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# Multiple Deuteration of Alkanes Synergistically-Catalyzed by Platinum and Rhodium on Carbon as a Mixed Catalytic System†

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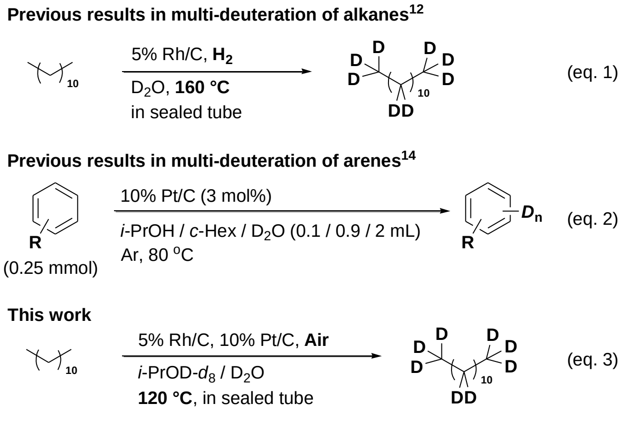
We have accomplished an efficient and mild multiple deuteration method for alkanes catalyzed by the combined use of heterogeneous platinum on carbon (Pt/C) and rhodium on carbon (Rh/C) catalysts in *i*-PrOD-$d_8$ and $D_2O$ as a mixed solvent. The present multi-deuteration could be initiated by the transition metal-catalyzed dedeuteration of *i*-PrOD-$d_8$ to produce $D_2$ and the subsequent C-H bond activation of alkanes catalyzed by the Pt/C and/or Rh/C-$D_2$ complex. This method could be applied to the deuteration of wide variety of linear, branched and cyclic alkanes as useful deuterated materials under mild conditions.

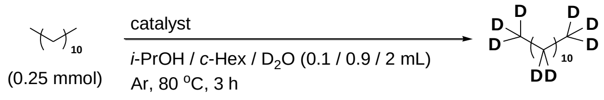
## Introduction

While deuterium-labeled compounds[1] are widely utilized in various analytical studies (e.g., microanalysis,[2] human metabolism,[3] and reaction mechanism[4]), and material chemistries (e.g., fiber optics[5] and heavy drugs[6]), multi-deuterated alkanes are also expected as an ecological and undetachable identification chemical marker for illegal diesel fuel laced with kerosene.[7] Although the direct deuteration [hydrogen (H)-deuterium (D) exchange] of the mother compounds based on the C-H bond activation[8] is a powerful and straightforward synthetic method to give the deuterium-labeled products, the multi-deuteration of the inactive alkanes is generally accomplished under comparatively harsh reaction conditions due to the poorly reactive nature of alkanes due to no coordinating functionalities with metal or acid catalysts.[8-12] Heterogeneous[9,12] or homogeneous[10] transition metal catalysts and various acidic reagents[11] have been utilized to facilitate the H-D exchange reaction of alkanes in the presence of the appropriate deuterium sources ($D_2O$, $D_2$, $C_6D_6$ etc.). In terms of the environmental and economical issues, the heterogeneous catalyst is useful due to the easiness to remove it from the reaction mixture and $D_2O$ as an inexhaustible natural deuterium source is greener for the H-D exchange reactions.[9c,12] We have also developed some H-D exchange reactions for various compounds catalyzed by heterogeneous platinum group metals on carbon (Pd/C, Pt/C, Rh/C, Ru/C and so on) in $D_2O$ as a deuterium source and solvent under atmospheric $H_2$ which could efficiently activate the platinum metal catalysts.[1d,13] Especially, the multi-deuteration of alkanes could be achieved under the Rh/C-catalyzed H-D exchange reaction using $D_2O$ in a sealed-tube at 160 °C under $H_2$ atmosphere (eq. 1).[12] On the other hand, we have recently established a Pt/C-catalyzed deuterium labeling method of arenes without the addition of flammable $H_2$ gas in a $D_2O$ and cyclohexane (*c*-hex) mixed solvent in the presence of 3 % *i*-PrOH as an internal hydrogen source (eq. 2).[14] In this reaction using a small amount of *i*-PrOH instead of $H_2$, a slight but sufficient $H_2$ was *in situ* generated by the Pt/C-catalyzed dehydrogenation of *i*-PrOH,[15] and Pt/C activated by $H_2$ promoted the multi-deuteration of arenes. Based on our previous perception, we have developed an efficient and mild multi-deuteration method of alkanes using a synergistic effect by the mixing of Rh/C and Pt/C in an *i*-PrOH (*i*-PrOD-$d_8$)/$D_2O$ mixed solvent at 120 °C (eq. 3).



