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Photocatalytic Multiple Deuteration of Polyethylene Glycol Derivatives Using Deuterium Oxide

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Deuterated molecules are of growing interest because of the specific characteristics of deuterium, such as stronger C–D bonds being stronger than C–H bonds. Polyethylene glycols (PEGs) are widely utilized in scientific fields (e.g., drug discovery and material sciences) as linkers and for the improvement of various properties (solubility in water, stability, etc.) of mother compounds. Therefore, deuterated PEGs can be used as novel tools for drug discovery. Although the H/D exchange reaction (deuteration) is a powerful and straightforward method to produce deuterated compounds, the deuteration of PEGs bearing many unactivated C(sp^3)–H bonds has not been developed. Herein, we report the photocatalytic deuteration of multiple sites of PEGs using tetra-*n*-butylammonium decatungstate (TBADT) and D_2O as an inexpensive deuterium source. This deuteration can be adapted to PEG derivatives bearing various substituents ((hetero)aryl, benzoyl, alkyl, etc.). The deuteration efficiencies of the α-oxy C(sp^3)–H bonds at the terminal positions of the PEGs were strongly influenced by the substituents. These reactivities were elucidated by density functional theory calculations of the reaction barriers towards the formation of radical intermediates, induced by the excited state of TBADT and the PEG substrate. In addition, the applicability of deuterated PEGs to internal standard experiments and Raman spectroscopy was demonstrated.

Introduction

Deuterium (D) is a nonradioactive isotope of hydrogen (H), and deuterated compounds are widely used in various scientific fields (e.g., drug discovery[1] elucidation of life phenomena,[2] materials such as organic electroluminescent devices,[3] and mechanistic studies in organic chemistry),[4] utilizing the specific properties of deuterium. For drug discovery, the deuterated compounds with less than 0.1% of the unlabeled compound remaining have been traditionally used as internal standards using mass spectrometry.[2] Live-cell Raman imaging of bioactive compounds using specific peaks of C–D bonds in the cell-silent region (1,800–2,700 cm^{-1}; wavenumber range where Raman peaks from endogenous intracellular molecules, such as proteins and lipids, have not observed) are also recently highlighted.[2b] Heavy drugs have also attracted considerable attention.[1] Deutetrabenazine and deucravacitinib were recently approved as heavy drugs by the Food and Drug Administration (Figure 1A). The deuterium switch (replacement of C–H bonds with C–D bonds) at the metabolic sites of drugs improves the bioavailability of H forms owing to the deuterium kinetic isotope effect (KIE) arising from the higher dissociation energy of the C–D bond compared with that of the C–H bond. Therefore, the development of practical deuteration protocols is of great interest and in high demand.

Meanwhile, polyethylene glycols (PEGs) are widely used in the field of drug discovery and related areas (Figure 1B); (1) small molecular drugs[5] (e.g., movantik, as astriction curative

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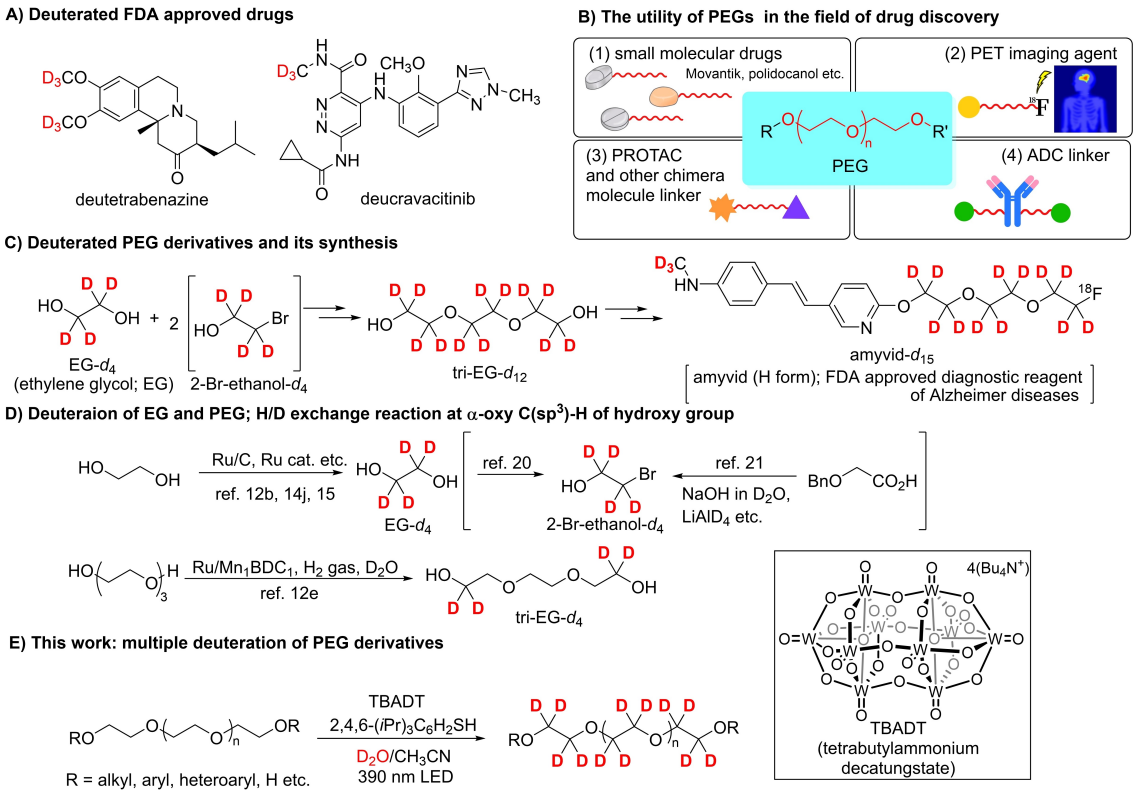


