Iridium-Catalyzed H/D Exchange

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The scope and limitation of an iridium-catalysed H/D exchange reaction has been investigated. Our results suggest a general mechanism for specific labelling at aromatic and non-aromatic double bonds by D_2O if an electron-donating group is in a 1,4-relation with the carbon where the H/D exchange takes place.

Introduction

The potential usage of catalytic isotope-exchange reactions varies from standards for NMR spectroscopy and mass spectrometry to highly specific labelling of promising drug candidates with tritium for physiological studies. Furthermore it can give new hints about the mechanism of catalytic processes and thus enable their improvement.

The ability of cyclooctadieneiridium(I) acetylacetonate (**1**)[1] (Figure 1) to act as a catalyst for the exchange of hydrogen at aromatic and non-aromatic double bonds by deuterium has been reported previously. The isotopic hydrogen is incorporated at a 1,4-position to a directing atom, where it is not particularly susceptible towards loss by metabolism or uncatalysed exchange (Scheme 1).

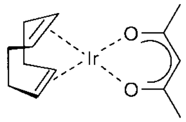
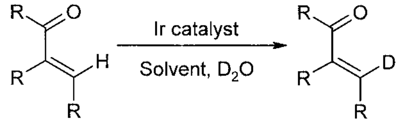


Figure 1. Cyclooctadieneiridium(I) acetylacetonate (**1**).



Scheme 1. General exchange pattern of a typical substrate.

Besides various carbonyl compounds it is possible to label acids, oximes and amines, with suitably high exchange rates. Although high deuteration grades have also been reported for specific systems with other catalysts, **1** is a good all-round system[2–8] as it not only accepts a broad set of functional groups as directors, but also tolerates coordinating substituents like methoxy and hydroxy groups. Furthermore, it shows an excellent stability towards light, heat and oxygen: even after three months storage it still retains its full catalytic power. Its neutral form grants a good solubility in both polar and non-polar solvents, thereby making exchange in nearly all possible substance classes possible.

Results and Discussion

Acids

In aromatic systems a carboxylic acid functional group has the ability to direct the H/D exchange in the *ortho* position. 2-Methoxybenzoic acid (**2**), which was used as our model substrate due to its high deuteration grade of 97.5% and ease of handling, undergoes H/D exchange at the unblocked *ortho* position. On the other hand, 4-nitrobenzoic acid (**3**) undergoes H/D exchange at both *ortho* positions (2×99%), while 3-(dimethylamino)benzoic acid (**4**) shows an exchange only in the unhindered C-6 position.

Carbonyls

Benzophenone (**5**) shows, as expected, an exchange in all four *ortho* positions. 2-Hydroxy-4-methoxyacetophenone (**6**) can tautomerise and have keto and enol forms. Therefore, instead of having the H/D exchange that generally occurs at the *ortho* position next to the carbonyl group, the exchange occurs at the methyl group. Acetophenone oxime (**7**), on the contrary, does not tautomerise; thus, the H/D exchange occurs exclusively at the two *ortho* positions.

It was not possible to label 2-methoxybenzaldehyde (**8**). A black precipitate was observed, which is presumably caused by reduction of the catalyst to Ir^0.

Amines and Alcohols

Benzylamines can be deuterated when catalysed by **1** whereas benzyl alcohols with similar structures cannot.

