

Iridium-Catalyzed H/D Exchange into Organic Compounds in Water

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Deuterium- and tritium-labeled compounds have a number of important uses, from solvents for NMR spectroscopy to reagents for mechanistic investigations.¹ Deuterium oxide (D₂O) is the most attractive isotopic source for the preparation of these materials due to its combined low cost and low toxicity. However, general procedures for the incorporation of deuterium into the C–H bonds of organic compounds which utilize D₂O are often limited to activated positions of the molecules.^{2,3}

An exception to this is the pioneering work of Garnett^{4–6} and Shilov,^{7,8} which showed that K₂PtCl₄ is a competent catalyst for homogeneous H/D exchange between D₂O and arenes or alkanes. It was found that the platinum-catalyzed process required the addition of several additives to proceed efficiently. First, a strong inorganic acid was used to prevent disproportionation of the catalyst to Pt(0) and Pt(IV). Additionally, an aromatic compound such as pyrene acted as an “olefin stabilizer” for Pt(II). Furthermore, the inclusion of an organic acid such as CH₃CO₂H was necessary to maintain homogeneity. For statistical reasons, the presence of these additives necessarily leads to a lower maximum deuterium exchange percentage. Reactions with halide salts of iridium⁹ and rhodium¹⁰ suffered from similar limitations. We report here that Cp*(PMe₃)IrCl₂ (**1**) efficiently catalyzes the exchange of deuterium from D₂O into organic molecules without added acid or stabilizers, and we discuss decomposition pathways of the catalyst that suggest future catalyst improvements.

We recently reported that the Ir complex [Cp*(PMe₃)IrH(CH₂Cl₂)] [B(C₆F₅)₃Me] (**2**) catalyzes low-temperature H/D exchange between C₆D₆ and a variety of organic substrates.¹¹ In search of an air-stable Ir(III) catalyst that could make use of D₂O as the deuterium source, we elected to study the aqueous H/D exchange behavior of Cp*(PMe₃)IrCl₂ (**1**). We believed that the aqueous medium would render the chloride ligands labile and lead to a catalytically active 16-e Ir fragment. Similar to the manner in which Periana and co-workers found that organic ligands altered the course of Pt(II) halide-catalyzed methane oxidation,¹² we were hopeful that a well-defined ancillary ligand set would lead to H/D exchange results better than those of the Ir(III) or Pt(II) systems studied previously.

Heating a variety of organic substrates with a catalytic amount (5 mol %) of the dichloride complex **1** in D₂O leads to extensive H/D exchange; Table 1 presents typical results.¹³ Emphasis was placed on substrates that had high water solubility, so that the reactions could be monitored by ¹H NMR spectroscopy.¹⁴ Choosing substrates with differently substituted carbon centers allowed issues of selectivity to be addressed. EI-MS was also used to confirm deuterium incorporation, although fragmentation of the parent ion of many of the substrates prevented this from being a definitive method for measuring deuterium content.¹⁵ Although **1** catalyzed extensive deuterium incorporation into many different types of unactivated C–H bond positions, some selectivity was observed

Table 1. H/D Exchange Results with 5 Mol % Cp*(PMe₃)IrCl₂^a

entry	substrate/selectivity	%D _{total}	entry	substrate/selectivity	%D _{total}
1			54		61
2		91	6		32
3		22	7		87
4		36	8		23

^a All reactions were performed with complex **3** in sealed glass containers containing 0.5 mL of D₂O at 135 °C for 40 h. For % D, ¹H NMR spectroscopy was used for analysis.

in those systems containing more than one type of C–H bond. For example, the internal methylene position of *n*-propanol is the least rapidly deuterated of the three positions available. When ibuprofen (entry 6 in Table 1) was used as the substrate, exchange into unactivated secondary and tertiary C–H bond positions was not observed. Similarly, sodium octanoate showed surprisingly high selectivity for the terminal position. Some preferential reaction at terminal sites has been seen previously in C–H activation/functionalization reactions and has been attributed to steric effects.^{8,16} We do not yet understand the physical basis of these selectivities, but the activation of stronger, primary C–H bonds is persuasive evidence against an exchange mechanism involving radicals. Exchange reactions using substrates which lack polar substituents, such as amylbenzene and naphthalene, led to low levels of deuterium incorporation (<10% overall) with use of the reaction conditions in Table 1.

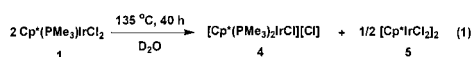
Deuterium incorporation into ethereal substrates, such as diethyl ether and tetrahydrofuran (THF), is also a facile process with the dichloride catalyst **1**. Monitoring the reactions by ¹H NMR spectroscopy reveals a preference for activation of the β-position in diethyl ether (presumably because these are primary hydrogens), whereas the α-position is attacked first in THF. Selective C–H activation of THF at the α-position had been previously observed in exchange reactions catalyzed by [Cp*(PMe₃)Ir(H)(CH₂Cl₂)] [B(C₆F₅)₃Me]¹¹ and in stoichiometric C–H activation reactions of Ir(III).¹⁷ Carmona and co-workers have reported that Tp^{Me}₂IrH₄ mediates H/D exchange between THF and D₂O by heating to 90 °C for 7 days. However, the levels of incorporation were very low and no selectivity for either the α- or β-positions was observed.¹⁸ The deuteration of sodium benzoate is significantly slower than that of benzoic acid (Table 1) because it leads to the formation of the less reactive Ir complex, Cp*(PMe₃)Ir(O₂CPh)₂ (**3**).

