Journal of Labelled Compounds and Radiopharmaceuticals
*J Label Compd Radiopharm* 2007; **50**: 73–78.
Published online 30 January 2007 in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1149

JLCR

Research Article

# Catalyst stability as a factor in iridium-mediated *ortho*-deuteration

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*Received 25 September 2006; Accepted 4 October 2006*

**Abstract:** Crossover experiments show that iridium complexes such as Ir(cod)(Py)($PCy_3$).$PF_6$ (**1**) and Ir(cod)($PPh_3$)$_2$.$BF_4$ are inactivated after a comparatively short period during deuterium exchange reactions. This effect can be limited to some extent by optimizing the concentration at which exchange is performed, but altering physical parameters and adding labile ligands in an effort to stabilize reactive intermediates does not improve matters. Complexes of bidentate arsines and PN ligands and, in some cases, bidentate phosphines, exhibit better stability. Unexpectedly, following hydrogenolysis, **1** is able to mediate deuterium exchange from deuterium oxide into amides and *N*-heterocycles at room temperature. Copyright © 2007 John Wiley & Sons, Ltd.

**Keywords:** iridium complexes; deuterium exchange; isotope exchange; catalyst stability; inactivation

## Introduction

Complexes of iridium(I) are now comparatively well-established as catalysts for the isotopic exchange of *ortho*-hydrogen in aromatic systems and, to a lesser extent, for exchange in heterocycles and adjacent to nitrogen in *N,N*-dimethylamides. Nevertheless, reproducibly quantitative levels of exchange can be elusive: if a high percentage of catalyst is used, exchange is rapid to start with, but the process slows and often stops after a period of only a few hours.[1,2] By comparison, Heys and co-workers demonstrated that, at a 2% loading, $IrH_2(Me_2CO)_2(PPh_3)_2BF_4$ was stable *in situ* over a period of some days.[3] In principle, if a complex mediates exchange into a substrate, deuterium incorporation should continue as long as excess deuterium and active catalyst are present. In practice, this does not occur with catalysts such as Ir(cod)Py($PCy_3$)$PF_6$ (**1**)[1] and Ir(cod)($PPh_3$)$_2BF_4$ (**2**)[2] although, with Ir(cod)($PPh_3$)$_3BF_4$ (**3**), exchange continues for 48 h and results in complete *ortho*-deuteration (Figure 1). Unfortunately, this complex has useful activity only toward *o*- and *m*-unsubstituted ketones.[4] A more promising system is Ir(cod)($Ph_2AsCH_2CH_2AsPh_2$)$BF_4$ (**4**), where complete exchange can take up to 5 days.[5] Crabtree has previously noted that catalysts formed by hydrogenolysis of the analogous systems, Ir(cod)(dppe)$PF_6$ and Ir(cod)($MePPh_2$)$_3PF_6$, had longer lifetimes than those formed from Ir(cod)($MePPh_2$)$_2PF_6$ or Ir(cod)Py(P-i-$Pr_3$)$PF_6$, although this improvement was at the cost of lower initial hydrogenation rates.[6] The question therefore arises whether the observed behaviour of **1** and **2** is actually a consequence of the catalyst being inactivated or sequestered, rather than of the system reaching equilibrium. Early catalyst inactivation would explain the poor correlation between ligand properties and the level of isotopic exchange for substrates whose binding kinetics are unfavourable or where initial exchange is slow.[7]

## Results and discussion

The deactivation of iridium catalysts during hydrogenation reactions is well known. Crabtree and co-workers[6,8] showed that deactivation is a consequence of the conversion of the metal complex to hydride-bridged dimers and trimers, which are catalytically inactive. It has also been suggested that deactivation may follow the dissociation of a phosphine ligand from the active species, even where the ligand is bound to a polymeric support.[9,10] A number of experiments were therefore devised in an effort to examine the factors influencing catalyst stability and means of enhancing it.[11]

