DOI: 10.1002/adsc.200606053

Synergistic Effect of a Palladium-on-Carbon/Platinum-on-Carbon Mixed Catalyst in Hydrogen/Deuterium Exchange Reactions of Alkyl-Substituted Aromatic Compounds

Nobuhiro Ito,[a] Tsutomu Watahiki,[a] Tsuneaki Maesawa,[a] Tomohiro Maegawa,[b] and Hironao Sajiki[b,]*

[a] Chemical Products Research Laboratories, Wako Pure Chemical Industries, Ltd., 1633 Matoba, Kawagoe 350-1101, Japan
Fax: (+81)-49-233-7953
[b] Laboratories of Medicinal Chemistry, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502-8585, Japan
Fax: (+81)-58-237-5979; e-mail: sajiki@gifu-pu.ac.jp

Received: February 15, 2006; Accepted: April 15, 2006

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: We have found a synergistic effect in the H-D exchange reaction of alkyl-substituted aromatic compounds using the Pd/C-Pt/C-D_2O-H_2 system. This system would lead to fully H-D exchange results even on the sterically hindered sites which were only low-deuterium incorporated by Pd/C or Pt/C independently. Since the reaction was general for a variety of aromatic compounds, it could be applied to the deuteration of dianiline derivatives as raw materials for polyimides.

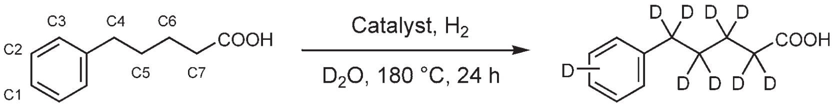
Keywords: catalysis; deuteration; palladium; platinum; synergistic effect

Deuterium-labeled compounds have been extremely useful in many different branches of science including analysis of drug metabolism, investigation of reaction mechanisms and kinetics etc.[1] Recently, deuterium-labeled polymers were recognized as new materials for wave guides in optical communication systems due to their transparency in the infrared wavelength region.[2] The post-synthetic incorporation of deuterium by the hydrogen isotope exchange reaction using D_2O, which is the cheapest deuterium compound, as a deuterium source is a cost-wise attractive method. A number of H-D exchange procedures of aromatic compounds in D_2O have been reported, for example, the H-D exchange reaction catalyzed by acids,[3] bases[4] or transition metals (Ir,[5] Ru,[6] Rh,[7] Pt[8] and Pd[9]) and supercritical[10] or microwave enhancement[6,8f] exchange reactions. However, many such methods involve contraindications with specific functionalities, low deuterium efficiency and/or the requirement of a vast amount of catalyst and special apparatus.

We have recently reported a characteristic H-D exchange reaction catalyzed by Pd/C or Pt/C using D_2O in the presence of a small amount of H_2 gas,[11] that is, Pd/C catalyzed the H-D exchange reaction at inactive alkyl chains[11b] and Pt/C catalyzed it at aromatic rings[11e] efficiently. We also applied the reaction to the stepwise deuteration of alkyl-substituted aromatic compounds using Pt/C and Pd/C and obtained high deuterium efficiency. Meanwhile, when we tried to examine the deuteration using Pd/C and Pt/C at the same time, and a surprisingly high deuterium efficiency by a synergistic effect was observed. Herein, we report the efficient deuterium incorporation into alkyl-substituted aromatic compounds by synergistic effect of the Pd/C-Pt/C-D_2O-H_2 system.

First, we examined the deuteration of 5-phenylvaleric acid using Pd/C and Pt/C independently or mixed them as a catalyst and Table 1 summarizes a comparison of the deuterium efficiencies. 5-Phenylvaleric acid and 10% Pd/C (10 wt%) in D_2O at 180°C under a small amount of hydrogen in a sealed tube for 24 h leads to high deuterium efficiency on the aromatic ring and alkyl chain, except for the C3 (*ortho*) position (entry 1). On the other hand, using 5% Pt/C (20 wt%) as a catalyst leads to high deuterium efficiency on the aromatic ring, except for the C3 (*ortho*) position (entry 3). The low deuterium efficiency of the C3 position is probably caused by steric hindrance of the alkyl chain, which was also reported by Matsubara[12] and Bergman.[13] Surprisingly, when the reaction was performed using a mixture of 10% Pd/C (10 wt%) and 5% Pt/C (20 wt%) as a catalyst, high deuterium efficiency was observed even at the C3 position which is a sterically hindered position, and fully deuterated 5-phenylvaleric acid-d_{13} was obtained in 84% isolated yield (entry 6). This high deuterium efficiency was not observed when 2-fold by weight of 10% Pd/C or 5%

