Microwave-Assisted H/D Exchange Reactions

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By

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STATEMENT

I hereby declare that this thesis has not been and will not be, submitted in whole or in part to another University for the award of any other degree.

Signed …… Alnomsy, Ayed khalaf

Date ……

ABSTRACT

This thesis describes a new microwave-assisted method for the synthesis of poly-deuterated anilines and pyridines. The microwave mediated deuteration of aniline derivatives both with and without a platinum catalyst has been studied. Selectivity and yields are compared, showing the well established electronic selectivity of deuteration in the absence of a platinum catalyst, and a selectivity governed by steric factors for the platinum catalysed exchange. Differences in percentage yield can be explained for each method but vary greatly with changes in substrate. The ability for platinum catalysed exchange to deuterate aliphatic positions has also been observed and a tentative mechanism is proposed for the exchange of protons on substituents. Following investigation into the two different catalysts, the yield for the microwave assisted procedure is good, and high levels of deuterium incorporation are observed with only a single cycle.

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ABBREVIATIONS

app	Apparent
c	Concentration
$CDCl_3$	Deuterated chloroform
d	Doublet
DCM	Dichloromethane
EI	Electron Impact
equiv	Equivalent
g	Gram(s)
GHz	Gigahertz
H/D	Hydrogen/ Deuterium
h	Hour(s)
Hz	Hertz
IR	Infra red
J	Coupling constant (in Hz)
KBr	Potassium bromide
L	Laevorotatory
m	Multiplet
m	*meta*
MAOS	Microwave–assisted organic synthesis
Me	Methyl
MHz	Megahertz
Mr	Molecular weight
Mr′	Average molecular weight
min	Minute(s)
ml	Millilitre
mmol	Millimole(s)
mol	Mole(s)
mp	Melting point
MS	Low–resolution mass spectra
MW	Microwave irradiation
nM	Nanomolar
NMR	Nuclear magnetic resonance
p	*para*
Phe	Phenyl
PSI	pound per square inch
R	Specified substituent
R.T.	Room temperature
s	Singlet
t	Triplet
tert	Tertiary
TLC	Thin layer chromatography
μM	Micromolar
°C	Celsius

1. Introduction

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1. Introduction

1.1. The Use of H/D-Exchange Reactions

During the 1960s and 70s the use of H/D-exchange reactions for the synthesis of deuterium containing compounds emerged as an area of considerable interest.[1] Despite considerable advances, interest in this process reduced dramatically in subsequent years until the mid 1990s when the development of this process was re-investigated.[1] This was primarily a consequence of the increase in demand for isotopically labelled compounds. Such compounds are used in pharmacokinetic and metabolic studies during drug development,[2,3] but are of equal importance in mechanistic investigations into catalysts and reaction pathways[4,5,6] and in C-H bond activation.[7,8] Deuterated internal standards provide an important quantitative handle in the study of human, animal and environmental samples. Similarities in physical and chemical properties of the substance under investigation result in deuterated standards generally exhibiting unchanged ionisation behaviour and retention times in LC/MS but differ on account of their mass difference. As a consequence, if the mass difference is large enough to separate signals from natural isotope patterns, quantitative analysis is possible.[1]

For the production of an isotopically labelled compound there are two possible strategies. Firstly it is possible to synthesise labelled compounds using the corresponding isotopically-labelled precursors. The second strategy is to directly exchange a carbon bonded hydrogen atom for a deuterium atom. This second method is commonly preferable as the first route often requires multi-step synthesis and the labelled precursors are generally expensive. In contrast the second strategy is a lot more efficient and cost-effective, because one can carry out the exchange reaction on the target molecule or a late intermediate in the synthesis. Other methods include halogen-deuterium exchange[9,10] and reductive deuteration.[11]

1.2.The First H/D-Exchange Reactions

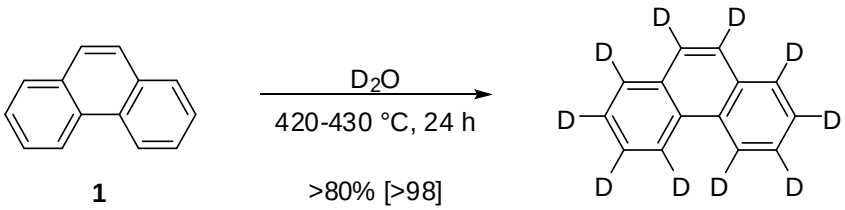
One of oldest methods for H/D exchange is pH dependent H/D exchange. Exchange occurs via base- or acid-catalysed formation of an enolate/enol, with H/D exchange occurring at the active positions in the molecule by application of deuterated Brønsted

acids. Such methods often require the deactivation of the compound to prevent the reverse exchange occurring.[1]

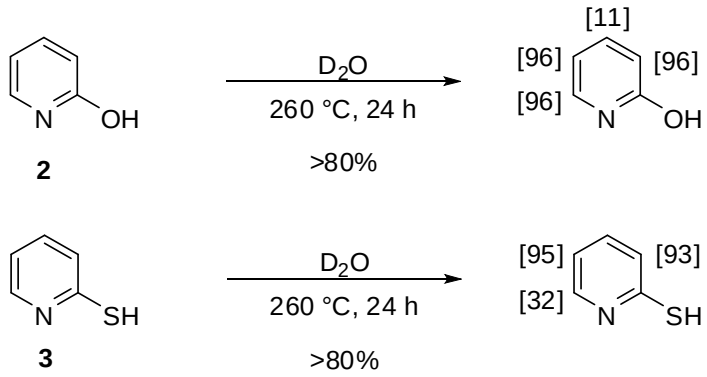
H/D exchange can also occur without the presence of an acid or base but just using deuterium oxide. This exchange occurs on acidic carbon-bonded hydrogen atoms, and works due to deuterium oxide's ability to act as either an acid or a base.

Such exchange is possible with a number of different compounds and the experimental conditions vary dramatically. For example, Junk and Catallo used conditions to achieve almost complete H/D exchange during the deuteration of phenanthrene (**1**) at 380-430 °C (**Scheme 1**).[12] Harsh conditions were used similarly by Werstiuk and Ju to carry out H/D exchange on pyridine derivatives, reporting good yields (>80%) and high levels of deuteration in the 3-, 5- and 6-positions of 2-hydroxypyridine (**2**) and 2-mercaptopyridine (**3**) (**Scheme 2**).[13]

Scheme 1. H/D exchange of phenanthrene (1)



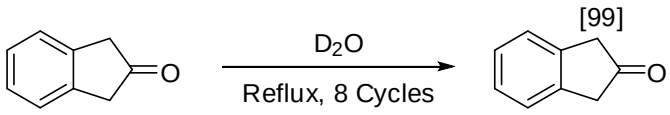
Scheme 2. H/D exchange of pyridine derivatives



Edlund and Berson showed that it is not always necessary to use such extreme conditions for H/D exchange.[14] During the synthesis of [1,1,3,3-D_4]2-indanone (**4**), exchange occurs by repeatedly heating the precursor in D_2O under reflux, to furnish the

deuterated product with high % deuteration. The milder conditions again led to high regioselectivity (**Scheme 3**).

Scheme 3. Highly regioselective deuteration of 2-indanone (4)



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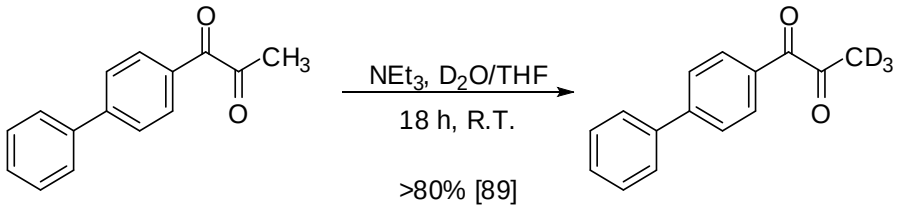
H/D exchange of methyl groups has also been reported under base catalysed conditions.[15] Berthelette and Scheigetz achieved such exchanges on methyl groups of aryl methyl ketones.[15] The exchange varied greatly with substrate, base and solvent but was achieved with high yield and percentage deuteration with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Deuteration of a base sensitive diketone **5** was also achieved without decomposition with the addition of triethylamine (**Scheme 4**).

Scheme 4. Deuteration of a base-sensitive diketone 5



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% = yields [ ] = % deuteration

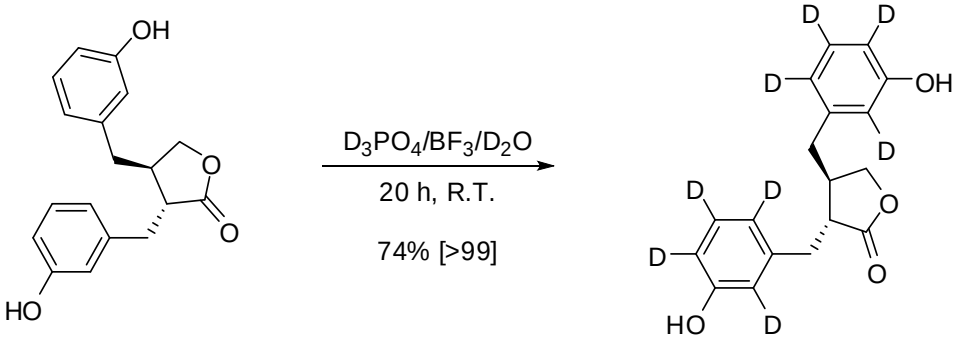
H/D exchange under conditions with or without the presence of a base has been successful in a number of cases, and is certainly not limited to the few examples mentioned above. However, one area of more relevance and a much larger field for this project is that of acid-catalysed H/D exchange.

1.3. Acid-Catalysed H/D Exchange

There are two possible exchange methods in acid-catalysed exchange: either strong deuterated Brønsted acids or alternatively a Lewis acid with a deuterium source can be used to deuterate an aromatic compound. The use of both of these deuteration methods combined together has also been researched. Wälälä *et al*. demonstrated this combination on a number of substrates including flavonoids, isoflavonoids and lignans.[16] With the use of a mixture of D_3PO_4, BF_3, and D_2O, good yields and high levels of deuteration at the activated positions were achieved at temperatures between 20 and 55 °C. The reaction involved many cycles over a period of one to four days.

Wälälä *et al*. did further work showing that with more severe conditions it was possible, using diadzein and enterolactone (**6**) as a substrate, to also deuterate at inactive positions.[17] The synthesis actually gave almost full deuteration of enterolactone (**6**) (>99%) including the inactive *meta* positions (**Scheme 5**).

Scheme 5. H/D exchange using both a Brønsted and Lewis acid



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H/D exchange reactions using methods in the presence of a Lewis acid are somewhat limited. The reactions are restricted to nonpolar arenes, as substrates such as aniline, phenol, anisole, and benzoic acid do not undergo exchange under these conditions. This is because of inhibition of the Lewis acid by complexation.[18]

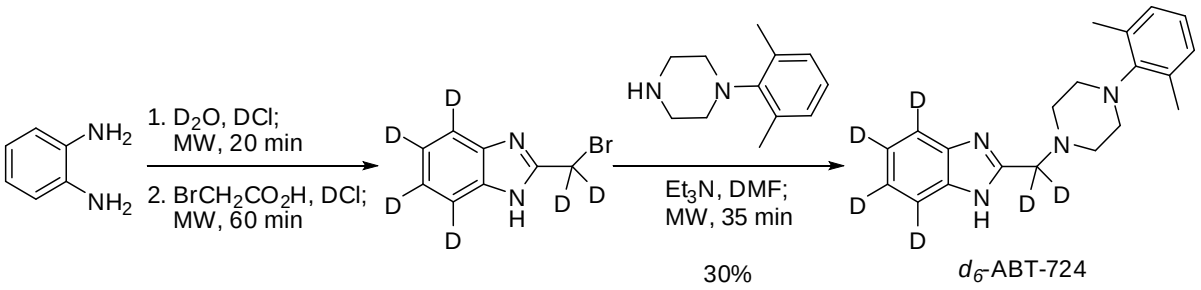
Acid-catalysed H/D exchange has also been reported in hydrocarbons. Sommer *et al*. reported deuteration using support-bound reagents.[19] The H/D exchange of isoalkanes with D_2SO_4 was observed, giving regioselective exchange of the isoalkanes with support-bound acids. Hydrogens bonded to a tertiary carbon were preferentially

exchanged whilst exchange on the linear hydrocarbons needed greater temperatures (>200 °C).

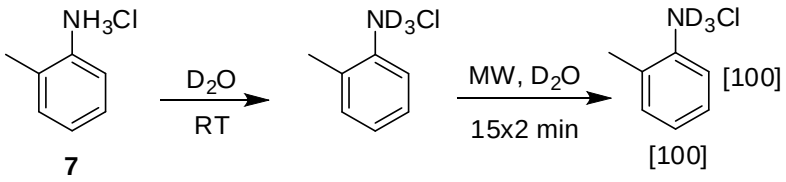
As with most areas of H/D exchange, acid-catalysed exchange is experiencing considerable growth enabled by microwave-assisted chemistry. This is due to advantages such as greatly reduced reaction times with similar percentage deuteration.[20,21] Vaidyanathan and Surber utilised this new method and its advantages in the isotopic labelling of ABT-724 (**Scheme 6**), with exchange occurring in minutes following H/D exchange on the diaminobenzene precursor; this was incorporated into a benzimidazole synthesis to elaborate d_6-ABT-724 in reasonable yield.[21]

One variant, which uses only D_2O during the deuteration process, was demonstrated by Jones and co-workers using the hydrochloride salt of 2-methylaniline (**7)** (**Scheme 7**).[22] This method has also been shown to be successful for aminopyridine derivatives.[23] Labile hydrogen atoms (NH) were exchanged by prior treatment with D_2O and then upon irradiation, deuteration was complete within a few minutes. Using this method high levels H/D exchange were achieved at the positions *ortho* and *para* to the amino group, depending upon substrate.

Scheme 6. Deuteration of ABT-724



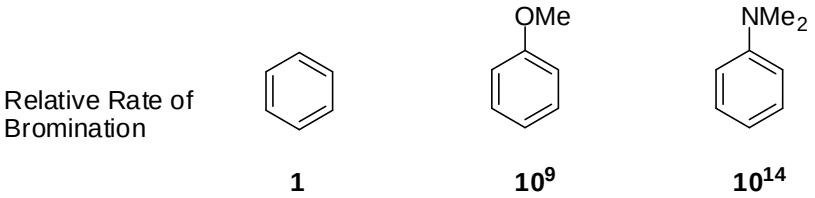
Scheme 7. Microwave-assisted H/D-exchange of anilines



Anilines are a comparatively reactive group of aromatic molecules, as opposed to phenols or benzene for example. This is due to the interaction of the lone pair on the nitrogen with the π system. This is also true of oxygen but its greater electronegativity

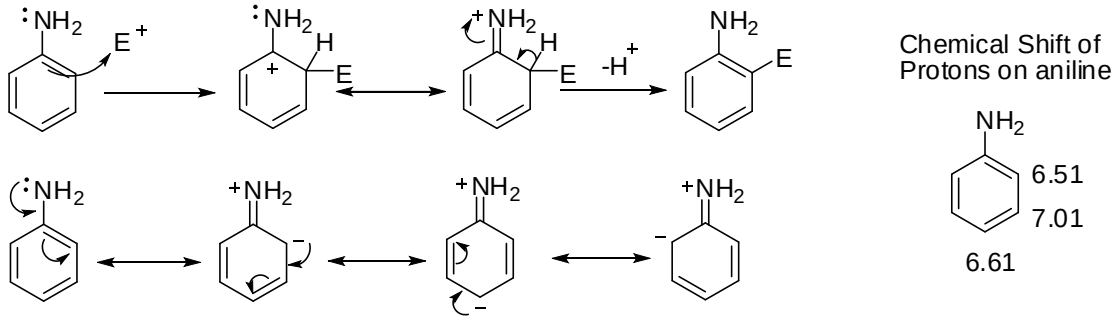
means that its lone pair does not interact to the same extent. The differences in reactivity attributed to this interaction can be seen in (**Figure 1**).[24]

Figure 1. Relative rates of bromination of aromatic compounds[24]



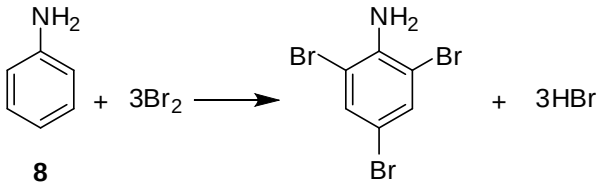
Anilines undergo electrophilic aromatic substitution with the regioselectivity of this process directing H/D exchange to the *ortho* and *para* positions. This is due to the stabilization of the positively changed transition state. The chemical shift of methines in the ^{1}H NMR of aniline reflects how electron density at the different positions is affected by its resonance forms. Both can be seen in **Scheme 8**. These factors mean that $\Delta G^{\ddagger}$ is lower, therefore giving a faster reaction at these positions.[24]

Scheme 8. Regioselectivity of electrophilic aromatic substitution[24]



The amino group is one of the most powerful *ortho, para*-directing groups in electrophilic substitution. If the conditions of the reaction are not too acidic, aniline (**8**) and its derivatives undergo rapid ring substitution. For example, aniline (**8**) like phenol, brominates three times under mild conditions (**Scheme 9**).[25]

Scheme* 9. *Anilines undergo bromination at* ortho *and* para *positions



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The selectivity of such aromatic compounds is well established and now chemists are looking towards altering such selectivity. One particularly interesting article was published by Phipps and Gaunt in 2009, in which the selectivity of reaction of aromatic compounds with an electron donating group was completely reversed to *meta* selectivity.[26]

1.4. H/D Exchange Using a Heterogeneous Metal Catalyst

Metal catalysed reactions provide great synthetic routes for the deuteration of many substrates and have become popular due to advantages such as milder conditions and, more importantly, their greater tolerance towards numerous functional groups. This means that fewer destructive side reactions occur, such as hydrolysis, dehalogenation, deuterium addition to multiple bonds, epimerisation and cleavage of protecting groups.[1] Furthermore difficulties brought about by the regioselectivity of substrates using other methods can frequently be overcome, while high percentage deuteration is still attained for both aromatic and aliphatic compounds under metal-catalysed exchange.

These methods also allow for the use of a number of deuterium sources, increasing the range of the substrates that can undergo exchange, *i.e.* [D_6]benzene is an appropriate deuterium source allowing for H/D exchange in less polar substrates.[1]

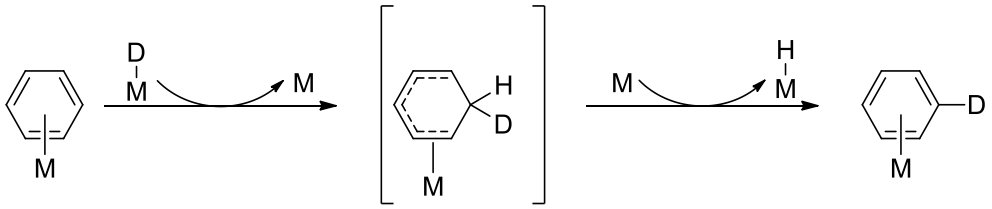
Heterogeneous metal catalysed exchange gives further advantages over that of homogeneous exchange. The ability to remove the catalyst by filtration is commonly possible. Furthermore, if there are no side products to the reaction there is no need for any work up.[27] The deuterium source is generally deuterium gas[28], D_2O or deuterated protic solvents.[29]

Two mechanisms are proposed to exist for the exchange: the associative π-complex mechanism and the dissociative π-complex mechanism (**Scheme 10**).[30] The extent to which each mechanism is involved in the exchange is dependent on the metal. For

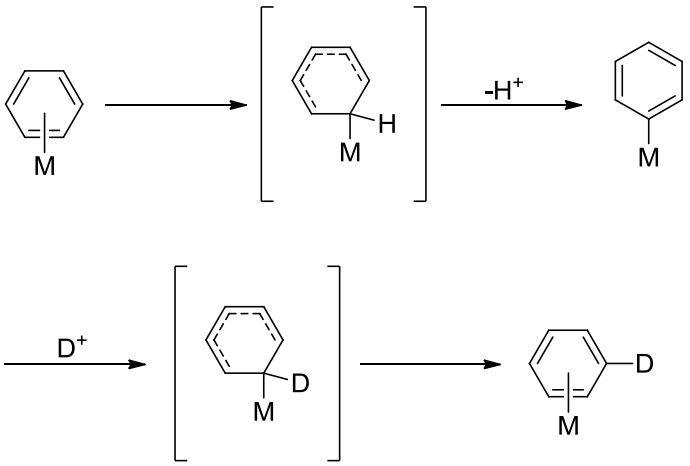
platinum-catalysed exchange reactions the dissociative mechanism is proposed to predominate, while for palladium the associative mechanism is proposed to predominate. Rhodium is thought to have equal involvement of both mechanisms.[31]

Scheme 10. Mechanisms of exchange using a heterogeneous metal catalyst

Associative mechanism:



Dissociative mechanism:



1.4.1. Palladium catalysis

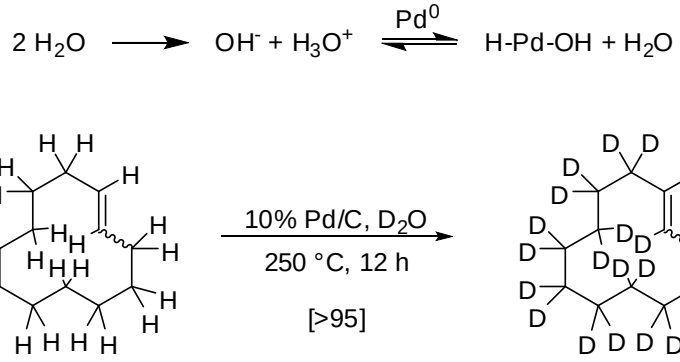
A lot of early methods developed for H/D exchange with heterogeneous palladium used deuterium gas as the source of deuterium.[32] Azran *et al*. developed a method using deuterium not as the solvent but to purge the catalyst surface of hydrogen and protic compounds.[33] This led to a highly effective Pd/C catalyst, and the complete and selective deuteration of benzylic protons could be achieved at room temperature within an hour for benzyl alcohol (using $[D_8]$-dioxane as the deuterium source) and dibenzyl ether (using D_2 gas as the deuterium source). A number of other substrates also experienced a high level of deuteration including benzylamine, dibenzyl and dibenzylamine. The deuteration of substrates was influenced by the deuterium source and catalyst/substrate ratios.

Myasoedov *et al*. used gaseous deuterium for the effective deuteration of amino acids and peptides using a method they developed called 'high-temperature solid-state catalytic isotope exchange' or HSCIE.[34,35,36] This method uses the action of the D_2 gas on a highly dispersed mixture of solid substrate with the catalyst.

A hydrothermal method for deuteration of aliphatic hydrocarbons, with deuteration occurring at temperatures up to 290 °C, has been reported by Möbius and Schaaf.[37] The compound is placed in an autoclave and subjected to a D_2/D_2O atmosphere at pressures of approximately 25 MPa, with a basket containing the catalyst placed above it.

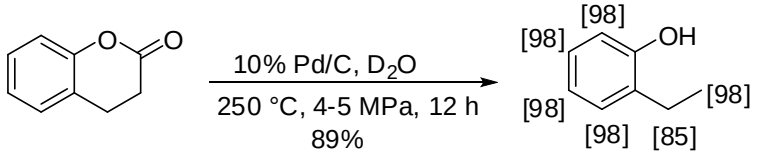
Under hydrothermal conditions, water dissociates a thousand times faster than at room temperature.[38] This means that the Pd^0 can readily oxidatively insert into the O-H bond to form the Pd^{II} species, which in turn catalyses the H/D exchange (**Scheme 11**).[39]

Scheme 11. H/D exchange under hydrothermal conditions



According to Matsubara *et al.*, completely deuterated aromatic or aliphatic hydrocarbons were formed under hydrothermal reaction conditions by decarboxylation of carboxylic acids. For example, the lactone **9** in D_2O afforded phenol derivative **10** with a high degree of deuteration in the presence of 10% Pd/C (5 mol%) at 250 °C and a pressure of 4-5 MPa (**Scheme 12**).[40]

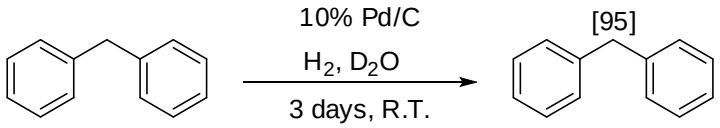
Scheme 12. H/D exchange of lactones under hydrothermal conditions



9 **10**

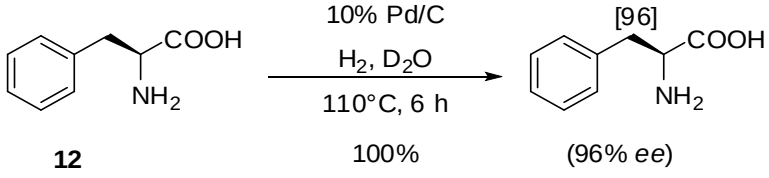
With previous knowledge of catalyst activation by initial occupation of the catalyst surface by hydrogen, Hirota and Sajiki have developed a 'one-pot' method for H/D exchange in which the palladium catalyst is activated by hydrogen *in situ*. Maximum exchange was achieved in the presence of catalytic amounts of hydrogen gas (0.45 equiv.) with no side reactions occurring to give the pure products. Substrates included diphenylmethane (**11**), 4-ethylbenzoate and 3-phenylpropanol. The deuteration of diphenylmethane (**11**) is shown below (**Scheme 13**).

Scheme 13. H/D exchange of diphenylmethane (11)



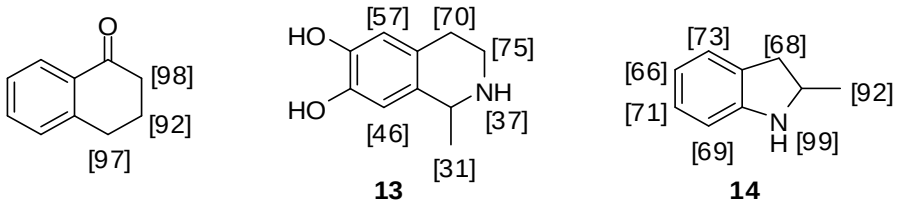
A method for the selective deuteration of the β-position of phenylaniline (**12**) without racemisation using a Pd/C-H_2/D_2O system has been developed by Maegawa *et al.*[41] H/D exchange occurs at 110 °C to give the L-enantiomer in 96% *ee* from starting material of 96% *ee* (**Scheme 14**). At 160 °C the α-position is also deuterated but racemisation occurs to give the product in only 17% *ee*.

Scheme 14. H/D exchange of phenylalanine (12)



The use of sodium borodeuterate for the *in situ* activation of the palladium catalyst in a method reported by Derau and Alzrodt, makes the reaction conditions suitable for microwave irradiation, due to the absence of gaseous reactants.[42] This meant that the reaction duration could once again be reduced by the application of microwave heating and still proceeds to give similar amounts of deuteration. Suitable substrates included carbocyclic compounds, isoquinone derivatives **13** and indole derivatives **14** (**Figure 2**).

