Heterogeneous Platinum Metal Catalyzed Deuterium Generation and Labeling Methods Using Hydrogen Gas and Deuterium Oxide as Key Reagents

Hironao Sajiki

Abstract Deuterium (heavy hydrogen, D or ^{2}H), a stable isotope of hydrogen (^{1}H) consists of one proton, one neutron and one electron and used extensively in a wide range of fields including science, chemistry, medicine, etc. We have developed quite simple and post-synthetic D labeled methods using a combination of platinum metal on carbon and deuterium oxide (D_2O) as the catalyst and a D source in the presence of organic substrates, and a highly pure D_2 gas preparation method occurred at room temperature (rt) via the catalytic H_2–D_2 exchange reaction between the H atom of the H_2 gas with the D atom of D_2O without any substrates. This review illustrates and describes such straightforward and useful methodologies.

Keywords Deuterium labeling · H–D exchange · C–H activation · Platinum-group metal on carbon · Deuterium gas preparation · Deuterium oxide · Hydrogen gas

Deuterated products have received attention not only as useful tools for the investigation of drug metabolisms [1, 2] or reaction mechanisms [3, 4] as tracers or surrogate compounds, but also as functional materials such as fully deuterated polymers as components of optical fibers for high-speed telecommunication, which are virtually free of any optical absorption based on the C–H stretching vibration [5]. Multi-deuterated alkanes are anticipated as internal markers to prevent the distribution of illegal (illicit) light diesel oil [6] and deuterated medicines are expected to become new drugs having a longer duration of action based on the isotopic effect (resistant to the drug metabolism) [7]. Since the atomic nucleus of D can be fused with a tritium (T or ^{3}H) nucleus into a helium (He) and a neutron together with the emission of a massive amount of energy (fusion energy) [8], it is expected as one of the most useful new sources of energy that avoids CO_2 generation.

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As summarized above, D is widely used in a variety of scientific fields as a representative nuclide of a stable isotope. The precedent preparation methods of D-labeled compounds can be classified into three types: (1) total synthetic methods starting from small deuterated raw materials; (2) reduction of reducible functionalities using deuterated reducing agents; and (3) post-synthetic direct deuteration (H–D exchange reaction). It is patently obvious that the catalytic reduction using D_2 gas (deuterogenation) as a part of (2) and the catalytic H–D exchange reaction of non-deuterated compounds as (3) are preferable and practical methodologies associated with less waste. By the way, what kind of deuterium source is desired to achieve the H–D exchange reactions? The cheapest and most productive one is D_2O. Natural water contains ca. 0.015% (150 ppm) of the D atom [9], which exists in the form of HDO by a disproportionation equilibrium. The D-abundance ratio that is highly enriched by the dual temperature isotope exchange process utilizing the difference in the chemical equilibrium constant between HDS and HDO in a temperature-dependent manner [H_2S obtains a deuterium atom from HDO at a higher temperature (ca. 125 °C) and H_2O obtains a deuterium from HDS at a lower temperature (ca. 25 °C); Girdler-Sulfide (GS) method] [10, 11]. Although nearly pure D_2O has been industrially manufactured using the GS method, D_2 gas is still produced by electrolysis of the incrassate (nearly pure) D_2O using an enormous amount of electric energy. Since D_2 gas, D_2O and some deuterated compounds are designated as international controlled materials and subject to rigid control regarding import and export under security trade control, the development of efficient, mild, easily handled and catalytic preparation methods of regulated and combustible D_2 gas would have to be developed in the respective countries, or even, each manufacturing site including laboratories in order to avoid the export, import and transportation problems.

In this review, we would like to describe the efficient platinum metal on carbon-catalyzed post-synthetic direct H–D exchange reactions using D_2O as the deuterium source under a H_2 atmosphere and a simple replacement method of sealed H_2 gas by D_2 gas via the Pd/C-catalyzed H_2–D_2 exchange reaction between H_2 and D_2O developed by us.