Table 1. Comparison of deuterium efficiencies of 5-phenylvaleric acid using Pd/C or Pt/C independently and by mixing them as a catalyst.[a]



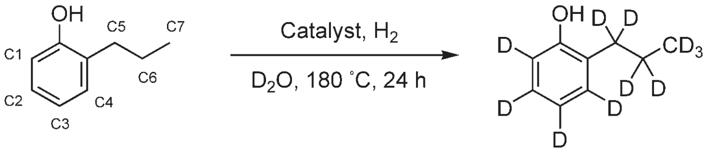
Entry	Catalyst (wt %)	D content [%][b]						Yield [%]
		C1	C2	C3	C4	C5, C6	C7	
1	10 % Pd/C (10 %)	96	96	14	98	96	96	88
2	10 % Pd/C (20 %)	>93	93	<36	98	97	97	82
3	5 % Pt/C (20 %)	97	97	19	28	8	10	92
4	5 % Pt/C (40 %)	95	95	13	6	2	7	92
5[c]	10 % Pd/C (10 %)	97	97	30	97	97	97	84
6	10 % Pd/C (10 %) + 5 % Pt/C (20 %)	97	97	97	97	97	94	84

[a] 500 mg (2.81 mmol) of the substrate were used and reactions were carried out under ordinary H_2 pressure using the catalyst in D_2O (99.9 % D content, 17 mL) in a sealed tube.

[b] D contents were determined by ^{1}H NMR after conversion of the carboxylic acid to the methyl ester on the basis of the integration of the methyl protons and confirmed by ^{2}H NMR, ^{13}C NMR and mass spectrometry.

[c] The product of entry 3 was used as starting material.

Table 2. Deuteration of 2-*n*-propylphenol using Pd/C and Pt/C as a mixed catalyst.[a]



Entry	Catalyst (wt %)	D content [%][b]							Yield [%]
		C1	C2	C3	C4	C5	C6	C7	
1	10 % Pd/C (10 %)	99	98	99	48	98	97	97	84
2	5 % Pt/C (20 %)	98	98	98	38	72	42	28	62
3	10 % Pd/C (10 %) + 5 % Pt/C (20 %)	97	97	97	87	97	97	97	55
4	5 % Pd/C (20 %) + 5 % Pt/C (20 %)	99	99	98	97	98	98	98	84

[a] 500 mg (3.67 mmol) of the substrate were used and reactions were carried out under ordinary H_2 pressure using the catalyst in D_2O (99.9 % D content, 17 mL) in a sealed tube.

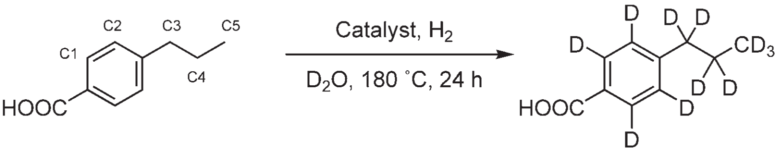
[b] D contents were determined by ^{1}H NMR and confirmed by ^{2}H NMR, ^{13}C NMR and mass spectrometry.

Pt/C was used as a catalyst (entries 2 and 4). Moreover, even stepwise deuteration, with 5 % Pt/C and subsequently with 10 % Pd/C-catalyzed deuteration could not give a high deuterium efficiency at the C3 position (entry 5). This result implies that mixing Pd/C with Pt/C as a catalyst brings about a synergistic effect in the H-D exchange reaction.

To explore the scope of this synergistic effect of the Pd/C-Pt/C-D_2O-H_2 system, the deuteration of 2-*n*-propylphenol was investigated (Table 2). 10 % Pd/C or 5 % Pt/C gave moderate deuterium efficiency at the C4 position which has steric hindrance of the alkyl chain (entries 1 and 2). As described previously, mixing 10 % Pd/C with 5 % Pt/C as a catalyst gave high deuterium efficiency (87 %) at the C4 position (entry 3). Furthermore, when 5 % Pd/C (20 wt %) and 5 % Pt/C (20 wt %) were used as a catalyst, fully deuterated 2-*n*-propylphenol-d_{11} was obtained (entry 4). This result indicated that a more dispersed catalyst shows high activity in the H-D exchange reaction in accordance with catalytic hydrogenation.

