Catalysis Today 139 (2008) 154–160

Contents lists available at ScienceDirect

Catalysis Today

journal homepage: www.elsevier.com/locate/cattod

Selective H–D exchange catalysed by aqueous phase and immobilised Pd nanoparticles

James A. Sullivan [a,*], Keith A. Flanagan [a], Holger Hain [a,b]

[a] UCD School of Chemistry and Chemical Biology, Belfield, Dublin 4, Ireland
[b] Institut fuer Anorganische Chemie, Universitaet Wuerzburg, Wuerzburg, Germany

ARTICLE INFO

Article history:
Available online 15 May 2008

Keywords:
Selective H–D exchange
Pd nanoparticles
Carbon nanotubes

ABSTRACT

Pd nanoparticles (with a mean diameter of 3.4 ± 0.5 nm) prepared through BH_4^- reduction of Na_2PdCl_4 can catalyse *selective* H–D exchange (through reaction with D_2O) at the carbon α to the N atom of a pyridine ring. Oxidised Pd(II) complex species also present as dissolved species in the nanoparticle dispersion play no part in the exchange.

We have studied the effects of several different variables on the rate of the selective H–D exchange activity for a model pyridine, *i.e.* 4-dimethylaminopyridine (DMAP). These variables include temperature, nanoparticle aging, nanoparticle re-reduction with H_2 and nanoparticle immobilisation onto multi-walled carbon nanotubes (MWCNTs). We have also extended the study to related pyridine containing molecules.

1. Introduction

The ability to selectively label molecules with deuterium is extremely important in pharmacological, chemical and environmental research especially in the investigation of reaction mechanisms [1] and kinetics [2] of carbon hydrogen bond activation processes. Deuterated molecules can also be used in stable isotopic tracer studies for use in GC or LC MS internal standardisation as well as in more specialist applications such as the development of non-linear optical materials [3]. Such labelling also provides a route to obtain analogous tritium labelled molecules for radiotracer studies [4]. Furthermore, using acid catalysed, base catalysed or metal catalysed processes [5], D and T labels can be introduced into organic substrates post-synthetically in contrast to the introduction of most ^{13}C labels and other isotopically labelled atoms. The post-synthetic formation of D-labelled materials has been the subject of recent reviews [2,6].

Specifically the selective labelling of pyridine and other N-hetero-aromatic units is of particular importance since these components find application in many important pharmaceutical (*e.g.* anti-tuberculosis agents such as isonicotinic hydrazide) [7], agrochemical (*e.g.* feed additives such as nicotinic acid) [8] and industrially relevant chemicals (*e.g.* polymer precursors such as 2-vinyl pyridine) [9] and thus, methods for selectively labelling these materials are important because of the proposed use of such deuterated materials in absorption, metabolism, environmental and toxico-kinetic radiotracer studies [10].

Pd/C catalysts have previously been used [11] to catalyse H–D exchange at activated sites within benzylic compounds using D_2 as a deuterium source while Pd/C and Pt/C have been used synergistically [12,13] to catalyse such reactions on activated and sterically hindered sites using D_2O.

There are also many publications dealing with the use of a variety of Pd-based catalysts to perform these reactions on various organic molecules (including N-containing heterocyclic molecules) but several seem to use conditions of relatively high temperature and pressure [14–16]. Activated Pd/C catalysts have also been frequently used in combination with D_2O as the D_2-source for labelling of benzylic as well as unactivated compounds [15,17–20,25].

Recently, we have described the preparation and characterisation of a relatively monodisperse aqueous phase DMAP stabilised Pd nanoparticle dispersion [21]. During the course of the characterisation of this dispersion it became apparent that (a) there existed within the dispersion an oxidised ionic Pd(II) species (which proved to be an active Suzuki coupling catalyst [22,23]) that formed from the reaction of the nanoparticles with air and (b) the nanoparticles within the dispersion were active in promoting selective H–D exchange of the protons α to the endocyclic N atom of the DMAP molecule through reaction with D_2O.

This selective H–D exchange of DMAP was previously confirmed using ^1H NMR, FTIR and high resolution mass spectrometry [21].

---

[*] Corresponding author. Tel.: +35 317162135; fax: +35 317162127.
E-mail address: james.sullivan@ucd.ie (J.A. Sullivan).

0920-5861/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.cattod.2008.03.031

