# Effective Synthesis of Deuterated n-Octylamine and Its Analogues

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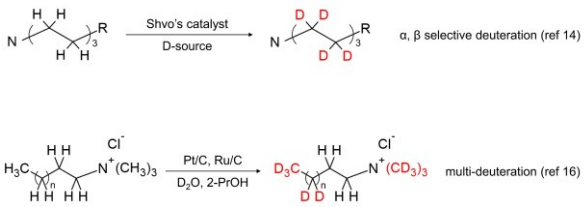
**Abstract.** In neutron scattering studies, deuterium-labelled compounds play a key role in controlling the contrast of organic samples and reducing the incoherent scattering background from the samples. As amine compounds play a vital role as functional molecules, we have developed a new synthesis method using an amide compound as a starting material to synthesize deuterated amines and their analogues. We determined the deuteration ratio of the obtained deuterated 1-octylamine by mass spectrometry, nuclear magnetic resonance (NMR), and neutron reflectometry techniques. As a result, the deuteration ratio was estimated to be ~60 %. The deuteration ratio of the synthesized 1-octylamine was not high because the method used did not deuterate its $\alpha$-protons and $NH_2$ group. However, this synthesis method is suitable for the large-scale synthesis of deuterated amine compounds for neutron research because it is easy to increase the synthetic scale.

## 1 Introduction

Deuterium ($^2H$) is a stable isotope of hydrogen and $^2H$-labelled compounds have been extensively used in a variety of research fields, beginning with its isolation in 1932 [1]. For example, various deuterated compounds have been used in the field of nuclear magnetic resonance (NMR), infrared spectrometry, mass spectrometry (MS), and neutron research [2–7].

Various compounds, such as carboxylic acids, aromatic compounds, and ionic liquids can be effectively deuterated using platinum group metal-catalyzed direct deuterium-labelling methods [8–12]. In contrast, even though amines are important functional molecules, there is no effective direct multi-deuteration method for amine compounds. Several direct deuteration methods (Scheme 1) that are selective for the $\alpha$-position or $\alpha,\beta$-position of alkylamines have been developed [13–15], with a recent advancement presented to a multi-deuteration via heterogeneous catalysts for ammonium/amine compounds [16]. Deuterium labelling methods are important in neutron scattering to control the contrast of the organic samples, and thus the prepared compounds reduce the incoherent scattering. However, the synthesis of deuterated amines with high deuteration ratios is preferable for neutron studies.

Herein, to synthesize amine compounds with a higher deuteration ratio, we have developed a new method for the synthesis of deuterated amines (Scheme 2). In this approach, we have used an amide compound as a starting material for deuterated amine synthesis because amide compounds can be deuterated directly using a Pd/C and Rh/C mixed catalyst system [17, 18] and amines can be easily synthesized by reducing amide compounds. Additionally, carboxylic acid compounds can also be synthesized by the hydrolysis of amide compounds in the presence of acids or bases. Therefore, we synthesized three deuterated compounds, namely amide, amine, and carboxylic acid, using the method shown in the Scheme 2. The deuteration ratio of these deuterated compounds was analyzed by electrospray ionization mass spectrometry (ESI-MS), NMR, and neutron reflectometry (NR) techniques.




**Scheme 1.** Direct deuteration method for amine compounds.

## 2 Materials and Methods

### 2.1 Reagents

*n*-Octanamide (TCI Chemicals Co., Ltd., Japan), deuterium oxide ($D_2O$, 99.9% D, Sigma-Aldrich), 2-propanol (FUJIFILM Wako Pure Chemical Co., Japan), Pd/C (10 wt% Pd, N.E. CHEMCAT Co., Japan), Rh/C (5 wt%, FUJIFILM Wako Pure Chemical Co., Japan), lithium aluminium hydride ($LiAlH_4$, Sigma-Aldrich),

