18. Multinuclear NMR Studies of Ligand-Exchange Reactions on Analogous Technetium(V) and Rhenium(V) Complexes. Relevance to Nuclear Medicine

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The kinetics of pyridine exchange on *trans*-$[MO_2(py)_4]^+$ have been followed by ^{1}H-NMR in CD_3NO_2 for M = Re, Tc: $k^{298}/s^{-1} = (5.5 \pm 0.1) \times 10^{-6}$, 0.04 ± 0.02; $\Delta H^{\neq}$/kJmol^{-1} = 111 ± 3, 101 ± 9; $\Delta S^{\neq}$/JK^{-1}mol^{-1} = +28 ± 10, +68 ± 35. For the Re^V complex, pyridine and oxygen exchanges have been measured simultaneously by ^{1}H- and ^{17}O-NMR in deuterated water: $k^{298}/s^{-1} = (8.6 \pm 0.2) \times 10^{-6}$ (py), $(14.5 \bullet 0.3) \times 10^{-6}$ (oxygen); $\Delta H^{\neq}$/kJmol^{-1} = 111 ● 1, 91 ± 1; $\Delta S^{\neq}$/JK^{-1}mol^{-1} = +32 ± 3, −32 ± 4. For both complexes, the rate law for pyridine exchange is first-order in complex and zero-order in pyridine; together with the activation parameter values, and the fact that the rate does not depend significantly on the nature of the solvent, this strongly implies the operation of a dissociative mechanism. The ratio of pyridine exchange rates for the Tc and Re complexes at room temperature is *ca.* 8000. The consequences of these observations for radiopharmaceutical synthesis are discussed.

Introduction. – The kinetics and mechanism of ligand substitution onto analogous Tc^V and Re^V centers are of fundamental interest in inorganic chemistry, since the relative reactivities of second- and third-row congeners have not been well studied and are thus poorly understood. However, understanding the fundamental factors which control these reactions is of more immediate concern to the field of nuclear medicine wherein ligand substitution onto Tc^V and Re^V centers forms the basis for many radiopharmaceutical syntheses [3] [4].

Prior to our work [2] [5], the only report known to us, wherein the relative rates of substitution of analogous Tc^V and Re^V complexes have been investigated, was that by *Fritzberg* and coworkers [6]. However, this study involves the unimolecular racemization of analogous penicillamine complexes and is thus not directly relevant to the reactions employed in radiopharmaceutical syntheses. To probe the possibility that analogous Tc^V and Re^V complexes undergo significantly different rates of ligand substitution, we have used NMR techniques to measure the rate of pyridine exchange on the cationic M^V complexes *trans*-$[MO_2(py)_4]^+$ (M = Tc, Re) in the nonaqueous solvent CD_3NO_2. A series of experiments was also performed on the Re complex in D_2O in order to determine the relative rates of pyridine and oxygen exchange on *trans*-$[ReO_2(py)_4]^+$, and to assess the solvent dependence for pyridine exchange on this complex.

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Experimental. – *Materials. Caution!* All references to Tc in this paper are to the isotope ^{99}Tc which emits a low-energy (0.292 MeV) β particle with a half-time of 212000 years. When this material is handled in mg amounts, it does not present a serious health hazard, since common laboratory materials provide adequate shielding. *Bremsstrahlung* is not a significant problem due to the low energy of the β particle emission, but normal radiation safety procedures must be used at all times, especially when dealing with solid samples, to prevent contamination and inadvertent inhalation.

The *trans*-dioxotetrakis(pyridine)metal(V) (M = Tc, Re) cations were prepared by standard literature procedures [7] [8] and isolated as the trifluoromethanesulfonate salts which were then crystallized three times from warm aq. solns. containing a small amount of free pyridine. The identities of the *trans*-$[MO_2(py)_4]F_3CSO_3$ salts were confirmed by elemental analyses and NMR (*vide infra*); each salt exhibited only one spot when subjected to two different TLC analyses. The ^{17}O-enriched $[ReO_2(py)_4]^+$ cation was prepared from ^{17}O-enriched water according to the procedure used by *Kashini* and *Murmann* to generate the ^{18}O-enriched analog [9].