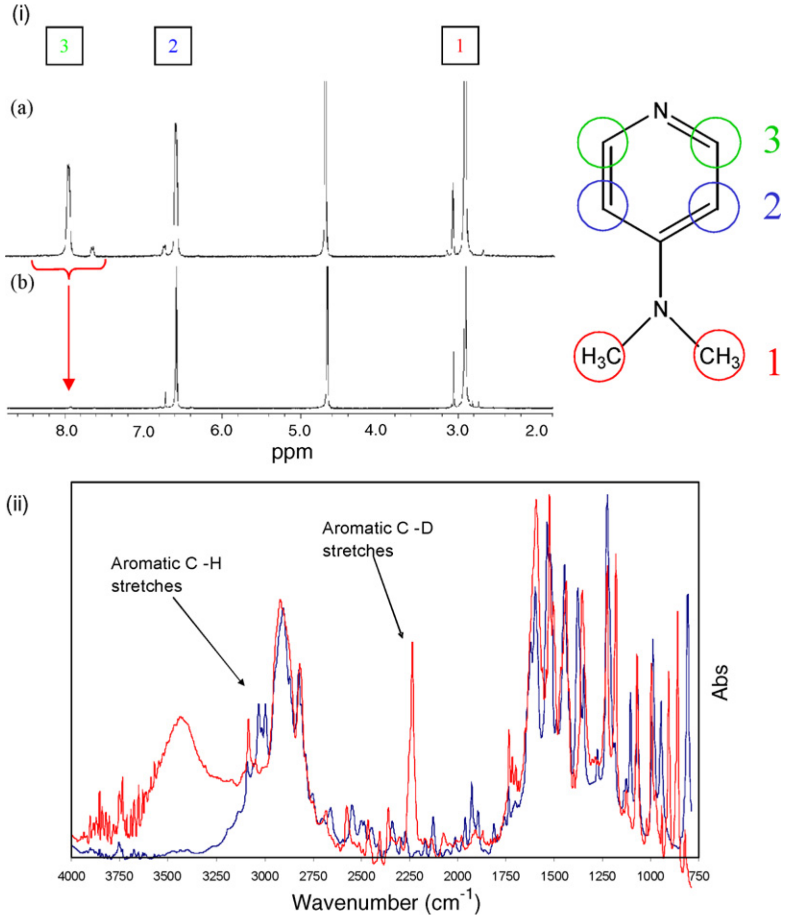


Fig. 1. (i) A comparison between the ^1H NMR spectra of the DMAP stabilised palladium nanoparticle dispersion in D_2O obtained (a) 1 h and (b) 2 days after preparation. (ii) A comparison of the DRIFTs spectrum of DMAP used in the initial dispersion preparation and DMAP subsequently isolated from the dispersion in D_2O.

Fig. 1(i) shows a ^1H NMR spectrum of a fresh dispersion and a dispersion which was held in D_2O. Fig. 1(ii) shows the DRIFTs spectrum of the 4-DMAP used in the initial nanoparticle dispersion preparation and the 4-DMAP isolated from such dispersions. The former spectra show the disappearance of resonances at $\delta \sim 8.0$ which are due to α protons in both the stabilising DMAP molecules and also in oxidised Pd(II) DMAP complexes which formed in the dispersion over time while the latter highlight the lower energy aromatic C–D vibrations (at $\sim$2240 cm^{-1} compared to aromatic C–H stretches at $\sim$3000 cm^{-1}). Analysis of the ^1H NMR spectra suggests these α protons are selectively exchanged with Deuterium from the D_2O over the period of 2 days with no such exchange seen on the aromatic β or methyl protons of the DMAP molecule. The mass spectrum of the post-exchanged DMAP molecules confirmed the replacement of two H atoms by two D atoms in all the isolated DMAP molecules.

In this manuscript we describe the use of Pd nanoparticles as a catalyst that promotes *selective* H–D exchange at the less activated α position of 4-substituted pyridines. We look at some factors which influence the rate and selectivity of this exchange reaction (temperature, age of the nanoparticle dispersion and the presence of $H_{2(g)}$). Furthermore, via judicious ligand exchange techniques, we develop a recyclable Pd-MWCNT composite material by immobilising the nanoparticles onto MWCNTs. We demonstrate that this composite material also catalyses the selective H–D exchange reaction for the 4-DMAP molecule and more importantly allows us to extend this catalytic activity to other pyridine-based substrates.

2. Experimental

All chemicals were used as supplied by the Sigma–Aldrich Chemical Company Ltd., unless otherwise stated. Sodium tetrachloropalladate(II) was purchased from Reagecon. All chemicals were used as received without further purification. Multi-walled carbon nanotubes (MWCNTs), prepared by a carbon arc discharge method, were supplied by the MER Corporation. Polycarbonate membrane filters (0.2 μm pore diameter) were purchased from Whatman-UK. The water used in all experiments was distilled-deionized Millipore-MilliQ water (18 MΩ cm^{-1}).

2.1. Catalyst preparation

2.1.1. Nanoparticle dispersions

Nanoparticle dispersions were prepared as previously reported [21]. Na_2PdCl_4 (0.127 mmol) was dissolved in distilled-deionized water (3 mL) and stirred vigorously. 4-Dimethylaminopyridine (DMAP) (0.682 mmol) was sonicated into 9 mL of distilled-deionised water and added to the stirring solution. The resulting mixture was stirred for 20 min. This solution was reduced by the addition of $NaBH_4$ (1% w/v, 1.100 mL) in 0.100 mL aliquots. A colour change from pale yellow to black was observed immediately. The resulting DMAP stabilised palladium nanoparticles were stirred vigorously for a further 30 min. TEM analysis has shown that the particles, which are stable in solution for more than 6 months, [22] have a mean diameter of 3.4 ± 0.5 nm.

To facilitate ^{1}H NMR characterisation of the nanoparticle dispersions and to analyse the selective H–D exchange activity of the prepared particles, the nanoparticles were also produced in D_2O. The preparation procedure was the same as described above except reduced to one third the amounts described above.

2.1.2. Thiol-modified multi-walled carbon nanotubes

To facilitate the immobilisation of the Pd nanoparticles we employ a previous observation that the DMAP stabilising ligand can be easily removed from the Pd nanoparticles and replaced with a thiol ligand [21].