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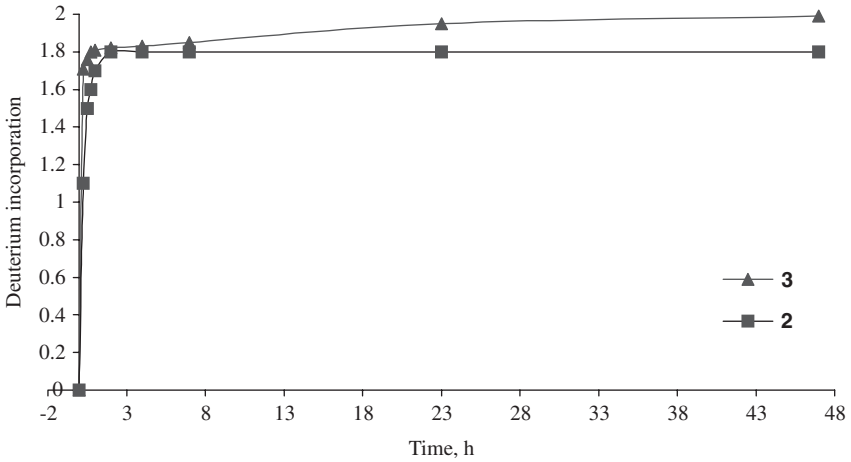


**Figure 1** Incorporation of deuterium into acetophenone as a function of time, using complexes **2** and **3**.

**Table 1** Crossover deuteration experiments with selected iridium catalysts[a]

| Pre-catalyst | $t_1$ (h) | Exchange into **A** | $t_2$ (h) | Exchange into **B** | Expected exchange into **B**[b] |
|---|---|---|---|---|---|
| Ir(cod)Py($PCy_3$)$PF_6$ (**1**) | 6 | 1.9 | 18 | 0.6 | 1.6 |
| Ir(cod)($PPh_3$)$_2BF_4$ (**2**) | 6 | 1.9 | 18 | 0.1 | 1.8[2] |
| Ir(cod)($PPh_3$)$_3BF_4$ (**3**) | 6 | 1.96 | 18 | 1.8 | 1.96[11] |
| **3** | 48 | 1.9 | 18 | 1.2 | 1.96[11] |
| Ir(cod)($Ph_2AsCH_2CH_2AsPh_2$)$BF_4$ (**4**) | 112 | 1.99 | 48 | 1.9 | 1.9[5] |
| Ir(cod)($Ph_2PCH_2CH_2CH_2PPh_2$)$BF_4$ (**5**) | 48 | 2.0 | 90 | 1.7 | 1.5[5] |
| Ir(cod)($Ph_2PCH_2CH_2PPh_2$)$BF_4$ (**6**) | 48 | 1.3 | 88 | 0.5 | 1.7[5] |
| Ir(cod)($Cy_2PCH_2CH_2PCy_2$)$BF_4$ (**7**) | 48 | 0.5 | 90 | 0.0 | 1.2[5] |
| Ir(cod)(BINAP)$BF_4$ (**8**) | 48 | 1.8 | 90 | 1.7 | 1.8[13] |
| Ir(cod)(Phox)$BF_4$ (**9**)[c] | 48 | 1.9 | 48 | 1.4 | 1.6[13] |
| Ir(cod)(QUINAP)$BF_4$ (**10**) | 48 | 1.9 | 88 | 1.45 | 1.45[13] |

[a] Method: 4-methylacetophenone (**A**) exchanged with $D_2$ and 100% catalyst during $t_1$; acetophenone (**B**) added to the mixture, and exchange continued with fresh $D_2$ during $t_2$.
[b] Exchange obtained when fresh catalyst is used.
[c] Phox is 2-(2-diphenylphosphinylphenyl)-4-phenyloxazoline.

## Crossover experiments

Although, at a 2% loading, $IrH_2(Me_2CO)_2(PPh_3)_2BF_4$ has been shown to be stable *in situ* for several days,[3] isotopic exchange in drug development candidates typically requires near-stoichiometric quantities or an excess of iridium complex to overcome futile binding to non-exchanging sites in the substrate.[12] The 1:2 catalyst/substrate ratio used in most of our work is more representative of this situation, in which there is no excess of binding substrate to aid complex stability. Crabtree has also noted that, at higher catalyst loadings, the rate of catalyst inactivation is substantially increased, simply because the catalyst concentration is higher.[6] In our earliest work,[1] we concluded that the catalyst formed on hydrogenolysis of **1** retained activity after 22 h, based on a crossover experiment, although the 4-phenylthiazole used in this case was chosen precisely because it was exchanged with some facility. However, a more rigorous investigation, using two electronically similar substrates with representative catalysts, gave somewhat different results (Table 1).

