UNIVERSITY OF SUSSEX

H/D Exchange Using Metal Colloids In Synthesis

A thesis submitted to University of Sussex

By

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In Candidature of
Doctor of Philosophy

February 2018

School of Life Sciences
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DECLARATION

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 …… Hussein Sharhan
Date ……

Acknowledgments

I would like to thank Prof. Mark Bagley for his constant support during all several difficulties met during this PhD and encouragement, trust and continued guidance throughout my work at University of Sussex and following me during my writing up, without him this thesis could hardly be concluded. Particular gratitude goes to Prof. John Spencer for his consistent encouragement to me. I would like to mention that it is a pleasure to work with my lab group, Yosef, Tyler. Thanks also extended to all the analytical and technical staff for all the help I've received, in particular Dr. Alaa Abdul Sada. Many thanks to Anna lzykowska for her help in the administration. Big thanks as well to Prof. Ray. Deeptima, Dr. Jose, Dr. Jessica, Dr. David, Dr. Ayed, Dr. abbas, basim, Dr. youssra, Dr. Majed, Dr. Asma, Dr. Dhai. Dr. Mohammed, Dr. Muntahdar, Dr. Ahmad, Dr. Ali, Hashem, Jalel, Ahmed, Mohamed, Fadhel, Ali, Mahdy, moued, kamal, Dr. Adnan and to all people who supported me in Iraq and in the UK, thank you very much for your support and praying. Finally, I would like to thank my family: my mother and father, my wife, my brothers and sisters and my children: Ahmed, Murtadha, Sajad, Nour Al-Huda and my baby Tuka. To them and to the soul of my brother Hassan I dedicate this thesis.

ABSTRACT

Microwave and conductive heating mediated H/D exchange reactions, the latter under continuous flow processing in the presence or absence heterogeneous or homogeneous catalysts have been studied in this thesis. The aim of this study was to validate an efficient way to introduce multiple deuterium atoms into compounds of interest. Such deuterated substrates could be useful for the investigation of pharmacological and metabolic properties. Aniline and aniline derivatives as well as a series of aminopyridine derivatives were used as substrates in this study, due to the importance of the corresponding labelled compounds as drug compounds or as precursors for the synthesis of clinical agents. Pd/C as a heterogeneous catalyst was employed under microwave–assisted and flow chemistry conditions and the %D incorporation and chemical yields were compared. The H/D exchange reaction using platinum as a homogeneous catalyst with aniline derivatives provided the means to incorporate deuterium efficiently at all aromatic positions. Furthermore, metal catalysis was able to facilitate exchange in alkyl side chains with high efficiency, provided that there was no quaternary centre in the alkyl group. The study also demonstrated that the H/D exchange of aniline derivatives in the absence of a metal catalyst proceeded as anticipated and was able, on deuterio-protio exchange under acidic conditions, to deliver *meta*-deuterated targets. The H/D exchange of aminopyridine derivatives using a platinum catalyst was also highly efficient, giving high deuterium incorporation in many cases. Mechanistic proposals have been put forwards for these processes. This research has provided a new method for the preparation of *meta* functionalized aniline- and highly functionalized pyridine-derivatives suitable for further elaboration. The Pt-catalyzed process has provided a means for deuteration at multiple aromatic positions in a single cycle, short reaction time and high efficiency.

Abbreviations

ADMET	**Absorption, distribution, metabolism and excretion - toxicity**
c	**Concentration**
$CDCl_3$	**Deuterated chloroform**
d	**Doublet**
DCM	**Dichloromethane**
DMSO	**Dimethyl sulfoxide**
EI	**Electron Impact**
Equiv.	**Equivalent**
EtOAc	**Ethyl acetate**
Et_2O	**Diethylether**
FDA	**Food and Drug Administration**
g	**Gram(s)**
GHz	**Gigahertz**
H/D	**Hydrogen/ Deuterium**
h	**Hour(s)**
Hz	**Hertz**
IR	**Infra-red**
J	**Coupling constant (in Hz)**
m	**Multiplet**
m	***Meta***
Me	**Methyl**
MeOH	**Methanol**
MHz	**Megahertz**
M_r	**Molecular weight**
Mr′	**Average molecular weight**
min	**Minute(s)**
mL	**Millilitre(s)**
mmol	**Millimole(s)**
mol	**Mole(s)**
mp	**Melting point**

NEt_3	**Triethylaniline**
nM	**Nanomolar**
NMR	**Nuclear magnetic resonance**
p	***Para***
Ph	**Phenyl**
PSI	**pound per square inch**
R.T.	**Room temperature**
s	**Singlet**
t	**Triplet**
tert	**Tertiary**

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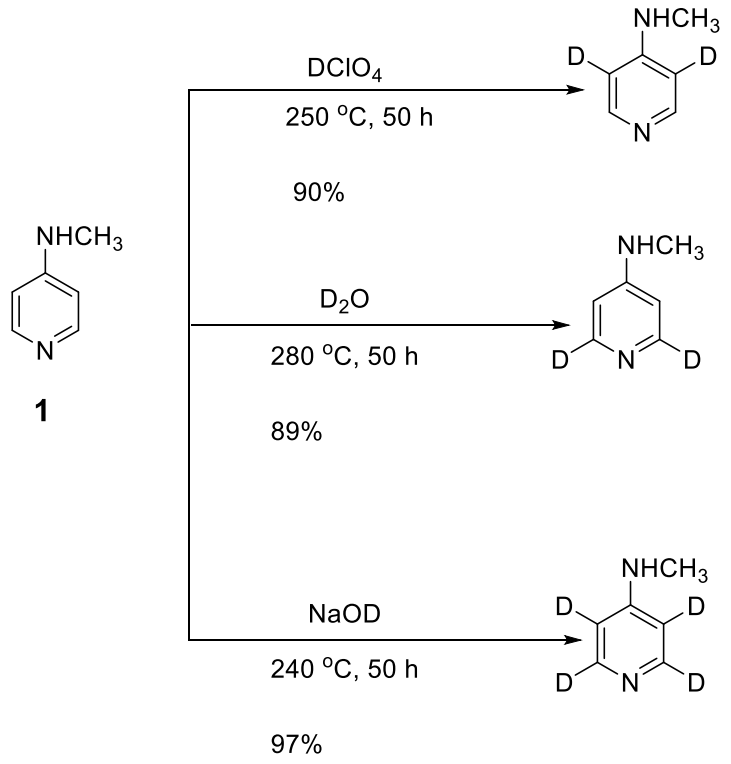
Chapter 1
Introduction

1.1. The Colloids

A colloid is a heterogeneous diffusion of two uninvolved forms, which is somewhat or fairly permanent, and has some characteristic features. It is possible that all fluids in the human body can be considered as examples of colloidal status.[1] In 1860 the Scottish chemist Thomas Graham, discovered that certain materials such as glue, gelatin and starch do not pass through particular semi-membranes, unlike real solutions; these materials were called colloids.

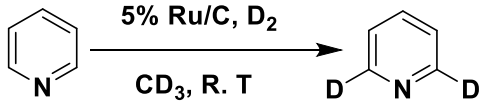
In 1925, Richard Zsigmondy conducted research on colloids including a study of particles scattered throughout another substance; by examining the way in which particles dispersed he noticed that more could be learned about the colloids.
There are synthetic colloids, such as hydroxyethyl starch, which became commercially available in the 1970s by using grains of maize to obtain the waxy starch. These colloids have several clinical features and properties. There are many benefits of industrial and consumer products that rely heavily on certain colloidal properties such as viscosity and flow.[2] Common examples include toothpaste lubricants, coatings and lotions. Colloids confer desirable flow properties on these products; in many cases, they also provide stability and non-separation of phas.

Recently, some colloidal materials that have been manufactured have been adapted to specific applications and have become widely available. Such manufactured colloids include colloidal carboxymethyl cellulose, fumed silica and microcrystalline cellulose.[3] Colloids have also found application as catalysts: Kathryn reported a high D incorporation catalysed by Pd colloid at room temperature between different N-heterocyclic substrates and D_2O[4] H/D exchange in different reactions between heterocyclic compounds which contain nitrogen[5] and deuterium has also been achieved using metal colloids as a catalysts with D_2O [6-9] or through the use of acid or base catalysts in D_2O source[10, 11]under high temperature conditions[12, 13]
(Scheme 1.1).



Scheme 1.1.H/D exchange of aminopyridine under various conditions.

Exchange at multiple positions in an aromatic or heterocyclic ring can be accomplished using these methods to give different proportions of deuterium incorporation and different regioselectivity of exchange. However, by using Ru or Rh as a catalyst dispersed in THF under a D_2 atmosphere in a solvent[14], deuterium incorporation can be achieved at a specific position of pyridine derivatives at room temperature. A similar result can also be obtained using 5% Ru / C as a catalyst in methanol-d_4, scheme (1.2).



2 **2a**

Scheme 1.2. H/D exchange at the α-position of pyridine under ambient conditions.[15]

Palladium colloid protected by poly-*N*-vinylpyrrolidone as a polymer was used in H/D exchange reactions as a catalyst for H/D exchange of pyridine and pyridine derivatives using D_2O as the deuterium source. A high level of H/D exchange was observed for pyridine and pyridine derivatives especially at the site adjacent to the endocyclic nitrogen under these reaction conditions. Within a short time, it provided a high

incorporation of deuterium and good chemical yield. H/D exchange not only occurred in the ring but was also observed in a side chain such as in a methyl group for the 4-methylpyridine substrate.[16]

1.2. Isotopes

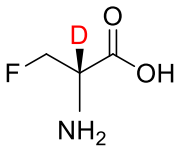
Each chemical element in the periodic table has certain number of protons and neutrons in its nucleus. If the number of neutrons changes, whereas the number of protons is fixed, then the new entity is different from the original chemical element. This is called an isotope of the element.[17,18] Accordingly, the isotope has an alternative mass number i.e. different atomic weight.

Some of the radioactive elements are not stable. They lose a number of neutrons and develop into an isotope or another element. The process of losing particles is called “decay”. In 1912, Frederick Soddy,[19,20] while investigating the process of decay, discovered new elements or isotopes starting with uranium (radioactive) until it changed into lead. The lost particles were released as alpha or beta radiation, depending on the particle emitted. Similarly Thomson discovered[21, 22] isotopes which had not been produced from radioactive decay. He found that some neon ions were deflected by a magnetic field more than other particles. These isotopes, in other words, were stable and non-radioactive. Furthermore, Aston[23] determined the atomic weight of these different isotopes using mass spectrometry.

The deuterium, (also known as heavy hydrogen) is one of two stable isotopes of hydrogen. Deuterium is a stable isotope of hydrogen which hydrogen has one proton in its nucleus. Since isotopes are atoms of the same element having the same number of protons whiles it have different numbers of neutrons, both hydrogen and deuterium are composed of one proton per each nucleus. The main difference between Hydrogen and Deuterium is that Deuterium atoms contain a neutron in their nucleus whereas Hydrogen atoms do not contain any neutrons in their nucleus. It was discovered by Harold Urey in 1931. Deuterium- containing compounds are of great value in analysing reaction mechanism and in determining the metabolism and distribution of a clinical drug.[24]

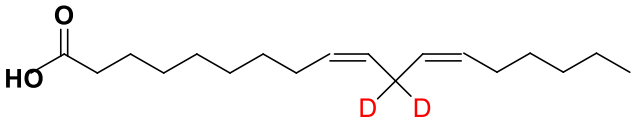
1.3. The use of isotopes in drugs

Various isotopes are used in many different industries; one being the pharmaceutical industry. In particular, the use of isotopes in an organic chemical reaction may well influence the rate of formation of the product. Depending upon the role of the isotope-containing species, its presence may cause a reaction to speed up or slow down, producing a so-called *isotope effect.*[25] This outcome can be attributed to many factors, but has at its basis the fact that the atomic masses of the isotopes are not the same. Sigma bonds to the heavier isotope are typically shorter and stronger with a lower zero point vibrational energy. These properties are very important when isotopes are introduced into drugs. For example replacing C-H bonds with C-D bonds can change the metabolism of a clinical agent, giving improved pharmacokinetic properties (Fig. 1.1).[26]



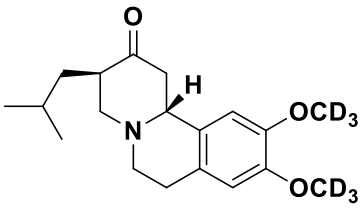
Fludalnine

3



RT001

4



SD-809

5

Fig 1.1. Structures of advanced clinical candidates containing deuterium: 1-DaxibotulinumtoxinA Topical Gel (RT001), Fludalnine and Deutetrabenazine (SD-809)

Isotopes can also be used to study the metabolism of a drug and form an essential part of the pharmacokinetic studies of ADMET properties of clinical agents that progress to market. These studies involve processes such as absorption of the drug, the distribution around the body and the excretion.[27] Since an isotope has a different

atomic mass, if a number of isotopes of the constituent elements are incorporated into a drug this gives the agent a characteristic isotopic label that is distinct from the natural abundance and thus the presence and distribution of the drug and any chemicals derived from the drug through metabolism can be identified and quantified.[28]

Teva's drug also known SD-809 and deutetrabenazine has been used since 1960s as a treatment for movement disorders, which currently undergoing review by the US FDA (Food and Drug Administration).

The structure of deutetrabenazine has two methoxy groups on its aryl ring (structure 5, Fig. 1. 1); the methoxy groups are metabolized by protodemethylated to the phenol/catechol. Deutatetrabenazine switches both from OCH_3 to OCD_3, and that is enough to slow the compound's clearance down to a useful degree. Actually, both the plain and the deuterated forms of tetrabenazine first get metabolized through reduction of the carbonyl group.[29- 30]

Replacing hydrogen atoms with a heavier deuterium in the molecule is one way to improve the metabolic behaviour of a drug. This is so because replacing deuterium with hydrogen makes the molecule break down more slowly as the carbon-deuterium bond is shorter and stronger than the carbon-hydrogen atom, making reactions from six to ten times slower. As a result, the deuterium can prolong the half-life of drugs and improve the patient's ability to tolerate certain drugs.[31]

1.4. The reactions of H/D exchange

H/D-exchange reactions at carbon centers[32] are found in many applications in modern synthetic organic chemistry; for example in the preparation of isotopically labelled compounds, in basic research on C–H bond activation,[33] or in mechanistic investigations on catalysts and reaction pathways.[32] The 1960s and 1970s, witnessed extensive research in this field. In the 1980s this slowed down considerably but was resumed again around mid-1990s due to the growing interest in catalytic C–H bond activation and the increasing demand for isotopically labeled compounds as a reference material in mass spectrometry.[34]

In the investigation of samples from the environment, animals, or humans, there is a particular advantage in the use of isotopically labelled internal standards in where matrix effects[35] can interfere with the quantification of toxins. This is because these effects can be almost totally excluded by the physical and chemical similarity of the

substance under investigation and the standard. The natural isotope pattern keeps signal overlap high. If the mass difference is selected to be large enough to keep signal overlap as low as possible, then quantitative determination will be possible.[36, 37] In addition to that, because of the production of very sophisticated and reliable mass spectrometers and their widespread availability, the demand for isotopically labelled internal standards has risen.

Essentially two procedures are often followed to synthesize isotopically labelled compounds. Perhaps the most common approach is to start from commercially available, stable, isotopically-labelled precursors, both ^{2}H-, as well as ^{13}C- and ^{15}N -labelled compounds, and prepare the targets by conventional synthesis. ^{15}N -labelled compounds are also useful for in vivo studies, for cases where deuterium-labelled compounds cannot be used because of the possibility of a different metabolism operating to the parent compound, or in cases where the metabolic loss of deuterium might be observed.[38]

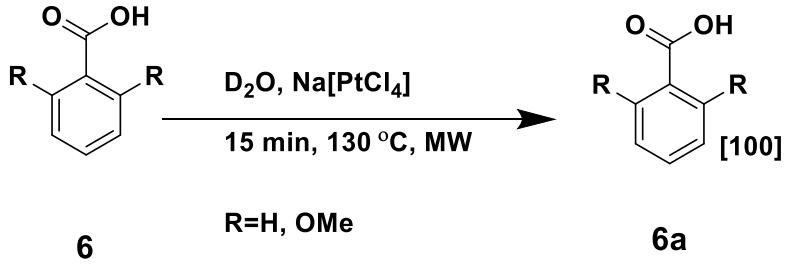
However, the length of synthetic routes and the high cost of ^{13}C- and ^{15}N -labelled starting materials must often be taken into account. In contrast, a molecule could be labelled considerably more rapidly and cost effectively by the direct exchange of a hydrogen atom (bonded to a carbon atom) for a deuterium atom. This method is particularly efficient for the synthesis of deuterated organic compounds since these exchange reactions can often be carried out directly on the target molecule or a late intermediate in the synthesis, and deuterium-containing reagents such as D_2O or D_2 gas can be used as the deuterium source. Deuterium can be inserted into a molecule by halogen/deuterium exchange[39] or by reductive deuteration.[40] although suitable precursors must frequently first be prepared.

In recent years, the introduction of automated parallel synthesis and further development of laboratory microwave apparatus have resulted in a very large number of studies on the preparation of deuterated substances by H/D exchange. The commercial interest in these approaches is evident from a series of patents.[41] In addition to the deuteration of organic molecules, exchange reactions have also been employed for the introduction of tritium (^{3}H, T). Here, H/D-exchange reactions are frequently used as reliable models for synthesis optimization for processes of tritiation. Furthermore, pharmacokinetic and metabolic studies often use radio-labelled pharmaceutical candidates of this type as part of drug development. One well-known

and important method for H/D exchange is metal catalyzed H/D exchange using homogeneous or heterogeneous catalysts.[42]

1.5. The use of homogenous catalysts for H/D exchange

Transition metal-mediated H/D-exchange reactions using soluble catalyst complexes offer many advantages over other methods. They have comparably mild reaction conditions and high tolerance towards a number of functional groups where dehalogenation, deuterium addition to multiple bonds, hydrolysis, epimerization, or the cleavage of protecting groups, which are undesirable side reactions, could occur. Another advantage is that, with these catalytic systems, very efficient deuterium incorporation with concomitant high regioselectivity can often be achieved, scheme (1.3). For this reason, they are in principle also suitable for the incorporation of tritium.



Scheme 1.3. H/D incorporation using platinum as a homogeneous catalyst.[43]

In addition to the use of deuterium gas and deuterium oxide as deuterium sources, deuterated solvents such as [D_6]-acetone or [D_6]-benzene are also suitable for H/D exchange on less polar substrates. Since fundamental studies of research groups of Garnett [44,45]in the early 1970s on H/D exchange by homogeneous catalysts, many efficient methods have been developed which have allowed high levels of incorporation of deuteration in both aromatic and aliphatic substrates.

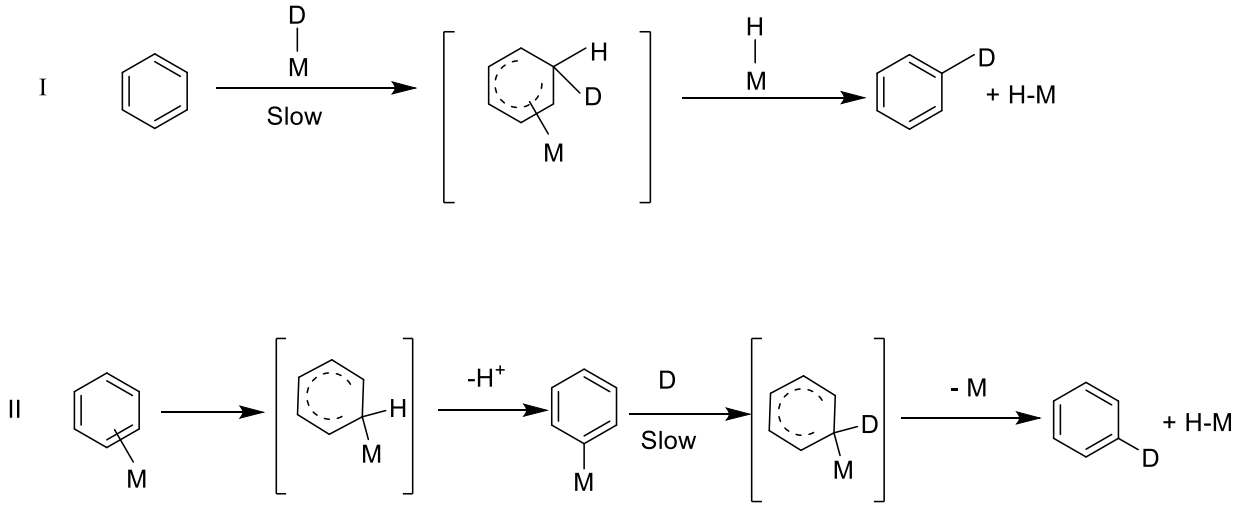
1.6. The use of heterogeneous catalyst for H/D exchange

A heterogeneous catalyst in chemical reactions has the possibility to be removed by simple filtration at the end of the process. Technically, this has an important advantage over homogeneous catalysis. Moreover, in exchange processes that occur without side reactions, no further work-up steps are necessary.[46] However, in heterogeneously catalyzed processes, it must be expected that the formation of dehalogenation, hydrogenation, and hydrolysis products could also occur; as well as

epimerization and racemization (under harsh conditions).[47] What cannot be usually avoided is the adjustment and optimization of reaction conditions for each substrate, in spite of the methodological improvements in recent years. With palladium, platinum, rhodium, nickel, and cobalt catalysts, high activity for H/D exchange has been achieved.[48]

1.7. The mechanisms of heterogeneous catalysis for H/D exchange

Garnett and co-workers have concluded that a π-complex mechanism is involved in heterogeneously catalyzed H/D exchange (Scheme 1.4),[49]since deuterium transfer in high yield is frequently observed only for substrates that contain a double bond or aromatic ring system. In addition to an associative mechanism I, kinetic investigations indicated that a competing dissociative π-complex mechanism II was also involved.[50] The notable difference between these two reaction pathways is that, in the associative mechanism I, direct substitution of a hydrogen atom by a deuterium atom occurs bound to the metal centre.



Scheme 1.4.Associative (I) and dissociative mechanism (II) for heterogeneous catalysis of H/D exchange in aromatic substrates[50].

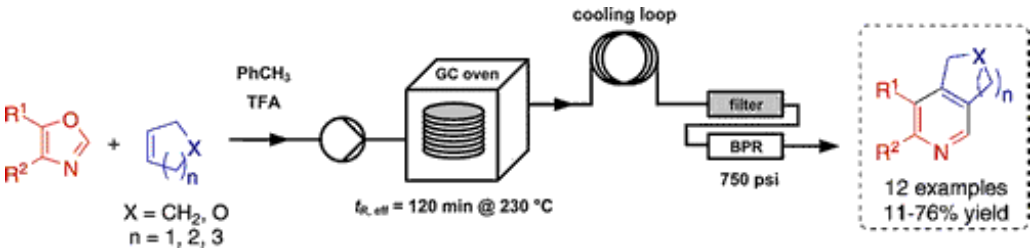
In the dissociative mechanism II, a proton of the initially formed π-complexis substituted by the metal atom.[51] Subsequently, this leads to the formation of an intermediate phenyl.[52] A substitution of the metal atom by deuterium would thence take place, only in the second step. Both mechanisms, it would seem, could be involved to a different extent in the formation of the product, depending on the

transition metal involved. A greater involvement of the dissociative mechanism is proposed in the case of platinum. For palladium, the associative mechanism predominates. In the case of rhodium, both mechanisms are involved equally. Aliphatic compounds are deuterated only under forcing conditions.[53]

1.8. Flow Chemistry

Flow chemistry exhibits some of the benefits related to microwave-assisted methods such as rapid reaction kinetics and sealed vessel technology. However since microwave irradiation must propagate through an organic medium the permeation depth is limited. Continuous flow processing technology provides a means to extend the processing power of microwave-assisted methods by using conductive heating in a flow cell at an elevated temperature and pressure under the control of a back-pressure regulator. A number of advantages are offered by this platform technology over batch processing methods, including small chemical stocks of reaction types, excellent temperature control, good heat transfer to mass, predictable mixing, ready automation and direct monitoring. Moreover, there are a number of different processing tools available, thus minimizing difficulties in the transfer of operating conditions to ensure continuous production.

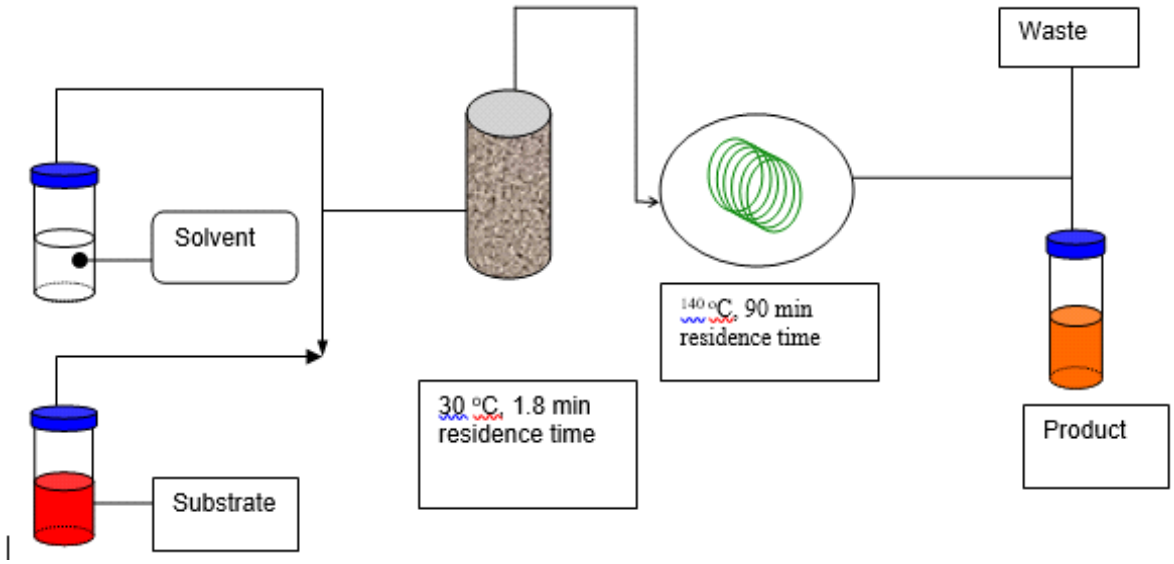
Many methods of pyridine synthesis have been transferred to continuous production and processing platforms. In 2013, Robert and Renner reported the reaction in flow to provide direct access to an annulated pyridine. The pyridines obtained through this one-step process constitute a valuable scaffold for medicinal chemistry.[54]



Scheme 1.5. Use of a flow reactor for the synthesis of pyridine derivatives.[54]

The synthesis of 5-arylpyridines under continuous processing has been reported to be replaced by a similar process (Scheme 1.5), a retro Diels-Alder reaction using continuous flow processing, in reasonable to excellent yields.[55] A variety of processes

have been described for the synthesis and reaction of N-substituted derivatives under flow conditions. Nowadays, a continuously flowing microfluidic reactor has been giving pyridine a more efficient, and rapid scalability profile, without using a transition metal as a catalyst.[56] In 2011, Martin reported the synthesis of pyridine suspense through a molecular inverted homogeneous electron demand-Diels-Alder reaction under constant flow conditions. Flow reactor chemistry (Scheme 1.6), controls the temperature of organic solvents beyond the boiling point, reducing the degree of toxicity and minimizes the difficulty of solvents in action such as nitrobenzene or chlorobenzene, which is commonly used in these reactions; these can be replaced to less harmful ones such as toluene. The process has developed a scalable flow, providing easy access to a series of newly constructed pyridine substrate.[57]



Scheme 1.6. Flow chemistry reactor for H/D exchange reactions.

1.9. Microwave

In organic chemistry, Gedye and Giguere first introduced the application of microwave technology in 1986.[58, 59]

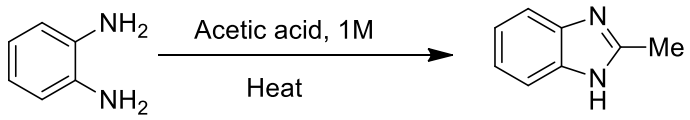
Commercial microwave reactors for chemical synthesis have become widely available in both academia and industry. At present, this technology has been exploited in organic synthesis, drug discovery, polymer chemistry and in the synthesis of metal colloids, amongst others.[60, 61]

According to the law of Arrhenius, heating chemical reactions using microwave irradiation in sealed vessels can significantly increase the solvent temperature above the atmospheric boiling point and thus increase the reaction rate (Equation 1).[62]

$$k = A\,EXP\left(\frac{-Ea}{RT}\right)$$

Equation 1. The Arrhenius Law

One example of this relationship of Arrhenius is the formation of benzimidazole from the reaction of 1,2-diaminobenzene with acetic acid where it was observed that the reaction at room temperature needed approximately 63 days to reach completion, whereas under high temperature conditions at 100 °C under conventional heating. However, the use of microwave irradiation in a closed vessel and at a temperature of 270 °C the process needed only 1 s to achieve suitable results. Thus, the use of microwave irradiation can reduce the reaction time considerably and thus increase production capability.[63, 64]



7 **8**

Scheme 1.7. Temperature of reaction mixture has a dramatic effect on reaction times.

Chemical reactions often require elevated temperatures to overcome unfavourable reaction kinetics. Conventional methods such as heating mantles, oil baths, gas burners and electrical baths are often unreliable inhomogeneous sources of heating. The use of microwave heating has been widely adopted as an efficient and quick method to reach the required temperatures to overcome kinetic barriers. Reaction

mixtures will heat under microwave irradiation by two mechanisms: dipole polarization and ionic conduction. Samples containing dipoles and ions respond to a rapidly oscillating electromagnetic field and as a result, the rapid transfer of energy to vibrational levels is observed. If this is combined with the use of a catalyst, then favourable and rapid reaction kinetics can be obtained.

This technology has been used in a wide range of important fields in synthetic chemistry, including the discovery of drugs,[65-69] chemistry of polymers and the preparation of inorganic nanocrystals as a synthesis of colloidal systems, amongst others.[70-73]

1.10. H/D exchange reactions for aniline derivatives

In the 1960s and 1970s, intensive study was conducted on H/D exchange methods,[74,75] leading to a number of practical strategies to use a C-H bond for exchange of hydrogen isotopes[76] under various metal catalyzed heterogeneous and homogeneous conditions. In the 1930s, the first investigation on isotopic-exchange was conducted using Platinum as a heterogeneous catalyst and was performed with aromatic hydrocarbons employing benzene chemisorption, followed by deuteron exchange using either absorbed D_2 gas or D_2O.[77] Many researchers have preferred the use of pre-reduced transition metals for this process, which has been available since 1957, along with isotopic water exchange driven by the need to prepare deuterated[74] or tritiated targets.[24, 78]

Due to of radiationless decomposition, there are challenges with the synthesis of tritiated targets with high activity tritium gas. Nevertheless, a reductive strategy using hydrogenation, under heterogeneous (Palladium in carbon) or homogeneous catalyst conditions[79] is still one of the most widely used methods for synthesis. The homogeneous salts of transition metals have been demonstrated in several studies as a viable approach. Since the early work of Garnett and Shilov[80-83] especially focusing on Pd and Pt catalysts as active catalysts for C-H functionalization of aromatic methane using isotopic water,[24,84-89] that can catalyze H/D exchange reactions for aromatic and aliphatic substrates, there are many efficient soluble transition metal catalysts for C-H functionalization,[90-97] including Iridium, Rhodium and Ruthenium.

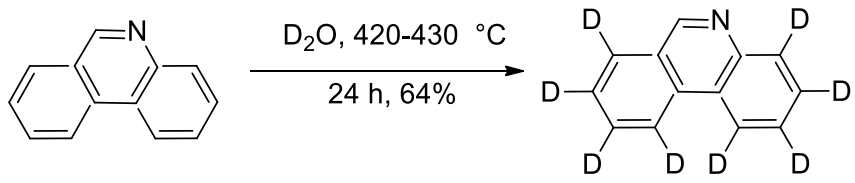
Recently with the improved performance of mass spectrometers and application of microwave technology for the synthesis of short-lived radiopharmaceuticals and a renaissance of interest in C-H bond activation[98] new metal-catalyzed H/D exchange methods have emerged[98-102], which improve the substrate scope over pH-dependent exchange methods Furthermore, even with an expansion of interest into C-H activation chemistry H/D exchange reactions often demand multiple cycles,[103] long reactions times[104] and/or strict conditions.[105]A method of microwave-assisted was developed for deuterium incorporation at aromatic ring and alkyl positions to substitute aniline derivatives that was effective with relatively mild conditions using a single cycle and isotopic water. Nowadays studies interesting in the development of new C-H functionalization procedures at unactivated positions for H/D exchange .[106]

There has been recent interest in the use of anilines for the synthesis of azo compounds[107], quinolones,[108], indoles,[109] quinolones,[110], isatoic anhydrides,[111] isatins[112] benzoxazoles,[113] carbazoles[114] acridines[115] and phenanthridines[116]

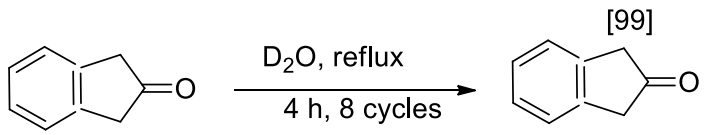
1.11. H/D exchange reactions for aminopyridine derivatives

Recently, the demand for multiple-labelled compounds containing stable isotopes has increased significantly.[35,76] Deuterium derivatives are important in drug development as internal standards of human and animal drug testing as well as in mechanical studies to determine pathway of reaction. Deuterated standards have the same physical and chemical properties of non-deuterated isotopologues and similar ionization properties. However, its mass is different from the mass of natural isotopes: the greater the difference, the easier the challenge to separate signals from natural isotopic forms, for quantification and analysis.[117]

The reactions for H/D exchange can occur in several ways. In some cases, activation technology for C-H are required involving metal catalysts,[85] whereas in other instances substrates can be exchanged using D_2O as a source of deuteration, mainly under extreme conditions or long reaction times.[12] For instance, the use of an autoclave at critical temperature of 420-430 °C has been used for the synthesis of phenanthridine (**9a**).[105] Conversely, d_4-indaone (**10a**) has been deuterated under neutral conditions at reflux in D_2O but required multiple cycles,[103] as depicted in (Scheme 1.8).



9 **9a**



10 **10a**

Scheme 1.8. H/D incorporation for phenanthridine (9) and indaone (10) using neutral D_2O.

1.12. Aims of this study

This project aimed to discover a rapid route of access to compounds labelled at multiple positions with deuterium by H/D exchange. The method should feature:

1. High %D exchange.
2. Incorporation at multiple positions.
3. Short reaction times and a single cycle.
4. Mild conditions using D_2O as deuterium source.
5. The preparation of *meta* functionalized aniline derivatives and pyridine derivatives suitable for biological application.

Chapter 2

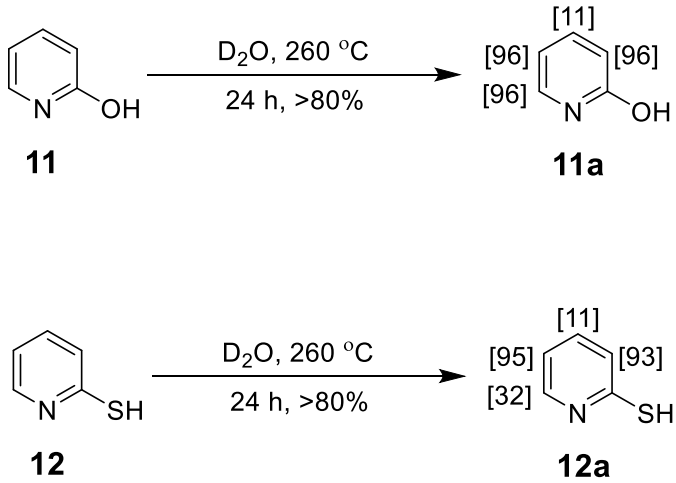
Investigating experimental parameters affecting H/D exchange reactions

2.1. Introduction

This chapter will report on the initial experiments conducted to establish effective methods for the promotion and analysis of deuterium exchange processes. The experimental studies will focus on H/D exchange under microwave irradiation; these studies will aid in establishing the required evidence to qualify reaction outcome. In particular, the experiments will investigate mass spectrometric and nuclear magnetic resonance (NMR) spectroscopic analysis of mixtures of isotopologues. In order to present results clearly, the study will aim to qualify the corresponding deuterium percentage incorporation at different positions.

In this study, when deuterium incorporation exceeds 50% at a particular position the product will be considered as containing the deuterium isotope at that position.

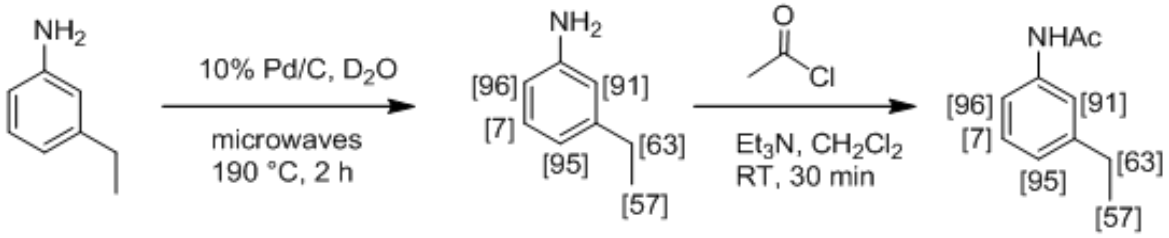
Many existing studies have reported significant results in H/D exchange reactions. For example, according to Werstiuk and Ju[12] experiments conducted in the absence of acid or base were able to incorporate D into pyridine derivatives with excellent isolated yields (>80%) and high levels of deuteration at certain positions (Scheme 2.1).



Scheme 2.1.Werstiuk and Ju's experiments on pyridine derivatives, giving high levels of deuteration at certain positions with good regioselectivity[12].

2.2. Initial studies using an heterogeneous catalyst

A heterogeneous catalyst in a chemical reaction has the possibility to be removed by simple filtration at the end of the process, an important advantage over homogeneous catalysts. Moreover, in exchange, processes that occur without side reactions and that do not require further purification, no further work-up operation would be required, simplifying the experimental procedure. However, in heterogeneously catalyzed processes, it is possible that the formation of dehalogenation, hydrogenation, and hydrolysis products could be observed, in addition to epimerization and racemization under harsh conditions. It might be anticipated that the adjustment and optimization of reaction conditions will be required for each substrate, in spite of improvements in methodology in recent years. With palladium, platinum, rhodium, nickel, and cobalt catalysts, high activity for H/D exchange has been described, with chemoselectivities for alkyl over aryl C-H bond activation that vary by metal. Thus, in order to review the methods and analytical procedures to qualify the efficiency, chemo- and regioselectivity of H/D exchange, a substrate bearing both alkyl and aryl groups was submitted to high temperature conditions (Scheme 2.2) in the presence of a deuterium source, varying the nature of the heterogeneous catalyst (Table 2.1). The high temperature conditions were obtained using microwave irradiation, varying the microwave power in order to maintain constant temperature as recorded by the instrument's in-built IR sensor.



