

SITE-SELECTIVE DEUTERIUM LABELING OF THE TETRABUTYLAMMONIUM CATION

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SUMMARY

Four separate selectively deuterated samples of tetrabutylammonium iodide have been prepared in which each one of the four nonequivalent alkyl carbons is separately and fully deuterated. These samples were prepared for nuclear magnetic resonance (NMR) studies of the aggregation of ion pairs in low polarity solvents.

INTRODUCTION

The aggregation of ion pairs in low polarity solvents has been a subject of interest for many years (1-7). However, until recently, only indirect evidence of this phenomenon could be obtained. We wished to use intercationic nuclear Overhauser effects (NOEs) between tetrabutylammonium cations in order to detect multi-ion aggregates. Because the cations within an aggregate are identical, there is no simple way of separating intra- from intercationic NOEs. We decided to prepare selectively deuterated samples of tetrabutylammonium iodide **1** in order to distinguish between intra- and intercationic NOEs. The present paper describes the syntheses of the four selectively ^2H -labeled tetrabutylammonium cations.

EXPERIMENTAL

All reagents were analytical grade and used without further purification. Proton Sponge (tradename for 1,8-(N,N,N',N'-tetramethyl)-naphthylenediamine), and lithium aluminum deuteride (98 atom % D) were purchased from Aldrich. (4,4,4-²H₃)-butyric acid (98 atom % D) and (3,3-²H₂)-butyric acid (98 atom % D) were purchased from Cambridge Isotopes, Inc.

NMR characterizations were performed on a Varian Unity 400 NMR spectrometer operating at 400 MHz for ¹H (100 MHz for ¹³C). ¹³C spectra were obtained in ¹H-decoupled mode. ¹H and ¹³C chemical shifts are reported in ppm relative to TMS. Matrix-assisted laser desorption ionization (MALDI) mass spectra were obtained on a Voyager DERP mass spectrometer using a linear delayed extraction method. A 50 μM sample of the compound to be analyzed was prepared in a solution of 30% acetonitrile and 0.01% trifluoroacetic acid in water. 2 μL of this sample was then placed in 10 μL of a matrix. The matrix used was 2,5-dihydroxybenzoic acid (10 mg/mL in 1:1 MeOH: H₂O). Spectra were taken in positive ion mode. Melting points were obtained on MelTemp II melting point apparatus.

1-(1,1-²H₂)-butanol 2

Procedure used was adapted from reference (8). 4.0 g (0.10 mol) of lithium aluminum deuteride (LAD) were placed in a 500 mL three-necked flask in an ice-water bath, and 200 mL of diethyl ether added slowly with stirring. A solution of 8.2 g (0.05 mol) of butyric anhydride in 20 mL of diethyl ether was added dropwise to the LAD mixture with stirring and cooling. The reaction was then refluxed for 2 hours. After cooling, the reaction was quenched with 3 mL water, followed by 5 mL of a 20% sodium hydroxide solution, and finally with 12 mL of water. The ether layer was decanted, the remaining residue was washed 2x with ether, and the ether extracts were combined. The ether was removed *in vacuo*, and the alcohol was distilled. Yield: 90%, b.p. 110°C -117°C, ¹H NMR: δ1.7 (OH), 1.6 (2-CH₂), 1.2 (3-CH₂), 0.9 (4-CH₃), ¹³C NMR: δ62.0 (1-CD₂), 34.5 (2-CH₂), 19.0 (3-CH₂), 14.0 (4-CH₃).

1-(1,1-²H₂)-iodobutane 3

The procedure used was adapted from reference (9). 8.9 g (0.063 mol) of phosphoric acid and 18.5 mL (0.27 mol) of 85% orthophosphoric acid were placed in a 100 mL round-bottomed flask. The mixture was stirred, and 45.5 g (0.27 mol) of potassium iodide and 5.0 g (0.06 mol) of **2** were added. The mixture was heated and stirred at 110°C for 5 hours. After the reaction cooled, 21 mL of water and 34 mL of diethyl ether were added. The ether layer was separated, shaken with 7 mL of a 10% Na₂S₂O₃ solution, washed with 27 mL of a cold saturated NaCl solution, and dried with 7 g of anhydrous Na₂SO₄. The ether was removed in vacuo. Yield: 50%, ¹H NMR: δ 1.8 (2-CH₂), 1.4 (3-CH₂), 0.9 (4-CH₃), ¹³C NMR: δ 7.0 (1-CD₂), 35.5 (2-CH₂), 24.0 (3-CH₂), 13.0 (4-CH₃).

