New synthesis of formaldehyde-d_2[1,2]

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A new and improved synthesis of formaldehyde-d_2 on a molar scale has been developed *via* the reactions:

$$CH_2Br_2 + D_2O \rightarrow CD_2Br_2 \rightarrow CD_2(OAc)_2 \rightarrow CD_2O$$

The yield from deuterated methylene bromide is 50%, and the deuterium content is over 98%.

Une nouvelle synthèse, à l'échelle molaire, du formaldéhyde-d_2, fondée sur les réactions suivantes, est rapportée:

$$CH_2Br_2 + D_2O \rightarrow CD_2Br_2 \rightarrow CD_2(OAc)_2 \rightarrow CD_2O$$

Le rendement à partir du bromure de méthylène deuterié est 50%, et le taux de deutérium dépasse 98%.

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Introduction

Formaldehyde-d_2 is a reagent of considerable utility as the starting point for further syntheses of deuterium labelled compounds (2) and for the study of reaction mechanisms (ref. 3 p. 213). The need for this material has grown considerably, and as part of a program to develop improved syntheses of labelled compounds, we have investigated and developed a new synthetic approach by which we have prepared up to 15 moles of formaldehyde-d_2.

The most satisfactory previous synthesis of formaldehyde-d_2 was that of Bannard, Morse, and Leitch (4) which consists of the lead tetraacetate cleavage of ethylene-d_4 glycol to yield pure, polymeric formaldehyde-d_2 in 75% yield. This procedure has the major disadvantage that the deuterated precursor is itself rather expensive, and, in addition, it is operationally difficult to carry out on a molar scale or larger. Elwyn *et al.* (5) have also described a synthesis in 33% yield by decarboxylation of dihydroxymaleic acid in heavy water followed by periodate cleavage of the resulting glycolaldehyde-d_4. Very recently, Olofson and Zimmerman (6) have reported a new synthesis of benzaldehyde-d_1 and formaldehyde-d_2 by exchange of a bisiminium cation with deuterium oxide, although the formaldehyde-d_2 was isolated only as a derivative. These latter preparations have the disadvantage that the product is obtained initially as a relatively dilute aqueous solution containing large amounts of inorganic salts so that a lengthy steam distillation is required in order to obtain pure material. Renaud and Leitch (7) have also recently described a novel preparation based on the Polonovsky reaction of trimethyl-d_9-amine oxide.

Results

The first step in the present synthesis was based on the discovery by Blanchard and Simmons (8) that methylene iodide could be exchanged in a basic solution of ethanol-OD and deuterium oxide. We have re-investigated this system extensively and have found that both methylene bromide and methylene iodide undergo ready exchange with refluxing, basic heavy water without the need of a co-solvent. By repeated exchange the deuterium content can be brought up to 99 atom % D and the partially depleted heavy water can be re-used in subsequent preparations.

$$CH_2Br_2 \xrightarrow{D_2O/OD^-} CD_2Br_2$$

$$CH_2I_2 \xrightarrow{D_2O/OD^-} CD_2I_2$$

Hydrolysis is very slow under these conditions and after 6–8 exchanges, 65–75% yields of fully deuterated halide were obtained. The exchange presumably proceeds through the dihalomethyl anion which reacts with D_2O much more rapidly

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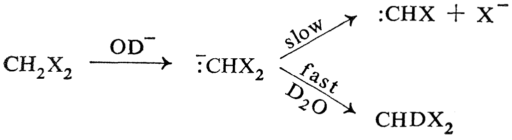
[1] Synthetic aspects of stable isotope chemistry. V. For Part IV, see ref. 1.