Electron-deficient aromatic compounds were less straightforward to achieve high deuterium efficiency, and the deuteration of 4-*n*-propylbenzoic acid was investigated (Table 3). Deuterium incorporation into the aromatic ring catalyzed by 10 % Pd/C was scarcely observed (entry 1). Even the aromatic ring-favorable 5 % Pt/C-catalyzed condition gave low deuterium efficiency, especially at the C2 position (entry 2). On the other hand, when 10 % Pd/C and 5 % Pt/C were used as a mixed catalyst, a moderate result was obtained (entry 3). Consequently, using a more dispersed catalyst, that is 5 % Pd/C and 5 % Pt/C as a mixed catalyst, gave higher deuterium efficiency (entry 4). Fur-

Table 3. Deuteration of 4-*n*-propylbenzoic acid using Pd/C and Pt/C as a mixed catalyst.[a]



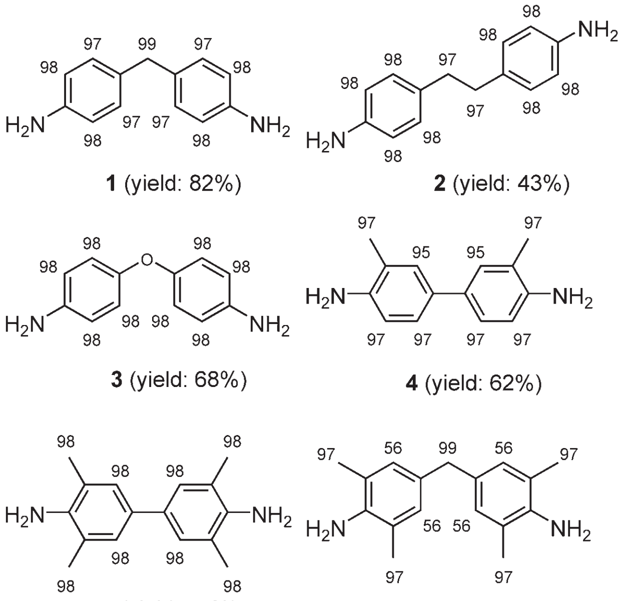
Entry	Catalyst (wt %)	D content [%][b]					Yield [%]
		C1	C2	C3	C4	C5	
1	10% Pd/C (10%)	3	4	96	93	92	64
2	5% Pt/C (20%)	62	17	15	12	11	84
3	10% Pd/C (10%) + 5% Pt/C (20%)	78	58	90	83	77	88
4	5% Pd/C (20%) + 5% Pt/C (20%)	94	92	96	96	95	92
5	1% Pd/C (100%) + 1% Pt/C (100%)	97	97	98	94	95	72
6	1% Pd/C (10%) + 1% Pt/C (10%)	16	4	57	33	23	87
7	1% Pd/C (1%) + 1% Pt/C (1%)	0	0	0	0	0	94

[a] 500 mg (3.05 mmol) of the substrate were used and reactions were carried out under ordinary H_2 pressure using the catalyst in D_2O (99.9% D content, 17 mL) in a sealed tube.

[b] D contents were determined by ^{1}H NMR after conversion of the carboxylic acid to the methyl ester on the basis of the integration of the methyl protons and confirmed by ^{2}H NMR, ^{13}C NMR and mass spectrometry.

thermore, when 1% Pd/C and 1% Pt/C (each 100 wt% of the substrate) were used as a mixed catalyst, excellent deuterium efficiency was achieved and fully deuterated 4-*n*-propylbenzoic acid-d_{11} was obtained (entry 5) although the reduction of the catalyst amount to 10 wt% and 1 wt% of the substrate gave disappointing results.

