DEUTERATION OF ORGANIC COMPOUNDS BY HYDROTHERMAL PROCESS

Miss Nattasiri Phaisarn

A Thesis Submitted in Partial Fulfillment of the Requirements
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ดิวทีเรชันของสารประกอบอินทรีย์โดยกระบวนการไฮโดรเทอร์มัล

น.ส.ณัฐสิริ ไพศาล

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By	Miss Nattasiri Phaisarn
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Thesis Advisor	Professor Dr. TIRAYUT VILAIVAN

Accepted by the FACULTY OF SCIENCE, Chulalongkorn University in Partial Fulfillment of the Requirement for the Master of Science

..... Dean of the FACULTY OF SCIENCE
(Professor Dr. POLKIT SANGVANICH)

THESIS COMMITTEE

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(Associate Professor Dr. PORNAPA SUJARIDWORAKUN)
..... Thesis Advisor
(Professor Dr. TIRAYUT VILAIVAN)
..... Examiner
(Professor Dr. SUMRIT WACHARASINDHU)
..... External Examiner
(Associate Professor Dr. Kwanruthai Tadpetch)

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สารประกอบติดฉลากดิวทีเรียมเป็นที่ต้องการเป็นอย่างมากในการประยุกต์ใช้ในงานที่หลากหลาย โดยเฉพาะอย่างยิ่งใช้เป็นสารมาตรฐานในเทคนิควิเคราะห์ต่าง ๆ วัตถุประสงค์ของงานวิจัยนี้คือการพัฒนาปฏิกิริยาการแลกเปลี่ยนระหว่างไฮโดรเจนกับดิวทีเรียม (HDx) และฮาโลเจนกับดิวทีเรียม (XDx) ภายใต้กระบวนการไฮโดรเทอร์มัล สำหรับปฏิกิริยาการแลกเปลี่ยนไฮโดรเจนและดิวทีเรียม ได้มีการศึกษากับตัวอย่างที่เป็นสารประกอบอะลิฟาติก อะลิไซคลิก อะโรมาติก เฮเทอโรไซคลิก และกรดอะมิโนหลายชนิด เพื่อศึกษารูปแบบความว่องไวของการเกิดปฏิกิริยาและขอบเขตของปฏิกิริยา โดยพบว่าการแลกเปลี่ยนระหว่างไฮโดรเจนกับดิวทีเรียมในดิวทีเรียมออกไซด์ภายใต้กระบวนการไฮโดรเทอร์มัลที่พัฒนาขึ้นมีความจำเพาะต่อไฮโดรเจนที่ตำแหน่ง *ออร์โธ-* และ *พารา-* ของสารประกอบกลุ่มฟีนอล และต่อไฮโดรเจนที่ตำแหน่งแอลฟาของกรดอะมิโน และกับตำแหน่งที่จำเพาะของสารประกอบกลุ่มเฮเทอโรไซคลิกบางชนิด อย่างไรก็ตามการเติมกรดหรือเบสสามารถช่วยเร่งปฏิกิริยาการแลกเปลี่ยนระหว่างไฮโดรเจนและดิวทีเรียมหรือเปลี่ยนรูปแบบความว่องไวของการเกิดปฏิกิริยา นอกจากนี้ยังพบอีกว่าดิวทีเรชันของกรดอะมิโนทำให้เกิดปฏิกิริยาอิพิเมอไรเซชันร่วมด้วย ในทางกลับกันการแลกเปลี่ยนระหว่างไฮโดรเจนและดิวทีเรียมของกรดคาร์บอกซิลิกหรือเอสเทอร์ของไฮโดรเจนที่ตำแหน่งแอลฟาเกิดได้ไม่ค่อยดีนักภายใต้ภาวะที่ไม่มีตัวเร่งปฏิกิริยา เพื่อหลีกเลี่ยงข้อจำกัดของการแลกเปลี่ยนระหว่างไฮโดรเจนกับดิวทีเรียมที่เกิดเฉพาะกับหมู่ C–H บางประเภท จึงได้มีการพัฒนาอีกวิธีการหนึ่งในการติดฉลากดิวทีเรียมโดยการแลกเปลี่ยนระหว่างฮาโลเจนกับดิวทีเรียม (XDx) ในปฏิกิริยา โดยในปฏิกิริยาแลกเปลี่ยนระหว่างฮาโลเจนกับดิวทีเรียมสารประกอบอะโรมาติกที่มีหมู่ฮาโลเจนร่วมกับหมู่ฟังก์ชันที่หลากหลายสามารถเกิดปฏิกิริยาดีฮาโลจีเนชันโดยใช้เกลือฟอร์เมตร่วมกับตัวเร่งปฏิกิริยาแพลเลเดียม/คาร์บอนในดิวทีเรียมออกไซด์ภายใต้สภาวะไฮโดรเทอร์มัล และที่สำคัญการใช้ฟอร์เมตที่ไม่ติดฉลากด้วยดิวทีเรียมสามารถให้อัตราส่วนของการแลกเปลี่ยนฮาโลเจนกับดิวทีเรียมต่อการแลกเปลี่ยนไฮโดรเจนกับดิวทีเรียมที่ยอมรับได้ในหลายกรณี (>80:20) ในกรณีของสารประกอบฟีนอล การแลกเปลี่ยนระหว่างไฮโดรเจนกับดิวทีเรียมที่ตำแหน่ง *ออร์โธ-* เป็นปฏิกิริยาข้างเคียงที่สำคัญ และสามารถลดได้โดยการใช้อุณหภูมิต่ำและใช้รีเอเจนต์ที่เป็นเบสน้อยกว่า ในกรณีที่อัตราส่วนของการแลกเปลี่ยนฮาโลเจนกับดิวทีเรียมต่อการแลกเปลี่ยนไฮโดรเจนกับดิวทีเรียมไม่ดีนักยังสามารถใช้โซเดียมฟอร์เมตที่ติดฉลากด้วยดิวทีเรียม ที่ได้จากปฏิกิริยาระหว่างกรดฟอร์มิกที่ติดฉลากด้วยดิวทีเรียมและโซเดียมคาร์บอเนต ซึ่งให้ผลที่ดีกว่าการใช้ฟอร์เมตที่ไม่ติดฉลาก วิธีการที่พัฒนาขึ้นทั้งสองวิธีเป็นวิธีการที่เป็นมิตรต่อสิ่งแวดล้อม มีประสิทธิภาพ และใช้งานได้จริงสำหรับการสังเคราะห์สารประกอบที่ติดฉลากดิวทีเรียม ถึงแม้ว่ายังต้องพัฒนาเพื่อเพิ่มประสิทธิภาพและขยายขอบเขตของการใช้งานของปฏิกิริยาต่อไป

สาขาวิชา	ปิโตรเคมีและวิทยาศาสตร์พอลิเมอร์	ลายมือชื่อนิสิต .....
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Nattasiri Phaisarn : DEUTERATION OF ORGANIC COMPOUNDS BY HYDROTHERMAL PROCESS. Advisor: Prof. Dr. TIRAYUT VILAIVAN

Deuterium-labeled compounds are in great demand in many applications, especially as reference standards for various analytical techniques. The objective of this study is to develop two complementary methods for deuterium labeling of organic compounds including the hydrogen-deuterium exchange (HDx) and halogen-deuterium exchange (XDx) reactions under hydrothermal conditions. For HDx, several aliphatic, alicyclic, aromatic, heterocyclic, and amino acid compounds were used as model substrates to determine the reactivity pattern and scope of the reaction. It was found that the HDx at the *ortho*- and *para*-Hs of phenolic compounds and a-position of amino acids as well as certain heteroaromatic compounds occurred efficiently in D_2O under the developed hydrothermal reaction without the need for any catalyst or additive. However, the addition of acid or base could accelerate the HDx reaction or change the reactivity pattern. Epimerization at the a-position of amino acids also occurred along the deuteration. On the other hand, the HDx at the a-position of carboxylic acids or esters proceeded poorly in the absence of a catalyst. To avoid the limitation of HDx that occurs only at specific types of C-H, the complementary strategy of deuterium labeling – namely halogen-deuterium exchange (XDx) was also developed. In the XDx, halogenated aromatic compounds bearing various functional groups were dehalogenated efficiently by formate salts in the presence of Pd/C as a catalyst in D_2O under hydrothermal conditions. Importantly, normal (i.e. non-deuterated) formates gave acceptable XDx:XHx ratios (>80:20) in several instances. In the case of phenol substrates, *ortho*-HDx was observed as a competing side reaction that could be minimized by performing the reaction at a lower temperature and with less basic reagents. In some cases where the XDx:XHx ratios were poor, the use of DCOONa generated in situ from DCOOD and Na_2CO_3 instead of HCOONa offered better results. The two developed methods provided a green, efficient, and practical method for the synthesis of deuterium-labeled compounds, although further improvements are still required to increase the efficiency and broaden the scope of the reactions.

Field of Study:	Petrochemistry and Polymer Science	Student's Signature .....
Academic Year:	2022	Advisor's Signature .....

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CHAPTER I

INTRODUCTION

1.1 Deuterium labeling

Isotopic labeling involves the replacement of one or more atoms in an organic molecule such as H, C, and N with their isotopes. Mostly, stable isotopes such as $^{2}H(D)$, ^{13}C, and ^{15}N are preferred due to their high stability and less toxicity. In most cases, physical and chemical characteristics are little affected by isotopic replacements, but the molecular masses are changed. This makes isotopic-labeled compounds useful as standards for quantitative mass spectrometry (MS)[1] and high-performance liquid chromatography (HPLC)[2] because they generally display the same retention and ionization behavior in LC/MS but differ on account of their mass difference. If the mass difference is large enough to minimize the signal overlap, a quantitative determination is possible.[1] Moreover, isotope labeling has been widely utilized as a technique for mechanistic studies on reactions and reaction pathways.[1, 3]

In nuclear magnetic resonance spectroscopy (NMR), deuterated solvents such as DMSO-d_6 or chloroform-*d* are routinely used due to the absence of an interfering signal in the proton frequency range. Also, the deuterium provided a lock frequency signal which is necessary for measuring the NMR signal. Furthermore, as shown by the bond dissociation energy the C–D bond (341.4 kJ/mol) is stronger than the C–H bond (338.4 kJ/mol),[4] thus it is more difficult to break. This can tremendously affect the properties of the molecules such as drug pharmacokinetics. Deuterated drugs are eliminated from the human body more slowly than non-deuterated drugs at the same dosage level.[5] In addition, the longer half-life of deuterated drugs reduces the dose and thus side effects of the drugs. Consequently, deuterated substances play a crucial role in medicinal chemistry. A wide variety of deuterated compounds are commercially available; however, they can be prohibitively expensive. As a result, efficient methods for synthesizing labeled compounds are still in great demand.[3]

1.2 Hydrogen-deuterium exchange (HDx)

Deuterium-labeled compounds can be prepared by conventional chemical synthesis starting from simple deuterated starting materials such as methanol-d_4. However, the substrates or reagents must be pre-labeled with deuterium, which is normally expensive, especially when considering that the final yield for synthesis can be low. Another commonly used method is the exchange of hydrogen by deuterium (HDx). The HDx reaction occurs efficiently when the hydrogen atom is attached to an atom with high electronegativities such as oxygen or nitrogen. However, such an exchange is rather dynamic in nature as it happens just by changing the solvent. As a result, labeling at heteroatom is not a practically useful reaction. The HDx reactions of hydrogen atoms attach to carbon are also possible when there are one or more electron withdrawing groups (EWG) attaching to the carbon atom. Fortunately, such C-D bonds are more stable and do not undergo a fast exchange back to the C-H bond like in the case of heteroatoms.

Typically, the HDx involves the transfer of one or more deuterium atoms between the substrate and a deuterium-containing reagent such as deuterium oxide (D_2O),[6, 7] dimethyl sulfoxide (DMSO-d_6),[8] methanol-d_4 (CD_3OD),[9] formic acid-d_2,[10] and D_2 gas produced by photocatalytic D_2O splitting.[10, 11] D_2O is an especially attractive deuterium source because of its low cost and low toxicity.[12] The HDx reaction is usually performed in the presence of acid[1], base or metal catalysts,[13] most importantly palladium and platinum.[14] The reaction may occur at ambient temperature, under conventional heating, microwave,[3] and hydrothermal processes.[6, 7]

1.2.1 Acid- and base-catalyzed HDx

The acid and base-catalyzed HDx of activated carbon centers in the presence of deuterium sources generally occur through enolization.[2] As a result, the α-CH connecting to various activating groups including ketone[15], aldehyde[16], ester[17], and carboxylic acids[18] can readily and selectively participate in the deuterium exchange reaction.[2] Also, several aromatic ring systems are readily deuterated via electrophilic substitution with D^+. In general, specific acid or base catalysts are required for each

type of substrate. Furthermore, the rate of HDx depends on the substrates and reaction conditions.

In 2007 Atzrodt et al.[1] reported a HDx reaction catalyzed by acids or bases using C_6D_6 as the deuterium source leading to the conversion of C–H bonds to C–D bonds. Lewis acids are used for the HDx such as $AlBr_3$, $EtAlCl_2$, $MoCl_5$, H_3PO_4, or BF_3. Especially, $MoCl_5$ was shown to be the most effective catalyst for HDx of nonpolar arenes substrates such as naphthalene (91% exchange) and isopropyl benzene (62% exchange). In the latter case, the exchange occurred only at the aromatic protons, suggesting the electrophilic substitution mechanism (**Figure 1.1**).

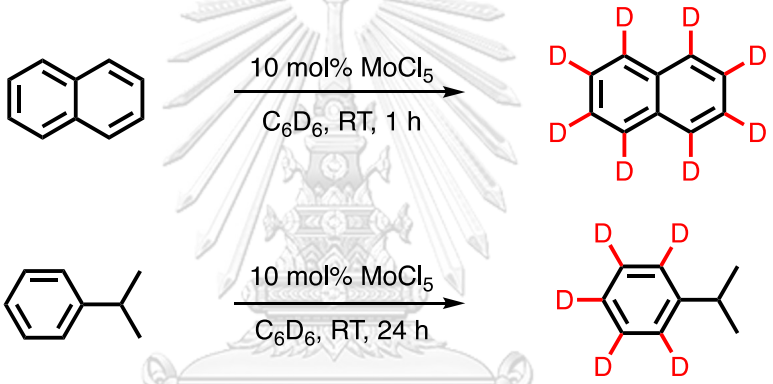


Figure 1.1 HDx of naphthalene and isopropyl benzene catalyzed by $MoCl_5$

In 2004, Wähälä et al.[19] demonstrated the HDx of polyphenolic substrates such as flavonoids, isoflavonoids, and lignans, in a mixture of D_3PO_4, BF_3, and D_2O. The reaction gave good yields and high deuteration percentages at the activated position of the arenes as shown in **Figure 1.2**. However, a long reaction time was required (7 days).

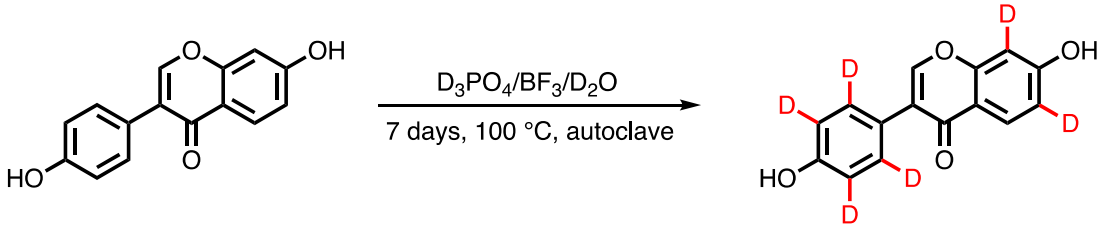


Figure 1.2 HDx of daidzein under acidic conditions

The acid-catalyzed HDx of phenols in D_2O is a well-known reaction. Resorcinol undergoes efficient HDx in D_2O containing dilute sulfuric acid.[20] The reaction occurred via the electrophilic aromatic substitution. The HDx selectively occurred at the C–H group *ortho*- and *para*- to the OH groups. This can be explained by the electrophilic attack of D^+ (or D_3O^+) at the most electron rich positions on the aromatic ring (**Figure 1.3**). No *meta*- HDx was observed according to ^1H NMR analysis (**Figure 1.4**).

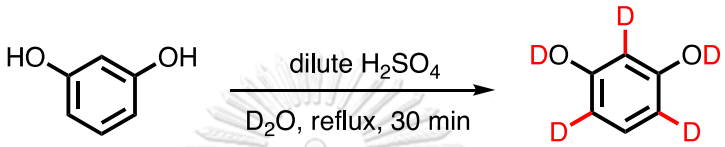


Figure 1.3 HDx of resorcinol in D_2O under acidic conditions

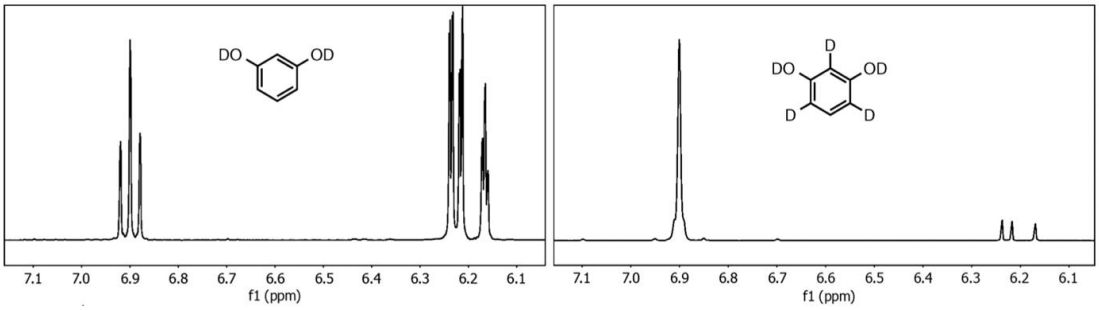


Figure 1.4 ^1H NMR spectra of resorcinol before (left) and after (right) HDx[20]

The deuteration of aryl methyl ketones and aryl methyl sulfones under basic conditions was studied by Berthelette and Scheigetz in 2004.[21] They reported that the HDx occurred exclusively at the methyl group of aryl methyl ketones. Triethylamine (TEA) was employed as a base allowing methyl group deuteration in ketone substrates without decomposition (**Figure 1.5**).

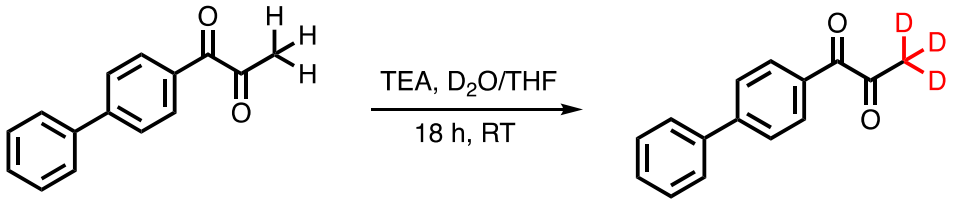


Figure 1.5 HDx of aryl methyl ketone in D_2O under basic conditions

In 2015, Zhan et al.[22] investigated the deuteration of phenols using NaOH as a catalyst and D_2O at 180 ℃ for 15 min under microwave irradiation. The HDx occurred regioselectively at the *ortho/para*-positions. The conditions were applied to various substituted phenols to evaluate the scope of the reaction. The deuterated products were obtained in the range of 87-97% yield (**Figure 1.6**).

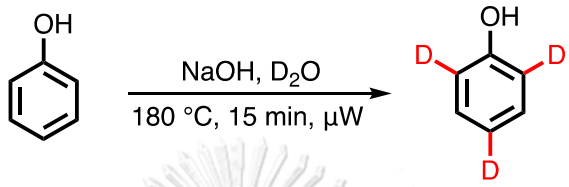


Figure 1.6 HDx of phenol using NaOH in D_2O under microwave irradiation

1.2.2 Metal catalyzed HDx

In the metal-catalyzed HDx, metal such as Pd activates the specific C–H bonds and makes them susceptible to the exchange reaction. Typically, aromatic and benzylic/allylic C–Hs are the most susceptible sites for the Pd-catalyzed HDx.

The high activity for HDx exchange has been found in Pd, Pt, Rh, Ni, and Co catalysts.[23] On the other hand, no particular exchange activity has been observed in heterogeneous reaction procedures with the metals iridium and ruthenium that are used successfully in homogeneous catalysis. Other metals such as manganese, chromium, and mercury had been used, but with little significance, for the metal-catalyzed HDx.[1]

In 2014 Krause-Heuer et al.[14] reported the HDx of arylamines such as diphenylamine, *N*-phenyl-o-phenylenediamine catalyzed by Pd/C or Pt/C in D_2O under heating conditions at 80 ℃ for 4-24 h. Primary and secondary aromatic amines were completely deuterated at all positions on the benzene ring in good yields (90-96%). However, no reaction was observed with tertiary aromatic amines because the availability of the nitrogen lone pair influences the deuteration reaction. It is expected that the metal catalyst can be located in the vicinity of the nitrogen atom of primary and secondary arylamines rather than tertiary arylamine since Pt and Pd have a quite high affinity for the nitrogen lone pair (**Figure 1.7**).

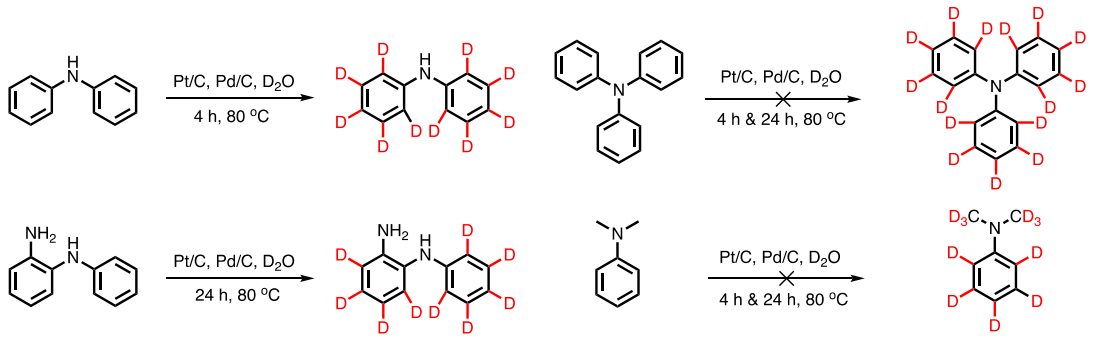


Figure 1.7 HDx of arylamine in D_2O catalyzed by Pd/C or Pt/C

The Pd catalyst can promote HDx at benzylic positions when used in combination with gaseous H_2 as a hydrogen source. In 2002 Sajiki et al. illustrated the HDx of diphenylmethane in the presence of 10% Pd/C and gaseous H_2 in D_2O at room temperature.[24] The reaction was developed in a one-pot fashion for the chemoselective HDx at the benzylic position in very high deuterium content under a mild reaction condition (**Figure 1.8**). No reaction was observed in the absence of H_2.

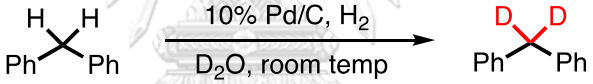


Figure 1.8 HDx of diphenylmethane with Pd/C-H_2-catalyzed in D_2O

In 2003, the Sajiki group further studied the HDx of heteroaromatic compounds catalyzed by palladium in the presence of H_2 and D_2O.[25] The HDx occurred selectively at the C2 and C8 positions in 48% yield (**Figure 1.9**).

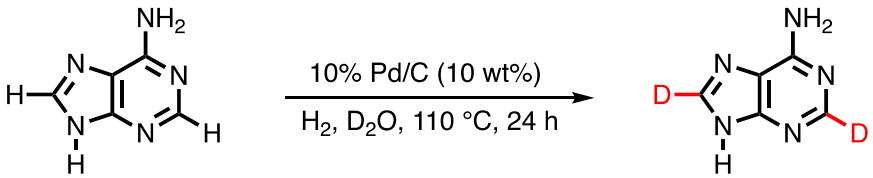


Figure 1.9 HDx of adenine in the presence of Pd/C-H_2-D_2O

Based on the abovementioned reactions, it was proposed that the Pd catalyst promoted the exchange reaction between H_2-D_2O to D_2-H_2O, and the in situ generated D_2 acted as the deuterating species. Such H-D exchange was

experimentally demonstrated in 2004 by Sajiki et al.[26] The procedure allowed a very simple method to generate D_2 that could be utilized for many deuteration reactions under mild conditions (**Figure 1.10**). The generated D_2 gas is easily applicable to the catalytic reduction of functionalized aromatic halides, epoxide, nitrile, and unsaturated hydrocarbons. For example, the reaction of 2-chlorobenzoic acid was performed under the mentioned conditions to give the benzoic acid-*d* in 98% yield. For 2-(3-chlorophenyl)oxirane as a representative of the epoxide substrate that was performed with H_2 gas and D_2O. The substrate was dechlorinated and the ring-opening of the epoxide occurred to form 2-phenylethanol-*d* in 69% yield (**Figure 1.11**). The reaction condition can be applied to halogen substrates and give excellent quantitative deuterium efficiencies.

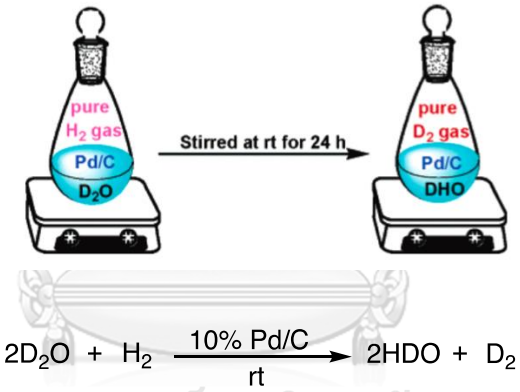


Figure 1.10 HDx with H_2 gas and D_2O in the presence of 10% Pd/C.[26] Reprinted (adapted) with permission from ref. 26 {Sajiki, H.; Kurita, T.; Esaki, H.; Aoki, F.; Maegawa, T.; Hirota, K. Complete Replacement of H_2 by D_2 via Pd/C-Catalyzed H/D Exchange Reaction. *Org. Lett.* **2004**, 6 (20), 3521-3523}. Copyright {2004} American Chemical Society.

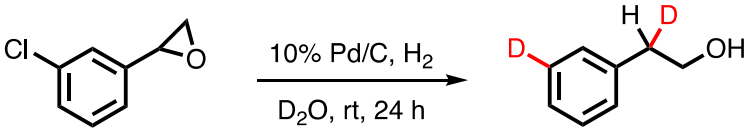


Figure 1.11 HDx of 2-(3-chlorophenyl)oxirane with H_2 gas and D_2O in the presence of 10% Pd/C[26]

1.2.3 Hydrothermal processes

Under hydrothermal conditions, the reactions are performed in a closed system under high temperature and pressure, often in water as the reaction medium. Under such conditions, water exists in subcritical or even supercritical states depending on whether the temperature is lower or higher than the critical point of water (or other reaction media).[27] Sub- or supercritical waters are more acidic and less polar and can dissolve the organic compounds that are normally insoluble in water. Many reactions can occur under such conditions without the requirement of a catalyst or additives including the HDx.[28] The most important advantage of such a procedure is its low cost and simplicity of operation.

For example, in 1994 Yao et al.[6] studied the HDx of aromatic compounds such as acetophenone, toluene, benzene, and dibenzothiophene in D_2O as a deuterium source at 400-500 °C. Under the mentioned conditions, the results showed that these conditions could not control the deuterium exchange position.

In 1996 Junk et al.[7] studied the HDx of 1-methylnaphthalene under supercritical conditions at 380-430 °C. The comparison of various conditions such as non-catalyzed, D_2O/Pd or ethylaluminium dichloride/benzene-d_6 was made. In the absence of catalyst, it was found that the completely deuterated product (1-methylnaphthalene-d_{10}, >97% exchange) was obtained. On the other hand, the deuteration only occurred at the aromatic proton in the presence of a catalyst (**Figure 1.12**).

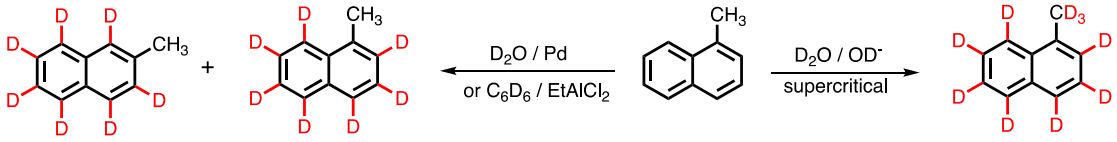


Figure 1.12 Deuteration of 1-methylnaphthalene in the absence and presence of D_2O/Pd or ethylaluminium dichloride/benzene-d_6 under supercritical condition

In 1989 Werstiuk and Ju[29] studied the HDx of pyridine derivatives in the absence of any catalyst in D_2O at 200-260 °C for 24 h. It was found that the HDx occurred at C3, C5, and C6 positions. The substrate was accomplished in high yield

and regioselectivity (**Figure 1.13**). When the pyridine was heated in D_2O at 300 °C for a prolonged period (62 h), the HDx occurred at all positions (C2, C3, C4, C5, C6) in more than 80% yield. Similarly, Yao et al.[6] reported in 1994 that the pyridine was heated with NaOD in D_2O at 400 °C for 10 min, and a complete deuteration (>80%) was observed at all positions.

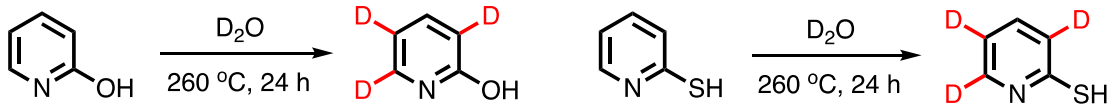


Figure 1.13 Deuteration of pyridine derivatives in D_2O

In 2004 Matsubara et al.[30] demonstrated the decarboxylative deuteration of carboxylic acids such as 4-hydroxyphenylpropionic acid in the presence of Pd/C in D_2O at 250 °C for 12 h. Under such conditions, the compound underwent both decarboxylation and complete deuteration at other positions as well (**Figure 1.14**).

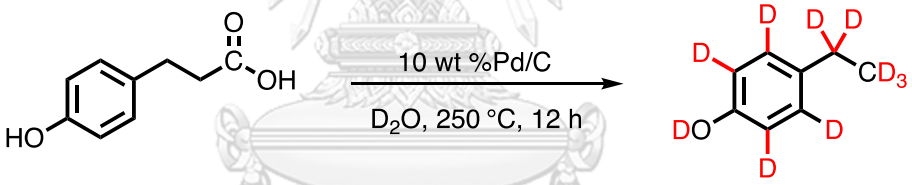


Figure 1.14 Decarboxylation and deuteration of 4-hydroxyphenylpropionic acid in D_2O in the presence of Pd/C

In 2004 Kubo et al.[28] investigated the site-selective HDx of phenol in sub- and supercritical water without any catalysts. The exchange was observed only at the *ortho/para*-positions at a temperature range of 210 to 300 °C. At higher temperature (400 °C), HDx at all positions were observed. The reaction rate is roughly 50% faster for the *ortho*- than the *para*-positions. It was proposed that the water was more localized near the hydroxyl group of the phenol. Therefore, the reactivity at the *ortho*-position, being closer to the hydroxyl group, was more greatly enhanced than the *para*-position.

In 2021 Darshana et al.[9] demonstrated a simple the XDx of indoles, pyrroles, carbonyl compounds, and steroids in CD_3OD. Prenyl or propargyl bromides were used as an initiator, presumably by generating deuterium halide (DX) upon reacting with CD_3OD. Next, the generated DX catalyzed the HDx of the substrates. The reaction took place cleanly under mild conditions, and no chromatographic purification was required to obtain the pure deuterated products (**Figure 1.15**).

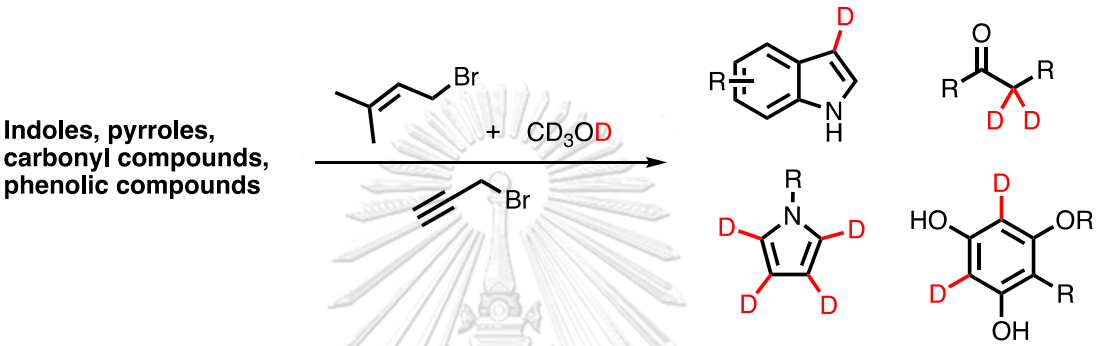


Figure 1.15 Deuteration of indoles, pyrroles, carbonyl and phenol compounds with prenyl or propargyl halides in CD_3OD

1.3 Halogen-deuterium exchange (XDx)

1.3.1 Halogen-hydrogen exchange (hydrodehalogenation)

Transition metals are well known for the activation of the C–X bond. Therefore, several reductive dehalogenation methods are catalyzed by a transitional metal in combination with hydride sources. Palladium is frequently used as the catalyst for reductive dehalogenation because of its renowned reactivity to the C–X bond through oxidative addition.[31] For example, in 1977 Cortese and Heck[32] reported that aromatic halides and nitro compounds are easily reduced at 50-100 °C to hydrocarbons and amines, respectively, with diethyl ammonium formate in the presence of palladium on carbon (Pd/C) or a soluble triarylphosphinepalladium acetate catalyst. It was also found that aryl halides are reduced to deuterium derivatives with formic acid-d_2.

In 2004 Arcadi et al.[33] demonstrated the hydrodechlorination of aryl chlorides bearing electron-withdrawing and electron-donating groups in the presence of 10% Pd/C in water using HCOONa as the hydrogen source. The reaction was accomplished

under mild conditions (room temperature, aqueous medium) and the dehalogenated products were obtained in the range of 16-100% yield. For instance, 4-chloroaniline gave 89% yield of aniline after 12 h.

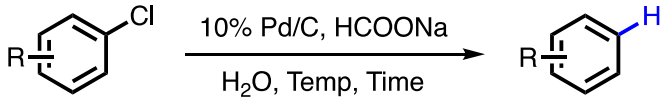


Figure 1.16 Hydrochlorination of aryl chlorides in water with HCOONa and catalytic 10% Pd/C

When the same reaction was performed under heating at 100 °C, further reduction of certain aromatic substrates to the corresponding alicyclic compounds was observed. For example, the dearomatization of 4-chlorophenol to cyclohexanol in **Figure 1.17**

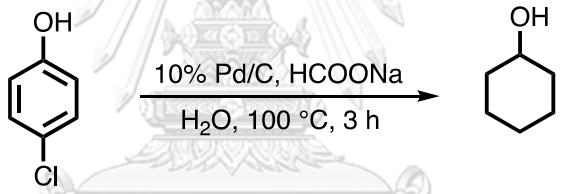


Figure 1.17 Dearomatization of 4-chlorophenol in water with HCOONa and catalytic 10% Pd/C at 100 °C for 3 h

In 2006 Logan and Oinen[34] illustrated the hydrodechlorination of substituted aryl chlorides bearing activating or deactivating groups using a homogeneous palladium catalyst prepared in situ from 2-(di-*tert*-butylphosphino)-biphenyl and $Pd(OAc)_2$. Sodium formate was used as a hydride source (**Figure 1.18**). The reactions were performed in refluxing methanol for 1-4 h to give the reduction product in 95-100% yield. For example, the hydrodechlorination of 4-chloroanisole gave anisole in 99% yield after 3 h.

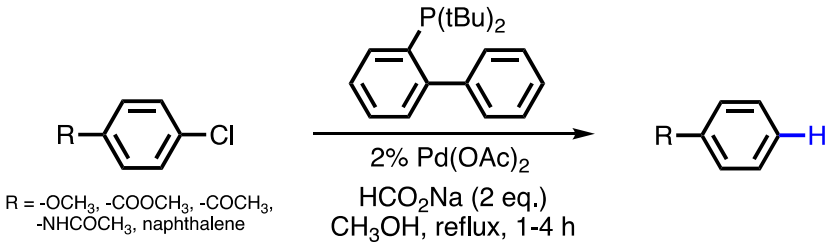


Figure 1.18 Hydrodechlorination of aryl chloride in with sodium formate in the presence of a homogeneous palladium catalyst

In 2007, Chen et al.[35] reported a catalytic transfer dehalogenation of highly functionalized aromatic halides and α-haloketones in the presence of palladium acetate, triphenylphosphine, and potassium carbonate using *n*-butanol as a hydrogen donor. The reactions were performed at 100 °C to give the dehalogenated products in the range of 15-90% yield (**Figure 1.19**). As an example, 1-bromo-3-methylbenzene was debrominated in 99% yield while 1-bromo-4-chlorobenzene could be selectivity debrominated to give chlorobenzene in 95% yield. 4-Fluoroanisole was inert under the same reaction conditions.

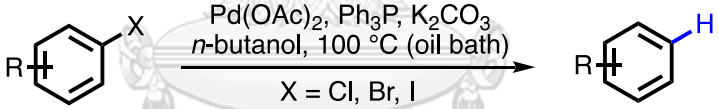


Figure 1.19 Pd-catalyzed dehalogenation of aromatic halides with alcohol as hydrogen donor

Recently, Tomanová et al.[36] developed a conceptually different reductive dehalogenation of (hetero)aryl bromides and iodides using sodium sulfite as the reducing agent in an aqueous medium. The reactions were performed in water at 130 °C for 3 h under microwave heating and required no other catalysts. 4-Bromophenol gave phenol as the only product in 88% isolated yield. 4-Bromoresorcinol was also readily debrominated under microwave irradiation to give the expected product in 96% yield (**Figure 1.20**). Only halogen atoms at the *ortho*- and *para*-positions of the OH group could be reduced according to the mechanism shown in **Figure 1.21.**

Therefore, the halogenated aromatics were subjected to the reaction with sodium sulfite in water such as 4-bromoaniline, 4-fluororesorcinol, 4-iodoanisole, and

4-chlororesorcinol. The results suggested that the outcome of a reaction was influenced by the nature of the halogen atoms (Br and I afford dehalogenation, while F and Cl afford sulfonation) and the structure of the reactive tautomer.

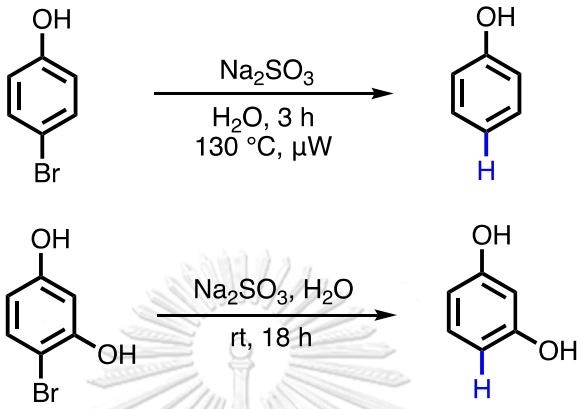


Figure 1.20 Debromination of 4-bromophenol and 4-bromoresorcinol with sodium sulfite[36]

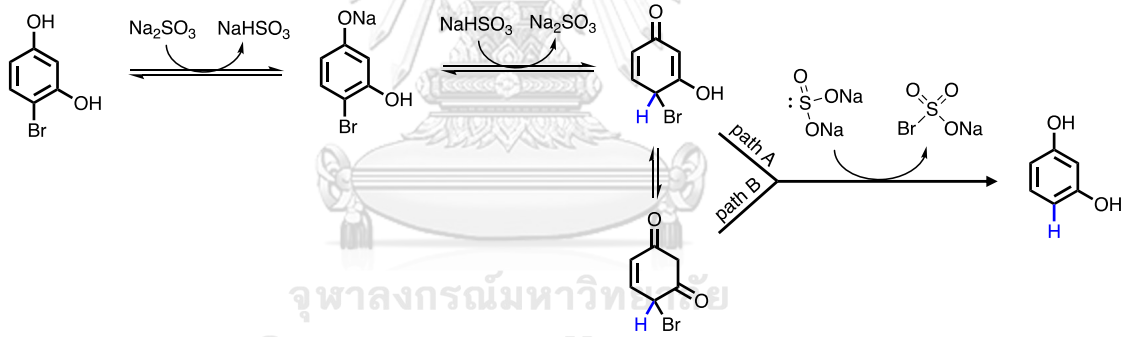


Figure 1.21 Proposed mechanism of the debromination of 4-bromoresorcinol[36]

From the previous reports, the successful exchange of halogen atoms attached to the aromatic/heteroaromatic ring systems with hydrogen paved the way for the replacement of the halogen by the deuterium atoms in the deuterohalogenation reactions.

1.3.2 Deuterodehalogenation (XDx)

In principle, if the hydrogen donor in the abovementioned hydrodehalogenation reactions was replaced by a deuterium donor, the C–X bound could be replaced by the C–D bond in the deuterodehalogenation reaction, which

will be referred to as X/D exchange or XDx. As an example, in 2014 Donald et al.[37] examined the XDx of halogenated heterocycles such as 3-bromoquinoline by using isopropanol-d_8 (d_8-IPA) or triethyl(silane-*d*) (Et_3SiD) as the deuterium source in the presence of a homogeneous palladium catalyst under microwave irradiation for 2.5 h to form 3-deuterioquinoline in 72% yield (**Figure 1.22**).

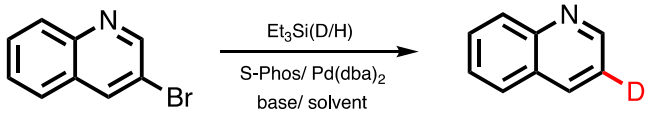


Figure 1.22 Deuteration of 3-bromoquinoline *in* triethyl(silane-*d*) under microwave condition[37]

Furthermore, XDx of halo-heterocyclic compounds such as 3-bromo-1-benzothiophene and 5-chloro-3-methyl-1-phenylpyrazole occurred readily in d_8-IPA to give the products in 59% and 91% yield, respectively (**Figure 1.23**).[37]

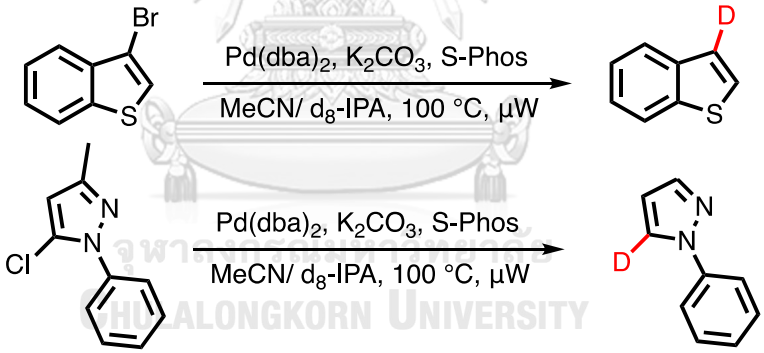


Figure 1.23 Deuteration of 3-bromo-1-benzothiophene and 5-chloro-3-methyl-1-phenylpyrazole with $Pd(dba)_2$ in d_8-IPA under microwave condition

In 2015, Zhang et al.[38] developed a Br/D exchange of aryl bromides carrying various functional groups. The reactions were performed with sodium formate-*d* (DCOONa) as the deuterium source in the presence of a Pd catalyst deriving from tris(dibenzylidene-acetone)dipalladium(0) ($Pd_2(dba)_3$) and *t*-Bu_3P. Under the same conditions, other aryl bromides bearing functional groups such as ester, ketone, phenol, nitrile, and amine afforded the deuterated compounds in 80-97% yield. For

example, ethyl 4-bromobenzoate gave ethyl 4-deuterobenzoate with 95% deuterium exchange.

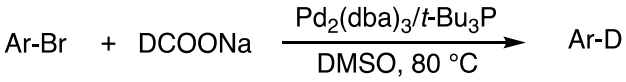


Figure 1.24 XDx of aryl bromide with DCOONa and palladium catalyst in DMSO

Moreover, palladium-catalyzed reductive dehalogenation was further developed by Helquist et al.[39] and Zoran et al.[40] In addition to reductive dehalogenation, Matsubara et al.[30] also illustrated that Pd/C could be used for reductive decarbonylation and decarboxylation under hydrothermal conditions. Also, Kozlowski et al.[41] reported in 2007 another palladium-catalyzed method for the decarboxylation of electron rich bis-*ortho*-substituted aromatic carboxylic acids using trifluoroacetic acid as the hydrogen source.

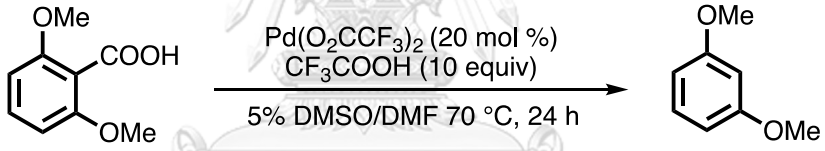


Figure 1.25 Palladium catalyzed decarboxylation of bis-ortho-substituted aromatic carboxylic acid

1.4 Rationale and objective of this work

As mentioned in the literature review, the available methods for HDx still have some limitations, including a time-consuming process with no selectivity and catalyst or additive required. Also, in the case of XDx, expensive deuterium sources such as benzene-d_6 and methanol-d_4 are needed. Furthermore, some reactions require homogeneous catalysts that were difficult to remove. Other reactions need prolonged heating.

In this work, we propose to investigate the suitable conditions for the hydrogen-deuterium exchange reaction under the hydrothermal conditions for a range of organic substrates with various functional groups including aliphatic, alicyclic, aromatic, and heterocyclic compounds (with special emphasis on amino acid and

simple aromatic compounds). In addition, the selectivity and limitation of HDx were studied. Furthermore, we aim to examine the suitable conditions for the halogen-deuterium exchange (XDx) of halogenated aromatic compounds with various functional groups. We expect that the study would provide a green, efficient, and inexpensive method for the synthesis of deuterium-labeled compounds that are useful in many applications.