1 Heterogeneous Platinum Metal Catalyzed Post-synthetic Deuterium Labeling Method Using D_2O as the Deuterium Source in the Presence of Hydrogen Gas

We have discovered that the H-atoms on the benzylic position of the substrate were time-dependently and site-selectively replaced with an equal number of D-atoms derived from D_2O under mild and Pd/C-catalyzed hydrogenation conditions (Fig. 1) [12–14].

The catalyst activity for the H–D exchange reaction under Pd/C–H_2–D_2O conditions was dramatically enhanced by the application of heat which facilitated the

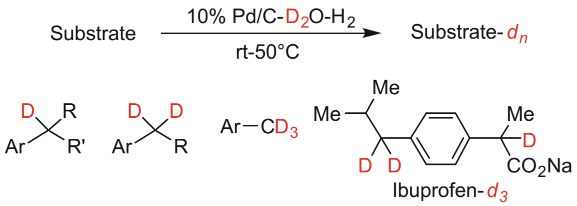


Fig. 1 H–D exchange reaction at the benzylic positions

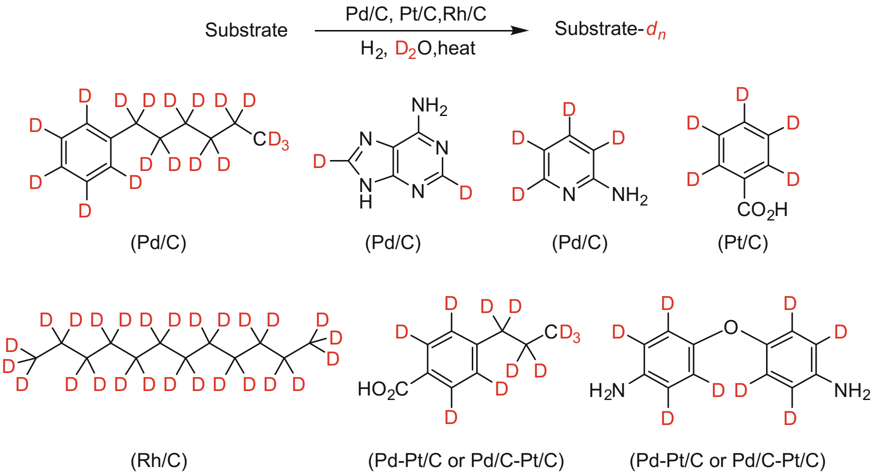


Fig. 2 Catalyst activity for the H–D exchange reaction

H–D exchange reaction at not only the benzylic sites, but also the inactive C–H bonds of alkyl-substituted aromatic compounds and heterocyclic nuclei [15–20]. Pt/C is an appropriate catalyst for the deuteration of aromatic nuclei, and the H–D exchange reaction smoothly proceeded under milder conditions [21, 22]. Furthermore, the mixed use of Pd/C and Pt/C or a bimetallic Pd–Pt on carbon was also found to be more efficient for the H–D exchange reaction in comparison to the independent use of Pd/C or Pt/C [23–25]. Furthermore, simple alkanes, which are inactive substrates by most definitions, could also be efficiently deuterated under the Rh/C-catalyzed heating conditions in a sealed tube (Fig. 2) [26].

The use of Ru/C enabled the regiospecific and efficient D incorporation at the α-position of alcohols at rt −80 °C and the results were applied as a regio- and stereoselective multi-deuteration method of sugar derivatives (Fig. 3) [27, 28].

H_2 gas is essential as an activating agent of the zero valent platinum group metal on carbon. Moreover, these H–D exchange methodologies are available to apply to the H–T (tritium, ^3H) exchange reaction using highly diluted tritiated water (THO) indicating a low level of radioactivity, and the multi-tritium incorporated products indicates a higher specific radioactivity in comparison to the HTO based on the suppression of the reverse reaction due to the isotope effect of T (Fig. 4) [29].

