rh(H$_3$tedta)Cl$_2$]·H$_2$O (0.7 g, 0.17 mmol) was refluxed in water (70 cm^3) until a clear yellow solution was formed. The volume was reduced to 25 cm^3 and on standing yellow crystals precipitated. These were recrystallised from hot water (0.4 g, 61%) (Found: C, 29.6; H, 4.0; N, 5.7. $C_{12}H_{21}N_2O_{10}RhS$ requires C, 29.6; H, 4.3; N, 5.8%). IR: 3583w, 3441m, 2977w, 2523vw, 2014w, 1724m, 1673 (sh), 1644s, 1625 (sh), 1373m, 1335m, 1239m, 896w, 768w, 690w and 348w cm^{-1}. UV/VIS (H$_2$O): 26 900 cm^{-1} (ε 483 dm^3 mol^{-1} cm^{-1}).

[Rh(H$_2$tedta)Cl]·H$_2$O. The complex [Rh(Htedta)]·2H$_2$O (0.2 g, 0.4 mmol) was dissolved in boiling water (12 cm^3) and concentrated hydrochloric acid (3 cm^3) added. A yellow precipitate formed after a few minutes. The mixture was refluxed for 2 h, filtered whilst hot and the yellow solid washed successively with water (10 cm^3), ethanol (10 cm^3) and diethyl ether (20 cm^3), and dried *in vacuo* (0.07 g, 45%) (Found: C, 28.5; H, 3.7; Cl, 7.8; N, 5.5. $C_{12}H_{20}ClN_2O_9RhS$ requires C, 28.5; H, 4.0; Cl, 7.0; N, 5.5%). IR: 3457m, 3004m, 1736s, 1637s, 1621 (sh), 1428m, 1392s, 1232m, 1204s, 1103w, 1000w, 917w, 790w, 712w, 625w and 402w cm^{-1}. UV/VIS (H$_2$O): 25 600 cm^{-1} (ε 900 dm^3 mol^{-1} cm^{-1}).

The complex [Rh(H$_2$tedta)Br] was prepared similarly from [Rh(Htedta)]·2H$_2$O (0.2 g), water (10 cm^3) and hydrobromic acid (48%, 3 cm^3), yield 41% (Found: C, 27.5; H, 3.4; Br, 14.7; N, 5.3. $C_{12}H_{18}BrN_2O_8RhS$ requires C, 27.1; H, 3.4; Br, 15.0; N, 5.3%). IR: 2973m, 1735s, 1619s, 1425m, 1388s, 1230m, 1200s, 1101w, 999w, 916w, 788w, 711w, 623w and 397w cm^{-1}. UV/VIS: 25 300 cm^{-1} (ε 1205 dm^3 mol^{-1} cm^{-1}).

The complex [Rh(H$_2$tedta)I]·2H$_2$O was prepared similarly from [Rh(Htedta)]·2H$_2$O (0.2 g), water (10 cm^3) and hydroiodic acid (50%, 3 cm^3). The dark solution produced was filtered, the brown solid isolated and washed as above. Yield 65% (Found: C, 23.5; H, 2.9; N, 4.4. $C_{12}H_{22}IN_2O_{10}RhS$ requires C, 23.4; H, 3.6; N, 4.5%). IR: 3437m, 3005m, 1732s, 1624s, 1424m, 1382s, 1230m, 1194s, 1098w, 1000w, 915w, 785w, 708w, 467w, 393w and 349w cm^{-1}. UV/VIS (H$_2$O): 22 600 (sh) and 30 300 cm^{-1} (ε 1140 dm^3 mol^{-1} cm^{-1}).

K$_2$[Rh(tedta)(NCS)]·2H$_2$O. The complex [Rh(Htedta)]·2H$_2$O (0.2 g, 0.4 mmol) was dissolved in the minimum amount of boiling water (30 cm^3) and KSCN (0.115 g, 1.2 mmol) added. The mixture was refluxed for 2 h, concentrated to *ca.* 15 cm^3, cooled and filtered. Methanol (15 cm^3) was added slowly to the filtrate causing immediate precipitation of a yellow solid. This was filtered off, rinsed with water (5 cm^3), ethanol (10 cm^3) and diethyl ether (10 cm^3), and dried *in vacuo* (0.117 g, 51%) (Found: C, 25.1; H, 3.1; K, 12.0; N, 6.8. $C_{13}H_{20}K_2N_3O_{10}RhS_2$ requires C, 25.0; H, 3.6; K, 12.5; N, 6.7%). IR: 3414s, 2983m, 2102s [ν(CN)], 1640s, 1371m, 1206w, 1097w, 903m, 792w, 618m and 480w cm^{-1}. UV/VIS: 27 100 cm^{-1} (ε 870 dm^3 mol^{-1} cm^{-1}).