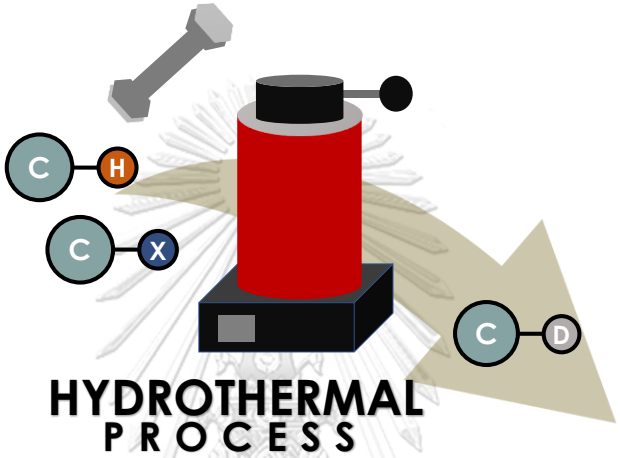


Figure 1.26 The concept of this work

CHAPTER II

EXPERIMENTAL SECTION

2.1 Materials

Stainless steel tubes with screw caps for constructing the reactors were purchased from Swagelok. All starting materials were purchased from standard suppliers and were used as received without further purification. Vanillin, 4-bromophenol, *trans*-4-hydroxy-L-proline, L-asparagine, 3-(4-hydroxyphenyl)propionic acid, 4-methoxyphenol, butyronitrile, α-methylbenzylamine, 4-bromophenol, 4-bromobenzoic acid, 4-chlorobenzoic acid, and ammonium formate ($HCOONH_4$) were purchased from Fluka. L-Leucine, L-lysine, L-tryptophan, L-tyrosine, L-threonine, phenylalanine, 4-hydroxyphenylacetic acid, γ-decalactone, 4-chloroacetanilide, and *p*-chlorocresol were purchased from Sigma-Aldrich. L-Aspartic acid, L-ascorbic acid, and anisole were purchased from BDH. *N*-Acetyl-*trans*-4-hydroxy-L-proline was purchased from Fluorochem. 4-Phenylbutyric acid was purchased from Thermo Scientific. 4-Picoline, 3-chloroperoxybenzoic acid (*m*-CPBA), sodium borohydride ($NaBH_4$), trifluoroacetic acid (TFA), and formic acid-d_2 were purchased from Acros Organics. Pyridine was purchased from Emsure. 4-Bromoacetanilide was purchased from Hopkin&Williams. 4-Chloroanisole, 4-chloroacetophenone, sodium formate (HCOONa), palladium 10% on carbon (10% Pd/C, wetted with ca. 55% water), and 4-Hydroxyindole was purchased from Tokyo Chemical Industry (TCI). Sodium oxalate ($Na_2C_2O_4$) was purchased from Alfa Aesar. Phenol and sodium bicarbonate ($NaHCO_3$) were purchased from Suksapan Panit. Salicylic acid, quinoline, benzyl cyanide, sodium sulfite (Na_2SO_3), ammonium acetate (CH_3COONH_4), sodium carbonate (Na_2CO_3), sodium hydroxide (NaOH), and acetic acid (CH_3COOH) were purchased from Merck. Diethyl ether, ethyl acetate, and ethanol were purchased from RCI Labscan. Deuterium oxide (D_2O, 99.8 atom% D), chloroform-*d* ($CDCl_3$), and dimethyl sulfoxide-d_6 (DMSO-d_6) were purchased from Cambridge Isotope Laboratories. Syringe filter (13 mm diam., 0.45 μm PTFE) was purchased from GVS life sciences. MilliQ water was obtained from a Milli-Q® Reference water purification system (type 1) equipped with a Millipak® 40 filter unit 0.22 μm, Millipore (USA). ^1H and ^{13}C NMR spectra were

recorded in a suitable deuterated solvent on a JEOL JNM-ECZ500R/S1 operating at 500 MHz (^{1}H) and 126 MHz (^{13}C). Mass spectra were recorded on a JEOL JMS-T100LP (AccuTOF^{TM} Dart) Mass spectrometer.

2.2 Methods

2.2.1 General procedure of hydrogen-deuterium exchange (HDx) reactions

All reactions were carried out in a screw-capped reactor made from stainless steel 316 tube with 9.5 mm OD, 1.2 mm wall thickness, and 6.0 cm length (total cell volume ~2.0 mL). In all reactions, 10 mg of the substrate and 500 µL of D_2O (0.1-0.3 M total concentration, depending on the substrate) were placed in the reactor and heated at the specified temperature for the specified period in a pre-heated electrical metal melting furnace (ToAuto, model SG-RRL-V.1.2-9KG-220V). After cooling to ambient temperature, the reactor was carefully opened and the obtained product(s) as a D_2O solution or suspension was transferred to the NMR tube by a disposable glass Pasteur pipette. The solution was then adjusted by D_2O to make the final volume of 560 µL before recording the ^{1}H NMR spectrum. If the obtained products were non-polar and insoluble in water, they were isolated by extraction with organic solvents (diethyl ether or ethyl acetate) followed by solvent removal prior to the characterization by the ^{1}H NMR analysis (in $CDCl_3$ or DMSO-d_6). For the reactions under acid- or base-catalyzed conditions, CH_3COOH (0.1 mmol, 5.7 µL for 4-bromophenol, and 0.076 mmol, 4.4 µL for *trans*-4-hydroxy-L-proline), trifluoroacetic acid (TFA, 10 µL), or $NaHCO_3$ (0.1 mmol, 8.4 mg for 4-bromophenol, 0.076 mmol, 6.4 mg for *trans*-4-hydroxy-L-proline) was added to the reaction before the heating as shown in **Table 2.1**.

Assuming no other competing reactions, the percent hydrogen-deuterium exchange (%HDx) was calculated from ^{1}H NMR spectrum using equation (1).

$$\%HDx = \frac{mol_{product}}{mol_{product} + mol_{substrate}} \times 100 \qquad (1)$$

Where $mol_{product}$ and $mol_{substrate}$ can be calculated from the peak areas of the signal of interest in the product and substrate, respectively.

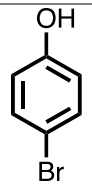
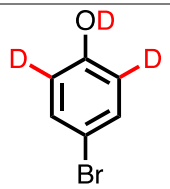
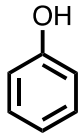
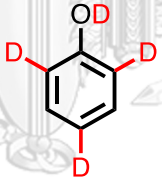
2.2.2 Scaled-up hydrogen-deuterium exchange (HDx) reactions

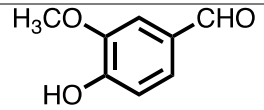
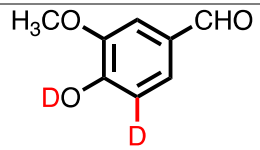
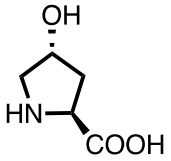
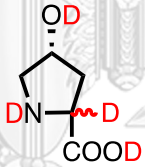
For the scaled-up syntheses, the reactions were performed in a Teflon-lined autoclave (10 mL in total volume). For the syntheses of maltol-d_3, 0.5 mmol (batch 1) and 2 mmol (batch 2) of the substrate, 3125 µL of D_2O, and 62.5 µL of TFA were placed in the reactor and heated at 230 °C for 1 h. After cooling to ambient temperature, the obtained product was extracted with diethyl ether, followed by drying with Na_2SO_4 and solvent removal by rotary evaporation. The crude products from the two batches were combined and purified by column chromatography [EtOAc:hexanes (1:4)] to afford maltol-d_4 (103 mg, 31.6% yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.73-7.70 (m, 1H), 6.42 (dd J = 5.5, 0.8 Hz, 1H), 2.39-2.34 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.1, 154.3, 149.0, 143.3, 113.1, 13.71.; MS (DART): *m/z* calcd for maltol-d_4: 130.0568 $[M]^+$ found: 130.0115, 131.0147.

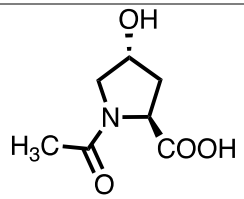
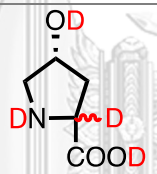
For ethyl maltol, 2 mmol of substrate and 3125 µL of D_2O in the presence of 62.5 µL of TFA were placed in the reactor. After cooling to ambient temperature, the obtained product was extracted with diethyl ether, followed by drying with Na_2SO_4 and solvent removal under vacuum. The crude product was purified by column chromatography [EtOAc:hexanes (1:4)] to afford ethyl maltol-d_3 (92 mg, 32.1% yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.74 (d J =5.5 Hz, 1H), 6.42 (d J = 5.5 Hz, 1H), 2.78-2.72 (m, 2H), 1.25 (t J = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.2, 154.5, 153.1, 142.4, 112.9, 10.8.; MS (DART): *m/z* calcd for ethyl maltol-d_3: 143.0662 $[M]^+$ found: 143.0424, 144.0237.

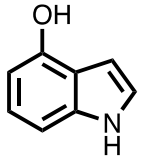
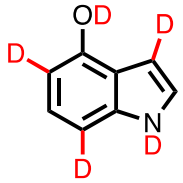
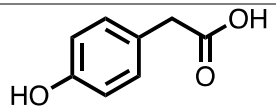
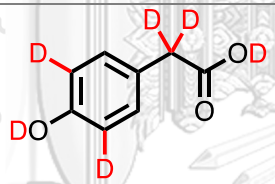
For furaneol, 3 mmol of substrate and 3125 µL of D_2O in the presence of 62.5 µL of TFA were placed in the reactor. After cooling to ambient temperature, the reaction product was transferred to a 15 mL centrifuge tube with water and freeze-dried to obtain the crude product as brown viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.37 (q J = 7.0 Hz, 2H), 1.47 (d J = 7.2 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 179.3, 66.6, 20.2.; MS (DART): *m/z* calcd for furaneol-d_4: 132.0725 $[M]^+$ found: 133.0937, 136.0538

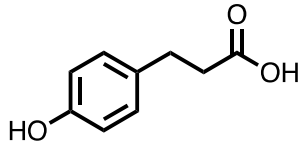
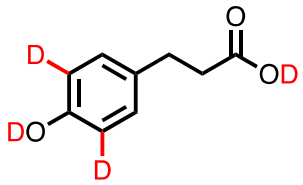
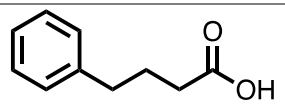
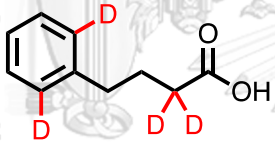
Table 2.1 Characterization of non-deuterated and deuterated compounds of HDx in this work

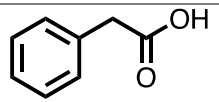
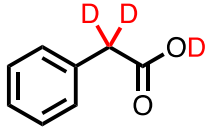
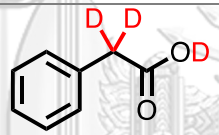
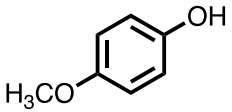
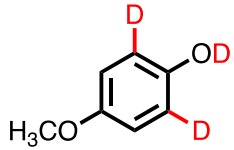
Substrate	Product(s)	Conditions	Residual proton signal
 4-Bromophenol ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.33 (d *J* = 8.9 Hz, 2H), 6.72 (d *J* = 8.9 Hz, 2H)	 4-Bromophenol-d_3 ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.33 (d, 2H), 6.72 (d *J* = 8.9 Hz, 2H)	150 °C, 1 h	H-2 @6.72 ppm (2H)
		200 °C, 1 h	H-2 @6.72 ppm (1.78H)
		250 °C, 1 h	H-2 @6.72 ppm (0.65H)
		250 °C, 2 h	H-2 @6.72 ppm (0.03H)
 Phenol ^{1}H NMR (500 MHz, D_2O) δ (ppm): 7.27 (t *J* = 8.0 Hz, 2H), 6.94 (t *J* = 7.4 Hz, 1H), 6.88 (d *J* = 8.6 Hz, 2H)	 Phenol-d_4 ^{1}H NMR (500 MHz, D_2O) δ (ppm): 7.31-7.26 (m, 2H), 6.95 (t *J* = 7.4 Hz, 1H), 6.88 (d *J* = 8.6 Hz, 2H)	230 °C, 1 h	H-2 @6.88 ppm (0.32H)
		230 °C, 2 h	H-2 @6.88 ppm (0.09H)

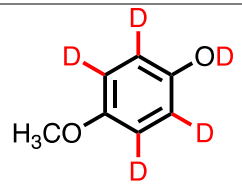
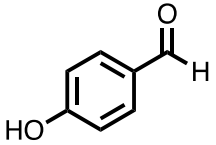
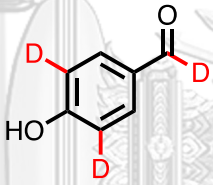
 Vanillin ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.38 (dd J = 8.1, 1.9 Hz, 1H), 7.34 (d J = 1.8 Hz, 1H), 6.92 (d J = 8.1 Hz, 1H)	 Vanillin-d_2 ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.38 (d J = 1.8 Hz, 1H), 7.34 (d J = 1.9 Hz, 1H)	250 °C, 1 h	H-1 @7.38 ppm (1H) H-5 @7.34 ppm (1H)
 *trans*-4-hydroxy-L-proline ^{1}H NMR (500 MHz, D_2O) δ (ppm): 4.45 (s, 1H), 4.13 (s, 1H), 3.27 (d J =	 *cis:trans*-4-hydroxy-L-proline ^{1}H NMR (500 MHz, D_2O) δ (ppm): 4.44 (s, 1H), 4.35 (s, 1H), 3.25 (d J =	150 °C, 1 h	H-2 @4.45 ppm (0.96H)
		200 °C, 1 h	H-2 (*trans*) @4.45 ppm (0.73H) H-2 (*cis*) @4.36 ppm (0.16H)

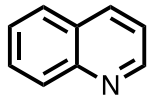
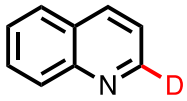
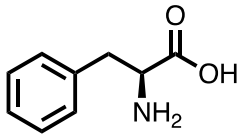
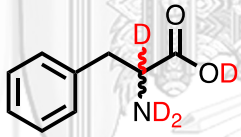
12.6 Hz, 1H), 3.14 (d *J* = 12.6, 1H), 2.22 (s, 1H), 1.94 (s, 1H)	12.6 Hz, 1H), 3.13 (d *J* = 14.9 Hz, 1H), 2.28 (d *J* = 9.6 Hz), 2.20 (d *J* = 14.1 Hz, 1H), 2.02 (d *J* = 14.2 Hz, 1H), 1.92 (d *J* = 18.4 Hz, 1H)	250 °C, 1 h	H-2 (*trans*-) @4.44 ppm (0.60H) H-2 (*cis*-) @4.35 ppm (0.42H)
 *N*-Acetyl-*trans*-4-hydroxy-L-proline ^{1}H NMR (500 MHz, D_2O) δ (ppm): 4.37 (dq *J* = 6.3, 2.1 Hz, 1H), 4.27 (t *J* = 8.5 Hz, 1H), 3.59 (dd *J* = 11.7, 4.1 Hz, 1H), 3.44 (ddt *J* = 21.4, 11.7, 2.0 Hz, 1H), 2.22-2.14 (m, 1H), 1.95 (ddd *J* = 13.6, 9.0, 4.5 Hz, 1H), 1.90 (s, 3H)	 *cis:trans*-4-hydroxy-L-proline ^{1}H NMR (500 MHz, D_2O) δ (ppm): 4.46-4.42 (m, 1H), 4.36 (ddd *J* = 6.1, 4.0, 1.8 Hz, 1H), 3.29-3.21 (m, 2H), 3.18-3.10 (m, 2H), 2.28 (dd *J* = 14.2, 4.5 Hz, 1H), 2.20 (d *J* = 14.1 Hz, 1H), 2.03 (dt *J* = 14.2, 1.9 Hz, 1H), 1.93 (dd *J* = 14.1, 4.3 Hz, 1H), 1.87-1.84 (m, 6H)	230 °C, 1 h	H-2 (*trans*-) @4.44 ppm (0.55H) H-2 (*cis*-) @4.36 ppm (0.40H)

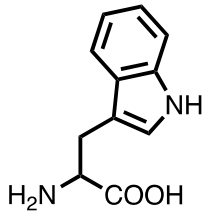
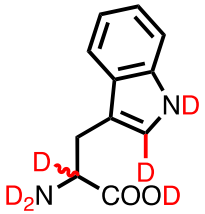
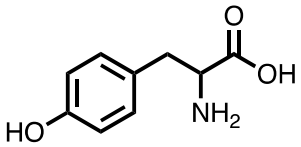
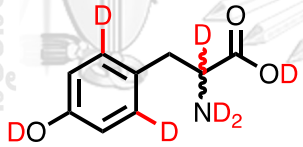
 4-Hydroxyindole ^{1}H NMR (500 MHz, D_2O) δ (ppm): 7.06 (d *J* = 3.2 Hz, 1H), 6.87 (d *J* = 4.7 Hz, 2H), 6.48 (d *J* = 3.2 Hz, 1H), 6.37-6.33 (m, 1H)	 4-Hydroxyindole-d_5 ^{1}H NMR (500 MHz, D_2O) δ (ppm): 7.00 (s, 1H), 6.81 (s, 2H), 6.42 (s, 1H), 6.32-6.28 (m, 1H)	230 °C, 1 h	H-3 @6.29 ppm (0.04H) H-5 @6.42 ppm (0.06H) H-7 @6.87 ppm (1.52H)
 4-Hydroxyphenylacetic acid ^{1}H NMR (500 MHz, D_2O) δ (ppm): 7.16 (d *J* = 8.5 Hz, 1H), 6.85 (d *J* = 8.5 Hz, 1H), 3.61 (s, 1H)	 4-Hydroxyphenylacetic acid-d_6 ^{1}H NMR (500 MHz, D_2O) δ (ppm): 7.14 (s, 1H), 6.83 (d *J* = 8.8 Hz, 1H), 3.58 (d *J* = 9.4 Hz, 1H)	230 °C, 1 h	H-2 @3.58 ppm (0.38H) H-4 @6.83 ppm (0.35H)
		230 °C, 2 h	H-2 @3.58 ppm (0.09H) H-4 @6.84 ppm (0.13H)

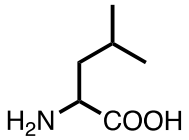
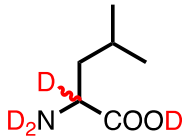
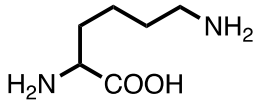
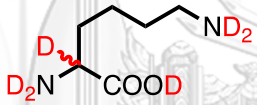
 3-(4-Hydroxyphenyl)propionic acid ^{1}H NMR (500 MHz, D_2O) δ (ppm): 7.14 (d *J* = 8.6 Hz, 1H), 6.82 (d *J* = 8.6 Hz, 1H), 2.83 (t *J* = 7.4 Hz, 1H), 2.62 (t *J* = 7.4 Hz, 1H)	 3-(4-Hydroxyphenyl)propionic acid-*d*$_4$ ^{1}H NMR (500 MHz, D_2O) δ (ppm): 7.12 (t *J* = 3.4 Hz, 1H), 6.80 (d *J* = 8.8 Hz, 1H), 2.80 (t *J* = 7.4 Hz, 1H), 2.60 (t *J* = 7.4 Hz, 1H)	230 °C, 1 h	H-5 @6.80 ppm (0.39H)
		230 °C, 2 h	H-5 @6.81 ppm (0.10H)
 4-Phenylbutyric acid ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.31-7.27 (m, 2H), 7.22-7.17 (m, 3H), 2.70-2.65 (m, 2H), 2.38 (t *J* = 7.5 Hz, 2H), 2.01-1.94 (m, 2H)	 4-Phenylbutyric acid-*d*$_4$ ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.32-7.27 (m, 2H), 7.20 (dd *J* = 12.4, 4.5 Hz, 3H), 2.70-2.65 (m, 2H), 2.38 (t *J* = 7.5 Hz, 2H), 2.01-1.94 (m, 2H)	TFA, 230 °C, 1 h	H-2 @2.38 ppm (1.76H) H-5 @2.81 ppm (2.81H)

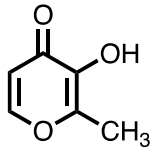
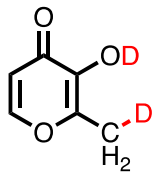
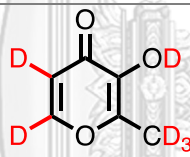
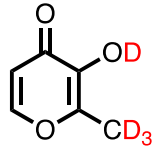
 Phenylacetic acid ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.36-7.27 (m, 5H), 3.65 (s, 2H)	 Phenylacetic acid-d_3 ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.36-7.27 (m, 5H), 3.64 (d *J* = 8.7 Hz, 2H)	230 °C, 1 h	H-2 @3.64 ppm (1.54H)
	 Phenylacetic acid-d_3 ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.37-7.26 (m, 5H), 3.66-3.62 (m, 2H)	TFA, 230 °C, 1 h	H-2 @3.64 ppm (0.32H)
 4-Methoxyphenol ^{1}H NMR (500 MHz, D_2O) δ (ppm): 6.89-6.86 (m, 2H), 6.84-6.81 (m, 2H), 3.74 (s, 3H)	 4-Methoxyphenol-d_3 ^{1}H NMR (500 MHz, D_2O) δ (ppm): 6.88 (d *J* = 8.5 Hz, 2H), 6.85-6.81 (m, 2H), 3.75 (s, 3H)	230 °C, 1 h	H-2 @6.83 ppm (1.35H)
		230 °C, 2 h	H-2 @6.80 ppm (0.73H)

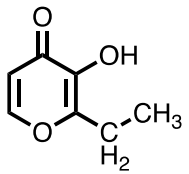
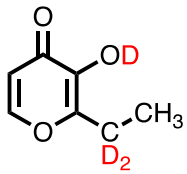
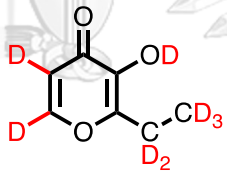
	 4-Methoxyphenol-d_5 ^{1}H NMR (500 MHz, D_2O) δ (ppm): 3.74 (s, 1H)	TFA, 230 °C, 1 h	H-2 @6.87 ppm (not observed) H-3 @6.83 ppm (not observed)
 *p*-Hydroxybenzaldehyde ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 10.61 (s, 1H), 9.79 (s, 1H), 7.78-7.74 (m, 2H), 6.94-6.91 (m, 1H)	 *p*-Hydroxybenzaldehyde-d_3 ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.78 (s, 1H), 7.77-7.74 (m, 2H), 6.93 (d *J* = 9.0 Hz, 2H)	230 °C, 1 h	H-2 @6.93 ppm (0.14H)

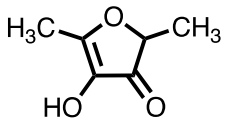
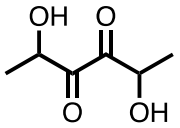
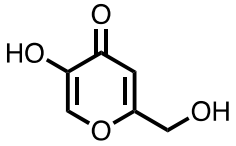
		230 °C, 1 h	H-2 @8.92 ppm (0.44H)
Quinoline ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.91 (dd *J* = 4.2, 1.7 Hz, 1H), 8.17-8.08 (m, 2H), 7.83-7.78 (m, 1H), 7.71 (ddd *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.53 (ddd *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.38 (dd *J* = 8.3, 4.2 Hz, 1H)	Quinoline-*d* ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.92 (dd *J* = 4.2, 1.7 Hz, 1H), 8.15 (dd *J* = 22.9, 4.4 Hz, 1H), 7.83 (dd *J* = 8.2, 0.8 Hz, 1H), 7.73 (ddd *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.56 (ddd *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.43-7.48 (m, 1H)		
		230 °C, 1 h	H-2 @3.82 ppm (0.06H)
Phenylalanine ^{1}H NMR (500 MHz, D_2O) δ (ppm): 7.33-7.16 (m, 5H), 3.87 (ddd *J* = 6.6, 5.1, 1.4 Hz, 1H), 3.16 (dd *J* = 14.2, 4.9 Hz, 1H), 3.00 (dd *J* = 13.8, 7.4 Hz, 1H)	Phenylalanine-d_4 ^{1}H NMR (500 MHz, D_2O) δ (ppm): 7.39-7.16 (m, 5H), 3.88-3.80 (m, 1H), 3.13 (d *J* = 14.4 Hz, 1H), 2.97 (d *J* = 14.5 Hz, 1H)		

 L-tryptophan ^{1}H NMR (500 MHz, D_2O) δ (ppm): 7.61 (d *J* = 7.9 Hz, 1H), 7.41 (d *J* = 8.2 Hz, 1H), 7.26-7.03 (m, 3H), 3.93 (dd *J* = 8.0, 4.9 Hz, 1H), 3.36 (dd *J* = 15.2, 4.8 Hz, 1H), 3.18 (dd *J* = 15.3, 8.1 Hz, 1H)	 L-tryptophan-d_6 ^{1}H NMR (500 MHz, D_2O) δ (ppm): 7.61 (d *J* = 7.5 Hz, 1H), 7.41 (d *J* = 7.8 Hz, 1H), 7.33-7.04 (m, 3H), 3.35 (d *J* = 15.3 Hz, 1H), 3.17 (d *J* = 15.4 Hz, 1H)	230 °C, 1 h	H-2 @3.93 ppm (not observed)
 L-tyrosine ^{1}H NMR (500 MHz, D_2O) δ (ppm): 6.72 (d *J* = 7.2 Hz, 2H), 6.42 (d *J* = 8.1 Hz, 2H), 3.90-3.78 (m, 1H), 2.81 (dd *J* = 14.3, 5.3 Hz, 1H), 2.68 (dd *J* = 14.6, 7.6 Hz, 1H)	 L-tyrosine-d_7 ^{1}H NMR (500 MHz, D_2O) δ (ppm): 6.24 (s, 4H), 2.35 (d *J* = 15.0 Hz, 1H), 2.21 (d *J* = 14.6 Hz, 1H), 1.97 (d *J* = 3.9 Hz, 1H)	230 °C, 1 h	H-2 @3.84 ppm (not observed) H-4 @6.24 ppm (2.84H)

 L-leucine ^{1}H NMR (500 MHz, D_2O) δ (ppm): 3.58 (dd *J* =8.2, 4.3 Hz, 1H), 1.63-1.48 (m, 3H), 0.81 (t *J* = 5.4 Hz, 6H)	 L-leucine-d_4 ^{1}H NMR (500 MHz, D_2O) δ (ppm): 1.64-1.52 (m, 3H), 0.84 (t *J* = 6.1 Hz, 6H)	230 °C, 1 h	H-2 @3.58 ppm (not observed)
 L-lysine ^{1}H NMR (500 MHz, D_2O) δ (ppm): 3.63 (t *J* =6.1 Hz, 1H), 2.95-2.87 (m, 2H), 1.78 (dt *J* = 10.8, 6.8 Hz, 2H), 1.66-1.56 (m, 2H), 1.45-1.26 (m, 2H)	 L-lysine-d_6 ^{1}H NMR (500 MHz, D_2O) δ (ppm): 2.94-2.87 (m, 2H), 1.76 (t *J* = 8.1 Hz, 2H), 1.66-1.55 (m, 2H), 1.44-1.27 (m, 2H)	230 °C, 1 h	H-2 @3.63 ppm (not observed)

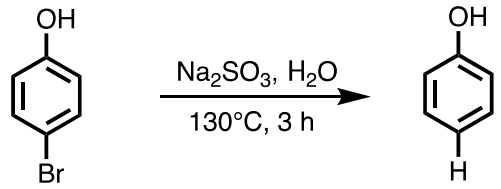
 Maltol ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.71 (d *J* = 5.5 Hz, 1H), 6.42 (d *J* = 5.5 Hz, 1H), 2.36 (s, 3H)	 Maltol-*d*$_4$ ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.73-7.70 (m, 1H), 6.42 (dd *J* = 5.5, 0.8 Hz, 1H), 2.39-2.34 (m, 3H)	230 °C, 1 h	CH_3-2 @2.36 ppm (1.83H)
		CH_3COOH, 230 °C, 1 h	CH_3-2 @2.36 ppm (0.98H)
	 No signal was observed (Maltol-*d*$_6$ or decomposition)	$NaHCO_3$, 230 °C, 1 h	Not observed
	 Maltol-*d*$_4$ ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.71 (d *J* = 5.6 Hz, 1H), 6.42 (d *J* = 5.5 Hz, 1H)	TFA, 230 °C, 1 h	CH_3-2 @2.36 ppm (not observed) H-5 @6.42 ppm (0.88H) H-6 @7.71 ppm (1H)

 Ethyl maltol ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.73 (d *J* = 5.5 Hz, 1H), 6.42 (d *J* = 5.6 Hz, 1H), 2.75 (q *J* = 7.6 Hz, 2H), 1.25 (t *J* = 7.6 Hz, 3H)	 Ethyl maltol-d_3 ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.74 (d *J* =5.5 Hz, 1H), 6.42 (d *J* = 5.5 Hz, 1H), 2.78-2.72 (m, 2H), 1.25 (t *J* = 7.6 Hz, 3H)	230 °C, 1 h	CH_2-2 @2.76 ppm (1.93H)
		TFA, 230 °C, 1 h	CH_2-2 @2.76 ppm (not observed)
	 No signal was observed (Ethyl maltol-d_8 or decomposition)	$NaHCO_3$, 230 °C, 1 h	CH_2-2 @2.75 ppm, CH_3-CH_2-2 @1.25 ppm, H-5 @6.42 ppm, and H-6 @7.73 ppm (not observed)

 Furaneol ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.49 (q *J* = 6.7 Hz, 1H), 2.26 (s, 3H), 1.45 (d *J* = 7.4 Hz, 3H)	 2,5-dihydroxyhexane-3,4-dione ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.37 (q *J* = 7.0 Hz, 2H), 1.47 (d *J* = 7.2 Hz, 6H)	TFA, 230 °C, 1 h	-
 Kojic acid ^{1}H NMR (500 MHz, D_2O) δ (ppm): 8.05 (s, 1H), 6.55 (s, 1H), 4.48 (s, 2H)	No signal was observed (decomposition)	230 °C, 1 h TFA, 230 °C, 1 h $NaHCO_3$, 230 °C, 1 h	Not observed

2.2.3 Procedures for halogen-deuterium exchange (XDx) reactions

2.2.3.1 Debromination of 4-bromophenol with sodium sulfite[36]



The reactions were carried out in the same screw-capped stainless steel reactor described in the HDx reactions. 4-Bromophenol (0.1 mmol, 17.4 mg) and Na_2SO_3 (1.2 mmol, 151.2 mg) were dissolved in 500 µL of H_2O and transferred to the reactor. The reaction was heated at 130 °C for 3 h in the same pre-heated electrical metal melting furnace used for the HDx reactions. After cooling to ambient temperature, the reactor was carefully opened and the obtained products as a H_2O solution were transferred to a microcentrifuge tube (2 mL). The reactor was washed with ethyl acetate (EtOAc) and the aqueous reaction mixture was extracted with EtOAc (2 mL × 3). The combined organics were dried over Na_2SO_4, filtered and the solvent was removed by rotary evaporation. After drying under vacuum, the product was analyzed by ^{1}H NMR.

2.2.3.2 Dehalogenative deuteration of 4-bromophenol with sodium sulfite

The same procedure as in **2.2.3.1** was followed but D_2O was used instead of H_2O. The other steps were the same, except that the reaction temperature was varied from 100-250 °C.

2.2.3.3 General procedure for halogen-hydrogen and halogen-deuterium exchange with formates

All reactions were carried out in the same screw-capped reactor as described above. The substrates (0.1 mmol), 10% Pd/C (10 mg, 1.0 mg Pd content, 0.01 mmol), and additives (0.1 mmol, optional) ($NaHCO_3$, CH_3COONH_4, $HCOONH_4$, HCOONa, DCOONa) were dissolved or suspended in 500 µL of H_2O or D_2O and transferred to the reactor. For the *in situ* preparation of DCOONa, formic acid-d_2 (1 mmol, 38 µL)

and Na_2CO_3 (0.5 mmol, 53.0 mg) were mixed in the reaction medium (D_2O). The reaction was heated at the specified temperature for the specified period of time. The other steps were the same as in **2.2.3.1** with the exception that the mixture was filtered over a syringe filter to remove the insoluble catalyst before the extraction.

Assuming no competing reactions other than halogen-hydrogen exchange (XHx) and halogen-deuterium exchange (XDx), the percent halogen-deuterium exchange (%XDx) was calculated from ^{1}H NMR spectrum using equation (2)

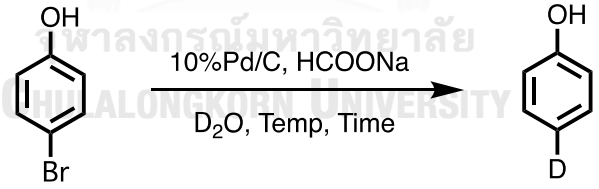
$$\%XDx = \frac{X\text{–}D}{X\text{–}D + X\text{–}H} \times 100 \qquad (2)$$

The conversion percentage of the XDx was calculated from ^{1}H NMR spectrum using equation (3)

$$\%conv. = \frac{X\text{–}D + X\text{–}H}{(X\text{–}D + X\text{–}H) + SM} \times 100 \qquad (3)$$

Where X–H and X–D can be calculated from the relative peak areas of the signal of interest in the product from the XHx and XDx reactions, respectively. SM represented the starting material that was left in the reaction.

2.2.3.4 Optimization of parameters

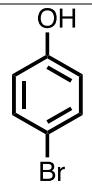
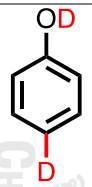
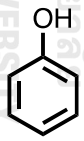


The mixture of 4-bromophenol (0.1 mmol) as a model substrate with 10% Pd/C (variable) and HCOONa (variable amounts) in 500 µL of D_2O were added to the reactor. The reaction was heated at 150 °C for 1 h. The remaining steps were the same as in **2.2.3.3**. The parameters including the quantity of Pd/C, HCOONa, reaction temperature, and reaction time were optimized as summarized in **Table 2.2** and the results are shown in **Table 2.3**.

Table 2.2 Parameters variation for optimization conditions

Parameter variation	10% Pd/C (mmol, mg)	HCOONa (mmol, mg)	Temp (°C)	Time (min)
10% Pd/C	0.0010, 1.0	0.15, 10.2	150	60
	0.0025, 2.0			
	0.0050, 5.0			
	0.0100, 10.0			
HCOONa	0.0025, 2.0	0.05, 3.4	150	60
		0.10, 6.8		
		0.15, 10.2		
		0.20, 11.6		
Temp	0.0025, 2.0	0.10, 6.8	100	60
			150	
			200	
			250	
Time	0.0025, 2.0	0.10, 6.8	150	30
				60
				120
				180

Table 2.3 Optimization of XDx parameters

Substrate	Product(s)	Conditions	Parameters		Key proton signals
		0.15 mmol HCOONa, 150 °C, 1 h	Pd/C (mmol)	0.0010	H-3 (XH+XD) @7.24 ppm (2.01H) H-4 (XH) @6.93 ppm (0.24H) H-2 (XH+XD) @6.83 ppm (2.00H)
				0.0025	H-3 (XH+XD) @7.24 ppm (2.09H) H-4 (XH) @6.93 ppm (0.16H) H-2 (XH+XD) @6.83 ppm (2.00H)
				0.0050	H-3 (XH+XD) @7.24 ppm (2.17H) H-4 (XH) @6.93 ppm (0.18H) H-2 (XH+XD) @6.84 ppm (2.00H)
				0.0100	H-3 (SM) @7.32 ppm (0.08H) H-3 (XH+XD) @7.24 ppm (2.45H) H-4 (XH) @6.92 ppm (0.21H) H-2 (XH+XD) @6.84 ppm (2.00H) H-2 (SM) @6.73 ppm (0.08H)
4-Bromophenol ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.33 (d *J* = 8.9 Hz, 2H), 6.72 (d *J* = 8.9 Hz, 2H)	Phenol-d_2 ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.24 (dd *J* = 7.6, 0.9 Hz, 2H), 6.93 (t *J* = 7.4 Hz, 1H), 6.83 (d *J* = 8.6 Hz, 2H)	0.0025 mmol Pd/C 150 °C, 1 h	HCOONa (mmol)	0.05	H-3 (SM) @7.33 ppm (4.95H) H-3 (XH+XD) @7.25 ppm (1.80H) H-4 (XH) @6.93 ppm (0.19H)
	 Phenol ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.26-7.22 (m, 2H), 6.93 (t *J* = 7.3 Hz, 1H), 6.84 (dd *J* = 8.7, 1.3 Hz,				

	2H)			H-2 (XH+XD) @6.84 ppm (2.00H) H-2 (SM) @6.72 ppm (4.93H)
			0.10	H-3 (SM) @7.33 ppm (0.03H) H-3 (XH+XD) @7.24 ppm (2.01H) H-4 (XH) @6.93 ppm (0.15H) H-2 (XH+XD) @6.84 ppm (2.00H) H-2 (SM) @6.72 ppm (0.05H)
			0.15	H-3 (XH+XD) @7.24 ppm (2.09H) H-4 (XH) @6.93 ppm (0.16H) H-2 (XH+XD) @6.83 ppm (2.00H)
			0.20	H-3 @7.24 ppm (2.48H) H-4 @6.93 ppm (0.17H) H-2 @6.84 ppm (2.00H)
		0.0025 mmol Pd/C, 0.05 mmol HCOONa, 1 h	Temp (°C) 100	H-3 (SM) @7.33 ppm (2.00H) H-3 (XH+XD) @7.25 ppm (0.29H) H-4 (XH) @6.93 ppm (0.03H) H-2 (XH+XD) @6.84 ppm (0.33H) H-2 (SM) @6.72 ppm (2.04H)
			150	H-3 (SM) @7.33 ppm (0.03H)

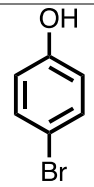
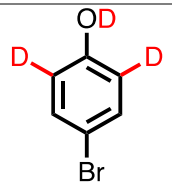
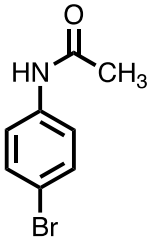
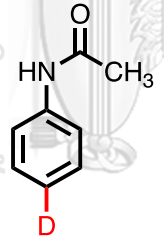
			H-3 (XH+XD) @7.24 ppm (2.01H) H-4 (XH) @6.93 ppm (0.15H) H-2 (XH+XD) @6.84 ppm (2.00H) H-2 (SM) @6.72 ppm (0.05H)
		200	H-3 (XH+XD) @7.25 ppm (4.42H) H-4 (XH) @6.93 ppm (0.25H) H-2 (XH+XD) @6.84 ppm (2.00H)
		250	H-3 (XH+XD) @7.25 ppm (48.12H) H-4 (XH) @6.93 ppm (0.95H) H-2 (XH+XD) @6.84 ppm (2.00H)
	0.0025 mmol Pd/C, 0.05 mmol HCOONa, 150 °C	Time (min) 30	H-3 (SM) @7.33 ppm (2.00H) H-3 (XH+XD) @7.25 ppm (1.04H) H-4 (XH) @6.93 ppm (0.11H) H-2 (XH+XD) @6.84 ppm (1.06H) H-2 (SM) @6.72 ppm (2.05H)
		60	H-3 (SM) @7.33 ppm (0.03H) H-3 (XH+XD) @7.25 ppm (2.01H) H-4 (XH) @6.93 ppm (0.15H)

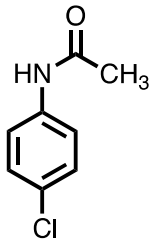
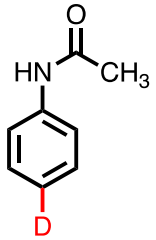
		H-2 (XH+XD) @6.84 ppm (2.00H)
		H-2 (SM) @6.72 ppm (0.05H)
	120	H-3 (XH+XD) @7.25 ppm (2.44H)
		H-4 (XH) @6.93 ppm (0.18H)
		H-2 (XH+XD) @6.84 ppm (2.00H)
	180	H-3 (XH+XD) @7.24 ppm (2.39H)
		H-4 (XH) @6.92 ppm (0.17H)
		H-2 (XH+XD) @6.84 ppm (2.00H)

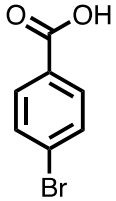
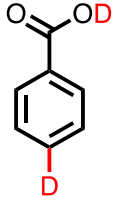
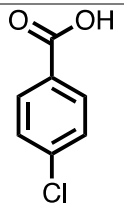
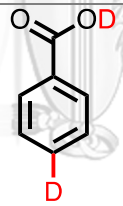
2.2.3.5 Evaluation of substrate scope for the XDx reactions

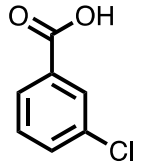
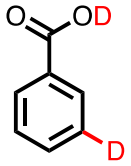
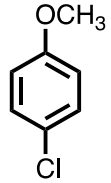
The optimal conditions obtained from **2.2.3.4** i.e. 0.1 mmol of the substrate, 2.0 mg (0.0025 mmol) of 10% Pd/C, and 6.8 mg (0.15 mmol) of HCOONa at 150 °C for 1 h were further applied to additional substrates including halogenated aromatic compounds with various functional groups and characterized as shown in **Table 2.4**.

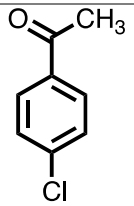
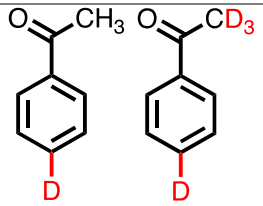
Table 2.4 Characterization of deuterated compounds of XDx using optimized conditions in this work

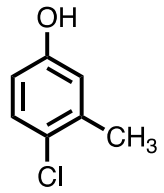
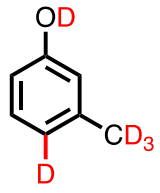
Substrate	Product(s)	Conditions	Key proton signals
		Optimized condition (0.1 mmol $Na_2C_2O_4$ was used instead of HCOONa)	H-2 (oHD) @6.72 ppm (1.78H) H-2 (SM) @7.33 ppm (2H)
4-Bromophenol ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.33 (d *J* = 8.9 Hz, 2H), 6.72 (d *J* = 8.9 Hz, 2H)	4-Bromophenol-d_3 ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.33 (d *J* = 8.9 Hz, 2H), 6.72 (d *J* = 8.9 Hz, 2H)		
		Optimized condition	H-2 (XH+XD) @7.55 ppm (3.04H) H-2 (SM) @7.46 ppm (0.73H) H-3 (XH+XD) @7.27 ppm (2.00H) H-4 (XH) @7.01 ppm (0.56H)
4-Bromoacetanilide ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.55 (d *J* = 8.9 Hz, 2H), 7.46 (d *J* = 8.9 Hz, 2H), 2.04 (s, 3H)	Acetanilide-*d* ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.55 (t *J* = 8.1 Hz, 2H), 7.46 (d *J* = 8.9 Hz, 2H), 7.30-7.35 (m, 2H), 7.01 (t *J* = 7.4 Hz, 1H), 2.03 (d *J* = 1.6 Hz, 3H)		

 4-Chloroacetanilide ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.60 (d J = 8.9 Hz, 2H), 7.33 (d J = 8.9 Hz, 2H), 2.04 (s, 3H)	 Acetanilide-*d* ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.60 (dd J = 8.8, 1.6 Hz, 2H), 7.56 (dd J = 8.4, 1.6 Hz, 2H), 7.33 (d J = 8.8 Hz, 2H), 7.30-7.25 (m, 2H), 7.01 (t J = 7.4 Hz, 1H), 2.04-2.02 (m, 3H)	Optimized condition	H-2 (SM) @7.60 ppm (0.31H) H-2 (XH+XD) @7.56 ppm (2.00H) H-3 (SM) @7.33 ppm (0.29H) H-3 (XH+XD) @7.28 ppm (1.95H) H-4 (XH) @7.01 ppm (0.51H)

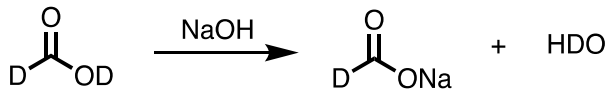
 4-Bromobenzoic acid ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.86 (d J = 8.6 Hz, 2H), 7.71 (d J = 8.6 Hz, 2H)	 Benzoic acid-d_2 ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.95 (d J = 8.2 Hz, 2H), 7.86 (d J = 8.5 Hz, 2H), 7.71 (d J = 8.6 Hz, 2H), 7.62 (t J = 7.4 Hz, 1H), 7.52-7.48 (m, 2H)	Optimized condition	H-2 (XH+XD) @7.95 ppm (2.70H) H-2 (SM) @7.86 ppm (2.75H) H-3 (SM) @7.71 ppm (2.70H) H-4 (XH) @7.62 ppm (0.30H) H-3 (XH+XD) @7.50 ppm (1.89H)
 4-Chlorobenzoic acid ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.94 (d J = 8.6 Hz, 2H), 7.56 (d J = 8.6 Hz, 2H)	 Benzoic acid-d_2 ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.96-7.92 (m, 2H), 7.62 (t J = 7.5 Hz, 1H), 7.57 (d J = 8.6 Hz, 2H), 7.50 (d J = 8.2 Hz, 2H)	Optimized condition	H-2 (XH+XD, SM) @7.94 ppm (2.97H) H-4 (XH) @7.62 ppm (0.10H) H-3 (SM) @7.57 ppm (2.00H) H-3 (XH+XD) @7.50 ppm (0.94H)

 3-Chlorobenzoic acid ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.87-7.83 (m, 2H), 7.66 (ddd *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.50 (t *J* = 8.1 Hz, 1H)	 3-Chlorobenzoic acid-d_2 ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.92-7.88 (m, 2H), 7.86-7.83 (m, 2H), 7.65 ppm (ddd *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.58 (d *J* = 7.4 Hz, 1H), 7.50 (d *J* = 8.1 Hz, 1H), 7.46 (dd *J* = 13.8, 5.7 Hz, 1H)	Optimized condition (0.15 mmol HCOONa was used)	H-2 (XH+XD) @7.90 ppm (2.00H) H-2 (SM) @7.85 ppm (0.40H) H-4 (SM) @7.65 ppm (0.20H) H-4 (XH+XD) @7.58 ppm (0.95H) H-3 (SM) @7.50 ppm (0.15H) H-3 (XH+XD, XH) @7.46 ppm (1.22H)
 4-Chloroanisole ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.24 (d *J* = 9.1 Hz, 2H), 6.83 (d *J* = 9.0 Hz, 2H), 3.79 (s, 3H)	Unidentifiable products	Optimized condition	H-3 (XH+XD) @7.48 ppm (2.00H) H-4 (SM) @7.24 ppm (0.14H) H-2 (XH+XD) @6.96 ppm (2.46H) H-3 (SM) @6.83 ppm (0.19H)

		Optimized condition	H-3 (SM) @8.06 ppm (0.30H)
			H-2 (XH+XD) @7.96 ppm (2.00H)
			H-3 (XH+XD of CD_3) @7.90 ppm (0.73H)
			H-2 (SM) @7.73 ppm (0.27H)
			H-4 (XH) @7.57 ppm (0.27H)
			H-3 (XH+XD) @7.47 ppm (1.77H)
			H-3 (XH+XD of CD_3) @7.44 ppm (0.71H)
4-Chloroacetophenone	Acetophenone-*d* and		
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.87 (d *J* = 8.7 Hz, 2H), 7.41 (d *J* = 8.7 Hz, 2H), 2.56 (s, 3H)	Acetophenone-d_4 ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.06 (d *J* = 8.5 Hz, H), 7.96 (d *J* = 8.3 Hz, 2H), 7.90 (d *J* = 8.6 Hz,), 7.73 (d *J* = 8.6 Hz,), 7.57 (t *J* = 7.4, 1H), 7.47 (d *J* = 8.3 Hz, 2H), 7.44 (d *J* = 8.7 Hz,)		

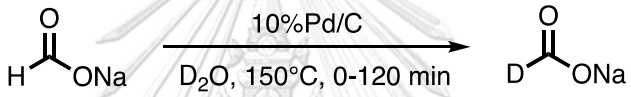
 *p*-Chlorocresol ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.17 (d *J* = 8.6 Hz, 1H), 6.71 (d *J* = 2.9 Hz, 1H), 6.61 (dd *J* = 8.6, 2.9 Hz, 1H), 2.31 (s, 3H)	 *p*-Chlorocresol-d_5 ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.17 (d *J* = 8.6 Hz, 1H), 7.13 (dt *J* = 7.7, 3.7 Hz, 1H), 6.75 (d *J* = 7.4 Hz, 1H), 6.72 (d *J* = 3.2 Hz, 1H), 6.66 (d *J* = 4.3 Hz, 1H), 6.64-6.59 (m, 1H), 2.31 (d *J* = 2.9 Hz, 3H)	Optimized condition	H-3 (SM) @7.17 ppm (1.13H) H-3 (XH+XD) @7.13 ppm (1.00H) H-4 (XH) @6.75 ppm (0.39H) H-6 (SM) @6.72 ppm (1.10H) H-2 (XH+XD) @6.66 ppm (1.57H) H-2 (SM) @6.62 ppm (1.55H)

2.2.3.6 Synthesis of sodium deuteroformate (DCOONa)



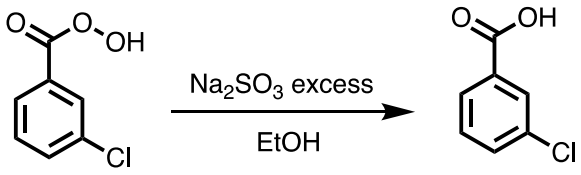
A mixture of formic acid-d_2 (3 mmol, 144.0 mg, 114 µL) and NaOH (3 mmol, 120.0 mg) was stirred overnight at room temperature. The water was removed by rotary evaporation. After drying under vacuum, the product was obtained as a white solid (149.1 mg, 100 %yield).