## Results and Discussion

During the multi-deuteration of arenes under Pt/C-*i*-PrOH-$D_2O$ conditions in a test tube containing atmospheric argon at 80 °C (eq. 2),[14] the excessive amount of *i*-PrOH could be a hydrogen source to facilitate the undesirable D-H exchange reaction (reverse reaction). Therefore, the reactions were performed in a combined solvent of a small amount of *i*-PrOH (0.1 mL) and an adequate amount of *c*-hex as the solubilizing agent of the arenes (*i*-PrOH, *c*-hex, $D_2O$; 0.1 mL, 0.9 mL, 2.0 mL, respectively). Meanwhile, the 10% Pt/C[16] (3 mol%)-catalyzed deuteration efficiency of *n*-dodecane was never promoted in the mixed solvent of *i*-PrOH, *c*-hex and $D_2O$ (Scheme 1). While the independent use of 5% Rh/C[12,17] possessing the high affinity toward alkanes instead of 10% Pt/C was also ineffective, the combined use of both 10% Pt/C and 5% Rh/C synergistically facilitated the deuteration of *n*-dodecane although the deuterium efficiency was low (average 5-6% D)



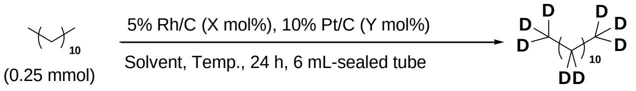
10% Pt/C (3 mol%) / $CD_2$: 0%, $CD_3$: 0%
5% Rh/C (3 mol%) / $CD_2$: 0%, $CD_3$: 0%
10% Pt/C (3 mol%) + 5% Rh/C (3 mol%) / $CD_2$: 5%, $CD_3$: 6%

**Scheme 1.** Synergistic effect of using Pt/C and Rh/C

On the other hand, the increment of the usage of 10% Pt/C and 5% Rh/C (each 15 mol%) at a higher temperature (120 °C) in a sealed tube dramatically improved the deuterium contents ($CD_2$, 81%; $CD_3$, 79%) of *n*-dodecane in the mixed solvent (*i*-PrOH, *c*-hex, $D_2O$; 0.1 mL, 0.9 mL, 2.0 mL) (Table 1, Entry 1). The use of 2-propanol-$d_8$ (*i*-PrOD-$d_8$) bearing no hydrogen source was slightly effective for the deuterium contents (Entry 2), and the removal of c-hex[18] led to the higher deuterium efficiencies of *n*-dodecane (Entry 3, in *i*-PrOD-$d_8$, $D_2O$; 0.1 mL, 2.0 mL). The single application of $D_2O$ as a solvent and deuterium source has significantly reduced the deuterium efficiency (Entry 4). These results indicated that the *i*-PrOH or *i*-PrOD-$d_8$ underwent the transition metal-catalyzed hydrogenation (dedeuteration), and the in situ-generated $H_2$, DH or $D_2$ effectively activated the metals on the carbon to facilitate the multiple deuteration of the simple linear alkane.[19] The increment of *i*-PrOD-$d_8$ (0.5 mL) was more effective to achieve the excellent deuterium contents ($CD_2$, 94%; $CD_3$, 96%) (Entries 3 *vs.* 5). Addition of *i*-PrOH (0.5 mL) was not very effective in comparison with that of *i*-PrOD-$d_8$ (0.5 mL) (Entries 5 *vs.* 6). The reaction at 120 °C was very adequate in comparison to 100 °C or 140 °C (Entries 5 *vs.* 7 and 8) ones, and the decrease in the use of Pt/C and Rh/C (each 10 mol% or 5 mol%) produced a slight, but obvious degradation of the deuterium efficiencies while it still relatively maintained the deuterium contents (entries 5 *vs.* 9 and 10). Although the single application of Pt/C or Rh/C (each 30 mol%) in the *i*-PrOD-$d_8$ and $D_2O$ combined solvent at 120 °C also promoted the multi-deuteration of *n*-dodecane and Pt/C-catalyzed reaction produced around 90% deuterium efficiencies (Entries 11 and 12), the synergistic use of Pt/C or Rh/C was found to be more effective (Entry 5). Since the transition metal-catalyzed dehydrogenation of secondary alcohols is favorable to that of primary alcohols,[15] the use of $CD_3OD$ (methanol-$d_4$) instead of *i*-PrOD-$d_8$ was less effective for the present multi-deuteration of *n*-dodecane (Entry 13).

