Research Article

Kinetic and High-Pressure Mechanistic Investigation of the Aqua Substitution in the Trans-Aquaoxotetracyanocomplexes of Re(V) and Tc(V): Some Implications for Nuclear Medicine

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A kinetic study of the aqua substitution in the [TcO(OH2)(CN)4]− complex by different thiourea ligands (TU = thiourea, NMTU = N-methyl thiourea, NNDMTU = N,N′-dimethylthiourea) yielded second-order formation rate constants (25°C) as follows: [NNDMTU, NMTU, TU, respectively]: k = 11.5 ± 0.1, 11.38 ± 0.04, and 7.4 ± 0.1 M−1 s−1, with activation parameters: ΔH°f = 55 ± 2, 42 ± 3, 35 ± 5 kJ mol−1; ΔS°f = −40 ± 8, −84 ± 11, −110 ± 17 J K−1 mol−1. A subsequent high-pressure investigation of the aqua substitution in the [ReO(OH2)(CN)4]− and [TcO(OH2)(CN)4]− complexes by selected entering ligands yielded ΔV°f values as follows: Re(V): −1.7 ± 0.3(NCS−), −22.1 ± 0.9 (TU) and for Tc(V): −3.5 ± 0.3(NCS−), −14 ± 1 (NNDMTU), and −6.0 ± 0.5 (TU) cm3 mol−1, respectively. These results point to an interchange associative mechanism for the negative NCS− as entering group but even a pure associative mechanism for the neutral thiourea ligands.

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1. INTRODUCTION

Technetium-99m is widely used in over 90% of all current diagnostic nuclear medicinal applications [1–5] due to its favourable nuclear properties (t1/2 = 6.02 hours, y = 140 keV 100%) and availability from a generator. It is routinely used for brain, heart, liver, kidney, and bone imaging. Technetium’s third-row congener and 5d analog, rhenium, also has applications in nuclear medicine since its imaging. Technetium-99m is widely used in over 90% of all current nuclear medicinal applications [1–5].

The development of technetium myocardial imaging agents commenced with work by Deutsch [9–12], who investigated the [99mTcCl2(dmpe)2]+ [dmpe = bis(1,2-dimethylphosphino)ethane] and [99mTcX2(diars)2]+ complexes (diars = o-phenylenedibis(dimethylarsine), X = Cl, Br) [12]. Studies on animal models indicated that the reduction of TcIII is biologically accessible for the cationic [99mTcCl2(dmpe)2]+ complex, yielding neutral [99mTcCl2(dmpe)2]. The latter then washes from the heart and becomes trapped in the liver. The reduction of ReIII to ReII [186ReIII–Cl2(dmpe)2]+ is 0.2 V more negative compared to the analogous Tc complex and is thus retained in the heart [10]. Kinetic, electrochemical, and structural work on the [Re/ TcCl2(dmpe)2] complexes has been published and illustrates its importance as initial models [13–18].

Currently, however, other monocationic complexes of technetium-99m are of significant interest because of their extensive use as 99mTc myocardial imaging agents [19, 20] with examples including Cardiolite or [99mTc(MIBI)6]+ (MIBI = 2-methoxy-2-methylpropylisocyanide) [21, 22] and Myoview [99mTcO2(Tetrofosmin)2]+. While the monocationic complexes are traditionally based on the [O=TCY=O]+, [Cl–TcIII–Cl]+, and Tc5 cores, a new class of myocardial imaging agents feature the [99mTcY=N]+ core, an example being the Tc–N–NOET complex (bis(N-methoxy-N-methylthiobiscarbamato)nitridotechnetium(V)).

Two technetium complexes, containing specifically phosphine ligands, currently used for myocardial imaging are the above-mentioned Myoview and Technecard.
structure of trans-fac-[ReO(OH2)(CN)4]− complex. Furthermore, the reactions involving [ReO(OH2)(TU)4]3+ and higher concentrations of the entering ligand showed typical limiting kinetics, while in the [ReO(OH2)(CN)4]− complex, no tendency of limiting kinetics was observed.