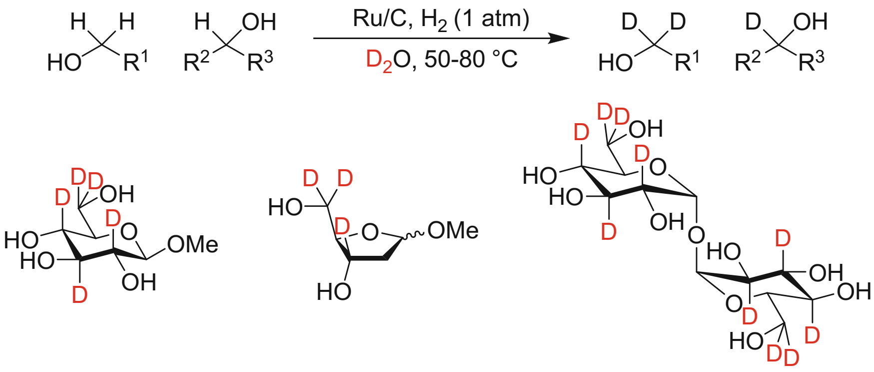


Fig. 3 Regiospecific deuterium incorporation at the α-positions of alcohols

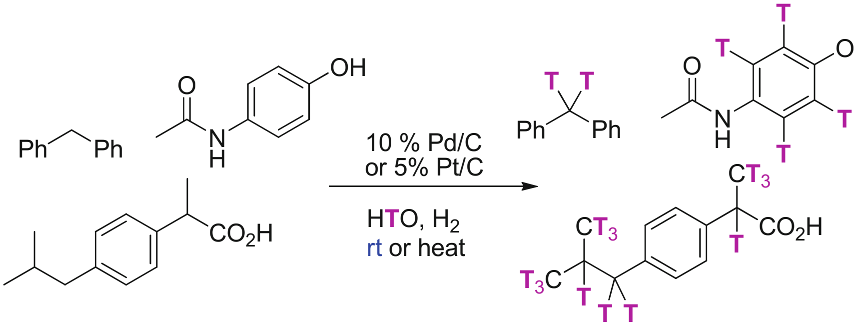


Fig. 4 H–T exchange reaction in highly diluted tritiated water

These deuterium and tritium labeling methods using the platinum group metal on carbon–D_2O–H_2 combination can be achieved under simple and mild conditions in comparison to conventional methods, and a wide variety of labeled compounds are obtained in good to quantitative yields and deuterium efficiencies [30–32].

2 Replacement of Hydrogen Gas by Deuterium Gas via Pd/C-Catalyzed H_2–D_2 Exchange Reaction Between H_2 and D_2O

As for the preparation methods of D_2 gas on a laboratory scale, the reaction of metals, such as sodium [33], iron [34], and magnesium [35] with D_2O, have been reported in the literature, although a large quantity of metal sludge is produced and drastic reaction conditions (several hundred degrees Celsius) are required. While numerous catalytic H_2–D_2 exchange reactions between H_2 and D_2O have also been

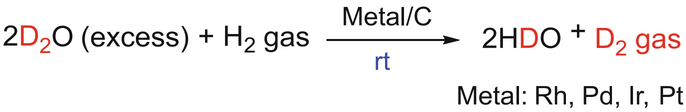


Fig. 5 Quantitative transmutation of H_2 gas into D_2 gas at room temperature

reported in the literature [36–44], such methods could not produce highly pure D_2 gas and also required a high pressure, the use of a special catalyst, and/or strongly basic or acidic reaction conditions.

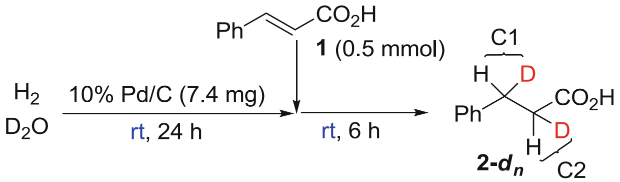
We have developed an efficient and quantitative in situ transmutation reaction of H_2 gas into D_2 gas utilizing the heterogeneous platinum group metal-catalyzed H_2–D_2 exchange reaction derived from D_2O as the deuterium source that occurs at rt [30–32, 45, 46]. H_2 gas sealed in the reaction flask is totally converted into nearly pure D_2 gas (Fig. 5), which can be used for the one-pot reductive deuteration (deuterogenation) of a wide variety of substrates possessing reducible functionalities within the molecule. Since Rh/C indicates the highest activity and Pd/C, Ir/C and Pt/C are also effective as catalysts, the H_2–D_2 exchange study was effected by the selection of Pd/C as the catalyst from the aspect of cost and ready availability.