Exchange with all substrates was observed to stop after heating at 135 °C for 40 h, with concomitant formation of a new Ir-containing material, observed by ³¹P NMR spectroscopy.¹⁹ The same species was found to be produced by heating Cp*(PMe₃)IrCl₂ in D₂O at 135 °C in the absence of organic substrate. Comparison

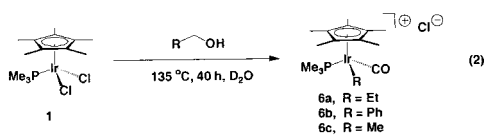
with authentic samples verified that the products were $[\text{Cp}^*(\text{PMe}_3)_2\text{IrCl}][\text{Cl}]$ (**4**) and $[\text{Cp}^*\text{IrCl}_2]_2$ (**5**) (eq 1).^{20,21} The equilibrium constant for this reaction is $K_{\text{eq}} = 0.6 \pm 0.1 \text{ L}^{1/2} \text{ mol}^{-1/2}$. Production of the Ir ion pair **4** is presumably the driving force for the disproportionation in the polar medium; no such disproportionation of **1** was observed by NMR spectroscopy in CD_2Cl_2 solution.

It was important to establish the catalytic properties of the disproportionation mixture of **4** and **5** toward the H/D exchange reaction. Bis(phosphine) complex **4** was shown to be completely inactive, and dimer **5** was shown to be moderately active (although substantially less active than dichloride **1**). More importantly, a 1:1 mixture of **4** and **5** was inactive. We therefore believe that **4** is an effective inhibitor of **5** by serving as a source of free chloride ion (vide infra).

Another decomposition route of dichloride complex **1** was encountered when primary alcohols were used as substrates in the exchange reactions. Although extensive H/D exchange was evident with *n*-propanol, complete formation of a new Ir species was observed after heating to 135 °C for 40 h. This new complex was



shown to be $[\text{Cp}^*(\text{PMe}_3)_2\text{Ir}(\text{CO})(\text{Et})][\text{Cl}]$ (**6a**) after subsequent isolation (61% yield) and characterization. Similarly, deuteration of benzyl and ethyl alcohol led to the isolation of $[\text{Cp}^*(\text{PMe}_3)_2\text{Ir}(\text{CO})(\text{Ph})][\text{Cl}]$ (**6b**, 72% yield) and $[\text{Cp}^*(\text{PMe}_3)_2\text{Ir}(\text{CO})(\text{Me})][\text{Cl}]$ (**6c**, 57% yield), respectively (eq 2).²² We believe that the production



of these carbonyl complexes is initiated by oxidation of the alcohol to form the corresponding aldehyde. Activation of the weak aldehydic C–H bond results in formation of an acyl complex, which undergoes facile decarbonylation to give the observed products.^{23,24} Further studies indicated that 2-propanol and phenol undergo H/D exchange, but catalyst decomposition leads to disproportionation products **4** and **5** because a decarbonylation pathway is not expected to be accessible.

We speculate that the mechanism of H/D exchange in this system is similar to the one observed by Shilov and Garnett.⁸ Dissociation of chloride from the Ir center produces a cationic 16-e fragment capable of C–H activation. Consistent with this, it was observed that added sodium chloride (10 equiv) completely inhibited the reaction. Because heterogeneous Pd and Pt catalysts have been shown to catalyze H/D exchange,¹ we considered the possibility of catalytically competent Ir colloids in our system. However, the addition of elemental mercury^{25,26} had no effect on the deuteration of *n*-propanol, providing evidence against this possibility.

These preliminary H/D exchange data involving dichloride **1** are very promising and in some cases even surpass the performance of the Pt(II) and Ir(III) halide salts mentioned earlier. We made our comparison using identical conditions to those in Table 1, meaning that 5 mol % of the catalyst was heated to 135 °C for 40 h with the substrate in D_2O and without any additives. Using those conditions, deuteration of Et_2O with **1** leads to a total incorporation level of 36%, whereas K_2PtCl_4 affords 7% and Na_3IrCl_6 yields 15%.²⁷ The results presented here are unique to aqueous chemistry. Neither the disproportionation nor the oxidation–decarbonylation

reaction with primary alcohols were observed when heating $\text{Cp}^*(\text{PMe}_3)_2\text{IrCl}_2$ under otherwise identical conditions in CD_2Cl_2 . This is most likely due to the fact that the chloride ligands of **1** are not labile in CD_2Cl_2 .²⁸ We are currently investigating ways to prevent the disproportionation of **2** and better understand the intimate mechanism of the H/D exchange reaction.

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Supporting Information Available: Synthetic procedures, characterization data for **3** and **6a–c**, and information about measurement of deuterium incorporation and equilibrium constant (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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