

The synthesis and isotopic analysis of $\text{CH}_3^{18}\text{OH}$ and $\text{CH}_3^{17}\text{OH}$ *

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(received on 25 June 1965)

SUMMARY

A number of methods of synthesis of methanol labelled with ^{18}O or with ^{17}O have been evaluated. The best method is considered to be the partial hydrolysis of trimethyl phosphate. Ethanol- ^{18}O can be prepared analogously by the partial hydrolysis of triethyl phosphate. The most accurate method for the isotopic analysis of oxygen in methanol is by pyrolysis in a specially designed vessel, the hydrogen being extracted through a palladium tube and the residual carbon monoxide analysed mass-spectrometrically.

INTRODUCTION.

Methanol labelled with one of the isotopes of oxygen is an extremely useful compound for the synthesis of other compounds and for studies of reaction mechanisms. Methanol- ^{18}O could, in principle, be prepared by fractional distillation of methanol⁽¹⁾ but this method of preparation is not a practical one, although it was once used⁽²⁾ in a study of the mechanism of esterification.

Various methods of synthesis of ^{18}O -labelled methanol have been described in the literature^(3,4,5) using ^{18}O -enriched water as a source of the isotope. We have made a critical examination of each of these methods and of some unreported alternatives and have found that most of them suffer from various serious disadvantages, which we hereby describe briefly.

Isotopic exchange with water.

The isotopic exchange of the oxygen of primary alcohols only occurs in acid solution and at relatively elevated temperatures⁽⁶⁾. Under these condi-

* This work was supported in part by a research grant from the U. S. Public Health Service.

tions, exchange is accompanied by ether formation, molecular rearrangements and elimination reactions to form olefines. With methanol, although only methyl ether can be formed as a side reaction, this method of preparation has not been used in practice since it is so slow. The rate of exchange of methanol has not been reported, but the first order rate coefficient for *n*-butanol ⁽⁶⁾, which is probably of the same order of magnitude, is $k_1 = 56 \times 10^{-8}$ sec. at 125° C in 0.917 N acid. A second disadvantage, particularly if highly enriched material is required, is the isotopic dilution inherent in any exchange process. Finally the considerable loss of material (and of isotope) by ether formation makes this an impractical method of synthesis.

The reaction of ¹⁸O-labelled oxygen with methyl magnesium iodide.

Wiberg reported ⁽³⁾ the synthesis of methanol-¹⁸O by a Grignard reaction. ¹⁸O-enriched water was electrolysed in a microcell and the isotopically enriched oxygen after thorough drying, was bubbled through a solution of methyl magnesium iodide in ether solution. The methanol was worked up in the usual way. Apart from the relative complexity of the apparatus required for the generation and drying of ¹⁸O-labelled oxygen we ⁽⁷⁾ have found that considerable isotopic dilution occurs unless very stringent precautions are taken to remove any oxygen originally present in the system. An added disadvantage is the relatively large losses in methanol on workup and the difficulty in separating all traces of solvent ether from the product. This disadvantage can be overcome ⁽⁷⁾ by the use of another solvent (such as tetrahydrofuran) but we have found that this reaction is only useful for the preparation of large quantities of methanol of low isotopic enrichment. This method of synthesis might, however, be used for the synthesis of highly enriched methanol-¹⁷O using oxygen-17 gas now available in high concentrations by thermal diffusion.

Alkaline hydrolysis of dimethyl sulphate.

It has been shown ⁽⁸⁾ that dimethyl sulphate hydrolyses with C-O bond fission in alkaline solution. This reaction has been used ⁽⁷⁾ to prepare ¹⁸O-labelled methanol. However, whenever concentrated solutions are used in order to conserve ¹⁸O-enriched water, the yield is considerably reduced due to the formation of dimethyl ether which reduces the yield and also leads to loss of isotope. In addition, the preparation of concentrated basic solutions without isotopic dilution is troublesome, since it requires large quantities of sodium amalgam or sodium in glass capillaries ⁽⁹⁾.