Scheme 2.2. Initial studies on H/D exchange of 3-ethylaniline using a heterogeneous catalyst.

Table 2.1 %D incorporation for 3-ethylaniline after microwave irradiation.

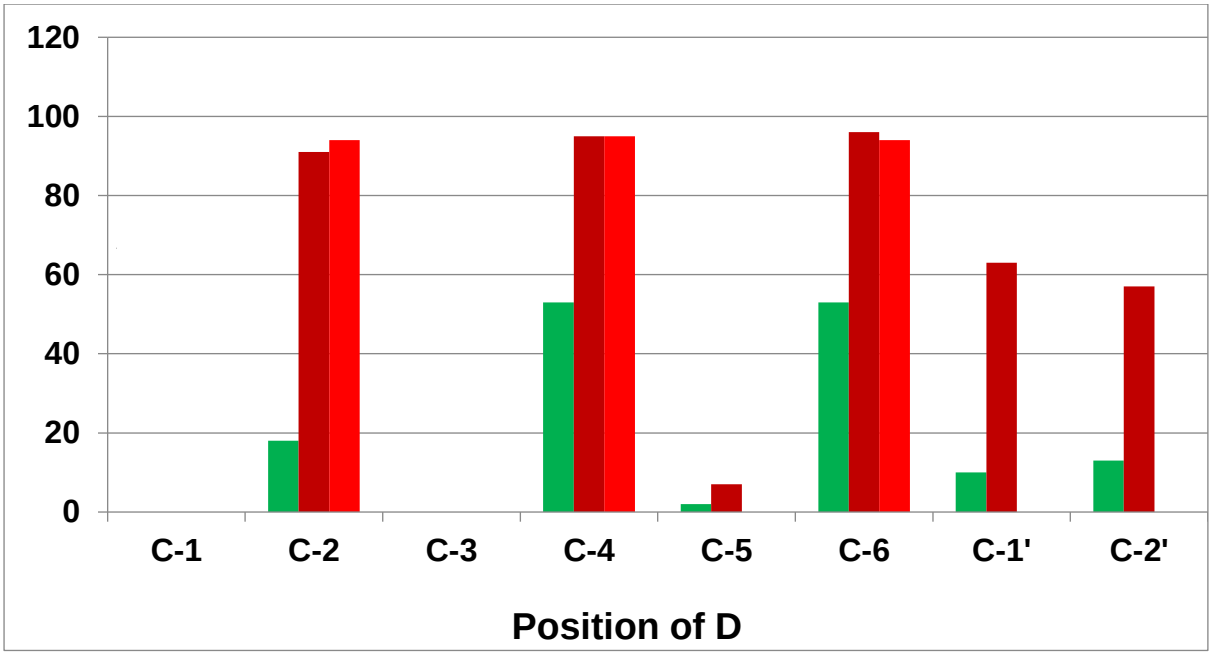
Entry	Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	Yield
1	%D*	18	….	53	2	53	10	13	80%
2	%D¥	91	….	95	7	96	63	57	87%
3	%D‡	94		95	0	94	0	0	50%

*%D incorporation at the corresponding position for the H/D exchange reaction after microwave irradiation of the substrate in the absence of a catalyst.

¥%D incorporation at the corresponding position for the H/D exchange reaction after microwave irradiation of the substrate using a Pd/C catalyst.

‡%D incorporation at the corresponding position for the H/D exchange reaction after microwave irradiation of the substrate using active charcoal.

Figure 2.1 illustrates deuteration for 3-ethylaniline by different methods, showing incorporation of deuterium at different positions. The first thing to note is that use of active charcoal influences the level of deuteration only at activated positions but does have a significant affect upon the kinetics of H/D exchange. However although use of Pd/C as a heterogeneous catalyst also gave good D incorporation at activated positions to a similar degree, there was no incorporation at the *meta* (C-5) position. Pd/C was able to promote the incorporation of D into the ethyl side chain, although the level of deuteration was slightly lower than the %D incorporation in the aromatic ring at activated positions. Nevertheless, this result was significant, certainly when compared with the use of D_2O alone. It would appear that palladium metal does not promote deuterium incorporation in the aromatic ring but does facilitate H/D exchange in the side chain. It was considered that Pt as a homogeneous catalyst might be better chosen for the deuteration of aromatic substrates and thus might be able to better promote aromatic exchange at unactivated positions.



Scheme 2.3.Impact of heterogeneous catalyst on deuteration levels for 3-ethylaniline.

▪deuteration levels for 3-ethylaniline without catalyst.

▪deuteration levels for 3-ethylaniline using a Pd/C heterogeneous catalyst.

▪deuteration levels for 3-ethylaniline using active charcoal.

2.3. Compound analysis after deuteration

2.3.1. Mass spectrometric analysis

Generally, the products of H/D exchange will display different levels of deuterium incorporation at different positions and this corresponds to a mixture of isotopologues and isotopomers. A consequence of the former is that the mixture is a series of deuterated species that are characterised by different isotopic distributions and thus different molecular masses. Mass spectrometry allows for the differentiation of all of these isotopologues during analysis and the resulting spectra displays the different relative abundances of the different masses of deuterated compounds. This should be readily apparent in the isotope distribution of the molecular ion peak, but may also be distinguished in fragments because of their distinctive shapes. The outcome of mass spectrometric analysis will be to identify the most prevalent isotopologue in the mixture. Referring to the cluster related with the substrate (peak main 130), this peak is confined to other signals besides representing isotopic species mentioned above.

Other clusters can be distinguished easily from fragments because of their distinctive shapes. This is clearly evident in Fig (2.1) for the mass spectrum of 3-ethylaniline.

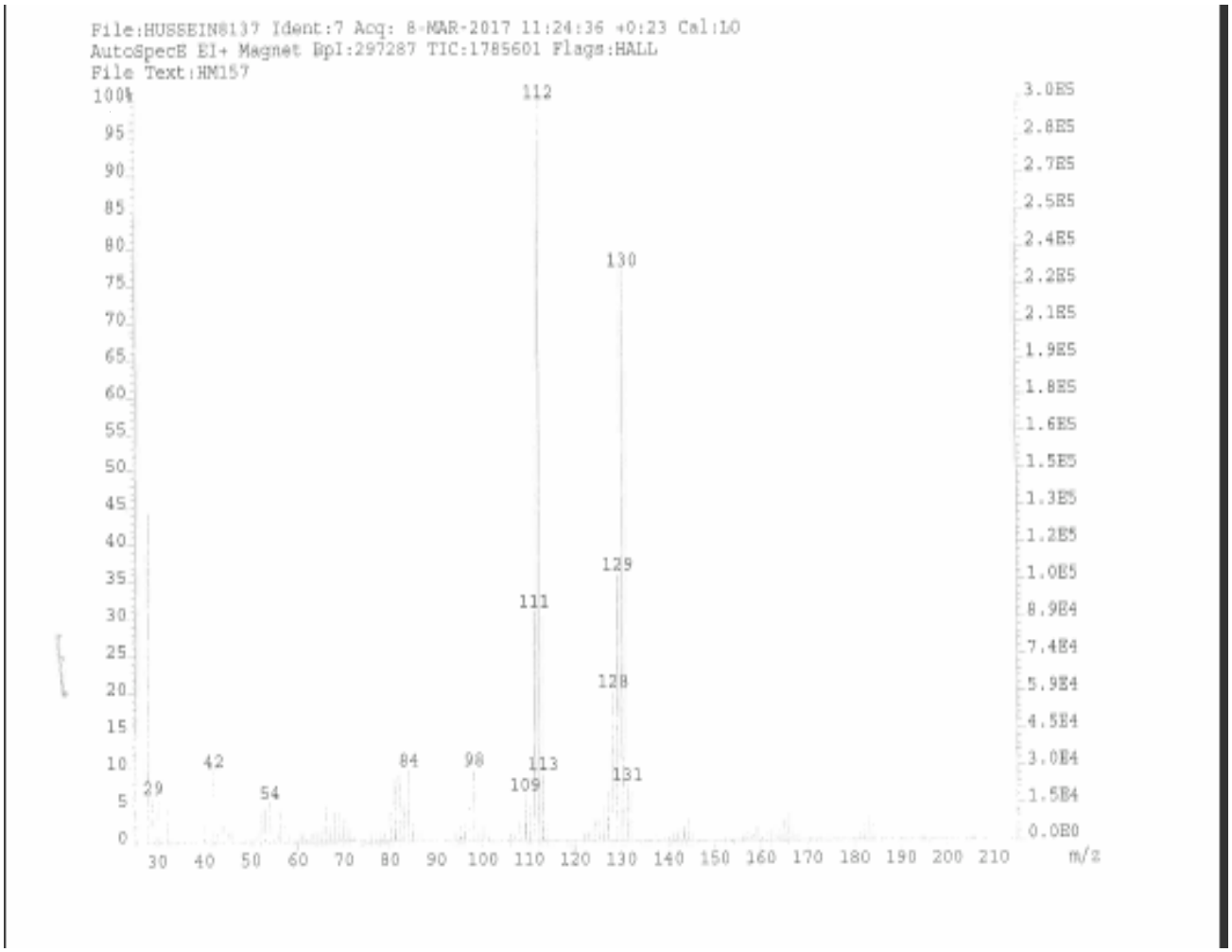


Fig (2.1).The mass spectrum for *d*$_9$- 3-ethylaniline.

2.3.2. ^{1}H NMRspectroscopic analysis

Although IR spectroscopy is a technique that is useful for distinguishing between labelled (C-D bonds) and unlabelled (C-H bonds) compounds, qualitatively, it would not be useful to quantify the subtle differences between mixtures of isotopologues produced in these H/D exchange reactions. Similarly, mass spectrometry cannot fulfil all the detailed quantification requirements for this study. Therefore, a different analytical method was required to be investigated; one that could provide easily quantifiable data, such as nuclear magnetic resonance spectroscopy. ^{1}H NMR spectroscopic analysis should be able to provide a reliable quantification on proton environments and so should indicate which positions have not exchanged for deuterium in the course of reaction and the relative extent to which exchange had occurred at other positions (see appendix 1a, 2a, 3a, 4a, 5a). However, the establishment of deuterium incorporation is not totally straightforward for each single position of a substrate as H positions in different isotopologues are not chemically equivalent. Figure 2.2 and 2.3 shows the significant difference in integration and multiplicity in the spectrum of aniline before and after H/D exchange, showing the ^{1}H-NMR spectroscopic proton signals (Fig. 2.2) compared with the corresponding deuterated isotopologues and isotopomers (Fig. 2.3) many of which were present in the sample.

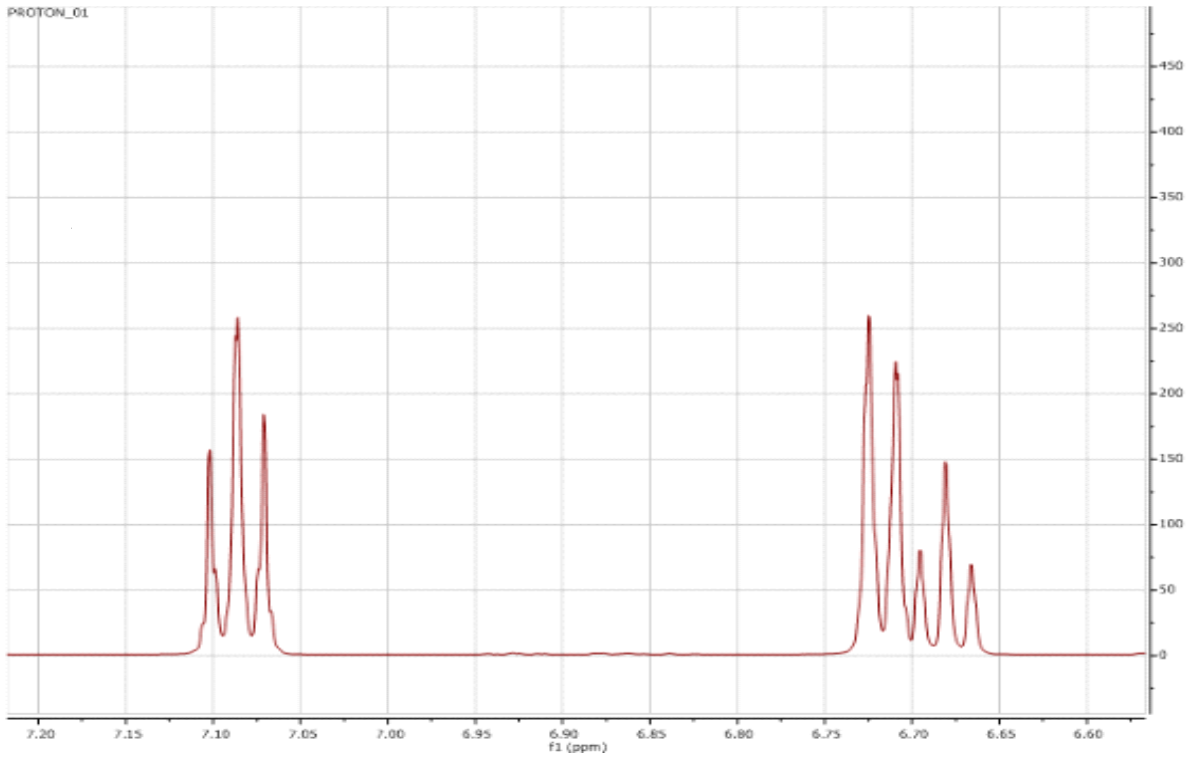


Fig 2.2.^{1}H NMR spectrum for aniline before deuterated

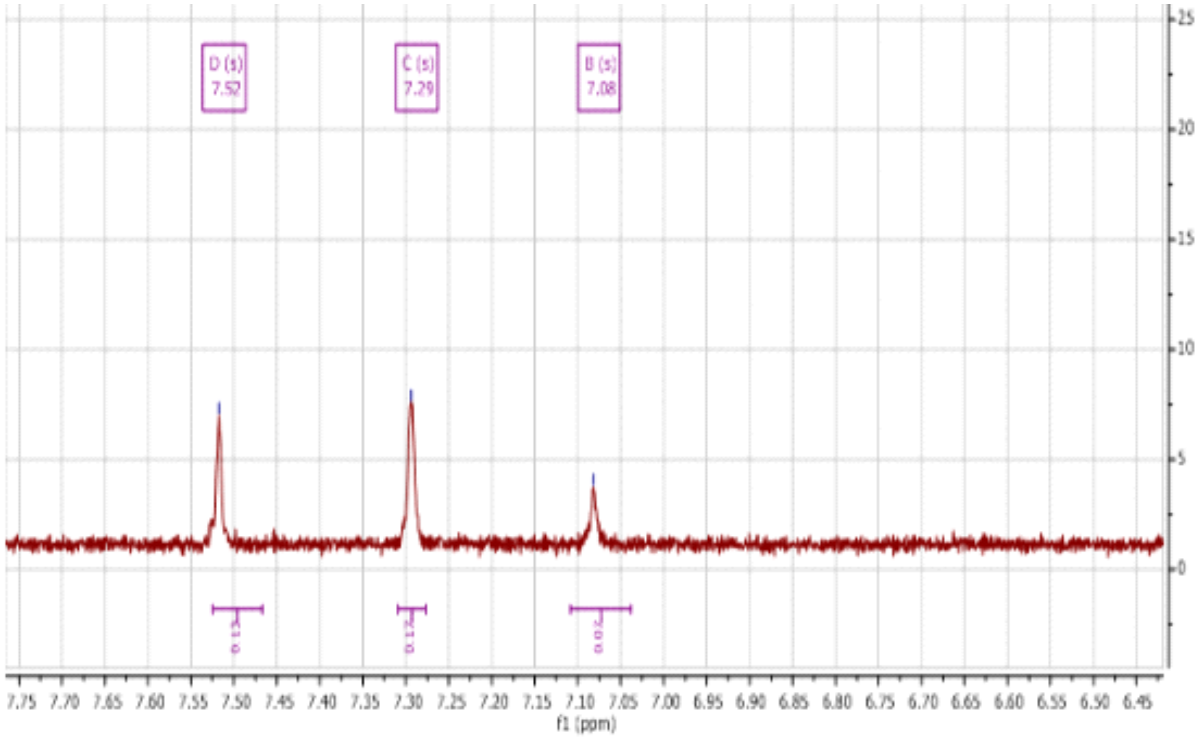
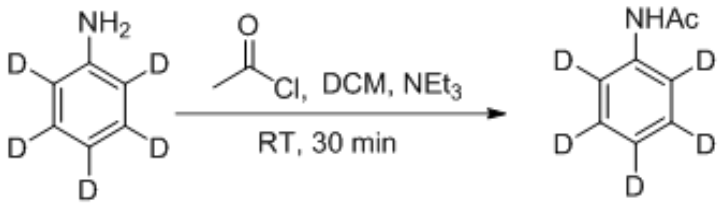


Fig 2.3.^{1}H NMR spectrum of d_5-aniline after deuterated

When H/D exchange is efficient, a high level of deuterium incorporation is present and thus the intensity of ^{1}H resonance is very low. Furthermore, it might not be possible to observe a particular coupling if the major isotopologue has exchanged the neighbouring position for D, depending upon the level of incorporation. Resonances from all of the different isotopologues are likely to overlap at a particular frequency, allowing one only to examine broadly, which positions are comparatively more deuterated than others. It should be possible to establish if there is deuterium incorporation at every position of the product provided a reference was present. Thus to quantify the absolute levels of D incorporation, an internal or external reference should be used – the former through chemical modification of the exchanged product and the latter by the addition of a known quantity of protic solvent. According to previous research on this topic, Derdau *et al.* preferred to quantify their deuterium analysis by the addition of tartaric acid.[118] However, another study by Guoet *et al,*[119]reported that 1,4-dioxane was a suitable external standard. This reference material was chosen as a suitable external reference standard for these studies on aromatic substrates because of the simplicity of the signal appearing as a singlet, its intensity and lastly the chemical shift, which is well removed in frequency from the aromatic region. However, use of an external standard was complemented by addition of an internal standard and for this operation; acetylation was chosen as a means to introduce a protic signal to compare ^{1}H resonances to in the product of H/D exchange. The integration values for the three protons of the added acetyl group could be compared to those present at other positions in the derivatized product, thereby providing internal reference. Acetyl chloride (AcCl) was considered as a suitable derivatizing agent since acetylation should be efficient for anilines and should occur without D/H back exchange if carried out under basic conditions (Scheme 2.4 and Figures 2.4, 2.5).



Scheme 2.4.General procedure for acetylation of deuterated aniline.

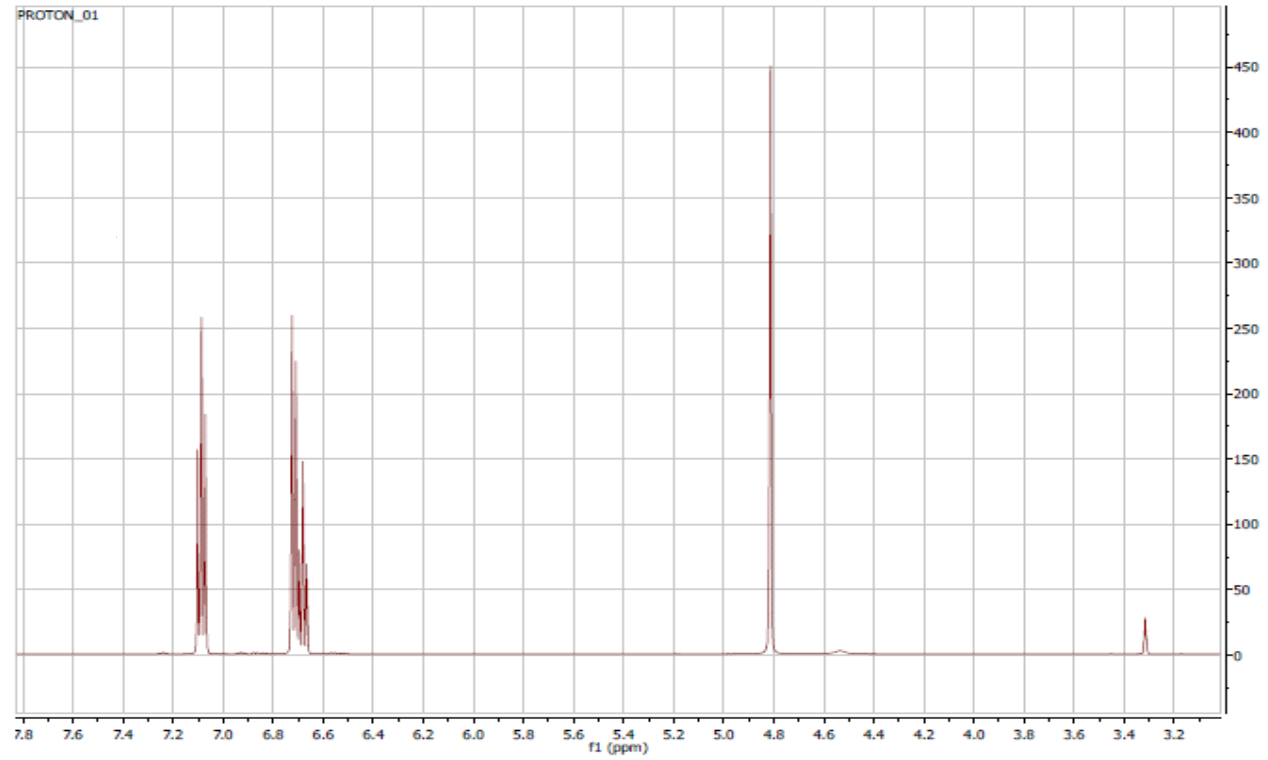


Fig 2.4.^{1}H NMR spectrum for aniline before deuteration.

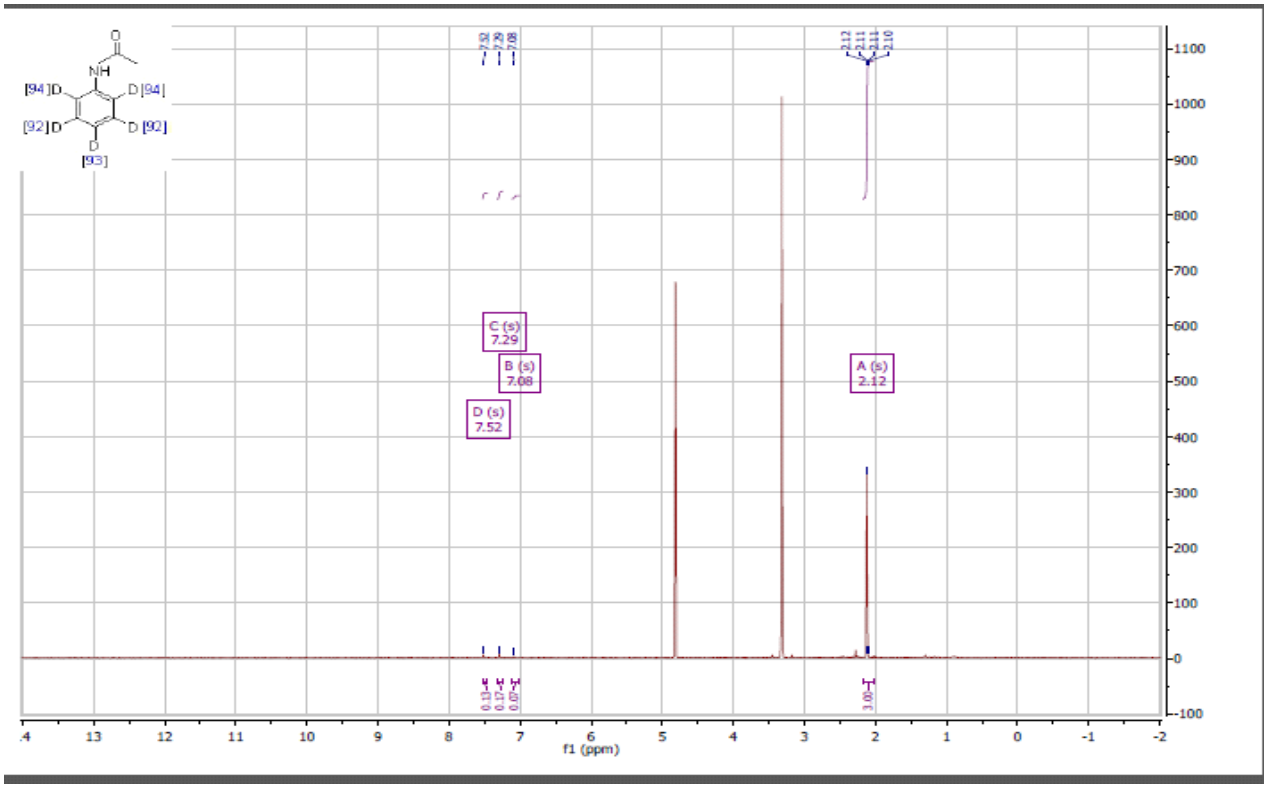


Fig 2.5.^{1}H NMR spectrum for 2,3,4,5,6-pentadeuteroaniline produced by H/D exchange. The signals on the aromatic region present as low intensity singlets with no coupling due to the high levels of deuterium incorporation.

Lastly, it would be vital to review the choice of deuterated solvent regularly for this analysis. It was anticipated that a change of solvent might be required due to solubility issues. The most suitable solvent was identified as d_4-methanol (CD_3OD) for aromatic compounds, as *d*-chloroform ($CDCl_3$) would probably not be suitable. Most anilines would exhibit proton resonances in the aromatic region in the ^1H NMR spectrum at a chemical shift in the region of δ 6-8 ppm and this could overlap with the chemical shift signal of $CHCl_3$ (δ 7.26 ppm); hence it might be tricky to accurately quantify data. Similarly, the use of d_6-dimethylsulfoxide (DMSO) in this case would show a peak due to the solvent isotopologue at δ 2.50 ppm and this may overlap with an internal reference from an acetyl signal at δ~2.10 ppm. This could complicate and mislead the integration operation and thus the quantification of findings. As a result of these considerations d_4-methanol was selected as the solvent of choice for NMR spectroscopic studies, with chemical shift signals for the methanol solvent isotopologue protic resonance (δ~3.31 ppm) and for HOD (δ~4.92 ppm) well removed from the region of interest. This should enable reasonably accurate quantification of deuterium incorporation for each aromatic position.

2.3.3. ^{13}C NMRspectroscopic analysis

Deuterium incorporation can give rise to significant changes in the ^{13}C NMR spectrum (see appendix 1b, 2b, 3b, 4b, 5b).. In Figure 2.5 and 2.6, the corresponding ^{13}C NMR spectrum for 4-*n*-butylaniline is shown before and after deuteration. Although these spectra are ^1H decoupled, deuterium has not been included in this decoupling method on account of difference in frequency of resonance. The consequence of this is that each carbon bound to a single deuterium (C-D) will appear as a deuterium triplet: the deuterium spin is 1 and the corresponding C-D coupling (*J*) results in 3 lines with the ratio of intensities equal to 1:1:1. It is significant to highlight that these signals will only be observed when the concentration of deuterated isotopologue and %D incorporation at that position is relatively high. Comparing ^{13}C NMR spectra before (Fig 2.6) and after (Fig 2.7) exchange, clear isotopologue peaks are observed at δ 128.5 and 115.3 ppm, the former in the presence of the dominant C-H signal.

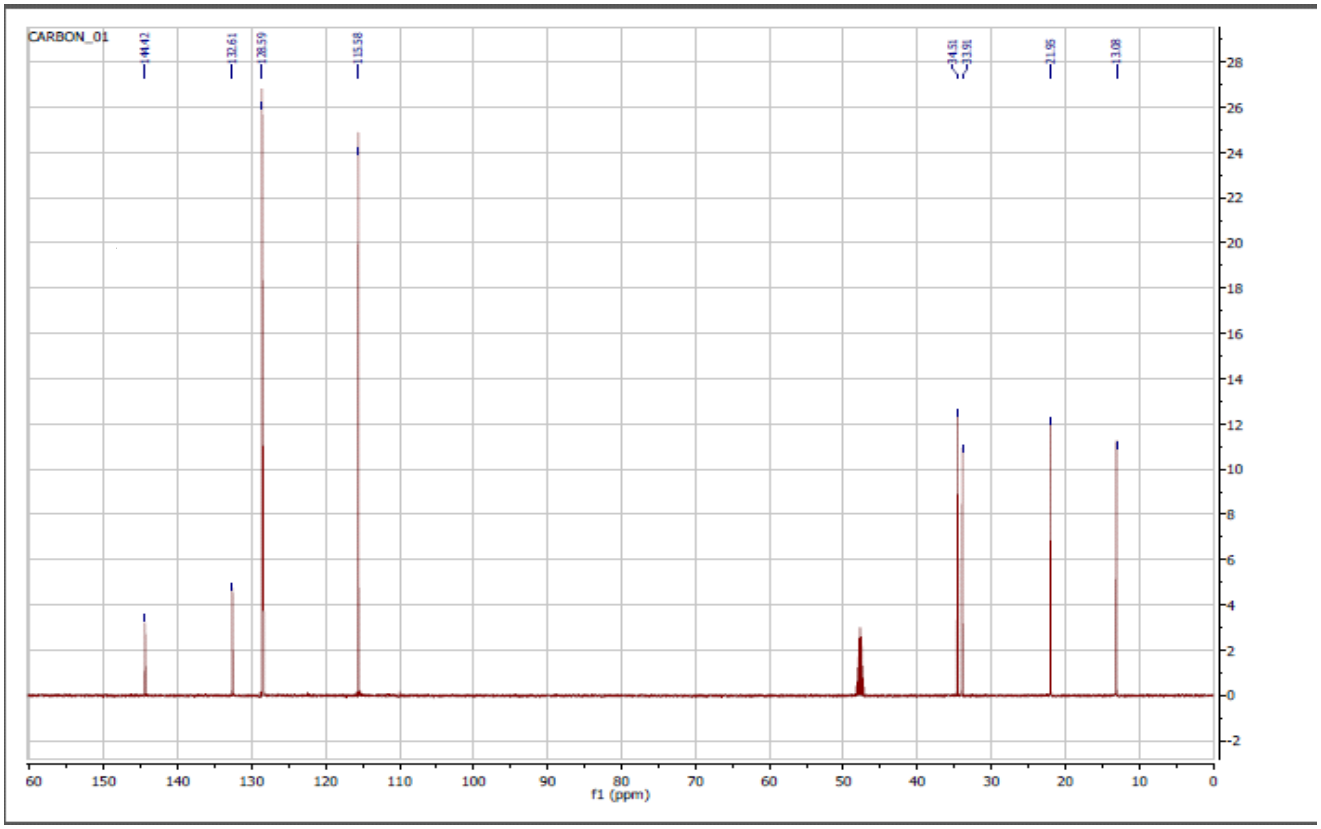


Fig 2.6.^{13}C NMR spectrum of 4-*n*-butylaniline, before deuteration

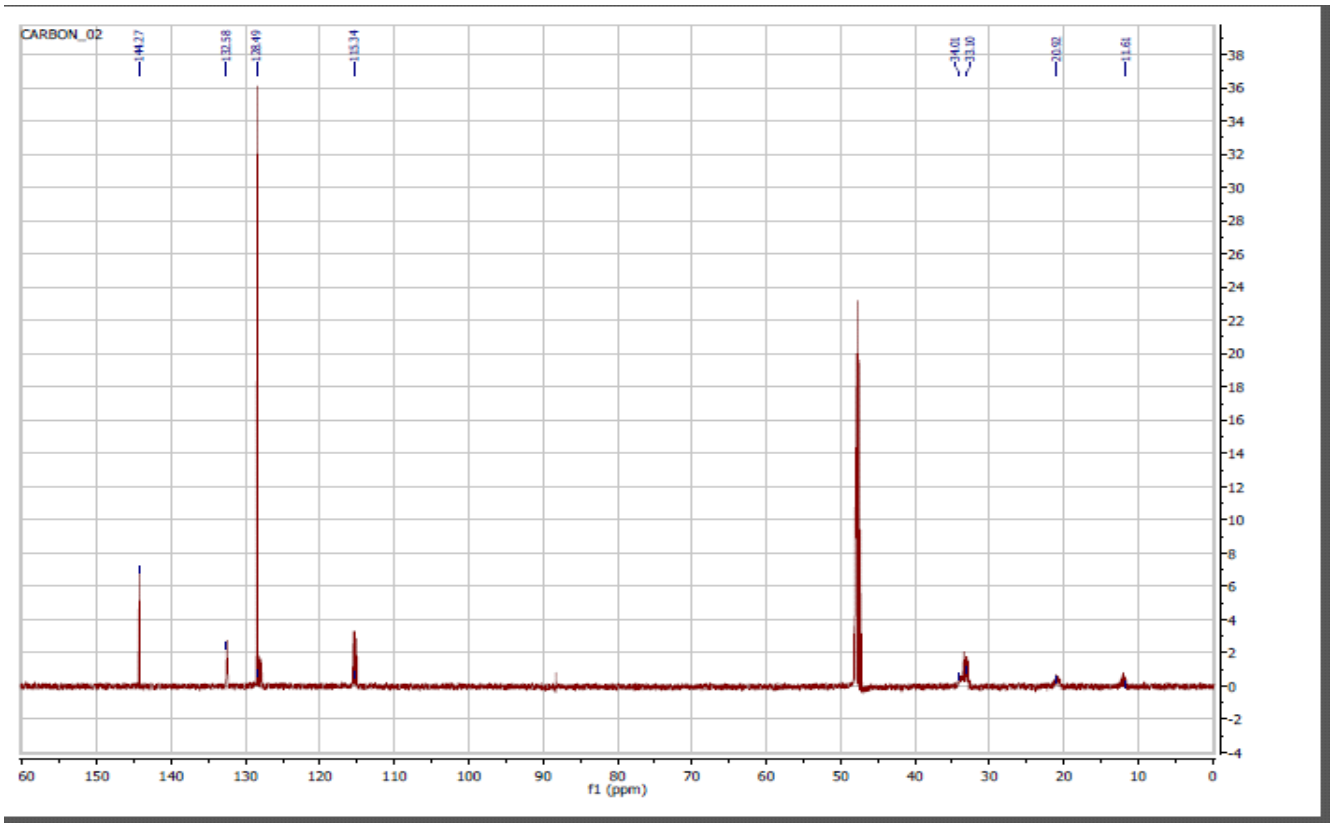
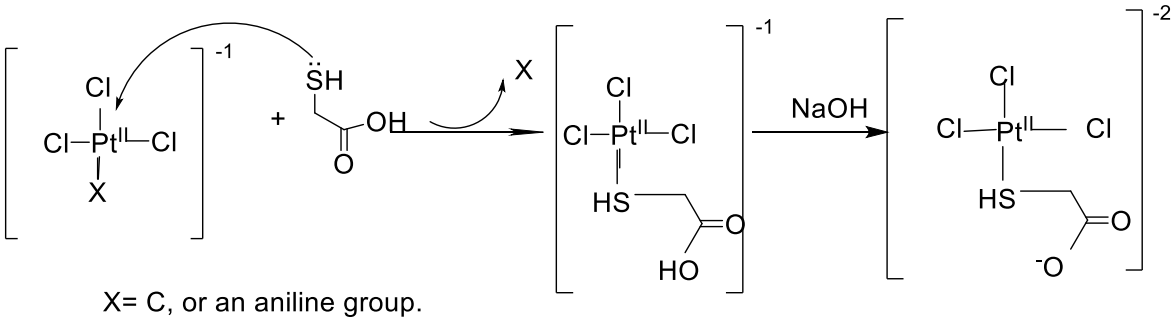


Fig 2.7.^{13}C NMR spectrum for d_{13}-4-*n*-butylaniline.

2.4. Removal of platinum contamination

Recently many studies were devoted to explore the advantages and applications of the use of deuterium in chemotherapy and pharmacology. However, the presence of heavy metal contaminants such as platinum complexes, introduced in processes to incorporate deuterium such as through use of a homogeneous catalyst, could cause many critical problems. It could affect antibiotic assay[120] and threaten accurate cytotoxicity assay as platinum causes toxicity in gastrointestinal and nephrology cases. In addition, heavy metal contamination can lead to deactivation of enzymes and proteins through binding with the sulfhydril (SH) group.[121] Due to their inherent toxicity, limits are placed on the contamination of medicines by heavy metals.

Thus the development of methods to introduce deuterium using homogeneous catalysts will need to incorporate methods to reduce any levels of Pt toxicity.[122] For this operation the use of a nucleophilic ligand with high Pt affinity was chosen, using an additive as a trap to scavenge the metal at the end of the reaction. Thioglycolic acid was chosen as one such scavenger of interest as thiol derivatives have high affinity for Pt and the carboxylate derivative could then be removed simply by aqueous work up. Scheme 2.5 shows how a ligand X could be replaced on Pt to produce a water soluble derivative that could be removed in base. Therefore, by incorporating the use of thioglycolic acid into a work up procedure a significant reduction in Pt contamination could be achieved.



Scheme 2.5.Thioglycolic acid as a nucleophilic scavenger.

The concentration of Pt in solution present following H/D exchange using a homogeneous Pt catalyst was measured using atomic absorption spectrometry. Aniline was chosen as a suitable substrate to investigate the ability of thioglycolic acid to reduce or remove the quantity of metal following simple work up. Thioglycolic acid

(4 equiv. in relation to the catalyst quantity) was added to the solution and then the mixture was stirred for 30 min. The absorbance amount of the platinum was quantified at 4.2 ppm after scavenging which was considered to be sufficiently low and acceptable, since this was in the absence of further purification. Comparing Pt contamination levels with the solution prior to scavenging (15 mg) demonstrated the high efficiency of the acid in reducing or removing platinum levels through ligand exchange. However if the quantity of catalyst required for efficient H/D exchange at poorly activated positions could be reduced still further this would serve to improve the utility of C-H activation methods in in the synthesis of deuterated compounds.

2.5. Acid effect

The incorporation of deuterium into aromatic substrates has been improved in certain instances under both acid-mediated and metal-catalyzed conditions using a deuterium source that is a strong deuterated acid, including both Brønsted and Lewis acids.[123]

It has been reported that high levels and greater yields of incorporation are achieved in arenes, especially at the activated position, at temperatures between 20 to 55 °C for polyphenolic substrates using a mixture of D_2O, BF_3 and D_3PO_4 following numerous reaction cycles for 1-4 days.[124]

By using microwave irradiation, the acid-catalyzed exchange should be dramatically accelerated in a H/D exchange reaction and this would offer a convenient method to elevate the temperature above the boiling point of the solvent. Microwave irradiation has been reported to reduce reaction times to a few minutes with high levels of deuterium incorporation in acid mediated processes.[125] In particular, using electrophilic aromatic substitution should enable exchange of the protons at *ortho* or *para* positions to electron donors under acidic conditions. For this reason, in order to bench mark the acid-mediated exchange, a study of the acid-catalyzed process was carried out under microwave irradiation (Table 2.2), comparing the reactivity of two different anilines.

