ISOTOPIC STUDIES OF THE HYDROGENATION AND EXCHANGE-LABELLING OF UNSATURATED HYDROCARBONS WITH HETERGENEOUS CATALYSTS

BY

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SUMMARY

This thesis describes investigations utilising isotopic hydrogen gas (D₂ and DT) and covering several areas of chemistry.

The initial studies involved the selective α-labelling of pyridine and other N-heterocyclics via new hydrogen-deuterium exchange catalysts, identified via a parallel-chemistry screening process. The new catalysts and associated methodology are applicable to labelling with tritium as well as deuterium and are a significant improvement upon existing labelling approaches.

The remaining studies involved the application of isotopes to studies of the hydrogenation of unsaturated hydrocarbons. Initially the hydrogenation, and isotopic exchange reactions, of simple unbranched C₅ alkenes and alkynes with D₂ gas were examined. Although many aspects of the hydrogenation chemistry of pentenes and pentynes have been studied there is an interest in obtaining close to 100% selectivity in the reactions of these important industrial feedstocks. The studies were subsequently extended to the hydrogenation of the less-volatile phenyl-C₃ unsaturated hydrocarbons, allowing studies with DT gas as well as D₂. The work carried out in these two chapters includes a comparison of a novel 1%Pd/Al₂O₃ catalyst developed by Johnson Matthey(JM) /Synetix with a standard catalyst 5% Pd/C catalyst routinely used for the hydrogenation of double bonds. Although these investigations are still in their initial stages, the results obtained suggest that the JM catalyst could prove more selective than the commonly used Pd/C.

The above DT studies also enabled an investigation of the application of a new development in ³H-NMR spectroscopy, the ³H cryo-probe. This new technology was shown to provide a significant advance for the analysis of tritiated compounds and mixtures containing low levels of radioactivity.

The last investigations concerned the facile exchange of isotope during the hydrogenation of terminal alkenes. This process was shown to be general and could well provide a novel methodology for the tritium labelling of this class of compounds.
ACKNOWLEDGEMENTS

I would like to thank my supervisors Prof J.R. Jones and Prof. W.J. S. Lockley for their encouragement and help throughout this project. I would also like to acknowledge the help and contribution of the other members of the ATHENA group during the project. Thanks are also due to EPSRC, who provided a research studentship, and to Johnson Matthey/Synetix for the loan of catalysts.

I would also like to thank Mr J. P. Bloxsidge for his enormous help with NMR spectroscopy, especially at the early stages of my PhD. Finally, many thanks to all the friends and colleagues in the division of chemistry for their encouragement and support during the last three years.
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CHAPTER 1:

INTRODUCTION
1.1: BACKGROUND

The work presented in this thesis is part of an EPSRC funded project entitled Advanced Technology in Catalytic Chemistry and Engineering for Novel Applications (ATHENA) and is under the overall leadership of Professor S. D. Jackson (Glasgow University, formerly of Synetix). As well as Glasgow University and Surrey University (Professors J. R. Jones and W. J. S. Lockley) three other UK universities are involved in the collaborative project – Professor L. F. Gladden (Cambridge University), Professor G. L. Hutchings (Cardiff University), and Professor J. M. Winterbottom (Birmingham University). In addition Northwestern University in the USA (Professor P. C. Stair) and the Fritz Haber Institute in Germany (Professor H. J. Freund) are involved. Industrial support has been provided by Synetix (Dr. F. King), which during the project became part of the Johnson Matthey Company.

Each centre has its own unique area of expertise and the research program was designed so as to concentrate on three kinds of reactions – hydrogenation, dehydrogenation and oxidation – and to focus on the catalyst selectivity. The industrial concerns- Johnson Matthey/Synetix- possesses catalysts and these were made available to the various research groups as and when required.

1.2: OBJECTIVES

The chemical industry is one of the UK's success stories, consistently making a profit (exports exceed imports) and thereby making a very valuable contribution to the balance of payments. Many of the chemicals produced involve several reaction steps, some or all of which may require a catalyst. It is important therefore that these catalysts are extremely efficient so that, ideally, the reactions proceed rapidly, at or close to room temperature and are very selective, so that the reaction yield is as close to 100% as possible and that little or no by-products or waste are produced. These various requirements are difficult to achieve. There is therefore a need to carry out more research so as to improve our understanding of how such
catalysts work. Only then will it be possible to design new, better and more cost efficient catalysts.

When one is studying a complex process such as a reaction mechanism it is wise to simplify the situation as far as possible, and it is here that isotopic substitution is very useful. Exchange reactions that involve the transfer of a proton, hydride or atomic hydrogen (H⁺, H⁻ or H) are amongst the simplest of reactions, but since even simple organic molecules often contain hydrogen in several different sites, the results of studies can be difficult to interpret. It is not surprising therefore that isotopes have played an important part in the study of such reactions.

Hydrogen has two heavy isotopes, deuterium (²H₁ or D) and tritium (³H₁ or T). The former is stable whereas the latter is radioactive – a weak β⁺ emitter with a half-life of 12.3 years. Liquid scintillation counting is usually employed to measure its radioactivity. Both deuterium and tritium have nuclear spins, I=1 for deuterium and I=1/2 for tritium. With the development of modern nuclear magnetic resonance (NMR) technology it is now possible to use ²H NMR and ³H NMR spectroscopy to measure both the degree of incorporation of isotope and also to define the site(s) labelled. These techniques were used extensively in the present research. They are particularly useful when studying hydrogen isotope exchange reactions, as these are different from other reactions such as hydrogenation as the product differs from the reactant only by virtue of substitution of an isotope. In other words but for these two techniques it would be difficult, but not impossible (one could use infra-red spectroscopy or mass spectrometry) to establish that hydrogen isotope exchange had taken place. One of the important aspects of the research was to see whether, when hydrogenation reactions take place, they are accompanied by hydrogen isotope exchange reactions, and if so, whether different catalysts behave in the same manner.

In view of the above comments this thesis is structured in the following manner:

In Chapter 2 the work on isotopically-labelled pyridine derivatives is presented. Pyridine and other N-heteroaromatic sub-units occur in many industrially important chemicals including a range of agrochemical and pharmaceutical agents. The work extends and significantly improves the earlier approach of Rubottom and Evain. Initially we envisaged that their experimental procedures might be changed, to
achieve α-deuteriated and, in particular, α-tritiated pyridine derivatives more efficiently.

In Chapter 3 the work on the hydrogenation of C₅ alkenes and alkynes using D₂ gas is reported. Although many aspects of the hydrogenation chemistry of pentenes and pentyynes have been studied there is an interest in obtaining close to 100% selectivity. The work carried out at Surrey includes a comparison of a novel 1%Pd/Al₂O₃ catalyst developed by Johnson Matthey/Synetix and a standard catalyst (Aldrich 5% Pd/C, cat. No. 27,870-7) routinely used for hydrogenation of double bonds. The analysis of the reactions was carried out by ¹H and ²H NMR. Chapter 4 further extends the work to studies of the hydrogenation of phenyl-C₃ unsaturated hydrocarbons. Once more the investigation of these substrates involves comparison of the two catalysts (5%Pd/C and 1%Pd/Al₂O₃). Chapter 5 provides a demonstration of how the sensitivity of ³H NMR spectroscopy, used in these studies, can be improved as a result of the application of a new development in ³H-NMR spectroscopy, the ³H cryo-probe accessory. As a result of this innovation, spectra can now be obtained by using microcurie levels of radioactivity, a factor of some 10³ lower than the amounts used in the first studies in the 1960's. The last chapter presents results from a series of five terminal alkenes showing that extensive hydrogen isotope exchange accompanies hydrogenation in all the selected cases.
CHAPTER 2:

HYDROGEN – DEUTERIUM EXCHANGE OF HETEROCYCLIC COMPOUNDS USING HETEROGENEOUS RHODIUM AND RUTHENIUM CATALYSTS
2.1: INTRODUCTION

Hydrogen-isotope exchange is both a very simple and very versatile reaction:

\[ AX + BY \rightarrow AY + BX \]

\[ X = H, Y = D \ (^{2}\text{H}) \text{ or T } (^{3}\text{H}) \]

Scheme 2.1

For these reasons it has been extensively studied and some of these are given below.

- It can be catalysed by acids, bases and metals and therefore be used to improve our understanding of reaction mechanisms and catalysts \(^{(1)}\).
- It can be studied under homogeneous conditions or heterogeneous conditions so that comparisons can be made \(^{(2)}\).
- It can be studied in a whole range of solvents so that solvent effects are better understood \(^{(3)}\).
- It can be used to prepare deuterium and tritium labelled compounds, which are widely used in the life sciences \(^{(4)}\).
- It can be used to study the selectivity of catalysts \(^{(5-6)}\).
- It can be used as a model to improve the efficiency of a reaction and to minimise the production of waste and particularly radioactive waste, which is expensive to store \(^{(7)}\).
- It can be used to study the effect of using an additional energy source e.g. ultrasound or microwaves so that reactions can be studied in a shorter time \(^{(8)}\).
- It can be used to train PhD students whose studies will require isotopic analysis techniques.

With the last point in mind it was interesting to see a report \(^{(9)}\) that 5% Ru/C selectively catalyses hydrogen-deuterium exchange of pyridine and a number of pyridine derivatives at the ortho positions (i.e. α to N). The reaction takes place at ambient temperature under very mild conditions:
Such an exchange obviates the need to prepare specific precursors and saves time. Previous studies (9) using different metal catalysts – Ni, Mo, Pt, Pd, Co – on a variety of supports (carbon, silica, alumina, or Kieselguhr) have also shown good selectivity but in all cases the reaction temperature was at 100°C or higher. The ability to effect hydrogen-deuterium exchange at lower temperature is useful for two reasons. Firstly, lower reaction temperatures reduce the risk of thermal decomposition (many pharmaceutical agents are very temperature sensitive) and slow the rate of competing side reactions. Secondly, previous studies of several catalytic systems have shown that as the reaction temperature is increased the selectivity is reduced, with deuteriation at undesired ring positions becoming significant. The results of Rubottom and Evain (9) are summarised in Table 2.1. The position of the incorporated deuterium was assigned by NMR spectroscopy (\(^1\)H, \(^2\)H, \(^13\)C as needed). The percentage incorporation was calculated using NMR integration and/or mass spectra data. The catalyst is commercially available and needed no pre-treatment. The reaction vessel was pressurised to 22psi of D\(_2\) and the reaction stirred at room temperature for 24hrs.

The method is clearly an attractive one but in order to make it amenable to a wider range of compounds and in particular its possible use in tritiation studies several questions need to be addressed:

- Can pressure be avoided?
- Is a labelled solvent necessary?
- Can the reaction time be reduced?
Table 2.1: 5% Ru/C deuteriation of pyridine and pyridine derivatives (9)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.jpg" alt="Pyridine" /></td>
<td><img src="image2.jpg" alt="Deuterated Pyridine" /></td>
</tr>
<tr>
<td><img src="image3.jpg" alt="Pyridine N-Methyl" /></td>
<td><img src="image4.jpg" alt="Deuterated Pyridine N-Methyl" /></td>
</tr>
<tr>
<td><img src="image5.jpg" alt="Pyridine N-Chloro" /></td>
<td><img src="image6.jpg" alt="Deuterated Pyridine N-Chloro" /></td>
</tr>
<tr>
<td><img src="image7.jpg" alt="Pyridine N-Ethyl" /></td>
<td><img src="image8.jpg" alt="Deuterated Pyridine N-Ethyl" /></td>
</tr>
<tr>
<td><img src="image9.jpg" alt="Pyridine N-Fluoride" /></td>
<td><img src="image10.jpg" alt="Deuterated Pyridine N-Fluoride" /></td>
</tr>
</tbody>
</table>

(a) All chemical yields were >90% and no major impurities were detected

Current tritium technology is centered around using T₂ gas at, or below, atmospheric pressure. It would therefore be unattractive if one had to employ higher pressures. There would also be the danger that other functional groups present in the substrate could be reduced. It would also reduce the attraction of the procedure if it was necessary to use a tritiated solvent as well as T₂ gas. For this reason it seemed
appropriate to study in some detail the role of the solvent. All the above aspects draw
attention to the fact that there can be significant differences when tritiated compounds
are being prepared, as compared to deuteriated compounds. For the above reasons a
research program was set up to:

1. See if the hydrogen-deuterium exchange reaction proceeded at
   atmospheric pressure.
2. See if CD$_3$OD was necessary for deuteriation.
3. If the answer to (2) is No, to investigate whether in the presence of other
   solvents and catalysts the reaction proceeded more rapidly so that the 24
   hrs previously used for the deuteriation can be reduced.
4. See if hydrogen/deuterium exchange of the kind

   \[ \text{D}_2 + \text{CH}_3\text{OH} \rightarrow \text{CH}_3\text{OD} + \text{HD} \]

   is important during the time taken to deuteriate the substrate.

When comparing different catalysts or assessing the importance of different solvents a
good deal of time can be saved if several reactions can be studied in parallel. Considerable
time was therefore spent in setting up such a parallel reaction capability.

2.2: EXPERIMENTAL

For single reactions which were performed at atmospheric pressure (or slightly above) a typical procedure was as follows:

To a 10ml capacity Discover glass tube (see Fig 2.1) designed
for microwave experiments, where considerable pressure may be generated, 20 µl of
substrate was inserted, followed by 10mg of catalyst and 1ml of CD$_3$OD solvent. The
D$_2$ gas is supplied in a 50L cylinder and after flushing a balloon with N$_2$ gas several
times, the D$_2$ gas is transferred. A stainless steel assembly was constructed (see Fig
2.2) to which the balloon could be attached. By opening the two valves the D$_2$ gas was
transferred to the reaction vessel which was then magnetically stirred for 24hrs at
room temperature (RT). The reaction vessel was disconnected, the catalyst filtered off
and the solvent removed by passing a stream of N$_2$ over the surface of the solution.
For $^1$H NMR analysis the substrate was dissolved in 500µl of CDCl$_3$ containing
tetramethylsilane (TMS). For $^2$H NMR analysis the CDCl$_3$ was removed (passing of N$_2$ over the solution surface) and replaced by CHCl$_3$. The NMR analysis was performed on either a Bruker AC-300MHz instrument or a Bruker DRX-500MHz instrument using standard conditions. For the 300MHz instrument the $^2$H frequency was 46.07MHz and for the 500MHz instrument 76.78MHz. All $^2$H and $^3$H NMR spectra are proton decoupled. In the case of either a $^2$H or $^3$H ($^1$H decoupled) spectra the experiment was performed by using a “WALTZ 16” composite pulse decoupling sequence on the proton channel. After it became clear that the deuteriation could take place at atmospheric pressure the balloon was dispensed with and a 300ml glass cylinder used as the D$_2$ reservoir (see Fig 2.2).