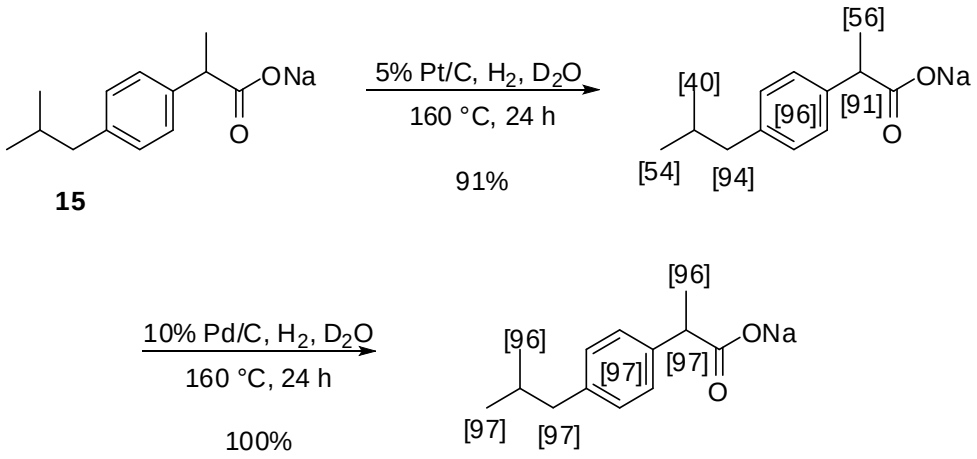
Figure 2. H/D exchange of substrates with in situ catalyst activation



1.4.2. Platinum catalysis

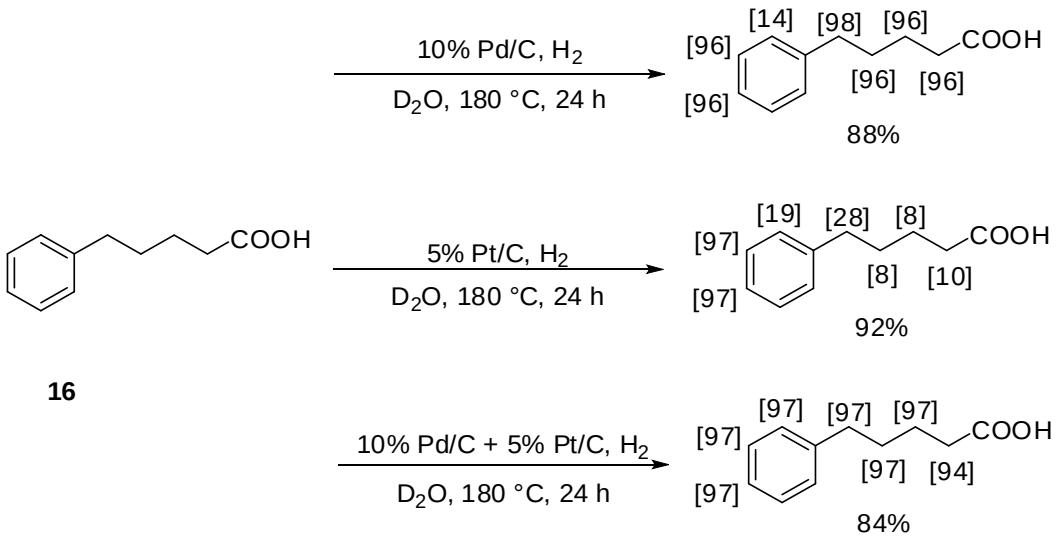
Heterogeneous platinum-catalysed H/D exchange is in many aspects, such as activation and scope, similar to heterogeneous palladium-catalysed H/D exchange.[43] However, it has been shown by comparative studies by Sajiki *et al*. that generally, while palladium catalysts preferentially deuterate aliphatic positions, platinum catalysts preferentially deuterate aromatic positions.[44] The difference in the catalyst's selectivity allows for more effective exchange for compounds with aliphatic and aromatic regions via stepwise deuteration. The advantages of this technique were demonstrated by Sajiki *et al*. in the deuteration of Ibuprofen[44] (**15**), giving an almost fully labelled product (**Scheme 15**).

Scheme 15. Stepwise H/D exchange of Ibuprofen (15)



It is also possible to combine the two catalysts. Such catalysis has been used in the deuteration of sterically hindered aromatic positions to great effect.[45] For the deuteration of 5-phenylvaleric acid (**16**) for example, the addition of palladium (10% Pd/C) gives only 14% deuteration of the *ortho* positions, and addition of platinum (5% Pt/C) gives only 19% deuteration. However, if the two systems are combined then almost complete deuteration of the *ortho* positions occurs (97% deuteration) (**Scheme 16**). This suggests a synergistic effect between the platinum and palladium complexes formed.

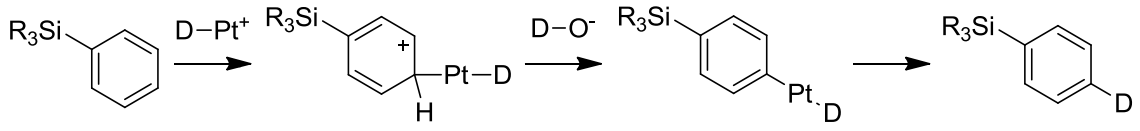
Scheme 16. Synergistic catalyst effects in the H/D exchange of phenylvaleric acid (16)



During the deuteration of aliphatic amines and amino acids catalysed by Adam's catalyst ($PtO_2 \cdot H_2O$), exchange selectivity is dependent upon the number and steric demand of substituents on the nitrogen atom. It is assumed that the nitrogen binds to the catalyst surface, inhibiting the catalysis of H/D exchange. This is supported by the decrease in reactivity with fewer substituents: tertiary>secondary>primary.[46]

A method using hydrothermal reaction conditions for platinum-catalysed exchange reactions has also been developed. Matsubara *et al*. reported the selective deuteration of aryl silanes, with anti *ortho* selectivity (**Scheme 17**). This was again proposed to be due to steric hindrance at the *ortho* position.[47]

Scheme 17. Anti ortho selectivity in H/D exchange of aryl silanes



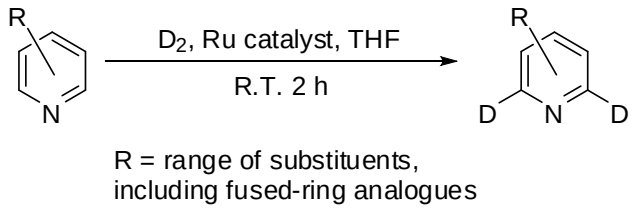
The proposed mechanism under hydrothermal conditions begins with the formation of metallic platinum during an inductive phase. The metallic platinum then inserts into the D_2O to give a D-Pt-OD complex. Dissociation of the complex follows to give the $D\text{-}Pt^+$ species that reacts with the aryl group to eventually give the deuterated product.[47]

Microwave irradiation methods are also compatible, giving shorter reaction times and frequently give fewer side reactions.[22]

1.4.3. Catalysis using other metals

Rhodium catalysed H/D exchange experienced a boom at the end of the 1980s, with a number of breakthroughs for heterogeneous methods in deuteration, using rhodium.[48-50] Lockley *et al*. developed a method for the *ortho* selective deuteration of *N*-heterocycles such as pyridines, quinolines and phthalazine derivatives, using rhodium and ruthenium in the presence of D_2 gas[51] (**Scheme 18**). Reasonable deuterium incorporation was achieved in just 2 hours.

Scheme 18. Ru-catalysed H/D exchange of N-heterocycles



These results are of interest to the project as deuteration is occurring selectively at positions electronically unfavourable for electrophilic substitution.

Nickel was first reported as a catalyst for H/D exchange in 1954 by Errede *et al.*[52], and since has generally been used for the deuteration of aromatic compounds.[53]

Microwave assisted exchange in the presence of a nickel catalyst is an efficient method of deuteration. This has been demonstrated with *N*-methylindole, to give complete deuteration with protic solvents, and C4-position selective deuteration with nonprotic solvents[23].

Cioffi *et al*. also reported the use of microwave irradiation in Raney nickel catalysed H/D exchange.[54] Deuterium incorporation was significant after very short reaction times (4 minutes) and high levels of H/D exchange could be achieved with longer time scales (6 minutes). Exchange occurred without decomposition or epimerization. The substrates used were sucrose and 1-*O*-methyl-β-D-galactopyranoside, and it was proposed that many other compounds containing vicinal OH groups would be suitable for this method. Raney copper is of less use in the catalytic exchange of hydrogen and deuterium but does offer methods for the deuteration of aromatic compounds via dehalogenation.[55]

1.5. H/D Exchange using a Homogeneous Metal Catalyst.

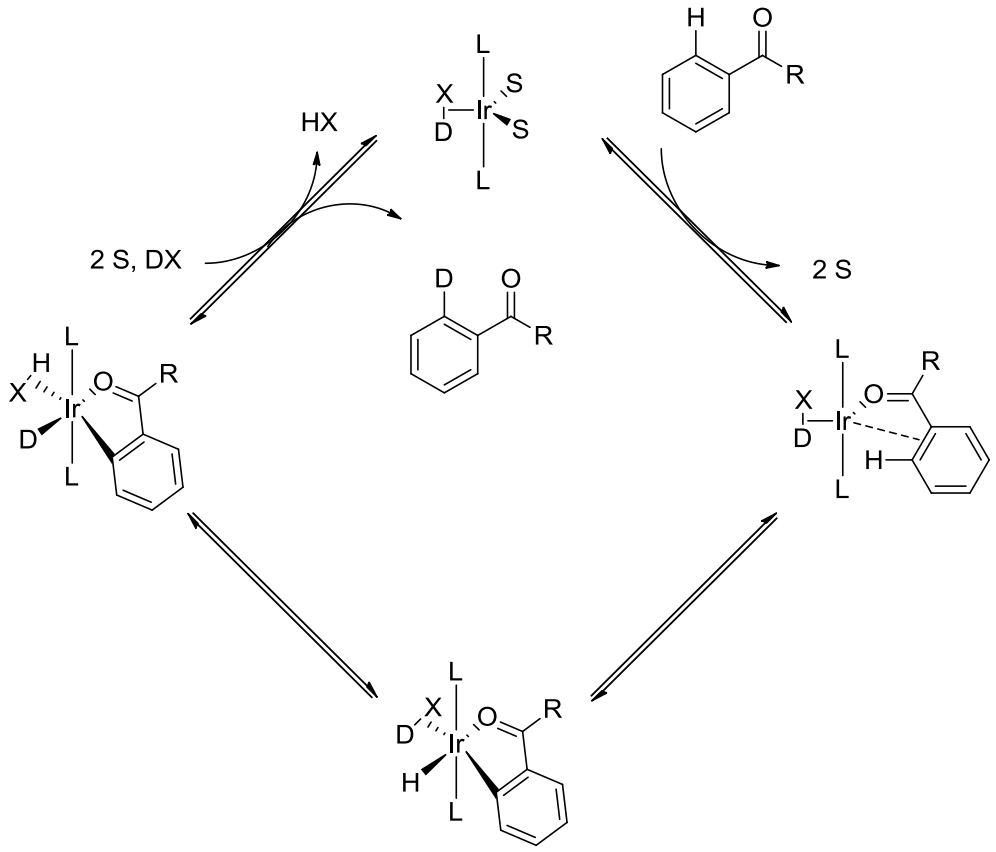
A great number of homogeneous catalysed exchange methods are available for the efficient deuteration of a wide range of substrates. Such reactions give the benefits of milder conditions and tolerance towards functional groups is common. Many familiar metals used in heterogeneous catalysed exchange have been used effectively in this area, such as platinum, palladium and rhodium, whilst also a number of other new metals are of huge importance. For example; at the forefront of homogeneous metal catalysed exchange reactions are those using cationic iridium complexes, with substantially more published examples than any other catalyst.[1]

1.5.1. Iridium catalysis

Cationic iridium complexes have been found to be of great importance in homogeneous metal catalysis for H/D exchange due to their great proficiency for activating C-H bonds. Investigation into the *ortho* deuteration of arylketones **17** and acetanilides **18** has been one of the most well covered areas for iridium catalysed exchange[56,57], with many studies into the effect of different factors, such as deuterium source, solvent, temperature, and duration[58], on the selectivity and the percentage of deuteration.

The proposed mechanism for the *ortho* deuteration (**Scheme 19**) begins with the coordination of the substrate to the cationic catalyst. Following complexation, oxidative insertion occurs to produce a five-membered metalocycle. H/D exchange followed by reductive elimination gives the *ortho* deuterated product and regenerates the catalyst.

Scheme 19. Mechanism of Ir-catalysed H/D exchange



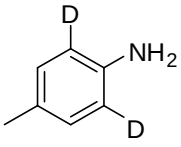
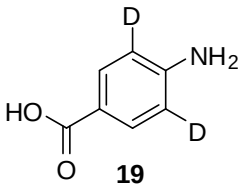
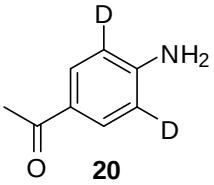
The substrates steric and electronic properties affect the success of the deuteration. Acetophenone amongst other substrates (benzamides, benzoic acid derivatives and acetanilides **18**) produce high degrees of *ortho* deuteration while other substituted derivatives give a reduced degree of deuteration.[56,57] Commonly used in these exchange reactions is the Crabtree catalyst $[Ir(cod)(PCy_3)(py)]PF_6$ (cod=1,5-cyclooctadiene, Cy=cyclohexyl, py=pyridine).

Fels *et al*. have reported the deuteration of α,β-unsaturated carbonyl compounds[58], with generally good deuteration in the β-position occurring via a similar mechanism to that shown in **Scheme 19**.

When using the catalyst [Ir(co)-(acac)] (acac = acetylacetonate), Fels *et al*. found that the regioselectivity of the exchange was dependent on the deuterium source used. Hence when using 2-methylbenzoic acid as a substrate, deuteration (45%) was observed solely in the *para* position as opposed to 98% deuteration in the *ortho* position. This is thought

to be due to the reduction of the ligand with simultaneous formation of elemental iridium. The precipitation of elemental iridium brings about the altered selectivity by a heterogeneous catalytic exchange reaction. Deuterium source dependent selectivity was also reported by Lockley *et al*. in the catalysed *ortho* deuteration of anilines (**Table 1**)[59] by using [Ir(cod)-(acac-F6)] (acac-F6 = hexafluoroacetylacetonate) and gaseous deuterium, an exclusively *ortho* H/D exchange relative to the position of the amino group was found. 4-Aminobenzoic acid (**19**) and 4-aminoacetophenone (**20**) are particularly interesting here, because they show reversed selectivity with gaseous D_2 compared with D_2O.

Table 1. Exclusively ortho H/D exchange of anilines using an Ir catalyst

Compound	Degree of deuteration[%]
	77
 **19**	80
 **20**	72

Bergmann *et al*. have shown that the activation of aliphatic, carbon-bonded hydrogens for H/D exchange is also possible and has been observed in a number of substrates including certain hydrocarbons, amides, carboxylic acids, alcohols, phenols and nonfunctionalised aromatic compounds.[60-62]

With the further development of iridium catalysts for homogeneous exchange reactions, it has been possible to deuterate an even greater number of substrates. Peris *et al*. have reported the efficient deuteration of substrates such as diethyl ether, ethyl methyl

ketone, isopropanol, and styrene using *N*-heterocyclic iridium-carbene complexes.[63] More recently still, Salter has observed the *ortho* directed deuteration of sp^3 carbons of *N*,*N*-dialkylamides, and other complex molecules containing multiple subsidiary groups, using $[(cod)Ir(PPh_3)_2]BF_4$.[64]

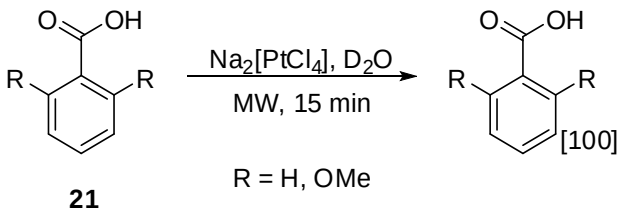
Developments with microwave synthesis equipment have also made it possible for iridium catalysed exchange to be accelerated, to give high percentage deuteration with reduced duration of reaction.[65]

1.5.2. Platinum Catalysis.

Platinum complexes were first established as important catalysts for H/D exchange by Garnett[66-69] and Shilov[70] during the 1960s and 1970s. Since then, the majority of exchange methods have used tetrachloroplatinate(II) salts as the exchange catalyst, which has for the majority been used in the deuteration of arenes.[1] Exchange reactions often use D_2O or AcOD as a deuterium source and due to the pH dependent stability and activity of the platinum catalyst, acidic conditions are required.

This may not be the case however for catalytic systems under microwave irradiation. Such reactions occur with reduced reaction duration, and could allow for acid free deuteration of arenes. Such an exchange has been reported by Jones *et al*. The H/D exchange reaction gave complete deuteration of the positions *meta* to the carboxylic acid group in benzoic acid derived **21** substrates (**Scheme 20**).[22]

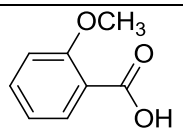
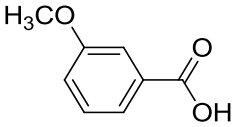
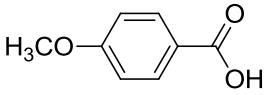
Scheme 20. Pt-catalysed H/D exchange of benzoic acids under microwave irradiation



21

Kański and Kańska also reported the deuteration of methoxybenzoic acids using a homogeneous platinum catalyst.[71] The rate constants for deuteration at different positions on the aromatic ring were calculated at 130 °C for the three different isomers of methoxybenzoic acid (**Table 2**).

Table 2. Rate constants for Pt-catalysed H/D exchange in methoxybenzoic acids

Compound	Rate Constant for Exchange, h^{-1}				
	k2	k3	k4	k5	k6
	-	0.087	0.22	0.2	0.045
	0.043	-	0.04	0.12	0.045
	0.0055	0.0135	-	0.0135	0.0055

The difference in rates was again proposed to be due to steric hindrance in which the bulky nature of the substituents to some extent prevents the formation of the σ-complex.[71]This was observed to a greater extent in the carboxylic acid group. This is most obviously seen in the example of 4-methoxybenzoic acid.

The work by Kański and Kańska above followed previous research into a number of other substrates.[72] Substrates including chloro, bromo, and nitrobenzoic acids where observed to give analogous reactivity to the table above with steric effects determining the rate constants for deuteration, supporting Garnett's original proposal of a predominant dissociative mechanism.[67]

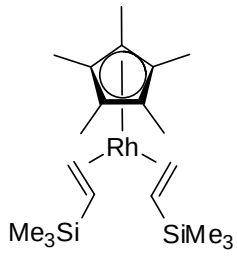
The most important pioneering work into platinum-catalysed hydrogen/deuterium exchange reactions was done by Garnett in the 1960's and 70's and is certainly of greatest relevance to this project. His work is summarised in more detail in the following paragraphs.

1.5.3. Rhodium and ruthenium catalysis

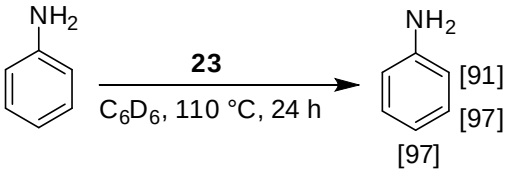
Less prominent in the area of H/D exchange catalysis is rhodium. While it has been shown to be proficient for such exchange reactions in arenes by Garnett *et al.*[73], very few methods involving rhodium have been reported. Brookhart *et al*. have achieved high percentage deuteration in substrates including aniline (**8**) and cylopentene (**22**)

(**Scheme 21**) using a rhodium-olefin complex **23**.[74] Joó *et al*. observed H/D exchange in the C-2 position of itaconic acid (**24**) following the reduction of the double bond, using soluble rhodium phosphate complexes with a mixture of H_2 and D_2O (**Scheme 22**).[75]

Scheme 21. H/D exchange using Rh-olefin complex 23



23



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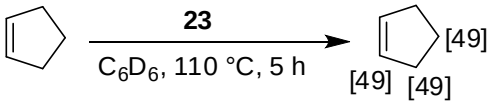
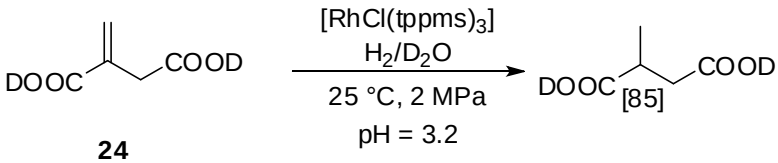


22

Scheme 22. Rh-catalysed H/D exchange of itaconic acid (24)

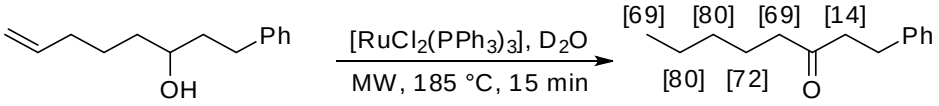


24

Lockley and Hesk more recently observed the deuteration of pyridine and a number of arene substrates using rhodium catalysts; $RhH[P(iPr)_3]_3$ and $[Rh(benzo[h]quinoline)(H)(PPh_2Bn)_2(acetone)]PF_6$ respectively.[51]

Ruthenium complexes can also be used in the homogeneous catalysis of H/D exchange. Matsubara *et al*. observed the catalysed deuteration of substrates with an electron donating group under microwave irradiation.[76] The scheme below (**Scheme 23**) shows the deuteration of an alkenol **25** in D_2O via a ruthenium-mediated migration of the double bond and isomerisation to ketone **17**.

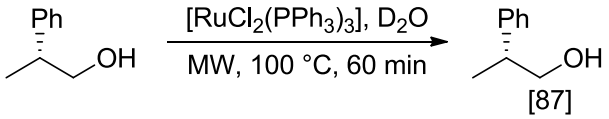
Scheme23. Ru-catalysed H/D exchange of alkenol 25



25

It was also shown that under similar conditions it was possible to selectively deuterate the α-position of primary alcohols **26** and amides (**Scheme 24**).[77] The reaction conditions were milder in this case to prevent deuteration of the stereocenter in alcohol **26** - the β position was unaffected at temperatures below 100 °C.

Scheme 24. Ru-catalysed exchange of a chiral alcohol 26



(99% *ee*) (99% *ee*)

Recent work done by Lockley and Hesk has shown the utility of ruthenium complexes in the homogeneous catalysed H/D exchange of alcohols, cyclic and aromatic substrates.[51] Regioselectivity in substituted aromatic precursors such as toluene is thought to be governed by steric factors with a greater selectivity at the *meta* (84%) and *para* (28%) positions over *ortho* (5%).

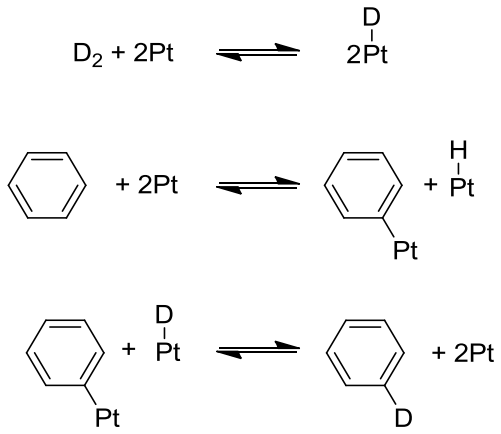
1.6. Garnett H/D Exchange using K_2PtCl_4

Garnett published a review called *"π-Complex Intermediates in Homogeneous and Heterogeneous Catalytic Exchange Reactions of Hydrocarbons and Derivatives with Metals"* in 1971 addressing the importance of platinum in H/D exchange reactions in unsaturated and aromatic hydrocarbons.[67] The proposed exchange mechanisms (dissociative and associative) are compared to previous classical mechanisms. Further studies of the exchange reactions revealed several problems with the classical mechanisms previously proposed by Farkas and Farkas[78] (dissociative) and Horiuti and

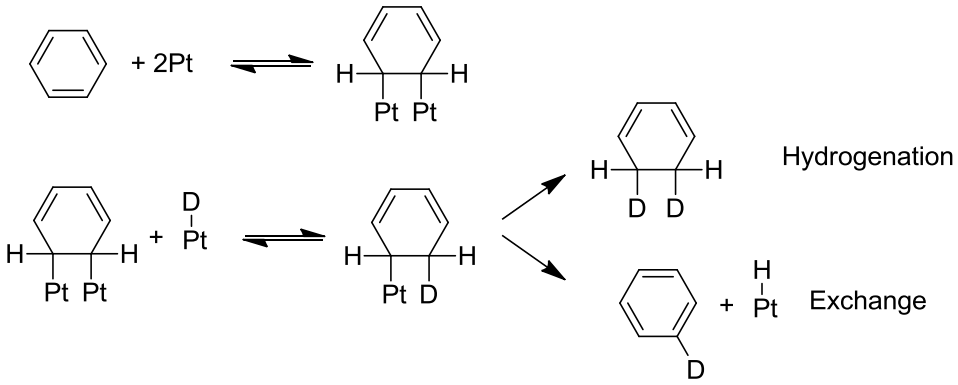
Polanyi (associative)[79] (**Scheme 25**). These problems will be discussed in the following paragraphs.

***Scheme 25*.**

Farkas and Farkas Dissociative Mechanism:



Horiuti and Polanyi Associative Mechanism:



Throughout the review, factors affecting the platinum-catalysed exchange are mentioned. Such factors include ionisation potential of functional groups, strength of adsorption to catalyst, sterics of functional groups and acidity of reaction mixture.

Exchange reactions carried out on monohalogenated aromatics showed that the rate and percentage of hydrogen / deuterium exchange was directly related to the ionisation potential of the halogen: fluorobenzene with the highest ionisation potential exhibited the greatest rate and percentage of exchange, whilst iodobenzene with the lowest proved the least effective substrate with both the lowest rate and percentage of exchange.

This effect was also seen when the exchange rate was compared between different delocalised systems. Naphthalene for example has a slower rate of exchange than

benzene because, due to its lower ionisation potential, delocalisation of its π-system occurs more readily to the catalyst, resulting in a stronger adsorption. This leads to preferential displacement of the deuterium leading to a slower rate of exchange.

These results could not be explained by the classical associative and dissociative mechanisms: the classical associative mechanism predicts a loss in resonance energy which does not occur. The classical dissociative mechanism predicts approximately equal chemisorption strengths which are also contradicted by Garnett's results.

The problems mentioned above can be resolved if π-electrons are used in the adsorption process. With classical association one would expect a loss of resonance energy. These observations led to the proposal of a new mode for aromatic adsorption by Garnett in 1960 (**Figure 3**).[67,80]

Figure 3.

Associative Transition State Classical Transition State

The new proposed adsorption mechanism was described as a donor-acceptor interaction in which there was a net flow of charge during the forward and backward donation of electrons. Quantum mechanically this is explained in terms of the complexity of the antibonding orbitals. The greater complexity leads to more nodal planes. This leads to the bonding orbital interaction predominating, causing net charge transfer to be in the direction of the metal.[67]

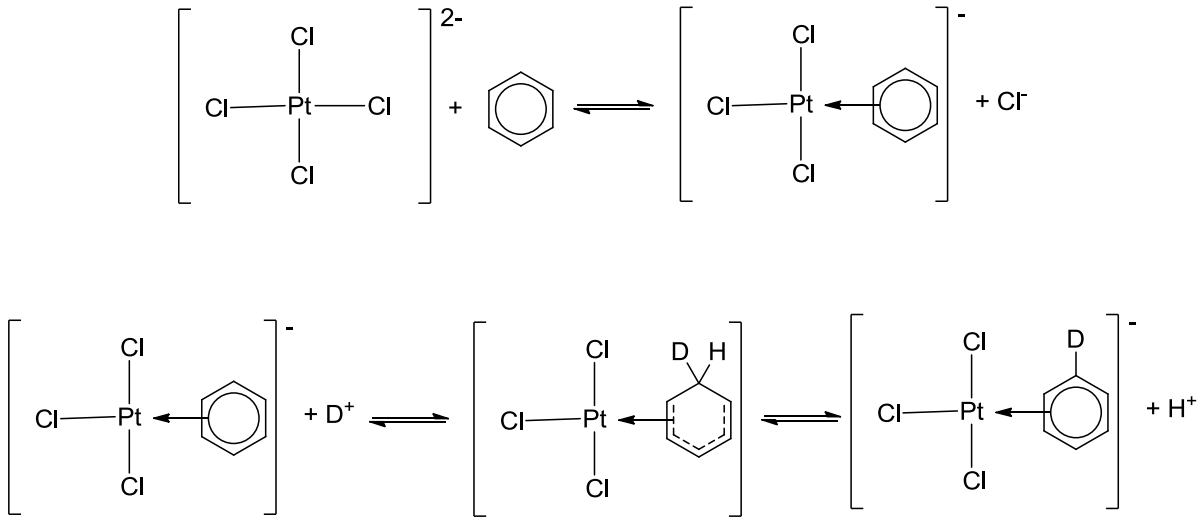
Garnett also reported a significant steric effect on the *ortho* position of monosubstituted alkylbenzenes (**Table 3**). Furthermore, Garnett showed that electronic factors no longer had an effect on selectivity, reporting very similar reactivity between trifluorotoluene and toluene in the catalysed homogeneous exchange (other than a steric effect reducing the number of 'active aromatic hydrogens').

Table 3. Absence of electronic effects on selectivity in Pt-catalysed H/D exchange

Compound	Deuteration, %	Amount of D in active aromatic hydrogens, %	Active Aromatic Hydrogens
Benzene	63	52	6
Toluene	66.6	16	5
Trifluorotoluene	77	14	3

Following analysis of the data for homogeneous catalysis, Garnett proposed two mechanisms to be occurring during the catalysis reaction. The homogeneous associative π-complex mechanism is shown below (**Scheme 26**). In this mechanism, the π-complex formed undergoes electrophilic attack by the deuteron with the formation of an associative intermediate. This occurs under acidic conditions to give the monodeuterated benzene following the loss of H^+ from the intermediate. Multiple deuteration is seen following rapid exchange cycles of the π-complex before the complex breaks.

