Chemistry of Re with *N*,*N*′-Bis(2-pyridylmethyl)ethylenediamine (H_2pmen): Hydrolysis, Dehydrogenation, and Ternary Complexes

Liang Xu, Jason Pierreroy, Brian O. Patrick, and Chris Orvig*

Medicinal Inorganic Chemistry Group, Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, B.C. V6T 1Z1, Canada

Received November 17, 2000

A number of Re complexes with *N*,*N*′-bis(2-pyridylmethyl)ethylenediamine (H_2pmen) have been made from [NH_4][ReO_4]. [$ReOCl_2$(H_2pmen)]Cl, [ReOCl(Hpmen)][ReO_4], and [ReO_2(H_2pmen)][ReO_4] are related by hydrolysis/HCl substitution. [ReOCl(Hpmen)][ReO_4] was structurally characterized and found to contain a water-stable amido−Re bond. Dehydrogenation of the N-donor ligand from each amine to imine with concomitant two-electron reduction of the Re center occurs readily in these systems. With suitable 3-hydroxy-4-pyrones, ternary complexes such as [Re^{III}Cl(ma)($C_{14}H_{14}N_4$)][ReO_4]·CH_3OH, **5**, were made from [NH_4][ReO_4], H_2pmen·4HCl and pyrones in one-pot syntheses. **5**, a seven-coordinate Re^{III} complex, was structurally characterized.

Introduction

Much rhenium research has been fueled by interest in technetium, whose radionuclide (^{99m}Tc) is the workhorse of diagnostic nuclear medicine.[1−7] Recently, however, the radioisotopes ^{186}Re and ^{188}Re, which have suitable β-emitting properties, have been investigated for potential use in therapeutic nuclear medicine.[4,6] For example, a ^{186}Re complex with hydroxyethylidene diphosphonate (HEDP) has been proven to be beneficial in clinical trials for the palliation of bone pain.[4,6,8] While some complexes of Tc and Re may be similar, their redox and kinetic behaviors tend to differ, with Re complexes, generally speaking, being more inert and easily oxidized. The implication of this difference is 2-fold. First is a practical challenge of reducing perrhenate and complexing it to a suitable ligand in a reasonable time frame. (^{188}Re has a half-life of 17 h and is generated from a [$^{188}WO_4$]$^{2-}$ generator as [$^{188}ReO_4$]$^-$.) Second, the biochemistry and medicinal chemistry of Re and Tc complexes may be totally different. For example, many Re complexes, whose Tc counterparts were shown to be easily demetalated by challenging ligands, would probably survive biological metal scavengers long enough to be useful.

Quite a few commercial Tc imaging agents owe their success to their interaction with the body. In general, the compound is distributed by perfusion but retained by biomodification. Thus, in a typical approach, a coordination complex is defined and its ligand is then modified to vary its metabolic biochemistry.[3,7] Alternatively, ternary complexes offer the possibility of biomodification on the metal site: substitution of one ligand would most likely affect the biochemistry of the complex. To approach this idea, one needs a "primary" ligand that not only forms a stable metal complex by itself but also forms ternary complexes incorporating a "secondary" ligand. Ultimately, this design strategy can be extended to making ternary complexes with, or interacting with, various biologically interesting endogenous ligands.

There is extensive literature on rhenium complexes with N-donor ligands.[9−17] With appropriate halides or oxygen donor ligands, these complexes are usually cationic and stable (or inert) in air and water in oxidation states III, IV, and V. Because these N donors are mostly neutral, their complexes commonly react with anionic oxygen donor ligands to form ternary complexes. This charge difference between N and O donors is an excellent tool in a one-pot synthesis to produce a self-assembled ternary complex. Reaction chemistry of ReL complexes (N-donor ligands) is rich, and a number of these reactions have implications in nuclear medicine. Most notable reactions, for our purposes, include oxygen-transfer reactions,[10,14,18] redox,[11,19] reduction/complexation (with, for example, organohydrazines),[20] and substitution with anionic ligands.[11] With a suitable chelate, these reactions usually do not lead to demetalation of the N-donor ligand. For instance, many air-stable Re complexes with tripodal N ligands have been made in III, IV, and V oxidation states, and the aforementioned reactions in complexes are common.[11,17,19,21] N-donor ligands are thus good candidates for our "primary ligands".

The chemistry of Tc/Re with 3-hydroxy-4-pyrones, a family of monoanionic bidentate O donor ligands, has been studied.[22,23]

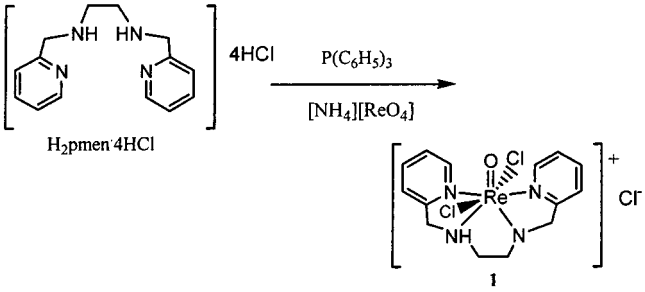
* To whom correspondence should be addressed. Phone: 604-822-4449. Fax: 604-822-2847. E-mail: orvig@chem.ubc.ca.

(1) Clarke, M.; Podbielski, L. *Coord. Chem. Rev.* **1987**, *78*, 253.
(2) Deutsch, E.; Libson, K.; Jurisson, S.; Lindoy, L. F. *Prog. Inorg. Chem.* **1983**, *30*, 75.
(3) Jurisson, S.; Desilets, C. P.; Jia, W.; Ma, D. *Chem. Rev.* **1993**, *93*, 1137.
(4) Dilworth, J. R.; Parrott, S. J. *Chem. Soc. Rev.* **1998**, *27*, 43.
(5) Tisato, F.; Refosco, F.; Bandoli, G. *Coord. Chem. Rev.* **1994**, *135*, 235.
(6) Volkert, W. A.; Hoffman, T. J. *Chem. Rev.* **1999**, *99*, 2269.
(7) Jurisson, S. S.; Lydon, J. D. *Chem. Rev.* **1999**, *99*, 2205.
(8) Deklerk, J. M. H.; Vanhetschip, A. D.; Zonnenberg, B. A.; Vandijk, A.; Quirijnen, J. M. S. P.; Blijham, G. H.; Vanrijk, P. P. *J. Nucl. Med.* **1996**, *37*, 244.
(9) Rouschias, G. *Chem. Rev.* **1974**, *74*, 531.
(10) Brown, S. N.; Mayer, J. M. *Inorg. Chem.* **1992**, *31*, 4091.
(11) Bohm, G.; Wieghardt, K.; Nuber, B.; Weiss, J. *Inorg. Chem.* **1991**, *30*, 3464.
(12) Paulo, A.; Domingos, A.; Santos, I. *Inorg. Chem.* **1996**, *35*, 1798.
(13) Paulo, A.; Domingos, A.; Marcalo, J.; de Matos, A. P.; Santos, I. *Inorg. Chem.* **1995**, *34*, 2113.
(14) Brown, S. N.; Mayer, J. M. *J. Am. Chem. Soc.* **1996**, *118*, 12119.
(15) DuMez, D. D.; Mayer, J. M. *Inorg. Chem.* **1998**, *37*, 445.
(16) Sugimoto, H.; Kamei, M.; Umakoshi, K.; Sasaki, Y.; Suzuki, M. *Inorg. Chem.* **1996**, *35*, 7082.
(17) Sugimoto, H.; Sasaki, Y. *Chem. Lett.* **1997**, 541.
(18) Abu-Omar, M. M.; Khan, S. I. *Inorg. Chem.* **1998**, 4979.
(19) Gisdakis, P.; Antoczak, S.; Rosch, N. *Organometallics* **1999**, *18*, 5044.
(20) Rose, D. J.; Maresca, K. P.; Nicholson, T.; Davison, A.; Jones, A. G.; Babich, J.; Fischman, A.; Graham, W.; DeBord, R. D.; Zubieta, J. *Inorg. Chem.* **1998**, *37*, 2701.

