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SYNTHESIS OF DEUTERATED CYCLODOPA WITH HYDROGEN/DEUTERIUM EXCHANGE

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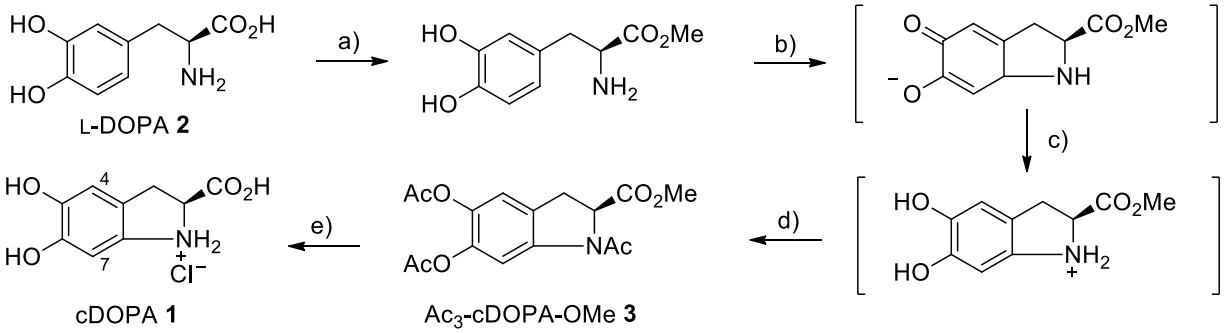
Abstract – CycloDOPA (5,6-dihydroxy-indoline-2-carboxylic acid, leukodopachrome) is one of metabolites derived from tyrosine, one of intermediate in melanin formation (mammalian) and betanidin main skeleton (betalain pigment in plant). Synthesis of deuterated cyclodopa via hydrogen/deuterium exchange by utilization of deuterium chloride (DCl) and deuterated triflic acid (TfOD) are reported. The novel fully deuterated aromatic cycloDOPA derivative can be formed depending on temperature and time of H/D exchange condition. The complete study of H/D exchange resulted in the selective deuterium between 4- and/or 7-position of aromatic hydrogen of cycloDOPA.

INTRODUCTION

CycloDOPA (5,6-dihydroxy-indoline-2-carboxylic acid, leukodopachrome, cDOPA, **1**, Scheme 1), known as metabolites of aromatic α-amino acid of tyrosine,[1] is one of intermediate in eumelanin pathway (melanin formation in mammalian)[2–4] and main skeleton of betanidin (betalain pigment in plant).[5,6] In spite of its simple structure, which can be constructed from intramolecular cyclization of L-DOPA **2**, a

This paper is dedicated to Prof. Dr. Tohru Fukuyama on the occasion of his 70th birthday.

few studies have been reported for the synthesis and its commercial source also limited. First synthesis of cDOPA has been reported on 1968.[7] Based on this study, cDOPA skeleton was generated once at early stage and isolated as its peracetylated formed of *O,O,N*-triacetyl cycloDOPA methyl ester (Ac_3-cDOPA-OMe, **3**, Scheme 1).



Scheme 1. Synthesis of cycloDOPA derivatives. a) $SOCl_2$, MeOH, reflux, 1 h, quant., b) $K_3[Fe(CN)_6]$, sodium phosphate (pH 8), 0 °C, 75 sec, c) $Na_2S_2O_4$, sodium phosphate (pH 8), 0 °C, 30 sec, d) Ac_2O, pyridine, rt, 4 h, 63% (3 steps), e) 6 M HCl, 80 °C, 5 h, quant.

Hydrogen/deuterium (H/D) exchange, the displacement of hydrogen bonded to carbon by deuterium, is one of the methods to broaden the variety of isotopically labeled material.[8] Based on the recent progress of the mass equipment, H/D exchange also provides analysis with stable isotopes to reveal the biosynthetic pathways.[9] Previously, the introduction of deuterated trifluoroacetic acid (TFA-*d*) for H/D exchange of hydrogen in aromatic ring of cDOPA was reported.[7] The selective H/D exchange (within ~50% deuterium incorporation) of hydrogen of aromatic moiety only at 7-position can be formed after the treatment at 83 °C and no incorporation was found when treated at 70 °C.

Although the deuterium incorporation in cDOPA can be utilized for analysis metabolic pathway, to date, the synthesis of fully deuterated cDOPA is not had been studied. An acid-catalyzed H/D exchange condition is known as an efficient method for incorporating deuterium into an aromatic moiety.[8,10] Recently, our detail analysis of chemical stability for cDOPA revealed that cDOPA was stable in acidic condition and easily broken over pH 4 to convert dihydroxyindole derivatives.[11] Moreover, deprotection of Ac_3-cDOPA-OMe **3** under acidic condition enabled cDOPA **1** formation also demonstrate stability of cDOPA[11] that indicating its potential for H/D exchange in acid condition. Since HCl system can be applied for deacetylation to result in cDOPA (Scheme 1), deuterium chloride (DCl) system is expected to introduce deuterium into cDOPA moiety.