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hydrochloric acid (FUJIFILM Wako Pure Chemical Co., Japan), magnesium sulfate (FUJIFILM Wako Pure Chemical Co., Japan), methanol (FUJIFILM Wako Pure Chemical Co., Japan), ethanol (FUJIFILM Wako Pure Chemical Co., Japan), anhydrous tetrahydrofuran (FUJIFILM Wako Pure Chemical Co., Japan), diethyl ether (FUJIFILM Wako Pure Chemical Co., Japan), 1,4-dioxane (FUJIFILM Wako Pure Chemical Co., Japan), $CDCl_3$ (FUJIFILM Wako Pure Chemical Co., Japan), and $CD_2Cl_2$ (FUJIFILM Wako Pure Chemical Co., Japan) were used without further purification. Silicon wafer (diameter = 5.08 cm, thickness = 2.0 mm) was supplied by Crystal Base Co. Ltd. (Osaka, Japan). Ultrapure water (18.2 MΩ.cm) was produced with a deionized purified water production system (RFU424TA system, ADVANTEC, Japan) and used throughout this study.

## 2.2 Instruments

ESI-MS spectra were recorded on a mass spectrometer EXTREM-MS-100P (JASCO Corporation). The percentage of deuteration of the molecules was calculated using isotope distribution analysis of different isotopologues [8, 12]. This was achieved by analysing the area under each MS peak which corresponds to a defined number of deuterium atoms. Based on the relative amount of carbon-13 ($^{13}C$) natural abundance found or estimated in the protonated version, the $^{13}C$ contribution to the value of the area under each MS signal was subtracted.

$^1H$ NMR (400 MHz) and $^2H$ NMR (61.4 MHz) spectra were recorded on a 400 MHz NMR spectrometer (JMTC-400/54/JJ/YH, JEOL Ltd., Tokyo, Japan).

In principle, the measurement was performed three times for each sample and the results were shown as mean deuteration ratios (with standard deviations).

## 2.3 Synthesis of deuterated *n*-octanamide

Deuteration reactions (Scheme 2) were carried out in a stainless-steel reactor (TSSR, TPR1-VSI-300, SUS316, Taiatsu Techno Corp., Tokyo, Japan) [19].

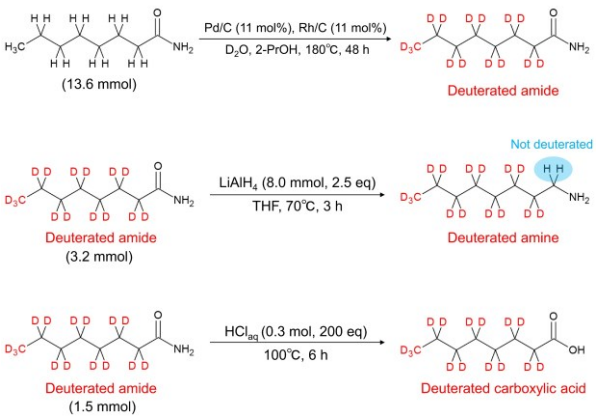
A mixture of *n*-octanamide (1.95 g, 13.6 mmol), Pd/C (10 wt% Pd, 1.60 g, 1.50 mmol (11 mol%)), and Rh/C (5 wt% Rh, 3.20 g, 1.55 mmol (11 mol%)) in 2-PrOH (40 mL)/$D_2O$ (80 mL) mixed solvent was loaded into the TSSR. The mixture was vacuum degassed for 10 min to remove oxygen. The reactor was purged with Ar for 10 s and then sealed. The mixture was heated to 180 °C and stirred continuously for 48 hours. After cooling to 20 °C, the mixture was filtered through a short plug of celite to remove the catalyst and washed a second time with EtOH (150 mL). The filtrate was evaporated to dryness under reduced pressure to yield deuterated *n*-octanamide (1.31 g, 64.3 %). $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.79–0.84 (m), 1.21–1.25 (m), 1.58 (residual signal), 2.12 (residual signal), 5.69 (s), 6.09 (s). $^2H$ NMR (61.4 MHz, $CDCl_3$) δ 0.78 (s), 1.21 (s), 1.54 (s), 2.13 (s), 5.74 (s), 6.11 (s).

