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COMMUNICATIONS

Published on Web 05/29/2002

Exceptional Kinetic Propensity of Hydroxymethyl Phosphanes toward Rh(III) Stabilization in Water

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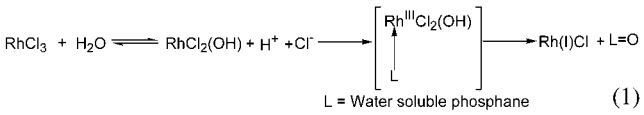
Received February 20, 2002

Since the discovery of Wilkinson's catalyst, $[RhCl(PPh_3)_3]$, numerous research efforts have been focused on the coordination chemistry of rhodium.[1,2] In recent years the chemistry of rhodium has attained considerable prominence in biomedicine.[3] For example, rhodium has Rh-105 radioisotope with ideal radiochemical properties (E_β = 560 keV (70%), 250 keV (30%); E_γ = 306 keV (5%), 319 keV (19%); $t_{1/2}$ = 36 h) and its radiotherapeutic agents have been implicated for use in the treatment of cancer.[3d−h] Stabilization of rhodium in +3 (or low-spin d^6) oxidation state is critical for biomedical applications because the low-spin d^6 electronic configuration confers both kinetic inertness and stability under in vivo conditions.[4] Bergman et al. and others have demonstrated coordination behavior of nitrogen-based ligands in stabilizing new rhodium compounds in +3 oxidation states even under reducing conditions.[4] Although phosphane ligands are ubiquitous in the coordination chemistry of rhodium, their role in stabilizing d^6 rhodium centers in aqueous media is unknown to date. Traditionally, water-soluble phosphanes (e.g., phosphatriazaadamantane (PTA) or sulfonated phosphanes) have been used to promote aqueous solubility and kinetic stability for transition metal compounds.[5] However, the reactions of water-soluble phosphanes with $RhCl_3 \cdot xH_2O$ are seldom straightforward and often result in complex reaction mixtures.[6] Specifically, Rh(III) in water readily oxidizes the hydrosoluble phosphanes even in the absence of oxygen.[6] Generally, the phosphane oxidation is facilitated by the formation of rhodium hydroxo species as depicted in eq 1. In fact, detailed redox studies by Larpent et al.[6c] have demonstrated the formation of transient hydroxorhodium (III) intermediate as outlined in eq 1. This means that if Rh(III) has to be stabilized, rhodium in +3 oxidation state must be coordinated and stabilized with specific ligands before hydroxorhodium (III) equilibrium sets in (eq 1). This can only be



(1)

achieved if the coordinating ligands have extraordinary kinetics toward complexation, whereby Rh(III) is stabilized before the hydroxointermediates are formed. Water-soluble ligands such as PTA and trisodium phosphinetriyltri-*m*-benzenesulfonate (TPPTS) are not capable of stabilizing Rh(III).[6] In this context, there is clearly a strong rationale for developing new insights into stabilizing Rh(III) complexes in aqueous media. As part of our ongoing studies on ligand design and coordination chemistry of metals/metallic isotopes for catalytic and biomedical applications,[7] we report herein the facile kinetics of a water-soluble bidentate phosphane (hydroxymethyl phosphinobenzene (HMPB) **1**) and also that of the water-soluble monodentate phosphane (tris-hydroxymethyl phosphine (THP) **2**), leading to the stabilization of Rh(III) complexes, *cis*-$[RhCl_2\{\eta^2\text{-}(HOCH_2)_2P(C_6H_4)P(CH_2OH)_2\}_2]Cl$ **3** and *fac*-$[RhCl_3(P(CH_2OH)_3)_3]$ **4**, respectively, in aqueous media.