Multi-walled carbon nanotubes (MWCNTs), prepared by a carbon arc discharge method, were supplied by the MER Corporation and thiolated using a slightly modified procedure to that described by Sainsbury and Fitzmaurice [24] as follows: as-received MWCNTs (0.003 g) were suspended in nitric acid (3 mL, 70% w/w) by sonication (15 min). The resulting black suspension was refluxed for 24 h at 130 °C and allowed to cool to room temperature. The suspension was then filtered through a polycarbonate membrane filter (Whatman-UK, 0.2 μm pore diameter) and washed with deionised-distilled water (1 L). The MWCNTs retained on the membrane filter were suspended in deionised-distilled water (10 mL) by sonicating the filter membrane (10 min). $KMnO_4$ (0.009 g, 5.696×10^{-5} mol) was added and the resulting dark-purple suspension cooled in an ice bath to 0 °C under magnetic stirring for 1 h. $HClO_4$ (3 mL, 70% w/w) was added to the solution, which was stirred at room temperature for 1 h. Citric acid monohydrate (0.186 g, 8.851×10^{-4} mol) was added and the suspension was stirred until it became grey in colour. The resulting suspension of MWCNTs was filtered through a polycarbonate membrane filter (Whatman-UK, 0.2 μm pore diameter) and washed with deionised-distilled water (1 L).

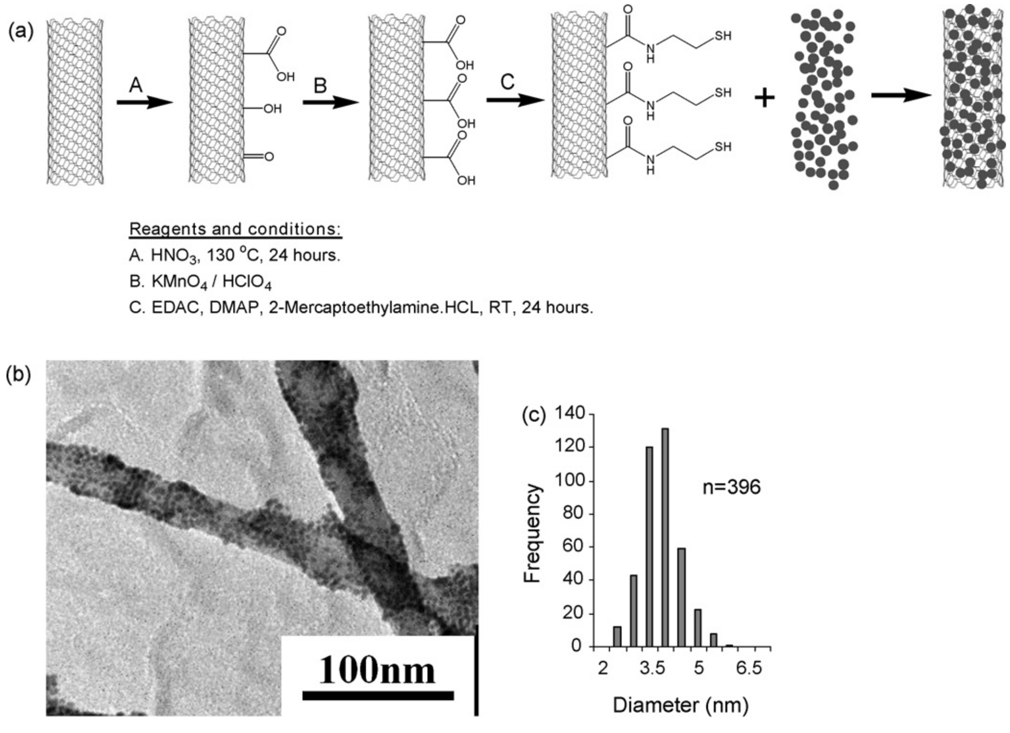
The retained MWCNTs were suspended in deionised-distilled water (10 mL) through sonication of the filter membrane. DMAP (0.003 g, 2.456×10^{-5} mol,) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDAC) (0.191 g, 9.963×10^{-3} mol) were added and stirred for 10 min. 2-Mercaptoethylamine hydrochloride (0.050 g, 4.401×10^{-4} mol) was added and the resulting suspension stirred for 24 h at room temperature. The suspension of MWCNTs was filtered through a polycarbonate membrane filter (Whatman-UK, 0.2 μm pore diameter) and washed with deionised-distilled water (1 L). The retained MWCNTs were again suspended in deionised-distilled water (10 mL) by sonication and were ready for use.

2.1.3. MWCNT/Pd-DMAP NP composites

Multi-walled carbon nanotube/DMAP stabilised Pd nanoparticle composites were prepared by the addition of a known amount of DMAP stabilised palladium nanoparticle dispersion to thiol-modified multi-walled carbon nanotubes.

In a typical composite preparation, 3 separate 1 mL aliquots of the prepared thiolated MWCNTs were sonicated for 5 min and the DMAP stabilised palladium nanoparticle dispersion (65 μL of an 887 ppm Pd dispersion) was added to each with brief mixing. Over the next 10 h the three resulting composite solutions precipitated twice and were subsequently re-dispersed by sonication for 10 s. The three separate composite solutions were then combined and left for 12 h to fully precipitate. The resulting clear supernatant was carefully removed and distilled-deionised water (3 mL) was added followed by sonication for 10 s.

