C–H Activation

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Mild and Efficient H/D Exchange of Alkanes Based on C–H Activation Catalyzed by Rhodium on Charcoal**

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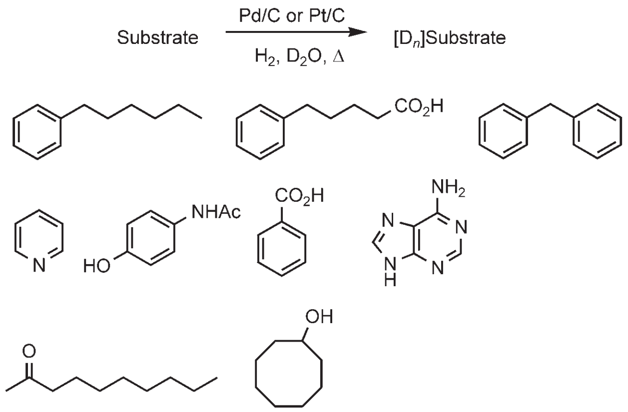
The C–H bond activation of organic compounds is one of the most useful synthetic methods for the fuctionalization of simple molecules.[1] The activation of unsaturated compounds can be achieved using transition-metal catalysts, and the coordination of a metal center to the π bond plays an important role in the reaction process.[1b] On the other hand, alkanes (saturated organic compounds) are known to be much less reactive towards C–H bond activation than unsaturated compounds because alkanes possess no coordination sites for metals. Therefore only a few processes, such as oxidation, H/D exchange, dehydrogenation, and radical reactions, have been reported as being C–H activation-induced, even though extensive efforts to activate alkanes have been made.[1] The H/D exchange reaction[2] is a basic transformation of alkanes. Deuterated products have received attention not only as useful tools for the investigation of human metabolism[3] or reaction mechanisms,[4] but also as functional materials[5] like deuterated polymers as components of optical fibers for high-speed telecommunications systems.[5a] Deuterated pesticides and pharmaceuticals are also effective for quantitative analyses and bioanalytical investigations as internal standards,[5b–d] while deuterated alkanes are expected to be applied as marker molecules to prevent the distribution of illegally mixed light diesel oil.[5e] Owing to this increasing interest, it is important to develop an efficient and facile H/D exchange method for alkanes. Since the first H/D exchange of alkanes was reported by Shilov and co-workers,[6] other H/D exchange reactions of alkanes have been developed.[1] Recently, Bergman and co-workers reported an efficient H/D exchange method for various substrates, including alkanes, by using a homogeneous cationic Ir hydride complex under mild conditions.[7] The H/D exchange reaction with deuterium oxide catalyzed by Pd/C under hydrothermal conditions has also been reported.[8]

We have recently established a method for deuterium incorporation into organic molecules by using a combination of Pd/C (or Pt/C) in D_2O under H_2, which has led to efficient H/D exchange for a variety of organic molecules such as aromatic compounds,[9,10] ketones, and alcohols[11] (Scheme 1). As part of an ongoing program for the development of H/D exchange reactions induced by heterogeneous catalysts, we have discovered a unique protocol for the C–H activation based deuteration of the C–H bond of alkanes, which do not possess functional groups. Herein we report deuteration of the C–H bond by the heterogeneous Rh/C-catalyzed multi-H/D exchange of simple alkanes. The reaction is carried out with D_2O as a solvent and as a deuterium source under nearly atmospheric pressure,[12] and the addition of cyclohexane as a co-solvent improves the efficiency of deuterium incorporation.



Scheme 1. Deuterium incorporation into alcohols, ketones, and aromatic compounds by using Pd/C (or Pt/C) in D_2O under H_2.

As an extension of our study, we examined the H/D exchange reaction of *n*-dodecane, which possesses no functional groups and thus cannot coordinate to metal catalysts. Unexpectedly, deuterium incorporation was observed on all the carbon atoms of *n*-dodecane with a 57–61% deuterium incorporation in the presence of Pd/C in D_2O under H_2 at 160°C. Encouraged by this result, we screened the effect of other Group VIII metal catalysts under the same reaction conditions. Rh/C was found to be the most effective catalyst for the deuteration of alkanes, where the deuterium incorporation increased to 81% (Table 1, entry 5). The hydrophobic catalyst support is essential for the reaction to proceed (Table 1, entries 6 and 7).