The H_2–D_2 exchange efficiency after 24 h of stirring of 7.4 mg of 10% Pd/C in D_2O (3.0 mL, 166 mmol) in a hydrogen filled sealed flask with an effective internal volume of 160 mL (6.5 mmol/H_2 at 25 °C; that is to say commercially designated as a 100 mL eggplant flask) at rt was determined by the incorporation ratio of the deuterium into dihydrocinnamic acid (**2-*d*$_n$**) by the 10% Pd/C-catalyzed hydrogenation and/or deuterogenation of cinnamic acid (**1**) at rt for 6 h in the H_2–D_2 exchanged sealed flask (Table 1). The deurterogenation of **1** efficiently proceeded by a 24 h pre-stirring (H_2–D_2 exchange reaction), and nearly 50% deuterium efficiencies (theoretical value) were observed on both the C1 and C2 methylenes (**2-*d*$_n$**, Entry 1). On the other hand, little deuteration was observed without the 24 h pre-stirring (Entry 2). The deuterium efficiency was reduced with an inclease in volume of H_2 using a larger flask (Entries 3 and 4). The D_2 purity is significantly affected by the use a ratio of H_2 and D_2O based upon the H_2–D_2 exchange efficiency under the same time frame and reaction temperature.

The replacement efficiency of H_2 by D_2 decreased with the deterioration in the deuterium content of D_2O (Entries 5–8). The significant decrease in the deuterium efficiency of the deuterogenated product was observed and 50% D_2O (HDO) led to virtually no incorporation of deuterium (Entry 7). Since the deterioration in purity of the D_2O caused a significant drop in the H_2–D_2 exchange efficiency, an excess amount of D_2O (3 mL, 166 mmol vs. 160 mL, 6.5 mmol of H_2) should be required to circumvent the drastic degradation of the D_2O purity.

The Pd/C-catalyzed H_2–D_2 exchange reaction is very likely proceeding via the illustrated reaction pathway shown in Fig. 6. The oxidative addition of the O–D bond of D_2O to the H_2-activated Pd metal on charcoal (**I**) produced the Pd(II) complex (**II**). Subsequently, the H–D exchange on a Pd(II) complex (**III**) and reductive elimination to give a HD-activated Pd metal on charcoal (**IV**).

Table 1 H_2–D_2 exchange efficiency under various conditions[a]



Entry	H_2 (mL/mmol)	D_2O (mL)	H_2O (mL)	D efficiency (%)[b]		Isolated yield (%)
				C1	C2	
1	160/6.5	3.0	0	48	46	98
2[c]	160/6.5	3.0	0	2	0	97
3	285/12.2	3.0	0	44	42	100
4	690/28.2	3.0	0	31	29	100
5	160/6.5	2.7	0.3	30	26	98
6	160/6.5	2.1	0.9	13	12	94
7	160/6.5	1.5	1.5	5	6	98
8	160/6.5	0.9	2.1	0	0	95

[a] The reaction was performed in a hydrogen-charged sealed flask using 7.4 mg of 10% Pd/C in D_2O or D_2O–H_2O mixed solvents (each 3.0 mL) at room temperature (25 °C) for 24 h. Subsequently, *trans*-cinnamic acid (**1**, 0.5 mmol) was added, and the reaction was quenched after 6 h

[b] The D content was determined by ^1H NMR on the basis of the integration of the aromatic protons

[c] Without initial 24 h-stirring prior to the addition of *trans*-cinnamic acid (**1**)