2.2.3.7 Sodium formate deuteration experiment



Sodium formate (0.3 mmol, 20.4 mg), sodium acetate (0.2 mmol, 16.4 mg) (as a reference compound), and 10% Pd/C (0.1 mmol, 10.0 mg) in 500 µL of D_2O were added to the reactor. The reaction was heated at 150 °C for 15, 30, 60, and 120 min. After cooling to ambient temperature, the reactor was carefully opened and the obtained products were transferred to the NMR tube. The final volume of solution was then adjusted by D_2O to 560 µL and the product was characterized by ^{1}H NMR and ^{13}C NMR spectroscopy.

2.2.3.8 Synthesis of 3-chlorobenzoic acid



A mixture of 3-chloroperoxybenzoic acid (0.5 mmol, 86.0 mg) and excess Na_2SO_3 (174.0 mg) was dissolved in EtOH (1 mL). The reaction mixture was stirred

overnight at room temperature. The solvent was removed by a gentle stream of nitrogen. Next, 2 N HCl (2 mL) and water (1 mL) were added to the residue. The solution was then extracted with EtOAc (5 mL × 3). The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent was removed by rotary evaporation. After drying, the product was obtained as a white solid (66.6 mg, 85 %yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.87-7.83 (m, 2H), 7.66 (ddd J = 8.0, 2.2, 1.1 Hz, 1H), 7.50 (t J = 8.1 Hz, 1H). The absence of the peroxide functional group was also confirmed by potassium iodide (KI), sulfuric acid (H_2SO_4), and starch which revealed colorless solution.

CHAPTER III

RESULTS AND DISCUSSION

3.1 Hydrogen-Deuterium Exchange (HDx) Reactions

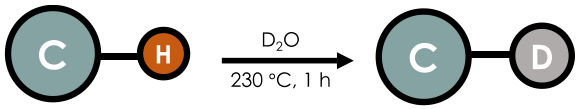


Figure 3.1 HDx of organic compounds

We proposed that the hydrogen-deuterium exchange reaction (HDx) could take place under hydrothermal conditions, which involves heating the substrate in D_2O at a high temperature and pressure in a closed system. Under such conditions, the water (or D_2O in this case) became more acidic and less polar. This makes it possible to dissolve organic compounds that are normally insoluble in water.[7] In this work, various substrates were examined to find suitable CH moieties that can undergo efficient HDx under hydrothermal conditions. Two potential candidates are the α-CH protons of amino acids and *ortho/para*-CH protons of aromatic rings.

3.1.1 Optimization of temperature

In a preliminary experiment to validate the concept, we initially used 4-bromophenol as a representative aromatic substrate and *trans*-4-hydroxy-L-proline as a representative amino acid substrate. The HDx of both compounds was performed in superheated D_2O without any added catalysts. The reaction temperature range of 150-250 °C was investigated with the same 1 h heating period. For 4-bromophenol, the HDx occurred exclusively at the *ortho*- position as confirmed by the disappearance of the *ortho*-proton signal at 6.72 ppm and the collapse of the *meta*-proton signal at 7.33 ppm into a broad singlet peak due to the loss of coupling with the adjacent *ortho*-protons (**Figure 3.2**). The %HDx could be estimated based on the ratio of the *meta*-protons from the starting material and the *ortho*-protons of the starting material and product. The results showed that at higher temperatures, the HDx became more efficient, but the reaction was not yet complete after heating at

250 °C for 1 h (67% exchange yield). With an extended reaction time from 1 to 2 h at the same temperature, the %HDx was increased to more than 97% indicating practically complete labeling.

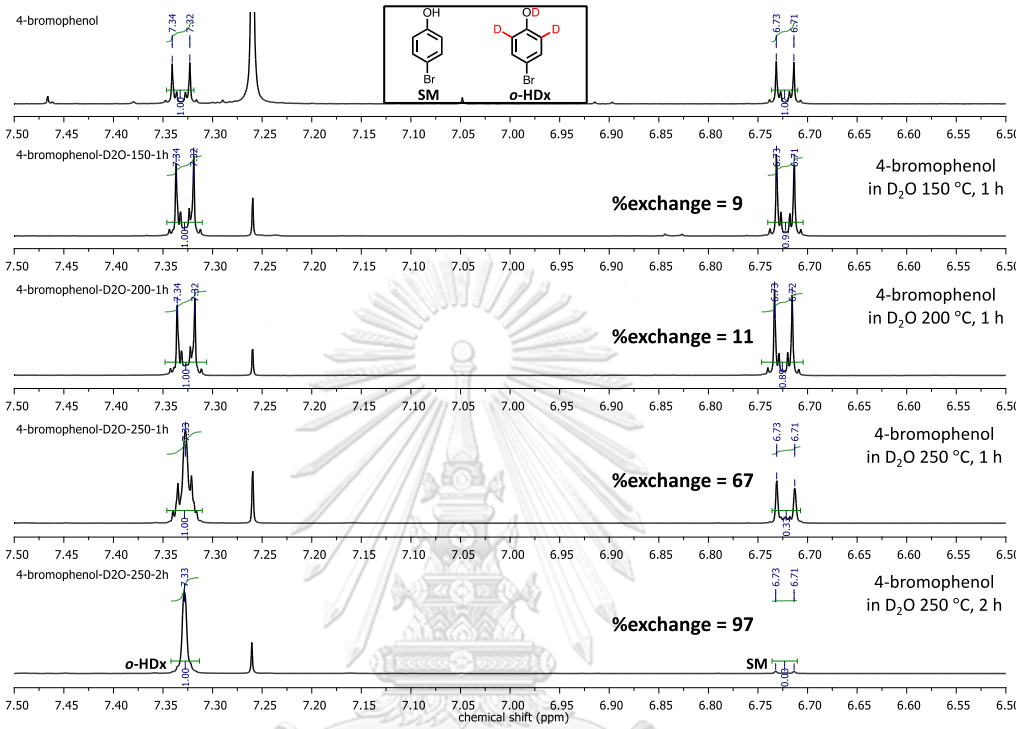


Figure 3.2 ^{1}H NMR spectra of the HDx reaction of 4-bromophenol at different temperatures

In the case of *trans*-4-hydroxy-L-proline (THLP), the deuteration was observed at 200 °C and it occurred exclusively at the α-position as shown by the decrease in the intensity of the α-CH signal at 4.45 ppm (**Figure 3.3**). For this substrate, the HDx was accompanied by epimerization as shown by the presence of two sets of signals, one corresponded to the *trans*-4-hydroxy-L-proline without the α-CH, which showed a somewhat simplified signal due to the absence of coupling with the α-proton. Another set of signals with a similar pattern, but slightly different chemical shifts were also observed. This was confirmed, by comparison with the authentic sample, to be the *cis*-4-hydroxy-D-proline (CHDP) which was the product of epimerization of *trans*-4-hydroxy-L-proline at the α-position. The ratio of *cis:trans* isomer increased with temperature and the value of 41:59 was obtained at 250 °C. No further change

was observed upon heating beyond this temperature or time suggesting that the epimerization reached its equilibrium, which was in agreement with the complete disappearance of the α-CH signal.

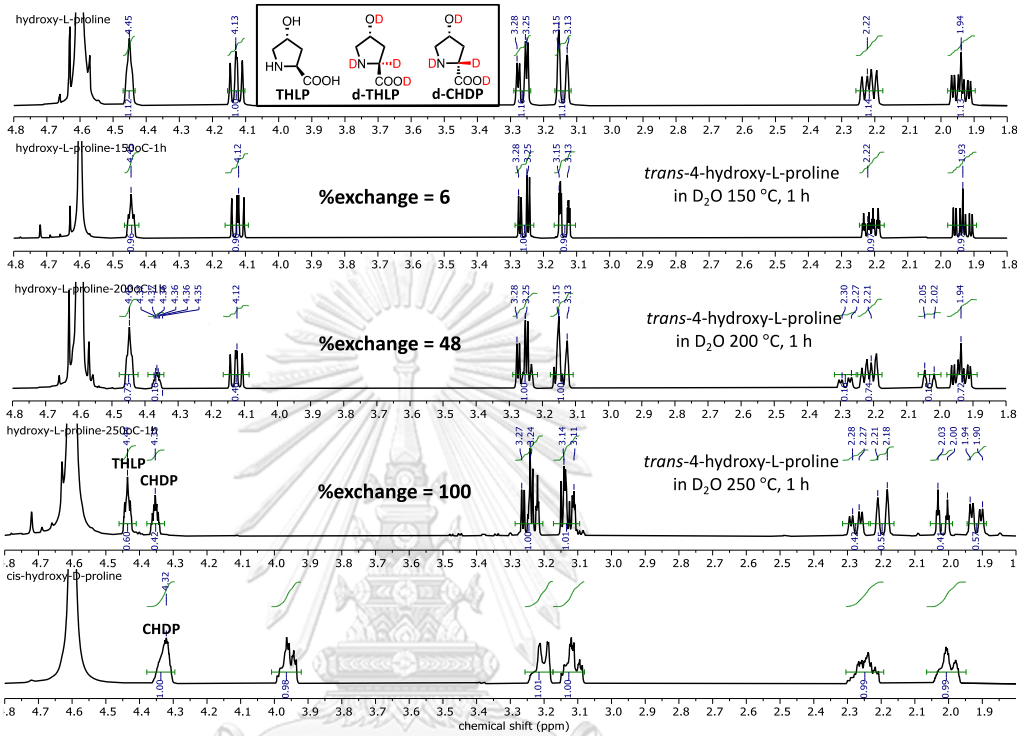


Figure 3.3 ^{1}H NMR spectra of the HDx reaction of *trans*-4-hydroxy-L-proline at different temperatures

3.1.2 Effect of pH on HDx

Next, the pH effects on the HDx of 4-bromophenol and *trans*-4-hydroxy-L-proline were evaluated (**Figure 3.4**). Acetic acid (CH_3COOH) and sodium bicarbonate ($NaHCO_3$) (1 equiv. each) were added as model acid and base catalyst, respectively. The reaction was performed at 230 °C for 1 h. The results indicated that the base could promote the HDx in both cases, probably by accelerating the deprotonation of the substrates. 4-Bromophenol underwent efficient HDx (98% exchange) at the *ortho*-position and *trans*-4-hydroxy-L-proline was also completely deuterated at α-position (97% exchange, *cis:trans* = 50:50). In contrast, 4-bromophenol gave smaller HDx (56% exchange) under acidic conditions while *trans*-4-hydroxy-L-proline underwent HDx (100% exchange, *cis:trans* = 42:58) at a similar extent to the basic conditions.

Furthermore, *trans*-4-hydroxy-L-proline underwent cleaner HDx under acidic conditions than basic conditions as confirmed by ^{1}H NMR spectra.

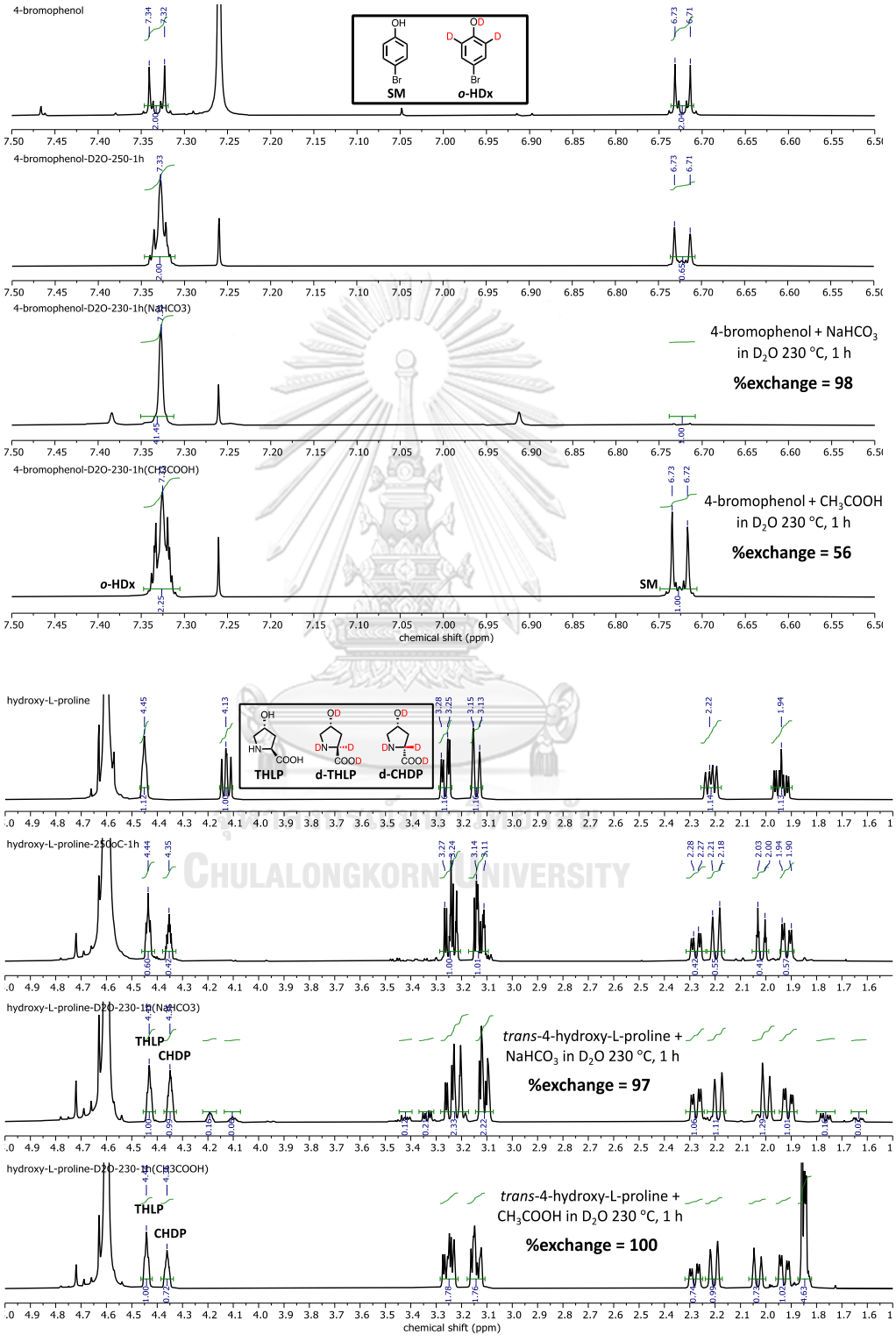


Figure 3.4 The pH effect of the HDx of 4-bromophenol and *trans*-4-hydroxy-L-proline

3.1.3 HDx of other substrates

Encouraged by the above results that the HDx could occur for both *ortho*-aromatic protons and α-protons of amino acids at a temperature in the range of 200 to 250 °C, additional substrates were further studied. An example includes vanillin, in which the deuterated derivative would be useful as a standard for the quantitation of vanillin by LC-MS.[42] The ^{1}H NMR spectra of vanillin before and after heating with D_2O for 1 hour at 230 °C are shown (**Figure 3.5**). This temperature was chosen based on practical consideration since this is the highest temperature that is still safe for a Teflon-lined reactor typically used for the scaled-up synthesis. The NMR spectra indicated a complete HDx (~100%) exclusively at the proton *ortho*- to the phenolic -OH group as shown by the complete disappearance of the proton signal at 6.92 ppm (d *J* = 8.1 Hz, 1H). In addition, the *ortho*-coupling with this proton (*J* = 8.1 Hz) was lost in the HDx product, while the *meta*-coupling (*J* = 1.8 Hz) between the other two protons was still present. Other signals remained the same indicating the compatibility of the present hydrothermal HDx with substrates carrying complex functional groups (in this case: ether, aldehyde, and phenol). Although decarbonylation had been previously reported to occur readily in the presence of Pd/C as a catalyst under hydrothermal conditions,[30] no such decarbonylation product was observed under the present conditions probably due to the lower reaction temperature and/or reaction time in the present work (230 °C for 1 h compared to 250 °C for 4-14 h in the previous work).

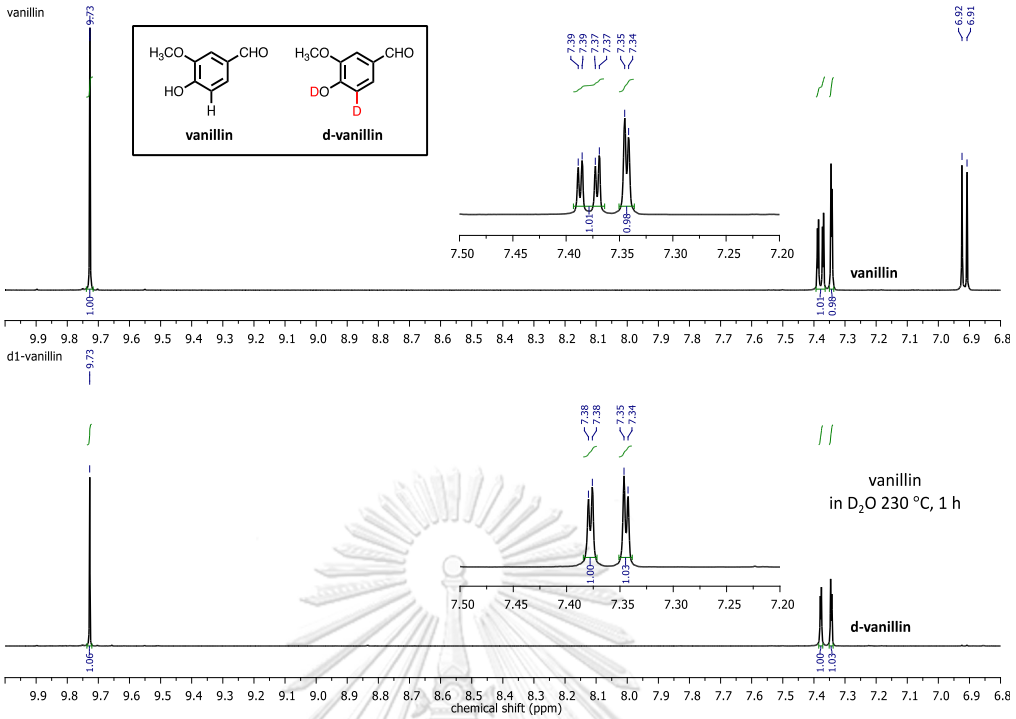


Figure 3.5 ^{1}H NMR spectra of vanillin before and after hydrothermal HDx

The hydrothermal HDx was further applied to additional substrates including aliphatic, alicyclic, aromatic, and heterocyclic compounds (mostly amino acid and simple aromatic compounds). The results are summarized in **Figure 3.12**.

The HDx of L-tryptophan and L-tyrosine also occurred efficiently in D_2O at 230 °C. In addition to the complete HDx at the α-positions, the HDx also occurred quantitatively at the indole C_2H of L-tryptophan and the phenolic *ortho*-CHs of L-tyrosine. The HDx of other amino acids including L-leucine and L-lysine occurred exclusively at the α-position. In all α-amino acids, the α-HDx presumably occurred with complete racemization, but this would not be observable by NMR as in the case of hydroxyproline since the racemized product would have an identical ^{1}H NMR spectrum to that of the starting compound. *N*-acetyl-*trans*-4-hydroxy-L-proline underwent a clean HDx with concomitant hydrolysis to form acetic acid as a byproduct. For L-aspartic acid, all signals disappeared which indicated that complete HDx might occur. This further suggested that the α-CH_2 linked to the carboxyl group might be susceptible to the HDx reaction. However, when a simple cyclic ester γ-decalactone was tested, the CH_2 adjacent to the ester group was found to be inert.

Therefore, the generality of HDx for a methylene group adjacent to only one electron-withdrawing group should be investigated further.

For aromatic compounds, in contrast to 4-bromophenol and vanillin which underwent almost quantitative HDx, no reaction was observed with anisole and benzoic acid. This suggests that only phenolic protons are effectively exchanged under this condition. For unsubstituted phenol, the results showed that the HDx occurred faster at the *ortho*- than the *para*-positions. The extent of HDx for the *ortho*-H was 68% and 91%, and for the *para*-H was 44% and 72% following heating with D_2O at 230 °C for 1 and 2 h, respectively. The mechanism of the HDx in phenols may involve keto-enol tautomerism between phenols and cyclohexadienones (**Figure 3.6**).

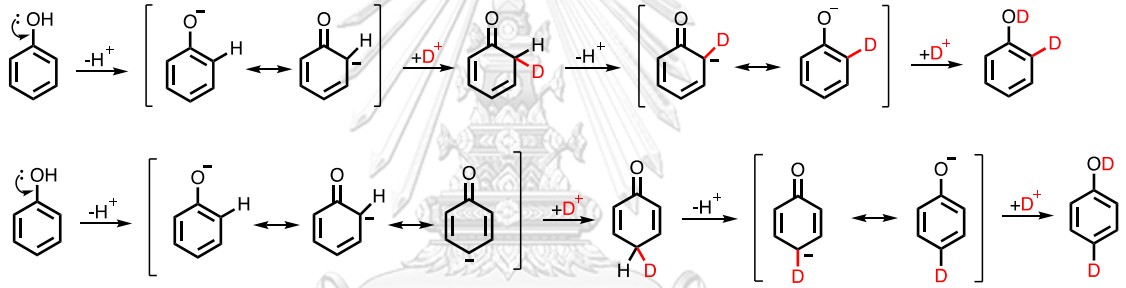


Figure 3.6 Proposed mechanism of the HDx of phenol via keto-enol tautomerism

The HDx of 4-hydroxyindole occurred at multiple positions. According to the reactivity pattern of phenol above, together with the susceptibility of indole C3 position to the electrophilic aromatic substitution, it was proposed that the CHs at the 3, 5, and 7 selectively underwent the HDx. This was further confirmed by ^{1}H NMR spectra which were assigned following Sun et al. report in 2007.[43]

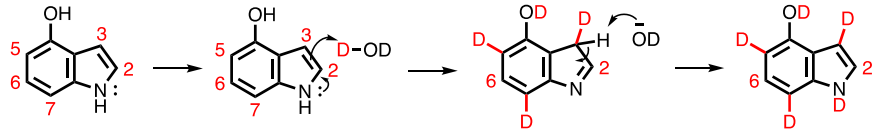


Figure 3.7 Proposed mechanism of the HDx of 4-hydroxyindole via keto-enol tautomerism and electrophilic aromatic substitution[9]

Electrophilic substitution of indole typically occurs at the C3 position rather than C2. This is because the attack at C3 does not disrupt the aromaticity of the benzene ring in the cationic intermediate.[44, 45]

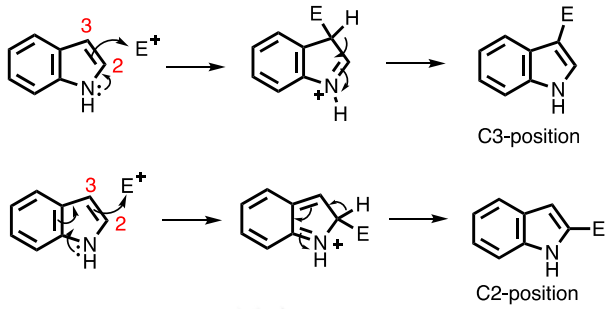


Figure 3.8 Electrophilic aromatic substitution of the indole ring at 2- and 3-positions.

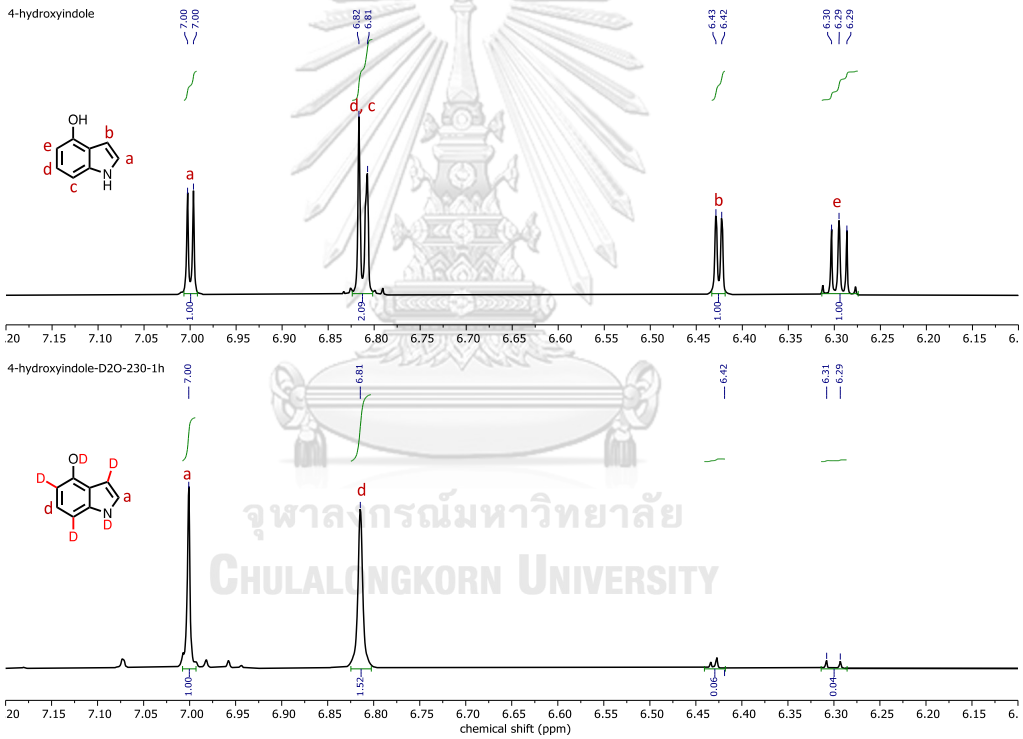


Figure 3.9 ^{1}H NMR spectra of 4-hydroxyindole before and after hydrothermal HDx

p-Hydroxybenzaldehyde also underwent a clean HDx at the *ortho*-position of the phenolic OH group. The HDx of 4-methoxyphenol in pure D_2O at 230 °C occurred exclusively at the phenolic *ortho*-position (1 h, 32% exchange). However, at the same temperature with an extended reaction time from 1 to 2 h, the %HDx was increased to 63%. Interestingly, when TFA (~2% v/v) was added, complete HDx at the *ortho*-

positions to both the phenolic and the methoxy groups while the methoxy CH_3 protons remained unexchanged. The acid could thus promote the exchange of the protons at the *ortho*-positions of both the phenolic and the methoxy group on the aromatic ring. In the presence of a base, the HDx selectively occurred at the *ortho*-position of the phenolic OH group. Importantly, the exchange occurred at a much faster rate compared to D_2O alone (**Figure 3.10**). The results suggest that the reactivity pattern can be fine-tuned by the appropriate choice of catalyst (acid, base, or no catalyst).

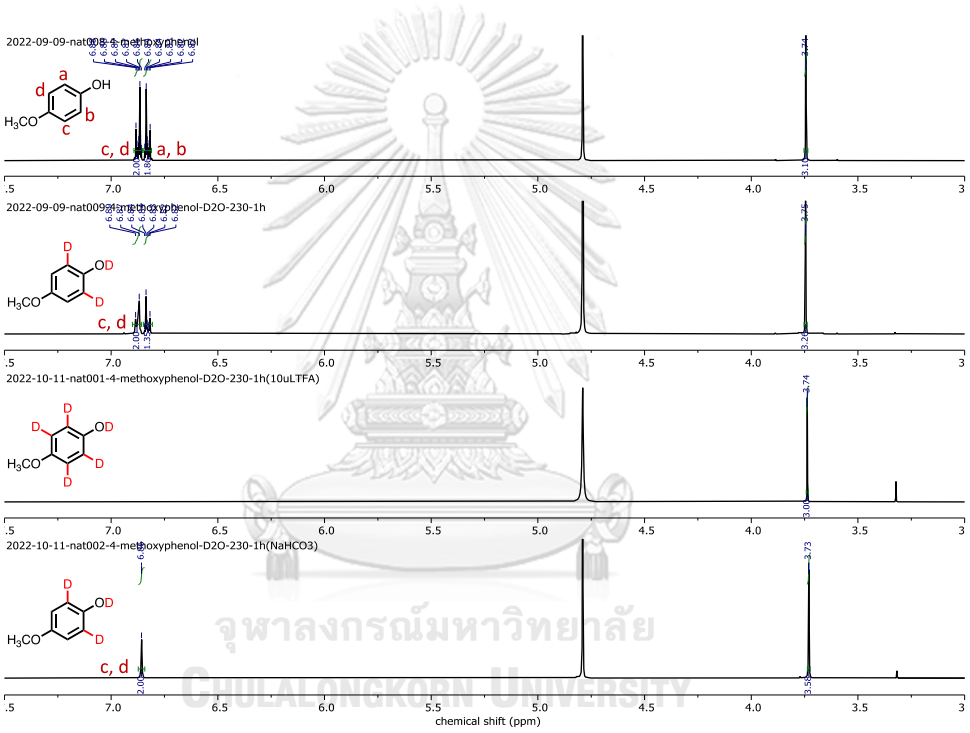


Figure 3.10 ^{1}H NMR spectra of 4-methoxyphenol in D_2O, acidic, and basic condition.

Phenylacetic acid was not a good substrate for HDx, with only 23% deuteration at the α-CH_2 group achieved under the standard conditions. However, in the presence of TFA as a catalyst, the %HDx increased to 84%. No HDx was observed at the aromatic ring which carried no electron-donating groups. Not unexpectedly, the HDx of 4-hydroxyphenylacetic acid occurred primarily at the *ortho*-position of the phenolic OH group and only little at the α-CH_2 in the absence of the acid catalyst. The HDx of 3-(4-hydroxyphenyl)propionic acid under non-catalyzed conditions selectively occurred at the phenolic *ortho*-position with very little reaction at the α-

CH_2. The results confirmed the low reactivity of the CH_2 adjacent to only one carboxylic group towards the HDx under non-catalyzed conditions.

When heterocyclic amines including pyridine, 4-picoline and quinoline were subjected to the standard HDx conditions, the HDx was observed only at the α-CH of quinoline. For pyridine and 4-picoline, the signal completely disappeared which might suggest decomposition rather than complete HDx which was considered unlikely based on the reactivity pattern of pyridine ring system.

Other compounds including L-asparagine, L-glutamic acid, L-theronine, salicylic acid, α-methylbenzylamine, and butyronitrile when subjected to the same hydrothermal HDx condition yielded complex mixtures possibly due to different rates of HDx at different positions or decomposition of the substrates/products. In the case of salicylic acid, the *para*-proton exchange as well as partial decarboxylation might also occur in addition to the expected *ortho*-HDx.[46] In the case of L-glutamic acid, ^{1}H NMR spectra indicated that a new product was formed, while the α-CH still remained. At first, it was proposed that the glutamic acid might cyclize to form pyroglutamic acid. However, the chemical shifts of the proton signals of the reaction product were quite different from the authentic sample of pyroglutamic acid. The product was tentatively assigned as 5-oxotetrahydrofuran-2-carboxylic acid or its lactone cyclization product.[47] Although further confirmation is required, it is clear that no HDx occurred at α-CH of glutamic acid under hydrothermal conditions.

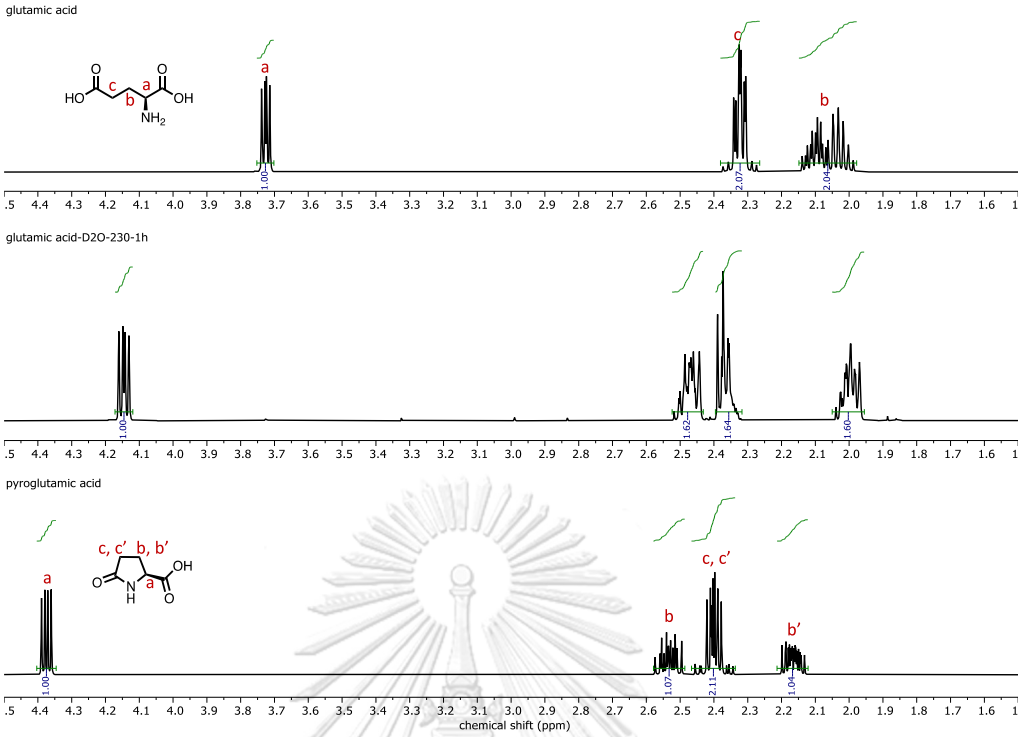
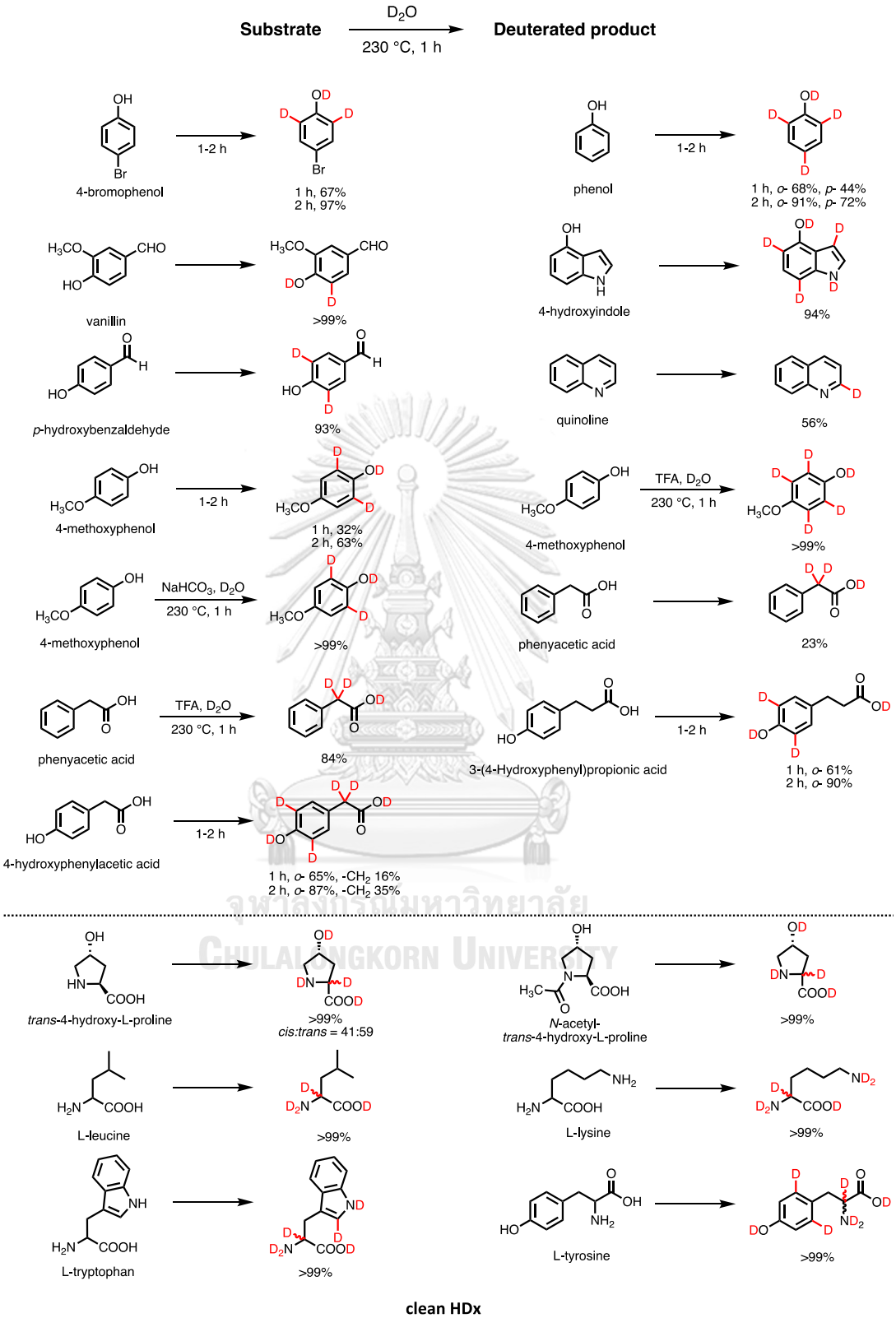


Figure 3.11 ^{1}H NMR spectra of glutamic acid before and after hydrothermal HDx


Substrate
D2O
230 °C, 1 h
Deuterated product
4-bromophenol
1-2 h
1 h, 67%
2 h, 97%
phenol
1 h, o- 68%, p- 44%
2 h, o- 91%, p- 72%
vanillin
>99%
4-hydroxyindole
94%
p-hydroxybenzaldehyde
93%
quinoline
56%
4-methoxyphenol
1 h, 32%
2 h, 63%
TFA, D2O
>99%
NaHCO3, D2O
phenyacetic acid
23%
84%
3-(4-Hydroxyphenyl)propionic acid
1 h, o- 61%
2 h, o- 90%
4-hydroxyphenylacetic acid
1 h, o- 65%, -CH2 16%
2 h, o- 87%, -CH2 35%
trans-4-hydroxy-L-proline
>99%
cis:trans = 41:59
N-acetyl-
trans-4-hydroxy-L-proline
L-leucine
L-lysine
L-tryptophan
L-tyrosine
clean HDx

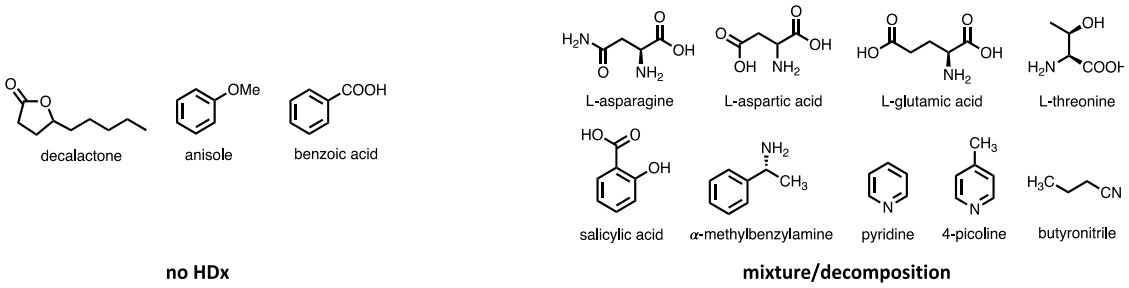


Figure 3.12 Deuterated substrates and HDx percentage in this work.

3.1.4 HDx of maltol, ethyl maltol, furaneol, and kojic acid

The developed hydrothermal HDx was further applied to other substrates including maltol, ethyl maltol, furaneol, and kojic acid. The deuterated version of these compounds is useful as internal standards for their quantitation by mass spectrometry.[48] Maltol has been used as an internal standard for the quantitation of furaneol which is an important flavoring agent.[49] Unfortunately, maltol is also naturally occurring, therefore it is necessary to deuterate to make it different from the naturally occurring maltol.

The HDx of maltol was studied in D_2O under neutral, acidic, and basic conditions (**Figure 3.13**). Under neutral and acidic conditions, the HDx occurred exclusively at the methyl group of maltol. However, only 39% exchange was observed under the standard condition (D_2O, 230 °C, 1 h). The addition of Pd/C with the hope to increase the reactivity of the allylic CH_3 was unsuccessful, and the extent of the exchange was practically the same as in the absence of Pd/C. On the other hand, more exchange (67%) was observed in the presence of acetic acid (0.89% v/v). Gratifyingly, a complete HDx at the CH_3 group was achieved when TFA (~2% v/v) which is a stronger acid was used instead of acetic acid. Under basic conditions ($NaHCO_3$), a complete disappearance of the signals was observed which might indicate complete exchange or decomposition (**Figure 3.14**). The ease of HDx at the methyl group was not obvious at the first sight. While the pyranone ring might get hydrolyzed to a triketone, the exchange should in principle be possible at multiple positions in addition to the methyl group. Thus, the HDx through the triketone intermediate is unlikely (**Figure 3.15**). However, when the C=O group was

protonated, the pyranone ring became aromatic, and thus the possibility of HDx at the CH_3 group adjacent to the $C=O^+$ became apparent.

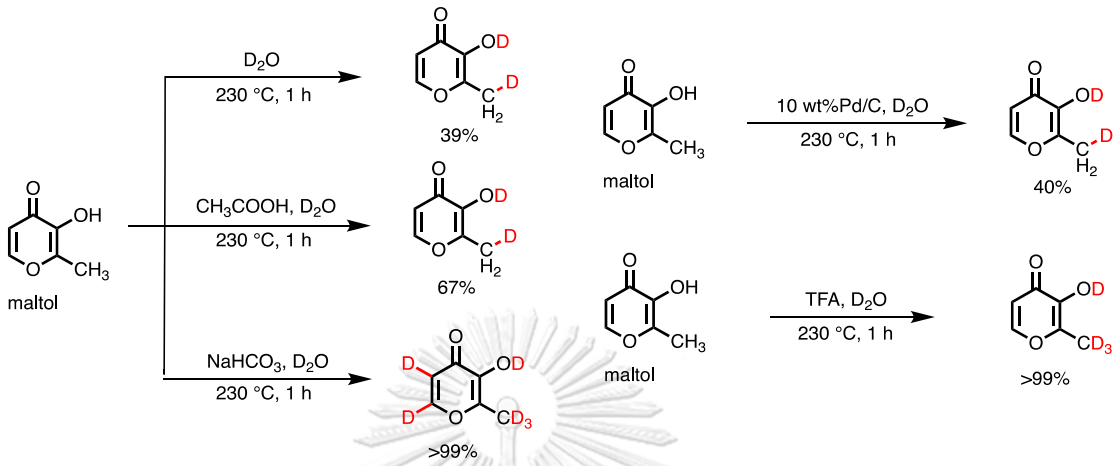


Figure 3.13 Deuteration of maltol in D_2O, acidic, and basic conditions.

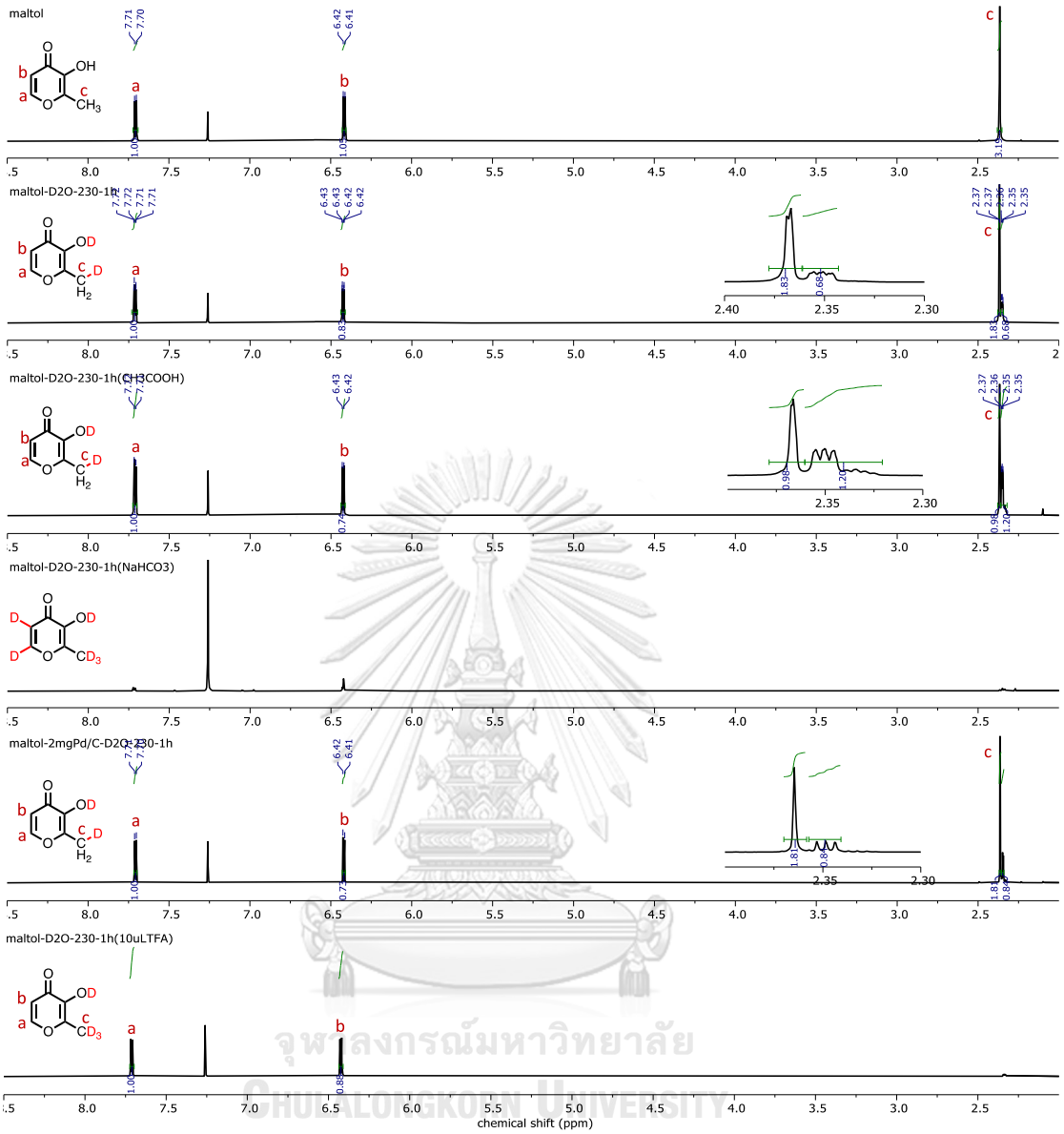


Figure 3.14 ^{1}H NMR spectra of maltol in D_2O, acidic, and basic conditions.

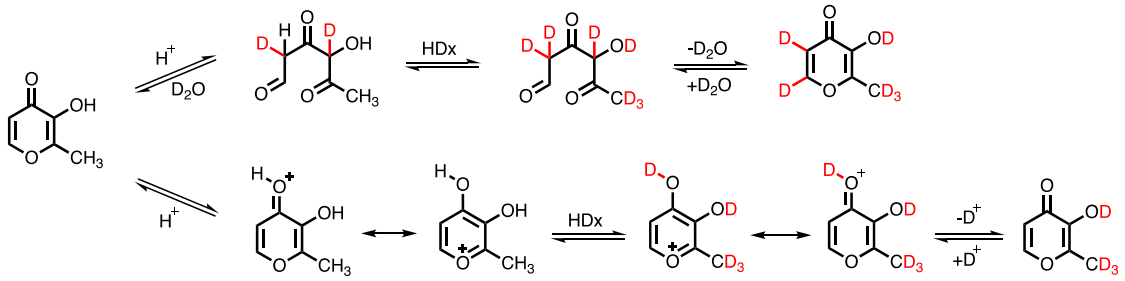


Figure 3.15 A proposed mechanism of the HDx of maltol

To test the generality of this selective HDx reaction at the alkyl group directly attached to a γ-pyrone ring at the α-position, the HDx of ethyl maltol as a homolog of maltol was next examined in D_2O under neutral, acidic, and basic conditions (**Figure 3.16**). The same reactivity pattern was observed as in the case of maltol, whereby the HDx occurred exclusively at the CH_2 group and not at the CH_3 group. Only little HDx (4%) was observed in D_2O alone under the standard conditions. However, the HDx increased to 99% in the presence of TFA. Under basic conditions, the complete disappearance of the signal was again observed. Since the CH_3 group located remotely from the C=O is not expected to undergo HDx in any circumstances, it is quite likely that the disappearance of signals was the consequence of decomposition rather than complete exchange (**Figure 3.17**).

