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Mild and Direct Multiple Deuterium-Labeling of Saturated Fatty Acids

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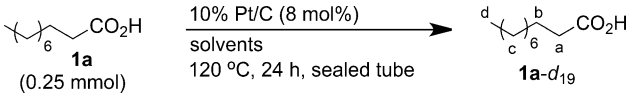
Abstract: We have established a mild and direct platinum on carbon (Pt/C)-catalyzed multi-deuterium labeling of various saturated fatty acids including bioactive compounds with high deuterium efficiencies in a mixed solvent of isopropyl alcohol and deuterium oxide (*i*-PrOH)/D_2O under neutral conditions at 120 °C without the external addition of deuterium or hydrogen gas.

Keywords: deuterium; fatty acids; isopropyl alcohol; platinum on carbon; valproic acid

During the past several decades, the utility of deuterium-labeled compounds has grown remarkably in various research fields,[1] such as microanalysis, reaction mechanisms, material chemistry, heavy drugs, etc.[2] Especially, in living organisms composed of various saturated fatty acids (aliphatic carboxylic acids), the deuterium-labeled derivatives are widely utilized in the elucidation of vital functionalities by the simplification and/or distinction of the spectroscopic data, evaluation of the cell death induced by the lipid peroxidation, etc.[3] While the partially-deuterated saturated fatty acids can be easily prepared by the reduction of the corresponding unsaturated substrates using the combination of a deuterium source and a catalytic or excess transition metal (e.g., $LiAlD_4$,[4a,c] D_2 gas[4a–d] in the presence of Wilkinson's catalyst, NaOD with Raney nickel[5] or D_2O with SmI_2[6]), the synthetic methods for multi- and fully-deuterated saturated fatty acids from non-labeled natural substrates are extremely limited. Although some deuterium-labeled materials are commercially available from chemical companies (e.g., Cambridge Isotope Laboratories, Inc., Wako Pure Chemical Industries, Ltd. etc., which are partially listed in the Supporting Information), the development of an easily handled and versatile synthetic method for targeted multi-deuterated saturated fatty acids is eagerly desired to investigate life phenomena. The reported direct and full deuteration [hydrogen (H)–deuterium (D) exchange] reactions of saturated fatty acids could be achieved under hydrothermal conditions (>220 °C, 2.3 MPa) using an autoclave in a strongly basic solution of D_2O in the presence of a platinum catalyst.[3a,i,7] However, repeated deuteration processes requiring a two to five day reaction for each cycle have been necessary to accomplish satisfactory deuterium levels. Although the iridium-catalyzed multi-deuteration of aliphatic carboxylic acids was also reported, the deuterium efficiencies were quite low.[8] We now report a Pt/C-catalyzed mild multi-deuteration method of saturated fatty acids including a bioactive compound (valproic acid) using an isopropyl alcohol (*i*-PrOH) and D_2O combined solvent at 120 °C for 24 h in a sealed tube.

We first examined the solvent efficiency for the direct multi-deuteration using capric acid (**1a**) as the substrate in the presence of 10% Pt/C (8 mol%) at 120 °C in a stainless-steel (SUS316) sealed tube (Taiatsu Techno®, Table 1). The deuteration in D_2O proceeded insufficiently to produce the multi-deuterated capric acid (**1a**-d_{19}) with very low D content (entry 1). On the other hand, the use of *i*-PrOH as a co-solvent with D_2O (*i*-PrOH/D_2O = 0.5/2 mL) dramatically improved the deuteration efficiency and the highly deuterated **1a**-d_{19} could be obtained (entry 2), even though *i*-PrOH can possibly become a hydrogen source and cause the undesired reverse D–H exchange reaction. A change in the D_2O ratio (*i*-PrOH/D_2O = 0.5/3 mL) could achieve a satisfactory D efficiency (92–96% D for **1a**) (entry 3). During the present deuteration, *i*-PrOH could be a mild hydrogen source *via* the Pt/C-catalyzed dehydrogenation[9] to acetone and H_2,[10] which would activate Pt/C[11] and facilitate the multi-deuteration[12,13] of **1a**. As collateral evidence of this hypothesis, the deuteration of **1a** satisfactorily proceeded in D_2O under a hydrogen at-