Certain trends are very much apparent from Table 1. Systems containing only simple phosphines, or a phosphine and a heterocyclic ligand, lost at least some of their activity within the course of a few hours. The system using **2** was clearly almost completely inactivated within 6 h, but **1** also lost much of its activity in the same period, and even the apparently stable **3**



DOI: 10.1002.jlcr

began to lose activity within 48 h. At the other extreme, the 1,2-bis(diphenylarsino)ethane complex (**4**) lost none of its activity after 112 h. The result with **4** does not translate directly to the corresponding diphosphinoalkane complexes: dppp complex **5** retains most of its activity after 48 h, but the dppe complex (**6**) has much-reduced activity after the same period, while the 1,2-bis(dicyclohexylphosphino)ethane complex (**7**) is completely inactivated. On the other hand, complexes **9** and **10**, using PN ligands, are consistently stable after at least 48 h. These complexes are cyclic analogues of **1**, and have useful activity for deuterium exchange in a number of substrate classes.[13] The relative stability of most bidentate systems is consistent with an inactivation pathway involving loss of one or more phosphine ligands as an important step.

## Concentration effects

If exchange mediated by either **1** or **2** genuinely reaches equilibrium within 24 h,[1,2] leaving deuteration runs for over 60 h should more than compensate for any rate effects from small changes in concentration. However, when deuteration of some simple substrates mediated by **1** is examined at a range of concentrations (keeping the catalyst/substrate ratio constant at 1:2), it appears that this is not always the case in practice. As illustrated in Figure 2, changing the concentration has little effect on incorporation into 2-phenylpyridine or 1-phenylpyrazole. However, with ethyl benzoate, there is a significant reduction in the extent of exchange at concentrations below 10 μmol/ml. Given the extended period allowed for exchange, the magnitude of this effect is very much greater than expected and, if the period of exchange at low concentration is extended (up to 112 h), there is no corresponding increase in deuterium incorporation. In line with the observations above, a reasonable interpretation of these results is that the active catalyst is degraded within the first 24 h in solution, and that this degradation is at least partly responsible for the 'equilibrium' observed after this time.

## The effect of deuterium oxide

The catalyst formed upon hydrogenolysis of $Ir(cod)(PPh_3)_3^+BF_4^-$ (**3**) may be more stable than those formed from either **1** or **2**, but it also suffers from a very limited substrate tolerance.[4] This is probably linked to the high steric demand associated with three phosphine ligands, and a better range of activity might be achievable if similar stability could be obtained by adding a labile (non-substrate) ligand to a system containing **1** or **2**. In earlier work using **1**, we had used a 1:1 catalyst/substrate ratio in the presence of deuterium oxide,[1] in the expectation that a small amount of coordinating solvent could stabilize the intermediate species by filling a vacant coordination site. However, we did not confirm that adding deuterium oxide was genuinely beneficial and so, to test the hypothesis, deuterium exchange of a series of substrates was carried out with and without added deuterium oxide, at 10 and 20 mM concentrations and using 50 and 100% of **1** (Table 2). The earlier data, obtained at the concentrations indicated, are included for comparison, and it is immediately clear that considerable variation in incorporation results simply from changing the catalyst/substrate ratio and adding deuterium oxide. It is interesting that the use of a 1:1 catalyst/substrate ratio generally does not