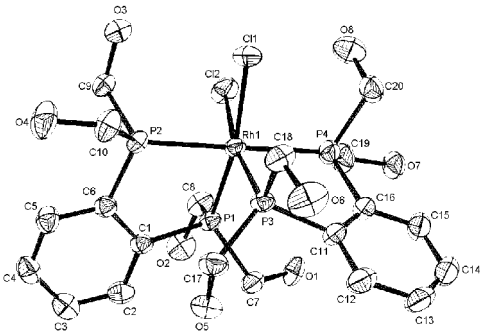


Figure 1. Molecular structure of *cis*-$[Rh(HMPB)_2Cl_2]Cl$ (**3**). Hydrogen atoms are omitted for clarity. Pertinent bond lengths (Å) and bond angles (deg) are as follows: Rh1−P1 = 2.280(2), Rh1−P2 = 2.345(2), Rh1−P3 = 2.292(2), Rh1−P4 = 2.333(2), Rh1−Cl1 = 2.452(2), Rh1−Cl2 = 2.441(2); P1−Rh1−P2 = 83.31(6), P3−Rh1−P4 = 83.40(6), Cl1−Rh1−Cl2 = 86.02 (7), P2−Rh1−P4 = 178.62(7).

The facile kinetics of a water-soluble bidentate phosphane (hydroxymethyl phosphinobenzene (HMPB) **1**) and also that of the water-soluble monodentate phosphane (tris-hydroxymethyl phosphine (THP) **2**), leading to the stabilization of Rh(III) complexes, *cis*-$[RhCl_2\{\eta^2\text{-}(HOCH_2)_2P(C_6H_4)P(CH_2OH)_2\}_2]Cl$ **3** and *fac*-$[RhCl_3(P(CH_2OH)_3)_3]$ **4**, respectively, in aqueous media.

The water-soluble rhodium (III) complex **3** was produced in good yields via the interaction of 3 equiv of $(HOCH_2)_2P(C_6H_4)P(CH_2OH)_2$ (HMPB) **1** with 1 equiv of $RhCl_3 \cdot xH_2O$ in aqueous media at 25 °C. This reaction is almost instantaneous and produced **3** as a predominant rhodium-containing species. The HCl generated during the dissolution of $RhCl_3 \cdot xH_2O$ (eq 1) abstracts 1 equiv of HMPB (**1**) resulting in its phosphonium salt.

The ^{31}P NMR spectrum of the reaction mixture showed two doublet of triplets in an A_2M_2X pattern centered at δ 56.40 and 49.22 attributable to **3**. A second rhodium species in less than 2% intensity appeared as a doublet at δ 53.04 ($^1J_{Rh-P}$ = 90 Hz) and was tentatively assigned to the corresponding *trans*-$[RhCl_2\{\eta^2\text{-}(HOCH_2)_2P(C_6H_4)P(CH_2OH)_2\}_2]Cl$. Single crystals suitable for X-ray diffraction analysis of the abundantly produced compound **3** were obtained by slow evaporation in methanol. The molecular structure of compound **3** as shown in Figure 1 confirms the cis configuration of the ligand in this Rh(III) compound. The water-soluble Rh(III) compound **3** represents the first X-ray crystal structure of a rhodium complex bearing a water-soluble bisphosphane in a cis coordination mode.

It may be conceived that the chelating ability of HMPB plays a critical role in stabilizing Rh in +3 oxidation state as discussed above. To evaluate if the monodentate analogues of HMPB exert similar kinetic influence in stabilizing Rh(III) under reducing

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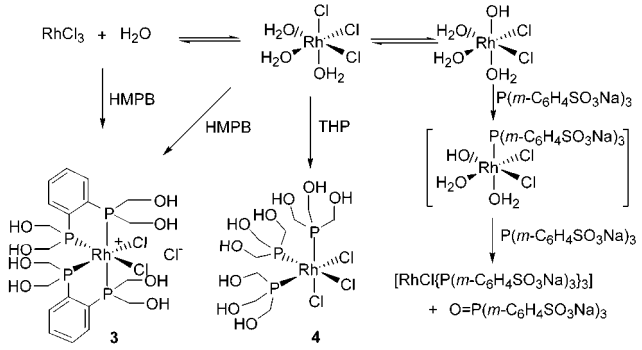
10.1021/ja025987e CCC: $22.00