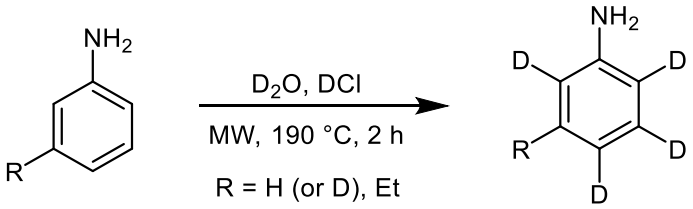


Table 2.2.The role of DCl in H/D exchange of aniline and 3-ethylaniline under microwave irradiation at 190 ºC.

Entry	Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	Yield
1	%D*	38	13	42	13	38	….	….	79%
2	%D¥	97	21	97	21	97	….	….	[a]86%
3	%D‡	18	….	53	2	53	10	13	80%
4	%D^	98	….	96	27	98	13	13	[a]89%

*%D incorporation for aniline using D_2O, calculated following acetylation.

¥%D incorporation for aniline using D_2O and DCl, calculated after microwave irradiation.

‡%D incorporation for 3-ethylaniline using D_2O, calculated after microwave irradiation.

^%D incorporation for 3-ethylaniline using D_2O and DCl, calculated after microwave irradiation.

[a]Unpublished findings, Jehan Al-HumaidiUniversity of Sussex and Princess Nourah Bint Abdul Rhman University, Saudi Arabia.

As Table 2.2 shows, in these experiments significant deuteration of aniline at activated positions was observed under acidic conditions (entry 2), as demonstrated by ^{1}H NMR spectroscopic analysis. Thus, these experiments clearly demonstrated the impact of DCl under similar reaction conditions. Comparing the same substrate in the absence of DCl (entry 1) low levels of D incorporation were observed under these neutral conditions.

It was decided to use an alternative substrate with an alkyl side chain in similar studies. Here, 3-ethylaniline was chosen (entries 3 and 4) and again 3-ethylaniline showed low levels of D incorporation in the absence of DCl (entry 3), especially at unactivated positions on the ring and in the side chain (both positions). The same substrate in the

presence of DCl incorporated deuterium efficiently at activated positions (entry 4); however, levels of side chain deuteration remained low.

Nevertheless, this result validated the importance of the use of metal catalysts in such experiments, in order to incorporate D at poorly activated positions.

Strong Brønsted acids, or as a substitute Lewis acids, could be used with a deuterium source and the use of DCl had been validated. Microwave irradiation had clearly promoted the acid-catalyzed H/D exchange and significantly reduced reaction times.

From the initial studies, deuterium chloride (DCl) was chosen as an inexpensive reagent for this project. Hence, it was decided to use it to conduct experiments due to the influence of this acid on deuteration.

2.6. The effect of temperature

Previous studies indicated that the temperature of reaction was one important parameter for H/D exchange, and a high temperature process with Pt^{II} as homogeneous catalysts was under consideration[127,128]. For this case, many experiments were reviewed to confirm the effect of suitable temperature on deuteration using microwave irradiation.[126] In order to determine the true effectiveness of microwave irradiation, the reaction was heated traditionally (reflux at 100° C for 24 hours); this was compared to a microwave-assisted procedure carried out in a sealed tube at a temperature above the boiling point of the solvent.[127,128] This essential aspect of microwave chemistry was relevant for a number of reasons. Firstly, it enabled a fast and practical way for deuteration to be tested under controlled conditions at high reaction temperatures using commercial instruments. Secondly, H/D exchange experiments could be carried out with faster optimization of conditions than traditional heating in oil baths; as a result, the first microwave reaction was set up without any additional catalyst at 190° C for 2 hours to establish the range of this process.

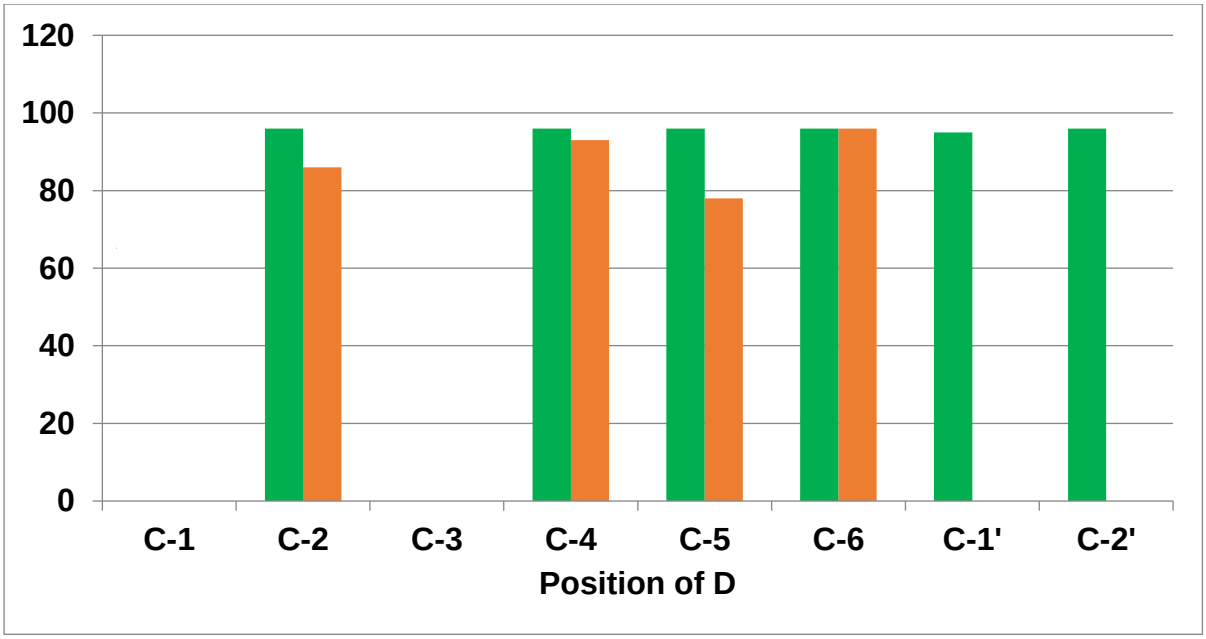
Table 2.3. Deuterium incorporation for 3-ethylaniline by use microwave irradiation and conductive heating, with Pt catalyst.

Entry	Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	Yield
1	%D*	96	….	96	96	96	95	96	87%
2	%D¥	86	….	93	78	96	0	0	96%

*%D Deuterium incorporation for 3 -ethylaniline after microwave irradiation.

¥%D Deuterium incorporation for 3 -ethylaniline under conductive heating.

There were two attempts (conductive heating- Microwave) made to discover the best way to achieve H/D exchange deuteration of the substrate. In fact, the study used 3-ethylaniline as a substrate. Table 2.3, depicts the levels of H/D exchange deuterium by using two methods. Clearly, the microwave method (entry 1) gave significant levels of H/D exchange at all positions including high incorporation in side chain according to the ^{1}H NMR spectroscopic analysis. Conversely, the conventional method (entry 2) using conductive heating achieved deuteration in the aromatic ring but there was no H/D exchange in the side chain. These two attempts were done by using same catalyst, quantity of acid and D_2O. However, due to being able to operate at elevated pressures under microwave synthesis, the device was able to perform reactions at temperatures more than 200 °C, and thus well above the boiling point of the solvent. As a result, the reaction conditions were significantly different in these two experiments (Scheme 2.6). Certainly, 190-200 °C appear as more suitable to be used in the microwave.



Scheme 2.6.Variation in deuteration levels based on a different method.

▪deuteration levels for 3-ethylaniline after conventional heating.

▪deuteration levels for 3-ethylaniline after microwave heating in a sealed tube.

2. 7. Catalyst effect

Table 2. 4. D% incorporation of 3- Ethylaniline after microwave irradiation.

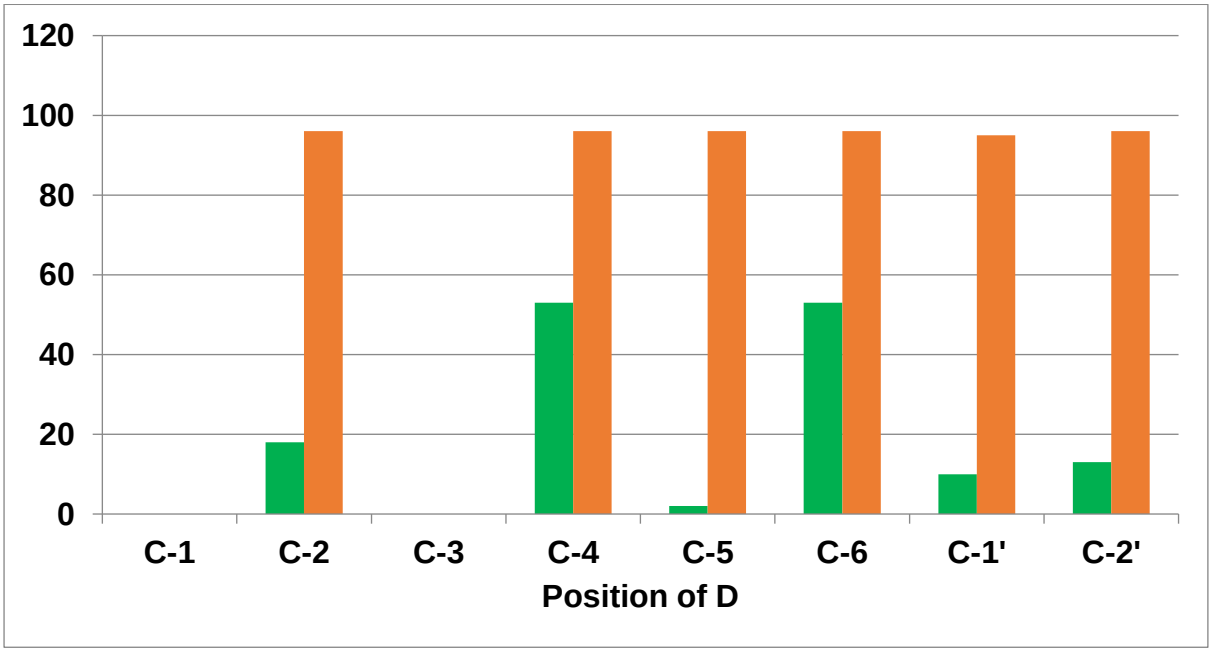
Entry	Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	Yield
1	%D*	18	….	53	2	53	10	13	80%
2	%D¥	96	….	96	96	96	95	96	87%

*%D Deuterium incorporation for 3-ethylaniline after using microwave irradiation without catalyst.

¥%D Deuterium incorporation for 3-ethylaniline after using microwave irradiation with a Pt catalyst.

Table 2.4 shows the effect that a Pt catalyst had on the percentage of D incorporation through protio/deuterio exchange. Furthermore, this study could be used for investigation of H/D exchange in a side chain. Therefore, 3-ethylaniline was chosen; this substrate has a chain. Of the two carbons with different reactivity, the amino group, with side chain in*meta* relationship, led to the analysis of electronic effect of two electron donor groups (amino and side chain) on all remaining positions

of the aromatic ring. Undoubtedly, the aromatic ring was significantly impacted by the amino group; thus all activated positions (*ortho* and *para*) were electron-rich and would exchange under either conditions whereas unactivated aromatic positions (C-5) needed the metal catalyst (Pt as homogeneous catalyst) to give significant levels of H/D exchange. In addition, the catalyst had a dramatic effect on C-H activation of the side chain (entry 2). These results are clearly depicted in scheme 2.7, which illustrates how the catalyst affects levels of D incorporation at all positions activated, unactivated aromatic and side chain C-H bonds; however, without the metal catalyst the deuteration levels were very low, especially at inactive and side chain positions.



Scheme 2.7.Impact of homogeneous catalyst on deuteration levels for 3-ethylaniline.

▪deuteration levels for 3-ethylaniline by use homogeneous catalyst.

▪deuteration levels for 3-ethylaniline without catalyst.

2.8. Calculation of the percentage of the deuteriation yield

Lastly it has been necessary to calculate the percentage yield, taking account of the ratio of different isotopologues of products as follows:

$$\text{Yield} = \frac{\text{mmol'}}{\text{mmol starting material}} \times 100$$

$$mmol' = \frac{Mr'}{\text{Mass of isolated product}}$$

To calculate mmol', M_r' should first be known.

$M_r' = M_r$ (starting material) + [Mr (D) –Mr (H)] (Levels of deuteration)

$M_r' = M_r$ (starting material) + 1.001 (D2%+D3%+D4%+D5%+D6%)

2.9. Conclusion

This chapter described studies of appropriate methods for developing microwave-mediated H/D exchange. The objective of this work was to validate an efficient method to replace hydrogen by deuterium in molecules of biological and pharmaceutical importance. Deuterated compounds are important in the study of chemical and biochemical pathways and in the investigation of pharmacology and metabolism of drugs. Using aniline derivatives as substrates, the corresponding labelled compounds would provide very useful building blocks for the synthesis of deuterated drugs. During these studies both homogeneous and heterogeneous catalysts were employed; their brief study established their potential for further in-depth investigation.

Quantification of %D incorporation was carried out by NMR spectroscopic analysis, by means of introducing an internal reference for ^{1}H NMR spectroscopy on acetylation which allowed calculation of deuterium incorporation at all positions in the molecular structure. To provide evidence in support of further study, different alkyl anilines were used, giving useful insights into catalyst activity, particularly with respect to reactivity at different positions. Lastly, all parameters impacting on H/D exchange were studied and suitable conditions and parameters were found. A temperature of 190-200 ^{o}C, the use of a homogeneous catalyst (K_2PtCl_4 2.5 mmol), DCl (4 equiv.), 2 h reaction time and D_2O as a solvent were found to be practical. The reactions carried out with microwave assistance were the most convenient. These homogeneous conditions appeared to give good yields and gave the potential to remove any metal contamination through scavenging. It also gave the best balance between time and cost.

Chapter 3

H/D exchange using Pd/C as a heterogeneous catalyst by microwave- and flow reactor-assisted chemistry.

3.1. Introduction

The aim of this study was to develop suitable methods and substrates for deuteration using microwave irradiation and a palladium or platinum catalyst in a modified Shilov-type procedure. For this task a set of aniline derivatives were chosen as the first substrates of study inspired by previous work of Garnett on the deuteration of such compounds. The evaluation of this process would lead us to quantify the role of a heterogeneous catalyst on the H/D exchange of different substrates. The efficiency of exchange as well as the chemical yield for the microwave-assisted procedure was also important.

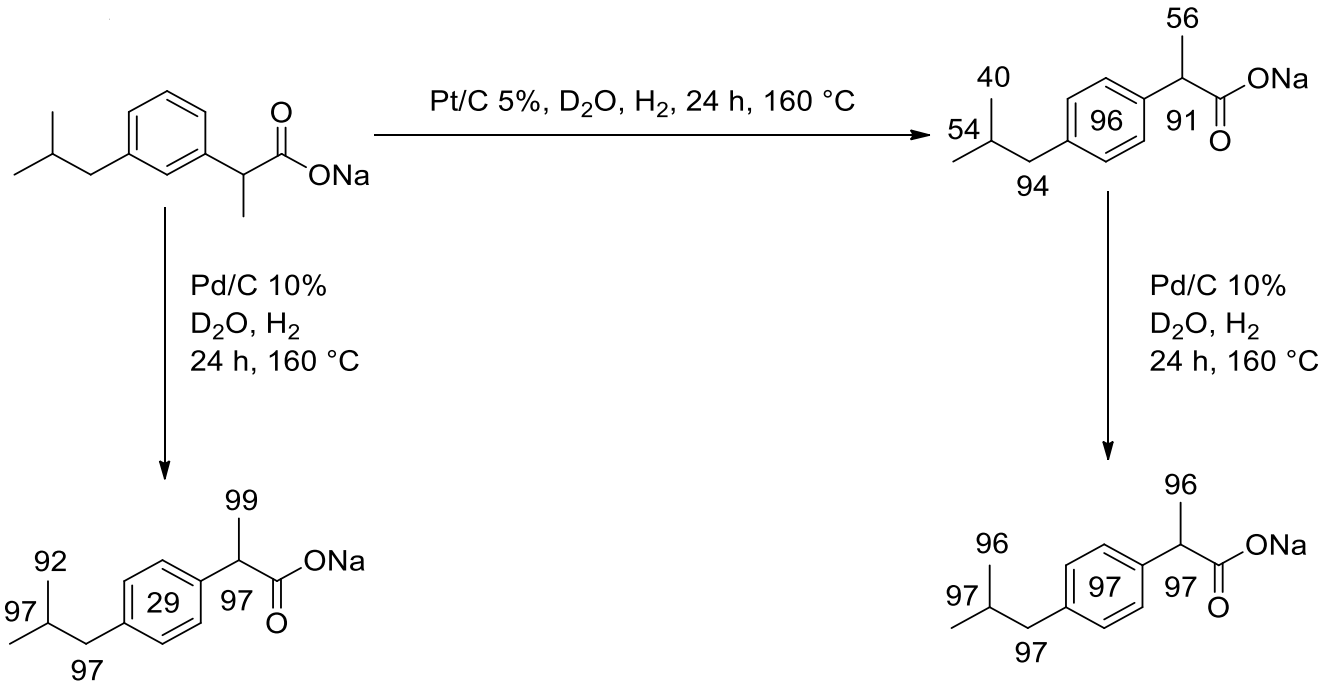
This goal was desirable for a number of reasons. A microwave-mediated modified Garnett procedure opens opportunities for rapid and efficient H/D exchange for a number of substrates that could be independent of electronic effects and enable efficient exchange at inactive positions. The precedent from Sanofi-Aventis, provided a foundation for us 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) actually make aniline derivatives ideal substrates.

3.2. Platinum vis Palladium

Both platinum-catalyzed and palladium-catalyzed H/D exchanges are essentially very similar mechanistically in how they bring about chemical changes and activate positions for exchange.[129,130] However, based on recent approaches, there is a significant variation in chemoselectivity (alkyl vs aryl), the kinetics of exchange and thus the required temperature, taking into account the rate of reaction. This distinction was validated by a study carried out by Sajiki et al[130, 131] their findings confirmed deuteration was higher using a platinum catalyst at aromatic positions, while aliphatic C-H positions were deuterated in palladium-catalyzed reactions.

The deuteration of phenol can be affected with almost quantitative D incorporation using a Pd-C catalyst although the reaction has to be heated to 180 °C whereas Pt-C can provide a comparable degree of D incorporation even at room temperature. This

is exemplified in work by Sajiki[131], in which the deuteration of Ibuprofen demonstrated that Pd and Pt catalysts exhibit different chemoselectivity, with Pt-C favoring reaction at aromatic C-H positions whereas Pd-C promoted aliphatic C-H activation (Scheme 3.1).



13

Scheme 3. 1. Platinum and palladium catalyzed H/D exchange of Ibuprofen.[131]

In considering the mechanism that might operate in a Garnett-type system, research confirms that platinum tetrachloride anion when subjected to a chemical process, in particular in an aqueous mixture, is stable. Even more, it adopts a stable square planar geometrical arrangement of atoms. Only 16 electrons enclose platinum in such chemical processes; this is contrary to the general principle whereby if the metal has 18 valence electrons it benefits from the stability of a noble gas configuration. Not satisfying the 18-electron rule, can lead to the ligation of π-electrons, which in turn can form π- or even σ-bonded compound structures. Such 16 electron catalysts can undergo oxidative addition reactions, although often the reactions have to operate under strongly acidic conditions.

An octahedral complex is the conclusive species in this chemical process, as the Pt is unlikely to be reduced under Garnett conditions and decrease its oxidation state from Pt^{II} to Pt^{0}. Although, this reaction has a high concentration of acid, nevertheless it does

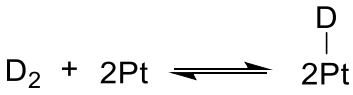
not rule out the presence of platinum tetrachloride as the catalytic species, rather than as a pre-catalyst. Garnett proposed and it has not been disputed that Garnett H/D exchange is likely to be directed by this catalyst, giving a clear role of a Pt(II)/Pt(IV) redox cycle.[132, 133]

3.3. Garnett's H/D exchange mechanism

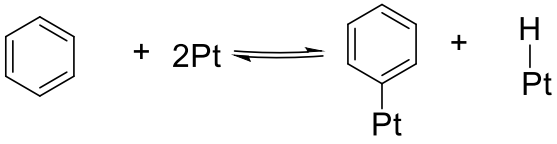
Garnett carried out a detailed study on H/D exchange mechanisms. The findings of the study are well recognised,[134] nevertheless, a detailed analysis has led to improved reasoning. According to Garnett's review of his works, H/D exchange is administered by using platinum as the substance in its pure state. On the other hand, further investigation found that this H/D exchange was not distinct. Furthermore, it was established that delocalized molecular orbitals could be vital in exchange mechanisms; in particular, the involvement of a π-complex in the Garnett system was proposed as a significant breakthrough (Garnett and Hodges).[135]Considering the reaction of π-systems

3.3.1.Farkas and Farkas Dissociative Mechanism[138]

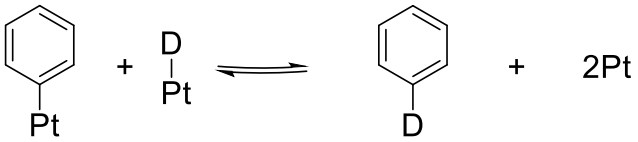
The first step is adsorption of deuterium on the surface of platinum.



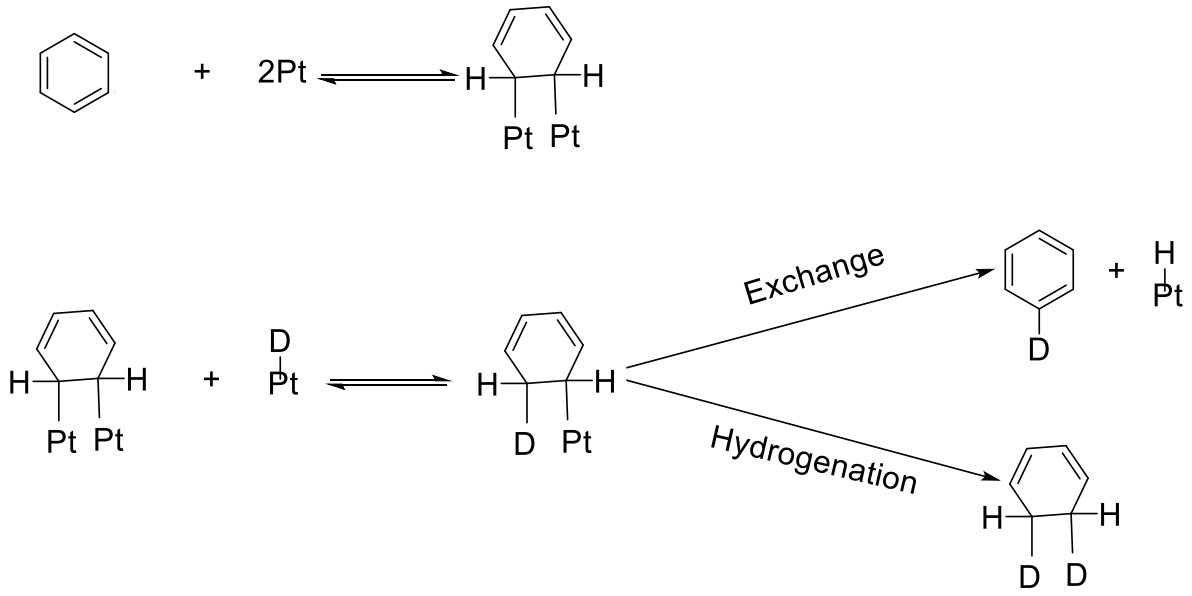
The second step involves substitution reaction between benzene ring and platinum.



Finally, the exchange occurs between platinum on the benzene ring and the deuterium adsorbed on the surface of platinum.



3.3.2. Horiuti and Polanyi Associative Mechanism[139]

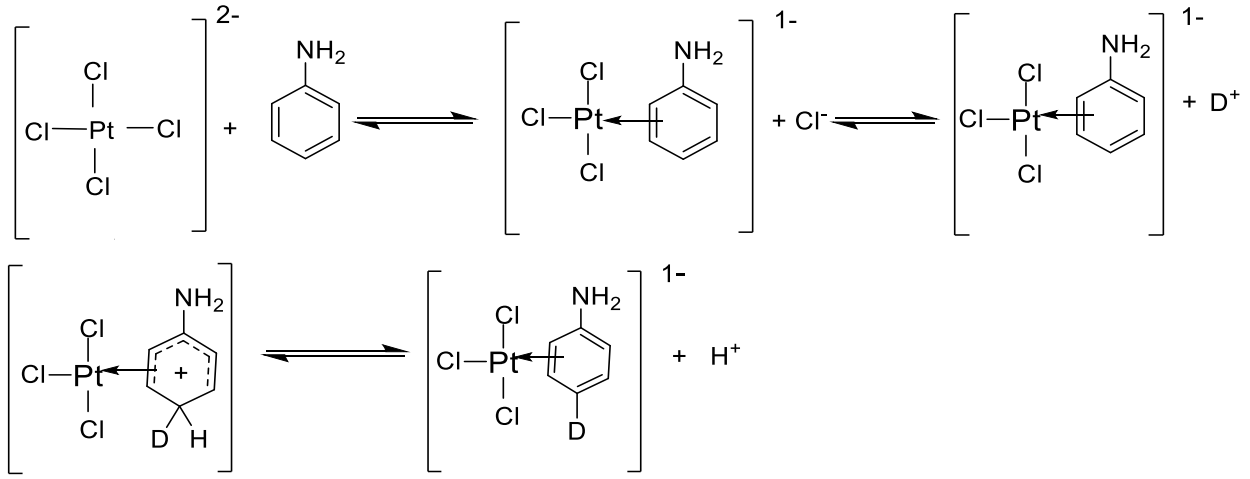


Scheme 3. 2. Classical associative intermediate and associative π-complex mechanism[140]

In this specific case, the metal is viewed as an acceptor using its empty d orbitals whereas C-H serves as a double-electron contributor (donor). Despite the fact that this definition for the most part alluded to metal-alkyl H/D exchange, some intriguing aspects could be relevant to the aromatic context because of the π electron-rich cloud and the metal empty orbitals.

3.3.3. Associative and Dissociative π-complex mechanism[80, 81]

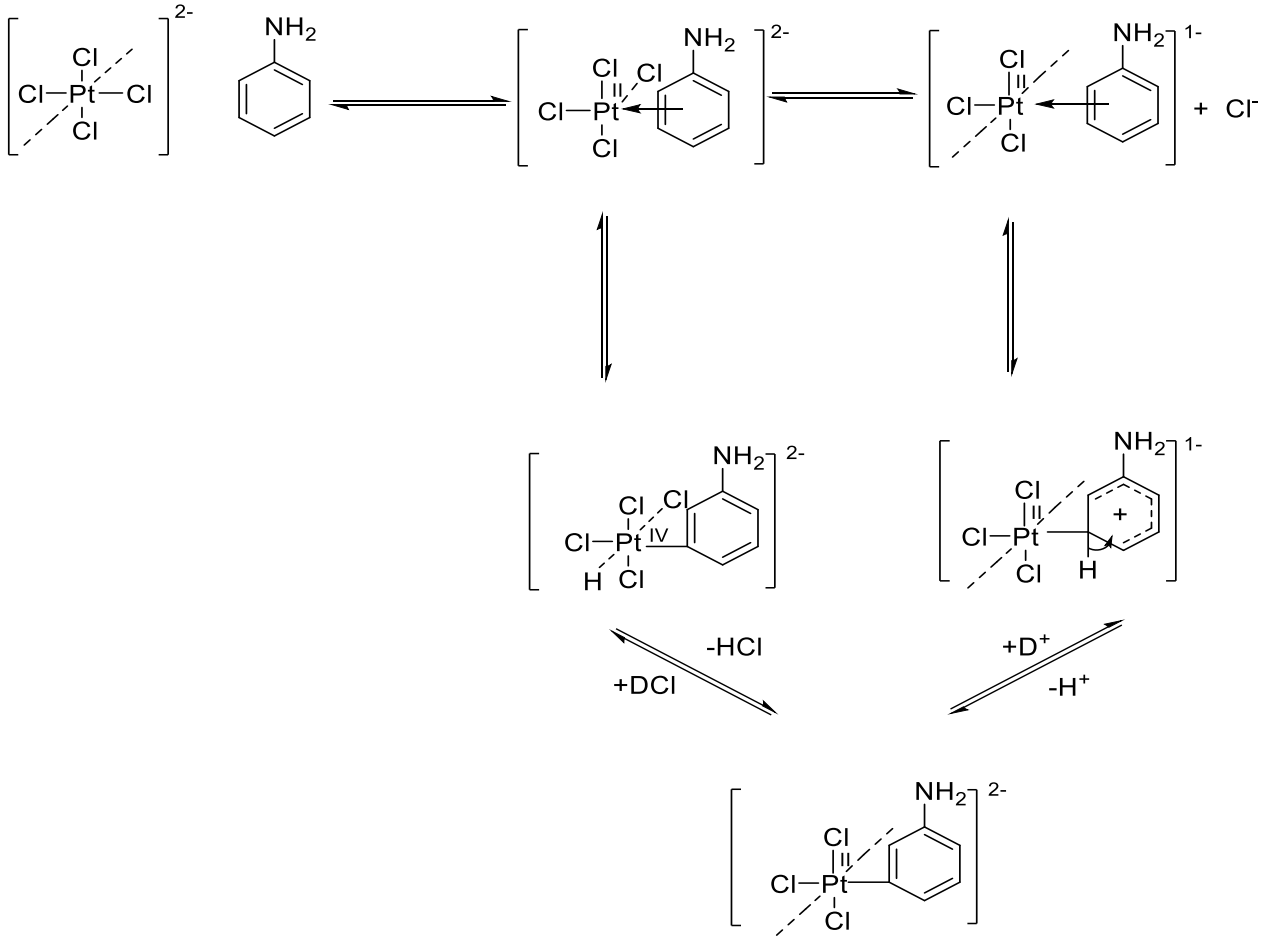
In his studies, Garnett established that activating and deactivating substituents on the aromatic ring did not impact the rate of exchange. This was later affirmed by the findings of Kanski and Kanska.[136,137] These findings were coherent with a dissociative mechanism operating for platinum–catalyzed H/D exchange (Scheme 3.3).



Scheme 3.3.Dissociative π-complex mechanism.

3.3.4. DIssociative and Dissociative π- complex mechanism[80]

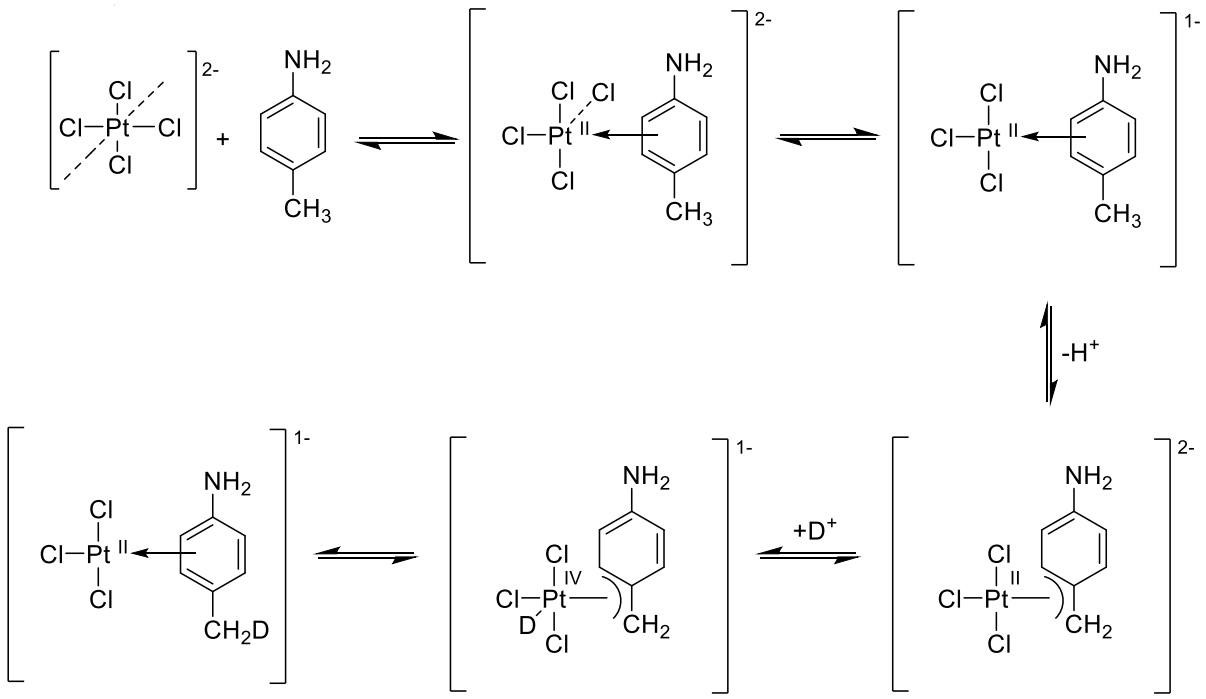
The scheme above depicts the main parts of H/D exchange mechanism anticipated by Garnett. Additionally, he likewise proposed a component where Pt(II) was the main metallic species included (Scheme 3.4).



Scheme 3.4.Dissociative π-complex mechanism.

3.3.5 Mechanism for alkyl H/D exchange[80].

The mechanism must be amended slightly for substrates containing alkyl groups to account for aliphatic C-H bond activation.



Scheme 3.5.Mechanism for alkyl H/D exchange.

The system depicted in Scheme 3.5 would be especially applicable for studies involving substrates containing an alkyl chain. In addition, as shown, the mechanistic procedures in both Scheme 3.3 and 3.4 cause one σ-bond to form between Pt and the phenyl ring. This last metal intermediate is by all accounts one of the best clarifications for various H/D exchange processes, which expect that a hydrocarbon experiences a nonstop (continuous) sequence of equilibrium exchange processes during the experiment. In particular, H/D exchange should happen subsequent to C-H activation mediated by Pt, with reversible C-H bond-cleavage and C-D bond-formation which takes place when the hydrocarbon particle is on the coordination sphere of Pt.

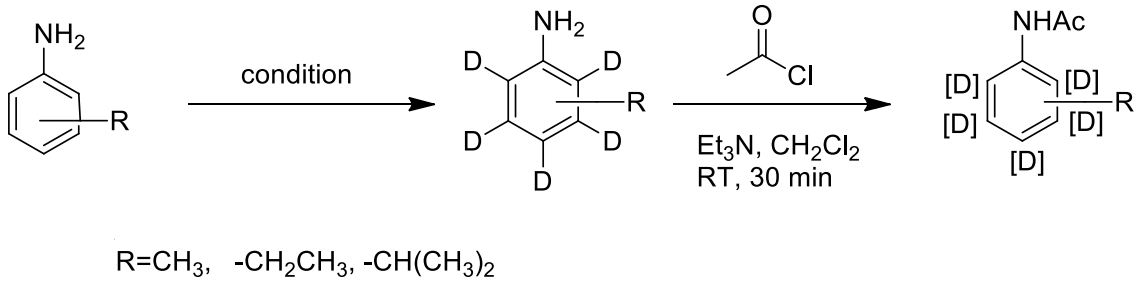
3.4. Palladium

In early methods[141] Pd catalysts were used with gaseous deuterium and applied in research into the use of heterogeneous deuterated catalysts for H/D exchange. Azran *et al*[142] investigated a process whereby both hydrogen and protic substances were constantly removed prior to using deuterium gas. Myasoedov and colleagues[143] proposed a study of how the use of gaseous deuterium on a solid surface can influence the function of the catalyst. Here, isotopic exchange proved successful allowing deuteration of the side chain of amino acids.[143-146] This technique was applied by Vert and colleagues during deuteration of lactides and glycolides; this process suggested using precursors nearest to the melting point of the species was the optimal temperature for the chemical reaction.

Given the literature success on the use of Pd or Pt on a surface for H/D exchange this system seemed worthy of further study, with the goal to develop methods applicable to anilines or heterocycles that used commercial catalysts and a single cycle to afford deuterated compounds suitable for further elaboration. Given the facility for Pd/C to mediate in particular aliphatic C-H activation and H/D exchange, a process much more challenging in the absence of a metal, this was the first heterogeneous catalytic system investigated in our laboratories.

3.5. H/D Exchange using a flow reactor

Flow chemistry is the performance of proceduresfor chemical reactions in the pipe or tube under reagent flow; it is commonly called plug flow, continuous flow chemistry or microreactor chemistry depending upon the experimental set up. For H/D exchange reactions involving complex exchange equilibria flow chemistry could offer interesting advantages and an opportunity to drive the process through reagent recycling, feedback loops or high temperature conditions. The starting materials for a reaction and solvent can be pumped together through a mixing connection into a temperature controlled tube or coil reactor. Flow chemistry can exhibit many advantages over conventional batch set ups such as quicker reactions due to high temperature conditions, safer procedures due to smaller reacting inventories, cleaner products due to the time-resolved separation of reagents and products, faster reaction optimization through automation, in-line monitoring and feedback, simple scale-up through scaling out multiple parallel reactors and incorporation of typically separate processes (like work-up, synthesis and analysis).



$R=CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$

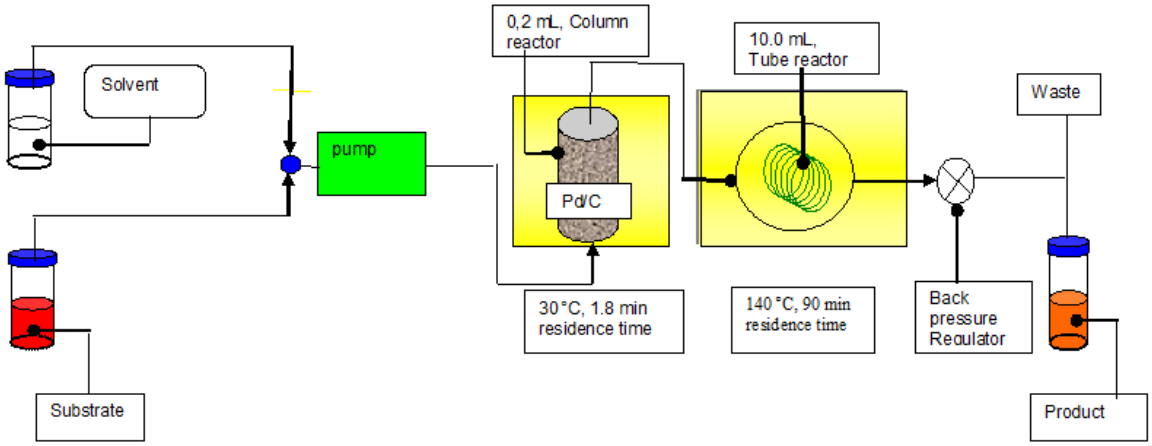


Fig 3.1.Schematic Flow Reactor Configuration.

