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# Mixed Pd/C and Pt/C as efficient catalysts for deuteration of Mesalamine

Sabera Bijani<sup>a</sup>, Vicky Jain<sup>a</sup>, Dharmarajan Padmanabhan<sup>b</sup>, Bipin Pandey<sup>a</sup>, Anamik Shah<sup>a,\*</sup>

<sup>a</sup> National Facility for Drug Discovery Centre, Department of Chemistry (UGC-DRS-II and DST-FIST-II Funded), Saurashtra University, Rajkot 360 005, India <sup>b</sup> Quality Control Programme, Radiopharmaceuticals, Board of Radiation and Isotope Technology, Sector 20, Vashi, Navi Mumbai 400 703, India

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# ABSTRACT

An unprecedent, efficient, and convenient lab-scale protocol for stable deuteration of Mesalamine, with mixed catalyst 10% Pd/C (10 wt %) and 10% Pt/C (25 wt %) at 145 °C, using D<sub>2</sub>O as deuterium source, in hydrogen atmosphere, is reported. The nature of reactive species with Pd/C-Pt/C-D<sub>2</sub>O-H<sub>2</sub> system is suggested to be of electrophilic nature D<sup>+</sup> type.



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# Introduction

Pharmaceutical companies<sup>1</sup> and leading new chemical entity (NCE) researchers in medicinal chemistry<sup>2</sup> are beginning to observe opportunities on the idea that simply switching of the C–H bond to the C–D bond in existing drugs can create drugs with altered physiological profiles. The kinetic isotope effect due to deuterium substitutions has significant pharmacological consequences on the metabolic profile, toxicity, efficacy, and various other important attributes required for NCE selection. Deuterated compounds are additionally required as reference internal standards in mass spectrometry studies during DMPK,<sup>2</sup> pesticides, and environmental pollutant studies. This has created a renaissance in the interest for developing synthetic methodologies for efficient deuteration.<sup>3</sup> One of the prominent methods of late stage deuteration is the use of transition metal catalysts or precious metals for example Ir,<sup>4</sup> Rh,<sup>5</sup> Re,<sup>6</sup> Pt,<sup>7</sup> Pd,<sup>8</sup> and Cr<sup>9</sup> with or without

E-mail address: anamik\_shah@hotmail.com (A. Shah).

carbon, including the oxidized form of metals like  $PtO_{2.}^{10}$  However, mostly single metal induced catalysis is reported.<sup>11</sup> This study reports a method consisting of the synergistic effect of the Pd/C-Pt/C-D<sub>2</sub>O-H<sub>2</sub> system for the tri-functional group attached to the aromatic ring, Mesalamine or 5-aminosalicylic acid **1a**. The critical parameter of methodology has been optimized with respect to initial purging and maintenance of the H<sub>2</sub> atmosphere, the role and % of individual catalysts, the substrate to mixed catalyst weight ratios, the role of temperature, and the duration of heating in a sealed tube. Additionally, the nature of reactive species as electron deficient as a D<sup>+</sup>, is suggested during deuteration with D<sub>2</sub>O and mixed catalysts. The relevance of mechanistic insights has been discussed in the light of weak co-ordinations of palladium charcoal<sup>12</sup> and the rapidly growing field of C–H activation.<sup>13</sup>

Recently, a large number of H–D exchange procedures for aromatic, aliphatic, and heterocyclic compounds, have been reported using D<sub>2</sub>O. Some of these exchanges are catalyzed by acids,<sup>14</sup> bases,<sup>15</sup> or transition metals. These synthetic challenges have led to the discovery of special deuterated reagents NaBD<sub>4</sub>,<sup>16</sup> 9-[<sup>2</sup>H]-9-phenylfluorene,<sup>17</sup> DMSO-D<sub>6</sub>,<sup>18</sup> etc. The use of Pd/C and Pt/C has been reported by Sajiki et al.<sup>19</sup> for mono-substituted





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<sup>\*</sup> Corresponding author. Tel.: +91 94284 66077, +91 98252 15656; fax: +91 (0281) 2577633/2583984.