NMR Measurements. The rate at which perdeuterated pyridine ((D_5)py) replaces pyridine (py) in the coordination sphere of *trans*-$[MO_2(py)_4]^+$ (M = Tc, Re) was monitored in CD_3NO_2 by recording 200-MHz ^{1}H-NMR spectra on a *Bruker CXP-200* spectrometer (4.7-T wide-bore magnet, 5-mm ∅ ^{1}H selective probe). 8-K data points were acquired using a frequency range of 3000 Hz and a pulse length of 2 μs. Twelve to 100 transients were added prior to *Fourier* transformation; 30–50 FIDs were measured in fixed time intervals and stored on disk.

The rate at which py and ^{17}O are replaced by (D_5)py and water-oxygen in the coordination sphere of ^{17}O-enriched *trans*-$[ReO_2(py)_4]^+$ were simultaneously monitored in D_2O by recording alternatively 400-MHz ^{1}H-NMR and 54.24-MHz ^{17}O-NMR spectra on a *Bruker AM-400* spectrometer (9.4-T wide-bore magnet, 10-mm ∅ broad-band probe). The experiments were performed automatically and both series of spectra stored separately on disk. The NMR parameters for ^{1}H (^{17}O) spectra were: 8-K (2-K) data points, 6000-Hz (50000-Hz) frequency range, 20-μs (14-μs) pulse width, 4–32 (15000 to 100000) transients added.

In the case of very slow substitution reactions ($k < 3 \times 10^{-4}$ s^{-1}), the solns. were rapidly prepared and transferred into the NMR probe. For the relatively fast substitutions on the Tc complex, as well as for the measurements on the Re complex at high temperatures ($T > 325$ K), the samples were mixed by help of a fast injection apparatus as described in [10]. The temp. was controlled by a *Bruker B-VT 1000* temp. controller and measured by substituting the sample tube by a tube containing a Pt resistor [11].

Data Treatment and Results. – *Pyridine Exchange on* trans-$[ReO_2(py)_4]^+$ *in* CD_3NO_2. The ^{1}H-NMR spectra of *trans*-$[ReO_2(py)_4]^+$ in CD_3NO_2 shows three multiplets corresponding to the three types of bound pyridine H-atoms (*Table 1*). All three are shifted to higher frequencies with respect to free pyridine resonances. The substitution reaction (*Eqn. 1*) was followed by recording the ^{1}H-NMR spectra as a function of time after

Table 1. *^{1}H-NMR Chemical-Shift Data of Free Pyridine,* trans-$[ReO_2(py)_4]^+$, *and* trans-$[TcO_2(py)_4]^+$ *in* CD_3NO_2 *Relative to TMS*

Protons at	δ/ppm		
	Pyridine	$[ReO_2(py_4)]^+$	$[TcO_2(py_4)]^+$
C(2), C(6)	8.55	9.14	9.31
C(3), C(5)	7.29	7.51	7.50
C(4)	7.70	7.73	7.95

$$trans\text{-}[MO_2(py)_4]^+ + 4\ (D_5)py \rightleftharpoons trans\text{-}[MO_2((D_5)py)_4]^+ + 4\ py\ (M = Tc, Re) \quad (1)$$

mixing CD_3NO_2 solutions of *trans*-$[ReO_2(py)_4]^+$ and of (D_5)pyridine. Since (D_5)pyridine is chemically equivalent to pyridine, all four steps of the substitution reaction are identical, and the kinetics of the net process can be analyzed as a single step, first-order approach to equilibrium. We use the integrals of the resonances of protons at C(2) and C(6) on bound and free pyridine (at 9.14 ppm and 8.55 ppm, respectively) to monitor the mole fraction x

of bound pyridine as a function of time. As shown in [12], the variation of x with time is given by *Eqn. 2*, where k represents the rate constant for the exchange of a particular

$$-\mathrm{d}x/\mathrm{d}t = k\,(x-x_\infty)/(1-x_\infty) \tag{2}$$

coordinated pyridine molecule and x_∞ is the mole fraction of bound pyridine at equilibrium. Integration of *Eqn. 2*, with the condition that at $t = 0$ the mole fraction of bound pyridine is x_0, leads to *Eqn. 3*. This equation was fitted to the mole fractions x using k, x_∞, and x_0 as adjustable parameters.

$$x = x_\infty + (x_0-x_\infty)\exp[-k\,\mathrm{t}/(1-x_\infty)] \tag{3}$$

In a first series of experiments performed at fixed temperatures, the initial concentrations of *trans*-$[ReO_2(py)_4]^+$ and (D_5)pyridine were varied. The resulting exchange rates k (*Table 2*) are independent of complex and free pyridine concentrations, leading to the rate-law (*Eqn. 4*).

$$-\mathrm{d}[MO_2(py)_4^+]/[MO_2(py)_4^+]\mathrm{d}t = k \tag{4}$$

In a second series of experiments, the temperature was varied and the results (*Table 3*) fitted to the *Eyring* equation: $k^{298}/s^{-1} = (5.5 \pm 0.1) \times 10^{-6}$, $\Delta H^{\neq}/kJmol^{-1} = 111.3 \pm 3$ and $\Delta S^{\neq}/JK^{-1}mol^{-1} = +27.8 \pm 10$.