System Parameters;

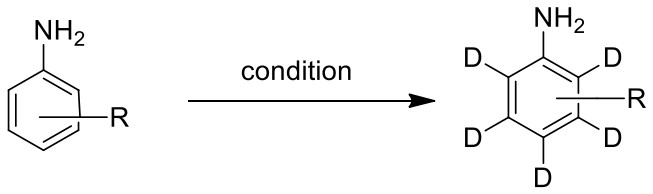
Solvent	D_2O
Substrate	Aniline derivatives in D_2O and DCl
Flow rate	0.111 mL/min
Tube reactor volume	10 mL
Column reactor volume	0.2 mL
Tube reactor temperature	140 °C
Column reactor temperature	30°C
Pressure	40 PSI

This experimental set up was used for H/D exchange. The flow reactor was configured using two reactors (a column reactor and tube reactor) as shown in (Fig 3.1). Aniline derivatives *(p*-toluidine, 3-ethylanilne, 4-ethylaniline and 2-isopropylaniline) were chosen for this investigation as ideal substrates because they contained different alkyl

groups and different positions. In this analysis appears incorporation and a high levels H/D exchange deuterated at all activated position.

In this study, this technique was used first to measure the activity of Pd/C catalyst at room temperature, the activity of the acid and D_2O with substrate was conducted at different temperature of 140 °C.

Table 3.1 shows the deuterium percentage for all positions and the isolated yields. It was apparent that the catalyst had not been greatly effective for H/D exchange by this method, especially no incorporation in inactivated (*meta*) aromatic positions. Moreover In the side chain minimal incorporation of deuterium had occurred and this could be attributed to essentially no effect of flowing through a Pd/C bed at this temperature. Although no relevant H/D exchanges were recorded in the experiment above, however that was good result for acid mediated H/D exchange. This investigation was for several of aniline derivatives with different side chains and different positions. It would indicate that under flow conditions at this temperature Pd leaching and thus catalysis by a homogeneous process or over nanoparticulate Pd in flow, released from the Pd-C, was minimal. Had leaching occurred one would have expected the heated coil reactor to have facilitated H/D exchange in the side chain but the extent of this was minimal, thus the study moved to microwave iradiation method.



R=CH_3, -CH_2CH_3, -$CH(CH_3)_2$

Table 3.1.%D incorporation of aniline derivatives deuterated by use of a flow reactor.

Entry	Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	Yield[a]
1	%D*	96	5	….	5	96	24	….	76%
2	%D¥	91	….	91	3	91	19	18	88%
3	%D‡	95	10	….	10	95	11	13	81%
4	%D^	….	10	86	14	85	23	41	72%

*%Deuterium incorporation for *p*-toluidine, calculated following acetylation.

¥%Deuterium incorporation for 3-ethylaniline, calculated following acetylation.

‡%Deuterium incorporation for 4-ethylaniline, calculated following acetylation.

^%Deuterium incorporation for 2-isopropylaniline, calculated following acetylation.

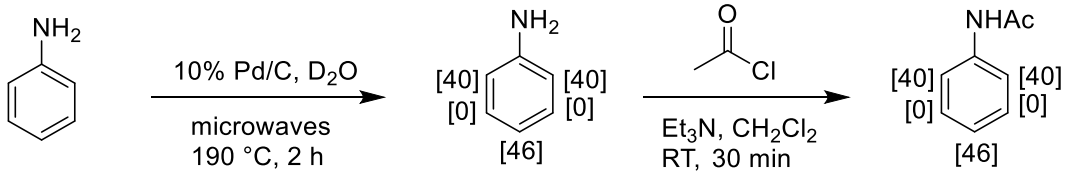
[a]Isolated yield for the H/D exchange reaction following acetylation.

H/D exchange using Pd/C as a heterogeneous catalyst by microwave- assisted.

3.6. Aniline

At the beginning of this investigation aniline was chosen as an ideal substrate of study containing only aromatic C-H bonds. Pd-C has been reported to only be poorly efficient in aromatic C-H functionalization and isotopic exchange so this would provide a good benchmark as to the efficiency of the process. A solution of aniline was added to a stirred mixture of the 10% Pd/C-catalyst and D_2O in a Pyrex tube and the mixture was irradiated at 190 °C in a sealed vessel for 2 hours. After the reaction hydrochloric acid was added to the mixture to liberate the aniline from the catalyst surface. Then the solution was filtered through Celite and neutralized by the addition of NaOH to give the d_3-aniline which was analyzed by ^1H NMR spectroscopy.

More derivatization by acetylation was carried out to quantify the degree of H-D exchange. A stirred solution of d_3-aniline was reacted with acetyl chloride in CH_2Cl_2 in the presence of NEt_3 (Triethylamine) under a N_2 atmosphere. The mixture was quenched and separated by the addition of hydrochloric acid to give the d_3- acetanilide. Acetylation was used to calculate the percentage deuteration of the various hydrogen environments by integrating each peak against the three-hydrogen integration of the acetyl methyl peak as an internal reference. In this analysis the peaks (δ = 7.15 ppm) corresponding to the protons at C-2/C-6 showed an integration after a simple subtraction that quantified an average of 0.80 of the 2.00 hydrogens had been exchanged for deuterium; this corresponded to 40% deuterium incorporation. However the corresponding protons at δ = 7.38 ppm *meta* to the amide (NH) exhibited an integration of 2.00 H, showing no incorporation at C-3/5 position for aniline by the Pd/C-catalyzed process. The isolated yield for the H-D exchange reaction was 84%. Table (3.2) shows that the aniline heated over a Pd catalyst in the presence of D_2O is only able to exchange at activated positions and such process is poorly inefficient in the absence of an acid catalyst. The lower than expected yield was due to the high solubility of aniline in D_2O. Given the poor result using aniline as a substrate, a more lipophilic precursor was chosen as an alternative system for study that also had the facility for aliphatic C-H activation to take advantage of the reported properties of Pd catalysts in these transformations.



14 **14a**

Table 3.2.%D incorporation of aniline after microwave irradiation using a Pd-C catalyst.

Position	C-2	C-3	C-4	C-5	C-6	Yield[a]
%D*	40	0	46	0	40	84%

*%D Deuterium incorporation calculated by ^{1}H NMR spectroscopic analysis following acetylation.

[a]Isolated yield after microwave irradiation following acetylation

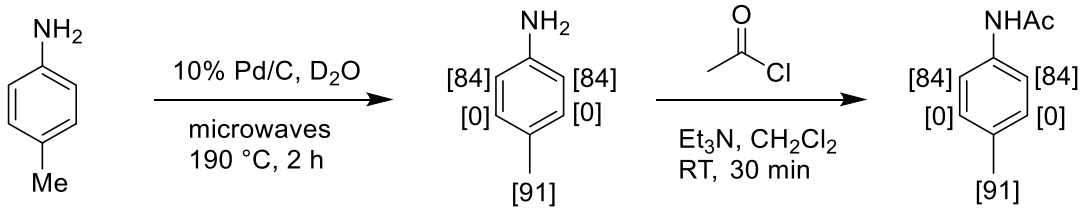
3.7. *p*-Toluidine

p-Toluidine was chosen as an ideal substrate because it contained an alkyl group to improve lipophilicity and enable study of aliphatic incorporation. An additional methyl group would also make the aromatic system more electron-rich and this could have an influence on metal-independent mechanisms of H/D exchange. A solution of *p*-toluidine was added to a stirred mixture of the 10% Pd/C-catalyst and D_2O in a Pyrex tube and irradiated at 190 °C for 2 hours as before. Hydrochloric acid was added to the mixture to liberate the *d_5-p*-toluidine from the catalyst surface. Work up and isolation procedures as before gave the *d_5-p*-toluidine for analysis by ^{1}H NMR spectroscopy.

Derivatization by acetylation was carried out to quantify the extent of H-D exchange using a stirred solution of the crude *d_5-p*-toluidine and acetyl chloride in CH_2Cl_2 and NEt_3 under a N_2 atmosphere. Acetylation was used to calculate the percentage deuteration of the various hydrogen environments by integrating each peak and comparing with the three hydrogen integration of the acetyl methyl peak as an internal reference. In this analysis the peaks at δ = 7.39 ppm corresponding to the protons at C-2/C-6 showed a proton integration of an average of 0.31 of the 2.00 hydrogens corresponding with 84% deuterium incorporation However the protons resonating at δ

= 7.11 ppm in the position *meta* to the amide (NH) exhibited an integration of 2.00 H, on the other hand, indicating no incorporation for the Pd/C-catalyzed process. Interestingly the C-1′ protons resonating at δ = 2.25 ppm gave an integration of 0.25 H. The isolated yield for the H-D exchange reaction was 83%.

It was apparent that the catalyst had been more effective in H/D exchange for this substrate than for aniline at activated positions, however no incorporation was observed at inactive (*meta*) aromatic positions. The improved incorporation could be as a consequence of increased rate of electrophilic aromatic substitution for a more electron-rich precursor although a metal-catalyzed process could not be ruled out for aromatic exchange. Side chain incorporation of deuterium had also proceeded with high efficiency and this was consistent with formation of Pd-alkyl σ-complex. This was encouraging for the development of a new rapid method for H/D exchange, in particular for side chain incorporation. It was noteworthy that despite reasonably efficient aliphatic C-H activation, *meta* functionalization had not been observed. To provide further evidence for and understanding of this process an alternative substrate was investigated containing a longer side chain and alternative substitution pattern.



15 ***d*$_5$,15**

Table 3.3.%D incorporation of *p*-toluidine after microwave irradiation using a Pd/C catalyst.

Position	C-2	C-3	C-4	C-5	C-6	C-1	Yield[a]
%D*	84	0	….	0	84	91	83%

*%D Deuterium incorporation calculated following acetylation.

[a]Isolated yield after microwave irradiation following acetylation.

3.*8.* 3-Ethylaniline

3-Ethylaniline was chosen as an ideal substrate because it contains an alkyl group to examine improved lipophilicity and incorporation into an alkyl side chain. This substrate would enable incorporation to be examined at both activated and poorly activated positions and should be able to decouple the effect of metal-catalyzed

exchange and acid-mediated exchange. A solution of 3-ethylanilinewas added to a stirred mixture of the 10% Pd/C-catalyst and D_2O in a Pyrex tube and irradiated at 190 °C for 2 hours as before. Hydrochloric acid was added to the mixture to liberate the d_8-3-ethylaniline from the catalyst surface. Then the solution was filtered through Celite and neutralized by the addition of NaOH to give the d_8-3-ethylaniline following work up which was analyzed by ^{1}H NMR spectroscopy.

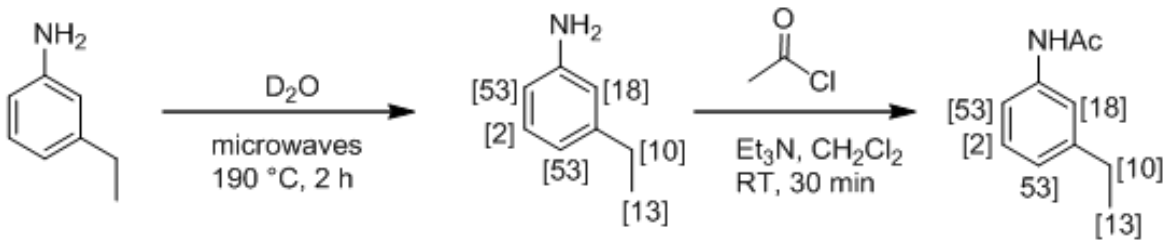
Subsequent derivatization by acetylation was carried out to quantify the extent of H-D exchange using acetyl chloride in CH_2Cl_2 and NEt_3 under a N_2 atmosphere. The acetanilide was used to calculate the percentage deuteration of the various hydrogen environments by integrating each peak against the three hydrogen integration of the acetyl methyl peak as an internal reference.

In this analysis the peak (δ = 7.20 ppm) corresponding to protons *meta*to amide NH exhibited an integration of 0.93 H for the Pt-catalyzed process. A simple subtraction quantified that an average of 0.07 of 1.00 hydrogens had been exchanged for deuterium as depicted in entry 2, table (3.4); this corresponded to 7% deuterium incorporation. High levels of incorporation were observed at all remaining positions of the aromatic ring. The isolated yield assuming the major isotopologue for the H-D exchange reaction was 86%. In the side chain, incorporation of deuterium had occurred albeit with slightly lower incorporation and this could be envisaged to happen by formation of a Pt-alkyl σ-complex.

The results of the experiments carried out in the presence of Pd-C were compared with incorporation experiments (entry 1, Table 3.4), using 3-ethylaniline under neutral conditions in the absence of catalyst. Relatively rapid exchange was observed at *para* position (C-4), where exchange was significant but slower, yet essentially no incorporation occurred in the *meta* and side chain positions. The uncatalyzed (metal-free) reaction, where the incorporation was lower, saw D incorporation at activated positions, but minimal incorporation at poorly activated positions. For the H-D exchange reaction, the yield was 86% in presence of the metal catalyst, whereas in the absence it was 80% (entries 1 and 2, table 3.4) confirming the efficiency of the isolation process from the catalyst. This evidence illustrated that the method was capable of high deuterium incorporation at *ortho* and *para* positions by using a metal catalyst and reasonable H/D exchange into an alkyl side chain. While without the catalyst, the H/D exchange was significantly lower than with the catalyst at activated

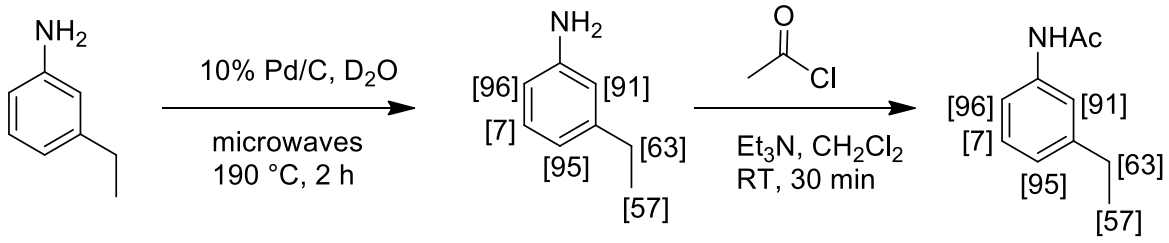
positions, in the absence of a metal there was also limited exchange at inactive positions. It was interesting that in the presence of the metal catalyst the efficiency of exchange at activated positions had increased. It would seem that this phenomenon could well be independent of the metal and could instead be a surface phenomenon. To provide further evidence on, and understanding of, this process an alternative

a. H/D-Exchange of 3-ethylaniline without a metal catalyst:



16 ***d₂*, 16**

b. H/D-Exchange of 3-ethylaniline using a heterogeneous catalyst:



17 ***d₈*, 17**

substrate was investigated containing an alternative substitution pattern.

Table 3. 4. %D incorporation of 3-ethylaniline after microwave irradiation.

Entry	Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	Yield[a]
1	%D*	18	….	53	2	53	10	13	80%
2	%D¥	91	….	95	7	96	63	57	86%

*Deuterium incorporation for 3-ethylaniline after heating in the absence of a catalyst, calculated following acetylation.

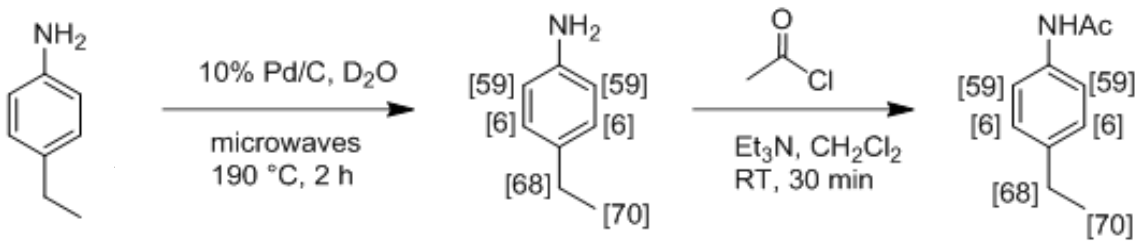
¥Deuterium incorporation for 3-ethylaniline after heating in the presence of Pd-C, calculated following acetylation.

[a]Isolated yield for the H/D exchange reaction following acetylation.

3.9.4-Ethylaniline

4-Ethylaniline was chosen as the next substrate of study to help confirm the effect of alkyl functionality on H/D exchange. A solution of 4-ethylaniline was added to a stirred mixture of the 10% Pd/C-catalyst and D_2O in a Pyrex tube and irradiated at 190 °C for 2 hours, as before. Hydrochloric acid was added to the mixture to liberate the 4-ethylaniline from the catalyst surface. Then the solution was filtered through Celite and neutralized by the addition of NaOH to give the d_7-4-ethylaniline which was analyzed by ^1H NMR spectroscopy.

More derivatization by acetylation was carried out to quantify the extent of H-D exchange by adding acetyl chloride to a stirred solution of d_7-4-ethylaniline in CH_2Cl_2 and NEt_3 under a N_2 atmosphere. The reaction was quenched by the addition of hydrochloric acid to give d_7-(4-ethylaniline)-derived acetanilide. Acetylation was used to calculate the percentage deuteration of the various hydrogen environments by integrating each peak against the three hydrogen integration of the acetyl methyl peak as an internal reference. In this analysis the peaks (δ = 7.42 ppm) corresponding to the protons at C-2/C-6 showed an integration that by simple subtraction quantified that an average of 0.83 of the 2.00 hydrogens had been exchanged for deuterium; this corresponded to 59% deuterium incorporation. However the protons resonating at δ = 7.13 ppm positioned *meta* to the amide (NH) exhibited an integration of 1.89 H whereas in the side chain reasonable incorporation of deuterium had occurred. Carrying out the reaction as before, the yield for the H-D exchange reaction was 84% as shown in table (3.5). All of this evidence illustrated that exchange in the side chain could occur and was more rapid than aromatic C-H activation using a Pd catalyst, especially at sterically encumbered positions. An *ortho* steric effect may have reduced metal exchange to the aniline by hindering formation of a Pd-aryl σ-complex. At C-3 and C-5 positions, exchange percentages were low, indicating that this phenomenon may well be dominant for 4-substituted precursors. Alternatively, the poor efficiency and rate of Pd-mediated aromatic exchange may simply indicate that H/D aromatic incorporation under these conditions is dominated by electrophilic aromatic substitution, perhaps with surface effects, with the metal only serving a role in C-H activation of the side chain.



18 ***d*7,18**

Table 3.5.%D incorporation of 4-ethylaniline after microwave irradiation using a Pd/C catalyst.

Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	Yield[a]
%D*	59	6	….	6	59	68	70	84%

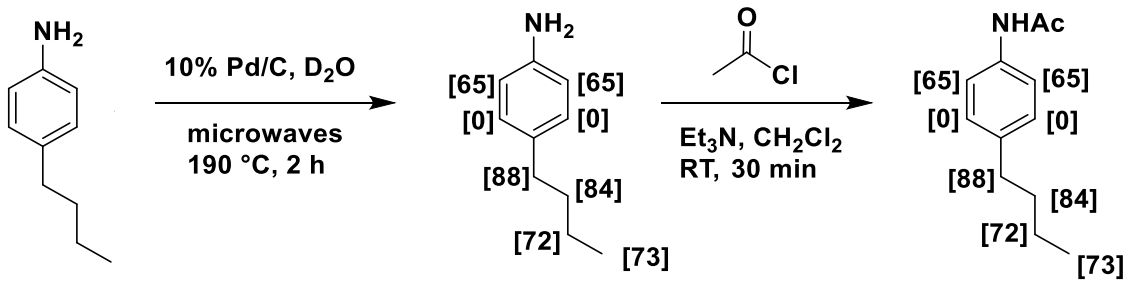
*%Deuterium incorporation calculated following acetylation.
[a]Isolated yield after microwave irradiation following acetylation.

3.10. *n*-Butylaniline

p-*n*-Butylaniline was selected as the next substrate of study to help confirm the effect of alkyl substitution on H/D exchange**.** A solution of *p*-*n*-butylaniline was added to a stirred mixture of the 10% Pd/C-catalyst and D_2O in a Pyrex tube and irradiated at 190 °C for 2 hours as before. Hydrochloric acid was added to the mixture to liberate the d_{11}-*n*-butylacetanilide from the catalyst surface. Then the solution was filtered through Celite and neutralized by the addition of NaOH to give the d_{11}-*p*-*n*-butylaniline which was analyzed by ^{1}H NMR spectroscopy.

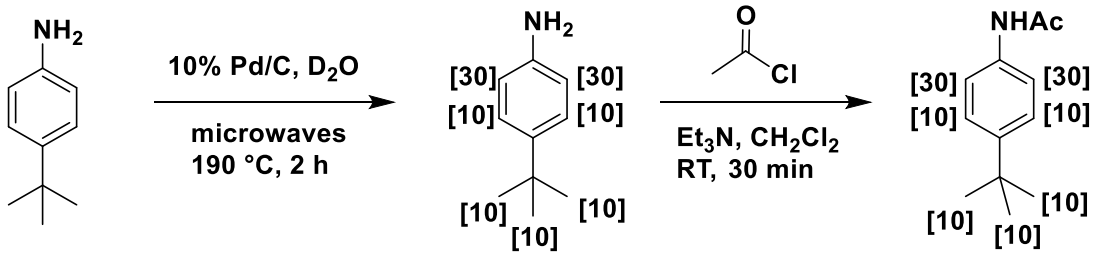
Derivatization by acetylation was carried out to quantify the degree of H-D exchange using acetyl chloride in CH_2Cl_2 and NEt_3 under a N_2 atmosphere to give the d_{11}-*n*-butylacetanilide. Acetylation was used to calculate the percentage deuteration of the various hydrogen environments by integrating each peak against the three hydrogen integration of the acetyl methyl peak as an internal reference.The isolated yield for the H-D exchange reaction was 73%. Using a Pd catalyst there was still good deuterium incorporation at C-2 and C-6. Elsewhere, was limited incorporation at C-3 and C-5 perhaps due to an *ortho*-steric effect, whereas in the side chain the role of the catalyst was clear in that there was high levels of exchange at all positions. Given the ready incorporation of deuterium in the side chain, this could be envisaged to occur by formation of a Pd-alkyl σ-complex entry 1.

a. H/D-Exchange of 4-*n*-butylaniline using a heterogeneous catalyst



19 **d_{11}, 19**

b. H/D-Exchange of *4-tert*-butylaniline using a heterogeneous catalyst



20 **20a**

Table 3.6.%D incorporation of 4-butylanilines after microwave irradiation using a Pd-C catalyst.

Entry	Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	Yield[a]
1	%D*	65	0	….	0	65	88	84	72	73	73%
2	%D¥	30	10	….	10	30	….	10	10	10	84%

*%D Deuterium incorporation for 4-*n*-butylaniline catalyst calculated following acetylation.

¥%D Deuterium incorporation for 4-*tert*-butylaniline calculated following acetylation.

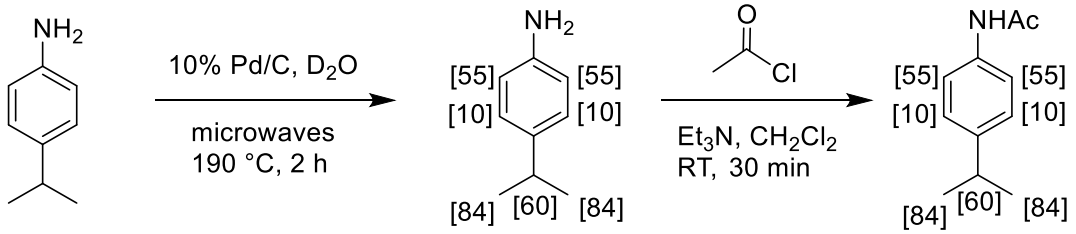
[a]Isolated yield for the H/D exchange reaction following acetylation.

The results for 4-*n*-butylaniline exchange were compared with experiments carried out using 4-*tert*-butylaniline. For this alternative substrate the yield for the H-D exchange reaction was 84%. In C-3 and C-5 positions the level of deuterium incorporation was similar, but with *tert*-butylaniline incorporation was even lower. This could have been a steric effect but it seemed plausible that other factors might be involved. However, as was expected in the deuterium exchange with branching in the side chain extremely low and probably insignificant D incorporation was observed in the alkyl group beyond the quaternary centre entry 2 (table 3.6).

3.11. Isopropylaniline

The table (3.7) shows 4-isopropylaniline as an additional substrate of study to confirm the effect of increased branching on H/D exchange. A solution of this aniline was added to a stirred mixture of the 10% Pd/C-catalyst and D_2O in a Pyrex tube and the mixture was irradiated at 190 °C in a sealed vessel for 2 hours as before. Hydrochloric acid was added to the mixture to liberate the 4-Isopropylaniline from the catalyst surface. Then the solution was filtered through Celite and neutralized by the addition of NaOH to give the d_9-4-isopropylaniline which was analyzed by ^{1}H NMR spectroscopy.

Derivatization by acetylation was carried out also as before to quantify the degree of H-D exchange using acetyl chloride in CH_2Cl_2 and NEt_3 under a N_2 atmosphere. Acetylation was used to calculate the percentage deuteration of the various hydrogen environments as an internal reference, as before. The yield for the H-D exchange reaction was 76%. All of this evidence illustrated that exchange does occur with branching in the side chain of the substrate as under Pd-catalysis the σ-complex can form providing there is not a quaternary centre. The 4-Isopropyl group displayed similarly low levels of D incorporation at C-3/5 to 4-ethylaniline due to these positions being sterically encumbered and/or poorly activated. This resulted in a very low percentage of deuterium incorporation at these positions. Similar considerations could be proposed for incorporation at C-1′ (60%), although it is interesting to compare the extent of incorporation into *p*-toluidine (section 3.3) which was deuterated at C-1′ to a much greater extent.



21 ***d*₉, 21**

Table 3.7.%D incorporation of 4-isopropylanilineafter microwave irradiation using Pd-C.

Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	Yield[a]
%D*	55	10	….	10	55	60	84	84	76%

*%Deuterium incorporation calculated following acetylation.

[a]Isolated yield after microwave irradiation following acetylation.

Lastly, the results of the initial experiments using the flow reactor (Table 3.1) were compared with the results of a microwave-assisted method (10% Pd/C, D_2O, 190 °C, 2h) (Table 3.8). Firstly (entry 1) when *p*-toludine was used as a substrate the microwave-assisted method was slightly more efficient in terms of chemical yield than the flow reactor process. The flow method gave higher levels of incorporation at activated positions but was not able to incorporate into the side chain indicating the process was essentially metal-catalyst free. Secondly, at unactivated aromatic positions deuterium incorporation was approximately the same in both methods and essentially not observed. The microwave-assisted method gave very high levels of H/D exchange in the side chain.

Table 3.1.%D incorporation of aniline derivatives deuterated by use of a flow reactor.

Entry	Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	Yield[a]
1	%D*	96	5	….	5	96	24	….	76%
2	%D¥	91	….	91	3	91	19	18	88%
3	%D‡	95	10	….	10	95	11	13	81%
4	%D^	….	10	86	14	85	23	41	72%

*%Deuterium incorporation for *p*-toluidine, calculated following acetylation.

¥%Deuterium incorporation for 3-ethylaniline, calculated following acetylation.

‡%Deuterium incorporation for 4-ethylaniline, calculated following acetylation.

^%Deuterium incorporation for 2-isopropylaniline, calculated following acetylation.

[a]Isolated yield for the H/D exchange reaction following acetylation.

Table 3.8.%D incorporation of aniline derivatives after microwave irradiation using a Pd-C catalyst.

Entry	Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	Yield[a]
1	%D*	83	0	….	0	83	91	….	83%
2	%D¥	91	….	95	7	96	63	57	86%
3	%D‡	60	11	….	11	60	68	70	84%

*%Deuterium incorporation for *p*-toluidine, calculated following acetylation.

¥%Deuterium incorporation for 3-ethylaniline, calculated following acetylation.

‡%Deuterium incorporation for 4-ethylaniline, calculated following acetylation.

[a]Isolated yield for the H/D exchange reaction following acetylation.

3.12. Conclusions

The deuteration of aniline using microwave irradiation did not give ideal results for palladium-catalyzed deuteration. Good selectivity for aliphatic over aromatic C-H activation was obtained but %D incorporation levels were not competitive. Aniline derivatives did show good incorporation of deuterium over a palladium catalyst at activated positions but this may well just be a surface phenomenon. The direct comparison, with the uncatalyzed process gave a greater insight into the selectivity and chemistry of the palladium-catalyzed exchange reactions.

It has been shown that the H/D exchange of aniline derivatives without palladium catalysis proceeded as expected and gave reduced H/D exchange at both activated and poorly-activated positions presumably by an acid-mediated mechanism. H/D exchange with the palladium catalyst provided efficient deuteration at activated aromatic positions only. Furthermore, palladium catalysis was able to facilitate exchange in alkyl side chains with quite high efficiency provided that there was no quaternary cent

Chapter 4

H/D exchange of aniline and aniline derivatives using an homogeneous metal catalyst

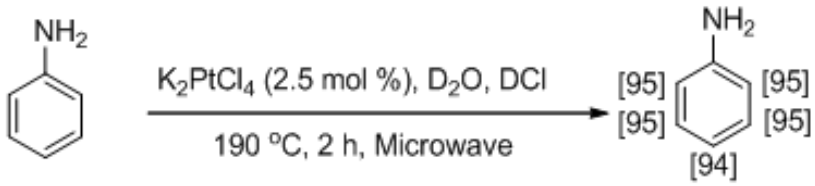
4.1. Introduction

Previously, a review of the early H/D exchange data was depicted and analyzed; this described the use of a heterogeneous catalyst including a few observations on the use of palladium and metal-complex developments. Regardless of the findings, the conclusions derived were significant to understand efficiencies instead of establishing methods for preparation of deuterated targets. Consequently, from the standpoint of the outcomes revealed in past sections, an investigation of the use of Pt in H/D exchange was deemed essential as a homogeneous catalyst. In spite of the fact that in the last section some mechanistic viewpoints were offered, in this chapter they will be extended. Based on existing studies.[145] Furthermore, a number of new anilines will be investigated as substrates to discover efficient methods for incorporating multiple isotopic labels efficiently and predictably. As per Garnett's review on viable substrates, alkyl-substituted precursors will be utilized. Therefore, an extensive assessment of Pt mediated H/D exchange both on aromatic rings and on alkyl side chains will be established.

4.2. Aniline

At the beginning of this investigation on the aromatic ring, aniline was chosen as it exhibits relatively high water solubility and hydrophilicity as a suitable starting substrate. A solution of aniline was added to a stirred mixture of Pt-catalyst and DCl in D_2O in a Pyrex tube; thereafter, the mixture was irradiated at 190 °C in a sealed vessel for 2 hours. Thioglycolic acid was added to the mixture after cooling to remove platinum contamination. This method liberated the aniline from the catalyst. Subsequently, the solution was neutralized by adding NaOH and extracted with CH_2Cl_2 to give the d_5-aniline which was analyzed by ^{1}H-NMR spectroscopy (see appendix 1a). Following the general procedure for H/D exchange, ^{1}H-NMR spectroscopic analysis of the crude product was quantified by addition of 1-4-dioxane (50 mol%) as an external standard. In this analysis the peak (δ = 7.09 ppm) corresponding to protons *meta* to amide NH exhibited an integration of 0.11 H for Pt-catalyzed process as depicted in table 4.1 entry 2. A simple subtraction quantified that

an average of 1.89 of the 2.00 hydrogens had been exchanged for deuterium; this corresponded to 95% deuterium incorporation. Similarly, the peaks corresponding to protons at C-2/C-6 (δ = 6.72 ppm) depicted an integration of 0.11 H, whereas at C-4 those resonating(δ = 6.68 ppm) displayed an integration of 0.06 H. The isolated yield for the H-D exchange reaction was (87%). The mass of d_5-aniline was confirmed as the major isotopologue by mass spectrometry which showed the major ion at *m/z* 98, for the catalyzed reaction. It was apparent that the catalyst had been effective for H/D exchange due to high levels of incorporation at all positions, and this could be envisaged to happen by the formation of a Pt-aryl σ-complex. In the absence of the catalyst a similar chemical yield was obtained following extraction (79%). This evidence illustrates high deuterium incorporation at all positions using a metal catalyst. Without the catalyst (entry 1), the H/D exchange was considerably lower than with the catalyst and occurred predominantly at the activated positions. At poorly activated positions there was minimal exchange under these conditions. To provide further evidence on an understanding of this process an alternative substrate was investigated containing an alkyl side chain.



22 **d_5, 22**

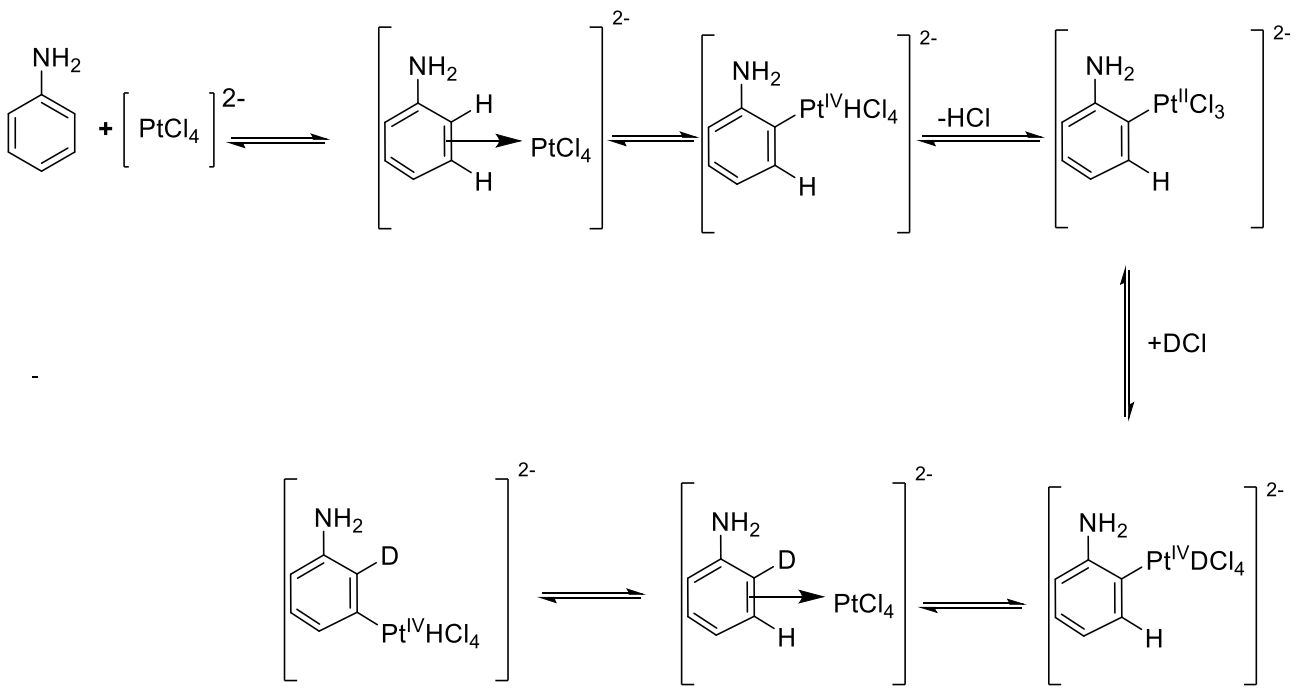
Table 4.1.%D incorporation of Aniline after microwave irradiation.

Entry	Position	C-2	C-3	C-4	C-5	C-6	Yield
1	%D*	38	13	42	13	38	79%
2	%D¥	95	95	94	95	95	87%

*%D Isolated yield% for the H/D exchange reaction after microwave irradiation of the substrate without catalyst.

¥%D Isolated yield% for the H/D exchange reaction after microwave irradiation of the substrate with catalyst.

Garnett noted that activating and deactivating substituents on the aromatic ring did not impact the rate of exchange. This was later confirmed by the findings of Kanski and Kanska.[136, 137] Ultimately these observations were consistent with a dissociative mechanism for platinum, proposed following their studies. The process incorporates formation of a π-complex preceding σ-bond formation between Pt and the phenyl ring in a series of equilibria. It could be expected that the substrate experiences a nonstop (continuous) sequence of such exchange processes within the experiment.

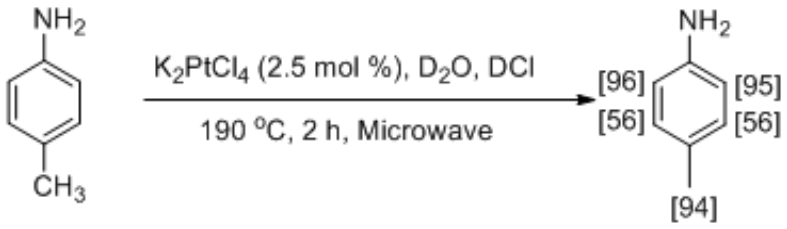


Scheme 4.1.Overview of mechanism of H/D exchange for an aromatic ring.

4.3. Toluidine

p-Toluidine was chosen as an ideal substrate because it contains an alkyl group to improve lipophilicity and examine incorporation into an alkyl side chain. It was anticipated that increased lipophilicity might alter both the efficiency of H/D exchange and product isolation. A solution of *p*-toluidine was added to a stirred mixture of Pt-catalyst and DCl in D_2O in a Pyrex tube and irradiated at 190 °C for 2 hours as before. Thioglycolic acid was added to the mixture after cooling to remove platinum contamination. This method liberated the aniline from the catalyst to give the d_7-*p*-toluidine following work up, for analysis by ^{1}H-NMR spectroscopy and mass spectrometry(see appendix 2a). ^{1}H-NMR spectroscopic analysis of the crude product was quantified by the addition of 1-4-dioxane (50 mol%) as an external standard. In

this analysis the peak (δ= 6.90 ppm) corresponding to protons *meta* to amide NH exhibited an integration of 0.89 H for the Pt-catalyzed process (Table 4.2). A simple subtraction quantified that an average of 1.11 of the 2.00 hydrogens had been exchanged for deuterium; this corresponded to 56% deuterium incorporation. However, the peak corresponding to protons at C-2/C-6 (δ = 6.64 ppm) showed an integration of 0.11 H, whereas at C-1′ those resonating protons (δ = 2.15 ppm) gave an integration of 0.18 H. The isolated yield for the H-D exchange reaction was improved (90%) perhaps as a consequence of increased lipophilicity aiding the isolation process. The mass of the d_7-*p*-toluidine major isotopologue was confirmed by mass spectrometry with the mean ion at *m/z* 114 for the catalyzed reaction. It was apparent that the catalyst had been effective for H/D exchange by giving high levels of incorporation at activated aromatic positions, and reasonable incorporation into the poorly activated (*meta*) aromatic positions probablydue to an *ortho*-steric effect by the methyl group. In the side chain, incorporation of deuterium had occurred with high efficiency and this might be envisaged to happen by the formation of a Pt-alkyl σ-complex. To provide further evidence on an understanding of this process an alternative substrate was investigated containing a longer side chain.