We have previously correlated different in vivo reactivities with in vitro behaviour [41] and attempted to link certain sites with biodistribution and bioactivity, but was, and still is, unable to do more detailed comparisons. Thus, since detailed mechanistic studies and data on substitution processes are fairly limited, it prompted us to reinvestigate the type of mechanism obeyed for the [ReO(OH2)(CN)4]− complex when reacted with different entering ligands and extending it to the Tc5+ complex, by specifically utilizing advanced high-pressure kinetics. This high-pressure study of the [MO(OH2)(CN)4]− complex (M = Re and Tc), with different entering ligands, is therefore reported here.

2. MATERIAL AND METHODS

All reagents and chemicals of analytical reagent grade, and double-distilled water was used in all experiments. All pH measurements were done with an Orion 701 pH meter and a combined glass/calomel electrode using standard buffer solutions and standardized hydrochloric acid solutions for calibration. The ionic strength was constant (μ = 1 M) in all the experiments, maintained with NaNO3 as noncoordinating electrolyte. In all calculations, pH = −log [H+]. Na3[ReO2(CN)4] and Na3[TcO2(CN)4] were prepared as previously described [37]. Caution: Technetium-99, although a low-energetic radio-active β-emitter (230 KeV, t1/2 = 2.1 × 105 y), should always be handled with care and under approved conditions.

Kinetic measurements were done on modified Durrum-Gibson Model D110 and Applied Photophysics SX.18 MV (control experiments; coupled with a J&M Tidas-16 diode array) stopped flow spectrophotometers equipped with constant temperature syringe and cell holder systems (accurate within 0.1 °C). These were coupled to a personal computer or Acorn Risc workstation capable of performing least-squares analyses on the absorption values versus time data obtained from the kinetic runs. The SCIENTIST [45] program was used to fit the data to selected functions. High-pressure studies were done on a GBC 916 spectrophotometer in a high-pressure vessel with pill box cells of path length ≈15 mm or in a stopped flow high-pressure vessel [46]. All kinetic runs were performed under pseudo-first-order conditions with the ligand in large excess. The solid lines in the figures represent computer least-squares fits of data, while the experimentally determined values are given as points. The [MO(L)(CN)4]2− complexes from the reactions between [MO(OH2)(CN)4]− and different entering ligands were characterised as previously described [43, 44].

3. RESULTS AND DISCUSSION

It was previously shown that the complete reaction scheme governing the substitution reactions on the protonated forms of the trans-[MO2(CN)4]3+ complexes is limited to the...
aqua species, trans-[MO(OH)\(_2\)(CN)\(_4\)]\(^{n^-}\) and with small contributions, under selected conditions from trans-[MO(OH\(_2\))(CN)\(_4\)]\(^{(n+1)-}\) [37]. Assumptions made and approximations have all been reported previously.

The \(pK_a\) value (of the [TcO(OH\(_2\))(CN)\(_4\)]\(^-\) complex, Scheme 1) was previously determined from the reaction between [TcO(OH\(_2\))(CN)\(_4\)]\(^-\) and NCS\(^-\) ions as 2.90(5) by Roodt et al. [44]. To further verify this by another ligand system, an independent kinetic \(pK_a\) determination was carried out for the reaction between [TcO(OH\(_2\))(CN)\(_4\)]\(^-\) and NNDMTU and is illustrated in Figure 1. NNDMTU was therefore completed for the reaction between the metal complex and NCS\(^-\) ions (2.90 ± 0.05) [44].

The data in Figure 1 was fitted to (1), and a \(pK_a\) value as reported in Table 1 was obtained. The acid dissociation constant thus determined from the reaction between [TcO(OH\(_2\))(CN)\(_4\)]\(^-\) and NNDMTU (2.99 ± 0.19) is in good agreement with the \(pK_a\) value reported for the reaction between the metal complex and NCS\(^-\) ions (2.90 ± 0.05) [44].