10.1021/ic0013025 CCC: $20.00 © 2001 American Chemical Society
Published on Web 03/21/2001

These anionic O-donor ligands stabilize M^V with an oxo or nitrido core, but their $M^{III/IV}$ complexes are ill-defined probably because of their reactivity in air and water. It is evident that these ligands alone are unable to stabilize the metal center very well. However, this inability is an attractive feature for a "secondary ligand" in a ternary complex; it would not displace the anchoring ligand. An added advantage of these ligands is that they are easily functionalized, providing the possibility of a wealth of bioconjugation chemistry.[24−29]

H_2pmen is a potential tetradentate ligand with four N donor atoms. Following a long line of amine/pyridine ligands, it promises stable Re complexes of intermediate oxidation states and presents the possibility of addition products with anionic ligands. We have previously reported a seven-coordinate complex $[ReOCl_2(H_2pmen)]Cl$ (**1**).[30] In this study, we investigated hydrolysis behavior of **1** and one-pot syntheses of ternary complexes from this ligand, $[NH_4][ReO_4]$, and 3-hydroxy-4-pyrones.



1

Experimental Section

Materials. Ethylenediamine, 3-hydroxyflavone, sodium borohydride, triphenylphosphine, potassium thiocyanide, and sodium hydroxide were all obtained from Aldrich or Alfa Chemicals and were used without further purification. Maltol (2-methyl-3-hydroxy-4-pyrone), ethylmaltol (2-ethyl-3-hydroxy-4-pyrone), and 5-hydroxymethyl-2-hydroxy-4-pyrene were obtained from Pfizer. $[NH_4][ReO_4]$ was received as a gift from Johnson-Matthey. $[(C_4H_9)_4N][ReOBr_4]$ was synthesized according to literature methods.[31] *N*,*N*′-Bis(2-pyridylmethyl)ethylenediamine tetrahydrochloride (H_2pmen·4HCl) and $[Re(H_2pmen)Cl_2]Cl$ (**1**) were prepared as previously reported.[30]

Instrumentation. IR (infrared) spectra were recorded as KBr disks in the range 4000−500 cm^{-1} on a Mattson Galaxy series 5000 FTIR spectrophotometer. Mass spectra (Cs^+, LSIMS (liquid secondary ion mass spectrometry)) were obtained on a Kratos Concept II H32Q with thioglycerol as the matrix. C, H, N, and Cl analyses were performed by Mr. Peter Borda in this department. NMR spectra were recorded at 200 MHz on a Bruker AC-200E (^{1}H, ^{1}H−^{1}H COSY) spectrometer and are reported as δ in ppm downfield from external TMS.

$[ReOCl(Hpmen)][ReO_4]$, 2. $[NH_4][ReO_4]$ (26 mg, 0.10 mmol) and H_2pmen·4HCl (38 mg, 0.10 mmol) were suspended in methanol (5 mL) with heating. Triphenylphosphine (52 mg, 0.20 mmol) was added to the suspension, and the mixture was heated at ∼60 °C for a few minutes, resulting in precipitation of a green crystalline material that was collected and dried under vacuum to yield 64 mg (87%). Anal. Calcd (found) for $C_{14}H_{17}ClN_4O_5Re_2$: C, 23.06 (23.22); H, 2.35 (2.36); N, 7.68 (7.59); Cl, 4.86 (5.05). Mass spectrum (LSIMS): m/z = 551 ($[ReO(C_{14}H_{15}N_4)(C_3H_9O_2S)]^+$, where $C_3H_9O_2S$ is the matrix, thioglycerol, and $C_{14}H_{15}N_4$ = H_2pmen-3H), 443 ($[ReO(C_{14}H_{16}N_4)]^+$, $[M - HCl]^+$). IR (cm^{-1}, KBr disk): 940, 909 ($\nu_{Re=O}$ for the complex cation and $[ReO_4]^-$, respectively). ^{1}H NMR: see Figure 1. Single crystals suitable for X-ray crystallographic analysis were grown from a water/methanol solution of $[ReOCl_2(H_2pmen)]Cl·CH_3OH$ (**1**) in a closed vial.

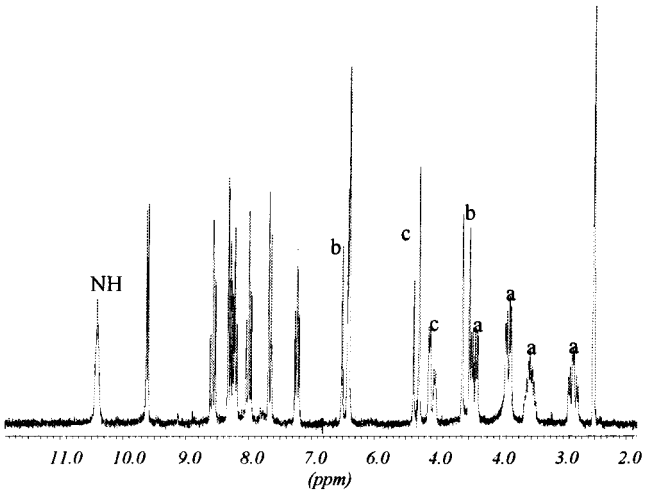


Figure 1. ^{1}H NMR spectrum of $[ReOCl(Hpmen)][ReO_4]$, **2**, in DMSO-d_6.