23 ***d*$_5$, 23**

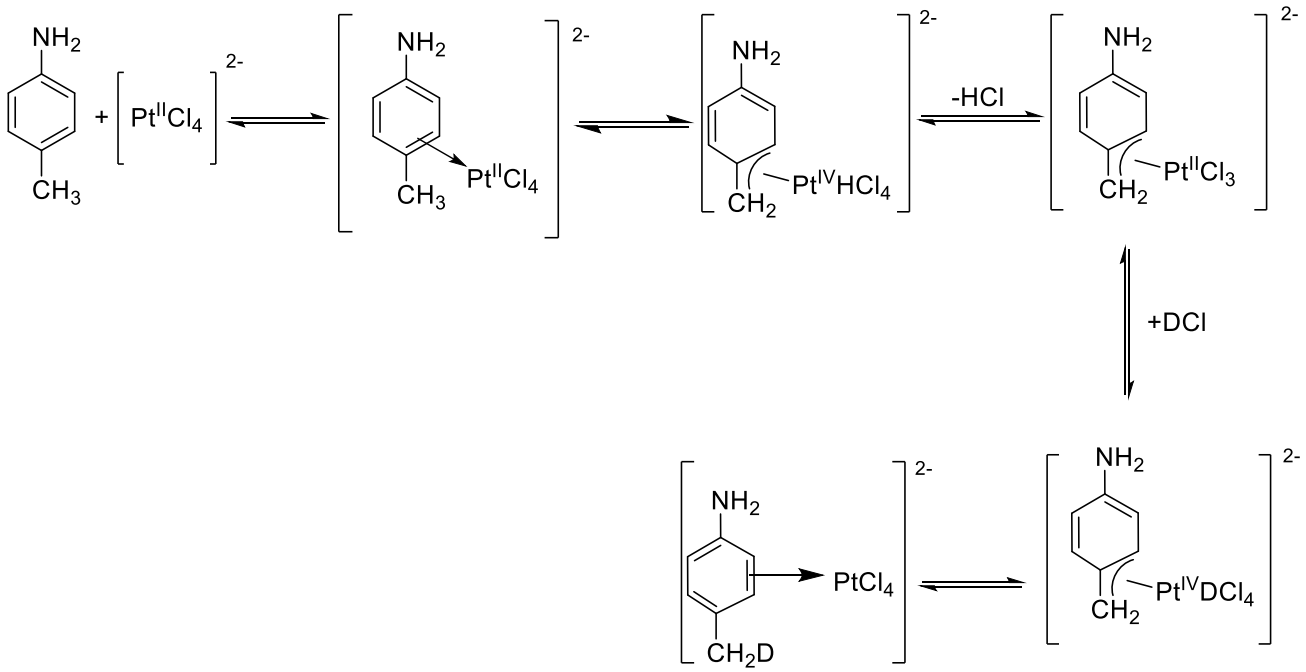
Table 4.2. %D incorporation of p-toluidine after microwave irradiation

Position	C-2	C-3	C-4	C-5	C-6	C-1′	Yield
%D*	96	56	…..	56	96	94	90

*%D Isolated yield% for the H/D exchange reaction after microwave irradiation of the substrate.

Garnett *et al*.[147] established that the H/D exchange mechanism for an alkyl chain demonstrates similar characteristics to the aromatic exchange process. Moreover, their study detected that alkyl chains on alkylbenzene were more responsive to metal-catalysed exchange in comparison to saturated aliphatic substrates. The simplest explanation could be that the π-electronic cloud proximity could promote alkyl chain exchange through conjugation and hyper-conjugation mechanisms. Therefore, they

suggested another alkyl dissociative π-complex mechanism was operating. Specifically, for this point a η3-allylplatinum species was proposed as an intermediate. As Khusnutdinova *et al*.[148] proved in their study, these complexes are by and large framed as an outcome of an allylic C-H deprotonation. Interestingly, considering plausible structures for intermediates, the procedure could be depicted by a hydride migration. Since the Pt acts as an electrophilic species, hydride could certainly be induced to migrate to the metal, forming a σ-bond. In spite of the fact that in reviews of related allylic metal complexes, where both cyclic and non-cyclic unsaturated frameworks have been discussed, aromatic rings were not considered mechanistically. Significant work by Driver *et al*.[149] formed the basis for extending this aspect to an aromatic context. Subsequent to highlighting the significance of π-electrons in activating the aliphatic hydrogen, Driver proposed that the exchange procedure relied on a reversible harmony between a π-arene complex and a π-allylic one. For this reason, the conduct of platinum towards the methyl group ought to be indicated. In the η3-allylic complex, Pt (II) has been transformed to Pt (IV) by reaction with DCl. Scheme 4.2 (see also Scheme 3.5).

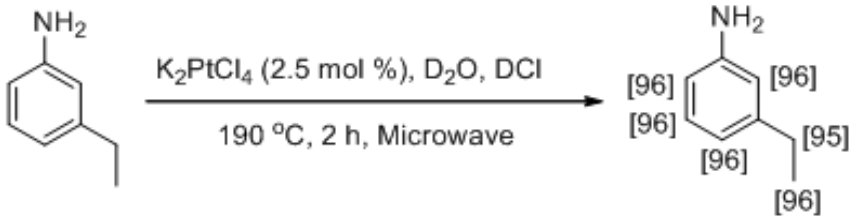


Scheme 4.2.Plausible mechanism of H/D exchange for a methyl group.

4.4. 3-Ethylaniline

3-Ethylaniline was chosen as an ideal substrate because it contains an alkyl group to improve lipophilicity and examine incorporation into an alkyl side chain. This substrate would also enable incorporation to be examined at both activated and poorly activated positions. A solution of 3-ethylaniline was added to a stirred mixture of Pt-catalyst and DCl in D_2O in a Pyrex tube and irradiated at 190 °C for 2 hours as before. Thioglycolic acid was added to the mixture after cooling to remove platinum contamination. This method liberated the 3-ethylaniline from the catalyst to give d_9-3-ethylaniline following work up, for analysis by ^{1}H-NMR spectroscopy and mass spectrometry (see appendix 3a,).^{1}H-NMR spectroscopic analysis of the crude product was quantified by addition of 1-4-dioxane (50 mol%) as an external standard. In this analysis the peak (δ = 7.08 ppm) corresponding to protons *meta*to amide NH exhibited an integration of 0.04 H for the Pt-catalyzed process. A simple subtraction quantified that an average of 0.96 of 1.00 hydrogen had been exchanged for deuterium as depicted in entry 1, table 4.3; this corresponded with 96% deuterium incorporation. However, the peaks corresponding to protons at C-2/C-6 (δ = 6.62 ppm) showed an integration of 0.04 H, whereas at C-4 those resonating at δ = 6.55 ppm gave an integration of 0.04 H. The isolated yield, considering the major isotopologue, for the H-D exchange reaction was 87%. The mass of the d_9-3-ethylaniline was confirmed by mass spectrometry by the main ion at *m/z* 130 for the catalyzed reaction. It was apparent that the catalyst had been effective for H/D exchange and gave high levels of incorporation at all positions. In the side chain, incorporation of deuterium had occurred with high efficiency and this could be envisaged to happen by formation of a Pt-alkyl σ-complex. However entry 2 in Table 4.3, depicts incorporation of 3-ethylaniline under conductive heating at reflux for 24 h in the same reagent system. Under these conditions, relatively rapid exchange was observed at *ortho* and *para* positions, metal exchange was significant but slower, yet no incorporation occurred in the side chain indicating that Garnett $C_{(sp3)}$-H activation required high temperature conditions. On the other hand, the uncatalyzed reaction, where the incorporation was lowered, occurred at activated position; however, there was no incorporation at poorly activated positions. For the H-D exchange reaction, the yield was good (87%) in the presence of the metal catalyst, using microwave irradiation and conductive heating methods (90%) (entries 1 and 2, Table 4.3). In the absence of the catalyst a similar chemical yield was obtained following

extraction (80%) (entry 3). This evidence illustrates that the method is capable of promoting high deuterium incorporation at all positions using a metal catalyst, including incorporation into an alkyl side chain. Without the catalyst, the H/D exchange was slightly lower and slower than when the catalyst was present at activated positions; however, at poorly activated positions there was no exchange especially at C-5, *meta* to both substituents. The uncatalyzed process gave very low exchange in the side chain. To provide further evidence towards understanding this process an alternative substrate was investigated containing a longer side chain.



24 ***d*$_9$, 24**

Table 4.3.%D incorporation of 3-ethylaniline after microwave irradiation for 2 h or conductive heating for 24 h.

Entry	Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	Yield
1	%D*	96	….	96	96	96	95	96	87%
2	%D¥	86	….	93	78	96	0	0	90%
3	%D‡	18	….	53	2	53	10	13	80%

*%D incorporation at the corresponding position for the H/D exchange reaction after microwave irradiation of the substrate with Pt catalyst.

¥%D incorporation at the corresponding position for the H/D exchange reaction after conductive heating for 24 h.

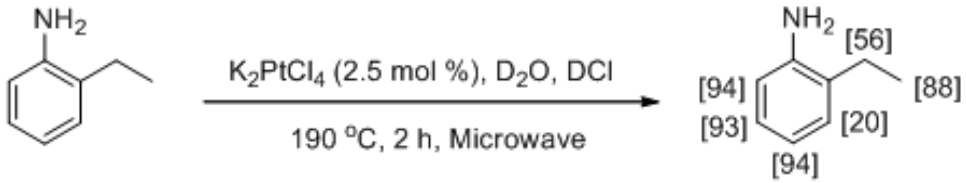
‡%D incorporation at the corresponding position for the H/D exchange reaction after microwave irradiation of the substrate in the absence of a Pt catalyst.

4.5. 2-Ethylaniline

2-Ethylaniline was chosen as the next substrate because it contained an alkyl group to improve lipophilicity and examine incorporation into an alkyl side chain but showed an alternative substitution pattern to establish the influence of a steric effect on the metal-catalyzed process. A solution of 2-ethylaniline was added to a stirred mixture of Pt-catalyst and DCl in D_2O in a Pyrex tube and irradiated at 190 °C for 2 hours as

before. Thioglycolic acid was added to the mixture after cooling to remove platinum contamination. This method liberated the 3-ethylaniline from the catalyst to give the d_8-2-ethylaniline following work up, for analysis by ^{1}H-NMR spectroscopy and mass spectrometry (see appendix 4a). ^{1}H-NMR spectroscopic analysis of the crude product was quantified by the addition of 1-4-dioxane (50 mol%) as an external standard. In this analysis the peak (δ = 7.00 ppm) corresponding to resonance of the proton at C-3 exhibited an integration of 0.80 H following the Pt-catalyzed process (Table 4.4). A significant *ortho*-steric effect was observed giving a level of deuterium incorporation that was much lower, 20% at C-3, than all other positions.

However, the peak corresponding to the proton at C-5 (δ = 6.95 ppm) showed an integration of 0.07 H, whereas those resonating at C-4 (δ = 6.71 ppm) displayed an integration of 0.06 H. The isolated yield for the H-D exchange reaction was 88%. The mass of the major isotopologue of 2-ethylaniline was confirmed by mass spectrometry by the main ion at *m/z* 129 for the catalyzed reaction. In the side chain, incorporation of deuterium had proceeded with good efficiency presumably by the formation of a Pt-alkyl σ-complex.



25 **d_8, 25**

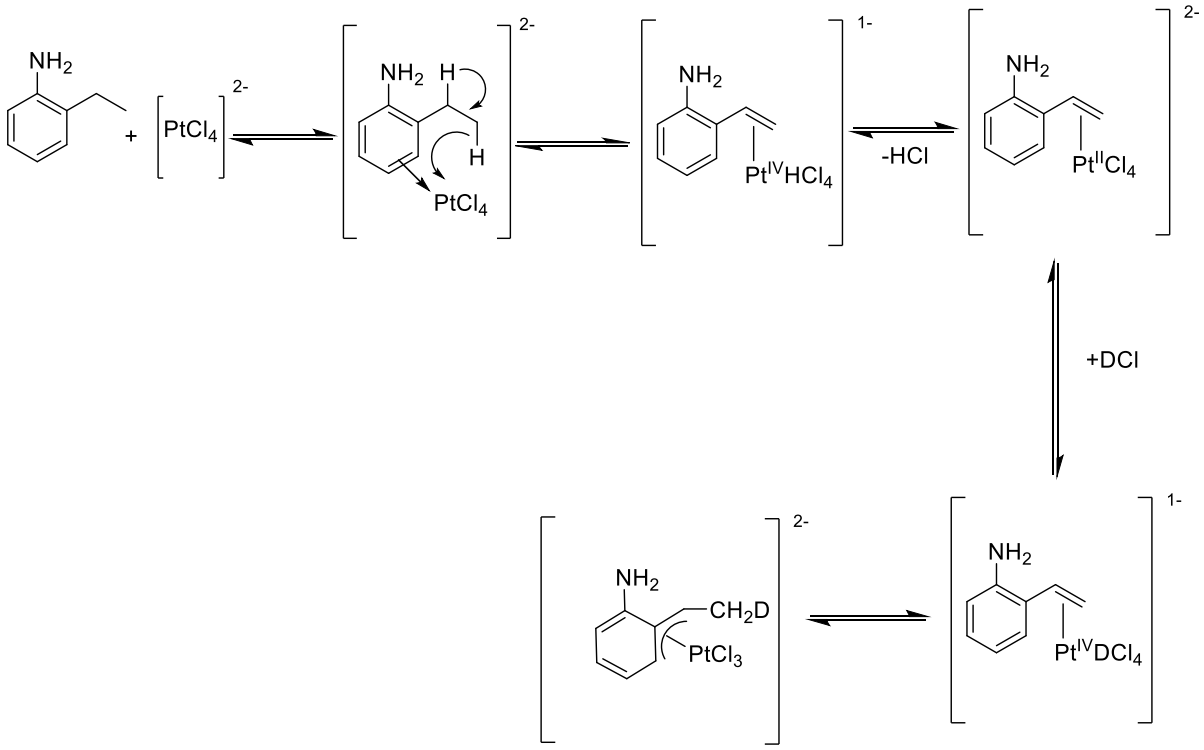
Table (4.4) %D incorporation of 2-Ethylaniline after microwave irradiation

Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	Yield
*%D	….	20	94	93	94	56	88	88%

*%D Isolated yield % for the H/D exchange reaction after microwave irradiation of the substrate.

The preferred position for rapid D incorporation could be dictated by steric elements. Steric considerations were perhaps not all that pertinent for exchange in 3-ethylaniline as congestion occurred at activated positions so under acidic conditions an alternative electrophle-mediated mechanism could operate to incorporate D with high efficiency. The significance of the steric factor was noticeably important for 2-ethylaniline exchange. The first step involves forming π-complexes between the aromatic ring and

platinum, and then formation of η3- π complexes through the migration of the hydride methyl group to form σ- bond, where platinum is bonding to the double bond in ethyl chain. In this step the π-allylic complexes are in equilibrium with the π- arene complexes. The Pt(II) ion is then converted into Pt(IV) by the addition of DCl and formation of σ-complexes, where studies have shown the presence of C-H…..Pt bond in these complex and through which enter the deuterium into ethyl group



Scheme 4.3.Plausible mechanism of H/D exchange at C-2'.

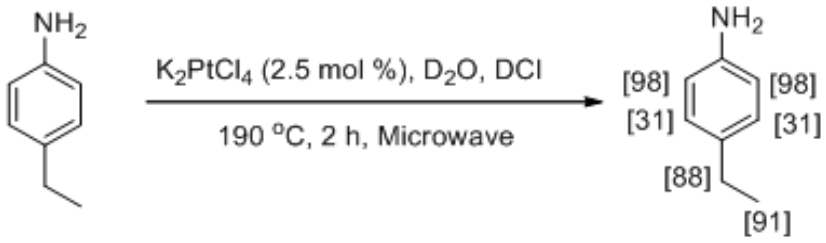
To provide further evidence on our understanding of this process an alternative substrate was investigated containing a longer side chain.

4.6. 4-Ethylaniline

4-Ethylaniline was chosen as a suitable substrate, because it contained an alkyl group to improve lipophilicity and examine incorporation into an alkyl side chain but showed an alternative substitution pattern to establish the influence of a steric effect on the metal-catalyzed process. A solution of 4-ethylaniline was added to a stirred mixture of Pt-catalyst and DCl in D_2O in a Pyrex tube and irradiated at 190 °C for 2 hours as before. Thioglycolic acid was added to the mixture after cooling to remove platinum contamination. This method liberated the 4-ethylaniline from the catalyst to give the d_7-4-ethylaniline following work up for analysis by ^{1}H-NMR spectroscopy and mass

spectrometry (see appendix 5a).^{1}H-NMR spectroscopic analysis of the crude product was quantified by the addition of 1-4-dioxane (50 mol%) as an external standard. In this analysis the peaks (δ = 6.94 ppm) corresponding to protons *meta*to amide NH exhibited an integration of 1.39 H for the Pt-catalyzed process (Table 4.5).

A simple subtraction quantified that an average of 0.61 of the 2.00 hydrogens had been exchanged for deuterium; this corresponded with 31% deuterium incorporation. A significant *ortho*-steric effect was observed for 4-substituted anilines, which now exhibited relatively slow *meta*-functionalization. Low levels of D-incorporation were observed at C-3 and C-5 of 4-ethylaniline. However, the peaks corresponding to protons at C2/C-6 (δ = 6.66 ppm) showed an integration of 0.05 H. The isolated yield for the H-D exchange reaction was 91% (Table 4.5). The mass of the 4-ethylaniline major isotopologue was confirmed by mass spectrometry and showed the main ion at *m/z* 128 for the catalyzed reaction. It was apparent that the catalyst had been effective for H/D exchange by giving high levels of incorporation at the activated aromatic positions, and low incorporation into the poorly activated (*meta*) aromatic positions due to an *ortho*-steric effect, prohibiting catalyst mediated exchange at C-3/5 of the aniline by hindering formation of a Pt-alkyl σ-complex. However in the side chain, incorporation of deuterium had accrued with high efficiency. To provide further evidence on an understanding of this process, an alternative substrate was investigated containing a bulkier side chain.



26 ***d*$_7$, 26**

Table 4.5. %D incorporation of 4-Ethylaniline after microwave irradiation:

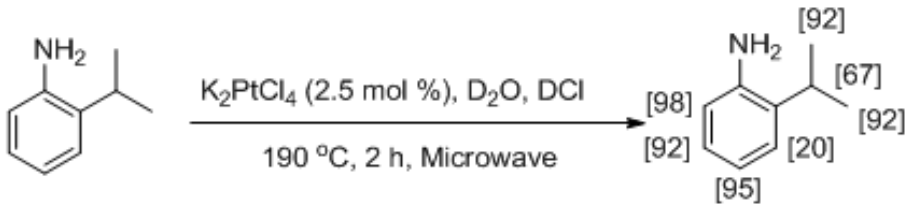
Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	Yield
%D*	98	31	….	31	98	88	91	91%

*%D Isolated yield % for the H/D exchange reaction after microwave irradiation of the substrate

4.7. Isopropylaniline

2-Isopropylaniline was chosen as an ideal substrate because it contained a larger alkyl group with increased branching to examine incorporation into an alkyl side chain and establish the influence of the *ortho*-steric effect on the metal catalyzed process. A solution of 2-isopropylaniline was added to a stirred mixture of Pt-catalyst and DCl in D_2O in a Pyrex tube and irradiated at 190 °C for 2 hours as before. Thioglycolic acid was added to the mixture after cooling to remove platinum contamination. This method liberated the 2-isopropylaniline to give the d_{10}-2-isopropylaniline following work up for analysis by ^{1}H-NMR spectroscopy. ^{1}H-NMR spectroscopic analysis of the crude product was quantified by the addition of 1-4-dioxane (50 mol%) as an external standard. In this analysis, the peak (δ = 7.08 ppm) corresponding to protons *meta* to the anilino NH group, at C-3, exhibited an integration of 0.80 H for Pt-catalyzed process; this corresponded with 20% deuterium incorporation, reduced due to an *ortho*-steric affect. However, the peaks corresponding to the proton at position C-6 (δ = 6.66 ppm) showed an integration of 0.02 H, whereas at C-4, those resonating at (δ = 6.71 ppm) displayed an integration of 0.05 H. The isolated yield for the H-D exchange reaction was 89% (Table 4.6). The mass of the 2-isopropylaniline product was confirmed by mass spectrometry and showed a main ion at *m/z* 144 for the catalyzed reaction. Moreover, in the side chain,

incorporation of deuterium had occurred with high efficiency and this maybe envisaged to happen by the formation of a Pt-alkyl σ-complex.



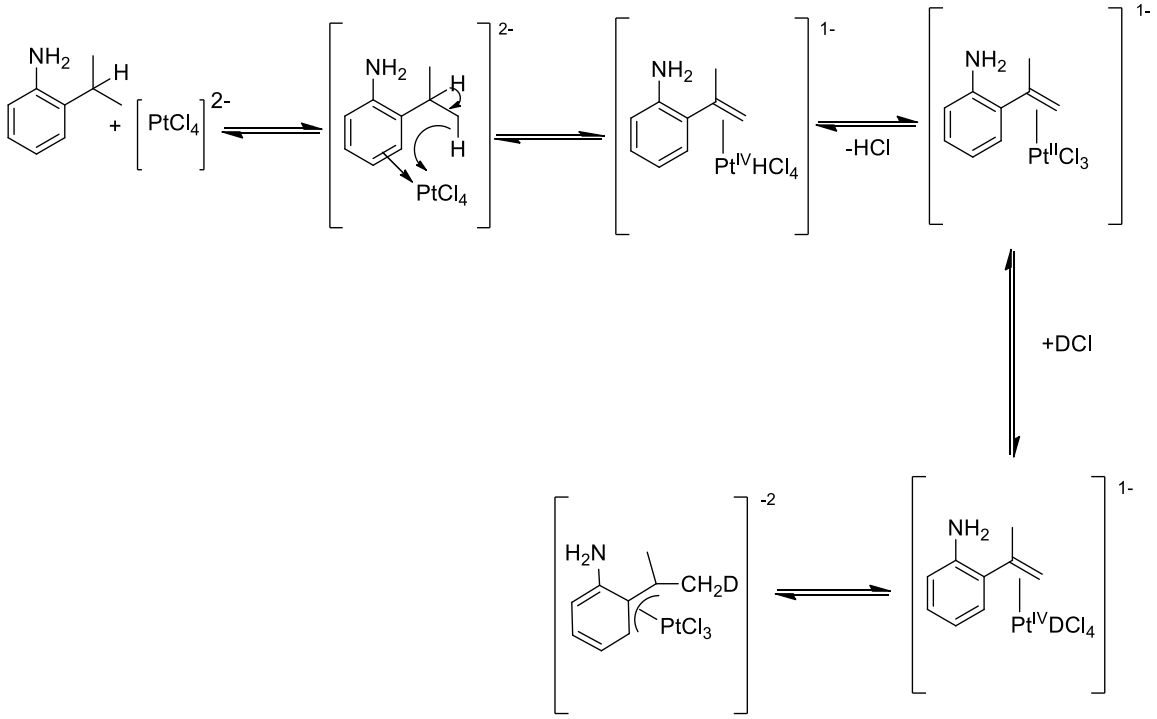
27 **d_{10}, 27**

Table 4.6. %D incorporation of 2-isopropylaniline after microwave irradiation

Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	Yield
%D*	….	20	95	92	98	67	92	92	89%

*%D Isolated yield % for the H/D exchange reaction after microwave irradiation of the substrate.

Additionally, it is relevant to present some mechanistic considerations about isopropyl H/D exchange. This system bears structural similarities with an ethyl chain, in Scheme 4.3. In the case of 2-isopropylaniline, steric hindrance is an important factor in deuterium incorporation and this effect is evident at position C-3 and C-1' where the percentage of deuterium incorporation is 20% and 67%, respectively. The deuterium incorporation into the two-methyl groups on the 2-isopropyl chain is equally rapid because they are enantiotopic. It would not be expected that the H-migration would be affected dramatically by the presence of an additional branch and this was observed to be the case, with similar D incorporation at C-2' (92%) as 2-ethylaniline (88%).



Scheme 4.4.Mechanism of H/D exchange in the isopropyl group.

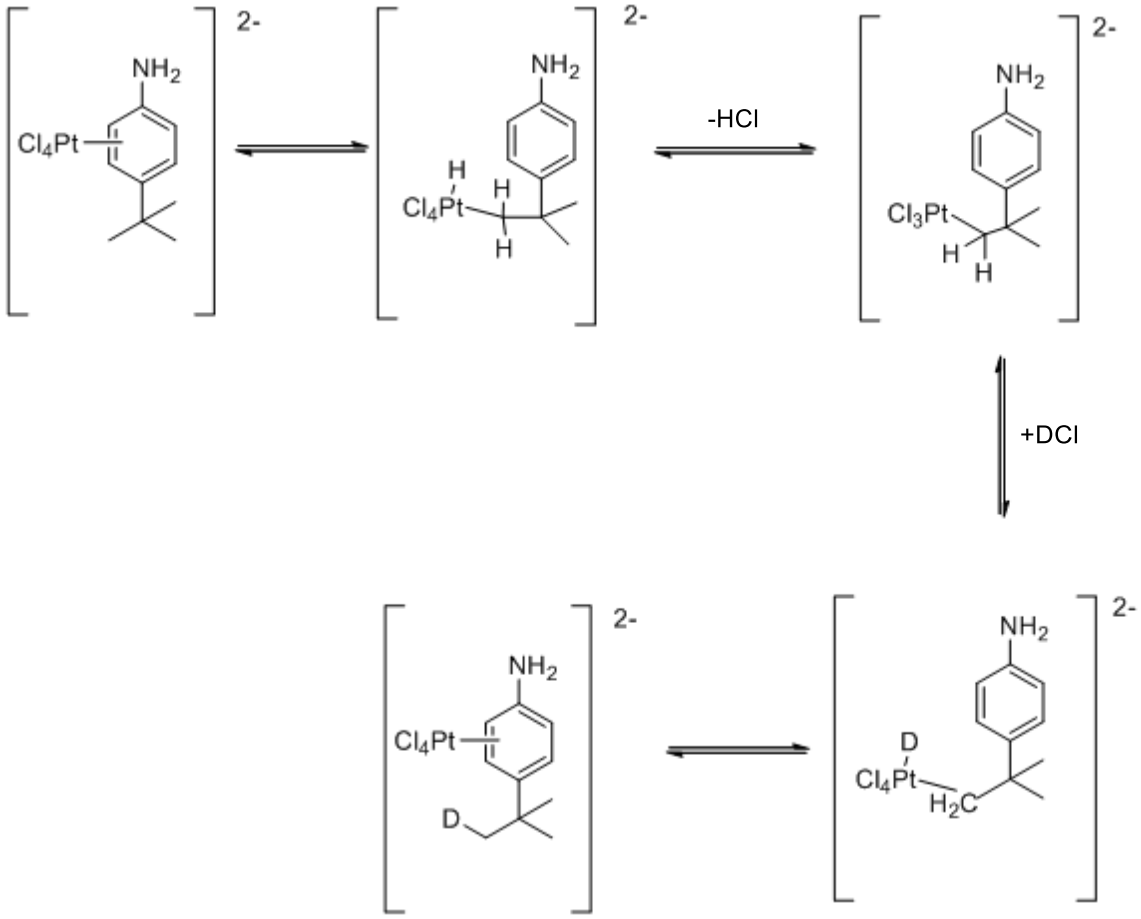
To provide further evidence on an understanding of this process an alternative substrate was investigated containing a bulkier side chain.

4.8. 4-*tert*-Butylaniline

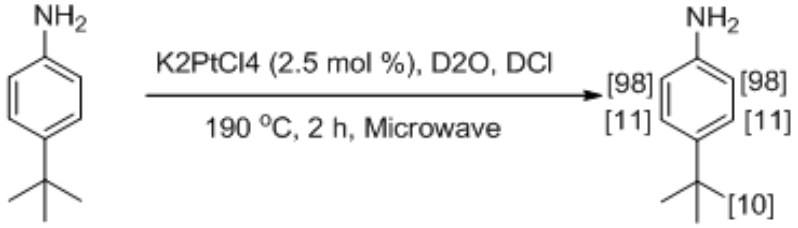
4-*tert*-Butylaniline was chosen as an ideal substrate because it contained a larger alkyl group, an alternative substitution pattern to establish the influence of a*ortho*-steric effect on the metal-catalyzed process, and the absence of a hydrogen atom at C-1' to examine the H-migration and side chain incorporation of D. A solution of 4-*tert*-

butylaniline was added to a stirred mixture of the Pt-catalyst and DCl in D_2O in a Pyrex tube and irradiated at 190 °C for 2 hours as before. Thioglycolic acid was added to the mixture after cooling to remove platinum contamination. This method liberated the 4-*tert*-butylaniline from the catalyst to give the *d_2*-4-*tert*-butylaniline following work up, for analysis by ^{1}H-NMR spectroscopy and mass spectrometry. ^{1}H-NMR spectroscopic analysis of the crude product was quantified by addition of 1-4-dioxane (50 mol%) as an external standard. In this analysis, the peaks (δ = 7.13 ppm) corresponding to protons *meta* to the anilino NH group exhibited an integration of 1.79 H following the Pt-catalyzed process (Table 4.7). A simple subtraction quantified that an average of 0.21 of the 2.00 hydrogens had been exchanged for

deuterium; this corresponded with 11% deuterium incorporation. The *ortho*-steric effect was most pronounced which showed slow incorporation at C-3/5. However, the peaks corresponding to the protons at C2/C-6 (δ = 6.67 ppm) showed an integration of 0.05 H,The isolated yield for the H-D exchange reaction was 82%. The mass of the 4-*tert*-butylaniline was confirmed as the major isotopologue by mass spectrometry by the main ion at *m/z* 152 for the catalyzed reaction. It was apparent that the method had been effective for H/D exchange by giving high levels of incorporation at the activated aromatic positions, but very low incorporation into the poorly activated (*meta*) aromatic positions. Overall, the steric impact of the *tert*-butyl chain despite any electron donor properties was responsible for the low deuterium level at C-3 and C-5, as depicted in Table 4.7. Furthermore, the side chain also had very low incorporation of deuterium; the lack of a proton at C-1' hindered formation of a Pt-alkyl σ-complex. Nevertheless, H/D exchange for tert-butyl chain could be occur by shifting from D3/D5 according to scheme (4.5). To provide further evidence on an understanding of this process an alternative substrate was investigated containing a longer side chain.



Scheme 4.5.Mechanism of H/D exchange for *tert*-butyl group.



28 ***d*₂, 28**

Table 4.7.%D incorporation of 4-*tert*-butylaniline after microwave irradiation.

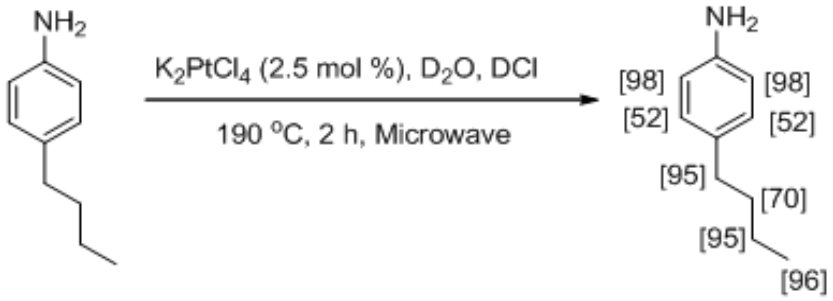
Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	Yield
%D*	98	11	….	11	98	….	10	82%

*%D Isolated yield% for the H/D exchange reaction after microwave irradiation of the substrate

4.9. 4-*n*-Butylaniline

4-*n*-Butylaniline was chosen as the next substrate to examine incorporation at 4 different positions in the alkyl side chain. This substrate would also enable incorporation to be examined at both activated and poorly activated aromatic positions.

A solution of 4-*n*-butylaniline was added to a stirred mixture of Pt-catalyst and DCl in D_2O in a Pyrex tube, and irradiated at 190 °C for 2 hours as before. Thioglycolic acid was added to the mixture after cooling to remove platinum contamination. This method liberated d_{13}-4-*n*-butylaniline, following work up for analysis by ^{1}H-NMR spectroscopy and mass spectrometry. ^{1}H-NMR spectroscopic analysis of the crude product was quantified by the addition of 1-4-dioxane (50 mol%) as an external standard. In this analysis the peaks corresponding to protons *meta* to the anilino NH (δ = 6.91ppm) exhibited an integration of 0.97 H for the Pt-catalyzed process. A simple subtraction quantified that an average of 1.03 of the 2.00 hydrogens had been exchanged for deuterium; this corresponded with 52% deuterium incorporation. However, the peak corresponding to protons at C2/C-6 (δ = 6.65 ppm) showed an integration of 0.04 H, The isolated yield for the H-D exchange reaction was 88% (Table 4.8). The mass of the d_{13}-4-*n*-butylaniline major isotopologue was confirmed by mass spectrometry by the major ion at *m/z* 160 for the catalyzed reaction. It was apparent that the catalyst had been partially effective for H/D exchange by giving high levels of incorporation at the activated aromatic positions, and reasonable incorporation into the poorly activated (*meta*) aromatic positions. However, in the side chain, incorporation of deuterium had occurred with high efficiency. Interestingly incorporation at C-1', C-3' and C-4' was highly efficient, but was less efficient at C-2'.



29 **d_{13}, 29**

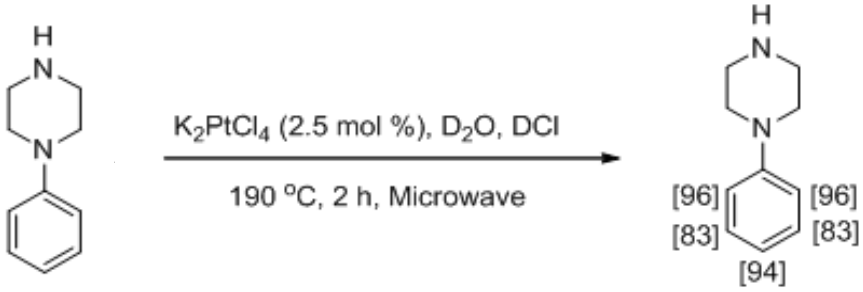
Table 4.8.%D incorporation of 4-*n*-butylanilne after microwave irradiation.

Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	Yield
%D*	98	52	….	52	98	95	70	95	96	88%

*%D Isolated yield % for the H/D exchange reaction after microwave irradiation of thesubstrate.

To provide further evidence on an understanding of this process an alternative substrate was investigated containing a differed substitution pattern.

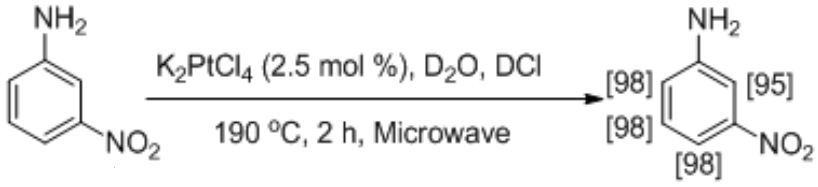
4.10. 1-Phenylpiperazine



30 **d_5, 30**

1-Phenylpiperazine was decidedly used for another specific branch of study. A solution of 1-phenylpiperazine was added to a stirred mixture of Pt-catalyst and DCl in D_2O in a Pyrex tube and irradiated at 190 °C for 2 hours as before. Thioglycolic acid was added to the mixture after cooling to remove platinum contamination. This method liberated the1-phenylpiperazine from the catalyst to give the d_5-1-phenylpiperazine following work up for analysis by ^{1}H-NMR spectroscopy and mass spectrometry. ^{1}H-NMR spectroscopic analysis of the crude product was quantified by the addition of 1-4-dioxane (50 mol%) as an external standard. In this analysis the peaks (δ = 7.22 ppm) corresponding to protons *meta* to the anilino NH exhibited an integration of 0.24 H following the Pt-catalyzed process. A simple subtraction quantified that an average of 1.76 of the 2.00 hydrogens had been exchanged for deuterium; this corresponded with 83% deuterium incorporation. However, the peak corresponding to protons at C2/C-6 (δ = 7.08 ppm) showed an integration of 0.08 H, whereas at C-4, those resonating (δ = 6.71 ppm) thus displayed an integration of 0.06 H. The isolated yield for the H-D exchange reaction was 96%. The mass of the 1-phenylpiperazine major isotopologue (d_5) was confirmed by mass spectrometry by the main ion at *m/z* 167 for the catalyzed reaction. C-5/C-3 positions demonstrated slightly lower deuterium incorporation which could be due to a change in the reactivity of the catalyst in the presence of an amine rather than aniline. In this substrate, the presence of an anilino alkyl chain (the heterocyclic ring) affected side chain incorporation, as *N*-phenylpiperazine displayed minimal incorporation in the heterocyclic $C_{(sp3)}$-H bonds.

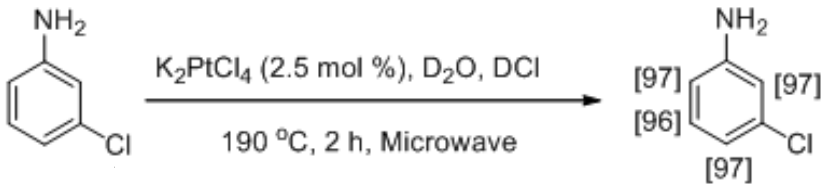
4.11. 3-Nitroaniline



31 ***d*$_4$, 31**

The use of 3-nitroaniline was investigated, as a substrate bearing an electron-withdrawing group to review alternative electronic effects. A solution of 3-nitroaniline was added to a stirred mixture of Pt-catalyst and DCl in D_2O in a Pyrex tube and irradiated at 190 ° for 2 hours as before. Thioglycolic acid was added to the mixture after cooling to remove platinum contamination. This method liberated the 3-nitroaniline to give the *d*$_4$-3-nitroaniline following work up for analysis by ^{1}H-NMR spectroscopy and mass spectrometry.^{1}H-NMR spectroscopic analysis of the crude product was quantified by the addition of 1-4-dioxane (50 mol%) as an external standard. In this analysis the peak (δ = 7.48 ppm) corresponding to protons *meta* to amide NH exhibited an integration of 0.02 H for the Pt-catalyzed process. A simple subtraction quantified that an average of 0.98 of the 1.00 hydrogens had been exchanged for deuterium, this corresponded with 98% deuterium incorporation. However, the peak corresponding to protons at C-6 (δ = 6.99 ppm) showed an integration of 0.05 H, whereas at C-4, those resonating (δ = 7.42 ppm) displayed an integration of 0.08 H. The isolated yield for the H-D exchange reaction was (92%). The mass of the *d*$_4$-3-nitroaniline major isotopologue was confirmed by mass spectrometry by the main ion at *m/z* 142 for the catalyzed reaction. It was apparent that the catalyst had been effective for H/D exchange by give high levels of incorporation at all positions. To provide further evidence on an understanding of this process an alternative substrate was investigated containing electron-withdrawing group.