Fig 2.1: 10ml capacity Discover glass tube

Fig 2.2: Stainless steel assembly
2.3: RESULTS AND DISCUSSION

The first thing investigated was whether the reaction could occur at atmospheric pressure (actually at a pressure just above atmospheric, by supplying deuterium from a balloon). This was done by choosing five substrates previously used by Rubottom and Evain\(^{(9)}\). The results of this first experiment can be seen below

Table 2.2: Isotopically labelled pyridine derivatives prepared according to Rubottom\(^{(9)}\) et al., but at 1atm.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>% labelling</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Picoline</td>
<td>91</td>
</tr>
<tr>
<td>4-Benzylpyridine</td>
<td>75</td>
</tr>
<tr>
<td>Isoquinoline</td>
<td>90 (1) and 100 (3)</td>
</tr>
<tr>
<td>2-Methoxypyridine</td>
<td>100</td>
</tr>
<tr>
<td>2-Benzylpyridine</td>
<td>89</td>
</tr>
</tbody>
</table>

A typical example of the results obtained for the substrates are given below. This shows the \(^1\text{H- and }^2\text{H (}^1\text{H decoupled)}\)-NMR spectra of isoquinoline isolated from the reaction.
The above and subsequent spectra have been processed as follows. Examination of the $^2$H-NMR of the exchanged substrate confirms the positions of exchange. By using integration of the $^1$H-NMR spectrum of the starting material and the exchanged material the percentage labelling in each position can be determined. If exchange has occurred the $^1$H-integration of the corresponding position will be decreased compared with the starting material. Thus, in the example of isoquinoline above we can calculate the amount of exchange as follows. In the starting material the integration for the positions o-nitrogen is 1 when normalized with respect to a resonance (7.9p.p.m) which is known to be unlabelled from the $^2$H-NMR. On the other hand at the exchanged material the normalized integrations of these same peaks are 0.11 and 0.08. From this the % deuterium labelling will be:

% labelling at position 1 = 0.11x100/1=11% ~90% labelling
% labelling at position 2 = 0.08x100/1=0.08%~100% labelling
The results obtained via this method are an approximation because the integration procedure carries an error of ca. 5-10%. Any labelling below the 10% level should therefore be treated with caution. The results of these experiments therefore showed promise as not only had we managed to obtain exchange at atmospheric pressure but the percentage of labelling was high and the specificity good.

The published method (9) utilised two deuterium donors, the deuterated solvent and the D$_2$-gas. We hoped that we might be able to eliminate [D$_4$]methanol which would enable us to convert the method for work with tritium. To investigate this further series of experiments were undertaken as follows:

1. Substrate + 5%Ru/C +[D$_4$]methanol (CD$_3$OD) stirred under N$_2$ gas at room temperature (RT) for 24h/
2. Substrate + 5%Ru/C + [H$_4$]methanol (CD$_3$OD) stirred under D$_2$ gas at room temperature (RT) for 24h.
3. Substrate + 5%Ru/C + [D$_4$]methanol stirred under H$_2$ gas at room temperature (RT) for 24h

Table 2.3: Isotopically labelled pyridine derivatives using different deuterium donors

<table>
<thead>
<tr>
<th>Reaction</th>
<th>% labelling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>93</td>
</tr>
</tbody>
</table>

The results obtained showed that when the reaction was attempted in the presence of nitrogen gas (absence of D$_2$ gas) no exchange was observed. In the presence of either hydrogen gas or undeuterated methanol exchange was observed but to differing degrees. It was observed that the % labelling in the case of (3) was higher than in the case of (2).

These results lead to the following conclusions. Firstly, that the following reaction is very important during the exchange of the substrate.

\[ D_2 + CH_3OH \rightarrow CH_3OD + HD \]

and hence that it was absolutely crucial to try to find a solvent that would not undergo exchange. Secondly in order for the exchange to occur, hydrogen or D$_2$ must be
present, (probably to activate the catalyst). Thirdly, that deuterium is originating from both the deuterated solvent and from the deuterium gas. This implied that we might be able to eliminate the deuterated solvent provided that an alternative inactive (non-exchangeable) solvent could be identified.

From this work we can see that the literature method (9) involved labelling of the substrate with deuterium from both of the possible donors present. Only by this dual approach were the very high percentages of labelling achieved. The current data does not enable us to differentiate between the several possible mechanisms below. Of course, more than one mechanism could be in operation.

\[
\begin{align*}
\text{D}_2\text{-gas} & \rightarrow \text{substrate} & \text{D}_4\text{-methanol} & \rightarrow \text{substrate} \\
(1) & & (2)
\end{align*}
\]

\[
\begin{align*}
\text{D}_2\text{-gas} & \rightarrow \text{D}_4\text{-methanol} & \text{D}_4\text{-methanol} & \rightarrow \text{D}_2\text{ gas} \\
(3) & & (4)
\end{align*}
\]

(scheme 2.3)

So direct catalytic exchange between the D2-gas and the substrate is possible, as is exchange of the CD3OD with the substrate. However, isotopic exchange between the CD3OD and the D2 gas is also likely. Hence either the CD3OD or the D2 gas (or both) could be the deuterium donor under the Rubottom conditions.

In summary, the reactions will proceed at 1 atmosphere pressure and labelling can occur in the absence of deuterated methanol. The next step was to identify a suitable alternative solvent to deuterated methanol. This is required because, as mentioned previously, the use of a labelled methanol solvent would be quite impractical for labelling with the tritium isotope.

Four solvents were investigated as possible alternatives; chloroform, acetone, methanol (undeuterated) and tetrahydrofuran (THF). The results obtained (Table 2.4 and 2.5) showed that, with the exception of chloroform, all the solvents could function as alternatives to [D4] methanol.
Table 2.4: % Labelling of 4-picoline in different solvents using Ru/C

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Solvent</th>
<th>% labelling</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Picoline</td>
<td>Chloroform</td>
<td>0</td>
</tr>
<tr>
<td>4-Picoline</td>
<td>Acetone</td>
<td>75</td>
</tr>
<tr>
<td>4-Picoline</td>
<td>Methanol</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 2.5: % Labelling of 4, 4-bipyridyl in different solvents using Rh

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Solvent</th>
<th>% Labelling</th>
</tr>
</thead>
<tbody>
<tr>
<td>4,4' Bipyridyl</td>
<td>Acetone</td>
<td>43</td>
</tr>
<tr>
<td>4,4' Bipyridyl</td>
<td>THF</td>
<td>46</td>
</tr>
<tr>
<td>4,4' Bipyridyl</td>
<td>Methanol</td>
<td>5</td>
</tr>
</tbody>
</table>

We decided to concentrate further work on THF because it is a very good organic solvent that will dissolve many organic compounds and because it does not undergo exchange reactions with tritium under normal conditions.

Before moving any further we decided that it would be wise to check if the literature procedure \(^{(9)}\) can proceed in less than 24h. A trial reaction for 7h gave results which showed very little exchange. We therefore thought that a new catalyst that would give good exchange in a shorter time than the 5%Ru/C used by Rubottom et al. was needed. A large number of catalysts were chosen (35 in total see Table 2.6) and a parallel reaction was attempted for 24h under D₂-gas at RT in THF using a model substrate (4-picoline). From the results of this screen three catalysts gave good exchange. These were Ru black, Rh black, and 5% Rh/Al₂O₃. The \(^1\)H-NMR data for reactions involving these three catalysts can be seen below:
Fig 2.5: $^1$H-NMR spectrum of labelled 4-picoline. CDCl$_3$ solvent. Rh black catalyst. (300MHz instrument).

Fig 2.6: $^1$H-NMR spectrum of labelled 4-picoline. CDCl$_3$ solvent. Ru black catalyst. (300MHz instrument).

Fig 2.7: $^1$H-NMR spectrum of labelled 4-picoline. CDCl$_3$ solvent. 5% Rh/Al$_2$O$_3$ catalyst. (300MHz instrument).
Table 2.6: Catalyst screening

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Performance</th>
<th>Catalyst</th>
<th>Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% Ru/Al₂O₃</td>
<td>1</td>
<td>Pd(II) oxide</td>
<td>0</td>
</tr>
<tr>
<td>Ru Black</td>
<td>3</td>
<td>Pd(II) acetylacetonate</td>
<td>0</td>
</tr>
<tr>
<td>5% Ru/C</td>
<td>2</td>
<td>1% Pd/Al₂O₃</td>
<td>0</td>
</tr>
<tr>
<td>Ru(VI) oxide</td>
<td>1</td>
<td>10% Pd/C</td>
<td>0</td>
</tr>
<tr>
<td>Ru(III) chloride trihydrate</td>
<td>1</td>
<td>Pd BaSO₄</td>
<td>0</td>
</tr>
<tr>
<td>Dicarbonylbis(triphenylphosphine) ruthenium(II) chloride</td>
<td>1</td>
<td>Wilkinson's Catalyst</td>
<td>0</td>
</tr>
<tr>
<td>Tris (triphenylphosphine)-ruthenium(II) chloride</td>
<td>1</td>
<td>Ir Black</td>
<td>1</td>
</tr>
<tr>
<td>5% Rh/C</td>
<td>1</td>
<td>Ir(IV) oxide</td>
<td>0</td>
</tr>
<tr>
<td>Rh Black</td>
<td>3</td>
<td>Ir(III) trihydrate chloride</td>
<td>0</td>
</tr>
<tr>
<td>5% Rh/Al₂O₃</td>
<td>3</td>
<td>Pt Black</td>
<td>0</td>
</tr>
<tr>
<td>Rh(III) chloride (anhyd.)</td>
<td>1</td>
<td>Pt(IV) oxide</td>
<td>0</td>
</tr>
<tr>
<td>3% Rh/Al₂O₃</td>
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<td>Pt(II) chloride</td>
<td>0</td>
</tr>
<tr>
<td>1% Rh/Al₂O₃</td>
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<td>5% Pt/CaCO₃</td>
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</tr>
<tr>
<td>Pd Black</td>
<td>0</td>
<td>Platinum dioxide</td>
<td>0</td>
</tr>
<tr>
<td>5% Pd CaCO₃</td>
<td>0</td>
<td>Au(III) oxide</td>
<td>0</td>
</tr>
<tr>
<td>Pd(II) acetate</td>
<td>0</td>
<td>Ni(II) chloride hexahydrate</td>
<td>0</td>
</tr>
<tr>
<td>5% Pd/C</td>
<td>0</td>
<td>Titanium(IV) oxide</td>
<td>0</td>
</tr>
</tbody>
</table>

(0 = no reaction or reduction, 1 = Ok, 2 = good and 3 = excellent)
Table 2.7: % Labelling of 4-picoline from catalyst screen

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Substrate</th>
<th>% Labelling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh Black</td>
<td>4-Picoline</td>
<td>67</td>
</tr>
<tr>
<td>Ru Black</td>
<td>4-Picoline</td>
<td>70</td>
</tr>
<tr>
<td>5% Rh/Al₂O₃</td>
<td>4-Picoline</td>
<td>63</td>
</tr>
</tbody>
</table>

Repetition of this parallel reaction on a smaller scale using only the three catalysts under the above conditions for 2h showed that the same amount of exchange had taken place as before, leading us to the conclusion that equilibrium could be achieved within ca. 2h.

Fig 2.8: $^1$H-NMR spectrum of labelled 4-picoline. CDCl₃ solvent. Rh black catalyst 2h reaction. (300MHz instrument).

The data generated up to this point was limited to a few substrates and hence the generality of the process had not been demonstrated for the new catalysts. The next step therefore was to repeat the parallel reaction using a larger number of substrates (16 in total). The results obtained showed a good degree of labelling. Moreover, in some cases exchange was achieved even for those substrates where the literature procedure had failed. One risk of using such highly active catalysts was the possibility of concomitant reduction of the pyridine nucleus under the reaction conditions. We thus investigated if any reduction was present and, if so, the amount of reduction, by using a combination of $^1$H-NMR, $^2$H-NMR and GC-MS. The results of this definitive screen are given below. In this table the data for the new catalysts is also compared with the original literature catalyst.
Table 2.8: Labelling of pyridines and other nitrogen heteroaromatics using various heterogeneous Ru and Rh catalysts with deuterium gas in tetrahydrofuran at ambient temperature and pressure.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Atom% D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rh Black&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3-Acetylpyridine</td>
<td>0</td>
</tr>
<tr>
<td>4-Acetylpyridine</td>
<td>99</td>
</tr>
<tr>
<td>3-Aminoquinoline</td>
<td>83</td>
</tr>
<tr>
<td>7,8-Benzoquinoline</td>
<td>90&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2-Benzylpyridine</td>
<td>99</td>
</tr>
<tr>
<td>4-Benzylpyridine</td>
<td>99</td>
</tr>
<tr>
<td>2,2'-Bipyridyl</td>
<td>35</td>
</tr>
<tr>
<td>4,4'-Bipyridyl</td>
<td>75</td>
</tr>
<tr>
<td>2-Bromopyridine</td>
<td>28</td>
</tr>
<tr>
<td>4-Me&lt;sub&gt;2&lt;/sub&gt;N-pyridine</td>
<td>100</td>
</tr>
<tr>
<td>Isoquinoline</td>
<td>89 (1)</td>
</tr>
<tr>
<td></td>
<td>88 (3)</td>
</tr>
<tr>
<td>2-Methoxypyridine</td>
<td>16</td>
</tr>
<tr>
<td>4-Picoline</td>
<td>98&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2-Phenylpyridine</td>
<td>20&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Phthalazine</td>
<td>61</td>
</tr>
<tr>
<td>Quinoline</td>
<td>99&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions: The substrate (20mg) and catalyst (10mg) were stirred under D<sub>2</sub> gas for 2 hours at ambient pressure and temperature, <sup>b</sup> indicates extensive reduction or other decomposition under the reaction conditions, <sup>c</sup> In addition there was 35 atom %D in the ortho-positions in the phenyl ring, <sup>d</sup> indicates a minor amount of reduction. <sup>*</sup> Original literature catalyst

In conclusion the work has shown that a wide range of pyridines and other nitrogen heteroaromatics can be labelled with deuterium at room temperature and pressure by isotopic exchange with deuterium gas in THF in the presence of ruthenium black, rhodium black or 5% rhodium on alumina. The new labelling method is rapid, isotope efficient and applicable to both electron-rich and deficient substrates. In a few cases a degree of reduction accompanies the exchange.
2.4 REFERENCES

CHAPTER 3:
METAL-CATALYSED HYDROGENATION OF C₅ ALKENES AND ALKYNES
3.1: INTRODUCTION

Heterogeneous catalysis plays an important role in the chemical industry and when we are looking for improvements selectivity is invariably the most important issue. If this can be achieved it follows that

- The consumption of reactants can be optimized.
- Subsequent separation steps can be avoided.
- The need to dispose of potentially polluting by-products is greatly reduced.