Crystal structure determination

Air-stable pale yellow crystals of [Rh(Htedta)]·3H$_2$O were grown from the reaction mixture. The X-ray data were recorded at room temperature using a Rigaku AFC7S diffractometer equipped with graphite-monochromated Mo-Kα radiation and a crystal of dimensions 0.17 × 0.12 × 0.10 mm.

Crystal data. $C_{12}H_{17}N_2O_8RhS·3H_2O$, M_r = 506.27, orthorhombic, space group $Pna2_1$, a = 7.185(2), b = 16.687(1), c = 14.631(1) Å, U = 1754.1(5) Å^3, Z = 4, D_c = 1.916 g cm^{-3}, F(000) = 1032, λ(Mo-Kα) = 0.710 69 Å, T = 300 K, μ(Mo-Kα) = 10.9 cm^{-1}.

Cell dimensions were obtained from 24 high-angle reflections (20.3 < 2θ < 33.9°) and the intensities of 1816 reflections were recorded (5 < 2θ < 50°; h 0–8, k 0–19, l −17 to 0) in ω–2θ mode. Data reduction with a ψ-scan empirical absorption correction (transmission: minimum 0.81, maximum 1.00) and decay correction (0.4%) gave 1416 unique observations of which 1087 with $F > 3\sigma(F)$ were used in the refinement. The space group from the absences was $Pna2_1$ (no. 33) or $Pnam$ (no. 62) of which the former was established from the analysis. Reflections in four parity groups were weak indicating a pseudo-C lattice. The Rh and S atom positions were readily established from the Patterson synthesis but their positions with y *ca.* 0.0 gave an electron-density map following a structure-factor calculation which had a (pseudo) mirror plane. Problems in the development of the model arose from this mirror but eventually a set of atomic positions was obtained. Hydrogen atoms bonded to C were introduced in calculated positions [d(C–H) 0.95 Å]. Full-matrix least-squares refinement minimising $\Sigma w\Delta^2$ gave R = 0.036 [174 parameters, 1087 reflections, $w^{-1} = \sigma^2(F) + 0.0005F^2$, anisotropic (Rh, S, O) and isotropic (N, C, H) atoms, maximum |shift/error| = 0.03, R' = 0.041]. The residual electron density was in the range 0.54 to −0.68 e Å^{-3}. No satisfactory model was found for the hydrogen atoms bonded to O. The absolute configuration for the crystal examined is as reported based on refinement of the enantiomorph and the final coordinates are given in Table 1. Neutral-atom scattering factors were taken from SHELX 76[15] and ref. 16 (Rh) and calculations were carried out using SHELX 76, SHELXS 86[17] and ORTEP[18] using a personal computer.

Complete atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1996, Issue 1.

Results and Discussion

The reaction of H$_4$tedta with RhCl$_3$·3H$_2$O in boiling water produced a yellow powder formulated as [Rh(H$_3$tedta)Cl$_2$]·H$_2$O on the basis of analytical data, and discussed further below. On boiling a solution of this material in water for 2 h complete loss of co-ordinated chloride occurred, and on cooling clear yellow crystals of [Rh(Htedta)]·2H$_2$O* separated. Dilute aqueous hydrohalogenic acids HX (X = Cl, Br or I) converted this complex into monohalides [Rh(H$_2$tedta)X]·nH$_2$O. The [Rh(Htedta)]·2H$_2$O was recovered unchanged from boiling dilute (10%) aqueous HF, reflecting the low affinity of the soft Rh^{III} for fluoride in aqueous solution. Concentrated (60%) HF did react with the complex on boiling but produced a complex mixture of products which were not identified. The reaction of [Rh(Htedta)]·2H$_2$O with KSCN in water formed the anionic rhodium complex K$_2$[Rh(tedta)(NCS)]·2H$_2$O. The structure of [Rh(Htedta)]·3H$_2$O was determined by X-ray diffraction and as it provides the starting point for a discussion of the chemistry in this system it is described first.