Triflic acid (TfOH), or so-called superacid, is known for its ability as catalyst that act as solvent for utmost amino acids.[12] Recently, we found that deuterated triflic acid (TfOD) can be used for H/D

exchange of aromatic amino acids such as phenylalanine and tyrosine,[13] or L-DOPA[14] under mild condition to give over 90% deuterium incorporation only in its aromatic moiety. Since cDOPA is stable at acidic condition, thus, TfOD also can be introduced for synthesis of deuterium labeled cDOPA derivatives. Here in this study, the comprehensive H/D exchange and analysis of deuterium incorporation of cDOPA is studied. The stable and readily synthesized cDOPA can be utilized for synthesis of the novel fully-deuterated aromatic moiety of cDOPA derivatives via H/D exchange. The introduction of DCl and TfOD system are expected to broaden the study of deuterium labeled cDOPA derivatives formation.

RESULTS AND DISCUSSION

The cDOPA **1** can be synthesized from oxidation of commercial available L-DOPA **2** and isolated as its peracetylated form of *O,O,N*-triacetyl cycloDOPA methyl ester (Ac_3-cDOPA-OMe, **3**, Scheme 1).[7] The further deacetylation of Ac_3-cDOPA-OMe **3** under strong acidic condition at 80 °C represents the stability of cDOPA **1**[11] is feasible for H/D exchange. Since acid-induced H/D exchange,[15] such as utilization with deuterium chloride (DCl) or deuterated triflic acid (TfOD), is known as the convenient method for H/D exchange of aromatic moiety, thus two possible exchangeable protons in aromatic ring of cDOPA at 4- and 7-position are enable to undergo H/D exchange. The cDOPA **1** skeleton was priorly subjected to 2D NMR analysis for ascertaining its each counterpart. Based on ^{1}H-NMR, the aromatic proton at 4-position was shown as singlet at δ = 6.84 ppm and 7-position was shown as singlet at δ = 6.90 ppm, respectively (Supplementary Material).

Since the deacetylation of Ac_3-cDOPA-OMe **3** by 6 M HCl conducted at 80 °C allowing the formation cDOPA **1** within fine yield (Scheme 1), thus the H/D exchange for synthesized deuterium labeled cDOPA derivatives was started by using DCl system. Accordingly, Ac_3-cDOPA-OMe **3** was then first subject to 20% DCl/D_2O at 80 °C and observed the deuterium incorporation from its unprotected form of cDOPA **1** by ^{1}H-NMR. In Figure 1 (a), when 20% DCl/D_2O was utilized, aromatic hydrogen of cDOPA at 7-position can be fully deuterated (99% D) meanwhile 4-position was deuterated up to 60% by within 4 h. In contrast, deuteration of 4-position was hampered meanwhile 7-position almost fully deuterated within less than 1 h. These large differences of deuterium incorporation between 4- and 7-position cannot be maintained due to long H/D exchange time can increase deuterium incorporation at 4-position (Figure 1 (a)).

The lower DCl concentration utilization of 5% and 10% DCl/D_2O showed 7-position was deuterated almost up to two times higher than 4-position dependent with time (Figure 1 (c) and (d)). In contrast with 20% DCl/D_2O utilization, lower DCl concentration needed longer H/D exchange time for deuterium at 7-position. At 7-position of cDOPA derivative, deuterium takes place about 80% and 95% after 6 h when

5% and 10% DCl/D_2O were utilized, respectively. Thus, the used of 5% or 10% DCl/D_2O is considered less suitable for H/D exchange of cDOPA.