Johnson Matthey (JM) has recently developed a 1% Pd/Al₂O₃ catalyst that is believed to be superior to some of the catalysts used in the past. It would make sense therefore to carry out a strict comparison and for this reason the Aldrich 5% Pd/C catalyst (No 27,870-7) was chosen.

The test reaction was the catalytic hydrogenation of a small number of C₅ alkenes and alkynes. Deuterium gas was used instead of H₂ and ²H NMR spectroscopy of the products used to determine the pattern of labelling, and therefore, the selectivity of the catalysts. Furthermore, some of the reactions were studied after completion i.e. in the presence of excess D₂ gas, whilst others were studied (deficiency of D₂ gas) after partial reaction had taken place. In this way it should be possible to study hydrogen-deuterium exchange reactions that might be taking place during the hydrogenation reaction.

Although not extensive there have been a number of investigations reported in the literature which are relevant to our own studies. Thus Rodriguez et al (¹) used a Ru/SiO₂ catalyst at elevated temperatures (>100°C) to study the hydrogenation of a number of linear and branched pentanes (1-pentene, 2-pentene (cis + trans), 2-methyl-2-butene and 2-methyl-1-butene). In all cases evidence of isomerisation (cis and trans isomerisation and double-bond migration), hydrogenolysis and homologation was obtained although hydrogenation was the predominant reaction.

Fourier transform infra-red spectroscopy (FTIR) was used by Lennon et al (²) to study the hydrogenation of 1,3- pentadiene over alumina- supported palladium catalyst. The reaction was seen to occur as a consecutive process, with the terminal double bond hydrogenated in advance of the internal double bond.

Jackson et al (³) used a Pd/C catalyst to study the hydrogenation of 1-pentyne, phenylacetylene, 2-pentyne and 1-phenyl-1-propyne and then set up
competitive hydrogenation reactions e.g. phenylacetylene/1-pentyne etc. With the exception of the 1-pentyne/2-pentyne couple, which revealed a rate enhancement for both alkynes, the competitive reactions result in a reduction of the hydrogenation rate for both alkynes.

The hydrogenation of 1- and 2-propyne (4) was used in order to study the characteristics of a PdZr alloy catalyst as well as a PdCuZr alloy (Cu is known to be beneficial with respect to selectivity). Under competitive conditions 1-pentyne was always the more reactive.

Laousarot et al (5) studied the hydrogenation of 1- and 2-pentyne and of 1,3-trans- and 1,3-cis-pentadiene catalyzed by toluene solutions of Ru₃(CO)₁₂, FeRu₂(CO)₁₂, FeRu(CO)₁₂, and Fe₃(CO)₁₂ and by the same clusters supported on γ-Al₂O₃. For all the systems studied the catalyst activity was higher for Ru₃(CO)₁₂-containing catalysts and lower for Fe₃(CO)₁₂-containing ones. For mixed metal catalysts, the activity decreased with increasing number of Fe atoms in the dodecacarbonyls. Anchorage of the clusters to γ-Al₂O₃ produced catalysts which were less active towards hydrogenation of 1- and 2-pentyne and more active towards hydrogenation of 1,3-cis and 1,3-trans-pentadiene but had no effect on product distribution.

In one of the most thorough of all studies Jackson and Kelly (6) studied the hydrogenation of a number of alkynes; 1- and 2-pentyne, 1- and 2-hexyne, phenylacetylene and 1-phenyl-1-propyne, over palladium catalysts. This combination allowed the authors to investigate the hydrogenation of a terminal alkyne compared with an internal alkyne and the effect of the size of the R group in

\[ R-C=O \quad \text{CH}_3 \]

The effect of an aromatic R group compared with an alkyl group, was also investigated as also were the kinetic aspects of the reactions. The results obtained could not be interpreted from what was already known about ethyne hydrogenation and suggest that the latter is a special case and further studies on higher molecular weight systems are necessary.
3.2: EXPERIMENTAL

For the hydrogenation experiments we chose the following five compounds:

\[ \text{1-pentene (1)} \quad \text{trans-2-pentene (2)} \quad \text{cis-2-pentene (3)} \quad \text{2-pentyne (4)} \quad \text{1-pentyne (5)} \]

All five compounds were commercially available (Aldrich) and their purity checked prior to use by $^1$H NMR.

Two types of reactions were performed: (a) Complete reactions, in which the substrate is completely converted to the final hydrogenation product by employing a molar excess of isotopic hydrogen and sufficient time. (b) Partial reactions where by changing the ratio of the concentration of the substrate and gas by employing a molar excess of substrate, we can control the extend of the reaction. The complete reaction allows the final isotopic distribution in the product to be defined. This derives from all the reductive and exchange-labelling processes which introduce isotope into the molecule. The partial reactions on the other hand allow an analysis of reactions that introduce an isotope, e.g., isotopic exchange reactions, but which would be unobservable by product analysis alone.

The catalyst that was received from JM was in the form of small grey pallets and was ground to fine powder prior to each experiment.
For complete reactions with 5%Pd/C and 1%Pd/Al₂O₃ catalysts the procedure was as follows:

A 10ml capacity (ca. 0.5 mmoles) Discover pressure tube was charged with the catalyst (10mg for 5%Pd/C or 50mg for 1%Pd/Al₂O₃). The Discover tube was then filled with D₂-gas and finally it was charged with the substrate (20μl ca. 0.22 mmoles). The resulting reaction mixture was stirred under D₂-gas for 30min at room temperature. For ¹H-NMR analysis the substrate was dissolved in 500μl of CDCl₃ containing TMS while for ²H-NMR analysis the substrate was dissolved in 500μl of CHCl₃. The NMR analysis was undertaken using the Bruker 500MHz spectrometer using standard conditions.

For partial reaction with 5%Pd/C and 1%Pd/Al₂O₃ catalyst the procedure was as follows:

A 10ml capacity Discover pressure tube was charged with the catalyst (10mg for 5%Pd/C or 50mg for 1%Pd/Al₂O₃). The Discover tube was then filled with D₂-gas and finally it was charged with the substrate (80μl ca.0.88 mmoles). The resulting reaction mixture was stirred under D₂-gas for 18h at room temperature. For ¹H-NMR analysis the substrate was dissolved in 500μl of CDCl₃ containing TMS while for ²H-NMR analysis the substrate was dissolved in 500μl of CHCl₃. The NMR analysis was undertaken using the Bruker 500MHz spectrometer using standard conditions.

The equipment that was used for this work was:

- An in-house hydrogen/deuterium distribution manifold based upon SSI stainless steel valves
- Discover pressure tubes (9cm length, 2cm diameter)
3.3: RESULTS AND DISCUSSION.
The experimental details are given in Table 3.4 and the NMR spectra ($^1$H of reactant, $^1$H of product(s), $^2$H ($^1$H decoupled) of product(s) are given in Figures 3.1-3.20).

Table 3.4: Experimental details

<table>
<thead>
<tr>
<th>Compound</th>
<th>Run No</th>
<th>Volume of substrate (µl)</th>
<th>Catalyst</th>
<th>Weight of catalyst (mg)</th>
<th>NMR spectra</th>
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<td>3.6 (a-c)</td>
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<td>3.11 (a-c)</td>
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<td>3.18 (a-c)</td>
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<td>1%Pd/Al$_2$O$_3$</td>
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<td>3.19 (a-c)</td>
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<td>5</td>
<td>20</td>
<td>80</td>
<td>1%Pd/Al$_2$O$_3$</td>
<td>50</td>
<td>3.20 (a-c)</td>
</tr>
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</table>
(Fig 3.1a): $^1$H NMR spectrum of 1-pentene in CDCl$_3$ solvent.

(Fig 3.1b): $^1$H NMR spectrum of 1-pentene hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig 3.1c): $^2$H NMR ($^1$H decoupled) spectrum of 1-pentene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.2a): $^1$H NMR spectrum of trans 2-pentene in CDCl$_3$ solvent.

(Fig 3.2b): $^1$H NMR spectrum of trans-2-pentene hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig 3.2c): $^2$H NMR ($^1$H decoupled) spectrum of trans-2-pentene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.3a): $^1$H NMR spectrum of cis-2-pentene in CDCl$_3$ solvent.

(Fig 3.3b): $^1$H NMR spectrum of cis-2-pentene hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig 3.3c): $^2$H NMR ($^1$H decoupled) spectrum of cis-2-pentene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.4a): $^1$H NMR spectrum of 2-pentyne in CDCl$_3$ solvent.

(Fig 3.4b): $^1$H NMR spectrum of 2-pentyne hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig 3.4c): $^2$H NMR ($^1$H decoupled) spectrum of 2-pentyne hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.5a): $^1$H NMR spectrum of 1-pentyne in CDCl$_3$ solvent.

(Fig 3.5b): $^1$H NMR spectrum of 1-pentyne hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig 3.5c): $^2$H NMR ($^1$H decoupled) spectrum of 1-pentyne hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.6a): $^1$H NMR spectrum of 1-pentene in CDCl$_3$ solvent.

(Fig 3.6b): $^1$H NMR spectrum of 1-pentene hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig: 3.6c): $^2$H NMR ($^1$H decoupled) spectrum of 1-pentene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.7a): $^1$H NMR spectrum of trans 2-pentene in CDCl$_3$ solvent.

(Fig 3.7b): $^1$H NMR spectrum of trans-2-pentene hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig: 3.7c): $^2$H NMR ($^1$H decoupled) spectrum of trans-2-pentene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.8a): $^1$H NMR spectrum of cis-2-pentene in CDCl$_3$ solvent.

(Fig 3.8b): $^1$H NMR spectrum of cis-2-pentene hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig 3.8c): $^2$H NMR ($^1$H decoupled) spectrum of cis-2-pentene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.9a): $^1$H NMR spectrum of 2-pentyne in CDCl$_3$ solvent.

(Fig 3.9b): $^1$H NMR spectrum of 2-pentyne hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig 3.9c): $^2$H NMR ($^1$H decoupled) spectrum of 2-pentyne hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.10a): $^1$H NMR spectrum of 1-pentyne in CDCl$_3$ solvent.

(Fig 3.10b): $^1$H NMR spectrum of 1-pentyne hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig 3.10c): $^2$H NMR ($^1$H decoupled) spectrum of 1-pentyne hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.11a): $^1$H NMR spectrum of 1-pentene in CDCl$_3$ solvent.

(Fig 3.11b): $^1$H NMR spectrum of 1-pentene hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig 3.11c): $^2$H NMR ($^1$H decoupled) spectrum of 1-pentene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.12a): $^1$H NMR spectrum of trans-2-pentene in CDCl$_3$ solvent.

(Fig 3.12b): $^1$H NMR spectrum of trans-2-pentene hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig 3.12c): $^2$H NMR ($^1$H decoupled) spectrum of trans-2-pentene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.13a): $^1$H NMR spectrum of cis-2-pentene in CDCl$_3$ solvent.

(Fig 3.13b): $^1$H NMR spectrum of cis-2-pentene hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig 3.13c): $^2$H NMR ($^1$H decoupled) spectrum of cis-2-pentene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.14a): $^1$H NMR spectrum of 2-pentyne in CDCl$_3$ solvent.

(Fig 3.14b): $^1$H NMR spectrum of 2-pentyne hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig: 3.14c): $^2$H NMR ($^1$H decoupled) spectrum of 2-pentyne hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.15a): $^1$H NMR spectrum of 1-pentyne in CDCl$_3$ solvent.

(Fig 3.15b): $^1$H NMR spectrum of 1-pentyne hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig 3.15c): $^2$H NMR ($^1$H decoupled) spectrum of 1-pentyne hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.16a): $^1$H NMR spectrum of 1-pentene in CDCl$_3$ solvent.

(Fig 3.16b): $^1$H NMR spectrum of 1-pentene hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig 3.16c): $^2$H NMR ($^1$H decoupled) spectrum of 1-pentene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.17a): $^1$H NMR spectrum of trans 2-pentene in CDCl$_3$ solvent.

(Fig 3.17b): $^1$H NMR spectrum of trans-2-pentene hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig: 3.17c): $^2$H NMR ($^1$H decoupled) spectrum of trans-2-pentene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.18a): $^1$H NMR spectrum of cis-2-pentene in CDCl$_3$ solvent.

(Fig 3.18b): $^1$H NMR spectrum of cis-2-pentene hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig 3.18c): $^2$H NMR ($^1$H decoupled) spectrum of cis-2-pentene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.19a): $^1$H NMR spectrum of 2-pentyne in CDCl$_3$ solvent.

(Fig 3.19b): $^1$H NMR spectrum of 2-pentyne hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig 3.19c): $^2$H NMR ($^1$H decoupled) spectrum of 2-pentyne hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
(Fig 3.20a): $^1$H NMR spectrum of 1-pentyne in CDCl$_3$ solvent.

(Fig 3.20b): $^1$H NMR spectrum of 1-pentyne hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent.

(Fig 3.20c): $^2$H NMR ($^1$H decoupled) spectrum of 1-pentyne hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent.
There are several aspects of the results that are worthy of comment. In all cases full hydrogenation with either catalyst gives pentane. We have assumed that under the experimental conditions equilibrium has been reached and for this reason we have concentrated on the pattern of labelling and not on the % deuterium incorporation.

Thus, in the Pd/C catalysed hydrogenation of 1-pentene the $^2$H NMR ($^1$H decoupled) spectrum (Fig 3.1c) shows two rather broad signals at $\delta=0.9$, 1.3p.p.m, consistent with what one would expect:

\[
\text{Pd/C} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2 \quad \text{CH}_3\text{CH}_2\text{CHDCH}_2\text{D} \\
\text{D}_2
\]

Scheme 3.1

The small peak at $\delta=1.6$p.p.m, which is observed in the other spectra as well, is due to the formation of HDO. There is a suspicion that the somewhat broader CH$_2$D peak might reflect the incorporation of deuterium at more than one methylene position but because of the similarity in the chemical shifts one can not be certain. Even when the signals are much sharper e.g. when $^3$H is used, and a shift reagent is used (with an appropriate substituent) it is still difficult to distinguish the various methylene groups.