Figure 1. The utility of deuterium and PEG in drug discovery and synthesis of deuterated PEGs.

drug, polidocanol as local anesthetic), (2) positron emission tomography (PET) imaging agents targeting β-amyloid protein aggregates[6] (e.g., amyvid and neuraceq for Alzheimer disease), (3) linker of proteolysis targeting chimera (PROTAC), phosphorylation targeting chimera (PhosTAC) and other chimera molecules,[7] (4) antibody-drug conjugate (ADC) or peptide drug conjugate linker.[8] Incorporating ethylene glycol (EG) or PEG units is known to enhance solubility in water and stability, resulting in decreased immunogenicity, dosing frequency, and optimization of pharmacokinetics.[5] In 2021, amyvid-d_{15}, bearing a deuterated PEG moiety, was reported to improve the ability of imaging agents for Alzheimer's disease in comparison with its H form (amyvid) owing to the KIE effect as stronger C–D bonds than C–H bonds (Figure 1C).[9]

H/D exchange reactions are powerful and straightforward deuteration methods for directly synthesizing deuterated compounds. Deuteration using D_2O as an abundant and inexpensive deuterium source has benefits in terms of cost and greenness compared to organic deuterium sources (CD_3OD, $CDCl_3$. C_6D_6 etc.).[10] H/D exchange at C(sp^3)–H bonds, neighboring heteroatoms (O,[11–15] N,[11,17] or S[11,19] atoms), is widely accomplished using transition metal catalysts (Raney nickel, Ru, Pt, Pd, Rh, Mo, Mn, Fe, and Ir catalysts) via C–H activation by the directing group effect of heteroatoms. Additionally, photocatalytic deuteration has recently gained attention as a mild reaction method, and direct deuteration at C(sp^3)–H bonds neighboring the heteroatoms of alkyl amines,[16b,18] *O*-alkyl phenol derivatives[16a] and alcohols[16b] has been reported. Meanwhile, there is no literature on H/D exchange at every position of the PEG C(sp^3)–H bonds because it is quite difficult for many unactivated α-oxy C(sp^3)–H bonds of the ether moiety on PEGs to undergo the replacement of H with D in a single reaction. H/D exchange at α-hydroxy C(sp^3)–H bonds of ethylene glycol (EG) as minimum unit of PEGs to EG-d_4 was achieved using heterogeneous Ru catalysts (Ru/C,[12d] Ru/Mn_1BDC_1),[12e] homogeneous Ru catalysts,[15] and Mn catalyst[14j] (Figure 1D). However, the α-oxy C(sp^3)–H bonds of the ether moiety (R^1O-CH_2R^2) on the PEGs did not undergo deuteration, as in the case of Ru/Mn_1BDC_1[12e] (Figure 1D). Therefore, as shown in Figure 1C, the PEG moiety of amyvid-d_{15} was needed to be synthesized by stepwise protocols using EG-d_4 and 2-bromo-ethanol-d_4, which can be alternatively prepared by mono-bromination of EG-d_4[20] or stepwise synthesis using NaOH in D_2O and expensive/moisture-sensitive deuteride reagents ($LiAlD_4$) from benzyloxy-acetic acid[21] (EG-d_4 and 2-bromo-ethanol-d_4 are commercially available, but very expensive).