Under conditions where dimethyl sulphate hydrolyses with both S-O and C-O bond fission the isotopic content of the product methanol is reduced even further.

Hydrolysis of methyl iodide.

The direct hydrolysis ⁽¹⁰⁾ of methyl iodide in concentrated aqueous solution is a slow reaction which suffers from the same disadvantage as the basic

hydrolysis of dimethyl sulphate, namely, ether formation. GRAGEROV *et al* ⁽⁵⁾ have described the preparation of ^{18}O -labelled methanol by a catalytic process in which methyl iodide is hydrolysed in sealed tubes at 100°C in the presence of large quantities of silver oxide. We have found ⁽⁷⁾ that the yield of methanol produced by this method is low and that considerable isotopic dilution occurs due to exchange between oxide and water. ^{18}O -labelled silver oxide could, in principle, be specially prepared for this purpose but it does not seem, in most cases, worthwhile doing so.

Acid hydrolysis of trimethyl phosphate.

BARNARD *et al* ⁽¹¹⁾ have shown that in initially neutral or acid solution, the first methyl group of trimethyl phosphate hydrolyses with purely C-O bond fission. Trimethyl phosphate is a readily obtainable starting material easily purified by fractional distillation under reduced pressure. If the reaction is allowed to proceed for only 10-20 % of its course, the product is uncontaminated by methanol formed by hydrolysis of the methyl groups of mono- and dimethyl phosphates where P-O bond cleavage ⁽¹²⁾ occurs. The ^{18}O -labelled methanol and excess water are readily removed by distillation in vacuo. The methanol is then separated by fractional distillation, and the remaining isotopically enriched water without further treatment. We consider that this is easily the best method of preparation of methanol labelled with oxygen isotopes, the main advantages being simplicity, absence of isotopic dilution, economy in the amount of isotope required, ease of recovery of the residual ^{18}O -enriched water, and the absence of by-product and contaminants. Details for the synthesis of methanol highly enriched in ^{18}O or in ^{17}O are described in the experimental section.

We have found that this method can also be used for the synthesis of ethanol labelled with isotopes of oxygen.

The isotopic analysis of oxygen in methanol.

Most high temperature methods of conversion ⁽¹³⁾ of methanol to carbon dioxide also produce significant quantities of dimethyl ether. The final traces of this ether are difficult to remove by fractionation on a vacuum line and, since it has the same mass, 46, as labelled carbon dioxide, serious errors in the isotopic analysis of methanol are caused by this contaminant. In some instances, it is possible to purify the carbon dioxide by vapour phase chromatography on a specially built column, as has been described for other alcohols by BOYD *et al* ⁽¹⁴⁾. In an alternative method BUNTON *et al* ⁽¹⁵⁾ have pyrolysed methanol in a graphite filled tube heated by an induction furnace and analysed the carbon *monoxide* formed mass-spectrometrically. Fairly large quantities of methanol are required for this method of analysis and we ⁽¹⁰⁾ have found that the accuracy and reproducibility is poor due to memory effects. ZEL-

VENSKII *et al* ^(1d) decomposed fairly large quantities of methanol on a zinc sulphide catalyst at 350° C and converted the carbon monoxide formed to carbon dioxide which was analysed in the usual way, whilst BAERTSCHI *et al* ^(1b) burnt the methanol with a known amount of oxygen of known isotopic composition and analysed the CO₂ formed after equilibrating it with the product water. LAUDER and co-workers ⁽¹⁶⁾ have described two methods for the isotopic analysis of oxygen in various organic compounds including methanol. These methods appear to be extremely complicated, requiring relatively large amounts of material and to be both time-consuming and inaccurate. Finally, an equilibration method ⁽¹⁷⁾ in which an alcohol is heated with CO₂ and a trace of sulphuric acid in a sealed tube for a given time at a known temperature is often used for isotopic analysis. This method, of isotopic analysis cannot be used for ethanol. However, the equilibration ⁽¹⁷⁾ and other methods are satisfactory in this case.