This subsequent MWCNT/Pd-DMAP NP composite solution was filtered through a polycarbonate membrane filter (Whatman-UK, 0.2 μm pore diameter) and the retained composite was washed with a further 100 mL of distilled-deionised water and 1 mL of D_2O. The retained composite was removed from the membrane by sonication into ~2 mL of D_2O and was ready for use. An aliquot of the resulting MWCNT/Pd-DMAP NP composite (10 μL) was deposited on a carbon-coated copper grid and was characterised



Reagents and conditions:
A. HNO_3, 130 °C, 24 hours.
B. $KMnO_4$ / $HClO_4$
C. EDAC, DMAP, 2-Mercaptoethylamine.HCL, RT, 24 hours.

Fig. 2. (a) Schematic of preparation procedure used to produce Pd/MWCNT composite material (b) TEM of resultant composite material (c) histogram showing particle size distribution.

by TEM. The average Pd nanoparticle size, as measured by TEM, is 3.6 ± 0.6 nm. Fig. 2 gives a schematic of the composite preparation procedure, a typical TEM and a histogram showing Pd nanoparticle size distribution.

2.2. Selective H–D exchange activity tests

The selective H–D exchange of the DMAP and other pyridine-based molecules was followed using ^{1}H NMR spectrometry by monitoring the various proton resonances against those of an appropriate internal standard (1,2-ethylene glycol). All ^{1}H nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Varian 300 MHz FT-NMR spectrometer using Mestrec software to evaluate relevant sample and internal standard peak integrations.

2.2.1. Selective H–D exchange of DMAP using the nanoparticle dispersion

In a typical experiment 0.040 mL of internal standard (0.078 mL 1,2-ethylene glycol in 2.00 mL D_2O) was added to 0.8 mL of a nanoparticle preparation (prepared as above) in D_2O. ^{1}H NMR spectra were run relatively frequently for the first 3 h following preparation of the dispersion and subsequently run at less frequent intervals (*e.g.* samples were left overnight *etc.*)

Parameters such as temperature (RT, 50 °C and 80 °C), age of the nanoparticle dispersion (fresh and 1 month old) and effect of H_2/Ar (3% H_2) treatment (flow rate ~200 mL/min for 30 min) were varied during these experiments. Typically, in a dispersion catalysed reaction the mol% of Pd (relative to DMAP substrate) was ~16%.

For experiments where fresh DMAP (16.4 μmols) in D_2O (50 μL) was added to the preformed nanoparticle dispersion (800 μL) the mol% of Pd (relative to the added DMAP substrate) was ~41%.

It should be noted that after certain periods of time the nanoparticles precipitated from solution. This time proved to be shorter at higher temperatures. However they could be re-dispersed with short sonication and no long-term deterioration of the nanoparticles was observed following such a precipitation.

2.2.2. Selective H–D exchange of DMAP and related pyridine-based molecules using MWCNT/Pd-DMAP NP composite

MWCNT/Pd-DMAP NP composite prepared as above was removed from the membrane by sonication for 30 s into 2 mL of the *reaction solution* (see below). The membrane was removed and washed with less than 1 mL of the *reaction solution*, if necessary, to ensure all composite was removed. The subsequent reaction mixture was heated to 50 °C for 5 h while H_2/Ar (3% H_2) was bubbled through the solution (~200 mL/min). The reaction mixture was cooled and sonicated periodically during this period. After 5 h the reaction was cooled and again sonicated to remove the composite from the walls of the reaction vessel. The reaction mixture was filtered through a polycarbonate membrane (Whatman-UK, 0.2 μm pore diameter). Another 1 mL of D_2O was added to the reaction vessel, sonicated and also filtered. The filtrate was analysed by ^{1}H NMR spectroscopy characterisation and compared to the ^{1}H NMR spectrum of the starting *reaction solution* to study the selectivity and yield of deuterated target molecule (Mestrec software used). The composite retained on the membrane was sonicated into the next *reaction solution* and was ready for reuse.

Note that the *reaction solution* involved a mixture of the target for selective H–D exchange (DMAP or other related pyridine-based molecule) (82 μmols) dissolved in 10 mL D_2O with sonication and 125 μL of EG standard solution was added (78 μL ethylene glycol in 2 mL D_2O). A ^{1}H NMR of this solution (800 μL) was run prior to any selective H–D exchange reaction.

Typically, in a recyclable composite catalysed reaction (given that 80% of Pd in a dispersion can be immobilised [22]) the mol% of Pd (relative to the moles of substrate) was ~8 mol%.

2.3. Catalyst characterisation techniques

All Transmission Electron Microscopy (TEM) images were recorded using a JEOL JEL-2000 EX electron microscope with a lattice resolution of 0.14 nm and a point-to-point resolution of 0.3 nm operating at 80 kV. Samples were prepared by evaporating a drop of the appropriate dispersion onto the surface of a carbon-coated 400 square mesh copper TEM grid.

3. Results and discussion

When considering the effects of different parameters on the rate of the selective H–D exchange activity for pyridine-containing molecules, it should firstly be stated that there is no H–D exchange noted at any stage in the absence of Pd in solution. Furthermore, experiments at extended times in the presence of $Pd(DMAP)_4(OH)_2$ complexes which can be isolated from the nanoparticle dispersion [21] also show no measurable (by ^{1}H NMR) deuterium exchange activity. This complex has previously been shown to contribute substantially to the catalytic activities of the Pd nanoparticle dispersions in the promotion of model Suzuki reactions [22,23]. Finally, the functionalised and non-functionalised MWCNTs do not promote H–D exchange in the absence of Pd nanoparticles. Therefore it is clear that it is the Pd nanoparticles that catalyse this reaction under the basic conditions of the nanoparticle dispersion (pH > 9).

