Inorg. Chem. **2003**, *42*, 2960–2967

Inorganic Chemistry
Article

Synthesis and Characterization of Novel ^{99g}Tc(V) and Re(V) Complexes with Water-Soluble Tetraaza Diamido Dipyridino Ligands: Single-Crystal X-ray Structural Investigations of Mono- and Dinuclear Complexes

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Received July 2, 2002

Rhenium and technetium are known for their useful applications in nuclear medicine with similar properties. In this study, new diamido dipyridino (N_4) water-soluble ligands $(2\text{-}C_5H_4NCH_2NHCO)_2CH_2$, **1** ($L^1H2$), $(2\text{-}C_5H_4NNHNHCO)_2CH_2$, **2**, and $[2\text{-}C_5H_4N^+(O)^-CH_2NHCO]_2CH_2$, **3**, were synthesized. Reaction of L^1H2 with $ReOCl_3(PPh_3)_2$ resulted in the novel six-coordinated rhenium(V) complex, *trans*-$ReO(L^1)(OEt)$, **4**. The complex was characterized by spectroscopic methods, and its X-ray crystallographic analysis revealed that rhenium is coordinated to four nitrogen atoms of the ligand and to two oxygen atoms from the deprotonated ethanol and the oxo group respectively in a distorted octahedral geometry. In solution, complex **4** was transformed to a new complex **5**, which was proved to be the dinuclear complex μ-oxo $[ReO(L^1)]_2O$. Reaction of **1** with $[n\text{-}Bu_4N][ReOCl_4]$ resulted in the neutral complex **6**, *trans*-$[ReO(L^1)]Cl$. Similarly, when ligand **1** was reacted with $[n\text{-}Bu_4N][^{99g}TcOCl_4]$, the neutral *trans*-$[^{99}TcO(L^1)]Cl$ complex **7** was formed, which upon dissolution transformed into a cationic complex **8**, *trans*-$[^{99}TcO(L^1)(OH_2)]^+Cl^-$. The single-crystal X-ray structure of **8** reveals that the coordination sphere about technetium is a distorted octahedron with four nitrogen atoms in the equitorial plane, while doubly bonded oxygen and coordinated water occupy the apical positions. Further dissolution of **8** resulted in the formation of dinuclear μ-oxo $[TcO(L^1)]_2O$, **9**. This study shows that Tc and Re have similar metal core structures in solution for diamido dipyridino systems, besides similarity in geometrical structure, proved by the X-ray structures on the same ligands.

1. Introduction

The chemistry of technetium and rhenium involves several oxidation states from I to VII.[1−3] ^{99m}Tc-based radiopharmaceuticals have received considerable attention owing to (a) the availability of high specific activity $^{99m}TcO_4^-$ generators, virtually in a majority of hospitals, (b) high diagnostic/clinical potential of ^{99m}Tc to image cancer, and (c) optimum decay energies (140 keV) that permit a minimum dose burden to patients.[4−6] Re, a congener of Tc, is also available as ^{186}Re (β^-, $t_{1/2} = 90.0$ h) and ^{188}Re ((β^-, $t_{1/2} = 17.0$ h) radioisotopes,

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(1) (a) Dilworth, J. R.; Parrott, S. J. The biomedical chemistry of technetium and rhenium. *Chem. Soc. Rev.* **1998**, *27*, 43−55. (b) Johannsen B; Spies, H. Technetium(V) chemistry as relevant to nuclear medicine. *Top. Curr. Chem.* **1996**, *176*, 79−121. (c) Barrera, J.; Burrell, A. K.; Bryan J. C. *Inorg. Chem.* **1996**, *35*, 335−341.

(2) Refosco T. F.; Bandoli G. Structural survey of technetium complexes. *Coord. Chem. Rev.* **1994**, *135/136*, 325−397.

(3) (a) Hjelstuen, O. K. Technetium-99m chelates in nuclear medicine. *Analyst* **1995**, *120*, 863−866. (b) Alberto, R. High and low valency organometallic compounds of Technetium and Rhenium. *Top. Curr. Chem.* **1996**, *176*, 149−187.

(4) (a) Jurisson, S.; Berning, D.; Jia, W.; Ma, D. *Chem. Rev.* **1993**, *93*, 1137−1156. (b) Schwochau, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2258−2267. (c) Eckelman, W. C. *Eur. J. Nucl. Med.* **1995**, *22*, 249−263. (d) Top, S. E.; Hafa, H.; Vessieres, A.; Quivy, J.; Vaissermann, J.; Hughes, D. W.; McGlinchey, M. J.; Mornon, J. P.; Thoreau, E.; Jaouen, G. *J. Am. Chem. Soc.* **1995**, *117*, 8372−8380 (e) Schubiger, P. A.; Alberto, R.; Smith, A. *Bioconjugate Chem.* **1996**, *7*, 165−179. (f) Hom, R. K.; Katzenellenbogen, J. A. *Nucl. Med. Biol.* **1997**, *24*, 485−498. (g) Alberto, R.; Schibli, R.; Egli, A.; Schubiger, A. P.; Abram, U.; Kaden, T. A. *J. Am. Chem. Soc.* **1998**, *120*, 7987−7988. (h) Spradau, T. W.; Katzenellenbogen, J. A. *Organometallics* **1998**, *17*, 2009−2017. (i) Waibel, R.; Alberto, R.; Willuda, J.; Finnern, R.; Schibli, R.; Stichelberger, A.; Egli, A.; Abram, U.; Mach, J. P.; Pluckthun, A.; Schubiger, P. A. *Nat. Biotechnol.* **1999**, *17*, 897−901.

10.1021/ic020434q CCC: $25.00

which have been used in oncology.[7−9] In fact, ^{99m}Tc and $^{186/188}$Re are complementary to each other for imaging and therapy, respectively. However, ^{99m}Tc is available at tracer levels, which does not permit characterization of Tc complexes by routine spectroscopic and analytical methods. Hence, studies are performed by using either the long-lived radionuclide ^{99g}Tc ($t_{1/2} = 2.2 \times 10^5$ years) or its congener, the nonradioactive Re. The extension of studies on Re and ^{99g}Tc to the corresponding radionuclides had a tremendous impact on the development of radiopharmaceuticals applied to clinical nuclear medicine.[10−13] Particularly, coordination studies of Tc(V) and Re(V) with tetradentate N_2S_2, N_2O_2, N_3S, N_2P_2, and S_2P_2 type ligands[14−18] that can be attached to the biomolecule of interest played an important role in the development of receptor-based tumor-specific diagnostic and therapeutic radiopharmaceuticals.

Pyridine-based ligands are soft donors and function as both good σ-donors and moderate π-acid ligands, which can form stable complexes with the transition metals.[1c] Recently, a hydrazinopyridine Tc complex[19] (HYNIC) was reported in high specific activity (3 Ci/μmol) although addition of coligands (e.g. phosphines, tricine, carboxylic acid) was required to improve the radiochemical purity of the eventual complex.[20] In general, radiopharmaceutical preparations in a clinical setting require that the preparative methods be simple, adoptable to formulation of instant kits using TcO_4^- as a starting material, and preferably amenable to one pot synthesis.[21] Hence, effort to design a multidonor framework with basic pyridine nitrogens and amide nitrogens for chelation to Tc or Re has resulted in new water-soluble tetraaza type chelating agents that can be functionalized through the acidic methylene protons of the malonamide backbone to obtain bifunctional chelating agents (BFCAs) for further attachment to a biomolecule of interest.

As a part of our investigations into the design and attachment of BFCAs to photoprobes,[22] receptor antagonist,[23] enzyme inhibitors,[24] and Fab fragments,[25] we report here the synthesis and characterization of tetradentate ligands that contain pyridine and amide nitrogen atoms for the formation

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(5) Hoffman, T.; Volkert, W. A. *Chem. Rev.* **1999**, *99*, 2269−2292. (b) Volkert, W. A. Ligand systems useful in designing high specific activity ^{99m}Tc or ^{186}Re;^{188}Re radiopharmaceuticals. In *Technetium and Rhenium in Chemistry and nuclear Medicine*, 4th ed.; Nicolini, M., Mazzi, U., Eds.; Cortina International: Verona, Italy, 1994; pp 239−242.

(6) (a) Volkert, W. A.; Jurisson S. Technetium-99m chelates as radiopharmaceuticals. In *Topics in Current Chemistry*; Yoshihara, K., Omori, T., Eds.; Springer-Verlag: Berlin, 1996; Vol. 176, pp 124−148.

