Solution Behaviour of a Monooxorhenium(V) Complex of 1,4,8,11-Tetraazacyclotetradecane

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Abstract

The reaction of $ReOCl_3(PPh_3)_2$ with cyclam gives a macrocyclic monooxorhenium(V) complex, $[ReO(cyclam)(OH_2)]Cl_3$ (**1**). This exists as a monocation in aqueous solution in which the cyclam ligand is doubly deprotonated $[ReO(C_{10}H_{22}N_4)(OH_2)]^+$ (**2**), the structure of which has been defined with the aid of NMR, visible spectrophotometric and FAB mass spectrometric methods.

Introduction

There have been relatively few reports of the macrocyclic coordination chemistry of rhenium [1]. In view of the current interest in higher valent oxo complexes of osmium and ruthenium as oxidation catalysts for organic transformations [2], this is rather surprising. Moreover, there is great interest in the related oxotechnetium(V) complexes which are used commonly in diagnostic nuclear medicine [3]. Monooxo complexes of the metastable isomer ^{99m}Tc (γ = 140 keV, $t_{1/2}$ = 6.02 h) are administered often as scanning agents for certain vital organs.

Dioxotechnetium(V) complexes of the macrocyclic ligand 'cyclam' (1,4,8,11-tetraazacyclotetradecane) have been characterised previously [4], and these complexes give rise to favourable biodistribution data in animals [5]. The present study was undertaken to compare the structure and solution chemistry of the related rhenium complexes to these structurally characterised technetium species. Such studies are also of concern to nuclear medicine in view of the potential use of the β-emitting radioisotopes of rhenium (^{186}Re, 1.07 MeV, $t_{1/2}$ 90 h; ^{188}Re, 2.12 MeV, $t_{1/2}$ 17 h) in radioimmunotherapy [6].

Experimental

$KReO_4$ and 1,4,8,11-tetraazacyclotetradecane were purchased from Aldrich Chemicals Co. and were used without further purification. Amberlite CG-50 (H^+ form) was purchased from Sigma, and all analytical grade solvents were further purified by standard literature methods [7]. *trans*-$ReOCl_3(PPh_3)_2$ was prepared according to the published method [8]. All other chemicals were of reagent grade and were used without further purification, unless otherwise stated.

Proton and ^{13}C NMR spectra were recorded on a Bruker AC-250 spectrometer, and all NMR chemical shifts are reported in ppm to higher frequency of Me_4Si. Fast atom bombardment mass spectra (FAB-MS) were recorded on a VG7070E instrument, using an aqueous glycerol matrix and fast argon atoms (8 keV accelerating voltage). Electronic spectra were measured on a Perkin-Elmer Lambda 3 spectrophotometer and the infrared spectra were obtained as KBr discs using a Perkin-Elmer 587 spectrophotometer. The magnetic susceptibility of powdered samples was measured by the Faraday method using a Sartorius microbalance in conjunction with a Bruker B-E10C8 research magnet equipped with a B-VT 1000 automatic temperature control, in the temperature range 110–293 K. Diamagnetic corrections were applied with the use of Pascal's constant [9].

$[Re^VO(cyclam)(OH_2)]Cl_3$

To a solution of 1,4,8,11-tetraazacyclotetradecane (cyclam) (0.05 g, 0.25 mmol) in chloroform (15 cm^3) was added *trans*-$[ReOCl_3(PPh_3)_2]$ (0.20 g, 0.24 mmol) and the solution was stirred at room temperature for five minutes. After filtration, diethyl ether was slowly added to yield a reddish-brown solid, which was filtered, washed with cold chloroform (2 × 5 cm^3) and ether (2 × 5 cm^3) and dried over P_2O_5 *in vacuo* (0.07 g, 57%).

Anal. Calc. for $C_{10}H_{26}N_4ReO_2Cl_3[0.5C_4H_{10}O]$: C, 25.53; H, 5.53; N, 9.93; Re, 33.01. Found: C, 25.70; H, 5.35; N, 9.83; Re, 33.10. Electronic spectrum (H_2O) [λ_{max} (nm) (ϵ (dm^3 mol^{-1} cm^{-1}))] 450 (90) 330(sh), 240(sh). IR: ν_{max} 3440 (H_2O), 3260(w, NH), 3040(w, NH) 1630(w, H_2O), 910(vs, ReO). Positive ion FAB-MS (H_2O–glycerol) (*m/z*): 419 (41), 417 (25), 401 (100), 399 (64) [$(C_{10}H_{24}N_4O_2Re)^+$ mol wt 419/417]. Magnetic susceptibility

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(110 to 293 K) $\chi_A = +195 \times 10^{-6}$ cgs units mol^{-1} (293 K) and $+205 \times 10^{-6}$ cgs units (110 K).