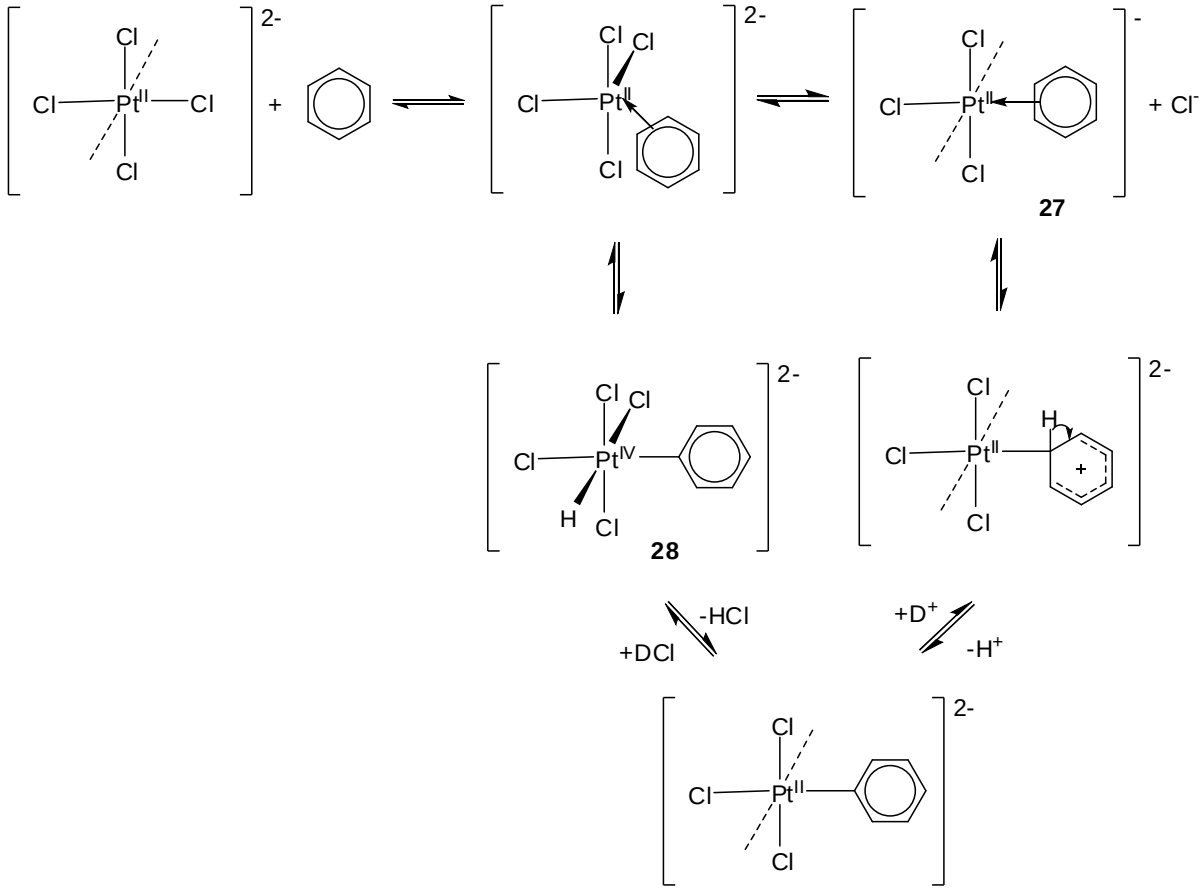
Scheme 26. Homogeneous associative π-complex mechanism



The second mechanism is the homogeneous dissociative π-complex mechanism (**Scheme 27**). This mechanism is proposed to predominate, as Garnett found that activating and deactivating substituents do not considerably affect the rate of exchange. This suggested that a mechanism with an associative intermediate would be very unlikely to predominate. This was supported by later work by Kański and Kańska.[71,72]

The homogeneous dissociative π-complex mechanism involves a reversible π-σ conversion. Such conversions had been observed before with ruthenium complexes.[81] The exchange step was proposed to be either a reversible electrophilic displacement of a proton from the π-bonded aromatic (**27**), or the formation of a six-coordinate hydride complex (**28**) in a reversible rearrangement that undergoes exchange involving the hydride group.

Scheme 27. Homogeneous dissociative π-complex mechanism



Deuteration has also been seen in the alkyl groups of alkyl substituted aromatic compounds. It was again observed that groups *ortho* to the alkyl substituents sterically hindered the catalytic exchange reducing the percentage of deuteration (**Table 3**).

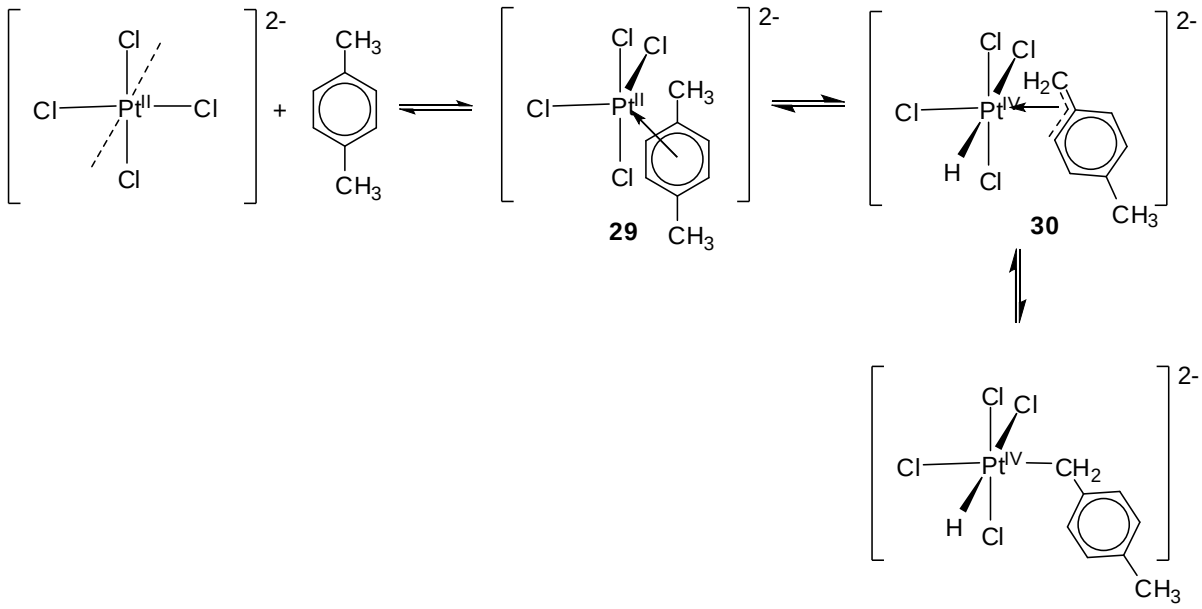
Table 3. Deuteration in alkyl group

Compound	Deuteration in alkyl group, %
Toluene	15.6
o-Xylene	6.6
m-Xylene	16.8
p-Xylene	20.2

Deuteration in the alkyl groups is analogous to the exchange in the aromatic positions with both stepwise and multiple exchange processes occurring.

Garnett's analysis of the M value (or Multiple exchange parameter) for *p*-xylene, suggested that multiple exchange is preferred and exchange occurs only on one methyl group for each interaction with the platinum catalyst. This led Garnett to propose an intermediate involving the localisation of a double bond, or the interaction of the ψ_2-orbitals of the *p*-xylene. This intermediate allows for the reversible π-aryl (**29**) to π-allylic complex (**30**) to form via proton elimination. Three mechanisms are proposed for the alkyl hydrogen deuterium exchange, one (**Scheme 28**) utilising the intermediate mentioned above is proposed to predominate.

Scheme 28. Proposed mechanism for alkyl H/D exchange



A second mechanism was proposed involving dealkylation without using the above intermediate for π-complexation.[ref] This has been discounted after studies showed conclusively that dealkylation does not occur as a predominant exchange mechanism. The second mechanism to be discounted was exchange via an increase in the hyper-conjugation in the alkyl group.

Garnett's review is of great importance to the work in this project and offers great insights into the chemistry taking place in the platinum-catalysed exchange reactions that have been studied.

1.4. The Goals of the project

Given the great capacity of Garnett's methods for homogenous Pt-catalysed H/D exchange, it seemed plausible that by combination with microwave heating, this approach could offer the potential to deuterate unactivated positions in much shorter reaction times. A similar phenomenon has been observed in heterogeneous systems.

It was proposed that a new method for facile H/D exchange of anilines, could be developed that featured:-

1- A single step / cycle;

2- The use of a commercial, readily available catalyst;

3- Microwave irradiation at readily accessible temperatures;

4- The incorporation of D at unactivated positions;

5- The facility to incorporate multiple D atoms;

6- The facility to exchange at side chain positions as well as aromatic methines;

7- Wide substrate scope so that the process will also work for electron poor systems.

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2.4.3. H/D Exchange of 4-tert-Butylaniline

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2.5.2. H/D Exchange of 3-Amino-2-methylpyridine

2.5.3. H/D Exchange of 5-Amino-2-methylpyridine

2.5.4. H/D Exchange of 3-Amino-5-methylpyridine

2.5.5. H/D Exchange of 3-Amino-4-methylpyridine

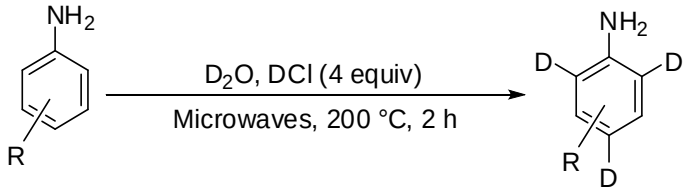
2. Results and Discussion

A variety of aniline derivatives and aminopyridines were selected as suitable substrates for deuteration using microwave irradiation with and without the presence of a platinum catalyst in a modified Garnett procedure. Evaluating both processes would allow for the quantification of the catalyst effect on the deuteration of the substrate. It was also important to establish the efficiency of exchange and yields for the new microwave-assisted procedure.

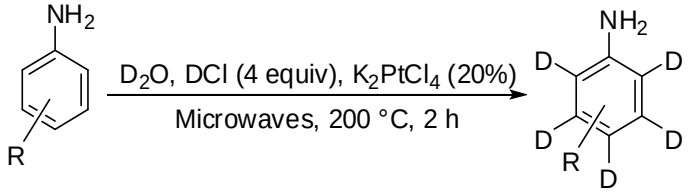
Such results are desirable for a number of reasons. A microwave-mediated modified Garnett procedure opens opportunities for rapid and efficient H/D exchange for a number of substrates that should be independent of electronic effects and enable efficient exchange at unactivated positions. Aniline derivatives were chosen as the first substrate of study in this project, as previous work by Garnett on the deuteration of such compounds, and precedent from Sanofi-Aventis (**Scheme 29**),[83] provided a foundation on which to build an understanding of this modified procedure. The combination of previous mechanistic understanding and the importance of aniline derivatives as useful building blocks in drug synthesis (in particular quinoline derivatives) make aniline derivatives ideal substrates.

Scheme 29. Overall goals and precedent (R = 3-Cl) for microwave-assisted Garnett H/D exchange of anilines

Uncatalysed Deuteration:



Catalysed Deuteration:

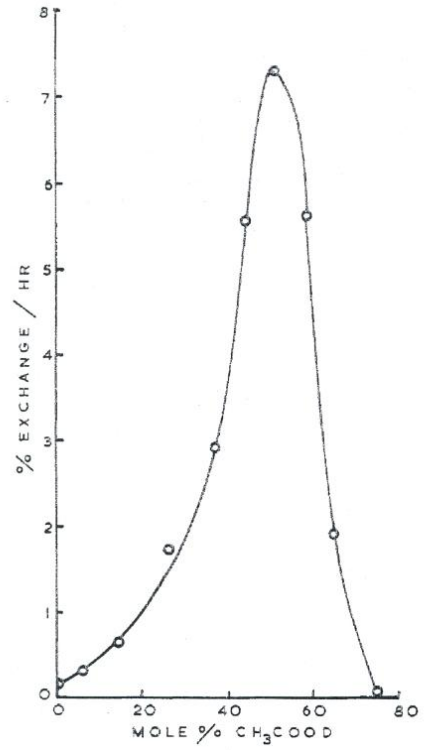


Subsequent to deuteration a number of techniques were employed to firstly purify the product and secondly establish the efficiency of the process, both in terms of chemical yield and the incorporation of deuterium.

Following the platinum-catalysed deuteration of a substrate, addition of thioglycolic acid was used to remove platinum contamination. Sulphur's high affinity for platinum gives rise to fast formation of a thiolate acid – platinum complex. The glycolic acid group then allows for easy removal of the platinum during the aqueous work up.

The use of deuterium oxide as the deuterium source was employed to minimise competing reactions, such as hydrogenation on the surface of the exchange catalyst. The lack of gaseous reagents is also beneficial when using microwave irradiation in synthesis.[42] The solvent plays an important factor in the catalysed exchange reactions. The relationship between acidity and percentage exchange/hour, as demonstrated by Garnett,[67] clearly indicates an optimum acidity of 50 mol% acetic acid (**Figure 4**). At lower concentrations the platinum catalyst precipitates quickly to give a lower concentration of catalyst in solution, hence the rate of exchange is reduced, complicating the process by the presence of heterogeneous Pt. At higher concentrations, D^+ competes with the aromatic compound for complex formation with the catalyst, again reducing the rate of exchange.

Figure 4. The relationship between acidity and H/D exchange[67]



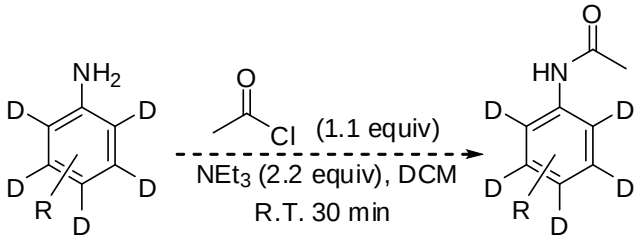
The temperature and time of the reaction are important in exchange. Garnett showed for nitrobenzene with $CH_3COOD–D_2O$ containing DCl (0.02 M) and K_2PtCl_4 (0.02 M), 2 h at 120 °C, gives deuteration of 90% *meta+para*, and 12% *ortho*.[67]

2.1. Calculating the Percentage Deuteration.

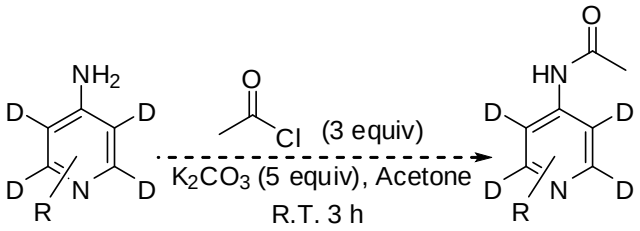
Following deuteration of the substrate it was considered important to establish both accurate percentage deuteration at each active hydrogen position and percentage yield of the deuterated substrate. This would be achieved by the introduction of an internal reference by acetylation of the amine group (**Scheme 30**) for analysis by ^{1}H NMR spectroscopy.

Scheme 30. Introduction of an internal reference

Acetylation of Aniline Substrates:

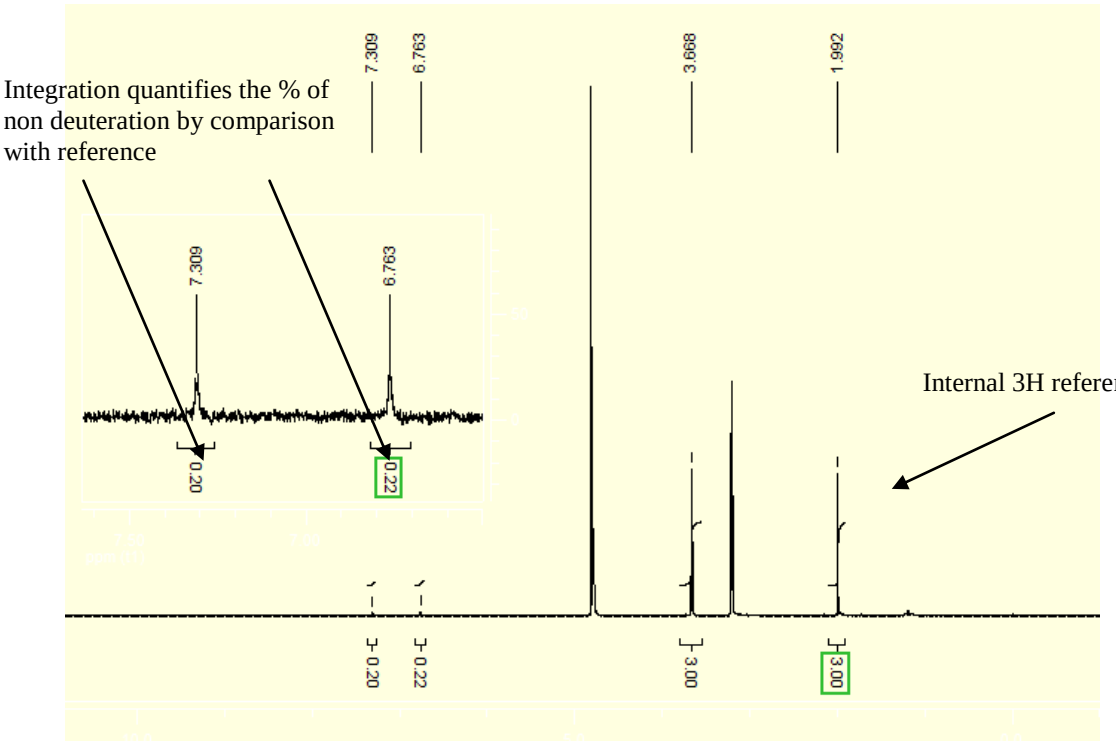


Acetylation of Pyridine Substrates:



With the addition of the acetyl group it was possible to calculate the percentage deuteration using ^{1}H NMR spectroscopic analysis with the methyl group as an internal reference peak. This is shown below in the example of d_4-*p*-anisidine (**Figure 5**).[82]

Figure 5. ***^{1}H NMR spectrum of d_4-N-(p-anisidine)acetamide where the acetyl group acts as an internal reference[82]***

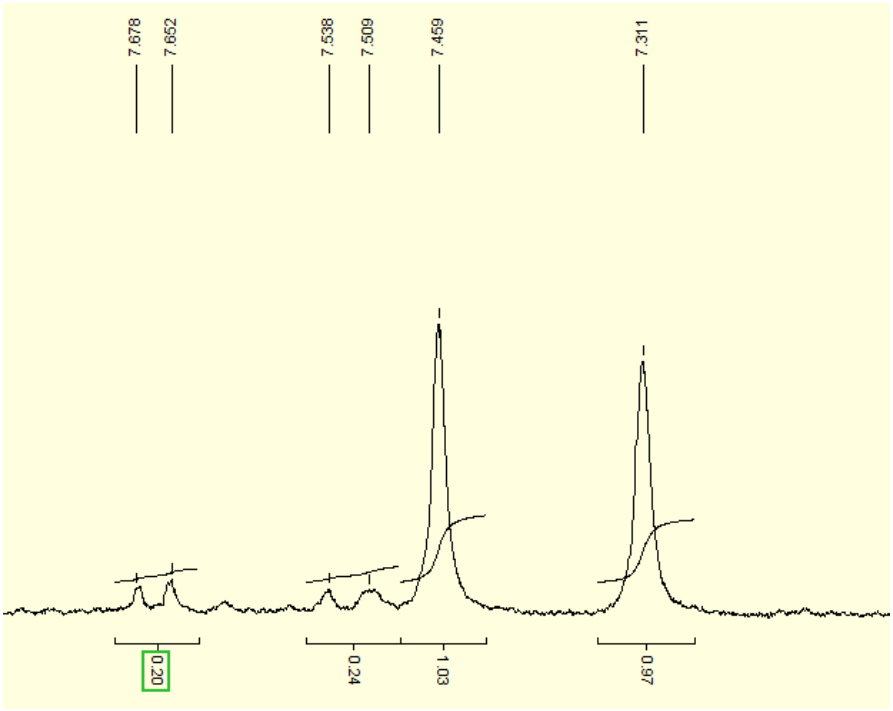


Using the acetyl methyl peak as a reference, it would be possible to accurately calculate the deuteration of the different hydrogen environments by integrating each peak against the three hydrogen integration of the acetyl methyl (δ = 1.99 ppm) peak. Only simple calculations would then be required to work out the percentage deuteration.

For example the peak corresponding to that of the protons *ortho* to the amide (δ = 7.31 ppm), have an integration of 0.20 H, as opposed to the undeuterated integration of 2.00 H. A simple subtraction quantifies that 1.80 of the 2.00 hydrogens have been exchanged for deuterium; this corresponds to 90% deuteration. The same calculations could then used for each environment to give the deuteration of each active hydrogen position. Peaks are assigned by the use of reference spectra. These would be produced by the acetylation of the corresponding undeuterated substrate, and thus are of great importance when assigning peaks. This is especially true in highly deuterated species, where it is not always possible to see each proton environment due to the high incorporation of deuterium in these positions.

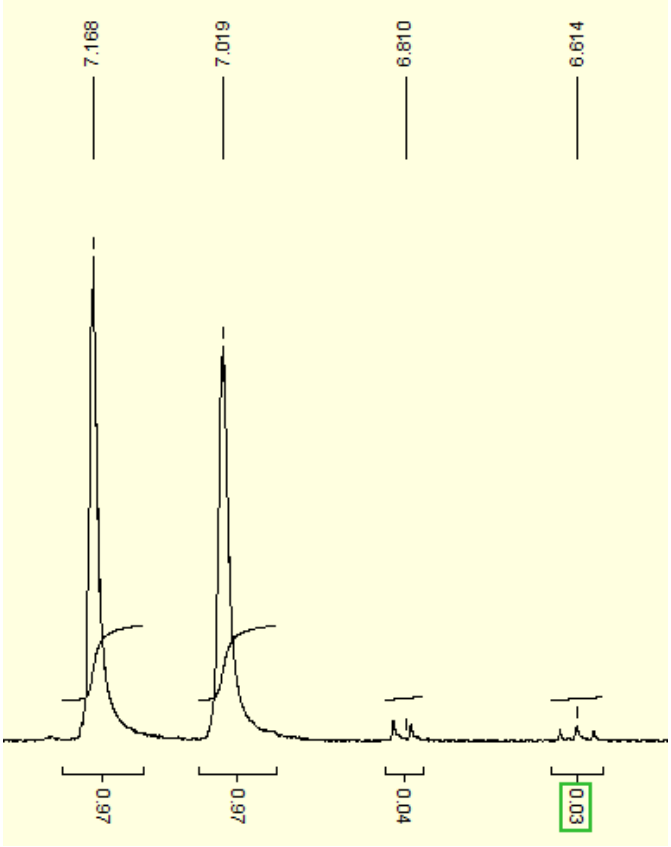
In certain spectra small impurities or overlaps between peaks of interest could be anticipated to make it difficult to obtain accurate levels of deuteration for all positions. This could then be overcome by the combined use of both the acetylated product spectrum and that of the unacetylated product. For this reason, it was considered important to analyze also the non-acetylated deuterated products in anticipation of any of these problems. An example of a poorly resolved acetamide spectrum is shown below for the H/D exchange of d_2-2-chloroaniline (**Figure 6**).[82]

***Figure 6. Integration of the aromatic region in the ^{1}H NMR spectrum of d_2-N-(2-chloroaniline)acetamide*[82]**



The impure nature of the spectrum and lack of complete resolution/separation of peaks meant that the majority of integrations shown were inaccurate. However, the peak corresponding to the proton in the 5-position (δ = 7.31 ppm) appeared unaffected by impurities and therefore has been used as a second reference in the spectrum of the unacetylated substrate (**Figure 7**).[82]

Figure 7. All aromatic peaks are resolved in the the ^{1}H NMR spectrum of d_2-2-chloroaniline[82]



Using this dual approach the percentage deuteration could be calculated accurately for problematic substrates and errors due to impurities accounted for.

2.2. Calculating the Percentage Yield

Once the percentage deuteration of the substrate had been calculated, it was possible to calculate an accurate average molecular weight (Mr′) for the product by simple calculation. Although the real percentage yield would not be expected to be at great disparity from that using the Mr of the starting material this level of rigour was carried out as a matter of course. This in turn would enable the calculation of accurate percentage yields in the usual manner:

$$Mr' = Mr_{\,starting\ material} + 1.001\,(D2\% + D3\% + D4\% + D5\% + D6\%)$$

M_r(D)-M_r(H) — Levels of Deuteration

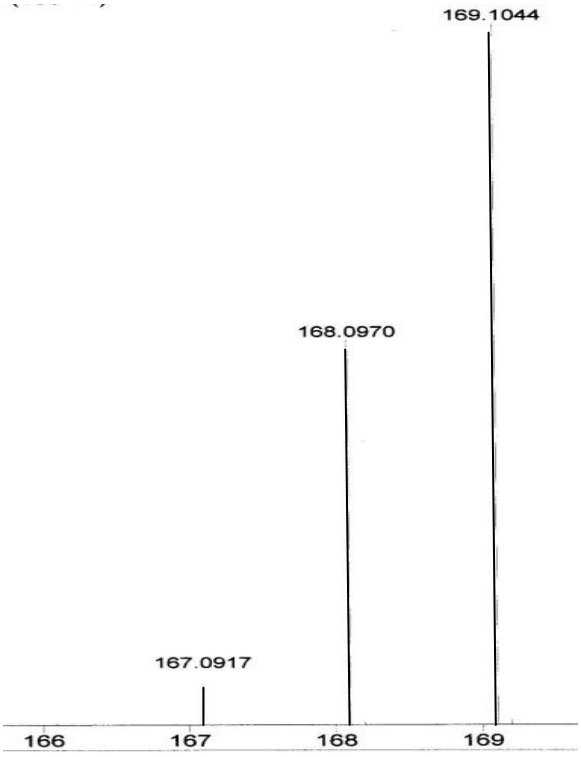
$$mMol' = \frac{M_r'}{Mass\ of\ Recovered\ Product}$$

$$Yield\ \% = \frac{mMol'}{mMol_{starting\ Material}} \times 100$$

2.3. Use of Other Characterisation Data

Supporting evidence was obtained by mass spectrometry, not only to provide information on the structure of the molecule but also to support the percentage deuteration data provided by the ^{1}H NMR spectroscopic analysis (**Figure 7**). ^{13}C NMR spectroscopy was also used where appropriate, to give information on not only the structure of the final product but also on the positions of high deuterium exchange. This is due to the difference in spin of deuterium giving a different multiplicity for the deuterated carbons than those bonded to a proton in a ^{1}H decoupled ^{13}C spectrum.[82] IR spectroscopy and melting points were also used to characterise the different compounds.

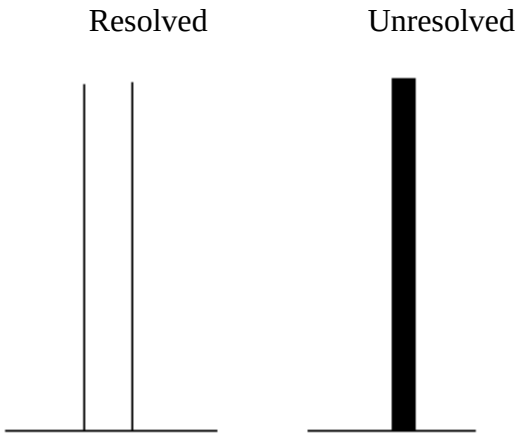
***Figure 8. Mass spectrum of N-(d_4-2-anisidin)acetamide*[82]**



For example, in the mass spectrum of *N*-(d_4-2-anisidin)acetamide (**Figure 8**),[82] one expects a mass of 169 with deuteration in four aromatic positions. This mass was confirmed by mass spectrometry whilst the expansion showed the different

isotopologues present. High resolution masses were obtained where possible although it was not always possible to separate the isotopologue peaks from those of the corresponding ^{13}C peaks (^{13}C is present at an isotopic natural abundance of 1.10%) of an isotopologue containing one less deuterium (**Figure 9**).

Figure 9.Resolution of isotopologue peaks in the mass spectrum



The resolution required can be calculated for each specific substrate. For example, for d_2-*p*-toluidine

$$Resolution = \frac{m}{\Delta m} = \frac{109.0829}{0.0032} \approx 34000$$

The resolution of the mass spectrometer used was ≈ 7000 and therefore the two peaks would be observed as a broad unresolved peak, thus preventing recovery of the highly resolved mass spectrometric data.

