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SYNTHESIS OF BASE-SELECTIVELY DEUTERIUM-LABELLED NUCLEOSIDES BY THE Pd/C-CATALYZED H-D EXCHANGE REACTION IN DEUTERIUM OXIDE

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Abstract – The D₂ gas-free and base-selective H-D exchange reaction of nucleosides was developed. It discloses a convenient route to the post-synthetic incorporation of deuteriums into the base moiety of nucleic acids with high deuterium efficiency.

INTRODUCTION

Nucleoside analogues represent a significant area of drug design. In the search for potential and selective antimetabolites such as antiviral and antitumor agents, a number of nucleoside analogues have been synthesized.¹ Deuterium-labelled nucleoside analogues are quite promising tools for the study of the mechanism of the biological activity, structure-activity relationship and metabolism of biologically active nucleosides² and higher-order structures of DNA.³ The catalytic and direct deuteration method of an unlabelled nucleoside is a favorable approach to the preparation of deuterated nucleosides. However, a number of reported methods are necessary to achieve laborious multi-step synthesis starting from commercially available deuterium-labelled small synthons⁴ since the lability of the glycosyl bond can not tolerate the use of harsh (especially acidic) reaction conditions. Although several direct incorporation methods of deuteriums into the base-moieties of nucleosides have been reported, such conventional post-synthetic procedures are often limited to acidic positions of the nucleosides,^{5a-c,e,g} leading to low levels of deuterium incorporation,^{5e-f} and require a vast amount of the catalyst,^{5d,f,g} addition of acidic or basic additives,^{5a-c,e,f} and/or expensive deuterium atmosphere.^{5d,f,g,6}

This paper is dedicated to the late Professor Kenji Koga.

Recently, we have reported a Pd/C-catalyzed efficient and regioselective H-D exchange reaction at the benzylic position between various benzylic derivatives and deuterium oxide at room temperature under hydrogen atmosphere.⁷ Under similar reaction conditions, H-D exchange reaction was achieved even on non-activated carbons by a rise in the reaction temperature.^{8,9} Based upon this background, we studied application of these H-D exchange reactions to the deuteration of nucleosides.¹⁰

RESULTS AND DISCUSSION

In our initial investigation, we explored the scope of the deuteration method toward uracil, cytosine and their derivatives (Table 1).

Table 1. Pd/C-catalyzed deuteration of uracil, cytosine and their derivatives in D₂O

Entry	X	R	Temp (°C)	Time (h)	D content (%) ^a		Yield (%)
					5-D	6-D	
1 ^b	O	H	140	48	—	—	—
2	O	H	160	24	98	97	100
3 ^b	O		140	48	—	—	—
4	O		160	24	94	35	100
5 ^b	NH	H	110	24	—	—	—
6	NH	H	160	48	95	96	98
7	NH		140	48	93	35	100

^a Determined by ¹H NMR spectroscopy using DSS as an internal standard. ^b Partial hydrogenation of the 5,6-double bond was observed.

The Pd/C-catalyzed reaction at 110-140 °C yielded the desired 5,6-dideuterated products, which unfortunately accompanied by partial hydrogenation of the 5,6-double bond of the pyrimidine ring (Table 1, Entries 1, 3 and 5). But it is notable that this defect could be entirely overcome with a rise in temperature up to 160 °C in a sealed tube (Table 1, Entries 2, 4 and 6). It is significant that the deuterium efficiency at the 6-position of pyrimidine nucleosides is lower (Table 1, Entries 4 and 7) compared to the

nearly quantitative deuterium incorporation at the 6-position of uracil and cytosine possessing no sugar moiety (Table 1, Entries 2 and 6).

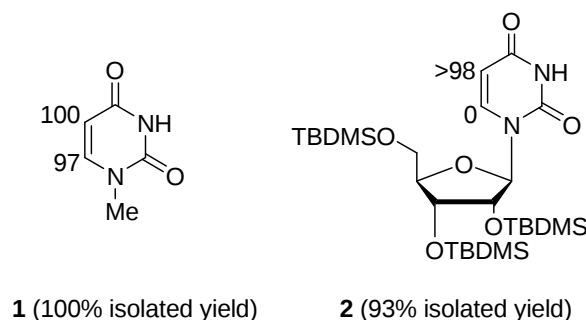


Figure 1. Deuteration efficiencies of **1** and **2** after the H-D exchange reaction at 160 °C for 24 h.

