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DEUTERIUM EXCHANGE LABELLING OF SUBSTITUTED AROMATICS USING $[IrH_2(Me_2CO)_2(PPh_3)_2]BF_4$

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ABSTRACT

Deuterium exchange labelling experiments were conducted on several series of compounds, including *para*-substituted benzoate esters, *para*-substituted N,N-dimethylbenzamides, and mono-*para*-substituted benzophenones, using $[IrH_2(Me_2CO)_2(PPh_3)_2]BF_4$ as catalyst and deuterium gas as the source of isotope. In most cases, labelling was efficient and regioselective, with deuterium appearing in the positions *ortho* to the carbonyl-containing functional group. Apparent from the results of these experiments was that, in each case the *para*-substituted rings were labelled more rapidly or to a greater extent than the corresponding unsubstituted rings, regardless of the identity of the substituent.

We have recently described[1,2] preliminary results of studies of deuterium exchange labelling of substrates with deuterium gas, catalyzed by $[IrH_2(Me_2CO)_2(PPh_3)_2]BF_4$, which displayed significant efficiency and regioselectivity in a range of substrate structural classes. We have continued to explore this area of exchange catalysis, with several aims: to learn something about the nature of the exchange process catalyzed by this complex, to expand the scope of the method, and to investigate the activity of related complexes. In this communication we report the results of exchange studies conducted on several series of substituted aromatics, with the objective to investigate the stereoelectronic effects of substituents on the exchange process.

A number of *p*-substituted benzoate esters were treated as shown in Scheme 1. The products were isolated by evaporation of the solvent and extraction of the residue with ether, then analyzed by ^1H NMR and MS in order to ascertain the amount and location of incorporated deuterium. In no case was a significant amount of any side reaction (e.g., reduction) detected, and recoveries were usually >90%. The deuterium labelling results are summarized in Table 1.

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Scheme 1

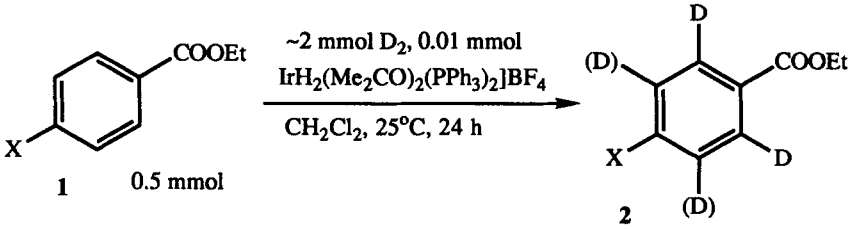


Table 1

Deuteriation of Benzoate Esters

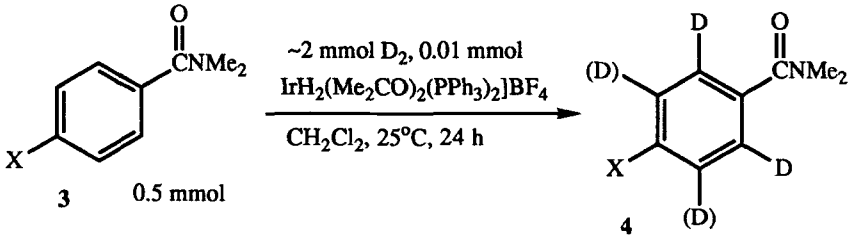
Entry	*para*-Substituent	mol D/mol, *ortho (meta)*
a	NMe_2	~0
b	OH	~1.9
c	OMe	~1.8
d	CMe_3	1.3-1.4
e	OC(O)Me	1.3-1.4
f	H	1.2
g	Ph	1.5-1.7
h	F	~1.5
i	Cl	~1.8
j	Br	~1.6
k	COOEt	1.3 (1.3)
l	$CONMe_2$	~0 (0.9)
m	CF_3	~1.0
n	CN	~0
o	NO_2	~1.0 (0.4)