The absence of any ReO_4^- impurity was confirmed by TLC (SiO_2, Me_2CO) and negative ion FAB-MS. The complex was further purified by cation exchange chromatography (Amberlite CG-50, carboxylic type, H^+ form). The complex was dissolved in the minimum volume of deionized water, loaded onto the column and eluted with a water–acetic acid–acetonitrile mixture (72:18:10). After removal of solvents under reduced pressure, and finally *in vacuo* a dark purple–red microcrystalline solid was obtained (tri-acetate salt, in the solid state). Attempts at isolating this complex as its ClO_4^- or PF_6^- salt led to oxidative decomposition. Indeed in aqueous solution at pH $\geqslant$ 8.5, the complex was unstable and irreversibly decomposed, forming ReO_4^- which was identified by TLC, electronic spectroscopy and negative ion FAB-MS. ^{13}C NMR (D_2O): δ 60.1, 56.1, 32.2. ^1H NMR (D_2O): δ 3.94 (2H, m) 3.90 (2H, m, CH_2N), 3.78 (4H, dd, CH_2N), 2.86 (4H, m, CH_2N), 2.75 (4H, dd, CH_2N), 2.31 (1H, m, CH_2CHCH_2), 2.23 (1H, m, $CH_2CH'CH_2$), 2.04 (s, $CH_3CO_2^- + CH_3CO_2H$), 1.97 (2H, m, $CH_2CH_2CH_2$). This purified complex, behaved identically in aqueous solution (pH 1 to 7) to the reddish-brown chloride complex **1**, isolated above, giving identical electronic and FAB-MS spectra and a similar IR spectrum [(KBr) ν_{max} 910 cm^{-1} (ReO)]. Both complexes were examined by cation exchange HPLC and co-eluted with a retention time characteristic of a monocationic complex. The complex, recovered from aqueous solution by evaporation, showed an unchanged Re=O stretching frequency at 910 cm^{-1}.

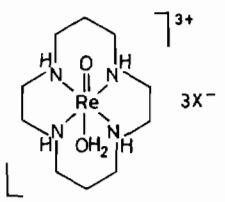
Results and Discussion

Reaction of equimolar amounts of $ReOCl_3(PPh_3)_2$ with 1,4,8,11-tetraazacyclotetradecane in chloroform at room temperature, led to a clean displacement of the phosphine ligands, giving a red–violet solution from which a reddish product, **1**, was isolated following addition of diethyl ether. The coordinated monooxo group was identified by its intense (ν(ReO)) stretching band at 910 cm^{-1}. This is a low value for a monooxorhenium(V) compound [10], and is comparable to values reported for technetium mono-oxo complexes in square pyramidal amine oxime complexes, [3]. This value may be compared to the value of 790 cm^{-1} reported for the *trans*-dioxotechnetium complex of cyclam $[Tc(O_2)cyclam]^+$ [4], and the value of 800 cm^{-1} reported for the *trans*-dioxorhenium complex of ethylenediamine, $[Re(O_2)[ethylenediamine]_2]^+$ [10]. The IR spectrum of the carefully dried complex also revealed a strong broad band at 3440 cm^{-1} and a second band at 1630 cm^{-1}, consistent with the presence of a coordinated water molecule [11]. In the polycrystalline state **1** exhibits a residual paramagnetic susceptibility value, χ_A, of $+195 \times 10^{-6}$ cgs units mol^{-1} (293 K). There was little variation in this value in the temperature range 110 to 293 K, and such temperature independent paramagnetic behaviour has been previously observed for other oxorhenium d^2 complexes [10].