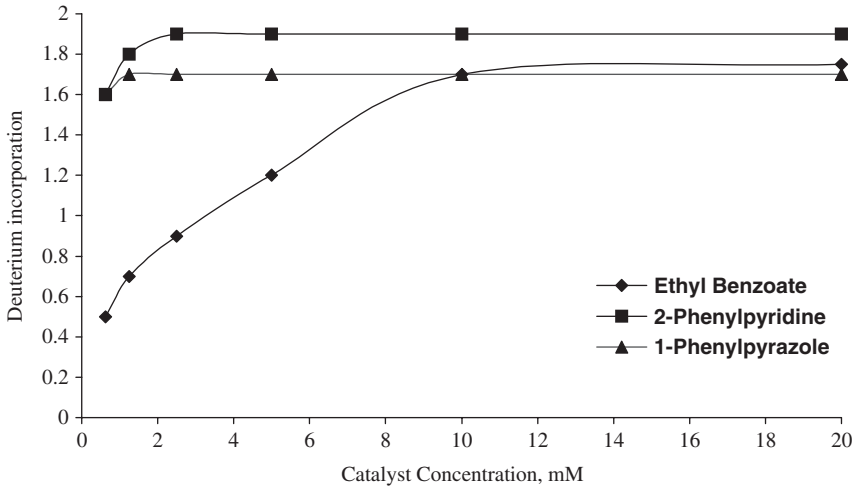


**Figure 2** Deuterium exchange into substrates, mediated by **1** (50%), as a function of concentration after 64–68 h.



DOI: 10.1002.jlcr

**Table 2** Effect of deuterium oxide upon deuteration mediated by **1**[a]

| Additive | None | None | None | $D_2O$[b] | $D_2O$[b] | $D_2O$[b] | $H_2O$[b] | $D_2O$[c] |
|---|---|---|---|---|---|---|---|---|
| Molar % of **1** | 50 | 50 | 100 | 50 | 50 | 100 | 50 | 50 |
| Concentration of **1** (mM) | 10 | 20 | 10 | 10 | 20 | D | 10 | 20 |
| *Substrate* | | | | | | | | |
| Acetophenone | 1.6 | 1.8 | 1.6 | 1.7 | — | 1.5 (22) | 1.0 | 0.0 |
| Ethyl benzoate | 1.7 | 1.75 | 1.85 | 0.3 | — | 1.6 (10) | 0.3 | 0.0 |
| *N,N*-dimethylbenzamide | 1.7 | 1.7 | 1.85 | 1.8 | 2.0 | 1.6 (40) | 0.9 | 0.4 |
| - in $NMe_2$ | 2.5 | 1.8 | 0.8 | 0.0 | 0.0 | 0.0 | 0.0 | 0.4 |
| Acetanilide | 1.8 | — | 1.7 | 0.3 | 2.0 | 0.8 (20) | 0.5 | 1.6 |
| 1-Phenylpyrazole | 1.1 | 1.7 | 0.7 | 0.9 | 1.1 | 2.0 (20) | 1.0 | 2.0 |
| 2-Phenylpyridine | 0.9 | 1.9 | 0.4 | 1.5 | 1.5 | 1.6 (16) | 0.9 | 1.4 |

[a] Figures are the number of deuterium atoms per molecule of substrate, determined by mass spectrometry, after exchange for 64–66h.
[b] 10 µl $^nH_2O$ per 10 ìmol of substrate.
[c] 0.1 ml $D_2O$ per 10 µmol of substrate—catalyst activated with $H_2$ (15 min) and exchange carried out under argon.
[d] Data from Ellmes *et al.*[1] concentrations (in mM) in brackets.

provide substantially better incorporation than a 1:2 catalyst/substrate ratio and that, in the case of 1-phenylpyrazole and 2-phenylpyridine, exchange is actually poorer than at the lower catalyst loading.

Since exchange is normally carried out without any special measures to exclude moisture, some water will inevitably be present. Nevertheless, adding powdered 4A molecular sieves to reduce the level of moisture present had essentially no effect on exchange. In contrast, the addition of deuterium oxide results, in the best cases, in a definite increase in *ortho*-deuteration of amide and *N*-heterocyclic substrates. The origin of this improvement becomes clearer when deuterium oxide is used as the sole deuterium source: pre-activating **1** with unlabelled hydrogen and carrying out the exchange with deuterium oxide under an argon atmosphere results in modest exchange into *N,N*-dimethylbenzamide, and good levels of exchange into acetanilide, 1-phenylpyrazole and 2-phenylpyridine. Exchange from deuterium gas and from deuterium oxide are not mutually exclusive and, in the best cases, complete *ortho*-exchange results. This type of behaviour is not surprising, since iridium-mediated exchange using deuterium or tritium oxide as the source of isotopic hydrogen is a well-known process,[14] However, such processes normally require elevated temperatures, whereas in this case exchange occurs at room temperature. Nevertheless, the addition of deuterium oxide abolishes exchange into the methyl groups of *N,N*-dimethylbenzamide despite the fact that some *N*-methyl exchange occurs upon its treatment with **1** and deuterium oxide alone.