The ligand concentration and temperature dependence study for each of the different thiourea entering ligands (TU, NMTU, and NNDMTU) was therefore completed for the [TcO(OH\(_2\))(CN)\(_4\)]\(^-\), with the data for NMTU as entering ligand shown in Figure 2.

These \(k_f\) versus temperature data sets were used in the Eyring equation [43] to calculate the activation parameters governing the \(k_f\) step (Table 1). The intercepts (\(k_r\)) in all these runs were zero within standard deviations, thus confirming a large \(k_f\) value (\(K_f = k_f/k_r\)) for each of the different nucleophiles.

The activation entropies (Table 1) for all the reactions studied suggest increased order in the transition state, indicative of association being important.

Following similar arguments used by Grundler et al. [35], and by our group [47], different pathways for the substitution process were therefore considered.
Table 1: Kinetic data for the reaction between \([\text{TcO(OH}_2\text{)(CN)}_4]\)^− and the different thiourea entering ligands; \(\mu = 1.0 \text{ M (NaNO}_3\text{)}, \text{pH} = 0.6\).
\(a\) L.S. fits to (2); \(b\) since small-negative intercepts were obtained in some cases, the value was fixed (\(= 0.00\)). The standard deviations reported are those from the first fits; \(c\) L.S. fits to (1).

| Parameter | \(T\) (°C) | NNMDTU | \(T\) (°C) | NMTU | \(T\) (°C) | TU |
|-----------|-------------|---------|-------------|-------|-------------|-----|
| \(k_f(\text{M}^{-1}\text{s}^{-1})\) \(a\) | 9.3 | 13.1(6) | 5.7 | 3.26(7) | 6.8 | 2.68(8) |
| | 16.5 | 6.1(1) | 15.9 | 5.95(6) | 15.8 | 5.0(1) |
| | 25.1 | 11.5(1) | 25.1 | 11.38(4) | 25.5 | 7.4(1) |
| \(k_r(s^{-1})\) \(a, b\) | 9.3 | 0.00(1) | 5.7 | 0.00(3) | 6.8 | 0.00(2) |
| | 16.5 | 0.00(4) | 15.9 | 0.00(5) | 15.8 | 0.00(3) |
| | 25.1 | 0.00(3) | 25.1 | 0.00(2) | 25.5 | 0.06(2) |
| \(pK_{a1}\) \(c\) | 24.8 | 2.99(19) | — | — | — | — |
| \(\Delta V_k^0 (\text{J K}^{-1} \text{mol}^{-1})\) | — | 55(2) | — | 42(3) | — | 35(5) |

Figure 2: Effect of \(k_{\text{obsd}}\) versus [NMTU] for the reaction between \([\text{TcO(OH}_2\text{)(CN)}_4]\)^− and NMTU at different temperatures, \(\mu = 1.0 \text{ M (NaNO}_3\text{)}, \lambda = 420 \text{ nm, pH} = 0.6, \text{and} [\text{M}] = 5 \times 10^{-5} \text{ M}.

Firstly, for an associative mechanism (Scheme 1, A, \(k_1\) and \(k_2\) pathway), the rate of the reaction is given by

\[
\text{Rate} = k_2[\text{MO(OH}_2\text{)(L)(CN)}_4\]^{n^-} - k_{-2}[\text{MO(L)(CN)}_4\]^{m^-}. \tag{3}
\]

If it is assumed that the \([\text{MO(OH}_2\text{)(L)(CN)}_4]\)\(^n^-\) complex is formed under steady-state conditions, its formation and decomposition would be equal yielding

\[
[\text{MO(OH}_2\text{)(L)(CN)}_4\]^{n^-} = k_2[\text{MO(OH}_2\text{)(L)(CN)}_4\]^{n^-} [L] + k_{-2}[\text{MO(L)(CN)}_4\]^{m^-} \frac{k_{-2} + k_2}{k_{-1}}. \tag{4}
\]