Pyridine Exchange on trans-$[TcO_2(py)_4]^+$ *in* CD_3NO_2. The ^{1}H-NMR spectrum of the Tc complex is very similar to that of the Re analog. The chemical shifts of the protons at

Table 2. *Pyridine-Substitution Rates on* trans-$[MO_2(py)_4]^+$ *in* CD_3NO_2 *at Various Sample Compositions*

M	T/K	10^2 [M]/m	10^2 [py]/m	$10^4 k/s^{-1}$
Re	334.4	1.1	4.1	8.0 ± 0.3
		1.0	12	7.5 ± 0.1
		1.1	37	8.2 ± 0.2
		2.6	9.7	8.4 ● 0.2
		0.39	4.3	8.0 ± 0.4
	333.0	0.26	1.4	5.9 ± 0.8
		0.97	9.9	6.0 ± 0.7
Tc	277.5	1.1	6.7	2.1 ± 0.1
		1.1	20	1.9 ± 0.1
		1.1	37	2.0 ± 0.1
		0.5	24	2.3 ± 0.1

Table 3. *Pyridine-Substitution Rates on* trans-$[MO_2(py)_4]^+$ *in* CD_3NO_2 *at Various Temperatures*

M = Re[a])		M = Tc			
T/K	$10^4 k/s^{-1}$	T/K	10^2 [Tc]/m	10^2 [py]/m	$10^4 k/s^{-1}$
295.7	0.041 ● 0.003	252.0	1.1	23	0.018 ± 0.0003
304.6	0.14 ± 0.03	258.3	0.50	29	0.091 ± 0.001
314.5	0.51 ± 0.01	268.1	0.51	22	0.39 ± 0.12
324.2	2.6 ± 0.1	277.5	1.1	20	1.9 ± 0.1
334.4	7.5 ● 0.1				
344.2	27 ± 2				

[a]) 10^2 [Re]/m = 1.0 and 10^2 [py]/m = 12.

C(2), C(4), and C(6) appear at slightly higher frequencies for the Tc^{V} complex relative to the Re^{V} analog (*Table 1*). The pyridine exchange rates were studied by the same general techniques as used for the Re^{V} system, and, as for the Re^{V} complex, variations in the complex and free pyridine concentration have no effect on the observed Tc^{V} exchange rates (*Table 2*). The experimentally accessible temperature range for this Tc^{V} system is smaller (*Table 3*), and thus the calculated activation parameters have larger associated errors: $k^{298}/s^{-1} = 0.04 \pm 0.02$, $\Delta H^{\neq}/kJmol^{-1} = 101.1 \pm 9$ and $\Delta S^{\neq}/JK^{-1}mol^{-1} = +68 \pm 35$.

Pyridine and Oxygen Exchange on trans-$[ReO_2(py)_4]^+$ *in* D_2O. The goals of this series of experiment were *i*) to compare, under the same experimental conditions, pyridine and oxygen exchange (*Eqn. 5*) on the Re^{V} complex, and *ii*) to provide some measure of the solvent dependence of pyridine exchange on this Re^{V} center. The experiments were

$$trans\text{-}[Re^{17}O_2(py)_4]^+ + 2D_2O \rightleftharpoons trans\text{-}[ReO_2(py)_4]^+ + 2D_2{}^{17}O \qquad (5)$$

performed in D_2O, and both reactions followed simultaneously after dissolution of 10% ^{17}O-enriched *trans*-$[ReO_2(py)_4]^+$ in D_2O containing (D_5)pyridine. The evolution with time of the mole fraction x of bound pyridine was followed as previously by integration of the ^1H-NMR signals of the protons at C(2) and C(6) on bound and free pyridine (*Fig., A*);