[2] Presented in part at the Second International Conference on Methods of Preparing and Storing Labelled Molecules, Brussels, Belgium. November 28–December 3, 1966.

than it decomposes to a halocarbene, thus accounting for the relatively high recovery even after a number of exchanges. By analogy with the addition of the trichloromethyl anion to aldehydes (9) and acid anhydrides (10), it might be expected that the dihalomethyl anion could be trapped by electrophilic species other than D^+, and such experiments would be of potential synthetic interest.[3]



Many attempts at the direct conversion of the methylene halides to formaldehyde confirmed their resistance to hydrolysis. This is a "textbook" reaction, but upon heating methylene iodide with water at 180° only carbon and iodine were obtained. Heating in a glass bomb with water and $Ba(OH)_2$, PbO, or Ag_2O caused the bomb to explode in each case. Heating with concentrated H_2SO_4 at 100° resulted in the liberation of iodine, and no reaction was observed with refluxing aqueous mixtures of silver oxide, silver carbonate, or silver acetate with either halide.

A two-step conversion to formaldehyde-d_2 was then developed when it was found that the methylene-d_2 halides would react with silver acetate or potassium acetate under anhydrous conditions to yield methylene-d_2 diacetate in 60-65% yields. The optimum conditions involved the reaction of 3–4 moles of potassium acetate with one mole of halide in refluxing acetic acid containing 5% of acetic anhydride. Methylene-d_2 bromide is preferred over the iodide because if any of the latter is left unreacted it is difficult to separate from methylene-d_2 diacetate. Methylene-d_2 diacetate is easily and rapidly hydrolyzed to formaldehyde-d_2 in over 80% yield. The formaldehyde solution thus obtained is very concentrated and contains only volatile materials, so that upon evaporation to dryness, pure polymeric formaldehyde-d_2 is readily obtained.

A very careful check on the deuterium content of the intermediate methylene-d_2 diacetate and the formaldehyde-d_2 showed that the latter had the same isotopic purity as the starting deuterated methylene halide. Thus, no back-exchange occurs in either of the hydrolytic steps.

$$CD_2Br_2 \xrightarrow[\text{HOAc}]{\text{excess KOAc}} CD_2.(OAc)_2$$

$$CD_2.(OAc)_2 + H_2O \rightarrow CD_2O + 2HOAc$$

Appendix

Several other much less successful approaches to the preparation of deuterated formaldehyde were investigated at some length and are included for the sake of completeness.

Leitch (11) has prepared acetaldehyde-1-d_1 from nitroethane-1,1-d_2 by hydrolysis of the sodium salt. When this reaction, or the modification introduced by Schechter and Williams (12) was applied to nitromethane, little if any formaldehyde was produced. Since this reaction would have led to an aqueous solution of formaldehyde-d_2 containing large amounts of inorganic salts, it was not investigated further.

$$CH_2{=}NO_2Na \quad \not\xrightarrow{H_2SO_4} \quad CH_2O$$

Dimethyl sulfoxide is known to react with electrophilic reagents to yield derivatives which can be hydrolyzed to formaldehyde (13). We have investigated the reaction of dimethyl-d_6-sulfoxide with hydrogen chloride gas in a hot benzene solution. With the protio compound, formaldehyde sublimed out of the reaction mixture in 45% yield, but from dimethyl-d_6-sulfoxide less than 10% yield of formaldehyde-d_2 resulted, the major product being dimethyl-d_6 sulfide.

The nature of the reduction reaction was not further investigated,[4] but it provides an interesting example of how an isotope effect may influence a multi-directional reaction when a C—H or C—D bond must be broken in one of the reaction paths.

A Polonovsky-type reaction between acetic anhydride and dimethyl-d_6-sulfoxide led to α-acetoxy dimethylsulfide-d_5 in 80% yield, hydrolysis of which led to formaldehyde-d_2 in less than 25% yield. The low yield was found to be due to the formation of the very stable dimethyl-d_6-

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[3] *Note added in proof*: The trapping of dihalomethyl lithium species with carbonyl compounds has recently been reported (15).

