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# Synthesis of three selectively deuterated propylene oxides

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**Three different selectively deuterated propylene oxides have been synthesized for use in quasi-elastic neutron scattering studies of the dynamics of propylene oxide within clathrate hydrate cages.**

**Keywords:** isotopic labeling; deuterium; propylene oxide; clathrate hydrates; synthesis; quasi-elastic neutron scattering

## Introduction

Clathrate hydrates are crystalline substances that form when host water molecules associate around a small guest molecule. Clathrate hydrates containing methane as the guest molecule are found in vast deposits on oceanic continental shelves. These methane hydrates store significant amounts of carbon so an understanding of their properties and stability is important to scientists' ability to predict potential responses to climate change-induced warming of the oceans. Methane hydrates are also a potential source of energy and clathrates could provide an efficient means of energy storage. In addition, efforts are underway to assess whether hydrates could provide a practical medium for the sequestration of carbon dioxide.

The success of efforts to predict how well hydrates could serve as a storage medium or how natural hydrate deposits will react to changes in climate depends to a great extent on how well thermal characteristics such as their glass-like thermal conductivity is understood.[1] The origin of their unusual thermal conductivity is thought to be interactions between the guest and host water molecules;[2] however, these interactions are not completely understood. One thing that is well known is that the size of the guest determines the extent to which it is free to move – rotate, rattle, or oscillate – inside the water cavity. Experimental studies of the motions of trimethylene oxide (TMO) guests in structure II clathrate hydrates[3] reveal that it has a great deal of rotational freedom, i.e. a weak interaction with the water cage.[4] These results are in strong contrast to the behavior of a comparatively large guest molecule such as propylene oxide (PO). Below 50 K, and in contrast to the behavior of TMO, PO molecules are essentially motionless. Above 50 K, a motion appears that most likely involves a rotation of PO about its lengthwise axis or alternatively a rotation of the methyl group. In addition, as temperature increases, a pronounced distortion of the water cavity appears, a clear indication of strong guest–host interactions.

We are interested in developing a better understanding of the processes involved in the formation of clathrate hydrates and of the fundamental properties of the hydrates, themselves, in particular, those which derive from interactions between the water host and the guest molecules as revealed by a study of the motions of the guest molecules. Tracked experimentally, the motion of the guest can be related to geometric factors – its size and shape relative to the host water cavity – as well as to guest-host dipole-dipole interactions.[5] For the study of guest dynamics of clathrate hydrates, a technique known as quasielastic neutron scattering (QENS) is well suited: the bound incoherent neutron scattering cross-section of $^{1}$H (80.27 barn, 1 barn = $10^{-24}$ cm$^2$) is large relative to that of $^{2}$H (2.05 barn).[6] The signal arising from a QENS experiment on a clathrate hydrate sample made with hydrogenated guest molecules and deuterated water thus produces a signal from only the $^{1}$H atoms that are in motion on the experimental time scale, allowing the geometry of the whole-molecule reorientations to be deduced. Moreover, the width of the quasielastic component provides information regarding the time scale of the motions and its temperature dependence reveals the energetics of any associated activation process(es).

QENS experiments of simple propylene oxide in a clathrate hydrate produce a complex signal where deconvolution of the signals from each of the three different types of protons is possible but the results cannot be assigned unambiguously to a single model of molecular motion. However, with the lower incoherent scattering intensity of deuterium atoms, relative to protons, having access to propylene oxides with two of the three positions labeled with deuterium would allow us to separately generate QENS data for each type of proton. We report here the synthesis of the three selectively deuterated propylene oxides needed for these studies.