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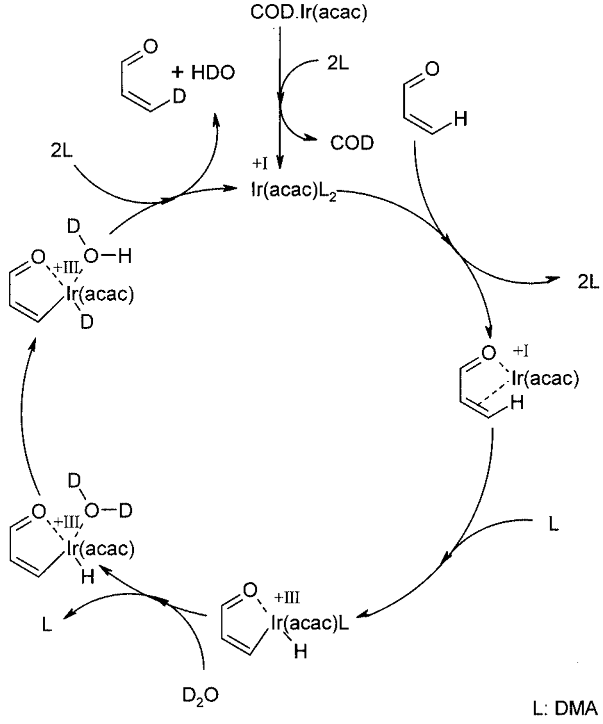
Using 2-methoxybenzylamine (**9**) as a test substrate, the deuteration grade obtained was above 50%. On the other hand, no deuteration of 2-methoxybenzyl alcohol (**10**) was observed. Following the HSAB concept, it is believed that amines can interact much better with iridium in the first coordinating step (Scheme 2) than alcohols due to their softer base character.



Scheme 2. Proposal of a simplified mechanism with deuterium oxide as the isotope source.

Non-Aromatic Systems

Assuming that the double-bond system of a conjugated carbonyl functional group could participate in deuteration in the same manner as the aromatic ring in **2**,[9] a number of compounds were examined. Two of those were *trans*-crotonic acid (**11**) and sorbic acid (**12**). Compound **11** can be deuterated to a deuteration grade higher than 60% whereas **12**, which has an extra conjugated double bond, cannot. It appears that **12** coordinates to iridium in a different way, thus suppressing the normal catalytic process. Further investigation was undertaken when the double bond is additionally conjugated to an aromatic system, as in *trans*-cinnamic acid (**13**) and *trans*-2,3-dimethoxycinnamic acid (**14**). In this case, the substrate is exclusively deuterated at the double bond in the β-position relative to the directing group. The deuteration grades achieved were 17% and 87%, respectively, thus demonstrating the electronic influence of the substituents.

As the α,β-unsaturated carbonyl group appeared to be as a suitable group for H/D exchange, a number of compounds that contain this system were screened. Some examples of these compounds include *trans*-1,2-dibenzoylethylene (**15**), which can be deuterated at multiple points, while, in contrast, 3-benzoylacrylic acid (**16**) shows more than 75% of deuteration, exclusively in the double bond at the β-position relative to the acid functional group. The result in the latter case indicates that the acid function is dominant over the carbonyl in directing the deuteration.

Chelate-Ring Size

With the assumption that **2** forms a five-membered metallacyclic intermediate when reacted with **1**,[10,11] further investigation was made to see if the six- and seven-membered intermediates also show deuteration. 2-Methoxyphenylacetic acid (**18**) and 3,4-dimethoxyphenylacetic acid (**19**) were used to study the six-membered metallacyclic intermediate system, whereas 3-(2-methoxyphenyl)propionic acid (**20**) was used to study the seven-membered intermediate system. The results show that no deuteration was detectable for both the six- and seven-membered intermediate systems.

Temperature/Solvent

Figure 2 shows the deuteration grade of **2** – the model substrate – at different temperatures when prepared in DMA or $CHCl_3$. Under similar conditions, the exchange rate is proportional to the temperature. This statement is clearly shown when DMA is used as a solvent. Under the same conditions to that of DMA, the exchange rate when $CHCl_3$ is employed remains at approximately 5%, though it increases to a small extent when temperature was raised. These values indicate that the solvent plays an important role in the exchange mechanism and must have a certain ligand characteristic, besides being polar and non-protic.

An exchange of solvent hydrogen by D_2O can be excluded in the case of DMA, as we have found high deuteration rates in our experiments. With $CHCl_3$, however, this could, in principle, be the reason for the low exchange rate of less than 5%, although we assume that this is mainly caused by the rather low coordination capability of $CHCl_3$.