(7) (a) Mäcke, H. R.; Heppeler, A.; Nock, B. In *Technetium, Rhenium and Other Metals in Chemistry and Nuclear Medicine 5*; Nicolini, M., Mazzi, U., Eds.; Padova, Italy, 1999; pp 77−91. (b) Fischman, A. J.; Babich, J. W.; Strauss, H. W. *J. Nucl. Med.* **1993**, *34*, 2253−2263. (c) Reubi, J. C. *J. Nucl. Med.* **1995**, *36*, 1825−1835. (d) Nock, B.; Maina, T.; Raptopoulou, C. P.; Terzis, A.; Chiotellis, E. *Inorg. Chem.* **2000**, *39*, 5197−5202.

(8) (a) Liu, S.; Edwards, D. S. *Chem. Rev.* **1999**, *99*, 2235−2268. (b) Hom, R. K.; Katzenellenbogen, J. A. *Nucl. Med. Biol.* **1997**, *24*, 485−498.

(9) Mullen, G. E. D.; Blower, P. J.; Price, D. J.; Powell, A. K.; Howard, M. J.; Went, M. J. *Inorg. Chem.* **2000**, *39*, 4093−4098. (b) Skaddan, M. B.; Katzenellenbogen, J. A. *Bioconjugate Chem.* **1999**, *10*, 119−129. (c) Bell, R. A.; McCarry, B. E; Vallient, J. F. *Inorg. Chem.* **1998**, *37*, 3517−3520.

(10) (a) Su, Z.-F.; Ballinger, J. R.; Rauth, A. M.; Abrams, D. N.; Billinghurst, M. W. *Bioconjugate Chem.* **2000**, *11*, 652−663. (b) Zhang, X.; Su, Z.-F.; Ballinger, J. R.; Rauth, A. M.; Pollak, A.; Thornback, J. R. *Bioconjugate Chem.* **2000**, *11*, 401−407. (c) Lente, G.; Shan, X.; Guzei, I. A.; Espenson, J. H. *Inorg. Chem.* **2000**, *39*, 3572−3576.

(11) (a) Hunter, D. H.; Luyt, L. G. *Bioconjugate Chem.* **2000**, *11*, 175−181. (b) Luyt, L. G.; Jenkins, H. A.; Hunter, D. H. *Bioconjugate Chem.* **1999**, *10*, 470−479. (c) Polyakov, V.; Sharma, V.; Dahlheimer, J. L.; Pica, C. M.; Luker, G. D.; Piwnica-Worms, D. *Bioconjugate Chem.* **2000**, *11*, 762−771. (d) Yamamura, N.; Magata, Y.; Arano, Y.; Kawaguchi, T.; Ogawa, K.; Konishi, J.; Saji, H. *Bioconjugate Chem.* **1999**, *10*, 489−495.

(12) Su, Z.-F.; Zhang, X.; Ballinger, J. R.; Rauth, A. M.; Pollak, A.; Thornback, J. R. *Bioconjugate Chem.* **1999**, *10*, 897−904.

(13) Auzeloux, P.; Papon, J.; Pasqualini, R.; Madelmont, J.-C. *J. Med. Chem.* **2001**, *44*, 1116−1121.

(14) (a) Rajagopalan, R.; Grummon, G. D.; Bugaj, J.; Halleman, L. S.; Webb, E. G.; Marmion, M. E.; Vanderheyden, J. L.; Srinivasan, A. *Bioconjugate Chem.* **1997**, *8*, 407−415. (b) Hom, R. K.; Katzenellenbogen, J. A. *J. Org. Chem.* **1997**, *62*, 6290−6297. (c) Grummon, G.; Rajagopalan, R.; Palenik, G. J.; Koziol, A. E.; Nosco, D. L. *Inorg. Chem.* **1995**, *34*, 1764−1772. (d) Rao, T. N.; Adhikesavaln, D.; Camerman, A.; Fritzberg, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 5798−5804. (e) Rao, T. N.; Adhikesavalan, D.; Camerman, A.; Fritzberg, A. R. *Inorg. Chim. Acta* **1991**, *180*, 63−67.

(15) Jurisson, S.; Halihan, M. M.; Lydon, J. D.; Barnes, C. L.; Nowotnik, D. P.; Nunn, A. D. *Inorg. Chem.* **1998**, *37*, 1922−1928.

(16) (a) Das. T.; Banerjee, S.; Samuel, G.; Kothari, K.; Unni, P. R.; Sarma, H. D.; Ramamoorthi, N.; Pillai, M. R. A. *Nucl. Med. Biol.* **2000**, *27*, 189−197. (b) Kniess, T.; Noll, S.; Noll, B.; Spies, H.; Johnansen, B. *J. Radioanal. Nucl. Chem.* **1999**, *240*, 657−660. (c) Decristoforo, C.; Mather, S. J. *Bioconjugate Chem.* **1999**, *10*, 431−438. (d) Guhlke, S.; Schaffland, A.; Zamora, P. O.; Sartor, J.; Diekmann, D.; Bender, H.; Knapp, F. F.; Biersack, H.-J. *Nucl. Med. Biol.* **1998**, *25*, 621−631. (e) Mardirossian, G.; Lei, K.; Rusckowski, M.; Chang, F.; Qu, T.; Egholm, M.; Hnatowich, D. J. *J. Nucl. Med.* **1997**, *38*, 907−913.

(17) (a) Van Gog, F. B.; Visser, G. W. M.; Klok, R.; Van der Schors, R.; Snow, G. B.; Van Dongen, G. A. M. S. *J. Nucl. Med.* **1996**, *37*, 352−262. (b) Hanson, L.; Taylor, A., Jr.; Marzilli, L. G. *Met.-Based Drugs* **1994**, *1*, 31−39. (c) Canney, D. J.; Billings, J.; Franscesconi, L. C.; Guo, Y. Z.; Haggerty, B. S.; Rheingold, A. L.; Kung, H. F. *J. Med. Chem.* **1993**, *36*, 1032−1040. (d) Noll, B.; Johhansen, B.; May, K.; Spies, H. *Appl. Radiat. Isot.* **1992**, *43*, 899−901. (e) Wong, E.; Fauconnier, T.; Benett, S.; Valliant, J.; Nguyen, T.; Lau, F.; Lu, L. F. L.; Pollak, A.; Bell, R. A.; Thornback, J. R. *Inorg. Chem.* **1997**, *36*, 5799−5808.

(18) (a) Prabhu, K. R.; Kishore, P. N.; Gali, H.; Katti, K V. *Curr. Sci.* **2000**, *78*, 431−439. (b) Prabhu, K. R.; Kishore, P. N.; Gali, H.; Katti, K V. *J. Am. Chem. Soc.* **2000**, *122*, 1554−1555. (c) Volkert, W. A.; Karra, S. R.; Gali, H.; Schibli, R.; Katti, K. V. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *144*, 489−492. (d) Katti, K. V. *Proc. Indian Acad. Sci., Chem. Sci.* **1999**, *111*, 425−436. (e) Gali, H, Karra, V, Reddy, S. R.; Katti, K. V. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2020−2023. (f) Karra, S R.; Schibli, R.; Gali, H.; Katti, K V.; Hoffman, T. J.; Higginbotham, C.; Sieckman, G. L.; Volkert, W A. *Bioconjugate Chem.* **1999**, *10*, 254−260. (g) Katti, K. V.; Gali, H.; Smith, C. J.; Berning, D. E. *Acc. Chem. Res.* **1999**, *32*, 9−17. (h) Cavel, R. G.; Hilts, R. W.; Luo; McDonald, R. *Inorg. Chem.* **1999**, *38*, 897−905.

(19) (a) Liu, S.; Edwards, D. S.; Harris, A. R.; Heminway, S. J.; Barrett, J. A. *Inorg. Chem.* **1999**, *38*, 1326−1335. (b) Rose, D. J.; Maresca, K. P.; Nicholson, T.; Davison, A.; Jones, A. G.; Babich, J.; Fischman, A.; Graham, W.; DeBord, J. R. D.; Zubieta, J. *Inorg. Chem.* **1998**, *37*, 2701−2716. (c) Ono, M.; Arano, Y.; Uehara, T.; Fujioka, Y.; Ogawa, K.; Namba, S.; Mukai, T.; Nakayama, M.; Saji, H. *Bioconjugate Chem.* **1999**, *10*, 386−394.

(20) Liu, S.; Edwards, D. S.; Looby, R. J.; Harris, A. R.; Poirier, M. J.; Barrett, J. A.; Heminway, S. J.; Carroll, T. R.; *Bioconjugate Chem.* **1996**, *7*, 63−71.

(21) Mary, J. H.; Jurisson, S. *Acc. Chem. Res.* **1999**, *32*, 1053−1060.