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## Experimental

### General methods

Commercially available starting materials were purchased from Acros or Aldrich unless otherwise specified. Anhydrous THF and dichloromethane were obtained by passing solvents through a pair of alumina columns under argon pressure using a PureSolv MD-3 solvent purification system. NMR spectra were recorded at 298 K on a Brüker Avance 500 Spectrometer using residual solvent peaks as internal standards ($CHCl_3$ at 7.26 ppm for $^1H$ and 77.0 ppm for $^{13}C$). Peaks in the $^{13}C$ spectra for deuterium-labeled carbons are given, with coupling information, only when the peaks were clearly distinguishable from the baseline noise. TLC was performed using Whatman silica gel plates ($F_{254}$, 0.25 mm) and compounds were visualized using UV light at 254 nm or by charring with either 10% phosphomolybdic acid in ethanol or vanillin with 1% $H_2SO_4$ in ethanol. Flash chromatography was carried out using MP Silica 32-63, 60 Å.

### 2-Oxo($^2H_5$)propyl 4-methylbenzenesulfonate (2)

[Hydroxy(tosyloxy)iodo]benzene (15.0 g, 38.2 mmol) was suspended in acetonitrile (160 mL). The suspension was heated to 50°C and acetone-$d_6$ (5.1 mL, 4.4 g, 69.4 mmol) was added to the hot mixture while the solution was stirred. The mixture was refluxed for 30 min, cooled to room temperature and stirred for 10 additional minutes. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (160 mL). The solution was washed with water (2 × 100 mL) and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure to yield the crude product (12.7 g). The crude product was purified by flash chromatography on silica, eluting first with 10% EtOAc/hexanes to remove the iodobenzene byproduct then with 100% EtOAc to isolate the product. The solvent was removed under reduced pressure to yield the purified product (7.45 g, 46% yield). $^1H$ NMR ($CDCl_3$, 500MHz) δ 7.82 (d, $J$ = 8.4 Hz, 2H), 7.38 (d, $J$ = 8.4 Hz, 2H), 2.47 (s, 3H). $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 201.2, 145.5, 132.3, 130.2, 128.0, 71.5 (quintet, $J_{C\text{-}D}$ = 23 Hz), 25.8 (septet, $J_{C\text{-}D}$ = 20 Hz), 21.87.

### 2-Hydroxy(1,1,3,3,3-$^2H_5$)propyl 4-methylbenzenesulfonate (3a)

2-Oxo($^2H_5$)propyl 4-methylbenzenesulfonate (**2**) (12.7 g, 54.4 mmol) was dissolved in methanol-d (25 mL) and the flask was cooled in an ice bath. While the solution was stirred, sodium borohydride (1.03 g, 27.2 mmol) was added slowly. Upon completion of the addition, the solution was stirred at 0°C for 5 min then the ice bath was removed and the solution was stirred for an additional 30 min as it warmed to room temperature. Saturated ammonium chloride (25 mL) was added and the mixture was stirred for 10 min at room temperature. The methanol was removed under reduced pressure and the resulting aqueous solution was extracted with dichloromethane (4 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure yielding the product as a clear oil which solidified to a white powder upon drying at high vacuum (9.28 g, 73%). $^1H$ NMR ($CDCl_3$, 500 MHz) δ 7.81 (d, $J$ = 7.8 Hz, 2H), 7.37 (d, $J$ = 7.8 Hz, 2H), 4.02 (s, 1H), 2.46 (s, 3H), 2.39 (br s, 1H). $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 145.0, 132.7, 129.9, 127.9, 74.2 (quintet, $J_{C\text{-}D}$ = 23 Hz), 65.4, 21.6, 17.7 (septet, $J_{C\text{-}D}$ = 19 Hz).