Although it appears that $^3$H studies would be more informative than $^2$H studies one must remember that compounds that we are working with are very low boiling liquids and containment and safe disposal of any radioactivity would be difficult.

For the corresponding hydrogenation of trans-2-pentene (2) and cis-2-pentene (3) the results (Fig 3.2c and 3.3c) are very similar to one another. Now the –CHD methylene peak is the major signal, as one would expect, but there is a significant amount of deuterium in the methyl group. In each case the –CHD signal shows signs of splitting consistent with the presence of deuterium at the expected central and penultimate methylene positions (which are unfortunately very close in chemical shift). The incorporation of deuterium in the methyl group can be explained if isomerisation takes place, either before, or in parallel, with the hydrogenation.
When we compare the results for the two catalysts, using the three substrates 1, 2 and 3, we see distinct similarities. Thus, compare:

Figs 3.1c and 3.6c 1-pentene Both show slightly broader CHD peak vs CH$_2$D peak
Figs 3.2c and 3.7c trans-2-pentene As above but CHD shows splitting.
Figs 3.3c and 3.8c cis-2-pentene. Broader CHD vs CH$_2$D due to resolution.

These results just highlight the need to improve NMR sensitivity and selectivity so that the spectra can be obtained quickly and we can follow the incorporation of the label into the various sites as a function of time. This is why the cryo-probe technology described in Chapter 5 is so important.

When we look at the results for the full hydrogenation of the pentynes (4) and (5) we again find similar $^2$H NMRs for both catalysts with the extent of the labelling somewhat more even for the 1% Pd/Al$_2$O$_3$ catalyst (compare Fig 3.9c and 3.10c with Fig 3.4c and particularly Fig 3.5c). In none of these methylene signals is there any sign of splitting.

The results of the partial hydrogenation experiments serve to highlight how useful this approach is in the study of catalysis. Now all the $^1$H NMR spectra of the reaction products are much more complex than hitherto. Following the same procedure adopted for the full hydrogenations studies we see that the Pd/C catalysed hydrogenation of 1-pentene give rise to a $^2$H NMR ($^1$H decoupled) spectrum (Fig 3.11c) in which there are 5 signals, some of which show signs of splitting. Two of these are for the -CHD and -CH$_2$D groups ($\delta$=1.2 and 0.9 p.p.m respectively) whilst the other, at 5.4 p.p.m (cis/trans 2-pentene), is similar to that witnessed previously for styrene tritiation and is due to the

\[
\begin{align*}
\text{R} & \quad \text{D} \\
\text{and} \\
\text{R} & \quad \text{R} \\
\text{D} & \quad \text{R}
\end{align*}
\]

hydrogen isotope exchange labelling of the rearranged by-product 2-pentene. The HDO signal that is probably due to two reasons one being because of the water existing in the catalyst and would exchange during the reaction and the second due to the work up procedure where chloroform that is known to adsorb molecules of water from the atmosphere is directly inserted in the reaction vessel just after the reaction and it is then shaken in order to adsorb as many moles of the substrate as possible,
during that time it is possible that the adsorbed water in the chloroform will exchange due to the traces of deuterium and the catalyst that are left in the reaction vessel, is probably hidden under that which appears at $\delta = 1.6 \text{ p.p.m}$ and which in the case of trans-2-pentene, itself shows splitting.

For both trans-2-pentene and cis-2-pentene the major signal is for the $-\text{CHD}-$, but again there is significant deuterium incorporation into the methyl group. These results are consistent with those obtained in the full hydrogenation experiments.

When we compare the results for the two catalysts, using the three substrates 1, 2 and 3, we again see distinct similarities.

Thus compare
Fig 3.11c and 3.16c 1-pentene virtually identical.
Fig 3.12c and 3.17c trans-2-pentene same apart from no splitting of signal at $\delta = 1.7 \text{ p.p.m}$.
Fig 3.13c and 3.18c cis-2-pentene major $-\text{CD}_2$ signal.

Finally when we compare (Figs 3.14c, 3.15c, 3.19c) the partial hydrogenation results for 2- and 1-pentynes (4 and 5 respectively) we can see that under the experimental conditions used we witness nearly exclusive deuteration to the labelled alkene accompanied by only a little H/D exchange and full reduction.

Although the C$_5$ hydrocarbons are simple molecules, their spectroscopic analysis is far from simple. Moreover, they are also liable to give rise to symmetrical intermediates and products during hydrogenation. This makes a complete analysis of such reactions problematic. In the following chapter the work on hydrogenation of double bonds tethered to an aryl moiety is presented. Because of the lack of symmetry, these systems are easier to analyse by NMR since the complications associated with the symmetry of the earlier C$_5$ reaction product (pentane) is removed. As a result all molecular sites in the reaction substrates, intermediates and products can be unambiguously interrelated.
3.4 REFERENCES

CHAPTER 4:
METAL-CATALYSED HYDROGENATION OF PHENYL-C₃ UNSATURATED HYDROCARBONS
In this chapter the work on hydrogenation of double bonds tethered to an aryl moiety is presented. The work derives from earlier studies on the hydrogenation of pentenes and pentynes reported in the previous chapter. In this instance though we are moving from simple molecules (e.g. cis-2-pentene) to more complex molecules (e.g. allylbenzene) in which the complications associated with the symmetry of the earlier C₅ reaction product (pentane) is removed. As a result all molecular sites in the reaction substrates, intermediates and products can be unambiguously interrelated. Once more the investigation of these substrates involved comparison of two catalysts (5%Pd/C and 1%Pd/Al₂O₃). In this instance, in addition to the use of D₂ gas, a mixture of DT gas was used. Unfortunately as a result of the partial decommissioning of the tritium laboratory pure (high specific activity) T₂ gas could not be used in the experiments. Instead its closest isotopomer DT gas was utilised at low specific activity in admixture with D₂ gas.

Baricelli (1,2) has published in this area. His work (1) was on the aqueous biphase hydrogenation of olefins using Ru(CO)₃(TPPMS)₂ and RuH₂(CO)(TPPMS)₃ where TPPMS is m-sulfophenyldiphenylphosphine. He has studied the hydrogenation 1-hexene, 1-decene, styrene, allylbenzene and cyclohexene. All the substrates investigated gave the saturated products with both catalysts. For allylbenzene there was no evidence of isomerisation to β-methylstyrene, the explanation for this was probably due to the fact that samples were taken after 2h during a 20h reaction. On the other hand for 1-decene and 1-hexene minor amounts, of isomerised products were observed. The order of reactivity for these reactions was as follows: 1-hexene > allylbenzene > 1-decene > styrene > cyclohexene. Later on Baricelli et al (2) further studied the hydrogenation of the substrates mentioned previously (1) but in this instance using the catalyst W (CO)₃(CH₃CN)(TPPTS)

Sakai, et. al (3) have worked on the hydrogenation of 1-phenyl-1-propyne using metallic nickel. Their results revealed that the main product was the alkene (Z) isomer with some traces of the (E) isomer. Further hydrogenation of the alkene gave the alkane.

Laren et. al (4) worked on a series of zero valent palladium complexes Pd(NN) (alkene) of bi- or tri-dentate nitrogen ligands of the general
formula 6-R''-C₃H₃N-(C(R')=NR)-2 (where R'' = H, Me, CH=NR', R' = H, Me and R=alkyl, aryl or amino group). The various complexes proved to have different stabilities under hydrogenation conditions. Pd-(C₅H₄N-(C(H)=N(CH₂)₂OH-2)(dmfu) gave good selectivity for the (Z)-alkene, however it decomposed before the full conversion of the alkyne. In the case of Pd-(C₅H₄N-(C(H)=Ni-Pr)-2)(dmfu) the stability and the selectivity was excellent.

Jackson's (⁵) work was based on the study of five competitive reactions. Phenylacetylene/1-pentyne, phenylacetylene/2-pentyne, 1-phenyl-1-propyne/1-pentyne, 1-phenyl-1-propyne/2-pentyne and 1-pentyne/2-pentyne. Initially the group examined the single systems as references. Their findings were reported to be as follows. The principal product was the alkene and only in the case of very high conversions was the alkane formed in a significant amount. When they moved to the competitive hydrogenation reactions e.g. phenylacetylene/1-pentyne etc. They found that with the exception of the 1-pentyne/2-pentyne couple, which revealed a rate enhancement for both alkynes, the competitive reactions result in a reduction of the hydrogenation rate for both alkynes.

To extend the range of study we chose the following three compounds:

allylbenzene (1)  trans-β-methyl styrene (2)  3-phenyl-1-propyne (3)

4.2: EXPERIMENTAL

Two types of reactions were carried out: (a) Complete reactions, in which the substrate is completely converted to the final hydrogenation product by employing an excess of isotopic hydrogen and sufficient time. (b) Partial reactions in which a deficiency of isotopic hydrogen is employed. The complete reaction allows the final isotopic distribution in the product to be identified. This derives from all the reductive and exchange-labelling processes which introduce isotope into the molecule. The partial reactions on the other hand allow an analysis of reactions which introduce isotope, e.g., isotopic exchange reactions, but which would be unobservable by product analysis alone.
For partial reactions with 5\%Pd/C and 1\%Pd/Al\textsubscript{2}O\textsubscript{3} catalysts the procedure was as follows:

A 10ml capacity Discover pressure tube was charged with the substrate (80\mu l), the catalyst (10mg for 5\%Pd/C or 50mg for 1\%Pd/Al\textsubscript{2}O\textsubscript{3}) and tetrahydrofuran (THF, 1ml) solvent. The resulting reaction mixture was stirred under D\textsubscript{2}-gas for 18h at room temperature. The solution was then filtered to remove catalyst and the solvent removed by passing a stream of N\textsubscript{2} over the surface of the solution. For \textsuperscript{1}H-NMR analysis the substrate was dissolved in 500\mu l of CDCl\textsubscript{3} containing TMS while for \textsuperscript{2}H-NMR analysis the substrate was dissolved in 500\mu l of CHCl\textsubscript{3}. The NMR analysis was undertaken using the Bruker 500MHz spectrometer using standard conditions.

For the reactions with 5\%Pd/C and 1\%Pd/Al\textsubscript{2}O\textsubscript{3} catalysts using DT gas the procedure was as follows:

Sodium hydroxide (100mg, 1 pellet) was dissolved in 20ml of D\textsubscript{2}O to which 155.5mg of NaBD\textsubscript{4} was added. An aliquot (10ml) of this solution was then used to dissolve the NaBT\textsubscript{4}. This produced 10ml of NaBD(T\textsubscript{4}) solution, aliquots of which (ca. 0.5ml) were then used for each reaction.

A 10 ml capacity Discover pressure tube was charged with the substrate (20-80mg), the catalyst (10mg for 5\%Pd/C or 50mg for 1\%Pd/Al\textsubscript{2}O\textsubscript{3}) and THF (1ml) solvent and sealed with a hydrogen-tight septum. After evacuation, flushing with nitrogen and re-evacuation, DT gas (9ml which was produced by the reaction of the 0.5ml of NaBD(T\textsubscript{4}) with the deuterated acetic acid existing in a mixture of CHCl\textsubscript{3}/ Toluene in the burette) was introduced from the burette. The resulting reaction mixture was stirred for 24h at room temperature. The solution was then filtered to remove the catalyst and the solvent removed by passing a stream of N\textsubscript{2} gas over the surface of the solution. For \textsuperscript{1}H NMR and proton-decoupled \textsuperscript{3}H NMR analysis the substrate was dissolved in 500\mu l of CDCl\textsubscript{3} containing TMS. The NMR analysis was undertaken using a Bruker 500MHz spectrometer using the standard conditions developed in our laboratories.
The equipment that was used for this work was:

- An in-house hydrogen/deuterium distribution manifold based upon SSI stainless steel valves
- An in-house deuterium/tritium distribution manifold based upon SSI stainless steel valves

- Discover pressure tubes (9cm length, 2cm diameter)
4.3: RESULTS AND DISCUSSION.

The experimental details are given in Table 4.1 and the NMR spectra (\(^1\)H of reactant, \(^1\)H of product(s), \(^2\)H (\(^1\)H decoupled) of product(s) and \(^3\)H (\(^1\)H decoupled) of product(s) are given in Figures 4.1-4.12).

Table 4.1: Experimental details.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Run no</th>
<th>Volume of substrate (μl)</th>
<th>Catalyst</th>
<th>Weight of catalyst (mg)</th>
<th>NMR spectra</th>
<th>Radioactivity (MBq)</th>
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<tr>
<td>1</td>
<td>1</td>
<td>20</td>
<td>5%Pd/C</td>
<td>10</td>
<td>4.1 (a-c)</td>
<td>10.6</td>
</tr>
<tr>
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<td>2</td>
<td>20</td>
<td>5%Pd/C</td>
<td>10</td>
<td>4.2 (a-c)</td>
<td>7.1</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>20</td>
<td>5%Pd/C</td>
<td>10</td>
<td>4.3 (a-c)</td>
<td>19.2</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>20</td>
<td>1%Pd/Al(_2)O(_3)</td>
<td>50</td>
<td>4.4 (a-c)</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>20</td>
<td>1%Pd/Al(_2)O(_3)</td>
<td>50</td>
<td>4.5 (a-c)</td>
<td>18.2</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>20</td>
<td>1%Pd/Al(_2)O(_3)</td>
<td>50</td>
<td>4.6 (a-c)</td>
<td>19.4</td>
</tr>
<tr>
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<td>7</td>
<td>80</td>
<td>5%Pd/C</td>
<td>10</td>
<td>4.7 (a-d)</td>
<td>11.6</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>80</td>
<td>5%Pd/C</td>
<td>10</td>
<td>4.8 (a-d)</td>
<td>30.5</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>80</td>
<td>5%Pd/C</td>
<td>10</td>
<td>4.9 (a-d)</td>
<td>21.3</td>
</tr>
<tr>
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<td>10</td>
<td>80</td>
<td>1%Pd/Al(_2)O(_3)</td>
<td>50</td>
<td>4.10 (a-d)</td>
<td>9.9</td>
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<td>80</td>
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<td>50</td>
<td>4.11 (a-d)</td>
<td>19.7</td>
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<tr>
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<td>1%Pd/Al(_2)O(_3)</td>
<td>50</td>
<td>4.12 (a-d)</td>
<td>9.6</td>
</tr>
</tbody>
</table>
(Fig: 4.1a): $^1$H NMR spectrum of allyl benzene in CDCl$_3$ solvent (500MHz instrument).