(alkyl, –OH, –NH<sub>2</sub>, –COOH, etc.) aromatics and concluded that Pd/C is suitable as an aliphatic substituent, while Pt/C is effective for aromatic deuteration. However, several of these methods lack in functional group tolerance, need vast amount of catalysts, or require a classy deuterium atmosphere with special apparatus, leading to low deuterium efficiency. There are very limited studies on poly-functional aromatics, much less on a drug. Recently, Sajiki et al.<sup>19</sup> have reported the deuteration of Ibuprofen, which has an aromatic and aliphatic component with –COOH far away from aromatics, by sequential use of Pd/C and Pt/C catalysts.

Mesalamine,<sup>20</sup> also known as Mesalazine or 5-aminosalicylic acid (5-ASA) **1a**, is the therapeutically active moiety of sulfasalazine<sup>21</sup> used to treat inflammatory bowel disease, such as ulcerative colitis and mild-to-moderate Crohn's disease. Chemically, –OH, –NH<sub>2</sub>, and –COOH are attached to the benzene ring, which makes it a poly-functional aromatic compound.

## **Results and discussion**

Initially, we studied the deuteration of 5-aminosalicylic acid using Rh/C, Pd/C, and Pt/C separately or mixed them as a catalyst and Table 1 summarizes a comparison of deuterium incorporation. Deuteration of Mesalamine **1a** was conducted by 25 weight percent of 10% Rh/C (Table 1, entry 1), 25 weight percent of 10% Pd/C (Table 1, entry 2), and 25 weight percent of 10% Pt/C at 150 °C for 48 h (Table 1, entry 3) in a sealed tube. All these studies involved purging and maintenance of the H<sub>2</sub> atmosphere. Mixed catalytic systems were also employed and unexpected variance in deuteration was observed. A combination of Pt and Rh afforded average deuterium incorporation, while a combination of Pd and Rh afforded notable regioselectivity (Table 1, entries 4 and 5).

From the above studies, Pd/C and Pt/C, mixed catalysts were chosen for further optimization (Table 2). As evidenced previously, Pt/C led to better deuteration of aromatic C–H than Pd/C, under identical conditions (Table 2, entries 1 and 2).

Although deuteration was incomplete in both cases (Table 2, entries 1 and 2), but marked regioselectivity in both studies was noteworthy (Fig. 1). In both the reactions, the C4 position was least deuterated, which is *para* to the carboxylic acid group and *meta* to the hydroxyl group (Fig. 1).

Indeed the regioselectivity indicates the presence of an electrophile type D<sup>+</sup> reactive species.<sup>22</sup> A careful examination of regioselectivity reported for aniline, benzoic acid, and 2-amino

#### Table 1

Comparison of deuteration efficiency of different catalytic systems

Entry	Catalysts			Temp	Time	% Deuteration <sup>b</sup>		
	10% Pt/C (% w/w)	10% Pd/C (% w/w)	10% Rh/C (% w/w)	(°C)	(h)	C3 (% of D)	C4 (% of D)	C6 (% of D)
1	_	_	25	150	48	79.0	76.0	84.0
2	-	25	-	150	48	40.8	23.8	37.9
3	25	_	-	150	48	78.6	58.9	80.8
4	25	_	10	150	48	70.0	53.0	72.0
5	_	25	10	150	48	77.0	21.0	12.0
6	20	5	_	150	48	94.7	92.0	90.5

phenol in recent literature<sup>19</sup> hints at the possibility of electrophilic type substitution in these reactions (Fig. 2).

Such pronounced regioselectivities are nullified, when *N*-acetylated Mesalamine **1c** is deuterated (Fig. 1). Such mechanistic insights are also substantiated by the fact that electron withdrawing groups for example -COOH,  $-NO_2$ , and  $-NHCOCH_3$  reduce reactivity, evidenced by lower levels of deuteration or longer reaction times or the requirement of more catalysts. Apparently, these mechanistic insights for C–H to C–D transformations may have a significant impact on the fast emerging field of C–H activation<sup>13</sup> and the weak coordination of Pd.<sup>12</sup>

With a view to enhancing the efficiency of deuteration, the role of a mixture of both catalysts was examined. Thus, entries 3-7(Table 2) describe the varying weight percent of 10% Pd/C and 10% Pt/C, which was heated for 48 h in a sealed tube in an atmosphere of H<sub>2</sub> gas. In these experiments, there is gradual increase of Pt/C, while maintaining an overall weight percent of mixed catalysts around 25–35% with respect to the substrate. As the results indicate, entry 7 with 10 weight percent of 10% Pd/C and 25 weight percent of 10% Pt/C, was found to afford optimum deuterium incorporation and the highest overall yields.