### (1,1,2-$^2H_3$)Propane-1,2-diol (6b)

Lithium aluminum deuteride (2.5 g, 59.5 mmol) was suspended in THF (50 mL) in a three-neck flask equipped with a pressure equalizing addition funnel, a mechanical stirrer and a reflux condenser and the mixture was cooled in an ice bath under argon. A solution of ethyl pyruvate (**5**) (5.1 mL, 5.3 g, 45.6 mmol) in THF (10 mL) was added dropwise to this mixture over a one hour period. The reaction was warmed to room temperature and then stirred for 24 h. The reaction was quenched by careful addition of water (20 mL), 1 M sodium hydroxide (30 mL) and water (40 mL). The resulting mixture was refluxed for 1 h. The mixture was cooled to room temperature, diluted with THF (90 mL) and filtered. The filtrate was dried over $MgSO_4$ and the solvent was removed to give a yellow oil (1.48 g, 41%). $^1H$ NMR ($CDCl_3$, 500 MHz) δ 3.56 (br s, 2H), 1.14 (s, 3H). $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 67.7 (t, $J_{C\text{-}D}$ = 22 Hz), 66.9 (quintet, $J_{C\text{-}D}$ = 21 Hz), 18.5.

### 1-(Benzyloxy)(3,3,3-$^2H_3$)propan-2-ol (10)

A solution of $d_3$-methylmagnesium iodide in THF (0.5 M; 73.6 mL, 36.8 mmol) was added to a stirred solution of 2-benzyloxyacetaldehyde (**9**) (4.60 g, 30.7 mmol) in THF (77 mL) at 0°C under argon and the solution was stirred for 2 h. Saturated ammonium chloride (10 mL) was added, the THF was removed under reduced pressure and the mixture was partitioned between ether (140 mL) and saturated ammonium chloride (140 mL). The organic layer was washed with sat. NaCl (100 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield a clear, colorless oil (3.86 g, 75%). $^1H$ NMR ($CDCl_3$, 500MHz) δ 7.36 (m, 5H), 4.59 (s, 2H), 4.01 (br d, $J$ = 7.7 Hz, 1H), 3.49 (dd, $J$ = 9.4, 3.1 Hz, 1H), 3.32 (dd, $J$ = 9.4, 8.1 Hz, 1H), 2.53 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 138.0, 128.4, 127.8, 127.7, 75.8, 73.3, 66.3.

### 1-(Benzyloxy)(3,3,3-$^2H_3$)propan-2-one (11)

DMSO (5.5 mL, 6.1 g, 78.1 mmol) was added dropwise, under argon, to a solution of oxalyl chloride (3.3 mL, 5.0 g, 39.4 mmol) in dichloromethane (175 mL) at −78°C and the solution was allowed to stir for 5 min. 1-(Benzyloxy)(3,3,3-$^2H_3$)propan-2-ol (**10**) (3.26 g, 19.3 mmol) in dichloromethane (36 mL) was added and the resulting solution was allowed to stir at −78°C for 1 h. Triethylamine (16.0 mL, 11.6 g, 114.6 mmol) was added to the reaction mixture, which was warmed to room temperature and stirred for 1 h. The reaction was then quenched with the slow addition of saturated ammonium chloride solution (250 mL) and the aqueous layer was extracted with dichloromethane (3 × 200 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified *via* flash chromatography (20 % ethyl acetate in hexanes) to yield the product as a clear, colorless oil (2.71 g, 84%). $^1H$ NMR ($CDCl_3$, 500 MHz) δ 7.38 (m, 5H), 4.62 (s, 2H), 4.08 (s, 2H). $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 206.8, 137.1, 128.5, 128.0, 127.8, 75.3, 73.3.

### 1-(Benzyloxy)(2,3,3,3-$^2H_4$)propan-2-ol (12)

1-(Benzyloxy)(3,3,3-$^2H_3$)propan-2-one (**11**) (2.35 g, 14.1 mmol) was dissolved in methanol (77 mL) and stirred for 10 min at 0°C. $NaBD_4$ (0.29 g, 6.9 mmol) was added, and the resulting solution was stirred for 20 min at 0°C then for 40 min at room temperature. Saturated ammonium chloride (40 mL) was added to the solution, which was allowed to stir for 10 min. The solvent

was removed under reduced pressure, and the aqueous layer was extracted with dichloromethane (3 × 40 mL). The organic layers were combined and dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield a clear, colorless oil (1.76 g, 74%). $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.37 (m, 5H), 4.59 (s, 2H), 3.50 (d, $J$ = 9.4 Hz, 1H), 3.32 (d, $J$ = 9.4 Hz, 1H), 2.10 (br s, 1H). $^{13}$C NMR ($CDCl_3$, 125 MHz δ 138.0, 128.4, 127.7, 127.6, 75.7, 73.3, 65.9 (triplet, $J_{C\text{-}D}$ = 22 Hz)).

