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PLATINUM CATALYZED H-D EXCHANGE REACTION OF VARIOUS AROMATIC COMPOUNDS UNDER HYDROTHERMAL CONDITION**

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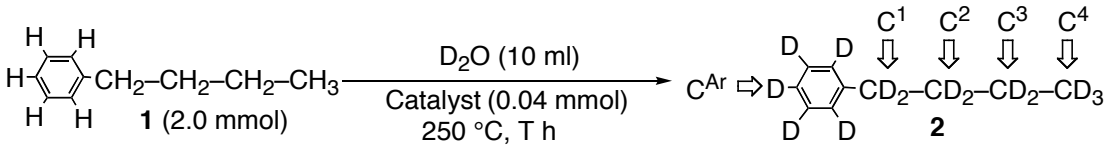
Abstract – Various aromatic compounds were treated with deuterium oxide under hydrothermal conditions in the presence of a catalytic amount of platinum (IV) oxide. An efficient H-D exchange reaction was observed, which gave various deuterium labeled aromatic compounds.

Introduction

The H-D exchange reaction of organic compounds has been attracted attention as a method for preparation of labeled compounds.[1,2] The H-D exchange reaction in deuterium oxide has been performed in various ways.[3] For example, a base catalyzed H-D exchange reaction in supercritical or subcritical deuterium oxide was applied for the reaction of phenol and aniline derivatives[4] and an acid-catalyzed H-D exchange reaction was applied for alkenes.[5] In addition, transition metal-catalyzed exchange reaction in deuterium oxide is a useful method.[6] We have demonstrated that H-D exchange reactions in alkanes and alkenes could be performed effectively with Pd/C catalyst in hydrothermal deuterium oxide[7a,b] and those in polystyrene samples could also be performed with PtO_2 catalyst in hydrothermal deuterium oxide.[7c] We also demonstrated that a ruthenium-catalyzed reaction under irradiation of microwaves in deuterium oxide could be a selective H-D exchange reaction at α-position of alcohols and amines.[8] In our findings, platinum catalyst is the most effective catalyst for H-D exchange reaction in an aromatic ring, as shown in Table 1. The mechanism of platinum-catalyzed H-D exchange reaction in aromatic ring may be considered to proceed *via* a Friedel-Crafts-type reaction.[9-11] In this sense, an electron rich heterocyclic compound or a benzene ring with an electron-donating group will show the more efficient H-D exchange reaction in hydrothermal deuterium oxide in the presence of

platinum catalyst.[4,6,11] Although easy deuteration is expected, the tolerances of these compounds under the hydrothermal conditions should be kept in mind. So, we will show some systematic platinum-catalyzed H-D exchange reactions of various heterocyclic compounds and aromatic compounds with electron-donating groups.

Table 1. Metal salt catalyzed deuteration of butylbenzene (**1**) under hydrothermal condition.[a,b]



run	Catalyst	T/h	C^{Ar}	C^1	C^2	C^3	C^4
1	Pd/C	2	20%	67%	42%	49%	43%
2	PdO	2	2	61	38	50	42
3	Pd black	2	<5	32	14	24	16
4	Raney Ni	2	3	28	10	13	5
5	PtO_2	2	28	42	26	32	30
6	PtO_2	4	65	58	49	48	40
7	PtO_2	6	81	75	59	65	56
8	PtO_2	14	96	95	94	95	83

[a] Substrate (2.0 mmol), catalyst (2 mol% Metal), and D_2O (20.0 g). [b]The ratios were determined by ^1H NMR, ^2H NMR, and MS spectra.

Results and Discussion

As shown in Figure 1, various aromatic compounds substituted with hetero-atoms were treated with hydrothermal deuterium oxide (250 °C) in the presence of 5 mol% of platinum(IV) oxide for 12 h, as shown in EXPERIMENTAL section. A complete H-D exchange reaction was observed in dibenzo-18-crown-6. In the case of triphenylamine, the electron-donating property of a nitrogen atom will benefit the acceleration of the H-D exchange reaction, but the steric hindrance at *ortho*-