$[ReO_2(H_2pmen)][ReO_4]$, 3. Method A. To H_2pmen·4HCl (205 mg, 0.846 mmol) in acetonitrile (3 mL) was added sodium acetate (145 mg, 1.76 mmol) in methanol. The resulting solution was purged with nitrogen for 20 min, and $[(C_4H_9)_4N][ReOBr_4]$ (430 mg, 0.563 mmol) in acetonitrile (5 mL) was added dropwise. The purple/black solution was stirred for 24 h at room temperature to yield a violet precipitate, which was filtered out and dried under vacuum.

Method B. $[NH_4][ReO_4]$ (27 mg, 0.10 mmol) and H_2pmen·4HCl (38 mg, 0.10 mmol) were dissolved in methanol (5 mL)/water (5 mL). Excess $NaBH_4$ (15 mg, 65 mmol) was added, resulting in effervescence, and the mixture turned dark-red. More $[NH_4][ReO_4]$ (31 mg, 0.11 mmol) was added, and the mixture was kept at room temperature for 24 h over which time dark-purple microcrystals precipitated. The precipitate was collected and dried to yield 10 mg (14%).

Method C. Crystals of $[ReOCl_2(H_2pmen)]Cl·CH_3OH$, **1**, were suspended in methanol in an open vial at 4 °C. Green crystals of $[ReOCl(Hpmen)][ReO_4]$, **2**, formed in a few days; subsequently, dark needles of $[ReO_2(H_2pmen)][ReO_4]$, **3**, were deposited. Conversion to **3** was complete in a few weeks. Alternatively **1** or **2** was treated with excess sodium acetate, and the dark-red material precipitated immediately. Anal. Calcd (found) for $C_{14}H_{18}N_4O_6Re_2$: C, 23.66 (24.19); H, 2.55 (2.54); N, 7.88 (7.84). Mass spectrum (LSIMS): m/z = 443 ($[M - H_2O]^+$ or $[ReO(C_{14}H_{16}N_4)]^+$, where $C_{14}H_{16}N_4$ = H_2pmen-2H). IR (cm^{-1}, KBr disk): 911, 788 ($\nu_{Re=O}$ for $[ReO_4]^-$ and $\nu_{trans\ ReO_2}$, respectively). ^{1}H NMR (DMSO-d_6) δ: 4.0 (d, 2H, H_{en}); 4.6 (two sets of overlapping doublets, 4H, H_{en} and NCH_2Py); 6.1 (d, 2H, NCH_2Py); 7.8 (td, 2H, H_{py}); 8.2 (td, 2H, H_{py}); 8.0 (d, 2H, H_{py}); 9.7 (d, 2H, H_{py}).

$[Re(NCS)_3(C_{14}H_{16}N_4)]$, 4. ($C_{14}H_{16}N_4$ = H_2pmen-2H). $[ReOCl(Hpmen)][ReO_4]$ (60 mg, 0.082 mmol) was suspended in 10 mL of methanol, and KNCS (15 mg, 0.15 mmol) was added. Green crystals of $[ReOCl(Hpmen)][ReO_4]$ dissolved in a few minutes followed by precipitation of a white crystalline material (a mixture of $K[ReO_4]$ and KCl). The supernatant was decanted and refrigerated, and dark-purple crystals precipitated in the red solution within a day. The supernatant was decanted off, and the crystals were dried to yield 10 mg (20%). Anal. Calcd (found) for $C_{17}H_{16}N_7ReS_3$: C, 33.99 (33.82); H, 2.68 (2.64); N, 16.32 (15.91). Mass spectrum (+LSIMS): m/z = 565 ($[Re(NCS)_3$-

(21) Takahira, T.; Umakoshi, K.; Sasaki, Y. *Acta Crystallogr., Sect. C* **1994**, *50*, 1870.
(22) Archer, C. M.; Dilworth, J. R.; Jobanputra, P.; Harman, M. E.; Hursthouse, M. B.; Karaulov, A. *Polyhedron* **1991**, *10*, 1539.
(23) Luo, H.; Rettig, S. J.; Orvig, C. *Inorg. Chem.* **1993**, *32*, 4491.
(24) Finnegan, M. M.; Rettig, S. J.; Orvig, C. *J. Am. Chem. Soc.* **1986**, *108*, 5033.
(25) Nelson, W. O.; Rettig, S. J.; Orvig, C. *J. Am. Chem. Soc.* **1987**, *109*, 4121.
(26) Finnegan, M. M.; Lutz, T. G.; Nelson, W. O.; Smith, A.; Orvig, C. *Inorg. Chem.* **1987**, *26*, 2171.
(27) Matsuba, C. A.; Nelson, W. O.; Rettig, S. J.; Orvig, C. *Inorg. Chem.* **1988**, *27*, 1045.
(28) Nelson, W. O.; Rettig, S. J.; Orvig, C. *Inorg. Chem.* **1989**, *28*, 3153.
(29) Zhang, Z.; Rettig, S. J.; Orvig, C. *Inorg. Chem.* **1991**, *30*, 509.
(30) Xu, L.; Setyawati, I. A.; Pierreroy, J.; Pink, M.; Young, V. G., Jr.; Patrick, B. O.; Rettig, S. J.; Orvig, C. *Inorg. Chem.* **2000**, *39*, 5958.
(31) Cotton, F. A.; Lippard, S. J. *Inorg. Chem.* **1966**, *5*, 9.

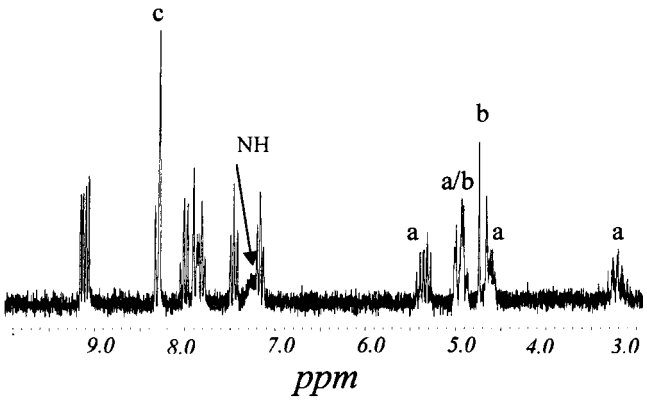


Figure 2. ^{1}H NMR spectrum of [Re($C_{14}H_{16}N_4$)($NCS)_3$], **4**, in acetone-d_6.

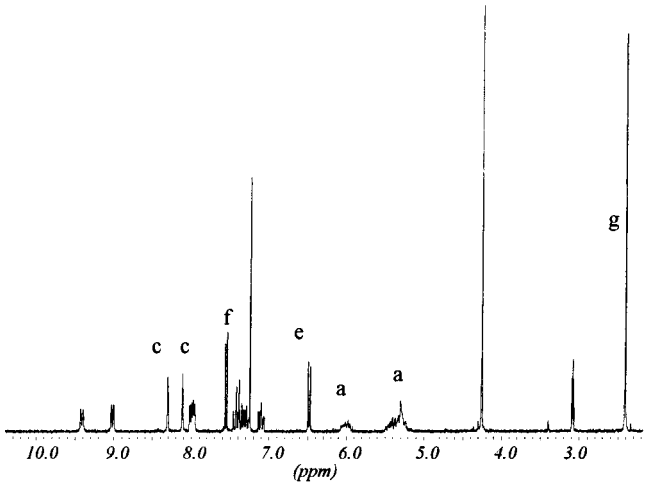


Figure 3. ^{1}H NMR spectrum of [ReCl(ma)($C_{14}H_{14}N_4$)][ReO_4], **5**, in $CDCl_3/CD_3OD$.