The regioselectivity of deuteriation is high except in the indicated cases, with *meta* labelling being undetectable by NMR. Nor was the ester ethyl group labelled to a detectable degree. The extent of labelling in the *ortho* positions is also high, in most cases more than 50% of theoretical, in spite of the relatively small excess of deuterium gas used. Equal deuteriation of all four aromatic positions of the symmetrical terephthalate diester **1k** was observed, as expected. The corresponding monoamide **1l** was labelled, as previously reported,[1,2] in the positions *ortho* to the amide function not adjacent to the ester, and a small amount of deuterium also appeared in the N-methyl groups. In addition, ethyl *p*-nitrobenzoate was deuteriated to a small extent in the *meta* position, consistent with the previously observed[2] ability of a nitro group to weakly mediate exchange into adjacent C-H bonds. The failure of the *p*-dimethylamino (**1a**) and *p*-cyano (**1n**) compounds to be labelled can be ascribed to strong coordination of these functions to the metal center, making it unavailable for the reversible interactions necessary for successful catalysis of exchange.

The entries of Table 1 are listed in order of the Hammet s_p value of the *p*-substitutent. No correlation of the level of deuterium incorporation with substituent s_p, nor to s_m, values is apparent in these results. In fact, most *p*-substituted compounds, regardless of whether the substituent is electron-donating or electron-withdrawing, are labeled to a greater extent under these conditions that the unsubstituted parent, ethyl benzoate, itself.

Previous results[1,2] had suggested that N,N-dimethylbenzamide does not become deuteriated under these reaction conditions. However, the positive results with the terephthalate derivatives **1k** and **1l** seemed inconsistent with that result. This issue has been further investigated. Although commercial N,N-dimethylbenzamide, regardless of source, fails in this reaction, careful purification of commercial material yields samples which do indeed undergo deuteriation. As in the benzoate ester series, this substrate is deuteriated in the aromatic ring only in the *ortho* positions. Excess deuterium as measured by mass spectrometry over that measured by ^1H NMR, as well as the presence of small amounts of (M + 3) ions, suggests the presence of a few percent excess deuterium in the N-methyl groups, as previously observed for **1k** and **1l**. A series of *p*-substituted N,N-dimethylbenzamides was then prepared and subjected to deuterium exchange conditions (Scheme 2), with the results shown in Table 2.

Scheme 2



3 0.5 mmol **4**

Table 2

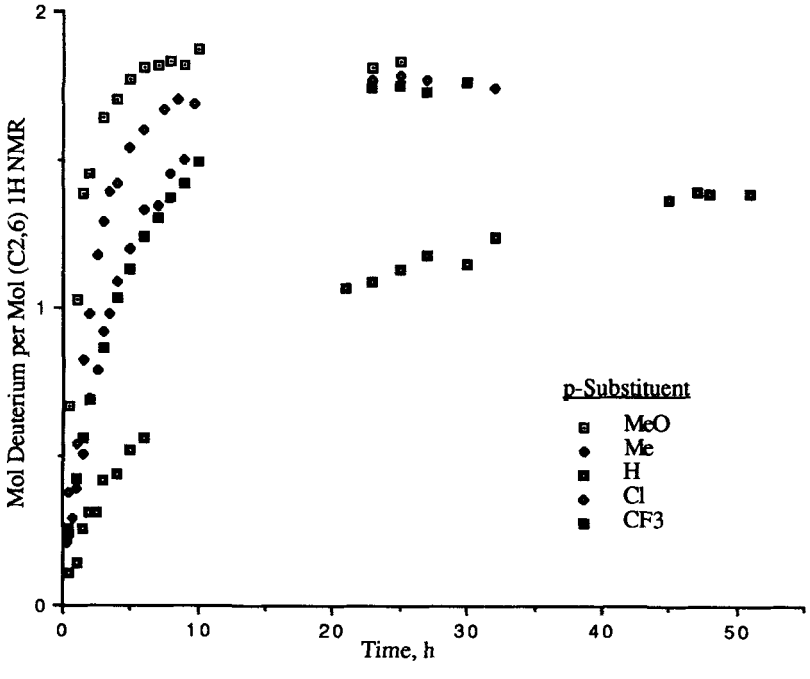
Deuteriation of N,N-Dimethylbenzamides

Entry	*para*-Substituent	mol D/mol *ortho (meta)*
a	OMe	1.1-1.2
b	H	~0.6
c	F	1.2-1.3
d	Cl	1.3-1.5
e	Br	~1.2
f	COOEt	0.9
g	C(O)NMe2	~0.6 (~0.6)
h	CF_3	1.0-1.2
i	NO_2	1.3-1.4 (0.4)