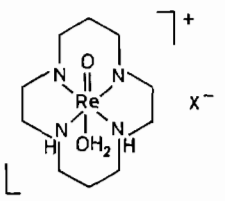
The complex although insoluble in common organic solvents (e.g. $CHCl_3$, Me_2CO) dissolves readily in water to afford a reddish-brown solution (λ_{max} 450 nm (90)). This visible band was unchanged in 6 M HCl solution. This suggests that a rhenium dioxo core is not present, as under these conditions successive protonation of the rhenium dioxo occurs, with the chromophore shifting to higher wavelengths [10]. Further information on the structure in solution was obtained from its positive ion FAB-MS spectrum in an aqueous glycerol matrix. It revealed a parent ion peak at $M^+ = 419/417$ and a daughter ion at 401/399, following loss of neutral water. This analysis was confirmed by a separate parent–daughter scan. The parent peak may correspond to $[ReO(OH_2)cyclam]^+$ minus two hydrogens, and the daughter therefore is [ReO-cyclam-2H]$^+$. Observed and calculated isotope patterns for these peaks showed excellent agreement, in support of these assignments. The ^{13}C NMR spectrum of the complex in D_2O was examined over the pH range 1–7. Three resonances were observed due to the rhenium–oxo complex, which were shifted to higher frequency ($\delta(D_2O)$ 60.1, 56.1, 32.2) compared to free ligand resonances ($\delta_c(D_2O)$ 49.2, 46.2, 24.7).

The solid complex **1** was dissolved in water and was analysed by cation exchange HPLC which revealed a peak due to a unipositive complex (as determined by its characteristic retention time). The rhenium–oxo complex which was separately purified by cation exchange chromatography, co-eluted with a solution of **1** on HPLC. The purified complex following cation exchange chromatography exhibited identical solution spectral characteristics to those observed upon dissolution of the complex **1** in water.

In concert, this information strongly suggests that the structure of the complex formed by dissolution of the trication **1** in water is that represented by the monocationic oxorhenium aquo complex **2**. The structure comprises a *trans*-$[ReO(OH_2)]^{3+}$ core spanned in the equatorial plane by two amine (NH) and two amide (*i.e.* deprotonated) nitrogens. Other workers have previously reported similar behaviour with monooxoruthenium(VI) aquo complexes [2, 12]. The deprotonation of amine and amide ligands is also well-defined in technetium(V) monooxo complexes in order to



1 [in solid]



2 [in solution]

satisfy the charge, geometrical and electronic requirements of the TcO^{3+} core [3]. The amine and amide nitrogens in complex **2** undergo rapid proton exchange in aqueous solution so that only three carbon resonances are observed at room temperature in the ^{13}C NMR spectrum. Although it is rather tempting to assign a rhenium dioxo structure to the isolated complex (by analogy with the corresponding $[TcO_2(cyclam)]^+$ complex [4] and the defined $[ReO_2(ethylenediamine)]^+$ cation), it is very clear that the complex has a monooxorhenium(V) core $(ReO)^{3+}$. The infrared stretch (910 cm^{-1}) is much higher than would be expected for a dioxo species (typically 800 cm^{-1}). In acidic solution the band at 450 nm is unchanged in high added acid (6 M HCl), conditions in which dioxo complexes would protonate with a shift to higher wavelength. Furthermore the complex was unstable above pH 8.5, irreversibly forming ReO_4^- and cyclam: rhenium dioxo complexes of amines are stable under such weakly basic conditions. The presence of the weakly bound water molecule *trans* to the Re=O band in **1** and the conjugate base **2** is supported by the infrared ($\nu(OH_2)$ 3440, 1630 cm^{-1}) and FAB mass spectrometric data. After dissolution of the complex **1** in H_2O, it may be recovered unchanged by evaporation and exhibits the same Re=O infrared stretching frequency (910 cm^{-1}).

The ^1H NMR spectrum of **2** was analysed with the aid of several selective decoupling experiments, and assignments were confirmed in a 2D COSY NMR spectrum of **2**. The presence of the apical rhenium oxo bond in **2** renders all of the methylene protons in the complex diastereotopic, and the protons in each geminal methylene group were observed to be chemical shift non-equivalent. For example, within the two five-membered chelate rings, the geminal CH_2N protons are non-equivalent (δ3.78 and 2.75 ppm) and are mutually coupled, while in the six-ring chelates the diastereotopic CH_2N protons (δ3.92 and 2.86 ppm) were additionally coupled to the adjacent non-equivalent CH_2 protons.

Interestingly, related acyclic N_4 tetraamines form stable rhenium dioxo cationic complexes [13] more reminiscent of the $[Re(ethylenediamine)_2O_2]^+$ complex with rhenium oxygen bond stretches of 810 cm^{-1}. These complexes are stable in the pH range 0 to 13 [and undergo successive protonation at lower pH (6 M HCl → 18 M H_2SO_4)] unlike the monooxo complex of cyclam which, although stable in 2 M HCl for prolonged periods (as monitored by spectrophotometry and ^1H NMR), is irreversibly oxidised to perrhenate above pH 8.5.

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