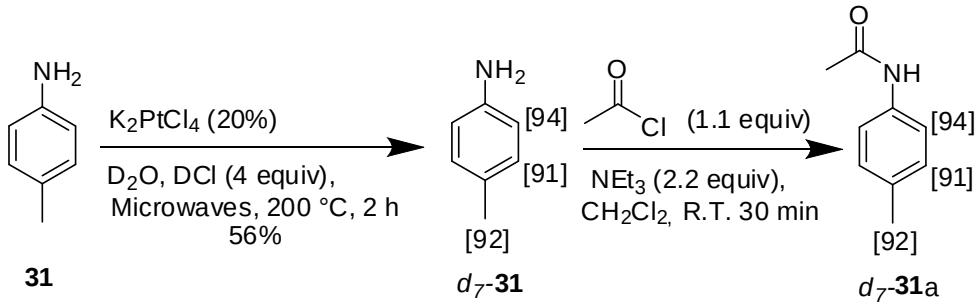
2.4. Pt-Catalyzed and Metal-Free H-D Exchange of Substituted Anilines

2.4.1. H/D-Exchange of *p*-Toluidine

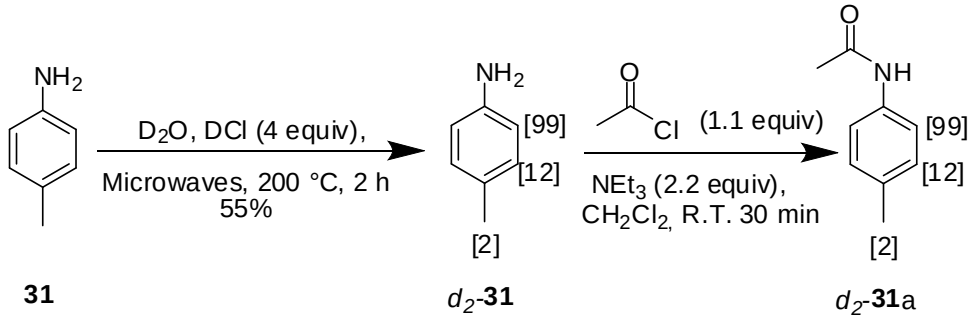
For the first reaction of study, the Pt-catalyzed H-D exchange of *p*-toluidine (**31**) was investigated under microwave irradiation. This substrate would demonstrate the influence of this catalyst system on both aryl and alkyl H/D exchange and could establish if an *ortho*-steric effect was in evidence in the Pt-catalysed process, as one might expect. A solution of *p*-toluidine was added to a stirred solution of the Pt catalyst and DCl in D_2O in a Pyrex tube and the mixture was irradiated at 200 °C in the sealed

vessel for 2 hours. Thioglycolic acid was added to the mixture after cooling in a stream of compressed air to remove platinum contamination. Then the solution was neutralized by the addition of NaOH and extracted with CH_2Cl_2 to give the *d_7-p*-toluidine (*d_7*-**31**) which was analyzed by ^{1}H NMR spectroscopy and mass spectrometry. Further derivatization by acetylation was carried out to quantify the overall degree of H-D exchange by adding acetyl chloride to a stirred solution of *d_7-p*-toluidine (*d_7*-**31**) in CH_2Cl_2 and NEt_3 on ice under a N_2 atmosphere. The mixture was warmed to room temperature and stirred for 30 min then quenched by the addition of hydrochloric acid to give the *d_7-N*-(4-toluidine)acetamide (*d_7*-**31**a) (**Scheme 31**). The same reaction was repeated but in the absence of the Pt catalyst to give the *d_2-N*-(4-toluidine)acetamide (*d_2*-**31**a) (**Scheme 32**).

Scheme 31. Pt-catalyzed deuteration of p-toluidine (31)



Scheme 32. Metal-free deuteration of p-toluidine (31)



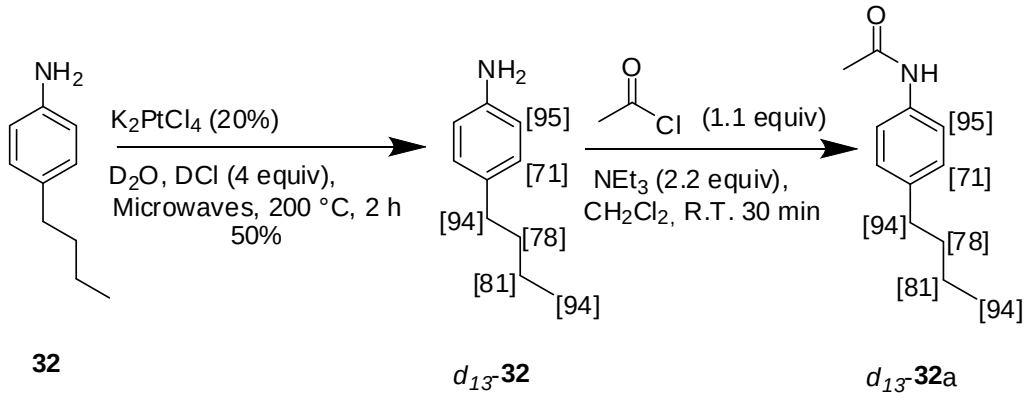
Acetylation as before was used to calculate the percentage deuteration of the different hydrogen environments by integrating each peak against the three hydrogen integration of the acetyl methyl peak as an internal reference. In this analysis the peak corresponding to the protons *meta* to the amide NH (δ = 6.91 ppm) exhibited an integration of 0.18 H for the Pt-catalyzed process, as opposed to the integration of the product of the uncatalyzed reaction, the ^{1}H NMR of which following deuteration showed an integration of 2.00 H. A simple subtraction quantified that an average of 1.82 of the 2.00 hydrogens had been exchanged for deuterium; this corresponded to 91%

deuterium incorporation. The same analysis of the peak corresponding to the protons at C-2/C-6 (δ = 6.91 ppm) showed an integration of 0.12 H, as opposed to the product from the metal-free reaction which showed an integration in this region of 1.76 H. The peak corresponding to the protons at C-1′ (δ = 2.16 ppm) displayed an integration of 0.23 H, as opposed to the product from the uncatalyzed reaction where the same resonance showed an integration of 2.99 H. The yield for the H-D exchange reaction was 56% and in the absence of the metal catalyst it was similar (55%). The mass of the product was confirmed using analysis by mass spectrometry and showed the major peak at *m/z* 160 for the catalyzed reaction and 151 in the absence of a catalyst. All of this evidence illustrates that without a Pt catalyst no significant exchange occurs at unactivated aromatic or alkyl side chain positions but there is good incorporation at C-2 and C-6. Using a Pt catalyst there is still good deuterium incorporation at C-2 and C-6, and at C-3/C-4/C-5 the metal has facilitated exchange. Given the ready incorporation of deuterium in the side chain, this could be envisaged to occur by formation of a Pt-alkyl σ-complex. The study of an alternative substrate containing a longer length of side chain would provide further evidence for and understanding of this process.

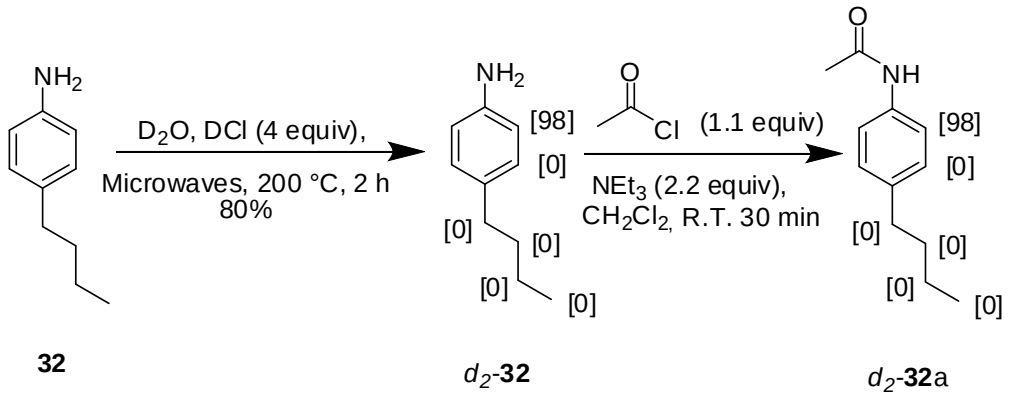
2.4.2. H/D-Exchange of *p*-*n*-Butylaniline

The Pt-catalyzed H-D exchange of *p*-*n*-butylaniline (**32**) was investigated under microwave irradiation as a substituted butylaniline to establish the effect of increasing chain length on the H/D exchange process. A solution of *p*-*n*-butylaniline (**32**) was added to a stirred solution of the Pt catalyst and DCl in D_2O in a Pyrex tube and the mixture was irradiated at 200 °C in the sealed vessel for 2 hours. Thioglycolic acid was added to the mixture after cooling in a stream of compressed air to remove platinum contamination. Then the solution was neutralized by the addition of NaOH and extracted with CH_2Cl_2 to give the d_{13}-4-*n*-butylaniline (d_{13}-**32**) which was analyzed by ^{1}H NMR spectroscopy and mass spectrometry. Further derivatization by acetylation was carried out to quantify the overall degree of H-D exchange by adding acetyl chloride to a stirred solution of d_{13}-4-*n*-butylaniline (d_{13}-**32**) in CH_2Cl_2 and NEt_3 on ice under a N_2 atmosphere. The mixture was warmed to room temperature and stirred for 30 min then quenched by the addition of hydrochloric acid to give the d_{13}-*N*-(4-*n*-butylphenyl)acetamide (d_{13}-**32**a) (**Scheme 33**). The same reaction was repeated but in the absence of the Pt catalyst to give the d_2-*N*-(4-*n*-butylphenyl)acetamide (d_2-**32**a) (**Scheme 34**).

Scheme 33. Pt-catalyzed deuteration of p-n-butylaniline (32)



Scheme 34. Metal-free deuteration of p-n-butylaniline (32)



Acetylation as before was used to calculate the percentage deuteration of the different hydrogen environments by integrating each peak against the three hydrogen integration of the acetyl methyl peak as an internal reference. In this analysis the peak corresponding to the protons *meta* to the amide NH (δ = 6.66 ppm) exhibited an integration of 0.57 H, as opposed to the integration of the product of the uncatalyzed reaction, the ^{1}H NMR of which following deuteration showed an integration of 2.00 H. A simple subtraction quantified that an average of 1.43 of the 2.00 hydrogens had been exchanged for deuterium; this corresponded to 71% deuterium incorporation. The same analysis of the peak corresponding to the protons at C-2/C-6,(δ = 6.91 ppm), showed an integration of 0.11 H, as opposed to the product from the metal-free reaction which showed an integration in this region of 0.5 H. The peak corresponding to the protons at C-1′ (δ = 2.44 ppm) displayed an integration of 0.13 H, as opposed to the product from the uncatalyzed reaction where the same resonance showed an integration of 2 H. Furthermore, the peak corresponding to the protons at C-2′ (δ = 1.47 ppm) exhibited an

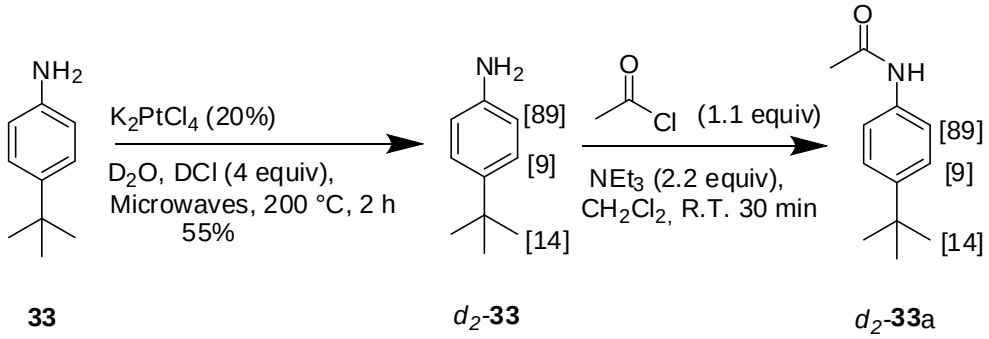
integration of 0.44 H, as opposed to the uncatalyzed reaction where no incorporation occurred at this position (integration of 2H). Similarly, the peak corresponding to the protons at C-3′ (δ = 1.26 ppm), displayed an integration of 0.39 H from the Pt-catalyzed reaction, as opposed to the product from the metal-free reaction which showed an integration of 2 H in this region. The yield for the H-D exchange reaction was 50% whereas in the absence of the metal catalyst it was 80%. The mass of the product was confirmed by analysis by mass spectrometry and showed the major peak at *m/z* 160 for the catalyzed reaction and *m/z* 151 in the absence of a catalyst. All of this evidence illustrates that without a Pt catalyst no significant exchange occurs at unactivated aromatic or alkyl side chain positions but there is good incorporation at C-2 and C-6 (**Scheme 34**). Using a Pt catalyst there is still good deuterium incorporation at C-2 and C-6, although this is reduced slightly due to increased exchange elsewhere, with good incorporation at C-3 and C-5, lowered due to an *ortho* steric effect; whereas in the side chain the role of the catalyst is clear in that there is high exchange at C-1′ and C-4′ and less significant exchange at C-2′ and C-3′ (**Scheme 33**). Given the ready incorporation of deuterium in the side chain, this could be envisaged to occur by formation of a Pt-alkyl σ-complex. The study of an alternative substrate containing a quaternary centre would provide further evidence for and understanding of this process.

2.4.3. H/D-Exchange of 4-*tert*-Butylaniline

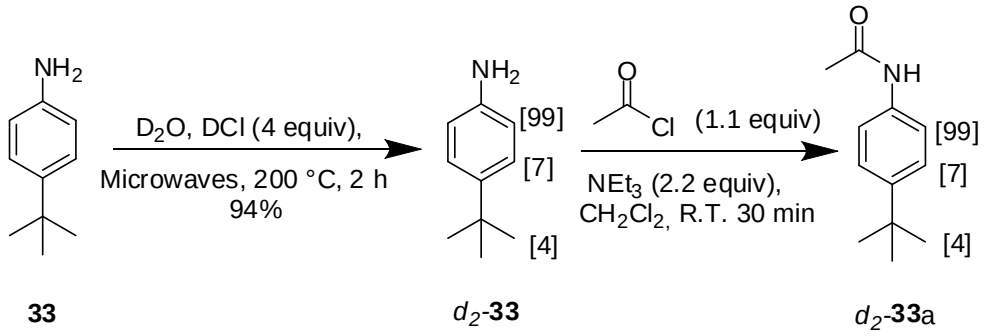
4-*tert*-Butylaniline (**33**) was selected as a substrate with a quaternary centre to see the effect of this structure on H-D exchange. A solution of 4-*tert*-butylaniline (**33**) was added to a stirred solution of the Pt catalyst and DCl in D_2O in a Pyrex tube and the mixture was irradiated at 200 °C in the sealed vessel for 2 hours. Thioglycolic acid was added to the mixture after cooling in a stream of compressed air to remove platinum contamination. Then the solution was neutralized by the addition of NaOH and extracted with CH_2Cl_2 to give the d_2-4-*tert*-butylaniline (d_2-**33**) which was analyzed by ^{1}H NMR spectroscopy and mass spectrometry. Further derivatization by acetylation was carried out to quantify the overall degree of H-D exchange by adding acetyl chloride to a stirred solution of d_2-4-*tert*-butylaniline (d_2-**33**) in CH_2Cl_2 and NEt_3 on ice under a N_2 atmosphere. The mixture was warmed to room temperature and stirred for 30 min then quenched by the addition of hydrochloric acid to give the d_2-*N*-(4-*tert*-butylphenyl)acetamide (d_2-**33**a) (**Scheme 35**). The same reaction was repeated but in the

absence of the Pt catalyst to give the d_2-*N*-(4-*tert*-butylphenyl)acetamide (d_2-**33**a) (**Scheme 36**).

Scheme 35. Pt-catalyzed deuteration of 4-tert-butylaniline (33)



Scheme 36. Metal-free deuteration of 4-tert-butylaniline (33)



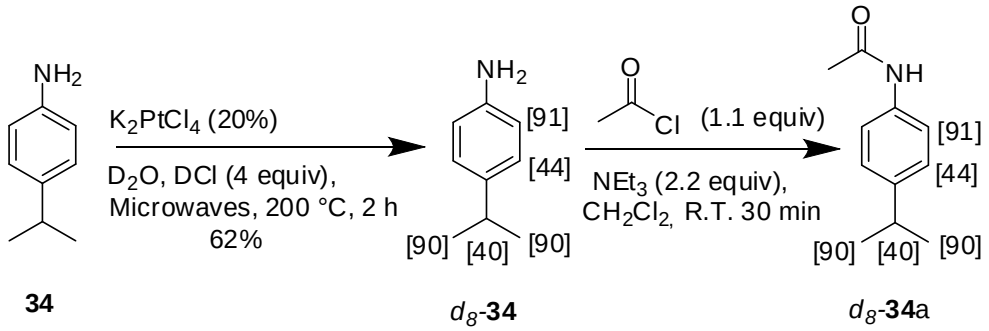
Acetylation as before was used to calculate the percentage deuteration of the different hydrogen environments by integrating each peak against the three hydrogen integration of the acetyl methyl peak as an internal reference. In this analysis the peak corresponding to the protons *meta* to the amide NH (δ = 7.13 ppm) exhibited an integration of 1.83 H, as opposed to the integration of the product of the uncatalyzed reaction, the ^{1}H NMR of which following deuteration showed an integration of 2.00 H. A simple subtraction quantified that an average of 0.17 of the 2.00 hydrogens had been exchanged for deuterium; this corresponded to 9% deuterium incorporation at each methine position. The same analysis of the peak corresponding to the protons at C-2/C-6 (δ = 6.67 ppm) showed an integration of 0.23 H, as opposed to the product from the metal-free reaction which showed an integration in this region of 0.02 H. The peak corresponding to the protons at C-1′ (δ = 1.25 ppm) displayed an integration of 7.72 H,

as opposed to the product from the metal-free reaction which showed an integration of 8.61 H in this region. The yield for the H-D exchange reaction was 55% whereas in the absence of the metal catalyst it was 94%. The mass of the product was confirmed by analysis by mass spectrometry and showed the major peak at *m/z* 151 for the catalyzed reaction and *m/z* 151 in the absence of a catalyst. All of this evidence illustrates that exchange cannot occur past a quaternary centre as the species cannot form the σ-complex. Furthermore, an *ortho* steric effect prevents metal exchange to C-3/5 of the aniline, as this would hinder formation of a Pt-alkyl σ-complex. The study of an alternative substrate containing branching in the side chain would provide further evidence for this process.

2.4.4. H/D-Exchange of 4-Isopropylaniline

4-Isopropylaniline (**34**) was selected as a substrate with increased branching to see the effect of this structure on H-D exchange. A solution of 4-isopropylaniline (**34**) was added to a stirred solution of the Pt catalyst and DCl in D_2O in a Pyrex tube and the mixture was irradiated at 200 °C in the sealed vessel for 2 hours. Thioglycolic acid was added to the mixture after cooling in a stream of compressed air again to remove platinum contamination. Then the solution was neutralized by the addition of NaOH and extracted to give the d_8-4-isopropylaniline (d_8-**34**) which was analyzed by ^{1}H NMR spectroscopy and mass spectrometry. Further derivatization by acetylation was carried out to quantify the overall degree of H-D exchange. Adding acetyl chloride to a stirred solution of d_8-4-isopropylaniline (d_8-**34**) in CH_2Cl_2 and NEt_3 on ice under a N_2 atmosphere gave the d_8-*N*-(4-isopropylphenyl)acetamide (d_8-**34**a) (**Scheme 37**).

Scheme 37. Pt-catalyzed deuteration of 4-isopropylaniline (34)



34 d_8-**34** d_8-**34**a

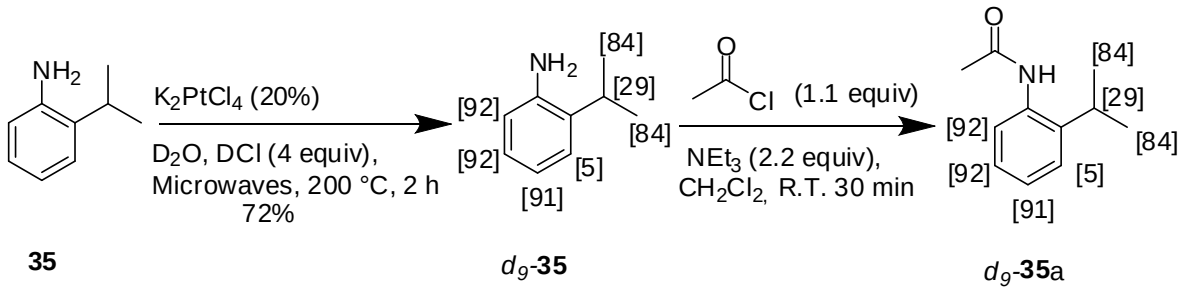
Each peak was integrated against the three hydrogen integration of the acetyl methyl peak as an internal reference. In this analysis the peak corresponding to the protons

meta to the amide NH (δ = 7.16 ppm) exhibited an integration of 1.12 H, the ^{1}H NMR of which should in the absence of exchange show an integration of 2.00 H. A simple subtraction quantified that an average of 0.88 of the 2.00 hydrogens had been exchanged for deuterium; this corresponded to 44% deuterium incorporation at each methine. The same analysis of the peak corresponding to the protons at C-2/C-6 (δ = 7.42 ppm) showed an integration of 0.19 H. The peak corresponding to the protons at C-1′ (δ = 2.46 ppm) displayed an integration of 0.60 H. The peak corresponding to the protons at C-2′ (δ = 1.14 ppm) displayed an integration of 0.60 H which corresponds to very high H/D exchange at this terminal position (90%). The yield for the H-D exchange reaction was 62%. The mass of the product was confirmed by analysis by mass spectrometry and showed the major peak at *m/z* 143 for the catalyzed reaction. All of this evidence illustrates that exchange does occur with branching in the side chain of the substrate as under Pt-catalysis the σ-complex will form providing there is not a quaternary centre. An *ortho* steric effect hinders metal exchange to aniline, by preventing formation of the Pt-alkyl σ-complex. The study of an alternative substrate with an alternative substitution pattern containing branching in the side chain would provide further evidence for this process.

2.4.5. H/D-Exchange of 2-Isopropylaniline

2-Isopropylaniline (**35**) was selected as a substrate with increased branching to see the effect of this structure on H-D exchange. A solution of 2-isopropylaniline (**35**) was added to a stirred solution of the Pt catalyst and DCl in D_2O in a Pyrex tube and the mixture was irradiated at 200 °C in the sealed vessel for 2 hours, as before. Thioglycolic acid was added to the mixture after cooling in a stream of compressed air to remove platinum contamination. Then the solution was neutralized by the addition of NaOH and extracted with CH_2Cl_2 to give the d_9-2-isopropylaniline (d_9-**35**) which was analyzed by ^{1}H NMR spectroscopy and mass spectrometry. Further derivatization by acetylation was carried out to quantify the overall degree of H-D exchange by adding acetyl chloride to a stirred solution of d_9-2-isopropylaniline (d_9-**35**) in CH_2Cl_2 and NEt_3 on ice under a N_2 atmosphere. The mixture was warmed to room temperature and stirred for 30 min then quenched by the addition of hydrochloric acid to give the d_9-*N*-(2-isopropylphenyl)acetamide (d_9-**35**a) (**Scheme 38**).

Scheme 38. Pt-catalyzed deuteration of 2-isopropylaniline (35)



35 d_9-**35** d_9-**35**a

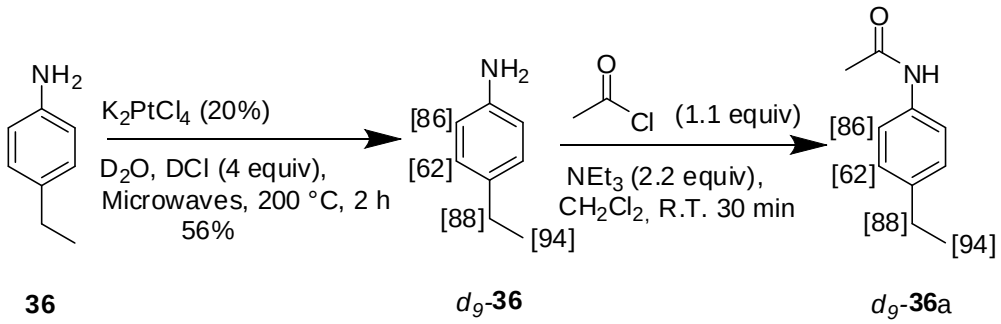
Each peak was integrated against the three hydrogen integration of the acetyl methyl peak as an internal reference. In this analysis the peak corresponding to the protons at C-6 (δ = 7.24 ppm) exhibited an integration of 0.08 H, the ^{1}H NMR of which following deuteration showed an integration of 2.00 H. A simple subtraction quantified that an average of 0.92 of the 2.00 hydrogens had been exchanged for deuterium; this corresponded to 92% deuterium incorporation. The same analysis of the peak corresponding to the protons at C-3 (δ = 7.34 ppm) showed an integration of 0.95 H. The same analysis of the peak corresponding to the protons at C-4 (δ = 7.18 ppm) showed an integration of 0.09 H. The same analysis of the peak corresponding to the protons at C-5 (δ = 7.18 ppm) demonstrated an integration of 0.08 H. The peak corresponding to the protons at C-1′ (δ = 3.13 ppm) displayed an integration of 0.71 H. The peak corresponding to the protons at C-2′ (δ = 1.58 ppm) displayed an integration of 0.98 H. The yield for the H-D exchange reaction was 72%. The mass of the product was confirmed by analysis by mass spectrometry and showed the major peak at *m/z* 144 for the catalyzed reaction. All of this evidence illustrates that exchange can occur with branching in the side chain and so a σ-complex must be forming. An *ortho* steric effect prevents metal-mediated exchange at the hindered positions of the aniline but efficient metal-mediated exchange is occurring at C-5; this could be envisaged to occur by formation of a Pt-alkyl σ-complex. The study of an alternative substrate containing a smaller side chain would provide further evidence for this process.

2.4.6. H/D-Exchange of 4-Ethylaniline

4-Ethylaniline (**36**)was selected as a substrate with increased chain length (over the toluidine) to see the effect of this structure on H-D exchange. A solution of 4-ethylaniline (**36**) was added to a stirred solution of the Pt catalyst and DCl in D_2O in a

Pyrex tube and the mixture was irradiated at 200 °C in the sealed vessel for 2 hours. Thioglycolic acid was added to the mixture after cooling in a stream of compressed air to remove platinum contamination. Then the solution was neutralized by the addition of NaOH and extracted with CH_2Cl_2 to give the d_9-4-ethylaniline (d_9-**36**) which was analyzed by ^{1}H NMR spectroscopy and mass spectrometry. Further derivatization by acetylation was carried out to quantify the overall degree of H-D exchange by adding acetyl chloride to a stirred solution of d_9-4-ethylaniline (d_9-**36**) in CH_2Cl_2 and NEt_3 on ice under a N_2 atmosphere. The mixture was warmed to room temperature and stirred for 30 min then quenched by the addition of hydrochloric acid to give the d_9-*N*-(4-ethylphenyl)acetamide (d_9-**36**a) (**Scheme 39**).

Scheme 39. Pt-catalyzed deuteration of 4-ethylaniline(36)



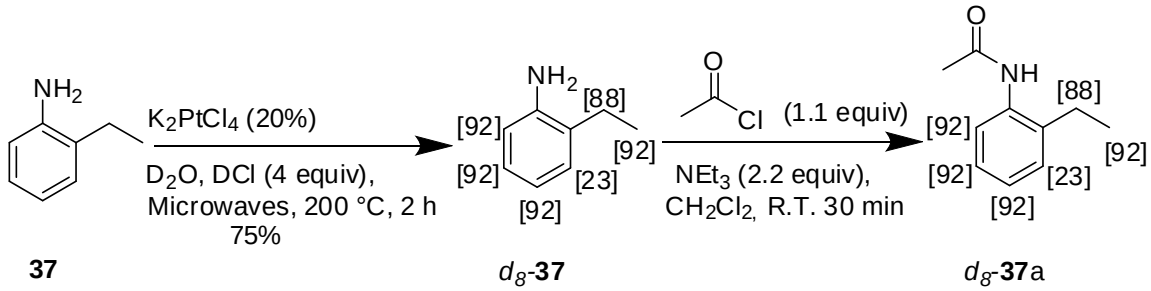
Each peak was integrated against the three hydrogen integration of the acetyl methyl peak as an internal reference. In this analysis the peak corresponding to the protons *meta* to the amide NH (δ = 7.15 ppm) exhibited an integration of 0.77 H, the ^{1}H NMR of which following deuteration showed an integration of 2.00 H. A simple subtraction quantified that an average of 1.23 of the 2.00 hydrogens had been exchanged for deuterium; this corresponded to 62% deuterium incorporation. The same analysis of the peak corresponding to the protons at C-2/C-6 (δ = 7.44 ppm) showed an integration of 0.27 H. The peak corresponding to the protons at C-1′ (δ = 1.19 ppm) displayed an integration of 0.24 H. The peak corresponding to the protons at C-2′ (δ = 2.58 ppm) displayed an integration of 0.17 H. The yield for the H-D exchange reaction was 56%. The mass of the product was confirmed by analysis by mass spectrometry and showed the major peak at *m/z* 130 for the catalyzed reaction. All of this evidence illustrates that exchange in the side chain can occur and is highly efficient at all positions. An *ortho* steric effect prevents metal exchange to the aniline by hindering formation of a Pt-alkyl

σ-complex. The study of an alternative substitution pattern would provide further evidence for this process.