### (2,3,3,3-$^2H_4$)Propane-1,2-diol (6c)

1-(Benzyloxy)(2,3,3,3-$^2H_4$)propan-2-ol (**12**) (1.70 g, 10.0 mmol) was dissolved in ethanol (82 mL) and treated with 10% Pd/C (0.37 g). The mixture was shaken under hydrogen at 35 psi overnight at room temperature on a Parr shaker. The mixture was then filtered through Celite and the solvent was removed under reduced pressure to give a viscous oil (0.68g, 85%). $^1$H NMR ($CDCl_3$, 500 MHz) δ 3.96 (br s, 2H), 3.63 (d, $J$ = 11.2 Hz, 1H), 3.41 (d, $J$ = 11.2 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 67.7.

### Tosylation of deuterated propanediols

(2,3,3,3-$^2H_4$)Propane-1,2-diol (**6c**) (0.68 g, 8.5 mmol) and triethylamine (1.2 mL, 0.87 g, 8.6 mmol) were added to a solution of *p*-toluenesulfonyl chloride (1.62 g, 8.5 mmol) in dichloromethane (11 mL) under argon. After stirring at room temperature under argon for 24 h, the reaction mixture was hydrolyzed with water (3.4 mL). The organic layer was extracted with dichloromethane (6.5 mL) and washed with saturated sodium bicarbonate (6.0 mL). The solution was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified *via* flash chromatography over silica (10% ethyl acetate in hexanes) to yield a viscous oil which solidified upon drying at high vacuum (0.73 g, 37%).

*2-Hydroxy(1,1,2-$^2H_3$)propyl 4-methylbenzenesulfonate (**3b**)*

Yield: 76%. $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.81 (d, $J$ = 8.2 Hz, 2H), 7.37 (d, $J$ = 8.2 Hz, 2H), 2.46 (s, 3H), 2.25 (br s, 1H), 1.16 (s, 3H). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 145.0, 132.6, 129.9, 127.8, 74.0 (quintet, $J_{C\text{-}D}$ = 23 Hz), 64.9 (t, $J_{C\text{-}D}$ = 22 Hz), 21.5, 18.4.

*2-Hydroxy(2,3,3,3-$^2H_4$)propyl 4-methylbenzenesulfonate (**3c**)*

$^1$H NMR ($CDCl_3$, 500 MHz) δ 7.81 (d, $J$ = 8.1 Hz, 2H), 7.37 (d, $J$ = 8.1 Hz, 2H), 3.99 (d, $J$ = 10.1 Hz, 1H), 3.87 (d, $J$ = 10.1 Hz, 1H), 2.46 (s, 3H), 2.36 (br s, 1H). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 145.0, 132.6, 129.9, 127.9, 74.7, 65.0 (t, $J_{C\text{-}D}$ = 22 Hz), 21.6.

### Formation of deuterated propylene oxides

Calcium oxide (2.06 g, 36.7 mmol, Fluka) was ground into a fine powder and dried at high vacuum for 1 h. 2-Hydroxy(1,1,3,3,3-$^2H_5$)-propyl 4-methylbenzenesulfonate (**3a**) (4.33 g, 18.4 mmol) was added to the flask containing the calcium oxide and the flask was attached to a short path distillation apparatus with a calcium chloride drying tube attached to the gas inlet. The reaction flask was submerged in an oil bath heated to 150°C causing the two solids to form a melt followed by slow distillation of product **4a**, collected in a flask cooled to −78°C, as a clear, colorless oil (0.92 g, 79%).