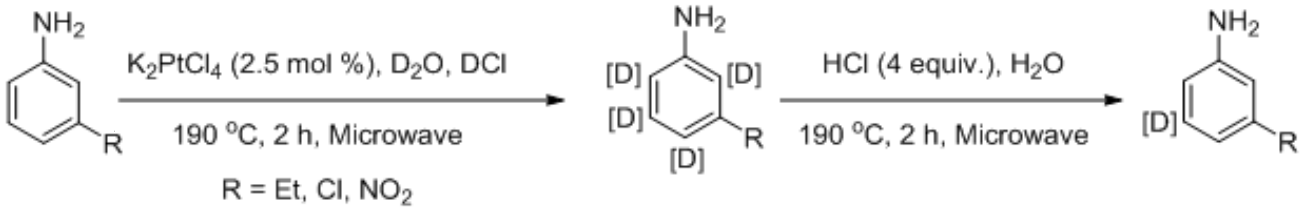
4.12. 3-Chloroaniline



32 ***d*$_4$, 32**

The considerable use of 3-chloroaniline was necessitated, as an electron-withdrawing group, for more study and investigation. A solution of 3-chloroaniline was added to a stirred mixture of Pt-catalyst and DCl in D_2O in a Pyrex tube and irradiated at 190 °C for 2 hours as before. Thioglycolic acid was added to the mixture after cooling to remove platinum contamination. This method liberated the 3-chloroaniline from the catalyst to give the *d*$_4$-3-chloroaniline following work up for analysis by ^{1}H-NMR spectroscopy and mass spectrometry.^{1}H-NMR spectroscopic analysis of the crude product was quantified by the addition of 1-4-dioxane (50 mol%) as an external standard. In this analysis the peak (δ = 7.01 ppm) corresponding to the proton *meta* to the anilino group exhibited an integration of 0.04 H for the Pt-catalyzed process. A simple subtraction quantified that an average of 0.96 of the 1.00 hydrogens had been exchanged for deuterium; this corresponded with 96% deuterium incorporation. However, the peaks corresponding to protons at C-6 (δ = 6.69 ppm) showed an integration of 0.03 H, whereas at C-4, those resonating (δ = 6.60 ppm) gave an integration of 0.03 H. The isolated yield for the H-D exchange reaction was 96%. The mass of the *d*$_4$-3-chloroaniline major isotopologue was confirmed by mass spectrometry by the main ion at *m/z* 131 for the catalyzed reaction. It was apparent that the catalyst had been effective for H/D exchange by giving high levels of incorporation at all positions.

4.13. Synthesis of *meta*-deuterated anilines

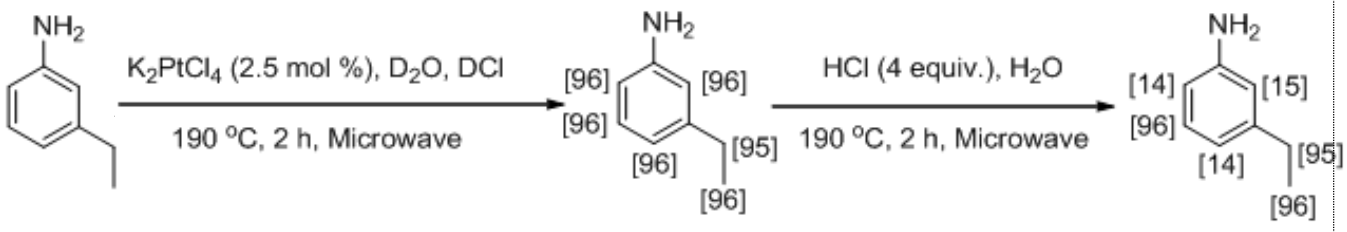


The Pt-catalyzed process had provided a means for deuteration at multiple aromatic positions of a series of substituted anilines. However, it would be a useful extension of this methodology if the process could be extended to provide anilines bearing D incorporation at only the unactivated *meta*positions, to take full advantage of the metal-catalyzed process and provide a new method for the preparation of *meta* functionalized anilines. It was felt this could be achieved if the product of the Pt-mediated process was resubmitted to acid-mediated deuterio-protio exchange under microwave-assisted conditions.

4.13.1. Reaction of d_9-3-ethylaniline

D_9-3-ethylaniline (from 4.4.1) was chosen as an ideal substrate because it contained a high level of D incorporation at the *meta* position. HCl (32%) (4 equiv.)and H_2O (5 mL) were added to d_9-3-ethylaniline. The mixture was irradiated at 190 °C for 2 hours as before; then the solution was neutralized by adding NaOH (1M, 10 mL) and extracted with DCM to give d_6-3-ethylaniline which was analyzed using ^{1}H-NMR spectroscopy. ^{1}H-NMR spectroscopic analysis of the crude product was quantified by the addition of 1,4-dioxane (50 mol%) as an external standard. In this analysis the peak corresponding to proton *meta* to the anilino NH_2 at C-5 (δ = 7.08 ppm) exhibited an integration of 0.04 H. A simple subtraction quantified that 96% deuterium incorporation had been maintained at this position throughout the acid-mediated deuterio-protio exchange reaction. However, the peaks corresponding to protons at C-2/C-6 (δ = 6.61-6.54ppm) showed an integration of 0.86 and 0.85 H, whereas those at C-4 (δ = 6.52 ppm) displayed an integration of 0.79 H. The isolated yield for the H-D exchange reaction was 87% (entry 2, Table 4.9). The mass of the d_6-3-ethylaniline as the major isotopologue was confirmed by mass spectrometry, which showed the main ion at *m/z* 127. In the side chain, the incorporation of deuterium was maintained at

high levels and was unaffected by the acid-mediated deuterio-protio exchange reaction.



24 ***d*$_6$, 24**

Table 4.9.%D incorporation of 3-ethylaniline after microwave irradiation in two steps.

Entry	Position	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	Yield
1	%D*	96	….	96	96	96	95	96	87%
2	%D¥	15	….	21	96	14	95	96	89%

*%D incorporation at respective positions following H/D exchange reaction 4.4.1 after microwave irradiation.

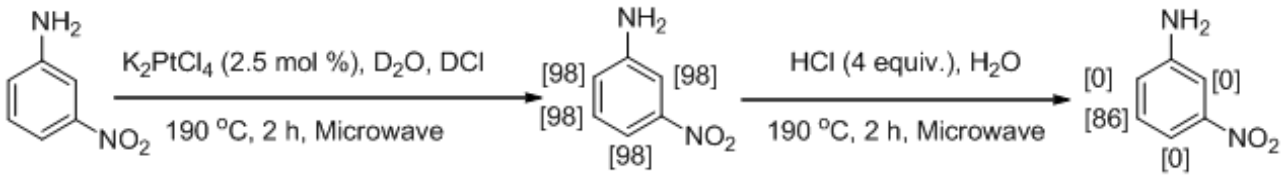
¥%D incorporation at respective positions following D/H exchange reaction after microwave irradiation of d_9-3-ethylaniline from 4.4.1 with HCl and H_2O.

To provide further evidence on an understanding of this process an alternative substrate was examined to obtain substrate selectively in *meta* position with high deuteration.

4.13.2. Reaction of d_4-3-nitroaniline

D_4-3-nitroaniline was chosen as the ideal next substrate of study because it contained a high level of D incorporation at the *meta* position but significantly different electronic properties. HCl (32%) (4 equiv.), in H_2O (5 mL) was added to the deuterated product of 4.10, d_4-3-nitroaniline, and the mixture was irradiated at 190 °C for 2 hours as before but in the absence of the Pt catalyst. The solution was neutralized by the addition of NaOH (1M, 10 mL) and extracted to give d_1-3-nitroaniline following work up for analysis by ^{1}H-NMR spectroscopy. ^{1}H-NMR spectroscopic analysis of the crude product was quantified by the addition of 1,4-dioxane (50 mol%) as an external

standard. In this analysis the peak corresponding to the proton *meta* to the anilino NH_2 group at C-5 (δ = 7.26 ppm) exhibited an integration of 0.14 H; this corresponded with 86% deuterium incorporation. However, the peaks corresponding to protons at all remaining positions integrated to 1.00 H in each case. The yield for the D-H exchange reaction was good (80%) (entry 2, Table 4.10). The mass of d_1-3-nitroaniline as the major isotopologue was confirmed by mass spectrometry which showed the main ion at *m/z* 139. To provide further evidence on an understanding of this process an alternative substrate was used to obtain substrate selectively in *meta* position with high deuteration.



31 ***d₁*, 31**

Table 4.10.%D incorporation of 3-nitroaniline after microwave irradiation in two steps.

Entry	Position	C-2	C-3	C-4	C-5	C-6	Yield
1	%D*	95	….	98	98	98	92%
2	%D¥	0	….	0	86	0	80%

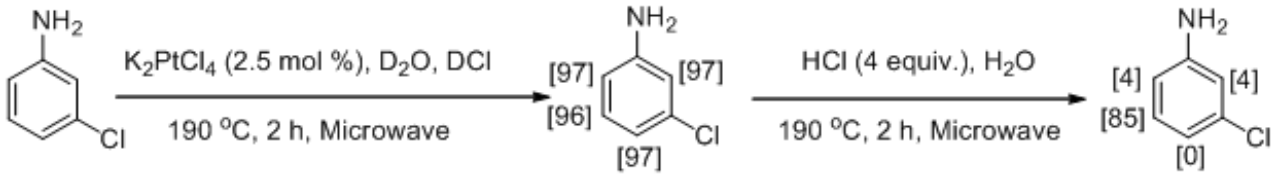
*%D incorporation at respective positions following H/D exchange reaction 4.10 after microwave irradiation

¥%D incorporation at respective positions following D/H exchange reaction after microwave irradiation of d_4-3-chloroaniline from 4.10 with HCl and H_2O.

4.13.3. Reaction of d_4-3-chloroaniline

D_4-3-chloroaniline was chosen as the ideal next substrate of study because it contained high D incorporation at the *meta* position but altered electronic properties, being more electron-poor but with an *ortho* and *para* directing 3-substituent. HCl (32%) (4 equiv.)and H_2O (5 mL) were added to d_4-3-chloroaniline and the mixture was irradiated at 190 °C for 2 hours as before. The solution was neutralized by the addition of NaOH (1M, 10 mL) and extracted to give the d_1-3-chloroaniline. ^{1}H-NMR spectroscopic analysis of the crude product was quantified by addition of 1,4-dioxane (50 mol%) as an external standard. In this analysis the peak corresponding to proton

meta to the anilino NH_2 at C-5 (δ = 7.00 ppm) exhibited an integration of 0.15 H. This indicated that 85% deuterium incorporation had been maintained at this position, a slightly lower percentage than before. However, the peak corresponding to protons at C2/C-6 (δ = 6.57 ppm) showed an integration of 1.92 H, whereas those at C-4 (δ = 6.67 ppm) displayed an integration of 1.00 H. The isolated yield for the D-H exchange reaction was 92% (entry 2, Table 4.11). The mass of d_1-3-chloroaniline was confirmed as the major isotopologue by mass spectrometry, showing the main ion at *m/z* 128.



32 ***d*₁, 32**

Table 4.11.%D incorporation of 3-chloroaniline after microwave irradiation in two steps.

Entry	Position	C-2	C-3	C-4	C-5	C-6	Yield
1	%D*	97	….	97	96	97	96%
2	%D¥	4	….	0	85	4	92%

*%D incorporation at respective positions following H/D exchange reaction 4.9 after microwave irradiation;

¥%D incorporation at respective positions following D/H exchange reaction after microwave irradiation of d_4-3-chloroaniline from 4.9 with HCl and H_2O.

4.14. Conclusions

In summary, the study demonstrated that the deuteration of a range of aniline derivatives was accelerated under microwave irradiation. The process gave good yields and predictable selectivities, providing a method for multiple deuteration of alkyl and aryl groups, even at poorly activated positions, using Pt-catalyzed methods in the absence of an *ortho*-steric effect.

Based upon bibliographic and experimental information, mechanisms for H/D aromatic and alkyl exchange have been considered and proposed. These dynamic equilibrium processes involving alkylaniline derivatives are affected by steric obstacles. It is proposed that an oxidation equilibrium between Pt (IV) / Pt (II) are the key species in

the metal-catalyzed process; formation of the π-complex was likewise an important part of such a procedure. The study also depicted that the H/D exchange of aniline derivatives in the absence of a metal catalyst proceeded as anticipated and was able to back-exchange at activated aromatic positions to give *meta*-deuterated targets. The H/D exchange reaction using a metal catalyst provided the means to incorporate deuterium at all aromatic positions. Furthermore, metal catalysis was able to facilitate exchange in alkyl side chains with high efficiency, provided that there was no quaternary centre. A proposed allyl complex was considered as intermediate and precursor to hydride and deuteride migration to give deuterated alkyl chains. The procedures discussed above were well-suited to the preparation of deuterated aniline derivatives but could find application to a wide range of substrates. Expanding the substrate scope will be the focus of subsequent chapters.

Chapter 5

H/D exchange of aminopyridine and aminopyridine derivatives using homogeneous catalyst:

5.1. Introduction

In this chapter, the focus will be on studying heterocyclic substrates in H/D exchange reactions. Previous studies established effective methods for exchange in electron-rich aniline systems. It was considered appropriate to validate these previous methods with a new set of substrates with significantly different electronic properties. As a result, the use of aminopyridines would seem to be particularly relevant for the aims of this study.

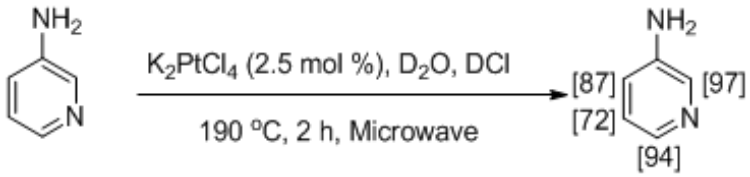
The electronic and steric parameters could affect the reactivity of every specific substrate differently. In addition, the range of H/D procedures already investigated and explained in previous chapters will be applied here. As a consequence, in some cases, appropriate reactions for measuring the extent of H/D exchange will be specifically introduced.

5.2. 3-Aminopyridine

An acceptable process had been established for H/D exchange of aniline and aniline derivatives; however further study was required, necessitating investigation of a series of different substrates in the process. Aminopyridine derivatives were chosen as they appear to have different electronic characteristics, and yet in heterocyclic chemistry they are valuable building blocks. Pyridine derivatives are considered as electron-poor aromatic compounds, in spite of the introduction of amino group as an electron-donating group. The Pt-catalyzed H-D exchange of 3-aminopyridine was first investigated under microwave irradiation as a specimen of a substituted methylpyridine. It was anticipated that metal-mediated exchange should be reasonably resilient to electronic properties but any acid-mediated exchange might not be. To investigate this hypothesis, a solution of 3-aminopyridine was added to a stirred solution of Pt catalyst and DCl in D_2O in a Pyrex tube and the mixture was then irradiated at 190 °C in a sealed vessel for 2 hours, as done under previous conditions. 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 adding NaOH

and extracted with CH_2Cl_2 to give the *d*$_4$-3-aminopyridine which was then analyzed by using ^{1}H-NMR spectroscopy and mass spectrometry^{1}H-NMR spectroscopic analysis of the crude product was quantified by addition of 1-4-dioxane (50 mol%) as an external standard.

In this analysis, the peak corresponding to the proton at position 2 (δ = 8.05 ppm) appeared with an integration of 0.03 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 proton at position 6 (δ = 7.97 ppm) depicted an integration of 0.06 H, whereas the peak corresponding to the protons at position 5 (δ = 6.94 ppm) displayed an integration of 0.28 H. The isolated yield for the H-D exchange reaction was 79% (Table 5.1). The mass of the product was confirmed as the major isotopologue by mass spectrometric analysis which showed the major ion at *m/z* 98 for the catalyzed reaction. As demonstrated in Chapter 4, Pt-catalyzed aromatic C-H activation could be facilitated by reversible σ-metal complex formation. So, a similar procedure has been here suggested for the heterocyclic context (Scheme 5.1). All this evidence depicts efficient ring H/D exchange. Positions 2 / 6 showed a high level of D incorporation, whereas position 5 was exchanged to a lower extent than another positions, perhaps due to being closer to the amino group. Interestingly D incorporation at C-5 *meta* to the amino group was relatively high and this could be indicative of the efficiency of the metal-mediated process and the fact it is relatively insensitive to electronic effects. The study of an alternative substrate would provide further evidence for and understanding of this process.

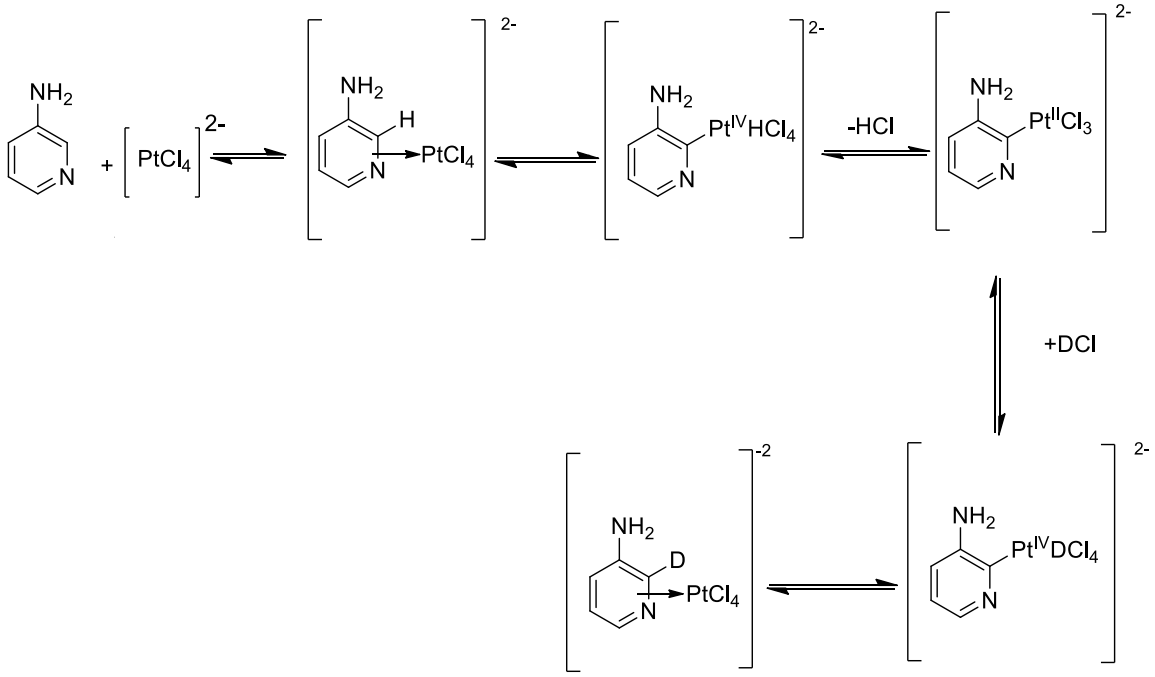


33 ***d*$_4$, 33**

Table 5.1. %D incorporation of 3-aminopyridine after microwave irradiation.

Position	C-2	C-3	C-4	C-5	C-6	Yield
%D*	97	….	87	72	94	79%

*%D Isolated yield % for the H/D exchange reaction after microwave irradiation of the substrate**.**

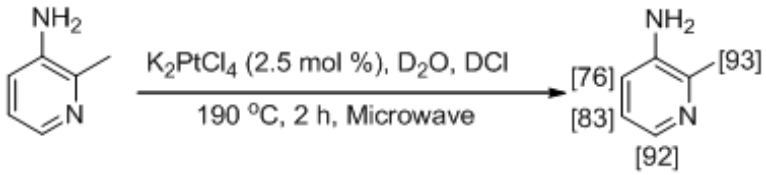


Scheme 5.1.Mechanism of aromatic H/D exchange on aminopyridine ring.

5.3. 3-Amino-2-methylpyridine

3-Amino-2-methylprydine was chosen as an alternative to 3-aminopyridine because it contained an alkyl group to improve lipophilicty and examine incorporation into an alkyl side chain. A solution of 4-amino-3-methylpyridine was added to a stirred solution of Pt catalyst and DCl in D_2O in a Pyrex tube and irradiated at 190 °C for 2 hours, as done under previous conditions. Work up using thioglycolic acid as before gave d_6-4-amino-3-methylpyridine for analysis by ^{1}H-NMR spectroscopy and mass spectrometry. ^{1}H-NMR spectroscopic analysis of the crude product was quantified by addition of 1-4-dioxane (50 mol%) as an external standard. In this analysis, the peak corresponding to the proton at position 6 (δ = 7.93 ppm) appeared to have an integration of 0.08 H. Moreover, a simple subtraction quantified that an average of 0.92 of the 1 hydrogen had been exchanged for deuterium; this corresponded to 92% deuterium incorporation. Similar analysis of the peak corresponding to the proton at position 5 (δ = 6.93 ppm) showed an integration of 0.24 H. The peak corresponding to the protons at position 4

(δ = 6.89 ppm) displayed an integration of 0.17 H. Furthermore, the peak corresponding to the methyl protons at δ = 2.36 ppm exhibited an integration of 0.20 H. The isolated yield for the H-D exchange reaction was good (83%) (Table 5.2). The mass of the product was confirmed as the major isotopologue by analysis done through mass spectrometry with the major ion at *m/z* 114 for the catalyzed reaction consistent with high levels of exchange at 2-Me. As demonstrate in previous Chapter, the Pt-catalyst could facilitate C_{sp3}-H activation by reversible conversion. A similar procedure has been suggested here in this heterocyclic context (Scheme 5.2) and clearly had proceeded with high efficiency. All the evidence illustrated excellent ring and alkyl H/D exchange. The hydrogens on positions 4 / 6 showed a high level of incorporation, unaffected by the presence of the methyl group. D incorporation at C-5 which should be promoted in electrophilic aromatic substitution by acid-mediated exchange by the presence of the methyl group, was, if anything, retarded. A further study of an alternative substrate would provide additional evidence for and understanding of this process.

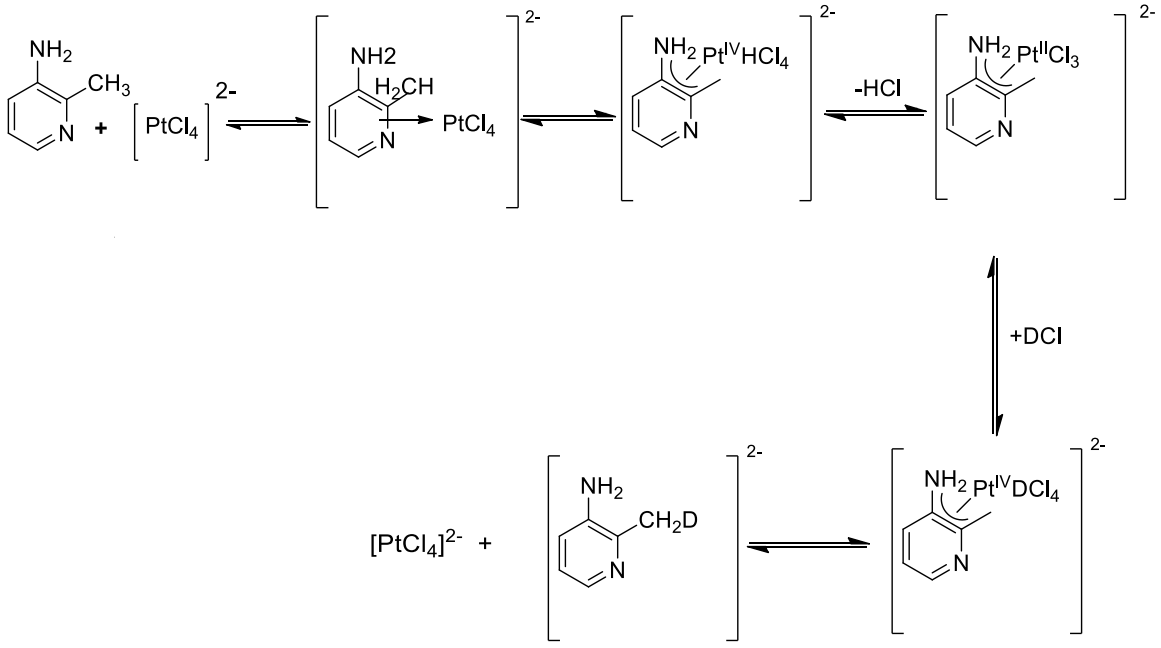


34 ***d*$_6$, 34**

Table 5.2. %D incorporation of 3-amino-2-methylpyridine after microwave irradiation

Position	C-2	C-3	C-4	C-5	C-6	C-1′	Yield
%D*	….	….	83	76	92	93	83%

*%D Isolated yield %for the H/D exchange reaction after microwave irradiation of the substrate**.**



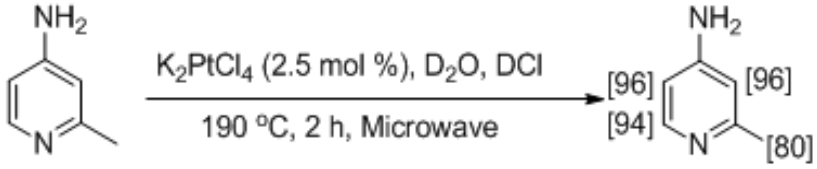
Scheme 5.2. Mechanism H/D exchange for side change in aminopyridine derivatives.

5.4. 4-Amino-2-methylpyridine

4-Amino-2-methylpyridine was chosen as an alternative substrate as it would appear different in its electronic characteristics but still contained an alkyl group to improve lipophilicty and examine incorporation into the alkyl side chain. The Pt-catalyzed H-D exchange of 4-amino-2-methylpyridine was investigated under microwave irradiation as another example of a substituted methylpyridine. A solution of 4-amino-2-methylpyridine was added to a stirred solution of Pt catalyst and DCl in D_2O in a Pyrex tube and irradiated at 190 °C for 2 hours, with thioglycolic acid work up as before, to give *d_6*-4-amino-2-methylpyridine following work up for analysis ^{1}H-NMR spectroscopy and mass spectrometry. Further derivatization was done by following the general procedure for H/D exchange; ^{1}H-NMR spectroscopic analysis of the crude product was quantified by adding 1-4-dioxane (50 mol%) as an external standard.

In this analysis, the peak corresponding to protons at position 3 (δ = 6.36 ppm) exhibited an integration of 0.04 H. A simple subtraction quantified that this corresponded to 96% deuterium incorporation. The same analysis of the peak corresponding to protons at position 6 (δ = 8.07 ppm) displayed an integration of 0.06 H; here, the peak corresponded to the protons at position 5 (δ = 6.32 ppm) displayed

an integration of 0.04 H. Furthermore, the peak corresponding to the protons at 2-Me (δ = 2.35 ppm) exhibited an integration of 0.58 H. The isolated yield for H-D exchange reaction was 82% (Table 5.3). The mass of the product was confirmed by analysis done using mass spectrometry showing the major ion at *m/z* 114 for the catalyzed reaction. All this evidence illustrated that excellent ring H/D exchange had occurred along with good exchange at 2-Me; especially high D incorporation had occurred at C3 and C-5 positions as a consequence of changing the position of the amino group. However, interestingly, D incorporation at C-6 had also increased. The study of an alternative substrate would provide further evidence for and understanding of this process.



35 ***d*$_6$, 35**

Table 5.3. %D incorporation of 4-amino-2-methylpyridine after microwave irradiation

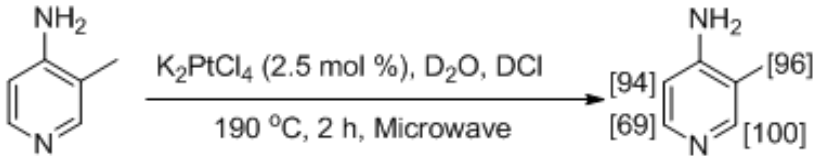
Position	C-2	C-3	C-4	C-5	C-6	C-1′	Yield
%D*	….	96	….	96	94	80	82%

*%D Isolated yield % for the H/D exchange reaction after microwave irradiation of the substrate

5.5. 4-Amino-3-methylpyridine

Here 4-amino-3-methylpyridine was chosen as alternative substitution pattern to gain further understanding into the high levels of D incorporation observed in the previous study, as well as establish the influence of streric effects on the metal-catalyzed H-D process. A solution of 4-amino-3-methylpyridine was added to a stirred solution of Pt catalyst and DCl in D_2O in a Pyrex tube and irradiated at 190 °C for 2 hours as before to give *d*$_6$-4-amino-3-methylpyridine following thioglycolic acid work up, for analysis by ^{1}H-NMR spectroscopy and mass spectrometry. Further derivatization was done following the general H/D exchange procedure; ^{1}H-NMR spectroscopic analysis of the crude product was quantified by adding 1-4-dioxane (50 mol%) as an external standard. In this analysis the peak corresponding to the proton at position 2 (δ = 8.05 ppm) appeared as an integration of 0.00 H; this corresponded to >98% (100%)

deuterium incorporation. The same analysis of the peak corresponding to the proton at position 6 (δ = 7.87 ppm) showed an integration of 0.36 H. The peak corresponding to the protons at position 5 (δ = 6.56 ppm) displayed an integration of 0.06 H. Furthermore, the peak corresponding to protons at 2-Me (δ = 2.05 ppm) exhibited an integration of 0.11 H. The isolated yield for H-D exchange reaction was 92% (Table 5.4). The mass of the d_6-4-amino-3-methylpyridine major isotopologue was confirmed by analysis using mass spectrometry by the major ion at *m/z* 114 for this catalyzed reaction. All this evidence illustrated that excellent ring H/D exchange has been enabled along with high H/D exchange at 3-Me.The hydrogens on positions C-2 and 5 showed high levels of D incorporation, whereas position 6 was exchanged to a lower extent than another positions, due to steric effect. The study of an alternative substrate would provide further evidence for and understanding of this process.



36 ***d*$_6$, 36**

Table 5.4.%D incorporation of 4-amino-3-methylpyridine after microwave irradiation.

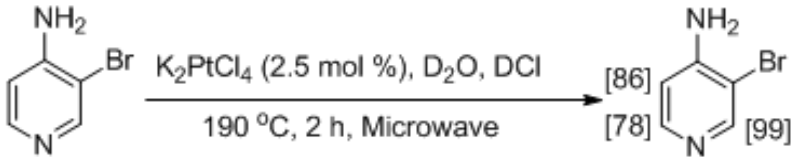
Position	C-2	C-3	C-4	C-5	C-6	C-1′	Yield
%D*	100	….	….	94	64	96	92%

*%D Isolated yield % for the H/D exchange reaction after microwave irradiation of the substrate**.**

5.6. 4-Amino-3-bromopyridine

4-amino-3-bromopyridine was chosen as this substrate possesses distinct and different electronic characteristics, as a substitute for methylpyridine to investigate of Pt-catalyzed H-D exchange using microwave irradiation. A solution of 4-amino-3-bromopyridine was added to a stirred solution of the Pt catalyst and DCl in D_2O in a Pyrex tube and irradiated at 190 °C for 2 hours as before. Thioglycolic acid work up gave d_3-4-amino-3-bromopyridine for analysis using ^{1}H-NMR spectroscopy and mass spectrometry. ^{1}H-NMR spectroscopic analysis of the crude product was quantified by

adding 1-4-dioxane (50 mol%) as an external standard. In this analysis, the peak corresponding to the proton at position 2 (δ = 8.20 ppm) appeared with an integration of 0.01 H. A simple subtraction quantified that an average of 0.99 of 1 hydrogen had been exchanged for deuterium; this corresponded to >98% (99%) deuterium incorporation. The same analysis of the peak corresponding to the proton at position 6 (δ = 7.93 ppm) showed an integration of 0.22 H. The peak corresponding to the protons at position 5 (δ = 6.71 ppm) displayed an integration of 0.14 H. The isolated yield for H-D exchange reaction was 92% (Table 5.5). The mass of the product was confirmed as the major isotopologue by mass spectrometric analysis with the major ion at *m/z* 175 for the catalyzed reaction. All this evidence illustrates excellent ring H/D exchange. So the hydrogen on positions 2 was a high level incorporation, whereas position 6 was exchanged to a lower extent than another position, due to steric effect. The study of an alternative substrate would provide further evidence for and understanding of this process.



37 ***d*3, 37**

Table 5.5.%D incorporation of 4-amino-3-bromopyridine after microwave irradiation.

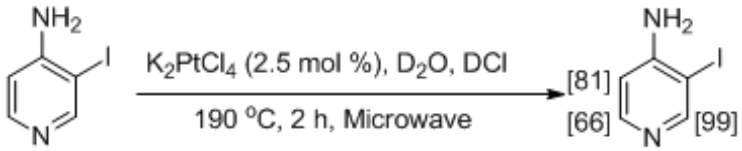
Position	C-2	C-3	C-4	C-5	C-6	Yield
%D*	99	….	….	86	78	92%

*%D Isolated yield % for the H/D exchange reaction after microwave irradiation of the substrate

5.7. 4-Amino-3-iodopyridine

Here, 4-amino-3-iodopyridine was chosen for its distinct electronic characteristics. It was anticipated that it should behave in a similar fashion to the previous substrate, but reduced electronegativity and increased mesomeric donation due to the halogen should attenuate D incorporation to a small degree. A solution of 4-amino-3-iodopyridine was added to a stirred solution of Pt catalyst and DCl in D_2O in a Pyrex tube, and irradiated at 190 ° for 2 hours, as already done before under similar conditions. Thioglycolic acid was added to the mixture after cooling in a stream of

compressed air to remove platinum contamination to give d_3-4- amino-3-iodopyridine for analysis by ^{1}H-NMR spectroscopy and mass spectrometry. Thereafter, ^{1}H-NMR spectroscopic analysis of the crude product was quantified by adding 1-4-dioxane (50 mol%) as an external standard. In this analysis the peak corresponding to proton at position 2 (δ = 8.38 ppm) exhibited an integration of 0.01H, A simple subtraction quantified that an average of 0.99 of the 1 hydrogens had been exchanged for deuterium, this corresponded to >98% (99%) deuterium incorporation. The same analysis of the peak corresponding to protons at position 6 (δ = 7.93 ppm) depicted an integration of 0.34 H, The peak corresponding to the protons at position 5 (δ = 6.71 ppm) displayed an integration of 0.19 H, The isolated yield for the H-D exchange reaction was 94% (Table 5.6). The mass of the product was confirmed as the major isotopologue by mass spectrometric analysis with the major ion at *m/z* 222 for the catalyzed reaction. All this evidence illustrates excellent ring H/D exchange. So the hydrogen on positions 2 was a high level incorporation, whereas position 6 was exchanged to a lower extent than another positions, due to steric effect. The study of an alternative substrate would provide further evidence for and understanding of this process.



38 ***d*$_3$, 38**

Table 5.6. %D incorporation of 4-amino-3-iodopyridine after microwave irradiation

Position	C-2	C-3	C-4	C-5	C-6	Yield
%D*	99	….	….	81	66	94%

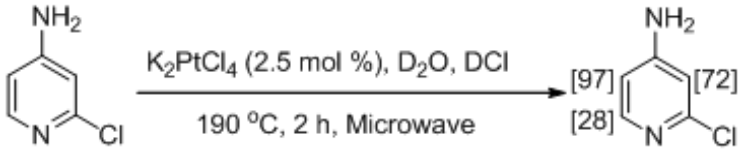
*%D Isolated yield % for the H/D exchange reaction after microwave irradiation of the substrate.

5.8. 4-Amino-2-chloropyridine

4-amino-2-chloropyridine were chosen as this substrate should exhibit very different electronic characteristics. A solution of 4-amino-2-chloropyridine was added to a stirred solution of Pt catalyst and DCl in D_2O in a Pyrex tube, and irradiated at 190 °C for 2 hours, as already done under previous conditions. Thioglycolic acid was added after cooling to give the d_2-4-amino-2-chloropyridine following work up for analysis by

^{1}H-NMR spectroscopy and mass spectrometry. Moreover, ^{1}H-NMR spectroscopic analysis of the crude product was quantified by adding 1-4-dioxane (50 mol%) as an external standard.

In this analysis the peak corresponding to proton at position 5(δ = 6.56 ppm) exhibited an integration of 0.03H. 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 protons at position 3 (δ = 6.49 ppm) showed an integration of 0.25 H. The peak corresponding to the protons at position 6 (δ = 7.75 ppm) displayed an integration of 0.72 H. The isolated yield for the H-D exchange reaction was 94% (Table 5.7). The mass of the d_2-4-amino-2-chloropyridine major isotopologue was confirmed by analysis done through mass spectrometry by the major ion at *m/z* 130 for the catalyzed reaction. The above evidence illustrates excellent H/D exchange at position 5 position, whereas a significant inactivated for two groups was observed giving a level of deuterium incorporation that was much lower 28% at position 6 than other position. The study of an alternative substrate would provide further evidence for and understanding of this process.



39 ***d*$_3$, 39**

Table 5.7.%D incorporation of 4-amino-2-chloropyridine after microwave irradiation.

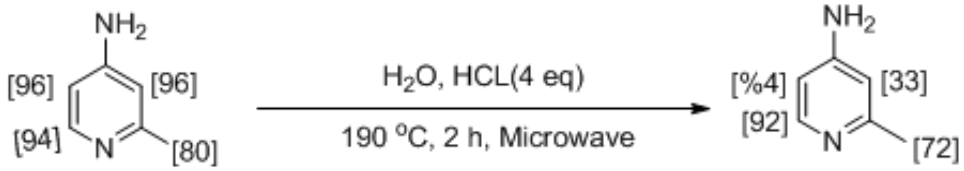
Position	C-2	C-3	C-4	C-5	C-6	Yield
%D*	….	75	….	97	28	94%

*%D Isolated yield % for the H/D exchange reaction after microwave irradiation of the substrate.

5.9. Synthesis of *meta*-deuterated aminopyridine

D_6-4-amino-2-methylpyridine was chosen as an ideal substrate because it contains high level of incorporation at all positions.

HCl (32%) (4 eq.) And H_2O (5 mL) were added to *d_6*-4-amino-2-methylpyridine. The mixture was irradiated at 190 °C in a sealed vessel for 2 hours. Then the solution was neutralized by adding NaOH (1M, 10 mL) and extracted with DCM to give *d_4*-4-amino-2-methylpyridine which was analyzed by ^{1}H-NMR spectroscopy and mass spectrometry. ^{1}H-NMR spectroscopic analysis of the crude product was quantified by addition of 1-4-dioxane (50 mol%) as an external standard. This analysis depicted that the peak corresponding to proton at position 5 (δ = 6.41 ppm) presented an integration of 0.96 H. A simple subtraction quantified that an average of 0.04 of the 1.00 hydrogens had been exchanged for deuterium (Table 5.8, entry 1); this corresponded to 4% deuterium incorporation. Moreover, the peak corresponding to proton at position 3 (δ = 6.37 ppm) showed an integration of 0.67 H, whereas at position 6 those resonating at δ = 7.82 ppm gave an integration of 0.08 H. The isolated yield for the H-D exchange reaction was 70% (Table 5.8). The mass of *d_4*-4-amino-2-methylpyridine was confirmed as the major isotopologue by mass spectrometry and the main ion at *m/z* 112. In the side chain, incorporation of deuterium had been maintained throughout the protio exchange process. This would imply that a conventional electrophile-driven acid-mediated process was probably not responsible for H/D exchange in the methyl group but that this was indeed a metal-mediated C_{sp^3}-H activation process.



35 ***d*$_4$, 35**

Table 5.8. %D incorporation of *d*$_6$-4-amino-2-methylpyridine after microwave irradiation by two steps

Entry	Position	C-2	C-3	C-4	C-5	C-6	C-1′	Yield
1	%D*	….	96	….	96	94	80	82%
2	%D¥	….	33	….	4	92	72	70%

*%D Isolated yield % for the H/D exchange reaction after microwave irradiation of the substrate.