Upon incorporation of the definition of \(K_{a1} (= [\text{MO(OH)}\text{(CN)}_4\]^{m^-})/\text{[H}^+\text{][MO(OH)}\text{(CN)}_4\]^{n^-})), \(M\text{[L]} (= [\text{MO(OH)}\text{(CN)}_4\]^{m^-} + \text{[MO(OH)(CN)}_4\]^{n^-})\) and substituting (4) into (3), integration of the rate law \([[L] \gg [M]]\), by assuming a fast \(k_2\) step (Scheme 1), \(5\) with \(k' = k_2/k_{-1} + k_2\), and defining the pseudo-first-order rate constant, is obtained:

\[
k_{\text{obsd}} = \frac{k_2'[L]}{1 + K_{a1}/[H^+]} + k_{-2}. \tag{5}
\]

Similar arguments may be used, considering an interchange pathway (Scheme 1, \(k_3\) and \(k_4\), incorporating the definition of \(K_{a1} (= [\text{MO(OH)}\text{(CN)}_4\]^{m^-})/\text{[H}^+\text{][MO(OH)}\text{(CN)}_4\]^{n^-})), \(M\text{[L]} (= [\text{MO(OH)}\text{(CN)}_4\]^{m^-} + \text{[MO(OH)(CN)}_4\]^{n^-})\), \(K_2 (= [\text{MO(OH)}\text{(L)(CN)}_4\]^{n^-} + \text{[MO(OH)}\text{(CN)}_4\]^{n^-})/\text{[MO(OH)}\text{(CN)}_4\]^{n^-})\), and \(\text{[L]} \gg [\text{MO(OH)}\text{(CN)}_4\]^{n^-})\), yielding an expression for the pseudo-first-order rate constant as given in (6), and assuming \(K_{a1}[L] \ll 1\),

\[
k_{\text{obsd}} = \frac{k_{-4}K_5[L]}{K_{a1}/[H^+] + 1} + k_{-4}. \tag{6}
\]

It is clear that (5) and (6) are similar and both adequately describe the experimental results (associative mechanism (5); \(k_f = k_2'\) and \(k_r = k_{-2};\) interchange mechanism (6); \(k_f = k_2K_5\) and \(k_r = k_{-4}\) and \(K_5 = k_3/k_{-3}\), and both simplify to (1) and (2), respectively.

The pressure dependence for the substitution process as studied here, at different pressures \(a\) and \(b\), is given by [47]

\[
\ln(k_{a}/k_{b}) = -\Delta V_{\text{exp}}^e(P_a - P_b)/RT. \tag{7}
\]

Since the contribution by the reverse step is negligible in all cases in this study as concluded above, this implies that \(\Delta V_{\text{exp}}^e \approx \Delta V_{k_f}^e\). The data obtained for the \(\text{trans-[TcO(OH}_2\text{(CN)}_4]\)\(^-\) complex are shown in Figure 3, where (7) was utilized to obtain \(\Delta V_{\text{exp}}^e\), and the results are reported in Table 1.

In order to compare the type of mechanism obeyed for \(\text{trans-aqua substitution in the [ReO(OH}_2\text{(CN)}_4]\)\(^-\) complex, a high pressure study with NCS\(^-\) ions and TU was also performed. Since the reaction between \([\text{ReO(OH)}\text{(CN)}_4]\)\(^-\) and L (L = NCS\(^-\) and TU) shows equilibrium constants of \(87 \pm 7\) and \(7.0 \pm 0.4\) \text{ M}^{-1}\), respectively [48, 49], similar arguments to the \(\text{Tc(V)}\) as mentioned above could be used to determine the activation volume, \(\Delta V_{\text{exp}}^e\), for which the values are reported in Table 2.