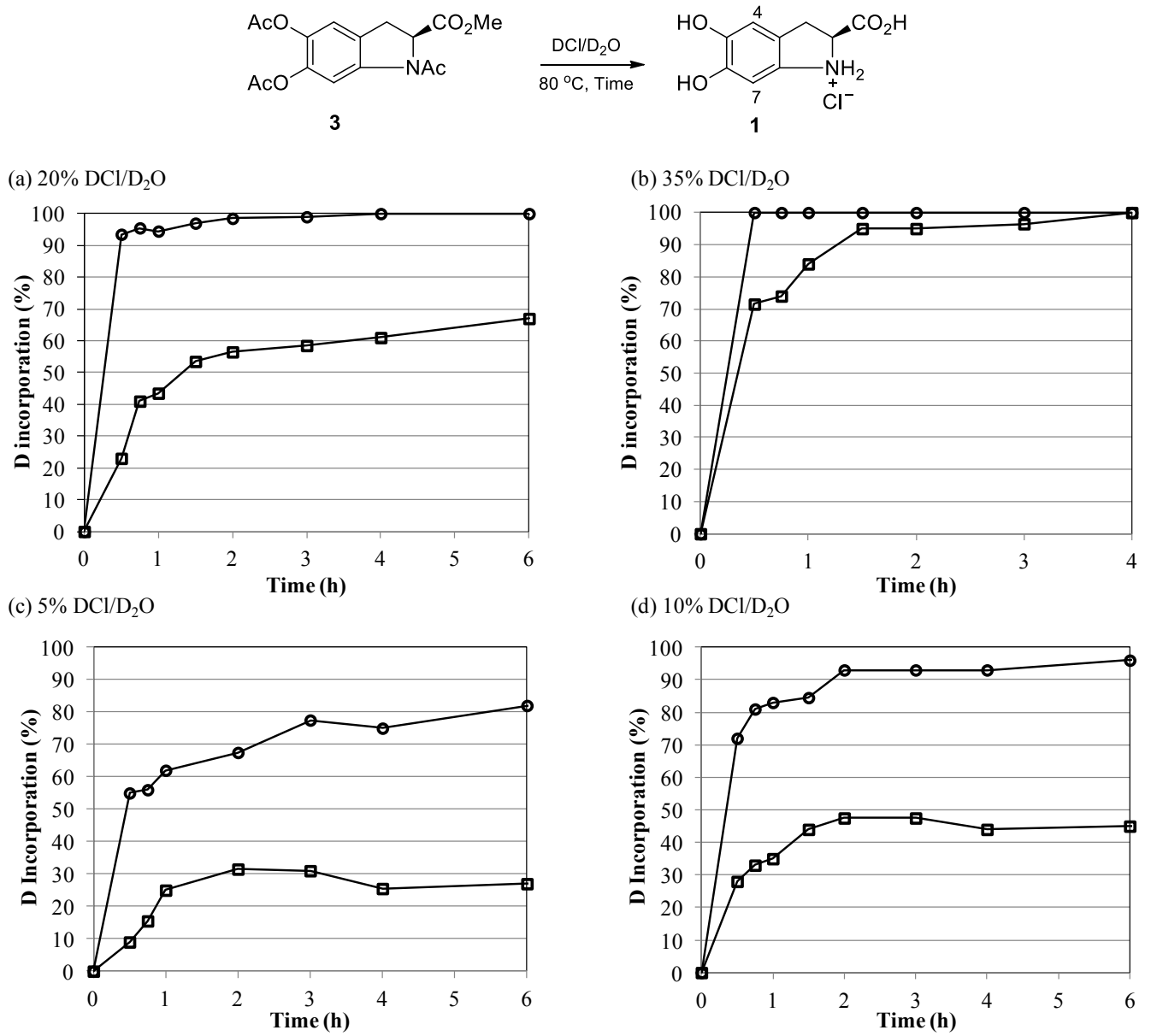
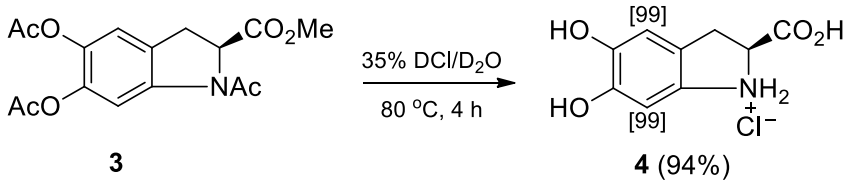


Figure 1. Deprotection and hydrogen/deuterium exchange of *O,O,N*-triacetyl cycloDOPA methyl ester (**3**) at 80 °C dependent on concentration of (a) 20% DCl/D_2O, (b) 35% DCl/D_2O, (c) 5% DCl/D_2O, and (d) 10% DCl/D_2O. The time-course H/D exchange was determined as cycloDOPA (**1**) which –□– present for 4-position and –○– present for 7-position.

When 35% DCl/D_2O was used at 80 °C (Figure 1 (b)), hydrogen of aromatic ring at 4- and 7-position were fully deuterated (99% deuterium incorporation) within 4 h. The high concentration of DCl is effective for rapid H/D exchange of both aromatic hydrogen of cDOPA at 4- and 7-position which suitable for synthesizing the fully-deuterated aromatic ring of cDOPA derivative. Thus, 35% DCl/D_2O

was subjected to Ac_3-cDOPA-OMe **3** for synthesis the fully deuterated cDOPA (**4**, Scheme 2). Compound **4** can be isolated by evaporation and removal of excess DCl with MeCN washing. During the isolation process, there are no loss of deuterated counterpart was observed by ^{1}H-NMR. Compound **4** is stable and feasible to undergo ^{13}C-NMR measurement in D_2O aqueous solution (Supplementary Material).



3 **4** (94%)

Scheme 2. Synthesis of deuterated cDOPA derivative (**4**)
Deuterium incorporation (% D) for each position is shown in square brackets.