Structure of [Rh(Htedta)]·3H$_2$O

The structure consists of discrete molecules containing an octahedrally co-ordinated Rh atom (Fig. 1). One carboxylate group remains unco-ordinated and is probably protonated. Examination of Fig. 1 and Table 1 shows that many of the atoms are related by the pseudo-mirror plane. Thus N(1)/N(2), O(2)/O(6) illustrate the 'mirror' and this only breaks down for the atoms bonded to C(6) and C(12). The ligand has been characterised once by X-ray studies on a copper complex[13] but showed a different co-ordination mode with the S atom bridging to two Cu atoms and one N and two O also co-ordinating to each metal centre. The related H$_4$edta has an

* Analytical data for the powdered material were consistent with two water molecules per rhodium, however the crystal structure revealed three water molecules in the crystal examined.

Table 1 Atomic coordinates for [Rh(Htedta)]·3H_2O

Atom	*x*	*y*	*z*
Rh	0.028 10(8)	0.000 14(6)	0.001 10
S	−0.242 6(3)	0.001 5(2)	−0.080 7(2)
O(1)	0.143 9(12)	0.089 0(4)	−0.072 3(5)
O(2)	0.205 1(13)	0.219 9(4)	−0.073 3(7)
O(3)	0.245 0(10)	0.015 8(4)	0.093 8(6)
O(4)	0.314 3(12)	0.078 3(5)	0.222 8(5)
O(5)	0.169 3(11)	−0.076 4(4)	−0.079 1(5)
O(6)	0.224 4(15)	−0.205 1(5)	−0.110 4(6)
O(7)	0.299 2(11)	−0.167 2(5)	0.103 5(5)
O(8)	0.243 8(11)	−0.145 0(5)	0.251 9(6)
O(9)	0.632 2(11)	−0.001 8(5)	0.277 5(6)
O(10)	0.563 3(15)	0.224 0(5)	0.230 3(6)
O(11)	0.409 6(12)	0.164 6(5)	0.777 2(6)
N(1)	−0.078 2(13)	0.094 5(5)	0.077 6(7)
N(2)	−0.075 5(13)	−0.107 3(5)	0.058 3(6)
C(1)	−0.349 4(17)	0.088 2(7)	−0.025 1(7)
C(2)	−0.288 7(16)	0.096 0(7)	0.075 2(8)
C(3)	−0.001 2(16)	0.171 8(7)	0.039 4(9)
C(4)	0.124 3(17)	0.160 5(7)	−0.041 9(8)
C(5)	−0.002 5(15)	0.082 9(7)	0.169 5(8)
C(6)	0.200 6(16)	0.057 3(7)	0.163 6(8)
C(7)	−0.366 2(17)	−0.080 3(7)	−0.025 5(8)
C(8)	−0.281 2(16)	−0.105 5(7)	0.063 9(8)
C(9)	−0.019 3(14)	−0.174 3(6)	−0.007 0(12)
C(10)	0.139 0(15)	−0.152 8(7)	−0.068 6(8)
C(11)	−0.011 3(15)	−0.129 7(7)	0.152 6(8)
C(12)	0.196 6(17)	−0.148 2(6)	0.162 7(7)

Table 2 Selected bond lengths (Å) and angles (°) for [Rh(Htedta)]·3H_2O

Rh–S	2.283(3)	O(1)–C(4)	1.28(1)
Rh–O(1)	2.011(7)	O(2)–C(4)	1.24(1)
Rh–O(3)	2.082(8)	O(3)–C(6)	1.28(1)
Rh–O(5)	2.009(7)	O(4)–C(6)	1.24(1)
Rh–N(1)	2.078(9)	O(5)–C(10)	1.30(1)
Rh–N(2)	2.114(9)	O(6)–C(10)	1.23(1)
S–C(1)	1.83(1)	O(7)–C(12)	1.18(1)
S–C(7)	1.82(1)	O(8)–C(12)	1.35(1)
N–C	1.46(1)–1.52(2)	C–C	1.50(2)–1.54(2)
N(1)–Rh–O(1)	83.2(3)	O(3)–Rh–O(1)	86.9(3)
N(1)–Rh–O(5)	169.1(4)	O(5)–Rh–O(3)	94.7(3)
N(1)–Rh–N(2)	107.5(4)	S–Rh–O(1)	93.7(3)
N(1)–Rh–O(3)	80.2(3)	S–Rh–N(1)	87.8(3)
N(2)–Rh–O(5)	82.5(3)	S–Rh–O(3)	167.8(2)
N(2)–Rh–O(1)	169.2(3)	S–Rh–N(2)	85.2(3)
N(2)–Rh–O(3)	96.4(3)	S–Rh–O(5)	97.5(2)
O(1)–Rh–O(5)	87.0(3)		