3.1. Effect of temperature

Fig. 3 shows the effect of temperature on the selective H–D exchange activity of three freshly prepared nanoparticle dispersions as monitored by the disappearance of the resonances attributed to the α protons of DMAP. It is clear that at elevated temperatures there is a more rapid exchange of the α protons. However, it should be noted that there is also a less desired side reaction seen at elevated temperatures where the β protons are also exchanged to a certain extent *e.g.* ~16% of the β protons were exchanged following 5 h of reaction at 80 °C. On the contrary no exchange of the β protons was noted from any nanoparticle dispersion which had been maintained at room temperature even following extended periods of time (>4 months).

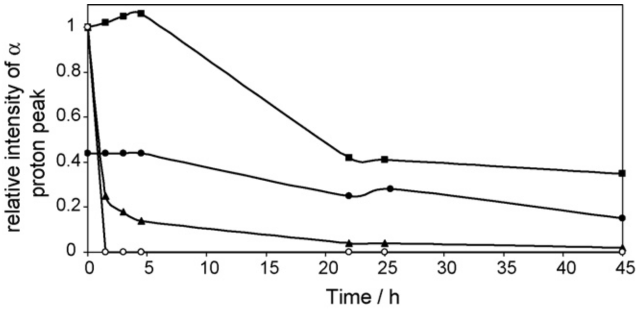


Fig. 3. Plot of α ^{1}H resonance intensity as a function of time in DMAP stabilised Pd nanoparticle dispersions. (■) Dispersion at room temperature, (▲) dispersion held at 50 °C, (○) dispersion held at 80 °C, (●) dispersion held at 50 °C with extra DMAP added following 25 h of H–D exchange—see text for details.

This suggests that the mode of co-ordination of the DMAP molecules becomes less selective at higher temperatures with perhaps the DMAP adsorbing side-on or face-on to the nanoparticles rather than through the endocyclic N atom.

3.2. Effect of extra DMAP addition

In order to determine whether the exchange of the α protons was a result of reactions taking place during the formation of the nanoparticle dispersion or whether it was due to some catalytic function of the nanoparticle dispersion an experiment was carried out where extra DMAP (at ~40% of the initial level) was added to a dispersion held at 50 °C approximately 25 h following its initial preparation, *i.e.* when more than 98% of the DMAP initially present had already undergone H–D exchange. The final profile (black circles) in Fig. 3 shows the exchange of the α protons from this sample as a function of time. Two features should be noted here. Firstly the added DMAP does undergo H–D exchange—proving that the formation of the nanoparticles is not a crucial step in the exchange process, and secondly, the rate of decrease of the signal attributed to the α protons is far lower than it was initially for fresh nanoparticles. An induction period of ~5 h is noted before exchange begins and over 30% of the α protons remained un-exchanged after ~50 h of further reaction at 50 °C. *Note*: In the case of the fresh nanoparticles approximately twice this concentration of DMAP underwent ~90% exchange at 50 °C in roughly 3 h.

The fact that extra DMAP added to the nanoparticle dispersion also undergoes H–D exchange is important when considering the possible modularity of this catalyst and extension of its activity to other related molecules (discussed later).

3.3. Effect of dispersion age

The final result above also suggests that the promotion of the H–D exchange reaction becomes less effective as the nanoparticles age. We envisage two possible explanations for this behaviour, *i.e.* the Pd surface becomes passivated due to the build-up of 2nd and subsequent layers of stabilising DMAP or the Pd surface becomes deactivated due to the formation of a passivating oxygen over-layer. To further assess this feature the activity of two differently aged nanoparticle dispersions in promoting the exchange of the α protons of freshly added DMAP was determined.

In Fig. 4 the H–D exchange profile of a fresh dispersion (at 50 °C) is compared to that of a dispersion which had been aged for 1 month (with additional DMAP added to ~40% of the concentration present in the initial preparation). It is clear that (as expected from the results shown in Fig. 3) the H–D exchange rate is far faster over the fresh dispersion than over the aged dispersion. Over 70% of the α protons of the DMAP added to the aged nanoparticle dispersion still remain un-exchanged after 170 h in D_2O.

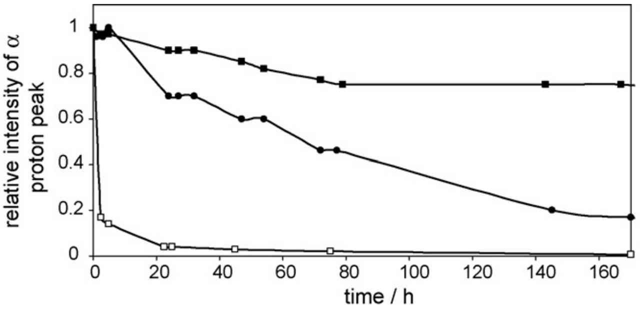


Fig. 4. Plot of α ^{1}H resonance intensity as a function of time in DMAP stabilised Pd nanoparticle dispersions held at 50 °C. (□) Fresh dispersion, (■) 1-month-old dispersion, (●) 1-month-old dispersion following a treatment in H_2/Ar.

3.4. Effect of treatment with H_2

Several authors [12,13,25,26] who have previously studied exchange reactions over group VIII metals have used "catalytic amounts" of H_2 within their reaction protocols. We assume (although it is not explicitly stated) that at least one function of H_2 is to keep the Pd in a reduced state although Esaki et al. [15,26] also postulate a direct role for H_2 in the reaction mechanism for the H–D exchange of the carbon skeleton of aliphatic alcohols. These authors also speculate that H_2 may keep Pd in a zero valent state.