DMA is the solvent of choice amongst the solvents that were examined. This could be due to the fact that it has a suitable structure that ensures it can participate in the reaction. The DMA molecule can act as a ligand and interact with the iridium atom. This renders the correct electronic environment that enables the exchange reaction.

DMF is another solvent of choice as, due to its structural similarity to DMA, it can participate in the same way. In any event, DMA is preferred due to its NMR spectrum as the aromatic region is clear of solvent resonances that could overlap with the product spectrum.[2]

Reaction Time

The deuteration grade increases continuously with longer reaction times. For **2** the equilibrium is reached after approximately two hours to yield 97±1% of labelling (Fig-

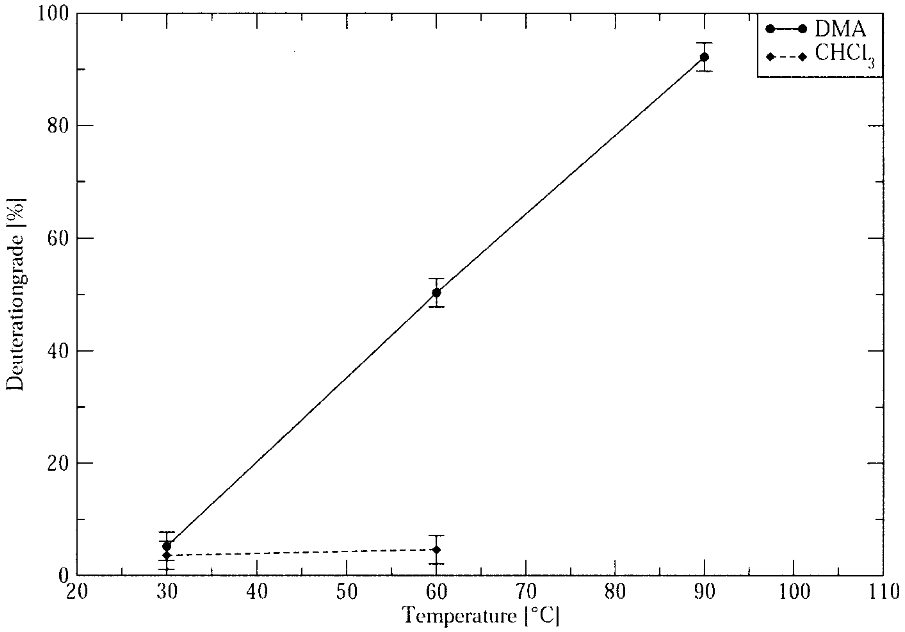


Figure 2. Influence of temperature and solvent on the deuteration grade of 2-methoxybenzoic acid (**2**).