(22) (a) Pandurangi, R. S.; Lusiak, P.; Platz, M. S.; Volkert, W. A.; Kuntz, R. R. *J. Org. Chem.* **1998**, *63*, 9019−9030. (b) Pandurangi, R. S.; Karra, S. R.; Katti, K. V.; Volkert, W. A.; Kuntz, R. R. *J. Org. Chem.* **1997**, *62*, 2798−2807. (d) Pandurangi, R. S.; Katti, K. V.; Volkert, W. A.; Kuntz, R. R. *Inorg. Chem.* **1996**, *35*, 3716−3718. (e) Pandurangi, R. S.; Kuntz, R. R.; Volkert, W. A.; Barnes, C. L.; Katti, K. V. *J. Chem. Soc., Dalton Trans.* **1995**, 565. (f) Pandurangi, R. S.; Karra, S. R.; Kuntz, R. R.; Volkert, W. A. *Photochem. Photobiol.* **1997**, *65*, 101−110. (g) Pandurangi, R. S.; Karra, S. R.; Kuntz, R. R..; Volkert, W. A. *Bioconjugate Chem.* **1995**, *6*, 630−637.

(23) Pandurangi, R. S. Unpublished results.

of novel oxotechentium(V)/oxorhenium(V) type complexes. The new tetraaza type water-soluble ligands [(2-$C_5H_4NCH_2$-$NHCO)_2CH_2$], **1** (L^1H_2), [(2-$C_5H_4NNHNHCO)_2CH_2$], **2**, and [{2-$C_5H_4N^+(O)^-CH_2NHCO]_2\}CH_2$], **3**, were synthesized in a single step by simple nucleophilic substitution of diethyl malonate with the corresponding pyridine. In this work, we have also studied the coordination of ligand **1** **(**L^1H_2) with ^{99g}Tc and Re and complexes of the general formulas MO(L^1) X and μ-oxo [MO(L^1)]$_2$O (M = Re or ^{99g}Tc, X = Cl, H_2O, or EtO). Furthermore, complexes *trans*-ReO(L^1)(OEt), **4**, μ-oxo [ReO(L^1)]$_2$O, **5**, and *trans*-[^{99g}TcO(L^1)(OH_2)]Cl, **8,** were isolated and characterized by single-crystal X-ray analysis. The crystal structure investigations on the long-lived isotope ^{99g}TcO (L^1) complex and ReO (L^1) complex constitute a novel report of structures of both metals on the same ligand.

2. Experimental Section

All synthetic procedures were conducted in a dry nitrogen atmosphere using standard techniques and prepurified solvents. Nuclear magnetic resonance spectra were recorded on a Bruker WH-250 spectrometer, and chemical shifts are reported in ppm downfield from $SiMe_4$ for ^1H NMR. Elemental analyses for the new compounds were done by Oneida Research Services, Inc., Oneida, NY. Elemental analyses of complexes were performed with a Perkin-Elmer 2400/II automated analyzer in the Institute of Radioisotopes-Radiodiagnostic Products, NCSR “Demokritos”, Athens, Greece. Mass spectra were obtained with a TSQ 7000 triple-quadrupole mass spectrometer (Thermoquest, San Jose, CA) operated in positive or negative ion electrospray ionization modes. Samples were introduced using a syringe pump in a corresponding solvent at a flow rate 400 mL/min. The temperature of the heated capillary was 350 °C, with electrospray voltage 4.5 kV (positive ions) or 3.0 kV (negative ions). IR spectra were recorded on KBr pellets on a Perkin-Elmer 1600 FT-IR spectrophotometer in the region 500−4000 cm^{-1} using polystyrene as a reference. All chemicals were reagent grade and were used as such unless otherwise noted. Ligands **1** and **2** were synthesized by nucleophilic substitution of diethyl malonate (vide supra), while ligand **3** was synthesized by the oxidation of ligand **1**. ^{99g}Tc was purchased from Oak Ridge National Laboratories, Oak Ridge, TN, as $NH_4{}^{99g}TcO_4$. The impure black solid was purified prior to use by overnight treatment with H_2O_2 and NH_4OH in MeOH. Evaporation of the solvent afforded $NH_4{}^{99g}TcO_4$ as a white powder, which was eventually converted to the [(*n*-$C_4H_9)_4N$] [$^{99g}TcOCl_4$] precursor by following a literature method.[26] Rhenium was purchased from Aldrich as $KReO_4$; it was converted to the $ReOCl_3(PPh_3)_2$[27] or the [(*n*-$C_4H_9)_4$][$ReOCl_4$] precursor[28] according to the published protocols.

Table 1. Summary of Crystal Data for Compounds **4**, **5**, and **8**

	complex **4**	complex **5**	complex **8**
formula	$C_{17}H_{19}N_4O_4Re$	$C_{31}H_{38}N_8O_{11}Re_2$	$C_{15}H_{20}ClN_4O_6Tc$
fw	529.56	1071.83	485.80
a, Å	23.664(2)	11.646(3)	13.957(9)
b, Å	8.291(1)	11.850(3)	17.14(1)
c, Å	18.655(2)	14.396(3)	7.768(6)
α, deg		78.725(7)	
β, deg	99.234(2)	76.133(7)	
γ, deg		67.656(8)	
V, Å^3	3612.6(5)	1771.8(7)	1858(2)
Z	8	2	4
D_{calcd}, Mg/m^3	1.947	2.007	1.736
space group	$C2/c$	$P1$	$P2_12_12_1$
temp, K	298	298	298
radiation; λ, Å	Cu Kα; 1.5418	Mo Kα; 0.710 73	Mo Kα; 0.710 73
abs coeff (μ), cm^{-1}	13.430	6.896	0.959
octants collcd	$\pm h, -k, l$	$\pm h, k, \pm l$	$h, \pm k, l$
GOF on F^2	1.059	1.071	1.032
R1	0.0310[a]	0.0248[b]	0.0304[c]
wR2	0.0837[a]	0.0638[b]	0.0774[c]

[a] For 2712 reflections with $I > 2\sigma(I)$. [b] For 5425 reflections with $I > 2\sigma(I)$. [c] For 2821 reflections with $I > 2\sigma(I)$.

2.1. Safety Note! ^{99g}Tc is a weak β emitter (292 keV) with a half-life of 2.12 × 10^5 years. All manipulations of solutions and solids containing this radionuclide were carried out in a dedicated laboratory supervised by radiation safety authorities. Safety protocols were followed at all times to prevent contamination. ^{99m}Tc is a γ emitter (141 keV) with a half-life of 6 h. Work with solutions containing this radionuclide was always performed behind sufficient lead shielding and following routine safety protocols.

2.2. X-ray Crystal Structure Determinations for Compounds 4, 5, and 8. Diffraction measurements for **5** and **8** were performed on a Crystal Logic Dual Goniometer diffractometer using graphite-monochromated Mo Kα radiation while, for **4**, diffraction data were collected on P2$_1$ Nicolet diffractometer upgraded by Crystal Logic using focusing graphite-monochromated Cu Kα radiation. Unit cell dimensions were determined and refined by using the angular settings of 25 automatically centered reflections and are listed in Table 1. Intensity data were recorded using a $\theta-2\theta$ scan. Three standard reflections monitored every 97 reflections showed less than 3% variation and no decay. Lorentz, polarization, and ψ-scan absorption corrections were applied using Crystal Logic software. The structures were solved by direct methods using SHELXS-86[29] and refined by full-matrix least-squares techniques on F^2 with SHELXL-98.[30] Further crystallographic details on **8**: $2\theta_{max} = 48.5°$; scan speed 2.0°/min; scan range 2.3 + $\alpha_1\alpha_2$ separation; reflections collected/unique/used = 3354/2988 [R_{int} = 0.0254]/2988, 325 parameters refined; R1/wR2 (for all data) = 0.0335/0.0799; $[\Delta\rho]_{min}/[\Delta\rho]_{max}$ = 0.328/−0.516 e/Å^3; $[\Delta/\rho]$ = 0.084. All hydrogen atoms were located by difference maps and were refined isotropically while all non-H atoms were refined anisotropically. Further crystallographic details on **4**: $2\theta_{max}$ = 125°; scan speed 4.5°/min; scan range 3.0 + $\alpha_1\alpha_2$ separation; reflections collected/unique/used = 2984/2882 [R_{int} = 0.0418]/2882; 301 parameters refined; R1/wR2 (for all data) = 0.0324/0.0854; $[\Delta\rho]_{min}/[\Delta\rho]_{max}$ = 1.037/−2.341 e/Å^3; $[\Delta/\rho]$ = 0.017. All hydrogen atoms (except methylene groups which were introduced at calculated positions as riding on bonded atoms) were located by difference maps and were refined isotropically, while all non-H atoms were refined anisotropically. Further crystallographic details on **5**: $2\theta_{max}$ = 50°; scan speed 2.0°/min; scan range 2.4 + $\alpha_1\alpha_2$ separation; reflections collected/unique/used = 6543/6216 [R_{int} = 0.0120]/6216; 595 parameters refined;

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(24) (a) Pandurangi, R. S.; Katti, K. V.; Stilwell, L.; Barnes, C. L. *J. Am. Chem. Soc.* **1998**, *120*, 11364−11373. (b) Pandurangi, R. S.; Rao, S. N.; Cieplak, P.; Stillwell, L. I.; Barnes, C. L.; Kuntz, R. R. *Int. Peptide Res.*, submitted for publication. (c) Pandurangi, R. S.; Lusiak, P.; Sun, Y.; Weber, K. T.; Kuntz, R. R. *Bioorganic Chem.* **1997**, *25*, 77−87.