The Rh/C and Pt/C synergistically catalyzed the multi-deuteration method in the *i*-PrOD-$d_8$ and $D_2O$ mixed solvent which could be applied to the wide variety of linear, branched and cyclic alkanes (Table 2). While the linear alkanes consisting of up to 20 carbons (*n*-dodecane, *n*-pentadecane and *n*-eicosane) were effectively deuterated with excellent deuterium contents (Table 1: Entry 5 and Table 2: Entries 1 and 2), the multi-deuteration of *n*-hexatriacontane ($C_{36}H_{74}$) gave a somewhat lower deuterium content due to its very low solubility and wax-like property (Table 2, Entry 3). Although the sterically-hindered positions of the branched alkane (2,2,4,4,6,8,8-heptamethylnonane) were especially less reactive (Entry 4), the axial and equatorial hydrogens of the cyclohexane derivatives (bicyclohexyl and trans-decaline) were smoothly exchanged with deuteriums with good deuterium efficiencies (Entries 5 and 6). Furthermore, adamantane and α-cholestane composed of rigidly-fixed condensed-ring structures also allowed the multi-deuteration but with rather in low deuterium contents (Entries 7 and 8). The additional *c*-hex could sometimes improve the deuterium efficiency with improvement of the solubility of substrates, consequently, the

**Table 1.** Optimization of H-D exchange reaction of *n*-dodecane

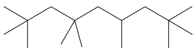
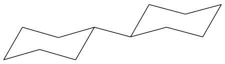
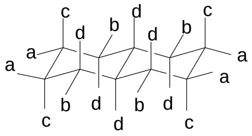
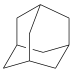
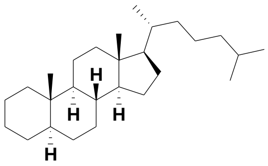
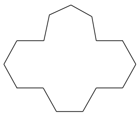


| Entry | X / Y (mol%) | Solvents (mL) | Temp. (°C) | D content (%)[a] $CD_2$ / $CD_3$ |
|---|---|---|---|---|
| 1 | 15 / 15 | *i*-PrOH / *c*-Hexane / $D_2O$ (0.1 / 0.9 / 2) | 120 | 81 / 79 |
| 2 | 15 / 15 | *i*-PrOD-$d_8$ / *c*-Hexane / $D_2O$ (0.1 / 0.9/ 2) | 120 | 84 / 81 |
| 3 | 15 / 15 | *i*-PrOD-$d_8$ / $D_2O$ (0.1 / 2) | 120 | 92 / 87 |
| 4 | 15 / 15 | $D_2O$ (2) | 120 | 36 / 37 |
| 5 | 15 / 15 | *i*-PrOD-$d_8$ / $D_2O$ (0.5 / 2) | 120 | 94 / 96 (100%)[b] |
| 6 | 15 / 15 | *i*-PrOH / $D_2O$ (0.5 / 2) | 120 | 84 / 86 |
| 7 | 15 / 15 | *i*-PrOD-$d_8$ / $D_2O$ (0.5 / 2) | 100 | 91 / 87 |
| 8 | 15 / 15 | *i*-PrOD-$d_8$ / $D_2O$ (0.5 / 2) | 140 | 88 / 89 |
| 9 | 10 / 10 | *i*-PrOD-$d_8$ / $D_2O$ (0.5 / 2) | 120 | 88 / 87 |
| 10 | 5 / 5 | *i*-PrOD-$d_8$ / $D_2O$ (0.5 / 2) | 120 | 89 / 85 |
| 11 | 0 / 30 | *i*-PrOD-$d_8$ / $D_2O$ (0.5 / 2) | 120 | 91 / 90 |
| 12 | 30 / 0 | *i*-PrOD-$d_8$ / $D_2O$ (0.5 / 2) | 120 | 39 / 40 |
| 13 | 15 / 15 | $CD_3OD$ / $D_2O$ (0.5 / 2) | 120 | 38 / 35 |

[a] The deuteration ratio was determined by $^1H$ and $^2H$ NMR with 1,4-dioxane (0.25 mmol) as the internal standard. [b] Isolated yield.