For further understanding of selective H/D exchange of cDOPA, unprotected cDOPA **1** was also directly subjected into H/D exchange at various temperatures. The H/D exchange of cDOPA **1** was started with utilization of 20% DCl/D_2O. This DCl concentration condition is considered suitable condition for the selective deuteration of cDOPA since within less than 1 h of Ac_3-cDOPA-OMe **3** subjection, the differences H/D exchange of 4- and 7-position can be detected (Figure 1 (a)). When cDOPA **1** was subjected with 20% DCl/D_2O at 80 ^{o}C, hydrogen at 7-position of aromatic cDOPA can be fully deuterated meanwhile 4-position can be only deuterated around 40% after 4 h. The slower H/D exchange within same DCl concentration and temperature for direct cDOPA **1** (Figure 2 (a)) rather than subjection of Ac_3-cDOPA-OMe **3** (Figure 1 (a)) might be the presence of accumulated acetic acid as byproduct of deacetylation that increase the system acidity during H/D exchange that can enhance the H/D exchange condition.

When 7-position can be fully deuterated after 4 h, decrease of temperature to 70 ^{o}C resulted in cDOPA aromatic moiety at 4-position deuterated only around 30% (Figure 2 (b)). Similarly, 4-position of cDOPA showed only around 20% deuterium incorporation and 7-position showed around 90% deuterium incorporation after 6 h when H/D exchange conducted at 60 ^{o}C (Figure 2 (c)). As for 50 ^{o}C (Figure 2 (d)), the same tendency also showed within prolonged time in which after 12 h of the treatment, 4-position of cDOPA showed only around 20% to be deuterium incorporation and 7-position showed around 90% deuterium incorporation. These result indicated that by lowering the temperature, the H/D exchange at 4-postion is slower than 7-position which depending on H/D exchange time. The further subjection of cDOPA **1** with 20% DCl at 60 ^{o}C for 6 h, followed with evaporation and removal of excess HCl, can result in deuterated cDOPA at 7-position derivative (compound **5**, Scheme 3). The selective

deuterium-labeled of compound **5** is stable and deuterated counterparts of 7-position (88% D) and 4-position (23% D) also showed no loss of deuterium incorporation during the isolation process.

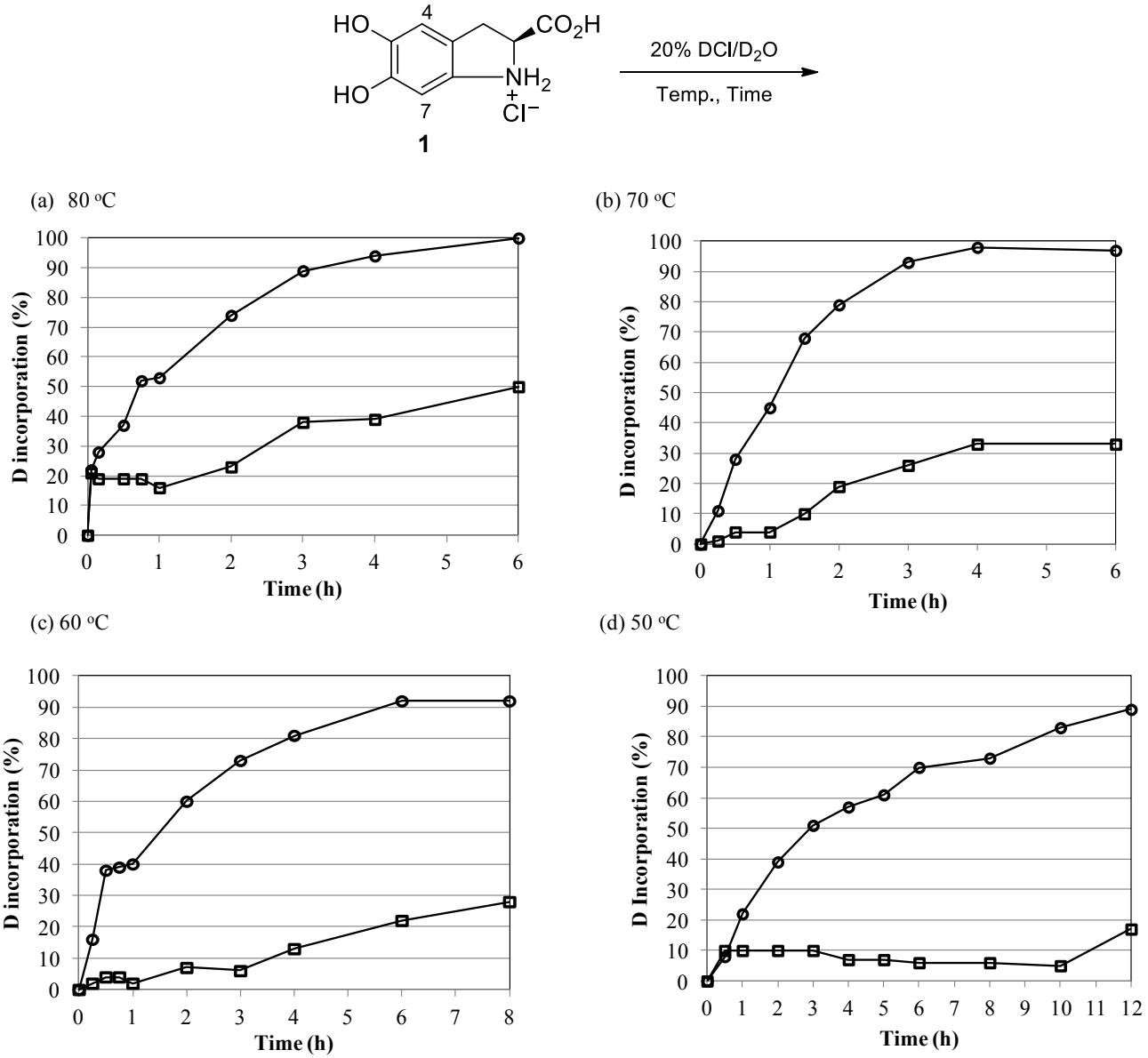
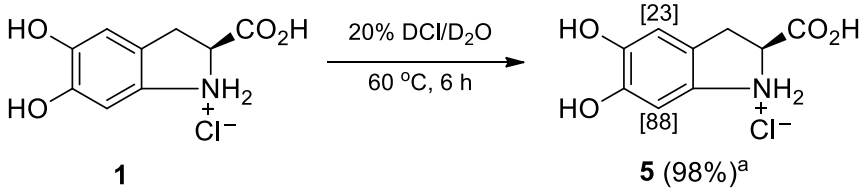