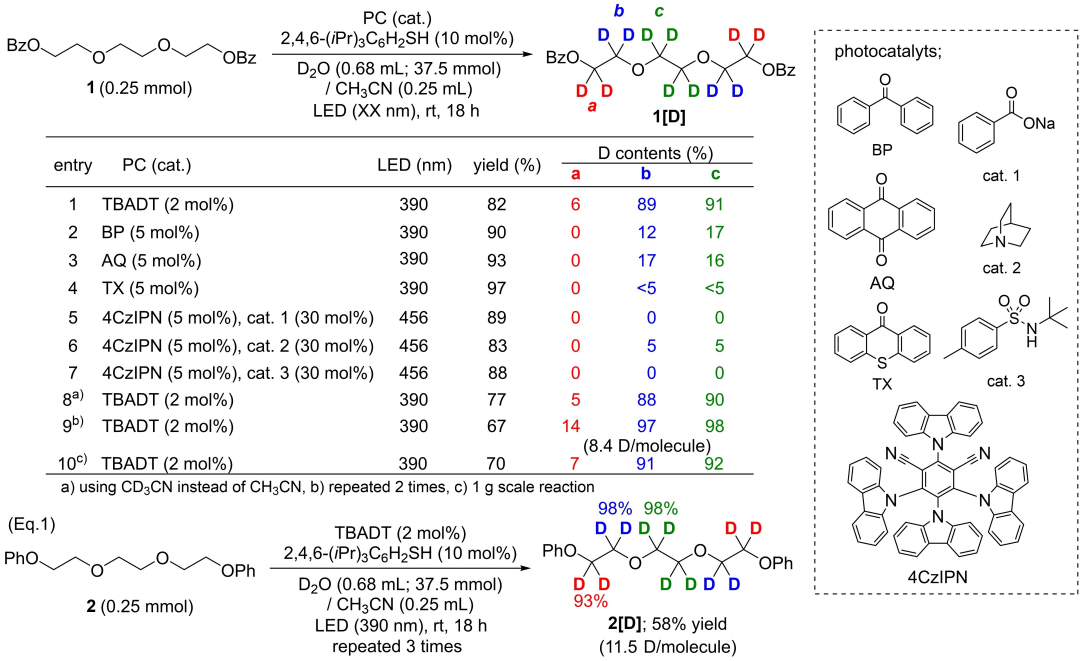
Herein, we demonstrate the direct and multiple H/D exchange reactions at the unactivated α-oxy C(sp^3)–H bonds of PEG derivatives, bearing the substituents at two terminal hydroxy groups (Figure 1E). The use of tetra-*n*-butylammonium decatungstate (TBADT) as a hydrogen atom transfer (HAT) catalyst and D_2O under 390 nm LED irradiation enabled multiple deuterations. Additionally, we revealed that the deuterium efficiencies of the α-oxy C(sp^3)–H bonds at the terminal positions of the PEG derivatives were strongly influenced by the substituents. These reactivities were elucidated using density

functional theory (DFT) calculations. Additionally, the applicability of the obtained deuterated PEGs for internal standard experiments in mass spectrometry and Raman analysis as basic experiments for molecular imaging was demonstrated.

Results and Discussion

First, the deuteration of the model compound di-benzoyl (Bz)-substituted triethylene glycol (**1**) was performed (Figure 2 and Table). The bond dissociation energy (BDE) of α-oxy C(sp^3)–H bond is known to be comparatively high, as shown in the literature[22b] (e.g., BDE of α-oxy C(sp^3)–H bonds; THF (92 kcal/mol) and 1,4-dioxane (96 kcal/mol)). Photocatalytic functionalization via a radical intermediate, resulting from the activation of the C–H bond bearing a high BDE, can be accomplished using HAT catalysts possessing strong hydrogen-atom abstraction properties (e.g., TBADT, benzophenone (BP), and anthraquinone (AQ)).[22] Inspired by previously-reported TBADT-catalyzed deuteration of C–H bonds adjacent to the oxygen atom of *O*-alkyl phenol,[16a] the use of TBADT[23] in the presence of 2,4,6-triisopropylbenzenethiol as a deuterium atom transfer (DAT) catalyst[16,18] in CH_3CN/D_2O under 390 nm LED irradiation gave the deuterated product (**1[D]**) with a high D content in 82% yield (entry 1). In this case, the deuterium content at the terminal (**a**; red) positions was low (6% D), and the internal (**b**; blue and **c**; green) positions efficiently underwent deuteration to give 89% D and 91% D, respectively. Meanwhile, the aromatic moiety of the Bz group was never deuterated because of the higher BDE of the aromatic C–H bonds (for example, the BDE of the C–H bond of benzene is 113 kcal/mol).[22b] BP, AQ, and thioxanthone (TX) were found to be insufficient HAT catalysts (entries 2–4). In addition, an indirect HAT protocol[22a] using a combination of 2,4,5,6-tetrakis(3,6-diphenylcarbazol-9-yl)-1,3-dicyanobenzene (4CzIPN) and sodium benzoate (cat. 1)/quinuclidine (cat. 2)/sulfone amide derivatives (cat. 3) resulted in little or no deuteration (entries 5–7), because the capacity for hydrogen-atom abstraction is known to be lower than that of TBADT[22c] (see the detailed optimization in the Supporting Information). The use of CD_3CN instead of CH_3CN gave a similar result (entries 1 *vs.* 8), indicating that the C(sp^3)–H bonds of CH_3CN did not function as a proton source, causing a decrease in deuterium content. The repeated reaction was found to improve the deuterated content (entries 9 *vs.* 1) and give **1[D]** with an average of 8.4 D atoms per molecule (8.4 D/molecule). 1 g-scale reaction of **1** was also accomplished to **1[D]** with a high D content (entry 10). Meanwhile, the deuteration of diphenyl (Ph)-substituted compound **2** proceeded effectively at all (terminal; red and internal; blue and green) α-oxy C(sp^3)–H positions of **2** with high D contents after the reactions, repeated three times (11.5 D/molecule: Equation (1), D contents after a single reaction; red: 50% D; blue: 86% D; green: 82% D). Intriguingly, the deuteration efficiencies of the α-oxy C(sp^3)–H bonds at the terminal positions of the PEG derivatives were found to be strongly influenced by the substituents (the details are presented in Figures 3 and 4).