The third profile in Fig. 4 shows the H–D exchange activity of an aged dispersion (at 50 °C) that had been pre-treated in bubbling H_2/Ar (3% H_2) for 30 min at this temperature prior to the addition of the extra DMAP.

It is obvious that the rate of H–D exchange over this aged and H_2-treated dispersion (while not being as rapid as that of the fresh catalyst) is significantly higher than that of the aged nanoparticle dispersion which has not been so treated. If it is assumed that the H_2 facilitates the reduction and removal of any Pd–O surface species (and it has been shown that H_2 can reduce particles of Pd–O below room temperature) [27–29] then we can suggest that a reason for decreased H–D exchange rate over older nanoparticle dispersions relates to the formation of an oxygen containing species which either blocks access to the surface or modifies the interaction of the pyridine-containing molecules with the surface in a manner that slows the reaction.

As an aside, these particular nanoparticles are oxidation sensitive and do rapidly oxidise under atmospheric conditions to yield a Pd(II) DMAP complex [21,22]. However, the rate of this atmospheric oxidation slows over time (such that the nanoparticles are stable for periods in excess of 6 months) and we assume that this is also due to the build-up of a passivating overlayer on the Pd surface.

Further experiments (results not shown) using nanoparticle dispersions which were aged for longer than that shown in Fig. 4 (4 month versus 1 month aged) showed similar activity profiles in the absence and presence of H_2. This shows that further aging does not severely further affect the activity of these nanoparticles.

To our knowledge there are no reports of the formation of any such oxygen over-layers on Pd nanoparticles following room temperature exposure to O_2. However, recent work, using model supported Pd nanoparticle systems, has shown that Pd nanoparticles chemisorb O_2 at temperatures below 400 K [30–32] and that the extent of this oxidation varies inversely as a function of the nanoparticle size. Thus it is not improbable that the nanoparticles described here are – to some extent – poisoned by O_2 following their preparation.

3.5. Immobilisation of the nanoparticles and recycling of the supported Pd catalyst

In order for this catalytic system to be of practical use in the production of selectively deuterated molecules for use in further kinetic, radiotracer or calibration functions it is obviously necessary to be able to remove the product molecules from the reaction mixture. Isolating the deuterated DMAP molecules from the nanoparticle dispersion following the exchange reaction, by necessity, involves precipitating the nanoparticles since the DMAP plays a vital role in stabilising the nanoparticles against aggregation and irreversible precipitation.

This is not ideal in terms of a modular catalytic process where a recyclable catalyst would be desired. Immobilising the nanoparticles onto a solid support offers a solution to this issue. Previously we have immobilised these nanoparticles onto thiolated multi-walled carbon nanotubes [22,23] (see Section 2.1.3) and have used

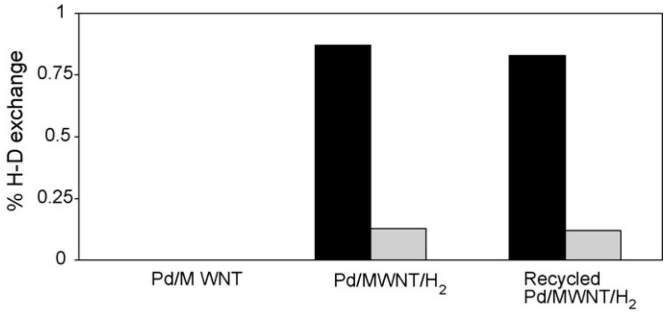


Fig. 5. Histogram showing normalised activity, selectivity and re-cyclability of the Pd-MWCNT composite material in promoting the selective H–D exchange reaction of DMAP molecules in the presence and absence of $H_{2(g)}$. The experiment involved a 5 h reaction at 50 °C. α proton selectivity (black columns), β proton selectivity (grey columns).

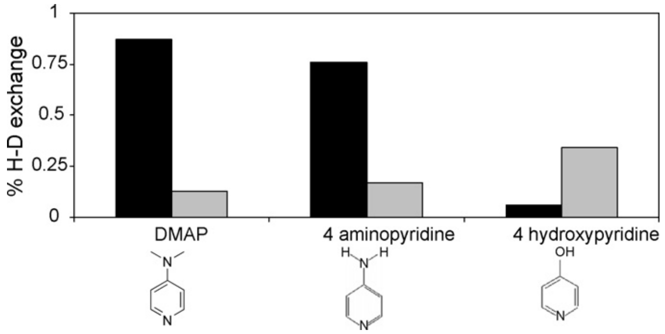


Fig. 6. Histogram showing normalised activity and selectivity of Pd-MWCNT composite catalyst in promoting the H–D exchange reaction of DMAP, 4-aminopyridine and 4-hydroxypyridine molecules in the presence of $H_{2(g)}$. The experiment involved a 5 h reaction at 50 °C. α proton selectivity (black columns), β proton selectivity (grey columns).

these composite materials as recyclable catalysts in model Suzuki coupling reactions [23] where they have shown no deterioration in activity following more than 5 reaction cycles under reaction conditions far harsher than those employed here.