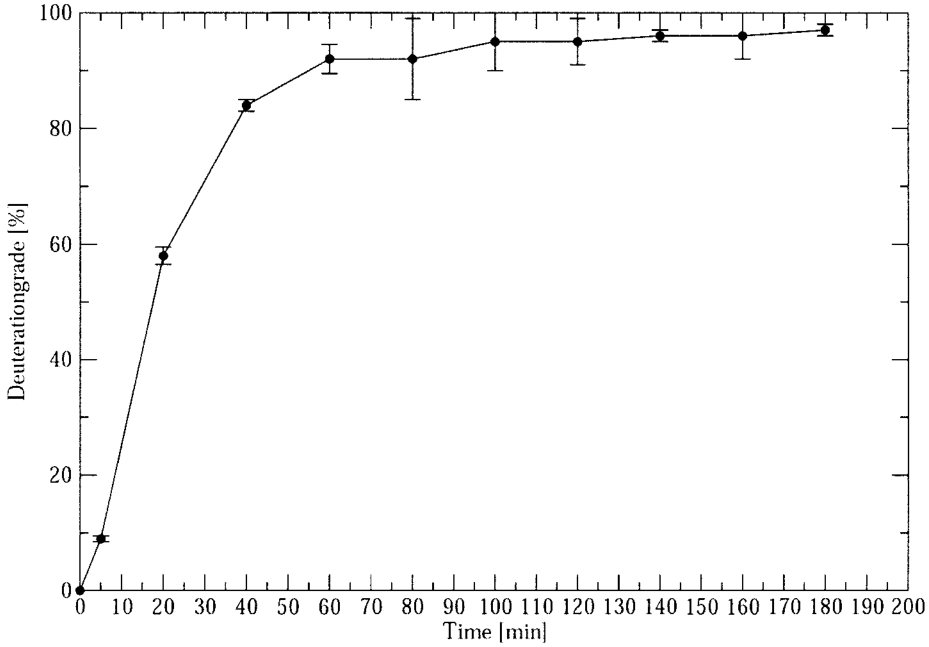


Figure 3. Influence of reaction time on the deuteration grade of 2-methoxybenzoic acid (**2**) at 90 °C.

ure 3). It appears that the achievable deuteration grade is only a function of time and isotopic dilution. In a few exemplary tries, also with less active compounds, the reaction time was increased, making practically quantitative H/D exchange achievable. For example, after three hours **7** showed only 2 × 12.5% exchange in the *ortho* position to the oxime, while after 48 h 2 × 82 ± 5% was reached.

Mechanism

The solvent influence on the overall exchange activity gives strong evidence that cyclooctadiene is replaced by solvent molecules, for example DMA, to form the real catalytically active compound. In addition, active Ir^{I}–DMA complexes are known from the literature and are generated in situ as catalytic intermediates.[12] This is in good agreement with reports of deuteration of cyclooctadiene when employing deuterium gas as the isotope source.[3]

After the first coordination of the substrate, iridium is inserted into the C–H bond. This can be formally described as oxidative addition. Subsequently, with coordination of D_2O, the exchange itself can take place. The reductive elimination then occurs and the deuterated substrate is released.

This proposed mechanism reflects the preferred square-planar coordination sphere for Ir^{I} and the octahedral coordination for Ir^{III}. The aforementioned scheme is in accordance with the 16/18-valence-electron rule.

Oxidative-addition reactions are typical for electron-rich, low-valent complexes of "late" transition metals like Ir. In principle, however, as an alternative to the oxidative addition/reductive elimination sequence a σ-bond metathesis mechanism may also be reasonable, although this type of reaction is more common for "early" transition metals, like for instance Sc.[13]

Analytics

The term deuteration grade is used to describe the amount of introduced deuterium atoms per possible position. It is given a value of 0% when there is no exchange, and 100% if the hydrogen has been completely replaced by deuterium. If multiple positions are present the results state different values for each possible position (Table 1).

For simple systems standard ^{1}H NMR techniques were used to assign the position and to calculate the deuteration grade from the corresponding integrals. It was very useful

Table 1. Deuterated products and their related data. Reactions were conducted at 90 °C for 2 h in DMA and D_2O, with a catalyst-to-substrate ratio of 1:25. Deviations from this standard procedure are given in the table.