EXPERIMENTAL.

Trimethyl phosphate was distilled *in vacuo*, the fraction boiling at 90 °C 22 mm/Hg being used for these experiments. ¹⁷O- and ¹⁸O-enriched water from the Isotope Separation Plant of the Weizmann Institute was used. It should be noted that this water is also highly enriched in deuterium.

¹⁸O-labelled methanol.

Trimethyl phosphate (8.5 g) and ¹⁸O-enriched water (8 g) were heated in a large sealed tube for 26 hrs at 105° C. The tube was opened and the mixture of excess water and methanol distilled off *in vacuo*. The mixture was then fractionally distilled at atmospheric pressure in a small Vigreux column, yielding two fractions (a) methanol-¹⁸O (0.85 g; b.p. 66-68° C) and (b) recovered ¹⁸O-enriched water (5.5 g). The methanol-¹⁸O is finally dried over a few grains of anhydrous potassium carbonate. This methanol contains deuterium in the hydroxyl group which can be removed by dissolving in a ten-fold excess of ordinary water and separation by fractional distillation as described above.

¹⁷O methanol was prepared in a similar manner from trimethyl phosphate (8 g) and ¹⁷O-enriched water (8 g), giving methanol fraction (1.2 g; b.p. 66-68° C) and recovered water (4.5 g).

Isotopic analysis of methanol.

Labelled methanol was analysed in the apparatus shown in the figure. The material to be analysed is placed in tube A and introduced through the stopcock and inlet tube B into the evacuated vessel C. The vessel has a volume of approximately 30 ml and sufficient methanol is vaporised to produce the saturated vapour pressure of 100 mm/Hg at room temperature (i.e. of the order 0.2 mM). The platinum wire D is heated electrically to about 900° C

in order to pyrolyse the methanol vapour. At this temperature virtually complete decomposition occurs as follows :

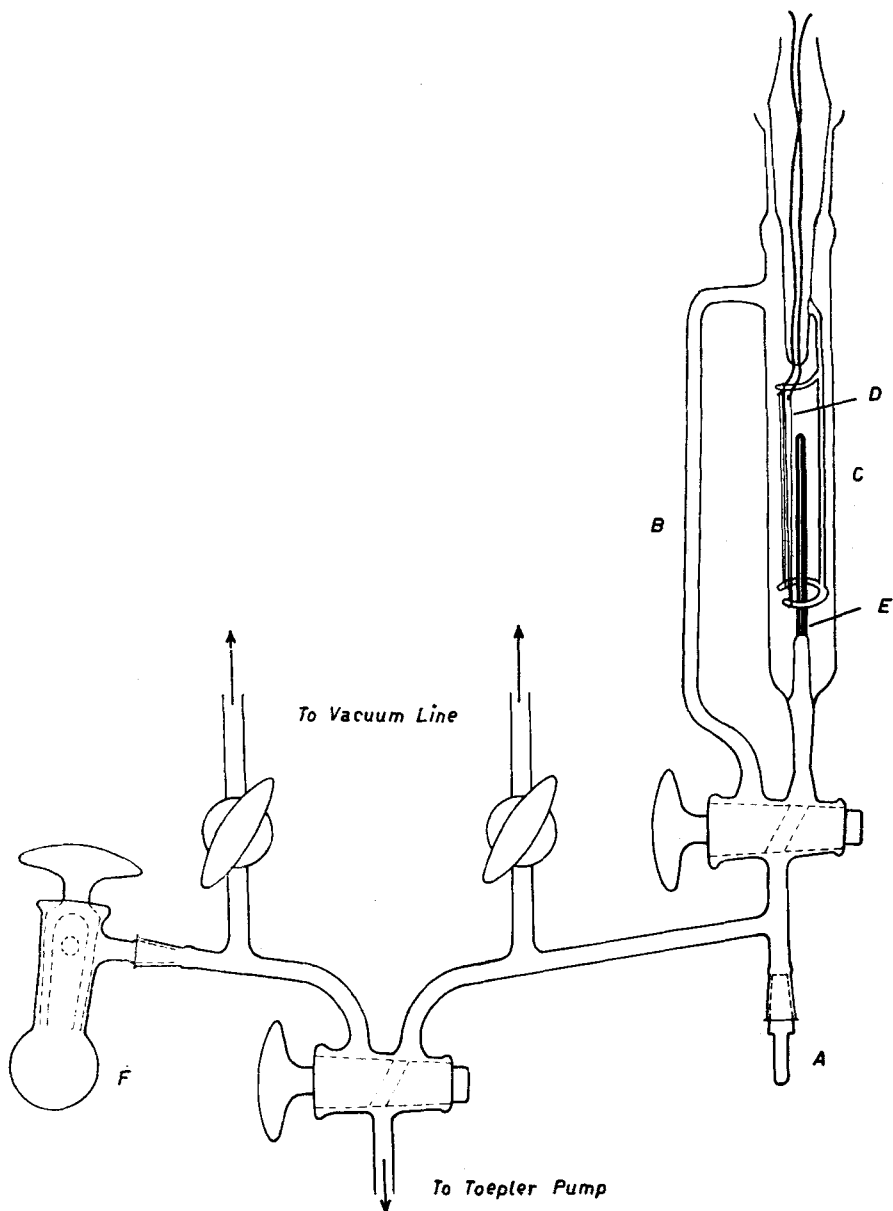
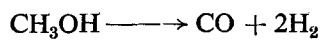