(25) Rajagopalan, R.; Sharma, U.; Kuntz, R. R.; Volkert, W. A.; Pandurangi, R. S. *J. Org. Chem.* **2002**, 6748−6757.

(26) Cotton, A.; Davison, A.; Day, W. M.; Gage, L. D.; Trop, H. S. *Inorg. Chem.* **1979**, *18*, 3024−3029.

(27) Chatt, J.; Rowe, G. A. *J. Chem. Soc.* **1962**, 4019−4033.

(28) Alberto, R.; Schibli, R.; Egli, A.; Schubiger, P. A.; Herrmann, W. A.; Artus, G.; Abram, U.; Kaden, T. *J. Organomet. Chem.* **1995**, *492*, 217−224.

(29) SHELXS-86: Sheldrick, G. M. *Structure Solving Program*; University of Gottingen: Gottingen, Germany, 1986.

(30) SHELXL-98: Sheldrick, G. M. *Crystal Structure Refining Program*; University of Gottingen: Gottingen, Germany, 1998.

R1/wR2 (for all data) = 0.0317/0.0673; $[\Delta\rho]_{min}/[\Delta\rho]_{max}$ = 0.950/−0.807 e/Å^3; $[\Delta/\rho]$ = 0.234. All hydrogen atoms of the tetradentate ligand and those of OW(L^1) were located by difference maps and refined isotropically. The remaining H-atoms were not included in the refinement. After the location of the three water solvates was completed, a number of peaks remained in the difference map which were modeled as disordered water and ethanol solvent molecules each refined in two positions with the total sum of their occupation factors fixed at 0.50. All the non-hydrogen atoms of the dinuclear complex and the three water solvates were refined anisotropically.

2.3. Synthesis of Ligands. Synthesis of 1 (L^1H_2 or N_2Py_2). A 100 mL round-bottom flask was flame-dried and purged with nitrogen gas. After cooling, it was charged with 10.81 g (100 mmol) of (aminomethyl)pyridine and 6.60 g (50 mmol) of dimethyl malonate. The reagents were dissolved in 25 mL of absolute ethanol. The reaction mixture was refluxed overnight before the solvent was removed completely in vacuo. The viscous residue (usually bright red in color) was purified by flash chromatography using CH_2Cl_2/2-propanol (5:1 ratio). After evaporation of the solvent, the sample was dried for 6−8 h on high vacuum to obtain ligand **1** as white crystals (yield: 46.5%). A slightly modified procedure was reported earlier for preparing the same ligand by Comba et al. in aqueous medium.[31] ^{1}H NMR ($CDCl_3$), δ: 8.67 (t, 2H), 8.48 (d, 2H), 7.73 (m, 2H), 7.33 (m, 2H), 7.24 (m, 2H), 4.40 (d, 4H), 3.25 (s, 2H). Anal. Calcd for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71. Found: C, 63.54; H, 5.64; N, 19.52.

Synthesis of $N_2(HyPy)_2$, 2. A 50 mL round-bottom flask was flame-dried and charged with 1.00 g (7.56 mmol) of dimethyl malonate and 1.815 g (16.63 mmol) of 2-hydrazinopyridine. The reactants were dissolved in 15 mL of absolute ethanol, and the reaction mixture was refluxed overnight. After the reaction mixture was cooled to room temperature, a white precipitate was formed. The solution was filtered, and the precipitate was washed with 10 mL of hexane and 10 mL of Et_2O to give a light brown colored product **2** (yield: 57%). ^{1}H NMR ($CDCl_3$), δ: 8.52 (d, 2H), 8.37 (d, 2H), 7.65 (m, 2H), 7.42 (m, 2H), 7.24 (m, 2H), 6.8 (d, 2H), 3.21 (s, 2H). ^{13}C NMR ($CDCl_3$), δ: 166.1, 159.4, 147.2, 137.3, 134.6, 114.4, 106.3. Anal. Calcd for $C_{13}H_{14}N_6O_2$: C, 54.54; H, 4.93; N, 29.36. Found: C, 54.36; H, 5.01; N, 29.17.

Synthesis of $N_2(PyNO)_2$, 3. A 100 mL round-bottom flask was charged with 1.00 g (3.517 mmol) of diamide **1** and 60 mL of dichloromethane. About 3.0 g (2.3 equiv) of mCPBA was also added and stirred overnight. The solution was filtered, taken up in 25 mL of DMF, and poured into 100 mL of Et_2O, which was vigorously stirred for 10 min to give a *N*-oxide product **3** (yield: 63%). ^{1}H NMR (DMSO-d_6), δ: 8.87 (b, 2H), 8.35 (d, 2H), 7.74 (m, 2H), 7.38 (m, 2H), 7.14 (m, 2H), 4.40 (d, 4H), 3.12 (s, 2H). ^{13}C NMR ($CDCl_3$), δ: 167.8, 166.4, 148.3, 139.2, 133.7, 131.0, 129.2, 125.0. Anal. Calcd for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.10; N, 17.71. Found: C, 56.45; H, 5.14; N, 17.85.

2.4. Synthesis of Rhenium and Technetium Complexes. ReO(L^1)(OEt), 4. To a stirred suspension of $ReOCl_3(PPh_3)_2$ (166 mg, 0.2 mmol) in EtOH (10 mL), 1 N CH_3COONa in EtOH (2 mL, 2 mmol) and a solution of **1** (H_2L, 57 mg, 0.2 mmol) in EtOH were added one after another. The resulting mixture was refluxed until the green-yellow color of the suspension turned yellow and a clear solution was formed. After the solution was cooled to room temperature, the Re complex **4** appeared as yellow needles suitable for X-ray studies. Complex **4** was soluble in chlorinated solvents, sparingly soluble in EtOH or MeOH, and insoluble in Et_2O. Yield: 60 mg (57%). ^{1}H NMR ($CDCl_3$), δ: 9.33 (d, 2H), 8.01 (m, 2H), 7.81 (m, 2H), 7.58 (t, 2H), 6.45 (d, 2H, ^1J = 19.57 Hz), 4.75 (d, 2H, ^1J = 19.57 Hz), 4.59 (d, 1H, ^1J = 15.49), 3.97 (d, 1H, ^1J = 15.41), 2.57 (q, 2H), 0.19 (t, 3H). IR (KBr, cm^{-1}): 3079, 2959, 2922, 2866, 2840, 1629 s, 1566, 1481, 1391 s, 1351, 1287, 1114, 1067, 1051, 934 s (Re=O), 905 s (Re−O), 888, 829, 770, 724 w, 619 w, 568 w, 546 w. MS: peaks at m/z = 485.2 and 483.2 corresponding to $[M{=}O]^+$ with OC_2H_5 fragmentation, i.e., $[(M{=}O)^+ - OC_2H_5]$ (M = 185 and 187 Re isotopes). Anal. Calcd for $C_{17}H_{19}N_4O_4Re$: C, 38.56; H, 3.62; N, 10.58. Found: C, 38.87; H, 3.97; N, 10.32.

$Re_2O_3(L^1)_2\cdot 3.5H_2O\cdot 0.5C_2H_5OH$, 5. Upon dissolution of the isolated yellow crystals of Re complex **4** in a mixture of CH_2Cl_2 and EtOH, a color transition was observed. The initial yellow solution turned pink. A few days later, slow evaporation of the solution yielded pink crystals of Re complex **5**, suitable for X-ray studies. Yield: 45.3%. ^{1}H NMR ($CDCl_3$), δ: 8.97 (d, 2H), 7.92 (m, 2H), 7.62 (m, 2H), 7.48 (t, 2H), 5.39 (d, 2H, ^1J = 20.39 Hz), 4.57 (d, 2H, ^1J = 19.97 Hz), 3.87 (d, 1H, ^1J = 17.61), 3.19 (d, 1H, ^1J = 17.83). IR (KBr, cm^{-1}): 3441 br, 3079 w, 2974 w, 2923 w, 2867 w, 1613 s, 1592 s, 1485, 1384, 1289 w, 1212 w, 1161 w, 1074, 1053, 1026, 923−935 w (ReO), 880 w, 829 w, 770, 655−680 s (Re−O−Re), 619 w, 562 w, 543 w. Anal. Calcd for $C_{30}H_{28}N_8O_{11}Re_2$, or better described as $C_{30}H_{28}N_8O_7Re_2\cdot 3.5H_2O\cdot 0.5C_2H_5OH$ (vide Experimental Section, crystallography): C, 34.76; H, 3.58; N, 10.46. Found: C, 35.10; H, 3.78; N, 10.79.