extensive co-ordination chemistry and of interest in the present context are [M(Hedta)(H_2O)] (M = Rh[19] or Ru[20]) where the ligand occupies five sites around the octahedrally co-ordinated M. The sixth site is occupied by water and there is one uncoordinated carboxylate residue. The Rh–N and Rh–O distances in the present compound (Table 2) agree well with those of the edta complex and the C–C and C–N are unexceptional.

Spectroscopic data

The yellow complex [Rh(Htedta)]·2H_2O is moderately soluble in cold water, and dissolved very easily in a phosphate buffer at pH 7.4. The ^{1}H NMR spectrum is complex and relatively uninformative, but the ^{13}C-{^{1}H} spectrum (Fig. 2 and Table 3) shows that the solid-state structure is retained in solution. The single free CO_2^- results in the absence of any plane of symmetry in the molecule and hence all the ligand CH_2 groups are inequivalent, leading to eight lines with equal intensities, in addition to the carboxylate carbon resonances which show the expected 3:1 grouping. The ^{103}Rh NMR spectrum of this solution shows a single sharp resonance at δ

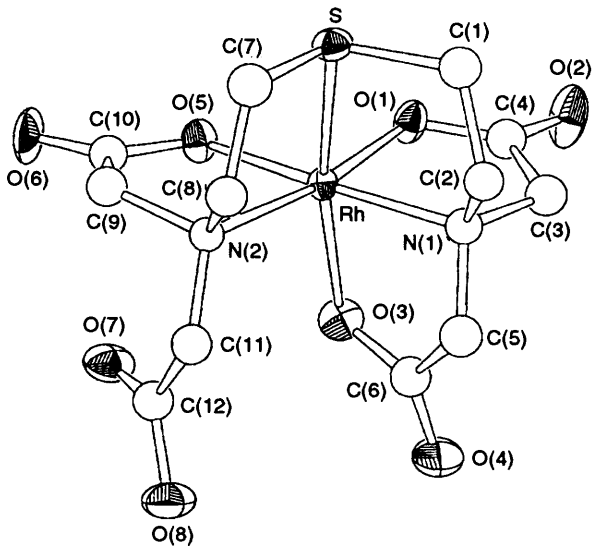


Fig. 1 View of the discrete molecule [Rh(Htedta)]·3H_2O showing the atom numbering scheme. Thermal ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity

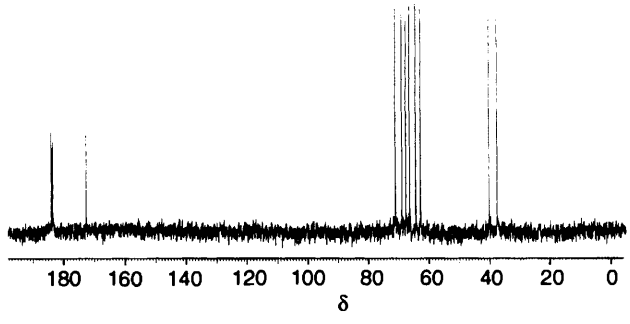


Fig. 2 The ^{13}C-{^{1}H} NMR spectrum of [Rh(Htedta)] in D_2O at 300 K

5576 (relative to Ξ = 3.16 MHz). The IR spectrum (KBr disc) (Fig. 3), although too complex to assign in full, shows characteristic fingerprints in the region 1000–2000 cm^{-1}.[21–23]