(1,1-²H₂)-tetrabutylammonium iodide 1a

0.44 g (0.003 mol) of ammonium iodide, 2.24 g (0.012 mol) of **3**, 2.61 g (0.012 mol) of Proton Sponge, and 4 mL of methanol were placed in a pressure tube and heated and stirred at 70°C for one week in the dark. The solid (mostly the hydroiodide of Proton Sponge) was removed by filtration, and the methanol was removed from the filtrate *in vacuo*. 6 mL of ether were added to the slushy residue of the filtrate, and after stirring for 2 hours, a solid dropped out. The solid (crude **1a**) was recrystallized from ethanol-ether. Yield: 43%, m.p. 134°C-135°C, ¹H NMR: δ 1.7 (2-CH₂), 1.4 (3-CH₂), 1.0 (4-CH₃), ¹³C NMR: δ 58.5 (1-CD₂), 24.5 (2-CH₂), 20.0 (3-CH₂), 14.0 (4-CH₃).

1-(1,1-²H₂)-propanol 4

This was prepared as was **2**, using 10.0 g (0.238 mol) of lithium aluminum deuteride, 400 mL of ether, and 15.5 g (0.119 mol) of propionic anhydride in 40 mL of ether. The mixture was quenched with 7 mL of water, 10 mL of a 20% sodium hydroxide solution, and 20 mL of water. Yield: 56%, ¹H NMR: δ 2.1 (OH), 1.5 (2-CH₂), 0.9 (3-CH₃), ¹³C NMR: δ 64.0 (1-CD₂), 26.0 (2-CH₂), 10.0 (3-CH₃).

1-(1,1-²H₂)-chloropropane 5

Procedure used was adapted from reference (10). 8.28 g (0.133 mol) of **4** and 11.6 g (0.146 mol) of pyridine were placed in a 100 mL three-necked flask fitted with a condenser, dropping funnel, and a liquid nitrogen trap. The solution

was cooled in an ice bath and stirred. 16.6 g (0.140 mol) of thionyl chloride was added dropwise. The ice bath was removed, and the mixture stirred for 4 hours. The contents of the flask and the liquid nitrogen trap were chilled and dried overnight with phosphorus pentoxide and distilled. Yield: 44%, fraction collected: 27°C-47°C, ^1H NMR: δ 1.8 (2-CH₂), 1.0 (3-CH₃), ^{13}C NMR: δ 46.0 (1-CD₂), 26.0 (2-CH₂), 11.0 (3-CH₃).

1-(1,1- $^2\text{H}_2$)-propyl magnesium chloride 6

Procedure used was adapted from reference (11). 1.56 g (0.064 mol) of magnesium turnings and a crystal of iodine were placed in a 100 mL three-necked flask fitted with a dropping funnel and a condenser. The flask was swept with nitrogen, and a solution of 6 mL of ether and 1 mL of **5** was added to the flask. The ether was refluxed gently in order to start the reaction. Stirring was started and sufficient ether was added to cover the magnesium. The remainder of **5** dissolved in 20 mL of ether were added over 45 minutes. Stirring was continued until the reaction subsided.

(2,2- $^2\text{H}_2$)-butyric acid 7

Procedure used was adapted from reference (12). 14.5 g of dry ice were crushed and placed in a 250 mL beaker. Grignard reagent **6** was poured over the dry ice, and the solid was stirred and allowed to stand until all of the dry ice had evaporated. A mixture of 35 g of crushed ice and 9 mL of concentrated hydrochloric acid was added slowly while the beaker was kept cool and stirring was continued. The ice bath was then removed, and the mixture stirred until there was a clean separation into 2 layers. The solution was poured into a separatory funnel, and the beaker was rinsed with 5 mL of ether. The upper layer was separated, and the aqueous layer was extracted with three 4-ml portions of ether. The ether extracts were combined and dried with anhydrous sodium sulfate. Ether was removed in vacuo. Yield: 32%, ^1H NMR: δ 8.5 (COOH), 1.6 (3-CH₂), 0.9 (4-CH₃), ^{13}C NMR: δ 180.0 (COOH), 36.0 (2-CD₂), 18.0 (3-CH₂), 14 (4-CH₃).

