

## Aromatic ring favorable and efficient H–D exchange reaction catalyzed by Pt/C

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**Abstract**—An effective and applicable Pt/C-catalyzed deuteration method of aromatic rings using D<sub>2</sub>O as a deuterium source under hydrogen atmosphere was developed. Five percent Pt/C would lead to quite effective H–D exchange results on the aromatic ring systems. The reaction is general for a variety of aromatic compounds including biologically active compounds.

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Biologically active compounds, such as drugs, pesticides, and environmental pollutants, labeled with deuteriums are widely used as research tools in life sciences.<sup>1</sup> Since a large number of drugs possess aromatic rings within the molecule, the substitution of deuterium for hydrogen by the hydrogen isotope exchange reaction of aromatic compounds in the presence of a catalyst is an attractive method for introducing deuteriums post-synthetically into the aromatic ring. Conventional deuterium-labeling procedures of aromatic compounds include H–D exchange catalyzed by acids,<sup>2</sup> bases<sup>3</sup> or transition metals (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>) and supercritical exchange reactions,<sup>10</sup> while many such methods include contraindication with specific functionalities, low deuterium efficiency and/or requirement of a vast amount of catalyst or extremely expensive deuterium atmosphere. Recently, Matsubara et al. developed a notable deuterium exchange method in hydrothermal D<sub>2</sub>O (ca. 250 °C/4 MPa) using Pd/C or PtO<sub>2</sub> as a catalyst<sup>11</sup> although only a few practical exchanges of the deuterium incorporation into aromatic ring systems, such as *t*-butylbenzene and biphenyl,<sup>11a</sup> *n*-butylbenzene,<sup>11b</sup> and sterically hindered arylsilanes<sup>11c</sup> were reported in the literature.

We also recently reported that 10% Pd/C efficiently catalyzed low (room)-temperature and chemoselective H–D exchange at the benzylic position<sup>12</sup> and high (110–160 °C)-temperature and multi-deuterium incorporation into many different types of unactivated alkyl chains<sup>13</sup> using D<sub>2</sub>O in the presence of a small amount of H<sub>2</sub> gas. In search of a heterogeneous catalyst that could promote especially effective deuterium exchange between aromatic ring systems and D<sub>2</sub>O, we decided to study the aqueous H–D exchange behavior of Pt on carbon (Pt/C) known as highly compatible with an aromatic ring under hydrogenation conditions.<sup>14</sup> We report here that 5% Pt/C would lead to quite effective H–D exchange results on the aromatic ring systems better than those of 10% Pd/C catalyst studied previously.

Typically, the reactions were carried under ordinary hydrogen pressure using 5% Pt/C (20 wt % of the substrate) in D<sub>2</sub>O at room temperature to 180 °C in a sealed tube. Examination of the <sup>1</sup>H NMR spectrum of the reaction product with *p*-anisic acid or dioxane as an internal standard shows quite efficient deuterium contents on the aromatic ring.

To explore the scope of this method, the deuteration of a number of aromatic substrates was investigated and Table 1 summarizes a comparison of deuterium efficiency of the aromatic ring using 5% Pt/C and 10% Pd/C as a catalyst under a variety of reaction temperatures.<sup>15</sup> Most of the substrates indicate satisfactory deuterium incorporation into the aromatic ring and

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**Table 1.** Comparison of deuterium efficiency of aromatic compounds using 5% Pt/C and 10% Pd/C as a catalyst<sup>a,b,c</sup>

Substrate		Catalyst, H <sub>2</sub> D <sub>2</sub> O, 24 h		Substrate-d <sub>n</sub>	
Entry	5% Pt/C			10% Pd/C	
1					
	rt (63%)			80 °C (60%) 180 °C (40%)	
2					
	rt (92%)			rt (92%)	
3					
	80 °C (76%)			80 °C (61%)	
4					
	rt (53%) 80 °C (59%)			80 °C (54%) 180 °C (48%)	
5					
	80 °C (79%) 180 °C (85%)			80 °C (85%) 180 °C (73%)	
6					
	80 °C (69%)			80 °C (88%)	
7					
	180 °C (69%)			180 °C (79%)	
8					
	rt (64%) 80 °C (59%)			180 °C (79%)	
9					
	80 °C (62%) 180 °C (62%)			80 °C (60%) 180 °C (63%)	
10					
	rt (58%) 80 °C (66%)			80 °C (60%) 180 °C (100%)	