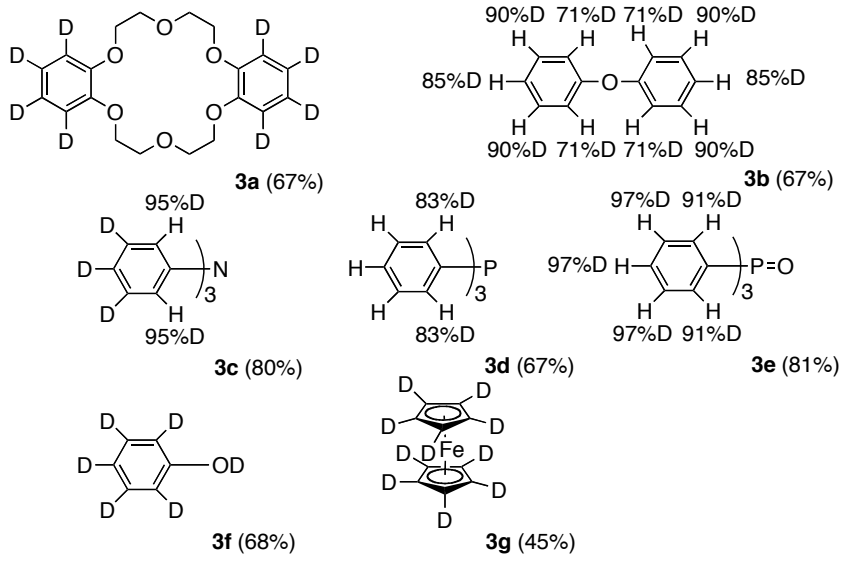


Figure 1. Results of H-D exchange reaction of aromatic compounds carrying hetero-atoms (5 mol% PtO_2, D_2O, 250 °C, 4 MPa).

position of triphenylamine makes the exchange reaction difficult. Selective H-D exchange at *ortho*-position of triphenylphosphine can be explained by coordination of phosphorous-atom with platinum catalyst.

In the case of heterocycles containing nitrogen-atoms, the H-D exchange reaction proceeded smoothly. As shown in Figure 2, efficient H-D exchange reactions were observed in all cases.

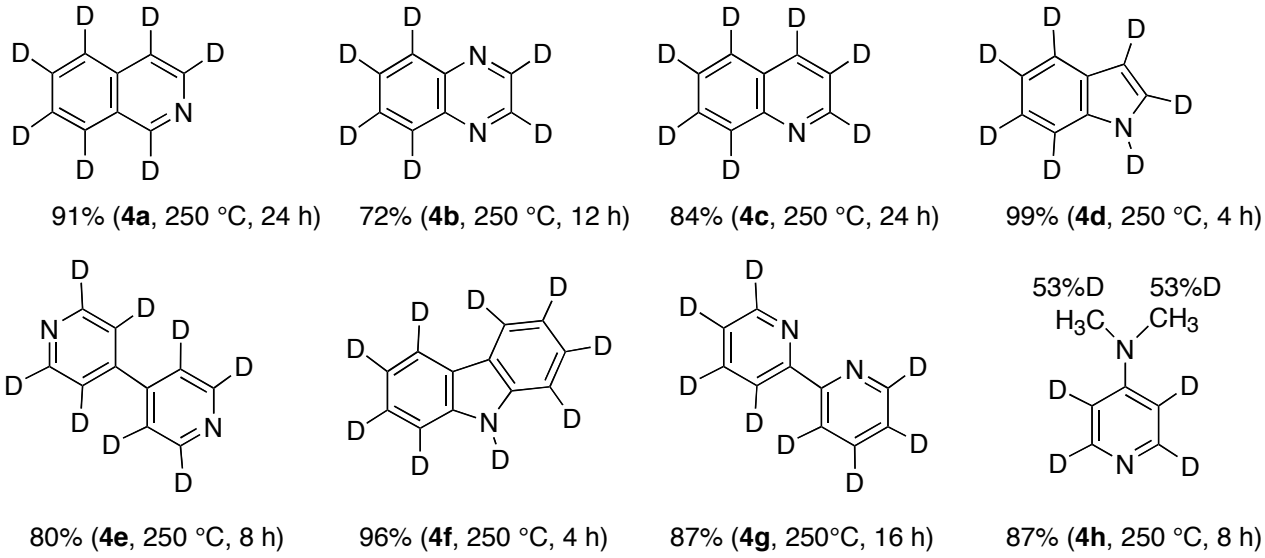
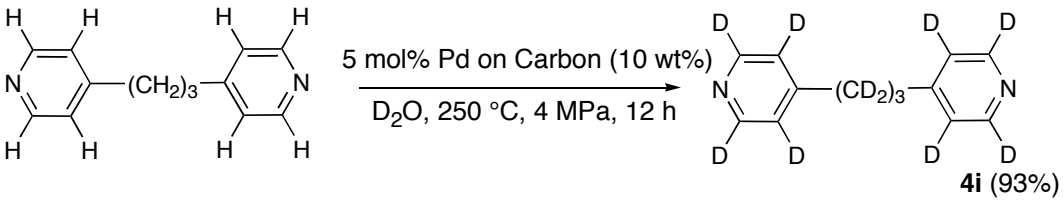


Figure 2. Results of H-D exchange reaction of N-atom containing heterocycles in deuterium oxide in the presence of 5 mol% platinum(IV) oxide (in parentheses, reaction temperature and reaction period).