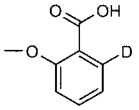
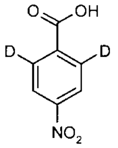
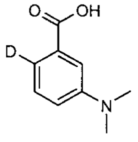
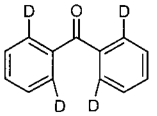
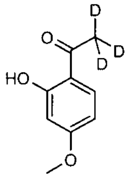
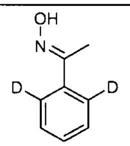
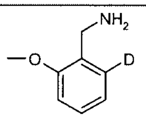
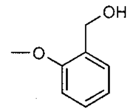
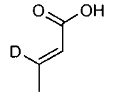
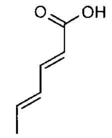
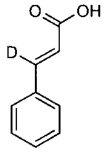
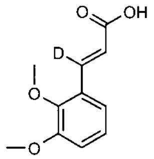
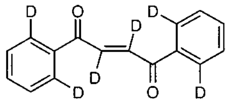
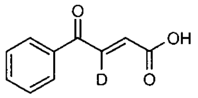
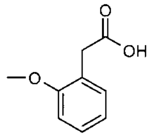
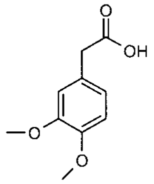
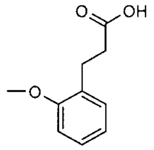
Entry	Product	Deuteration grade	Data
2		97.5%	δ_H ($CDCl_3$) = 4.06 (s, 3 H), 7.10 (m, 2 H), 7.56 (t, 1 H); *m/z* (EI) = 153 ($M^{-\bullet}$)
3		2 × 99%	δ_H ($CDCl_3$) = 8.35 (s, 2 H); *m/z* (EI) = 169 ($M^{+\bullet}$)
4		45% only in position 6, position 2 is hindered by the dimethylamino group	δ_H ($CDCl_3$) = 3.05 (s, 6 H), 7.02 (d, 1 H), 7.36 (m, 1 H), 7.52 (m, 1.55 H); δ_{igd} (CD_3COCD_3) = 117.25 (t, 0.47), 117.86 (s, 1.00), 129.24 (s, 0.65), 129.36 (s, 0.82), 131.51 (s, 0.62), 131.58 (s, 0.80)
5		4 × 5%	δ_H ($CDCl_3$) = 7.52 (m, 6 H), 7.81 (m, 3.8 H)
6		3 × 99% at the methyl group, no exchange at ring carbons	δ_H ($CDCl_3$) = 3.86 (s, 3 H), 6.34 (m, 2 H), 7.57 (d, 1 H), 12.69 (s, 1 H)
7		2 × 12.5% at the ring, after 3 hours, methyl group remains unlabelled	δ_H ($CDCl_3$) = 2.25 (s, 3 H), 7.37 (m, 3 H), 7.68 (m, 1.75 H)
9		61%	δ_H ($CDCl_3$) = 2.68 (br, 2 H), 3.87 (s, 3 H), 4.41 (d, 2 H), 6.96 (m, 2 H), 7.22 (t, 1 H), 7.39 (m, 0.39 H)
10		0%	δ_H (CD_3COCD_3) = 3.84 (s, 3 H), 4.70 (s, 2 H), 6.95 (m, 2 H), 7.25 (t, 1 H), 7.46 (d, 1 H)
11		69% after 4 hours	δ_H (CD_3COCD_3) = 2.10 (br, 3 H), 5.86 (br, 1 H), 6.96 (m, 0.31 H); δ_{igd} (CD_3COCD_3) = 16.9 (s, 1.27), 17.1 (s, 0.98), 122.8 (s, 1.22), 122.9 (s, 0.98), 144.0 (t, 1.14), 144.3 (s, 1.00)

Table 1. *(continued)*.

Entry	Product	Deuteration grade	Data
12		0% after 4 hours	δ_H ($CDCl_3$) = 1.92 (s, 3 H), 5.82 (d, 1 H), 6.27 (m, 2 H), 7.53 (m, 1 H)
13		17%	δ_H ($CDCl_3$) = 6.58 (d, 1 H), 7.45 (m, 3 H), 7.69 (m, 2.83 H)
14		75%	δ_H ($CDCl_3$) = 3.91 (s, 6 H), 6.53 (m, 1 H), 7.14 (m, 3 H), 8.09 (d, 0.25 H); δ_{igd} ($CDCl_3$) = 118.88 (s, 3.48), 118.99 (s, 1.00), 128.31 (s, 3.16), 128.39 (s, 1.00), 140.85 (t, 3.17), 141.15 (s, 1.00)
15		2 × 7.5% at the double bound, with additional 15% at ring carbon atoms in diverse pattern	δ_H (CD_3COCD_3) = 7.71 (m, 6 H), 8.02 (s, 1.85 H), 8.15 (m, 4 H); *m/z* (EI) = 236 ($C_{16}H_{12}O_2$ 70%), 238 ($C_{16}H_{10}D_2$ 15%)
16		75% exclusively at the double bound	δ_H ($CDCl_3$) = 6.93 (m, 1 H), 7.62 (m, 3 H), 8.04 (m, 2.25 H)
17		0%	δ_H ($CDCl_3$) = 3.63 (s, 2 H), 3.84 (s, 3 H), 6.96 (m, 2 H), 7.27 (m, 2 H)
18		0%	δ_H ($CDCl_3$) = 3.33 (s, 2 H), 3.64 (m, 6 H), 6.64 (m, 3 H)
19		0%	δ_H ($CDCl_3$) = 2.59 (t, 2 H), 2.93 (t, 2 H), 3.87 (s, 3 H), 6.94 (m, 2 H), 7.23 (m, 2 H)