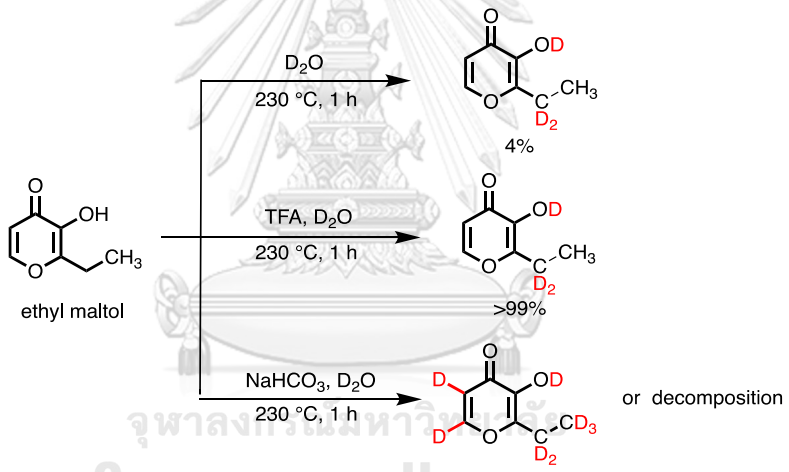


Figure 3.16 Deuteration of ethyl maltol in D_2O, acidic, and basic conditions.

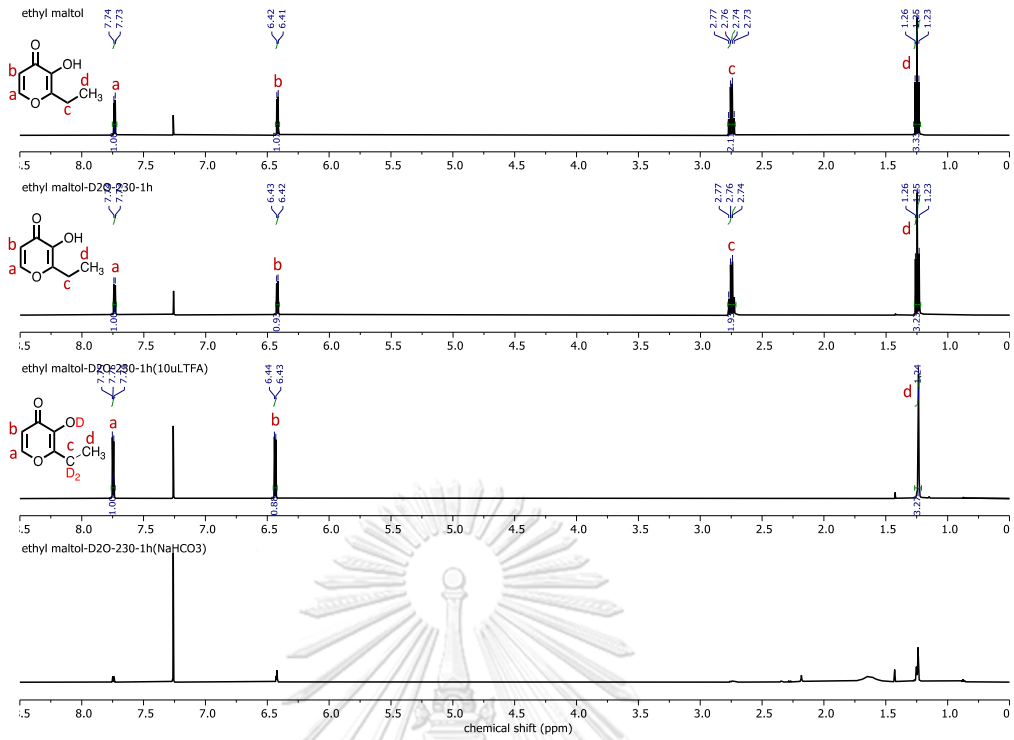


Figure 3.17 ^{1}H NMR spectra of ethyl maltol in D_2O, acidic, and basic conditions.

Kojic acid is a naturally occurring compound that shares the same γ-pyrone core as maltol. It is therefore another interesting target for the hydrothermal HDx. When kojic acid was heated in D_2O under the standard, acidic, and basic conditions, ^{1}H NMR spectra showed complete disappearance of proton signals in all cases. These results indicated that decomposition had occurred.

The acid-catalyzed HDx condition was also applied to furaneol which bears some structural similarity to maltol. Thus, furaneol was heated in D_2O in the presence of TFA at 230 °C for 1 h. The product was isolated by freeze-drying and was obtained as a brown viscous oil. ^{1}H NMR spectra of this product showed the disappearance of the singlet proton signal at 2.3 ppm corresponding to the allylic methyl group (**Figure 3.19**). This seems to suggest that only the methyl group connecting to the alkene underwent the HDx as in the case of maltol. Upon more careful observation, it was found that the proton signals were slightly shifted from the furaneol starting material. To confirm that the obtained product was indeed furaneol-d_4 as expected, ^{13}C NMR spectra were recorded (**Figure 3.20**). However, the ^{13}C signals were inconsistent with the structure of the expected product. Based on

the small number of ^{13}C signals, the product should be rather symmetrical. Therefore, it was hypothesized that the reaction product from the heating of furaneol and D_2O in the presence of TFA was 2,5-dihydroxyhexane-3,4-dione. This is the ring-opening product of furaneol which was confirmed by DART-MS as shown *m/z* in **Figure A68** as 149.0955. In addition, the reaction of furaneol with D_2O was monitored at the reaction time of 10, 30, and 60 min at the same 230 °C in the presence of TFA. ^1H NMR spectra showed that the ring opening reaction was completed within 10 min after heating at 230 °C and prolonged heating lead to decomposition (**Figure 3.21**).

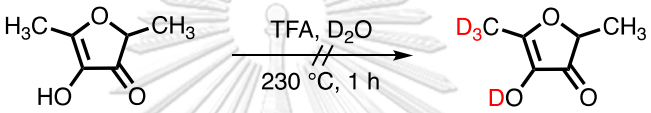


Figure 3.18 HDx of furaneol in the presence of TFA in D_2O.

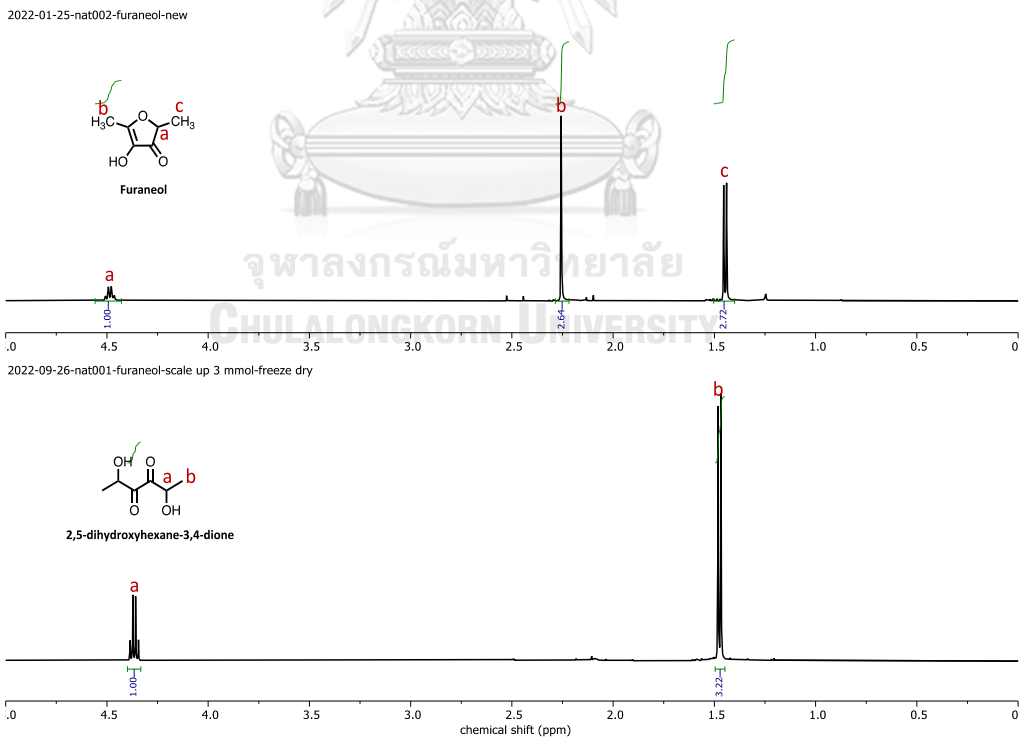


Figure 3.19 ^1H NMR spectra of furaneol hydrothermal HDx

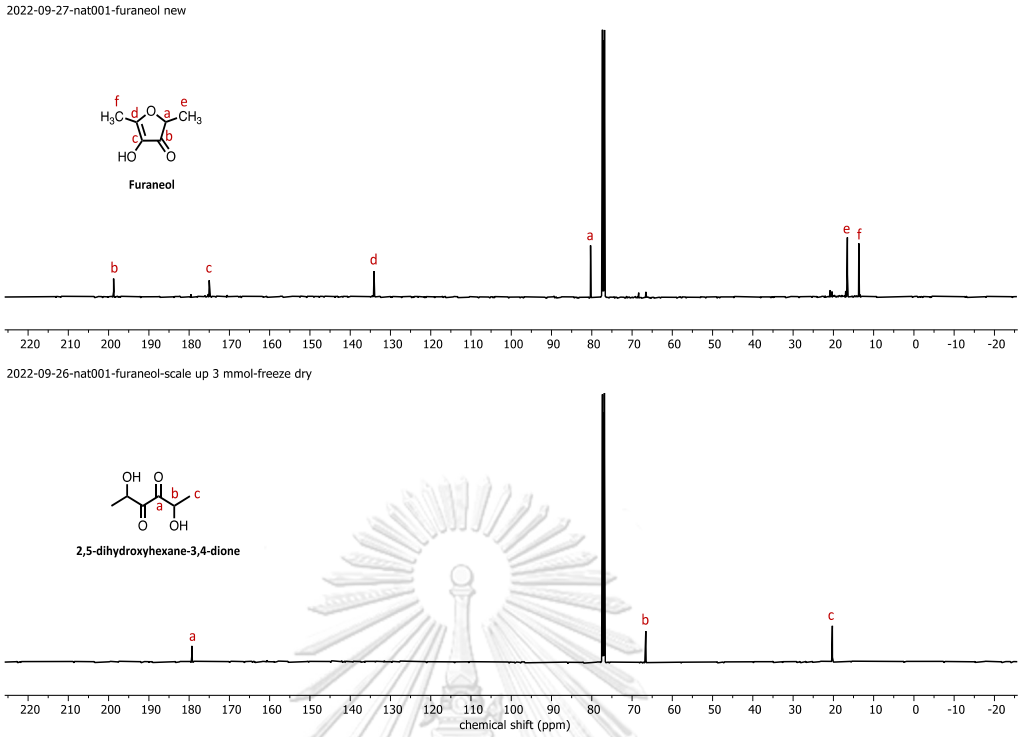


Figure 3.20 ^{13}C NMR spectra of furaneol hydrothermal HDx

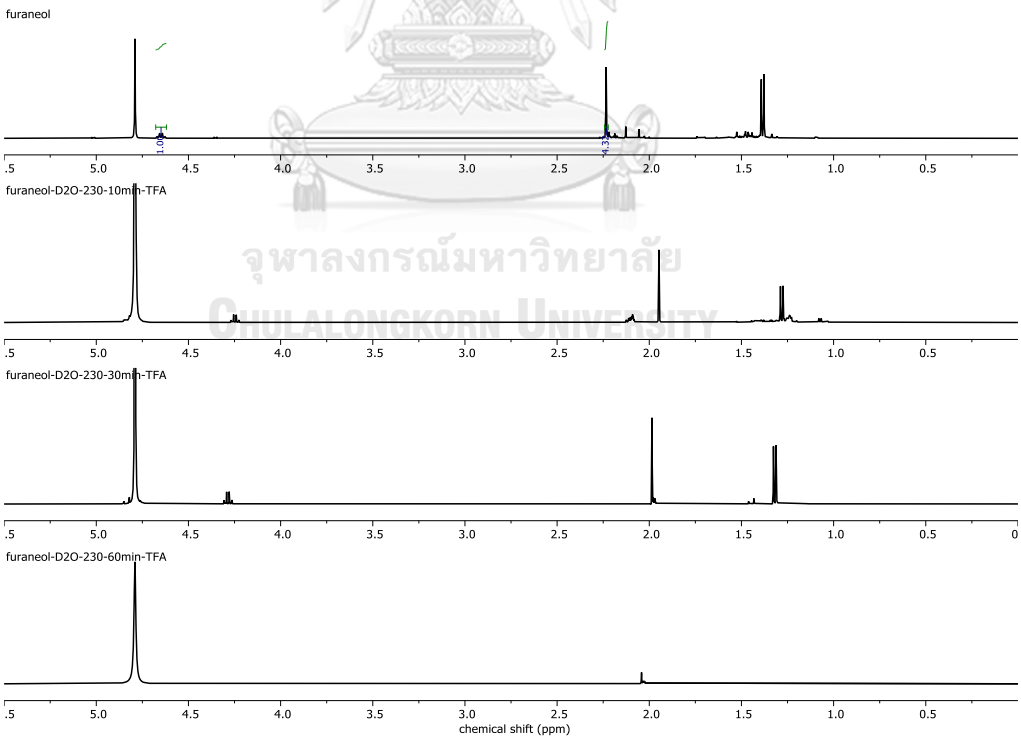


Figure 3.21 ^{1}H NMR spectra of furaneol kinetic in TFA at different reaction time

The TFA-catalyzed deuteration reactions were successfully scaled up in the case of maltol and ethyl maltol. The deuterated products (maltol-d_4 and ethyl maltol-d_3) were obtained in 31.6% and 32.1% yield, respectively at 0.79 and 0.64 mmol reaction scales after purification by column chromatography. The degree of deuteration was more than 99% in both cases. This indicated the practicality of the hydrothermal HDx method for the synthesis of deuterium-labeled compounds.

3.1.5 Concluding remarks for the HDx studies

In summary, this study successfully demonstrated a hydrogen-deuterium exchange (HDx) reaction of various organic compounds in D_2O in the absence of any catalyst under hydrothermal conditions. The results showed that the efficient HDx occurred at the *ortho/para*-positions of aromatic ring with phenolic group and α-position of amino acids. Furthermore, HDx at the α-position of amino acids occurred with complete epimerization/racemization. Moreover, the α-CH_2 adjacent to the carboxyl group poorly exchanged under the non-catalyzed conditions and even extended the reaction time, but rapidly exchanged in the presence of an acid catalyst. Some compounds were inert and others gave complex mixtures under the developed hydrothermal HDx condition.

3.2 Halogen-Deuterium Exchange (XDx) Reactions

In the aforementioned HDx reaction, the reactivity of the substrate determined the success of the exchange reaction. Only the relatively acidic C-Hs at the *ortho*- and *para*-positions of phenols, certain heteroaromatic ring systems (quinoline and indole), and α-CH of amino acids underwent clean HDx reactions in the absence of any catalyst. Less reactive substrates including the CH_2 attached to a carboxyl group or C_2-alkylated γ-pyrones required an acid catalyst to promote the efficient HDx. Thus, it was not possible to replace the H atom with the D atom at any desired positions using this strategy. A recent literature report on sodium sulfite-mediated reductive dehalogenation of aryl halides in water[36] suggests the potential of applying the same reaction for XDx if the reaction medium was replaced by D_2O. Initially, the debromination of 4-bromophenol in water under hydrothermal conditions was performed instead of the microwave condition that was used in the literature.[36]

3.2.1 Debromination of 4-bromophenol (XHx)

To investigate the debromination of 4-bromophenol as a model reaction, Na_2SO_3 was initially employed as the reducing agent. The reaction was performed in water at 130 °C for 3 h (**Figure 3.22**). The results showed that the debromination occurred, but was not yet complete. When the reaction temperature was increased to 250 °C for 1 h, complete debromination was observed to give unsubstituted phenol as the only product within 1 h as confirmed by ^{1}H NMR (**Figure 3.23**).

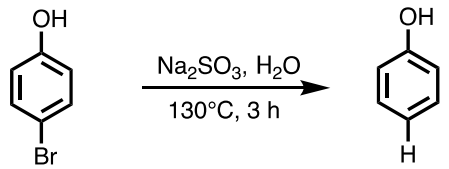


Figure 3.22 Debromination of 4-bromophenol in water under hydrothermal conditions at 130 °C for 3 h

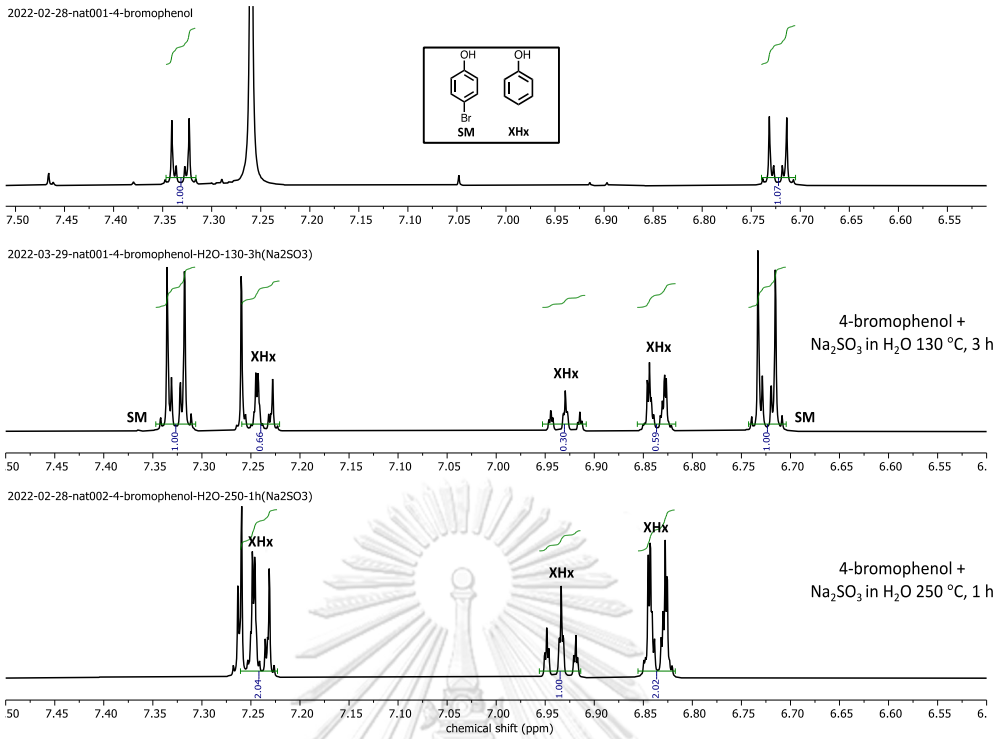


Figure 3.23 ^{1}H NMR spectra of debromination of 4-bromophenol in water under hydrothermal condition at 130 °C for 3 h and 250 °C for 1 h

3.2.2 Effects of temperature and time on the deuteration of 4-bromophenol with Na_2SO_3

Encouraged by the results from the model debromination of 4-bromophenol promoted by Na_2SO_3 in water, the reaction was next repeated in D_2O at a temperature between 100-250 °C (**Figure 3.24**). The results showed that the XDx began at 150 °C as shown by the ^{1}H NMR signal at 7.25 ppm after 1 h heating period. However, the reaction was not clean, and other byproducts were observed in addition to the expected XDx product. These include the *ortho*-HDx and *ortho*-HDx+XDx products as shown by the broad signals at 7.33 and 7.24 ppm, respectively. Also, substantial amounts of the 4-bromophenol starting material remained. When the temperature was increased to 200 °C and 250 °C, no signals were observed by ^{1}H NMR which indicated either complete deuterium exchange or decomposition. Hence, 150 °C was chosen as the temperature for further study.

Next, the reaction time was then increased to 2 h and 3 h while the temperature was fixed at 150 °C. The results showed that at 2 h reaction time, the

signal of the 4-bromophenol almost disappeared. However, the XDx signal became smaller too and the broad signals at 7.33 and 7.24 ppm corresponding to the *ortho*-HDx and *ortho*-HDx+XDx products were stronger. The results indicated that the *ortho*-HDx occurred as a significant competing reaction with the desired XDx. Based on the ratio of the *ortho*-HDx and XDx products according to ^{1}H NMR integration, the *ortho*-HDx appeared to be faster than the XDx by at least 10-fold. When the heating was prolonged to 3 h, the trideuterated product (*ortho*-HDx & XDx) became the major product. However, since the ^{1}H NMR signal at 7.33 ppm indicated the presence of bromine in the product, it can be concluded that the debromination was not complete after heating at 150 °C for 3 h. Based on ^{1}H NMR integration, the reaction mixture consisted of the starting material (SM), XDx, *ortho*-HDx + SM, *ortho*-HDx, and *ortho*-HDx & XDx products at 3.4, 2.6, 31.5, 28.1, and 62.5 mol%, respectively (**Figure 3.25**).

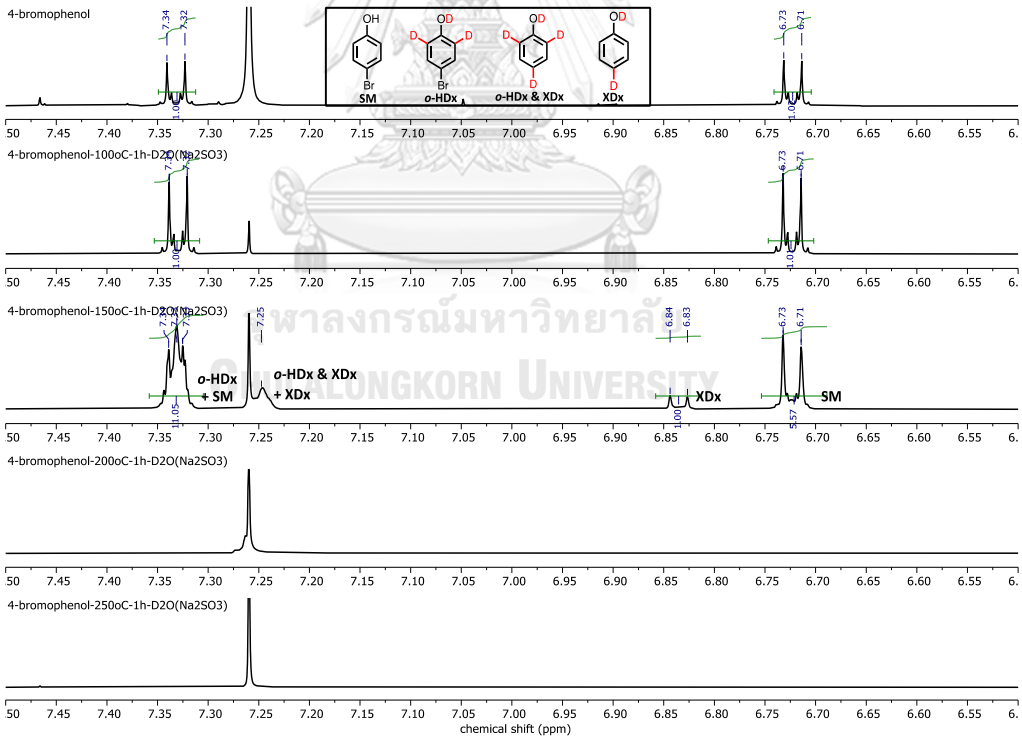


Figure 3.24 ^{1}H NMR spectra of XDx of 4-bromophenol mediated by Na_2SO_3 in D_2O under hydrothermal conditions at 100, 150, 200, and 250 °C

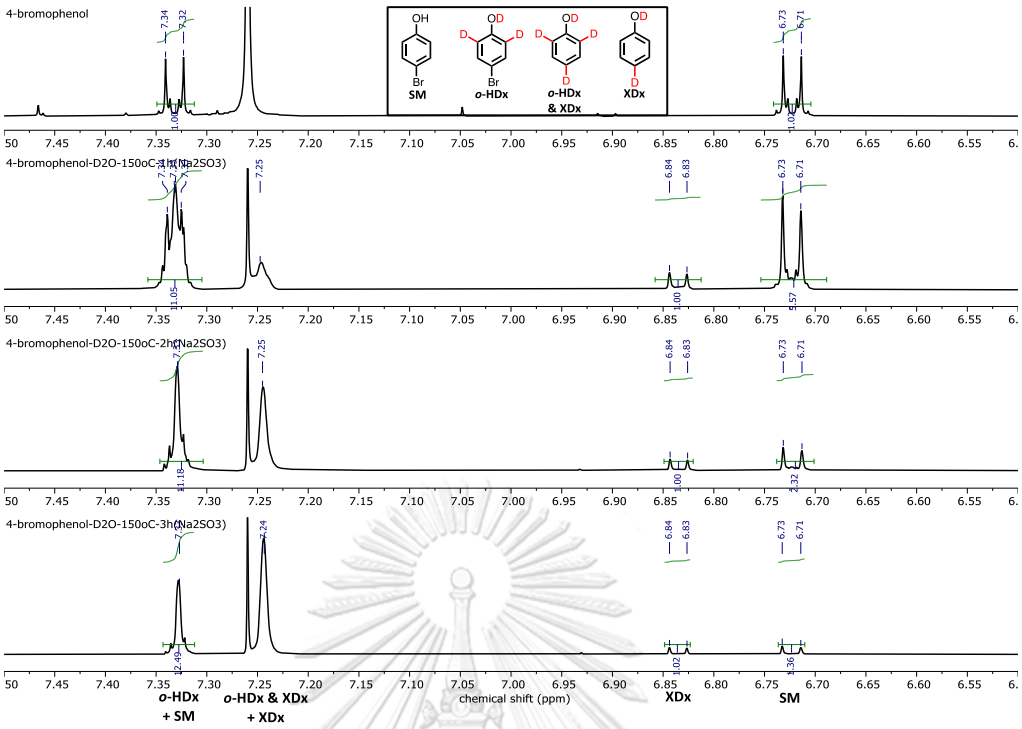


Figure 3.25 ^{1}H NMR spectra of XDx of 4-bromophenol mediated by Na_2SO_3 in D_2O under hydrothermal conditions with different the reaction time

3.2.3 Deuteration of 4-bromophenol in the absence of Na_2SO_3

The reaction of 4-bromophenol with D_2O in the absence of Na_2SO_3 to determine whether the *ortho*-HDx occurred spontaneously or was promoted by the presence of Na_2SO_3. When 4-bromophenol was heated in D_2O at 150 °C for 1 h, no change was observed based on the NMR spectra, suggesting that the *ortho*-HDx was insignificant under such condition. This is in agreement with the HDx experiments (**section 3.1.1**) whereby a higher temperature (230-250 °C) was required for the exchange. Indeed, when the reaction temperature was raised to 250 °C, a complete *ortho*-HDx of 4-bromophenol was achieved within 2 h. This was confirmed by the disappearance of the *ortho*-proton signal at 6.72 ppm and the collapse of the *meta*-proton signal at 7.33 ppm into a singlet peak due to the loss of coupling with the adjacent *ortho*-protons (**Figure 3.26**).

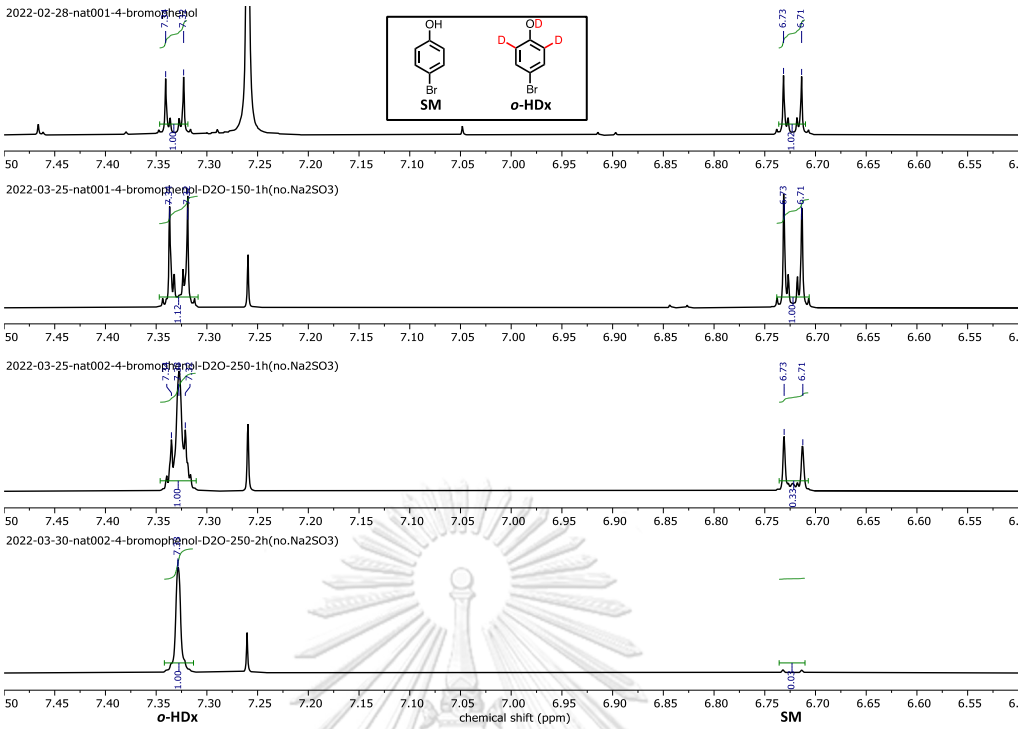


Figure 3.26 ^{1}H NMR spectra of deuteration of 4-bromophenol in the absence of Na_2SO_3

Based on the preliminary results above, it was decided that the Na_2SO_3-mediated debromination was not suitable for the selective XDx due to the competing *ortho*-HDx under hydrothermal conditions. The strong basicity of Na_2SO_3 could promote the *ortho*-HDx to occur at a faster rate than the XDx. Fortunately, it was found that $HCOONH_4$ in the presence of Pd/C[33] gave a satisfactory performance in the reductive dehalogenation of 4-bromophenol (XHx) to give phenol (98% conversion) under hydrothermal conditions. Importantly, when the reaction was performed in D_2O the expected XDx product was obtained together with some XHx product (95% conversion, XDx:XHx = 81:19) even though the fully protonated $HCOONH_4$ was used. Encouraged by these results, the optimization of the formate-mediated XDx reaction was performed next.

3.2.4 Deuteration of 4-bromophenol in the presence of 10% Pd/C with $HCOONH_4$

To investigate the debromination of 4-bromophenol (0.1 mmol) in the presence of 10% Pd/C (10 mg, 0.01 mmol, 10 mol%) with $HCOONH_4$ (0.1 mmol, 6.3 mg) in water (500 µL), the reaction was heated at 150 °C for 1 h (**Figure 3.27**). The results showed that the debromination was almost complete. When the reaction medium was changed from H_2O to D_2O, the XDx occurred as shown by the proton signals at 7.25 and 6.84 ppm (the *meta*- and *ortho*-protons of the phenolic OH group, respectively). The ratio of the two sets of protons was close to 1:1. The signal due to the *ortho*-proton of the starting material at 6.72 ppm almost completely disappeared and some small signals of the *para*-proton of the XHx product were also observed (**Figure 3.28**). Based on the ^1H integration data, the conversion of 4-bromophenol to XDx + XHx products was 95% complete and the ratio of XDx:XHx was 81:19. Gratifyingly, no significant *ortho*-HDx was observed presumably by the lower basicity of $HCOONH_4$ when compared to Na_2SO_3 (pK_a of HCOOH = 3.75, pK_a of H_2SO_3 = 1.81).[50]

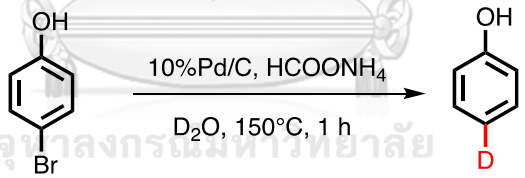


Figure 3.27 Deuteration of 4-bromophenol in the presence of 10% Pd/C with $HCOONH_4$

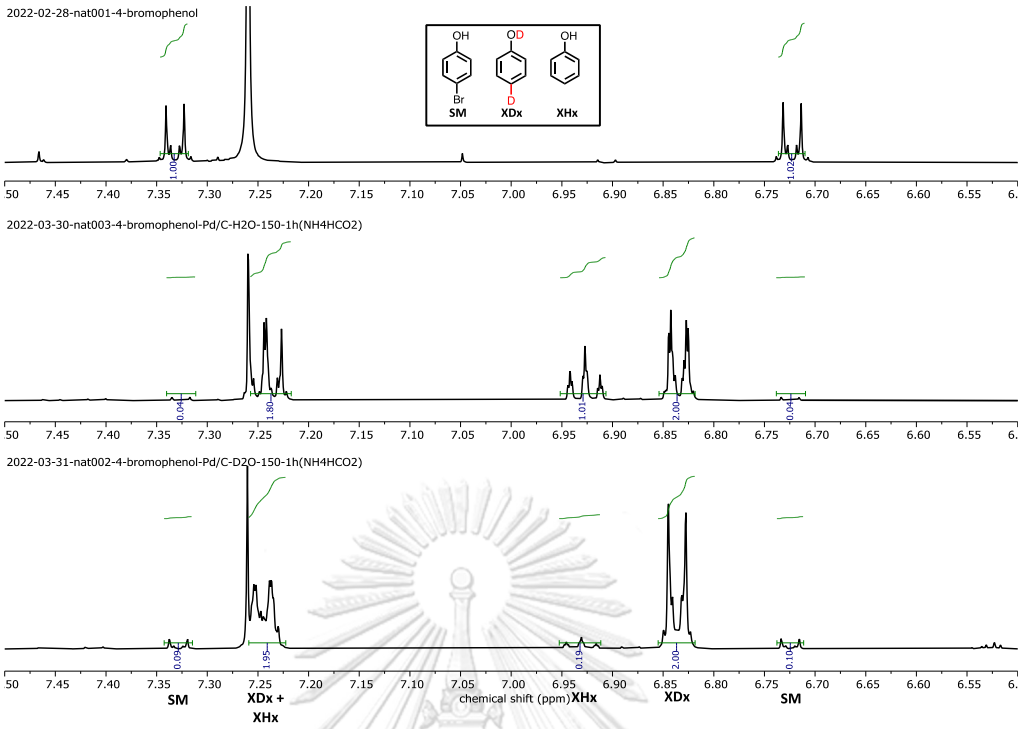


Figure 3.28 ^{1}H NMR spectra of the reaction products from the XDx and XHx of 4-bromophenol mediated by $HCOONH_4$ and Pd/C in H_2O and D_2O under hydrothermal conditions

Control reactions were also performed without $HCOONH_4$ in the presence of 10% Pd/C in H_2O and D_2O (**Figure 3.29**). The results showed that the debromination did not occur and the starting material remained unchanged. The results confirmed that $HCOONH_4$ was essential for the XHx and XDx reactions.

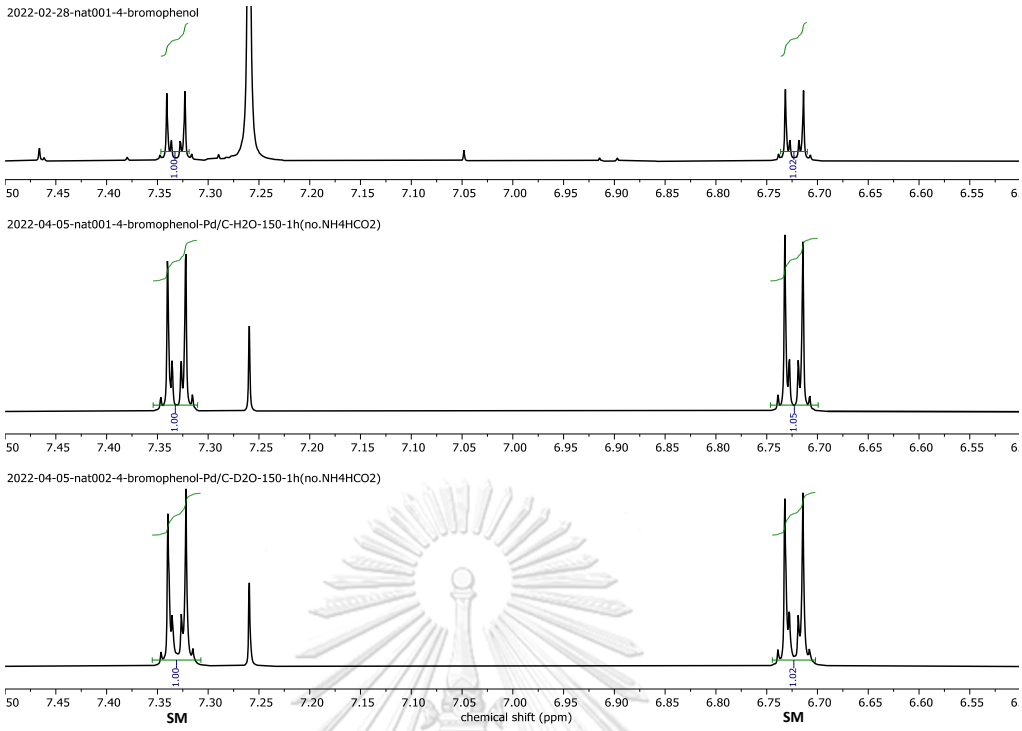


Figure 3.29 ^{1}H NMR spectra of the reaction products from the XHx and XDx of 4-bromophenol by Pd/C in H_2O and D_2O under hydrothermal conditions in the absence of $HCOONH_4$

3.2.5 XHx and XDx in the presence of different additives

To further confirm the active role of $HCOONH_4$, the XHx and XDx reactions were performed in the presence of other additives including CH_3COONH_4, $NaHCO_3$, and HCOONa[33] in H_2O and D_2O (**Figures 3.30, 3.31**).

When 4-bromophenol was heated with the abovementioned additives in the presence of 10% Pd/C in H_2O at 150 °C for 1 h, the successful debromination with the formation of phenol was observed only in the cases of $HCOONH_4$ and HCOONa (**Figure 3.30**). Likewise, the same set of reactions in D_2O gave the XDx product in the presence of $HCOONH_4$ and HCOONa. No reactions were observed in the case of CH_3COONH_4. Interestingly, significant *ortho*-HDx (36% exchanged) was observed in the case of $NaHCO_3$ without the formation of the XDx product (**Figure 3.31**). The experiments demonstrated that formate salts were essential for the XDx, and that basic conditions promoted only the *ortho*-HDx.

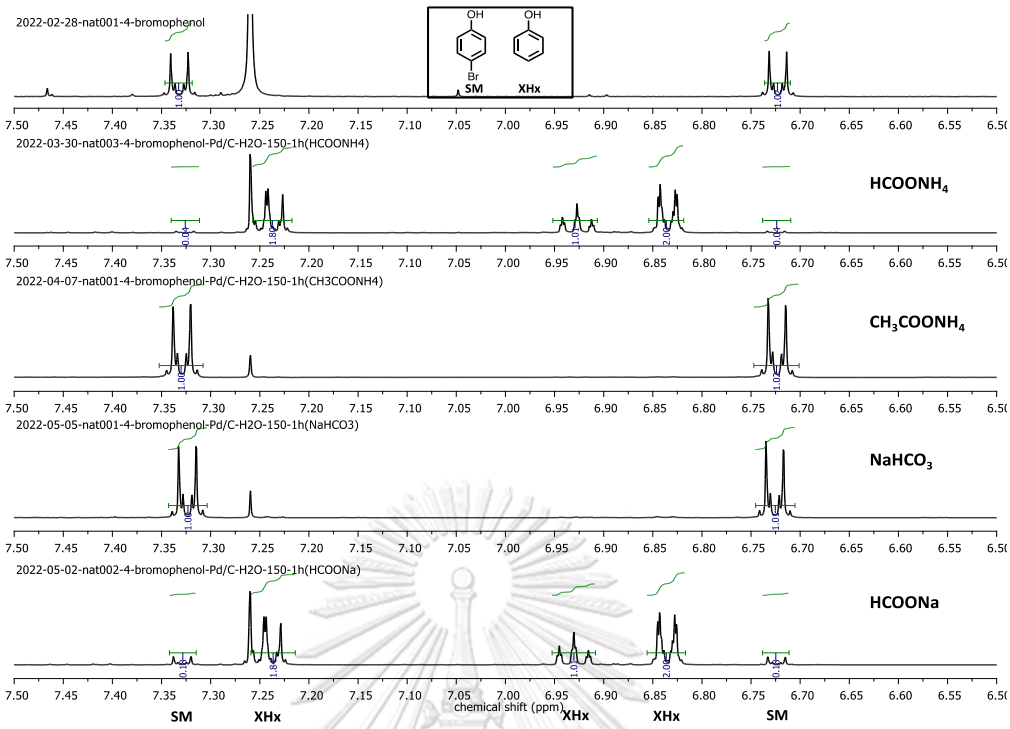


Figure 3.30 ^{1}H NMR spectra of the reaction products from the XHx of 4-bromophenol with different additives in H_2O

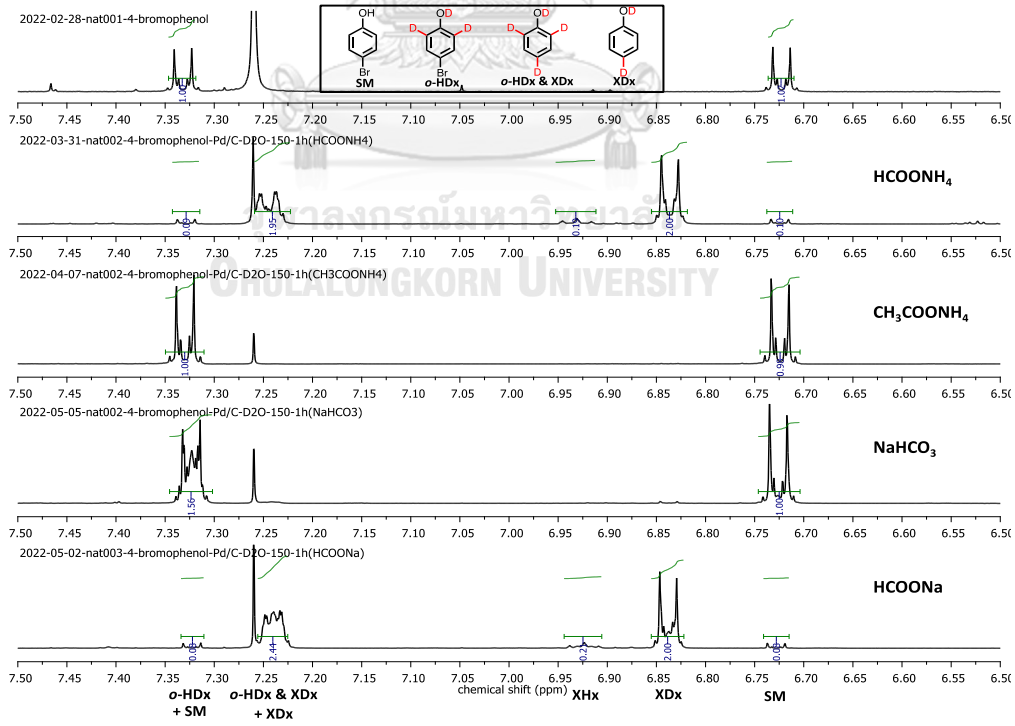


Figure 3.31 ^{1}H NMR spectra of the reaction products from the XDx of 4-bromophenol with different additives in D_2O

3.2.6 Deuteration of 4-bromophenol in the presence of sodium formate and Pd/C

In order to maximize the XDx:XHx ratio, attempts were made to eliminate all proton sources from the reaction. Since $HCOONH_4$ contains extra protons from the ammonium group, it was thought that HCOONa might give better results. Thus, 4-bromophenol was heated with HCOONa in the presence of 10% Pd/C in H_2O and D_2O at 150 °C for 1 h. ^1H NMR analyses indicated that almost complete debromination occurred in both H_2O (92%) and D_2O (97%). For the reaction performed in D_2O, the XDx:XHx ratio was calculated to be 83:17 which was in the same range as $HCOONH_4$ (**Figure 3.32**)

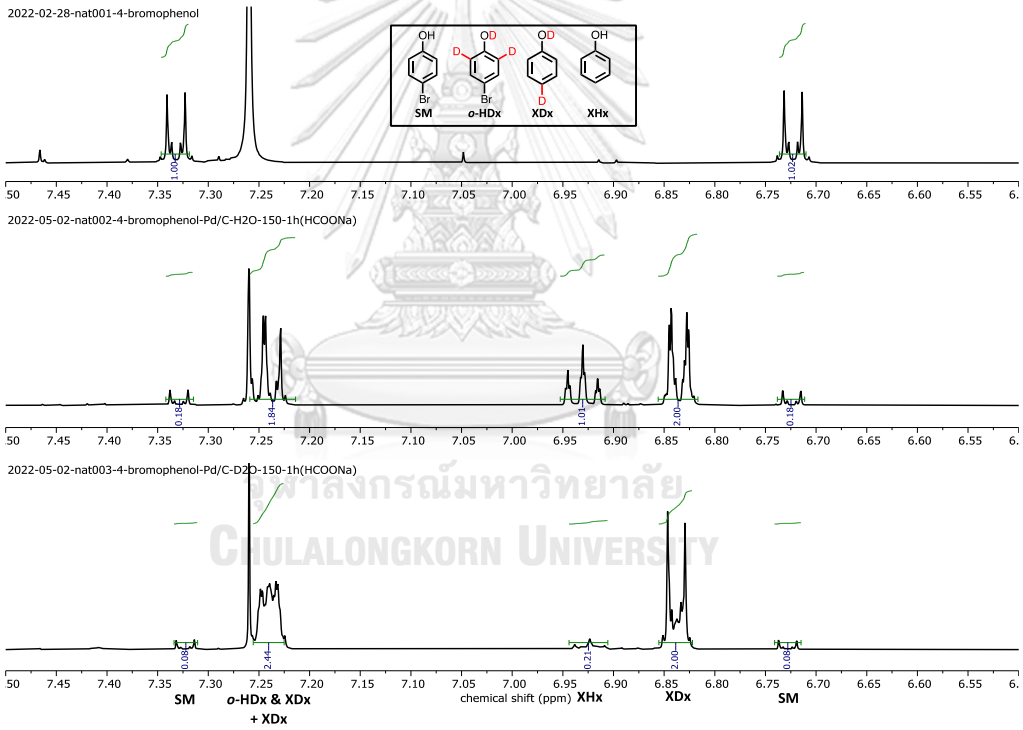


Figure 3.32 ^1H NMR spectra of the reaction products from the XDx and XHx of 4-bromophenol mediated by HCOONa and Pd/C in H_2O and D_2O under hydrothermal conditions

3.2.7 Comparison of the XDx of 4-bromophenol in the presence of sodium formate or sodium deuteroformate with Pd/C

In another attempt to eliminate the proton source, DCOONa was prepared from formic acid-d_2 and NaOH and was used instead of HCOONa. ^{1}H NMR spectra of the XDx product of 4-bromophenol in the presence of DCOONa (0.1 mmol, 6.9 mg) and 10 mol% Pd/C showed that the starting material still remained. The conversion was only 35% and the XDx:XHx ratio of 87:13. On the other hand, the reaction using HCOONa gave 98% conversion with XDx:XHx ratio of 85:15 (**Figure 3.33**). Although the results are difficult to rationalize, HCOONa was chosen because it gave better conversion and the acceptable XDx:XHx ratio that was comparable to DCOONa.