Table 1. Solvent efficiency.[a,b]



Entry	Solvents	D content [%]				Yield
		a	b	c	d	
1	D_2O (2 mL)	13	13	9	18	100%
2	*i*-PrOH/D_2O (0.5/2 mL)	89	90	93	92	93%
3	*i*-PrOH/D_2O (0.5/3 mL)	96	95	92	94	97%
4[c]	D_2O (2 mL)	92	91	89	85	95%
5[c]	cyclohexane/D_2O (0.5/2 mL)	81	86	88	73	97%
6[d]	*i*-PrOH/D_2O (0.5/3 mL)	35	53	65	68	81%
7	*i*-PrOD-d_8/D_2O (0.5/2 mL)	98	99	96	94	96%
8	*i*-PrOD-d_8/D_2O (0.1/2 mL)	32	51	58	61	98%
9	*i*-PrOD-d_8/D_2O (0.25/1 mL)	38	49	57	66	100%
10	MeOD-d_4/D_2O (0.5/2 mL)	8	8	5	8	88%
11	*i*-PrOD-d_8 (0.5 mL)	63	68	65	60	96%

[a] During the deuteration using isopropyl alcohol as a co-solvent, the generation of a small amount of the corresponding deuterated isopropyl ester derived from **1a** was observed. Therefore, only **1a**-d_{19} was isolated after the hydrolysis of the isopropyl ester (refer to Supporting information for details).

[b] The deuteration ratio was determined by ^1H and ^2H NMR using 1,4-dioxane (0.25 mmol) as an internal standard.

[c] Under an H_2 atmosphere.

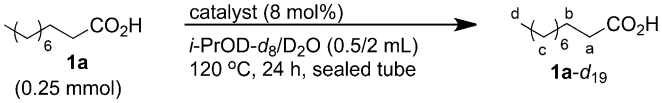
[d] At 80 °C.

mosphere, which indicated that H_2 was a key element in the direct multi-deuteration (entry 4).[13,14] Although the addition of cyclohexane as a co-solvent with D_2O could often improve the deuterium efficiency in the previously reported multi-deuteration reactions of arenes and alkanes due to the increase of solubility,[13] an addition effect could not be observed in the present deuteration of **1a** (entries 4 *vs.* 5). The deuterium source derived from D_2O was also consumed in the deuteration of cyclohexane.[13b] The deuterium efficiency of **1a** significantly decreased at a lower temperature (80 °C, entry 6). The deuterium efficiency at the α-position of **1a** was slightly lower than that at the other carbons, which was caused by the steric repulsion of the Pt metal-coordinated carboxylic acid and/or undesirable D–H exchange reaction with the hydrogen sources derived from excess *i*-PrOH and generated DHO by keto-enol tautomerization. These results related to the solubility and reaction temperature indicated that the heating at 120 °C was an important factor to effectively control the equilibrium between H–D and D–H exchange reactions, and obtain an efficiently deuterated **1a**-d_{19}. The present reaction using the combined solvent of *i*-PrOH and D_2O as a hydrogen carrier and a deuterium source without the additional use of flammable H_2 gas is obviously an adequate methodology not only from the viewpoint of safety and easy handling, but also for the volumetric efficiency of the reactors. The use of isopropyl alcohol-d_8 (*i*-PrOD-d_8; 0.5 mL) without a hydrogen source instead of *i*-PrOH as a co-solvent of D_2O could achieve slightly higher and nearly quantitative D contents of **1a**-d_{19} (entries 2 *vs.* 7).[10] On the other hand, the decrease of *i*-PrOD-d_8 or both *i*-PrOD-d_8 and D_2O provided lower D contents of **1a**-d_{19} (entries 7 *vs.* 8 and 9). The quantities of hydrogen (H_2, HD and D_2 gases), which was generated by the dehydrogenation of isopropyl alcohol as an activating agent of platinum metal, and total deuterium sources were also important factors to give the efficiently deuterated **1a**-d_{19}. The use of MeOD-d_4 instead of *i*-PrOD-d_8 was inefficient (entry 10),[15] and the deuteration of **1a** in only *i*-PrOD-d_8 as a solvent and a deuterium source (without D_2O) was also not too efficient (entry 11).