to employ substrates that contained, for example, a methyl or methoxy group that can be used as internal standard.[4] The results were occasionally verified by mass spectrometry, which always showed a very good agreement.

For more complex systems inverse gated decoupled ^{13}C NMR spectra were recorded. These carbon spectra, which can be integrated, allow absolutely clear assignment of the deuteration position from the coupling pattern. A normal C–D coupling shows a triplet, whereas the C–H coupling remains as a singlet (Figure 4). Their integration reflects the deuteration grade very precisely. These results can even be improved, because normally the neighbouring carbons split up and also allow integration.

Isotope Source

Due to the inconvenience of handling D_2 gas, nearly all experiments were carried out with D_2O as the isotope source. To adapt this technique for tritium labelling of drug candidates a suitable radioactive source is required. The high risk related to the usage of tritiated water prohibits its employment in standard methods.[10,14] Consequently, the catalyst system was tested with deuterium gas and **2** as model compound. A deuteration grade of 45% was observed, but surprisingly at the C-4 position, *para* to the acid and *meta* to the methoxy group (Figure 5), thus indicating that a different mechanism from the one described above

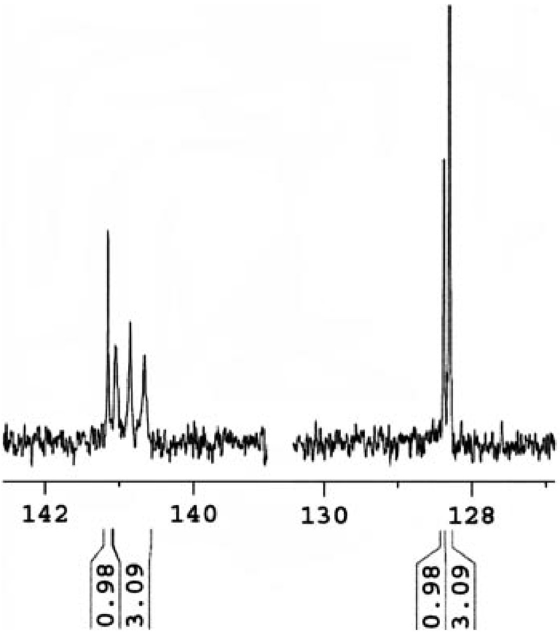


Figure 4. Representative C–D (left) and split up C–H (right) coupling in *trans*-2,3-dimethoxycinnamic acid (**14**) with corresponding integrals.

has taken place (Scheme 2). A similar experiment using **5** showed diverse exchange over the aromatic ring, although not the expected *ortho* exchange: deuterium was mainly positioned *meta* and *para* to the carbonyl group, with an overall exchange rate of 30%.

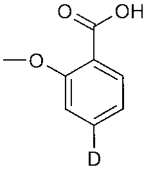


Figure 5. With deuterium gas as the isotope source rather than D_2O, 2-methoxybenzoic acid (**2**) shows exchange *para* to the acid and *meta* to the methoxy group, with no labelling *ortho* to the carboxylic acid.

In contrast to our exchange reaction with D_2O, we observed precipitation of iridium when D_2 was employed as the isotope source. This finding parallels the experiments of Hickey et al.,[15] in which 4-aminobenzoic acid was labelled with D_2 in the *meta* position rather than in the *ortho* position In this case the results were explained by formation of an iridium colloid cluster that is able to exchange in positions other than *ortho*.