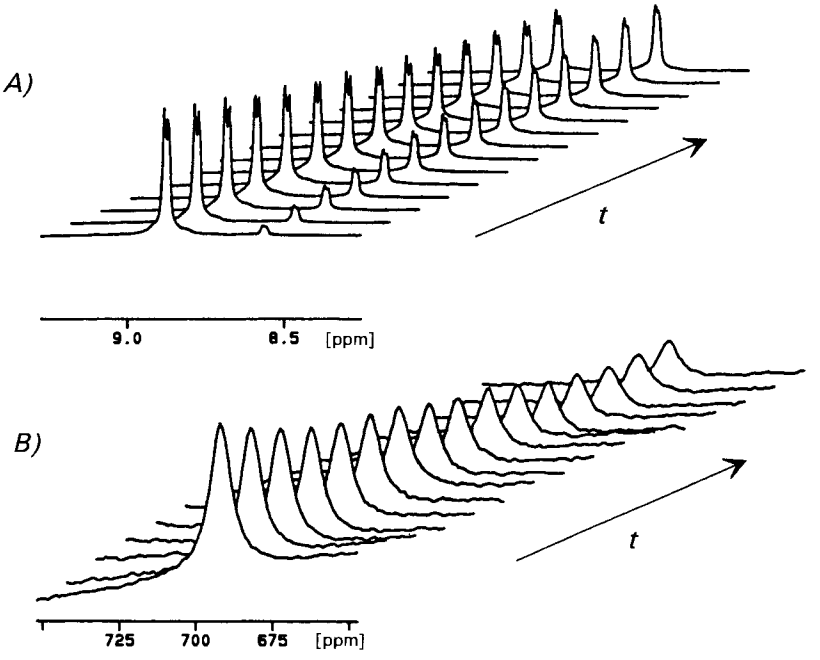

Figure. *Pyridine and oxygen exchange on* trans-$[ReO_2(py_4)]^+$ *in* D_2O *at 296.6 K.* A) *Decrease of the* ^1H*-NMR signal of bound pyridine* (protons at C(2) and C(6)) *and increase of the signal of the corresponding protons on free pyridine due to pyridine exchange.* B) *Decrease of of the* ^{17}O*-NMR signal with time due to exchange between the bound* ^{17}O*-enriched site with the non-enriched* D_2O. The time interval between plotted spectra is 147 min in both cases.

exchange rates of the O-atoms of the Re^{V} complex were also assessed within *Eqn. 3*. The ^{17}O-NMR spectrum of *trans*-$[Re^{17}O_2(py)_4]^+$ shows the oxo signal (line width = 287 Hz at 307.8 K) 524 ppm downfield from the $D_2{}^{17}O$ signal. To obtain the evolution of the mole fraction of bound ^{17}O as a function of time, it was not possible to perform a direct electronic integration of the two resonances lines due to the large difference in intensity of the two sites observed. The procedure used was to plot both ^{17}O resonances on different scales, measure the hights and widths of the signals with a ruler, and finally calculate the mole fractions from these data by taking into account the proper scaling factors. The calculated exchange rates, obtained at four temperatures, are reported in *Table 4*. These

Table 4. *Pyridine- and Oxygen-Exchange Rates on* trans-$[ReO_2(py)_4]^+$ *in* D_2O (pH 7.61) *at Various Temperatures*

T/K	10^2 [Re]/m	10^2 [py]/m	$10^4 k$ (pyridine)/s^{-1}	$10^4 k$ (oxygen)/s^{-1}
296.6	0.66	13	0.068 ± 0.001	0.12 ± 0.003
312.9	0.74	15	0.73 ± 0.01	0.84 ± 0.03
324.0	0.72	14	3.4 ± 0.1	3.0 ± 0.4
308.3	0.70	1.9	0.62 ± 0.01[a])	0.97 ± 0.06[a])

[a]) Values obtained at very low free-pyridine concentration.

values were used to calculate the activation parameters for pyridine exchange: $k^{298}/s^{-1} = (8.6 \pm 0.2) \times 10^{-6}$, $\Delta H^{\neq}/kJmol^{-1} = 111 \pm 1$, $\Delta S^{\neq}/JK^{-1}mol^{-1} = +32 \pm 3$ and for oxygen exchange: $k^{298}/s^{-1} = (14.5 \pm 0.3) \times 10^{-6}$, $\Delta H^{\neq}/kJmol^{-1} = 91 \pm 1$, $\Delta S^{\neq}/JK^{-1}mol^{-1} = -32 \pm 4$. The value of k^{298} observed for oxygen exchange by ^{17}O-NMR is very similar to the value observed under similar conditions by *Kashani* and *Murmann* using classical ^{18}O-exchange techniques (12×10^{-6} s^{-1} at very low pyridine concentrations) [9].