Figure 2. Hydrogen/deuterium exchange of cycloDOPA (**1**) by 20% DCl/D_2O dependent on temperature of (a) 80 °C, (b) 70 °C, (c) 60 °C, and (d) 50 °C. The time-course H/D exchange was determined which –□– present for 4-position and –○– present for 7-position.



Scheme 3. Synthesis of deuterated cDOPA derivative (**5**)

[a] Recovery percentage. Deuterium incorporation (% D) for each position is shown in square brackets.

Triflic acid (TfOH) is categorized as strong Brønsted acid and known for its ability to solve mostly amino acid skeleton.[12,13,16] The deuterated triflic acid (TfOD) can be used to promote H/D exchange[12] of aromatic amino acid such as phenylalanine and tyrosine,[13] or L-DOPA[14] under mild condition (rt or 0 °C) to give over 90% deuterium incorporation only in its aromatic moiety. To complete the synthesis of deuterated cDOPA derivatives, cDOPA **1** was then also treated with TfOD. At room temperature (Figure 3(a)), about 90% deuterium incorporation takes place at 4- and 7-position of cDOPA aromatic ring after 1 h. The degree of exchange did not change with longer incubation time.

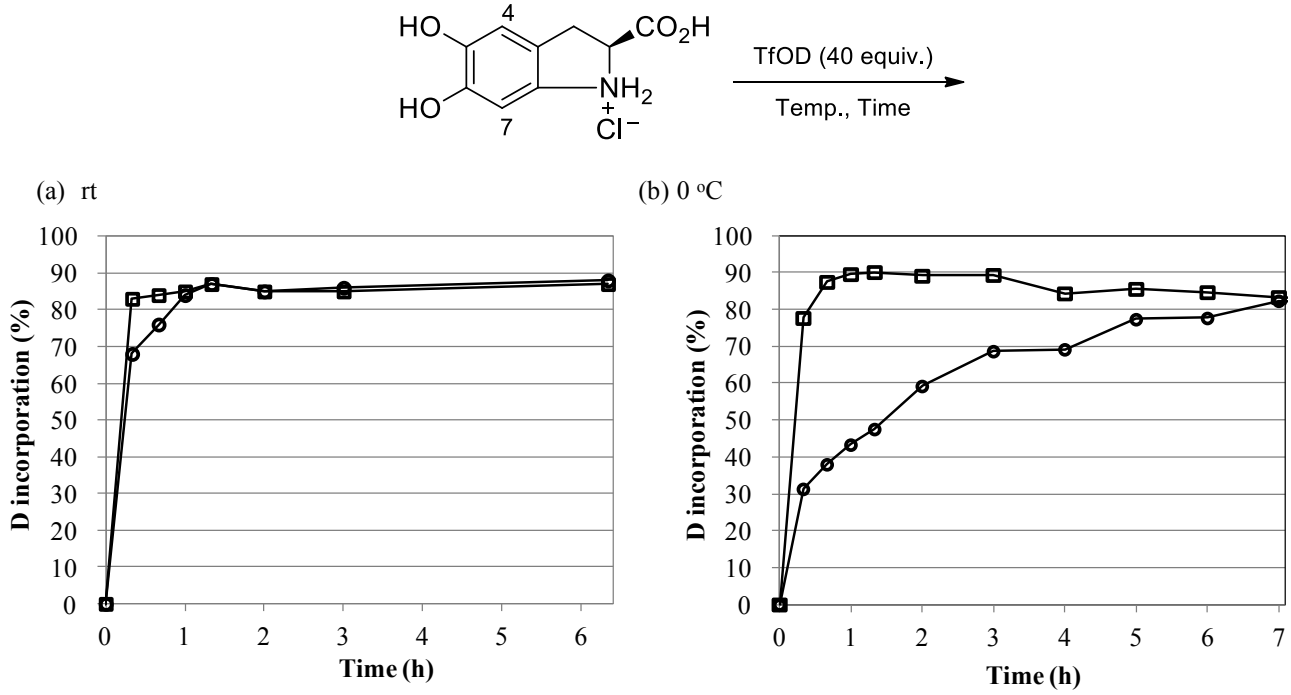
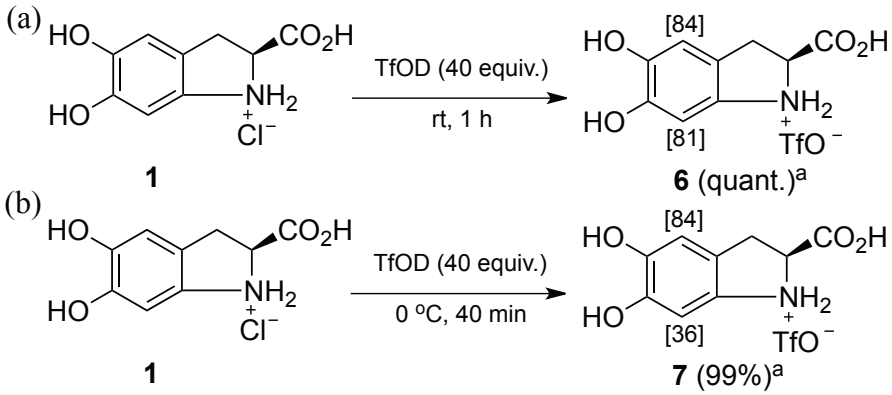


Figure 3. Hydrogen/deuterium exchange of cycloDOPA (**1**) with triflic acid (TfOD, 40 equiv.) at (a) rt and (b) 0 °C The time-course H/D exchange was determined which –□– present for 4-position and –○– present for 7-position.

In Figure 3(b), H/D exchange of cDOPA at lower temperature (0 °C) showed 4-position is faster to be exchanged rather than 7-position. Within 40 min, proton at 4-position deuterium can be achieved 84% D and 7-position was deuterated about 34% D based on observation with ^{1}H-NMR. Elongation time for H/D exchange at 0 °C showed that the two sites can be deuterated around 90% after 6 h. TfOD is suitable for H/D exchange of cDOPA aromatic moiety at room temperature (about 90% deuterium incorporation after 1 h, Figure 3(a)), compared with previous utilization with TFA-*d* that needed high temperature to conduct only around 50% deuterium at 7-position.[7] It possible due to TfOD is known to relatively strong acid rather than TFA-*d*.[12,17] By utilizing TfOD at rt for 1 h, full deuterated aromatic moiety of cDOPA derivatives **6** can be formed (Scheme 4 (a)). Next, the selective deuterated cDOPA at 4-position of compound **7** can be synthesized by utilizing TfOD at 0 °C for 40 min (Scheme 4 (b)). Further treatment