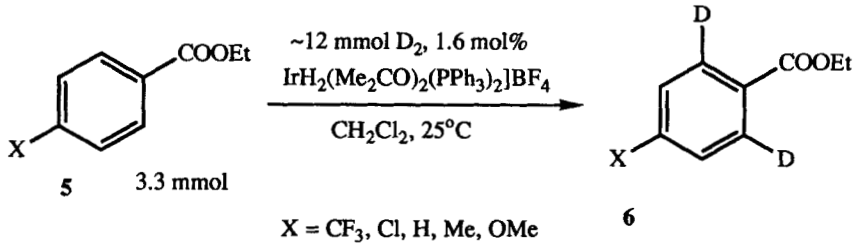
As in the previous series, analogs with *p*-substituents are labelled to a greater extent than the *p*-unsubstituted parent. In these compounds as well, the presence of a few percent of trideuterio species observed in the mass spectra of products suggests that some deuterium was incorporated into the N-methyl groups. However, this has not been confirmed by independent means. These two series of experiments appear to indicate that there is not a large substituent effect on the labeling process (except perhaps that the mere presence of a *para* substituent, whatever its character, improves the labelling result).

Since the reactions were not checked before the end of the 24-hour time period, substituent effects on the rate of deuteriation at shorter reaction times could not be observed. In order to investigate the time course of deuteriation more closely, the deuteriation of a subset of benzoate esters was monitored. Details of the reactions are outlined in Scheme 3. The reactions were run under one atmosphere of pressure, which consisted of about 150 mm of solvent vapor pressure and 610 mm of D_2. Small samples of the reaction mixtures were removed at intervals, worked up, and the products examined carefully by ^1H NMR to measure the extent of deuterium incorporation into the *ortho* positions. The data are summarized in Figure 1. These data clearly show that ethyl benzoate is deuteriated more slowly than any of the *para*-substituted derivatives. Careful repurification of the ethyl benzoate did not alter the rate of its deuteriation, indicating that the slower labelling is not caused by an impurity in the material. Nor was the catalyst activity being reduced by other means. This was demonstrated by adding ethyl *p*-methoxybenzoate to a reaction mixture of ethyl benzoate and catalyst after a three-day reaction time, after the labelling of ethyl