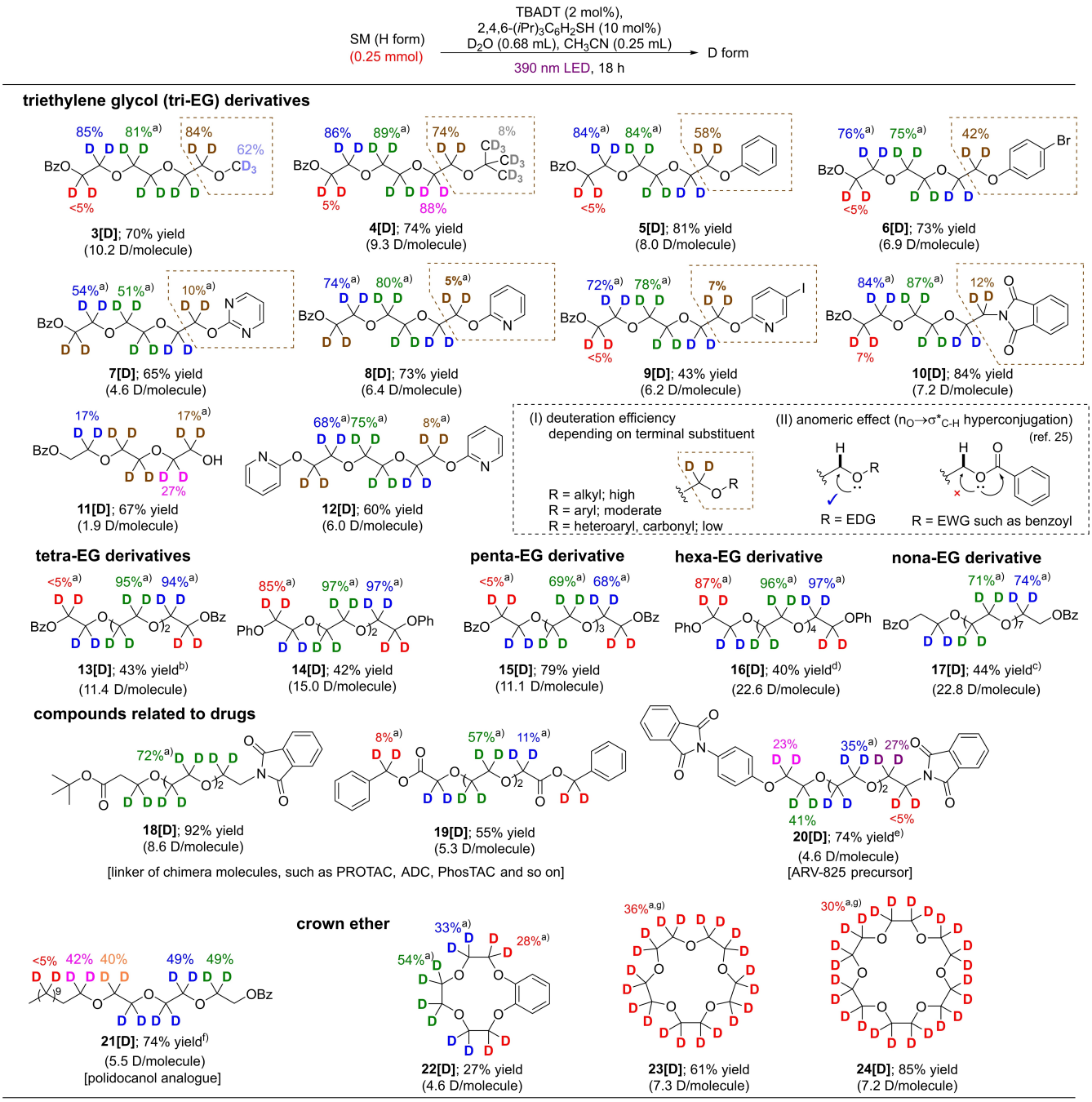
Next, we investigated the substrate scope of the TBADT-catalyzed multiple H/D exchange reactions (Figure 3). Additionally, the substituent effects at the terminal positions of the triethylene glycol (tri-EG) derivatives (**3**–**11**), bearing Bz group and another moiety were also examined. In all cases, the internal α-oxy C(sp^3)–H bonds (blue, green) were efficiently deuterated, and a lower D content at the C(sp^3)–H bonds (red) neighboring the OBz moiety was observed. The α-oxy C(sp^3)–H