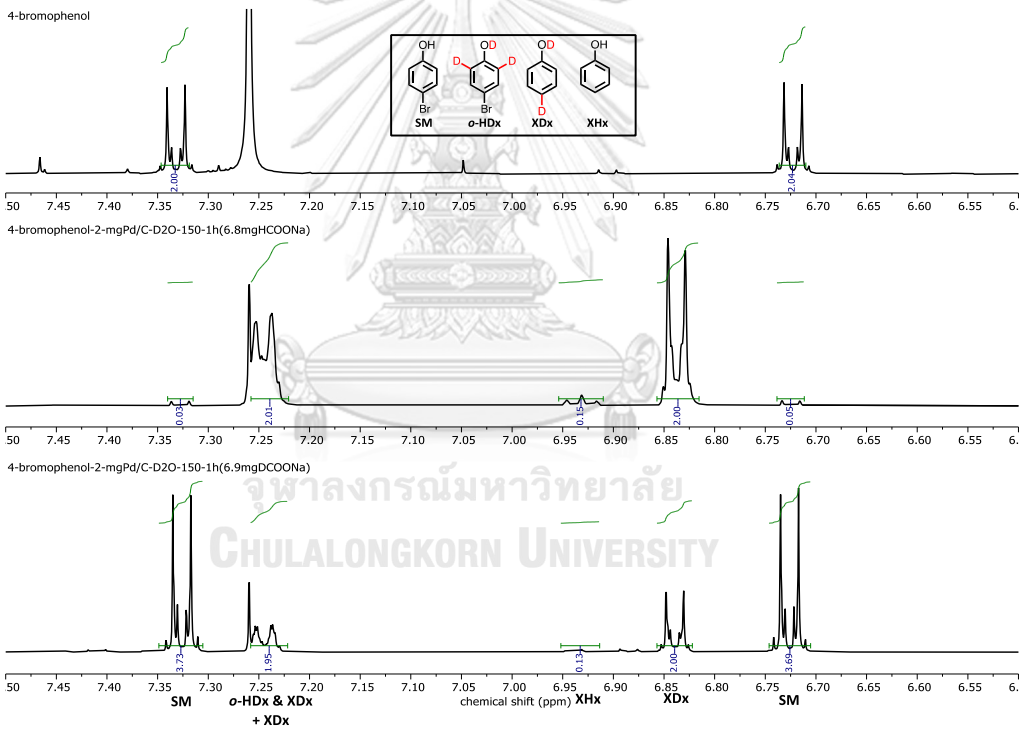


Figure 3.33 ^{1}H NMR spectra of the reaction products from the XDx of 4-bromophenol with sodium formate and sodium deuteroformate in the presence of Pd/C

3.2.8 Conditions optimization for the XDx of 4-bromophenol

3.2.8.1 Effects of the amounts of 10% Pd/C

To investigate the suitable amount of 10% Pd/C, the XDx reactions were performed in the presence of different amounts of the catalyst. In all cases, the conversion was more or less complete. However, as the amount of the catalyst was increased, the ratio of XDx also increased. Nevertheless, the proportion of the undesirable *ortho*-HDx also increased. From the results in **Table 3.1**, 0.0025 mmol of 10% Pd/C per 0.1 mmol of the substrate (2.5 mol%) was chosen because it gave a good compromise between conversion, XDx:XHx, and *ortho*-HDx.

Table 3.1 Optimization of the amounts of Pd/C[a]

Entry	Pd/C (mol%)	Conv. (%)	XDx:XHx	*o*-HDx (%)
1	1.0	100	76:24	0.5
2	2.5	100	85:15	4.3
3	5.0	100	83:17	8
4	10.0	94	83:17	18

[a] 17.4 mg, 0.1 mmol of 4-bromophenol was used, 10% Pd/C, 10.2 mg and 0.15 mmol HCOONa in 500 µL of D_2O (99.9% D content) at 150 °C for 1 h

3.2.8.2 Effects of the amounts of sodium formate

Next, the effects of the amounts of HCOONa were investigated in the range of 0.05 – 0.20 mmol/0.1 mmol of the substrate (0.5 – 2 equiv.). The results in **Table 3.2** indicated that the originally used 0.10 mmol of HCOONa (1 equiv) should be appropriate. Under this condition, high conversion (98%) and good XDx:XHx (85:15) were achieved. Similar conversion and XDx:XHx value was obtained at higher amounts of HCOONa, but the *ortho*-HDx became more significant. This may be explained by the basicity of excess HCOONa in the system.

Table 3.2 Optimization of the amounts of HCOONa[a]

Entry	HCOONa (mmol)	Conv. (%)	XDx:XHx	*o*-HDx (%)
1	0.05	27	79:21	0
2	0.10	98	85:15	0.5
3	0.15	100	85:15	4.3
4	0.20	100	87:14	19

[a] 0.1 mmol of 4-bromophenol was used, 2 mg, 0.0025 mmol 10% Pd/C and HCOONa in 500 µL of D_2O at 150 °C for 1h

3.2.8.3 Effects of reaction temperature

To investigate the effect of reaction temperature, the reactions were performed over the temperature range of 100 – 250 °C for the same 1 h period. The results in **Table 3.3** showed that 150 °C should be the optimal reaction temperature because a low conversion was observed at lower temperature and *ortho*-HDx became more significant competing reactions at higher temperatures.

Table 3.3 Optimization of reaction temperature[a]

Entry	Temp (°C)	Conv. (%)	XDx:XHx	*o*-HDx (%)
1	100	12	100:0	0
2	150	98	85:15	0.5
3	200	100	89:11	55
4	250	100	96:4	96

[a] 0.1 mmol of 4-bromophenol was used, 0.0025 mmol 10% Pd/C, and 0.1 mmol HCOONa in 500 µL of D_2O for 1h

3.2.8.4 Effects of reaction time

To study the effect of reaction time, the reactions were performed at the same temperature (150 °C) and different reaction times in the range of 30 – 180 min (0.5 – 3 h). The results in **Table 3.4** showed that the reaction time of 60 min should be the appropriate reaction time. As with other parameters, the *ortho*-HDx became more pronounced side reactions at longer reaction times.

Table 3.4 Optimization of reaction time[a]

Entry	Time (min)	Conv. (%)	XDx:XHx	*o*-HDx (%)
1	30	34	79:21	0
2	60	98	85:15	0.5
3	120	100	85:15	18
4	180	100	86:14	16

[a] 0.1 mmol of 4-bromophenol was used, 0.0025 mmol 10% Pd/C, and 0.1 mmol HCOONa in 500 µL of D_2O at 150 °C

3.2.8.5 Effect of D_2O volume

To study the effect of D_2O volume, the reaction was performed at the same temperature in a variable volume of 250 – 1000 µL of D_2O for 1 h. The ^1H NMR spectra showed that the volume of D_2O as 500 µL should be appropriate the volume in the reaction. Under this condition, both high conversion (98%) and good XDx:XHx (85:15) were achieved.

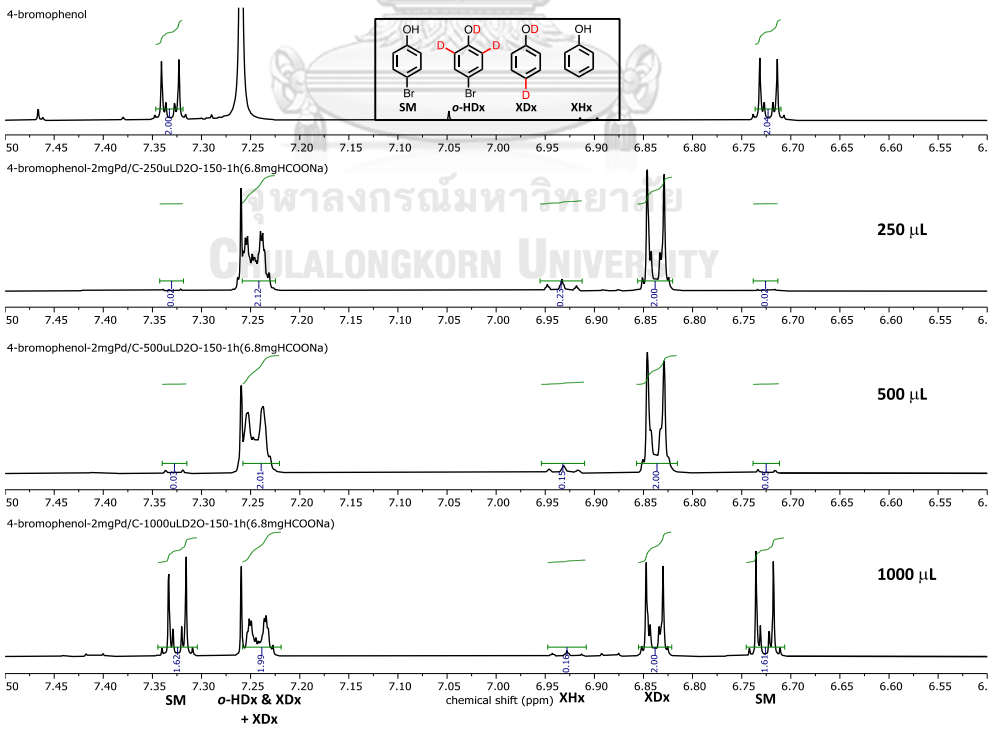
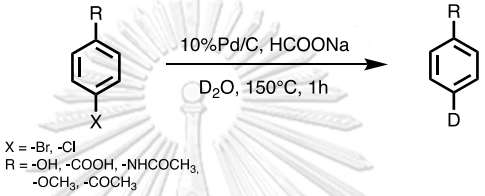
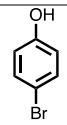
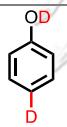
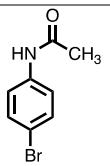
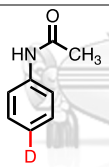
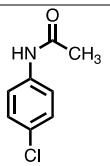
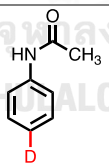
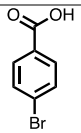
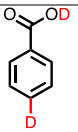
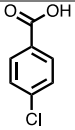
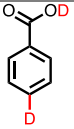
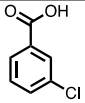
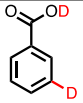
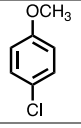


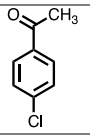
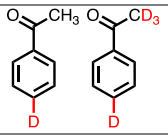
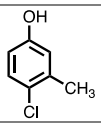
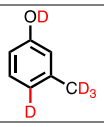
Figure 3.34 ^1H NMR spectra of the reaction products from the XDx of 4-bromophenol in different volume of D_2O

In summary, the optimized condition for the hydrothermal XDx of 4-bromophenol (at 0.1 mmol scale) was 0.0025 mmol of 10 wt% Pd/C (2.5 mol%), 0.1 mmol of HCOONa (1 equiv) in 500 µL of D_2O at 150 °C for 1 h. This condition was further applied to other halogenated aromatic compounds with various functional groups as shown in **Table 3.5**.

Table 3.5 XDx of various halogenated aromatic substrates in the presence of HCOONa and Pd/C



Entry	Substrate	Product(s)	Conv. (%)	XDx:XHx	Conv. XHx (%)[a]
1			98[b]	85:15[b]	85
2			73	44:56	31
3			87	49:51	43
4			39	70:30	41
			94[c]	70:30[c]	-
5			48	89:11	30
6			83[d]	73:28[d]	91
7		-	Unidentifiable products		

8			cannot be calculated due to formation of several products		
9			47	61:39	50

Standard condition: 0.1 mmol SM + 0.0025 mmol 10 wt% Pd/C + 0.1 mmol HCOONa in 500 µL of D_2O at 150 °C for 1 h

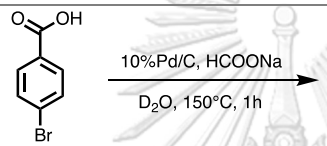
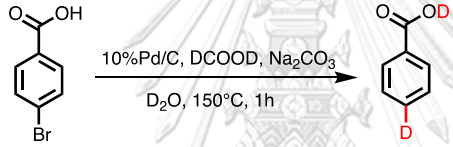
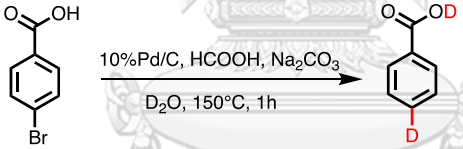
[a] standard condition D_2O to H_2O, [b] %*o*-HDx = 0.5, [c] 0.2 mmol HCOONa, [d] 0.15 mmol HCOONa

From the results in **Table 3.5**, the optimized condition for the XDx of 4-bromophenol was also applicable to other substrates. However, the conversion percentage and ratio of XDx:XHx seemed to be varied among different substrates. 4-Chloro and 4-bromoacetanilide gave good conversion but low XDx:XHx ratios in the range of 1:1. Only low conversion and XDx:XHx ratio were obtained for 4-bromobenzoic acid (39%, 70:30) under the standard XDx conditions. 4-Chlorobenzoic acid gave a somewhat better conversion and XDx:XHx ratio (48%, 89:11). 3-Chlorobenzoic acid gave good conversion but low XDx:XHx ratio (83%, 73:28) (at 1.5 equiv of HCOONa). In the case of 4-bromobenzoic acid, the conversion was improved to 94% when the amounts of HCOONa was doubled to 2.0 equiv. but the XDx:XHx ratio remained the same. For 4-chloroanisole (entry 7) the ^{1}H NMR signals of the starting material disappeared, but no XDx and HDx occurred as shown by the remaining *para*-substituted aromatic pattern after the reaction. For 4-chloroacetophenone (entry 8), the XDx occurred as evidenced by ^{1}H NMR spectra but the conversion and XDx:XHx ratio could not be calculated due to the formation of several products. In addition, the disappearance of the CH_3 group suggested that the relatively acidic methyl ketone also underwent the HDx. In the case of *p*-chloro-*m*-cresol, poor conversion and low XDx:XHx ratio (47%, 61:39) were obtained. Furthermore, some HDx at the CH_3 group (39%) was also observed as shown by the reduced intensity of the CH_3 signal relative to the aromatic signals.

Due to the poor conversion and low XDx:XHx ratio of 4-bromobenzoic acid under the standard XDx conditions, this compound was selected for further optimization (**Table 3.6**). When DCOONa (generated in situ from formic acid-d_2 (1 mmol) and Na_2CO_3 (0.5 mmol)) was used instead of HCOONa, the XDx:XHx ratio was

improved to 82:18. Unexpectedly, the conversion was also dramatically increased to 92%. This could be due to the solubility of the substrate in aqueous Na_2CO_3 used for the preparation of the DCOONa. When the combination of HCOOH and Na_2CO_3 was used, the conversion percentage was similar to the result of DCOOD with Na_2CO_3. However, the XDx:XHx ratio was poor.

Table 3.6 Comparison of additives effect with 4-bromobenzoic acid by using HCOONa, DCOOD with Na_2CO_3, and HCOOH with Na_2CO_3

Entry	Reactions	Conv. (%)	XDx:XHx
1		39	70:30
2		92	82:18
3		91	60:40

3.2.9 Proposed mechanism of XDx

For the mechanism of XDx in the presence of HCOONa in D_2O catalyzed by Pd/C, we proposed that Pd catalyzed the dissociation of formate generated according to equation (1) into carbonate ion (CO_3^{2-}) and H_2 as shown in equation (2).[51]

$$HCOONa \rightleftharpoons HCOO^- + Na^+ \quad (1)$$

$$2HCOO^- \xrightleftharpoons{D_2O} 2DCO_3^- + H_2 \quad (2)$$

Next, the Pd-bound H_2 may directly reduce the C–X bond to form the C–H (XHx). On the other hand, based on the previous study of Sajiki et al.[26] we propose

that the H–D exchange should readily occur in D_2O to give the Pd-bound D_2. This Pd-bound D_2 could then reduce the C–X to C–D bond (XDx) on the Pd surface (**Figure 3.35**).

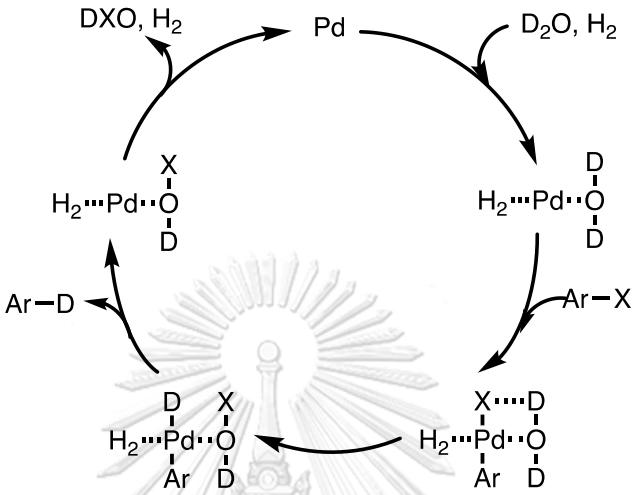


Figure 3.35 A plausible mechanism of XDx on the Pd surface.[26, 52]

To determine the fate of sodium formate (HCOONa) when heated in D_2O in the presence of Pd/C, ^1H and ^{13}C NMR spectra were recorded at 150 °C for 0, 15, 30, 60, and 120 min in the presence of sodium acetate as a reference are shown in **Figures 3.36** and **3.37**. The results from ^1H NMR showed that the decomposition of HCOONa started at 30 min and was completed at 120 min. ^{13}C NMR revealed that most of the HCOONa (δ_C $HCOO^-$ = 172.2 ppm)[53] were converted to HCO_3^- (or DCO_3^-) as shown by the disappearance of the signal at 171.1 ppm and the formation of a new signal at 160.6 ppm (δ_C HCO_3^- = 161.7 ppm; CO_3^{2-} = 169.3 ppm).[54, 55] Nevertheless, some ^{13}C signal at the original position of the formate also remained, but with a distinctive splitting pattern that indicated the formation of deuteroformate ($DCOO^-$) ion.

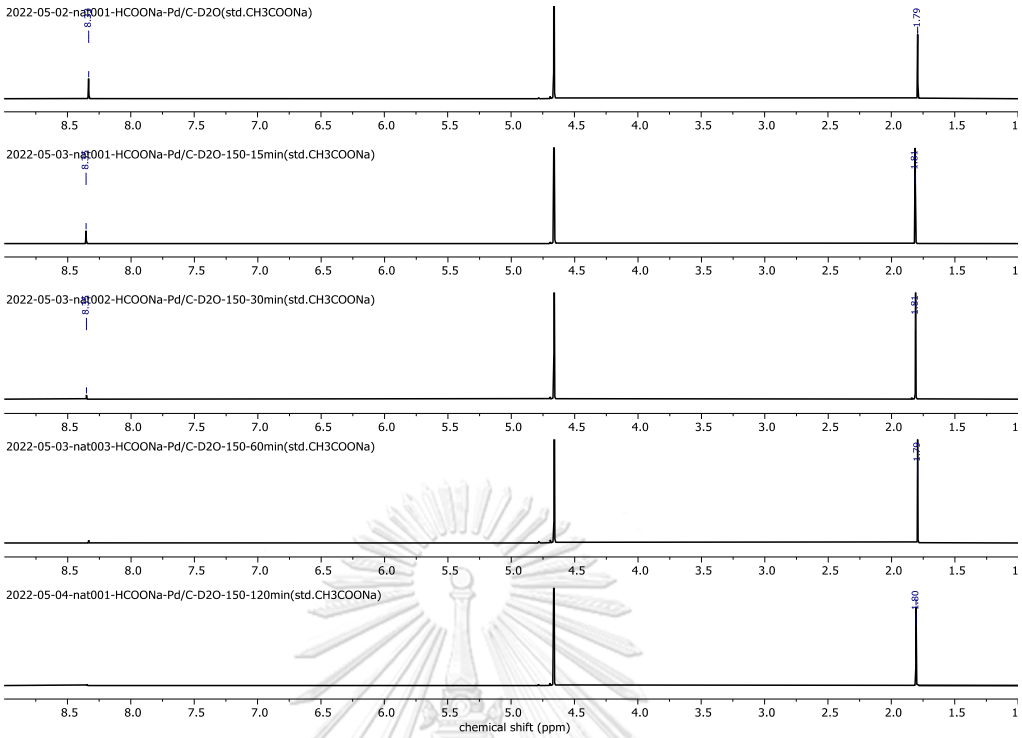


Figure 3.36 ^{1}H NMR spectra of the reaction products from the HDx of HCOONa in D_2O with CH_3COONa under hydrothermal conditions with different reaction time

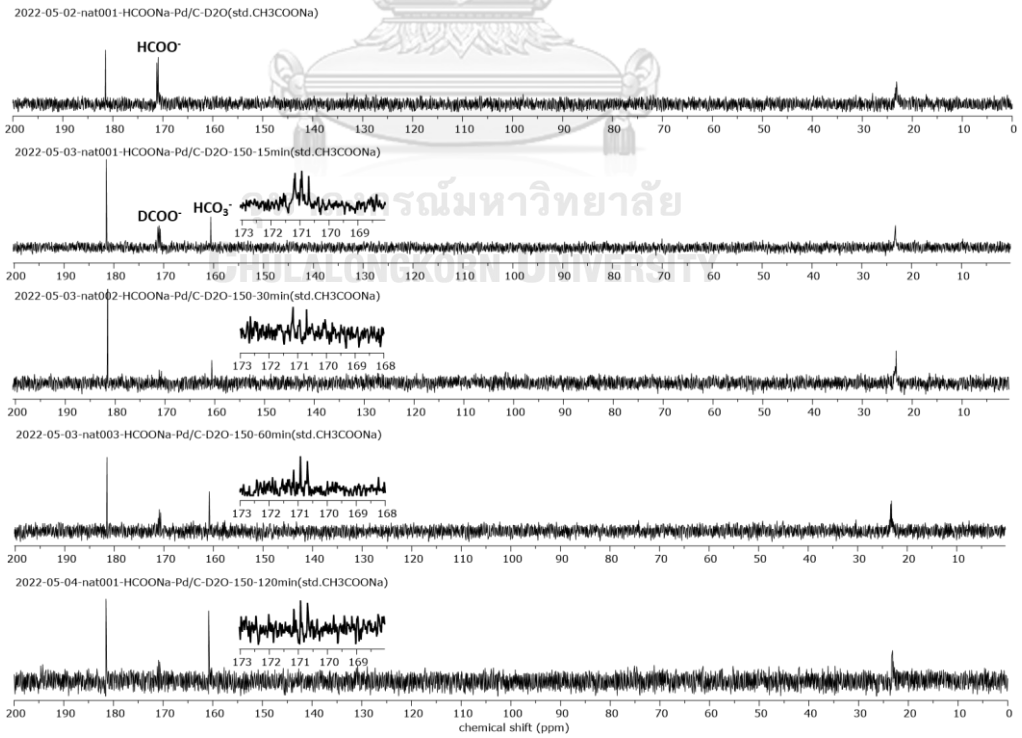


Figure 3.37 ^{13}C NMR spectra of the reaction products from the HDx of HCOONa in D_2O with CH_3COONa under hydrothermal conditions with different reaction time

Based on the information above, the fate of HCOONa is proposed as shown in **Figure 3.38**. The formate undergoes a Pd-catalyzed dehydrogenation in D_2O to form deuterocarbonate and hydrogen gas (likely in the Pd-bound form). The deuterocarbonate could then be reduced to deuteroformate, either by the Pd-bound hydrogen or Pd-bound deuterium arising from the HDx on the Pd surface. In the presence of the C-X substrate, the deuteroformate would ultimately transfer the deuterium to the product and be converted to carbonate/bicarbonate.

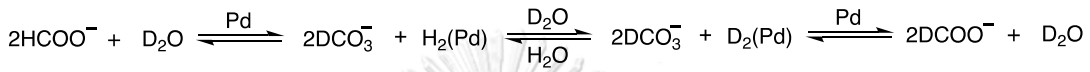


Figure 3.38 A proposed mechanism for the HDx of sodium formate

Formate can also be converted to oxalate, which is also a powerful reducing agent.[56] Since the chemical shift ^{13}C signal of oxalate (δ_C $C_2O_4^{2-}$ = 162.1 ppm)[57] and carbonate/bicarbonate (δ_C HCO_3^- = 161.7 ppm) were similar, it was not possible to ascertain this by ^{13}C NMR. To confirm that the reaction pathway does not occur via sodium oxalate intermediate. The debromination and deuteration of 4-bromophenol in the presence of $Na_2C_2O_4$ was investigated in H_2O and D_2O, under the standard conditions (**Figure 3.39**). No reaction was observed in H_2O and only partial *ortho*-HDx (11%) was observed in D_2O. The results confirmed that the reaction did not proceed through the oxalate intermediate.

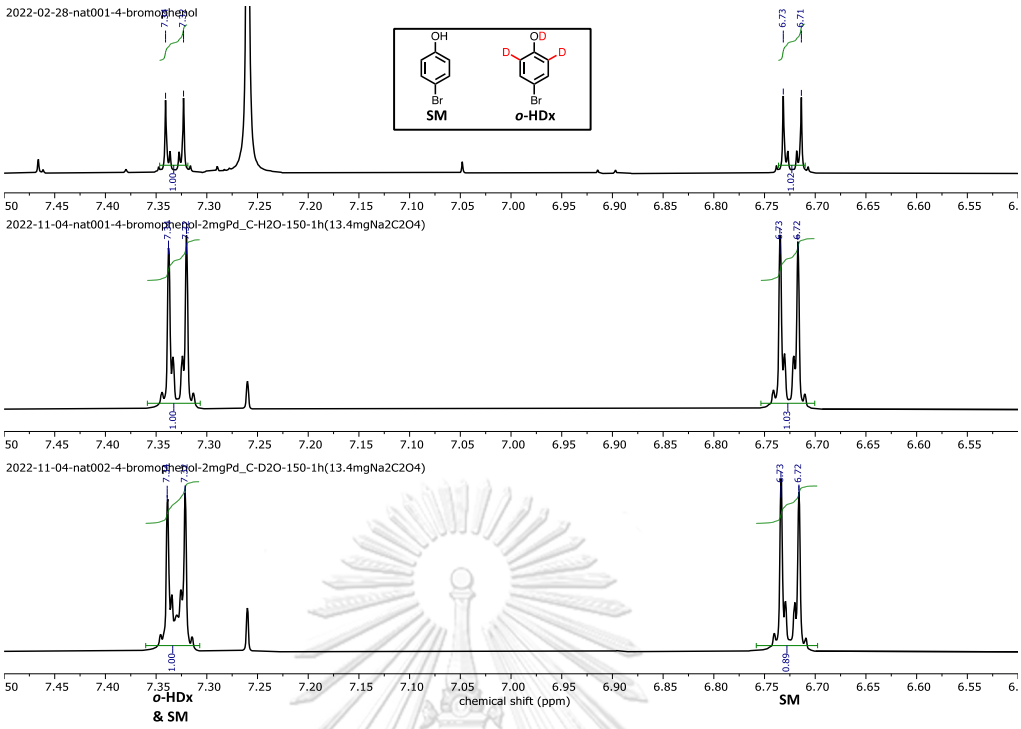


Figure 3.39 ^{1}H NMR spectra of the reaction products from the XHx and XDx of 4-bromophenol in the presence of $Na_2C_2O_4$

To confirm that 10% Pd/C is required, the deuteration of $HCOONH_4$ was examined in the absence and presence of 10% Pd/C. In the presence of 10% Pd/C, the formate signal disappeared as it was converted to CO_3^{2-} as shown in **Figure 3.40**. On the other hand, in the absence of Pd, the formate signal remained unchanged indicating that the Pd/C was essential.

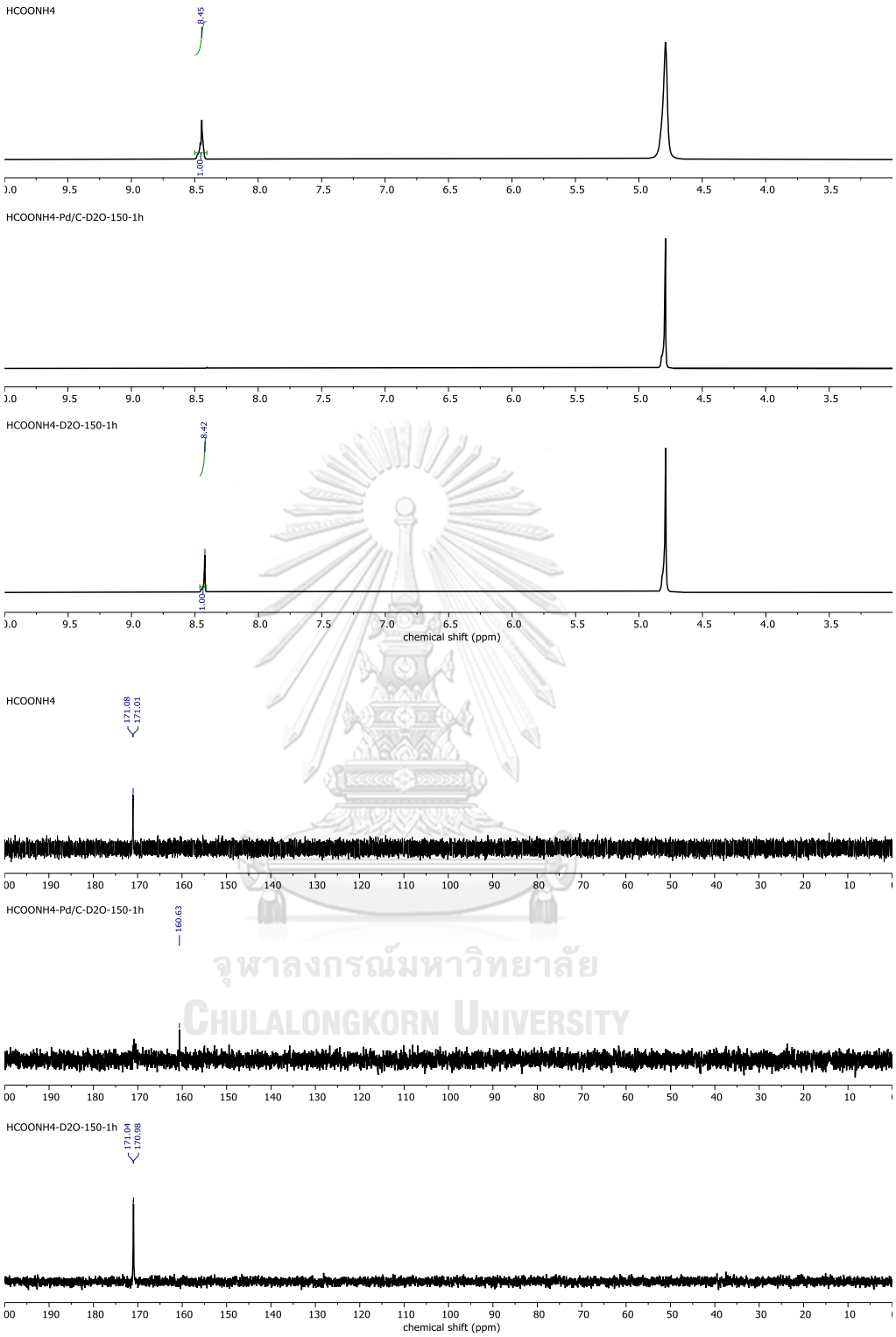


Figure 3.40 ^{1}H NMR and ^{13}C NMR spectra from the HDx of $HCOONH_4$ in the presence and absence of 10% Pd/C

3.2.10 Concluding remarks for the XDx studies

We have also explored the halogen-deuterium exchange (XDx) reaction using a formate salt and Pd/C in D_2O under hydrothermal conditions. The conditions were optimized using 4-bromophenol as a model substrate and it was found that HCOONa (0.1 mmol, 6.8 mg) and Pd/C (0.0025 mmol, 2.0 mg) in D_2O (500 µL) at 150 °C for 1 h gave the good conversion and little *ortho*-HDx. Surprisingly, although non-deuterated formate was used as the reducing agent, the XDx:XHx ratio was relatively good probably due to the facile Pd-catalyzed HDx process in the presence of excess D_2O. Acceptable results were obtained when the same reaction condition was applied to other halogenated aromatic compounds except for certain substrates that exhibit poor solubilities in water, even under subcritical conditions. In some cases, improved results were obtained with the use of DCOONa generated *in situ* from DCOOD and Na_2CO_3 instead of HCOONa. In other cases, improvement is still needed. The solubility problem can be solved by using a solubilizing agent such as a surfactant or co-solvent. It was later realized that the palladium catalyst used contains significant amounts of water and thus drying the catalyst or replacing water in the catalyst with D_2O further should improve the XD:XH ratio further.

CHAPTER IV

CONCLUSION

In this thesis, the hydrogen-deuterium exchange reactions (HDx) of organic compounds with various functional groups (aromatic, alicyclic, heterocyclic, and amino acids) have been investigated under hydrothermal conditions. The reactions were performed by heating the substrates in D_2O at 230 °C for 1 h in a screw-capped stainless steel reactor, optionally in the presence of acid or base catalyst. α-Amino acids and phenols are good substrates for the hydrothermal HDx. In the absence of any catalyst, the HDx occurred readily and selectively at the α-CH and *ortho/para*-positions, respectively. The addition of a base further promoted the *ortho*-HDx of phenolic substrates, while the addition of acid could promote the HDx at other positions on the aromatic ring. The α-CH_2 group adjacent to the carboxyl group exchanged slowly unless an acid catalyst was present. Thus, selective deuteration can be achieved by selecting the appropriate conditions (no catalyst, acidic, basic). The limitations of the methodology include 1) some compounds were inert or gave complex mixtures under the developed hydrothermal HDx conditions 2) for scaling up the reaction, the maximum temperature was limited to 230 °C because this is the maximum temperature that can be used with the Teflon-lined reactor used for scaling up.

In addition, a complementary strategy for the preparation of deuterium-labeled compounds namely the halogen-deuterium exchange (XDx) reaction was also investigated. Various aromatic halides underwent efficient XDx when heated with a formate salt and Pd/C in D_2O under hydrothermal conditions. In a model XDx reaction of 4-bromophenol, the reaction took place readily at 150 °C for 1 h with only little competing *ortho*-HDx. Remarkably, the XDx:XHx product ratio was good even if the non-deuterated formate salt was used as the reducing agent due to the facile Pd-catalyzed HDx process in the presence of excess D_2O. However, when the same reaction condition was applied to other halogenated aromatic compounds, poor results were obtained with certain substrates. Nevertheless, satisfactory results were obtained with the use of DCOONa generated in situ from DCOOD and Na_2CO_3

instead of HCOONa. Further improvement is still required for other substrates, for example by the use of a solubilizing agent to improve the water solubility of the substrate and/or by drying the Pd catalyst to remove the contaminated water.

In conclusion, the developed methods could provide two complementary approaches for preparing deuterated compounds with high efficiency. The reaction should be further investigated to determine the generality/limitation of the reaction and to expand the substrate scope.

APPENDIX

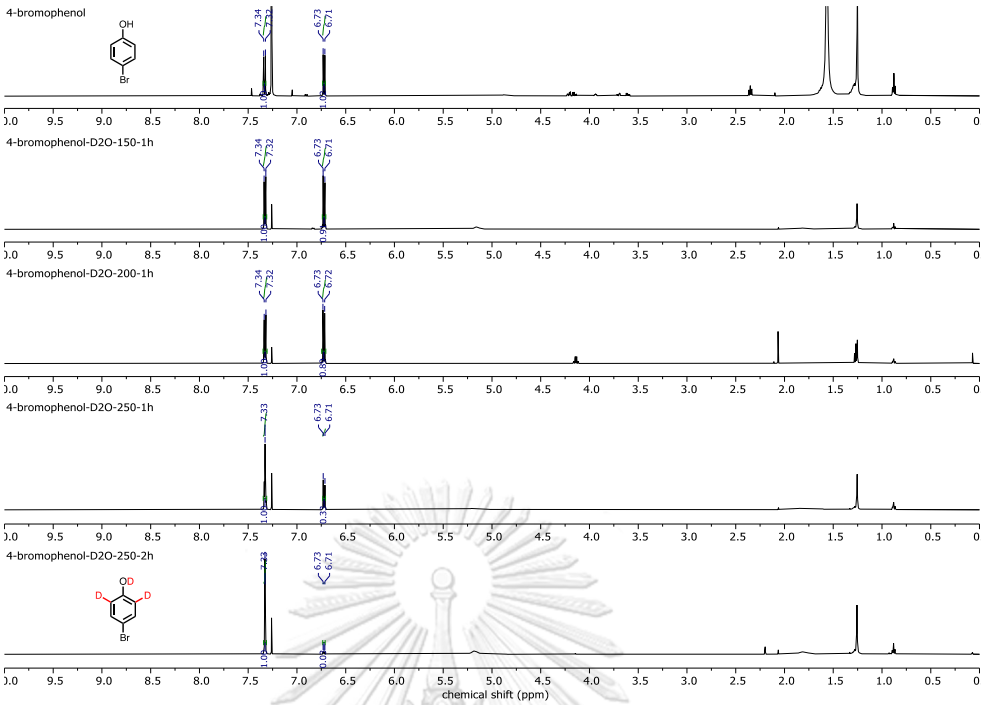


Figure A1 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the HDx reaction of 4-bromophenol at 150-250 °C for 1-2 h

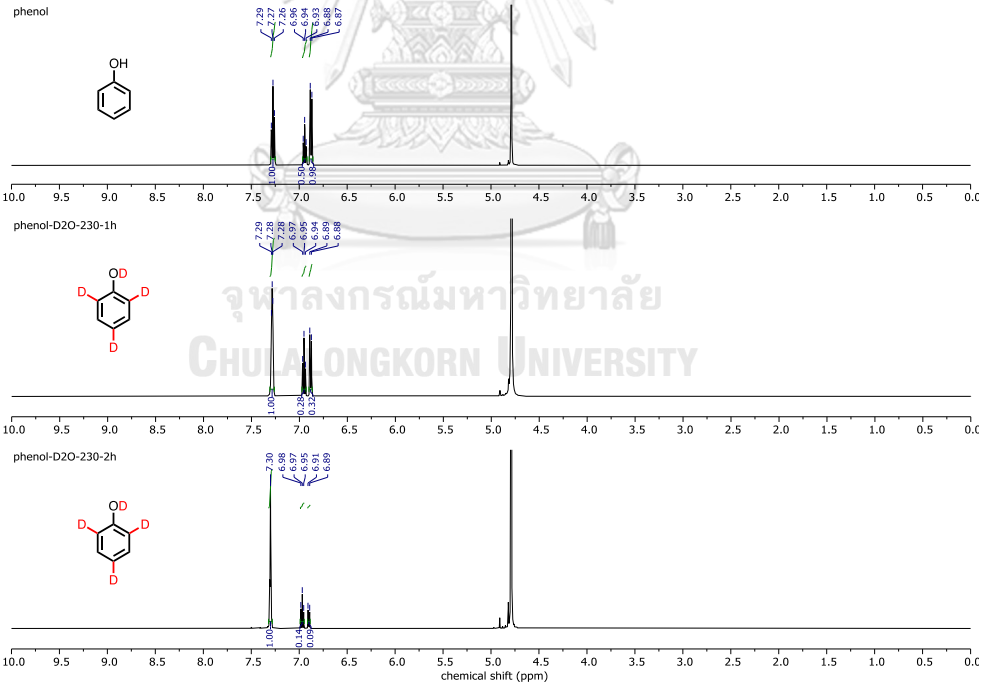


Figure A2 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of phenol at 230 °C for 1-2 h

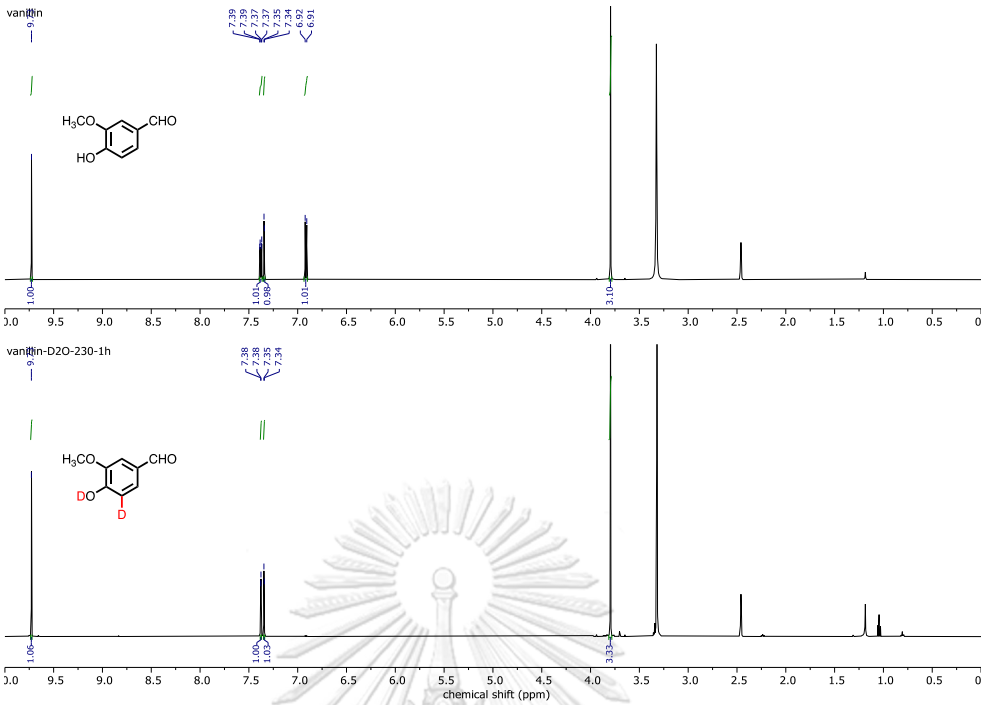


Figure A3 ^{1}H NMR (500 MHz, DMSO-d_6) NMR spectrum of the HDx reaction of vanillin at 230 °C for 1 h

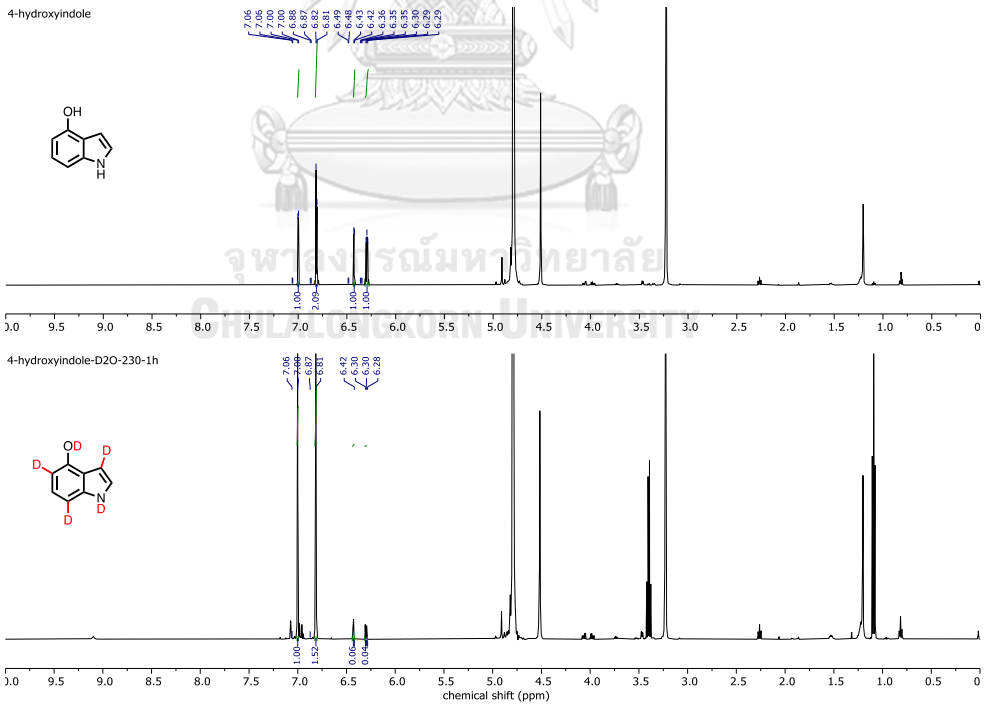


Figure A4 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of 4-hydroxyindole at 230 °C for 1 h

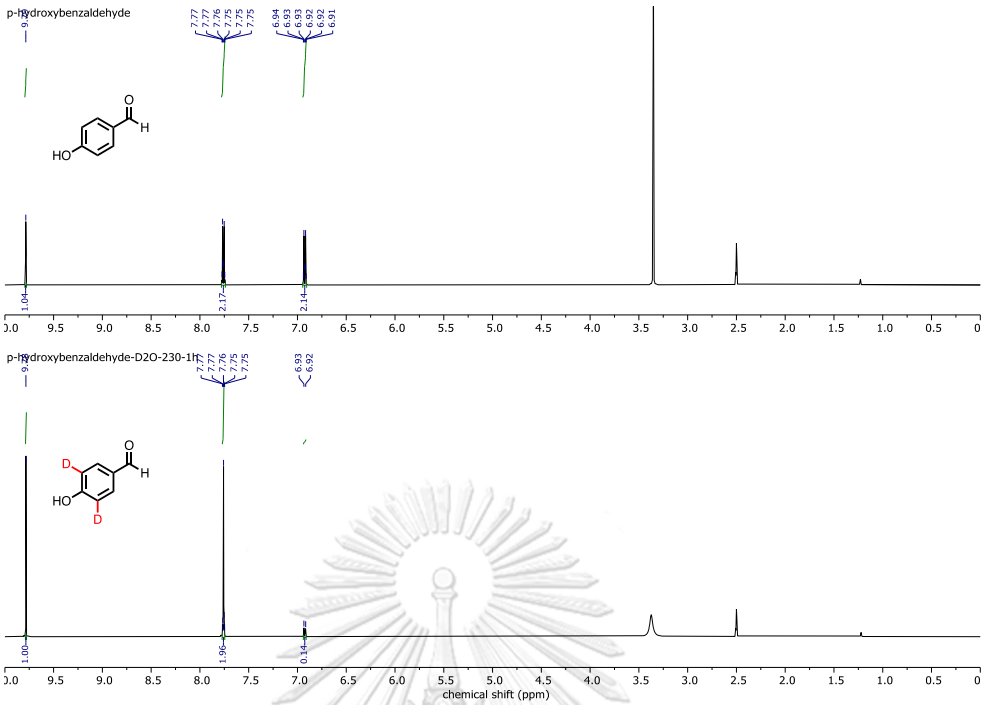


Figure A5 ^{1}H NMR (500 MHz, DMSO-d_6) NMR spectrum of the HDx reaction of *p*-hydroxybenzaldehyde at 230 °C for 1 h

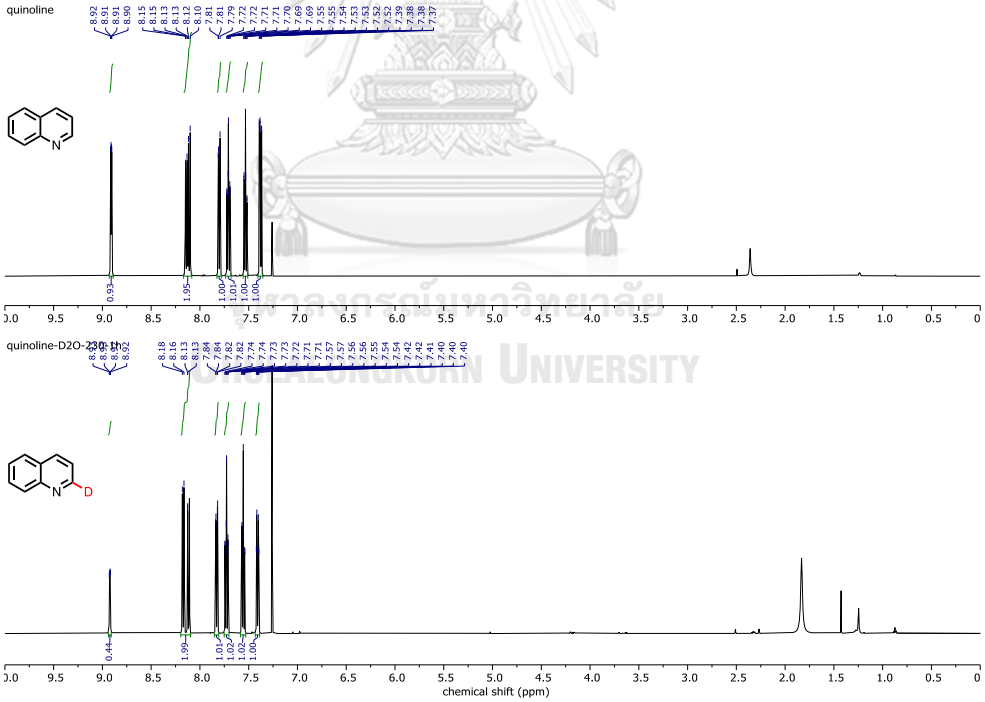


Figure A6 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the HDx reaction of quinoline at 230 °C for 1 h