($C_{14}H_{14}N_4$)·H_2O]$^+$, $C_{14}H_{14}N_4$ = H$_2$pmen-4H). IR (cm^{-1}, KBr disk): 2081, 2059 ($\nu_{N\equiv C}$). ^{1}H NMR: see Figure 2.

[ReCl(ma)($C_{14}H_{14}N_4$)][ReO_4]·CH_3OH, 5 ($C_{14}H_{14}N_4$ = H$_2$pmen-4H). [NH_4][ReO_4] (27 mg, 0.10 mmol), H$_2$pmen·2HCl (38 mg, 0.10 mmol), and 2-methyl-3-hydroxy-4-pyrone (maltol, Hma, 42 mg, 0.33 mmol) were combined in methanol (3 mL), and the solution was heated for 20 h at 70 °C. To the resulting hot dark-green solution was added more [NH_4][ReO_4] (27 mg, 0.10 mmol), and single crystals suitable for a structural determination precipitated upon slow cooling. The crystals were collected, washed with methanol, and dried to yield 50 mg (58%). Anal. Calcd (found) for $C_{21}H_{23}ClN_4O_8Re_2$: C, 29.08 (29.43); H, 2.67 (2.60); N, 6.46 (6.55); Cl 4.09 (3.98). Mass spectrum (+LSIMS): m/z = 585 ([ReCl(ma)($C_{14}H_{14}N_4$)]$^+$). IR (cm^{-1}, KBr disk): 909 ($\nu_{Re=O}$). ^{1}H NMR: see Figure 3.

[ReCl(ema)($C_{14}H_{14}N_4$)][ReO_4], 6 ($C_{14}H_{14}N_4$ = H$_2$pmen-4H). The synthesis was the same as that for [ReCl(ma)($C_{14}H_{14}N_4$)][ReO_4] except that 2-ethyl-3-hydroxy-4-pyrone (ethylmaltol, Hema, 42 mg, 0.30 mmol) was used. Yield: 40 mg (47%). Anal. Calcd (found) for $C_{21}H_{21}ClN_4O_7Re_2$: C, 29.70 (29.51); H, 2.49 (2.45); N, 6.60 (6.30). Mass spectrum (+LSIMS): m/z = 599 ([ReCl(ema)($C_{14}H_{14}N_4$)]$^+$). IR (cm^{-1}, KBr disk): 909 ($\nu_{Re=O}$).

[ReCl(koj)($C_{14}H_{14}N_4$)][ReO_4], 7 ($C_{14}H_{14}N_4$ = H$_2$pmen-4H). The synthesis was the same as that for [ReCl(ma)($C_{14}H_{14}N_4$)][ReO_4] except that 5-hydroxymethyl-2-hydroxy-4-pyrone (kojic acid, Hkoj, 42 mg, 0.30 mmol) was used. Yield: 38 mg (45%). Anal. Calcd (found) for $C_{20}H_{19}ClN_4O_8Re_2$: C, 28.56 (28.70); H, 2.62 (2.34); N, 6.34 (6.25). Mass spectrum (+LSIMS): m/z = 601 ([ReCl(koj)($C_{14}H_{14}N_4$)]$^+$). IR (cm^{-1}, KBr disk): 909 ($\nu_{Re=O}$).

[ReCl(flv)($C_{14}H_{14}N_4$)][ReO_4], 8 ($C_{14}H_{14}N_4$ = H$_2$pmen-4H). [NH_4]-[ReO_4] (0.027 g, 0.10 mmol), H$_2$pmen·4HCl (0.038 g, 0.10 mmol), and 3-hydroxyflavone (Hflv, 34 mg, 0.14 mmol) were combined in methanol (3 mL), and the solution was heated for 20 h at 70 °C. This resulted in a dark-green solution and a dark-purple crystalline material. The crystals were collected and dried. Yield: 55 mg (58%). Anal. Calcd (found) for $C_{29}H_{23}ClN_4O_7Re_2$: C, 36.77 (37.04); H, 2.45 (2.47); N, 5.91 (5.97). Mass spectrum (+LSIMS): m/z = 697 ([ReCl(flv)-($C_{14}H_{14}N_4$)]$^+$), 662 ([M − Cl]$^+$), 621 ([M − C_6H_4]$^+$). IR (cm^{-1}, KBr disk): 910 ($\nu_{Re=O}$).

[ReOCl$_2$($C_{14}H_{14}N_4$)][ReO_4], 9 ($C_{14}H_{14}N_4$ = H$_2$pmen-4H). [NH_4]-[ReO_4] (0.027 g, 0.10 mmol), H$_2$pmen·4HCl (0.038 g, 0.10 mmol), and the HCl salt of 2,5-diazo-*N*,*N*′-dimethylhexyl-1,6-bis(phenylphosphinic acid) (98 mg, 0.20 mmol) were combined in methanol (3 mL), and the solution was heated for 70 h at 70 °C. The resulting dark-red solution was cooled to room temperature and left in the open air for a few days over which time a yellow microcrystalline solid precipitated. The precipitate was collected to yield 20 mg (26%). Anal. Calcd (found) for $C_{14}H_{14}Cl_2N_4O_5Re_2$: C, 22.08 (21.68); H, 1.85 (1.93); N, 7.36 (7.19). Mass spectrum (+LSIMS): m/z = 511 ([ReOCl$_2$($C_{14}H_{14}N_4$)]$^{2+}$). IR (cm^{-1}, KBr disk): 942, 910 ($\nu_{Re=O}$ for the complex cation and perrhenate, respectively). ^{1}H NMR (DMSO-d_6) δ: 4.5 (s, 4H, H_{en}); 8.1 (m, 2H, H_{py}); 8.8 (m, 2H, H_{py}); 8.6 (d, 2H, H_{py}); 9.4 (s, 2H, NC*H*Py); 9.6 (d, 2H, H_{py}).