**Table 2.** Multi-deuteration of various alkanes

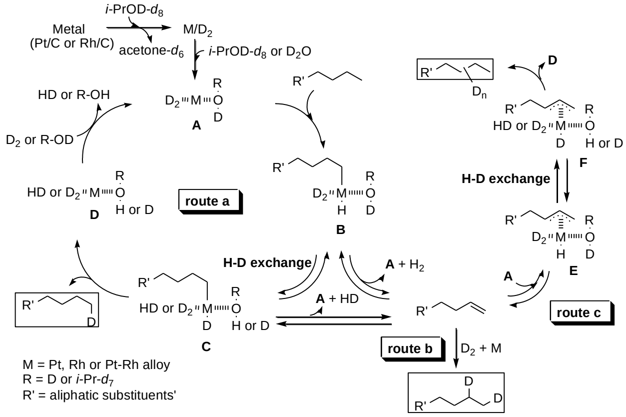
$$\underset{(0.25\ \text{mmol})}{\text{Substrate}} \xrightarrow[\substack{i\text{-PrOD-}d_8\ /\ D_2O\ (0.5\ /\ 2\ \text{mL}) \\ 120\ °\text{C, 24 h, 6 mL-sealed tube}}]{\text{5\% Rh/C (15 mol\%), 10\% Pt/C (15 mol\%)}} \text{Substrate-}\boldsymbol{d}_\text{n}$$

| Entry | Substrate | D content (%)[a] | Yield (%) |
|---|---|---|---|
| 1 | Pentadecane ($C_{15}H_{32}$) | $CD_3(CD_2)_{13}CD_3$<br>97 92 97 | 92 |
| 2 | *n*-Eicosane ($C_{20}H_{42}$) | $CD_3(CD_2)_{18}CD_3$<br>94 94 94 | 95 |
| 3[b] | *n*-Hexatriacontane ($C_{36}H_{74}$) | $CD_3(CD_2)_{34}CD_3$<br>78 86 78<br>(87 86 87[c]) | 69 (89[c]) |
| 4 | 2,2,4,4,6,8,8-Heptamethylnonane | <br>CD 53; $CD_2$ 17; $CD_3$ 62<br>(CD 43; $CD_2$ 15; $CD_3$ 74[c]) | 100 (99[c]) |
| 5 | Bicyclohexyl | <br>equatrial 75; axial 71 | 86 |
| 6 | *trans*-Decaline |  <br>a 97; b 95; c 87; d 94 | 85 |
| 7 | Adamantane | <br>CD 35; $CD_2$ 39 | 99 |
| 8 | *α*-Cholestane |  <br>ave. 19[b] (14[c]), (39[b,d]) | 82[b] (82[c]), (90[b,d]) |
| 9 | Cyclopentadecane | <br>$CD_2$ 96 | 99 |

[a] The deuteration ratio was determined by $^1$H and $^2$H NMR with 1,4-dioxane (0.25 mmol or 0.125 mmol) as the internal standard. [b] 0.125 mmol of substrate, 10% Pt/C (30 mol%) and 5% Rh/C (30 mol%) were used. [c] 0.125 mmol of substrate, 10% Pt/C (30 mol%) and 5% Rh/C (30 mol%), and *i*-PrOD-$d_8$ / $D_2O$ (1 / 2 mL) were used. [d] 0.1 mL of cyclohexane was added as a co-solvent.

deuterium contents of *α*-cholestane were obviously improved by the additional *c*-hex (0.1 mL) (Entry 8).[20] Meanwhile, cyclopentadecane as a flexible cyclic compound was efficiently deuterated to give a nearly quantitative deuterated product (Entry 9). In the cases using *n*-hexatriacontane, 2,2,4,4,6,8,8-heptamethylnonane and *α*-cholestane as substrates (Entries 3, 4 and 8), the significant improvement of the deuteration efficiencies was not observed by the increment use of *i*-PrOD-$d_8$ (0.5 to 1.0 mL).