Other recent reports have shown a similar exchange pattern for naphthyl and phenyl substrates in the presence of Ir^{III} catalysts and deuterium gas.[16,17] We assume that deuterium gas can reduce the acetylacetone and subsequently form an active Ir^{III} species, which enables exchange in positions other than those labelled with D_2O. It seems that only electronic effects in the aromatic ring are relevant to this exchange reaction, and that there is no evidence for an influence of directing groups in the substrate.

Conclusions

Screening a number of compounds has shown that the iridium catalyst has the ability to catalyze H/D exchange in an array of compounds. These include unsaturated carboxylic acids, ketones and amines whose hydrogens at the double-bond position can be exchanged. Complex **1** catalyzes deuteration in a 1,4-relation relative to a directing atom, via a five-membered metallacyclic intermediate, providing that there is no steric hindrance or blockage from other functional groups.

Complex **1** is considered to be an all-round catalyst. It can catalyze the H/D exchange at relatively low catalyst/substrate molar ratios and in relatively short reaction times. The standard conditions used throughout our experiment employ a catalyst/substrate molar ratio of 1:25 and a reaction time of two hours. Moreover, **1** catalyzes the reaction at moderate reaction temperatures of 60–90 °C and it can easily be prepared from its precursor $[Ir(COD)Cl]_2$. Under these conditions, H/D exchange varied between 5 and 99% at a specific positions.

The mechanism presumably involves displacement of cyclooctadiene by a solvent molecule, which later on is replaced by a substrate, which in our case is an α,β-unsaturated carbonyl group, or a benzylamine. In addition, the solvent molecule presumably plays an important role in the oxidation/reduction cycle of iridium on which the H/D exchange is based. The presence of a hetero atom in an unsaturated compound in a position that allows the formation of a five-membered metallacycle with iridium is a prerequisite for a successful exchange reaction. With respect to the heteroatom, softer bases coordinate more effectively to the catalyst.

The proposed mechanism is only applicable to the exchange of hydrogen by D_2O. Employment of D_2 as labelling reagent yields, under identical conditions, isotopic exchange in positions that can not be rationalised by the five-membered metallacyclic intermediate. This result will be the object of further investigations in our laboratory.

Experimental Section

General Remarks: All solvents were purified by standard procedures and were distilled prior to use. Reagents obtained from commercial sources were used without further purification. The NMR spectra were measured with Bruker ARX 200 and Bruker AV 500 instruments. Mass spectra were recorded with a Finnigan MAT 8230 instrument.

Catalyst: To prepare cyclooctadieneiridium(I) acetylacetonate (**1**), $[Ir(COD)Cl]_2$ (250 mg, 0.372 mmol) was treated with degassed diethyl ether (2 mL), and stirred under argon at room temperature for 20 min until it had dissolved completely. Acetyl acetone (80 μL, 0.773 mmol) was added dropwise with a syringe to the reaction mixture. After 5 min stirring 1 N KOH (1.25 mL) was added dropwise to the reaction mixture with a syringe. The reaction mixture was stirred for an additional 10 min, then distilled water (2.0 mL) was added dropwise with a syringe. The solution became darker as distilled water was added and finally became dark brown. A yellow solid could also be observed. The reaction mixture was stirred for an additional hour before diethyl ether was evaporated. The yellow solid was filtered from the aqueous solution and washed three times with portions of distilled water (3 mL). The crystals were dried overnight to yield 215 mg (0.538 mmol, 73%) of fine, yellowish crystals of **1**. ^{1}H NMR (CDCl$_3$): δ = 1.66 (d, J = 7.6 Hz, 4 H), 2.04 (s, 6 H), 2.28 (m, 4 H), 4.02 (s, 4 H), 5.55 (s, 1 H) ppm.[1,2]

Reaction: The reactions were carried out mostly in the same manner. This consists of stirring a mixture of substrate and **1** in the solvent (DMA) under argon at 90 °C for 2 h. However, in some cases, the reaction conditions were modified slightly. The modifications include the adjustment of the volume of solvent and D$_2$O, the use of D$_2$ gas instead of D$_2$O, alteration of the substrate to catalyst ratio, omitting to use a condenser when the reaction was carried out in a mini-reactor, and adjustment of temperature and reaction time. The following paragraphs explain how the deuteration reactions for sample compounds of each class were prepared.