(Fig: 4.1b): $^1$H NMR spectrum of allyl benzene hydrogenation experiment using DT gas. CDCl$_3$ solvent. (500MHz instrument.).* residual THF

(Fig: 4.1c): $^3$H NMR ($^1$H decoupled) spectrum of allyl benzene hydrogenation experiment using DT gas. CHCl$_3$ solvent. (500MHz instrument).
(Fig: 4.2a): $^1$H NMR spectrum of trans-$\beta$-methyl styrene hydrogenation experiment using DT gas. CHCl$_3$ solvent. (500MHz instrument + cryo-probe.). * residual THF

(Fig: 4.2b): $^1$H NMR spectrum of trans-$\beta$-methyl styrene hydrogenation experiment using DT gas. CDCl$_3$ solvent. (500MHz instrument + cryo-probe.). * residual THF

(Fig: 4.2c): $^3$H NMR ($^1$H decoupled) spectrum of trans-$\beta$-methyl styrene hydrogenation experiment using DT gas. CHCl$_3$ solvent. (500MHz instrument + cryo-probe).
(Fig: 4.3a): $^1$H NMR spectrum of 3-phenyl-1-propyne in CDCl$_3$ solvent. (500MHz instrument).

(Fig: 4.3b): $^1$H NMR spectrum of 3-phenyl-1-propyne hydrogenation experiment using DT gas. CDCl$_3$ solvent. (500MHz instrument.). * residual THF

(Fig: 4.3c): $^3$H NMR ($^1$H decoupled) spectrum of 3-phenyl-1-propyne hydrogenation experiment using DT gas. CHCl$_3$ solvent. (500MHz instrument).
(Fig: 4.4a): $^1$H NMR spectrum of allyl benzene in CDCl$_3$ solvent. (500MHz instrument).

(Fig: 4.4b): $^1$H NMR spectrum of allyl benzene hydrogenation experiment using DT gas. CDCl$_3$ solvent. (500MHz instrument + cryo-probe). * residual THF

(Fig: 4.4c): $^3$H NMR ($^1$H decoupled) spectrum of allyl benzene hydrogenation experiment using DT gas. CHCl$_3$ solvent. (500MHz instrument + cryo-probe).
(Fig: 4.5b): $^1$H NMR spectrum of trans-$\beta$-methyl styrene hydrogenation experiment using DT gas. CDCl$_3$ solvent. (500MHz instrument). * residual THF

(Fig: 4.5c): $^3$H NMR (1'H decoupled) spectrum of trans-$\beta$-methyl styrene hydrogenation experiment using DT gas. CHCl$_3$ solvent. (500MHz instrument).
(Fig: 4.6a): $^1$H NMR spectrum of 3-phenyl-1-propyne in CDCl$_3$ solvent. (500MHz instrument).

(Fig: 4.6b): $^1$H NMR spectrum of 3-phenyl-1-propyne hydrogenation experiment using DT gas. CDCl$_3$ solvent. (500MHz instrument.). * residual THF

(Fig: 4.6c): $^1$H NMR ($^1$H decoupled) spectrum of 3-phenyl-1-propyne hydrogenation experiment using DT gas. CHCl$_3$ solvent. (500MHz instrument).
(Fig: 4.7a): $^1$H NMR spectrum of allyl benzene in CDCl$_3$ solvent.. (500MHz instrument).

(Fig: 4.7b): $^1$H NMR spectrum of allyl benzene hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent. (500MHz instrument).

(Fig: 4.7c): $^2$H NMR ($^1$H decoupled) spectrum of allyl benzene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent. (500MHz instrument).

(Fig: 4.7d): $^3$H NMR ($^1$H decoupled) spectrum of allyl benzene hydrogenation experiment using DT gas. CHCl$_3$ solvent. (500MHz instrument + cryo-probe).
(Fig: 4.8a): $^1$H NMR spectrum of trans-$\beta$-methyl styrene in CDCl$_3$ solvent. (500MHz instrument).

(Fig: 4.8b): $^1$H NMR spectrum of trans-$\beta$-methyl styrene hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent. (500MHz instrument).

(Fig: 4.8c): $^2$H NMR ($^1$H decoupled) spectrum of trans-$\beta$-methyl styrene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent. (500MHz instrument).

(Fig: 4.8d): $^3$H NMR ($^1$H decoupled) spectrum of trans-$\beta$-methyl styrene hydrogenation experiment using DT gas. CHCl$_3$ solvent. (500MHz instrument + cryo-probe).
(Fig: 4.9a): $^1$H NMR spectrum of 3-phenyl-1-propyne in CDCl$_3$ solvent. (500MHz instrument).

(Fig: 4.9b): $^1$H NMR spectrum of 3-phenyl-1-propyne hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent. (500MHz instrument.).

(Fig: 4.9c): $^2$H NMR ($^1$H decoupled) spectrum of 3-phenyl-1-propyne hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent. (500MHz instrument).

(Fig: 4.9d): $^3$H NMR ($^1$H decoupled) spectrum of 3-phenyl-1-propyne hydrogenation experiment using DT gas. CHCl$_3$ solvent. (500MHz instrument).
(Fig: 4.10a): $^1$H NMR spectrum of allyl benzene in CDCl$_3$ solvent. (500MHz instrument).

(Fig: 4.10b): $^1$H NMR spectrum of allyl benzene hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent. (500MHz instrument.)

(Fig: 4.10c): $^2$H NMR ($^1$H decoupled) spectrum of allyl benzene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent. (500MHz instrument).

(Fig: 4.10d): $^3$H NMR ($^1$H decoupled) spectrum of allyl benzene hydrogenation experiment using DT gas. CHCl$_3$ solvent. (500MHz instrument + cryo-probe)
(Fig: 5.1b): $^1$H NMR spectrum of trans-β-methyl styrene hydrogenation experiment using D$_2$ gas. CDC$_3$ solvent. (500MHz instrument).

(Fig: 4.1c): $^1$H NMR ($^1$H decoupled) spectrum of trans-β-methyl styrene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent. (500MHz instrument).

(Fig: 4.1d): $^3$H NMR ($^1$H decoupled) spectrum of trans-β-methyl styrene hydrogenation experiment using DT gas. CHCl$_3$ solvent. (500MHz instrument + cryo-probe).
(Fig: 4.12a): $^1$H NMR spectrum of 3-phenyl-1-propyne in CDCl$_3$ solvent. (500MHz instrument).

(Fig: 4.12b): $^1$H NMR spectrum of 3-phenyl-1-propyne hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent. (500MHz instrument.).

(Fig: 4.12c): $^2$H NMR ($^1$H decoupled) spectrum of 3-phenyl-1-propyne hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent. (500MHz instrument).

(Fig: 4.12d): $^3$H NMR ($^1$H decoupled) spectrum of 3-phenyl-1-propyne hydrogenation experiment using DT gas. CHCl$_3$ solvent. (500MHz instrument + cryo-probe).
When allylbenzene (1) is fully hydrogenated uneven addition of isotope across the double bond takes place with both catalysts (Figs 4.1c and 4.4c). This suggests that some hydrogen-tritium exchange is taking place at the same time as the hydrogenation occurs. In addition some exchange at the benzylic position (δ=2.6 p.p.m) also occurs. The behaviour of the two catalysts is very similar although the small signal at δ=1.9 p.p.m is absent when the 1%Pd/Al₂O₃ catalyst is used.

When only partial hydrogenation is possible the ²H (Figs 4.7c and 4.10c) and ³H (Figs 4.7d and 4.10d) spectra contain extra signals which come about as a result of H/T or H/D exchange. With DT as our isotope source we must remember that with our specific activity (in the mCi/mmol ratio than Ci/mmol) most of the molecules will be made up of DH and only a trace of DT. This means that the tritiated product will be made of many isotopomers each containing one tritium. Thus from Fig 4.4c we have

\[
\begin{align*}
R-\text{CH}_2\text{-CH}_2\text{-CH}_2\text{T} \\
R-\text{CH}_2\text{-CHT-CH}_3 \\
R-\text{CHT-CH}_2\text{-CH}_3 \text{ etc... seen as } R\text{-CHT-CHT-CH}_2\text{T} \\
&2.6 \quad 1.6 \quad 0.9 \text{ p.p.m}
\end{align*}
\]

Similarly from Fig 4.7d we have, in addition to the above hydrogenation isotopomers, the following reactant isotopomers

\[
\begin{align*}
R-\text{CH}_2\text{-CH=CHT} \\
R-\text{CH}_2\text{-CH=CTH} \\
R-\text{CH}_2\text{-CT=CHT} \\
R-\text{CH}_2\text{-CT=CH}_2 \text{ etc.... seen as } R\text{-CH}_2\text{-CT=CT}_2 \\
&6 \quad 5 \text{ p.p.m}
\end{align*}
\]

With more time it would have been interesting to carry out radiochromatographic separation of the products/reactants as these are less volatile than pentenes/pentyynes studied previously.

The hope was that the 1%Pd/Al₂O₃ catalyst would turn out to be more selective than the Pd/C catalyst and there is some support for this in the present
results. The small signals at $\delta = 5.97$ and $6.45$ p.p.m (clearer in Figs 4.7c than 4.7d) are thought to arise from the double bond migration of the reactant to give the product

$$ R-\text{CH}=\text{CH}-\text{CH}_3 $$

$$ 6.45 \quad 5.97 \quad 2 \text{ p.p.m} $$

But these are absent (Figs 4.10c and 4.10d) for the $1\%\text{Pd/Al}_2\text{O}_3$ catalyst. In addition the signal at $\delta = 2$ p.p.m is of much lower intensity for this catalyst.

The results for trans-$\beta$-methylstyrene (2) (Figs 4.2c and 4.5c) again show that the $1\%\text{Pd/Al}_2\text{O}_3$ catalyst give a cleaner product (absence of signal at $\delta = 0.9$ p.p.m) and this behaviour is again witnessed in the case of 3-phenyl-1-propyne hydrogenation (compare Fig 4.3c and 4.6c) where the reason for the difference of isotope distribution is due to the fact that except from hydrogenation there is also hydrogen-deuterium exchange taking place. The partial hydrogenation results for 3-phenyl-1-propyne for both catalysts (compare Figs 4.9d and 4.12d) are also very similar and highlight a very important point, namely that the pattern of labelling in hydrogenation reactions can be varied widely and that this may represent a splendid opportunity when synthetic procedures can be difficult and time consuming.

Overall, the results obtained with all the substrates are consistent with the expected cis-addition of deuterium during hydrogenation. However, significant isotopic exchange and/or isomerisation takes place with some substrates, especially with the 5% palladium on carbon catalyst. The results obtained for the JM palladium on alumina catalyst show signs of greater selectivity, with less isotope exchange and isomerisation.
4.4: REFERENCES

CHAPTER 5:
DEVELOPMENT AND APPLICATION OF A TRITIUM CRYO-PROBE
5.1: INTRODUCTION

Nuclear magnetic resonance spectroscopy (NMR) is probably the single most important technique as far as the research chemist is concerned. Provided the nuclide in question has a non-zero spin it can be detected by NMR spectroscopy. However, each nuclide has its own sensitivity (See Table 5.1 for the NMR properties of isotopes of the more common elements). Here one can see that tritium ($^3$H or T) is even more detectable than protium. In fact it is the most sensitive of all NMR active nuclei. This would suggest that $^3$H NMR spectroscopy would be widely used, but apart from the major pharmaceutical companies and a small number of academic centres specialising in tritium chemistry this is not the case. The reason for this is that tritium is radioactive and few groups possess expertise in (and facilities for) both NMR-spectroscopy and radiochemistry. The situation is unfortunate since tritium is one of the least hazardous radionuclides, emitting very weak $\beta^-$-particles. Their energy is such that no special shielding is necessary for work with the isotope.

Table 5.1: Nuclear properties of some important isotopes

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Natural abundance</th>
<th>Nuclear spin</th>
<th>Resonance frequency (MHz at 2.114T)</th>
<th>Relative sensitivity (for equal number of nuclei at constant field)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H</td>
<td>99.984%</td>
<td>$\frac{1}{2}$</td>
<td>90</td>
<td>1</td>
</tr>
<tr>
<td>$^2$H(D)</td>
<td>0.0156%</td>
<td>1</td>
<td>13.8</td>
<td>9.65X$10^{-3}$</td>
</tr>
<tr>
<td>$^3$H(T)</td>
<td>&lt;10$^{-16}$</td>
<td>$\frac{1}{2}$</td>
<td>96</td>
<td>1.21</td>
</tr>
<tr>
<td>$^{12}$C</td>
<td>98.89</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$^{13}$C</td>
<td>1.11</td>
<td>$\frac{1}{2}$</td>
<td>22.6</td>
<td>1.59X$10^{-2}$</td>
</tr>
<tr>
<td>$^{14}$C</td>
<td>&lt;10$^{-10}$</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$^{14}$N</td>
<td>99.63</td>
<td>1</td>
<td>6.5</td>
<td>1.01X$10^{-3}$</td>
</tr>
<tr>
<td>$^{15}$N</td>
<td>0.37</td>
<td>$\frac{1}{2}$</td>
<td>9.12</td>
<td>1.04X$10^{-3}$</td>
</tr>
<tr>
<td>$^{16}$O</td>
<td>99.76</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$^{17}$O</td>
<td>0.037</td>
<td>$\frac{5}{2}$</td>
<td>12.2</td>
<td>2.91X$10^{-2}$</td>
</tr>
<tr>
<td>$^{18}$O</td>
<td>0.20</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

When we review the various NMR spectrometers that have been used to obtain $^3$H NMR spectra at Surrey (Table 5.2) over the last forty years we see that much improvement in the magnet design has taken place, with much higher fields now available. This means that less radioactivity is required to obtain
satisfactory spectra, as measured by a good signal (S) to noise (N) ratio. This has been particularly important for a radioactive nucleus such as tritium. Nevertheless the quantity of radioactivity required (25$\rightarrow$ 1mCi) for a useable NMR spectrum is still considerably higher than the amounts required for liquid scintillation counting (less than 1μCi). This simply reflects the fact that NMR spectroscopy in general is not a particularly sensitive technique.