for removal of excess TfOD was difficult to conduct. Although deuterium incorporation of deuterated cDOPA derivatives synthesis using TfOD showed no significant differences after the treatment, pH adjustment with NaOD, freeze drying, and then gel filtration chromatography (Sephadex G-10 eluted by HCl (pH = 3) to isolate. (see Supplementary Material for details).



Scheme 4. Synthesis of deuterated cDOPA derivatives (**6** and **7**)

[a] %Yield measured from UV-Vis spectra (TfOD/D_2O). Deuterium incorporation (% D) for each position is shown in square brackets.

The full and partially deuterated cDOPA derivatives (**4**–**7**) via H/D exchange can be formed by the utilization of DCl and TfOD system. The deuterium counterpart of deuterated cDOPA derivatives of **4**–**7** can be determined by ^{1}H-NMR (Figure 4). Based on ^{1}H-NMR (Figure 4, Supplementary Material), there is no change of proton NMR signal integrations corresponding to heterocyclized side chain of deuterated cDOPA derivatives. Thus, indicated the H/D exchanges were occurred specific only in aromatic moiety of cDOPA. H/D exchange basically is complex process with complicated intermediate that can be affected by temperature, deuterium source, and pH. Thus, the site-selectivity between H/D exchanges of 4- and 7-position aromatic ring of cDOPA treated with DCl or TfOD possibly due to differences of acidity activity. H-4 is suggested to be more difficult to conduct H/D exchange than H-7 and since TfOH is categorized as superacid which have higher acidity than HCl, thus at lower temperature H-4 can be selectively deuterated. Moreover, H/D exchange in TfOD system might be occurred selectively due to intramolecular exchange between sites that having approximately equal proton affinity in the conjugate acid.[18] However, the controllable deuterated cDOPA derivatives can be use to infer biological macromolecules due to its beneficial detection with spectroscopic methods.