X-ray Crystallographic Analysis. Crystals of **2** and **5** were mounted on glass fibers and data were collected at 20 and −100 °C, respectively, on a Rigaku/ADSC CCD area detector. Two sets of scans were collected for each crystal (φ = 0.0−190.0°, χ = 0.0°; and ω = −18.0 to 23.0°, χ = −90°; 0.50° oscillations, 81.0 s exposures for **2**; φ = 0.0−190.0°, χ = −90°; and ω = −18.0 to 23.0°, χ = −90°, 0.50° oscillations; 15.0 s exposures for **5**). The data were processed using the d*TREK program[32] and corrected for Lorentz and polarization effects. Both structures were solved by direct methods[33] and expanded using Fourier techniques.[34,35]

Results and Discussion

As reported earlier, when stoichiometric amounts of ammonium perrhenate, H$_2$pmen·4HCl, and triphenylphosphine were heated in methanol at 70 °C, the solution turned immediately green and then in about an hour it turned yellow and yielded [ReOCl$_2$(H$_2$pmen)]Cl (**1**).[30] A green crystalline material was isolated in high yield when excess [NH_4][ReO_4] was used and the reaction mixture was heated only for a few minutes. This green material was characterized as [ReOCl(Hpmen)]-[ReO_4] (**2**). The elemental analysis fits, the LSIMS(+) spectrum shows a prominent [ReO(pmen)]$^+$ ([M − HCl]$^+$) peak at m/z = 443, and Re═O stretches of both perrhenate (ν_{ReO} = 908 cm^{-1}) and the complex (ν_{ReO} = 939 cm^{-1}) are prominent in the IR spectrum. Surprisingly, this formulation suggests the formation of an amido−Re bond in a wet acidic solution (the reaction started with H$_2$pmen·4HCl, which rendered the solution acidic). Water-stable M−amido bonds (M = Tc or Re) are rare, but the few existing examples are well-known in the field of nuclear medicine. Tc═O complexes of hexamethylpropylene amine oxime (HM−PAO) and ethylcysteinate dimer ECD, both containing amido donors, are successful brain-imaging agents.[3]

Single crystals of **2** precipitated from a methanol/water solution of [ReOCl$_2$(H$_2$pmen)]Cl·CH_3OH (**1**), and an X-ray crystallographic analysis of **2** confirmed the formulation. One oxo O, one Cl, and four N atoms coordinate to the rhenium center, forming a distorted octahedron with the O and Cl atoms in cis positions (Figure 4 and Tables 1 and 2). Except for a remarkable right angle formed by O−Re−Cl, the remaining

(32) d*TREK: Area Detector Software, version 4.13; Molecular Structure Corporation: Texas, 1996−1998.
(33) Altomare, A.; Burla, M. C.; Cammalli, G.; Cascarano, M.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, A. *J. Appl. Crystallogr.* **1999**, *32*, 115.
(34) Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; de Gelder, R.; Israel, R.; Smits, J. M. M. *The DIRDIF-94 program system*; Technical Report; Crystallography Laboratory: The Netherlands, 1994.
(35) *teXsan, Crystal Structure Analysis Package*; Molecular Structure Corporation: Texas, 1985, 1992.

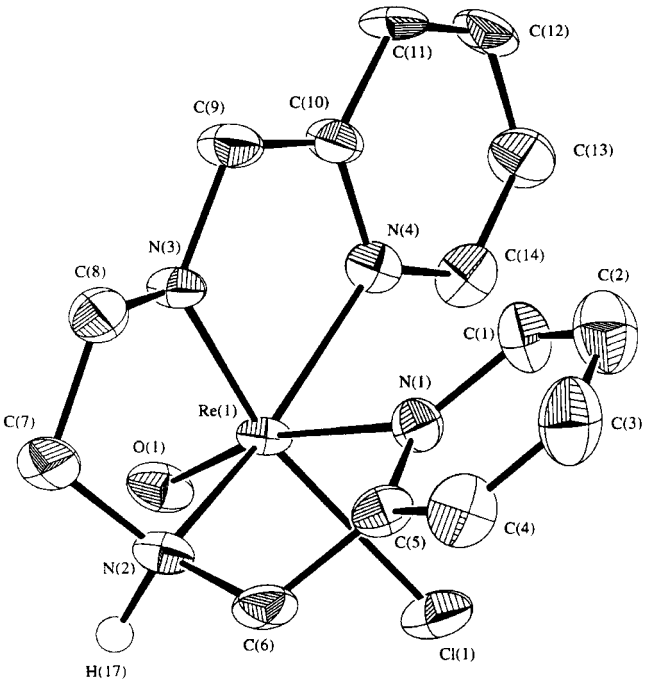


Figure 4. ORTEP drawing of the $[ReOCl(Hpmen)]^+$ cation in **2**, showing the crystallographic numbering. Thermal ellipsoids for the non-hydrogen atoms are drawn at the 33% probability level.

Table 1. Selected Crystallographic Data for **2** and **5**

	2	**5**
empirical formula	$C_{14}H_{17}N_4O_5Re_2Cl$	$C_{21}H_{23}N_4O_8Re_2Cl$
fw	729.18	867.29
color, habit	green, platelet	red-brown, block
crystal system	triclinic	monoclinic
space group	$P\bar{1}$	$P2_1/n$
a, Å	9.3975(7)	8.4833(2)
b, Å	10.648(2)	18.7387(7)
c, Å	10.779(2)	15.0656(6)
α, deg	68.78(1)	
β, deg	74.13(1)	91.47(1)
γ, deg	68.36(1)	
V, Å^3	922.3(2)	2394.1(1)
Z	2	4
ρ_{calc}, g/cm^3	2.626	2.403
radiation	Mo Kα	Mo Kα
μ, mm^{-1}	13.30	10.28
transm coeff	0.466−1.000	0.684−1.000
R; R_w[a]	0.044; 0.118	0.027; 0.072

[a] $R = \sum||F_o| - |F_c||/\sum|F_o|$, $I > 3\,\sigma(I)$; $R_w = (\sum(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2)^{1/2}$, all data

coordinating atoms are squeezed toward one another and away from the oxo O atom. This distortion is consistent with other $[Re{=}O]^{3+}$ complexes and can be rationalized by the spatial and electronic demands of an oxo ligand and/or strain imposed by five-membered ring chelation.[23,36−40] An amido−Re bond is confirmed by its short length (Re−N(3) = 1.896 Å) and by the (almost) planar sp^2-hybridized N(3). The rest of the Re−N lengths, as well as Re=O (1.691 Å) and Re−Cl lengths, are in the expected range with Re−N(1) being longest (2.296 Å), consistent with coordination trans to an oxo ligand.

The ^{1}H NMR spectrum (Figure 1) shows that **2** retains its solid-state structure in solution. All 17 H atoms are seen: 16 in the ligand backbone (positions a, b, c; see drawing of **2**) and 1 amine H, which disappears on addition of D_2O. In a correlation spectroscopy (COSY) experiment, the amine proton is shown to couple to one of the methylene protons next to the pyridine. As expected, coupling patterns of the ethylene H atoms are complex (each couples to the other three); those of NCH_2py are simple (geminal coupling only), and those of pyridine H atoms are unique (each couples to the others on the same pyridine ring in a predictable fashion). All ^{1}H NMR signals are well resolved, suggesting a rigid solution structure.