Polyimides are important materials in the electronics industry due to their superior thermostability and workability. Recently, deuterated polyimides[14] are being seen as materials for wave guides in optical communication systems, because the replacement of hydrogen in the polyimides to deuterium brings about an enhancement of transparency by reduction of the C–H bond vibrational absorption in the infrared (IR) wavelength region and its overtones in the near IR to visible region.[2] Hence H-D exchange of several dianiline derivatives for the raw materials of polyimide synthesis was investigated to extend applications of the Pd/C-Pt/C-D_2O-H_2 system (Figure 1). As expected, 4,4′-diaminodiphenylmethane **1** and 4,4′-diaminodiphenylethane **2** achieved excellent deuterium efficiency and yields on use of a mixture of 10% Pd/C (10 wt%) and 5% Pt/C (20 wt%). Additionally, an ether derivative, such as 4,4′-diaminodiphenyl ether **3**, showed excellent deuterium incorporation as in alkyl-substituted derivatives. Furthermore, when 3,3′-dimethylbenzidine **4** and 3,3′,5,5′-tetramethylbenzidine **5** were used as the substrate, excellent deuterium efficiency was observed even at the steric hindrance position (2, 2’ of **4** and 2, 2′, 6, 6’ of **5**). On the other hand, 4,4′-dimethylenedi-2,6-xylidine **6** was low-deuterium incorporated under the same conditions, while using a mixture of 1% Pd/C (100 wt%) and 1% Pt/C (100 wt%) as a mixed catalyst leads to high deuterium efficiency (average 87% D content). Condensation of these deuterated substrates and pyromellitic dianhydride gave highly deuterated polyimides.



1 (yield: 82%) **2** (yield: 43%)

3 (yield: 68%) **4** (yield: 62%)

5 (yield: 54%) **6** (yield: 57%, 1% Pd/C-1% Pt/C)

Figure 1. Deuteration of dianiline derivatives using the 10% Pd/C-5% Pt/C-D_2O-H_2 system at 180 °C for 24 h.

In summary, we have found a synergistic effect in the H-D exchange reaction using the Pd/C-Pt/C-D_2O-H_2 system. This system could efficiently incorporate deuterium into a variety of alkyl-substituted aromatic compounds even at sterically hindered sites. It can be applied not only to optical materials but also to biologically active compounds. It is not known exactly why a synergistic effect arises on mixing Pd/C with

Pt/C, and we are currently investigating the process to elucidate the mechanism.

Experimental Section

Typical Experimental Procedure

A substrate (500 mg, 2.8–3.7 mmol) and 10% Pd/C (50 mg, 10 wt% of the substrate) and 5% Pt/C (100 mg, 20 wt% of the substrate) in D_2O (17 mL) were stirred at 180 °C in a sealed tube under an H_2 atmosphere for 24 h. The reaction mixture was diluted with ether (20 mL) and the mixture was filtered to remove the catalyst. The filtered catalyst was washed with ether (5 mL × 2). The combined ethereal layer was washed with H_2O (20 mL), dried ($MgSO_4$), and concentrated under vacuum. The residue was purified by silica gel column chromatography or preparative TLC. The D content (%) was determined by ^1H NMR using dioxane or benzene as an internal standard and confirmed by ^2H and ^{13}C NMR and mass spectrometry.

References

[1] T. Junk, W. J. Catallo, *Chem. Soc. Rev.* **1997**, *26*, 401–406.

[2] a) T. Kaino, K. Jinguji, S. Nara, *Appl. Phys. Lett.* **1982**, *41*, 802–804; b) T. Kaino, K. Jinguji, S. Nara, *Appl. Phys. Lett.* **1983**, *42*, 567–569.

[3] a) J. L. Garnett, R. J. Hodges, *J. Am. Chem. Soc.* **1967**, *89*, 4546–4547; b) J. L. Garnett, R. J. Hodges, *J. Chem. Soc. Chem. Commun.* **1967**, 1001–1003; c) G. P. Bean, A. R. Johnson, A. R. Katritzky, B. J. Ridgewell, A. M. White, *Aust. J. Chem.* **1995**, 1219–1223; d) M. A. Long, J. L. Garnett, R. F. W. Vining, T. Mole, *J. Am. Chem. Soc.* **1972**, *94*, 8632–8633; e) N. H. Werstiuk, T. Kadai, *Can. J. Chem.* **1974**, *52*, 2169–2171.

[4] a) M. Tashiro, K. Nakayama, *J. Chem. Soc., Perkin Trans. 1* **1983**, 2315–2318; b) G. Y. Iranzo, J. Elgureo, *J. Labelled Compd. Radiopharm.* **1990**, *28*, 967–970; c) M. Okazaki, N. Uchino, N. Nozaki, K. Kubo, *Bull. Chem. Soc. Jpn*, **1995**, *68*, 1024–1029.