## 2.4 Synthesis of deuterated 1-octylamine

Deuterated *n*-octanamide (0.48 g, 3.2 mmol) was dissolved in 5 mL of tetrahydrofuran, and 1.0 M $LiAlH_4$/THF solution (8 mL, 8 mmol (2.5 eq)) was slowly added dropwise to the deuterated *n*-octanamide solution under moderate stirring. The mixture was then heated at 70 °C for 3 hours. After cooling the mixture in an ice bath, cold water was added slowly until the reaction was complete. The mixture was then extracted with diethyl ether (3×30 mL). The combined extracts were dried with anhydrous magnesium sulfate, filtered, and evaporated to dryness under reduced pressure to yield deuterated 1-octylamine (0.40 g, 91.7 %). $^1H$ NMR (400 MHz, $CD_2Cl_2$) δ 0.79–0.86 (m), 1.20–1.44 (m), 2.57 (s, 2H). $^2H$ NMR (61.4 MHz, $CD_2Cl_2$) δ 0.82 (s), 1.23 (s), 1.35 (s), 1.48 (s).

## 2.5 Synthesis of deuterated 1-ocanoic acid

Deuterated *n*-octanamide (0.23 g, 1.5 mmol) was dissolved in 50 mL of 6 M HCl aq (0.3 mol, 200 eq), and the mixture was heated at 100 °C for 6 hours. After cooling to 20 °C, the mixture was extracted with diethyl ether (3×20 mL). The combined extracts were dried with anhydrous magnesium sulfate, filtered, and evaporated to dryness under reduced pressure to yield deuterated 1-octanoic acid (0.18 g, 80.2 %). $^1H$ NMR (400 MHz, $CD_2Cl_2$) δ 0.86 (residual signal), 1.28 (residual signal), 1.56 (residual signal), 2.29 (residual signal). $^2H$ NMR (61.4 MHz, $CD_2Cl_2$) δ 0.79 (s), 1.20 (s), 1.52 (s), 2.25 (s).




**Scheme 2.** Synthesis of deuterated amide, amine, and carboxylic acid in this study.

## 2.6 Neutron reflectivity measurement

NR measurements were performed at a polarized neutron reflectometer (BL17 SHARAKU, Japan) with a horizontal scattering geometry installed at the Materials and Life Science Experimental Facility (MLF) at J-PARC [20, 21]. The incident beam power of the proton accelerator was 800 kW (peak neutron flux at 10 meV [n/eV·s·cm$^2$] was about 4.8×10$^{12}$) for all measurements. Pulsed neutron beams were generated in a mercury target at 25 Hz, and the NR data were measured using the time-of-flight (TOF) technique. The wavelength ($\lambda$) range of the incident neutron beam was tuned to approximately 2.2–8.8 Å for the unpolarized neutron

mode by disk choppers. The covered scattering vector ($Q_z$) range was 0.008–0.09 Å$^{-1}$, where $Q_z = (4\pi/\lambda)\sin\theta$ ($\theta$ represents the angle of incidence). A 10 mm beam footprint was maintained on the sample surface using six different types of collimating slits. TOF neutron data were collected using a $^3$He gas tube detector without spatial resolution. All measurements were taken at ambient temperature. The MLF uses the event recording method as a standard data acquisition system [22]. Data reduction, normalization, and subtraction procedures were performed using a program installed at BL17 SHARAKU. Motofit software [23] was used to fit the NR profiles using the least-squares approach to minimize the deviation of the fit. The scattering length density (SLD) value was evaluated using Motofit. The molar composition and physical density of the sample can be used to determine the SLD value, which is a nuclear property of individual atoms. Therefore, the deuteration ratio of the sample can be calculated using the SLD value.

A sample cell for NR experiments developed at BL17 SHARAKU was used for this experiment. The Si-substrate was placed in the sample cell and deuterated *n*-octylamine was added. Then, the sample cell was mounted on the reflectometer sample stage.

## 3 Results and Discussions

### 3.1 Synthesis of deuterated compounds

The deuteration reaction of *n*-octanamide was carried out as shown in the Scheme 2. This reaction gave the deuterated *n*-octanamide in a moderate yield (64.3 %). The pressure of the TSSR reactor reached 0.2 MPa at 20 °C after the reaction, indicating that some of the *n*-octanamide decomposed during the reaction. On the other hand, the other reactions in the Scheme 2 proceeded quantitatively.