Next, several commercial Rh/C catalysts, obtained from different suppliers, were used for the H/D exchange reaction

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Table 1: Examination of Group VIII metal catalysts.[a]

$$CH_3(CH_2)_{10}CH_3 \xrightarrow[\text{160 °C, 12 h, sealed tube}]{\textbf{catalyst}\text{, }H_2\text{, }D_2O} CD_3(CD_2)_{10}CD_3$$

Entry	Catalyst[b]	D content [%] $CD_3(CD_2)_{10}CD_3$
1	10% Pd/C (10 wt%)	57 61 57
2	10% Ru/C (10 wt%)	12 14 12
3	10% Ir/C (10 wt%)	45 34 45
4	5% Pt/C (20 wt%)	18 18 18
5	10% Rh/C (10 wt%)	80 81 80
6	5% Rh/Al_2O_3 (20 wt%)	0 0 0
7	$RhCl_3\ 3\,H_2O$ (1.6 mol%)[c]	0 0 0

[a] The reaction was carried out with the given catalyst in D_2O (2 mL) under H_2 at 160 °C. [b] Catalysts were provided by N.E. Chemcat, except for Pt/C (Aldrich). Amount of catalyst used is shown in parentheses. [c] The amount of Rh metal used in the reaction was the same as for entry 5.

because it is known that the activity of supported metal catalysts is variable depending on the commercial source[13] (Table 2). The 5% Rh/C provided by Aldrich had a better catalyst activity, and nearly fully deuterated *n*-dodecane was obtained (Table 2, entry 3). The reason for the varied outcome of the reaction (depending on the source of catalyst) is still unclear. This inconsistency might be caused by the quality of the activated carbon in the catalyst, by the remaining acid (a contaminant from the process purification of catalyst) on the activated carbon, or by the valence of Rh on the activated carbon.

Table 2: Effect of catalyst obtained from different suppliers.

$$CH_3(CH_2)_{10}CH_3 \xrightarrow[\text{160 °C, 24 h, sealed tube}]{\text{Rh/C, }H_2\text{, }D_2O} CD_3(CD_2)_{10}CD_3$$

Entry	Supplier	D content [%] $CD_3(CD_2)_{10}CD_3$
1	N.E. Chemcat (10% Rh/C, 10 wt%)	80 81 80
2	Wako Chemical (5% Rh/C, 20 wt%)	81 80 81
3	Aldrich (5% Rh/C, 20 wt%)	96 92 96
4	Merck (5% Rh/C, 20 wt%)	50 52 50

[a] The reaction was carried out with the catalyst in D_2O (2 mL) under H_2 at 160 °C.

The above Rh/C-catalyzed H/D exchange method was applied to the deuteration of various linear alkanes (Table 3).[14] Linear alkanes bearing less than 28 carbon atoms underwent H/D exchange at all of the carbon centers with over 90% deuterium incorporation and with high to quantitative yields of each isolated product (Table 3, entries 1 and 3–5). In the case of *n*-hexatriacontane (36 carbon atoms), however, deuterium incorporation was moderate (up to 59%, Table 3, entry 6). No H/D exchange was observed under the H_2-free reaction conditions (Table 3, entry 2).

Table 3: H/D exchange of linear alkanes.[a]

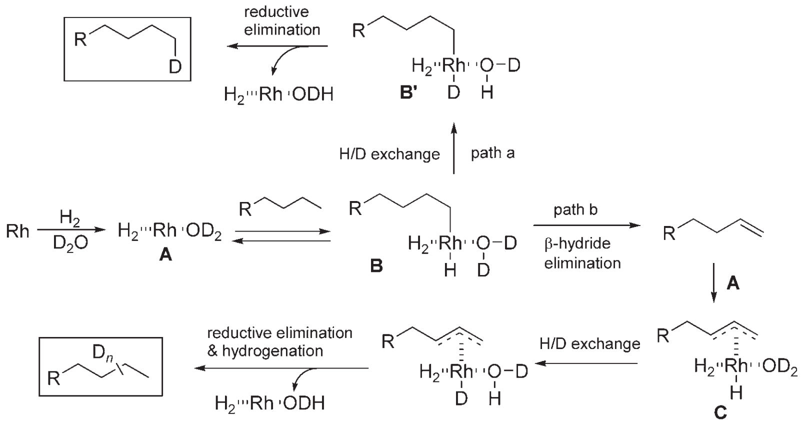
$$\text{Substrate} \xrightarrow[\text{160 °C, 12 h, sealed tube}]{\text{Rh/C (Aldrich), }H_2\text{, }D_2O} [D_n]\text{Substrate}$$