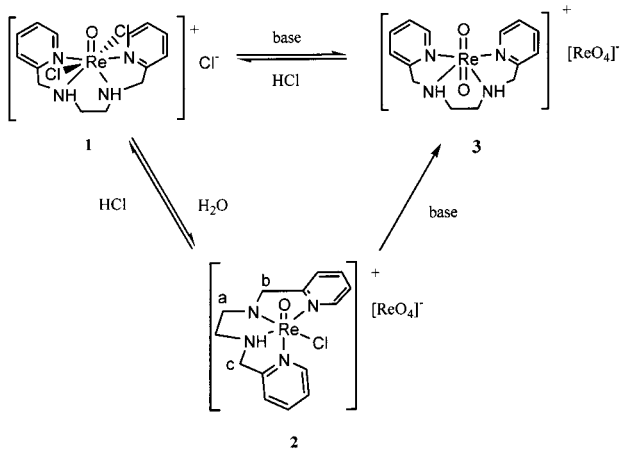
Table 2. Selected Bond Lengths (Å) and Bond Angles (deg) in the Complex Cations in **2** and **5**

	$[ReOCl(Hpmen)]^+$, **2**	$[ReCl(C_{14}H_{14}N_4)(ma)]^+$, **5**
Re−O(1)	1.691(5)	2.134(4)
Re−O(2)		2.034(4)
Re−N(1)	2.296(6)	2.091(4)
Re−N(2)	2.137(6)	2.090(5)
Re−N(3)	1.896(6)	2.056(5)
Re−N(4)	2.089(6)	2.102(4)
Re−Cl(1)	2.464(2)	2.499(1)
N(2)−C(6)	1.49(1)	1.287(7)
N(3)−C(9)	1.465(9)	1.307(7)
Cl(1)−Re−O(1)	90.0(2)	80.6(1)
O(2)−Re−O(1)		77.3(2)
N(1)−Re−O(1)	165.6(2)	161.9(2)
N(2)−Re−O(1)	98.4(3)	121.3(2)
N(3)−Re−O(1)	109.6(3)	73.0(2)
N(4)−Re−O(1)	102.3(2)	90.2(2)
N(1)−Re−N(2)	75.1(2)	73.1(2)
N(1)−Re−N(3)	82.4(3)	124.7(2)
N(1)−Re−N(4)	87.3(2)	91.7(2)
N(1)−Re−Cl(1)	78.2(2)	93.2(1)
N(2)−Re−N(3)	81.2(3)	68.5(2)
O(2)−Re−N(1)		85.1(2)
O(2)−Re−Cl(1)		82.1(1)
O(2)−Re−N(4)		83.3(3)
Re−N(3)−C(9)	120.4(5)	119.4(4)
Re−N(3)−C(8)	119.8(5)	118.4(4)
C(8)−N(3)−C(9)	115.0(6)	121.8(5)

Figure 1. Selected Bond Lengths (Å) and Bond Angles (deg) in the Complex Cations in **2** and **5**

Interestingly, from a mixture of $[NH_4][ReO_4]$ and H_2pmen·4HCl, when $NaBH_4$ was used as a reductant instead of triphenylphosphine, $[ReO_2(H_2pmen)][ReO_4]$ (**3**) was isolated as a dark crystalline solid. The IR spectrum of the complex is marked by a prominent asymmetric stretch of trans ReO_2 (ν_{ReO2} = 787 cm^{-1}), diagnostic of such species,[41] and the LSIMS(+) spectrum shows a $[M - H_2O]^+$ peak at m/z = 443. The ^{1}H NMR spectrum of **3** shows the complex to be either C_2 or C_s symmetric with a coupling pattern similar to that of **1**, but the chemical shifts of the corresponding protons of **1** and **3** are markedly different, reflecting differences in their coordination environments.

Conversion among **1**, **2**, and **3** is colorful and interesting. In



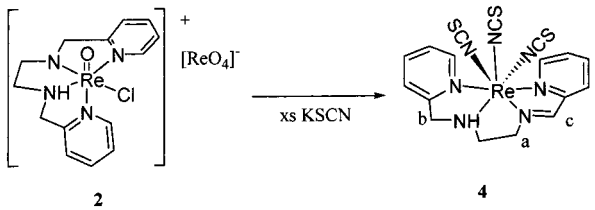
a methanol/water solution in air, $[ReOCl_2(H_2pmen)]Cl$ (**1**, yellow) slowly converts to $[ReOCl(Hpmen)][ReO_4]$ (**2**, green)

(36) Herrmann, W. A.; Rauch, M. U.; Artus, R. J. *Inorg. Chem.* **1996**, *35*, 1988.
(37) Gilli, G.; Sacerdoti, M.; Bertolasi, V.; Rossi, R. *Acta Crystallogr.* **1982**, *B38*, 100.
(38) Banbery, H. J.; McQuillan, F.; Hamor, T. A.; Jones, C. J.; McCleverty, J. A. *J. Chem. Soc., Dalton Trans.* **1989**, 1405.
(39) van Bommel, K. J. C.; Verboom, W.; Kooijman, H.; Spek, A. L.; Reinhoudt, D. N. *Inorg. Chem.* **1998**, *37*, 4197.
(40) Luo, H.; Liu, S.; Rettig, S. J.; Orvig, C. *Can J. Chem.* **1995**, *73*, 2272.

and finally to $[ReO_2(H_2pmen)][ReO_4]$ (**3**, red). From seven-coordinate **1** to six-coordinate **2** involves loss of 1 equiv of HCl, with formation of an amido−Re bond. An analogy can be drawn to the conjugate base-catalyzed dissociative mechanism (D_{cb}) that is accepted in the substitution of Co^{III} amine complexes; a proton on an amine ligand is extracted by a base, forming an amido−Co bond with concomitant loss of a ligand (for example, a chloride), and the highly reactive five-coordinate intermediate accepts a donor ligand, completing the substitution reaction.[42,43] The proposed five-coordinate intermediate, however, has not been isolated (or observed) in Co complexes with simple amines. Complex **2**, owing to the inertness of Re and its structurally constraining ligand, lends some support to the D_{cb} mechanism.