**Table 1 (continued)**

Entry	5% Pt/C	10% Pd/C
9 <sup>d</sup>		
	80 °C (70%) 180 °C (66%)	180 °C (90%)
10		
	180 °C (58%)	180 °C (57%)
11 <sup>d</sup>		
	180 °C (100%)	180 °C (98%)
12		—
	rt (72%)	
13		—
	180 °C (88%)	
14		—
	rt (73%)	
15		—
	80 °C (88%)	

<sup>a</sup> 500 mg (3.0–5.4 mmol) of the substrate was used and reactions were carried out under ordinary H<sub>2</sub> pressure using 5% Pt/C (20 wt % of the substrate) or 10% Pd/C (10 wt % of the substrate) in D<sub>2</sub>O (99.9% D content, 17 mL) in a sealed tube and isolated yields were indicated in parentheses.

<sup>b</sup> D contents were determined by <sup>1</sup>H NMR and confirmed by <sup>2</sup>H NMR and mass spectrum and indicated in small figures in the table.

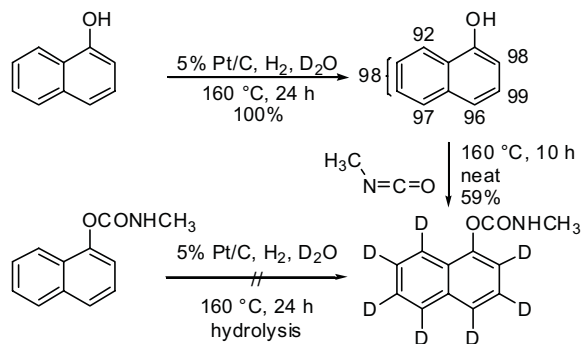
<sup>c</sup> Deuterium efficiency was indicated as the average D content in the case of a symmetrical structure.

<sup>d</sup> D contents were determined by <sup>1</sup>H NMR after the conversion of carboxylic acid into the corresponding methyl ester on the basis of the integration of the methyl protons.

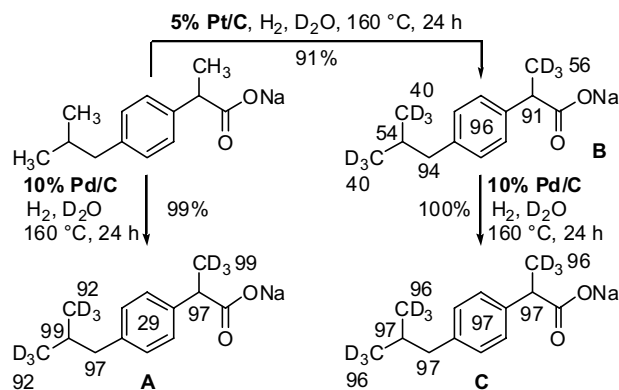
5% Pt/C-catalyzed reaction conditions always gave apparently better deuterium efficiency on the aromatic ring at the same or lower temperature. The efficiency into the side alkyl chain (propyl, entries 2 and 5; methyl, entry 4) was indicated to be better under the 10% Pd/C-catalyzed conditions. Even at room temperature (ca. 20 °C) nearly quantitative incorporation was observed in phenol<sup>16</sup> although 10% Pd/C required 180 °C to acquire the equivalent result (entry 1). In addition, 2-pro-