*2-($^2H_3$)Methyl(3,3-$^2H_2$)oxirane (**4a**)*

$^1$H NMR ($CDCl_3$, 500 MHz) δ 2.94 (s, 1H). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 47.9, 47.2 (quintet, $J_{C\text{-}D}$ 27 Hz), 17.0 (septet, $J_{C\text{-}D}$ 19 Hz).

*2-Methyl($^2H_3$)oxirane (**4b**)*

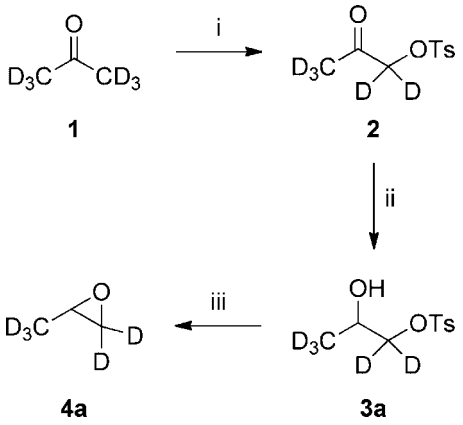
Yield: 74%. $^1$H NMR ($CDCl_3$, 500 MHz) δ 1.32 (s, 3H).

*2-($^2H_3$)Methyl(2-$^2H$)oxirane (**4c**)*

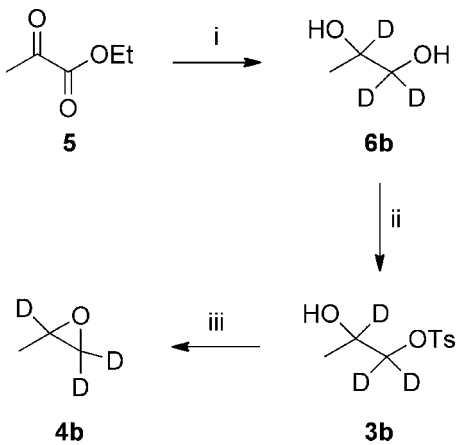
Yield: 79%. $^1$H NMR ($CDCl_3$, 500 MHz) δ 2.77 (d, $J$ = 5.3 Hz, 1H), 2.46 (d, $J$ = 5.3 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 47.9.

## Results and discussion

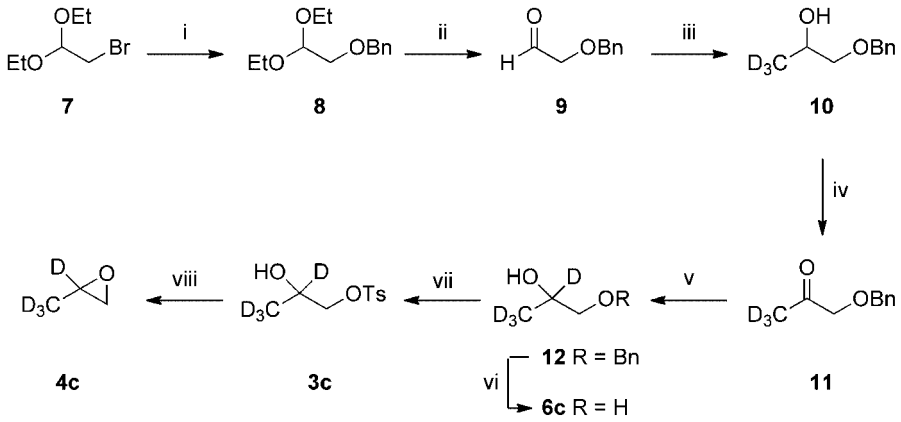
The syntheses of the three targeted, selectively deuterated propylene oxides each required a separate approach, although the final step in each sequence was identical. The first synthesis, of the $d_5$ derivative, was the simplest and most efficient (Scheme 1). The sequence began with the direct tosyloxylation of acetone-$d_6$, which occurred in 46% yield, based on the initial amount of acetone-$d_6$.[7] The resulting α-tosyloxyacetone, **2**, was found to be highly susceptible to hydrogen-deuterium exchange at the position between the ketone and the tosyloxy group so it must either be immediately subjected to the next reaction or stored under carefully anhydrous conditions. The synthesis continued with the reduction of α-tosyloxyacetone by sodium borohydride in 73% yield. The reduction was carried out in methanol-d as the solvent to further minimize exchange at