Another benefit of such immobilisation would be that selective H–D exchange reactions could be performed on pyridine-containing molecules that do not themselves stabilise the Pd nanoparticles. This is in contrast with the nanoparticle dispersion catalysed system discussed above where only molecules that can absorb onto the nanoparticle surface, form an electrical double layer and thus prevent irreversible aggregation may undergo selective H–D exchange in this manner. Other advantages in this process are that any work-up procedure would be considerably simplified in the presence of a heterogeneous catalyst and the possibility of Pd atom incorporation into the product molecules is much decreased.

Fig. 5 shows the H–D exchange levels observed using the Pd-MWCNT composite as a catalyst following a 5 h reaction at 50 °C. The levels of Pd present in the reaction mixtures were approximately 1.3 μmol, *i.e.* ~8 mol% of the reaction mixture.

The first set of data indicates that no H–D exchange whatsoever is observed under these reaction conditions using the Pd-MWCNT composite material directly following its preparation.

The second data set shows that there is a dramatic increase in reactivity when the reactions are carried out in the presence of bubbling H_2/Ar. The activity is dramatically increased but there is a decrease in selectivity, with a certain amount (~13%) of the β protons also becoming exchanged.

We can attribute the increased reactivity to the presence of H_2 which removes Pd–O species from the surface of the catalyst thereby freeing adsorption sites for the added DMAP to adsorb and undergo the exchange reaction.

The formation of a certain amount of β exchanged DMAP molecules is also not a surprise given the elevated temperature of this reaction. Under these conditions the nanoparticle dispersion itself (see above) also catalyses a certain amount of non-selective aromatic H–D exchange. Thus it is clear that carrying out the exchanges at lower temperatures leads to slower but more selective reactions.

The final set of data shows that the composite material can behave as a recyclable catalyst following filtration and washing. In a repeat H–D exchange experiment using the same sample of catalytic composite with freshly added DMAP, it is observed that the activity and selectivity of the composite is not significantly altered (α exchange falls from 87% to 83% and the level of β exchange falls from 13% to 12%). Therefore it can be concluded that the composite is an active and recyclable catalyst for this particular exchange reaction.

3.6. Extending the H–D exchange reaction to related substrates

While the prepared composite can be used and reused to promote the selective exchange reaction of the α protons in DMAP, it would be exceptionally useful if the selectivity and reactivity of the material could be extended to other related substrates. In our first attempt to extend the activity and selectivity of the composite to related substrates of interest the two analogues 4-aminopyridine and 4-hydroxypyridine were chosen for further study. It should be noted that previously Werstiuk and Ju [33] have exchanged the aromatic protons on 2-hydroxy pyridine and 2-mercapto pyridine using D_2O as a deuterium source. These authors noted a certain amount of selectivity in the reaction with hydrogen at C3, C5 and C6 preferentially exchanging in both molecules. However, these reactions were carried out at temperatures of 200 °C and 260 °C in the absence of any catalyst. We would hope that the process described here would provide H–D exchange selectivity under far more benign conditions.

Fig. 6 shows the level of H–D exchange observed for the α and β protons of these molecules using the Pd-MWCNT composite following the same reaction regime as was used in the reactions shown in Fig. 5 (*i.e.* a 5 h reaction at 50 °C). The reactivity and selectivity of the exchange reaction using DMAP as the substrate and composite as the catalyst are also shown to aid comparison.

The first alternative substrate analysed for selective H–D exchange was 4-aminopyridine. The H–D exchange characteristics (level of α and β exchange) following such a 5 h reaction in D_2O with the composite material in the presence of bubbling H_2/Ar are similar to those of the DMAP molecule, *i.e.* 76% α exchange and 17% β exchange (compared to 87% and 13% respectively for DMAP). This shows that the 4-aminopyridine has similar adsorption and reaction properties to its dimethylated analogue.

When the substrate is further altered (to 4-hydroxy pyridine) the H–D exchange reactivity is much decreased and the α/β selectivity is inverted, *i.e.* the overall level of aromatic H–D exchange is lower than in the previous cases and the selectivity is altered in that the β protons of the aromatic ring (34% exchanged after 5 h) are more rapidly exchanged than the α protons (6% exchanged after 5 h). This suggests that the 4-hydroxypyridine co-ordinates in a different manner to the surface of the Pd nanoparticles than the aminopyridine-type molecules and that this co-ordination is of extreme importance in the reaction process.

These reactions were also repeated with recycled composite materials and the activity/selectivity profiles were not significantly different from those shown in Fig. 6 (results not shown).

4. Conclusions

An aqueous phase dispersion of Pd nanoparticles with a mean diameter of 3.4 ± 0.5 nm can catalyse the selective H–D exchange reaction at carbons α to the endocyclic N atom of the aromatic ring of pyridine-containing compounds through reaction with D_2O.

Increasing the temperature increases the rate of this exchange but decreases the selectivity of the reaction with minor amounts of H–D exchange also occurring at the β position of the aromatic ring.

The reaction is slower using aged nanoparticles and this decrease in activity is ascribed to the growth of an oxygen overlayer with time following the initial preparation of the dispersion. This effect can be ameliorated by pretreatment of the particles in H_2 prior to reaction or by the continuous bubbling of $H_{2(g)}$ into the reaction mixture.

The system can be heterogenised by immobilisation of the Pd nanoparticles onto functionalised (thiolated) multi-walled carbon nanotubes thereby generating a Pd-MWCNT composite. This composite material is active in promoting the H–D exchange reaction at the α position of DMAP and 4-aminopyridine.

