Preparation of [^{2}H]-Paraformaldehyde

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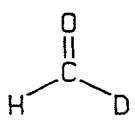
SUMMARY

Polymeric [^{2}H]-formaldehyde, which is useful for the synthesis of a variety of labelled molecules, is prepared from bromoform in four steps. The isotopic purity of the final product depends on that of the [^{2}H]-bromoform made in the first step, and is measured after conversion of the [^{2}H]-formaldehyde to [2-^{2}H]-5,5-dimethyl-1,3-dioxane.

KEY WORDS: [^{2}H]-Paraformaldehyde, deuterium labelling.

INTRODUCTION

[^{2}H]-Formaldehyde, **1**, is a potentially useful reagent in the preparation of a wide variety of regioselectively deuterated molecules.[1]



1

The compound has previously been prepared by Bannard, Morse, and Leitch through the conversion of acetylene to [1,2-$^2H_2$]-ethylene glycol and subsequent oxidative cleavage with lead tetraacetate.[2] This synthesis has the advantage of producing gaseous monomeric **1** directly, but is somewhat inconvenient because special apparatus is required for the handling of gases. Numerous spectroscopic studies of **1** have been described in the literature, and have used [^{2}H]-formaldehyde either prepared from the above procedure or obtained from commercial but somewhat expensive sources.[3a-d] In the present paper, a convenient four-step synthesis of polymeric [^{2}H]-formaldehyde from bromoform is reported. Additionally, in order to determine its isotopic purity, **1** has been transformed to

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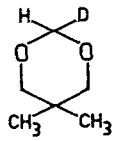
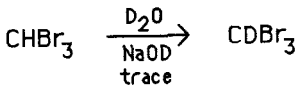
[2-^{2}H]-5,5-dimethyl-1,3-dioxane (2).



2

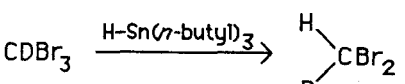
DISCUSSION

The present synthesis is based on the known conversion of [$^2H_2$]-methylene bromide to [$^2H_2$]-formaldehyde.[4] Thus, [^{2}H]-methylene bromide (5) is required to make 1. An exchange procedure (^2H_2O/base) cannot be used to obtain 5 in a pure isotopic state, although the dideuterated compound is readily prepared by such means.[4] Bromoform appeared to be a suitable starting material since it is readily available, and its proton undergoes exchange with ^2H_2O in the presence of base.[5] [^{2}H]-Bromoform (4) (isotopic purity 96+%) was thus prepared by two successive ^2H_2O exchanges. A higher isotopic purity could have been obtained with an additional exchange step.



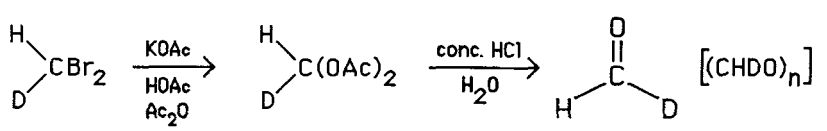
3 4

The [^{2}H]-bromoform (4) was then reduced to 5 in 80% yield by tri(*n*-butyl)tin hydride. This reduction proceeds via a free radical chain reaction under non-exchanging conditions, and the [^{2}H]-methylene bromide (5) formed in the reaction is reduced much more slowly than is 4.[6a,b,c]



4 5

The remaining steps, shown below, follow those of the previous synthesis of [$^2H_2$]-formaldehyde.[4]

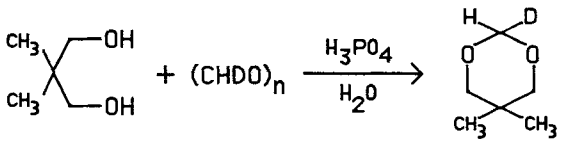


5 6 1

The isotopic purity of the [^{2}H]-formaldehyde depends solely on the isotopic purity of the

[^{2}H]-bromoform, since the subsequent stages of the synthesis take place without any exchange.

The cyclic acetal (**2**) was prepared from **1** and the diol **7** and was obtained in a pure state as the only volatile product from the reaction mixture.[7] This compound has previously been made by a different method.[8]



7 **2**

The chemical shift of the CHD proton in the NMR spectrum of **2** appears upfield (0.0293 ppm) from that of the residual undeuterated **2**, and allows the isotopic purity to be determined by integration (at least in a high-field NMR spectrometer).