Discussion. – The data of *Table 1* show that, as expected, both cationic M^{V} centers cause the proton signals of the coordinated pyridine ligands to shift downfield from those of noncoordinated pyridine. Also, as expected, this simple inductive effect of the cationic center is most strongly felt at C(2) and C(6) which are closest to the metal center, and least felt at the remote C(4). Somewhat more surprisingly, the Tc^{V} center effects a significantly larger shift in the positions of the signals of the protons at C(2), C(6), and C(4) than does the Re^{V} center, while both centers have the same effect on the position of the protons at C(3) and C(5). While the greater effect on the signals of the protons at C(2), C(6), and C(4) may readily be ascribed to the more acidic character of Tc^{V} relative to Re^{V}, the equivalent effect of the two centers on the protons at C(3) and C(5) must result from a combination of σ- and π-electronic interactions. A complete understanding of these interaction will have to await additional studies on analogous Tc^{V} and Re^{V} complexes. Coordination of oxygen to the acidic Re^{V} core also causes the chemical shift of this atom to move downfield from that in noncoordinated water. The ^{17}O chemical shift observed within the +1 charged *trans*-$[ReO_2]^+$ core (524 ppm) is about one-half of that observed within the +2 charged *trans*-$[UO_2]^{2+}$ core (1121 ppm) [13].

Sequential displacement of the four py ligands of $[MO_2(py)_4]^+$ by an incoming ligand X potentially involves the four intermediate complexes *trans*-$[MO_2(py)_3X]^+$, *trans*(O), *trans*(X)-$[MO_2(py)_2X_2]^+$, *trans*(O),*cis*(X)-$[MO_2(py)_2X_2]^+$, and *trans*-$[MO_2(py)X_3]^+$, in ad-

dition to the starting complex *trans*-$[MO_2(py)_4]^+$ and the product *trans*-$[MO_2X_4]^+$. Thus, studies wherein X is a ligand different from py are inherently complicated and difficult to interpret [14]. For this reason, we chose to evaluate the kinetics of the pyridine exchange reaction (*Eqn. 1*), wherein the entering and leaving groups are identical. In this system, the exchange follows strict first-order kinetics, and interpretation of the kinetic data is straightforward.

The rate law for pyridine exchange (*Eqn. 1*) is first-order in concentration of complex and zero-order in concentration of (D_5)py; this implies that for both Tc and Re complexes the rate-determining step in the pyridine exchange process is dissociative in character. While both centers undergo pyridine exchange by the same rate law, the actual rates governing this exchange process are markedly different (*Table 5*). The rate of ligand exchange on the Re^V complex is so slow that the solutions must be heated in order to promote a reasonable rate of reaction (at 25° the extrapolated half-life for pyridine exchange on *trans*-$[ReO_2(py)_4]^+$ is *ca.* 35 h). Contrariwise, the rate of pyridine exchange on the Tc^V complex is so rapid that the solutions must be cooled in order to attain a reasonable rate of reaction (at 25° the extrapolated half-life for pyridine exchange on *trans*-$[TcO_2(py)_4]^+$ is *ca.* 15). Thus, the ratio of pyridine exchange rates for the Tc and Re complexes, k^{Tc}/k^{Re}, at room temperature is *ca.* 8000. This very large ratio of exchange rates for a neutral ligand situated *cis* to a M=O linkage is remarkably similar to the ratio of exchange rates we have observed for an anionic ligand situated *trans* to a M=O linkage [2] [5] [15]: for *trans*-$[MO(OH_2)(CN)_4]^-$, the ratio of rates governing replacement of water by thiocyanate is $k^{Tc}/k^{Re} = 6400$ at room temperature.

All the data obtained in this study are consistent with pyridine exchange on *trans*-$[MO_2(py)_4]^+$ (M = Tc, Re) centers occurring by a predominantly dissociative process: *i*) the rate law is independent of the concentration of excess pyridine, *ii*) the entropies of activation are positive, and *iii*) for the single complex evaluated (M = Re) the rate is not sensitive to whether the solvent is CD_3NO_2 or D_2O. The conclusion that M^V–py bond cleavage dominates the activation process is entirely consistent with observations made by *Lu* and *Clarke* on the reactions of *trans*-$[TcO_2(py)_4]^+$ in a variety of nonaqueous solvents (*Table 5*) [14]. Of further mechanistic interest is the observation that, for