entry	PC (cat.)	LED (nm)	yield (%)	D contents (%) a	b	c
1	TBADT (2 mol%)	390	82	6	89	91
2	BP (5 mol%)	390	90	0	12	17
3	AQ (5 mol%)	390	93	0	17	16
4	TX (5 mol%)	390	97	0	<5	<5
5	4CzIPN (5 mol%), cat. 1 (30 mol%)	456	89	0	0	0
6	4CzIPN (5 mol%), cat. 2 (30 mol%)	456	83	0	5	5
7	4CzIPN (5 mol%), cat. 3 (30 mol%)	456	88	0	0	0
8[a)]	TBADT (2 mol%)	390	77	5	88	90
9[b)]	TBADT (2 mol%)	390	67	14	97	98
					(8.4 D/molecule)	
10[c)]	TBADT (2 mol%)	390	70	7	91	92

a) using CD_3CN instead of CH_3CN, b) repeated 2 times, c) 1 g scale reaction

Figure 2. Screening of photocatalysts in multiple α-oxy C(sp^3)–H deuteration of di-benzoyl triethylene glycol (**1**) and comparison of deuterium efficiency between 1 and di-phenyl triethylene glycol (**2**).



a) average of D contents on the same color of D atom, b) repeated 2 times, c) using 2.04 mL D_2O, d) repetaed 3 times, e) using CH_3CN (0.25 mL) and CH_2Cl_2 (0.5 mL), f) reaction time is 48 h
g) deuterium content was calculated using by tetrachloroethane as an internal standard.

Figure 3. Substrate scope in multiple H/D exchange reaction of PEGs.

bonds substituted with alkyl groups (methyl (**3[D]**) and *tert*-butyl (*t*Bu-; **4[D]**)) or aryl groups (phenyl (**5[D]**), and *p*-Br-C_6H_4- (**6[D]**) at the oxygen atoms underwent efficient deuteration. Meanwhile, the electron-deficient heteroaromatics on the 2-pyrimidyl (**7[D]**), 2-pyridyl (**8[D]**), and 4-iodo-2-pyridyl (**9[D]**) substrates resulted in less deuteration of the substituted α-oxy C(sp^3)–H bonds (brown). The α-amino C(sp^3)–H bonds, substituted by phthalimide, on **10[D]** was also less deuterated. The present H/D exchange reaction was proposed to proceed via a radical intermediate at the α-positions of oxygen atom (see Figure 4). The α-oxy C(sp^3)–H bonds are known to be activated by anomeric effect, $n_O \rightarrow \sigma^*_{C-H}$ hyperconjugation (Figure 3-(ii)).[24,25] In the case of substrates bearing an alkyl group as the electron-donating group (EDG) at the terminal and internal oxygen atoms, the anomeric effect efficiently facilitated the desired deuteration via C(sp^3)–H bond activation (Figure 3-(i)). Meanwhile, when using an electron-withdrawing Bz-substituted substrate, the O lone pair was deactivated by interactions (resonance) with the carbonyl group; namely, the weakened anomeric assistance resulted in low deuteration efficiency.