CONCLUSION

In conclusion, H/D exchange of cDOPA derivatives under DCl and TfOD allowing the formation of full and partially deuterated cDOPA derivatives (**4**–**7**). When DCl was utilized at 60 °C, H/D exchange of

cDOPA was shifted as 7-position is faster than 4-position. In contrast, utilization with TfOD at 0 °C was enable the H/D exchange of 4-position to be faster than 7-position of aromatic cDOPA moiety. The deuterated cycloDOPA derivatives formed from by utilizing DCl simpler to be isolated rather than TfOD subjection. H/D exchange in cDOPA might simplify the analysis of complex biomolecules with stable isotopes to reveal the biosynthetic pathways for further study in the field of biomolecular chemistry.

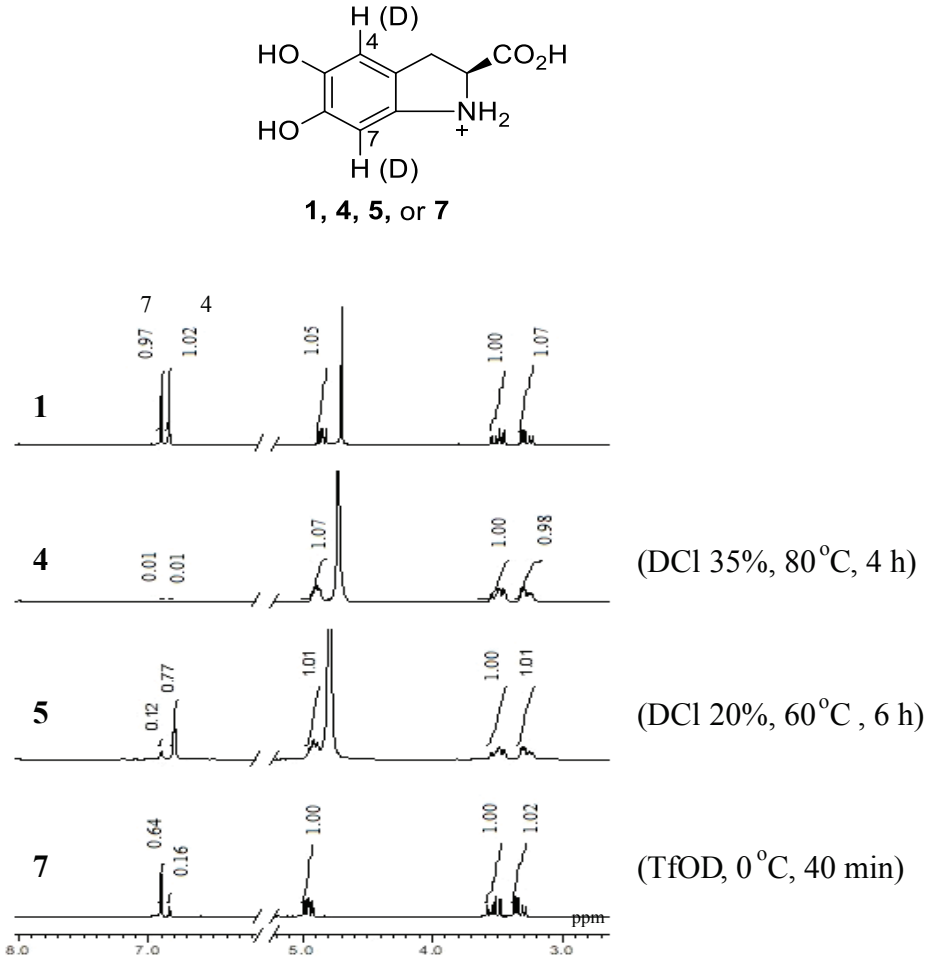


Figure 4. Selected ^{1}H-NMR profile of cDOPA (**1**) and deuterated cDOPA derivatives (**4**–**5**, **7**)

EXPERIMENTAL

General methods. ^{1}H-NMR spectra were measured by a Jeol EX 270 spectrometer (JEOL, Tokyo, Japan) for determining the H/D exchange proportion. MS data were obtained with a Waters LCT Premier XE instrument. HRMS-ESI spectra were obtained with a Waters UPLC ESI-TOF mass spectrometer (Waters, Milford, CT, USA). All reagents used were of analytical grade. Optical rotations were measured at 23 °C on JASCO DIP370 polarimeter (JASCO, Tokyo, Japan). TfOD (98% D) was purchased from Sigma–Aldrich. DCl (35 wt% in D_2O, 99% D) was purchased from Wako. The cycloDOPA derivatives (**1** and **3**) were synthesized by reported methods with slightly modification.