The catalyst efficiency was next investigated (Table 2): **1a** was efficiently multi-deuterated using 8 mol% of 10% Pt/C in *i*-PrOD-d_8/D_2O combined solvents (entry 1). The reduction of 10% Pt/C from 8 mol% to 5 mol% resulted in a lowering of the deuterium efficiency (entries 1 *vs.* 2). While 10% Rh/C and Ir/C exhibited low catalyst activities for the deuteration of **1a** (entries 3 and 4), the deuteration using Pd/C and Ru/C never proceeded (entries 5 and 6).

We next examined the versatility of the substrate applicability in the Pt/C-catalyzed direct multi-deuteration using the combined solvent [conditions A (Table 1, entry 3); *i*-PrOH/D_2O (0.5/3 mL) bearing the advantage of cost performance and conditions B

Table 2. Catalyst efficiency.[a,b]



Entry	Catalysts	D content [%]				Yield
		a	b	c	d	
1	10% Pt/C	98	99	96	94	96%
2[c]	10% Pt/C	87	95	93	91	100%
3	10% Rh/C	7	10	10	29	84%
4	10% Ir/C	27	42	36	64	98%
5	10% Pd/C	0	0	0	0	100%
6	10% Ru/C	0	0	0	0	100%

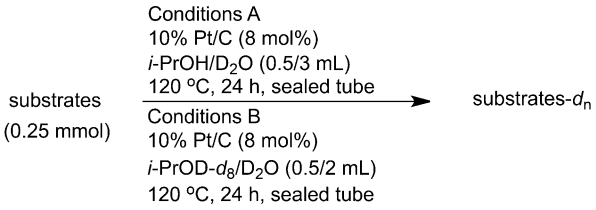
[a] During the deuteration using isopropyl alcohol as a co-solvent, the generation of a small amount of the corresponding deuterated isopropyl ester derived from **1a** was observed. Therefore, only **1a**-d_{19} was isolated after the hydrolysis of the isopropyl ester (refer to the Supporting Information for details).

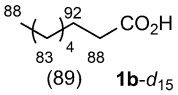
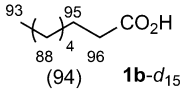
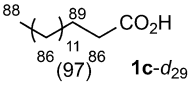
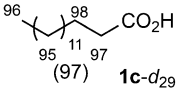
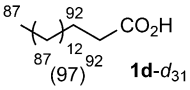
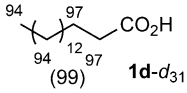
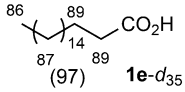
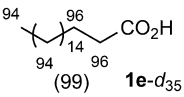
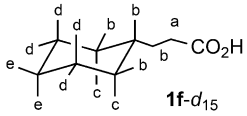
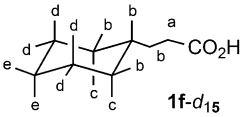
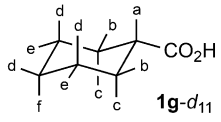
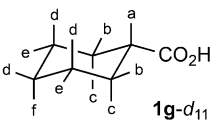
[b] The deuteration ratio was determined by ^1H and ^2H NMR using 1,4-dioxane (0.25 mmol) as an internal standard.

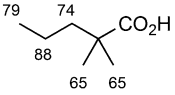
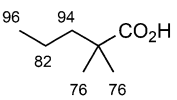
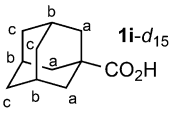
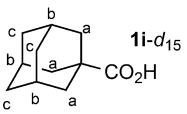
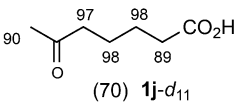
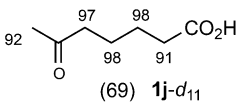
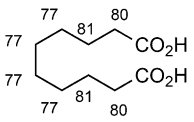
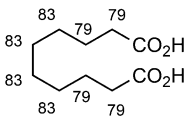
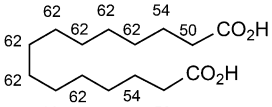
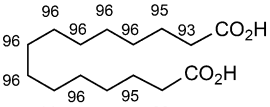
[c] 5 mol% of 10% Pt/C was used.