ReO(L^1)Cl, 6. To a 5 mL stirred solution of $[n\text{-}Bu_4N][ReOCl_4]$ (117.4 mg, 0.2 mmol) in EtOH was added **1** (57 mg, 0.2 mmol) in EtOH. Upon addition of the ligand, a pink solid was separated from the reaction mixture. The solid was insoluble in alcohols, ether, and chlorinated solvents. Yield: 65 mg (63%). IR (KBr, cm^{-1}): 3091 w, 2927 w, 2886 w, 1641 s, 1633 s, 1568, 1485, 1434, 1359 s, 1291, 1221 w, 1161 w, 1102 w, 1063, 1052 s, 1030, 1017 sh, 965 s (Re=O), 880 w, 830 w, 768 s, 722, 655 w, 623 w, 569 w, 522 w, 472 w, 447, 363 s (Re−Cl). Anal. Calcd for $C_{15}H_{14}N_4O_3ReCl$: C, 34.65; H, 2.71; N, 10.78. Found: C, 34.46; H, 2.96; N, 10.61.

2.5. Synthesis of Technetium Complexes. ^{99g}TcO[(L^1)Cl, 7, and $[^{99g}TcO[(L^1)(H_2O)]^+Cl^-\cdot 2H_2O$, 8. To a stirred solution of $[(n\text{-}C_4H_9)_4N][^{99g}TcOCl_4]$ (100 mg, 0.2 mmol) in EtOH (10 mL) was added a solution of **1** (57 mg, 0.2 mmol) in EtOH (2 mL). Within a few minutes, a brown solid appeared and the precipitate was washed with EtOH and Et_2O. The solid, complex **7**, was soluble in chlorinated solvents and insoluble in alcohols or Et_2O. Yield: 60 mg (70%). IR (KBr, cm^{-1}): 3072 w, 2923 w, 2884 w, 1641 s, 1626 s, 1567, 1485, 1431, 1358 s, 1291, 1221 w, 1161 w, 1098 w, 1050 s, 1028, 1017, 945 s (Tc=O), 879 w, 830 w, 765 s, 721, 653 w, 621 w, 570 w, 519 w, 474 w, 443, 374 s (Tc−Cl). During recrystallization of **7** from a EtOH/CH_2Cl_2 mixture, brown needle-like crystals were formed while a brown solid remained in the bottom of the flask. The crystals were suitable for X-ray crystallographic analysis and proved to be complex **8**. Yield: 30 mg (44% based on **7**). ^{1}H NMR (DMSO-d_6), δ: 9.68 (d, 2H), 8.24 (m, 2H), 7.98 (m, 2H), 7.82 (m, 2H), 6.03 (d, 2H, ^1J = 20.41 Hz), 5.00 (d, 2H, ^1J = 20.54 Hz), 4.39 (d, 1H, ^1J = 14.65), 3.37 (d, 1H, ^1J = 14.65). IR (KBr, cm^{-1}): 3425, 3079 w, 2920 w, 2863 w, 1637 s, 1623 s, 1567, 1486, 1430, 1375, 1294, 1220 w, 1160 w, 1100 w, 1052 s, 1030 w, 967 s (Tc=O), 892 w, 831 w, 778, 722, 658 w, 619 w, 573 w. Anal. Calcd for $C_{15}H_{20}ClN_4O_4Tc$: C, 37.02; H, 4.14; N, 11.51. Found: C, 37.18; H, 4.29; N, 11.32.

The IR spectrum of the brown solid showed the following peaks (KBr, cm^{-1}): 3420 s, 3079 w, 2922 w, 2865 w, 1640−1580 br, s, 1568, 1485, 1428, 1413, 1370, 1291, 1219 w, 1161 w, 1100 w,

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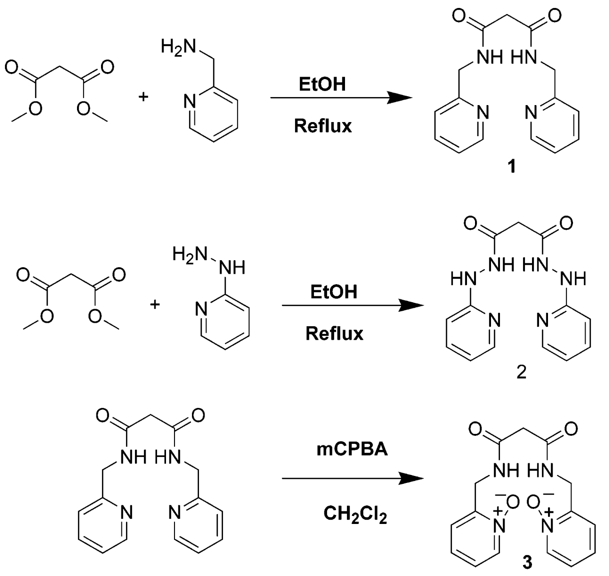
(31) Comba, P.; Goll, W.; Nuber, B.; Varnagy, K. *Eur. J. Inorg. Chem.* **1998**, 2041−2049.

Scheme 1



1078 w, 1051 s, 1026 w, 967, 945, 889 w, 831 w, 765, 720, 680−658 s, 613 w, 572 w. Further attempts to recrystallize the brown solid from a $EtOH/CH_2Cl_2$ mixture failed.

3. Results and Discussion

3.1. Synthesis of Ligands. Diethyl malonate is a useful substrate for nucleophilic substitution to incorporate a chelating agent for metals at one end while the acidic proton of the CH_2 group can be used for incorporating the biomolecule of interest at the other end. For example, reaction of (aminomethyl)pyridine with diethyl malonate in alcohol, under reflux conditions, gave N_2Py_2, **1** (L^1H_2), in a single step. Similarly, nucleophilic substitution of diethyl malonate with hydrazinopyridine yielded $N_2(HyPy)_2$, **2,** in high yield (Scheme 1). Ligands **1** and **2** are designed with a purpose of chelating ^{99m}Tc and Re metals with a tetraaza type of coordination through the amide nitrogens and pyridine nitrogens. Further oxidation of pyridine nitrogens on **1** using the oxidizing agent *m*-chloroperbenzoic acid (mCPBA) resulted in $N_2(PyO)_2$, **3**. All the ligands were characterized by proton NMR and elemental analysis. The key point of note here is that all the pyridine-based chelating agents are water soluble rendering them useful in aqueous conditions for formulating potential radiopharmaceuticals. Preliminary studies on radiolabeling of ligands **1**−**3** showed that they form ^{99m}Tc complexes at tracer level through the ligand exchange reaction with ^{99m}Tc glucoheptonate.[23]

3.2. Synthesis of Re Mono- and Dinuclear Complexes 4 and 5. Reaction of **1** (L^1H_2) with $ReOCl_3(PPh_3)_2$ in ethanol with sodium acetate as a deprotonating agent resulted in oxorhenium complex $ReO(L^1)(OEt)$, **4**, as pale yellow crystals (Scheme 2). The complex **4** was characterized by spectroscopic methods, elemental analysis, and single-crystal X-ray analysis.

The IR spectrum of the complex **4** showed a peak at 934 cm^{-1}, which can be assigned to the Re═O stretching band of the complex **4**.[27,32] Proton NMR of **4** revealed the interesting splitting of peak corresponding to methylene protons (^1J = 19.57 Hz) attached to amide group and CH_2 protons attached to pyridine (^1J = 15.41 Hz, AB pattern). Similar inequavalency of CH_2 protons attached to amide groups was observed in MAG3−Re type complexes.[33] X-ray structure analysis revealed that Re complex **4** is a distorted octahedron with NNNN donor set arising from the deprotonation of two amide groups and from the pyridine nitrogens forming two covalent and two coordinate bonds, respectively.

The tetraaza type coordination of Re complex has all the nitrogens occupying equitorial positions, while the oxo group occupies an axial position. A solvent ethanol molecule occupies the sixth position by deprotonation of CH_2OH group. When the Re complex **4** is redissolved in dichloromethane/ethanol mixture, a slow color transition from yellow to pink was observed. The pink solid **5** showed a weak peak at 923−935 cm^{-1} and a peak at 655−690 cm^{-1}. The first peak can be attributed to the characteristic Re═O stretching, while the second one can be assigned to Re−O−Re according to the literature.[32,34] Proton NMR of the dinuclear complex **5** also reveals a similar AB pattern for the CH_2 protons bonded to amide groups (^1J = 20.39 Hz) and methylene protons attached to the pyridine ring (^1J = 17.61 Hz) as observed for the mononuclear complex. The final structure of the dinuclear complex **5** was established by single-crystal X-ray crystallography (vide supra) and was proved to be the dinuclear μ-oxo $[ReO(L^1)]_2O$.