The complex [Rh(Htedta)]·2H_2O was converted into monohalides [Rh(H_2tedta)X]·*n*H_2O (X = Cl, Br or I) on boiling with dilute aqueous HX. They were isolated as yellow (X = Cl or Br) or brown (X = I) powders, poorly soluble in water, but which dissolved easily in the phosphate buffer. However hydrolysis to reform [Rh(Htedta)] occurred rapidly at ambient temperatures as demonstrated by the ^{13}C-{^{1}H} NMR spectra. This is in contrast to the equivalent complex with dtpa, [Rh(H_3dtpa)Cl], which, on treatment in boiling water, undergoes only partial loss of halide,[24] presumably a reflection of the increased *trans*-labilising effect of thioether over amine. The ^{103}Rh NMR spectra, which required several hours accumulation even from saturated solutions, showed [Rh(Htedta)] as the only significant species. Hydrolysis was slower at lower temperatures, and ^{13}C-{^{1}H} NMR spectra recorded from aqueous buffer solutions freshly prepared and maintained at 275 K revealed simple patterns (Table 3). The presence of only four CH_2 and two CO_2 resonances requires the molecules to have a plane of symmetry, and unequivocally demonstrates the structure of the halides are as in **I** (see also Scheme 1). Small systematic shifts in δ(CH_2) were observed as the halogen present varied (Table 3). The IR spectra (Fig. 3) reveal characteristic fingerprints, which distinguish the complexes from the halide-free starting material.

The thiocyanato complex was obtained as the dipotassium salt (deprotonated carboxylates) due to the different pH at which the preparation was conducted. The presence of a single strong and broad ν(CN) stretch at 2102 cm^{-1} was interpreted as isothiocyanato (*N*CS) co-ordination,[25] but the ν(CS) and

Table 3 Selected ^{13}C NMR data[a]

Compound	$\delta(SCH_2)$	$\delta(NCH_2)$	$\delta(CCH_2)$	$\delta(CO_2)$
H_4tedta[b]	28.6	56.2	60.0	175.4
[Rh(Htedta)]·$2H_2O$	37.6, 40.4	62.8, 64.4	66.4, 67.6, 69.0, 71.1	172.7, 183.5, 183.6, 184.1
[Rh(H_2tedta)Cl]·H_2O	34.9	62.5	66.3, 67.4	173.1, 183.9
[Rh(H_2tedta)Br]	34.7	62.1	67.0, 68.1	173.4, 183.2
[Rh(H_2tedta)I]·$2H_2O$	34.5	61.3	68.5, 69.5	173.8, 184.6
K_2[Rh(tedta)(NCS)]·$2H_2O$	36.5, 39.2	61.6, 63.1	65.2, 66.6, 67.9, 69.3	181.1, 181.3, 182.3, 183.7
[Rh(H_3tedta)Cl_2]·H_2O[c] A	31.9, 40.5	54.3, 65.7	60.0,[d] 71.1	(172.6, 172.7, 185.0, 185.4, 185.5, 185.6)[e]
B	33.2, 42.3	54.4, 65.8	60.0,[d] 71.5	

[a] Relative to $SiMe_4$, solution in water–D_2O (10:1) containing potassium phosphate buffer pH 7.4. [b] In D_2O containing NaOD. [c] Two isomers A (minor) and B (major). [d] CH_2NH^+ group. [e] Carboxylate CO_2 resonances not assigned to individual isomers due to overlap.