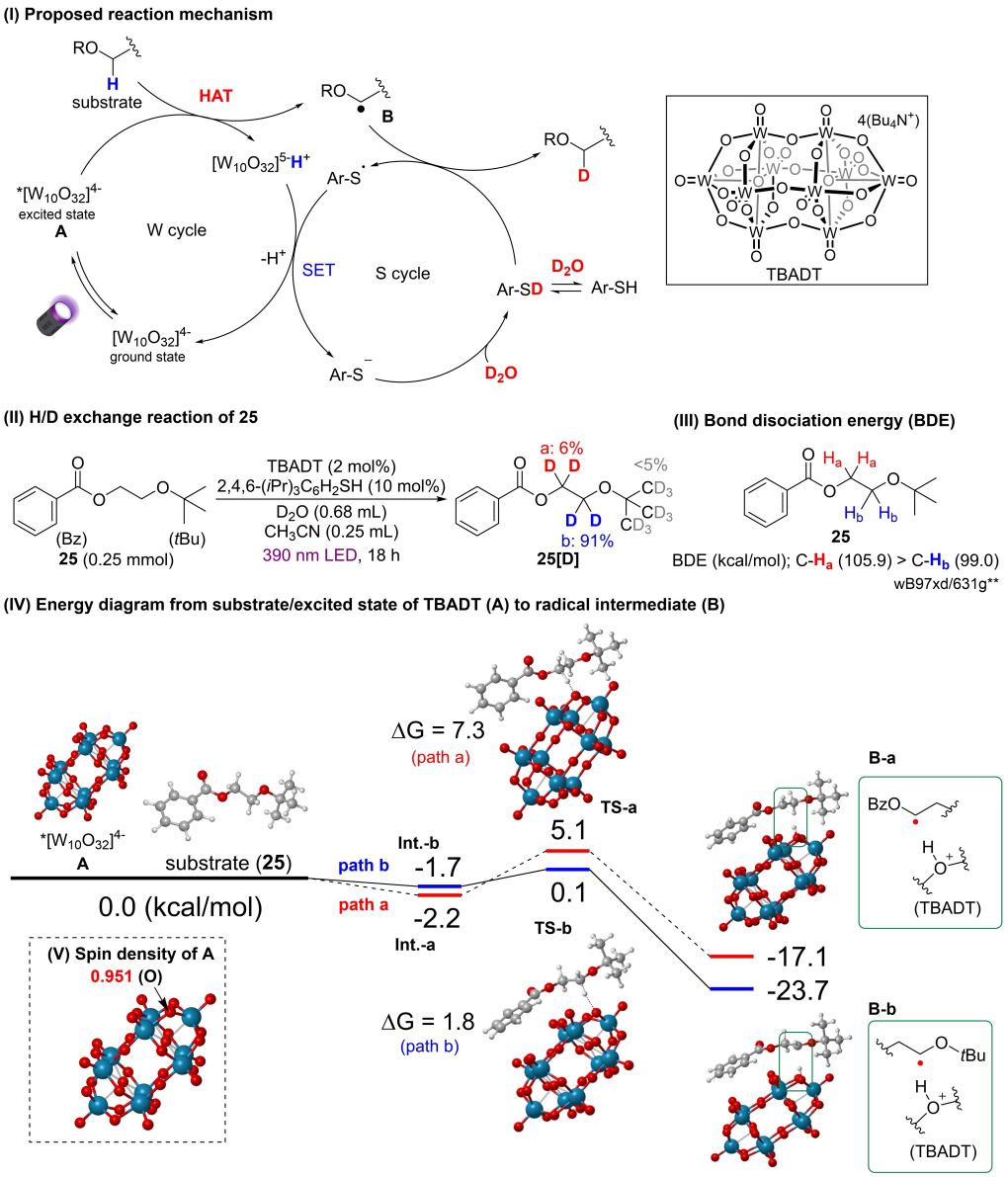


Figure 4. Mechanistic study.

Electron-deficient heteroaromatics also exhibited a weakened anomeric assistance.

In addition, a hydroxy-free substrate (**11**) was adapted for deuteration, and di-2-pyridyl substrate (**12**) underwent efficient deuteration at the internal α-oxy C(sp^3)–H bonds. Furthermore, tetra-EG (**13** and **14**), penta-EG (**15**), hexa-EG (**16**), and nona-EG (**17**) derivatives bearing Bz or Ph groups were also multiply deuterated with deuteration efficiencies similar to those of **1** and **2**. Various multi-O-containing substrates (**18**–**21**), related to bioactive compounds (linkers of PROTAC, ADC, PhosTAC, etc.,[7,8] synthetic precursors of ARV-825[26] and drug analogs (polidocanol)[5]) could also undergo multiple deuterations at α-oxy C(sp^3)–H bonds. In addition, benzo 12-crown 4-ether (**22**), 15-crown 5-ether (**23**) and 18-crown 6-ether (**24**) were deuterated.

As a proposed reaction mechanism in deuteration of α-oxy C(sp^3)–H bond, the photoexcitation of TBADT ($[W_{10}O_{32}]^{4-}$) would first generate the excited state (triplet) of TBADT (**A**; $[W_{10}O_{32}]^{4-*}$), and HAT between α-oxy C(sp^3)–H bond on substrate and **A** affords the radical intermediate **B** (Figure 4-I). Meanwhile, the deuterated thiol catalyst (Ar-SD),[16,18] generated from the H/D exchange of Ar-SH with D_2O, converts the deuterium atom into **B** to give the deuterated product. Similar deuterations are repeated at almost α-oxy C(sp^3)–H bonds of the PEGs to give multiple deuterated products. During this process, the deuteration efficiency at the C(sp^3)–H bond linked by O-electron-deficient substituents (e.g., OBz) was low, as shown in Figures 2 and 3.

Next, we attempted to elucidate these different deuteration efficiencies in terms of the BDE and the energy barrier to form radical intermediates using DFT calculations. The calculation