This high pressure kinetic study on the reaction between \([\text{TcO(OH)}\text{(OH}_2\text{)(CN)}_4]\)\(^-\) and NCS\(^-\) ions, NNMDTU and TU
Table 2: Comparative table for the kinetic data and activation parameters for the ligation reactions of $[\text{ReO(OH}_2\text{)}\text{(CN)}_4]^{-}$ and $[\text{TcO(OH}_2\text{)}\text{(CN)}_4]^{-}$ at 25°C. ([a]References [37, 48], [b]this work.)

| Parameter         | Metal        | NCS $^{-}$ | NNDMTU | NMTU | TU    | HN$_3$ |
|-------------------|--------------|------------|--------|------|-------|--------|
| $k_f$ (M$^{-1}$s$^{-1}$) | Re$^{(a)}$   | 0.00348(4) | 0.059(2) | 0.067(2) | 0.0399(9) | 0.0064(2) |
|                   | Tc$^{(b)}$   | 22.2(3)$^{(a)}$ | 11.5(4) | 11.38(4) | 7.4(1) | — |
| $k_f/T_c/k_f$Re   | —           | 6321       | 195    | 170  | 185   | — |
| $\Delta S^a_{k_f}$ (J K$^{-1}$ mol$^{-1}$) | Re$^{(a)}$ | −11(6)     | −119(40) | −125(10) | −95(3) | −87(6) |
|                   | Tc$^{(b)}$   | −9(12)     | −40(8)  | −84(11) | −110(17) | — |
| $\Delta H^a_{k_f}$ (kJ mol$^{-1}$) | Re$^{(a)}$ | 17.4(1.9)  | 45(11) | 42(3) | 52(1) | 60(2) |
|                   | Tc$^{(b)}$   | 62(4)      | 55(2)  | 42(3) | 35(5) | — |
| $\Delta V^a_{k_f}$ (cm$^3$ mol$^{-1}$) | Re$^{(a)}$ | −1.7(3)    | —      | —    | −22.1(9) | — |
|                   | Tc$^{(b)}$   | −3.5(3)    | −14(1) | —    | −6.0(5) | — |

Figure 3: The effect of pressure on the second-order formation rate constant for the reaction between $[\text{TcO(OH}_2\text{)}\text{(CN)}_4]^{-}$ and NCS$^{-}$, NNDMTU, and TU at 25°C, pH = 0.6, [M] = 5 $\times$ 10$^{-5}$ M, $\lambda = 420$ nm, $a$ refers to left axis, $b$ refers to the right axis. [NCS$^{-}$] = 0.2 M, [NNDMTU] = [TU] = 0.05 M, $\mu$ = 1.0 M (NaNO$_3$).

Figure 4: The effect of pressure on the second-order formation rate for the reaction between $[\text{ReO(OH}_2\text{)}\text{(CN)}_4]^{-}$ and NCS$^{-}$ ions and TU at 25°C, pH = 0.3, [M] = 1.5 $\times$ 10$^{-3}$ M, $a$ refers to left axis, $b$ refers to right axis. [NCS$^{-}$] = 0.6 M, $\lambda_{\text{NCS}^{-}} = 420$ nm; [TU] = 1.0 M, $\lambda_{\text{TU}} = 350$ nm, $\mu$ = 1.0 M (NaNO$_3$).

[Figure 3], yields $\Delta V^a_{\text{expt.}}$ values of $-3.5 \pm 0.3$, $-14 \pm 1$, and $-6.0 \pm 0.5$ cm$^3$/mol, respectively. Similarly, the data for the Re(V), as represented in Figure 4 gave $\Delta V^a_{\text{expt.}}$ values of $-1.7 \pm 0.3$ and $-22.1 \pm 0.9$ cm$^3$/mol for NCS$^{-}$ ions and TU respectively. It is clear that all these indicate small to large negative values, contrary to the experiments on Alberto’s ReI complexes$^{[35]}$.

