

Investigation of $[\text{IrH}_2(\text{Me}_2\text{CO})_2(\text{PPh}_3)_2]\text{BF}_4$ as a Catalyst of Hydrogen Isotope Exchange of Substrates in Solution

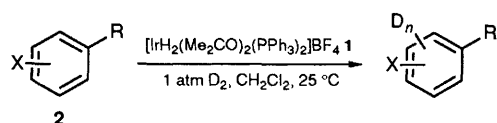
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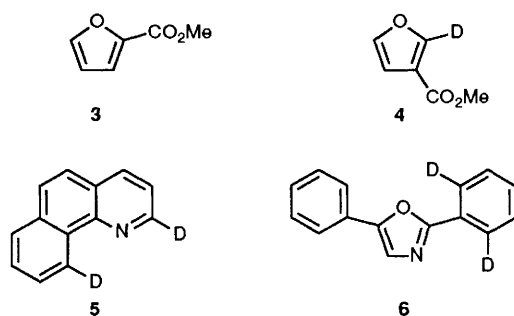
The title complex is found to catalyse the efficient and regioselective exchange of deuterium gas with hydrogens in several substrate structural types; exchange is observed only at aromatic sites in proximity to certain nitrogen or oxygen containing functional groups, but not all such sites undergo exchange.

Of the various preparative approaches to compounds labelled with deuterium or tritium, catalytic hydrogen isotope exchange of the unlabelled compound is attractive for its simplicity, as it avoids the need for synthesis. Many catalytic exchange methods with varying degrees of efficiency and selectivity have been reported.¹ We have become interested in exploring the ability of certain homogeneous organotransition metal complexes, already known to be capable of carbon-hydrogen bond activation,² to catalyse the exchange of isotopic hydrogen gas with hydrogens of compounds in solution. Such systems may provide increased efficiency and/or selectivity compared to existing hydrogen isotope exchange methods.

We now report our preliminary results showing that the complex $[\text{IrH}_2(\text{Me}_2\text{CO})_2(\text{PPh}_3)_2]\text{BF}_4$ **1**³ efficiently catalyses the exchange of deuterium gas with compounds of several structural types, resulting in regioselective incorporation of the isotope. Complex **1** has previously been shown to catalyse the exchange of deuterium for hydrogen in specific methyl groups of caffeine (N-4-CH₃) and 8-methylquinoline, without significant exchange of the isotope into either the ligands of **1** or the solvent.⁴ The present results, summarized in Table 1, show that a 1.5–2.5 mol% ratio of catalyst to substrate in the presence of only 2–3 fold molar excess of deuterium gas can result in high levels of deuterium incorporation at specific sites in the compounds. Net deuterium enrichment of products was analysed by mass spectrometry, and the location of deuterium by ¹H and/or ²H NMR spectroscopy. Peak integrations in ¹H NMR spectra of products were carefully compared with those of unlabelled references, and ²H NMR studies were conducted in a few cases to confirm or supplement other data. Results are estimated to be accurate to within 10% at active sites and less than 0.10 D (¹H NMR) or 0.05 D (²H NMR) at 'unlabelled' sites. Most experiments were run at least twice; replicates agreed to within 10% of total deuterium incorporation by mass spectrometry. Results shown are averages of replicates. Reaction workup is simple and high yields of pure products are obtained in most cases. No attempt has been made to maximize deuterium incorporation; rather, the aim was to compare substrates' relative propensities for exchange.



Scheme 1



With the exception of compound **5** (where 50% of incorporated deuterium is at C-2), the regioselectivity of deuterium exchange is consistent with coordination of the metal centre with a heteroatom adjacent to the aromatic ring, followed by reversible C–H insertion to form a five-membered metallocycle intermediate. This is preceded for **1**, from which isolable complexes could be made containing 8-methylquinoline⁴ and benzo[*h*]quinoline⁵ as ligands. These complexes were found to have Ir–N bonds, and either an agostic interaction between metal and a C–H bond of the methyl (8-methylquinoline) or an Ir–C-10 bond (benzo[*h*]quinoline), resulting in five-membered metallocycles. However, in the present study only aryl C–H bonds and not alkyl C–H bonds interact with the metal centre, as evidenced by the absence of labelling in the methyl groups of propiophenone **2c** and α,α -dimethylpropiophenone **2d**. Moreover, several other cyclic and acyclic alkyl ketones and esters with methyl or methylene groups