Subsequent optimization studies were focused on the duration of heating at 145 °C, by maintaining catalyst weight, and a ratio similar to entry 7. The efficiency of deuteration was examined at 4 h, 8 h, 12 h, 16 h, 20 h, 24 h, and 36 h (Table 2, entries 8–14). As data indicate, the best results could be obtained in 24 h (Table 2, entry 13) itself, which was half the time required in entry 7 (48 h). Thus, excellent deuterium efficiency was achieved with ~99.8% deuteration of 5-aminosalicylic acid **1a** to get deuterated 5-aminosalicylic acid **1b** (Table 2, entry 13).

The relevance of  $H_2$  purging and the maintenance of the  $H_2$  atmosphere was further confirmed by performing the reaction without/in absence of hydrogen using the same reaction conditions (Table 2, entry 15),<sup>23</sup> but results indicate that the presence of hydrogen is essential. Additionally, the role of temperature was also examined and the optimized reaction conditions of entry 13 were subjected to deuteration at room temperature, under identical conditions. Once again, a significant lowering in deuteration efficiencies was observed. The catalyst used in the reaction was found to be satisfactorily recycled up to three catalytic cycles.

The position of deuterium substitution in the aromatic ring and degree of deuteration have been determined by <sup>1</sup>H NMR measurements. Observed typical coupling patterns and *J* values in <sup>1</sup>H NMR

<sup>a</sup> 300 mg (1.96 mmol) of **1a** was used and reactions were carried out under a H<sub>2</sub> atmosphere using the catalyst in D<sub>2</sub>O (99.9% D content, 12 mL) in a sealed tube. <sup>b</sup> Deuterium incorporation was determined by quantitative NMR spectroscopy with *tert*-butanol as an internal reference.

#### Table 2

Optimization studies for deuterated 5-aminosalicylic acid 1a, using Pd/C or/and Pt/C<sup>a</sup>



Entry	Catalyst		Temp	Time	% Deuteration <sup>b</sup>			Yield <sup>d</sup>
	10% Pd/C (% w/w)	10% Pt/C (% w/w)	(°C)	(h)	C3 (% of D)	C4 (% of D)	C6 (% of D)	(%)
1	25	_	150	48	40.8	23.8	37.9	96
2	-	25	150	48	78.6	58.9	80.8	94
3	20	5	150	48	94.7	92.0	90.5	86
4	15	10	145	48	95.6	96.2	97.4	88
5	10	15	145	48	96.2	91.5	97.6	88
6	10	20	145	48	98.3	96.7	99.2	70
7	10	25	145	48	99.7	99.8	99.8	95
8	10	25	145	4	91.6	80.8	94.7	94
9	10	25	145	8	96.2	91.5	97.6	92
10	10	25	145	12	97.2	93.8	96.8	95
11	10	25	145	16	98.6	96.6	99.0	93
12	10	25	145	20	98.0	97.3	97.6	96
13	10	25	145	24	99.8	99.8	99.7	96
14	10	25	145	36	99.8	99.5	99.0	90
15 <sup>c</sup>	10	25	145	24	Traces			
16	10	25	rt	24	92.4	95.0	73.5	98
17 <sup>e</sup>	10	25	145	24	97.0	97.0	96.7	95

Bold entry demonstrates the best optimized condition.

<sup>a</sup> 300 mg (1.96 mmol) of the substrate was used and reactions were carried out under a H<sub>2</sub> atmosphere using the catalyst in D<sub>2</sub>O (99.9% D content, 12 mL) in a sealed tube. <sup>b</sup> Deuterium incorporation was determined by quantitative NMR spectroscopy with *tert*-butanol as an internal reference.