We previously concluded that with regard to the mechanism, due to the large distortion (metal displaced out of the plane formed by the four cis ligands bonded to the metal, away from the trans-oxo) observed for the $[\text{MO(L)(CN)}_4]^{n-}$ complexes of Mo$^{IV}$, W$^{IV}$, Re$^{V}$, and Tc$^{V}$, a dissociative activation would be favoured during trans-aqua substitution reactions$^{[44, 47]}$. A positive volume of activation ($+10.6 \pm 0.5$ cm$^3$/mol) was observed for the reaction between the corresponding isosstructural $[\text{WO(OH}_2\text{)}\text{(CN)}_4]^{2-}$ complex and N$_3^{-}$, forming an important basis of the mechanistic assignment.

However, the current high-pressure study on the $[\text{ReO(OH}_2\text{)}\text{(CN)}_4]^{-}$ and $[\text{TcO(OH}_2\text{)}\text{(CN)}_4]^{-}$ complexes clearly indicates a negative volume of activation for all these reactions (Table 2), ranging from slightly negative for the anionic NCS$^{-}$ as entering ligand, to substantially negative for the neutral thiourea ligands. This yields important evidence, along with the large negative $\Delta S^a$ values, that an associative (A) mechanism or an associative interchange ($I_a$) mechanism is operative for the activation step during these trans-aqua substitution reactions on the M(V) metals. In principle, this is actually quite acceptable, since the $[\text{MO(OH}_2\text{(CN)}_4]^{n-}$ complexes of Mo$^{IV}$, W$^{IV}$, Re$^{V}$ and Tc$^{V}$ are all classic 16 electron species. Clearly, the M(IV) metal centres are softer than the corresponding Re$^{V}$ and Tc$^{V}$, allowing easier dissociation of the aqua ligand in the rate determining step. This is confirmed by the solid state structures of the $[\text{MO(NCS)(CN)}_4]^{2-}$ complexes, wherein both of the NCS$^{-}$ ligands where nitrogen bound$^{[43, 44]}$.

The formation of the $[\text{MO(L)(CN)}_4]^{m-}$ complex in Scheme 1 in an A mechanism yields an activation volume $\Delta V^a_{\text{expt.}} = \Delta V^a_{k_f} = \Delta V^a_{k_f}$, which is expected to be large negative, and holds true for the reactions between both $[\text{ReO(OH}_2\text{(CN)}_4]^{-}$ and TU ($\Delta V^a_{k_T} = -22.1$ (9) cm$^3$/mol$^{-1}$) and $[\text{TcO(OH}_2\text{(CN)}_4]^{-}$ and NNDMTU.
(ΔV* k = -14(1) cm³ mol⁻¹) and to a lesser extend for [TcO(OH₂)(CN)₄]⁻ and TU (ΔV* k = -6.0 ± 0.5 cm³ mol⁻¹). It is therefore realistic that the neutral ligands will associate more easily with the [MO(OH₂)(CN)₄]⁻ species, compared to association between two negative species ([MO(OH₂)(CN)₄]⁻ and the NCS⁻ ligand), supporting the assumption of an associative process. Furthermore, the reaction between [MO(OH₂)(CN)₄]⁻ and NCS⁻ yielded activation values of -1.7 ± 0.3 and -3.5 ± 0.3 cm³ mol⁻¹ for ReV and TcV, respectively. These are considered too small negative values to support a pure associative activation, although electrostriction between the negatively charged complex and entering NCS⁻ ligand might affect the total value of ΔV* exp of.

For an I₄ mechanism, the volume of activation can be expressed as the sum of the individual contributions for each step in Scheme 1 (8), where k₄ = k₃k₅ and ΔV* k₃,5 = reaction volume for the equilibrium reaction defined by K₅:

ΔV* exp = ΔV* k₃ + ΔV* k₅.

(8)
The k₄ step is associated with a simultaneous bond breaking/formation process, and therefore ΔV* k₄ is expected to be slightly negative in an interchange associative process. Furthermore, ΔV* k₃ can be expressed in terms of its individual components (9):

ΔV* k₃ = ΔV* k₁ - ΔV* k₃.