Figure 1
Time Course of Benzoate Ester Deuteriation



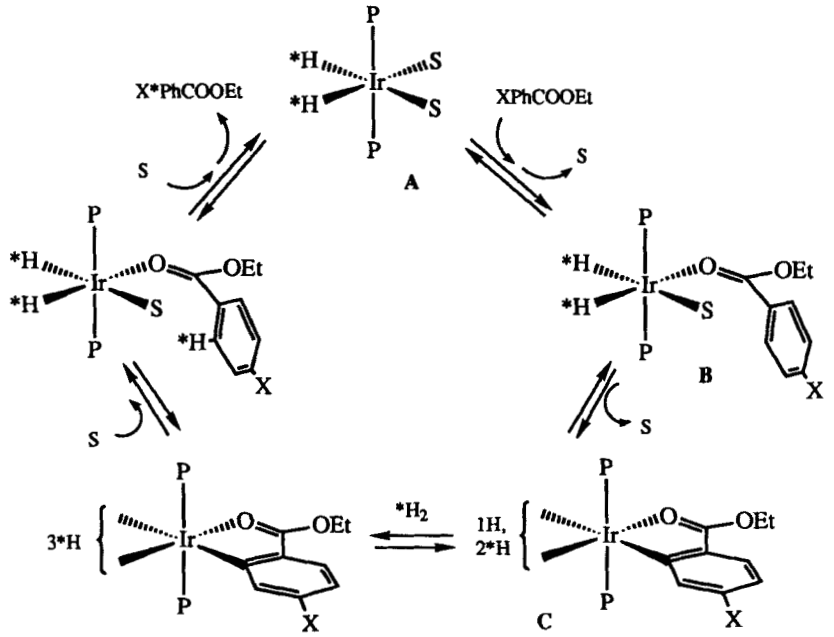
Scheme 3



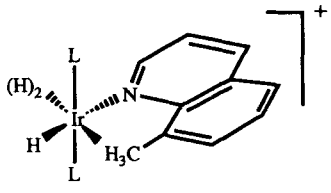
benzoate had reached a maximum. Within the next 24 h, the ethyl *p*-methoxybenzoate had become deuteriated to nearly the same extent (^{1}H NMR analysis) as it had in separate reactions with fresh catalyst. **These results demonstrate that the catalyst remains essentially fully active for at least four days under these reaction conditions.**

The most likely mechanism for H-D exchange based on the known reactivity[3] of iridium complexes such as the present one is depicted partially in Scheme 4. Initial reversible coordination of the ester oxygen to iridium takes place by displacement of loosely coordinated acetone from the starting complex A, to give B. Subsequent insertion of the iridium center of B into the *ortho* C-H bond of the ligated ester, with concurrent loss of the second acetone ligand, constitutes the oxidative addition step to give C.

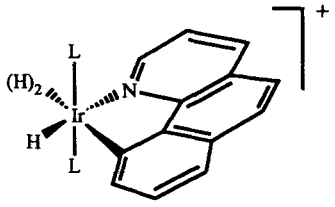
Scheme 4



All three hydrogens (the two original hydrides plus the *ortho* hydrogen of the substrate) could be retained in C, as a hydride ligand and a dihydrogen ligand, as precedented by known complexes such as D[4] and E[5]. Such complexes are fluxional,[6] with all hydrogens exchanging easily with each other and with atmospheric hydrogen.



D



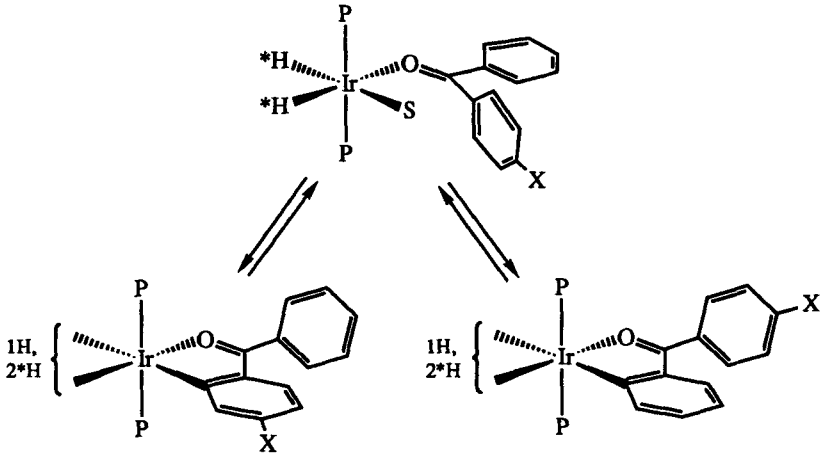
E

Such a reaction scheme explains the *ortho* regioselectivity of H-D exchange which is observed. However, the acceleration of the rate of deuteriation by both electron-donating and electron-withdrawing substituents is inconsistent with simple aromatic electrophilic or nucleophilic substitution mechanisms being involved in the rate determining step. Moreover, it is not clear from these data whether the initial coordination step or the oxidative addition-reductive elimination stage, or the exchange of hydride ligands with atmospheric deuterium determines the rate of substrate deuteriation.

It was thought that insight into the latter question could be obtained by observing the relative rates of H-D exchange in the two rings of mono-*p*-substituted benzophenone. If any difference in the rate of deuteriation of the two rings is observed, this would indicate that some aspect of the C-H bond insertion process is rate determining, and exclude the initial iridium-carbonyl coordination and the exchange of iridium-bound hydride for deuteride as being kinetically important, see Scheme 5. The parent benzophenone itself was found to become maximally exchanged within two hours--much faster than the benzoate esters, under the same conditions by which they were labelled (Scheme 1). Therefore, exchange reactions of *p*-methoxy- *p*-methyl-, *p*-chloro- and *p*-trifluoromethylbenzophenone were set up under similar conditions, and sampled at early time points, as well as after 24 h, when complete equilibration would be expected to have been established. ^{1}H NMR analysis of the isolated samples allowed the amount of deuterium in the *ortho* positions of the substituted and unsubstituted rings to be separately measured. The results are presented in Table 3.