Entry	Substrate	D content [%]	Yield [%]
1	*n*-dodecane ($C_{12}H_{26}$)	$CD_3(CD_2)_{10}CD_3$ 91 90 91	76
2[b]	*n*-dodecane ($C_{12}H_{26}$)	$CD_3(CD_2)_{10}CD_3$ 0 0 0	76
3	*n*-pentadecane ($C_{15}H_{32}$)	$CD_3(CD_2)_{13}CD_3$ 92 92 92	93
4	*n*-eicosane ($C_{20}H_{42}$)	$CD_3(CD_2)_{18}CD_3$ 87 90 87	93
5	*n*-octacosane ($C_{28}H_{58}$)	$CD_3(CD_2)_{26}CD_3$ 96 92 96	100
6[c]	*n*-hexatriacontane ($C_{36}H_{74}$)	$CD_3(CD_2)_{34}CD_3$ 59 52 59	96

[a] The reaction was carried out with the substrate (0.25 mmol) and 5% Rh/C (20 wt%) in D_2O (2 mL) under H_2 at 160 °C. [b] Under argon. [c] 24 h.

Branched and cyclic alkanes were also deuterated under the same reaction conditions. The H/D exchange of secondary and tertiary methyl groups within the branched alkanes proceeded smoothly with high deuteration efficiencies (Table 4, entries 1–4). Cyclic alkanes, such as cyclopentadecane and pentadecylcyclohexane, were also deuterated with moderate to excellent efficiencies (Table 4, entries 5–7). In contrast α-cholestane, possessing a rigid cholesterol skeleton, had a lower deuterium incorporation ratio (Table 4, entry 8). The deuterated products were spectroscopically pure and did not require chromatographic purification.

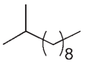
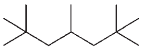
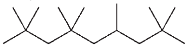
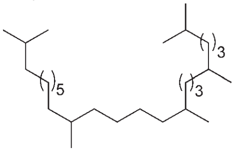
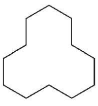
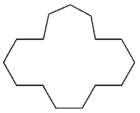
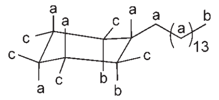
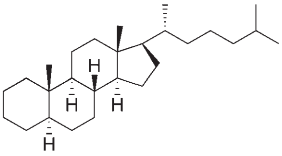
For the H/D exchange reaction of alkanes, the oxidative insertion of Rh into the C–H bonds should be the key step. Since H_2 at atmospheric pressure is essential for the deuteration reaction (Table 3, entry 2) it might act as an activator of the Rh catalyst (as a so-called mild ligand). There are two plausible mechanisms (Scheme 2).[9g] Firstly, the H_2-and D_2O-activated Rh species **A** could insert into the C–H bond of the alkane followed by H/D exchange with D_2O to form **B′**. Then reductive elimination from **B′** gives the corresponding deuterated alkane (path a). Alternatively, the Rh–substrate complex **B** could undergo β-hydride elimination to produce an alkene, which can react with **A** to form the Rh–π-allyl complex **C**. Subsequent H/D exchange, reductive elimination,



Scheme 2. Plausible mechanisms.

Table 4: H/D exchange of branched and cyclic alkanes.[a]

$$\text{Substrate} \xrightarrow[\text{160 °C, sealed tube}]{\text{Rh/C (Aldrich), H}_2\text{, D}_2\text{O}} [D_n]\text{Substrate}$$

Entry	Substrate	*t* [h]	D content [%]	Yield [%]
1	2-methylundecane	12	 CD_3 92; CD_2 93; CD 96	90
2	2,2,4,6,6-pentamethylheptane	12	 CD_3 85; CD_2 80; CD 91	96
3	2,2,4,4,6,8,8-heptamethylnonane	24	 CD_3 88; CD_2 90; CD 90	60
4	squalane	24	 CD_3 99; CD_2 99; CD 100	92
5	cyclododecane	24	 CD_2 84	66
6	cyclopentadecane	24	 CD_2 94	78
7	pentadecylcyclohexane	24	 a 69; b 82; c 77	88
8	α-cholestane	24	 D 36(average)	97

[a] The reaction was carried out with 5% Rh/C (20 wt%) in D_2O (2 mL) under H_2 at 160°C.