Table 5.2: Various $^3$H NMR Spectrometers used at Surrey

<table>
<thead>
<tr>
<th>Year</th>
<th>Details</th>
<th>Frequency (MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1968-69</td>
<td>Perkin Elmer R10</td>
<td>64</td>
</tr>
<tr>
<td>1970-88</td>
<td>Bruker WH 90</td>
<td>96</td>
</tr>
<tr>
<td>1988-present</td>
<td>Bruker AC 300</td>
<td>320</td>
</tr>
<tr>
<td>1997-present</td>
<td>Bruker DRX 500</td>
<td>533.5</td>
</tr>
</tbody>
</table>

Although the information for a direct comparison of the sensitivity of these instruments is unavailable, there is no doubt that improvements in magnet design over the last forty years have led to the production of NMR spectrometers that operate at much higher magnetic fields and which are considerably more sensitive. One estimate suggests that there has been as much as three orders of magnitudes improvement in sensitivity. This however has not been brought about without a corresponding increase in cost. A new 500MHz NMR spectrometer would cost in the region of £400K whilst an 800MHz instrument would be in the region of £700K making it too expensive for many small chemistry departments. An alternative strategy was therefore adopted at the University of Surrey. Instead of seeking ever-increasing field strength and hence higher sensitivity, new technological developments made it possible to seek a reduction in the background noise in the detector via cryonic technology. An investment was therefore made in a cryo-probe at a cost of ~ £90k. This therefore represents excellent value for money.

Bruker have been at the forefront of cryo-probe development\(^{(1)}\). Cooling the RF coils of a probe to cryogenic temperatures improves the RF efficiency and reduces the noise generated by the coils. Further improvements can be achieved if the pre-amplifier is also cooled to cryogenic temperatures, as in this way the thermal noise generated in the circuit is reduced. These objectives, despite the formidable challenges presented by the need to keep the sample temperature stable at close to room temperature, whilst the RF coils nearby, are cooled to below 35K, have now
been achieved \(^{1}\). Results are available for \(^1\)H\(^{2-3}\) and a preliminary study with \(^3\)H has also been reported \(^{4}\). In this last case a tritiated sample of ortho-
methoxyacetophenone \((o{-}\text{MeO}-C_6H_4\text{COCH}_2\text{T})\) was prepared by a base-catalysed hydrogen-isotope exchange procedure. Four solutions, containing 165, 15, 2.5 and 0.4MBq (where 1Bq = 2.7x10\(^{-11}\)Ci) of radioactivity were made up in CDCl\(_3\) solution. Each sample was then run on the following instruments using a 16h accumulation time using standard analytical conditions in each case:

(a) Bruker AC-300 spectrometer with a 5mm dual proton/tritium probe for tritium observation at 330.13 MHz.

(b) Bruker DRX-500 spectrometer with the 5mm leak proof selective excitation proton/tritium probe for tritium observation at 533.5 MHz.

(c) Bruker DRX-500 spectrometer with the 5mm selective excitation proton/tritium cryo-probe for tritium observation at 533.5 MHz.

The results obtained are summarised in Table 5.3

Table 5.3: Improvements in signal-to-noise ratio from using the tritium cryo-probe.

<table>
<thead>
<tr>
<th>Sample number</th>
<th>Radioactivity (MBq)</th>
<th>Radioactivity (μCi)</th>
<th>S/N Ratios</th>
<th>AC-300</th>
<th>DRX-500</th>
<th>DRX500*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>165</td>
<td>4460</td>
<td></td>
<td>910</td>
<td>2230</td>
<td>7350</td>
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<tr>
<td>2</td>
<td>15</td>
<td>405</td>
<td></td>
<td>55</td>
<td>170</td>
<td>870</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>68</td>
<td></td>
<td>12</td>
<td>32</td>
<td>147</td>
</tr>
<tr>
<td>4</td>
<td>0.4</td>
<td>11</td>
<td></td>
<td>-</td>
<td>-</td>
<td>21</td>
</tr>
</tbody>
</table>

* + Cryo-probe

The improvement in S/N using the cryo-probe was 4.3 ±0.7 as mentioned previously, which equates to close on a 20-fold saving in time. With the tritium located specifically in the methyl position a sharp singlet is obtained. However in most labelled compounds the tritium may well be located in several molecular positions and it is in this area that the use of the cryo-probe could prove most useful since it should be possible to detect weak signals. For these reasons we carried out partial catalytic hydrogenations of four substrates using low specific activity deuterium tritide gas over two different catalysts.
1-phenyl-1-propyne (1)  trans-β-methyl styrene (2)  allyl benzene (3)

3-phenyl-1-propyne (4)

5.2: EXPERIMENTAL

The experimental procedure is similar to the one described in Chapter 4 and the equipment used is also the same.

5.3: RESULTS AND DISCUSSION

The experimental details are given in Table 5.4 and the NMR spectra ($^3$H ($^1$H decoupled) of product(s) using the $^1$H/$^3$H probe and the $^1$H/$^3$H cryo-probe are given in Figures 5.1-5.12).

Table 5.4: Experimental details.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Volume of substrate (μl)</th>
<th>Catalyst</th>
<th>Weight of catalyst (mg)</th>
<th>NMR spectra</th>
<th>Radioactivity (MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>5%Pd/C</td>
<td>10</td>
<td>5.1 (a-b)</td>
<td>9.5</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>5%Pd/C</td>
<td>10</td>
<td>5.2 (a-b)</td>
<td>7.1</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>5%Pd/C</td>
<td>10</td>
<td>5.3 (a-b)</td>
<td>10.6</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>1%Pd/Al₂O₃</td>
<td>50</td>
<td>5.4 (a-b)</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>1%Pd/Al₂O₃</td>
<td>50</td>
<td>5.5 (a-b)</td>
<td>9.9</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>1%Pd/Al₂O₃</td>
<td>50</td>
<td>5.6 (a-b)</td>
<td>9.6</td>
</tr>
</tbody>
</table>
(Fig 5.1a): $^3$H NMR ($^1$H decoupled) of 1-phenyl-1-propyne hydrogenation experiment using DT gas. CDCl$_3$ solvent, (500MHz instrument).

(Fig 5.1b): $^3$H NMR ($^1$H decoupled) of 1-phenyl-1-propyne hydrogenation experiment using DT gas. CDCl$_3$ solvent, (500MHz instrument & cryo-probe).
(Fig 5.2a): $^3$H NMR ($^1$H decoupled) of *trans*-β-methyl styrene hydrogenation experiment using DT gas. CDCl$_3$ solvent, (500MHz instrument).

(Fig 5.2b): $^3$H NMR ($^1$H decoupled) of *trans*-β-methyl styrene hydrogenation experiment using DT gas. CDCl$_3$ solvent, (500MHz instrument & cryo-probe).
(Fig 5.3a): $^3$H NMR ($^1$H decoupled) of allylbenzene hydrogenation experiment using DT gas. CDCl$_3$ solvent (500MHz instrument).

(Fig 5.3b): $^3$H NMR ($^1$H decoupled) of allylbenzene hydrogenation experiment using DT gas. CDCl$_3$ solvent (500MHz instrument & cryo-probe).
(Fig 5.4a): $^3$H NMR ($^1$H decoupled) of allylbenzene hydrogenation experiment using DT gas. CDCl$_3$ solvent, (500MHz instrument).

(Fig 5.4b): $^3$H NMR ($^1$H decoupled) of allylbenzene hydrogenation experiment using DT gas. CDCl$_3$ solvent, (500MHz instrument & cryo-probe).
(Fig 5.5a): $^3$H NMR ($^1$H decoupled) of allylbenzene hydrogenation experiment using DT gas. CDCl$_3$ solvent, (500MHz instrument).

(Fig 5.5b): $^3$H NMR ($^1$H decoupled) of allylbenzene hydrogenation experiment using DT gas. CDCl$_3$ solvent, (500MHz instrument & cryo-probe).
(Fig 5.6a): $^3$H NMR ($^1$H decoupled) of 3-phenyl-1-propyne hydrogenation experiment using DT gas. CDCl$_3$ solvent, (500MHz instrument).

(Fig 5.6b): $^3$H NMR ($^1$H decoupled) of 3-phenyl-1-propyne hydrogenation experiment using DT gas. CDCl$_3$ solvent, (500MHz instrument & cryo-probe).
The $^3$H NMR spectra ($^1$H-decoupled) of the four tritiated compounds are given in Figures 5.1-5.6. In each case we can compare the results obtained on the Bruker DRX 500 spectrometer both with and without the cryo-probe. The signal assignments have been given in Chapter 4 and the time used to acquire the spectra (12h) was the same in each case. In some cases weak signals e.g at $\delta=0.9$ p.p.m in Fig 5.1a become more visible when the cryo-probe is used. In Fig 5.6b there are two weak signals at $\delta=0.9, 1.6$ p.p.m that are not visible without the use of the cryo-probe.

Until recently the signal (S) to noise (N) ratio was calculated manually but with the development of new computer software this can be done automatically. To take a specific example (Fig 5.7), the S/N ratio for signal A is 26.5 when the cryo-probe was used but only 5.3 in its absence, giving an enhancement of 5. For signal B the improvement was 6.4 and for signal C, 5.97. The overall improvement was 5.8. For the six spectra the enhancements are summarised (Table 5.5). The mean value, $4.3\pm 1.1$ is the same as that observed for the tritiated acetophenone previously although the standard deviation ($\pm 1.1$ compared with $\pm 0.7$) is somewhat higher.

(Fig 5.7): $^3$H NMR ($^1$H decoupled) of allylbenzene hydrogenation experiment using DT gas. CDCl$_3$ solvent (500MHz instrument and 500MHz instrument & cryo-probe)
Table 5.5: Signal to noise enhancement from using the cryo-probe

<table>
<thead>
<tr>
<th>3H NMR spectra</th>
<th>S/N Enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1a-b</td>
<td>2.8</td>
</tr>
<tr>
<td>5.2a-b</td>
<td>3.7</td>
</tr>
<tr>
<td>5.3a-b</td>
<td>2.7</td>
</tr>
<tr>
<td>5.4a-b</td>
<td>5.6</td>
</tr>
<tr>
<td>5.5a-b</td>
<td>5.4</td>
</tr>
<tr>
<td>5.6a-b</td>
<td>5.8</td>
</tr>
<tr>
<td><strong>Average value</strong></td>
<td><strong>4.3 ±1.1</strong></td>
</tr>
</tbody>
</table>

In the early days of 3H NMR spectroscopy 10mCi samples were used in an NMR spectrometer operating at 64 MHz. Now we can use 11μCi in an NMR spectrometer operating at 533.5MHz but with a cryo-probe accessory. In both cases overnight accumulation was necessary. This 1000-fold improvement in sensitivity (over 40 years) still leaves us using much higher levels of radioactivity than are used in liquid scintillation counting. Since the natural abundance level of tritium is <10⁻¹⁶% the potential for further improvements in detectability via increase in sensitivity or reduction in noise is enormous. With this potential, many benefits are likely to emerge and hence it is worth looking at such possibilities.

For the chemist making analytical measurements the customary attitude to noise is that it should be minimised whenever possible in order to detect the signal(s). This is usually referred to as passive signal processing. The limit of detection (LOD) is defined as three times the average noise level and the limit of quantitation (LOQ) is ten times the average noise level. When S≈N the signal cannot be distinguished from the noise (background).

The development of computer technology has played a big part in many areas of chemistry, not least instrumentation. It now looks as if sensitivity of many instruments can be dramatically improved through the development of active signal processing (ASP), based on quantum resonance interferometry (QRI), which can detect weak signals, in some cases more than four orders of magnitude less than the background noise. The signal is now detected as a disturbance to the noise rather than filtering out the noise, as is done in all passive signal processing. So far ASP has only been used for the analysis of DNA arrays but its potential in other areas...
has been anticipated. How long it will be before $^3$H NMR spectroscopy and other techniques can benefit from this development is uncertain at this time but as mentioned before the potential benefits are enormous for this isotope.
5.3 REFERENCES


CHAPTER 6:

SOME FURTHER EXAMPLES OF TERMINAL METHYLENE HYDROGEN ISOTOPE EXCHANGE
**6.1: INTRODUCTION**

In some of the earlier work presented in this thesis (see Chapter 4) it was clear that the process of hydrogenation was accompanied by hydrogen isotope exchange. It was therefore of some interest to see whether this second reaction could also be observed in a wider range of substrates and it is these results which feature in the present chapter. One of the early reported investigations (1, 2) was concerned with the hydrogenation of styrene (1) using a range of catalysts, both homogeneous and heterogeneous. Uneven addition of tritium across the double bond was observed as revealed in the $^3$H NMR spectrum. Some of the results obtained using different catalysts are summarised in Table 6.1.

![Scheme 6.1](image)

**Scheme 6.1**

Table 6.1: Tritium distribution (relative %) in ethyl benzene and styrene using different catalysts

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Relative tritium distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ethyl benzene</td>
</tr>
<tr>
<td></td>
<td>(a)</td>
</tr>
<tr>
<td>5% Pd/C</td>
<td>23</td>
</tr>
<tr>
<td>5% Pt/C</td>
<td>54</td>
</tr>
<tr>
<td>5% Pt/Al$_2$O$_3$</td>
<td>28</td>
</tr>
<tr>
<td>5% Rh/C</td>
<td>48</td>
</tr>
<tr>
<td>Raney Nickel</td>
<td>62</td>
</tr>
<tr>
<td>5% Ru/C</td>
<td>37</td>
</tr>
</tbody>
</table>
In the case of the ethyl benzene product (2) the ratio of the methyl to methylene labelling was in the range 2-4.6. By employing a lower amount of T₂ gas so that complete saturation of the double bond was not possible analysis of the unreacted starting material shows that hydrogen isotope exchange also takes place with formation of species such as (3) and (4). This therefore explains the uneven addition across the double bond observed for (2). It is now clear that there are two reactions – hydrogen isotope exchange and reduction - taking place. This is a very interesting observation since the reactions have the useful benefit of increasing the maximum specific activity that can be obtained in reduction processes when such catalysts are used. The introduction of two tritium atoms can give a maximum specific activity of ca. 56 Ci/mmol whereas three will give ca. 84 Ci/mmol. The observation also holds out the prospect of labelling alkenes by exchange under conditions where complete reduction is not possible. In the case of Raney-Ni hydrogen/isotope exchange is less important than for the other catalysts (Table 6.1). One homogeneous catalyst (Wilkinson’s) has also been used and similar observations were made. As the concentration of catalyst was increased the labelling became more symmetric.

\[
\begin{align*}
(3) & \quad \text{H} & \quad \text{T} & \quad \text{Ph} & \quad \text{H} \\
(4) & \quad \text{H} & \quad \text{H} & \quad \text{Ph} & \quad \text{T}
\end{align*}
\]

In both the heterogeneous and homogeneous studies H₂:T₂ mixtures in the ratio 10:1 (v/v) were used. When the rate of the gas exchange reaction

\[
\text{H}_2 + \text{T}_2 \rightarrow 2\text{HT}
\]

is fast the \(^3\text{H}\) NMR spectrum should not show any sign of T-T coupling and this indeed was the case for all the heterogeneous catalysts but this was not so for the Wilkinson catalyst, suggesting, quite reasonably, that the exchange reaction was much slower under these homogeneous conditions.