General procedures for H/D exchange with DCl. The *O,O,N*-triacetyl cycloDOPA methyl ester (**3**, 45 mg, 0.13 mmol) or cycloDOPA (**1**, 45 mg, 0.19 mmol) was dissolved in DCl (2.34 mL) and stirred at specific temperature. The part of reaction mixture (250 μL) was diluted with D_2O (200 μL) in ice bath and then subject into ^{1}H-NMR depend on time.

General procedures for H/D exchange with TfOD. The cycloDOPA (**1**, 45 mg, 0.19 mmol) was dissolved in TfOD (672 μL, 7.6 mmol) and stirred at specific temperature. The part of reaction mixture (67.2 μL) was diluted with D_2O (500 μL) for subjection into ^{1}H-NMR depend on time.

CycloDOPA-4,7-*d*$_2$ (4) The *O,O,N*-triacetyl cycloDOPA methyl ester (**3**, 49.3 mg, 0.15 mmol) was dissolved in 35% DCl (2.56 mL, 28.7 mmol). The reaction mixture was stirred at 80 ^{o}C for 4 h, and concentrated under high pressure. The residue was washed with MeCN and diluted by small amount of D_2O, then centrifuged. The supernatant liquid then concentrated to afford product as brown amorphous mass (32.1 mg, 0.14 mmol, 94%). $[\alpha]_D$ –73 (c 1.0, D_2O). ^{1}H-NMR (270 MHz, D_2O) δ: 6.90 (0.01H, s), 6.82 (0.01H, s), 4.89 (1H, t, *J* = 9.7 Hz), 3.50 (1H, dd, *J* = 16.2, 9.6 Hz), 3.28 (1H, dd, *J* = 16.2, 6.6 Hz) ppm. ^{13}C-NMR (67.5 MHz, D_2O) δ: 172.4, 146.8, 145.1, 127.0, 126.0, 112.6 (*J* = 21.2 Hz), 106.9 (*J* = 23.2 Hz), 61.5, 33.3 ppm. HRMS (ESI): calcd for $C_9H_8D_2NO_4$ $[M + H]^+$ 198.0735, found 198.0724.

CycloDOPA-7-*d* (5) The cycloDOPA (**1**, 49.2 mg, 0.21 mmol) was dissolved in 20% DCl (2.56 mL, 16.6 mmol). The reaction mixture was stirred at 60 ^{o}C for 6 h, and concentrated under high pressure. The residue was washed with MeCN and diluted by small amount of D_2O, then centrifuged. The supernatant liquid then concentrated to afford product as brown amorphous mass (48.2 mg, 0.21 mmol, 98%). $[\alpha]_D$ –76 (c 1.0, D_2O). ^{1}H-NMR (270 MHz, D_2O) δ: 6.90 (0.12H, s), 6.80 (0.77H, s), 4.91 (1H, t, *J* = 7.9 Hz), 3.50 (1H, dd, *J* = 16.2, 9.6 Hz), 3.27 (1H, dd, *J* = 16.2, 6.6 Hz) ppm. ^{13}C-NMR (67.5 MHz, D_2O) δ: 172.3, 146.8, 145.1, 126.8, 126.0, 112.8, 106.7 (*J* = 23.2 Hz), 61.5, 33.3 ppm. HRMS (ESI): calcd for $C_9H_9DNO_4$ $[M + H]^+$ 197.0673, found 197.0666.

CycloDOPA-4-*d* (7) The cycloDOPA (**1**, 4.4 mg, 0.019 mmol) was dissolved in TfOD (67.2 μL, 0.76 mmol) and stirred at 0 ^{o}C for 40 min. The reaction mixture was diluted with D_2O (500 μL), measured the deuterium incorporation by ^{1}H-NMR and UV-Vis spectroscopy (UV (TfOD/D_2O): λ_{max} (ε) = 285 (4328) nm, 99%). $[\alpha]_D$ –78 (c 0.78, TfOD/D_2O). ^{1}H-NMR (270 MHz, D_2O) δ: 6.90 (0.64H, s), 6.84 (0.16H, s), 4.95 (1H, dd, *J* = 9.7, 6.8 Hz), 3.53 (1H, dd, *J* = 16.2, 9.6 Hz), 3.32 (1H, dd, *J* = 16.2, 6.8 Hz) ppm. ^{13}C-NMR (67.5 MHz, D_2O) δ: 173.1, 146.8, 145.2, 127.2, 126.3, 112.8 (*J* = 21.2 Hz), 107.3, 62.0, 33.5 ppm. HRMS (ESI): calcd for $C_9H_9DNO_4$ $[M + H]^+$ 197.0630, found 197.0679.

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