[5] a) J. L. Garnett, M. A. Long, A. B. McLaren, K. B. Peterson, *J. Chem. Soc., Chem. Commun.* **1973**, 749–750; b) J. R. Heys, A. Y. L. Shu, S. G. Senderoff, N. M. Phillips, *J. Labelled Compd. Radiopharm.* **1993**, *33*, 431–438; c) C. A. Lukey, M. A. Long, J. L. Garnett, *Aust. J. Chem.* **1995**, *48*, 79–91; d) S. R. Klei, J. T. Golden, T. D. Tilley, R. G. Bergman, *J. Am. Chem. Soc.* **2002**, *124*, 2092–2093; e) M. J. Hickey, J. R. Jones, L. P. Kingston, W. J. S. Lockley, A. N. Mather, B. M. McAuley, D. J. Wilkinson, *Tetrahedron Lett.* **2003**, *44*, 3959–3961.

[6] a) M. Takahashi, K. Oshima, S. Matsubara, *Chem. Lett.* **2005**, *34*, 192–193; b) K. Ishibashi, M. Takahashi, Y. Yokota, K. Oshima, S. Matsubara, *Chem. Lett.* **2005**, *34*, 664–665.

[7] a) M. R. Blake, J. L. Garnett, I. K. Gregor, W. Hannan, K. Hoa, M. A. Long, *J. Chem. Soc., Chem. Commun.* **1995**, 930–932; b) D. Hesk, J. R. Jones, W. J. S. Lockley, *J. Labelled Compd. Radiopharm.* **1990**, *28*, 1427–1436; c) D. Hesk, J. R. Jones, W. J. S. Lockley, *J. Pharm. Sci.* **1991**, *80*, 887–890.

[8] a) W. G. Brown, J. L. Garnett, *J. Am. Chem. Soc.* **1958**, *80*, 5272–5274; b) R. R. Fraser, R. N. Renaud, *J. Am. Chem. Soc.* **1966**, *88*, 4365–4370; c) J. L. Garnett, R. J. Hodges, *J. Am. Chem. Soc.* **1967**, *89*, 4546–4547; d) E. Buncel, O. Clement, *J. Chem. Soc., Perkin Trans. 2* **1995**, 1333–1338; e) M. Yamamoto, K. Oshima, S. Matsubara, *Chem. Commun.* **2004**, 1714–1715; f) M. Yamamoto, K. Oshima, S. Matsubara, *Org. Lett.* **2004**, *6*, 5015–5017.

[9] a) C. Hardacre, J. D. Holbrey, S. E. J. McMath, *Chem. Commun.* **2001**, 367–368; b) S. Matsubara, Y. Yokota, K. Oshima, *Chem. Lett.* **2004**, *33*, 294–295.

[10] a) T. Junk, W. J. Catallo, L. D. Civils, *J. Labelled Compd. Radiopharm.* **1997**, *36*, 625–630; b) T. Junk, W. J. Catallo, *Tetrahedron Lett.* **1996**, *37*, 3445–3448, c) T. Junk, W. J. Catallo, J. Elguero, *Tetrahedron Lett.* **1997**, *38*, 6309–6312.

[11] a) H. Sajiki, K. Hattori, F. Aoki, K. Yasunaga, K. Hirota, *Synlett* **2002**, 1149–1151; b) H. Sajiki, F. Aoki, H. Esaki, T. Maegawa, K. Hirota, *Org. Lett.* **2004**, *6*, 1485–1487; c) T. Maegawa, A. Akashi, H. Esaki, F. Aoki, H. Sajiki, K. Hirota, *Synlett* **2005**, 845–847; d) H. Sajiki, H. Esaki, F. Aoki, T. Maegawa, K. Hirota, *Synlett* **2005**, 1385–1388; e) H. Sajiki, N. Ito, H. Esaki, T. Maesawa, T. Maegawa, K. Hirota, *Tetrahedron Lett.* **2005**, *46*, 6995–6998.

[12] M. Yamamoto, K. Oshima, S. Matsubara, *Org. Lett.* **2004**, *6*, 5015–5017.

[13] M. B. Skaddan, C. M. Yung, R. G. Bergman, *Org. Lett.* **2004**, *6*, 11–13.

[14] a) T. P. Russell, A. Karim, A. Mansour, G. P. Felcher, *Macromolecules* **1988**, *21*, 1890–1893; b) S. F. Tead, E. J. Kramer, T. P. Russell, W. Volksen, *Polymer* **1992**, *33*, 3382–3387; c) N. C. Stoffel, S. Chandra, E. J. Kramer, *Polymer* **1997**, *38*, 5073–5078.