The present multi-deuteration by the combined use of Pt/C and Rh/C in *i*-PrOD-$d_8$ and $D_2O$ can proceed via various possible reaction pathways. First of all, a portion of *i*-PrOD-$d_8$ is transformed to $D_2$ gas by the Pt or Rh-catalyzed dedeuteration, and the generated $D_2$ and *i*-PrOD-$d_8$ or $D_2O$ coordinate with the metal(s) to produce an active species (**A**) (Scheme 2).[14,21] The subsequent oxidative addition of a C-H bond of the alkane to **A** gives an intermediate **B**, then an H-D exchange takes place on the metal to form the intermediate **C**, which undergoes the reductive elimination to produce the deuterium-labeled alkane (route a). Alternatively, the *β*-hydride elimination of intermediate **B** or **C** gives an alkene, which reacts with $D_2$ gas in the presence of Pt/C or Rh/C as a catalyst to produce a deuterated alkane (route b). Furthermore, the active species (**A**) could also form a *π*-allyl complex (**E**) with the alkene (route c) and the subsequent H-D exchange reaction of metal-H of **E** and the deuterium incorporation provides the deuterated alkane. These possible reactions are repeated to produce the corresponding multi-deuterated alkanes. Although HD, $H_2$ and *i*-PrOH-$d_n$ result in the undesirable D-H exchange generated during the reaction process or when using non-labeled *i*-PrOH as an activating source, the desirable H-D exchange of the alkane preferentially proceeds to give the multi-deuterated alkane due to the stable isotope effect.



**Scheme 2.** Synergistic effect of using Pt/C and Rh/C

## Conclusion

We have developed an efficient multi-deuteration of alkanes synergistically-catalyzed by the mixed use of Pt/C and Rh/C in *i*-PrOD-$d_8$ and $D_2O$. The present H-D exchange reaction proceeds under mild and neutral conditions to produce the corresponding multi-deuterated cyclic and linear alkanes without the further addition of gaseous $H_2$. Therefore, the safe and efficient deuterium-labeling method of alkanes is expected to be utilized in practical fields.

## Experimental

### Typical procedure for Pt/C and Rh/C-catalyzed multi-deuteration of alkanes (Table 1 and Table 2, Entries 1-2, 4-7 and 9)

A suspension of an alkane (0.25mmol), 10% Pt/C (15 mol%) and 5% Rh/C (15 mol%) in *i*-PrOD-$d_8$ (0.5 mL) and $D_2O$ (2 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) to remove the catalysts. The filtrate was extracted with $Et_2O$ (20 mL) and $H_2O$ (20 mL), and then the aqueous layer was further extracted with $Et_2O$ (10 mL x 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtrated and concentrated in vacuo to give the deuterated product.

### Procedure for Pt/C and Rh/C-catalyzed multi-deuteration of alkane (Table 2. Entry 3)

A suspension of an alkane (0.125 mmol), 10% Pt/C (30 mol%) and 5% Rh/C (30 mol%) in *i*-PrOD-$d_8$ (0.5 mL) and $D_2O$ (2 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) to remove the catalysts. The filtrate was extracted with hexane (20 mL) and $H_2O$ (20 mL), and then the aqueous layer was further extracted with hexane (10 mL x 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtrated and concentrated in vacuo to give the deuterated product.

### Procedure for Pt/C and Rh/C-catalyzed multi-deuteration of alkane (Table 2. Entry 8)

A suspension of an alkane (0.125 mmol), 10% Pt/C (30 mol%) and 5% Rh/C (30 mol%) in *i*-PrOD-$d_8$ (0.5 mL), $D_2O$ (2 mL) and cyclohexane (0.1 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) to remove the catalysts. The filtrate was extracted with hexane (20 mL) and $H_2O$ (20 mL), and then the aqueous layer was further extracted with hexane (10 mL x 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtrated and concentrated in vacuo to give the deuterated product.

*n*-Dodecane-$d_{26}$ (Table 1, entry 5) : Colorless oil, $^1H$ NMR (500 MHz, $CDCl_3$): δ 1.24–1.18 (m, 1.26H), 0.80 (m, 0.27H); $^2H$ NMR (61 MHz, $CHCl_3$): δ 1.20 (brs), 0.83 (brs).

*n*-Pentadecane-$d_{32}$ (Table 2, entry 1) : Colorless oil, $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.24–1.17 (m, 1.52H), 0.81 (m, 0.15H); $^2H$ NMR (61 MHz, $CHCl_3$): δ 1.20 (brs), 0.83 (brs).

*n*-Eicosane-$d_{42}$ (Table 2, entry 2) : Colorless solid, $^1H$ NMR (500 MHz, Benzene-$d_6$): δ 1.28–1.50 (m, 1.17H), 0.86 (m, 0.32H); $^2H$ NMR (61 MHz, Benzene): δ 1.20 (brs), 0.82 (brs).