A substrate in Scheme 1, 1,3-bis(4-pyridyl)propane, has three methylene groups between two nitrogen atom containing heterocycles. In this case, the use of a palladium catalyst instead of a platinum one gave the corresponding fully deuterated product. The reaction with platinum(IV) catalyst could not exchange the protons on the center methylene group perfectly.



Scheme 1.

Thus, transition metal catalyzed H-D exchange reactions under hydrothermal deuterium oxide can be applied to various aromatic compounds and heterocycles. Although the hydrothermal condition means that the reaction is performed under 200~250 °C / 1.5~5 MPa, the surrounding water (or D_2O) also prevents the decomposition of organic compounds. The hydrothermal reaction is different from direct heating.

EXPERIMENTAL

The H-D exchange reactions were performed as follows. The vessel in Figure 3 is designed to release the internal overpressure.[7a] It is commercially available from Shikokurika Co., Ltd., Kochi, Japan. In a teflon vessel, platinum(IV) oxide (22.7 mg, 0.1 mmol), deuterium oxide (15 mL), and aromatic compound (2.0 mmol) were added. After the vessel was placed in autoclave and sealed, the whole was placed in oven (250 °C). After the autoclave was heated for the period indicated in the text, it was cooled to rt. The obtained mixture was extracted with chloroform. Teflon vessel absorbs organic compounds. To extract the product completely, the vessel washed with chloroform and water using ultra sonic cleaner for 15 min each. These solvents used for wash were extracted with chloroform. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The obtained product was purified by a short silica-gel column chromatography. Instead of the vessel in Figure 1, glass sealed tube is also possible. In the sealed tube case, however, the reaction should be taken care concerning about explosion, as the internal pressure is quite high. The deuteration ratio was determined by ^1H and ^2H NMR spectrum using an internal standard ($CHBr_3$ for ^1H NMR spectrum and $CDCl_2$-$CDCl_2$ for ^2H NMR spectrum).

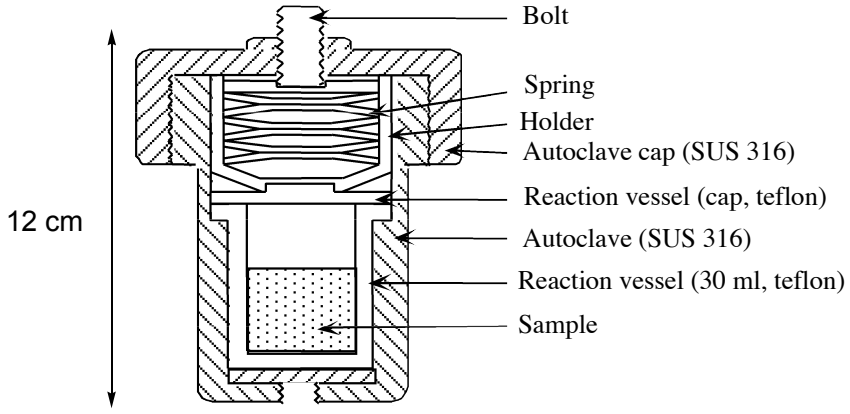


Figure 3. 30mL Teflon© lined autoclave

Deuterated Dibenzo-18-Crown-6 (3a)

^1H-NMR (300 MHz, $CDCl_3$): δ 4.25-3.6 (m, 16H); ^2H-NMR (40 MHz, $CHCl_3$): δ 7.4-6.8 (m, 8D); MS: 368 (M^+).

Deuterated Diphenyl ether (3b)

^1H-NMR (300 MHz, $CDCl_3$): δ 7.25 (m, 0.4H), 6.99 (m, 0.3H), 6.95 (m, 1.16H); ^2H-NMR (40 MHz, $CHCl_3$): δ 7.25 (m, 3.6H), 6.9 (m, 4.5H).

Deuterated Triphenylamine (3c)

^1H-NMR (300 MHz, $CDCl_3$): δ 7.05 (m, 0.3H); ^2H-NMR (40 MHz, $CHCl_3$): δ 7.7-7.0 (m, 14.7D); MS: 260 (M^+).