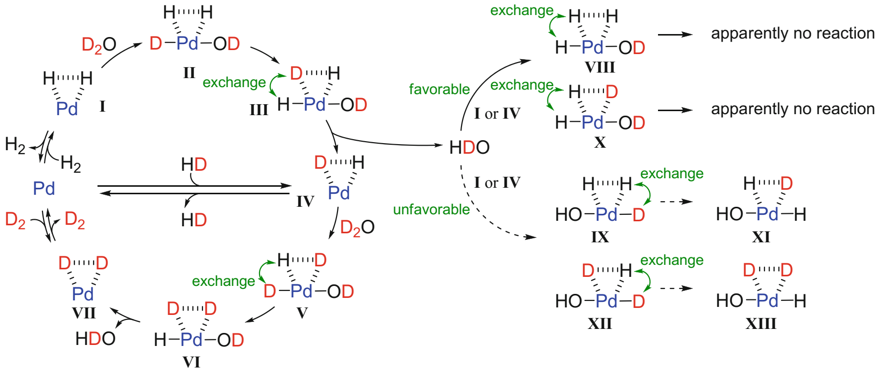


Fig. 6 Plausible reaction mechanism

Further oxidative addition of excess D_2O to **IV**, H–D exchange, reductive elimination and discharge of D_2 gas could turn over the catalyst cycle.

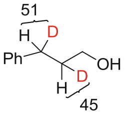
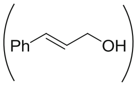
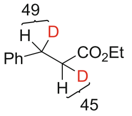
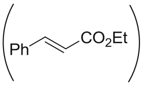
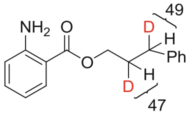
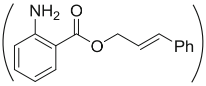
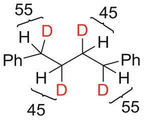
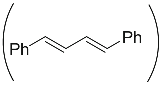
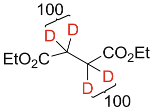
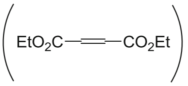
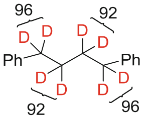
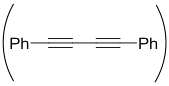
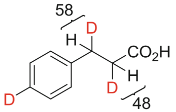
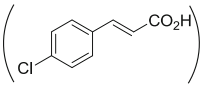
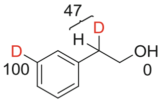
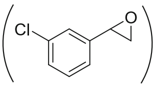
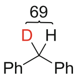
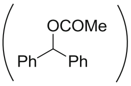
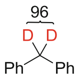
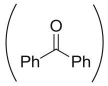
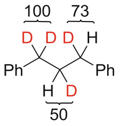
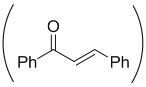
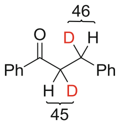
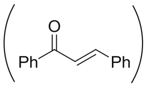
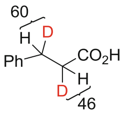
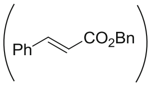
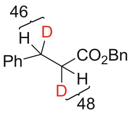
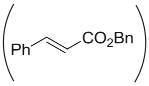
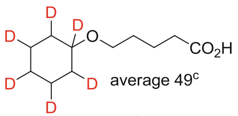
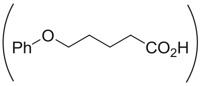
The reaction progress is clearly controlled by the isotopic effect between H and D. The oxidative addition of HDO to H_2 or HD-activated Pd metal on charcoal (**I** or **IV**) should preferably occur at the O–H bonds (**VIII** or **X**) compared to the O–D bond (**IX** or **XII**) and virtually no reaction was observed as a result of the H–H exchange on **VIII** or **X**. Therefore, the formation of the complex (**II** or **V**) derived from D_2O and **I** or **IV** should be necessary to generate HD or D_2. The oxidative addition of the HD–activated Pd metal (**IV**) to D_2O gave the complex (**V**), which would undergo the intramolecular H–D exchange, leading to the D_2 generation via complex **VI**. Namely, increasing the H_2O content in D_2O with the ratio of 50% or more would result in no reaction due to the complexation with HDO or H_2O and Pd metal (**I** or/and **IV**) followed by the intramolecular H–H exchange based on the isotopic effect (see also Table 1, Entries 7 and 8). Therefore, the use of a reasonably excess molar number of D_2O compared with the use of H_2 to avoid the unfavorable H–H exchange process should be required for the efficient generation of pure D_2 gas.