<sup>c</sup> Reaction was carried out without H<sub>2</sub> atmosphere.

<sup>d</sup> Isolated vield.

<sup>e</sup> N-Acetylated Mesalamine.







**Figure 2.** Regioselective deuterium incorporation<sup>a,b</sup> of related compounds. <sup>19a</sup>Numbers in the figure represent the % of deuteration on the adjacent carbon. <sup>b</sup>Numbers in the parenthesis represent the isolated yields.

for Mesalamine, fixing the position of C3, C4, and C6 protons, and the quantitative degree of deuteration were determined by a comparison of integration of methyls in *tert*-butanol, which was used as internal reference. The absence of peaks in <sup>13</sup>C NMR for deuterated carbons (C3, C4, and C6) in DEPT 90 and 135 was also indicative of complete deuteration for products **1b** (Table 2, entries 7 and 13). Triplets in <sup>13</sup>C NMR for deuterated carbons with a coupling constant of 20–22 Hz confirmed aromatic deuteration.

Further evidence of complete deuteration was obtained from satisfactory LC–MS and MS data. The chromatographic analysis was performed by using LC–MS with Acquity<sup>TM</sup> BEH C18 (50 mm × 2.1 mm i.d., 1.7  $\mu$  particle size) column and a flow rate of 0.3 ml/min. The mobile phase consisted of 3 mM Ammonium acetate with pH 6: Acetonitrile. Detection was monitored by an MS detector with the ESI mode. Detection was operated by a full scan mode with a range of 50–1200 Da with a 0.5 s scan time and a 0.02 s inter-scan delay. The Ion source temperature was maintained at 150 °C and a desolvation temperature of 600 °C. Desolvation gas flow at 1200 L/h and a gas flow of 60 L/h for sample, capillary, and extractor were maintained at 30 v, 3000 v, and 3 v, respectively.

## Conclusion

In summary, an unprecedent, efficient, and convenient late stage, post synthetic deuteration methodology for C–H to C–D transformation for a bulk drug Mesalamine has been developed, involving the synergistic effect of the Pd/C–Pt/C–D<sub>2</sub>O–H<sub>2</sub> system, for the tri-functional group attached to the aromatic ring, with catalysts 10% Pd/C (10 wt %) and 10% Pt/C (25 wt %) at 145 °C, using D<sub>2</sub>O as the deuterium source, under a hydrogen atmosphere. The role of H<sub>2</sub> gas purging and atmosphere, ratio of individual catalyst, substrate to mixed catalyst ratio, duration of heating, and temperature has been examined to achieve efficient deuteration. The rationale for observed pronounced regioselectivity at a lower level of deuteration in Mesalamine has been suggested to involve the electrophilic nature of the reactive species D<sup>+</sup> and substantiated with similar regioselectivity observed in the recent literature. This study opens up a new frontier of exploring reactivity and selectiv-

ity of the C–H to the C–D transformation with mixed catalysts. Further, studies are required to understand the exact role of synergistic effects associated with mixed catalysts.

# Experimental

To a solution of 5-aminosalicylic acid **1a** (300 mg, 1.96 mmol) in  $D_2O$  (12 mL), 10% Pd/C (30 mg, 10 wt % of **1a**) and 10% Pt/C (75 mg, 25 wt % of **1a**) were charged, under a  $H_2$  atmosphere and the reaction mixture was heated at 145 °C in a sealed tube, for a designated time, as noted in Table 2. The workup involved the treatment of the reaction mixture with methanol (40 mL), stirring, and filtering the catalyst. The filtrate was concentrated under reduced pressure and the residue was triturated with *n*-hexane to yield the desired product, which was filtered and dried in an oven for further analysis.

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- 22. The observed regioselectivity, due to D<sup>+</sup> type electrophilic nature of reactive species, is true for partial deuteration only. This may not be true for complete deuteration example, where >99% deuteration is observed.
- 23. The role of initial hydrogen bubbling and positive pressure during deuteration is to deoxygenate the solvent and maintain elemental reactive state of Pd and Pt on charcoal, in a reductive atmosphere.