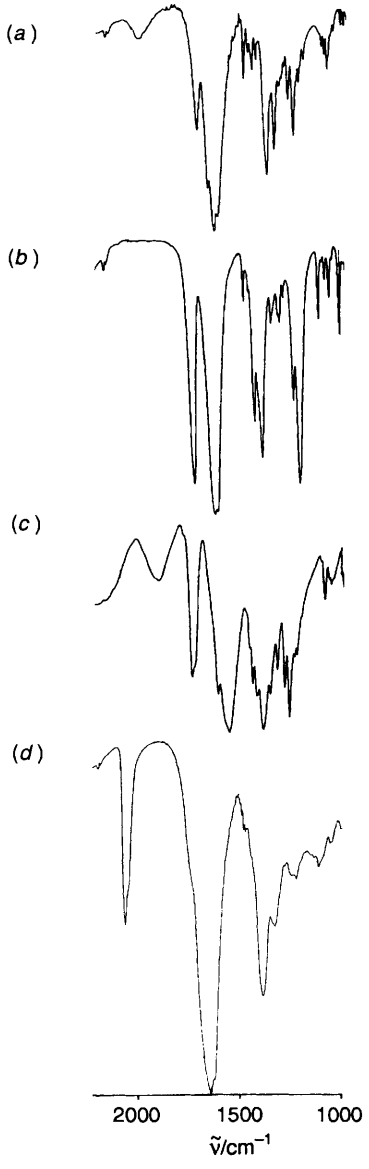
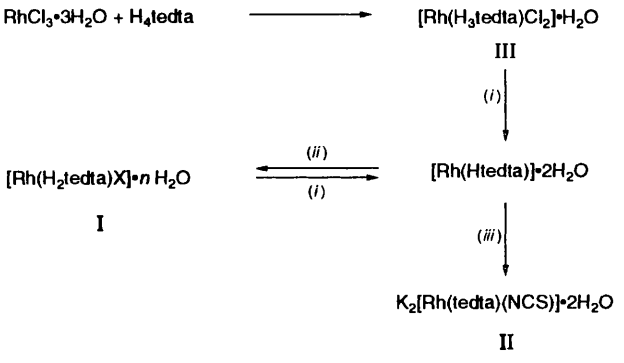
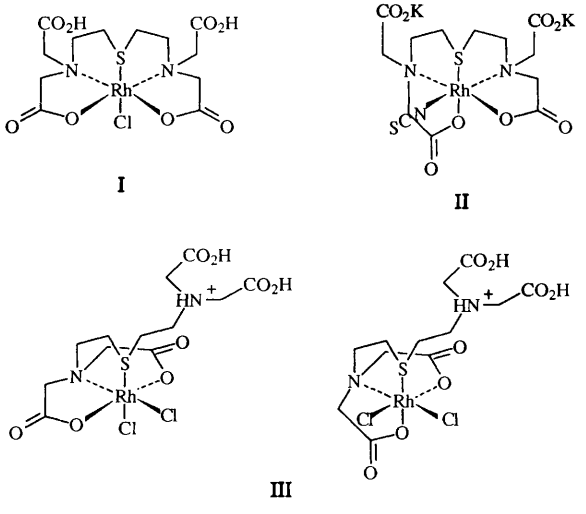


Fig. 3 Infrared spectra (KBr discs) of (*a*) [Rh(Htedta)]·$2H_2O$, (*b*) [Rh(H_2tedta)Cl]·H_2O, (*c*) [Rh(H_3tedta)Cl_2]·H_2O and (*d*) K_2[Rh(tedta)(NCS)]·$2H_2O$

δ(NCS) vibrations were not identified due to the complex vibrations of the tedta ligand in appropriate regions. Further support for the presence of an *N*CS rather than *S*CN linkage is provided by the UV/VIS spectrum compared to those of the monohalides, where the lowest energy d–d band ($^1A_{1g} \longrightarrow {}^1T_{1g}$ in O_h symmetry) gives the spectrochemical series NCS > Cl > Br > I, typical of *N*CS co-ordination, whereas *S*CN linkages usually place the thiocyanato complex between Br and I.[25]



Scheme 1 (*i*) water; (*ii*) HX (X = Cl, Br or I); (*iii*) KSCN



The IR spectrum of this complex confirms the absence of protonated CO_2H groups. However, in contrast to the monohalides with structure **I**, the ^{13}C-{^1H} NMR spectrum at 275 K of the thiocyanato complex contains eight CH_2 resonances (Table 3) showing the absence of a plane of symmetry and identifying the isomer as **II**. The ^{13}C-{^1H} spectrum also contains a number of much weaker resonances at similar frequencies to those of the major species, which may be due to the presence of a second isomer or to hydrolysis products.

Whilst the synthesis of the other complexes from [Rh(Htedta)] is straightforward, the [Rh(H_3tedta)Cl_2]·H_2O formed by the initial reaction of H_4tedta and $RhCl_3$·$3H_2O$ is difficult to obtain cleanly. This may at least in part be due to the variable constitution of commercial rhodium trichloride.[26] The ^{13}C-{^1H} NMR spectrum (Table 3) is consistent with a mixture of two isomers both with low symmetry and possessing two bound and two free carboxylates, while the IR spectrum (Fig. 3) in addition to the characteristic features due to bound and free carboxylate groups exhibits a broad feature at *ca.* 2500 cm^{-1}

indicative of protonated amine. Possible structures for these isomers are shown in **III**. The complex was not regenerated even on prolonged reflux of [Rh(Htedta)] with concentrated HCl.