We assumed that the lower deuterium efficiency was attributable to the lack of the acidic hydrogen at the 1-position and/or the existence of free hydroxyl groups of the sugar moiety,^{8a} so we investigated the H-D exchange reaction of 1-methyluracil (**1**) and 2',3',5'-tris-O-TBDMS-uridine (**2**), which possesses fully protected hydroxyl groups of the furanose ring, under the reaction conditions. As a result, nearly quantitative deuterium efficiency was achieved at both the 5 and 6-positions of the uracil ring in the case of 1-methyluracil (**1**) (Figure 1). On the other hand, no deuterium incorporation into the 6-position of **2** was observed, although the 5-position was quantitatively deuterated. Therefore, it is obvious that the acidic hydrogen at the 1-position and free hydroxyl groups were not responsible for the deuterium efficiency at the 6-position of uridine derivatives while the actual reason for the lowering of the deuterium efficiency at the 6-position of uridine derivatives is not clear yet.

Table 2. Pd/C-catalyzed deuteration of thymidine derivatives in D₂O

Entry	R	Solvent	Temp (°C)	D content (%) ^a		Yield (%)
				5-Me	6-D	
1	H	D ₂ O	110	97	96	89
2 ^b		D ₂ O	140	71	7	53
3		CD ₃ OD	110	0	0	98
4		CD ₃ OD	160	26	0	99

^a Determined by ¹H NMR spectroscopy using DSS as an internal standard. ^b Partial hydrolysis (ca. 10%) at glycosyl bond was observed.

While uracil, cytosine and their derivatives were hydrogenated at the 5,6-double bond at 110-140 °C, thymine possessing a methyl group at the 5-position of the pyrimidine ring was entirely deuterated at 110 °C without the partial hydrogenation of the 5,6-double bond (Table 2, Entry 1). Partial hydrolysis of the glycosyl bond was unfortunately observed when thymidine, a 2'-deoxy-pyrimidine nucleoside, was used as the substrate^{10,11} (Table 2, Entry 2), and hence purification using column chromatography was required. When CD₃OD was used as a solvent and D source instead of D₂O in order to prevent the hydrolysis, the D content at both the 5-methyl group and the 6-position of the thymine ring was strongly depressed although there was no hydrolysis of the glycosyl bond (Table 2, Entries 3 and 4).

Table 3. Pd/C-catalyzed deuteration of adenine derivatives in D₂O

Entry	R	Temp (°C)	D content (%) ^a		Yield (%)
			2-D	8-D	
1	H	110	95 ^b	95 ^b	99
2		110	95	92	99
3		160	95	96	98
4		110	96	96	81

^a Determined by ¹H NMR spectroscopy using 3-trimethylsilyl-1-propanesulfonic acid sodium salt (DSS) as an internal standard. ^b Indicates the average D content.

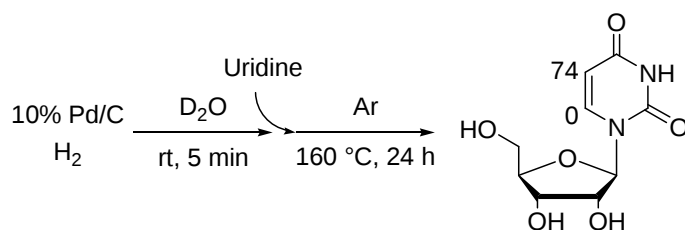
Table 4. Pd/C-catalyzed deuteration of guanosine, inosine, and hypoxanthine in D₂O

Substrate		10% Pd/C, H ₂ , D ₂ O 110 °C (reflux), 24 h	Substrate-d _n
Entry	Substrate	D content (%) ^a	Yield (%)
1			92
2			100
3			92

^a Determined by ¹H NMR spectroscopy using DSS as an internal standard.