Figures 1–3 show the spectra of $^1$H NMR, $^2$H NMR, and ESI-MS of deuterated *n*-octanamide, 1-octylamine, and 1-octanoic acid, respectively. The obtained deuteration ratios of these deuterated materials by the ESI-MS analysis were 73 % (±0.2 %) for *n*-octanamide, 60 % (±0.1 %) for 1-octylamine, and 75 % (±0.7 %) for 1-octanoic acid, respectively. Since the $\alpha$-position of the 1-octylamine was not deuterated, the deuteration ratio of deuterated 1-octylamine is lower than that of other deuterated compounds. In addition, as mentioned in the following section, the deuteration ratio of 1-octylamine was calculated to be lower than that of other compounds because the $NH_2$ group in 1-octylamine contains two protons.

Moreover, the deuteration ratios of the alkyl-chain moiety of these deuterated materials were determined by $^1$H NMR analysis using 1,4-dioxane as an internal standard. The obtained deuteration ratios of these deuterated materials by the $^1$H NMR analysis were 73 % (±0.2 %) for *n*-octanamide, 60 % (±0.2 %) for 1-octylamine, and 69 % (±0.3 %) for 1-octanoic acid. The difference in the obtained deuteration ratio between the ESI-MS and $^1$H NMR analysis was within 4.3 %. Therefore, the $^1$H NMR and ESI-MS analysis results are consistent.

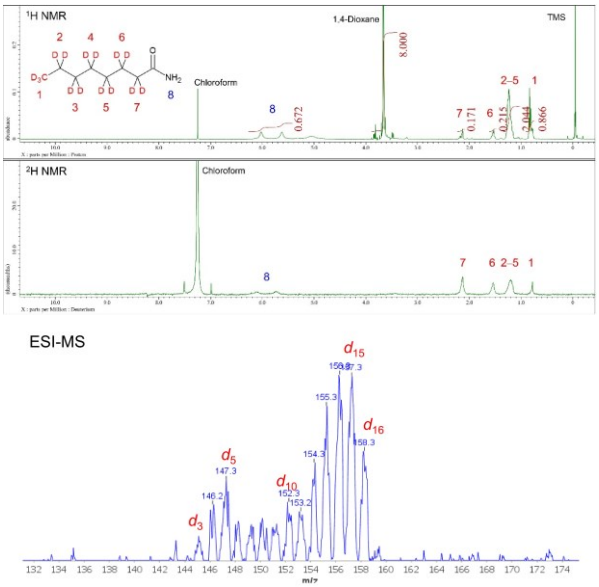



**Figure 1.** $^1$H NMR ($CDCl_3$, 400 MHz), $^2$H NMR ($CDCl_3$, 61.4 MHz), and ESI-MS data of deuterated *n*-octanamide. ESI-MS in negative mode of *n*-octanamide showing the mass distribution of the different isotopologues, which ranges from $d_3$–$d_{17}$. The distribution of the isotopologues is as follows $[M–H]^-$: 1.6 %, $d_3$; 4.0 %, $d_4$; 7.1 %, $d_5$; 2.9 %, $d_6$; 3.1 %, $d_7$; 3.6 %, $d_8$; 3.8 %, $d_9$; 4.6 %, $d_{10}$; 4.5 %, $d_{11}$; 6.6 %, $d_{12}$; 12.3 %, $d_{13}$; 17.6 %, $d_{14}$; 17.6 %, $d_{15}$; 10.0 %, $d_{16}$; 0.7 %, $d_{17}$.