Deuterated Triphenylphosphine (3d)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.8-7.1 (m, 10H); ^{2}H-NMR (40 MHz, $CHCl_3$): δ 7.7-7.0 (m, 4.9D). The regio of deuteration was determined after conversion into triphenylphosphine oxide by oxone. Deuterated triphenylphosphine oxide: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.8-7.7 (m, 1H), 7.65-7.3 (m, 9H); ^{2}H-NMR (40 MHz, $CHCl_3$): δ 7.8-7.7 (m, 5D).

Deuterated Triphenylphosphine oxide (3e)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.8-7.7 (m, 0.6H), 7.65-7.3 (m, 0.27H); ^{2}H-NMR (40 MHz, $CHCl_3$): δ 7.8-7.0 (m, 14.1D).

Deuterated Phenol (3f)

^{1}H-NMR (300 MHz, $CDCl_3$): no signal; ^{2}H-NMR (40 MHz, $CHCl_3$): δ 7.2 (br s, 2D), 6.9 (br s, 1D), 6,8 (br s, 2D).

Deuterated Ferrocene (3g)

^{1}H-NMR (300 MHz, $CDCl_3$): no signal; ^{2}H-NMR (40 MHz, $CHCl_3$): δ 4.1 (br s, 10D).

Deuterated Isoquinoline (4a)

^{1}H-NMR (300 MHz, $CDCl_3$): no signal; ^{2}H-NMR (40 MHz, $CHCl_3$): δ 9.2 (br s, 1D), 8.5 (br s, 1D), 7.9 (br s, 1D), 7.7 (br s, 1D), 7.6-7.3 (br s, 3D); MS: 136 (M^+).

Deuterated Quinoxaline (4b)

^{1}H-NMR (300 MHz, $CDCl_3$): no signal; ^{2}H-NMR (40 MHz, $CHCl_3$): δ 8.9 (br s, 2D), 8.2 (br s, 2D), 7.8 (br s, 2D); MS: 136 (M^+).

Deuterated Quinoline (4c)

^{1}H-NMR (300 MHz, $CDCl_3$): no signal; ^{2}H-NMR (40 MHz, $CHCl_3$): δ 8.9 (br s, 1D), 8,15 (br s, 1D), 8.1 (br s, 1D), 7.8 (br s, 1D), 7.7 (br s, 1D), 7.5 (br s, 1D), 7.3 (br s, 1D); MS: 136 (M^+).

Deuterated Indole (4d)

^{1}H-NMR (300 MHz, $CDCl_3$): no signal; ^{2}H-NMR (40 MHz, $CHCl_3$): δ 7.8 (br s, 1D), 7.6 (br s, 1D), 7.5-7.0 (m, 4D), 6.6 (br s, 1D); MS: 124 (M^+).

Deuterated 4,4'-Dipyridyl (4e)

^{1}H-NMR (300 MHz, $CDCl_3$): no signal; ^{2}H-NMR (40 MHz, $CHCl_3$): δ 8.7 (br s, 4D), 7.5 (br s, 4D); MS: 164 (M^+).

Deuterated Carbazole (4f)

^{1}H-NMR (300 MHz, $CDCl_3$): no signal; ^{2}H-NMR (40 MHz, $CHCl_3$): δ 7.95 (br s, 2D), 7.45 (br s, 3D), 7.15 (br s, 2D); MS: 176 (M^+).

Deuterated 2,2'-Dipyridyl (4g)

^{1}H-NMR (300 MHz, $CDCl_3$): no signal; ^{2}H-NMR (40 MHz, $CHCl_3$): δ 8.6 (br s, 2D), 8.4 (br s, 2D), 7.7 (br s, 2D), 7.2 (br s, 2D); MS: 164 (M^+).

Deuterated 4-(Dimethylamino)pyridine (4h)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.0 (m, 2.8H); ^{2}H-NMR (40 MHz, $CHCl_3$): δ 8.2 (br s, 2D), 6.5 (br s, 2D), 2.9 (br s, 3.2D).

Deuterated 4,4'-Trimethylenedipyridine (4i)

^{1}H-NMR (300 MHz, $CDCl_3$): no signal; ^{2}H-NMR (40 MHz, $CHCl_3$): δ 8.5 (br s, 4D), 7.1 (br s, 4D), 2.6 (br s, 4D), 1.9 (br s, 2D); MS: 212 (M^+).