1-(2,2- $^2\text{H}_2$)-butanol 8

This was prepared similarly to **2**, using 1.38 g (.0373 mol) of lithium aluminum hydride, 63 mL of ether, and 1.68 g (.0187 mol) of **7** dissolved in 6 mL of ether. The reaction was quenched with 1 mL of water, 2 mL of a 20% sodium

hydroxide solution, and 3 mL of water. Yield: 70%, ^1H NMR: δ 2.0 (OH), 3.6 (1- CH_2), 1.3 (3- CH_2), 0.9 (4- CH_3), ^{13}C NMR: δ 62.0 (1- CH_2), 34.0 (2- CD_2), 19.0 (3- CH_2), 14.0 (4- CH_3).

1-(2,2- $^2\text{H}_2$)-iodobutane 9

This was prepared similarly to 3, using 1.79 g (.0128 mol) of phosphoric acid, 3.7 mL (.056 mol) of 85% orthophosphoric acid, 9.19 g (.0556 mol) of potassium iodide, and 1.00 g (.0132 mol) of 8. After the reaction cooled, 11 mL of water, and 19 mL of ether were added. The ether layer was shaken with 4 mL of a 10% $\text{Na}_2\text{S}_2\text{O}_3$ solution, 15 mL of a cold saturated NaCl solution, and dried with 4 g of anhydrous Na_2SO_4 . Yield: 55%, ^1H NMR: δ 3.2 (1- CH_2), 1.4 (3- CH_2), 0.9 (4- CH_3), ^{13}C NMR: δ 7.0 (1- CH_2), 24.0 (3- CH_2), 13.0 (4- CH_3).

(2,2- $^2\text{H}_2$)-tetrabutylammonium iodide 1b

This was prepared similarly to 1a. 0.26 g (.0018 mol) of ammonium iodide, 1.34 g (0.007 mol) of 9, 1.54 g (0.007 mol) of Proton Sponge and 4 mL of methanol were used. Yield: 7%, ^1H NMR: δ 3.4 (1- CH_2), 1.4 (3- CH_2), 1.0 (4- CH_3). ^{13}C NMR: δ 59.4 (1- CH_2), 23.8 (2- CD_2), 19.8 (3- CH_2), 13.9 (4- CH_3).

1-(3,3- $^2\text{H}_2$)-butanol 11

This was prepared similarly to 2. 3.7 g (.098 mol) of lithium aluminum hydride, 178 mL of ether, 4.0 g (.044 mol) of (3,3- $^2\text{H}_2$)-butyric acid in 20 mL of ether were used. The reaction was quenched with 3 mL of water, 3 mL of a 20% NaOH solution, and 13 mL of water. Yield: 93%, ^1H NMR: δ 2.6 (OH), 3.6 (1- CH_2), 1.4 (2- CH_2), 0.8 (4- CH_3), ^{13}C NMR: δ 62.0 (1- CH_2), 35.0 (2- CH_2), 18.0 (3- CD_2), 14.0 (4- CH_3).

1-(3,3- $^2\text{H}_2$)-iodobutane 12

This was prepared similarly to 3. 5.4 g (0.04 mol) of phosphoric acid, 11 mL (0.16 mol) of 85% orthophosphoric acid, 27.4 g (0.16 mol) of potassium iodide, and 3.09 g (.0410 mol) of 11 were used. After cooling, 12 mL of water and 20 mL of ether were added. The ether layer was shaken with 4 mL of 10% $\text{Na}_2\text{S}_2\text{O}_3$, followed by 16 mL of a cold saturated NaCl solution, and dried with 4 g of anhydrous sodium sulfate. Yield: 59%, ^1H NMR: δ 3.2 (1- CH_2), 1.8 (2- CH_2), 0.9 (4- CH_3), ^{13}C NMR: δ 0.7 (1- CH_2), 36.0 (2- CH_2), 12.0 (4- CH_3).

(3,3-²H₂)-tetrabutylammonium iodide 1c

This was prepared similarly to **1a**, using 2.24 g of **12**. Yield: 3.6 %. m.p. 135°C-137°C. ¹H NMR: δ3.4 (1-CH₂), 1.7 (2-CH₂), 1.0 (4-CH₃), ¹³C NMR: δ59.5 (1-CH₂), 24.4 (2-CH₂), 17.5 (3-CD₂), 13.8 (4-CH₃).