Conclusion

This work provides essential background for the development of therapeutic rhodium products using H_4tedta as a bifunctional chelating agent.

Acknowledgements

We thank the EPSRC for financial support (to A. M. H.) and for funds to purchase an X-ray diffractometer. Also for access to the Chemical Database System at Daresbury. We thank Mr. G. R. Henderson for experimental assistance.

References

1 B. Grazman and D. E. Troutner, *Appl. Radiat. Isot.*, 1988, **39**, 257.
2 A. T. M. Vaughn, A. Keeling and S. C. S. Yankuba, *Int. J. Appl. Radiat. Isot.*, 1985, **36**, 803.
3 G. L. DeNardo and S. J. DeNardo, in *Radioimmunoimaging and Radioimmunotherapy*, eds. S. W. Burchiel and B. A. Rhodes, Elsevier, Amsterdam, 1983, p. 41.
4 D. J. Hnatowich, W. W. Layne and R. L. Childs, *Int. J. Appl. Radiat. Isot.*, 1982, **33**, 327.
5 M. Li and C. F. Meares, *Bioconjugate Chem.*, 1991, **2**, 26.
6 G. Ergun Efe, M. R. A. Pillai, E. O. Schlemper and D. E. Troutner, *Polyhedron*, 1991, **10**, 1617.
7 M. R. A. Pillai, J. M. Lo, C. S. John and D. E. Troutner, *Nucl. Med. Biol.*, 1990, **17**, 419.
8 W. J. Kruper, jun., D. K. Pollock, W. A. Fordyce, M. J. Fazio and M. N. Inbasekaran, *U.S. Pat.*, 4 994 560, 1987.
9 M. J. Abrams, G. J. Bridger, S. K. Larsen, B. A. Murrer, N. Powell, R. T. Skerlj and J. F. Vollano, *U.S. Pat. Appl.*, 08/235 318, 1994.
10 G. Schwarzenbach, H. Senn and G. Anderegg, *Helv. Chim. Acta*, 1957, **40**, 1886.
11 P.-K. Tse and J. E. Powell, *Inorg. Chem.*, 1985, **24**, 2727.
12 P. J. Peerce, H. B. Gray and F. C. Anson, *Inorg. Chem.*, 1979, **18**, 2593.
13 J. M. Berg and K. O. Hodgson, *Inorg. Chem.*, 1986, **25**, 1800.
14 N. R. Champness, W. Levason, D. Pletcher and M. Webster, *J. Chem. Soc., Dalton Trans.*, 1992, 3243.
15 G. M. Sheldrick, SHELX 76, Program for Crystal Structure Determination, University of Cambridge, 1976.
16 *International Tables for X-Ray Crystallography*, Kynoch Press, Birmingham, 1974, vol. 4, pp. 99–101, 149–150.
17 G. M. Sheldrick, SHELXS 86, Program for the Solution of Crystal Structures, University of Göttingen, 1986; *Acta Crystallogr., Sect. A*, 1990, **46**, 467.
18 C. K. Johnson, ORTEP II, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN, 1976.
19 G. H. Y. Lin, J. D. Leggett and R. M. Wing, *Acta Crystallogr., Sect. B*, 1973, **29**, 1023.
20 K. Okamoto, J. Hidaka, I. Iida, K. Higashino and K. Kanamori, *Acta Crystallogr., Sect. C*, 1990, **46**, 2327.
21 M. L. Morris and D. H. Busch, *J. Am. Chem. Soc.*, 1956, **78**, 5178.
22 R. E. Seivers and J. C. Bailar, jun., *Inorg. Chem.*, 1962, **1**, 174.
23 T. G. Appleton, J. R. Hall and M. A. Williams, *Inorg. Chim. Acta*, 1982, **61**, 51.
24 N. A. Ezerskaya, T. P. Solovykh, Ya. V. Salyn', O. N. Evstaf'eva and L. K. Shubochkin, *Russ. J. Inorg. Chem.*, 1982, **27**, 707.
25 A. H. Norbury, *Adv. Inorg. Chem. Radiochem.*, 1975, **17**, 231.
26 B. E. Mann and C. Spencer, *Inorg. Chim. Acta*, 1982, **65**, L57.

Received 21*st August* 1995; *Paper* 5/05534B