However, the reaction of N_2Py_2, **1** (L^1H_2), with the different precursor $[n\text{-}Bu_4N][ReOCl_4]$ yielded a pink solid **6.** Unfortunately, this solid was insoluble in all common organic solvents. The IR spectrum of **6** showed a peak at 965 cm^{-1} which can be assigned to Re═O stretching vibration and bands associated with the presence of the ligand **1** except for the bands associated with the N−H bonds indicating that the amides have been deprotonated. On the basis of the above data and the elemental analysis, we can assume that **6** is complex of the type $ReO(L^1)Cl$, where the chlorine atom occupies the sixth coordination site, trans to oxygen.

3.3. Synthesis of ^{99g}Tc Complexes. The synthesis of ^{99g}Tc complex using the precursor $[(n\text{-}C_4H_9)_4N]$ $[^{99g}TcOCl_4]$ in ethanol yielded a brown solid **7**. The IR spectrum of **7** was similar to **6** except that it showed a shift of Tc═O stretching vibration to 945 cm^{-1}. Since the shift of the stretching vibration peak is common between oxotechnetium and oxorhenium complexes,[35] we can reasonably assume that **7** is the complex of type $TcO(L^1)Cl$, similar to **6**. Complex **7**

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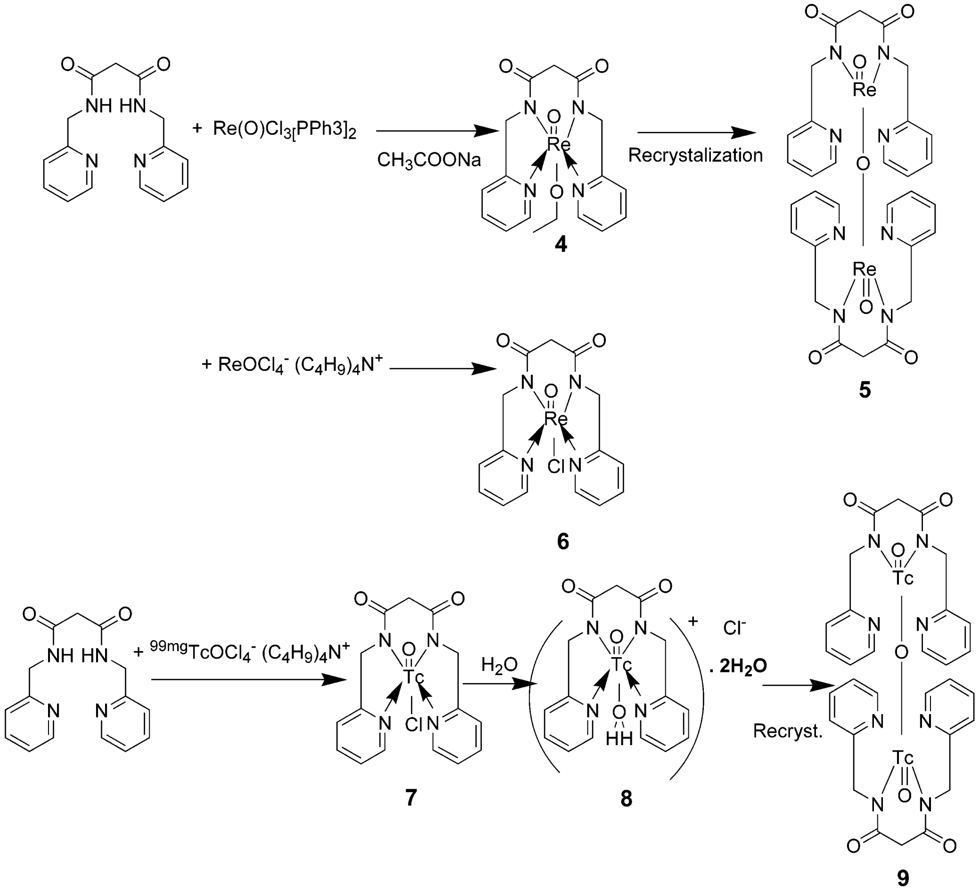
(32) Tisato, F.; Mazzi, U.; Bandoli, G.; Cros, G.; Darbieu, MH.; Coulias, Y.; Guiraud, R. *J. Chem. Soc., Dalton Trans.* **1991**, 1301−1307.

(33) Lipowska, M.; Hanson, L.; Xu, X.; Marzilli, P.; Taylor, A.; Marzilli, L. G. *Inorg. Chem.* **2002**, *41*, 3032−3041 and references therein.

(34) (a) Tisato, F.; Refosco, F.; Mazzi, U.; Bandoli, G.; Dolmella A. *Inorg. Chim. Acta* **1989**, *164*, 127. (b) Battistuzzi. G.; Bonamartini-Conardi, A.; Dallari, D.; Saladini, M.; Battistuzzi, R. *Polyhedron* **1999**, *18*, 57−63.

(35) Papadopoulos, M.; Pirmettis, I.; Pelecanou, M.; Raptopoulou, C.; Terzis, A.; Stassinopoulou, C.; Chiotellis, E. *Inorg. Chem.* **1996**, *35*, 7377−7387. (b) O'Neil, J.; Wilson, S.; Katzenellenbogen, J. *Inorg. Chem.* **1994**, *33*, 319−323. (c) Mahmood, A.; Baidoo, K. E.; Lever, S. In *Technetium and Rhenium in Chemistry and Nuclear Medicine 3*; Nicolini, M., Bandoli, G., Mazzi, U., Eds.; Raven Press: New York, 1990; p 119.

Scheme 2



was unstable in solution, presumably due to the high lability of the sixth site of the coordination in the complex. Traces of the moisture in the solvent or prolonged contact with air can lead to the removal of labile chlorine changing the neutral complex **7** to cationic aqua complex **8**. In fact, attempts to recrystallize solid **7** in a mixture of ethanol and CH_2CL_2 yielded brown crystals **8** and a brown solid remaining at the bottom of the flask. The IR spectrum of the crystal selected for X-ray analysis showed a peak at 967 cm^{-1}, shifted from 945 cm^{-1} in **7**, suggesting the change in the coordination sphere of the metal.[36] The proton NMR spectrum of **8** is very similar to mononuclear Re complex **4** showing a similar splitting of CH_2 protons bonded to amide groups (AB pattern, $^1J = 20.41$ Hz) and for methylene protons connected to the pyridine ring ($^1J = 14.65$ Hz). Further, the X-ray analysis of the crystal was proved to be the cationic complex **8,** $[TcO(L^1)(H_2O)]^+Cl^-$, with chlorine as a counterion and two water of crystallization (see below).

The IR spectrum of the remaining brown solid from the reaction showed 3 peaks at 967, 945, and 680 cm^{-1}. The peak at 680 cm^{-1} can be attributed to Tc−O−Tc dinuclear complex **9** (Scheme 2), similar to the Re complex **5**.[34−37]

The remarkable similarity of Tc and Re complexes although prepared from different precursors shows that similar reaction mechanism is taking place in solution for both Tc and Re complexes. The nature of the complexes isolated and observed in each case, however, depend on their solubility, the precursor, the solvent, the deprotonating agent, and the reaction conditions. Tc(V) chemistry in general is dominated by $[Tc{=}O]^{3+}$ or trans $[O{=}Tc{=}O]^+$ cores. However, the factors that determine which of these cores is preferred in solution are not completely understood.[38] For example, π-donor ligands such as Schiff base ligands coordinated in the equitorial plane orthogonal to the Tc═O linkage seem to favor the $[Tc{=}O]^{3+}$ core,[39,40] while π-acceptor and saturated tetraamine ligands stabilize the *trans*-dioxo moiety.[41] On the basis of the similarity of Re and Tc complexes of N_2Py_2, previous studies,[35] and the data presented in this work, the following reaction mechanism may be suggested:

$$\mathbf{1} + TcOCl_4^- \rightarrow TcO(L^1)Cl\ (\mathbf{7}) \rightarrow [TcO(L^1)(H_2O)] + Cl^- \rightarrow [TcO(L^1)]_2O$$

3.4. Single-Crystal X-ray Analysis. $[^{99g}TcO(L^1)(H_2O)]^+Cl^-\cdot 2H_2O$. The summary of crystal data for compounds **4**,

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[36] Stassinopoulou, Ch.; Mastrostamatis, S.; Papadopoulos, M.; Vavouraki, H.; Terzis A.; Hountas, A.; Chiotellis, E. *Inorg. Chim. Acta* **1991**, *189*, 219−224.