Table 5. *Rate Constants and Activation Parameters for Substitution Reactions onto* trans-$[MO_2(py)_4]^+$ (M = Re, Tc) *in Various Solvents*

		k^{298}/s^{-1}	$\Delta H^{\neq}/kJmol^{-1}$	$\Delta S^{\neq}/JK^{-1}mol^{-1}$	Ref.
trans-$[ReO_2(py)_4]^+$ in					
CD_3NO_2	py exchange	$(5.5 \pm 0.1) \times 10^{-6}$	111.3 ± 3	$+27.8 \pm 10$	this work
D_2O[a])	py exchange	$(8.6 \pm 0.2) \times 10^{-6}$	111 ± 1	$+32 \pm 3$	this work
	O exchange	$(14.5 \pm 0.3) \times 10^{-6}$	91 ± 1	-32 ± 4	this work
trans-$[TcO_2(py)_4]^+$ in					
CD_3NO_2	py exchange	0.04 ± 0.02	101.1 ± 9	$+68 \pm 35$	this work
MeOH	py substitution[b])	0.10	97.6 ± 3	$+63.5 \pm 2.5$	[14]
EtOH	py substitution[b])	0.05	94.2 ± 6	$+46.2 \pm 4$	[14]
MeOH/DMF	py substitution[b])	0.16	99.6 ± 3	$+74.1 \pm 3$	[14]
DMF	py substitution[b])	0.19	74.0 ± 5	-10.6 ± 1	[14]

[a]) From data at 296.6, 312.9, and 324.0 K in *Table 4*.

[b]) For the reaction: *trans*-$[TcO_2(py)_4]^+ + apy \rightarrow$ *trans*-$[TcO_2(py)_3(apy)]^+ + py$, where apy = 4-aminopyridine.

trans-$[ReO_2(py)_4]^+$ in D_2O, the values of the normalized oxygen-exchange rate and normalized pyridine-exchange rate are very similar; *e.g.*, at 298 K $2k(\text{oxygen})/10^6 s^{-1} = 29 \pm 1$ and $4k(\text{pyridine})/10^6 s^{-1} = 34 \pm 1$. This implies that oxygen exchange occurs upon essentially every pyridine exchange, and thus the two exchange processes may well be coupled. Such coupling would likely occur through the existence of a common intermediate, many of which can be readily hypothesized for this system; the structure of one such intermediate is given by *Kashani* and *Murmann* [9].

In conclusion, this study establishes definitively that for analogous Tc^V and Re^V complexes the Tc species undergoes ligand substitution significantly more rapidly than does its Re congener. When our current results on the *trans*-$[MO_2(py)_4]^+$ complexes are combined with our other studies on the *trans*-$[MO(OH_2)(CN)_4]^-$ complexes [2] [5] [15], it is clear that the phenomenon is independent of whether the complexes are cationic or anionic, whether substitution occurs *cis* or *trans* to the M=O linkage, or whether the reaction is conducted in aqueous or nonaqueous media. For all conditions, the Tc^V complexes react three to four orders of magnitude faster than do the Re^V analogs. This observation has direct consequences for radiopharmaceutical syntheses; *i.e.*, it can be anticipated that reaction conditions optimized for the transfer of Tc^V 'cores' will *not* directly apply to the transfer of analogous Re^V 'cores'. This in turn means that new reaction conditions must be developed to synthesize Re analogs to existing Tc radiopharmaceuticals.

Moreover, all mechanistic evidence acquired to date implies that substitution onto Tc^V and Re^V centers is dissociative in character; that is, the substitution process is dominated by bond cleavage and not by bond formation. Thus, rate effects generated by varying the nature of the entering ligand will be minimal. This observation again has direct consequences for radiopharmaceutical syntheses. Specifically, within a given system the most effective means that can be used to increase the rate of substitution reactions on Re^V will *not* be to vary the nature of the entering group, but rather to vary the nature of the non-reacting end of the leaving groups. Finally, it may be possible to utilize the greater tendency of Re (relative to Tc) to expand its coordination number, in order to generate totally different mechanisms for ligand exchange on Re which would circumvent the inherently slower kinetics of ligand substitution on Re centers.

The results already obtained from these initial studies into the kinetics and mechanisms of ligand substitution reactions on analogous Re and Tc centers are clearly relevant to the development and understanding of new radiopharmaceuticals. Further fundamental studies are planned to increase our understanding of the various factors governing the relative reactivities of Tc and Re complexes that are important in nuclear medicine.

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