



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



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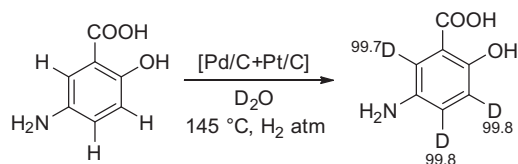
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ABSTRACT

An unprecedented, 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 D₂O as deuterium source, in hydrogen atmosphere, is reported. The nature of reactive species with Pd/C–Pt/C–D₂O–H₂ system is suggested to be of electrophilic nature D⁺ type.



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Introduction

Pharmaceutical companies¹ and leading new chemical entity (NCE) researchers in medicinal chemistry² 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,² pesticides, and environmental pollutant studies. This has created a renaissance in the interest for developing synthetic methodologies for efficient deuteration.³ One of the prominent methods of late stage deuteration is the use of transition metal catalysts or precious metals for example Ir,⁴ Rh,⁵ Re,⁶ Pt,⁷ Pd,⁸ and Cr⁹ with or without

carbon, including the oxidized form of metals like PtO₂.¹⁰ However, mostly single metal induced catalysis is reported.¹¹ This study reports a method consisting of the synergistic effect of the Pd/C–Pt/C–D₂O–H₂ 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 H₂ 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⁺, is suggested during deuteration with D₂O and mixed catalysts. The relevance of mechanistic insights has been discussed in the light of weak co-ordinations of palladium charcoal¹² and the rapidly growing field of C–H activation.¹³

Recently, a large number of H–D exchange procedures for aromatic, aliphatic, and heterocyclic compounds, have been reported using D₂O. Some of these exchanges are catalyzed by acids,¹⁴ bases,¹⁵ or transition metals. These synthetic challenges have led to the discovery of special deuterated reagents NaBD₄,¹⁶ 9-[²H]-9-phenylfluorene,¹⁷ DMSO-D₆,¹⁸ etc. The use of Pd/C and Pt/C has been reported by Sajiki et al.¹⁹ for mono-substituted

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(alkyl, –OH, –NH₂, –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.¹⁹ 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,²⁰ also known as Mesalazine or 5-aminosalicylic acid (5-ASA) **1a**, is the therapeutically active moiety of sulfasalazine²¹ used to treat inflammatory bowel disease, such as ulcerative colitis and mild-to-moderate Crohn's disease. Chemically, –OH, –NH₂, 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 H₂ 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⁺ reactive species.²² A careful examination of regioselectivity reported for aniline, benzoic acid, and 2-amino

phenol in recent literature¹⁹ 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, –NO₂, and –NHCOCH₃ 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 activation¹³ and the weak coordination of Pd.¹²

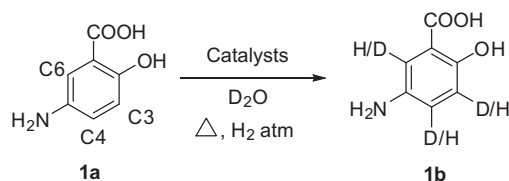
With a view to enhancing the efficiency of deuteration, the role of a mixture of both catalysts was examined. Thus, entries 3–7 (Table 2) describe the varying weight percent of 10% Pd/C and 10% Pt/C, which was heated for 48 h in a sealed tube in an atmosphere of H₂ gas. In these experiments, there is 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 H₂ purging and the maintenance of the H₂ atmosphere was further confirmed by performing the reaction without/in absence of hydrogen using the same reaction conditions (Table 2, entry 15),²³ 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 ¹H NMR measurements. Observed typical coupling patterns and *J* values in ¹H NMR

Table 1
Comparison of deuteration efficiency of different catalytic systems^a



Entry	Catalysts			Temp (°C)	Time (h)	% Deuteration ^b		
	10% Pt/C (% w/w)	10% Pd/C (% w/w)	10% Rh/C (% w/w)			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

^a 300 mg (1.96 mmol) of **1a** was used and reactions were carried out under a H₂ atmosphere using the catalyst in D₂O (99.9% D content, 12 mL) in a sealed tube.

^b Deuterium incorporation was determined by quantitative NMR spectroscopy with *tert*-butanol as an internal reference.

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