A more consistently deleterious effect is observed when excess unlabelled water is added. With substrates where exchange is observed using deuterium oxide alone, this effect could be attributed to exchange from water competing with that from deuterium gas. However, this suppression of exchange is also observed with acetophenone and ethyl benzoate, which do not incorporate deuterium from deuterium oxide, and in these cases the effect is likely to result from a reduction in rate resulting from competitive binding of water to the metal.

## The effect of other additives

A number of other species have been examined as additives, and some examples are shown in Table 3. Most of those examined do result in a marginal improvement in exchange into acetophenone, which may or may not result from stabilization of the active catalyst. More generally, however, most additives simply have no effect, or suppress exchange either partly or (using dimethylsulfoxide and hexachloroacetone) completely. The enhanced exchange into 2-phenylpyridine using deuteromethanol is likely to be another example of the effect observed with deuterium oxide. Even acetone, which has been reported by Crabtree as an effective inhibitor of degradation with bis(phosphine) catalysts,[6] was not effective in improving exchange using **1**. The only exceptions, then, are the improved incorporations observed into the methyl groups of *N,N*-dimethylbenzamide using either pyridine-1-oxide or tris(pentafluorophenyl)phosphine. However, the factors underlying this enhancement, and the control of exchange into amide *N*-alkyl groups generally, remain unclear.

## The effect of the counterion

Pfaltz and co-workers[15] have reported that the tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($BAr_F$)



DOI: 10.1002.jlcr

**Table 3** Effect of various Additives upon deuteration mediated by **1**[a]

| Additive | [None] | Dimethyl-acetamide | Succinimide[b] | Acetone | MeOD | $Bu_3PO$ | Pyridine-1-oxide | $P(C_6F_5)_3$ | 18-crown-6 |
|---|---|---|---|---|---|---|---|---|---|
| *Substrate* | | | | | | | | | |
| Acetophenone | 1.6 | 1.7 | 1.8 | 1.8 | 1.7 | 1.8 | 1.8 | 1.5 | 1.7 |
| Ethyl benzoate | 1.7 | 0.3 | 0.0 | 0.3 | 0.3 | 1.5 | 0.2 | 1.6 | 0.15 |
| *N,N*-dimethylbenzamide | 1.7 | 1.2 | 1.6 | 1.4 | 1.4 | 1.4 | 0.9 | 0.7 | 1.4 |
| -in $NMe_2$ | 2.5 | 0.4 | 0.4 | 0.6 | 1.8 | 1.5 | 3.4 | 3.0 | 0.4 |
| Acetanilide | 1.8 | 1.0 | 1.4 | 1.4 | 1.6 | 1.2 | 1.2 | 0.8 | 0.9 |
| 1-Phenylpyrazole | 1.1 | 0.6 | 0.6 | 0.0 | 0.6 | 0.7 | 0.45 | 0.3 | 1.4 |
| 2-Phenylpyridine | 0.9 | 0.5 | 0.2 | 1.1 | 1.4 | 0.7 | 0.4 | 0.6 | 1.0 |

[a] Figures are the number of deuterium atoms per molecule of substrate, as determined by mass spectrometry; runs carried out with 50% catalyst at 10 mM (2 eq. Additive unless other wise stated).
[b] 1 mol. eq.

counterion is efficient at stabilizing homochiral iridium PN complexes during asymmetric hydrogenation. Although complexes $Ir(cod)L_2Cl$, where the anion is coordinated to the metal centre, are substantially inactive as deuterium exchange catalysts,[16] Ir(cod)(Py)($PCy_3$).$BAr_F$ (**11**) could represent an intermediate stage between such neutral species and cationic complexes such as **1**. However, **11** was also inactive as a catalyst for deuterium exchange. At this point, then, the prospect of improving exchange by using different counterions appears remote.