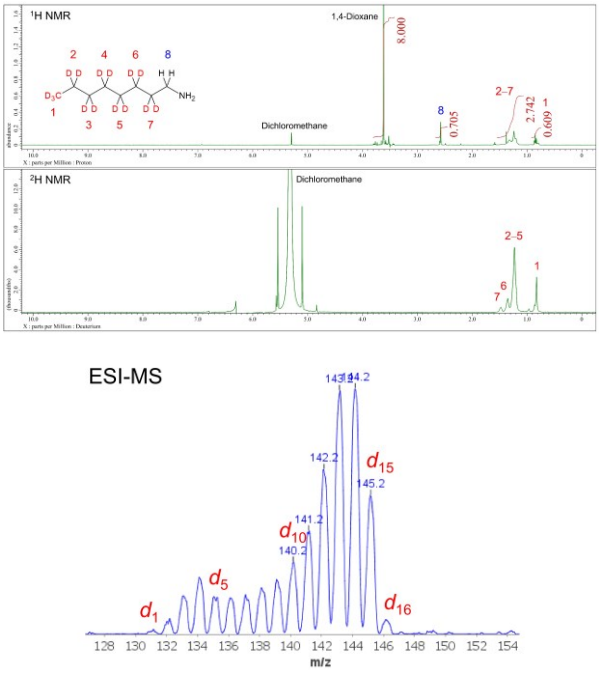



**Figure 2.** $^1$H NMR ($CD_2Cl_2$, 400 MHz), $^2$H NMR ($CD_2Cl_2$, 61.4 MHz), and ESI-MS data of deuterated 1-octylamine. ESI-MS in positive mode of 1-octylamine showing the mass distribution of the different isotopologues, which ranges from $d_1$–$d_{15}$. The distribution of the isotopologues is as follows $[M+H]^+$: 0.2 %, $d_1$; 0.8 %, $d_2$; 2.7 %, $d_3$; 4.0 %, $d_4$; 2.7 %, $d_5$; 2.6 %, $d_6$; 2.8 %, $d_7$; 3.4 %, $d_8$; 3.8 %, $d_9$; 5.2 %, $d_{10}$; 7.6 %, $d_{11}$; 12.8 %, $d_{12}$; 19.7 %, $d_{13}$; 19.7 %, $d_{14}$; 10.9 %, $d_{15}$; ; 1.0 %, $d_{16}$.

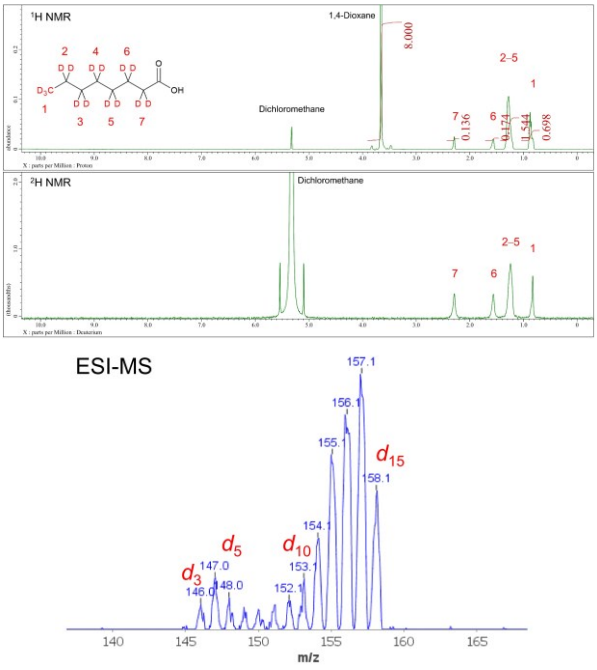



**Figure 3.** $^{1}$H NMR ($CD_2Cl_2$, 400 MHz), $^{2}$H NMR ($CD_2Cl_2$, 61.4 MHz), and ESI-MS data of deuterated 1-octanoic acid. ESI-MS in negative mode of 1-octanoic acid showing the mass distribution of the different isotopologues, which ranges from $d_3$–$d_{15}$. The distribution of the isotopologues is as follows $[M–H]^-$: 1.8 %, $d_3$; 6.4 %, $d_4$; 2.2 %, $d_5$; 1.1 %, $d_6$; 1.2 %, $d_7$; 2.2 %, $d_8$; 2.1 %, $d_9$; 2.9 %, $d_{10}$; 7.5 %, $d_{11}$; 14.5 %, $d_{12}$; 21.7 %, $d_{13}$; 25.2 %, $d_{14}$; 11.5 %, $d_{15}$.