**Scheme 1.** (i) PhI(OTs)OH, $CH_3CN$, 50°C, 46% (ii) $NaBH_4$, $CH_3OD$, 73% (iii) CaO, 150°C, 79%.




**Scheme 2.** (i) $LiAlD_4$, THF, 41% (ii) *p*-TsCl, $Et_3N$, $CH_2Cl_2$, 76% (iii) CaO, 150°C, 74%.




**Scheme 3.** (i) BnOH, NaH, *n*-$BuN_4I$, reflux, 70% (ii) HCl, reflux, 83% (iii) $CD_3MgI$, THF, 75% (iv) DMSO, $(COCl)_2$, $Et_3N$, −78°C, 84% (v) $NaBD_4$, $CH_3OH$, 74% (vi) $H_2$ (35 psi), 10% Pd/C, 85% (vii) *p*-TsCl, $Et_3N$, $CH_2Cl_2$, 37% (viii) CaO, 150°C, 79%.

the most enolizable carbon. In the final step of the sequence, solid compound **3a** was mixed with pulverized calcium oxide and submerged in an oil bath heated to 150°C. The two solids formed a melt that reacted to form the propylene oxide product, which was isolated directly by distillation in 79% yield. The product, as initially isolated, was contaminated with small amounts of acetone, water and propionaldehyde. The impurities could be removed by preparative gas chromatography.

The sequence required to form the $d_3$ derivative was also straightforward (Scheme 2). This compound has been previously reported in the literature but the paper describing its synthesis does not give any experimental details so we chose to follow a different route.[8] Ethyl pyruvate was reduced with lithium aluminum deuteride in 41% yield to form selectively deuterated 1,2-propanediol, **6b**. The propanediol was then treated with *p*-toluenesulfonyl chloride to form compound **3b**, resulting from selective tosylation at the primary alcohol, in 76% yield. This reaction also formed a small amount (5%) of the ditosylated product, which could be separated from the desired product by column chromatography. The final step to form the $d_3$ propylene oxide was identical to the reaction used in the first sequence.

The synthesis of the $d_4$ derivative was the most challenging of the three. Several relatively direct approaches were initially considered without success. These approaches included attempts to exchange deuterium into pyruvic acid,[9] which did not proceed with complete enough incorporation of deuterium, and reaction of $CD_3MgBr$ with diethyl oxalate to form ethyl pyruvate with a labeled methyl group,[10,11] which produced the product with unsatisfactory yield and purity. In the end, we settled on an eight-step sequence from a commercially available starting material. 2-Benzyloxyacetaldehyde, **9**, was formed in two steps by a known method.[12] This compound was reacted with $CD_3MgI$ in 75% yield to form protected propanediol, **10**, with label incorporated at the methyl group. This compound was then subjected to Swern oxidation (84% yield) and the resulting ketone was reduced back to the alcohol with sodium borodeuteride in 74% yield to incorporate the final, necessary deuterium atom. Removal of the benzyl protecting group by hydrogenolysis in 85% yield produced the appropriately labeled propanediol, **6c**, which was converted to the tosylate and subjected to ring formation, as before (Scheme 3).

## Conclusions

We have developed effective syntheses of three different labeled propylene oxides, each incorporating deuterium atoms at two of the three carbons atoms. These compounds will be used to study the dynamics of propylene oxide within a clathrate hydrate cage using QENS.

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