2.4.7. H/D-Exchange of 2-Ethylaniline

2-Ethylaniline (**37**) was selected as an alternative substrate in to see the effect of this structure on H-D exchange. A solution of 2-ethylaniline (**37**) was added to a stirred solution of the Pt catalyst and DCl in D_2O in a Pyrex tube and the mixture was irradiated at 200 °C in the sealed vessel for 2 hours. Thioglycolic acid was added to the mixture after cooling in a stream of compressed air to remove platinum contamination. Then the solution was neutralized by the addition of NaOH and extracted with CH_2Cl_2 to give the d_8-2-ethylaniline (d_8-**37**) which was analyzed by ^{1}H NMR spectroscopy and mass spectrometry. Further derivatization by acetylation was carried out to quantify the overall degree of H-D exchange by adding acetyl chloride to a stirred solution of d_8-2-ethylaniline (d_8-**37**) in CH_2Cl_2 and NEt_3 on ice under a N_2 atmosphere. The mixture was warmed to room temperature and stirred for 30 min then quenched by the addition of hydrochloric acid to give the d_8-*N*-(2-ethylphenyl)acetamide (d_8-**37**a) (**Scheme 40**).

Scheme 40. Pt-catalyzed deuteration of 2-ethylaniline (37)



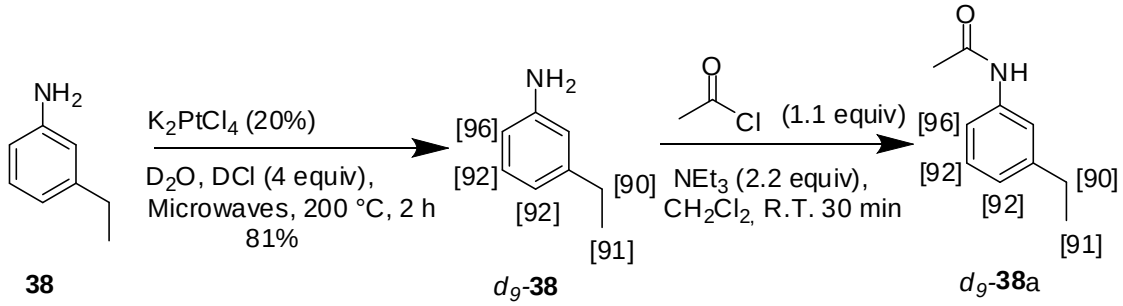
Each peak was integrated against the three hydrogen integration of the acetyl methyl peak as an internal reference. In this analysis the peak corresponding to the protons *meta* to the amide NH (δ = 7.21 ppm) exhibited an integration of 0.77 H, the ^{1}H NMR of which following deuteration showed an integration of 2.00 H. A simple subtraction quantified that an average of 0.23 of the 1 hydrogen had been exchanged for deuterium; this corresponded to 23% deuterium incorporation. The same analysis of the peak corresponding to the protons at C-4/C-5 (δ = 7.12 ppm) showed an integration of 0.15 H. The peak corresponding to the protons at C-6 (δ = 7.32 ppm) displayed an integration of 0.08 H. The peak corresponding to the protons at C-1′ (δ = 2.55 ppm)

displayed an integration of 0.23 H. The peak corresponding to the protons at C-2′ (δ = 1.05 ppm) displayed an integration of 0.25 H. The yield for the H-D exchange reaction was 75%. The mass of the product was confirmed by analysis by mass spectrometry and showed the major peak at *m/z* 129 for the catalyzed reaction. All of this evidence illustrates that exchange can occur in the side chain of this alternative substrate. Again, an *ortho* steric effect prevents metal exchange at the hindered positions by inhibiting the formation of a Pt-alkyl σ-complex. The study of the last isomer would provide further evidence for this process.

2.4.8. H/D-Exchange of 3-Ethylaniline

3-Ethylaniline (**38**) was selected to complete this part of the study to see the effect of this structure on H-D exchange. With this substrate, all hindered positions are activated towards electrophilic aromatic substitution. A solution of 3-ethylaniline (**38**) was added to a stirred solution of the Pt catalyst and DCl in D_2O in a Pyrex tube and the mixture was irradiated at 200 °C in the sealed vessel for 2 hours. Thioglycolic acid was added to the mixture after cooling in a stream of compressed air to remove platinum contamination. Then the solution was neutralized by the addition of NaOH and extracted with CH_2Cl_2 to give the d_9-3-ethylaniline (d_9-**38**) which was analyzed by ^{1}H NMR spectroscopy and mass spectrometry. Further derivatization by acetylation was carried out to quantify the overall degree of H-D exchange by adding acetyl chloride to a stirred solution of d_9-3-ethylaniline (d_9-**38**) in CH_2Cl_2 and NEt_3 on ice under a N_2 atmosphere. The mixture was warmed to room temperature and stirred for 30 min then quenched by the addition of hydrochloric acid to give the d_9-*N*-(3-ethylphenyl)acetamide (d_9-**38**a) (**Scheme 41**).

Scheme 41. Pt-catalyzed deuteration of 3-ethylaniline (38)



38 d_9-**38** d_9-**38**a

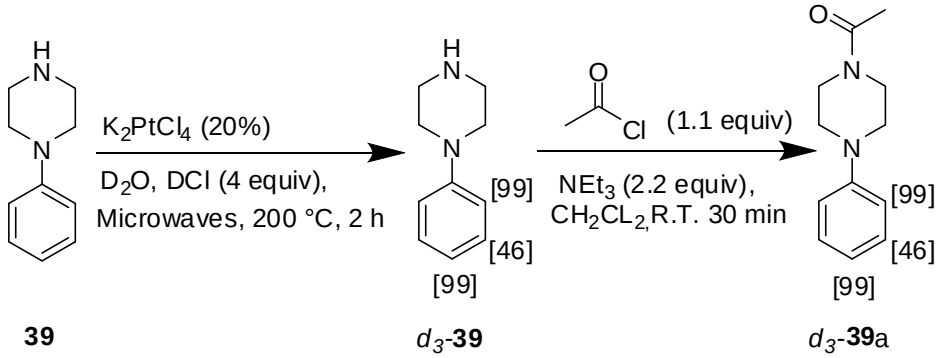
Each peak was integrated against the three hydrogen integration of the acetyl methyl peak as an internal reference. In this analysis the peak corresponding to the protons at C-2/C-6 (δ = 7.37 ppm) exhibited an integration of 0.08 H, the ^{1}H NMR of which

following deuteration showed an integration of 2.00 H. A simple subtraction quantified that an average of 1.92 of the 2.00 hydrogens had been exchanged for deuterium; this corresponded to 96% deuterium incorporation. The same analysis of the peak corresponding to the protons at C-4 (δ = 7.33 ppm) showed an integration of 0.09 H. The peak corresponding to the protons at C-5 (δ = 7.19 ppm) displayed an integration of 0.08 H. The peak corresponding to the protons at C-1′ (δ = 2.57 ppm) displayed an integration of 0.21 H. The peak corresponding to the protons at C-2′ (δ = 1.16 ppm) displayed an integration of 0.28 H. The yield for the H-D exchange reaction was 81%. The mass of the product was confirmed by analysis by mass spectrometry and showed the major peak at *m/z* 130 for the catalyzed reaction. All of this evidence illustrates that now all positions undergo H/D exchange – the *ortho* steric effect being countered by electronic activation towards electrophilic aromatic substitution. However what was not clear from these experiments was whether H/D exchange could occur in a side chain beyond a heteroatom. The study of an alternative substrate containing a heteroatom in the side chain would provide further evidence for this process.

2.4.9. H/D-Exchange of *N*-Phenylpiperazine

N-Phenylpiperazine (**39**) was selected as a substrate bearing a heteroatom in the side chain to see the effect of this structure on H-D exchange. A solution of the phenylpiperazine (**39**) was added to a stirred solution of the Pt catalyst and DCl in D_2O in a Pyrex tube and the mixture was irradiated at 200 °C in the sealed vessel for 2 hours. Thioglycolic acid was added to the mixture after cooling in a stream of compressed air to remove platinum contamination. Then the solution was neutralized by the addition of NaOH and extracted with CH_2Cl_2 to give the d_3-1-phenylpiperazine (d_3-**39**) which was analyzed by ^{1}H NMR spectroscopy and mass spectrometry. Further derivatization by acetylation was carried out to quantify the overall degree of H-D exchange by adding acetyl chloride to a stirred solution of d_3-1-phenylpiperazine (d_3-**39**) in CH_2Cl_2 and NEt_3 on ice under a N_2 atmosphere. The mixture was warmed to room temperature and stirred for 30 min then quenched by the addition of hydrochloric acid to give the d_3-*N*-(1-phenylpiperazine)acetamide (d_3-**39a**) (**Scheme 42**).

Scheme 42. Pt-catalyzed deuteration of phenylpiperazine (39)



39 d_3-**39** d_3-**39**a

Each peak was integrated against the three hydrogen integration of the acetyl methyl peak as an internal reference. In this analysis the peak corresponding to the protons at C-2/C-6 (δ = 7.09 ppm) exhibited an integration of 0.05 H, the ^{1}H NMR of which following deuteration showed an integration of 2.00 H. A simple subtraction quantified that an average of 1.95 of the 2.00 hydrogens had been exchanged for deuterium; this corresponded to 99% deuterium incorporation. The same analysis of the peak corresponding to the protons at C-3/C-5 (δ = 7.24 ppm) showed an integration of 1.07 H. The peak corresponding to the protons at C-4 (δ = 6.96 ppm) displayed an integration of 0.02 H. The yield for the H-D exchange reaction was 83%. The mass of the product was confirmed by analysis by mass spectrometry and showed the major peak at *m/z* 165 for the catalyzed reaction. All of this evidence illustrates that exchange cannot occur in the side chain past a heteroatom which could be because the π-allylic complex is not forming (see **Scheme 28** in the Introduction for comparison) and/or it could be because the Pt-alkyl σ-complex is not able to form. This represents a limit of the methodology; that a heteroatom in the side chain would seem to prevent further H/D exchange.

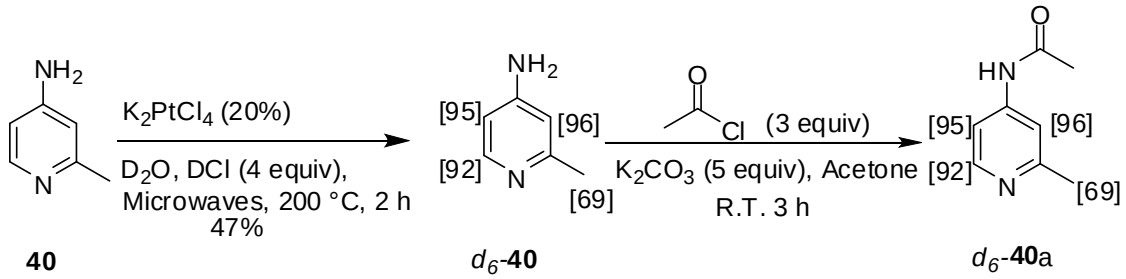
2.5. Pt-Catalyzed and Metal-Free H-D Exchange of Substituted Pyridines

2.5.1. H/D-Exchange of 4-Amino-2-methylpyridine

With a suitable method established for H/D exchange of anilines, it now remained to establish the scope of the process by investigating a series of alternative substrates. Thus, aminopyridines were chosen as they exhibit different electronic properties and yet are valuable building blocks in heterocyclic chemistry. Pyridines are electron-poor

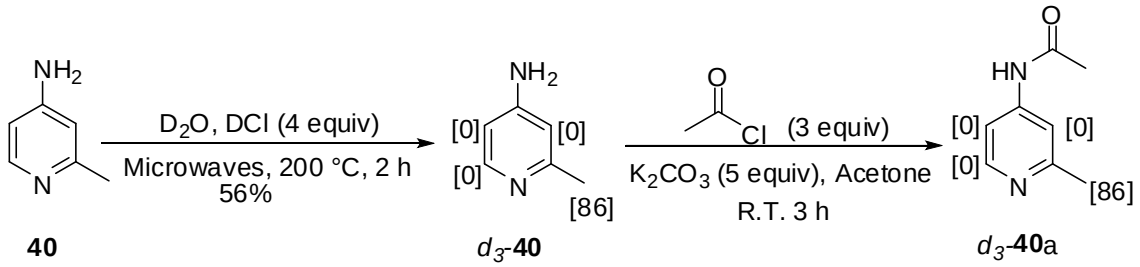
aromatic compounds and do not ordinarily undergo electrophilic aromatic substitution with ease, although the introduction of an electron-donating group (such as an amino group) can facilitate this process. The Pt-catalyzed H-D exchange of 4-amino-2-methylpyridine (**40**) was first investigated under microwave irradiation as an example of a substituted methylpyridine. A solution of 4-amino-2-methylpyridine (**40**) was added to a stirred solution of the Pt catalyst and DCl in D_2O in a Pyrex tube and the mixture was irradiated at 200 °C in the sealed vessel for 2 hours, as before. Thioglycolic acid was added to the mixture after cooling in a stream of compressed air to remove platinum contamination. Then the solution was basified by the addition of NaOH and extracted with CH_2Cl_2 to give the d_6-4-amino-2-methylpyridine (d_6-**40**) which was analyzed by ^{1}H NMR spectroscopy and mass spectrometry. Further derivatization by acetylation was carried out to quantify the overall degree of H-D exchange by adding acetyl chloride to a stirred solution of d_6-4-amino-2-methylpyridine (d_6-**40**) in K_2CO_3. The mixture was stirred for 3 h then quenched by the addition of water to give the d_6-*N*-(pyridine-2-methyl-4-yl)acetamide (d_6-**40**a) (**Scheme 43**). The same reaction was repeated but in the absence of the Pt catalyst to establish the behaviour of this electron-rich pyridine under the metal-free conditions (**Scheme 44**).

Scheme 43. Pt-catalyzed deuteration of 4-amino-2-methylpyridine (40)



40 d_6-**40** d_6-**40**a

Scheme 44. Metal-free deuteration of 4-amino-2-methylpyridine (40)



40 d_3-**40** d_3-**40**a

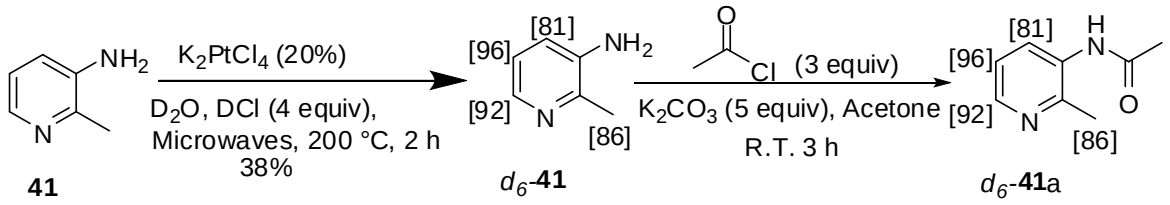
Each peak was integrated against the three hydrogen integration of the acetyl methyl peak as an internal reference. In this analysis the peak corresponding to the protons at C-3 (δ = 6.42 ppm) exhibited an integration of 0.04 H, as opposed to the integration of the product of the uncatalyzed reaction, the ^{1}H NMR of which following deuteration showed an integration of 1 H. A simple subtraction quantified that an average of 0.96 of the 1 hydrogens had been exchanged for deuterium; this corresponded to 96% deuterium incorporation. The same analysis of the peak corresponding to the protons at C-5 (δ = 6.37 ppm) showed an integration of 0.05 H, as opposed to the product from the metal-free reaction which showed an integration in this region of 1 H. The peak corresponding to the protons at C-6 (δ = 7.83 ppm) displayed an integration of 0.08 H, as opposed to the product from the uncatalyzed reaction where the same resonance showed an integration of 1 H. Furthermore, the peak corresponding to the protons at 2-Me (δ = 2.27 ppm) exhibited an integration of 0.94 H, as opposed to the product from the metal-free reaction which showed an integration of 0.42 H in this region. The yield for the H-D exchange reaction was 47% whereas in the absence of the metal catalyst it was 56%. These yields seemed reduced in comparison to the aniline series and this was considered to be a consequence of reduced efficiency in the work up and isolation procedure. The mass of the product was confirmed by analysis by mass spectrometry and showed the major peak at *m/z* 114 for the catalyzed reaction and *m/z* 110 in the absence of a catalyst. All of this evidence illustrates that without a Pt catalyst poor ring exchange has occurred whereas good exchange is in evidence at 2-Me. Using a Pt catalyst, excellent ring exchange is now in evidence, whereas at the 2-Me group the level of exchange is reduced presumably due to ready incorporation in the ring. The study of an alternative substrate would provide further evidence for and understanding of this process.

2.5.2. H/D-Exchange of 3-Amino-2-methylpyridine

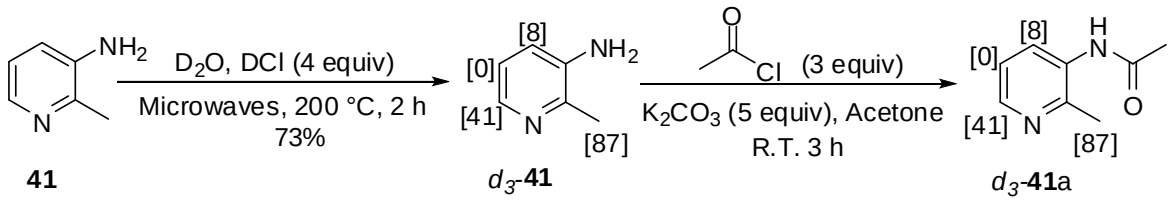
The Pt-catalyzed H-D exchange of 3-amino-2-methylpyridine (**41**) was investigated under microwave irradiation as an alternatively substituted methylpyridine. A solution of 3-amino-2-methylpyridine (**41**) was added to a stirred solution of the Pt catalyst and DCl in D_2O in a Pyrex tube and the mixture was irradiated at 200 °C in the sealed vessel for 2 hours. Thioglycolic acid was added to the mixture after cooling in a stream of compressed air to remove platinum contamination. Then the solution was neutralized by

the addition of NaOH and extracted with CH_2Cl_2 to give the d_6-3-amino-2-methylpyridine (d_6-**41**) which was analyzed by ^{1}H NMR spectroscopy and mass spectrometry. Further derivatization by acetylation was carried out to quantify the overall degree of H-D exchange by adding acetyl chloride to a stirred solution of d_6-3-amino-2-methylpyridine (d_6-**41**) in K_2CO_3. The mixture was stirred for 3 h then quenched by the addition of water to give the d_6-*N*-(pyridine-2-methyl-3-yl)acetamide (d_6-**41**a) (**Scheme 45**). The same reaction was repeated but in the absence of the Pt catalyst to give the d_3-*N*-(2-methyl-3-yl)acetamide (d_3-**41**a) (**Scheme 46**).

Scheme 45. Pt-catalyzed deuteration of 3-amino-2-methylpyridine (41)



Scheme 46. Metal-free deuteration of 3-amino-2-methylpyridine (41)



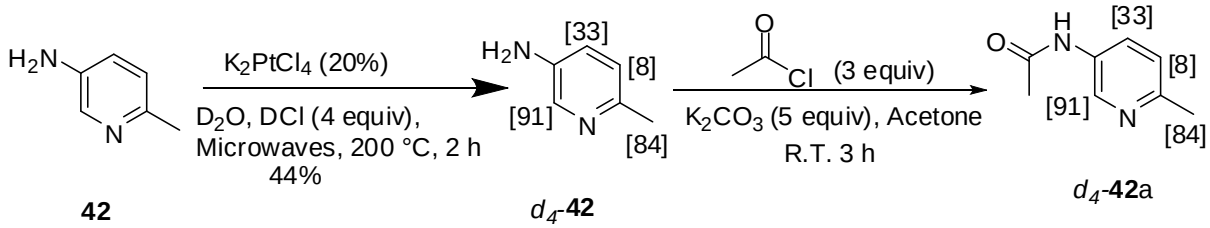
Each peak was integrated against the three hydrogen integration of the acetyl methyl peak as an internal reference. In this analysis the peak corresponding to the protons at C-4 (δ = 8.25 ppm) exhibited an integration of 0.19 H, as opposed to the integration of the product of the uncatalyzed reaction, the ^{1}H NMR of which following deuteration showed an integration of 1 H. A simple subtraction quantified that an average of 0.81 of the 1 hydrogens had been exchanged for deuterium; this corresponded to 81% deuterium incorporation. The same analysis of the peak corresponding to the protons at C-5 (δ = 7.88 ppm) showed an integration of 0.04 H, as opposed to the product from the metal-free reaction which showed an integration in this region of 1 H. The peak corresponding to the protons at C-6 (δ = 7.28 ppm) displayed an integration of 0.08 H, as opposed to the product from the uncatalyzed reaction where the same resonance showed an integration of 0.59 H. Furthermore, the peak corresponding to the protons at 2-Me (δ = 2.46 ppm) exhibited an integration of 0.41 H, as opposed to the product from the metal-free reaction which showed an integration of 0.37 H in this region. The yield

for the H-D exchange reaction was again low at 38% whereas in the absence of the metal catalyst it was 73%. The mass of the product was confirmed by analysis by mass spectrometry and showed the major peak at *m/z* 114 for the catalyzed reaction and *m/z* 111 in the absence of a catalyst. All of this evidence illustrates that without a Pt catalyst poor ring exchange and good exchange at in the 2-methyl group is occurring, whereas with the catalyst excellent ring exchange is facilitated by Pt, with a corresponding reduction in exchange in the side chain due to ready incorporation in ring perhaps. Interestingly, H/D exchange at C-4 was reduced and this could be due to the *ortho* substituent and pyridines preference for electrophilic aromatic substitution directed towards the β-position. The study of an alternative substrate would provide further evidence for and understanding of this process.

2.5.3. H/D-Exchange of 5-Amino-2-methylpyridine

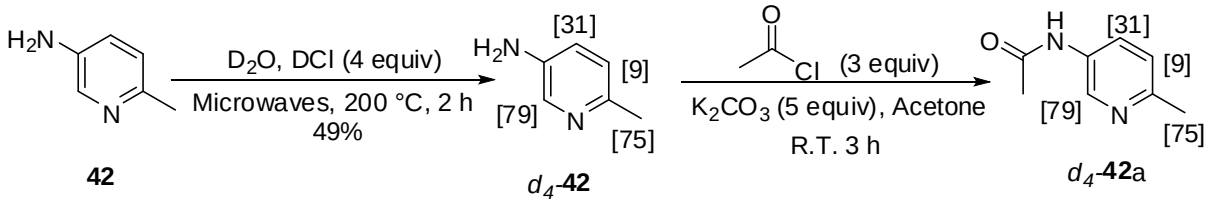
The Pt-catalyzed H-D exchange of 5-amino-2-methylpyridine (**42**) was investigated under microwave irradiation as another example of a substituted methylpyridine. A solution of 5-amino-2-methylpyridine (**42**) was added to a stirred solution of the Pt catalyst and DCl in D_2O in a Pyrex tube and the mixture was irradiated at 200 °C in the sealed vessel for 2 hours. Thioglycolic acid was added to the mixture after cooling in a stream of compressed air to remove platinum contamination. Then the solution was neutralized by the addition of NaOH and extracted with CH_2Cl_2 to give the d_4-5-amino-2-methylpyridine (d_4-**42**) which was analyzed by ^{1}H NMR spectroscopy and mass spectrometry. Further derivatization by acetylation was carried out to quantify the overall degree of H-D exchange by adding acetyl chloride to a stirred solution of d_4-5-amino-2-methylpyridine (d_4-**42**) in K_2CO_3. The mixture was stirred for 3 h then quenched by the addition of water to give the d_4-*N*-(pyridine-2-methyl-5-yl)acetamide (d_4-**42**a) (**Scheme 47**). The same reaction was repeated but in the absence of the Pt catalyst to give the d_4-*N*-(2-methyl-5-yl)acetamide (d_4-**42**a) (**Scheme 48**).

Scheme 47. Pt-catalyzed deuteration of 5-amino-2-methylpyridine (42)



42 d_4-**42** d_4-**42**a

Scheme 48. Metal-free deuteration of 5-amino-2-methylpyridine (42)



42 d_4-**42** d_4-**42**a

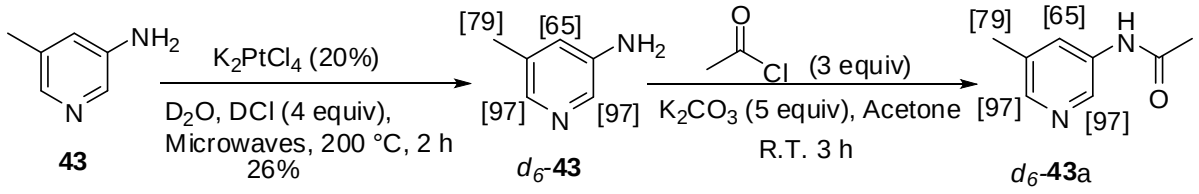
Each peak was integrated against the three hydrogen integration of the acetyl methyl peak as an internal reference. In this analysis the peak corresponding to the protons at C-3 (δ = 7.26 ppm) exhibited an integration of 0.92 H, as opposed to the integration of the product of the uncatalyzed reaction, the ^{1}H NMR of which following deuteration showed an integration of 1 H. A simple subtraction quantified that an average of 0.08 of the 1 hydrogens had been exchanged for deuterium; this corresponded to 8% deuterium incorporation. The same analysis of the peak corresponding to the protons at C-4 (δ = 7.95 ppm) showed an integration of 0.67 H, as opposed to the product from the metal-free reaction which showed an integration in this region of 0.69 H. The peak corresponding to the protons at C-6 (δ = 8.58 ppm) displayed an integration of 0.09 H, as opposed to the product from the uncatalyzed reaction where the same resonance showed an integration of 0.21 H. Furthermore, the peak corresponding to the protons at 2-Me (δ = 2.45 ppm) exhibited an integration of 0.50 H, as opposed to the product from the metal-free reaction which showed an integration of 0.75 H in this region. The yield for the H-D exchange reaction was again low both in the presence (44%) and absence (49%) of the metal catalyst and so isolation issues could not be ruled out. The mass of the product was confirmed by analysis by mass spectrometry and showed the major peak at *m/z* 112 for both the catalyzed and metal-free reactions. All of this evidence illustrates that without a Pt catalyst incorporation has improved at C-6 and in the methyl group but at C-3 it has not increased due to an *ortho* steric effect. The study of an alternative substrate would provide further evidence on understanding of this process.

2.5.4. H/D-Exchange of 3-Amino-5-methylpyridine

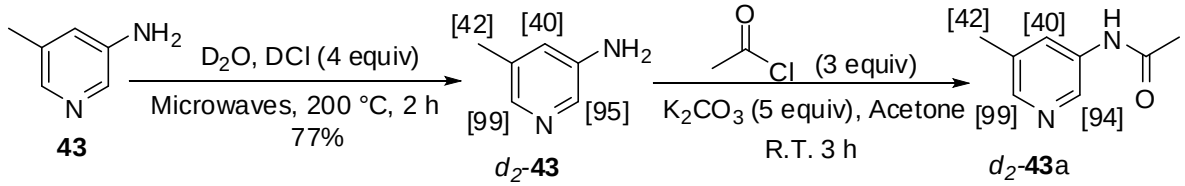
The Pt-catalyzed H-D exchange of 3-amino-5-methylpyridine (**43**) was investigated under microwave irradiation on a substituted methylpyridine. A solution of 3-amino-5-methylpyridine (**43**) was added to a stirred solution of the Pt catalyst and DCl in D_2O in a Pyrex tube and the mixture was irradiated at 200 °C in the sealed vessel for 2 hours.

Thioglycolic acid was added to the mixture after cooling in a stream of compressed air to remove platinum contamination. Then the solution was neutralized by the addition of NaOH and extracted with CH_2Cl_2 to give the d_6-3-amino-5-methylpyridine (d_6-**43**) which was analyzed by ^{1}H NMR spectroscopy and mass spectrometry. Further derivatization by acetylation was carried out to quantify the overall degree of H-D exchange by adding acetyl chloride to a stirred solution of d_6-3-amino-5-methylpyridine (d_6-**43**) in K_2CO_3. The mixture was stirred for 3 h then quenched by the addition of water to give the d_6-*N*-(pyridine-5-methyl-3-yl)acetamide (d_6-**43**a) (**Scheme 49**). The same reaction was repeated but in the absence of the Pt catalyst to give the d_2-*N*-(5-methyl-3-yl)acetamide (d_2-**43**a) (**Scheme 50**).