*n*-Hexatriacontane-$d_{74}$ (Table 2, entry 3) : Colorless solid, $^1H$ NMR (500 MHz, $CDCl_3$): δ 1.19–1.25 (m, 6.66H), 0.86 (m, 1.35H); $^2H$ NMR (61 MHz, $CHCl_3$): δ 1.20 (brs), 0.83 (brs).

*n*-Hexatriacontane-$d_{74}$ (Table 2, entry 3[c]) : Colorless solid, $^1H$ NMR (500 MHz, $CDCl_3$): δ 1.19–1.25 (m, 8.26H), 0.82–0.89 (m, 0.68H); $^2H$ NMR (61 MHz, $CHCl_3$): δ 1.19 (brs), 0.82 (brs).

2,2,4,4,6,8,8,-Heptamethylnonane-$d_{34}$ (Table 2, entry 4) : Colorless oil, $^1H$ NMR (500 MHz, $CDCl_3$): δ 1.59 (m, 0.47H), 1.03–1.27 (m, 4.97H), 0.85–0.97 (m, 10.21H); $^2H$ NMR (61 MHz, $CHCl_3$): δ 1.57 (brs), 1.22 (brs), 0.87–0.94 (brd).

2,2,4,4,6,8,8,-Heptamethylnonane-$d_{34}$ (Table 2, entry 4[c]) : Colorless oil, $^1H$ NMR (500 MHz, $CDCl_3$): δ 1.59 (m, 0.56H), 1.04–1.24 (m, 5.08H), 0.85–0.97 (m, 7.03H); $^2H$ NMR (61 MHz, $CHCl_3$): δ 1.54 (brs), 1.18–1.20 (brs), 0.84–0.91 (brd).

Bicyclohexyl-$d_{22}$ (Table 2, entry 5) : Colorless oil, $^1H$ NMR (500 MHz, $CDCl_3$): δ 1.62–1.64 (m, 2.14H), 0.88–1.24 (m, 3.00H); $^2H$ NMR (61 MHz, $CHCl_3$): δ 1.65 (m), 0.90–1.13 (m).

*trans*-Decaline-$d_{18}$ (Table 2, entry 6) : Colorless oil, $^1H$ NMR (500 MHz, $CDCl_3$): δ 1.66 (m, 0.12H), 1.41 (m, 0.18H), 1.23 (m, 0.44H), 0.86 (m, 0.32H); $^2H$ NMR (61 MHz, $CHCl_3$): δ 1.61 (brs), 1.49 (brs), 1.17 (brs), 0.87 (brs).

Adamantane-$d_{16}$ (Table 2, entry 7) : Colorless solid, $^1H$ NMR (500 MHz, $CDCl_3$): δ 1.85 (m, 2.60H), 1.75 (brd, 7.20H); $^2H$ NMR (61 MHz, $CHCl_3$): δ 1.81 (brs), 1.69 (brs).

$\alpha$-Cholestane-$d_{48}$ (Table 2, entry 8[c]) : Colorless solid, $^1$H NMR (500 MHz, $CDCl_3$): δ 0.63–1.95 (m, 33.84H); $^2$H NMR (61 MHz, $CHCl_3$): δ 0.92–1.16 (m).

$\alpha$-Cholestane-$d_{48}$ (Table 2, entry 8[d]) : Colorless solid, $^1$H NMR (500 MHz, $CDCl_3$): δ 0.63–1.93 (m, 26.67H); $^2$H NMR (61 MHz, $CHCl_3$): δ 0.82–1.78 (m).

Cyclopentadecane-$d_{30}$ (Table 2, entry 9) : Colorless solid, $^1$H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 0.91H); $^2$H NMR (61 MHz, $CHCl_3$): δ 1.27 (brs).

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## Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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18 We have also previously reported that *c*-hex was an efficient co-solvent for the multi-deuteration of alkanes using the Rh/C catalyst under $H_2$ atmospheric conditions, because the H-D exchange reaction of relatively small cyclic compounds, such as *c*-hex, has been quite difficult to occur.(Ref. 12) Meanwhile, the present multi-deuteration of alkanes by the combined use of Pt/C-Rh/C in *i*-PrOD-$d_8$ and $D_2O$ at 120 $^{o}$C might facilitate the multi-deuteration of *c*-hex to prevent the desirable deuteration of *n*-dodecane, which has clearly indicated that the present reaction system was more efficient for the H-D exchange reaction than the previous methodology (Rh/C-$H_2$-$D_2O$) at 160 $^{o}$C. The deuterated *c*-hex could not be detected due to the easy vaporization.

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