In contrast, the H-D exchange reaction of purine derivatives including nucleosides such as adenosine, guanosine and inosine gave excellent deuterium efficiencies at the 2 and 8-positions of the purine rings with high isolated yields even at 110 °C (Table 3 and Table 4). No significant differences in the D content and the isolated yield were observed at 160 °C (Table 3, Entry 3). It is noteworthy that nearly quantitative deuteration was achieved in the case of 2'-deoxyadenosine without hydrolysis of the glycosyl bond (Table 3, Entry 4).

In the presented deuteration method using the Pd/C-H₂-D₂O system, no H-D exchange proceeded in the absence of hydrogen gas.^{7,8a} To investigate the role of hydrogen gas, we examined the following reaction. 10% Pd/C (10 wt% of the substrate) was suspended in 1 mL of D₂O in a test tube (10 mL) and pre-stirred under H₂ atmosphere for 5 minutes at room temperature. After two vacuum/Ar cycles to remove hydrogen gas from the reaction tube, uridine was added and stirred at 160 °C in a sealed tube under Ar atmosphere for 24 h. Consequently, the H-D exchange reaction at the 5-position of uridine progressed while the deuterium efficiencies at the 5 and 6-positions were rather depressed compared with the deuterium efficiencies in Table 1, entry 4 (Scheme 1). It is obvious that the existence of a small amount of hydrogen gas for the activation of the palladium surface is essential for the H-D exchange reaction. It is likely that hydrogen gas acts as a so-called ligand of the Pd metal in this reaction.



Scheme 1. Investigation of the role of H₂ in this deuterating method

In summary, an efficient base selective H-D exchange reaction can be achieved with the Pd/C-H₂-D₂O system under heating conditions.¹² This deuteration method does not require the use of D₂ gas and special apparatus, and is applicable to a variety of nucleic acids under neutral reaction conditions. The reactions are very clean and the products were obtained in excellent yields without chromatographic purification. This chemoselective deuterating method should contribute to extensive studies of nucleic acids chemistry.

EXPERIMENTAL

General

¹H, ²H, and ¹³C NMR spectra were recorded on a JEOL AL 400 spectrometer or JEOL EX 400 spectrometer (¹H NMR: 400 MHz, ²H NMR: 61 MHz, ¹³C NMR: 100 MHz). Chemical shifts (δ) are given in ppm relative to residual solvent or 3-trimethylsilyl-1-propanesulfonic acid sodium salt (DSS) as

an internal standard. EI and FAB MS spectra were taken on a JEOL JMS-SX102A machine. Optical rotations were measured using a JASCO DIP-360 Digital Polarimeter.

10 % Pd/C was purchased from Aldrich Chemical Co. and deuterium oxide (99.7% isotopic purity) was purchased from Cambridge Isotope Laboratories. All of the substrates were used without further purification.

Typical procedure for deuteration of adenosine (Table 3, Entry 3): After two vacuum/H₂ cycle to remove air from the reaction tube, adenosine (66.8 mg, 0.25 mmol) and 10% Pd/C (6.7 mg, 10 wt% of the substrate) in D₂O (1 mL) was stirred at 160 °C in a sealed tube for 24 h. After cooling, the reaction mixture was filtered using a membrane filter (Millipore Millex[®]-LG, 0.20 μm). The filtered catalyst was washed with boiling water (50 mL) and the combined filtrates were concentrated in vacuo to give adenosine-*d*₂ as a white powder (66.3 mg, 98%). The deuterium content (%) was determined by ¹H NMR spectroscopy and confirmed by ²H NMR spectroscopy and MS spectrum. $[\alpha]_D^{20}$ -55° (c 0.38, H₂O) [adenosine¹³ $[\alpha]_D^{11}$ -62° (c 0.71, H₂O)]. MS (EI): *m/z* (%) = 269 (3) [M+2] (21% *d*₁, 56% *d*₂, 23% *d*₃). ¹H NMR (DMSO-*d*₆): 8.37 (s, 0.05H), 8.12 (s, 0.04H), 7.34-7.30 (br s, 2H), 5.90 (d, *J* = 6.4 Hz, 1H), 5.45-5.41 (m, 2H), 5.20 (d, *J* = 4.9 Hz, 1H), 4.63 (dd, *J* = 4.9, 6.4 Hz, 1H), 4.16 (dd, *J* = 3.4, 4.4 Hz, 1H), 3.99 (dd, *J* = 3.4, 3.4 Hz, 1H), 3.72-3.67 (m, 1H), 3.60-3.54 (m, 1H). ¹³C NMR (DMSO-*d*₆): 156.2, 152.3 (small multiplet), 149.0, 139.9 (small mutiplet), 119.3, 87.9, 85.9, 73.4, 70.6, 61.6. ²H NMR (DMSO): 8.02 (br).