[37] Bandoli, G.; Mazzi, U.; Nicolini, M.; Refosco, F. *J. Chem. Soc.* **1984**, 2505−2511.

[38] Trop, H. S.; Jones, A. G.; Davison, A. *Inorg. Chem*. **1980**, *19*, 1993−1997.

[39] Franklin, K. J.; Howard-Lock, H. E.; Lock, C. J. L. *Inorg. Chem*. **1982**, *21*, 1941−1946.

[40] Zuckman, S.; Freeman, G. M.; Troutner, D. E.; Volkert, W. A.; Holmes, R. A.; Van Der Veer, D. G.; Barefield, E. K. *Inorg. Chem.* **1981**, *20*, 2386−2389.

[41] Clarke, M. J.; Podbielski, L. *Coord. Chem Rev*. **1987**, *78*, 253−331.

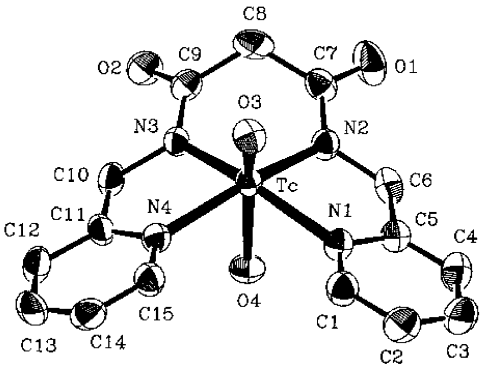

Figure 1. Ortep diagram for $[^{99}TcO(L^1)(H_2O)]^+Cl^-$ complex **8**.

Table 2. Selected Bond Distances (Å) and Angles (deg) for **8** (^{99g}Tc) and **4** (Re)

Tc−N(1)	2.170(4)	Re−N(1)	2.194(4)
Tc−N(2)	1.980(4)	Re−N(2)	1.999(4)
Tc−N(3)	1.968(4)	Re−N(3)	1.998(4)
Tc−N(4)	2.145(4)	Re−N(4)	2.194(3)
Tc−O(3)	1.641(3)	Re−O(3)	1.692(3)
Tc−O(4)	2.188(3)	Re−O(4)	1.924(3)
O(3)−Tc−N(3)	107.9(2)	O(3)−Re−N(3)	104.6(2)
O(3)−Tc−N(2)	107.8(2)	O(3)−Re−N(2)	103.2(2)
N(3)−Tc−N(2)	90.9(2)	N(3)−Re−N(2)	94.5(2)
O(3)−Tc−N(4)	92.1(2)	O(3)−Re−N(4)	86.2(2)
N(3)−Tc−N(4)	78.0(2)	N(3)−Re−N(4)	76.8(1)
N(2)−Tc−N(4)	156.5(2)	N(2)−Re−N(4)	168.6(2)
O(3)−Tc−N(1)	93.2(2)	O(3)−Re−N(1)	87.9(2)
N(3)−Tc−N(1)	158.3(2)	N(3)−Re−N(1)	166.4(2)
N(2)−Tc−N(1)	77.6(2)	N(2)−Re−N(1)	77.7(2)
N(4)−Tc−N(1)	106.8(2)	N(4)−Re−N(1)	109.3(2)
O(3)−Tc−O(4)	162.4(2)	O(3)−Re−O(4)	161.1(2)
N(3)−Tc−O(4)	84.3(2)	N(3)−Re−O(4)	87.4(2)
N(2)−Tc−O(4)	84.0(2)	N(2)−Re−O(4)	90.1(2)
N(4)−Tc−O(4)	77.8(2)	N(4)−Re−O(4)	82.3(1)
N(1)−Tc−O(4)	76.3(1)	N(1)−Re−O(4)	81.8(2)

5, and **8** is given in Table 1. The structure of **8** consists of cationic oxotechentium complex, Cl as an anion, and two water molecules of crystallization. The ORTEP diagram of **8** is shown in Figure 1, and selected bond distances and angles are listed in Table 2. The coordination about technetium is distorted octahedral with the four nitrogen atoms of the ligand in the equatorial plane while the doubly bonded oxygen and the coordinated water occupy the apical positions. Technetium lies 0.35 Å out of the equitorial plane toward the oxo group. The two five-membered rings in the coordination sphere adopt the stable envelope conformation with the deprotonated amide nitrogens being out of the mean plane of the remaining four atoms [∼0.31 Å for both N(2) and N(3)]. On the other hand, in the six-membered chelating ring, technetium and C(8) are displaced by 0.52 and 0.60 Å out of the mean plane defined by N(2), C(7), C(9), and N(3). The Tc−N amide bond distances [Tc−N(2) = 1.980(4) Å, Tc−N(3) = 1.968(4) Å] are comparable with those found in analogous complexes containing deprotonated amide nitrogens coordinated to technetium.[42] The Tc−N pyridine bond distances [Tc−N(L^1) = 2.170(4) Å, Tc−N(4) = 2.145(4) Å] are in the ranges observed in well-known complexes.[43] The Tc−O water bond length is 2.188(3) Å. A plethora of hydrogen bonds between the coordinated and lattice water molecules, the chlorine counterion, and the carbonyl oxygens is formed (Table 3).

Table 3. Hydrogen Bonds Formed in Compound **8**^{a}

interaction	H···A, Å	D···A, Å	DH···A, deg
O(4)−HO(4A)···OW(1)^{i}	1.814	2.550	160.7
O(4)−HO(4B)···OW(1)^{i}	1.849	2.642	166.5
OW(1)−HW(1A)···Cl^{ii}	2.349	3.017	168.4
OW(1)−HW(1B)···O(1)^{iii}	1.913	2.686	153.3
OW(2)−HW(2A)···O(2)^{iv}	2.059	2.849	161.7
OW(2)−HW(2B)···Cl^{v}	2.046	3.049	161.7

^{a} A = acceptor, D = donor. Symmetry operations: (i) $1 - x, y - 0.5, 0.5 - z$; (ii) $x - 1, y, z$; (iii) $x - 0.5, 0.5 - y, 1 - z$; (iv) $x - 1, 1 + y, z - 1$; (v) $1 - x, 0.5 + y, 0.5 - z$.

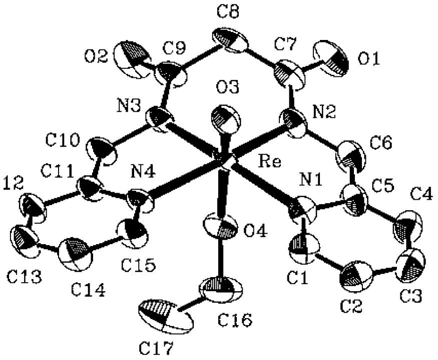

Figure 2. Ortep diagram for $[ReO(L^1)OC_2H_5]$ complex **4**.

$ReO(N_2Py_2)(OC_2H_5)$, 4. The ORTEP diagram of **4** is given in Figure 2, and selected bond distances and angles are listed in Table 2. Rhenium is coordinated to the four nitrogen atoms of the ligand and to two oxygen atoms coming from the deprotonated ethanol and the oxo group in a distorted octahedral geometry. The four nitrogens occupy the equitorial plane, out of which rhenium lies at 0.18 Å toward the oxo group. The five-membered rings in the coordination sphere exist in the envelope configuration with N(2) and N(3), the deprotonated amide nitrogens, displaced by 0.31 and 0.41 Å, respectively. Similar to Tc complex **8**, the six-membered chelating ring is in the coordination sphere. The Re metal and C(8) are displaced by 0.27 and 0.57 Å, respectively. The Re−N amide bond distances [Re−N(2) = 1.999(4) Å, Re−N(3) = 1.998(4) Å] are comparable with those found in analogous complexes containing deprotonated amide nitrogens.[42] The Re−N pyridine bond distances [Re−N(L^1) = 2.194(4) Å, Re−N(4) = 2.194(3) Å] are in the ranges observed in well-known complexes.[44] The Re−O ethanol bond length is 1.924(3) Å.

$[Re_2O_3(L^1)_2]\cdot 3.5H_2O\cdot 0.5C_2H_5OH$, 5. The ORTEP diagram of the dinuclear complex **5** is given in Figure 3, and selected hydrogen bond distances and angles are listed in Table 4. The dinuclear complex is formed due to the almost linear bridging of a divalent oxygen atom between the two Re metal ions [Re(L^1)−O(7)−Re(2) = 174.3(2)°]. The coordination sphere about each rhenium is distorted octa-

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(42) Papadopoulos, M.; Nock, B.; Maina, T.; Pirmettis, I.; Raptopoulou, C.; Tasiopoulos, A.; Troganis, A.; Kabanos, T.; Terzis, A. C.; Chiotellis, E. *J. Biol. Inorg. Chem.* **2001**, *6*, 159−165.