Acids: 2-Methoxybenzoic acid (**2**; 102 mg, 0.67 mmol) and **1** (10.2 mg, 0.026 mmol) were placed in a 1-mL mini-reactor under argon. DMA (0.65 mL) was added to the mini-reactor and stirred until all the solid had dissolved. D$_2$O (0.1 mL) was added dropwise whilst stirring. The reaction mixture was heated at 90 °C for 2 h and then left to cool. The mixture was then treated with 20 mL of H$_2$O and acidified with 5 mL of 1 N HCl before being extracted three times with 20 mL of diethyl ether. The organic phase was dried with MgSO$_4$ and filtered. The solvent was removed and the deuterated product was obtained. ^{1}H and ^{13}C NMR and mass spectra were measured.

Neutral Compounds: Acetophenone oxime (**7**; 100.0 mg, 0.74 mmol) and **1** (11.6 mg, 0.029 mmol) were placed in a 50-mL, round-bottomed flask. DMA (7.6 mL) was added to the flask and stirred until all the solid had dissolved. D$_2$O (2.4 mL) was added dropwise whilst stirring. The reaction mixture was put under argon gas and heated at 90 °C for 2 h and then left to cool. The mixture was then treated with 20 mL of H$_2$O before being extracted three times with 15 mL of diethyl ether. The organic phase was dried with MgSO$_4$ and filtered. The solvent was removed and the deuterated product was obtained. ^{1}H and ^{13}C NMR spectra were measured.

Amines and Alcohols: Complex **1** (10.1 mg, 0.025 mmol) was placed in a 1-mL mini-reactor under argon. DMA (0.40 mL) was added to the flask and stirred until all the solid had dissolved. 2-Methoxybenzylamine (**9**; 80 μL, 0.65 mmol) was added to the mini-reactor and then D$_2$O (0.1 mL) was added dropwise whilst stirring. The reaction mixture was heated at 90 °C for 2 h and then left to cool. The mixture was then treated with 20 mL of 12.5% NH$_3$ before being extracted three times with 20 mL of diethyl ether. The organic phase was dried with MgSO$_4$ and filtered. The solvent was removed and the deuterated product was obtained. A ^{1}H NMR spectrum was measured.

Allylic Systems: *trans*-Crotonic acid (**11**; 74.0 mg, 1.16 mmol) and **1** (13.5 mg, 0.034) were placed in a 10-mL, round-bottomed flask. DMA (2.0 mL) was added to the flask and stirred until all the solid had dissolved. Deuterium oxide (1.0 mL) was added dropwise whilst stirring. The reaction mixture was put under argon gas, heated at 90 °C for 4 h and then left to cool. The mixture was then treated with 10 mL of 1 N HCl before being extracted three times with 5 mL of 1-butanol. The organic phase was filtered, the solvent was removed and the deuterated product was obtained after drying at high vacuum for 2 h. A ^{1}H NMR spectrum was measured.

Deuterium Gas: 2-Methoxybenzoic acid (**2**; 102 mg, 0.67 mmol) and **1** (10.2 mg, 0.026 mmol) were placed in a 50-mL, round-bottomed flask. The reaction vessel was evacuated and flushed with argon to remove oxygen. DMA (7.6 mL) was added to the flask and stirred until all the solid had dissolved. Then, a balloon containing roughly 50 mL of D$_2$ was attached to the apparatus. The gas phase consisted of approximately two parts deuterium to one part argon. The reaction mixture was heated at 90 °C for 2 h, changing colour from yellowish to dark brown and forming a black precipitate. The mixture was then treated with 20 mL of H$_2$O and acidified with 5 mL of 1 N HCl before being extracted three times with 20 mL of diethyl ether. The organic phase was dried with MgSO$_4$ and filtered. The solvent was removed and the deuterated product was obtained. ^{1}H and ^{13}C NMR and mass spectra were measured.

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