¥%D Isolated yield % for the H/D exchange reaction after microwave irradiation of the *d*$_6$-4-amino-2-methylpyridine, with HCl and H_2O

5-10. Conclusion

The incorporation of D into aminopyridines under microwave irradiation proceeded for the most part in high efficiency for these platinum-catalyzed deuteration experiments. Good selectivity for aliphatic and certain aromatic C-H positions was observed depending upon the substrate. Moreover, according to previous studies, a reversal in the reaction without catalyst demonstrated that aminopyridine compounds undergo rapid H/D exchange just at the α-position. Furthermore, aminopyridine derivatives did show high levels of H\D exchange using a homogeneous Pt catalyst at all positions. The effect of halogen substituents did vary with position by way of a halogen at position 3 gave high efficiency and regioselectivity for position 2, whereas a 2-chloride did exchange very slowly at position 6 perhaps as a consequence of its reduced basicity. Interestingly, the 3-iodide exhibited relatively high D incorporation at both α-positions similar to the 3-bromide. It was noted that alkyl groups exhibited high levels of H/D exchange in the side-chain apparently as a consequence of a metal-mediated mechanism. However, in 4-amino-3-methylpyridne was slightly lower H/D exchange at position 5, presumably as a consequence of steric effects.

Chapter 6

Experimental

6.1 General procedure

All reagents were commercially available and were used without further purification. Analytical thin layer chromatography was performed using aluminium-backed plates coated with Merck Kieselgel 60 GF254 that were visualized under UV light (at 254 and/or 360 nm). Microwave irradiation experiments were carried out using a self-tunable CEM Discover focused monomodal microwave synthesizer at the given temperature, measured using the instrument's in-built IR sensor, by varying the irradiation power (initial power given in parentheses). a Perkin–Elmer 1600 series FTIR spectrometer was used to record the Infra-red (IR) spectra in the range 4000-600 cm-1 using an ATR probe and thin films between NaCl plates for liquid samples or as a nujol mull and are reported in cm-1. While a Varian VNMRS instrument operating at 400 or 500 MHz was used to measure the nuclear magnetic resonance (NMR) spectra, the measurements were carried out in $CDCl_3$ 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 obtained using electron ionization (EI) Fisons Instruments VG Autospec. 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.

6.1.1General procedure for metal-free H/D exchange

D_2O (5 mL) was added to the aniline derivative.in a Pyrex tube. The vessel was sealed and then irradiated at 190 ºC for 2 h using a CEM Explorer microwave synthesizer (maximum pressure 150 psi) by modulation of the initial microwave power (300 W). The mixture was cooled in a stream of compressed air and then extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated *in vacuo*.

6.1.2General procedure for deuteration using Pd/C catalyst

A solution of the aniline derivative (1 equiv.) in D_2O (1 mL) was added to a stirred suspension of 10% Pd/C (0.9 equiv) in D_2O (3 mL). The mixture was irradiated at 190 °C (initial power 300 W; maximum pressure 150 psi) in a sealed vessel for 2 hours, then cooled in a stream of compressed air and filtered through Celite. The filtered solid

was washed with HCl (1M, 10 mL). The filtrates were combined, neutralized by the addition of aqueous NaOH solution (1M, 10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford the product.

6.1.3 General procedure for acetylation

Acetyl chloride (1.1 equiv) was added to a stirred solution of the aniline derivative and NEt_3 (2.2 equiv) in CH_2Cl_2 (3 mL) at 0 ºC under N_2. The mixture was warmed to room temperature and stirred for 30 min. Hydrochloric acid (1M; 10 mL) was added and then the organic layer was further washed with hydrochloric acid, dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by column chromatography on silica, eluting with petroleum ether-ethyl acetate (2:1) gave the acetylated product.

6.1.4General procedure for deuteration using K_2PtCl_4

Different substituted derivatives of aniline and aminopyridine (1 equiv.) in D_2O (1 mL) were added to a stirred solution of K_2PtCl_4 (2.5 mol%) and DCl (35%) (4 equiv.)in D_2O (3 mL) .The mixture was irradiated at 190 °C (initial power 300 W; maximum pressure 150 psi) in a sealed vessel for 2 hours. Then the solution was neutralized by the addition of aqueous NaOH solution (1M, 10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). . The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated *invacuo* to afford the product.

6.1.5 General procedure for Synthesis of *meta*-deuterated

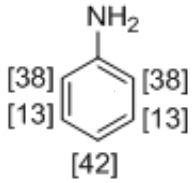
A solution of HCl (32%) (4 equiv.)in H_2O (5 mL) was added to a deuterated derivative of aniline or aminopyridine. The mixture was irradiated at 190 °C (initial power 300 W; maximum pressure 150 psi) in a sealed vessel for 2 hours. Then the solution was neutralized by the addition of aqueous NaOH solution (1M, 10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated *in vacuo*.

6.1.6 General procedure for determination of %D incorporation by the addition of an external standard

Following general procedure for H/D exchange, ^1H NMR spectroscopic analysis of the crude product was quantified by the addition of dioxane (50 mol%) as an external standard.

6.1.1. Experimental procedures for metal-free H/D exchange

Aniline (36)

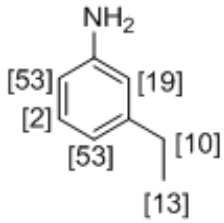


36

Aniline (300 mg, 294 µL, 3.16 mmol, 1 equiv.) was added to D_2O (5 mL) and reacted according to General Procedure 6.1.1 to give the *title compound***1** (244 mg, 79%) as a brown oil. A sample of **1** (200 mg, 2.0 mmol, 1 equiv.), acetyl chloride (154 µL, 2.28 mmol, 1.1 equiv.), NEt_3 (612 µL, 4.46 mmol, 2.2 equiv.) and CH_2Cl_2 (10 mL) were reacted according to General Procedure 6.1.3 to give an analytical sample of the acetanilide (213 mg, 81%) as a brown solid; δ_H(500 MHz; CD_3OD) *7.52 (1.23H, m), *7.30 (1.74H, s), *7.08 (0.58H, m), 2.12 (3H, s).

*Signals from multiple isotopologues

3-Ethylaniline (16)



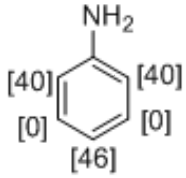
16

3-Ethylaniline (300 mg, 307 µL, 2.48 mmol, 1 equiv.) was added to D_2O (5 mL) and reacted according to General Procedure 6.1.1 to give the *title compound*d_2-3-ethylaniline (**2**) (280 mg, 87%) as a brown oil. A sample of d_2-3-ethylaniline (200 mg, 1.79 mmol, 1 equiv.), acetyl chloride (177 µL, 1.7 mmol, 1.1 equiv.), NEt_3 (725 µL, 3.38 mmol, 2.2 equiv.) and CH_2Cl_2 (10 mL) were reacted according to General Procedure 6.1.3 to give an analytical sample of d_9-*N*-(3-ethylphenyl)acetamide (256 mg, 96%) as a yellow oil; δ_H(500 MHz; CD_3OD) *7.35 (0.93H, s), *7.18 (0.98H, s), *6.91 (0.8H, s), *2.60 (1.79H, s), 2.10 (3H, s), *1.21 (2.61H, m).

*Signals from multiple isotopologues

6.1.2. Experimental procedures for H/D exchange using Pd/C catalyst

Aniline (14)

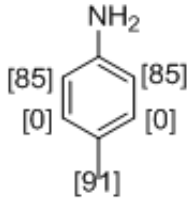


14

Aniline (300 mg, 294 µL, 3.22 mmol, 1 equiv.), was added to a stirred suspension of 10% Pd/C (30.7 mg, 2.89 mmol, 0.9 equiv), in D_2O (5 mL) and reacted according to General Procedure 6.1.2 to give the title compound (120 mg, 38%) as a brown oil. A sample of aniline **3** (110 mg, 1.12 mmol, 1 equiv.), acetyl chloride (85 µL, 1.23 mmol, 1.1 equiv), NEt_3 (337 µL, 2.46 mmol, 2.2 equiv) and CH_2Cl_2 (10 mL) were reacted according to General Procedure 6.1.3 to give an analytical sample of the acetanilide (221 mg, 84%) as a brown solid; δ_H (500 MHz; CD_3OD) *7.52 (1.19H, s), 7.30 (2.00H, s), *7.08 (0.54H, s), 2.12 (3H, s).

*Signals from multiple isotopologues

***p*-Toluidine (15)**

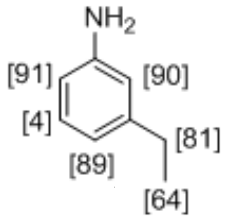


15

p-Toluidine (300 mg, 2.8 mmol, 1 equiv) was added to a stirred solution of 10% Pd/C (26.8 mg, 2.52 mmol, 0.9 equiv) in D_2O (5 mL) and reacted according to General Procedure 6.1.2 to give the *title compound*d_5-*p*-toluidine (**4**) (179 mg, 56%) as a brown oil. A sample of d_5-*p*-toluidine (**4**) (120 mg, 1.1 mmol, 1 equiv), acetyl chloride (110 µL, 1.21 mmol, 1.1 equiv), NEt_3 (499 µL, 2.41 mmol, 2.2 equiv) and CH_2Cl_2 (10 mL) were reacted according to General Procedure 6.1.3 to give an analytical sample of the acetanilide (140 mg, 83%) as a colourless solid; δ_H (500 MHz; CD_3OD) *7.39 (0.31H, s), 7.11 (2.00H, s), *2.25 (0.25 H, m), 2.10 (3H, s).

*Signals from multiple isotopologues

3-Ethylaniline (17)

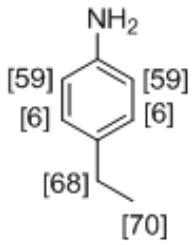


17

3-ethylaniline (300 mg, 307 µL, 2.48 mmol, 1 equiv), was added to a stirred suspension of 10% Pd/C (23.4 mg, 2 mmol, 0.9 equiv), in D_2O (5 mL) and reacted according to General Procedure 6.1.2 to gave the title compound (260 mg, 81%) as a brown oil. A sample of *d_8*-3-ethylaniline (200 mg, 1.79 mmol, 1 equiv), acetyl chloride (177 µL, 1.7 mmol, 1.1 equiv), NEt_3 (725 µL, 3.38 mmol, 2.2 equiv) and CH_2Cl_2 (10 mL) were reacted according to General Procedure 6.1.3 to gave an analytical sample of the *d_8*-3- ethylphenyl acetamide (256 mg, 96%) as a yellow oil; δ_H (500 MHz; CD_3OD), *7.38 (0.10H, s), *7.34 (0.11H, s), *7.17 (0.96H, s), *6.90 (0.09H, s), *2.55 (0.38H, s), 2.09 (3H, s) *1.16 (1.08H, s).

*Signals from multiple isotopologues

4-Ethylaniline (18)

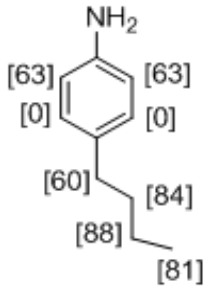


18

4-ethylaniline (300 mg, 309 µL, 2.48 mmol, 1 equiv), was added to a stirred suspension of 10% Pd/C (23.7 mg, 2.22 mmol, 0.9 equiv) in D_2O (5 mL),and reacted according to General Procedure 6.1.2 to give the title compound d9-4-ethylaniline (210 mg, 65%) as a brown oil. A sample of *d_7*-4-ethylaniline (200 mg, 1.53 mmol, 1 equiv), acetyl chloride (154 µL, 1.7 mmol, 1.1 equiv), NEt_3 (631 µL, 3.58 mmol, 2.2 equiv) and CH_2Cl_2 (10 mL) were reacted according to General Procedure 6.1.3 to give an analytical sample of the *d_7*-(4- ethylphenyl)acetamide (221 mg, 84%) as a brown solid. δ_H (500 MHz; CD_3OD) *7.42 (0.83H, s), *7.13 (1.89H, m), *2.59 (0.64 H, m), 2.10 (3H, s), *1.17 (0.89H, m).

*Signals from multiple isotopologues

4-*n*-Butylaniline (19)

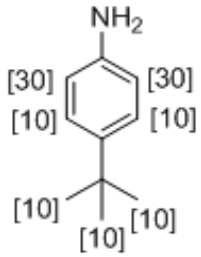


19

4-n-Butylaniline (300 mg, 317 µL, 2.0 mmol, 1 equiv) was added to a stirred suspension of 10% Pd/C (19.15 mg, 1.8 mmol, 0.9 equiv) in D_2O (5 mL) and reacted according to General Procedure 6.1.2 to give the title compound d_{11}-4-n-butylaniline (275 mg, 86%) as a brown oil. A sample of d_{11}-4-n-butylaniline (270 mg, 1.78 mmol, 1 equiv), acetyl chloride (186 µL, 1.95 mmol, 1.1 equiv), and NEt_3 (819 µL, 3.9 mmol, 2.2 equiv) and CH_2Cl_2 (10 mL) were reacted according to General Procedure 6.1.3 to give an analytical sample of the d_{11}-N-(4- n-butylphenyl)acetamide (263 mg, 73%) as a colourless solid. δ_H (500 MHz; CD_3OD) *7.41 (0.75H, s), 7.12 (2.00H, m), *2.50 (0.33H, s), 2.11 (3H, s), *1.54 (0.32H, m), *1.25 (0.80H, m), *0.91 (0.56H, m)

*Signals from multiple isotopologues

4-*tert*-Butylaniline (20)



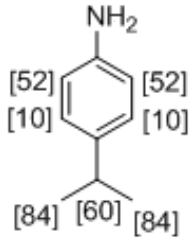
20

4-tert-Butylaniline (300 mg, 318 µL, 2.01 mmol, 1 equiv) was added to a stirred suspension of 10% Pd/C (19.19 mg, 1.8 mmol, 0.9 equiv) in D_2O (5 mL) and reacted according to General Procedure 6.1.2 to give the title compound *d*-4-tert-butylaniline (120 mg, 39%) as a brown oil. A sample of *d*-4-tert-butylaniline (120 mg, 0.8 mmol, 1 equiv), acetyl chloride (80 µL, 0.88 mmol, 1.1 equiv), NEt_3 (363 µL, 1.76 mmol, 2.2 equiv) and CH_2Cl_2 (10 mL) were reacted according to General Procedure 6.1.3 to give an analytical sample of the *d*-N-(4-tert-butylphenyl)acetamide (131 mg, 84%) as a

colourless solid. δ_H (500 MHz; CD_3OD) *7.44 (1.40H, s), *7.34 (1.80H, d), 2.11(3H, s), *1.31 (8.10H, s).

*Signals from multiple isotopologues

4-Isopropylanline (21)



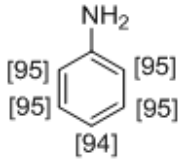
21

4-Isopropylaniline (300 mg, 303 µL, 2.22 mmol, 1 equiv), was added to a stirred suspension of 10% Pd/C (21.3 mg, 2 mmol,) in D_2O (5 mL) and reacted according to General Procedure 6.1.2 to give the title compound *d*$_9$-4-isopropylaniline (209 mg, 62%) as a brown oil A sample of *d*$_9$-4-isopropylaniline (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) and CH2Cl2 (10 mL) were reacted according to General Procedure 6.1.3 to give an analytical sample of the *d*$_9$-N-(4- isopropylphenyl)acetamide (216 mg, 76%) as a yellow solid. δ_H (500 MHz; CD_3OD) *7.42 (0.97H, m), *7.16 (1.80H, s), *2.26 (0.80H, m) 2.11 (3H, s), *1.19 (0.94H, s).

*Signals from multiple isotopologues

6.1.3. Experimental procedures for H/D exchange using K_2PtCl_4 catalyst

***d*$_5$-Aniline (22)**



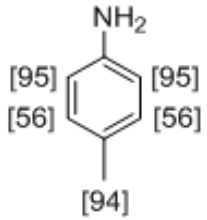
22

A solution of aniline (300 mg, 294 µL, 3.22 mmol, 1 equiv.) in D_2O (1 mL) was added to a stirred solution of K_2PtCl_4 (33.2 mg, 0.08 mmol, 2.5 mol%) and DCl (35%) (1.02 mL, 12.88 mmol, 4 equiv.)in D_2O (3 mL) and reacted according to General Procedure 6.1.4.Thioglycolic acid (17 µL, 0.25 mmol, 10 mol%) was added and the mixture was stirred for 30 min, then submitted to aqueous work up according to General Procedure

6.1.4 to give the *title compound* (273 mg, 87%) as a brown oil; IR v_{max} /cm^{-1} 3351, 3219, 2274, 2513, 1618, 1568, 1428, 1398, 1303, 1197; δ_H (500 MHz; CD_3OD) *7.09 (0.11H, s), *6.72 (0.11H, s), *6.68 (0.06H, s),**;** δc (125 MHz, CD_3OD) 147.0 (s, C-NH_2)**),** 128.4 (t,C-D, $J_{C\text{-}D}$25 Hz), 117.68 (t, C-D, $J_{C\text{-}D}$25), 115.14 (t, C-D, $J_{C\text{-}D}$25); *m/z* (EI) 98 (100, $C_6H_2D_5N^{\cdot+}$), 97 (44, $C_6H_3D_4N^{\cdot+}$), 96 (15, $C_6H_4D_3N^{\cdot+}$),

*Signals from multiple isotopologues

d_5, p- toluidine (23)

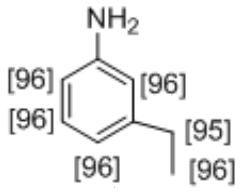


23

A solution of 4-methylaniline (300 mg, 2.8 mmol, 1 equiv.) in D_2O (1 mL) was added to a stirred solution of K_2PtCl_4 (32.3 mg, 0.078 mmol, 2.5 mol %.) and DCl (35%) (662 µL,8.04 mmol, 4 eq.) in D_2O (5 mL) and reacted according to the general procedure 6.1. 4. Thioglycolic acid (21.7 µL, 0.312 mmol, 10 mol%) was added and the mixture was stirred for 30 min, then submitted to aqueous work up according to General Procedure 6.1.4 to give the title compound (284 mg, 90%) as a yellow powder, 40 °C; (IR) vmax /cm-1 3417, 3337, 3222, 3026, 2264, 2048, 1619,1591, 1476, 1462,1441, 1295, 1256 and 1238; δ_H (500 MHz; CD_3OD) *6.90 (0.89H, s), *6.64 (0.11H, s), *2.15 (0.18H, m); δ c (150 MHz, CD_3OD) 144.0 (s, C-NH_2),128.0 (m, C-D), 126.0 (s, C-CD_3), 115.0 (m, C-D), 18.0 (m, CD_3); *m/z* (EI) 114 (38, $C_7H_2D_7N^{\cdot+}$), 113 (61, $C_7H_3D_6N^{\cdot+}$), 112 (100, $C_7H_4D_5N^{\cdot+}$), 111 (36, $C_7H_5D_4N^{\cdot+}$), 110 ($C_7H_6D_3N^{\cdot+}$).

*Signals from multiple isotopologues

***d_9*, 3-Ethylaniline (24)**

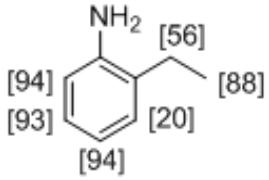


24

A solution of 3-ethylaniline (300 mg, 307 µL, 2.48 mmol, 1 equiv) was added to a stirred solution of K_2PtCl_4 (25.73mg, 0.062 mmol, 2.5 mol %.) and DCl (35%) (816 µL, 9.92 mmol, 4equiv.)in D_2O (3 mL) and reacted according to General Procedure 6.1.4. Thioglycolic acid (17 µL, 0.25 mmol, 10 mol%) was added and the mixture was stirred for 30 min, then submitted to aqueous work up according to General Procedure 6.1.4 to give the title compound (282 mg, 87 %) as a brown oil; (IR) vmax /cm-1 3442, 3351, 3221, 2934, 1616, 1564, 1399, 1301, 1257, 1053; δ_H (500 MHz; CD_3OD), *7.08 (0.04H, s), *6.62 (0.04H, s), *6.55 (0.4H, s), *6.52 (0.4H, s), *2.54 (0.12H, s), *1.17 (0.13H, s); δc(125 MHz, CD_3OD) 146.0 (s, C-NH_2), 144.0(s, C-C), 127.0 (t,C-D, $J_{C\text{-}D}$ 25), 117.0 (t, C-D, $J_{C\text{-}D}$ 25), 114.0 (t, C-D, $J_{C\text{-}D}$ 25), 112.0 (t, C-D, $J_{C\text{-}D}$ 25), 27.0(m, CD_2), 13.0 (m, CD_3); *m/z* (EI) 130 (61, $C_8H_2D_9N^{\cdot+}$), 129 (47, $C_8H_3D_8N^{\cdot+}$), 112 (69), 92 (34), 74 (15), 47 (100).

*Signals from multiple isotopologues

***d_8*, 2-Ethylaniline (25)**



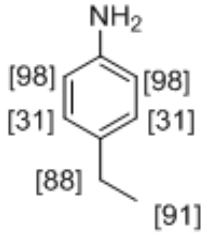
25

A solution of 2-ethylaniline (300 mg, 293 µL, 2.48 mmol, 1 equiv.) in D_2O (1 mL) was added to a stirred solution of K_2PtCl_4 (25.73mg, 0.062 mmol, 2.5 mol %.) and DCl (35%) (816 µL, 9.92 mmol, 4equiv.)in D_2O (3 mL) and reacted according to the general procedure 6.1. 4. Thioglycolic acid (17 µL, O.25mmol, 10 mol%). was added and the mixture was stirred for 30 min, then submitted to aqueous work up according to General Procedure 6.1.4 to give the title compound (280 mg, 88%) as a yellow oil; (IR) vmax /cm- 13431, 3333, 2297, 1618, 1598, 1561, 1505, 1424, 1330, and 1227;

δH (500 MHz; CD_3OD) *7.0 (0.80H, s), *6.95 (0.07H, m), *6.71(0.06H, s), *6.66 (0.06H, d), *2.50 (0.88H, m), *1.17 (0.36H, m); δc (125 MHz, CD_3OD) 144.0 (s, C-NH_2), 128.0 (s, C-C), 127.0 (s, C-H), 125.0 (m, C-D), 117.0 (m, C-D) ,115.0 (m, C-D), 23.0 (m, CD_2), 11.0 (m, CD_3); *m/z* (EI) 130 (9, $C_8H_3D_8N^{\cdot+}$), 129 (37, $C_8H_4D_7N^{\cdot+}$), 128 (22, $C_8H_5D_6N^{\cdot+}$), 112 (35), 111 (100), 110 (38).

*Signals from multiple isotopologues

d_7, 4-Ethylaniline (26)

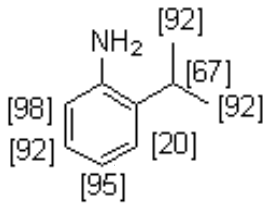


26

A solution of 4-ethylaniline (300 mg, 309 µL, 2.48 mmol, 1 equiv.) in D_2O (1 mL) was added to a stirred solution of K_2PtCl_4 (25.73mg, 0.062 mmol, 2.5 mol %.) and DCl (35%) (816 µL, 9.92 mmol, 4eq.)in D_2O (3 mL) and reacted according to the general procedure 6.1. 4. Thioglycolic acid (17 µL,0.25 mmol, 10 mol%) was added and the mixture was stirred for 30 min, then submitted to aqueous work up according to General Procedure 6.1.4 to give the title compound (289 mg, 91%)as a brown oil; (IR) vamx /cm-1 3349, 3022, 2933, 2220, 1618, 1475, 1462 and 1053; δH (500 MHz; CD_3OD) *6.94 (1.39H, s), *6.66 (0.05H, m), *2.47 (0.24 H, m), *1.12 (0.27 H, m); δc (125 MHz, CD_3OD) 144.0 (s, C-NH_2), 133.0 (s, C-C), 128.0 (m, C-D), 115.0 (m, C-D), 27.0 (m, CD_2), 14.0 (m, CD_3); *m/z* (EI) 129 (25, $C_8H_3D_8N^{\cdot+}$), 128 (52, $C_8H_4D_7N^{\cdot+}$), 127 (45, $C_8H_5D_6N^{\cdot+}$), 111 (78), 110 (100), 109 (80), 92 (22), 74 (6), 47(42).

*Signals from multiple isotopologues

d_{10}-2-Isopropylaniline (27)

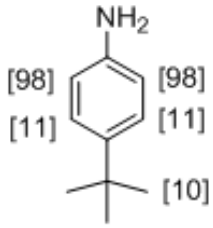


27

A solution of 2-isopropylaniline (300 mg, 314 µL, 2.22 mmol, 1 equiv.) in D_2O (1 mL) was added to a stirred solution of K_2PtCl_4 (23 mg, 0.05 mmol, 2.5 mol %.) and DCl (35%) (731 µL, 8.88 mmol, 4 eq.)in D2O (3 mL) and reacted according to the general procedure 6.1. 4. Thioglycolic acid (14 µL, 0.2 mmol, 10 mol%) was added and the mixture was stirred for 30 min, then submitted to aqueous work up according to General Procedure 6.1.4 to give the title compound (287 mg, 89%) as a brown oil; (IR) vmax /cm-13376, 2931, 3060 , 2216, 2126, 2067, 1617, 1559,1445,1303 and 1058; δ_H (500 MHz; CD_3OD) *7.08 (0.80H, s), *6.97(0.02H, s), *6.93 (0.05H, m), *6.70 (0.08H, m), *2.95 (0.33H, m), *1.19 (0.51H, d), δc (125 MHz, CD_3OD) 144.0 (s, C-NH_2), 134.0 (s, C-C), 127.0 (t, C-D, $J_{C\text{-}D}$ 23), 127.0 (s, C-H), 115.0 (t, C-D, $J_{C\text{-}D}$ 24), 115.0 (t, C-D,$J_{C\text{-}D}$ 24), 26.0 (s, C-H), 14.0 (m, CD_3); *m/z(*EI) 145 (63, $C_9H_3D_{10}N^{\cdot+}$), 144 (47, $C_9H_4D_9N^{\cdot+}$), 128 (64), 127 (100), 126 (82), 92 (42), 81 (17), 74 (12), 47, (72).

*Signals from multiple isotopologues

d_2-4-*tert*-Butylaniline (28)



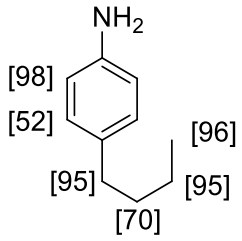
28

A solution of 4-tert-butylaniline (300 mg, 318 µL, 2.01 mmol, 1 equiv.) in D_2O (1 mL) was added to a stirred solution of K_2PtCl_4 (20.75 mg, 0.05 mmol, 2.5 mol %.) and DCl (35%) (661µL,8.04 mmol, 4 eq.)in D_2O (5 mL) and reacted according to the General procedure 6.1.4. Thioglycolic acid (20.75 µL, 0.2 mmol, 10 mol%) was added and the

mixture was stirred for 30 min, then submitted to aqueous work up according to General Procedure 6.1.4 to give the title compound (251 mg, 82%) as a brown oil; (IR) vmax /cm-1 3350, 3217, 3064, 2957, 2928, 2868, 2253, 1619, 1478, 1261, 1043 and 897; δ_H (500 MHz; CD_3OD) *7.13(1.83H, s), *6.67(0.05H, d), *1.25 (8.07H, s); δ c (150 MHz, CD_3OD) 143.0 (s, C-NH_2), 140.0 (s, C-C), 125.0 (s, C-H), 115.0 (t, C-D, J_{C-D} 23), 33.0 (m, C-CD_3), 30.0 (m, CD_3); m/z (EI) 154 (10, $C_{10}H_{10}D_5N^{\cdot+}$), 153 (18, $C_{10}H_9D_4N^{\cdot+}$), 152 (22, $C_{10}H_8D_3N^{\cdot+}$), 151 (13, $C_{10}H_7D_2N^{\cdot+}$), 138 (60), 137 (100), 136 (82), 108 (55), 96 (46).

*Signals from multiple isotopologues

d_{13}-4-*n*-Butylaniline (29)

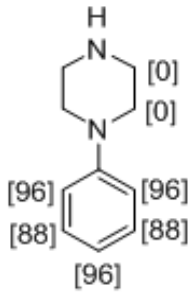


29

A solution of 4-n-butylaniline (300 mg, 317 µL, 2.01 mmol, 1 equiv.) in D_2O (1 mL) was added to a stirred solution of K_2PtCl_4 (20.75 mg, 0.05 mmol, 2.5 mol %.) and DCl (35%) (661 µL, 8.04 mmol, 4 equiv.)in D_2O (5 mL) and reacted according to the general procedure 6.1.4. Thioglycolic acid (14 µL, 0.2 mmol, 10 mol%) was added and the mixture was stirred for 30 min, then submitted to aqueous work up according to General Procedure 6.1.4 to give the title compound (285 mg, 88 %); as a brown oil; (IR) vmax /cm-1 3347, 3021, 2981, 2900, 2213, 1617, 1500, 1462, 1441, 1300 and 1256; δ_H (500 MHz; CD_3OD) *6.91(0.97H, s), *6.65(0.04H, m), *2.43(0.11H, s), *1.47 (0.60H, m), *1.26 (0.15H, m), *0.85 (0.13H, m); δc (150 MHz, CD_3OD) 144.0 (s, C-NH2), 132.0 (s, C-C), 128.0 (s, C-H), 115.0 (m, C-D), 33.0 (m, CD_2) , 24.0 (m, CD_2), 11.0 (m, CD_3); m/z (EI) 162 (4, $C_{10}H_2D_{13}N^{\cdot+}$), 161 (9, $C_{10}H_3D_{12}N^{\cdot+}$), 160 (12, $C_{10}H_4D_{11}N^{\cdot+}$), 159 (10, $C_{10}H_5D_{10}N^{\cdot+}$), 158 (5, $C_{10}H_6D_9N^{\cdot+}$), 112 (50), 111 (100), 110 (95).

*Signals from multiple isotopologues

d$_5$-Phenylpiperazine (30)

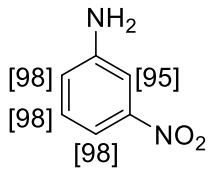


30

A solution of 1-phenylpiperazine (300 mg, 282 µL, 1.85 mmol, 1 equiv.) in D_2O (1 mL) was added to a stirred solution of K_2PtCl_4 (19.1 mg, 0.046 mmol, 2.5 mol %.) and DCl (35%) (609 µL, 7.4 mmol, 4 equiv.)in D_2O (5 mL) and reacted according to the general procedures 6.1.4. Thioglycolic acid (12 µL, 0.184 mmol, 10 mol%) was added and the mixture was stirred for 30 min, then submitted to aqueous work up according to General Procedure 6.1.4 to give the title compound (276 mg, 89%) as a yellow oil; (IR) vmax /cm-1 3290, 2946, 2821, 2272, 1567, 1429, 1396, 1326, 1254 and 1223; δ_H (500 MHz; CD_3OD) *7.22 (0.24H, s), *7.08 (0.08H, d), *6.95 (0.04H, d), *3.09 (2.99H, dt), *2.95 (4H, dt); δc (150 MHz, CD_3OD) 151.0 (s, C-NH_2), 128.0 (s, C-H), 119.0 (t, C-D, $J_{C\text{-}D}$ 24), 117.0 (t, CD, $J_{C\text{-}D}$ 24), 50.0 (s, CH_2), 45.0 (s, CH_2); m/z (EI) 167 (23, $C_{10}H_9D_5N_2^{\cdot+}$), 166 (12, $C_{10}H_9D_4N_2^{\cdot+}$), 125 (100), 124 (51), 110 (25), 109 (34), 108 (15), 82 (47), 81 (28).

*Signals from multiple isotopologues

d$_4$-3-Nitroaniline (31)



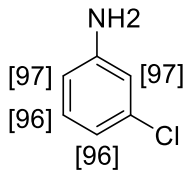
31

3-Nitroaniline (300 mg, 2.17 mmol, 1 equiv.) in D_2O (1 mL) was added to a stirred solution of K_2PtCl_4 (23 mg, 0.053 mmol, 2.5 mol %.) and DCl (35%) (714 µL, 8.68 mmol, 4 eq.)in D_2O (3 mL) and reacted according to the general procedure 6.1. 4. Thioglycolic acid (16 µL, 0.22 mmol, 10 mol%) was added and the mixture was stirred

for 30 min, then submitted to aqueous work up according to General Procedure 6.1.4 to give the title compound (282 mg, 92%) as a yellow powder, mp 117 °C; (IR) vmax /cm-1 3370, 2938, 2220, 2075, 1618, 1516, 1417, 1380, 1303, 1259, and 1172; δ_H (500 MHz; CD3OD) *7.48(0.02H, s), *7.42(0.02H, s), *7.24 (0.02H, s), *6.99 (0.02H, s); δc(125 MHz, CD_3OD) 149.0 (s, C-NO_2), 1148.0 (s, C-NH_2), 129.0 (t, C-D, $J_{C\text{-}D}$ 25), 119.0 (t, C-D, $J_{C\text{-}D}$ 24), 110.0 (t, C-D, $J_{C\text{-}D}$ 25), 107.0 (t, C-D, $J_{C\text{-}D}$ 25); m/z (EI) 142 (100, $C_6H_2D_4N_2O_2^{\cdot+}$), 112 (7), 96 (88), 92 (27), 84 (14), 69 (53), 47 (39).

*Signals from multiple isotopologues

d$_4$-3-Chloroaniline (32)

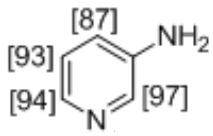


32

A solution of 3-chloroaniline (300 mg, 250 µL, 2.3 mmol, 1 equiv.) in D_2O (1 mL) was added to a stirred solution of K_2PtCl_4 (23.3 mg, 0.056 mmol, 2.5 mol %.) and DCl (35%) (750 µL, 9.2 mmol, 4 eq.)in D_2O (3 mL) and reacted according to the general procedure 6.1. 4. Thioglycolic acid (16 µL, 0.22 mmol, 10 mol%) was added and the mixture was stirred for 30 min, then submitted to aqueous work up according to General Procedure 6.1.4 to give the title compound (291 mg, 96%) as a brown oil; (IR) vmax /cm-1 3361, 3224, 2262, 1618, 1571, 1557, 1401, 1375, 1298, 1216, and 925;δ_H (500 MHz; CD_3OD), *7.01 (0.04H, s), *6.69 (0.03H, s), *6.60(0.03H, s), *6.58 (0.030H, s), δc(125 MHz, CD_3OD) 149.0 (s, C-NH_2**),** 133.0 (s, C-Cl), 129.0 (t, C-D, $J_{C\text{-}D}$24), 116.0 (t, C-D, $J_{C\text{-}D}$24), 114.0 (t, C-D, $J_{C\text{-}D}$24), 112.0 (t, C-D, $J_{C\text{-}D}$ 24); *m/z* (EI)133 (34, $C_6H_2D_4\,^{37}ClN^{\cdot+}$), 131 (100, $C_6H_3D_3\,^{37}ClN^{\cdot+}$), 130 (27, $C_6H_4D_2\,^{37}ClN^{\cdot+}$), 96 (15), 28 (26).

*Signals from multiple isotopologues

d$_4$-3-Aminopyridine (33)

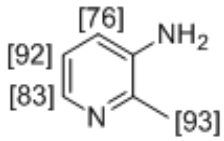


33

A solution of 3-aminopyridine (300 mg, 3.19 mmol, 1 equiv.) in D_2O (1 mL) was added to a stirred solution of K_2PtCl_4 (33 mg, 0.08 mmol, 2.5 mol%) and DCl (35%) (1 mL, 12.7 mmol, 4 equiv) in D_2O (3 mL) and reacted according to the General Procedure 6.1.4. Thioglycolic acid (30 mg, 22.6 µL, 0.32 mmol, 10 mol%) was added and the mixture was stirred for 30 min, then submitted to aqueous work up according to General Procedure 6.1.4 to give the title compound (247 mg, 79%) as a colourless powder, mp 48-52 ºC; IR vmax / cm-1 3334, 3213, 2246, 1627, 1559, 1434,1402, 1202; δ_H (500 MHz; CD_3OD) *8.05 (0.03H, s), *7.97 (0.06H, s), *7.26 (0.07H, s), *6.94 (0.13H, s); δc (125 MHz, CD_3OD), 144.0 (s, C-NH_2), 136.0 (t, C-D, $J_{C\text{-}D}$ 24), 135.0 (t, C-D, J_{CD} 23), 123.0 (t, C-D, $J_{C\text{-}D}$ 23), 121.0 (s, C-H); m/z (EI) 98 (100, $C_5H_2D_4N_2^{\cdot+}$), 97 (80, $C_5H_3D_3N_2^{\cdot+}$), 96 (28, $C_5H_4D_2N^{\cdot+}$), 95 (10, $C_5H_4D_1N_2^{\cdot+}$), 71 (23), 70 (22), 69 (15)..

*Signals from multiple isotopologues

d$_6$-3-Amino-2-methylpyridine (34)



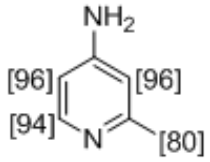
34

A solution of 3-amino-2-methylpyridine (300 mg, 2.77 mmol, 1 equiv.) in D_2O (1 mL) was added to a stirred solution of K_2PtCl_4 (28.6 mg, 0.069 mmol, 2.5 mol %.) and DCl (35%) (0.9 mL, 11.08 mmol, 4 equiv) in D_2O (3 mL) and reacted according to the general procedure 6.1.4. Thioglycolic acid (25 µL, 0.276 mmol, 10 mol%) was added and the mixture was stirred for 30 min, then submitted to aqueous work up according to General Procedure 6.1.4 to give the title compound (262 mg, 83%) as a colourless powder: mp 91-97 ºC; IR vmax /cm-1 3444, 3310, 3159, 2537, 2289, 2195, 1629, 1575,

1412, 1265, 1198, 1042 and 878; δ_H (500 MHz; CD_3OD), *7.93 (0.08H, d, J_{H-H} 5.13), *6.93 (0.17H, s), *6.89 (0.24H d, J_{H-H} 8.05), *2.36 (0.20 H, m); δc (125 MHz, CD_3OD),142.0 (s, C-NH_2), 142.0 (s, C-CD_3), 136.0 (t, C-D, J_{C-D} 27), 121.0 (t, C-D, J_{C-D} 25), 121.0 (s, C-D, J_{C-D} 24), 17.0 (m, CD_3); m/z (EI) 114 (100, $C_6H_2D_6N_2^{\cdot+}$), 113 (87, $C_6H_3D_5N_2^{\cdot+}$), 112 (60, $C_6H_4D_4N_2^{\cdot+}$), 111 (28, $C_6H_5D_3N_2^{\cdot+}$), 85 (60), 84 (77), 68 (15).