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REFERENCES

1. (a) T. Junk and W. J. Catallo, *Chem. Soc. Rev.,* 1997, **26**, 401. (b) N. Elander, J. R. Jones, S.-Y. Lu, and S. Stone-Elander, *Chem. Soc. Rev.,* 2000, **29**, 239. (c) J. L. Garnett, *Catal. Rev.,* 1971, **5**, 229. (d) T. Kametani, K. Katoh, M. Tsubuki, and T. Honda, *J. Am. Chem. Soc*., 1986, **108**, 7055. (e) M. Ihara, K. Noguchi, T. Ohsawa, K. Fukumoto, and T. Kametani, *J. Org. Chem*., 1983, **48**, 3150.
2. (a) T. Kurihara, N. Ooba, S. Toyoda, and T. Maruno, *Oyobuturi,* 2002, **71**, 1708. (b) T. Kaino, K. Jinguji, and S. Nara, *Appl. Phys. Lett.,* 1983, **42**, 567. (c) A. Koshino and T. Tagawa, *J. Appl. Polym. Chem. Soc.,* 1965, **9**, 117. (d) M. S. Miller and I. M. Klotz, *J. Am. Chem. Soc*., 1973, **95**, 5694.
3. (a) J. T. Golden, R. A. Andersen, and R. G. Bergman, *J. Am. Chem. Soc.,* 2001, **123**, 5837. (b) A. E. Shilov and A. A. Steinman, *Coord. Chem. Rev.,* 1977, **24**, 97. (c) J. L. Ganet and R. J. Hodges, *J. Am. Chem. Soc.,* 1967, **89**, 4546.
4. J. Yao and R. F. Evilia, *J. Am. Chem. Soc.,* 1994, **116**, 11229.
5. N. H. Werstiuk and T. Kadai, *Can. J. Chem.,* 1974, **52**, 2169.
6. (a) F. A. L. Anet and M. St. Jacques, *J. Am. Chem. Soc*., 1966, **88**, 2585. (b) J. L. Ganett and R. J. Hodges, *J. Am. Chem. Soc*., 1967, **89**, 4545. (c) O. Desponds and M. Schlosser, *Tetrahedron Lett*., 1996, **37**, 47. (d) H. Sajiki, K. Hattori, F. Aoki, K. Yasunaga, and K. Hirota, *Synlett,* 2002, 1149; H. Sajiki, F. Aoki, H. Esaki, T. Maegawa, and K. Horita, *Org. Lett.,* 2004, **6**, 1485. (e) C. Hardacre, J.

D. Holbrey, and S. E. J. McMath, *J. Chem. Soc., Chem. Commun.,* 2001, 367. (f) J. G. Atkinson, M. O. Luke, and R. S. Stuart, *Can. J. Chem.*, 1967, **45**, 1511. (g) J. R. Jones, W. J. S. Lockley, S.-Y. Lu, and S. P. Thompson, *Tetrahedron Lett.*, 2001, **42**, 331. (h) T. Maegawa, A.Akashi, H. Esaki, F. Aoki, H. Sajiki, and K. Hirota, *Synlett*, 2005, 845. (i) H. Sajiki, H. Esaki, F. Aoki, T. Maegawa, and K. Hirota, *Synlett*, 2005, 1385.

7. (a) S. Matsubara, Y. Yokota, and K. Oshima, *Chem. Lett.,* 2004, **33**, 294. (b) S. Matsubara, Y. Yokota, and K. Oshima, *Org. Lett.,* 2004, **6**, 2071. (c) M. Yamamoto, Y. Yokota, and K. Oshima, and S. Matsubara, *Chem. Commun.,* 2004, 1714. (d) S. Matsubara and K. Oshima, *J. Org. Synth. Soc. Jpn.,* 2005, **63**, 154.
8. (a) M. Takahashi, K. Oshima, and S. Matsubara, *Chem. Lett.,* 2005, **34**, 192. (b) K. Ishibashi, M. Takahashi, Y. Yokota, K. Oshima, and S. Matsubara, *Chem. Lett.,* 2005, **34**, 664.
9. S. J. Pastine, S. W. Youn, and D. Sames, *Org. Lett.,* 2003, **5**, 1055.
10. M. Yamamoto, K. Oshima, and S. Matsubara, *Org. Lett.,* 2004, **6**, 5015.
11. T. Yoshida, T. Matsuda, T. Okano, T. Kitani, and S. Otsuka, *J. Am. Chem. Soc.,* 1979, **101**, 2027.

**This paper is dedicated to Professor Dr. Barry M. Trost as we celebrate his 65th birthday.