## The effect of temperature and pressure

Given the limited value of additives as a means to improve stability, a further means to circumvent the problem of catalyst stability might be to carry out exchange processes at elevated temperature or pressure. Of these parameters, temperature is least likely to be beneficial since, although the rate of exchange may be increased, species such as **1** and its hydrogenated forms suffer from significant instability above room temperature.[6] In practice, the results obtained after 18 h at 55°C are at best only a marginal improvement upon those obtained at room temperature, and generally somewhat poorer (Table 4). Surprisingly, carrying out exchange for a longer period at −20°C also resulted in incorporations that were at best comparable to those obtained at room temperature.

The results obtained from exchange runs carried out at room temperature under pressure (Table 4) do not assist in the improvement of isotopic incorporation, but are of interest nonetheless. Deuterium incorporation into acetophenone was essentially quantitative; 2-phenylpyridine was also more efficiently exchanged than at atmospheric pressure. However, the effect upon exchange into other substrates was much less beneficial, and in the case of amide substrates especially, the extent of exchange after 18 h under pressure was very much poorer than that obtained after a longer period at ambient pressure. A plausible explanation, assuming that the exchange pathway is basically the same for all substrates, is that the rate-determining step in the process with amides involves the dissociation of deuterium from a catalytic intermediate, whereas that with acetophenone and 2-phenylpyridine involves the coordination of deuterium. For the remaining substrates, the rate-determining step presumably does not involve association or dissociation of deuterium.

**Table 4** Effect of temperature and pressure upon deuteration mediated by **1**[a]

| Temperature | 20 | 55 | −20 | 20 |
|---|---|---|---|---|
| Time (h) | 64 | 18 | 118 | 18 |
| Pressure (atm) | 1 | 1.2 | 1 | 15 |
| *Substrate* | | | | |
| Acetophenone | 1.6 | [b] | 1.8 | 2.0 |
| Ethyl benzoate | 1.7 | 1.8 | 1.75 | 1.7 |
| *N,N*-dimethylbenzamide | 1.7 | 1.4 | 1.5 | 1.1 |
| -n $Nme_2$ | 2.5 | 1.6 | 1.9 | 0.5 |
| Acetanilide | 1.8 | 1.5 | 0.8 | 0.9 |
| 1-Phenylpyrazole | 1.1 | — | 0.7 | 1.3 |
| 2-Phenylpyridine | 0.9 | — | 0.4 | 1.5 |

[a] Figures are the number of deuterium atoms per molecule of substrate, as determined by mass spectrometry; runs carried out with 50% catalyst at 10 mM.
[b] Not recovered.

## Conclusion

Neither variation of physical parameters nor the addition of labile ligands is an effective means to enhance the stability of iridium complexes during deuterium exchange. The problems of instability can be overcome to some extent by carrying out reactions at concentrations above 10 μmol/ml where this is



DOI: 10.1002.jlcr

practical. Nevertheless, given that it is generally preferable to carry out exchange processes under the simplest conditions, the most attractive catalyst systems appear to be those involving bidentate arsine, phosphine, or *PN* ligands.

### Experimental

Exchange and analytical methods were as described previously.[1,2,5] Crabtree's catalyst (**1**) and bis(1,5-cyclooctadiene)diiridium(I) dichloride was obtained from Strem; complexes **2**–**8** and **10** were prepared *in situ* as described previously,[2,4,5] and complex **9** was prepared as described by Pfaltz *et al.*[15]

### Typical procedure for crossover experiment

A solution of **1** (8.0 mg; 10 μmol) in DCM (1 ml) containing 4-methylacetophenone (1.5 μl, 10 μmol), was degassed and flushed with deuterium, then sealed and stirred for 6 h. The system was evacuated briefly, acetophenone (1.2 μl, 10 μmol) was added, and the mixture was again degassed and flushed with deuterium. After stirring for a further 18 h, volatiles were evaporated and the product was subjected to GC-MS analysis.

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DOI: 10.1002.jlcr