cost using the combination of PEG derivatives, bearing many C–H bonds, and TBADT as a bulky catalyst would be high; therefore, the deuteration of a simple substrate, giving similar deuteration efficiency, should be accomplished. The EG derivative **25**, bearing Bz and *t*Bu groups on each oxygen atom, was chosen as a simple model substrate for TBADT-catalyzed deuteration (Figure 4-II). As expected, the C(sp^3)–H bond (position b; blue) linked by *t*BuO moiety was efficiently deuterated with 91% D content, whereas the deuteration efficiency at the BzO-linked C(sp^3)–H bond (position a; red) was lower (6% D). BDEs, calculated by DFT, clearly indicated less reactivity of BzO-linked C(sp^3)–H bond (BDE; C–H_a (red; 105.9 kcal/mol) > C–H_b (blue; 99.0 kcal/mol)) (Figure 4-III). The energy diagram of the HAT process from **A** and **25** to the radical intermediate (**B**) also supports the different deuteration efficiencies between the C–H_a and C–H_b bonds (Figure 4-IV). The spin density was mostly located at the O atom (+0.951) at the bridge position (Figure 4-V), which shows that this position of **A** is the most reactive for C–H abstraction of the substrate.[27] In the deuteration of **25**, two radical intermediates (carbon radical, neighboring BzO moiety (**B-a**) or *t*BuO moiety (**B-b**)), resulting from the abstraction of H_a or H_b atoms from **25**) are considerable. The energy barrier from intermediate-a (**Int.-a**), in which O atoms bearing a high spin density on **A** and H_a atoms on **25** are near, to transition state-a (**TS-a**) is higher than that from **Int.-b** to **TS-b** (ΔG (kcal/mol) = 7.3 vs. 1.8). **TS-b** is more stable than **TS-a** because of the greater anomeric effect of the electron-donating alkyl group substituted at the O atom, as shown in Figure 3-(II).[25] Additionally, the radical intermediate-b (**B-b**) was more stable than **B-a** because of a similar anomeric effect. These results clearly indicate that the deuteration of *t*BuO-linked C(sp^3)–H bond of **25** proceeds preferentially, which is consistent with the actual experimental results.

As mentioned in the introduction, deuterated compounds are widely utilized in various scientific fields. Therefore, the applicability of the deuterated PEG products as internal standards for drug discovery and live-cell Raman imaging was evaluated (Figure 5). To use the deuterated compounds as internal standards in mass spectrometry, the deuterium-labeled product with protonated ion greater than four (M + 4) is ideal in comparison with mother compound (H form; M), and less 0.1% of the unlabeled compound remaining is required. (M means monoisotopic mass of molecular ion, protonated ion, deprotonated ion, etc.). The H/D exchange reaction may give a mixture of non-deuterated substrate (M) and fully deuterated products. Therefore, the distribution of the mass (*m/z*) of **1[D]**, obtained in Figure 2, Table and entry 1, as the tri-EG derivative was evaluated by mass analysis and theoretical calculations, considering the natural isotopic masses of C and O (Figure 5-A; see the details in the Supporting Information). Consequently,**1[D]**-D_8 (M + 8) was found to be the major component and less than 0.1% of **1[D]**-D_3 ([M + 3]) as minimum mass (*m/z*) was observed. The minimum mass (*m/z*) of **13[D]** as tetra-EG derivative was M + 7. The flavonoid dimer **26**, consisting of hexa-EG moiety and two 4-hydroxyflavone, has been reported to modulate DOX activity against multidrug resistant protein 1 (MRP1).[28] Deuterated flavonoid dimer (**26[D]**) was prepared from **16[D]** and the distribution of its mass (*m/z*) was found to be greater than M + 18. These results indicate that this convenient multiple deuteration method is useful for the preparation of internal standards for drugs bearing PEG moieties (the metabolic study using rat