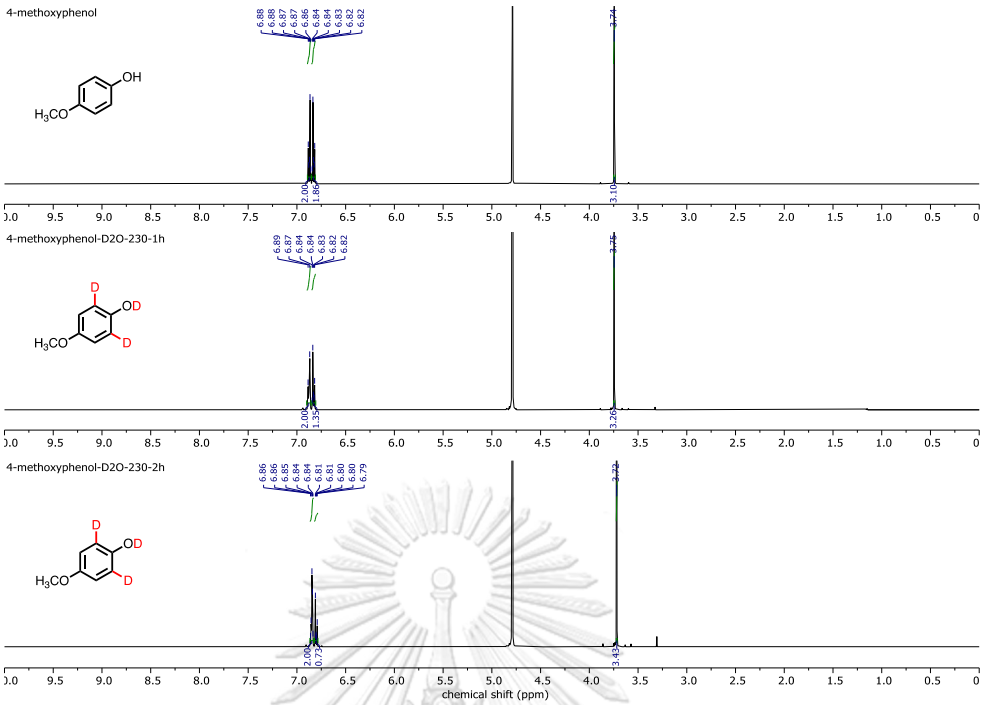


Figure A7 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of 4-methoxyphenol at 230 ℃ for 1-2 h

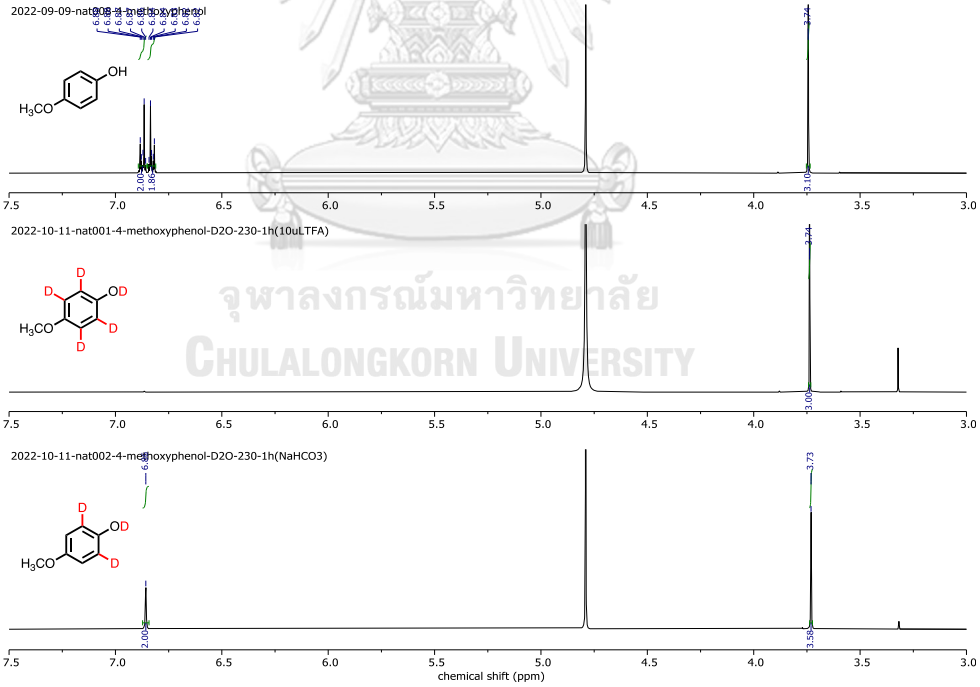


Figure A8 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of 4-methoxyphenol in the presence of TFA and $NaHCO_3$ at 230 ℃ for 1 h

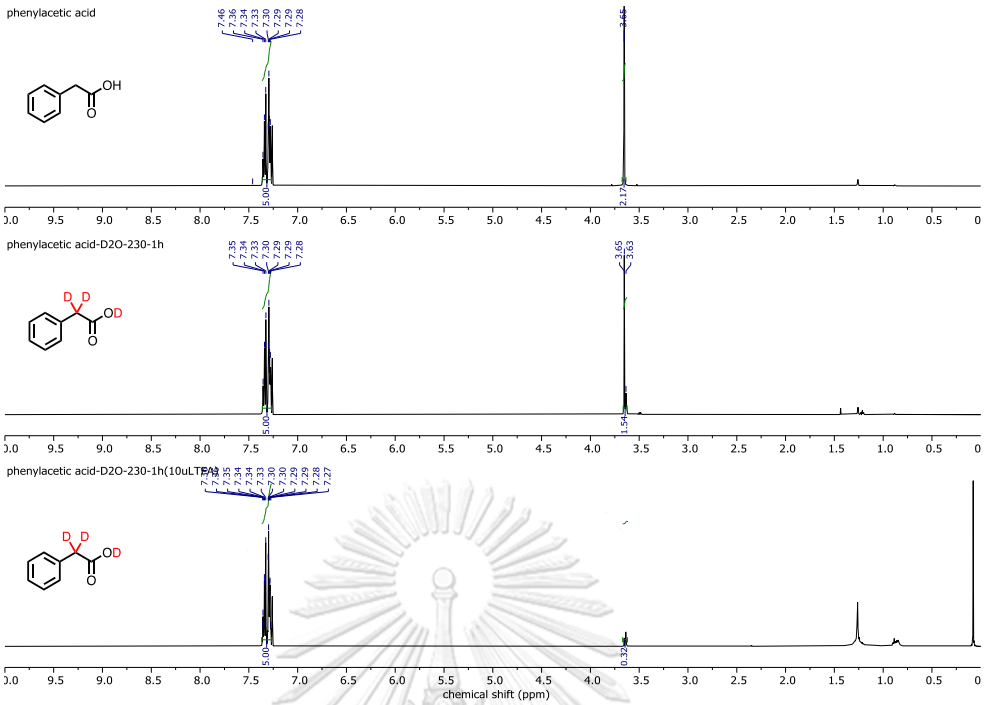


Figure A9 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the HDx reaction of phenylacetic acid at 230 °C in D_2O and TFA for 1 h

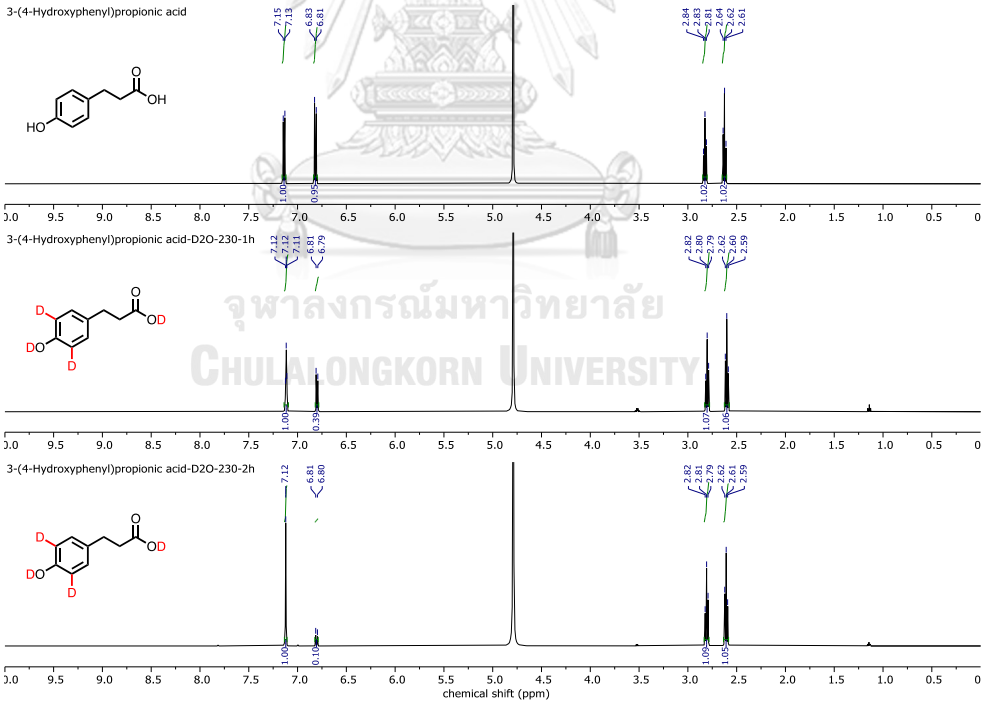


Figure A10 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of 3-(4-hydroxyphenyl)propionic acid at 230 °C for 1-2 h

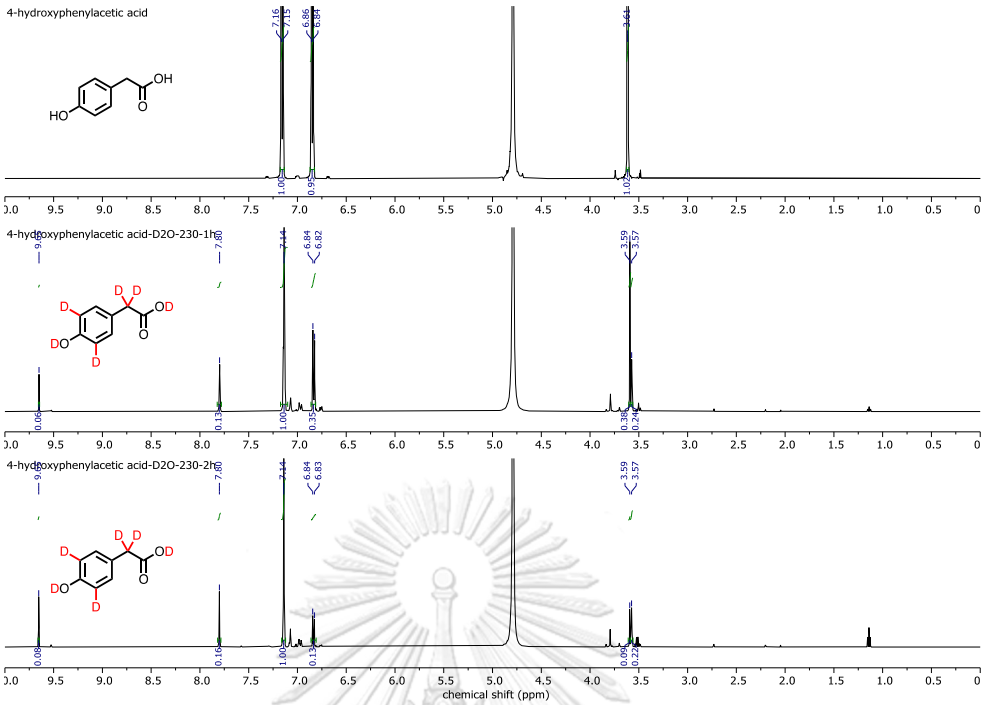


Figure A11 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of 4-hydroxyphenylacetic acid at 230 °C for 1-2 h

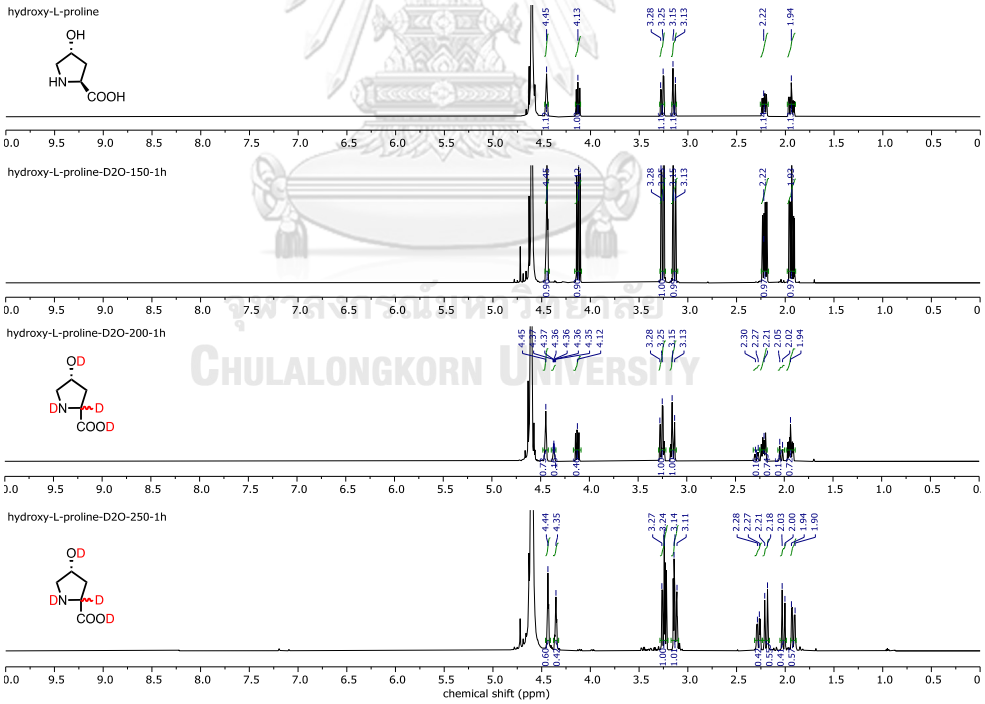


Figure A12 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of *trans*-4-hydroxy-L-proline at 150-250 °C for 1 h

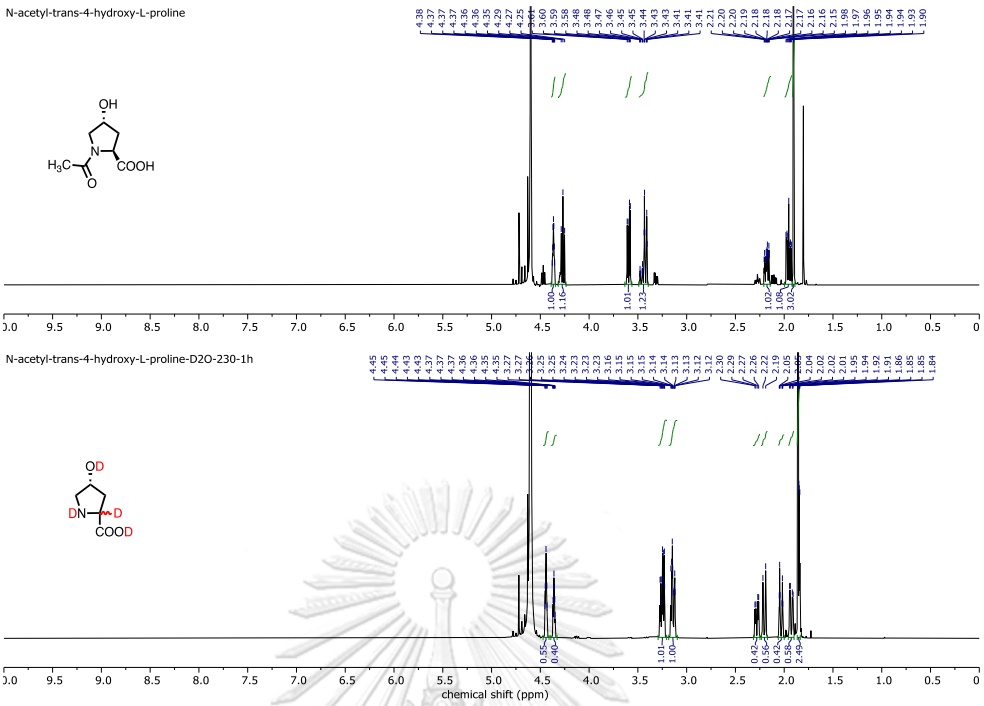


Figure A13 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of *N*-acetyl-*trans*-4-hydroxy-L-proline at 230 °C for 1 h

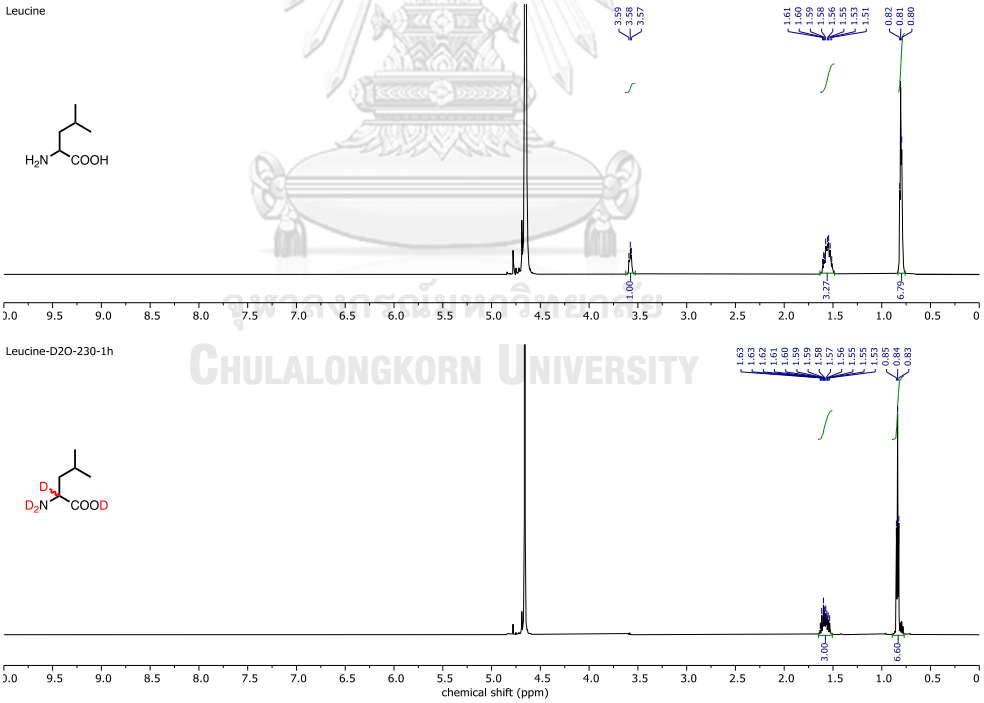


Figure A14 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of L-leucine at 230 °C for 1 h

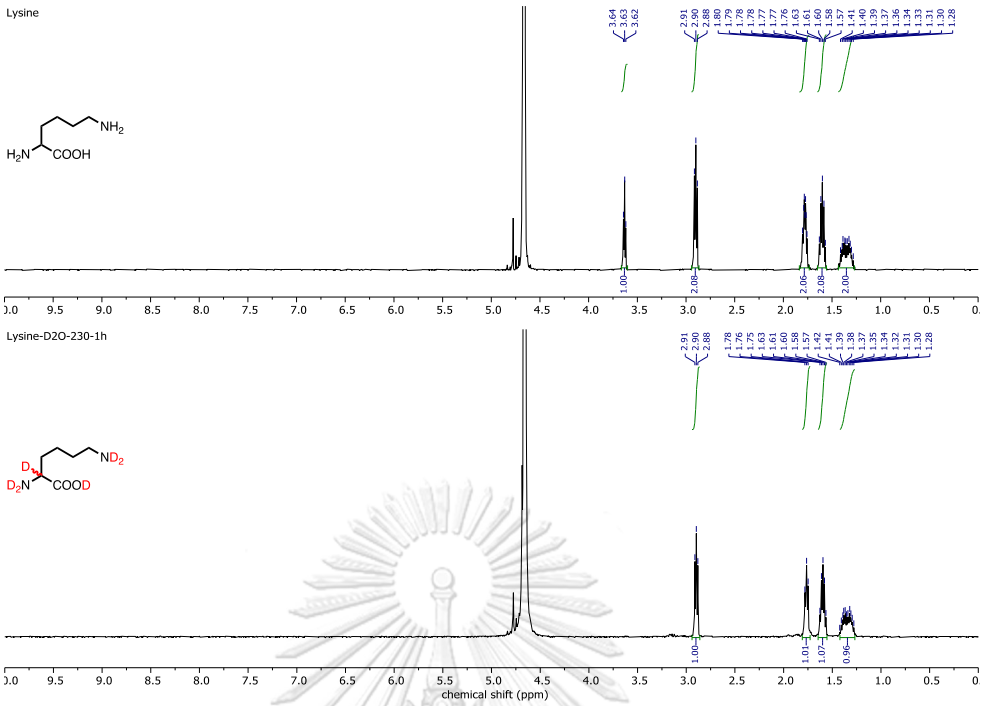


Figure A15 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of L-lysine at 230 °C for 1 h

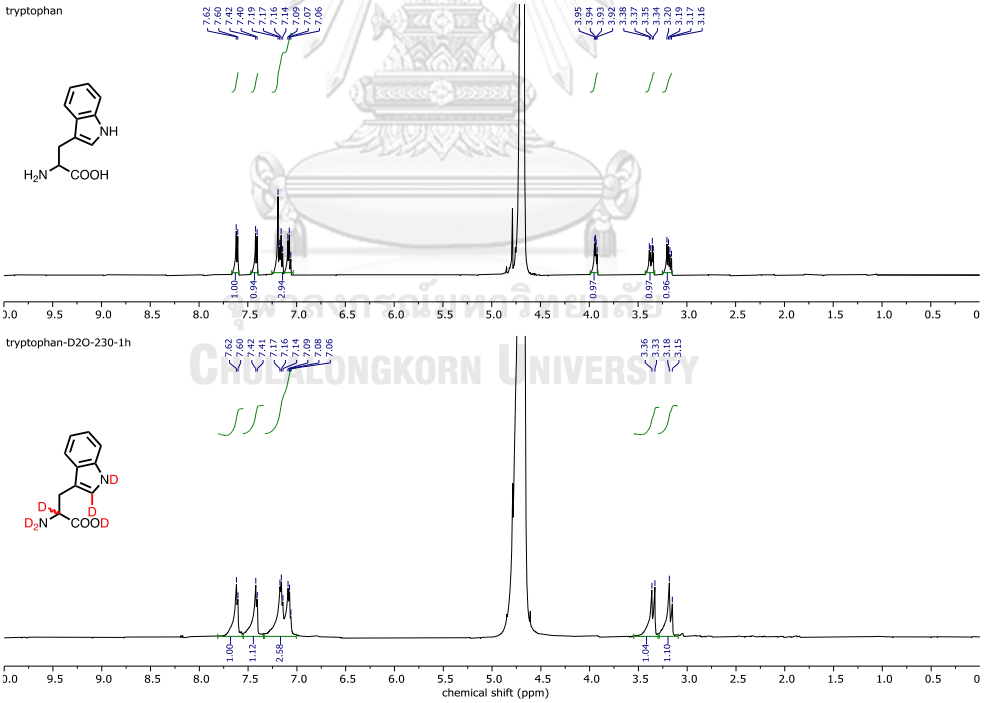


Figure A16 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of L-tryptophan at 230 °C for 1 h

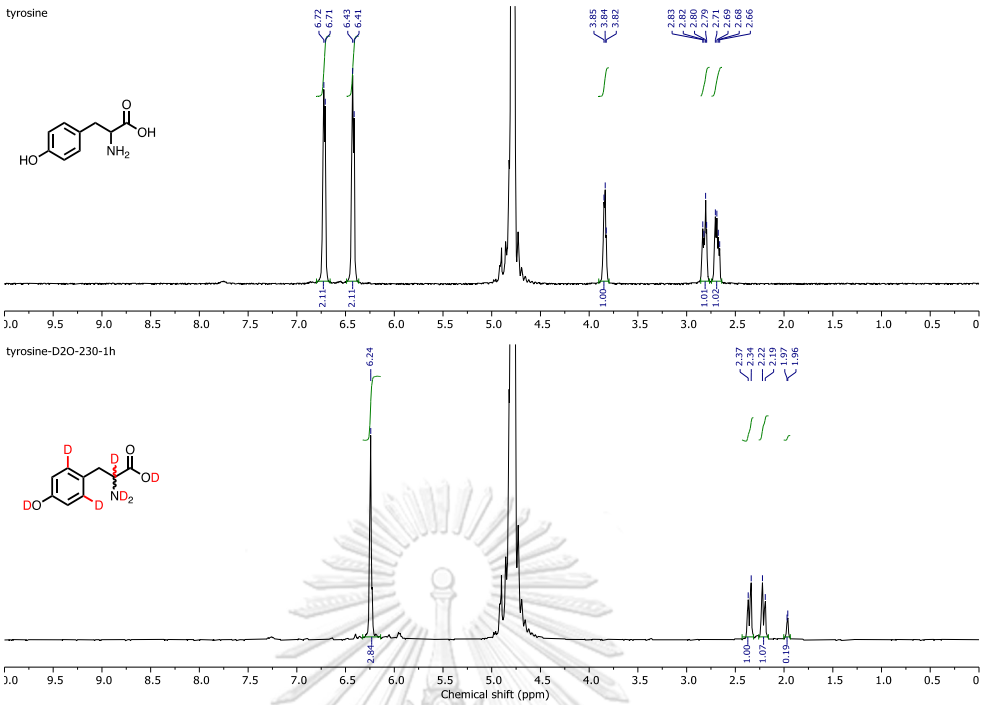


Figure A17 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of L-tyrosine at 230 °C for 1 h

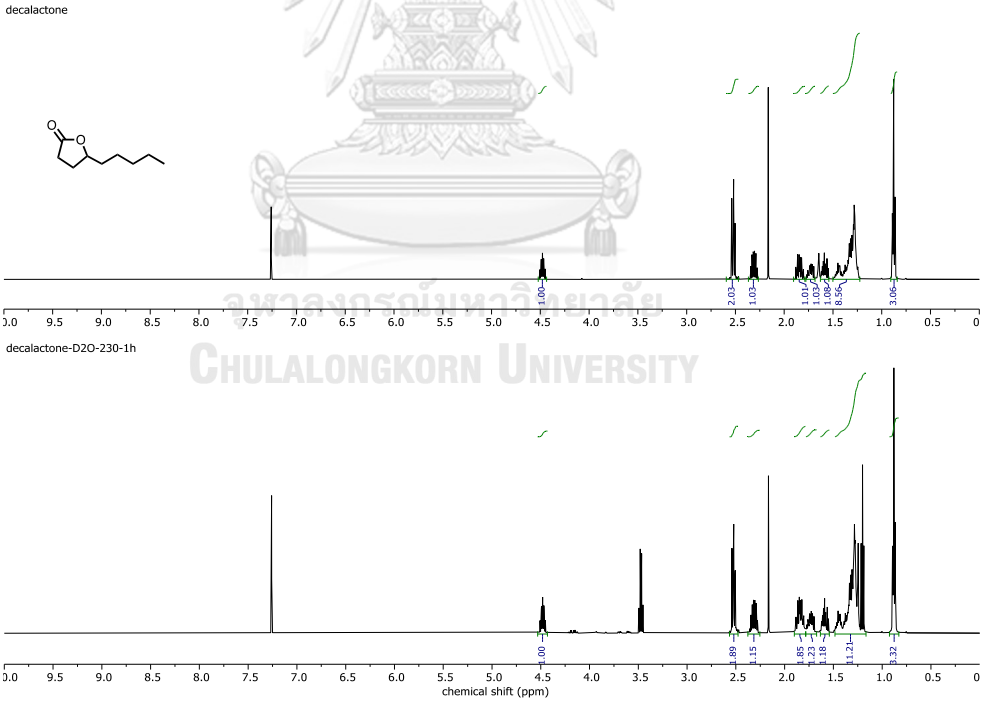


Figure A18 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the HDx reaction of decalactone at 230 °C for 1 h

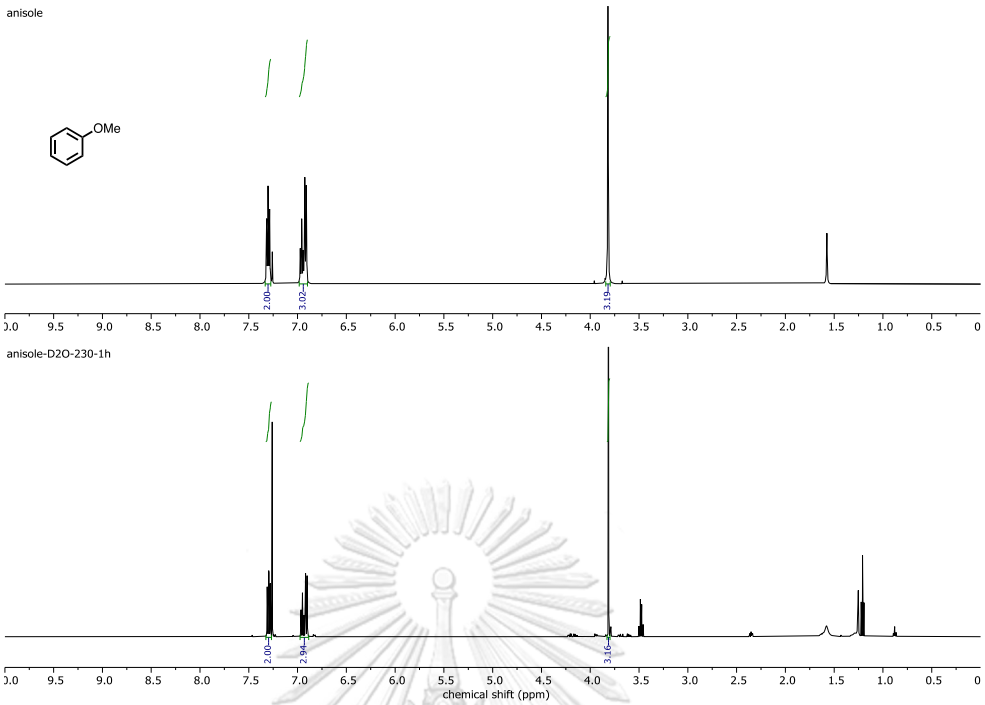


Figure A19 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the HDx reaction of anisole at 230 ℃ for 1 h

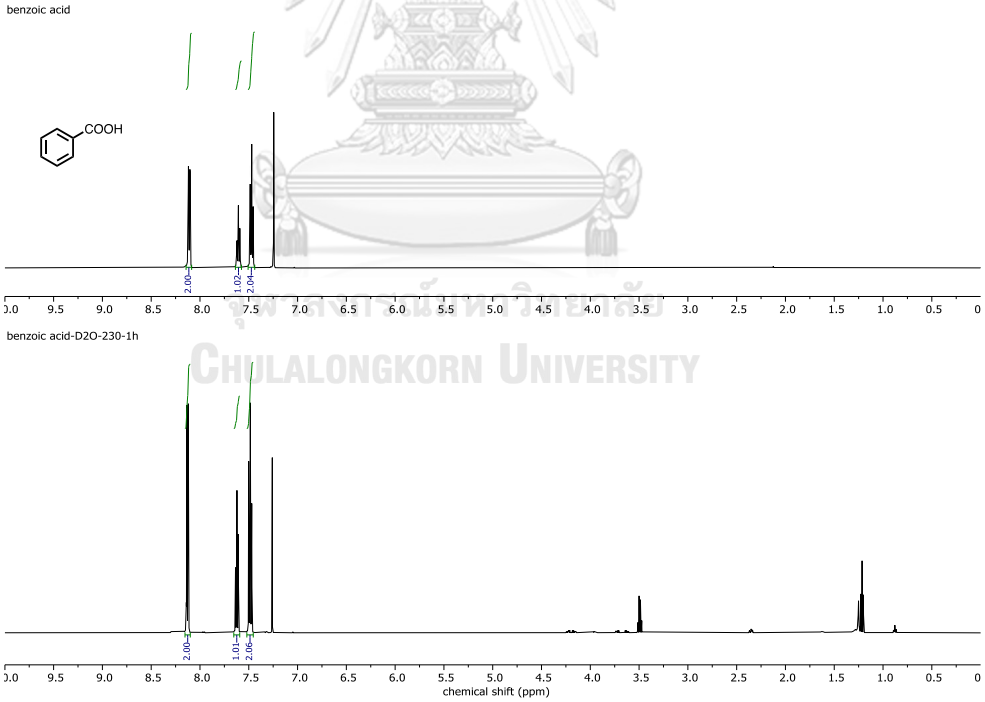


Figure A20 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the HDx reaction of benzoic acid at 230 ℃ for 1 h

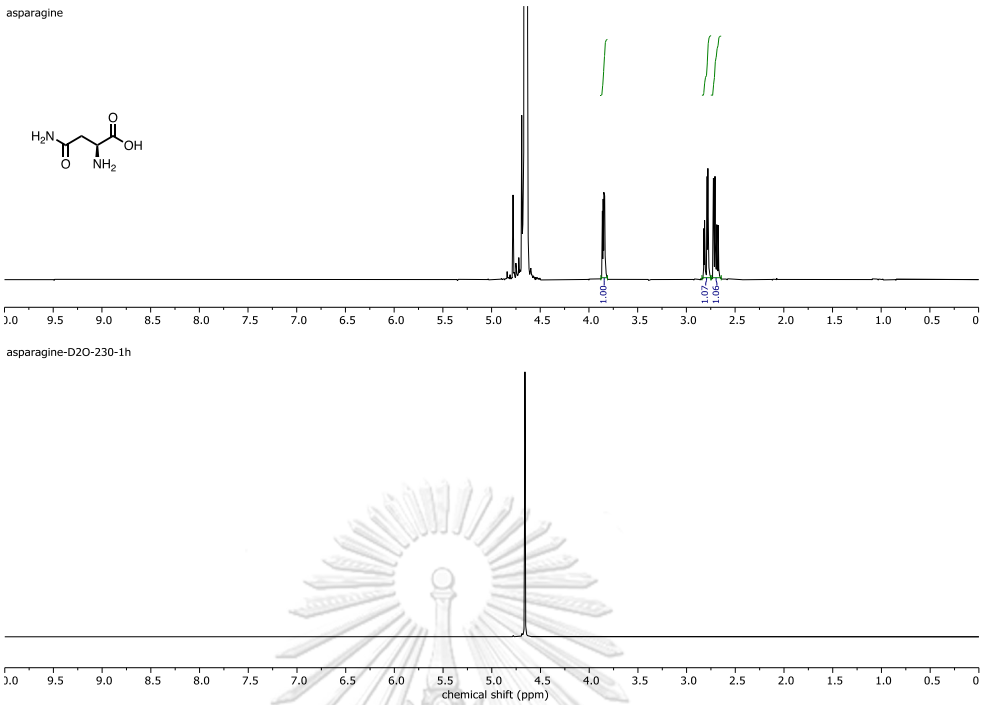


Figure A21 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of L-asparagine at 230 ℃ for 1 h

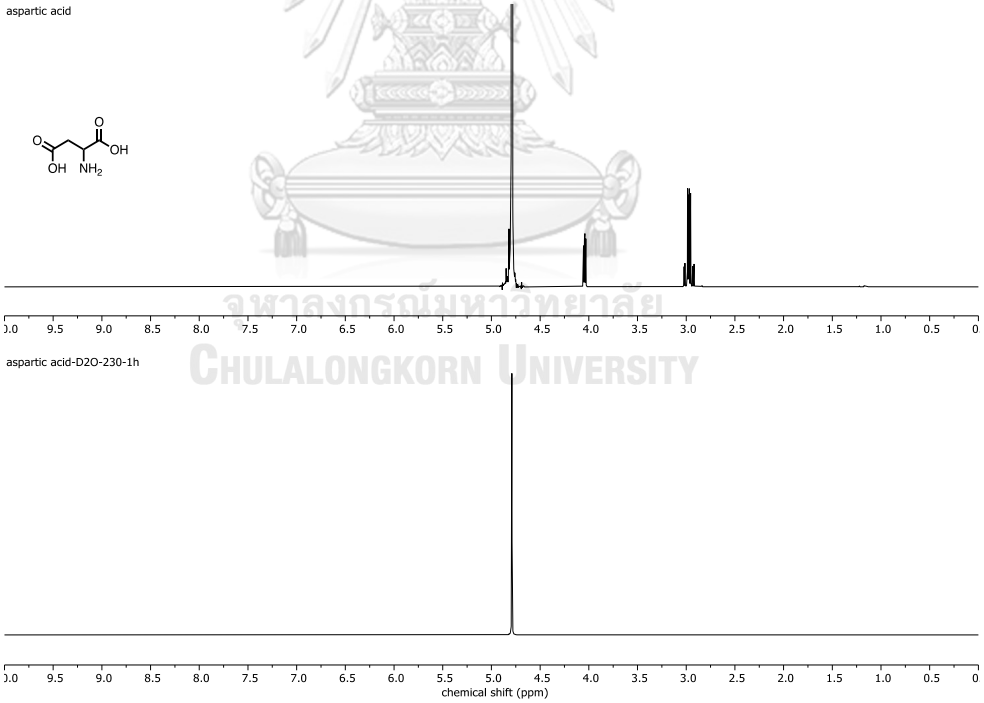


Figure A22 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of L-aspartic acid at 230 ℃ for 1 h

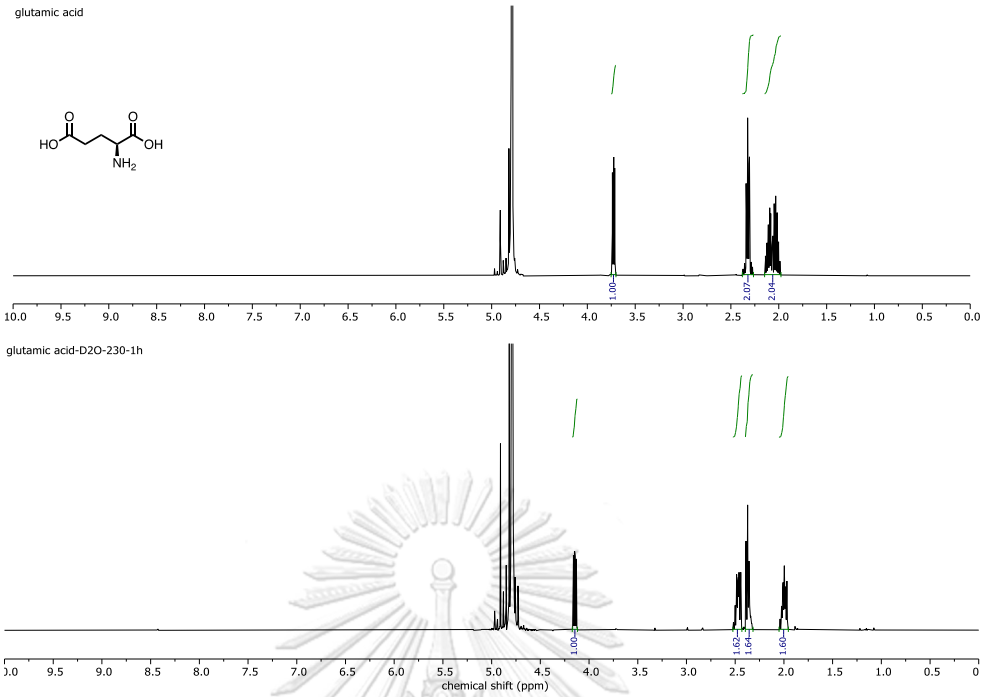


Figure A23 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of L-glutamic acid at 230 ℃ for 1 h

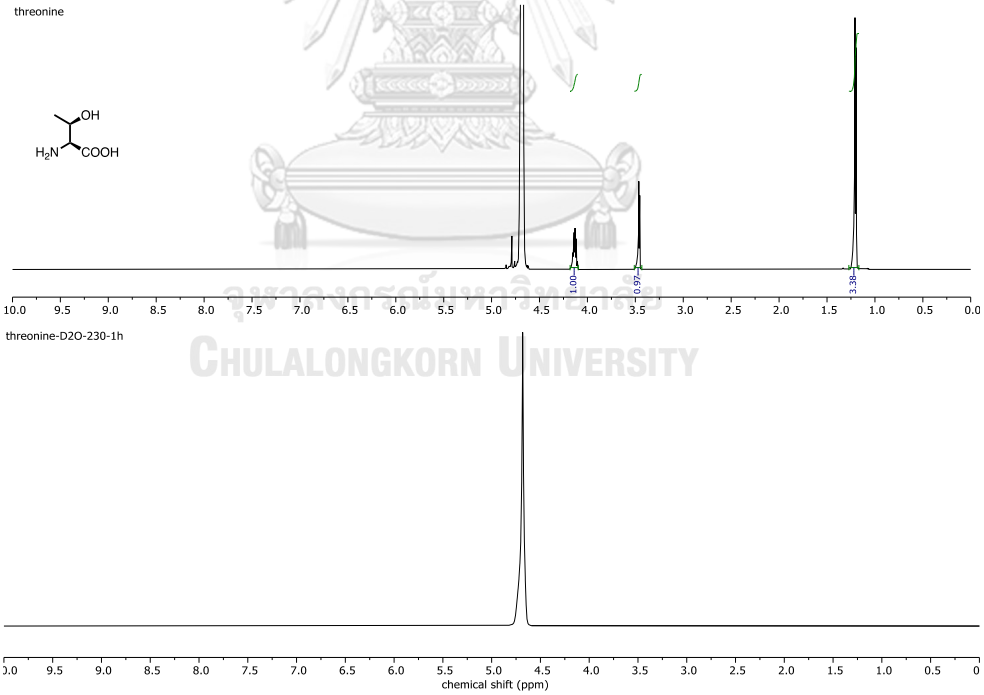


Figure A24 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of L-threonine at 230 ℃ for 1 h

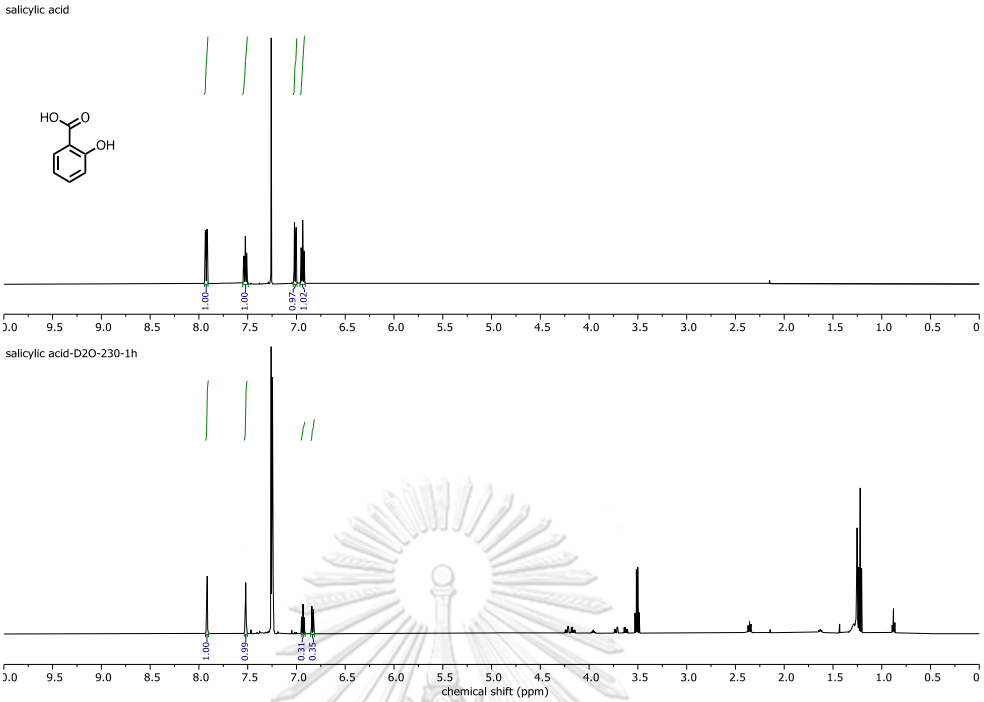


Figure A25 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the HDx reaction of salicylic acid at 230 °C for 1 h

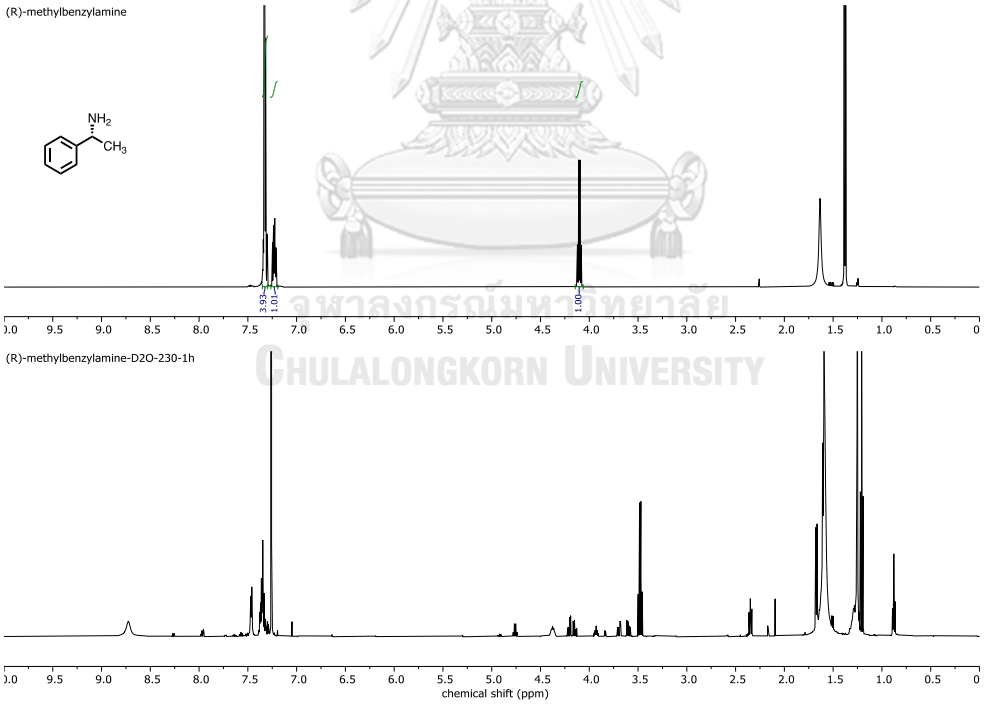


Figure A26 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the HDx reaction of α-methylbenzylamine at 230 °C for 1 h