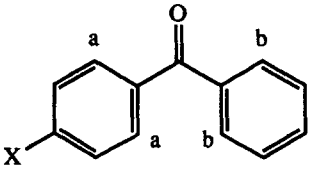
These results clearly show that in each case the *ortho* positions of the substituted ring become deuteriated faster than those of the unsubstituted ring, especially in the early stages of the exchange. At long reaction times, the ratios decline to unity, and the total amount of deuterium incorporated is near maximal based on the initial excess of deuterium gas over substrates. These results support and extend those obtained above in the case of benzoate esters and amides. They demonstrate that it is not the initial coordination event, nor the exchange of hydride ligands with deuterium which is rate determining, but rather some aspect of the oxidative addition-reductive elimination (C-H insertion) sequence.

Scheme 5



Additional experiments are required to determine why rings containing both electron donating and electron withdrawing substituents undergo labelling faster than unsubstituted rings, and what this fact implies for the detailed mechanism of exchange. The *ortho* C-H bond cleavage depicted above, required for the H-D exchange to occur, might proceed by a classical, three-center, oxidative addition of a transient Ir^I center (a relatively nucleophilic process), or alternatively by something more equivalent to an electrophilic aromatic

Table 3
Deuteriation of Monosubstituted Benzophenones



X =	CF3	Cl	Me	OMe
25 min				
ratio D_a/D_b	**1.4**	**1.6**	**1.3**	**2.1**
total D at a & b	1.8	2.0	2.1	2.2
55 min				
ratio D_a/D_b	**1.3**	**1.2**	**1.1**	**1.4**
total D at a & b	2.2	2.4	2.6	2.4
24 h				
ratio D_a/D_b	**1.0**	**1.0**	**1.0**	**1.0**
total D at a & b	3.2	3.3	3.4	3.4

substitution by an electron-poor Ir^{III} species.[7] It is possible that either or both of these mechanisms is involved, depending upon the particular substrate. Moreover, in some related rhodium systems,[8] it is actually the prior h^2-coordination of metal to arene ring which is rate determining, not the C-H bond cleavage itself. Further investigations into these issues continue.

EXPERIMENTAL

^1H NMR spectra were recorded on a Bruker AM 400 instrument using $CDCl_3$, CD_2Cl_2 or C_6D_6 as solvent, and tetramethylsilane or residual $CHCl_3$ as internal standard. Mass spectra were measured in the chemical ionization mode on a Finnegan 4610 instrument. Rate constants were calculated using standard regression analysis. Commercially available compounds were reagent grade or better, and were distilled before use. Other substrates were prepared by treatment of the appropriate acyl chloride with ethanol or with aqueous dimethylamine, worked up by organic/aqueous partition, washed with aqueous HCl then aqueous $NaHCO_3$, stripped of solvent, and distilled. Repurification of N,N-dimethylbenzamide and ethyl benzoate was accomplished by acid/base extraction, followed by silica gel chromatography, and finally distillation.

Typical reaction procedure: A 100 mg portion of substrate and a 10 mg portion of $[IrH_2(Me_2CO)_2(PPh_3)_2]BF_4$ were dissolved in 5 mL of methylene chloride in each of four 10- or 15-mL flasks. The flasks were attached via a four-way distribution adaptor to the vacuum line. The solutions were frozen in lN_2, the apparatus evacuated, and deuterium gas was added to atmospheric pressure. The solutions were allowed to warm to room temperature, excess pressure being released through a Firestone valve during warming. The solutions were stirred vigorously for the desired time. Time course studies with ethyl benzoates were conducted singly in 500 mL flasks, and the solutions were allowed to thaw and warm up to rt before introducing deuterium (time 0). Workups were accomplished by evaporating the solvent, suspending the residue in diethyl ether, filtering to remove catalyst, and evaporating the filtrate.

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