.*Signals from multiple isotopologues

d$_6$-4-Amino-2-methylpyridine (35)

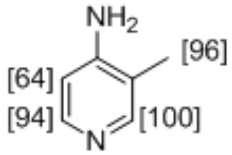


35

A solution of 4-amino-2-methylpyridine (300 mg, 2.77 mmol, 1 equiv.) in D_2O (1 mL) was added to a stirred solution of K_2PtCl_4 (28.6 mg, 0.069 mmol, 2.5 mol %.) and DCl (35%) (0.9 mL, 11.08 mmol, 4 equiv) in D_2O (3 mL) and reacted according to the general procedure 6.1.4. Thioglycolic acid (25 µL, 0.276 mmol, 10 mol%) was added and the mixture was stirred for 30 min, then submitted to aqueous work up according to General Procedure 6.1.4 to give the title compound (259 mg, 82 %) as a colorless solid; mp 96 ºC; IR vmax /cm-1 3325, 3065, 1662, 1639, 1577, 1436, 1407, 1261, 958 and 705 cm-1. δ_H (500 MHz; CD_3OD), *8.07 (0.06H, d, J = 6 Hz, 6-H), *6.36 (0.0.4H, d, J = 2 Hz, 3-H), *6.32 (0.04H, d, J = 2 Hz, 5-H), *2.35 (0.58H, m, 1′- H). δc (125 MHz, CD_3OD), 156.0 (s, C-N), 155.0 (s, C-C), 147.0 (tD, J = 25 Hz, CD), 107.0 (s, CH), 105.0 (s, CH), 20.0 (D, J = 23 Hz, CD_3).m/z (EI) 115 (10, $C_6H_2D_6N_2^{\cdot+}$), 114. (95, $C_6H_3D_5N_2^{\cdot+}$), 113 (100, $C_6H_4D_4N^{\cdot+}$), 112 (60, $C_6H_5D_3N_2^{\cdot+}$), 111 (23, $C_6H_6D_2N_2^{\cdot+}$), 85 (33), 84 (45), 72 (24).

*Signals from multiple isotopologues

d_6-4-Amino-3-methylpyridine (36)

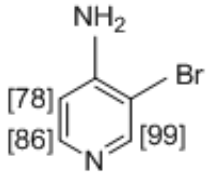


36

A solution of 4-amino-3-methylpyridine (300 mg, 2.77 mmol, 1 equiv.) in D_2O (1 mL) was added to a stirred solution of K_2PtCl_4 (28.6 mg, 0.069 mmol, 2.5 mol %.) and DCl (35%) (0.9 mL, 11.08 mmol, 4 equiv) in D_2O (3 mL) and reacted according to the general procedure 6.1.4. Thioglycolic acid (25 µL, 0.276 mmol, 10 mol%) was added and the mixture was stirred for 30 min, then submitted to aqueous work up according to General Procedure 6.1.4 to give the title compound (290,5 mg, 92%) as a colourless solid; mp 104 ºC; IR vmax /cm-1 3408, 3312, 3125, 2536, 2404, 2367, 2247, 2200, 2053, 1648, 1573, 1549, 1467, 1436, 1367, 1273, 1203, 1036, 884 cm-1. δ_H (500 MHz; CD_3OD), *8.05 (0.00H, s, 2-H), *7.87 (0.31H, s), *6.56 (0.06H, s, 5-H), *2.05(0.11H, s, Me). δc (125 MHz, CD_3OD), 153.0 (s, C-N), 147.0 (s, CHa), 147.0 (s, *J*=24 Hz CH*), 145.0 (tD, *J* = 28 Hz, CD), 116.0 (s, C-C), 107.0 (s, *J*=23 Hz CH), 12.0 (s, Me).m/z (EI) 115 (8, $C_6H_2D_6N_2^{\cdot+}$), 114 (95, $C_6H_3D_5N_2^{\cdot+}$), 113 (83, $C_6H_4D_4N_2^{\cdot+}$), 112 (52, $C_6H_4D_4N_2^{\cdot+}$), 111 (25, $C_6H_5D_3N_2^{\cdot+}$), 85 (48), 84 (100), 68 (12).

*Signals from multiple isotopologues

d_3-4-Amino-3-bromopyridine (37)



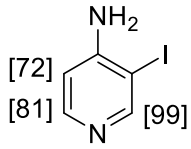
37

A solution of 4-amino-3-bromopyridine(300 mg, 1.73 mmol, 1 equiv.) in D_2O (1 mL) was added to a stirred solution of K_2PtCl_4 (18 mg, 0.043 mmol, 2.5 mol %.) and DCl (35%) (0.5 mL, 6.92 mmol, 4 equiv) in D_2O (3 mL) and reacted according to the General procedure 6.1.4 .Thioglycolic acid (12.2 µL, 0.172 mmol, 10 mol%) was added and the mixture was stirred for 30 min, then submitted to aqueous work up according to General Procedure 6.1.4 to give the title compound (247 mg, 92%) as a colorless powder; mp 73 ºC. IR vmax /cm-1 3435, 3294, 3093, 2264, 1626, 1562, 1466,

1442, 1396, 1377, 1353, 1266, 1187, 1080, 978 and, 831 cm-1.δ_H (500 MHz; CD_3OD), *8.20 (0.01H, s, 2-H), *7.93 (0.22H, d, *J* = 6 Hz, 6-H), *6.71 (0.14H, d, *J* = 6 Hz, 5-H). δc (125 MHz, CD_3OD), 152.0 (s, C-N), 149.0 (tD, *J* = 28 Hz, CD), 147.0 (s, CH), 109.0 (s, *J*=28 Hz CH), 105.0 (s, C).m/z (EI) 177 (72, $C_5H_2D_3BrN_2^{\cdot+}$), 175(100, $C_5H_3D_2BrN_2^{\cdot+}$), 174 (50, $C_5H_4D_1BrN_2^{\cdot+}$), 98 (50), 96 (47), 68 (36), 53(18).

.*Signals from multiple isotopologues

d$_3$-4-Amino-3-iodopyridine (38)

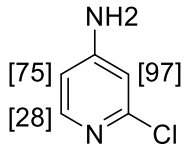


38

A solution of 4-amino-3-iodopyridine (300 mg, 1.36 mmol, 1 equiv.) in D_2O (1 mL) was added to a stirred solution of K_2PtCl_4 (14 mg, 0.034mmol, 2.5 mol %.) and DCl (35%) (0.4 mL, 5.5 mmol, 4 equiv) in D_2O (3 mL) and reacted according to the general procedure 6.1.4. Thioglycolic acid (10 µL, 0.0.136 mmol, 10 mol%) was added and the mixture was stirred for 30 min, then submitted to aqueous work up according to General Procedure 6.1.4 to give the title compound (284 mg, 94%) as a colourless powder mp 97 ºC; IR vmax /cm-1 3434, 3297, 3086, 2248, 1631, 1572, 1474, 1400, 1369, 1269, 1186, 829 and 785 cm-1.δ_H (500 MHz; CD_3OD), *8.38 (0.01H, s, 2-H), *7.93 (0.28H, d, *J* = 6 Hz, 6-H), *6.55 (0.19H, s, 5-H). δc (125 MHz, CD_3OD), 155.0 (tD, *J* = 19 Hz, CD), 154.0 (s, C-N), 147.0 (s, CH), 108.0 (s, CH), 79.0 (s, C). m/z (EI) 223 (10, $C_5H_2D_3IN_2^{\cdot+}$), 222 (75, $C_5H_3D_2BrN_2^{\cdot+}$), 221.(100, $C_5H_4DBrN_2^{\cdot+}$), 95 (40, 94 (54), 67 (32), 66 (26).

*Signals from multiple isotopologues

d$_3$-4-Amino-2-chloropyridine (39)



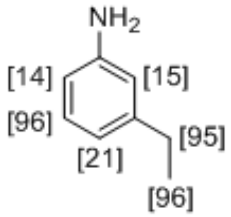
39

A solution of 4-amino-2-chloropyridine (300 mg, 2.33 mmol, 1 equiv.) in D_2O (1 mL) was added to a stirred solution of K_2PtCl_4 (24 mg, 0.06 mmol, 2.5 mol %.) and DCl

(35%) (0.73 mL, 9.32 mmol, 4 equiv) in D2O (3 mL) and reacted according to the General procedure 6.1.4. Thioglycolic acid (20.6 µL, 0.224 mmol, 10 mol%) was added and the mixture was stirred for 30 min, then submitted to aqueous work up according to General Procedure 6.1.4 to give the title compound (285 mg, 94%) as a colorless solid; mp 95-98 ºC; IR vmax /cm-1 3350, 3305, 3144, 2739, 1656, 1573, 1549, 1451, 1403, 1380, 1273, 978, 831 and 764 cm-1. δ_H (500 MHz; CD_3OD), *7.75 (0.72H, d, *J* = 6 Hz, 6-H), *6.56 (0.03H, d, *J* = 2 Hz, 3-H), *6.49 (0.25H, dd, *J* = 6, 2 Hz, 5-H). δc (125 MHz, CD_3OD), 157.0 (s, C-N), 151.0 (s, C-N), 148.0 (s, CH), 108.0 (s, *J*=26 Hz CH), 107.0 (s, *J*=24 Hz CH). m/z (EI) 132 (30, $C_5H_2D_3ClN_2^{\cdot+}$), 130 (72, $C_5H_3D_2ClN_2^{\cdot+}$), 129 (33, $C_5H_4D_1ClN_2^{\cdot+}$), 95 (100), 94 (68), 68 (43), 67 (41).

.*Signals from multiple isotopologues

6.1.4. Experimental procedures for Synthesis of *meta*-deuterated *d_6*-3-Ethylaniline (40)

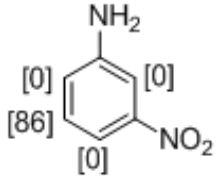


40

HCl (32%) (520 µL, 6.92mmol, 4 eq.) in H_2O (5 mL) was added to *d_9*- 3-ethylaniline (210 mg, 1.73 mmol, 1 eq.) the rest of the the work up followed the General procedure (6.1.5), to give the title compound (201 mg, 89 %) as a brown oil; (IR) vmax /cm-1 3353, 3220, 3032, 2222, 1616, 1581, 1441, 1316, 1290 and 1054; δ_H (500 MHz; CD_3OD), *7.08 (0.04H, s), *6.61 (0.79H, s), *6.54 (0.86H, s), *6.52 (0.85H, s), *2.55 (0.10H, s), 1.16 (0.11H, s),δc (125 MHz, CD_3OD) 146.0 (s, C-NH_2**),** 145.0 (s, C-C), 120.00 (t,C-D,), 117.0 (t, C-D), 114.0 (t, C-D), 112.0 (t, C-D), 27.0 (m, CD_2), 14.0 (m, CD_3). *m/z* (EI) 128 (12, $C_8H_4D_7N^{\cdot+}$), 127 (90, $C_8H_5D_6N^{\cdot+}$), 126 (37, $C_8H_6D_5N^{\cdot+}$), 125 (16, $C_8H_7D_4N^{\cdot+}$), 109 (100).

*Signals from multiple isotopologues

d₁-3-Nitroaniline (41)

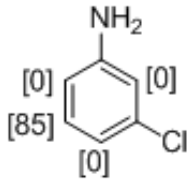


41

HCl (32%) (517 µL, 6.9 mmol, 4 eq.) in H_2O (5 mL) was added to *d₄*-3-Nitroaniline (220 mg, 1.72 mmol, 1 eq.), the rest of the the work up followed the General procedure (6.1.5), to give the title compound (196 mg, 80 %): as a yallow powder, mp 106-112 °C; (IR) vmax /cm-1 3372, 2937, 2220, 2074, 1618, 1572, 1489, 1418, 1289, 1257, and 1145; δ_H (500 MHz; CD_3OD) 7.56 (1.00H, s), 7.48 (1.00H, s), *7.26 (0.14H, s), 6.94 (1.00H, s)**;** δc(125 MHz, CD_3OD) 148.0 (s, C-NO_2)**,** 147.0 (s, C-NH_2), 120.0 (t, C-D), 117.0 (t, C-D), 113.0 (t, C-D), 108.0 (t, C-D). *m/z* (EI) 139 (35, $C_6H_5DN_2O_2^{\cdot+}$), 93 (100), 81 (20), 66 (68).

*Signals from multiple isotopologues

d₁-3-Chloroaniline (42)

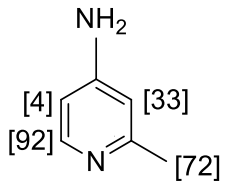


42

HCl (32%) (485 µL, 6.5 mmol, 4 eq.)in H_2O (5 mL) was added to *d₄*-3-chloroaniline (225 mg, 1.63 mmol, 1 eq.). ,the rest of the the work up followed the General procedure (6.1.5), to give the title compound (200 mg, 92%): as a brown oil; (IR) vmax /cm-1 3360, 3215, 3056, 1618, 1572, 1593, 1443,1311, 1259, 1163, and 992; δ_H (500 MHz; CD_3OD), *7.00 (0.15H, s), 6.67 (1.00H, s), 6.57 (1.94H, s), δc(125 MHz, CD_3OD) 149.0 (s, C-NH_2)**,** 134.0 (s, C-Cl), 129.0 (t, C-D), 116.0 (t, C-D), 114.0 (t, C-D), 112.0 (t, C-D), *m/z* (EI) 130 (56, $C_6H_5D^{37}ClN^{\cdot+}$), 128 (100, $C_6H_5D^{35}ClN^{\cdot+}$) 93 (58), 66 (57).

*Signals from multiple isotopologues

d_6-4-Amino-2-methylpyridine (43)



43

HCl (32%) (4 equiv.). and, H_2O (5 mL) was added to *d_6*-4-amino-2-methylpyridine (200 mg, 1.75 mmol, 1 equiv) and reacted according to General Procedure 6.1.5, to give the title compound (137 mg, 70 %) as a colorless solid, mp 96-99 ºC. IR; vmax /cm-1 3324, 3065, 2911, 2848, 2366, 1638, 1602, 1559, 1495, 1345, 1297, 1261, 985, 705 cm-1. δ_H (500 MHz; CD_3OD), *7.82 (0.04H, d), 6.41 (0.96H, d) *6.37 (0.67H, d), *2.27 (0.083H, s,). δc (125 MHz, CD_3OD), 157.0 (s, C-N), 155.0 (s, C-C), 147.0 (tD, J = 26 Hz, CD), 108.0 (s, CH), 106.0 (s, CH), 21.0 (D, *J* = 19 Hz, CD_3). *m/z* (EI) 113 (32, $C_6H_4D_4N_2^{\cdot+}$), 112 (100, $C_6H_5D_3N_2^{\cdot+}$), 111 (80, $C_6H_6D_3N_2^{\cdot+}$), 110 (33, $C_6H_7D_2N_2^{\cdot+}$), 84 (22), 83 (34), 82 (20), 71 (11).

*Signals from multiple isotopologues

Future work

Currently H/D exchange reactions represent an important branch of studies. In this thesis, Pd/C as a heterogeneous catalyst was used under microwave–assisted and flow chemistry conditions due to the importance of the corresponding labelled compounds as drug compounds or as precursors for the synthesis of clinical agents. Their use could have a relevant role in defining fully deuterated syntheses for biological active compounds in future. The incorporation of aniline derivatives using palladium as a heterogeneous catalyst could be a reaction that would be worthy of future studies.

This study has revealed flow reactor chemistry can be used for H/D exchange and is, however, perhaps the most promising field of study for the future. In this study flow reactor, chemistry was used for H/D exchange in a single cycle. We are extremely excited at the possibilities that this process could be improved in the future by changing the metal, by investigating different colloidal system or by finding a means to perturb the equilibrium by removing protio solvents in flow It is anticipated that extending these studies the improve methods and application of flow chemistry reactors in a catalytic process.

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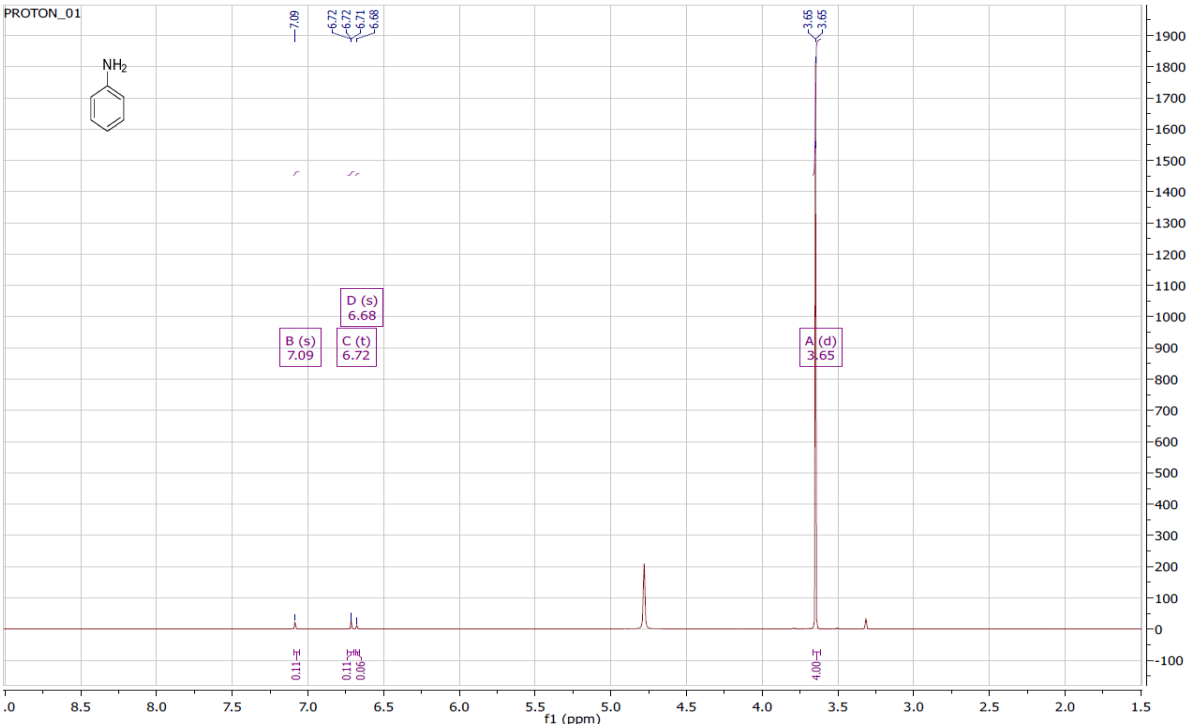
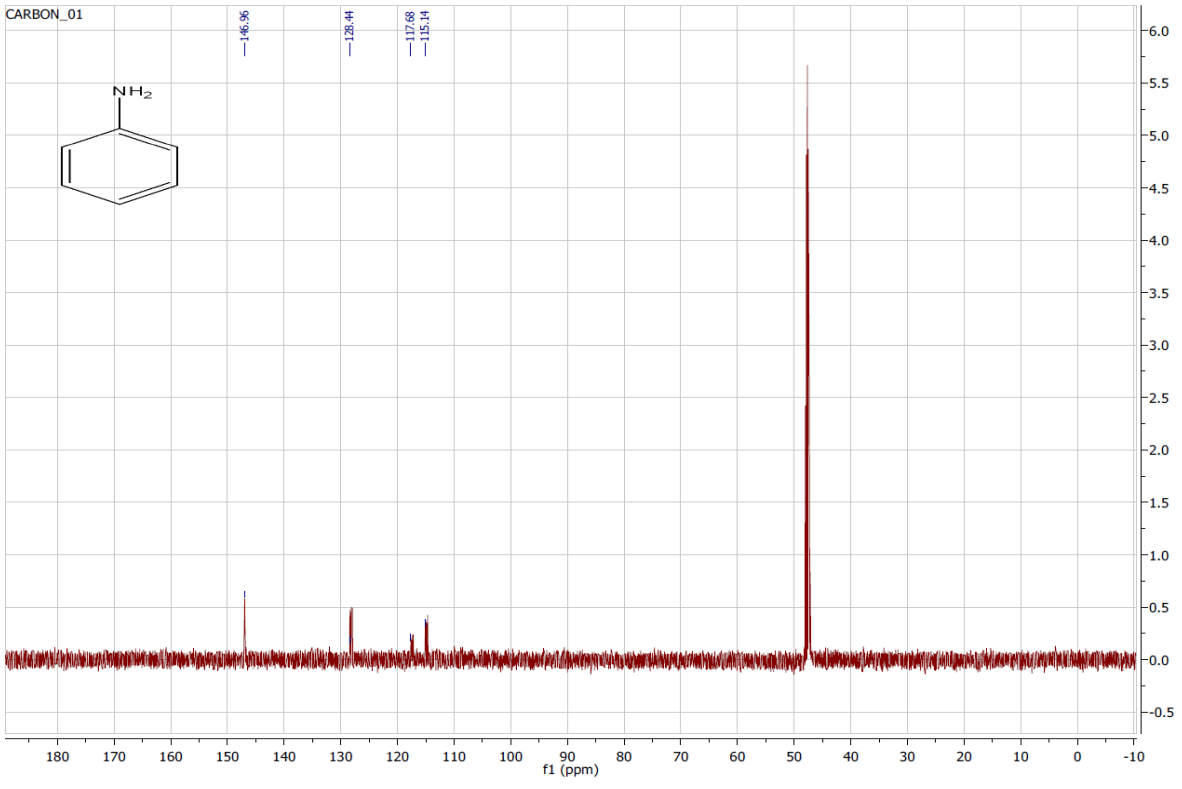
Appendix

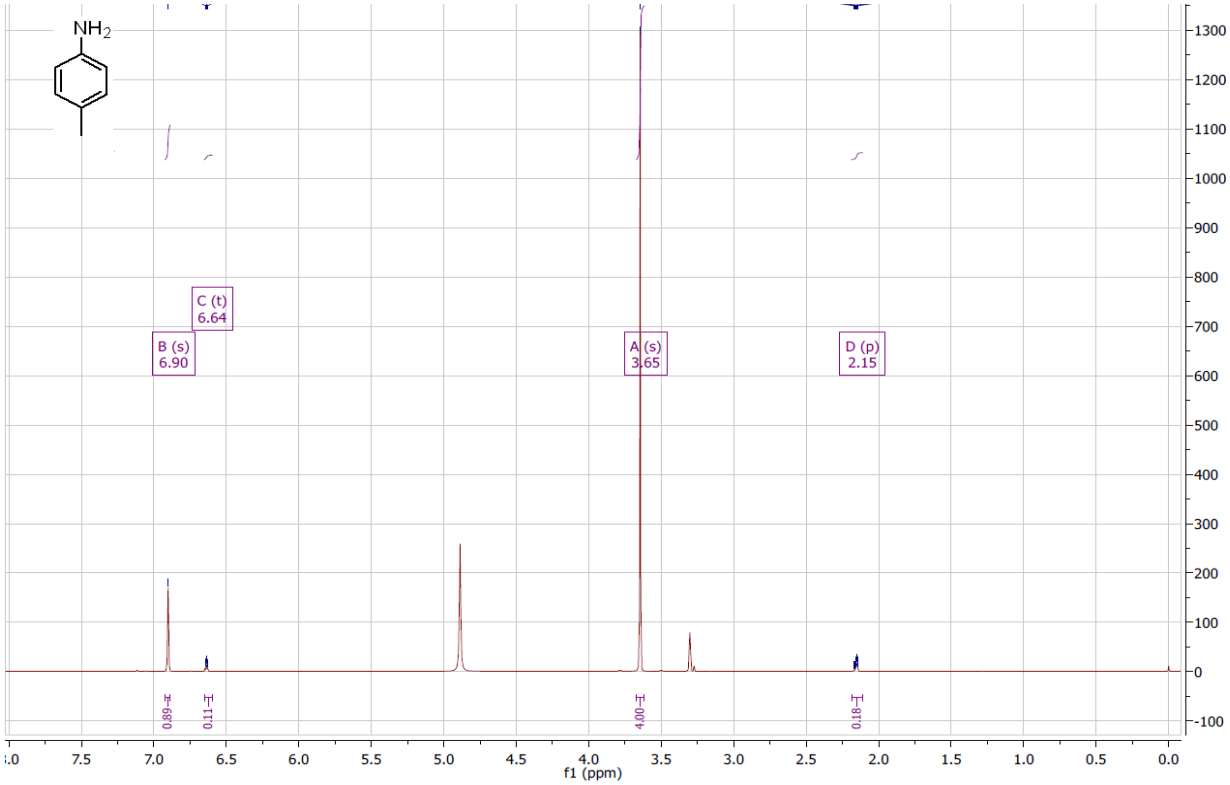
1a. ^{1}H NMR spectrum (500 MHz, CD_3OD) for d_5- Aniline



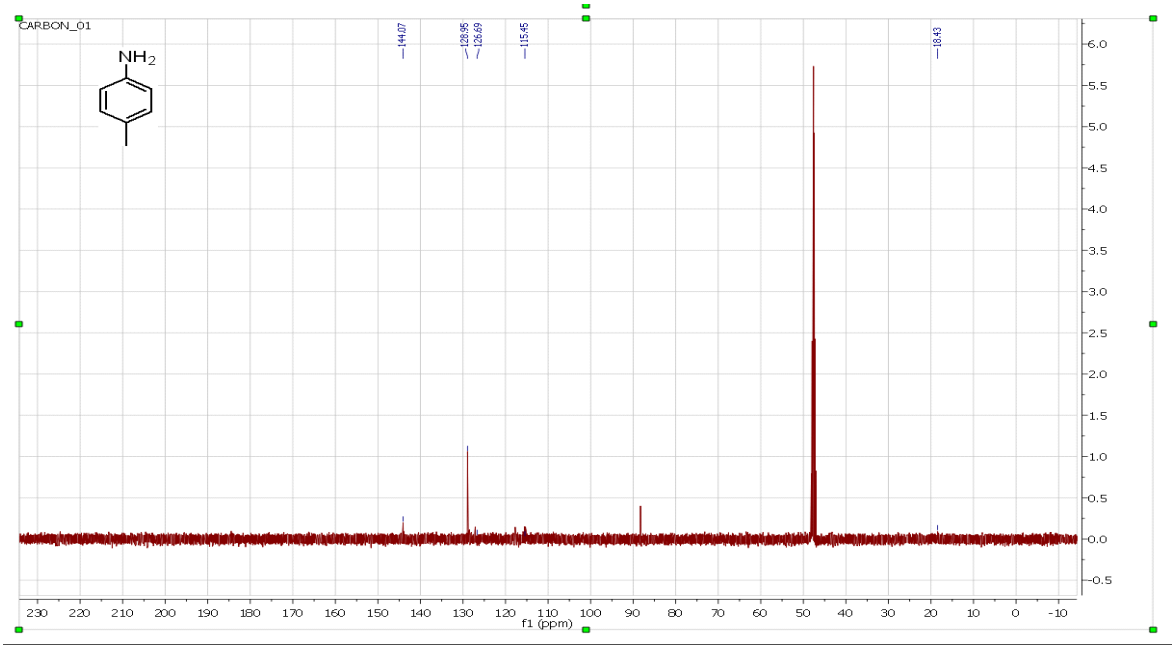
1b. ^{13}C NMR spectrum (150 MHz, CD_3OD) for d_5- Aniline



2a. ^{1}H NMR spectrum (500 MHz, CD_3OD) for *d_7-P*-toludine

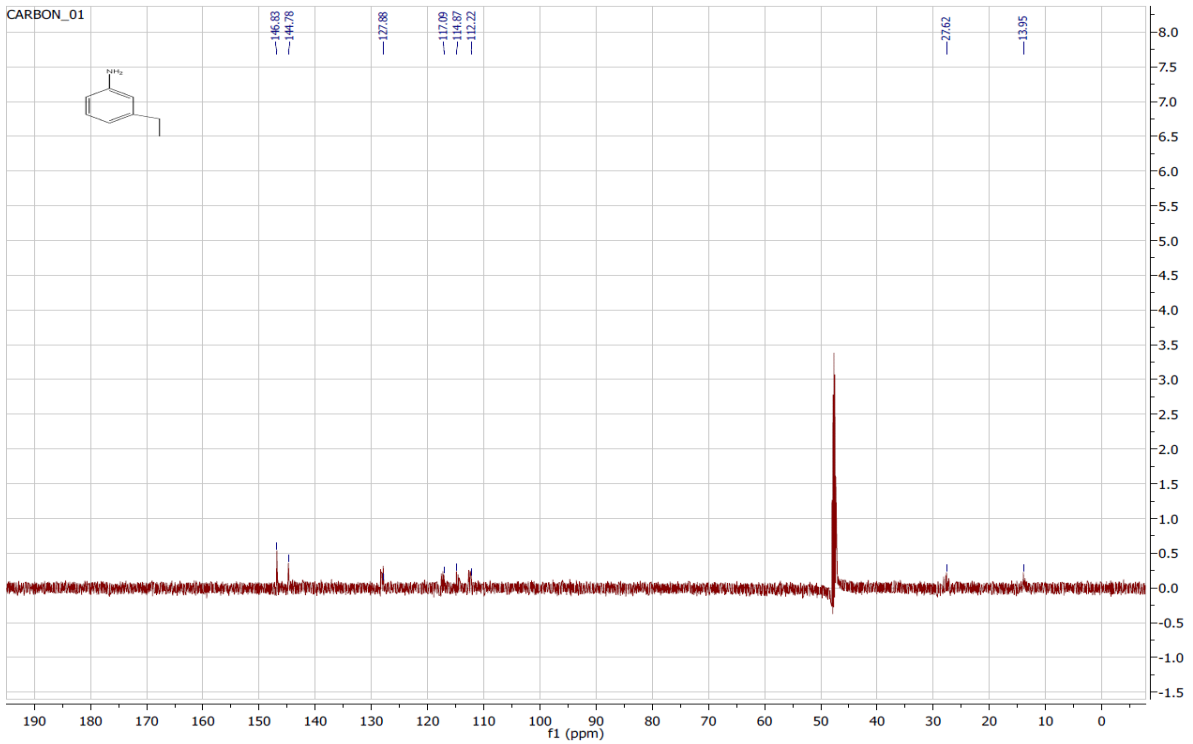


2b. ^{13}C NMR spectrum (150 MHz, CD_3OD) for *d_7-P*-toludine

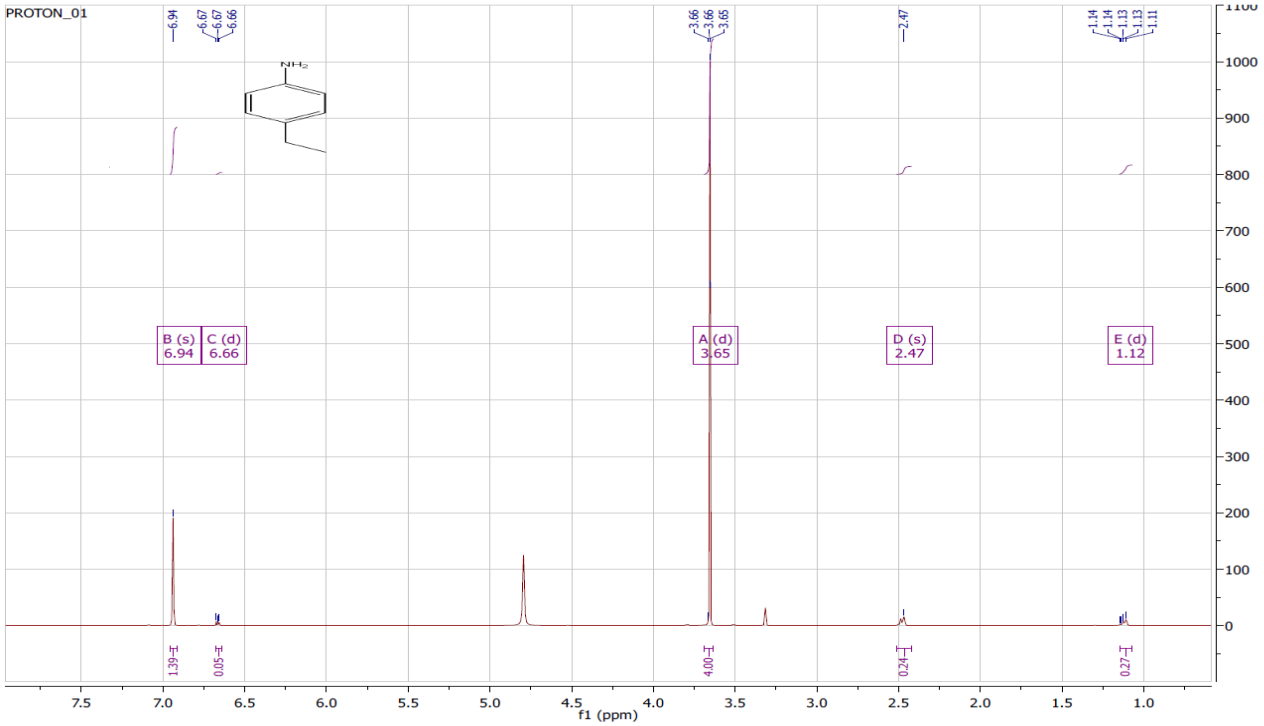


3a. ^{1}H NMR spectrum (500 MHz, CD_3OD) for d_9-3-Ethylaniline

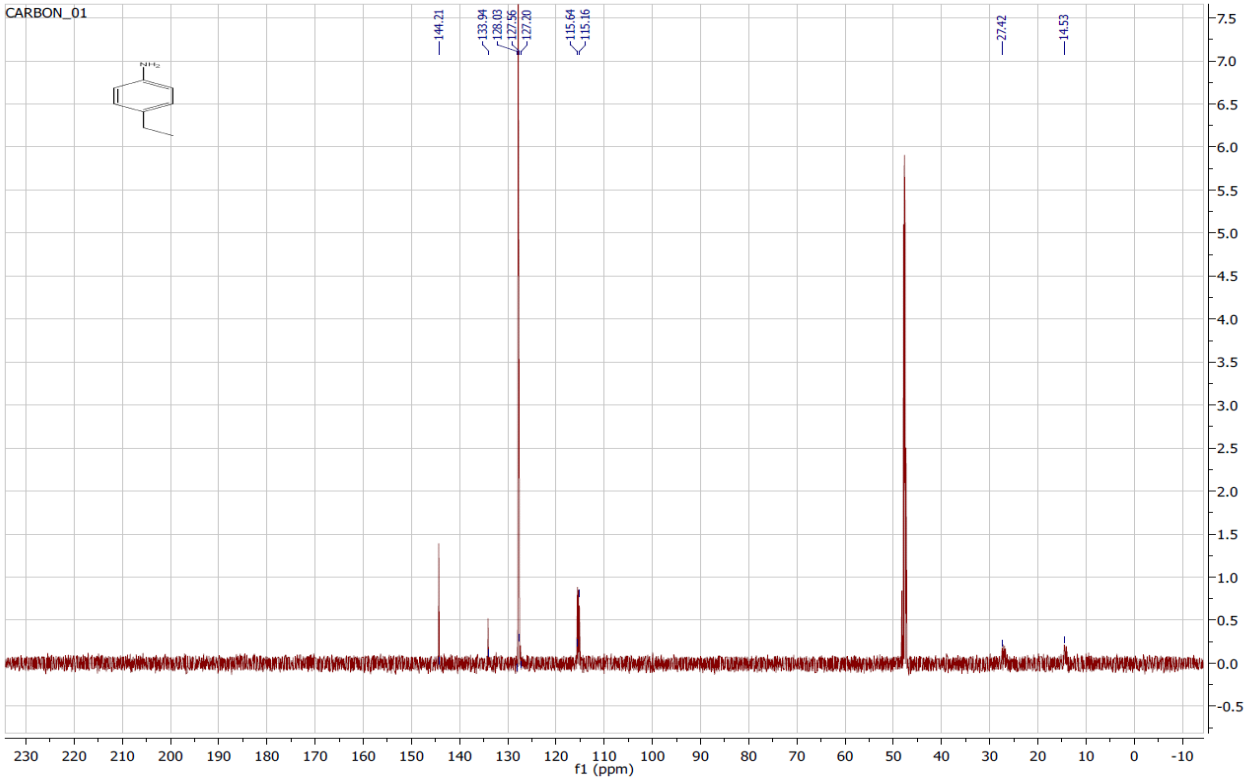
3b. ^{13}C NMR spectrum (150 MHz, CD_3OD) for d_9-3-Ethylaniline



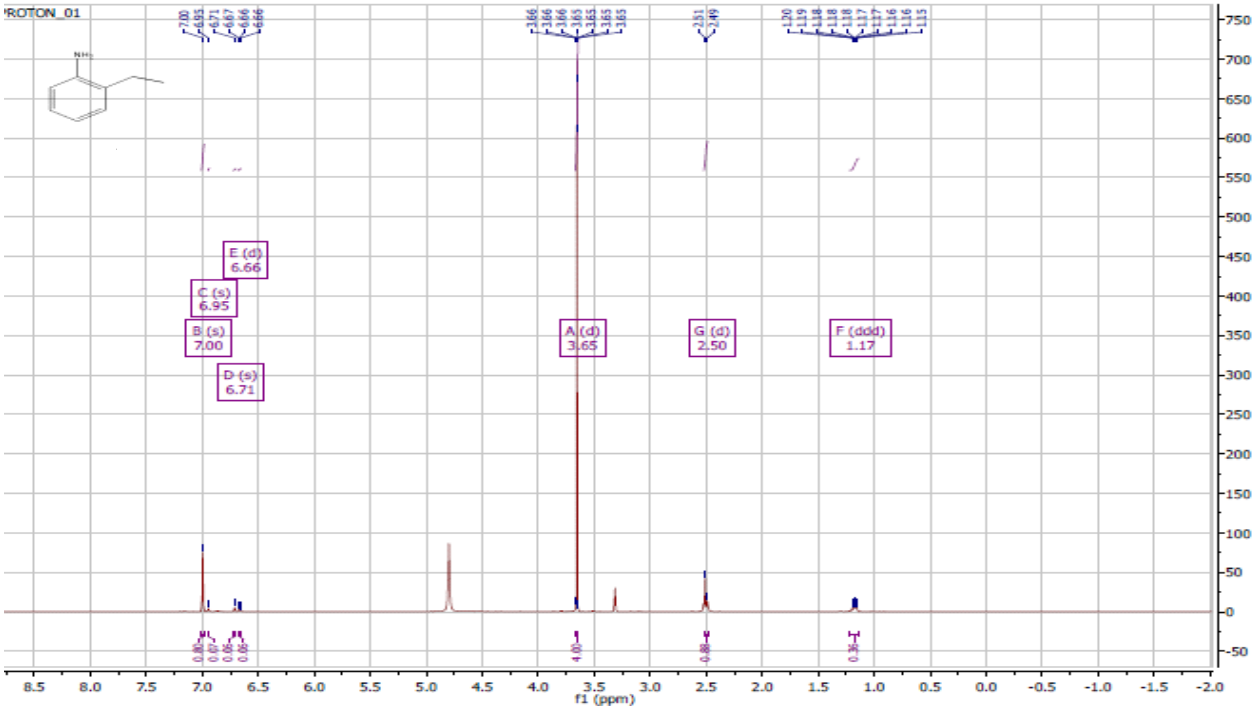
4a. ^{1}H NMR spectrum (500 MHz, CD_3OD) for *d*$_9$-4-Ethylaniline



4b. ^{13}C NMR spectrum (150 MHz, CD_3OD) for *d*$_9$-4-Ethylaniline



5a. ^{1}H NMR spectrum (500 MHz, CD_3OD) for *d*$_9$-2-Ethylaniline



5b. ^{13}C NMR spectrum (150 MHz, CD_3OD) for *d*$_9$-2-Ethylaniline