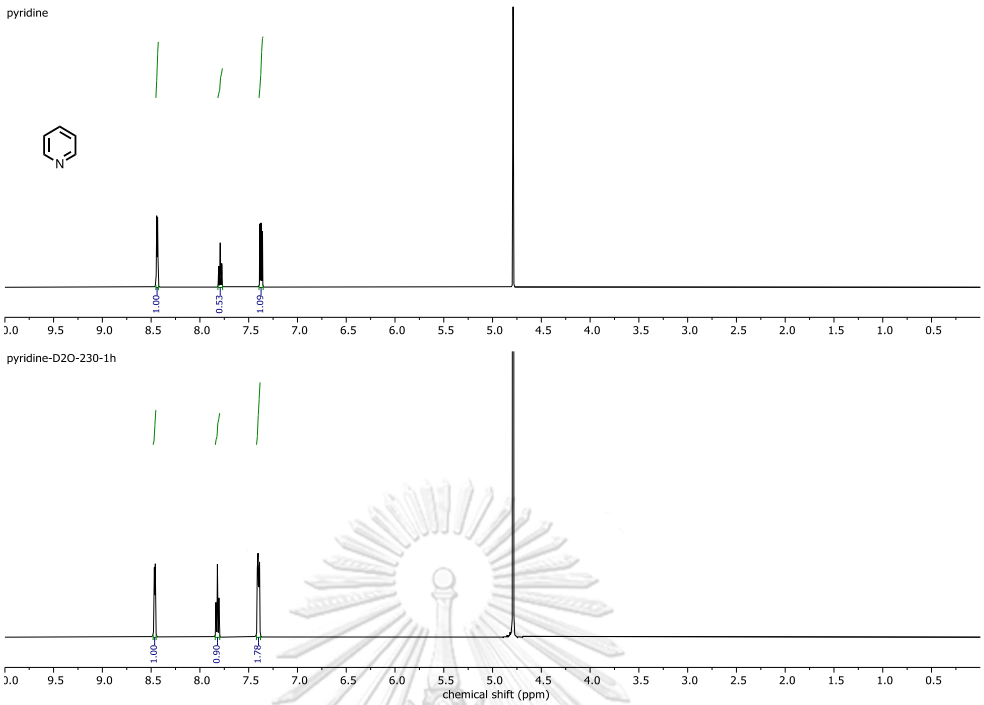


Figure A27 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of pyridine at 230 °C for 1 h

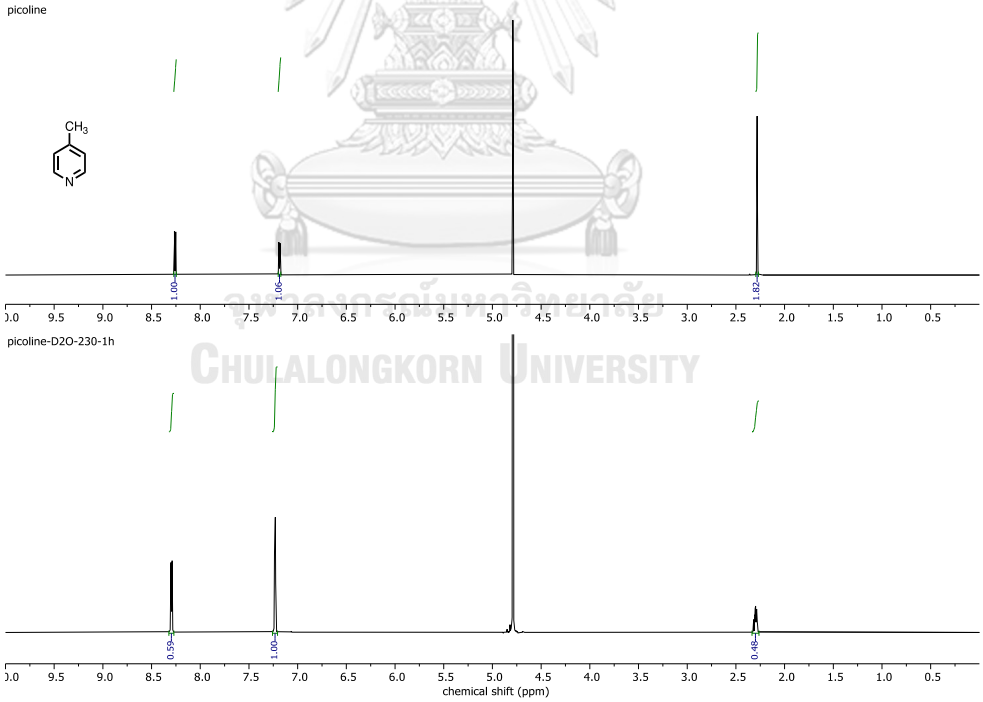


Figure A28 ^{1}H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of 4-picoline at 230 °C for 1 h

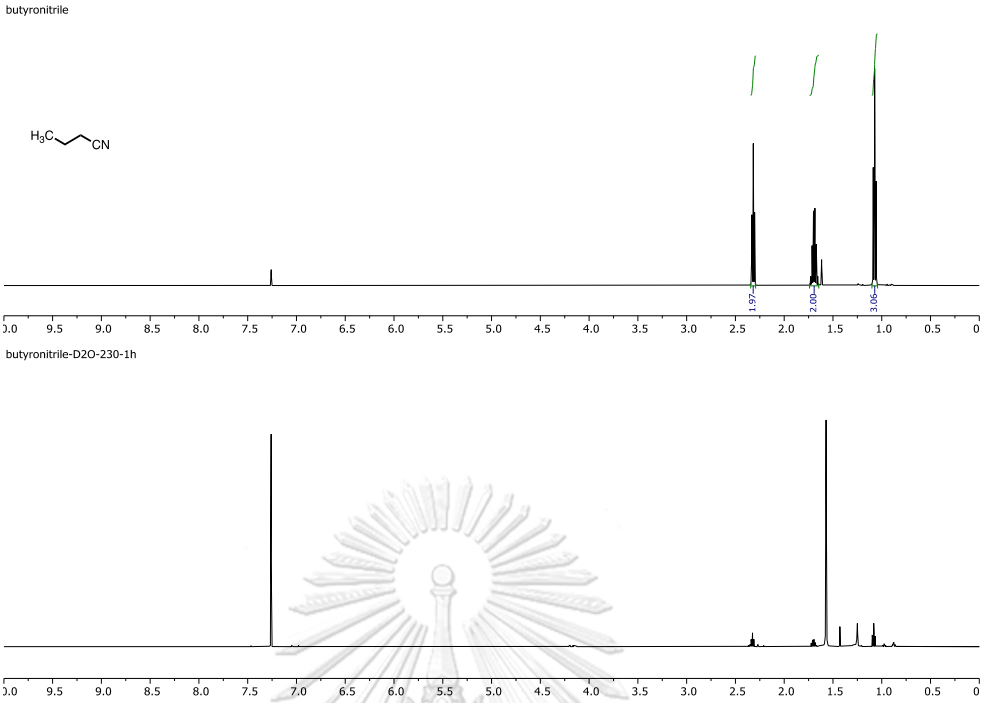


Figure A29 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the HDx reaction of butyronitrile at 230 ℃ for 1 h

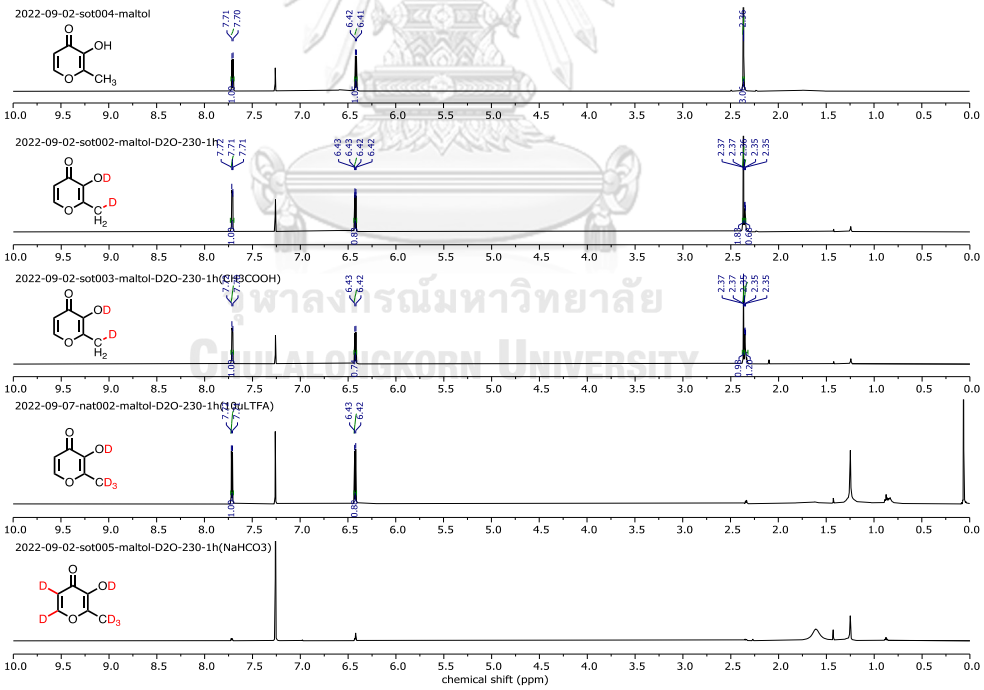


Figure A30 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the HDx reaction of maltol at 230 ℃ for 1 h under neutral, acid, and base conditions

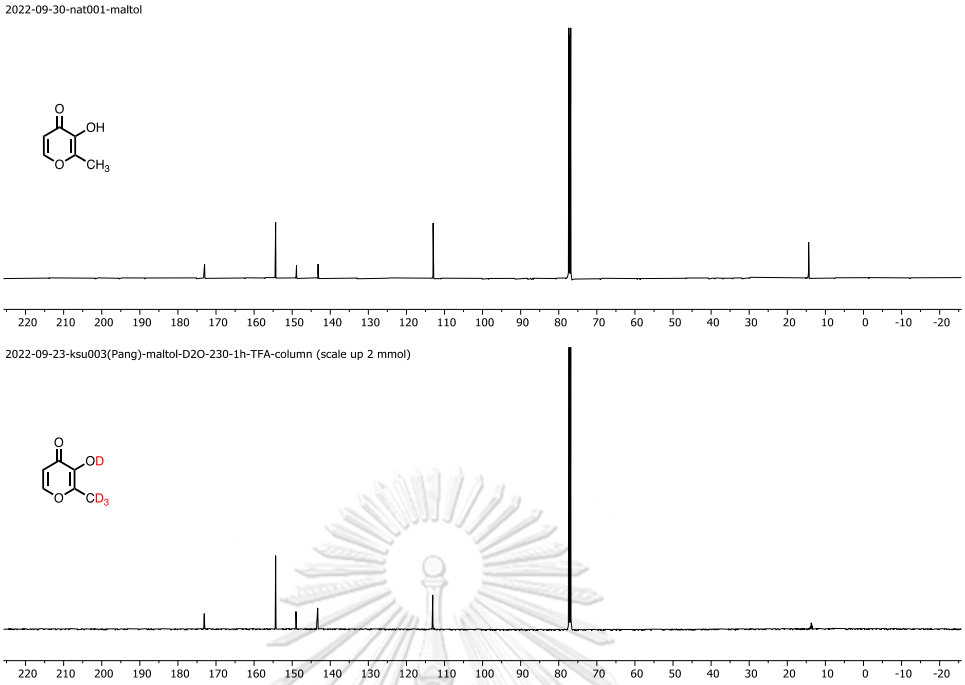


Figure A31 ^{13}C NMR (126 MHz, $CDCl_3$) NMR spectrum of maltol and maltol-d_4

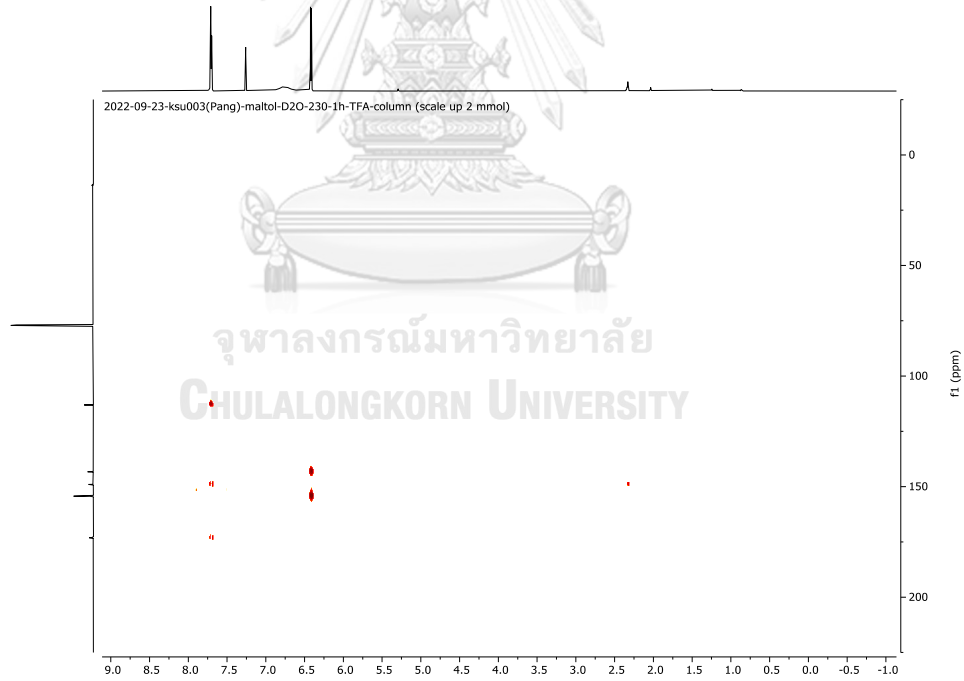


Figure A32 2D HMBC NMR (500 MHz, $CDCl_3$) NMR spectrum of maltol-d_4

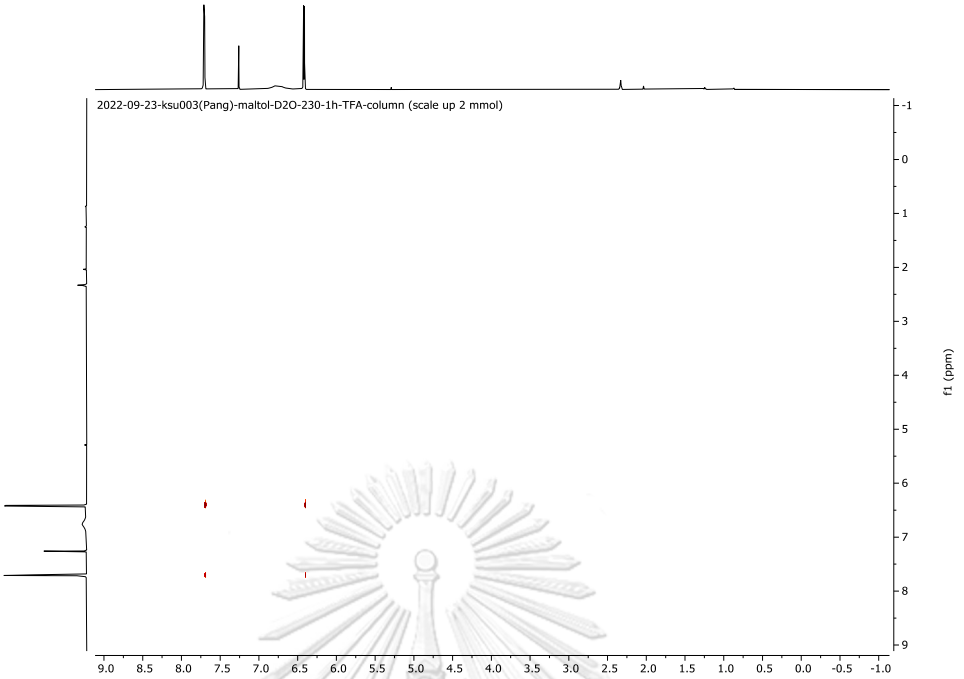


Figure A33 2D COSY NMR (500 MHz, $CDCl_3$) NMR spectrum of maltol-d_4

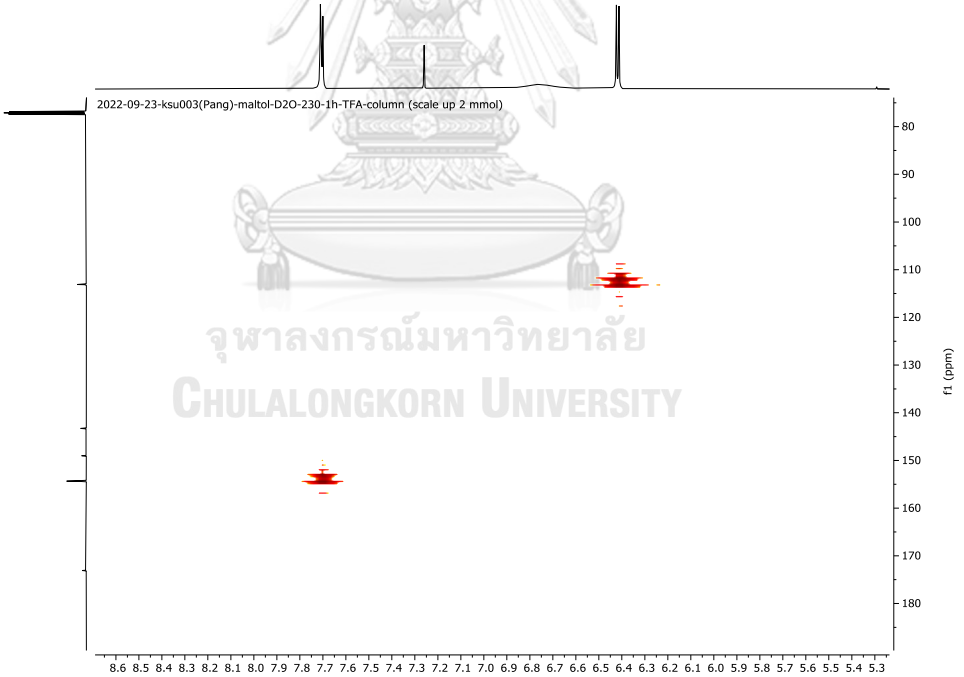


Figure A34 2D HSQC NMR (500 MHz, $CDCl_3$) NMR spectrum of maltol-d_4

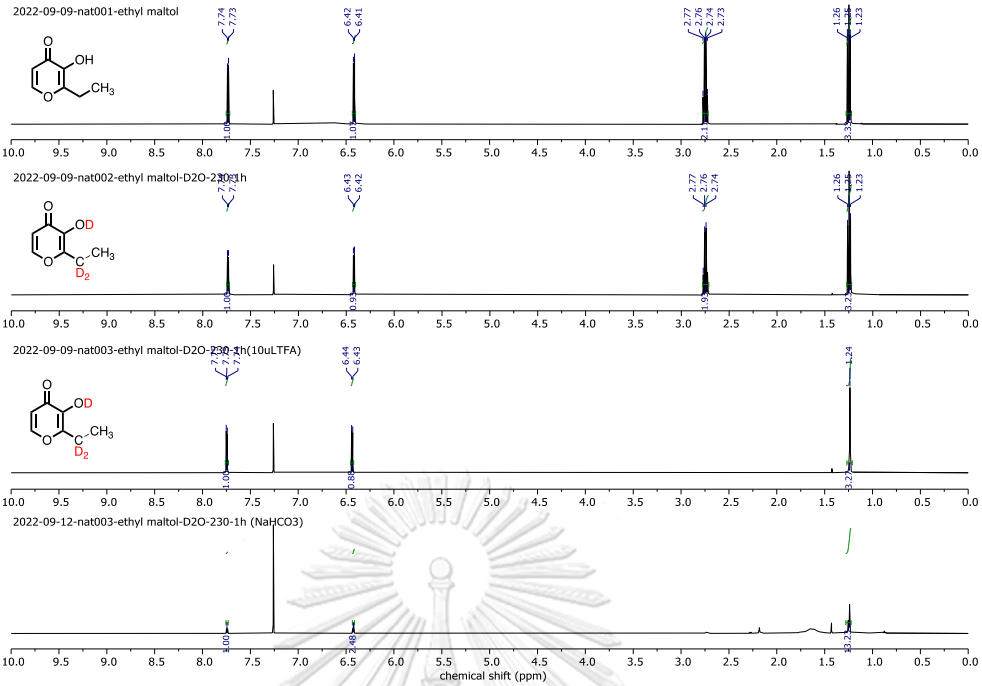


Figure A35 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the HDx reaction of ethyl maltol at 230 °C for 1 h under neutral, acid, and base conditions

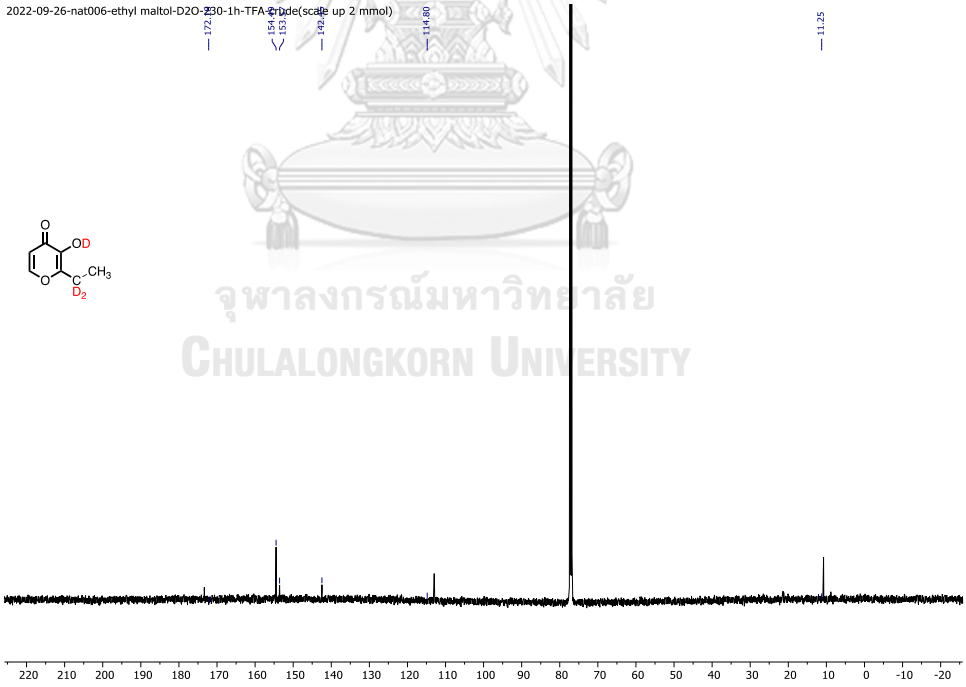


Figure A36 ^{13}C NMR (126 MHz, $CDCl_3$) NMR spectrum of ethyl maltol-d_3

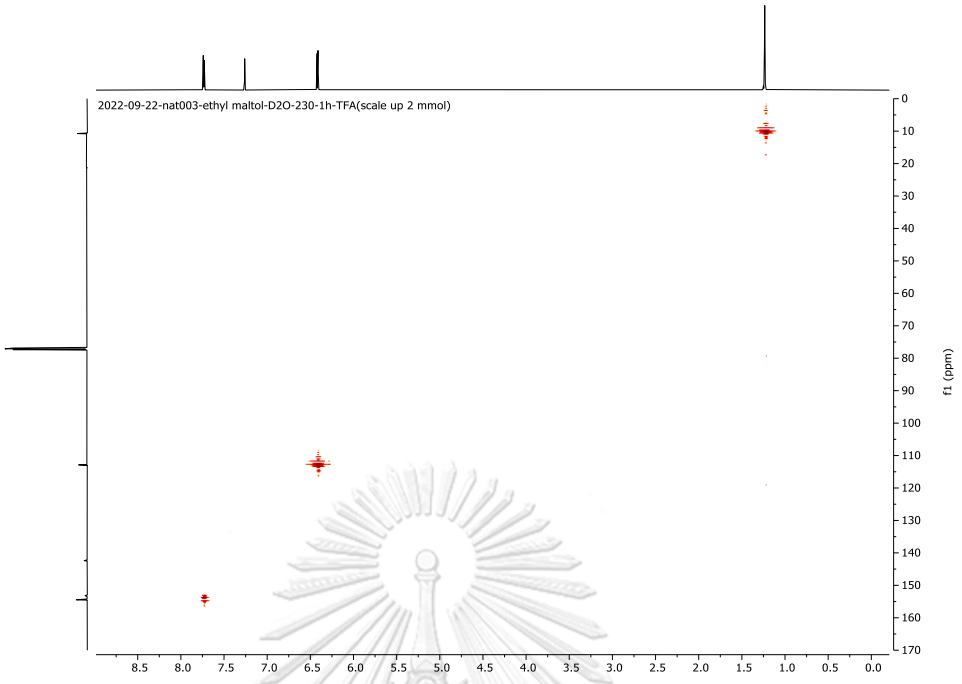


Figure A37 2D HSQC NMR (500 MHz, $CDCl_3$) NMR spectrum of ethyl maltol-d_3

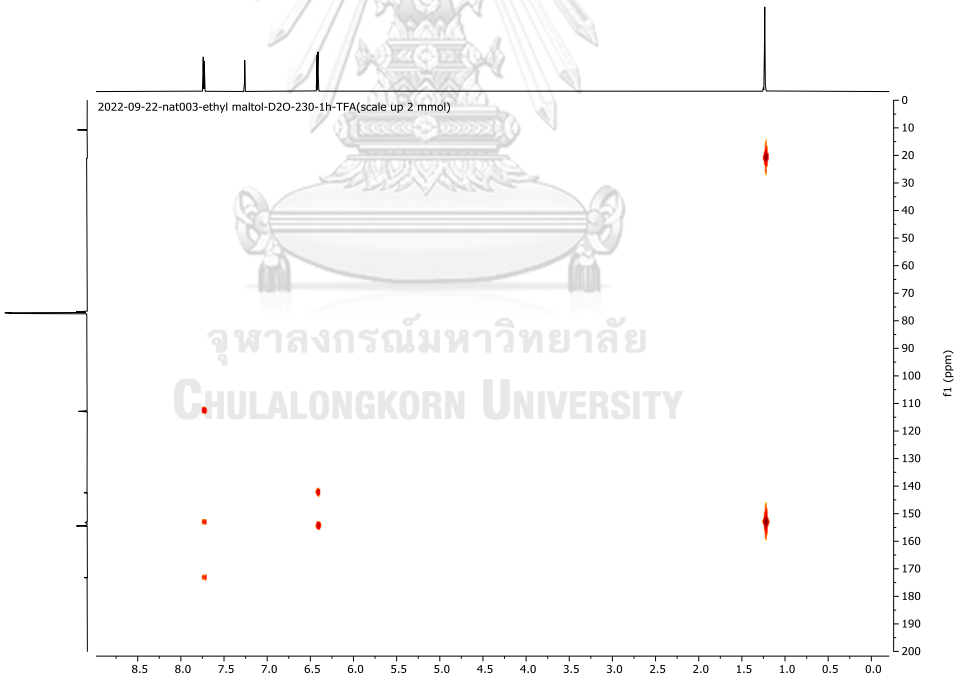


Figure A38 2D HMBC NMR (500 MHz, $CDCl_3$) NMR spectrum of ethyl maltol-d_3

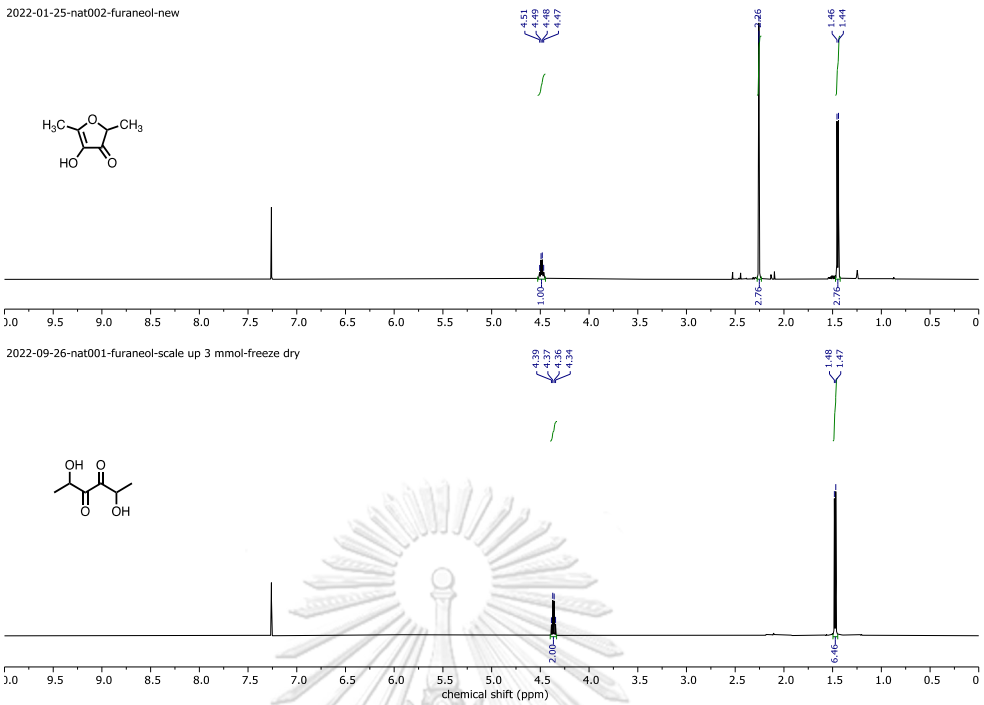


Figure A39 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the HDx reaction of furaneol and 2,5-dihydroxyhexane-3,4-dione

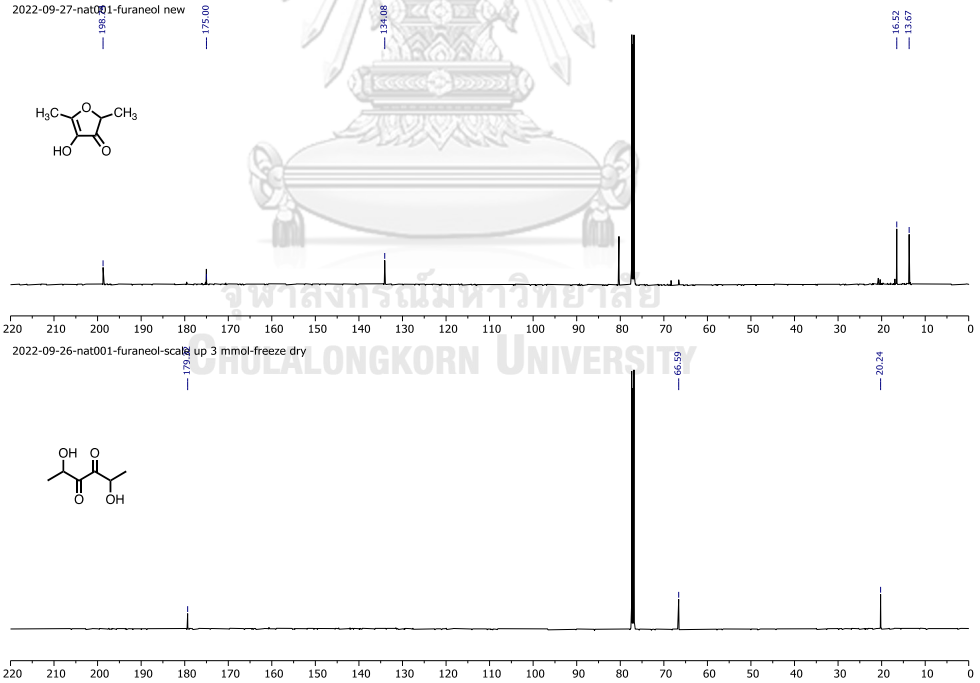


Figure A40 ^{13}C NMR (126 MHz, $CDCl_3$) NMR spectrum of furaneol and 2,5-dihydroxyhexane-3,4-dione

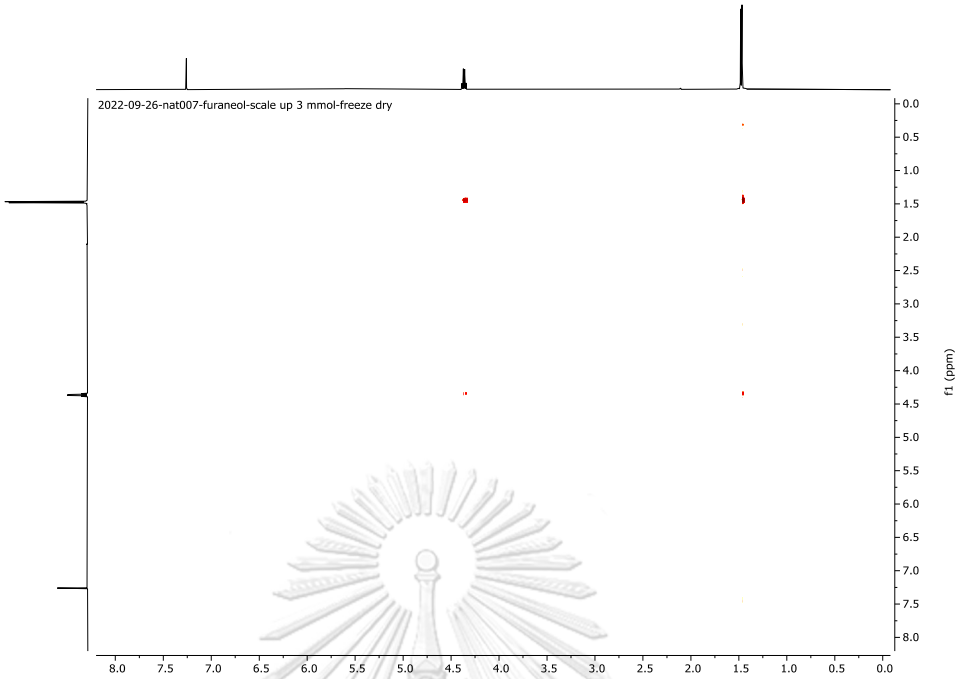


Figure A41 2D COSY NMR (500 MHz, $CDCl_3$) NMR spectrum of 2,5-dihydroxyhexane-3,4-dione

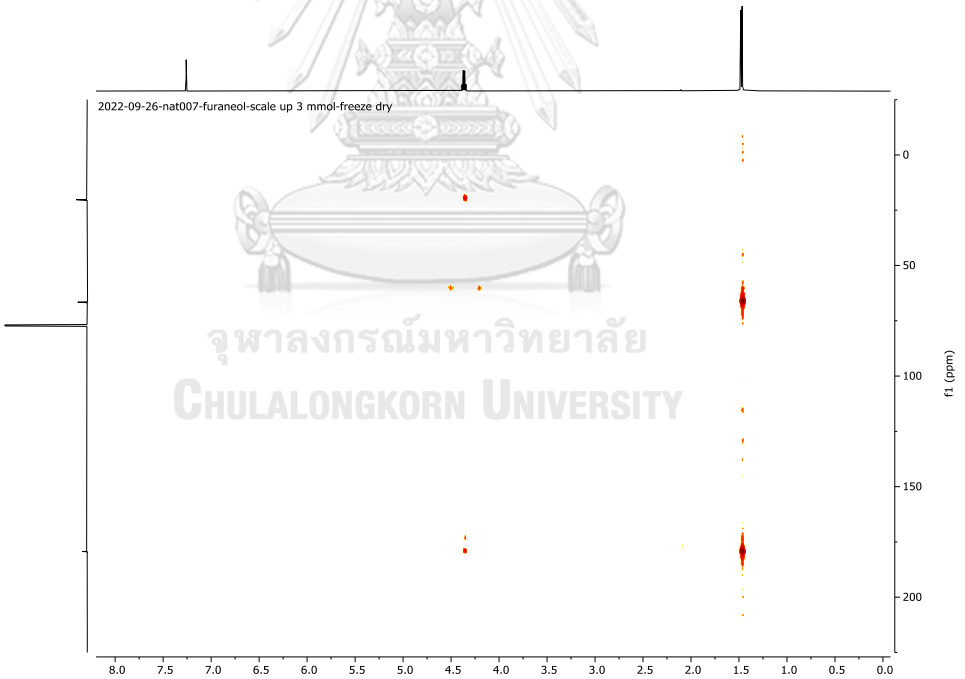


Figure A42 2D HMBC NMR (500 MHz, $CDCl_3$) NMR spectrum of 2,5-dihydroxyhexane-3,4-dione

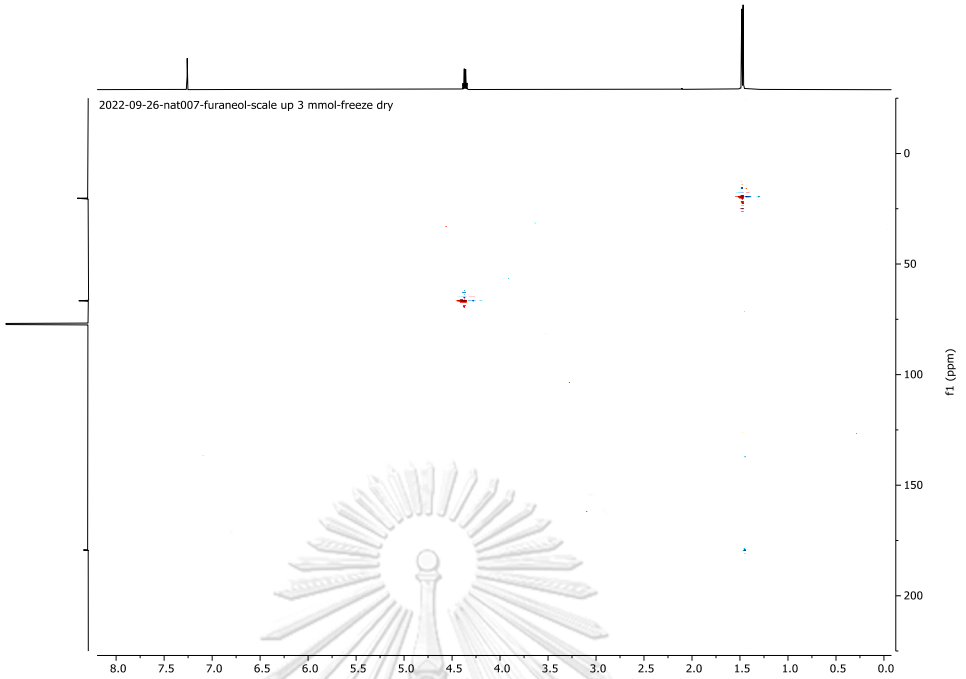


Figure A43 2D HSQC NMR (500 MHz, $CDCl_3$) NMR spectrum of 2,5-dihydroxyhexane-3,4-dione

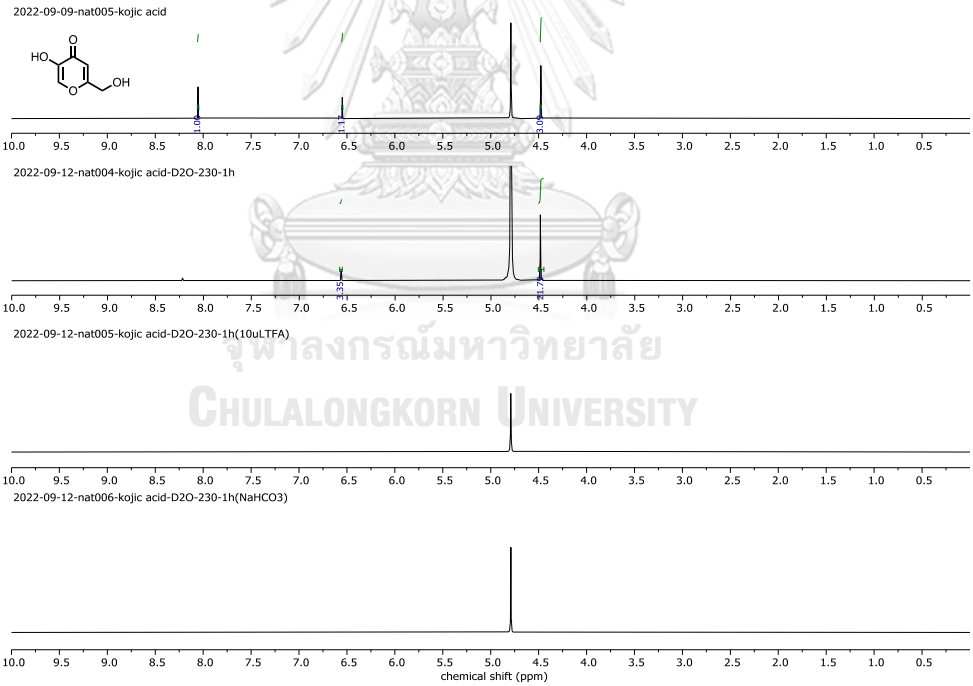


Figure A44 ^1H NMR (500 MHz, D_2O) NMR spectrum of the HDx reaction of kojic acid at 230 °C for 1 h under neutral, acid, and base conditions

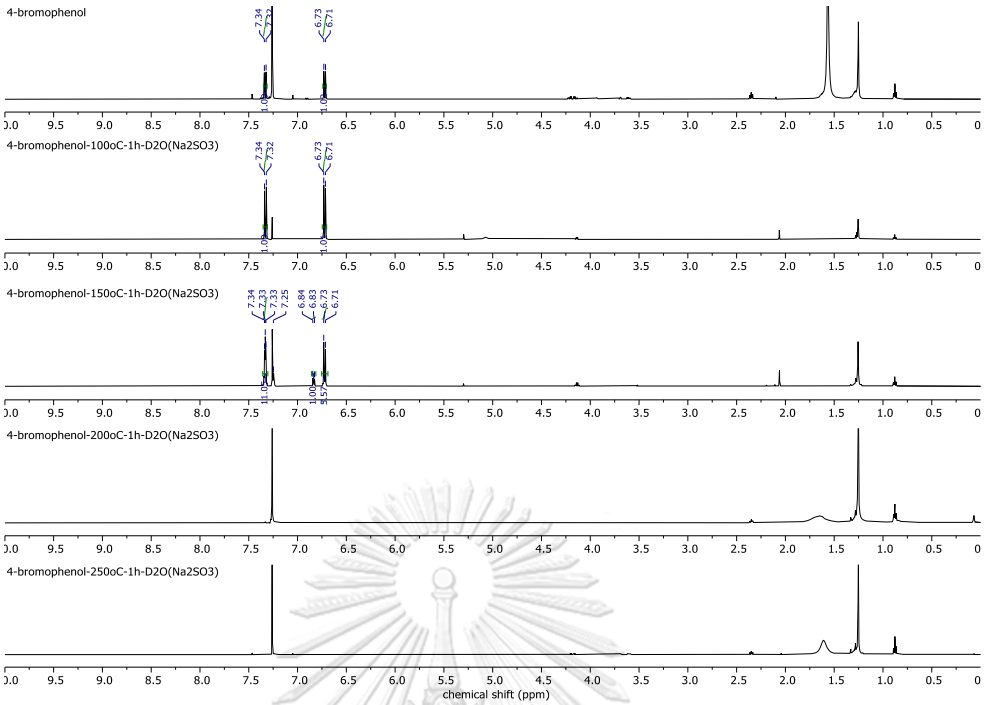


Figure A45 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the XDx reaction of 4-bromophenol in the presence of Na_2SO_3 with various amount of reaction temperature for 1 h

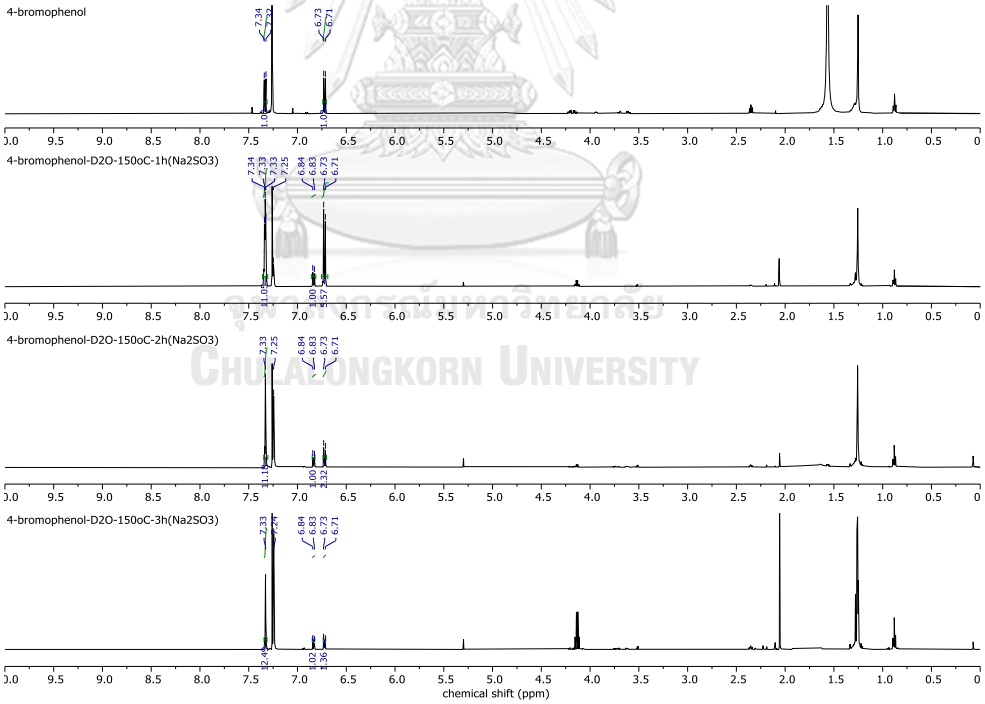


Figure A46 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the XDx reaction of 4-bromophenol in the presence of Na_2SO_3 with various amount of reaction time

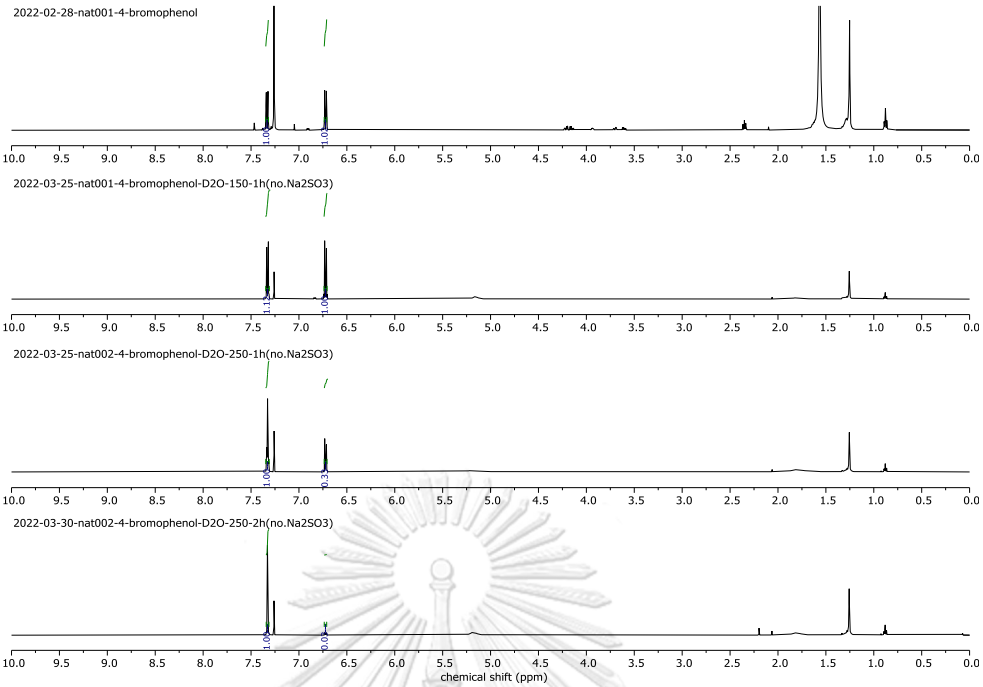


Figure A47 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the XDx reaction of 4-bromophenol in the absence of Na_2SO_3 at 150-250 °C for 1-2 h