[²H]-Uracil (Table 1, Entry 2): MS (EI): *m/z* (%) = 114 (100) [M+2] (4% *d*₁, 88% *d*₂, 7% *d*₃, 1% *d*₄). ¹H NMR (DMSO-*d*₆): 10.91 (br, 2H), 7.41 (s, 0.03H), 5.47 (s, 0.02H), ²H NMR (DMSO): 7.40 (br s), 5.46 (br s).

[²H]-Uridine (Table 1, Entry 4): $[\alpha]_D^{21}$ +5° (c 0.27, H₂O) [uridine¹³ $[\alpha]_D^{20}$ +4° (c 2)]. MS (EI): *m/z* (%) = 245 (4) [M+1], 246 (3) [M+2] (27% *d*₀, 36% *d*₁, 24% *d*₂, 13% *d*₃). ¹H NMR (DMSO-*d*₆): 11.09 (br, 1H), 7.91 (s, 0.65H), 5.81 (d, *J* = 5.3 Hz, 1H), 5.68-5.65 (m, 0.06H), 5.41 (br s, 1H), 5.13 (br s, 2H), 4.04 (s, 1H), 3.98 (s, 1H), 3.86 (d, *J* = 3.4 Hz, 1H), 3.65-3.55 (m, 2H). ¹³C NMR (DMSO-*d*₆): 163.2, 150.8, 140.7, 101.8 (small mutiplet), 87.7, 84.9, 73.6, 69.9, 60.9. ²H NMR (DMSO): 7.90 (br), 5.58 (br).

[²H]-Cytosine (Table 1, Entry 6): MS (EI): *m/z* (%) = 113 (100) [M+2] (2% *d*₀, 9% *d*₁, 79% *d*₂, 9% *d*₃, 1% *d*₄). ¹H NMR (DMSO-*d*₆): 10.32 (br s, 1H), 7.35 (s, 0.04H), 7.09 (br s, 2H), 5.61 (s, 0.04H). ¹³C NMR (DMSO-*d*₆): 166.9, 157.3, 142.8 (small multiplet), 92.4 (small multiplet). ²H NMR (DMSO): 7.32 (br s), 5.58 (br s).

[²H]-Cytidine (Table 1, Entry 7): $[\alpha]_D^{21}$ +25° (c 0.26, H₂O) [cytidine¹³ $[\alpha]_D^{25}$ +31° (c 0.7, H₂O)]. MS (EI): *m/z* (%) = 244 (1) [M+1], 245 (1) [M+2] (26% *d*₀, 32% *d*₁, 29% *d*₂, 13% *d*₃). ¹H NMR (DMSO-*d*₆):

7.87 (s, 0.65H), 7.21 (br s, 2H), 5.79 (d, $J = 3.4$, 1H), 5.20 (s, 0.07H), 5.32 (br, 1H), 5.09 (br, 2H), 3.95 (br s, 2H), 3.84 (br s, 1H), 3.69-3.42 (m, 2H). ^2H NMR (DMSO): 7.87 (br), 5.79 (br s).

[^2H]-1-Methyluracil (1): MS (EI): m/z (%) = 128 (2) [$\text{M}+2$] (4% d_1 , 82% d_2 , 14% d_3). ^1H NMR (DMSO- d_6): 11.2 (br s, 1H), 7.65 (s, 0.03H), 5.55 (s, 0.004H). ^2H NMR (DMSO): 7.40 (br s), 5.46 (br s).