However, attempts to extend this activity and selectivity to other related molecules have shown that the presence of other functional groups within the substrate of interest can have detrimental consequences for both the activity and the selectivity of the reaction. We ascribe this effect to varied modes of coordination of the substrates to the Pd nanoparticle surface resulting in different selectivities.

Acknowledgements

We gratefully acknowledge funding from EPA Ireland and invaluable discussions with Prof M. Brust. We also acknowledge funding to allow JAS to attend the Helsinki workshop from the COST network through COST action D36 and funding for HH through the EU Socrates-Erasmus exchange programme.

References

[1] D.M. Marcus, K.A. McLachlan, M.A. Wildman, J.O. Ehresmann, P.W. Kletnieks, J.F. Haw, Angew. Chem. 118 (2006) 3205–3208.
[2] T. Junk, W.J. Catallo, Chem. Soc. Rev. 26 (1997), 26, 401.
[3] M. Okazaki, N. Uchino, N. Nozaki, K. Kubo, Bull. Chem. Soc. Jpn. 68 (1995) 1024.
[4] M. Saljoughian, P.G. Williams, Curr. Pharm. Des. 6 (2000) 1029.
[5] N. Elander, J.R. Jones, S.-Y. Lu, S. Stone-Elander, Chem. Soc. Rev. 29 (2000) 239.
[6] J. Atzrodt, V. Derdau, T. Fey, J. Zimmermann, Angew. Chem. Int. Ed. 46 (2007) 7744.
[7] A.E. Perelman, B.I. Vishnevskii, G.I. Vavilin, T.B. Ilina, T.M. Yakovleva, V.A. Kropachev, L.B. Trukhmanova, Pharm. Chem. J. 11 (1977) 1573.
[8] Y. Higashio, T. Shoji, Appl. Catal. A: Gen. 260 (2004) 251.
[9] A.R. Sherman, Encyclopedia of Reagents for Organic Synthesis, J. Wiley and Sons, New York, 2004.
[10] E. Alexakis, J.R. Jones, W.J.S. Lockley, Tetrahedron Lett. 47 (2006) 5025.
[11] J. Azran, M. Shimoni, O. Buchman, J. Catal. 148 (1994) 648.
[12] N. Ito, T. Watahiki, T. Maesawa, T. Maegawa, H. Sajiki, Adv. Synth. Catal. 348 (2006) 1025.
[13] H. Sajiki, N. Ito, H. Esaki, T. Maesawa, T. Maegawa, K. Hirota, Tetrahedron Lett. 46 (2005) 6995.
[14] T. Maegawa, A. Akashi, H. Esaki, F. Aoki, H. Sajiki, K. Hirota, Synlett 5 (2005) 845.
[15] H. Esaki, F. Aoki, T. Maegawa, K. Hirota, H. Sajiki, Heterocycles 66 (2005) 361.
[16] H. Esaki, F. Aoki, M. Umemura, M. Kato, T. Maegawa, Y. Monguchi, H. Sajiki, Chem. Eur. J. 13 (2007) 4052.
[17] V. Derdau, J. Atzrodt, SynLett 12 (2006) 1918.
[18] H. Sajiki, F. Aoki, H. Esaki, T. Maegawa, K. Hirota, Org. Lett. 6 (9) (2004) 1485.
[19] H. Esaki, N. Ito, S. Sakai, T. Maegawa, Y. Monguchi, H. Sajiki, Tetrahedron 62 (2006) 10954.
[20] V. Derdau, J. Atzrodt, W. Holla, J. Label Compd. Radiopharm. 50 (2007) 295–299.
[21] K.A. Flanagan, J.A. Sullivan, H. Mueller-Bunz, Langmuir 23 (2007) 12508.
[22] K.A. Flanagan, PhD Thesis, UCD, 2007.
[23] J.A. Sullivan, K.A. Flanagan, H. Hain, Catal. Today, submitted for publication.
[24] T. Sainsbury, D. Fitzmaurice, Chem. Mater. 16 (2004) 2174.
[25] H. Sajiki, K. Hattori, F. Aoki, K. Yasunaga, K. Hirota, Synlett 7 (2002) 1149.
[26] H. Esaki, R. Ohtaki, T. Maegawa, Y. Monguchi, H. Sajiki, J. Org. Chem. 72 (2007) 2143.
[27] K. Muto, M. Katada, M. Niwa, Appl. Catal. A: Gen. 134 (1996) 203.
[28] Z. Karpinski, Adv. Catal. 37 (1990) 45.
[29] C.B. Wang, H.K. Lin, C.M. Ho, J. Mol. Catal. A: Chem. 180 (2002) 285.
[30] T. Schalow, B. Brandt, D.E. Starr, M. Laurin, S.K. Shaikhutdinov, S. Schauermann, J. Libuda, H.J. Freund, Angew. Chem., Int. Ed. 45 (2006) 3693.
[31] T. Schalow, B. Brandt, M. Laurin, S. Guimond, D.E. Starr, S.K. Shaikhutdinov, S. Schauermann, J. Libuda, H.J. Freund, Top. Catal. 42 (2007) 387.
[32] T. Schalow, B. Brandt, D.E. Starr, M. Laurin, S.K. Shaikhutdinov, S. Schauermann, J. Libuda, H.J. Freund, Phys. Chem. Chem. Phys. 9 (2007) 1347.
[33] N.H. Werstiuk, C. Ju, Can. J. Chem. 67 (1989) 5.