Scheme 49. Pt-catalyzed deuteration of 3-amino-5-methylpyridine (43)



Scheme 50. Metal-free deuteration of 3-amino-5-methylpyridine (43)



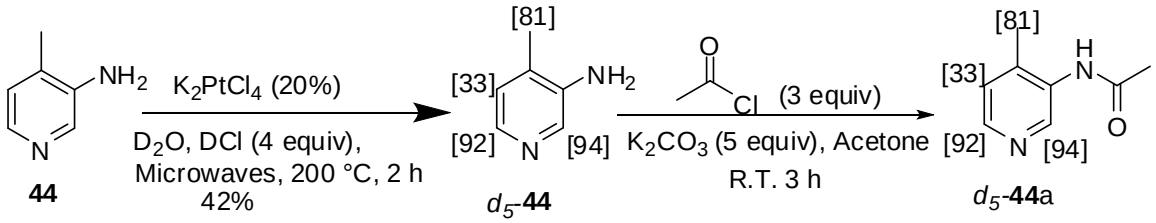
Each peak was integrated against the three hydrogen integration of the acetyl methyl peak as an internal reference. In this analysis the peak corresponding to the protons at C-2 (δ = 8.09 ppm) exhibited an integration of 0.03 H, as opposed to the integration of the product of the uncatalyzed reaction, the ^{1}H NMR of which following deuteration showed an integration of 1 H. A simple subtraction quantified that an average of 0.97 of the 1 hydrogens had been exchanged for deuterium; this corresponded to 97% deuterium incorporation. The same analysis of the peak corresponding to the protons at C-4 (δ = 7.93 ppm) showed an integration of 0.35 H, as opposed to the product from the metal-free reaction which showed an integration in this region of 0.60 H. The peak corresponding to the protons at C-6 (δ = 8.51 ppm) displayed an integration of 0.03 H, as opposed to the product from the uncatalyzed reaction where the same resonance

showed an integration of 0.01 H. Furthermore, the peak corresponding to the protons in the methyl group (δ = 2.31 ppm) exhibited an integration of 0.61 H, as opposed to the product from the metal-free reaction which showed an integration of 1.76 H in this region. The yield for the H-D exchange reaction was again low (26%) whereas in the absence of the metal catalyst it was 77%, perhaps indicating in this case that complexation to the metal was reducing the efficiency of the isolation procedure. The mass of the product was confirmed by analysis by mass spectrometry and showed the major peak at *m/z* 114 for the catalyzed reaction and *m/z* 110 in the absence of a catalyst. All of this evidence illustrates that with a Pt catalyst exchange does improve at C-4 but is impeded by an *ortho* steric effect; without the Pt catalyst exchange is very good at activated positions, although reduced exchange is observed in the methyl group as it is less acidic at C-5. Higher exchange is observed under both sets of conditions at C-2 and C-6 as these positions are now activated by the amino group. The study of an alternative substrate would provide further evidence for and understanding of this process.

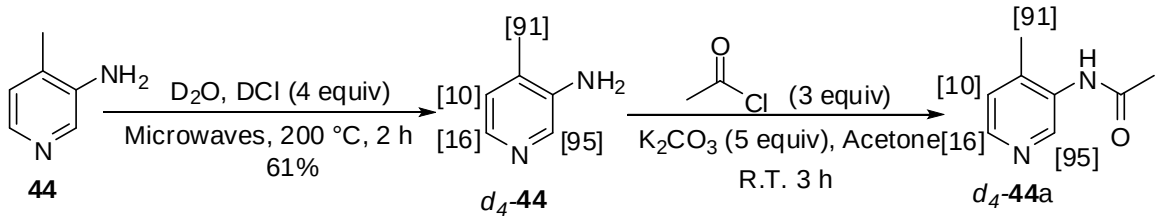
2.5.5. H/D-Exchange of 3-Amino-4-methylpyridine

The Pt-catalyzed H-D exchange of 3-amino-4-methylpyridine (**44**) was investigated under microwave irradiation as an alternatively substituted methylpyridine. A solution of 3-amino-4-methylpyridine (**44**) was added to a stirred solution of the Pt catalyst and DCl in D_2O in a Pyrex tube and the mixture was irradiated at 200 °C in the sealed vessel for 2 hours. Thioglycolic acid was added to the mixture after cooling in a stream of compressed air to remove platinum contamination. Then the solution was neutralized by the addition of NaOH and extracted with CH_2Cl_2 to give the d_5-3-amino-4-methylpyridine (d_5-**44**) which was analyzed by ^{1}H NMR spectroscopy and mass spectrometry. Further derivatization by acetylation was carried out to quantify the overall degree of H-D exchange by adding acetyl chloride to a stirred solution of d_5-3-amino-4-methylpyridine (d_5-**44**) in K_2CO_3. The mixture was stirred for 3 h then quenched by the addition of water to give the d_5-*N*-(pyridine-4-methyl-3-yl)acetamide (d_5-**44**a) (**Scheme 51**). The same reaction was repeated but in the absence of the Pt catalyst to give the d_4-*N*-(4-methyl-3-yl)acetamide (d_4-**44**a) (**Scheme 52**).

Scheme 51. Pt-catalyzed deuteration of 3-amino-4-methylpyridine (44)



Scheme 52. Metal-free deuteration of 3-amino-4-methylpyridine (44)



Each peak was integrated against the three hydrogen integration of the acetyl methyl peak as an internal reference. In this analysis the peak corresponding to the protons at C-2 (δ = 8.21 ppm) exhibited an integration of 0.06 H, as opposed to the integration of the product of the uncatalyzed reaction, the ^{1}H NMR of which following deuteration showed an integration of 1 H. A simple subtraction quantified that an average of 0.94 of the 1 hydrogens had been exchanged for deuterium; this corresponded to 94% deuterium incorporation. The same analysis of the peak corresponding to the protons at C-6 (δ = 8.45 ppm) showed an integration of 0.08 H, as opposed to the product from the metal-free reaction which showed an integration in this region of 0.84 H. The peak corresponding to the protons at C-5 (δ = 7.25 ppm) displayed an integration of 0.67 H, as opposed to the product from the uncatalyzed reaction where the same resonance showed an integration of 0.90 H. Furthermore, the peak corresponding to the protons in the methyl group (δ = 2.31 ppm) exhibited an integration of 0.57 H, as opposed to the product from the metal-free reaction which showed an integration of 0.27 H in this region. The yield for the H-D exchange reaction was 42% whereas in the absence of the metal catalyst it was 61%. The mass of the product was confirmed by analysis by mass spectrometry and showed the major peak at *m/z* 113 for the catalyzed reaction and *m/z* 112 in the absence of a catalyst. All of this evidence illustrates that with a Pt catalyst reduced exchange was observed in the side chain due to increased incorporation elsewhere and high incorporation occurred at C-6, whereas at C-5 it was lower than expected due to the *ortho* steric effect.

All-in-all, this series of aminopyridines demonstrated that the microwave-assisted method that had been successful for substituted anilines was also appropriate for different targets. Alternative substitution patterns have probed the *ortho*-steric effect and although yields were lower than the aniline series the study was considered a success. Not only was this method able to facilitate exchange in a β-methyl group but this study has shown it can also alter and improve the deuteration of a pyridine ring.

3. Conclusion

The deuteration of aniline derivatives using microwave irradiation has given an insight into the selectivity and efficiency of both acid and platinum-catalysed deuteration. While the understanding of acid-catalysed electrophilic substitution is well established, the combination of such reactions with the analogous platinum-catalysed process allowed for direct comparison, giving a greater insight into the selectivity and chemistry of the platinum-catalysed exchange reactions.

It has been shown that the H/D exchange of aniline derivatives without platinate catalysis proceeded as expected giving deuteration at activated positions and the H/D exchange with the platinum catalyst provided deuteration at all aromatic positions, undergoing H/D exchange providing there is no *ortho* steric affect. Furthermore, platinum catalysis was able to facilitate exchange in alkyl side chains with high efficiency providing there was no quaternary centre.

The H/D exchange of pyridine derivatives without platinum catalysis proceeded as expected giving deuteration at activated positions and in the methyl group but the deuteration was reduced for some substrates due to *ortho* steric affect. Sometimes good exchange occurred at all positions even though there were *ortho* substituents when a platinum catalyst was used.

In general, the yield for the microwave assisted procedure is good, varying between 73 to 81%. The reactions are relatively short, and high levels of deuterium incorporation are observed with only a single cycle/pass. Furthermore, the method requires no chromatographic purification and is simple to carry out.

In conclusion, this is a useful procedure for the synthesis of deuterated targets that should find use in the chemist's modern toolkit.

4. Experimental

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4. Experimental

4.1. General Procedures

Commercially available reagents were used without further purification. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF254 that were visualised under UV light (at 254 and/or 360 nm). Microwave irradiation experiments were performed using a self-tunable CEM Discover focused monomodal microwave synthesiser at the given temperature, measured using the instrument's in-built IR sensor, by varying the irradiation power (initial power given in parentheses). Infra-red (IR) spectra were recorded in the range 4000-600 cm-1 using KBr disks for solid samples and thin films between NaCl plates for liquid samples or as a nujol mull and are reported in cm-1. Nuclear magnetic resonance (NMR) spectra were recorded in CDCl3 at 25 °C unless stated otherwise and were reported in ppm; J values were recorded in Hz and multiplicities were expressed by the usual conventions. Low-resolution mass spectra (MS) were determined using electron ionization (EI). In vacuo refers to evaporation at reduced pressure using a rotary evaporator and diaphragm pump, followed by the removal of trace volatiles using a vacuum (oil) pump.

4.1.1. General Procedure for Pt-Catalysed H/D Exchange

A solution of aniline derivatives or pyridines derivatives was added to a stirred solution of K_2PtCl_4) (20 mol %.) and DCl (35%) in D_2O (3 mL) in a 10 mL Pyrex tube. The mixture was irradiated at 200 °C using a CEM Discover microwave synthesiser by moderating the initial power (300 W) with maximum pressure of 150 psi in a sealed vessel for 2 hours. The reaction mixture was cooled to room temperature. To the solution thioglycolic acid was added. Then the solution was neutralized by the addition of NaOH (1M; 10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined, dried (MgSO4), filtered and evaporated under vacuum.

4.1.2. General Procedure for Metal-Free H/D Exchange

A solution of an aniline derivative or pyridine derivative was added to a stirred solution of DCl (35%) in D_2O (3 mL) in a 10 mL Pyrex tube. The mixture was irradiated at 200 °C using a CEM Discover microwave synthesiser by moderating the initial power (300 W) with a maximum pressure of 150 psi in sealed vessel for 2 hours. The reaction

mixture was cooled to room temperature. To the solution thioglycolic acid was added. Then the solution was neutralized by the addition of NaOH (1M; 10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum.

4.1.3. General Procedure for Acetylation

4.1.3.1 Acetylation of Aniline Derivatives

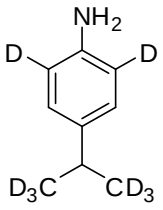
Acetyl chloride was added to a stirred solution of the aniline derivative in CH_2Cl_2 (5 mL) and NEt_3 on ice under a N_2 atmosphere. The mixture was warmed to room temperature and stirred for 30 min. Hydrochloric acid was added and the organic layer was washed with hydrochloric acid, dried ($MgSO_4$), and evaporated under vacuum.

4.1.3.2 Acetylation of Pyridine Derivatives

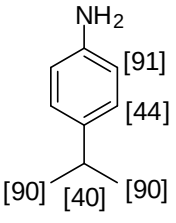
A solution of the pyridine derivative was dissolved in acetone (20 mL) and K_2CO_3 was added, followed by the dropwise addition of acetyl chloride in acetone (5 mL). The reaction mixture was stirred for 3 h. The solution was quenched by water, then the solvent was evaporated *in vacuo* and the crude extracted three times with CH_2Cl_2. The organic phase was dried by Na_2SO_4 and filtrated. Then the solvent was evaporated *in vacuo*.

4.2.Experimental Data for Pt-Catalysed H/D Exchange

d_8-4-Isopropylaniline (*d_8*-34)



d_8-**34**



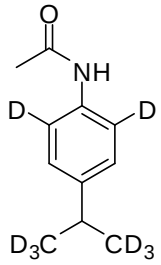
d_8-**34**

According to General Procedure 4.1, using 4-isopropylaniline (**34**) (300 mg, 303 µL, 2.22 mmol, 1 equiv), K_2PtCl_4 (182 mg, 0.44 mmol, 20 mol%), DCl (35%; 731 µL, 8.88 mmol, 4 equiv) in D_2O (3 mL), thioglycolic acid (124 µL, 1.76 mmol, 4 equiv), and aqueous NaOH solution (1 M; 10 mL) gave the *d_8*-4-isopropylaniline (*d_8*-**34**) (209 mg,

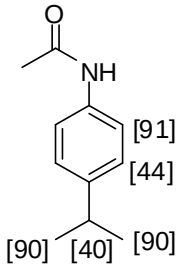
62%) as a brown oil (Found $M^{\bullet+}$, 143.1678. $C_9H_5D_8N$ [$M^{\bullet}$] requires 143.1676); ν_{max} (KBr) 3349, 3216, 3022, 2927, 2889, 2211, 2125, 2065, 1618, 1477, 1460, 1259; δ_H (400 MHz; CD_3OD) [a]6.93 (0.40H, s), [a]6.68 (0.19H, s), [a]2.46 (0.40H, s), [a]1.14 (0.60H, s), [a]0.91 (0.42H, s); δ_c (125 MHz, CD_3OD) 145.8 (s, C-N**)**, 140.2 (s, C-C), 127.7 (s, CH), 116.7 (t, 2CD, $J_{C\text{-}D}$ 23.5), 34.2 (s, CH), 23.9 (m, $2CD_3$); *m/z* (EI) 143 ($M^{\bullet+}$, 60%), 125 (100), 96 (20).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

***d*$_8$-*N*-(4-Isopropylphenyl)acetamide (*d*$_8$-34a)**



d$_8$-**34**a

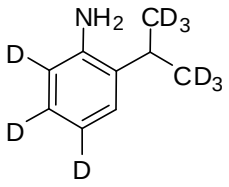


d$_8$-**34**a

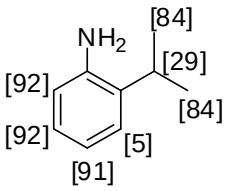
According to General Procedure 4.1, using *d*$_8$-4-isopropylaniline (*d*$_8$-**34**) (166 mg, 1.16 mmol, 1 equiv), acetyl chloride (92.43 μL, 1.3 mmol, 1.1 equiv), NEt_3 (337 μL, 2.5 mmol, 2.2 equiv) in CH_2Cl_2 (10 ml) at 0 °C under a N_2 atmosphere gave the *d*$_8$-*N*-(4-isopropylphenyl)acetamide (*d*$_8$-**34**a) (128 mg, 60%) as a yellow solid (Found $M^{\bullet+}$, 185.1783. $C_{11}H_7D_8NO$ [$M^{\bullet}$] requires 185.1781), mp 91 °C; ν_{max} (KBr) 3284, 3240, 3167, 3095, 3041, 2963, 2934, 2893, 2213, 2125, 2065, 1662, 1604, 1540, 1515, 1370, 1306; δ_H (400 MHz; CD_3OD) 7.42 (0.19H, m), 7.16 (1.12H, s), 2.82 (0.88H, s), 2.10 (3H, s), 1.18 (0.53H, m); δ_c (125MHz, CD_3OD) 171.6 (s, C=O), 146.1 (s, C-N), 137.4 (s, C-C), 127.4 (s, 2CH), 121.2 (m, 2CD), 34.4 (s, CH), 23.7 (s, CH_3), 23.5 (m, CH_3), 13.5 (m, $2CD_3$); *m/z* (EI) 185 ($M^{\bullet+}$, 90%), 168 (60), 125 (100), 96 (40). 143 (35), 107 (10).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

***d*$_9$-2-Isopropylaniline** (*d*$_9$-**35**)



d$_9$-**35**

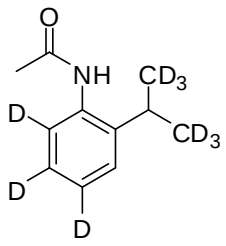


d$_9$-**35**

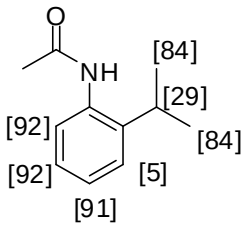
According to General Procedure 4.1, using 2-isopropylaniline (**35**) (300 mg, 314 μL, 2.22 mmol, 1 equiv), K_2PtCl_4 (184 mg, 0.44 mmol, 20 mol%), DCl (35%; 731 μL, 8.88 mmol, 4 equiv) in D_2O (3 mL), thioglycolic acid (125 μL, 1.76 mmol, 4 equiv), and NaOH solution (1 M;10 mL) gave the *d*$_9$-2-isopropylaniline (*d*$_9$-**35**) (229 mg, 72%) as a brown oil (Found $M^{\bullet+}$, 144.1615. $C_9H_4D_9N$ [$M^{\bullet}$] requires 144.1613); ν_{max} (KBr) 3464, 3375, 3228, 3060 , 2929, 2278, 2216, 2067, 1619, 1561, 1446, 1383, 1302; δ_H (400 MHz; CD_3OD) 7.08 (0.95H, s), [a]6.92 (0.09H, s), [a]6.70 (0.17H, m), 2.97 (0.71H, m), [a]1.22 (0.98H, d, $^3J_{H\text{-}H}$ 7); δ_c (125 MHz, CD_3OD) 144.9 (s, C-N**)**, 134.4 (s, C-C), 126.8 (t, CD, $^1J_{C\text{-}D}$ 24), 126.0 (s, CH), 119.6 (t, 1CD, $^1J_{C\text{-}D}$ 24), 117.0 (t, 1CD,$^1J_{C\text{-}D}$ 24), 28 (m, CH), 22.5 (m, CD_3); *m/z* (EI) 144 ($M^{\bullet+}$, 30%), 125 (100), 96 (20), 107 (15).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

***d*$_9$-*N*-(2-Isopropylphenyl)acetamide** (*d*$_9$-**35**a)



d$_9$-**35**a



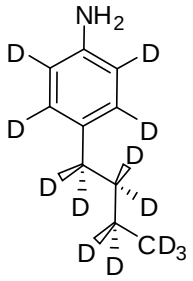
d$_9$-**35**a

According to General Procedure 4.1, using *d*$_9$-2-isopropylaniline (*d*$_9$-**35**) (180 mg, 1.23 mmol, 1 equiv), acetyl chloride (92 μL, 1.3 mmol, 1.1 equiv), and NEt_3 (379 μL, 2.70 mmol, 2.2 equiv) in CH_2Cl_2 (10 ml) at 0 °C under a N_2 atmosphere gave the *d*$_9$-*N*-(2-isopropylphenyl)acetamide (*d*$_9$-**35**a) (162 mg, 72%) as a yellow solid (Found $M^{\bullet+}$, 186.1787. $C_{11}H_6D_9NO$ [$M^{\bullet}$] requires 186.1781), mp 43 °C; ν_{max} (KBr) 3289, 3013,

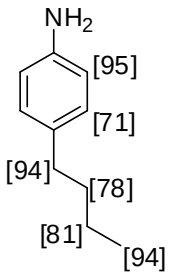
2959, 2952, 2780, 2269, 2210, 2130, 2066, 1653, 1522, 1289, 1011, 973, 694, 608; δ_H (400 MHz; CD_3OD) 7.34 (0.95H, s), [a]7.24 (0.09H, d,$^3J_{H\text{-}H}$ 8), [a]7.18 (0.17H, d, $J_{H\text{-}H}$ 7), 3.13 (0.71H, m), 2.14 (3H, s), 1.58 (0.98H, d, $J_{H\text{-}H}$ 7); δ_c (125 MHz, CD_3OD) 172.7 (s, C=O), 145.6 (s, C-N), 135.3 (s, C-C), 128.0 (m, CD), 126.9 (t, CD, $^1J_{C\text{-}D}$ 24), 126.8 (s, CH), 28.8 (m, CH), 23.5 (m, $2CD_3$), 22.9 (s, CH_3); *m/z* (EI) 186 ($M^{\bullet+}$, 92%), 141 (90), 124 (100), 96 (40). 168 (30), 107 (25).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

***d*$_{13}$-4-*n*-Butylaniline (*d*$_{13}$-32)**



d$_{13}$-**32**

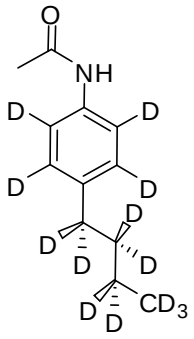


d$_{13}$-**32**

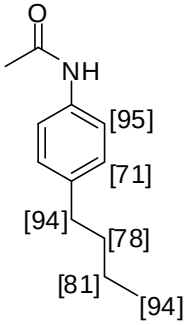
According to General Procedure 4.1, using 4-*n*-butylaniline (**32**) (300 mg, 317 μL, 2.01 mmol, 1 equiv), K_2PtCl_4 (166 mg, 0.40 mmol, 20 mol%), DCl (35%; 662 μL, 8.04 mmol, 4 equiv) in D_2O (3 mL), thioglycolic acid (113 μL, 1.61 mmol, 4 equiv), and NaOH solution (1 M;10 mL) gave the *d*$_{13}$-4-*n*-butylaniline (*d*$_{13}$-**32**) (160 mg, 50%) as a brown oil (Found $M^{\bullet+}$, 160.1895. $C_{10}H_4D_{11}N$ [$M^{\bullet}$] requires 160.1895); ν_{max} (KBr) 3444, 3349, 3214, 3019, 2901, 2212, 2102, 1619, 1499, 1462, 1442, 1300, 1256; δ_H (400 MHz; CD_3OD) [a]6.91 (0.11H, s), 6.66 (0.57H, t, $J_{C\text{-}D}$ 4), [a]2.44 (0.13H, s), [a]1.47 (0.44H, m), 1.26 (0.39H, m), [a]0.86 (0.18H, m); δ_c (125 MHz, CD_3OD) 145.9 (s, C-N**)**, 134.1 (s, C-C), 129.9 (s, CH), 117.0 (m, CD), 35.8 (m, CD), 35.2 (m, CD), 23.3 (m, CD), 14.3 (m, CD); *m/z* (EI) 160 ($M^{\bullet+}$, 80%), 111 (100), 96 (30).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

d_{13}-*N*-(4-*n*-Butylphenyl)acetamide (*d_{13}*-32a)



d_{13}-**32**a

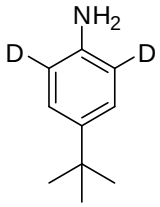


d_{13}-**32**a

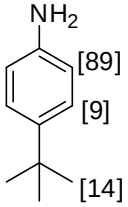
According to General Procedure 4.1, using *d_{13}*-4-*n*-butylaniline (*d_{13}*-**32**) (130 mg, 0.89 mmol, 1 equiv), acetyl chloride (63 μL, 0.88 mmol, 1.1 equiv), and NEt_3 (247 μL, 1.77 mmol, 2.2 equiv) in CH_2Cl_2 (10 ml) at 0 °C under a N_2 atmosphere gave the *d_{13}*-*N*-(4-*n*-butylphenyl)acetamide **(*d_{13}*-32a)** (59 mg, 36%) as a colourless solid (Found $M^{\bullet+}$, 202.1997. $C_{12}H_6D_{11}NO[M^{\bullet}]$ requires 202.2001), mp 101 °C; ν_{max} (KBr) 3267, 3124, 2916, 2930, 2854, 2200, 2213, 2120, 2067, 1660, 1514, 1451, 1371, 1291; δ_H (400 MHz; CD_3OD) [a]7.43 (0.22H, m), 7.11 (1.13H, s), [a]2.53 (0.26H, m), 2.10 (3H, s), [a]1.53 (0.88H, s), [a]1.29 (0.78H, m), [a]0.88 (0.54H, m); δ_c (125 MHz, CD_3OD) 171.5 (s, C=O), 139.9 (m, C-N), 137.3 (s, C-C), 129.5 (s, 2CH), 121.3 (m, 2CD), 36.0 (m, 2CD), 34.9 (m, 2CD), 23.7 (s, CH_3), 23.3 (m, 2CD), 14.2 (m, 3CD); *m/z* (EI) 202 ($M^{\bullet+}$, 45%), 160 (35) 111 (90).

[a]Signal arises duo to the presence of isotopologues and/or isotopomers.

d_2-4-*tert*-Butylaniline (*d_2*-33)



d_2-**33**



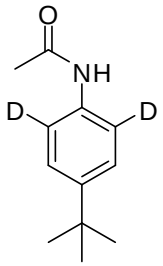
d_2-**33**

According to General Procedure 4.1, using 4-*tert*-butylaniline (**33**) (300 mg, 318 μL, 2.01 mmol, 1 equiv), K_2PtCl_4 (166 mg, 0.40 mmol, 20 mol%), DCl (35%; 662 μL, 8.04 mmol, 4 equiv) in D_2O (3 mL), thioglycolic acid (113 μL, 1.61 mmol, 4 equiv), and NaOH solution (1 M;10 mL) gave the *d_2*-4-*tert*-butylaniline (*d_2*-**33**) (167 mg, 55%) as a brown oil (Found $M^{\bullet+}$, 151.1334. $C_{10}H_{13}D_2N$ $[M^{\bullet}]$ requires 151.1330); ν_{max} (KBr) 3434,

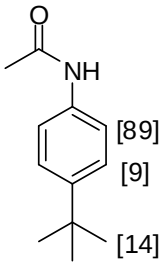
3353, 3215, 3063, 3034, 2927, 2868, 2253, 2212, 2169, 1619, 1500, 1216, 1043, 898; δ_H (400 MHz; CD_3OD) 7.13 (1.83H, s), [a]6.67 (0.23H, d, $^3J_{H\text{-}H}$ 9), 1.25 (7.72H, s); δ_c (125 MHz, CD_3OD) 145.1 (s, C-N**)**, 142.1 (s, C-C), 116.2 (t, 2CD, $J_{C\text{-}D}$ 24.7), 34.5 (m, C-CD_3), 31.7 (tt, $3CD_3$, $^1J_{C\text{-}D}$ 19.2, $^2J_{C\text{-}D}$ 2.8); *m/z* (EI) 151 ($M^{\bullet+}$, 40%), 137 (100), 108 (40), 96 (30).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

***d*$_2$-*N*-(4-*tert*-Butylphenyl)acetamide (*d*$_2$-33a)**



d$_2$-**33**a

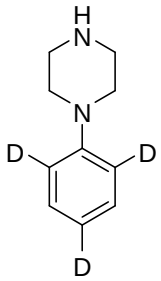


d$_2$-**33**a

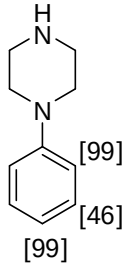
According to General Procedure 4.1, using *d*$_2$-4-*tert*-butylaniline (*d*$_2$-**33**) (127 mg, 0.84 mmol, 1 equiv), acetyl chloride (66 μL, 0.84 mmol, 1.1 equiv), NEt_3 (260 μL, 1.85 mmol, 2.2 equiv) in CH_2Cl_2 (10 mL) at 0 °C under a N_2 atmosphere gave the *d*$_2$-*N*-(4-*tert*-butylphenyl)acetamide (*d*$_2$-**33**a) (102 mg, 63%) as a colourless solid (Found $M^{\bullet+}$, 193.1435. $C_{12}H_{15}D_2NO$ [$M^{\bullet}$] requires 193.1436), mp 154 °C; ν_{max} (KBr) 3289, 3248, 3172, 3096, 3034, 2958, 2926, 2865, 2167, 1688, 1670, 1604, 1537, 1471, 1382, 1321, 1266, 1043, 1010, 969, 899, 765; δ_H (400 MHz; CD_3OD) [a]7.41 (0.23H, m), 7.34 (1.83H, s), 2.10 (3H, s), 1.30 (7.72H, s); δ_c (125 MHz, CD_3OD) 171.5 (s, C=O), 148.1 (s, C-N), 137.0 (s, C-C), 126.0 (s, 2CH), 120.0 (t, 2CD, $J_{C\text{-}D}$ 24), 35.0 (m, C-CD_3), 31.5 (tt, $3CD_3$, $^1J_{C\text{-}D}$ 19.2, $^2J_{C\text{-}D}$ 2.8), 23.7 (s, CH_3); *m/z* (EI) 193 ($M^{\bullet+}$, 45%), 137 (100), 179 (80).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