(Table 1, entry 7); *i*-PrOD-d_8/D_2O (0.5/2 mL) resulting in the slightly higher D contents to prepare multi-deuterated carboxylic acid derivatives possessing satisfactory D efficiencies]. Linear fatty acids, such as caprylic acid (**1b**), pentadecylic acid (**1c**), palmitic acid (**1d**) and stearic acid (**1e**) were effectively multi-deuterated with an average of *ca.* 90% deuterium efficiencies under conditions A (Table 3, entries 1–4, left column). The use of *i*-PrOD-d_8 instead of *i*-PrOH (conditions B) gave higher and excellent deuterium contents on all the carbons (entries 1–4, right column). Although the H–D exchange reactions of stearic acid (**1e**) bearing a longer aliphatic chain in comparison with **1a** in *i*-PrOH/D_2O (1/3 mL) and *i*-PrOH/cyclohexane/D_2O (0.5/0.5/3 mL) were also performed to be designated for the purpose of the further identification of the addition effect of cyclohexane, the deuterium efficiency was also never improved as in Table 1, entries 4 *vs.* 5 (see also the Supporting Information). Substrates possessing a cyclohexane ring within the molecule (**1f** and **1g**) and the branched aliphatic carboxylic acid (**1h**) could also undergo the multi-deuteration in mod-

Table 3. Scope of substrates.[a,b]



Entry	Substrates-d_n[c] Conditions A (Yield [%])	Substrates-d_n[c] Conditions B (Yield [%])
1	 (89) **1b**-d_{15}	 (94) **1b**-d_{15}
2	 (97) **1c**-d_{29}	 (97) **1c**-d_{29}
3	 (97) **1d**-d_{31}	 (99) **1d**-d_{31}
4	 (97) **1e**-d_{35}	 (99) **1e**-d_{35}
5	 **1f**-d_{15} a; 82, b; 96, c; 85, d; 84, e; 83 (90)	 **1f**-d_{15} a; 72, b; 97, c; 83, d; 88, e; 84 (95)
6	 **1g**-d_{11} a; 47, b; 79, c; 58, d; 71, e; 35, f; 88 (92)	 **1g**-d_{11} a; 39, b; 86, c; 51, d; 74, e; 35, f; 74 (95)

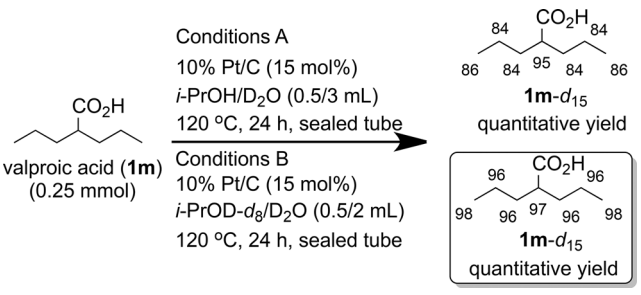
Entry	Substrates-d_n[c] Conditions A (Yield [%])	Substrates-d_n[c] Conditions B (Yield [%])
7	 (100) **1h**-d_{13}	 (97) **1h**-d_{13}
8	 **1i**-d_{15} a; 58, b; 66, c; 68 (97)	 **1i**-d_{15} a; 91, b; 98, c; 97 (94)[d]
9	 (70) **1j**-d_{11}	 (69) **1j**-d_{11}
10	 (97) **1k**-d_{16}	 (99) **1k**-d_{16}
11	 (95) **1l**-d_{26}	 (97)[d] **1l**-d_{26}

[a] During the deuteration using isopropyl alcohol as a co-solvent, the generation of a small amount of the corresponding deuterated isopropyl ester derived from **1a** was observed. Therefore, only **1a**-d_{19} was isolated after the hydrolysis of the isopropyl ester (refer to the Supporting Information for details).
[b] Isolated yields are shown in parentheses.
[c] The deuteration ratio was determined by ^1H and ^2H NMR using 1,4-dioxane (0.25 mmol) as an internal standard.
[d] 15 mol% of 10% Pt/C.