Table 1 Hydrogen–deuterium exchange of substituted benzenes (Scheme 1)^a

Compound	R ^b	X	Deuterium incorporated ^c	Location ^d
2a	CO ₂ Et	H	1.1	C-2,6
2b	CH ₂ CO ₂ Et	H	<0.01	—
2c	C(O)Et	H	1.7 ^e	C-2,6
2d	C(O)Bu ^t	H	1.8	C-2,6 ^f
2e	CO ₂ Et	2-Me	0.68	C-6
2f	CO ₂ H	2-Me	0.16	C-6
2g	CO ₂ Et	3-OMe	1.0	C-2(85%), C-6(15%)
2h	CO ₂ Et	3-Br	1.5	C-2(67%), C-6(33%) ^f
2i	CO ₂ Et	3-NO ₂	0.89	C-2(50%), C-4(8%), C-6(42%)
2j	CO ₂ Et	4-CO ₂ Et	2.5	C-2,3,5,6
2k	CO ₂ Et	4-C(O)NMe ₂	1.3	C-3,5(68%), Me(32%) ^f
2l	C(O)NMe ₂	4-C(O)NMe ₂	2.3	C-2,3,5,6 (55%), Me(45%) ^f
2m	C(O)NMe ₂	H	<0.05	—
2n	CH ₂ NMe ₂	H	<0.05	—
2o	NO ₂	H	0.18	C-2,6 ^f
2p	Imidazol-2-yl	H	1.4	C-2,6
2q	Imidazol-4-yl	H	<0.05	—
2r	2-Pyridyl	H	1.8	C-2,6 ^f
2s	2-Pyridyl-methyl	H	<0.05	—
3	—	—	<0.03	—
4	—	—	0.87 ^f	—
5	—	—	0.57 ^g	—
6	—	—	1.7	—

^a 100 mg of substrate and 10 mg of **2** stirred in 5 ml of methylene chloride under ca. 35 ml deuterium gas at 1 atm for 16–24 h at room temperature; workup by evaporation of solvent and extraction of product from residue with diethyl ether. ^b Designated position 1. ^c mol deuterium/mol substrate, determined by CI-MS (chemical ionization mass spectrometry). ^d Determined by 400 MHz ¹H NMR spectroscopy. ^e 10–25% reduced to 1-phenylpropan-1-ol. ^f Deuterium substitution additionally determined by ²H NMR spectroscopy. ^g 15–25% reduced to 1,2,3,4-tetrahydrobenzo[*h*]quinoline.

available for formation of five-membered metallocycles (not shown) do not undergo exchange at all. Significantly, homologues of successful substrates, such as ethyl phenylacetate **2b** and 2-benzylpyridine **2s**, which would require formation of six-membered metallocycle intermediates, are not labelled under these conditions.

Substantial levels of exchange at the C-2 positions of *meta*-substituted benzoate esters **2g-i** reveal the absence of significant steric or electronic impediments to labelling; in fact in **2g** and **2h** the extent of labelling at C-2 is substantially greater than at the less hindered C-6, in spite of the fact that aryl bromo and *O*-alkyl ether groups alone fail to mediate exchange. Some other more striking results are observed. Whereas *N,N*-dimethylbenzamide **2m** is not labelled, *N,N,N',N'*-tetramethylbenzene-1,4-dicarboxamide **2l** becomes deuteriated both in the ring and the methyl groups; moreover, the related monoester-monoamide **2k** becomes deuteriated, not *ortho* to the ester group as expected, but adjacent to the amide group instead (as well as in the methyl groups). The failure of ethyl 2-furoate **3** to undergo labelling may be rationalized by invoking chelate formation of the metal with the ester and furan oxygens leading to an inactive complex. However, the origin of the specificity of deuteriation of ethyl 3-furoate **4** at C-2 and not C-4, and the reason for the contrast between the successful labelling of 2-phenylimidazole **2p** and the lack of labelling of 4-phenylimidazole **2q**, are as yet unclear.

Addition of small amounts (5 mol% relative to substrate) of *N,N*-dimethylbenzamide or *N,N*-dimethylbenzylamine to reaction mixtures of **2c** abolish exchange labelling of the latter. This seems to presage lower reactivity of carbonyl-containing substrates also possessing one of the other two functional groups; however, the results with substrates **2k** and **2l** suggest that interactions between functional groups in the same molecule can lead to labelling even in the presence of apparently inhibitory functions. In contrast to the results with carbonyl-containing substrates, the level of 2-phenylimidazole deuteriation is not greatly diminished even in the presence of an equimolar amount of *N,N*-dimethylbenzamide or *N,N*-dimethylbenzylamine.

In other experiments (results not shown) it was found that benzylic amine, hydroxy and ether groups alone do not promote exchange. Aryl nitriles are inert in terms of both exchange and reduction, as are aryl and primary alkyl bromides; aryl nitro groups alone are weak mediators of deuterium exchange and are not reduced. Isolated carbon-carbon double bonds are easily reduced, however, and α,β -unsaturated esters are reduced to saturated esters having

only a slight preponderance of deuterium in the β -position. Simple benzylic double bonds are more slowly reduced, possibly owing to competing formation of η^6 -aryl complexes as previously reported.⁶

The results described were acquired using methylene chloride as solvent, but other solvents were found to be suitable for use in some cases. Acetone was found to remain completely unlabelled even when stirred for 65 h with complex **1** under a deuterium atmosphere. When used as a solvent in exchange reactions, the extent of labelling of 2-phenylimidazole was undiminished compared to that in methylene chloride solution. However, the labelling of propiophenone was completely abolished. Similar results were obtained with tetrahydrofuran as solvent. In contrast, the use of acetonitrile as solvent reduced the labelling even of 2-phenylimidazole to very low levels.

The above results show that $[\text{IrH}_2(\text{Me}_2\text{CO})_2(\text{PPh}_3)_2]\text{BF}_4$ can catalyse the deuterium exchange labelling of compounds of several structural types. The labelling is regioselective, and in most cases very efficient. This catalytic exchange procedure is simple to conduct and high-yielding, making it potentially practical and effective, were tritium gas to be substituted for deuterium, for the direct tritiation of certain classes of compounds to high specific activity.

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