pylphenol was regioselectively deuterated at the 4, 5, and 6 positions of the aromatic ring at room temperature using 5% Pt/C as a catalyst (entry 2). Electron-sufficient aromatic compounds were well deuterated by using 5% Pt/C (entries 1–8). For electronically neutral and electron-deficient aromatic compounds, the desired H–D exchange reaction is less straightforward and relatively higher reaction temperature is necessary to achieve satisfactory results (entries 9–12)<sup>17</sup> although it is difficult to determine exactly the reason for the lower reactivity (electronic<sup>18</sup> or steric hindrance<sup>4i,11a,11c</sup> effect). On the other hand, 10% Pd/C-catalyzed H–D exchange reaction of electron-deficient aromatic rings reveals quite low deuteration efficiency even at 180 °C (entries 9–11). It is worth noting that the 5% Pt/C and 10% Pd/C-catalyzed deuteration tolerates carboxylic acid (entries 9 and 11)<sup>19</sup> and ester (entry 10) although the reaction mixture was heated up to 180 °C in the aqueous medium. Moreover, 5% Pt/C exerts excellent catalytic activity toward deuterium incorporation of a biphenyl and the thoroughly deuterated biphenyl-*d*<sub>10</sub> was obtained even at 80 °C (entry 13). The catalyst could be recovered almost quantitatively after simple filtration and it could be reused. The recovered 5% Pt/C was also effective in the 2nd and the 3rd reactions, and the isolated yields and deuterium efficiency of the 2nd and 3rd runs were comparable to those of the first run.

To reliably identify the residual pesticides, pharmaceuticals, environmental pollutants and so on in foods, water, atmospheric air, etc., using Mass or GC–mass spectrometry, analytical samples should be fortified with surrogate compounds (internal standards).<sup>20</sup> Since surrogate compounds should possess nearly equal physical properties to those of analytical mother samples, multi-deuterated mother samples may be employed for such purpose. As illustrated in [Scheme 1](#), 5% Pt/C-catalyzed deuteration process can also be useful for deuteration of carbaryl as a bactericide of domestic animals and carbaryl-*d*<sub>7</sub> can be applied to the microanalysis of residual carbaryl of meat as a surrogate compound. Carbaryl-*d*<sub>7</sub> was prepared in two steps starting from  $\alpha$ -naphthol with good chemical yield (59% two steps total yield) and deuterium efficiency without significant overreduction of the aromatic ring, because carbaryl was not stable enough under the aqueous deuteration conditions.



**Scheme 1.** Synthesis of carbaryl-*d*<sub>7</sub> as a surrogate compound.



**Scheme 2.** Stepwise synthesis of ibuprofen- $d_{17}$ .

We recently reported the excellent deuterium incorporation into the inactivated alkyl side chains of ibuprofen, an antiinflammatory drug, by 10% Pd/C-catalyzed H–D exchange reaction while the deuterium efficiency of the aromatic ring was only 29% (Scheme 2, A).<sup>13</sup> A useful application of 5% Pt/C and 10% Pd/C-catalyzed deuteration methods is to transform an aromatic compound possessing an alkyl side chain, such as ibuprofen, into an entirely deuterated product (C) via 5% Pt/C-catalyzed aromatic ring favorable deuteration of a mother aromatic compound with accompanying subsequent 10% Pd/C-catalyzed aliphatic side chain favorable deuteration of intermediary B as shown in Scheme 2.

In summary, we have developed a method for effective and applicable Pt/C-catalyzed deuteration of aromatic rings using D<sub>2</sub>O as a deuterium source under hydrogen atmosphere. The reaction is general for a variety of aromatic compounds including biologically active compounds. Further investigations directed toward elucidation of the detailed scope and limitation of those reactions are in progress.

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15. Exchange reactions using a nonaromatic substrate, for example, octanoic acid, led to almost no deuterium incorporation even at 180 °C with use of 5% Pt/C as a catalyst in analogy with the Pd work.<sup>13a</sup>
16. No deuterium incorporation was observed in the absence of hydrogen atmosphere (under nitrogen atmosphere) at room temperature for 24 h.<sup>12,13a</sup>
17. Recently, Skaddan et al. reported homogeneous Ir complex-catalyzed and effective deuterium-labeling method of aromatic compounds using acetone-*d*<sub>6</sub> as a deuterium source although the introduction of electron-withdrawing groups, such as ester, amide, carboxylic acid, and aldehyde, into the aromatic nucleus lowered the deuterium incorporation.<sup>41</sup>
18. The 5% Pt/C-catalyzed deuteration of nitrobenzene possessing a strong electron-deficient nitro group gave nearly no deuterium incorporation even at 180 °C and 60% of nitrobenzene was recovered without reduction of the nitro group.
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