The generated deuterium gas in a sealed flask is easily applicable for the one-pot deuterogenation of various substrates possessing a wide variety of reducible functionalities within the molecule, and the desired deuterium-incorporated products are obtained in excellent to quantitative deuterium efficiencies as shown in Table 2. The heterogeneous catalyst can be recovered by simple filtration, and the acidic deuterium atoms on the carboxylic acid, alcohol and amine functionalities were replaced by hydrogen atoms during the aqueous workup.

The *chemoselective* one-pot deuterogenation was also possible by the addition of a catalyst poison [47–53]. For example, the chemoselective one-pot deuterogenation of an olefin in the presence of an aromatic ketone or benzyl ester within the molecule proceeded with excellent deuterium efficiencies by the addition of a very low loading (0.01 equiv) of diphenylsulfide (Ph_2S) as a catalyst poison (Table 2, **14-*d₂*** and **16-*d₂***), while the deuterogenation of the aromatic ketone or benzyl ester cannot be avoided without the addition of Ph_2S (Table 2, **13-*d₄*** and **15-*d₂***) [45, 46]. Furthermore, a quite mild and fruitful deuterogenation of an aromatic nucleus is also possible. A partially (nearly 50%) deuterated cyclohexane derivative (**17-*d₆***) can be easily obtained by the use of 10% Rh/C as a catalyst under gentle heating conditions (50 °C) [54–57].

It is noteworthy that almost pure and dried (waterless) D_2 gas can be collected in a rubber balloon or gas collection bag via a drying tube from a pressure-resistant reaction vessel with an internal volume of 170 mL after the H_2–D_2 exchange reaction at rt although the increased use of 10% Pd/C (30–40 mg) and D_2O (6–10 mL) under medium H_2 pressure (3–4 atm) was required. The collected waterless D_2 gas can be applied to the anhydrous deuterogenation and deuteration reactions, while the one-pot and in situ method is not applicable to water-sensitive substrates and reactions.

Table 2 Deuterium efficiency of deuteration using in-situ generated D_2 gas[a,b,]

 **3**-d_2 83 %		 **4**-d_2 82 %	
 **5**-d_2 80 %		 **6**-d_4 95 %	
 **7**-d_4 93 %		 **8**-d_8 100 %	
 **9**-d_3 89 %		 **10**-d_2 95 %	
 **11**-d_1 100 %		 **12**-d_2 80 %	
 **13**-d_4 88 %		 **14**-d_2 91 %[c]	
 **15**-d_2 96 %		 **16**-d_2 85 %[c]	
 **17**-d_6 49 %[d,e]			

[a] The substrate is indicated in parentheses

[b] Digits located adjacent to each D atom indicate the deutrium efficiency

[c] 0.01 equiv of Ph^{2}S were added as a catalyst poison

[d] 10% Rh/C was used as a catalyst instead of 10% Pd/C

[e] The theoretical D-efficiency is 55%

In summary, the H–D and H_2–D_2 exchange reactions introduced in this manuscript are readily and independently available at each laboratory and manufacturing site when necessary. Interestingly, these results strongly indicate that the H–H exchange reaction between the H_2 gas, substrates and protic solvents, such as H_2O, MeOH, etc. without the influence of the isotopic effect must frequently and continuously occur under the hydrogenation conditions, while the reaction seems to apparently undergo no reaction. This review should be helpful for the various international research groups who need the presented methodologies to prepare D labeled compounds and D_2 gas. Since the methodologies in this review have already been put to practical use by Wako Pure Chemical Industries, Ltd. (deuterium labeled reagents and contract manufacturing service), it is possible to use such a service according to your needs.

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