***d*$_3$-1-Phenylpiperazine (*d*$_3$-39)**



d$_3$-**39**

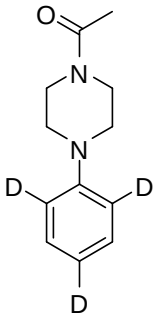


d$_3$-**39**

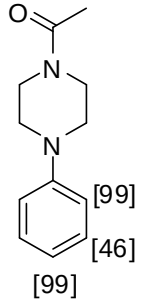
According to General Procedure 4.1, using phenylpiperazine (**39**) (300 mg, 282 μL, 1.85 mmol, 1 equiv), K_2PtCl_4 (153 mg, 0.37 mmol, 20 mol%), DCl (35%; 609 μL, 7.4 mmol, 4 equiv) in D_2O (3 mL), thioglycolic acid (113 μL, 1.61 mmol, 4 equiv), NaOH solution (1 M;10 mL) gave the *d*$_3$-1-phenylpiperazine (*d*$_3$-**39**) (257 mg, 83%) as a yellow oil (Found $M^{\bullet+}$, 165.1470. $C_{10}H_{11}D_3N_2$ [$M^{\bullet}$] requires 165.1471); ν_{max} (KBr) 3302, 3047, 2947, 2828, 2275, 1575, 1550, 1436, 1381, 1326, 1274; 1227; δ_H (400 MHz; CD_3OD) [a]7.23 (1.07H, s), [a]7.10 (0.05H, m), [a]6.96 (0.02H, t, $J_{H\text{-}H}$ 4.3), 3.10 (4H, m), 2.95 (4H, m); δ_c (125 MHz, CD_3OD) 153.0 (s, C-N**)**, 129.8 (s, 2CH), 120.7 (m, 1CD), 117.5 (t, 2CD,$J_{C\text{-}D}$ 25.2), 51.1 (s, 2C-$NCOCH_3$), 46.4 (s, 2C-$NCOCH_3$); *m/z* (EI) 165 ($M^{\bullet+}$, 45%), 124 (90), 109 (50), 136 (25), 95 (10).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

***d*$_3$-*N*-(1-Phenylpiperazine)acetamide (*d*$_3$-39a)**



d$_3$-**39**a

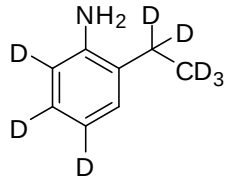


d$_3$-**39**a

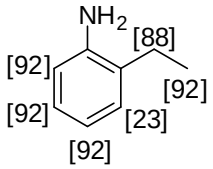
According to General Procedure 4.1, using *d*$_3$-1-phenylpiperazine (*d*$_3$-**39**) (191 mg, 1.09 mmol, 1 equiv) acetyl chloride (94 μL, 1.20 mmol, 1.1 equiv), NEt_3 (242 mg, 2.40 mmol, 1 equiv) in CH_2Cl_2 (10 ml) at 0 ^oC under a N_2 atmosphere gave the d_3-*N*-(1-phenylpiperazine)acetamide (*d*$_3$-**39a**) (56 mg, 24%) as a colourless solid (Found $M^{\bullet+}$,

207.1569. $C_{12}H_{13}D_3N_2O$ [$M^{\bullet}$] requires 207.1576), mp 43 °C; ν_{max} (KBr) 3282, 2916, 2849, 2815, 1627, 1573, 1428, 1277, 1254, 1226, 1043, 1002, 985; δ_H (400 MHz; CD_3OD) 7.24 (1.07H, s), 7.09 (0.05H, s), 6.96 (0.02H, s), 3.73 (2H, m), 3.69 (2H, m), 3.18 (2H, m), 3.13 (2H, m), 2.14 (3H, s); δ_c (125 MHz, CD_3OD) 171.7 (s, C=O), 152.4 (s, C-N), 129.9 (s, 2CH), 126.4 (s, 2CH), 117.7 (t, 2CD, $J_{C\text{-}D}$ 23.7), 51.0 (s, C-$NCOCH_3$), 50.3 (s, C-$NCOCH_3$), 47.4 (s, C-N), 42.7 (s, C-N), 21.1 (s, CH_3); *m/z* (EI) 207 ($M^{\bullet+}$, 100%), 109 (35), 169 (40), 136 (25).

d_8-2-Ethylaniline (d_8-37)



d_8-**37**

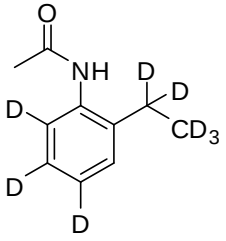


d_8-**37**

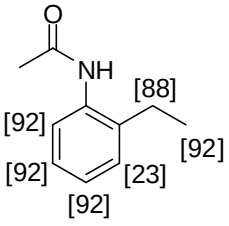
According to General Procedure 4.1 using 2-ethylaniline (**37**) (300 mg, 293 μL, 2.48 mmol, 1 equiv), K_2PtCl_4 (205 mg, 0.48 mmol, 20 mol%), DCl (35%; 816 μL, 9.92 mmol, 4 equiv) in D_2O (3 mL), thioglycolic acid (136 μL, 1.92 mmol, 4 equiv), NaOH solution (1 M;10 mL) gave the d_8-2-ethylaniline (d_8-**37**) (239 mg, 75%) as a yellow oil (Found $M^{\bullet+}$, 129.1397. $C_8H_3D_8N$ [$M^{\bullet}$] requires 129.1394); ν_{max} (KBr) 3227, 3184, 3107, 3046, 3012, 2929, 2784, 2279, 2219, 2168, 2144, 2069, 1648, 1566, 1524, 1374, 1272; δ_H (500 MHz; CD_3OD) 6.99 (0.77H, s), [a]6.94 (0.08H, m), [a]6.71 (0.08H, s), [a]6.66 (0.08H, m), [a]2.49 (0.36H, m), [a]1.53 (0.24H, m); δ_c (125 MHz, CD_3OD) 145.6 (s, C-N**)**, 129.9 (s, C-C), 129.2 (s, CH), 127.3 (m, CD), 119 (m, CD) , 116.6 (m, CD), 24.5 (m, CD), 13.3 (m, CD); *m/z* (EI) 129 ($M^{\bullet+}$, 50%), 111 (100), 96 (10).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

d_8-*N*-(2-Ethylphenyl)acetamide (d_8-37a)



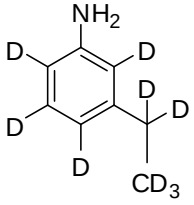
d_8-**37**a



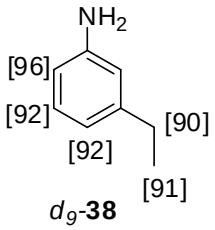
d_8-**37**a

According to General Procedure 4.1, using d_8-2-ethylaniline (d_8-**37**) (96 mg, 0.74 mmol, 1 equiv), acetyl chloride (65 μL, 0.81 mmol, 1.1 equiv), NEt_3 (228 μL, 1.63 mmol, 2.2 equiv) in CH_2Cl_2 (10 ml) at 0 ^oC under a N_2 atmosphere gave the d_8-*N*-(2-ethylphenyl)acetamide (d_8-**37**a) (39 mg, 31%) as a yellow solid (Found $M^{\bullet+}$, 171.1500. $C_{10}H_5D_8NO$ [$M^{\bullet}$] requires 171.1499), mp 106 °C; ν_{max} (KBr) 3459, 3374, 3227, 3048, 3006, 2936, 2271, 2221, 2072, 1619, 1561, 1446; δ_H (400 MHz; CD_3OD) 7.32 (0.08H, s), 7.21 (0.77H, s), 7.12 (0.15H, m), 2.55 (0.23H, m), 2.04 (3H, s), 1.05 (0.25H, m); δ_c (125 MHz, CD_3OD) 172.5 (s, C=O), 140.5 (s, C-N), 136.3 (s, C-C), 129.8 (s, 1CH), 127.9 (m, CD**)**, 127.0 (m, CD), 126.9 (m, CD), 25.3 (m, CD), 24.2 (s, CH_3), 13.5 (m, CD); *m/z* (EI) 171 ($M^{\bullet+}$, 60%), 111 (100), 128 (90), 97 (10).

d_9-3-Ethylaniline (d_9-**38)**



d_9-**38**

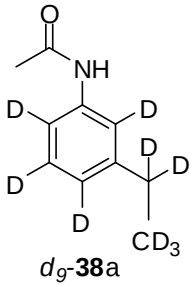


d_9-**38**

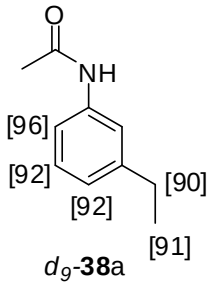
According to General Procedure 4.1 using 3-ethylaniline (**38**) (300 mg, 307 μL, 2.48 mmol, 1 equiv), K_2PtCl_4 (205 mg, 0.48 mmol, 20 mol%), DCl (35%; 816 μL, 9.92 mmol, 4 equiv) in D_2O (3 mL), thioglycolic acid (141 μL, 1.99 mmol, 4 equiv), NaOH solution (1 M;10 mL) gave the d_9-3-ethylaniline (d_9-**38**a) (260 mg, 81%) as a brown oil (Found $M^{\bullet+}$, 130.1452. $C_8H_2D_9N$ [$M^{\bullet}$] requires 130.1456); ν_{max} (KBr) 3442, 3350, 3220, 2934, 2223, 2091, 2071, 1618, 1518, 1400, 1301, 1258, 1053; δ_H (400 MHz; CD_3OD) [a]6.99 (0.08H, s), [a]6.59 (0.09H, s), [a]6.54 (0.16H, s), [a]2.48 (0.21 H, s), [a]1.13 (0.28 H, s); δ_c (125 MHz, CD_3OD) 148.2 (s, C-N**)**, 146.1 (s, C-C), 129.4 (t, 1CD, $J_{C\text{-}D}$ 23.9), 118.7 (t, 1CD, $J_{C\text{-}D}$ 24.3), 116.0 (t, 1CD, $J_{C\text{-}D}$ 22.9), 113.8 (t, 1CD, $J_{C\text{-}D}$ 23.4), 29.1 (m, CD_2), 15.2 (m, CD_3); *m/z*(EI) 130 ($M^{\bullet+}$, 80%), 112 (100), 96 (20).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

d_9-*N*-(3-Ethylphenyl)acetamide (d_9-38a)



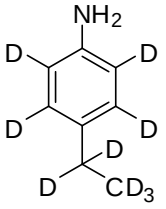
d_9-**38**a



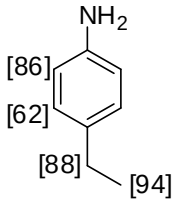
d_9-**38**a

According to General Procedure 4.1 using d_9-3-ethylaniline (d_9-**38**) (200 mg, 1.79 mmol, 1 equiv), acetyl chloride (127 μL, 1.79 mmol, 1.1 equiv), NEt_3 (503 μL, 3.59 mmol, 2.2 equiv) in CH_2Cl_2 (10 ml) at 0 ^oC under a N_2 atmosphere gave the d_9-*N*-(3-ethylphenyl)acetamide (d_9-**38**a) (281 mg, 87%) as a yellow oil (Found $M^{\bullet+}$, 172.1562. $C_{10}H_4D_9NO$ [$M^{\bullet}$] requires 172.1562); ν_{max} (KBr) 3301, 3152, 3104, 3054, 2931, 2860, 2278, 2224, 2136, 2096, 2070, 1667, 1537, 1393, 1269, 1127, 835; δ_H (400 MHz; CD_3OD) 7.37 (0.08H, s), 7.33 (0.09H, s), 7.19 (0.08H, s), 6.93 (0.09H, s), 2.57 (0.21H, s), 2.11 (3H, s), 1.16 (0.28H, m); δ_c (125 MHz, CD_3OD) 171.4 (s, C=O), 145.7 (s, C-N), 139.5 (s, C-C), 129.1 (t, 1CD, $J_{C\text{-}D}$ 24.2), 124.2 (t, 1CD, $J_{C\text{-}D}$ 24.2), 120.2 (t, 1CD, $J_{C\text{-}D}$ 24.2), 118.1 (t, 1CD, $J_{C\text{-}D}$ 24.6), 28.8 (m, CD_2**)**, 23.9 (s, CH_3), 15.0 (m, CD_3); *m/z* (EI) 172 ($M^{\bullet+}$, 20%), 130 (50), 112 (35), 149 (15), 98 (10).

d_9-4-Ethylaniline (d_9-36)



d_9-**36**



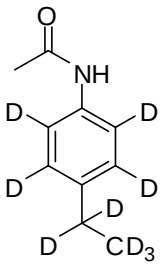
d_9-**36**

According to General Procedure 4.1, using 4-ethylaniline (**36**) (300 mg, 309 μL, 2.48 mmol, 1 equiv), K_2PtCl_4 (205 mg, 0.48 mmol, 20 mol%), DCl (35%; 816 μL, 9.92 mmol, 4 equiv) in D_2O (3 mL), thioglycolic acid (136 μL, 1.92 mmol, 4 equiv), NaOH solution (1 M;10 mL) gave the d_9-4-ethylaniline (d_9-**36**) (180 mg, 56%) as a brown oil (Found $M^{\bullet+}$, 130.1456. $C_8H_2D_9N$ [$M^{\bullet}$] requires 130.1456); ν_{max} (KBr) 3349, 2960, 2220, 2100, 2069, 1617, 1477, 1463, 1442, 1301, 1254; δ_H (400 MHz; CD_3OD) ^{a}6.93 (0.77H, s), ^{a}6.67 (0.27H, m), ^{a}2.46 (0.17H, m), ^{a}1.05 (0.24H, m); δ_c (125 MHz, CD_3OD) 145.7

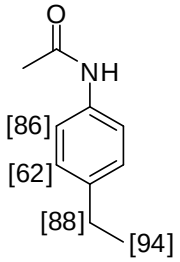
(s, C-N), 135.5 (s, C-C), 128.9 (m, 2CD), 116.9 (m, 2CD), 28.1 (m, CD_2), 15.8 (m, CD_3); *m/z* (EI) 130 ($M^{\bullet+}$, 50%), 111 (100), 97 (10).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

***d*$_9$-*N*-(4-Ethylphenyl)acetamide (*d*$_9$-36a)**



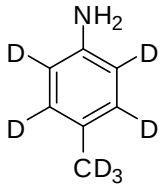
d$_9$-**36**a



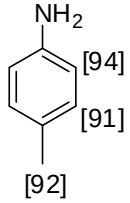
d$_9$-**36**a

According to General Procedure 4.1, using *d*$_9$-4-ethylaniline (*d*$_9$-**36**) (150 mg, 1.22 mmol, 1 equiv), acetyl chloride (95 μL, 1.34 mmol, 1.1 equiv), NEt_3 (270 μL, 2.68 mmol, 2.2 equiv) in CH_2CL_2 (10 mL) at 0 ^oC under a N_2 atmosphere gave the *d*$_9$-*N*-(4-ethylphenyl)acetamide (*d*$_9$-**36**a) (210 mg, 95%) as a brown solid (Found $M^{\bullet+}$, 172.1560. $C_{10}H_4D_9NO$ [$M^{\bullet}$] requires 172.1562), mp 45 °C; ν_{max} (KBr) 3298, 3094, 3227, 2962, 2222, 1664, 1593, 1524, 1372, 1313, 1264; δ_H (400 MHz; CD_3OD) 7.44 (0.27H, m), 7.15 (0.77H, s), 2.58 (0.17H, m), 2.12 (3H, s), 1.19 (0.24H, m); δ_c (150 MHz, CD_3OD) 171.5 (s, C=O), 140.5 (s, C-N), 137.3 (s, C-C), 128.6 (t, 2CD, $J_{C\text{-}D}$ 24.3), 121.1 (m, 2CD**)**, 28.5 (m, CD_2), 23.8(s, CH_3), 15.3 (m, CD_3); *m/z* (EI) 172 ($M^{\bullet+}$, 65%), 129 (50), 111 (95), 98 (10).

***d*$_7$-*p*-Toluidine (*d*$_7$-31)**



d$_7$-**31**



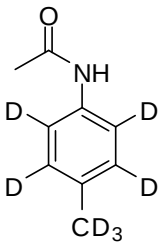
d$_7$-**31**

According to General Procedure 4.1, using *p*-toluidine (**31**) (300 mg, 2.8 mmol, 1 equiv), K_2PtCl_4 (233 mg, 0.56 mmol, 20 mol%), DCl (35%; 921 μL, 1102 mmol, 4 equiv) in D_2O (3 mL), thioglycolic acid (156 μL, 2.24 mmol, 4 equiv), NaOH solution (1 M;10 mL) gave the *d*$_7$-*p*-toluidine (*d*$_7$-**31**) (179 mg, 56%) as a brown oil (Found $M^{\bullet+}$,

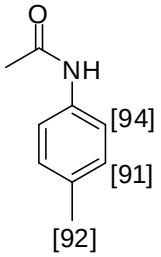
114.1170 $C_7H_2D_7N$ [$M^{\bullet}$] requires 114.1174), mp 34 °C; ν_{max} (KBr) 3417, 3343, 3220, 3022, 3006, 2499, 2264, 2244, 2191, 2114, 2077, 2224, 2048, 1617, 1597, 1477, 1463,1442, 1294, 1254, 1239; δ_H (400 MHz; CD_3OD) [a]6.91 (0.18H, s), [a]6.91 (0.12H, s), 2.16 (0.23 H, m); δ_c (125 MHz, CD_3OD) 145.3 (s, C-N**)**, 130.1 (t, C-D, J_{C-D} 23.8), 128.5 (s, C-CD_3), 116.7 (t, C-D, J_{C-D} 23.9), 19.6 (m, CD_3); *m/z* (EI) 114 ($M^{\bullet+}$, 40%), 112 (100), 98 (10).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

***d*$_7$-*N*-(4-Toluidine)acetamide (*d*$_7$-31a)**



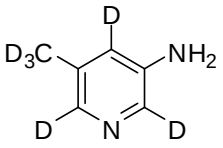
d$_7$-**31**a



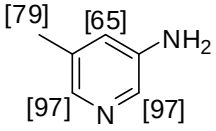
d$_7$-**31**a

According to General Procedure 4.1, using *d*$_7$-*p*-toluidine (*d*$_7$-**31**) (125 mg, 1.21 mmol, 1.1 equiv), acetyl chloride (85 μL, 1.21 mmol, 1.1 equiv), NEt_3 (340 μL, 2.41 mmol, 2.2 equiv) in CH_2CL_2 (10 mL) at 0 °C under a N_2 atmosphere gave the *d*$_7$-*N*-(4-toluidine)acetamide (*d*$_7$-**31**a) (136 mg, 79%) as a colorless solid (Found $M^{\bullet+}$, 156.1281 .$C_9H_4D_7NO$ [$M^{\bullet}$] requires 156.1280), mp 121 °C; ν_{max} (KBr) 3289, 3245, 3166, 3092, 3031, 2930, 2852, 2782, 2277, 2222, 2202, 2115, 2048, 1660, 1597, 1533, 1367, 1314, 1263, 1038, 1013; δ_H (400 MHz; CD_3OD) 7.38 (0.07H, m), 7.10 (0.79H, s), 7.15 (0.08H, s), 2.25 (0.19, m,), 2.09 (3H, s); δ_c (125 MHz, CD_3OD) 171.5 (s, C=O), 137.2(s, C-N)**,** 134.6 (s, C-CD_3), 23.7 (s, CH_3); *m/z* (EI) 156 ($M^{\bullet+}$, 45%), 147 (15), 112 (100).

***d*$_6$-3-Amino-5-methylpyridine (*d*$_6$-43)**



d$_6$-**43**

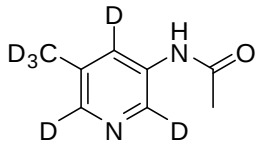


d$_6$-**43**

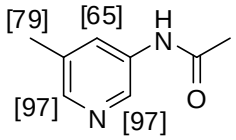
According to General Procedure 4.1, using 3-amino-5-methylpyridine (**43**) (300 mg, 2.7 mmol, 1 equiv), K_2PtCl_4 (224 mg, 0.54 mmol, 20 mol%), DCl (35%; 889 μL, 10.8 mmol, 4 equiv) in D_2O (3 mL), thioglycolic acid (153 μL, 2.16 mmol, 4 equiv), NaOH solution (1 M;10 mL) gave the d_6-3-amino-5-methylpyridine (d_6-**43**) (153 mg, 26%) as a yellow solid (Found $M^{\bullet+}$, 114.1064. $C_6H_2D_6N_2[M^{\bullet}]$ requires 114.1064), mp 53 ºC; ν_{max} (KBr) 3334, 3210, 2235, 1627, 1589, 1575, 1410, 1389, 1259, 884; δ_H (400 MHz; CD_3OD) [a]7.76 (0.03H, s), [a]7.61 (0.03H, s), [a]6.92 (0.35H, s), [a]2.20 (0.61H, m); δ_c (125 MHz, CD_3OD) 145.9 (d, C-N, $J_{C\text{-}D}$ 7.59), 138.7 (t, 1C-D, $J_{C\text{-}D}$ 26.5), 138.6 (t, C-CD_3, $J_{C\text{-}D}$ 4.4), 134.3 (t, 1CD, $J_{C\text{-}D}$ 27.0), 123.7 (s, 1 CH), 17.6 (m, CD_3); *m/z* (EI) 114 ($M^{\bullet+}$, 60%), 95 (5).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

d_6-*N*-(5-Methylpyridin-3-yl)acetamide (d_6-43a)



d_6-**43**a

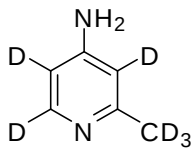


d_6-**43**a

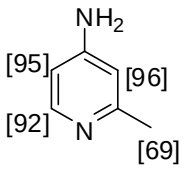
According to General Procedure 4.1, using d_6-3-Amino-5-methylpyridine (d_6-**43**) (100 mg, 0.88 mmol, 1 equiv), dissolved in acetone (20 mL), K_2CO_3 (607 mg, 4.4 mmol, 5 equiv), acetyl chloride (207 mg, 187 μL, 2.6 mmol, 3 equiv) in acetone (5 ml) to give the d_6-*N*-(5-methylpyridin-3-yl)acetamide (d_6-**43**a) (100 mg, 95%) as a yellow solid (Found $M^{\bullet+}$, 156.1175. $C_8H_4D_6N_2O$ $[M^{\bullet}]$ requires 155.1170), mp 125 °C; ν_{max} (KBr) 3224, 2922, 1691, 1602, 1531, 1409, 1387, 1289, 1018, 881, 769; δ_H (400 MHz; CD_3OD) 8.51 (0.03H, s), 8.09 (0.03H, s), 7.93 (0.35H, s), 2.31 (0.61H, m), 2.15 (3H, s); δ_c (125 MHz, CD_3OD) 171.8 (s, C=O), 145.0 (t, 1CD, $J_{C\text{-}D}$ 26.5), 138.6 (t, 1CD, $J_{C\text{-}D}$ 28.8), 137 (d, C-NH_2, $J_{C\text{-}D}$ 8.8) 135.2 (m, C-CD_3), 128.9 (t, 1CD, $J_{C\text{-}D}$ 27.6), 23.8 (s, CH_3), 17.7 (m, CH_3); *m/z* (EI) 156 ($M^{\bullet+}$, 40%), 113 (80).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

d_6-4-Amino-2-methylpyridine (d_6-40)



d_6-**40**

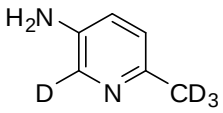


d_6-**40**

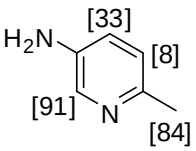
According to General Procedure 4.1, using 4-amino-2-methylpyridine (**40**) (300 mg, 2.7 mmol, 1 equiv), K_2PtCl_4 (224 mg, 0.54 mmol, 20 mol%), DCl (35%; 889 μL, 10.8 mmol, 4 equiv) in D_2O (3 mL), thioglycolic acid (153 μL, 2.16 mmol, 4 equiv), NaOH solution (1 M;10 mL) gave the d_6-4-amino-2-methylpyridine (d_6-**40**) (141 mg, 47%) as a colourless solid (Found $M^{\bullet+}$, 114.1068.$C_6H_2D_6N_2$ [$M^{\bullet}$] requires 114.1064), mp 77 ºC; ν_{max} (KBr) 3332, 3197, 3090, 2919, 2568, 2515, 2400, 2302, 1584, 1492, 1440, 1247, 964; δ_H (400 MHz; CD_3OD) [a]7.83 (0.08H, s),[a]6.42 (0.04H, s), [a]6.37 (0.05H, s), [a]2.27 (0.94H, m); δ_c (125 MHz, CD_3OD) 158.6 (s, C-NH_2), 157.1 (s, C-CD_3), 148.7 (t, 1CD, $J_{C\text{-}D}$ 26.5), 109.0 (t, 1CD, $J_{C\text{-}D}$ 24.7), 107.6 (t, 1CD, $J_{C\text{-}D}$ 25.2), 22.9 (m, CD_3); *m/z* (EI) 114 ($M^{\bullet+}$, 65%), 95 (5).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

d_4-5-Amino-2-methylpyridine (d_4-42)



d_4-**42**



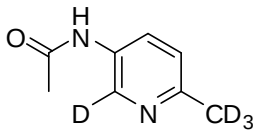
d_4-**42**

According to General Procedure 4.1, using 5-amino-2-methylpyridine (**42**) (300 mg, 2.7 mmol, 1 equiv), K_2PtCl_4 (224 mg, 0.54 mmol, 20 mol%), DCl (35%; 889 μL, 10.8 mmol, 4 equiv) in D_2O (3 mL), thioglycolic acid (153 μL, 2.16 mmol, 4 equiv), NaOH solution (1 M;10 mL) gave the d_4-5-amino-2-methylpyridine (d_4-**42**) (132 mg, 44%) as a colourless solid (Found $M^{\bullet+}$, 112.0936. $C_6H_4D_4N_2$ [$M^{\bullet}$] requires 112.0939), mp 78 ºC; ν_{max} (KBr) 3396, 3323, 3269, 3030, 2928, 2497, 2402, 2232, 2052, 1909, 1635, 1597, 1564, 1460, 1371, 1301, 1250, 1153, 1086, 1042, 914; δ_H (400 MHz; CD_3OD) [a]7.85 (0.09H, s), [a]7.04 (0.67H, d, J_1 8.48), [a]6.92 (0.92H d, J_1 8.48,), [a]2.32 (0.50H, m); δ_c (125

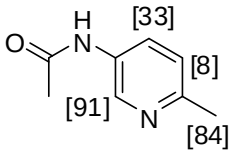
MHz, CD_3OD) 147.3 (s, C-NH_2)**,** 143.5 (s, C-CD_3)**,** 148.7 (t, 1CD, $J_{C\text{-}D}$ 26.8), 124.8 (s, 1CH), 124.5 (s, 1CH), 22.1 (m, CD_3); *m/z* (EI) 112 ($M^{\bullet+}$, 20%), 145 (55).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

***d*$_4$-*N*-(2-Methylpyridin-5-yl)acetamide** (*d*$_4$-**42**a)



d$_4$-**42**a

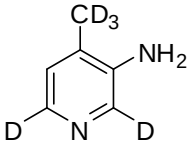


d$_4$-**42**a

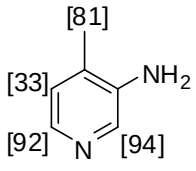
According to General Procedure 4.1, using *d*$_4$-5-amino-2-methylpyridine (*d*$_4$-**42**) (100 mg, 0.88 mmol, 1 equiv), dissolved in acetone (20 mL), K_2CO_3 (607 mg, 4.4 mmol, 5 equiv), acetyl chloride (207 mg, 187 µL, 2.6 mmol, 3 equiv) in acetone (5 ml) to give the *d*$_4$-*N*-(2-methylpyridin-5-yl)acetamide (*d*$_4$-**42**a) (67 mg, 50%) as a colourless solid (Found $M^{\bullet+}$, 154.1046 .$C_8H_6D_4N_2O$ [$M^{\bullet}$] requires 154.1044), mp 110 °C; ν_{max} (KBr) 3395, 3296, 3232, 3163, 3090, 3009, 2871, 2236, 2151, 2054, 1851, 1685, 1610, 1582, 1463, 1452, 1295, 1139, 1006, 826; δ_H (400 MHz; CD_3OD) 8.58 (0.09H, s), 7.95 (0.67H, d, J_1 8.48), 7.26 (0.92H, d, J_1 8.48), 2.45 (0.50 H,m), 2.14 (3H, s); δ_c (125 MHz, CD_3OD) 171.9 (s, C=O), 154.2 (s, C-NH), 140.8 (m, 1CD), 134.8 (s, C-CD_3), 129.7 (s, 1CH), 124.7 (s, 1CH), 23.6 (s, CH_3), 22.4 (m, CH_3); *m/z* (EI) 154 ($M^{\bullet+}$, 30%), 112 (60), 95 (5).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

***d*$_5$-3-Amino-4-methylpyridine (*d*$_5$-44)**



d$_5$-**44**



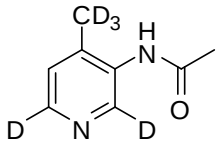
d$_5$-**44**

According to General Procedure 4.1, using 3-amino-4-methylpyridine (**44**) (300 mg, 2.7 mmol, 1 equiv), K_2PtCl_4 (224 mg, 0.54 mmol, 20 mol%), DCl (35%; 889 µL, 10.8 mmol, 4 equiv) in D_2O (3 mL), thioglycolic acid (153 µL, 2.16 mmol, 4 equiv), NaOH

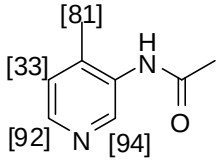
solution (1 M;10 mL) gave the d_5-3-amino-4-methylpyridine (d_5-**44**) (126 mg, 42%) as a colourless solid (Found $M^{\bullet+}$, 113.1064 .$C_6H_3D_5N_2O$ [$M^{\bullet}$] requires 113.1064, mp 55 ^oC; v_{max} (KBr) 3950, 3880, 3807, 3745, 3464, 2806, 2634, 2254, 2053, 1420, 1388, 1252, 953, 852; δ_H (400 MHz; CD_3OD) [a]7.75 (0.08H, s), [a]7.62 (0.06H, s), [a]6.93 (0.67H, s), [a]2.21 (0.57H, m); m/z (EI) 113 ($M^{\bullet}$+, 60%), 95 (5).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

***d*$_5$-*N*-(4-Methylpyridin-3-yl)acetamide** (d_5-**44**a)



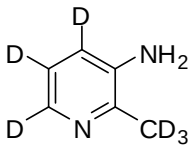
d_5-**44**a



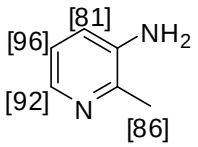
d_5-**44**a

According to General Procedure 4.1, using d_5-3-amino-4-methylpyridine (d_5-**44**) (126 mg, 1.12 mmol, 1 equiv), dissolved in acetone (50 mL), K_2CO_3 (772 mg, 5.6 mmol, 5 equiv), acetyl chloride (207 mg, 187 μL, 2.6 mmol, 3 equiv) in acetone (5 ml) to give the d_5-*N*-(4-methylpyridin-3-yl)acetamide (d_5-**44**a) (96 mg, 55%) as a colourless solid (Found $M^{\bullet+}$, 155.1110 .$C_8H_5D_5N_2O$ [$M^{\bullet}$] requires 155.1170), mp 105 °C; v_{max} (KBr) 3950, 3886, 3802, 3745, 2806, 2634, 2546, 2486, 2414, 2254, 1420; δ_H (400 MHz; CD_3OD) 8.45 (0.08H, s), 8.21 (0.06H, s), 7.25 (0.67H, s), 2.31 (0.57 H, m), 2.15 (3H, s); *m/z* (EI) 155 ($M^{\bullet+}$, 85%), 113 (100).