As stated above, compounds with higher deuteration ratio are preferable for neutron experiments. In the case of the deuteration of malonamide compounds using the same catalyst system, the deuteration ratio increased with increasing of the reaction temperature. However, this also accelerates the decomposition reaction of malonamides [18]. It is inferred that *n*-octanamide probably has similar properties, and the deuteration ratio of *n*-octanamide will increase in exchange for the increased decomposition rate of *n*-octanamide. For enhancing the deuteration ratio of *n*-octanamide, it is recommended to optimize the reaction temperature. It is worth noting that reusing the deuterated *n*-octanamide for a second cycle with new $D_2O$ and catalyst would lead to a higher deuteration ratio of *n*-octanamide. It is considered that this method can obtain *n*-octanamine with a high deuteration ratio without worrying about the decomposition of *n*-octanamine.

### 3.2 Neutron reflectivity analysis

In neutron studies, the SLD profile is the main factor for analyzing the fine structure of nano-materials. However, it is difficult to accurately determine the SLD value of 1-octylamine by $^{1}$H NMR and ESI-MS methods because the $NH_2$ protons are easily exchanged with the surrounding solvent ($D_2O$ and/or $H_2O$). However, neutron scattering techniques can be successfully applied to determine the SLD value (and deuteration ratio) of organic samples [24, 25]. Therefore, in this study, we determined the SLD value of deuterated 1-octylamine using NR.

The NR data were obtained using a BL17 SHARAKU neutron reflectometer. Figure 4 shows the NR profiles obtained from the deuterated 1-octylamine/Si substrate sample and the fitting curve of the sample obtained using Motofit software. Although a few experimental points at around $Q_z = 0.03$ Å$^{-1}$ which is a data stitching zone deviated significantly from the fitting curve, data analysis didn't have any issues. The SLD value of deuterated 1-octylamine was estimated to be $3.63\times10^{-6}$ Å$^{-2}$. Since the calculated SLD values for protonated ($NH_2$) species and deuterated ($ND_2$) species are $3.67\times10^{-6}$ Å$^{-2}$ and $4.36\times10^{-6}$ Å$^{-2}$, respectively, it can be suggested that the $NH_2$ protons of deuterated 1-octylamine are not deuterated. Therefore, we have concluded that two protons of the $NH_2$ group in 1-octylamine were protonated during the synthesis procedure, and as a result, the obtained SLD values of deuterated 1-octylamine appeared to be smaller.

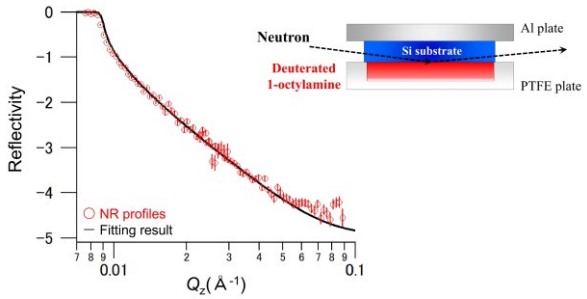



**Figure 4.** NR profiles obtained from the deuterated 1-octylamine/Si substrate sample and its fitting curve. The inset shows an image of the NR sample system.

## 4 Summary

In this study, we have efficiently synthesized three deuterated compounds with high deuteration ratios, *n*-octanamide, 1-octylamine, and 1-octanoic acid, using the synthesis method shown in Scheme 2. In particular, deuterated 1-octylamine with alkyl chains having a high deuteration ratio. If the $LiAlD_4$ catalyst system [26, 27] was used in the reduction reaction, the SLD value and deuteration ratio of deuterated 1-octylamine can be improved to $5.16\times10^{-6}$ Å$^{-2}$ and 77.1 %, respectively. Therefore, fully deuterated amine synthesis using the $LiAlD_4$ catalyst system seems to be an attractive option for the use of deuterated amines in neutron studies.

This work was supported by JSPS KAKENHI (Grant Number) 21K05121. Direct deuteration reactions were conducted at the User Experiment Preparation LabIII (CROSS). $^{1}$H NMR, $^{2}$H NMR, and ESI-MS spectroscopy experiments were conducted at the Deuteration Laboratory in J-PARC MLF. Neutron experiments were conducted at the BL17 SHARAKU apparatus in J-PARC, Tokai, Japan (Proposal No. 2022A0001).

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