[^2H]-2',3',5'-Tris-*O*-TBDMS-uridine (2): $[\alpha]_{\text{D}}^{21} +18^\circ$ (c 0.74, CH_3Cl) [$2',3',5'$ -tris-*O*-TBDMS-uridine $[\alpha]_{\text{D}}^{22} +22^\circ$ (c 0.83, CH_3Cl)]. MS (FAB+): m/z (%) = 588 (17) [$\text{M}+1$] (4% d_0 , 58% d_1 , 31% d_2). ^1H NMR (CDCl_3): 7.94 (s, 1H), 5.80 (d, $J = 3.38$ Hz, 1H), 5.60 (small multiplet, 0.01H), 4.10-3.99 (m, 3H), 3.91 (d, $J = 11.6$ Hz, 1H), 3.68 (d, $J = 11.6$ Hz, 1H), 0.87 (s, 9H), 0.83 (s, 9H), 0.81 (s, 9H), 0.15-0.00 (m, 18H). ^2H NMR (DMSO): 5.63 (br s).

[^2H]-Thymine (Table 2, Entry 1): MS (EI): m/z (%) = 130 (100) [$\text{M}+4$] (1% d_2 , 12% d_3 , 80% d_4 , 6% d_5 , 1% d_6). ^1H NMR (DMSO- d_6): 11.0 (br, 1H), 10.6 (br, 1H), 7.23 (s, 0.04H), 1.68 (s, 0.10H). ^2H NMR (DMSO): 7.23 (br s), 1.66 (br s).

[^2H]-Thymidine (Table 2, Entry 2): $[\alpha]_{\text{D}}^{25} +28^\circ$ (c 0.27, CH_3OH) [thymidine 13 $[\alpha]_{\text{D}}^{20} +31^\circ$ (c 1.03)]. MS (EI): m/z (%) = 243 (5) [$\text{M}+1$], 244 (5) [$\text{M}+2$] (31% d_0 , 37% d_1 , 23% d_2 , 9% d_3). ^1H NMR (DMSO- d_6): 11.3 (br s, 1H), 7.72 (s, 1H), 6.19 (t, 1H), 5.25 (d, $J = 3.9$ Hz, 1H), 5.04 (t, 1H), 4.26 (br s, 1H), 3.78 (m, 1H), 3.64-3.53 (m, 2H), 2.15-2.07 (m, 2H), 1.80-1.76 (m, 0.88H). ^2H NMR (DMSO): 1.67 (br s).

[^2H]-Thymidine (Table 2, Entry 4): MS (EI): m/z (%) = 243 (4) [$\text{M}+1$], 244 (3) [$\text{M}+2$], 245 (1) [$\text{M}+3$] (33% d_0 , 36% d_1 , 22% d_2 , 9% d_3). ^1H NMR (DMSO- d_6): 11.3 (br s, 1H), 7.72 (s, 1H), 6.19 (t, 1H), 5.24 (d, $J = 3.9$ Hz, 1H), 5.04 (t, 1H), 4.26 (br s, 1H), 3.78 (d, $J = 2.9$ Hz, 1H), 3.64-3.55 (m, 2H), 2.15-2.07 (m, 2H), 1.80-1.78 (m, 2.23H). ^2H NMR (DMSO): 1.76 (br s).

[^2H]-Adenine (Table 3, Entry 1): MS (EI): m/z (%) = 137 (100) [$\text{M}+2$] (2% d_0 , 6% d_1 , 78% d_2 , 13% d_3 , 1% d_4). ^1H NMR (DMSO- d_6): 12.79 (br 1H), 8.14 (s, 0.05H), 8.11 (s, 0.05H), 7.10 (br s, 2H). ^2H NMR (DMSO): 8.11 (br s).

[^2H]-Adenosine (Table 3, Entry 2): $[\alpha]_{\text{D}}^{19} -60^\circ$ (c 0.38, H_2O) [adenosine 13 $[\alpha]_{\text{D}}^{11} -62^\circ$ (c 0.71, H_2O)]. MS (EI): m/z (%) = 269 (2) [$\text{M}+2$] (5% d_0 , 20% d_1 , 50% d_2 , 25% d_3). ^1H NMR (DMSO- d_6): 8.37 (s, 0.08H), 8.17 (s, 0.05H), 7.35 (br s, 2H), 5.90 (d, $J = 6.3$ Hz, 1H), 5.45-5.43 (m, 2H), 5.20 (d, $J = 4.8$ Hz, 1H), 4.63 (dd, $J = 2.9, 5.8$ Hz, 1H), 4.17 (dd, $J = 2.1, 4.2$ Hz, 1H), 3.99 (dd, $J = 1.4, 2.9$ Hz, 1H), 3.71-3.67 (m, 1H), 3.60-3.58 (m, 1H). ^2H NMR (DMSO): 8.02 (br s).