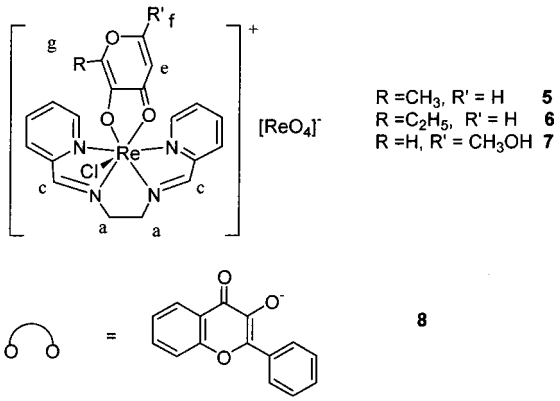
Following this analogy to Co chemistry and assuming that **2** is indeed the coordinatively unsaturated intermediate, the amido complex is expected to continue base-catalyzed hydrolysis or to revert to $[ReOCl_2(H_2pmen)]Cl$ in excess HCl. The conversion from **2** to **3** can be viewed as loss of one HCl and gain of one H_2O, effectively equivalent to hydrolysis. A drop of base completes the conversion from **1** or **2** to **3** instantly, and solutions of **2** or **3** turn yellow (to **1**) when HCl is added. This process is notable because it supports conjugated base-catalyzed hydrolysis and provides a rare example of an intermediate thereof in a Re system.[42,43]

A coordinatively unsaturated complex also promises facile reactions (most likely via an initial addition step). **2** reacted rapidly with KSCN, forming a number of products that were hard to isolate except for one: a dark-purple crystalline solid precipitated from a cold reaction mixture of **2** and KSCN. Elemental analysis of the material fits a 1:1:3 ratio of Re/L/NCS and indicates that the complex has no other non-hydrogen atoms. The IR spectrum shows no Re=O stretch but strong CN stretches from thiocyanate ($\nu_{C\equiv N}$ = 2081 and 2059 cm^{-1}), and the frequencies of the signals suggests that they are N-bound.[44] (+)LSIMS shows an interesting species of the formula $[Re(NCS)_3(C_{14}H_{14}N_4)]^+ \cdot H_2O$, in which four H atoms on H_2pmen are missing. While it is common to observe [L − 4H] peaks in the mass spectra of metal diamine complexes, they do not necessarily suggest that the formation of an imine complex should be possible on a synthetic scale. More telling evidence of the imine formation comes from the ^1H NMR spectrum (Figure 2). A total of 16 H atoms are seen, and one disappears (δ 7.2−7.3, broad) on D_2O exchange. Of the remaining 15, six H-atom resonances spread out in the range δ 3.0−5.5 ppm (positions a and b; see drawing for assignment), a range that is expected from the eight methylene hydrogens on H_2pmen; two H atoms are missing. *Nine* H atoms resonate between δ 7.0 and 9.3, in the range one would expect to find hydrogen atoms on unsaturated carbons, i.e., the *eight* pyridine H atoms. The extra hydrogen is a singlet, overlapping with half of a pyridine H doublet, at δ 8.25 ppm (position c). This resonance at 8.25 ppm can only be explained by a −C*H*=N linkage, in order to rationalize the integration of the spectrum, and the single exchangeable (amine) H in the D_2O experiment. The complex is thus formulated as **4**, a neutral seven-coordinate Re^{III} complex with three NCS ligands, and the N_4 ligand coordinates through the two pyridine N, one intact amine N, and one imine N atoms.



2 **4**

Perhaps more convincing evidence for the formulation of **4**, and indeed the reaction that produces it, comes from the synthesis of **5**. **5** is a very dark-green crystalline product that



precipitated from a heated methanolic solution of $[NH_4][ReO_4]$, $H_2pmen \cdot 4HCl$, and maltol and is formulated as $[Re^{III}Cl(ma)(C_{14}H_{14}N_4)][ReO_4] \cdot CH_3OH$, where $C_{14}H_{14}N_4$ is the diimine analogue of H_2pmen. The formation of **5** is supported by the elemental analysis, agreeing with the above formulation; by LSIMS, showing a prominent M^+ peak at m/z = 585; and by IR spectroscopy, showing bands from both ligands and a characteristic ν_{ReO} (= 908 cm^{-1}) of $[ReO_4]^-$. The ^1H NMR spectrum of **5** shows all 19 H atoms from the diimine N4 ligand and maltol, indicating that the complex is asymmetric (Figure 3). The H resonances of the maltolato ligand shift from that of the free pyrone, evincing its coordination (positions e−g; see drawing of **5** for assignment). In addition to the four ethylenediamine hydrogen resonances (two sets of multiplets, position a) and eight pyridine H signals (well-resolved), two singlet imine resonances at 8.3 and 8.1 ppm are unmistakable (position c) and are within the range of known imine complexes.

X-ray quality crystals of **5** precipitated from a slow cooling methanolic reaction mixture of $[NH_4][ReO_4]$, $H_2pmen \cdot 4HCl$, and maltol. Crystallographic analysis showed that the complex cation contains a seven-coordinate Re center complexed by one Cl, two O, and four N atoms (Figure 5, Tables 1 and 2). The coordination geometry resembles a capped trigonal prism with N(1)−N(4), N(2)−N(3), and O(1)−Cl(1) defining the vertexes and O(2) capping the N(1)N(4)Cl(1)O(1) face. The imine formation is supported by short C(2)−N(6) and C(9)−N(3) bond distances and by the planarity at the respective sp^2 C and N atoms. The resulting shape of the complex cation is noteworthy; the Re center is coordinated by a flat ligand (maltolate) and by two flat ligand fragments (the conjugated imine−pyridine units of the $C_{14}H_{14}N_4$ ligand). The flatness of the N-donor ligand is only disrupted at the sp^3 carbons of the ethylenediamine unit, where it bends. Seven-coordinate Re^{III} complexes are common, and notable examples are the monocapped trisdioxime species of formula $ReX(dioxime)_3BR$, where R is a variety of organic groups and X is a monodentate anion.[45,46] Tc analogues of these dioxime complexes, BATO, represent a family of successful heart-imaging agents. Except for a long Re−Cl bond, bond

(41) Fergusson, J. E. *Coord. Chem. Rev.* **1966**, 459.
(42) Tobe, M. In *The Role of Ion-Association in the Substitution Reactions of Octahedral Complexes in Nonaqueous Solution*; Gould, R. F., Ed.; American Chemical Society: Washington, DC, 1965; p 24.
(43) Basolo, F.; Pearson, R. G. *Mechanism of Inorganic Reactions*, 2nd ed.; Wiley: New York, 1967.
(44) Nakamoto, K. *Infrared and Raman Spectra of Inorganic Coordination Compounds*; John Wiley & Sons: New York, 1986.