EXPERIMENTAL

[^{2}H]-Bromoform (**4**): Deuterium oxide (99.8 % D, 70 g) was added to a 500 ml round-bottomed flask containing bromoform (30 g). About 0.2 ml of 0.5 M NaOD was then added. The flask was protected from light, and the mixture was stirred for 30 h under nitrogen. After this time, the upper deuterium oxide layer was removed and 60 g fresh deuterium oxide was added. About 0.2 ml of 0.5 M NaOD was again added, and the mixture was stirred in the dark under nitrogen for an additional 30 h. The mixture was allowed to settle, and the lower bromoform layer was removed and dried over anhydrous sodium sulfate to give 25.8 g (86%) of **4**. NMR analysis showed the deuterium content to be 96+ atom % D.

[^{2}H]-Methylene bromide (**5**): To a stirred solution of [^{2}H]-bromoform (2.0 ml, 22.8 mmol) in a 50 ml round-bottomed flask fitted with a condenser was added slowly via a syringe 6.13 ml (6.63 g, 22.8 mmol) of tri(*n*-butyl)tin hydride (Aldrich Chemical Co., 99%). The mixture was refluxed under nitrogen for 25 h. The resulting brown liquid was distilled to yield 3.31 g (83%) of **5** as a clear liquid. Proton NMR (200 MHz in deuteriochloroform): ∂ (ppm) 4.9162 (1:1:1 triplet, J_{HD}=0.86 Hz).

[^{2}H]-Methylene diacetate (**6**): [^{2}H]-Methylene bromide (12.0 g, 68.6 mmol) was placed in a 300 ml round-bottomed flask and glacial acetic acid (44 ml) and acetic anhydride (4.8 ml) were added. The mixture was stirred and 21 g anhydrous potassium acetate was added as quickly as possible without hindering stirring. A reflux condenser fitted with a calcium sulfate drying tube was attached, and the mixture was refluxed for 40 h. The solution was allowed to cool with continued stirring and 120 ml diethyl ether was added. [Exposure to atmospheric moisture is deleterious to reaction yields and should be kept to a minimum.] The precipitated KBr was filtered off and washed several times with ether. The filtrates were combined and refiltered to remove additional solids which had precipitated. A distillation apparatus with a Vigreux fractionating column was assembled and the filtrate was distilled at atmospheric pressure to remove first the ether and then the

acetic acid. The yellow solution which remained in the flask was allowed to cool and 40 ml ether was added. More KBr precipitated and was filtered off. The ether was removed using a rotary evaporator, and the remaining yellow liquid was distilled, b.p. 39-44 °C/3mm, to give 5.5 g (60%) of **6** as a clear liquid. Proton NMR (60 MHz in deuteriochloroform): ∂ (ppm) 2.11 (s, 6 H, -CH_3), 5.68 (broad, 1 H, CHD).

[^{2}H]-Paraformaldehyde (**1**): [^{2}H]-Methylene-diacetate (5.5 g) was placed in a 25 ml round-bottomed flask and water (0.11 ml) was added. The mixture was stirred and 0.15 ml of conc. hydrochloric acid was added. After being refluxed for 18 h, the solution was taken to dryness at 2 mm pressure to leave **1** as a white powder (0.734 g, 59%), m.p. 154-157 °C.

[2-^{2}H]-5,5-Dimethyl-1,3-dioxane: 2,2-Dimethyl-1,3-propanediol (**7**) (100 mg, 0.96 mmol) and **1** (29 mg, 0.96 mmol) were placed in a 10 ml round-bottomed flask. Water (0.2 ml) and several drops of 85% phosphoric acid were added and the mixture was stirred and refluxed overnight. A short-path still-head/condenser was then attached to the reaction flask, and the product (a couple of drops) was collected in a small round-bottomed flask. This collection flask was then rinsed with deuteriochloroform for NMR sample preparation. Proton NMR (500 MHz in deuteriochloroform): ∂ (ppm) 0.9671 (s, 3 H, -CH_3), 0.9877 (s, 3 H, -CH_3), 3.4987 (s, 4 H -CH_2-), 4.7764 (broad singlet, 1 H, CHD). The deuterium content of the final product was determined to be 97 atom % D. The deuterium isotope shifts in the methyl groups of **2** are of conformational origin and will be discussed in a separate paper.[8]

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