In a somewhat similar study Tang et al. studied the hydrogenation of 2-acetamidocinnamic acid (5) using T₂ gas to give N-acetyl [2, 3-\(^3\text{H}\)] phenylalanine (6).
Very even addition across the double bond occurred with the relative intensities of the methylene and methine signals being in the ratio of 54:46 and the specific activity 60 Ci/mmol. In sharp contrast to these results the reduction of 2-acetamidoacrylic acid (7) to give N-acetyl [2, 3-$^3$H] alanine (8) gave 95% of the tritium at the methyl position and only 5% at the methine position. The specific activity of the product was now 85 Ci/mmol, the theoretical maximum for the complete addition of three tritium atoms. The $^3$H NMR ($^1$H decoupled) spectrum revealed multiple signals caused by the primary isotope effects CT$_3$ (δ 1.33), CT$_2$H (δ 1.35), CTH$_2$ (δ 1.37) and by tritium-tritium coupling CT$_3$-CT (δ 1.28, 1.35). When deliberate under-reduction experiments were performed two additional tritium signals appeared, consistent with a tritium-hydrogen exchange process. Radio-gas chromatography on a series of styrene–type compounds also served to confirm the importance of vinylic exchange in these reduction reactions.

More recently Ursine et al (4) have reported their findings on the solid state catalytic hydrogenation of alkyl and alkyl benzenes:
Scheme 6.4
This is a reaction that has been developed and used by Myasaedov \(^5\) and colleagues to synthesise a whole range of highly tritiated compounds. The nature of the metal as well as the support, the reaction temperature and the ratio of the substrate to catalyst all influence the degree of conversion. The study was hampered by the facts that no direct measurement of the isotopic distribution was made. The authors relied on \(^1\)H NMR spectroscopy to see if any decrease in the \(^1\)H signals occurred. Nevertheless it was clear that once again hydrogen isotope exchange accompanied the reduction process.

To extend the range of the study we chose the following five compounds:

- Allyl phenylether (11)
- 4-Allylanisole (12)
- 4-Allyl-1,2-dimethoxybenzene (13)
- Allyl butyrate (14)
- Allylurea (15)
6.2: EXPERIMENTAL

For partial reactions with 5%Pd/C and 1%Pd/Al$_2$O$_3$ catalyst the procedure was as follows:

A 10ml capacity Discover pressure tube was charged with the substrate (80-360μl), the catalyst (10mg for 5%Pd/C or 50mg for 1%Pd/Al$_2$O$_3$) and THF (1ml) solvent. The resulting reaction mixture was stirred under D$_2$-gas for 18h at room temperature. The solution was then filtered to remove catalyst and the solvent removed by passing a stream of N$_2$ over the surface of the solution. For $^1$H-NMR analysis the substrate was dissolved in 500μl of CDCl$_3$ containing TMS while for $^2$H-NMR analysis the substrate was dissolved in 500μl of CHCl$_3$. The NMR analysis was undertaken using the Bruker 300MHz and 500MHz spectrometers using standard conditions.

The equipment that was used for this work was:

- An in-house hydrogen/deuterium distribution manifold based upon SSI stainless steel valves
- Discover pressure tube (9cm length, 2cm diameter)

6.3: RESULTS AND DISCUSSION.

The experimental details are given in Table 6.2 and the NMR spectra ($^1$H of reactant, $^1$H of product(s), $^2$H ($^1$H decoupled) of product(s) are given in Figures 6.1-6.13).

Table 6.2: Experimental details.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Run No</th>
<th>Weight of substrate (mg)</th>
<th>Catalyst</th>
<th>Weight of catalyst (mg)</th>
<th>NMR spectra</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>1</td>
<td>80</td>
<td>5%Pd/C</td>
<td>10</td>
<td>6.1 (a-c)</td>
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<tr>
<td>12</td>
<td>2</td>
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<td>5%Pd/C</td>
<td>10</td>
<td>6.2 (a-c)</td>
</tr>
<tr>
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<td>5%Pd/C</td>
<td>10</td>
<td>6.3 (a-c)</td>
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<tr>
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<td>4</td>
<td>80</td>
<td>5%Pd/C</td>
<td>10</td>
<td>6.4 (a-c)</td>
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<tr>
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<td>6.5 (a-c)</td>
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<tr>
<td>11</td>
<td>6</td>
<td>80</td>
<td>1%Pd/Al$_2$O$_3$</td>
<td>50</td>
<td>6.6 (a-c)</td>
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<tr>
<td>12</td>
<td>7</td>
<td>80</td>
<td>1%Pd/Al$_2$O$_3$</td>
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<td>6.7 (a-c)</td>
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<tr>
<td>13</td>
<td>8</td>
<td>80</td>
<td>1%Pd/Al$_2$O$_3$</td>
<td>50</td>
<td>6.8 (a-c)</td>
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<tr>
<td>14</td>
<td>9</td>
<td>80</td>
<td>1%Pd/Al$_2$O$_3$</td>
<td>50</td>
<td>6.9 (a-c)</td>
</tr>
<tr>
<td>15</td>
<td>10</td>
<td>80</td>
<td>1%Pd/Al$_2$O$_3$</td>
<td>50</td>
<td>6.10 (a-c)</td>
</tr>
<tr>
<td>14</td>
<td>11</td>
<td>80</td>
<td>1%Pd/Al$_2$O$_3$</td>
<td>50</td>
<td>6.11 (a-c)</td>
</tr>
<tr>
<td>14</td>
<td>12</td>
<td>160</td>
<td>1%Pd/Al$_2$O$_3$</td>
<td>50</td>
<td>6.12 (a-c)</td>
</tr>
<tr>
<td>14</td>
<td>13</td>
<td>320</td>
<td>1%Pd/Al$_2$O$_3$</td>
<td>50</td>
<td>6.13 (a-c)</td>
</tr>
</tbody>
</table>
(Fig: 6.1a): $^1$H NMR spectrum of allyl phenylether in CDCl$_3$ solvent. (300MHz instrument).

(Fig: 6.1b): $^1$H NMR spectrum of allyl phenylether hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent, (300MHz instrument.).

(Fig: 6.1c): $^2$H NMR ($^1$H decoupled) spectrum of allyl phenylether hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent, (500MHz instrument).
(Fig: 6.2a): $^1$H NMR spectrum of 4-allylanisole in CDCl$_3$ solvent. (300MHz instrument).

(Fig: 6.2b): $^1$H NMR spectrum of 4-allylanisole hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent, (300MHz instrument).

(Fig: 6.2c): $^2$H NMR ($^1$H decoupled) spectrum of 4-allylanisole hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent, (500MHz instrument).
(Fig: 6.3a): $^1$H NMR spectrum of 4-allyl-1,2-dimethoxybenzene in CDCl$_3$ solvent. (300MHz instrument).

(Fig: 6.3b): $^1$H NMR spectrum of 4-allyl-1,2-dimethoxybenzene hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent, (300MHz instrument).

(Fig: 6.3c): $^2$H NMR ($^1$H decoupled) spectrum of 4-allyl-1,2-dimethoxybenzene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent, (500MHz instrument).
(Fig: 6.4a): $^1$H NMR spectrum of allyl butyrate in CDCl$_3$ solvent. (300MHz instrument).

(Fig: 6.4b): $^1$H NMR spectrum of allyl butyrate hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent, (300MHz instrument).

(Fig: 6.4c): $^2$H NMR ($^1$H decoupled) spectrum of allyl butyrate hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent, (500MHz instrument).
(Fig: 6.5a): $^1$H NMR spectrum of allylurea in CDCl$_3$ solvent. (300MHz instrument).

(Fig: 6.5b): $^1$H NMR spectrum of allylurea hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent, (300MHz instrument).

(Fig: 6.5c): $^2$H NMR ($^1$H decoupled) spectrum of allylurea hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent, (500MHz instrument).
(Fig: 6.6a): $^1$H NMR spectrum of allyl phenylether in CDCl$_3$ solvent. (300MHz instrument).

(Fig: 6.6b): $^1$H NMR spectrum of allyl phenylether hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent, (300MHz instrument).

(Fig: 6.6c): $^2$H NMR ($^1$H decoupled) spectrum of allyl phenylether hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent, (500MHz instrument).
(Fig: 6.7a): $^1$H NMR spectrum of 4-allylanisole in CDCl$_3$ solvent. (300MHz instrument).

(Fig: 6.7b): $^1$H NMR spectrum of 4-allylanisole hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent, (300MHz instrument).

(Fig: 6.7c): $^2$H NMR ($^1$H decoupled) spectrum of 4-allylanisole hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent, (500MHz instrument).
(Fig: 6.8a): $^1$H NMR spectrum of 4-allyl-1,2-dimethoxybenzene in CDCl$_3$ solvent. (300MHz instrument).

(Fig: 6.8b): $^1$H NMR spectrum of 4-allyl-1,2-dimethoxybenzene hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent, (300MHz instrument).

(Fig: 6.8c): $^2$H NMR ($^1$H decoupled) spectrum of 4-allyl-1,2-dimethoxybenzene hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent, (500MHz instrument).
(Fig: 6.9a): $^1$H NMR spectrum of allyl butyrate in CDCl$_3$ solvent. (300MHz instrument).

(Fig: 6.9b): $^1$H NMR spectrum of allyl butyrate hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent, (300MHz instrument).

(Fig: 6.9c): $^2$H NMR ($^1$H decoupled) spectrum of allyl butyrate hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent, (500MHz instrument).
(Fig: 6.10a): $^1$H NMR spectrum of allylurea benzene in CDCl$_3$ solvent. (300MHz instrument).

(Fig: 6.10b): $^1$H NMR spectrum of allylurea hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent, (300MHz instrument).

(Fig: 6.10c): $^2$H NMR ($^1$H decoupled) spectrum of allylurea hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent, (500MHz instrument).
(Fig: 6.11a): $^1$H NMR spectrum of allyl butyrate in CDCl$_3$ solvent. (300MHz instrument).

(Fig: 6.11b): $^1$H NMR spectrum of allyl butyrate hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent, (300MHz instrument).

(Fig: 6.11c): $^2$H NMR ($^1$H decoupled) spectrum of allyl butyrate hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent, (500MHz instrument).
(Fig: 6.12a): $^1$H NMR spectrum of allyl butyrate in CDCl$_3$ solvent. (300MHz instrument).

(Fig: 6.12b): $^1$H NMR spectrum of allyl butyrate hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent, (300MHz instrument).

(Fig: 6.12c): $^2$H NMR ($^1$H decoupled) spectrum of allyl butyrate hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent, (500MHz instrument).
(Fig: 6.13a): $^1$H NMR spectrum of allyl butyrate in CDCl$_3$ solvent. (300MHz instrument).

(Fig: 6.13b): $^1$H NMR spectrum of allyl butyrate hydrogenation experiment using D$_2$ gas. CDCl$_3$ solvent, (300MHz instrument).

(Fig: 6.13c): $^2$H NMR spectrum ($^1$H decoupled) of allyl butyrate hydrogenation experiment using D$_2$ gas. CHCl$_3$ solvent, (500MHz instrument).
There are many interesting features to the results. To take the allyl phenyl ether results first we see in Fig 6.1c that there are two large peaks at 1.0 and 1.8 p.p.m. consistent with the formation of the reduced product (16). They are approximately of the same area/integrals. The peak at 7.2 p.p.m. present in all of the $^2$H NMR spectra is due to the solvent. As mentioned previously (Chapter 1) the deuterium signals are much broader than the $^1$H and $^3$H signals and this can be a problem when there are similar chemical shifts.

\[ \text{OCCH_2CHDCH_2D} \]

(16)

There are in Fig 6.1c additional, small signals at 5.0, 5.4 and 5.45 p.p.m., consistent with the formation of compound (17) as a result of hydrogen isotope exchange having taken place. This evidence is stronger in Fig 6.6c where the 1% Pd/Al$_2$O$_3$ catalyst has been employed.

\[ \text{OCH_2CD=CD_2} \]

(17)

two isotopomers

6.03 p.p.m

D. \( \equiv \) D 5.40 p.p.m

R

H

D \( \equiv \) H

R

D 5.45 p.p.m

Comparison of the results for 4-allylanisole (12) and 4-allyl-1,2-dimethoxybenzene (11) shows that they are very similar (Fig 6.2, 6.3). In both cases the deuterium incorporation has been more uneven than was the case for allyl phenyl ether and hydrogen-deuterium exchange more extensive. The deuterium exchange signals are thought to arise from the following isotopomers:
These studies highlight the advantages of $^3$H NMR over $^2$H NMR despite the radioactivity of tritium. In fact the latter can be a distinct advantage as radiochromatography can be used to separate the various species present and hence simplify the NMR spectra.

The results for both allyl butyrate (Fig 6.4) and allylurea (Fig 6.5) again show that extensive isotope exchange has taken place in parallel with the hydrogenation reaction. Comparison of the two catalysts (5% Pd/C & 1% Pd/Al$_2$O$_3$), for compound (11) (Figs 6.1 and 6.6), for compound (12) (Figs 6.2 and 6.7), for compound (14) (Figs 6.3 and 6.8) and for compound (15) (Figs 6.5 and 6.10) shows that there is very little difference in behaviour.

The final part of the study involved an experiment in which the amount of substrate (allyl butyrate) was varied – Figures 6.11-6.13. The addition of deuterium across the double bond takes place fairly evenly and varies little with increasing quantity of substrate. However the amount of hydrogen-deuterium exchange taking place increases with the weight of substrate (Fig 6.14). For the purpose of quantification the deuterium signal for the CH$_2$D group was set at 100% and the two signals at 5.4, 5.5 p.p.m used to calculate the degree of exchange.
We can conclude from this study that the hydrogen isotope exchange at the terminal position of allyl species during their hydrogenation reactions over heterogeneous catalysts is facile and general. In our case no significant differences were observed with the two catalysts. An experiment showed that by increasing the quantity of substrate one could vary the ratio of hydrogenated product to exchanged substrate and that, hence, the reaction of allyl compounds over the palladium catalysts used could be used as a practical method for the labeling of allyl systems with hydrogen isotopes. The method could be of benefit in the labeling of target allyl compounds provided satisfactory chromatographic separation could then be achieved from the saturated sytems. This is usually the case in reversed phase HPLC due to the significant differences in lipophilicity and geometry between the alkane and alkene systems.