Figure — Apparatus used for the isotopic analysis of methanol.

The hydrogen is pumped off as it is formed through the palladium tube E which is kept hot by the glowing filament. The carbon monoxide is then transferred to the bulb F by means of a Toepler pump. The CO may contain up to 2 % hydrogen which does not affect the mass-spectrometric analysis. Using a CEC mass spectrometer Model 21-401, the reproducibility of this method is ± 0.5 % for consecutive ^{18}O analyses. This is close to the limit of the present accuracy of this mass-spectrometer.

The isotopic results of two typical separate syntheses are given in the table :

	Starting water	Methanol	Recovered water
$\text{CH}_3^{18}\text{OH}$	97 atom % ^{18}O	92 atom % ^{18}O	96 atom % ^{18}O
$\text{CH}_3^{17}\text{OH}$	9.0 atom % ^{17}O	7.2 atom % ^{17}O	8.0 atom % ^{17}O

The water was analysed (18) by equilibration with carbon dioxide. The slight lowering of isotopic content in both alcohol and water is probably due to a small proportion of hydrolysis of the diester. This is shown by the fact that the ^{17}O synthesis was heated longer (41 hours) than the ^{18}O synthesis (26 hours). Shorter heating times would produce even lower isotopic dilution, but also, of course, smaller yields. Attempts to use smaller quantities of ^{18}O -enriched water in order to conserve it (trimethyl phosphate 12 g; water, 2 ml) give considerably poorer yields of methanol with a much lower isotopic content.

^{18}O -labelled ethanol.

Triethyl phosphate (12 g) and ^{18}O -enriched water (10 ml containing 98.5 atom percent ^{18}O) were heated in a sealed tube for 18 hours at 150°C . The tube was broken open and the mixture of ethanol and excess water distilled off in vacuo. The mixture was fractionally distilled at atmospheric pressure, yielding two fractions (a) ethanol ^{18}O azeotrope (1.7 g), (b) recovered ^{18}O -enriched water (10.5 g). The ethanol was dried (twice) with anhydrous potassium carbonate, redistilled (b.p. 78°C) analysed by direct mass-spectrometry and found to contain 97 atom ^{18}O .

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