erate to high deuterium efficiencies under both conditions A and B (entries 5–7). It is noteworthy that the multi-deuteration of adamantanecarboxylic acid (**1i**) smoothly proceeded under conditions B and the corresponding deuterium-labeled **1i**-d_{15} was obtained with excellent D contents by using an increased amount (15 mol%) of 10% Pt/C (entry 8, right column). Furthermore, 6-oxoheptanoic acid (**1j**) was effectively multi-deuterated with a highly deuterium efficiency without the influence of a ketone (entry 9).[16] Sebacic acid (**1k**) and pentadecanedioic acid (**1l**) as dicarboxylic acids also underwent smooth multi-deuteration (entries 10 and 11).[17]

Deuterium-labeled medicines (heavy drugs) have recently been the focus of attention due to a prolongation of their biological half-time in the human body.[2] For example, valproic acid (**1l**) as a branched aliphatic carboxylic acid, is widely utilized as an antiepileptic agent and the partially deuterium-labeled valproic acids (**1l**-d_n: $n=4$,[18a] 6[18b] or 14[18a]) are valuable for metabolic and pharmacokinetic studies. While the partially deuterium-labeled valproic acids (**1l**-d_n) were prepared *via* a multistep synthesis using expensive deuterated precursors, such as 1-bromopropane-d_3, 1-bromopropane-d_7 and D_2 gas, there has been no synthetic method for the fully-deuterated valproic acid (**1l**-d_{15}). Our present method could be applied to the direct and easy preparation of **1l**-d_{15} from the non-labeled valproic acid (**1l**) especially using D_2O as a deuterium source in the presence of *i*-PrOD-d_8 at 120 °C for 24 h with excellent D contents under conditions B using an increased amount (15 mol%) of 10% Pt/C (Scheme 1).[17]

In conclusion, we have developed a mild, efficient and direct multi-deuteration method for saturated fatty acids (aliphatic carboxylic acids) catalyzed by Pt/C in a D_2O/*i*-PrOH (*i*-PrOD-d_8) combined solvent at 120 °C. Various deuterated fatty acids including valproic acid-d_{15} could be easily prepared under milder reaction conditions (at 120 °C) in comparison with the previously reported hydrothermal conditions (> 220 °C, 2.3 MPa). The present method without the external addition of H_2 gas is valuable and is expected to be utilized for analytical and metabolism studies and the development of heavy drugs.



Scheme 1. Multi-deuteration of a bioactive compound (valproic acid).

Experimental Section

General Procedure

A suspension of an aliphatic carboxylic acid (0.25 mmol), 10% Pt/C (8 mol%), *i*-PrOH (0.5 mL) and D_2O (3 mL) in a 6-mL stainless-steel sealed tube was stirred at 120 °C under atmospheric conditions. After stirring for 24 h, the mixture was cooled to room temperature and filtered by a membrane filter (Milipore, Millex®-LH, 0.2 μm) using Et_2O (20 mL) and H_2O (20 mL) to remove the catalysts, and then concentrated under vacuum to remove Et_2O. To the aqueous layer, NaOH (50 mg) was added and the mixture was stirred at 70 °C for 24 h. After cooling to room temperature, aqueous HCl (5 N) was added to the reaction mixture until pH < 2 which was then extracted with Et_2O (10 mL × 5). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to give the deuterated product.

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[15] The transition metal-on-carbon-catalyzed dehydrogenation of primary alcohols in H_2O under reduced pressure effectively produces the carboxylic acids as desirable products accompanied by the generation of H_2. The undesirable cleavage of the intermediate aldehyde occurs under normal atmospheric pressure to give

carbon monoxide (CO) and so on as side-products, which maybe inhibit the present deuteration of carboxylic acids by the strong coordination on to platinum metal. See ref.[9b]

[16] Although polar by-products were detected by TLC analysis, they could not be isolated and assigned.

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Mild and Direct Multiple Deuterium-Labeling of Saturated Fatty Acids

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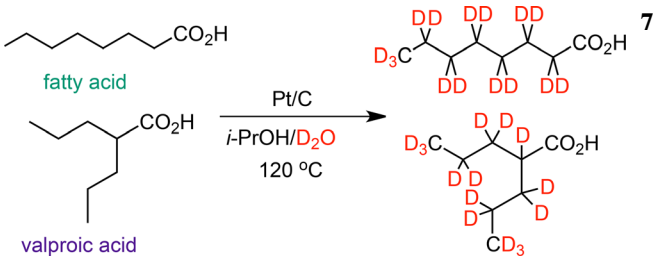

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