(43) (a) Bandoli, G.; Dolmella, A.; Porchia, M.; Refosco, F.; Tisato, F. *Coord. Chem. Rev.* **2001**, *214*, 43−90. (b) Tisato, F.; Refosco, F.; Bandoli, G. *Coord. Chem. Rev.* **1994**, *135/136*, 325−397.

(44) Chang, L.; Rall, J.; Tisato, F.; Deutsch, E.; Heeg, M. *Inorg. Chim. Acta* **1993**, *205*, 35−44.

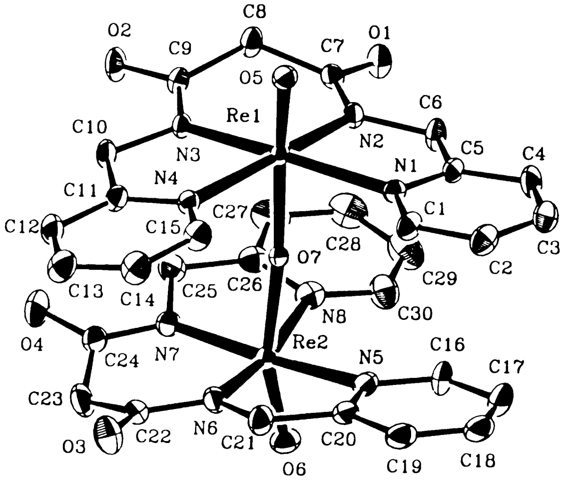

Figure 3. Ortep diagram for $[ReO(L^1)]_2O{\cdot}3.5H_2O{\cdot}0.5C_2H_5OH$, **5**.

Table 4. Selected Bond Distances (Å) and Angles (deg) in the Dimeric Re Complex **5**

Re(1)−N(1)	2.211(4)	Re(2)−N(5)	2.200(4)
Re(1)−N(2)	2.015(4)	Re(2)−N(6)	1.998(4)
Re(1)−N(3)	2.014(4)	Re(2)−N(7)	1.999(4)
Re(1)−N(4)	2.197(4)	Re(2)−N(8)	2.209(4)
Re(1)−O(5)	1.717(3)	Re(2)−O(6)	1.704(3)
Re(1)−O(7)	1.910(3)	Re(2)−O(7)	1.937(3)
O(5)−Re(1)−O(7)	162.7(1)	O(6)−Re(2)−O(7)	161.3(2)
O(5)−Re(1)−N(3)	99.3(1)	O(6)−Re(2)−N(6)	101.1(2)
O(7)−Re(1)−N(3)	92.1(1)	O(7)−Re(2)−N(6)	92.7(1)
O(5)−Re(1)−N(2)	99.1(2)	O(6)−Re(2)−N(7)	101.8(2)
O(7)−Re(1)−N(2)	92.6(1)	O(7)−Re(2)−N(7)	89.4(1)
N(3)−Re(1)−N(2)	95.5(1)	N(6)−Re(2)−N(7)	95.5(2)
O(5)−Re(1)−N(4)	86.9(1)	O(6)−Re(2)−N(5)	87.8(2)
O(7)−Re(1)−N(4)	85.8(1)	O(7)−Re(2)−N(5)	82.8(1)
N(3)−Re(1)−N(4)	77.9(1)	N(6)−Re(2)−N(5)	77.5(2)
N(2)−Re(1)−N(4)	171.7(1)	N(7)−Re(2)−N(5)	169.1(2)
O(5)−Re(1)−N(1)	87.2(1)	O(6)−Re(2)−N(8)	86.9(2)
O(7)−Re(1)−N(1)	82.9(1)	O(7)−Re(2)−N(8)	80.8(1)
N(3)−Re(1)−N(1)	717.3(1)	N(6)−Re(2)−N(8)	170.4(2)
N(2)−Re(1)−N(1)	77.7(1)	N(7)−Re(2)−N(8)	77.5(2)
N(4)−Re(1)−N(1)	108.4(1)	N(5)−Re(2)−N(8)	108.5(2)

hedral with the four nitrogen atoms of the tetradentate ligand in the equitorial plane while the oxo group and the bridging oxygen occupy the apical positions. Each rhenium is displaced out of the equitorial plane toward the oxo group by 0.100 and 0.144 Å for $Re(L^1)$ and Re(2), respectively. The two N_4 equitorial planes are almost parallel forming an angle of 3.67°. The five-membered rings in the coordination sphere of each rhenium adopt the stable envelope configuration with C(6), $Re(L^1)$, C(21), and N(7) displaced by 0.139, 0.176, −0.750, and 0.176 Å, respectively. The six-membered chelating ring of each rhenium exists in the chair configuration with $Re(L^1)$ and C(8) displaced by 0.178 and 0.329 Å and Re(2) and C(22) displaced by 0.203 and 0.129 Å, respectively. The Re−N amide bond distances [$Re(L^1)$−N(2) = 2.015(4), $Re(L^1)$−N(3) = 2.014(4), Re(2)−N(6) = 1.998(4), and Re(2)−N(7) = 1.999(4) Å] and the Re−N pyridine [$Re(L^1)$−$N(L^1)$ = 2.211(4), $Re(L^1)$−N(4) = 2.197(4), Re(2)−N(5) = 2.200(4), and Re(2)−N(8) = 2.209(4) Å] are consistent with those found in the mononuclear species. The Re−O bridging bond distances are almost equal [$Re(L^1)$−O(7) = 1.910(3) and Re(2)−O(7) = 1.937(3) Å] and are comparable with the Re−O ethanol bond length found in the mononuclear complex. A complex network of hydrogen bonds is formed due to the presence of donor and acceptor atoms in the dinuclear complex as well as in the lattice (Table 5).

Table 5. Hydrogen Bonds Formed in the Dimeric Complex **5**[a]

interaction	H⋯A, Å	D⋯A, Å	DH⋯A, deg
OW(1)−HW(1A)⋯O(1)^{i}	1.808	2.754	160.6
OW(1)−HW(1B)⋯O(5)^{ii}	2.106	2.876	145.4
OW(2)⋯OW(2)^{iii}		2.669^{b}	
OW(2)⋯OW(3)^{ii}		2.784^{b}	
OW(2)⋯O(2)^{I}		2.800^{b}	
OW(3)⋯OW(1)^{ii}		2.802^{b}	
OW(3)⋯O(2E)^{ii}		2.896^{b}	
OW(4)⋯O(3)^{iv}		2.922^{b}	
OW(5)⋯OW(7)^{v}		2.441^{b}	
O(2E)⋯O(6)^{vi}		2.801^{b}	

[a] A = acceptor, D = donor. Symmetry operations: (i) −*x*, 1 − *y*, 1 − *z*; (ii) *x*, *y*, *z*; (iii) −*x*, −*y*, 1 − *z*; (iv) 1 − *x*, -*y*, 1 − *z*; (v) −*x*, −*y*, −*z*; (vi) *x*, *y*, −1 + *z*. [b] These distances can be possibly attributed to hydrogen-bonded interactions although the hydrogen atoms have not been located.

4. Conclusion

In conclusion, the new pyridine-based ligands are water soluble and prepared in a single step. Particularly, we have shown that ligand **1** (L^1H_2) allows stabilization of both rhenium and technetium in oxidation state V within similar cores in solution. The provision for attaching biomolecules of interest is feasible through the nucleophilic substitution of acidic methylene protons on the malonamide backbone. The reported X-ray crystal structures of ^{99g}Tc and Re on the same chelating framework establishes the similarity in geometry as well as in the type of metal−oxygen cores in solution, which can be extended safely to clinically useful ^{99m}Tc and $^{186/188}$Re. However, further studies particularly on the electrochemical behavior, nature of biodistribution in vivo, and long-term stability of the reported complexes at tracer level will determine their potential utility as radiopharmaceuticals.

Acknowledgment. This work was carried out with the funds from American Heart Association (Heartland Affiliate, 9951387Z, R.S.P.) and NIH (CA 72421, R.R.K.). The authors are indebted to Professor Silvia Jurisson for using her authorization for storing ^{99g}Tc complex. The authors also thank Dr. Wycoff for handling the ^{99g}Tc sample for proton NMR.

Supporting Information Available: Tables and CIF files of crystal structure data for **4**, **5**, and **8**, including atomic coordinates and equivalent isotropic displacement parameters, selected interatomic distances, torsional angles, displacement parameters for hydrogen atoms, and intensity data, Ortep figures, and proton NMR of ligands and complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

IC020434Q