Table 5: The effect of co-solvent.[a]

$$CH_3(CH_2)_{34}CH_3 \xrightarrow[\text{160 °C, 24 h, sealed tube}]{\text{Rh/C (Aldrich), H}_2\text{, D}_2\text{O}} CD_3(CD_2)_{34}CD_3$$

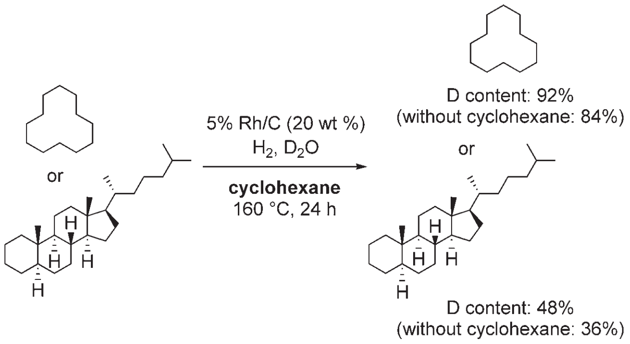
co-solvent

Entry	Co-solvent	D content [%] CD_3	$(CD_2)_{34}$	CD_3
1	none	43	41	43
2	cyclohexane	93	94	93
3	$CHCl_3$	13	25	13
4	1,2-dichloroethane	37	40	37
5	toluene	28	30	28

[a] The reaction was carried out with the substrate (0.1 mmol) and 5% Rh/C (20 wt%) in D_2O (1 mL) and co-solvent (0.1 mL) under H_2 at 160°C.

and hydrogenation gives the deuterated alkane (path b). Further deuterium incorporation may occur by repetition of the processes described as paths a and b. The reaction may occur on the Rh metal interface of the support, as the activated carbon plays an important role in the reaction progress (Table 1).

Notably, the H/D exchange reaction of alkanes described herein efficiently proceeds in D_2O even though alkanes are only slightly soluble in D_2O. It is likely that the activated carbon helps to dissolve and/or concentrate the alkanes into the carbon micropores (enrichment effect of the substrate), and therefore the alkanes can easily come into contact with the Rh catalyst. We envisioned that a co-solvent for dissolving alkanes would improve the efficiency of the deuteration process. Several solvents for the deuteration of *n*-hexatriacontane were explored. Interestingly, only cyclohexane enhanced the deuterium efficiencies up to 94% (Table 5, entry 2); in contrast, other solvents such as $CHCl_3$, 1,2-dichloromethane, and toluene all decreased the deuterium efficiency (Table 5, entries 3–5). We also carried out H/D exchange reactions on a branched alkane and a cyclic alkane using cyclohexane as the co-solvent. Consequently, the deuterium incorporated onto the substrates was significantly improved (Scheme 3; for comparison see Table 4, entries 5 and 8).



Scheme 3. The H/D exchange reaction using cyclohexane as the co-solvent.

In conclusion, we have developed an efficient Rh/C-catalyzed H/D exchange reaction of alkanes under nearly atmospheric conditions based on the C–H activation process. This method can be applied to diverse alkanes with good to high deuterium incorporation. The addition of cyclohexane as a co-solvent significantly improves the deuteration efficiency.

Experimental Section

In a hydrogen atmosphere, a suspension of D_2O (2 mL), 5% Rh/C (20 wt%), and substrate (0.25–0.5 mmol) was stirred at 160°C for 12–24 h. After the reaction was complete, the mixture was extracted with Et_2O and the ethereal layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give the deuterated product. The deuterium content of the product was calculated by using ^{1}H NMR spectra with 1,4-dimethoxybenzene as an internal standard. The deuterium incorporation was confirmed by ^{2}H NMR spectroscopy and the amount of deuterium incorporated was also determined by mass spectrometry.

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