(9)
Since ΔV* k₁,3 is expected to be positive (associated with bond breaking), and ΔV* k₃ in turn is slightly negative, ΔV* k₃ is expected to be either small positive or slightly negative. It is thus clear from (9), that depending on the relative magnitude of the volume change associated with K₃ and K₄, that either an I₄ or I₃ mechanism is possible. However, since an overall negative tendency for ΔV* exp, was obtained, an associative interchange mechanism is considered more likely for the NCS⁻ reaction, since there should be significant electrostriction between the NCS⁻ and [M]⁻ species. For the neutral thiourea ligands, an even larger negative activation volume is observed, and a pure associative mode of activation could well be operative.

Upon comparison of the trans-substitution reactions on the [ReO(OH₂)(CN)₄]⁻ and [TcO(OH₂)(CN)₄]⁻ complexes (Table 2), a few other interesting observations are also made.

Firstly, for the [ReO(OH₂)(CN)₄]⁻ complex, the order of reactivity for the ligands are: NMTU > NNDMTU > TU > NCS⁻ > HN₃ and for the [TcO(OH₂)(CN)₄]⁻ complex: NCS⁻ > NNDMTU > NMTU > TU. It is clear that the NCS⁻ ligand shows the fastest reaction with the Tc centre (ca. 6300 times faster), but the slowest reaction with the Re centre [see relative ratio of k₃/Tc/k₅/Re in Table 2]. A comprehensive explanation of this rate difference is not yet possible. It is, however, known that the TcV centre can more readily accept electron density than does the ReV [50, 51] and to some extent favour, in spite of the negative charge on the NCS⁻ as entering ligand, association with the TcV centre. This is, however, not manifested in the activation volumes. The rate constants of the thiourea ligands are more comparable, showing a great deal of consistency for both metal centres, although a slight dependence on steric bulk/electron density of the TU ligands is apparent, but cannot currently be convincingly explained, see below.

Secondly, since it is known that methyl substituents on a ligand can increase the pKa value and therefore the electron donating ability thereof (see examples in Table 3 [52]), it is expected in an associative mechanism that the methyl substituted thiourea will react slightly faster than TU, as was concluded from this work on the ReV system.

Thirdly, the [MO(OH₂)(CN)₄]⁻ compounds of TcV and ReV react both according to an associative mechanism or partly associative, while the MoIV and WIV compounds react via a dissociative mechanism. From this, it is clear that the work done on the MoIV and WIV centres, although all isostructural d² species, cannot be applied directly to the TcV and ReV centres, as assumed previously [13]. It also implies that the higher-oxidation state of the TcV and ReV centres favour the more associative activation, while the MoIV and WIV could favour a dissociative activation mode.

However, even more detailed high-pressure studies, to enable construction of complete volume profiles, are required in future.

These results, along with the fact that the Tc(V) centre is much more reactive than the Re(V), is of particular relevance to nuclear medicine. In the preparation of ⁹⁹mTc radiopharmaceuticals or in the labelling of antibodies with ⁹⁹mTc, “transfer” ligands are often used to stabilize the required oxidation state, and then the actual labelling is accomplished by simple ligand substitution onto the “transfer complex” [53]. From this work, the best way of optimizing labelling conditions would be to use a S-donor transfer ligand instead of a C- or N-donor transfer ligand so that the exchange process would be dissociative in nature. This would imply that the transfer ligand, rather than the concentration of the antibody or chelating moiety attached to the antibody, would influence the reaction rate and yield a much “cleaner” reaction mixture (concentration of unlabeled antibody in solution would be low). Furthermore, the greater reactivity of Tc compared to Re must be taken into account when developing therapeutic radio-rhenium analogues to known diagnostic ⁹⁹mTc radiopharmaceuticals. For example, more drastic conditions are required in the preparation of ¹⁸⁶Re diphosphonates (for bone imaging) than in the preparation of ⁹⁹mTc diphosphonates [54]. These differences in reactivities between TcV and ReV centres needs to be taken into account before procedures that are needed for ⁹⁹mTc.
available for certain technetium complexes are applied to the preparation of the rhenium analogues.

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