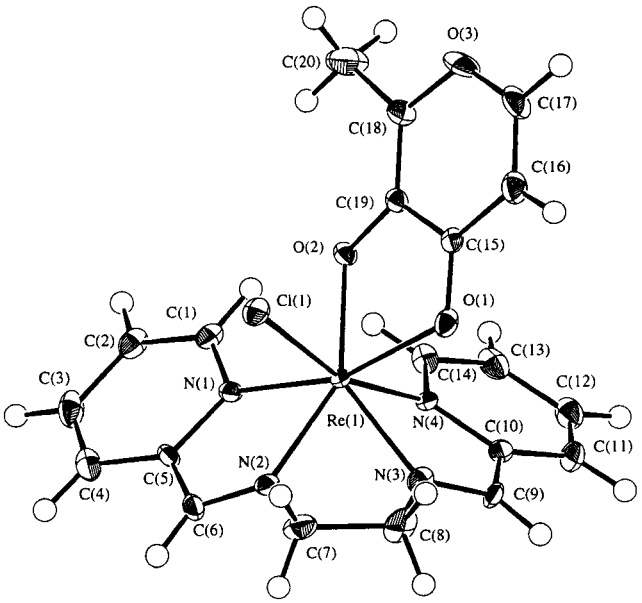


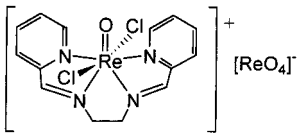
Figure 5. ORTEP drawing of the $[ReCl(ma)(C_{14}H_{14}N_4)]^+$ cation in **5**, showing the crystallographic numbering. Thermal ellipsoids for the non-hydrogen atoms are drawn at the 33% probability level.

distances of **5** are within the expected range for the respective bonds. The Re−N bond lengths vary little, from 2.056 to 2.102 Å, and are comparable to those of $ReX(dioxime)_3BR$.[45] The Re−O bond lengths reflect the difference between enolato O(2) coordination (2.034 Å) and carbonyl O(1) coordination (2.314 Å).

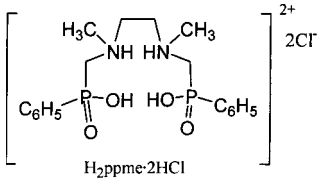
Two more ternary complexes with the 3-hydroxy-4-pyrones, ethylmaltol, and kojic acid (**6** and **7,** respectively) and one with 3-hydroxy-4-flavone (**8**) were similarly synthesized in one-pot syntheses, indicating the general nature of this reaction. In a ^{1}H NMR experiment where a 1:1:1 mixture of $[NH_4][ReO_4]$, H_2pmen·4HCl, and maltol were heated, only the ternary product was formed and all of the ligands were consumed. Considering the complexity of the system, this result is quite remarkable.

Although the mechanism is unclear, the reaction can be characterized as a dehydrogenation in which two amines on H_2-pmen are oxidized to imines with a concomitant four-electron reduction of perrhenate (Re^{VII}) to Re^{III}. Dehydrogenation of amines in metal complexes is common, especially in macrocyclic amines, but the metals usually retain their oxidation state.[47−49] Amine dehydrogenation by a metal in a high oxidation state with concomitant reduction of the metal has been reported but is much less common.[49] An analogy can also be drawn to 2-hydrazinopyridine (HYPY) reactions with $[MO_4]^-$ (M = Tc/Re), where two HYPY molecules reduce $[MO_4]^-$ to M^{III} with the hydrazines being dehydrogenated and complexed to the metals in their oxidized forms, essentially equivalent to dehydrogenations.[50]

We were curious about the role of the 3-hydroxy-4-pyrones in this reaction and the possibility of making ternary complexes with other anionic ligands. We found that the 3-hydroxy-4-pyrones are crucial in this dehydrogenation and that they most likely facilitate the reaction by thermodynamically stabilizing, or trapping, the ternary complex. When $[NH_4][ReO_4]$ reacted with H_2pmen·4HCl in the absence of a 3-hydroxy-4-pyrone, a small amount of very dark-red, intractable material was produced over a few days, with most of the starting amine left unreacted. A host of other coligands, such as cysteine, glycine, iminodiacetic acid, and catechol, was used instead of a 3-hydroxy-4-pyrone, and the reactions produced this mysterious dark-red material with variable success. The formation of the red complex (or complexes) was somewhat clarified when the HCl salt of 2,5-diazo-*N*,*N*′-dimethylhexyl-1,6-bis(phenylphosphinic acid) (H_2ppme·2HCl), a N_2O_2 ligand at our disposal, was used in the reaction. The dark-red material was produced in sufficient quantity so that when it was left in the open air in a methanol suspension, a yellow crystalline solid was produced, and this was characterized as $[ReOCl_2(C_{14}H_{14}N_4)][ReO_4]$ (**9**). The



9



H_2ppme·2HCl

production of this complex can be rationalized by the following. The dehydrogenation does occur in all of the above reactions, and it produces the dark-red product(s); the red material presumably contains the $Re^{III}(C_{14}H_{14}N_4)$ unit and oxidizes to **9** in air. It is unclear, however, why **9** was produced in a better yield in the presence of H_2ppme·2HCl. **9** was formulated on the basis of the elemental analysis, the IR spectrum ($\nu_{Re=O}$ = 942, 910 cm^{-1} for the complex cation and perrhenate, respectively), the mass spectrum, (+LSIMS, with a prominent $[M]^+$ peak), and the ^{1}H NMR spectrum (C_{2v} symmetric with en H atoms in dynamic exchange). In light of a seven-coordinate structural motif of Re^V=O complexes proposed earlier, the structure of **9** can be predicted.[30]

Facile reduction of perrhenate under mild conditions is useful in radiopharmaceutical applications. Production of **1**−**3** and **5**−**8** should translate readily to kit conditions. The hydrolysis behavior of **1**−**3** hints that a few exchanging complexes may be present in a solution, but it also promises interesting biochemistry. Reactivity of **5**−**8** is yet to be explored, but preliminary results indicate that they have curious reactions with endogenous ligands.

Acknowledgment. The authors gratefully acknowledge DuPont Pharmaceuticals for its support, the Natural Sciences and Engineering Research Council for grants, and Mr. Peter Borda for elemental analysis.

Supporting Information Available: Crystallographic file, in CIF format, for structures **2** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

IC0013025

(45) Jurisson, S.; Halihan, M. M.; Lydon, J. D.; Barnes, C. L.; Nowotnik, D. P.; Nunn, A. D. *Inorg. Chem.* **1998**, *37*, 1922 and references therein.
(46) Al-Shihri, A. S. M.; Dilworth, J. R.; Howe, S. D.; Silver, J.; Thompson, R. T. *Polyhedron* **1993**, *12*, 2297.
(47) Mahoney, D. F.; Berttie, J. K. *Inorg. Chem.* **1973**, *12*, 2561.
(48) Brown, G. M.; Weaver, T. R.; Keene, F. R.; Meyer, T. J. *Inorg. Chem.* **1976**, *15*, 190.
(49) Bernhard, P.; Bull, D. J.; Burgi, H. B.; Osvath, P.; Raselli, A.; Sargeson, A. M. *Inorg. Chem.* **1997**, *36*, 2804.
(50) Hirsch-Kuchma, M.; Nicholson, T.; Davison, A.; Davis, W. M.; Jones, A. G. *Inorg. Chem.* **1997**, *36*, 3237.