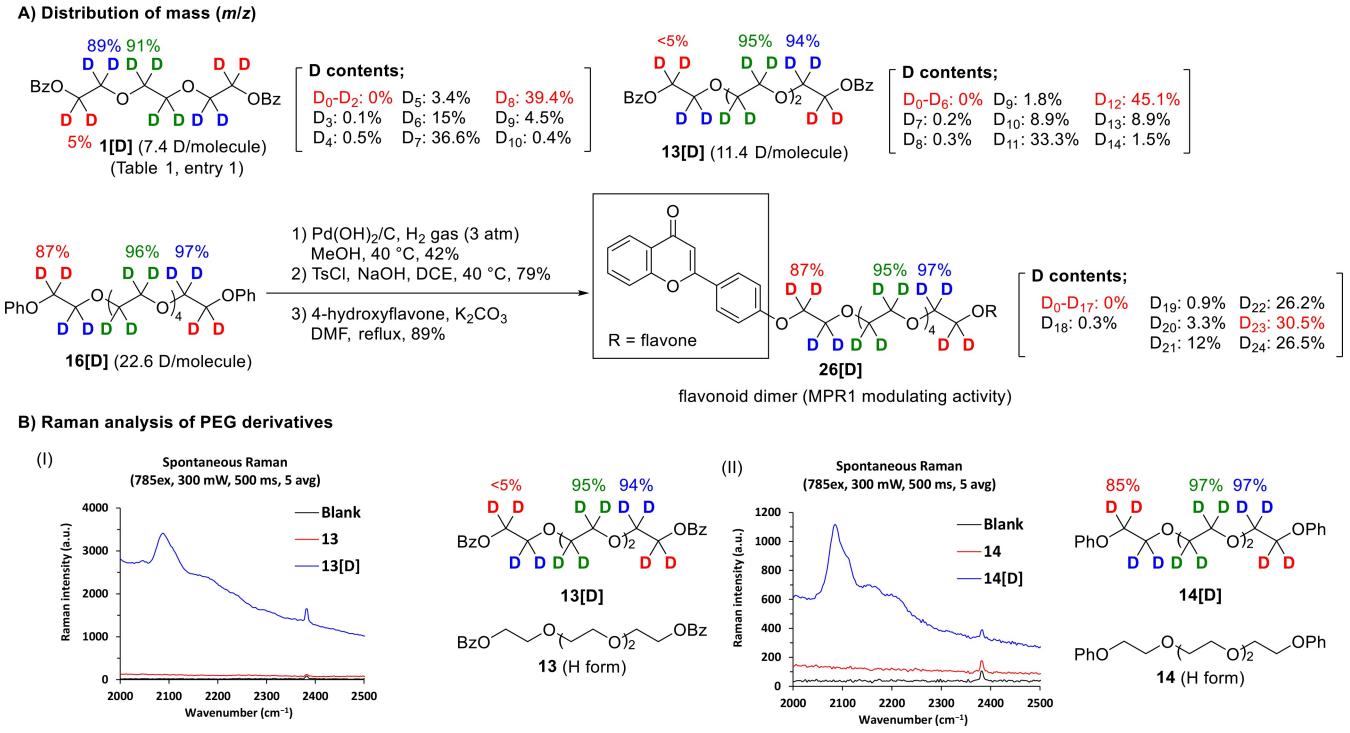


Figure 5. Evaluations of applicabilities of deuterated PEGs for internal standard in drug discovery and Raman analysis.

liver microsomes produced no significant KIE between **26[D]** and **26** (H form); see Supporting Information).

Meanwhile, deuterium labels have been used as Raman tags for biological species such as fatty acids, amino acids, sterols, and glucose,[2b] because deuterium labeling has a significantly limited effect on biological activities compared to fluorescent tags etc. Therefore, the identification of C–D bonds with distinct vibrational frequencies in the cell-silent region is crucial as a preliminary investigation for live-cell Raman imaging. Unique Raman peaks of **13[D]** and **14[D]** were observed[29] at approximately 2057 cm^{-1}~2129 cm^{-1} in the silent region (Figure 5B–I and 5B-II; blue lines). Bioactive compounds bearing deuterated PEG derivatives are expected to be utilized for live-cell Raman imaging in the future.

Conclusions

We successfully established a multiple deuteration method for PEG derivatives via photocatalytic α-oxy C(sp^3)–H activation in the presence of TBADT using D_2O as an inexpensive deuterium source. It is noteworthy that the deuteration efficiency of the terminal PEGs was strongly influenced by substituents. A mechanistic study using DFT calculations revealed these differences in the deuteration efficiencies. Mass spectrometry of the deuterated PEG derivatives demonstrated their applicability as internal standards for drug discovery research. Additionally, Raman analysis of deuterated PEG derivatives showed unique peaks, derived from C–D bonds, in the silent region. This result is expected to provide important information, such as the intracellular localization of bioactive compounds consisting of a PEG moiety, by live-cell Raman imaging. This first accomplishment of multiple deuteration of PEG skeletons will contribute to develop the future deuterium science, including medicinal chemistry.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Polyethylene glycol · Photocatalytic reaction · H/D exchange reaction · Deuterium oxide

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[29] Raman spectra of **13**, **13[D]**, **14**, **14[D]** were measured in 1.5 mL polypropylene microtubes. The Blank measurement without compounds exhibits the background signal mainly derived from the container material (polypropylene). No solvent was used for the measurement. Note; higher background observed for the Raman spectra of deuterated compounds might be due to a very small amount of fluorescent impurities introduced during the deuteration reaction.

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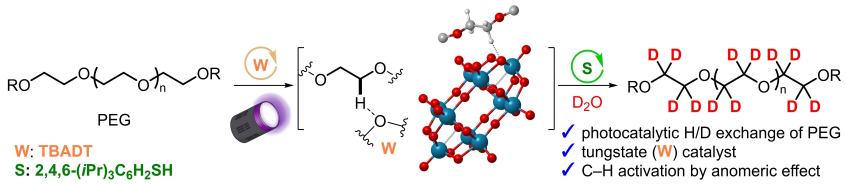

Supporting information for this article is given via a link at the end of the document.We successfully established a multiple deuteration for PEG derivatives via photocatalytic α-oxy C(sp^3)–H activation in the presence of TBADT using D_2O as an inexpensive deuterium source. The mechanistic study using DFT calculation etc. revealed deuteration reactivity. This first accomplishment of multiple deuterium incorporation to PEG skeleton will contribute to develop the future deuterium science and medicinal chemistry.

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Photocatalytic Multiple Deuteration of Polyethylene Glycol Derivatives Using Deuterium Oxide