***d*$_6$-3-Amino-2-methylpyridine (*d*$_6$-41)**



d_6-**41**



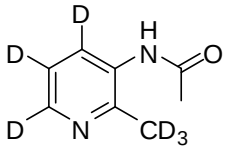
d_6-**41**

According to General Procedure 4.1, using 3-amino-2-methylpyridine (**41**) (300 mg, 2.7 mmol, 1 equiv), K_2PtCl_4 (224 mg, 0.54 mmol, 20 mol%), DCl (35%; 889 μL, 10.8

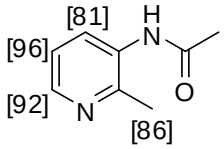
mmol, 4 equiv) in D_2O (3 mL), thioglycolic acid (153 μL, 2.16 mmol, 4 equiv), NaOH solution (1 M;10 mL) gave the d_6-3-amino-2-methylpyridine (d_6-**41**) (116 mg, 38%) as a colourless solid (Found $M^{\bullet+}$, 114.1061. $C_6H_2D_6N_2$ [$M^{\bullet}$] requires 114.1064), mp 91 ºC; ν_{max} (KBr) 3345, 3311, 3164, 2536, 2404, 2367, 2288, 2237, 2194, 1631, 1553, 1436, 1264, 1197, 1042, 877; δ_H (400 MHz; CD_3OD) [a]7.70 (0.04H, s), [a]7.06 (0.19H, s), [a]6.99 (0.05H d, J_1 8.05), [a]2.32 (0.40H, m); δ_c (125 MHz, CD_3OD) 144.5 (s, C-NH_2), 144.4 (s, C-CD_3), 137.9 (t, 1CD, $J_{C\text{-}D}$28.0), 123.5 (t, 1CD, $J_{C\text{-}D}$ 25.0), 123.9 (s, 1CH), 19.5 (q, 1CD_3, $J_{C\text{-}D}$ 20); *m/z* (EI) 114 ($M^{\bullet+}$, 75%), 96 (5).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

d_6-*N*-(2-Methylpyridin-3-yl)acetamide (d_6-**41**a)



d_6-**41**a

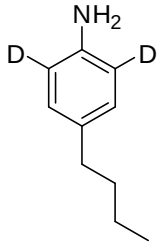


d_6-**41**a

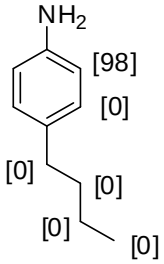
According to General Procedure 4.1, using d_6-3-amino-2-methylpyridine (d_6-**41**) (88 mg, 0,77 mmol, 1 equiv), dissolved in acetone (50 mL), and K_2CO_3 (772 mg, 5.6 mmol, 5 equiv), acetyl chloride (207 mg, 187 μL, 2.6 mmol, 3 equiv) in acetone (5 ml) to give the d_6-*N*-(2-methylpyridin-3-yl)acetamide (d_6-**41**a) (50 mg, 41%) as a colourless solid (Found $M^{\bullet+}$, 156.116 .$C_8H_4D_6N_2O$ [$M^{\bullet}$] requires 156.1170), mp 46 °C; ν_{max} (KBr) 3841, 3296, 3077, 3006, 2926, 2850, 2785, 2262, 1660, 1567, 1511, 1377, 1174, 1013, 954, 705; δ_H (400 MHz; CD_3OD) 8.25 (0.19H, s), 7.88 (0.03H, s), 7.28 (0.08H, s), 2.46 (0.41H, m), 2.18 (3H, s); δ_c (125 MHz, CD_3OD) 172.3 (s, C=O), 153.8 (s, C-NH), 146.5 (t, 1CD, $J_{C\text{-}D}$ 26.8), 134.7 (t, 1CD, $J_{C\text{-}D}$ 24.3), 134.1 (s, C-CD_3), 122.7 (s, 1CD, $J_{C\text{-}D}$ 26.8), 23.1 (s, CH_3), 20.1 (m, CH_3); *m/z* (EI) 156 ($M^{\bullet+}$, 80%), 112 (100), 95 (5).

4.3. Experimental Data for Metal-Free H/D Exchange

***d*$_2$-4-*n*-Butylaniline** (*d*$_2$-**32**)



d$_2$-**32**

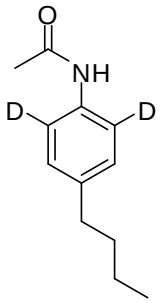


d$_2$-**32**

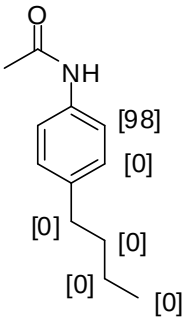
According to General Procedure 4.1, using 4-*n*-butylaniline (**23**) (300 mg, 317 μL, 2.01 mmol, 1 equiv), DCl (35%; 662 μL, 8.04 mmol, 4 equiv) and D_2O (3 mL) the *d*$_2$-4-*n*-butylaniline (*d*$_2$-**32**) (243 mg, 80%) was obtained as a brown oil (Found $M^{\bullet+}$, 151.1328. $C_{10}H_{13}D_2N$ [$M^{\bullet}$] requires 151.1330); ν_{max} (KBr) 3425, 3349, 3214, 3020, 1499, 1405, 1376, 1314, 1196, 1104, 1060; δ_H (400 MHz; CD_3OD) [a]6.91 (0.05H, m), 6.65 (1.92H, s), 2.47 (2H, t, *J*), 1.52 (2H, m), 1.32 (2H, t), 0.91 (3H, t, *J*); *m/z* (EI) 151 ($M^{\bullet+}$, 50%), 121 (20), 108 (100).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

***d*$_2$-*N*-(4-*n*-Butylphenyl)acetamide (*d*$_2$-32a)**



d$_2$-**32**a



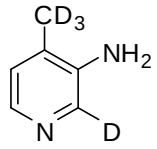
d$_2$-**32**a

According to General Procedure 4.1, using *d*$_2$-4-*n*-butylaniline (*d*$_2$-**32**) (204 mg, 1.35 mmol, 1 equiv), acetyl chloride (105μL, 1.5 mmol, 1.1 equiv) and NEt_3 (416.6 μL, 2.97 mmol, 2.2 equiv) in CH_2Cl_2 (10 ml) at 0 ^oC under a N_2 atmosphere gave the *d*$_2$-*N*-(4-*n*-butylphenyl)acetamide (*d*$_2$-**32**a) (188 mg, 72%) as a colourless solid (Found $M^{\bullet+}$, 193.1997. $C_{12}H_{15}D_2NO$ [$M^{\bullet}$] requires 193.2001); ν_{max} (KBr) 3166, 3119, 2854, 1640, 1514, 1459, 1361, 1281; δ_H (400 MHz; CD_3OD) [a]7.41 (0.06H, m), 7.11 (1.97H, s), 2.57

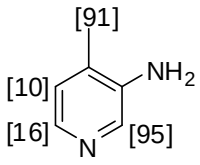
(2H, t, *J*), 2.10 (3H, s), 1.57 (2H, m), 1.34 (2H, t), 0.93 (3H, t, *J*); *m/z* (EI) 193 ($M^{\bullet+}$, 45%), 151 (30), 111 (90).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

***d*$_4$-3-Amino-4-methylpyridine (*d*$_4$-44)**



d$_4$-**44**

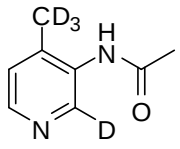


d$_4$-**44**

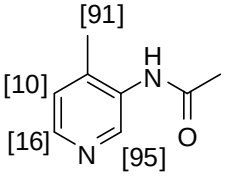
According to General Procedure 4.1, using 3-amino-4-methylpyridine (**44**) (300 mg, 2.7 mmol, 1 equiv), DCl (35%; 889 μL, 10.8 mmol, 4 equiv) in D_2O (3 mL) the *d*$_4$-3-amino-4-methylpyridine (*d*$_5$-**44**) (183 mg, 61%) was obtained as a colourless solid (Found $M^{\bullet+}$, 112.1064. $C_6H_4D_4N_2$ [$M^{\bullet}$] requires 112.1064); ν_{max} (KBr) 3442, 3204, 2960, 2696, 2526, 1375, 1324; δ_H (400 MHz; CD_3OD) [a]7.89 (0.05H, s), [a]7.70 (0.84H, d), [a]7.02 (0.90H, s), [a]2.14 (0.27H, m); *m/z* (EI) 112 ($M^{\bullet+}$, 100%), 113 (20).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

***d*$_4$-*N*-(4-Methylpyridin-3-yl)acetamide** (*d*$_4$-**44**a)



d$_4$-**44**a

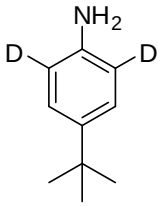


d$_4$-**44**a

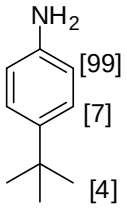
According to General Procedure 4.1 using *d*$_4$-3-amino-4-methylpyridine (*d*$_4$-**44**) (142 mg, 1.3 mmol, 1 equiv), dissolved in acetone (50 mL), and K_2CO_3 (894 mg, 6.4 mmol, 5 equiv), acetyl chloride (305 mg, 276 μL, 3.8 mmol, 3 equiv) in acetone (5 ml) to give the *d*$_4$-*N*-(4-methylpyridin-3-yl)acetamide (*d*$_4$-**44**a) (26 mg, 14%) as a yellow solid (Found $M^{\bullet+}$, 154.1175. $C_8H_6D_4N_2O$ [$M^{\bullet}$] requires 154.1170); ν_{max} (KBr) 3905, 3892, 3886, 3881, 3874, 3865, 3760, 3752, 3736, 3670, 3656, 3629, 2814, 2415, 2169, 2092;

δ_H (400 MHz; CD_3OD) 8.51 (0.05H, s), 8.24 (0.84H, d), 7.33 (0.90H, d), 2.27 (0.27H, s), 2.19 (3H, s); *m/z* (EI) 154 ($M^{\bullet+}$, 100%), 112 (100).

***d*$_2$-4-*tert*-Butylaniline (*d*$_2$-33)**



d$_2$-**33**

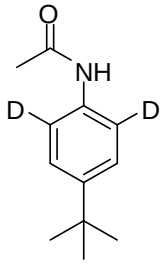


d$_2$-**33**

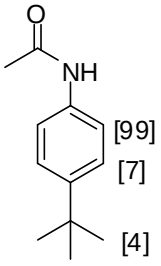
According to General Procedure 4.1, using 4-*tert*-butylaniline (**33**) (300 mg, 318 µL, 2.01 mmol, 1 equiv), DCl (35%; 662 µL, 8.04 mmol, 4 equiv) D_2O (3 mL) to give the *d*$_2$-4-*tert*-butylaniline (*d*$_2$-**33**) (286 mg, 94%) as a brown oil (Found $M^{\bullet+}$, 151.1335. $C_{10}H_{13}D_2N$ [$M^{\bullet}$] requires 151.1330); ν_{max} (KBr) 3851, 3836, 3743, 3674, 3585, 2915, 2848, 1699, 1684, 1652, 1558, 668; δ_H (400 MHz; CD_3OD) [a]7.14 (1.86H, s), [a]6.68 (0.02H, d, $J_{H\text{-}H}$ 9), [a]1.25 (8.61H, s); δ_c (125 MHz, CD_3OD) 145.1 (s, C-N), 142.1 (s, C-C), 116.2 (t, 2CD, $^1J_{C\text{-}D}$ 24.7), 34.5 (m, C-CMe_3), 31.7 (tt, $3CD_3$, $J_{1\ C\text{-}D}$ 19.2, $J_{2\ C\text{-}D}$2.8); *m/z* (EI) 151 ($M^{\bullet+}$, 60%), 136 (100), 108 (50), 96 (30).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

***d*$_2$-*N*-(4-*tert*-Butylphenyl)acetamide (*d*$_2$-33a)**



d$_2$-**33**a



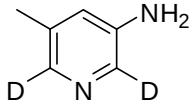
d$_2$-**33**a

According to General Procedure 4.1, using *d*$_2$-4-*tert*-butylaniline (*d*$_2$-**33**) (127 mg, 0.84 mmol, 1 equiv), acetyl chloride (65.8µL, 0.88 mmol, 1.1 equiv) and NEt_3 (259.5µL, 1.85 mmol, 2.2 equiv) in CH_2Cl_2 (10 ml) at 0 ^oC under a N_2 atmosphere to give the *d*$_2$-*N*-(4-*tert*-butylphenyl)acetamide (*d*$_2$-**33**a) (110 mg, 67%) as a colourless solid (Found $M^{\bullet+}$, 193.1429. $C_{12}H_{15}D_2NO$ [$M^{\bullet}$] requires 193.1436); ν_{max} (KBr) 3288, 3171, 3097,

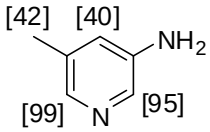
2961, 2865, 1685, 1669, 1654, 1593, 1518, 1483, 1420, 1382, 1361, 1317, 1039, 1010, 979, 898, 765; δ_H (400 MHz; CD_3OD) [a]7.41 (0.02H, m), 7.33 (1.86H, s), 2.10 (3H, s), 1.30 (8.61H, s); δ_c (125 MHz, CD_3OD) 171.5 (s, C=O), 148.1 (s, C-N), 137.0 (s, C-C), 126.4 (s, 2CH), 120.7 (t, 2CD, $^1J_{C\text{-}D}$ 24.3), 35.0 (m, C-CD_3), 31.5 (tt, $3CD_3$, $J_{1\ C\text{-}D}$ 19.2, $J_{2\ C\text{-}D}$2.8), 23.7 (s, CH_3); *m/z* (EI) 193 ($M^{\bullet+}$, 30%), 136 (50), 178 (40).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

d_2-3-Amino-5-methylpyridine (d_2-43)



d_2-**43**

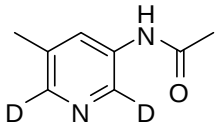


d_2-**43**

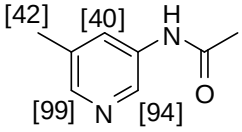
According to General Procedure 4.1, using 3-amino-5-methylpyridine (**43**) (100 mg, 0.93 mmol, 1 equiv), DCl (35%; 305 μL, 3.7 mmol, 4 equiv) and D_2O (3 mL) to give the d_2-3-amino-5-methylpyridine (d_2-**43**) (81 mg, 77%) as a yellow solid (Found $M^{\bullet+}$, 110.0810. $C_6H_6D_2N_2$ [$M^{\bullet}$] requires 110.0813); ν_{max} (KBr) 3324, 2235, 1627, 1589, 1575, 1410, 1389, 1259, 864; δ_H (400 MHz; CD_3OD) [a]7.76 (0.06H, s), [a]7.61 (0.01H, s), [a]6.93 (0.60H, s), [a]2.21 (1.76H, m); *m/z* (EI) 110 ($M^{\bullet+}$, 60%), 95 (5).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

d_2-*N*-(5-Methylpyridin-3-yl)acetamide (d_2-43a)



d_2-**43**a



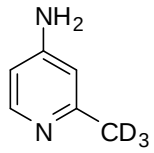
d_2-**43**a

According to General Procedure 4.1, using d_2-3-amino-5-methylpyridine (d_2-**43**) (70 mg, 0.61 mmol, 1 equiv), dissolved in acetone (20 mL), and K_2CO_3 (423 mg, 3.07 mmol, 5 equiv), acetyl chloride (144 mg, 131 μL, 1.84 mmol, 3 equiv) in acetone (5 ml) to give the d_2-*N*-(5-methylpyridin-3-yl)acetamide (d_2-**43**a) (25 mg, 27%) as a yellow solid (Found $M^{\bullet+}$, 152.0915 .$C_8H_8D_2N_2O$ [$M^{\bullet}$] requires 152.0919); ν_{max} (KBr) 3234, 2933, 1681, 1622, 1531, 1409, 1387, 1289, 1018, 881, 769; δ_H (400 MHz; CD_3OD) 8.51

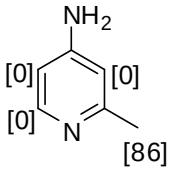
(0.01H, s), [a]8.10 (0.06H, s), [a]7.93 (0.60H, s), 2.34 (1.76 H, m), 2.15 (3H, s); *m/z* (EI) 152 ($M^{\bullet+}$, 45%), 110 (100).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

d_3-4-Amino-2-methylpyridine (d_3-40)



d_3-**40**

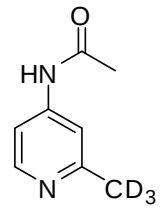


d_3-**40**

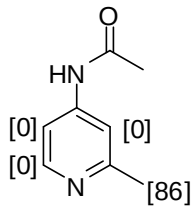
According to General Procedure 3.1, using 4-amino-2-methylpyridine (**40**) (150 mg, 1.4 mmol, 1 equiv), DCl (35%; 457 μL, 5.6 mmol, 4 equiv) in D_2O (3 mL) to give the d_3-4-amino-2-methylpyridine (d_3-**40**) (99 mg, 56%) as a colourless solid (Found $M^{\bullet+}$ 110.0812. $C_6H_5D_3N_2$ [$M^{\bullet}$] requires 110.0813); ν_{max} (KBr) 3233, 3199, 3088, 2965, 1247, 994; δ_H (400 MHz; CD_3OD) 7.83 (1H, d), 6.42 (1H, d), 6.37 (1H, dd), [a]2.26 (0.42H, m); *m/z* (EI) 110 ($M^{\bullet+}$, 100%), 95 (5).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

d_3-*N*-(2-Methylpyridin-4-yl)acetamide (d_3-**40**a)



d_3-**40**a

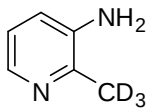


d_3-**40**a

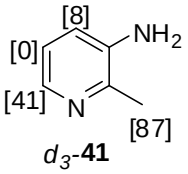
According to General Procedure 3.1, using d_3-4-amino-2-methylpyridine (d_3-**40**) (70 mg, 0.61 mmol, 1 equiv), dissolved in acetone (20 mL), and K_2CO_3 (423 mg, 3.07 mmol, 5 equiv), acetyl chloride (144 mg, 131 μL, 1.84 mmol, 3 equiv) in acetone (5 ml) to give the d_3-*N*-(2-Methylpyridin-4-yl)acetamide (d_3-**40**a) (25 mg, 27%) as a yellow solid (Found $M^{\bullet+}$, 153.0982. $C_8H_7D_3N_2O$ [$M^{\bullet}$] requires 153.0981); ν_{max} (KBr) 3235, 2916, 2849, 2242, 1672, 1606, 1585, 1569, 1536, 1469, 1373, 1300, 1040, 963, 893; δ_H (400 MHz; CD_3OD) 7.95 (1H, d), [a]7.25 (1H, d), [a]7.04 (1H, dd), 2.34 (0.42H, m), 2.14 (3H, s); *m/z* (EI) 153 ($M^{\bullet+}$, 60%), 112 (100).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

d_3-3-Amino-2-methylpyridine (d_3-41)



d_3-**41**

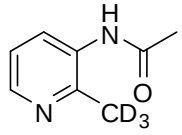


d_3-**41**

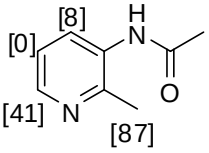
According to General Procedure 3.1, using 3-amino-2-methylpyridine (**41**) (150 mg, 1.4 mmol, 1 equiv), DCl (35%; 457 μL, 5.5 mmol, 4 equiv) in D_2O (3 mL) to give the d_3-3-amino-2-methylpyridine (d_3-**41**) (112 mg, 73%) as a colourless solid (Found $M^{\bullet+}$ 111.0878. $C_6H_5D_3N_2$ [$M^{\bullet}$] requires 111.0876); ν_{max} (KBr) 3846, 3756, 3639, 2583, 2913, 2361, 1658, 1370, 1264, 1197, 1042, 877; δ_H (400 MHz; MeOD) 7.70 (0.59H, d), 7.06 (0.92H, d), 6.99 (1H, m), [a]2.31 (0.37H, m); *m/z* (EI) 111 ($M^{\bullet+}$, 25%), 94 (5).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

d_3-*N*-(2-Methylpyridin-3-yl)acetamide (d_3-41a)



d_3-**41**a

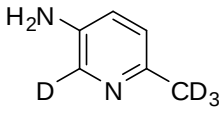


d_3-**41**a

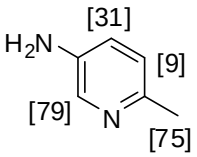
According to General Procedure 3.1, using d_3-3-amino-2-methylpyridine (d_3-**41**) (100 mg, 0.87 mmol, 1 equiv), dissolved in acetone (20 mL), and K_2CO_3 (605 mg, 4.4 mmol, 5 equiv), acetyl chloride (207 mg, 187 μL, 2.6 mmol, 3 equiv) in acetone (5 ml) to give the d_3-*N*-(2-methylpyridin-3-yl)acetamide (d_3-**41**a) (23 mg, 18%) as a colourless solid (Found $M^{\bullet+}$, 153.0986. $C_8H_7D_3N_2O$ [$M^{\bullet}$] requires 153.0981); ν_{max} (KBr) 3246, 3011, 2916, 2849, 2348, 2251, 1670, 1591, 1574, 1525, 1441, 1396, 1463, 1370, 1294, 1246, 1186, 1114, 1039, 1014, 856, 804; δ_H (400 MHz; CD_3OD) 8.25 (0.59H, d), 7.88 (0.92H, d), 7.27 (1H, m), [a]2.25 (0.37 H, m), 2.18 (3H, s); *m/z* (EI) 153 ($M^{\bullet+}$, 45%), 111 (100), 94 (5).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

d_4-5-Amino-2-methylpyridine (d_4-42)



d_4-**42**

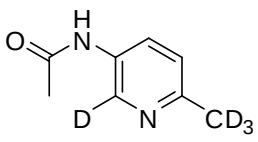


d_4-**42**

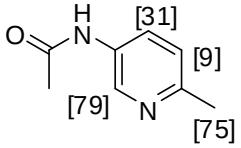
According to general procedure 3.1 using 5-amino-2-methylpyridine (**42**) (150 mg, 1.4 mmol, 1 equiv), DCl (35%; 457 μL, 5.5 mmol, 4 equiv) in D_2O (3 mL) to give the d_4-5-amino-2-methylpyridine (d_4-**42**) (76 mg, 49%) as a colourless solid (Found $M^{\bullet+}$ 112.0936. $C_6H_4D_4N_2$ [$M^{\bullet}$] requires 112.0939); v_{max} (KBr) 3584, 3390, 3269, 3030, 2928, 2264, 1635, 1596, 1363, 1460, 1371, 1301, 1250, 1115, 1086, 1042, 914; δ_H (400 MHz; CD_3OD) [a]7.85 (0.21H, d), 7.04 (0.78H, d, J_3 8), 6.92 (0.69H d, J_3 8), [a]2.32 (0.75H, m); *m/z* (EI) 112 ($M^{\bullet+}$, 65%), 117(20).

[a]Signal arises due to the presence of isotopologues and/or isotopomers.

d_4-*N*-(2-Methylpyridin-5-yl)acetamide (d_4-**42**a)



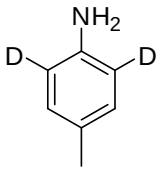
d_4-**42**a



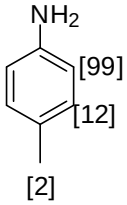
d_4-**42**a

According to General Procedure 4.1 using d_4-5-amino-2-methylpyridine (d_4-**42**) (70 mg, 0.62 mmol, 1 equiv), dissolved in acetone (20 mL) and K_2CO_3 (423 mg, 3.1 mmol, 5 equiv), acetyl chloride (144 mg, 130 μL, 1.8 mmol, 3 equiv) in acetone (5 mL) to give the d_4-N-(2-Methylpyridine-5-yl)acetamide (20 mg, 22%) as a colourless solid (Found $M^{\bullet+}$, 154.1013. $C_8H_6D_4N_2O$ [$M^{\bullet}$] requires 154.1013); v_{max} (KBr) 3584, 3296, 2917, 2849, 2289, 1738, 1582, 1538, 1463, 1452, 1282, 1129, 1116, 931; δ_H (400 MHz; CD_3OD) 7.95 (0.87H, s), 7.44 (0.21H, d, J_3 8), 7.25 (0.69H, d, J_1 8.48), 2.45 (0.75 H, m), 2.14 (3H, s); *m/z* (EI) 154 ($M^{\bullet+}$, 85%), 111 (100), 97 (5).

***d*$_2$-*p*-Toluidine (*d*$_2$-31)**



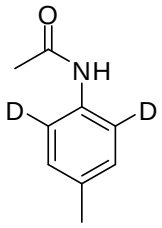
d$_2$-**31**



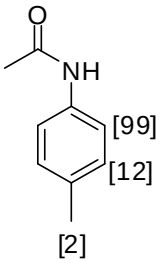
d$_2$-**31**

According to General Procedure 3.1, using *p*-toluidine (300 mg, 2.8 mmol, 1 equiv), DCl (35%; 921μL, 11.2 mmol, 4 equiv) in D_2O (3 mL) to give the *d*$_2$-*p*-toluidine (*d*$_2$-**31**) (169 mg, 55%) as a beige solid (Found $M^{\bullet+}$, 109.1335. $C_7H_7D_2N$ [$M^{\bullet}$] requires 109.1330); δ_H (400 MHz; CD_3OD,) 6.91 (1.76H, s), 6.65 (0.06H, d, $J_{H\text{-}H}$ 8.6), 2.21 (2.99H, m); *m/z* (EI) 109 ($M^{\bullet+}$, 70%), 108 (100).

***d*$_2$-*N*-(4-Toluidine)acetamide (*d*$_2$-31a)**



d$_2$-**31**a



d$_2$-**31**a

According to General Procedure 3.1, using *d*$_2$-*p*-toluidine (*d*$_2$-**31**) (100mg, 0.88 mmol, 1 equiv), acetyl chloride (68.3μL, 0.96 mmol, 1.1 equiv), NEt_3 (271μL, 1.95 mmol, 2.2 equiv) in CH_2Cl_2 (10 ml) at 0 ^{o}C under a N_2 atmosphere to give the *d*$_2$-*N*-(4-toluidine)acetamide *(d*$_2$-**31**a) (84.6 mg, 63 %) as a white solid (Found $M^{\bullet+}$, 151.1235. $C_9H_9D_2NO$ [$M^{\bullet}$] requires 151.1320); ν_{max} (KBr) 3291, 3176, 3104, 3005, 2954, 1662, 1599, 1540, 1371, 1316; δ_H (400 MHz; CD_3OD) 7.10 (1.76H, s), 2.29 (2.99H, m), 2.10 (3H, s); *m/z* (EI) 109 ($M^{\bullet+}$, 100%), 151 (50).

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