Future studies would benefit from being able to withdraw samples at fixed time intervals and obtain the \(^2\text{H}\) NMR spectra rapidly so that the kinetics of the hydrogenation/hydrogen isotope exchange reactions can be investigated in more detail. This is one of the reasons why the development of cryo-probe technology is so important.
6.5 REFERENCES


CHAPTER 7:
OVERALL CONCLUSIONS
In the Chapter 2 I have carried out experimental studies on the deuteriation of a number of pyridine-type compounds based on the previous work from Rubottom and Evain, where 5% Ru/C selectively catalyses hydrogen-deuterium exchange at the \textit{ortho} positions (i.e. \(\alpha\) to N). The reaction takes place at ambient temperature under very mild conditions. Their approach although very attractive it brings the drawback that it cannot be applicable for use with tritium. Keeping that in mind we decided to make a number of changes which included changes in the reaction time, elimination of pressure and change of the reaction solvent form deuterated methanol to THF that will lead to a better understanding of the mechanism and provide improvements which can be of value for the deuteriation and also tritiation of a number of industrial pharmaceutical compounds.

In Chapter 3 I have reported on the hydrogenation of a number of C\(_5\) alkenes and alkynes using D\(_2\) gas and two catalysts (5% Pd/C and a 1% Pd/Al\(_2\)O\(_3\) catalyst developed by Johnson Matthey). The results have been analyzed by \(^1\text{H}\) and \(^2\text{H}\) NMR. Although the C\(_5\) hydrocarbons are simple molecules, their spectroscopic analysis is far from simple. Moreover, they are also liable to give rise to symmetrical intermediates and products during hydrogenation. This makes a complete analysis of such reactions problematic. Our results show that in some cases more selective hydrogenation is observed.

Chapter 4 is essentially a development of the work carried out in Chapter 3 the work on hydrogenation of double bonds tethered to an aryl moiety is presented. Because of the lack of symmetry, these systems are easier to analyse by NMR since the complications associated with the symmetry of the earlier C\(_5\) reaction product (pentane) is removed. Overall, the results obtained with all the substrates are consistent with the expected \textit{cis}-addition of deuterium during hydrogenation. However, significant isotopic exchange and/or isomerisation take place with some substrates, especially with the 5% palladium on carbon catalyst. The results obtained for the JM palladium on alumina catalyst show signs of greater selectivity, with less isotope exchange and isomerisation.

In Chapter 5 I show how, by using a cryo-probe in the NMR spectrometer, the selectivity of \(^3\text{H}\) NMR spectroscopy can be improved by a factor of approximately 4 (equivalent to a saving in time of 16 fold). This has tremendous potential, as the amount of radioactivity required in the future will considerably less than hitherto.
Finally in Chapter 6 I show how extensive hydrogen-deuterium exchange in a number of allyl systems can provide a new labelling procedure that will be of benefit in the labelling of target allyl compounds provided satisfactory chromatographic separation could then be achieved from the saturated systems.
PRESENTATIONS-PAPERS

- 3/10/2005 International Isotope Society (UK group) meeting in Hixton
- 26/10/2005 Surrey University postgraduate symposium
- 28/08/2005 ATHENA (catalysis consortium) presentation Chicago
- 14-17/05/2005 ATHENA (catalysis consortium) presentation Billingham
- 12-15/05/2004 Johnson Matthey symposium in Nottingham
- 02/10/2004 International Isotope Society (UK group) meeting in Hixton
- 3/10/2004 ATHENA (catalysis consortium) presentation Berlin
- 14/10/2004 Surrey University postgraduate symposium
- 08/07/2003 ATHENA (catalysis consortium) presentation Paris
- 12-15/05/2003 Johnson Matthey symposium in Nottingham
- 08/10/2003 ATHENA (catalysis consortium) presentation Sunderland
- one published paper
  “One-step Exchange-labelling of Piperidines, Piperazines and Dialkylamines with Deuterium Oxide: Catalysis by Various Ruthenium Complexes.”
  Efstathios Alexakis\textsuperscript{a}, Michael J. Hickey\textsuperscript{b}, John R. Jones\textsuperscript{a}, Lee P. Kingston\textsuperscript{b}, William J. S. Lockley\textsuperscript{a}, Andrew N. Mather\textsuperscript{b}, Traci Smith\textsuperscript{a} and David J. Wilkinson\textsuperscript{b}. Tetrahedron Letters:
  \textsuperscript{a} School of Biological and Molecular Sciences, University of Surrey, Guildford, Surrey GU2 7XH, UK \textsuperscript{b} AstraZeneca R&D Charnwood, Bakewell Rd, Loughborough, Leics. LE11 5RH,
- one papers in final draft
  “Efficient Deuterium Exchange-Labelling of Pyridines and other Aromatic Nitrogen Heterocyclics using a Deuterium Gas Donor at Room Temperature and Pressure.”
  Department of Chemistry, School of Biological and Molecular Sciences, University of Surrey, Guildford, Surrey GU2 7XH,
One-step Exchange-labelling of Pyridines and other $N$-Heteroaromatics using Deuterium Gas: Catalysis by Heterogeneous Rhodium and Ruthenium Catalysts.

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Department of Chemistry, School of Biological and Molecular Sciences, University of Surrey, Guildford, Surrey GU2 7XH, UK.

Abstract

A wide range of pyridines and other nitrogen heteroaromatics can be labelled with deuterium at room temperature and pressure by isotopic exchange with deuterium gas in THF in the presence of ruthenium black, rhodium black or 5% rhodium on alumina. The labelling is rapid, isotope efficient and applicable to both electron-rich and poor substrates. In a few cases a degree of reduction accompanies the exchange.

Keywords: pyridine, N-heteroaromatic, a-exchange, deuteration, ruthenium black, rhodium black, rhodium on alumina, isotope-exchange, deuterium gas.

Pyridine and other $N$-heteroaromatic sub-units occur in many industrially important chemicals including a range of agrochemical and pharmaceutical agents. Methods for labelling these units with isotopes of hydrogen are therefore of interest since they provide routes to the tritium-labelled compounds for use in environmental, disposition and other ADMET radiotracer studies. They also provide access to the deuterium-labelled compounds for use in stable-isotope tracer studies or for GC-MS or LC-MS internal standardisation.

Methods for labelling such $N$-heterocyclics via isotopic exchange are often quite limited. Many involve a requirement for a directing group within the labelling substrate, to facilitate ortho-labelling or of some other activating substituent. Others necessitate the use of isotopic water in conjunction with a Group VIII metal with the consequent problems of potential radiotoxicity or of product radiolysis should high specific activity tritium-labelling be required. Sometimes reaction conditions involve acid catalysis or high temperatures. In many cases labelling of the pyridine moiety has been observed as an artefact along with the labelling of the targeted molecular sites.

Only a few methods describe the direct exchange-labelling of unactivated N-heteroaromatics using an isotopic hydrogen gas donor with commonly available catalysts. One such report, describes the use of a deuterium gas donor in conjunction with a 5% ruthenium on carbon catalyst for the labelling of pyridines using deuterium gas and deuterated methanol. Unfortunately, we have now shown that the isotopic labelling achieved with this method results to a significant degree from the deuterated solvent as well as from the D$_2$ gas. An additional drawback of the method is that the activity of the catalyst is very low, necessitating the use of pressurised D$_2$, an undesirable operation with the tritium isotope.

Recognising all the above limitations we have carried out a screen of other potential Group VIII metal catalysts for this type of deuterium gas exchange process (Scheme) so as to identify systems with greater potential for use with both the deuterium and tritium isotopes.

A wide range of supported and unsupported noble metal catalysts were screened and three catalysts were identified which transferred the isotope efficiently from deuterium gas to the substrate. Moreover, these catalysts were far more active than the literature catalyst, allowing their use at ambient temperature and pressure in non-hydroxylic solvents. Three particularly effective catalysts were identified from the screen; rhodium black, ruthenium black and 5%
rhodium on alumina. Next, these new catalysts were evaluated against a panel of pyridines and other N-heteroaromatics specifically selected to investigate various stereo-electronic and regiochemical aspects of the labelling processes.

\[
\begin{align*}
\text{D}_2 / \text{GpVIII metal catalyst} \\
\text{THF / RT / 2h} \\
R = \text{range of substituents including fused-ring analogues}
\end{align*}
\]

The results of this study are summarised in the Table.

**Table: Labelling of Pyridines and Other Nitrogen Heteroaromatics using Various Heterogeneous Ru and Rh Catalyst with Deuterium Gas in Tetrahydrofuran at Ambient Temperature and Pressure**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Atom% D</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rh Black</td>
<td>Ru Black</td>
<td>5% Rh/Alumina</td>
<td>5% Ru/Carbon</td>
</tr>
<tr>
<td>3-Acetylpyridine</td>
<td>99%</td>
<td>99%</td>
<td>99%</td>
<td>0%</td>
</tr>
<tr>
<td>4-Acetylpyridine</td>
<td>99%</td>
<td>0%</td>
<td>83%</td>
<td>0%</td>
</tr>
<tr>
<td>3-Aminoquinoline</td>
<td>83%</td>
<td>99%</td>
<td>43%</td>
<td>0%</td>
</tr>
<tr>
<td>7,8-Benzoquinoline</td>
<td>90%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>2-Benzylpyridine</td>
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<td>8%</td>
<td>22%</td>
<td>0%</td>
</tr>
<tr>
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<td>0%</td>
<td>76%</td>
<td>0%</td>
</tr>
<tr>
<td>2,2'-Bipyridyl</td>
<td>35%</td>
<td>0%</td>
<td>19%</td>
<td>0%</td>
</tr>
<tr>
<td>4,4'-Bipyridyl</td>
<td>75%</td>
<td>47%</td>
<td>75%</td>
<td>0%</td>
</tr>
<tr>
<td>2-Bromopyridine</td>
<td>28%</td>
<td>0%</td>
<td>0%</td>
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<td>4-Dimethylaminopyridine</td>
<td>100%</td>
<td>47%</td>
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<tr>
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<td></td>
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<td>87%(3)</td>
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<td>85%</td>
<td>83%</td>
<td>0%</td>
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<tr>
<td>Quinoline</td>
<td>99%</td>
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<td>53%</td>
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</tbody>
</table>

(a) Conditions: The substrate (Xmmol) and catalyst (XXmg) were stirred under D₂ gas for 2 hours at ambient pressure and temperature, (b) indicates a minor amount of reduction, (c) indicates extensive reduction or other decomposition under the reaction conditions, (d) In addition there was 35 atom %D in the ortho-positions in the phenyl ring.

Overall, the data shows that many N-heteroaromatics can be efficiently labelled using this simple procedure. Moreover, the procedure leads to highly regioselective (mostly regiospecific) labelling in positions α to nitrogen.

Six of the substrates (3- & 4-acetylpyridine, 7,8-benzoquinoline, 2-phenylpyridine, 4-dimethylaminopyridine and 2-methoxy pyridine) were selected to check for concomitant
labelling at other favourable sites via base-catalysed, ortho-directed\textsuperscript{1} or heteroatom-directed methyl/methylene labelling processes.\textsuperscript{14,14d} However only one example of such behaviour was observed: both \( \alpha \)- and ortho-labelling\textsuperscript{1} was observed with 2-phenylpyridine.

Previous work has shown that tight binding of the substrate to the catalyst surface can inhibit labelling in metal catalysed exchange\textsuperscript{3b,3l,6b} and indeed 2,2'-bipyridyl does show a reduced extent of labelling in comparison with the 4,4'-linked analogue, consistent with the expected bidentate complexation with the surface. However phthalazine, another bidentate substrate, and 2-bromopyridine, both of which are able to bind strongly, and which were indeed recovered unlabelled from a previous study\textsuperscript{6b}, are nevertheless labelled by the new catalysts.

In common with many other metal-catalysed isotopic exchange methods\textsuperscript{5} the procedure appears to be applicable to both electron-rich and electron-poor substrates. Moreover, variously fused-ring pyridine analogues are labelled. Both these behaviours bode well for the general applicability of the method.

In a few cases a degree of reduction accompanies the isotope exchange, though for most substrates examined this behaviour is absent or of marginal significance.

An important parameter for any labelling reaction is the isotopic incorporation and this was satisfactorily high under the simple protocol utilised. Indeed for faster-reacting substrates it was close to the equilibrium value (XXXD/molecule) calculated for the exchangeable hydrogen isotope pool in the reaction, assuming no isotope effects.

The method has also proved amenable to use with the tritium isotope, at least at low specific activity. Thus [3,3'-\(^{3}\text{H}\)]4,4'-bipyridyl was obtained with the tritium label exclusively in the \( \alpha \)-positions, via a single high-yielding exchange step using the rhodium black catalyst, and without any detectable decomposition.

In summary, the labelling procedure is highly regioselective, simple to carry out, product isolation is generally straightforward and recoveries are high. The procedure used for a typical small-scale deuteration reaction is given later\textsuperscript{5} The scale of this preparation was chosen to model the preparation of tritiated compounds or of MS internal standards (where a small scale is often required by the efficient utilisation of the tritium isotope or the limited availability of the substrate or analyte) however it has been successfully scaled-up by many fold.

Acknowledgements

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References


8. [2,6′,2″,6″-2H4]4′,4″-Bipyridyl (22 mg) and rhodium black (10 mg) were dissolved in THF (1 ml) and stirred at room temperature and pressure for 5 h. During this period the deuterium gas was replaced five times. The catalyst was filtered off and the solvent removed under a stream of nitrogen to yield essentially pure labelled bipyridyl (15mg), which was dissolved in a minimum of dichloromethane and treated with hexane to yield crystalline [2,6′,6″-2H4]4′,4″-bipyridyl (22mg, 97.5%, 112-113°).
(authentic standard 112-113°C), $^1$H-NMR (CDCl$_3$) δ 7.56 (4H, multiplicity, β-protons), 8.76 (4H, residual α-protons) p.p.m. $^2$H-NMR (CHCl$_3$) δ 8.76 (singlet, α-deuterons) p.p.m., MS (M+4D) gives 160.093 a.m.u., $C_{10}H_4D_4$ requires 160.093 a.m.u. The overall deuteration achieved in this single step was 3.5D/molecule.