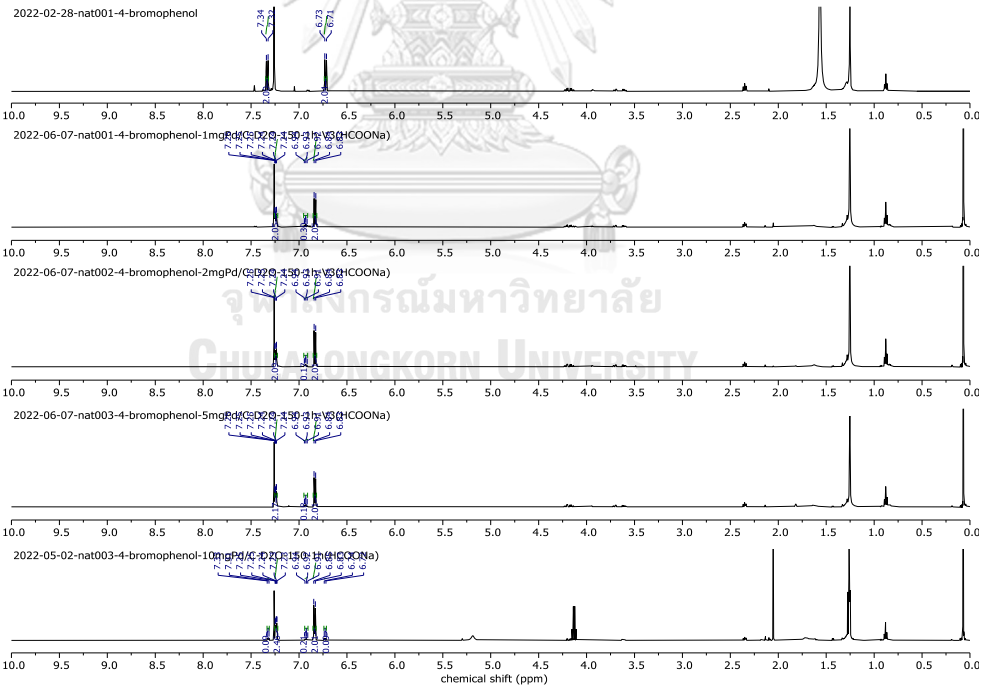


Figure A48 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the XDx reaction of 4-bromophenol with various amount of Pd/C at 150 °C for 1 h

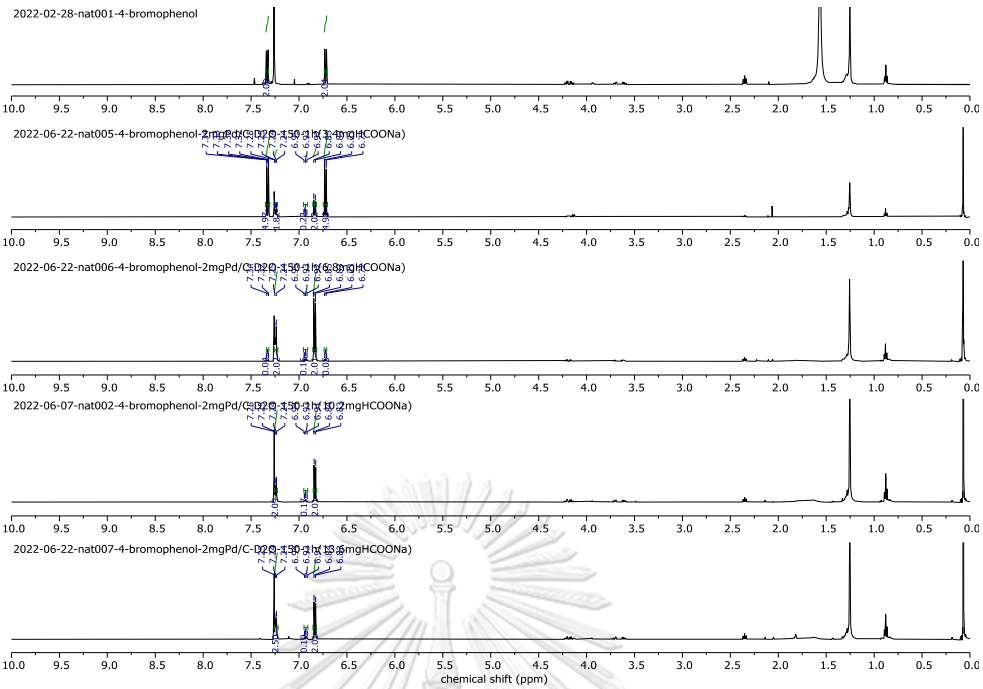


Figure A49 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the XDx reaction of 4-bromophenol with various amount of HCOONa at 150 ℃ for 1 h

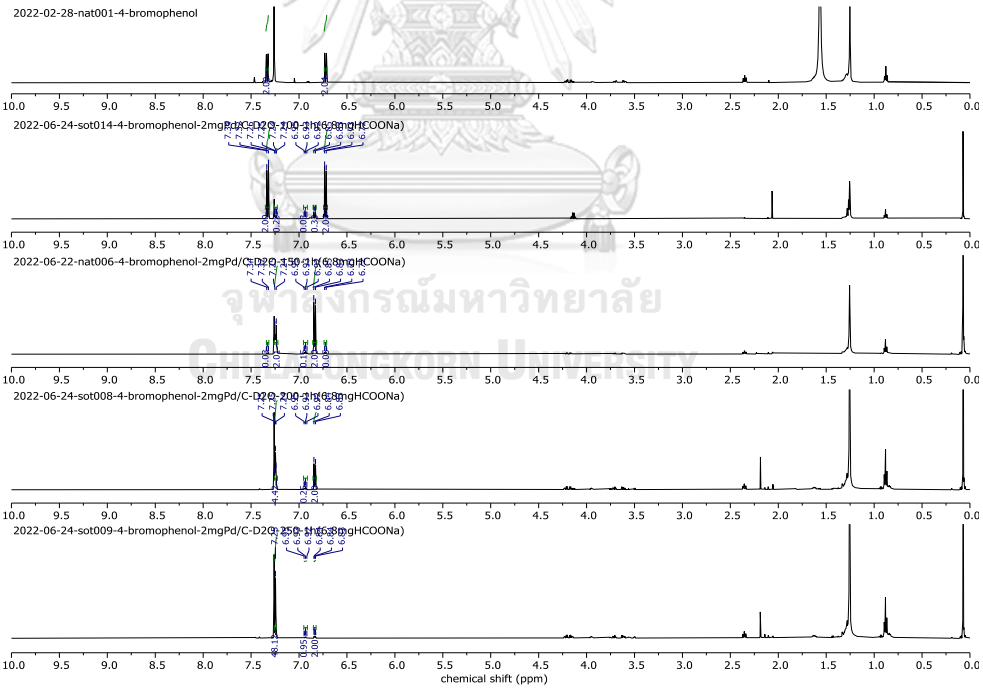


Figure A50 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the XDx reaction of 4-bromophenol with various amount of reaction temperature for 1 h

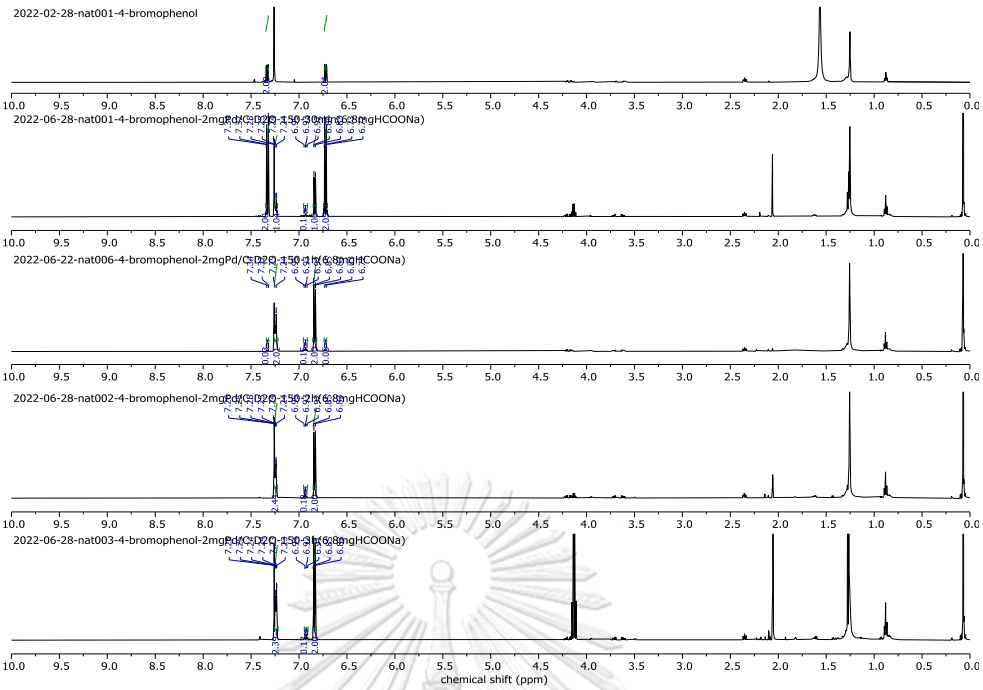


Figure A51 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the XDx reaction of 4-bromophenol with various amount of reaction time at 150 °C

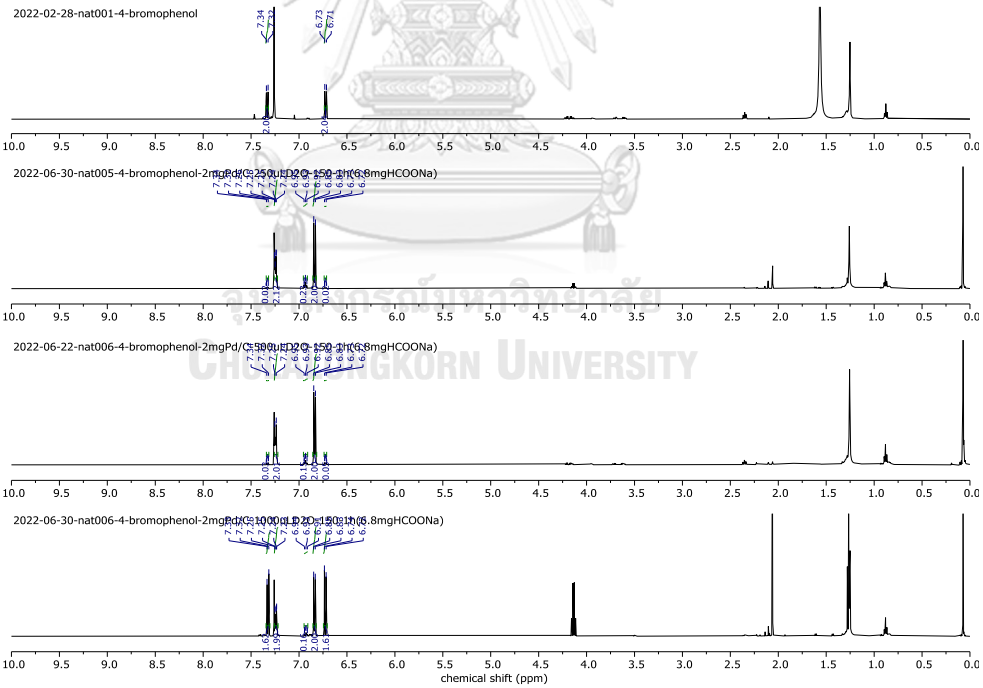


Figure A52 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the XDx reaction of 4-bromophenol with various amount of D_2O at 150 °C for 1 h

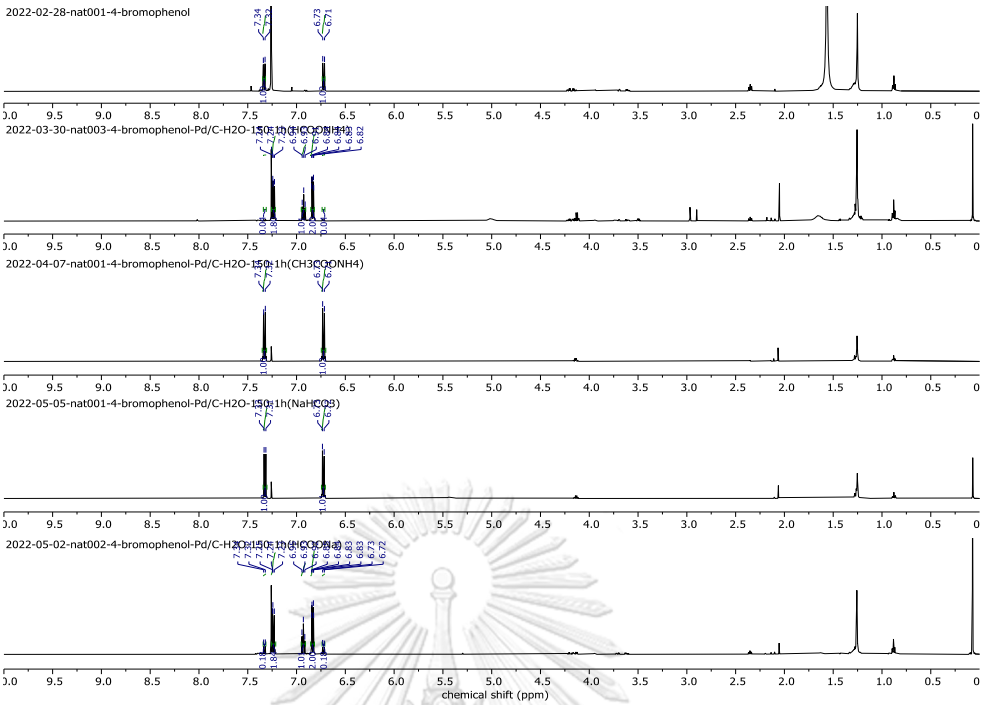


Figure A53 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the XHx reaction of 4-bromophenol with various amount of additives at 150 ℃ for 1 h

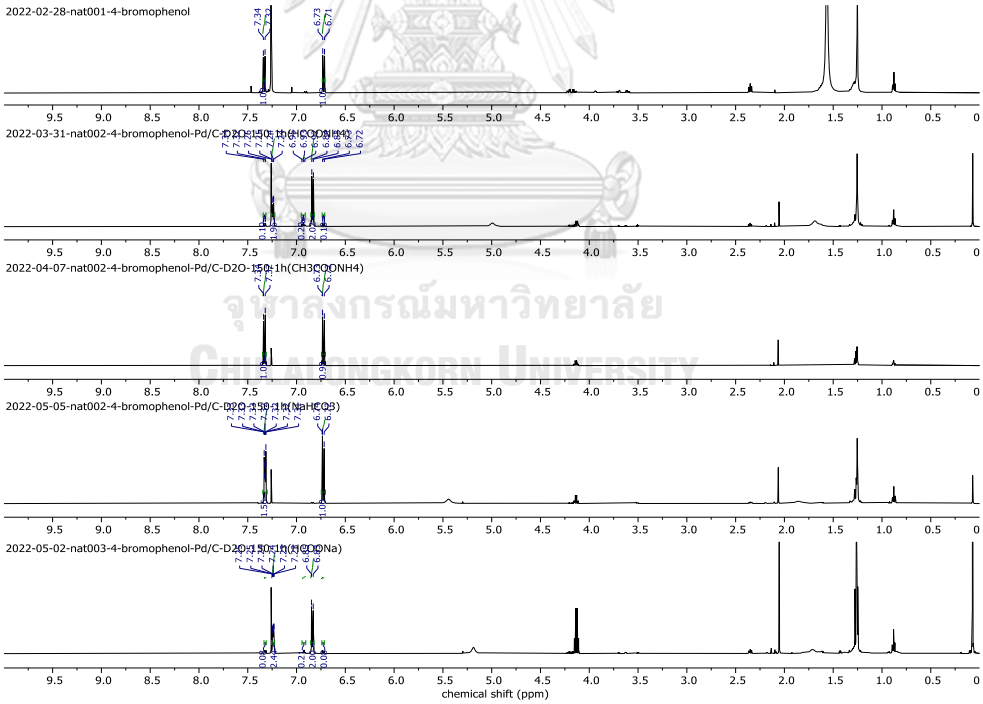


Figure A54 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the XDx reaction of 4-bromophenol with various amount of additives at 150 ℃ for 1 h

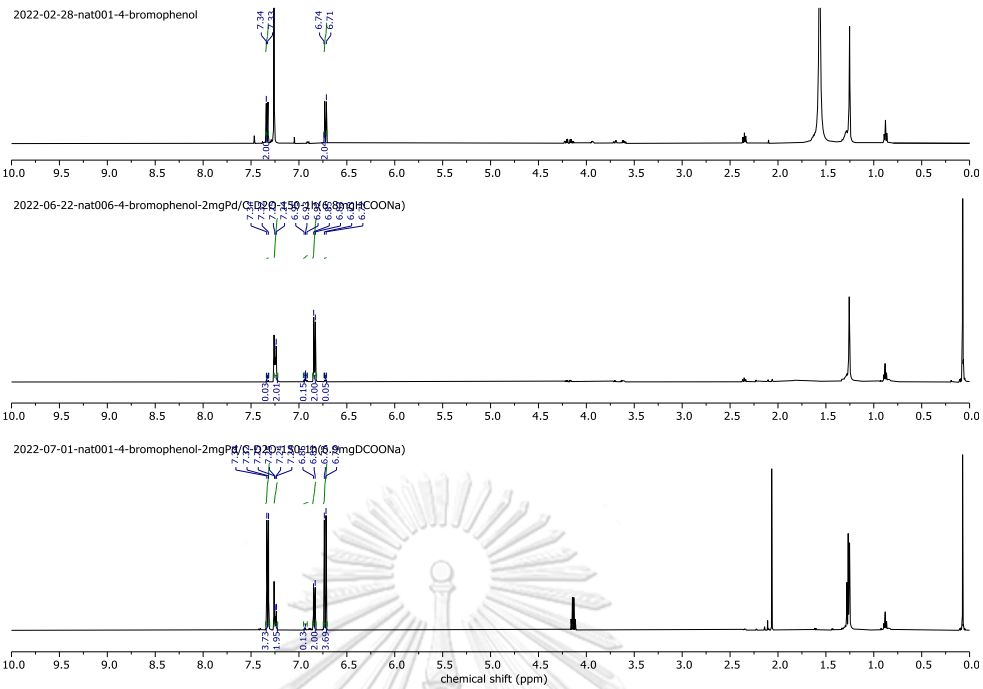


Figure A55 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the XHx and XDx reaction of 4-bromophenol with optimized condition

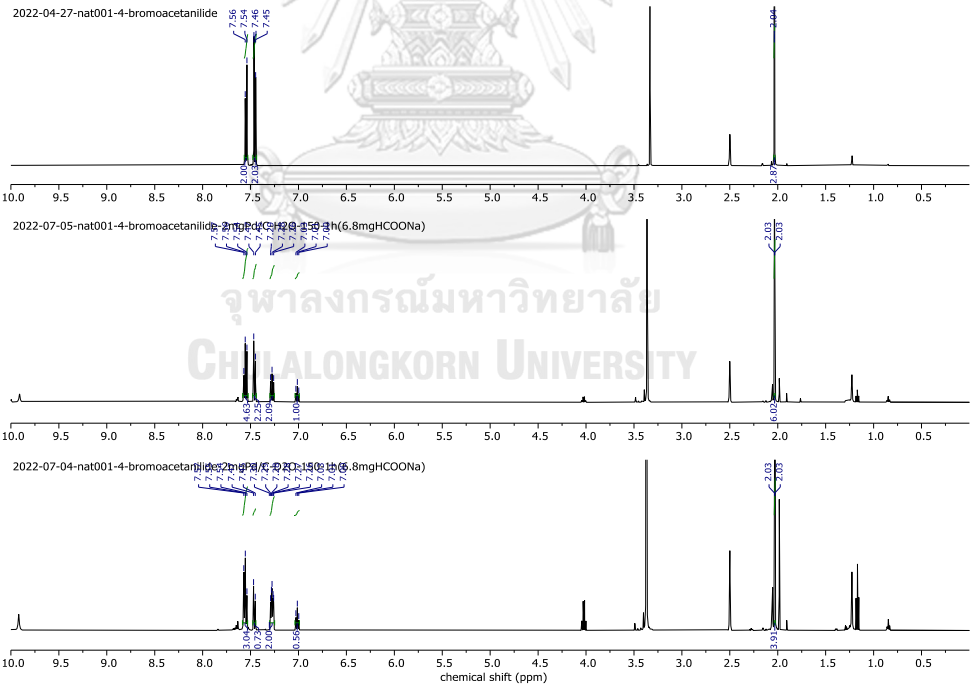


Figure A56 ^{1}H NMR (500 MHz, DMSO-d_6) NMR spectrum of the XHx and XDx reaction of 4-bromoacetanilide with optimized condition

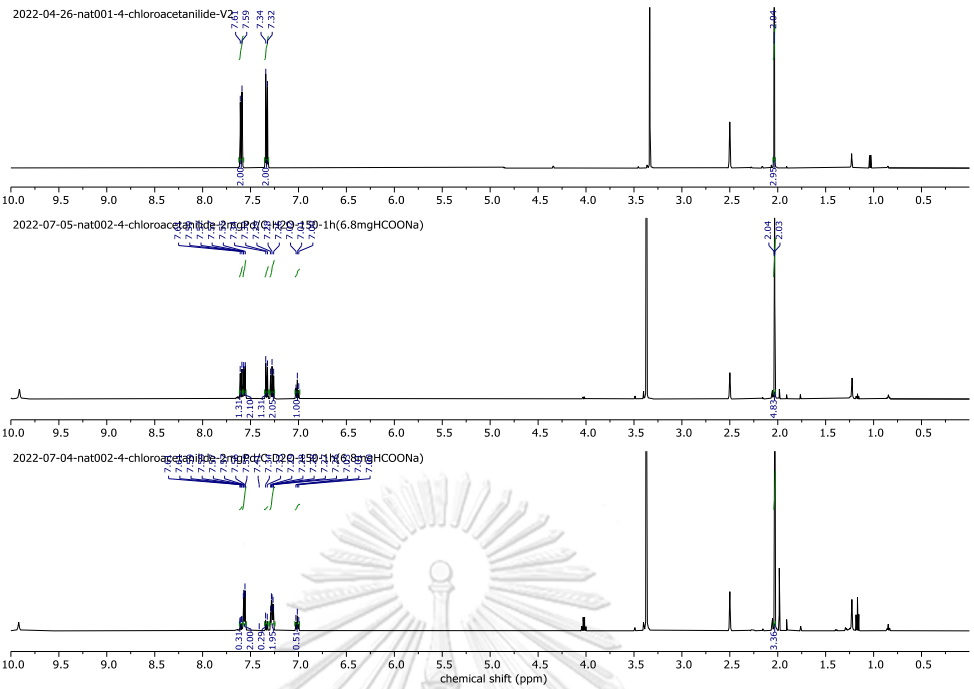


Figure A57 ^{1}H NMR (500 MHz, DMSO-d_6) NMR spectrum of the XHx and XDx reaction of 4-chloroacetanilide with optimized condition

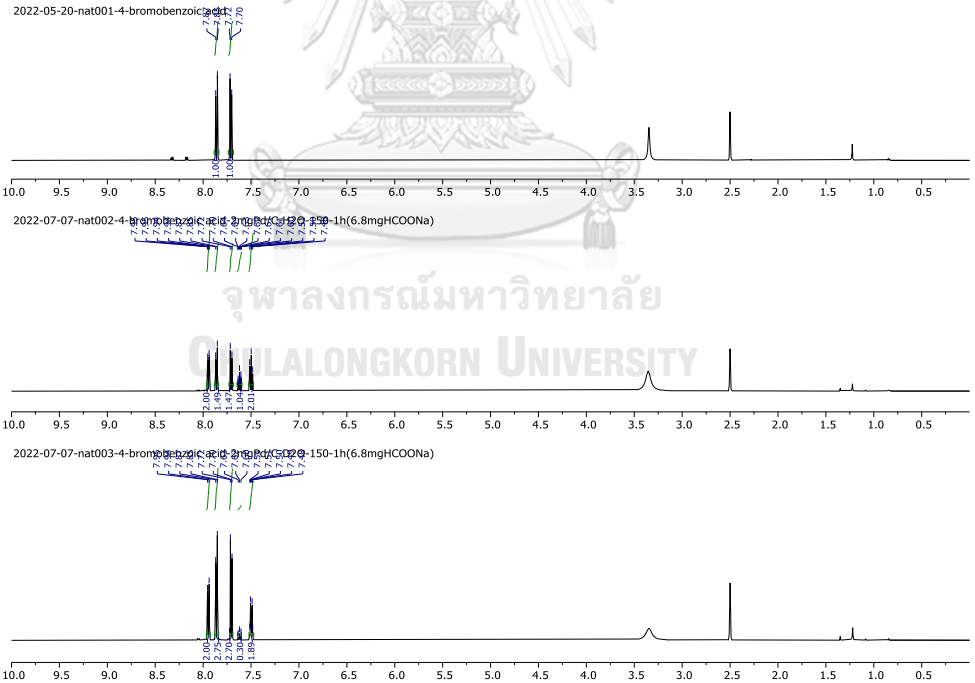


Figure A58 ^{1}H NMR (500 MHz, DMSO-d_6) NMR spectrum of the XHx and XDx reaction of 4-bromobenzoic acid with optimized condition

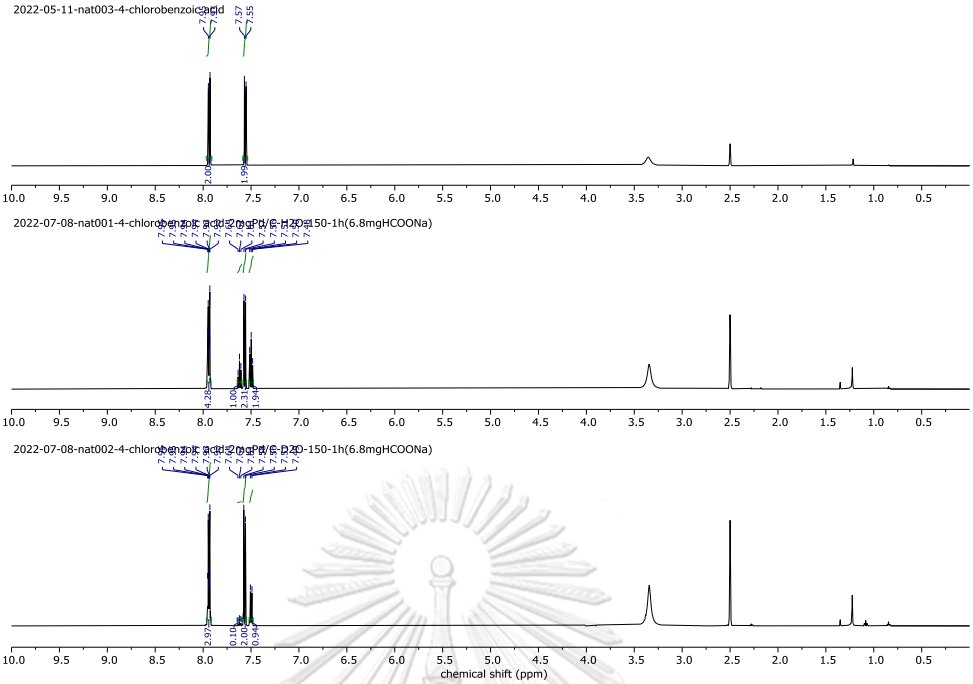


Figure A59 ^{1}H NMR (500 MHz, DMSO-d_6) NMR spectrum of the XHx and XDx reaction of 4-chlorobenzoic acid with optimized condition

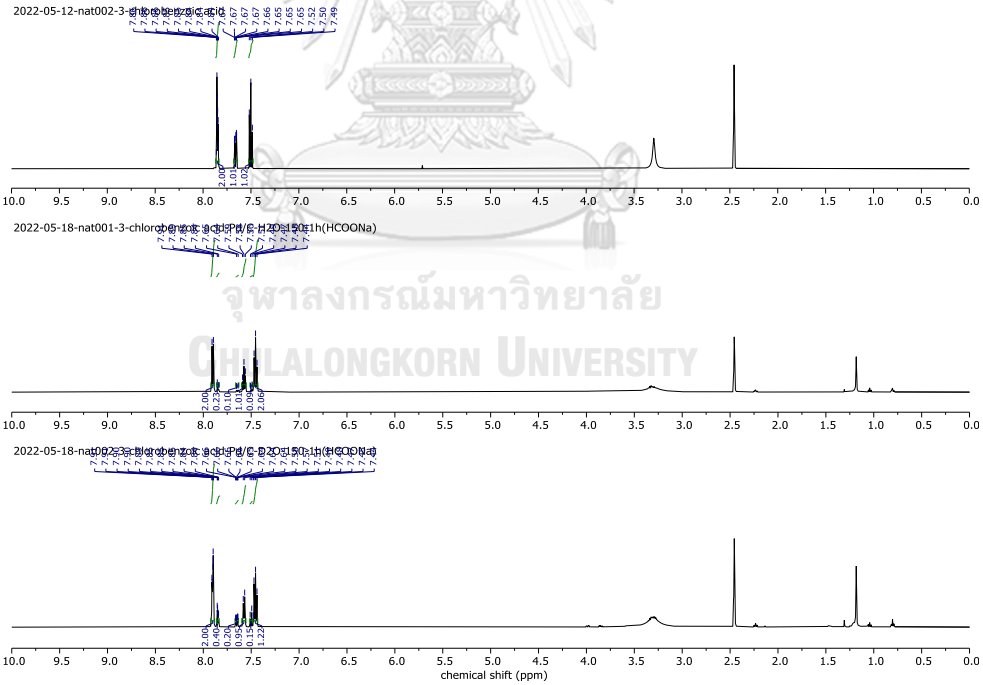


Figure A60 ^{1}H NMR (500 MHz, DMSO-d_6) NMR spectrum of the XHx and XDx reaction of 3-chlorobenzoic acid with 0.15 mmol HCOONa and Pd/C at 150 °C for 1 h

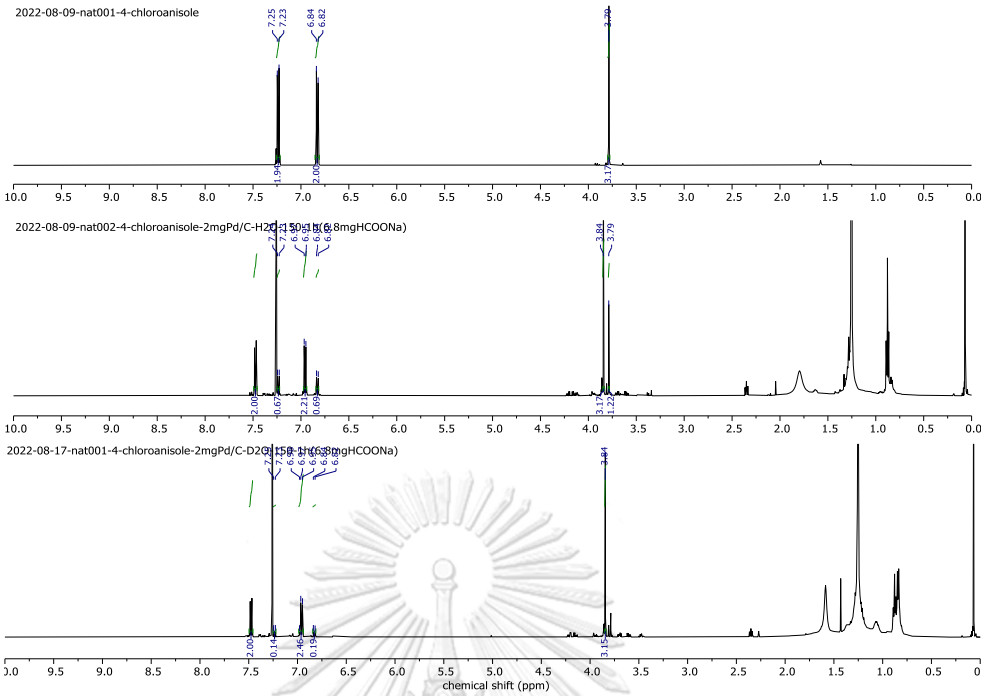


Figure A61 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the XHx and XDx reaction of 4-chloroanisole with optimized condition

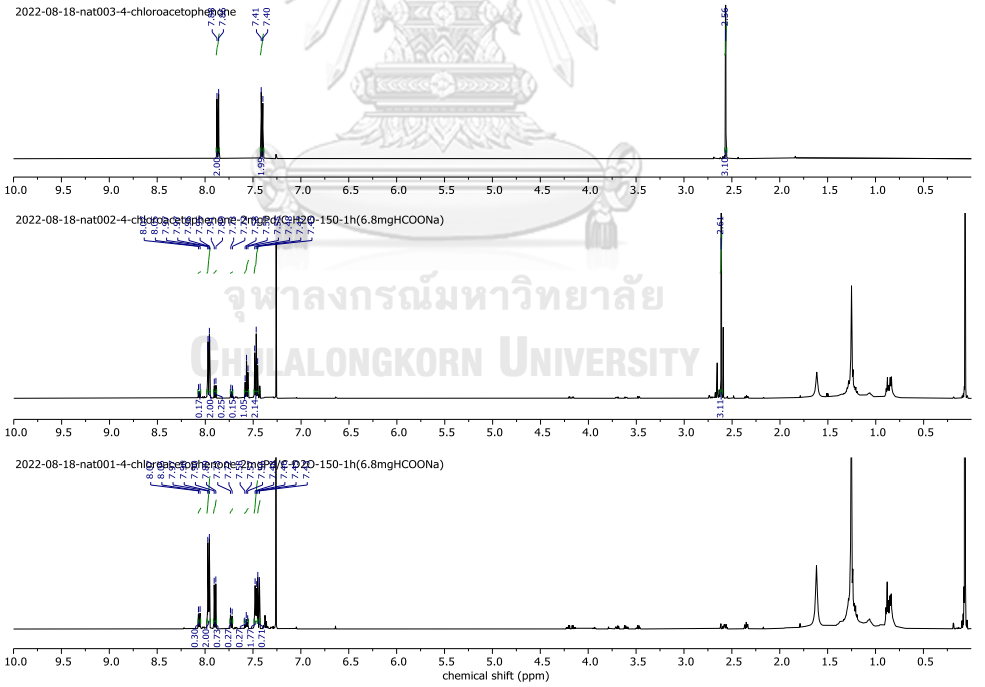


Figure A62 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the XHx and XDx reaction of 4-chloroacetophenone with optimized condition

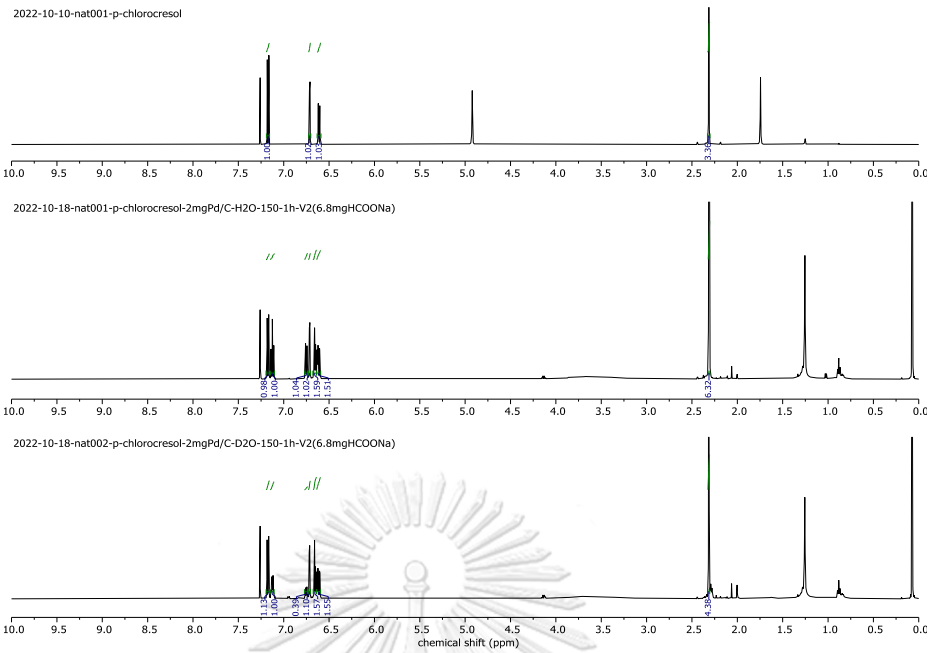


Figure A63 ^{1}H NMR (500 MHz, $CDCl_3$) NMR spectrum of the XHx and XDx reaction of *p*-chlorocresol with optimized condition

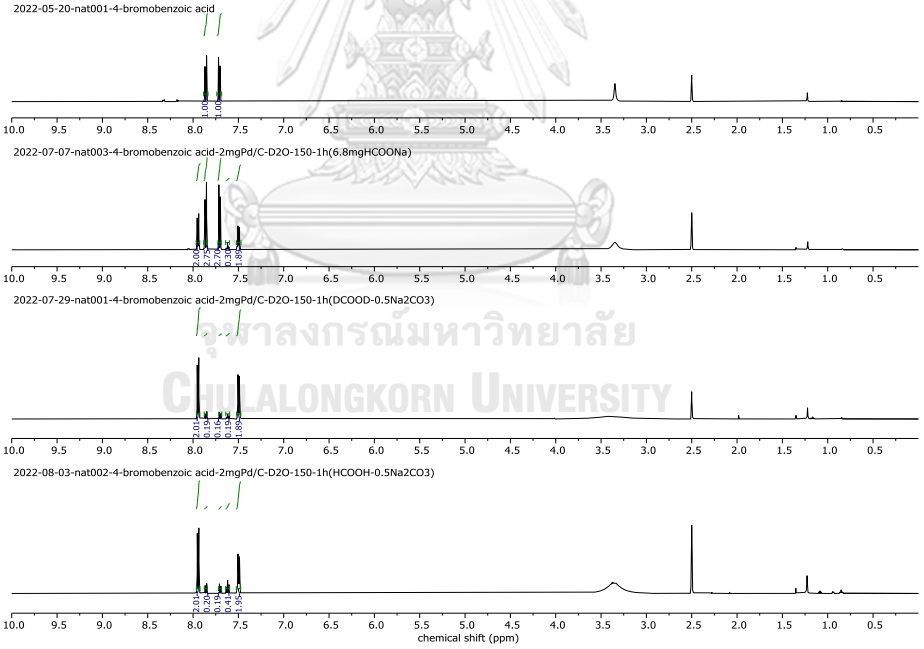


Figure A64 ^{1}H NMR (500 MHz, DMSO-d_6) NMR spectrum of the XDx reaction of 4-bromobenzoic acid using HCOONa, DCOOD with Na_2CO_3, and HCOOH with Na_2CO_3 in the presence of Pd/C at 150 °C for 1 h

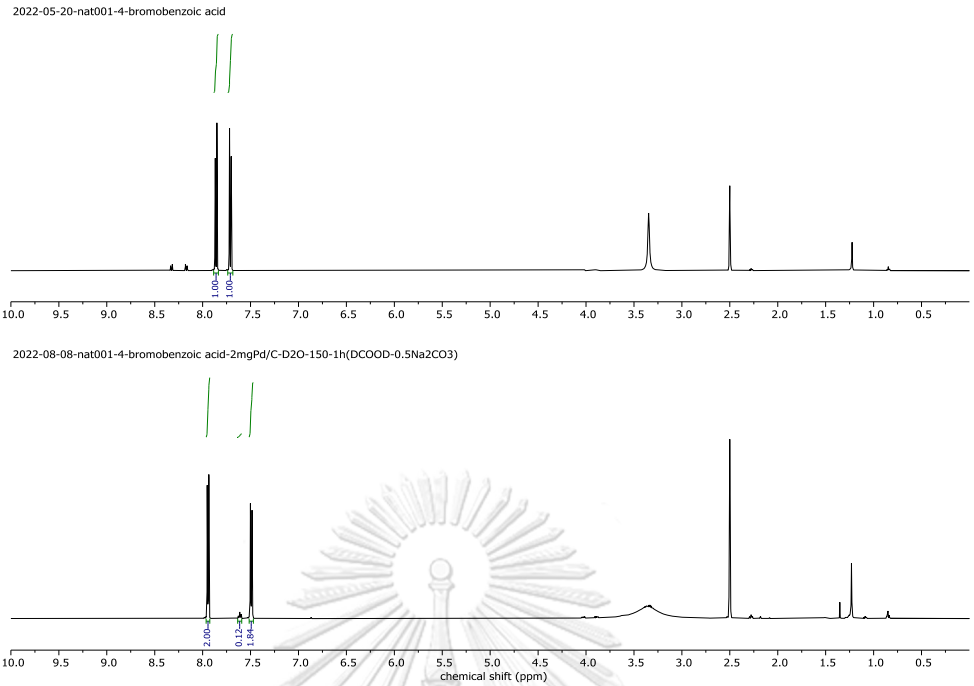


Figure A65 ^{1}H NMR (500 MHz, DMSO-d_6) NMR spectrum of the XDx reaction of 4-bromobenzoic acid using DCOOD with Na_2CO_3 and Pd/C at 150 °C for 1 h

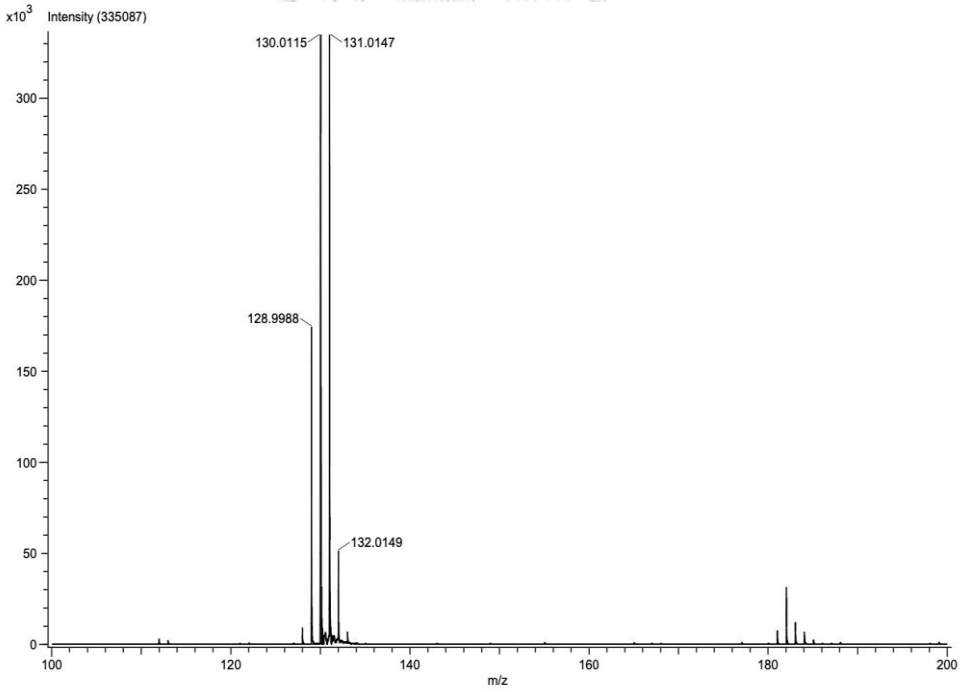


Figure A66 MS (DART) of maltol-d_4

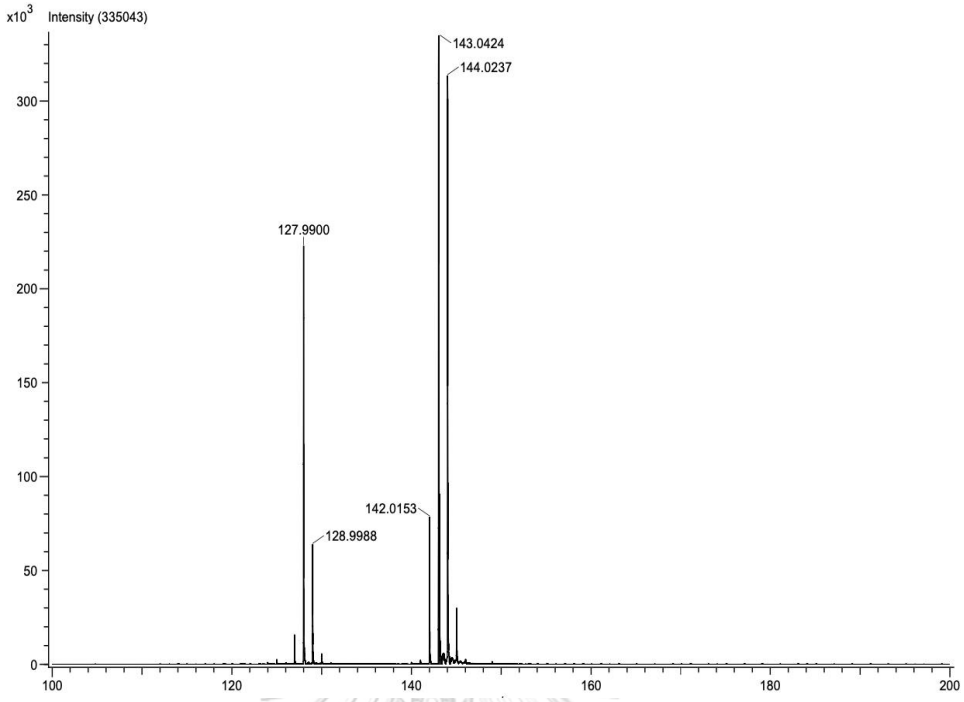


Figure A67 MS (DART) of ethyl maltol-d_3

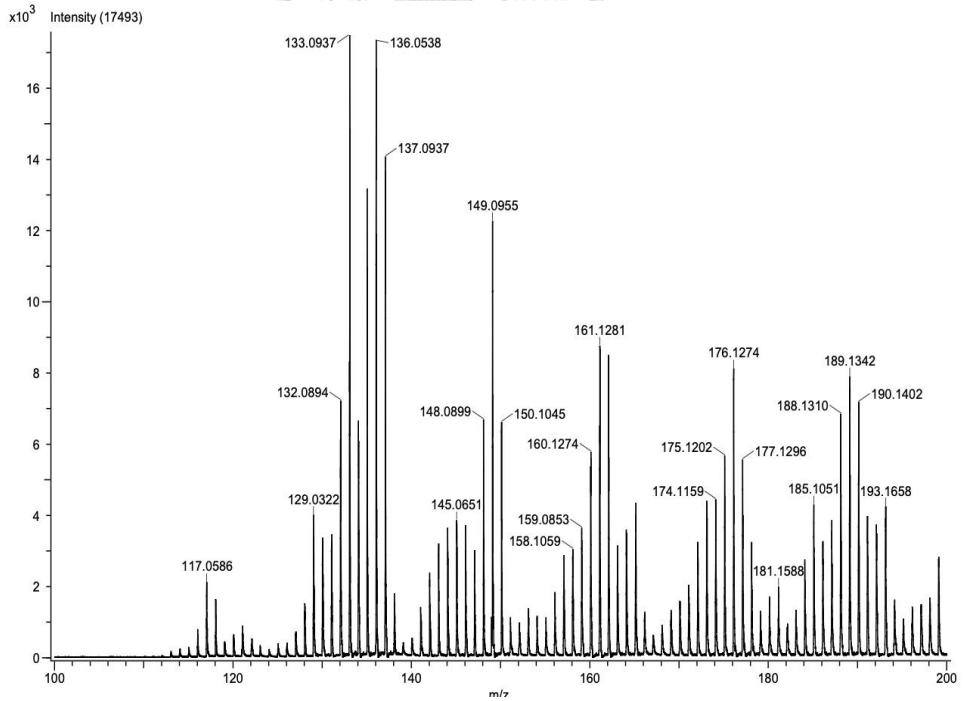


Figure A68 MS (DART) of HDx product of furaneol in TFA at 230 °C for 1 h

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VITA

NAME	Nattasiri Phaisarn
DATE OF BIRTH	30 April 1997
PLACE OF BIRTH	Bangkok, Thailand
INSTITUTIONS ATTENDED	Bachelor's Degree of Science (Chemistry) in 2020
PUBLICATION	Phaisarn N.; Vilaivan T. Deuteration of Organic Compounds by Hydrothermal Process. Proceedings of the 48th International Congress on Science Technology and Technology-based Innovation (STT48), Nakhon Si Thammarat, Nov 29 -Dec 1, 2022; pp 206-213.