[4] The reduction of sulfoxides to sulfides by iodide ion is a well-known reaction, see ref. 14.

thioacetal of the aldehyde. This approach was abandoned because of the low yield and the presence of sulfur impurities in the formaldehyde-d_2 which were difficult to remove.

$$CD_3 \cdot SO \cdot CD_3 + Ac_2O \rightarrow CD_3 \cdot S \cdot CD_2 \cdot OAc + DOAc$$

$$2CD_3 \cdot S \cdot CD_2 \cdot OAc + H_2O \rightarrow CD_2O + (CD_3 \cdot S)_2 \cdot CD_2 + 2HOAc$$

Experimental

Nuclear magnetic resonance (n.m.r.) spectra were run on a Varian A60-A instrument and mass spectra were performed by the Morgan-Schaeffer Corporation, Montreal, Quebec.

Methylene-d_2 Bromide

A heterogeneous mixture of 500 g of methylene bromide and 210 g of a 10% solution of sodium deuteroxide in deuterium oxide was stirred and refluxed for 24 h. The organic layer was separated and further exchanged with successively decreasing amounts of 10% sodium deuteroxide (160, 150, 130, 100, 100, and 100 g). The organic layer was finally distilled through a short Vigreux column. A water–methylene-d_2 bromide azeotrope was first collected, followed by the bulk of the dry methylene-d_2 bromide. The azeotropic mixture was dried by passage over phosphorous pentoxide on a vacuum line and combined with the dry material from the distillation, to give a yield of 319 g (63%). Nuclear magnetic resonance and mass spectral analyses showed the methylene-d_2 bromide to contain 99 atom % D.

Methylene-d_2 Diacetate

To a mechanically stirred solution of methylene-d_2 bromide (176 g, 1.0 moles) in 600 ml glacial acetic acid containing 30 g of acetic anhydride was added potassium acetate (294 g, 3.0 moles) at such a rate as not to prevent stirring. On heating the mixture to reflux, all of the potassium acetate dissolved and after 1 h potassium bromide began to crystallize from the solution. Stirring and refluxing was continued for 24 h, after which time the solution was allowed to cool with continued stirring in order to avoid cake formation. To the cooled reaction mixture was added 1500 ml of ether, and the precipitate was filtered off and washed with ether until no odor of acetic acid remained.[5]

The filtrate and washings were combined and distilled at atmospheric pressure to remove the ether and the bulk of the acetic acid. If more solid was seen to crystallize at this point, the dilution with ether and filtration were repeated. If not, the distillation was continued at 12 mm pressure and, after removal of acetic acid and acetic anhydride, a fraction was collected at 61–63 °C to yield 83 g (0.62 moles, 62%) of methylene-d_2 diacetate. The deuterium content of the methylene group was found by n.m.r. analysis to be 99%.

Formaldehyde-d_2

A mixture of methylene-d_2 diacetate (240 g, 1.79 moles), 45 ml of water, and 5 ml of concentrated hydrochloric acid was refluxed for 17 h. Upon cooling of the solution, some polymeric formaldehyde-d_2 crystallized out and was filtered off. The filtrate was taken to dryness in vacuum to leave the bulk of the product as a white solid. A second distillation of the solvent mixture was necessary to recover all of the product. The combined crops of formaldehyde-d_2 were dried at 0.5 mm and 100 °C in order to remove the last traces of acetic acid and gave a yield of 49.4 g (1.54 moles, 86%); m.p. 172–174 °C, which corresponds to that of α-polyoxymethylene (ref. 3 p. 158).

The dimedone derivative had a m.p. 188–190 °C and mixture m.p. of 188–189 °C.

Analysis of Formaldehyde-d_2

A mixture of polymeric formaldehyde-d_2 (0.50 g, 15.6 mmoles), methanethiol (10 g, 208 mmoles), and ether (15 ml) was stirred for 18 h in a stoppered flask. After removal of the volatile materials, formaldehyde-d_2 dimethylthioacetal was distilled at 38–40 °C/5 mm in a yield of 1.2 g (10.9 mmoles, 70%). Nuclear magnetic resonance analysis showed the methylene group to contain 98.5 atom % D.

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[5] This operation must be carried out as quickly as possible to minimize exposure since methylene diacetate reacts very rapidly with atmospheric moisture with a resulting lowering of yield.