Scheme 1. Synthesis of Water-Soluble Rhodium Complexes



conditions, the reactions of tris-hydroxymethyl phosphane ($P(CH_2OH)_3$ **2**) with $RhCl_3 \cdot xH_2O$ in aqueous media were performed. It is significant to note that the monodentate tris-hydroxymethyl phosphane produced the corresponding *fac*-$[RhCl_3(P(CH_2OH)_3)_3]$ (**4**) complex in good yields (Scheme 1). The ^{31}P NMR of the reaction mixtures showed a singular peak corresponding to the Rh(III) complex **4**. The molecular constitution of **4** was further confirmed by single-crystal X-ray analysis. The ORTEP plot and the salient bonding parameters are outlined in Figure 2.

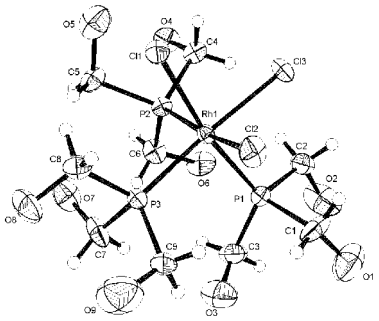


Figure 2. Molecular structure of *fac*-$[Rh(THP)_3Cl_3]$ (**4**). Pertinent bond lengths (Å) and bond angles (deg) are as follows: Rh1−P1 = 2.295(2), Rh1−P2 = 2.286(2), Rh1−P3 = 2.2985(19), Rh1−Cl1 = 2.442(2), Rh1−Cl2 = 2.433(2); Rh1−Cl3 = 2.433 (2); P1−Rh1−P2 = 96.86(8), P2−Rh1−P3 = 95.34(7), P1−Rh1−P3 = 96.01(8).

The equilibrium of the rhodium chloro to the corresponding hydroxo species is commonly encountered in all reactions of $RhCl_3 \cdot xH_2O$ preformed in aqueous media.[6] However, the reaction of $RhCl_3 \cdot xH_2O$ with hydroxymethyl phosphane ligands **1** and **2**, as depicted in Scheme 1, demonstrates the ability of the mono- and bidentate water-soluble phosphanes to coordinate with Rh(III) and consequently stop the onset of the rhodium−hydroxo equilibrium. To put our results (on the efficacy of hydroxymethyl phosphane ligands **1** and **2** to trap the rhodium in +3 oxidation state) in perspective, the results from the corresponding reactions of $RhCl_3 \cdot xH_2O$ with PTA and TPPTS ($P(m\text{-}C_6H_4SO_3Na)_3$) in aqueous media are compared.[6] In every instance, the hydrophilic PTA and TPPTS are readily oxidized by Rh(III), presumably via the hydroxorhodium (III) intermediate $[RhCl_2(OH)]$, and consequently the Rh(I) coordination complexes are formed.[6] In this context, our findings demonstrate that the efficacy of **1** and **2** toward complex formation with Rh(III) clearly outweighs the rate of dissociation of $RhCl_3 \cdot xH_2O$ to $[RhCl_2(OH)]$.

The hydrophilic Rh(III) complexes **3** and **4** exhibits remarkable kinetic inertness in water. In particular, no Cl to H_2O exchange were observed as evidenced by NMR spectroscopic experiments.[8] The coordination chemistry of hydroxymethyl phosphane ligands **1** and **2** and the associated kinetic stabilities exerted to the metal center provide new opportunities in the design and development of in vivo stable Rh-105 labeled therapeutic agents for potential use in the treatment of cancer.

Acknowledgment. This work was supported by the U.S. Department of Energy, Department of Radiology, and the University of Missouri Research Reactor.

Supporting Information Available: Synthesis, NMR characterization details, crystal data, structure refinement, atomic coordinates, bond lengths and angles for **3** and **4** (PDF). X-ray crystallographic files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) ^{31}P NMR experiments of **3** and **4** in aqueous media for a duration of over three weeks showed no spectral changes. These data infer kinetic inertness of Rh−Cl bonds in **3** and **4**.

JA025987E