[^2H]-Deoxyadenosine (Table 3, Entry 4): $[\alpha]_{\text{D}}^{20} -19^\circ$ (c 0.36, CH_3OH) [deoxyadenosine $[\alpha]_{\text{D}}^{20} -20^\circ$ (c 0.36, CH_3OH)]. MS (EI): m/z (%) = 253 (5) [$\text{M}+2$] (24% d_1 , 51% d_2 , 25% d_3). ^1H NMR (DMSO- d_6): 8.35 (s, 0.04H), 8.15 (s, 0.04H), 7.30 (br s, 2H), 6.36 (t, 1H), 5.32 (d, $J = 3.9$ Hz, 1H), 5.25 (t, 1H), 4.43 (dd, J

= 2.9, 2.9 Hz, 1H), 3.91 (dd, J = 2.4, 4.4 Hz, 1H), 3.99 (dd, J = 3.4, 3.4 Hz, 1H), 3.67-3.62 (m, 1H), 3.57-3.51 (m, 1H), 2.77-2.71 (m, 1H), 2.30-2.25 (m, 1H). ^2H NMR (H_2O): 8.10 (br).

[^2H]-Guanosine (Table 4, Entry 1): $[\alpha]_{\text{D}}^{20}$ -59° (c 0.25, 0.02 N NaOH) [guanosine $[\alpha]_{\text{D}}^{20}$ -61° (c 0.30, 0.02 N NaOH)]. MS (ES+): m/z (%) = 284 (1) $[\text{M}+1]$ (43% d_1 , 38% d_2 , 19% d_3). ^1H NMR ($\text{DMSO}-d_6$): 10.65 (br s, 1H), 7.95 (s, 0.03H), 6.50 (br s, 2H), 5.72 (d, J = 6.3 Hz, 1H), 5.41 (d, J = 5.8 Hz, 1H), 5.14 (d, J = 3.9 Hz, 1H), 5.05 (t, 1H), 4.42 (dd, J = 2.8, 5.6 Hz, 1H), 4.11 (dd, J = 2.2, 4.4 Hz, 1H), 3.90 (dd, J = 1.7, 3.4 Hz, 1H), 3.67-3.52 (m, 1H). ^2H NMR (DMSO): 7.96 (br).

[^2H]-Inosine (Table 4, Entry 2): $[\alpha]_{\text{D}}^{21}$ -46° (c 0.34, H_2O) [Inosine 13 $[\alpha]_{\text{D}}^{18}$ -49° (c 0.9, H_2O)]. MS (EI): m/z (%) = 270 (1) $[\text{M}+2]$ (30% d_1 , 40% d_2 , 30% d_3). ^1H NMR ($\text{DMSO}-d_6$): 12.45 (br s, 1H), 8.37 (s, 0.04H), 8.11 (s, 0.03H), 5.90 (d, J = 5.9 Hz, 1H), 5.54 (br s, 1H), 5.26 (br s, 1H), 5.12 (br s, 1H), 4.51 (br s, 1H), 4.15 (br s, 1H), 3.96 (d, J = 3.9 Hz, 1H), 3.74-3.62 (m, 1H), 3.60-3.56 (m, 1H). ^2H NMR (DMSO): 8.06 (br).

[^2H]-Hypoxanthine (Table 4, Entry 3): MS (EI): m/z (%) = 138 (100) $[\text{M}+2]$ (3% d_0 , 8% d_1 , 76% d_2 , 12% d_3 , 1% d_4). ^1H NMR ($\text{DMSO}-d_6$): 13.3 (br, 1H), 12.3 (br, 1H), 8.14 (s, 0.02H), 8.01 (s, 0.03H). ^2H NMR (DMSO): 7.99 (br d).

ACKNOWLEDGEMENTS

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