1-(4,4,4-²H₃)-butanol 14

This was prepared similarly to **2**. 6.0 g (.16 mol) of lithium aluminum hydride, 230 mL of ether, 5 g (.06 mol) of (4,4,4-²H₃)-butyric acid in 20 mL of ether were used. The reaction was quenched with 3 mL of water, 5 mL of a 20% sodium hydroxide solution, and 13 mL of water. Yield: 40%, b.p. 115°C-116°C, ¹H NMR: δ2.3 (OH), 3.6 (1-CH₂), 1.5 (2-CH₂), 1.3 (3-CH₂), ¹³C NMR: δ61.5 (1-CH₂), 34.5 (2-CH₂), 19.0 (3-CH₂), 13.0 (4-CD₃).

1-(4,4,4-²H₃)-iodobutane 15

This was prepared similarly to **3**. 3.23 g (0.023 mol) of phosphoric acid, 6.7 mL (0.10 mol) of 85% orthophosphoric acid, 16.55 g (0.10 mol) of potassium iodide, and 1.85 g (0.024 mol) of **14** were used. After cooling, 7 mL of water and 12 mL of ether were added. The ether layer was shaken with 3 mL of 10% sodium thiosulfate solution, 10 mL of cold saturated aqueous sodium chloride, and dried with 3 g of anhydrous sodium sulfate. Yield: 50%. ¹H NMR: δ3.2 (1-CH₂), 1.8 (2-CH₂), 1.4 (3-CH₂), ¹³C NMR: δ7.0 (1-CH₂), 35.5 (2-CH₂), 19.0 (3-CH₂), 12.0 (4-CD₃).

(4,4,4-²H₃)-tetrabutylammonium iodide 1d

This was prepared similarly to **1a**, using 2.24 g of **15**. Yield: 28 %. m.p. 138°C. ¹H NMR: δ3.4 (1-CH₂), 1.7 (2-CH₂), 1.4 (3-CH₂), ¹³C NMR: δ59.5 (1-CH₂), 24.5 (2-CH₂), 19.8 (3-CH₂), 13.2 (4-CD₃).

DISCUSSION

The ²H-labeled tetrabutylammonium iodides (**1a-1d**) prepared as described here have all been successfully used for intercationic NOE studies (Heinsen & Pochapsky, unpublished results). The completeness of deuteration was confirmed in each case by the absence of ¹H signals at the appropriate positions in the ¹H NMR spectra greater than 1% of the integrated signal intensity of completely

protonated positions. More importantly, control NOE difference spectra obtained for pure compounds **1a-1d** confirm that no intracationic NOEs are observed at the deuterated positions upon inversion of the signal of the adjacent protons. Typically, NOEs between adjacent protons in the fully protonated tetrabutylammonium cation range between 10%-20% of full signal intensity. Based on these observations, we expect that the isotopic purity of the labels in all four products are essentially undiluted from that of the starting materials (98% minimum ^2H per labeled site) (see Table I).

	Calc. mass (daltons):	Obsvd. mass (daltons)
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{N}^+\text{I}^-$	242.5	241.9
1a $\text{CH}_3\text{CH}_2\text{CH}_2\text{CD}_2\text{N}^+\text{I}^-$	250.5	249.9
1b $\text{CH}_3\text{CH}_2\text{CD}_2\text{CH}_2\text{N}^+\text{I}^-$	250.5	249.7
1c $\text{CH}_3\text{CD}_2\text{CH}_2\text{CH}_2\text{N}^+\text{I}^-$	250.5	249.8
1d $\text{CD}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{N}^+\text{I}^-$	254.6	253.8

Table I. Results from MALDI mass spectral analysis of compounds **1a-1d**, as well as unlabeled tetrabutylammonium iodide. See text for details.

All four compounds, **1a-1d**, were prepared by the same method, with similar crude yields. The reported yields for the recrystallized material vary from 3.6% to 43%, since each recrystallization performed on a compound results in some loss. The lower yield reported for **1c** is due to it being recrystallized two more times than **1a**, **1b**, or **1d**. The low yield of **1b** was due to the fact that recrystallizations tend to give better yields on large scale. **1b** was made from just over half as many moles of reactants as were **1a**, **1c**, or **1d**, so although the crude percent yield was on the order of the other tetrabutylammonium iodides, there was insufficient compound with which to do a high-yield recrystallization.

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