SYNTHESES WITH STABLE ISOTOPES: METHANOL-^{13}C, METHANOL-^{13}C-D_4 AND METHANOL-^{12}C.

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SUMMARY

Hydrogenation of carbon dioxide at mild temperature and pressure utilizing a copper-zinc-chromium catlyst has been developed for small- and large-scale preparations of methanol and is applicable to various isotope isomers.

INTRODUCTION

Kilogram quantities of acetic-$^{13}C_2$ acid at ca. 90 atom percent carbon-13 have been required for a program demonstrating the lack of adverse biological effects from incorporation of high levels of the isotope into biological systems [1] and the usefulness of stable isotopes for clinical diagnostic applications [2-4], in addition to its uses as a general synthetic intermediate. From a consideration of the chemical form of the enriched isotope (carbon-^{13}C monoxide) from the production facility [5] and the scale of the preparations, the synthetic route to acetic acid chosen as most efficacious was that involving carbonylation of methanol-^{13}C [6].

Various methods have been devised for the efficient preparation of isotopically labeled methanol [7]; however, most of these are not readily applicable to a multimolar scale. Catalytic hydrogenation of carbon monoxide is a common industrial method and has also been used for isotopic syntheses [8]:

$$CO + 2H_2 \xrightleftharpoons{\text{Catalyst, Heat, Pressure}} CH_3OH$$

Although carbon monoxide is the starting material most readily available for syntheses with carbon-13, we observed that carbon dioxide was very readily and quantitatively reduced in the presence of a catalyst designed for the industrial production of methanol from carbon monoxide at relatively low pressure [9] and that deterioration of the catalyst, which can occur with the monoxide, was not significant with the dioxide.

$$CO_2 + 3H_2 \xrightarrow[\text{200-250°}]{\text{Cu-Zn-Cr}} CH_3OH + H_2O$$

Carbon dioxide is very simply prepared by oxidation of carbon monoxide over copper oxide at 400°. Hydrogenation of carbon dioxide produces a mole of water for each mole of methanol. Often this mixture can be used directly without separation; however, when anhydrous methanol is required, bulb-to-bulb vacuum distillation from molecular sieve is a simple and effective procedure.

DISCUSSION AND RESULTS

A schematic diagram of the large-scale apparatus, with a production capacity of about 5 to 10 moles per day, is shown in Fig. 1. Construction is of stainless steel, total volume of the system is 17 dm^3, volume of the catalyst bed is 0.4 dm^3, circulation rate produced by the vane pump is 10 dm^3/min, and the condenser is cooled with chilled water. The heat exchanger significantly reduces the requirements for heating the catalyst bed and for cooling the condenser. Efficient condensation is required because of the reversible nature of the reaction and for convenient isolation of product.

The apparatus illustrated in Fig. 2 was devised for smaller scale (primarily polyisotopic) syntheses; it should be useful (although not yet applied) to preparation of other isotope isomers (e.g., with oxygen-17, oxygen-18, carbon-14, and tritium). With one-fiftieth the volume of the larger apparatus, its production

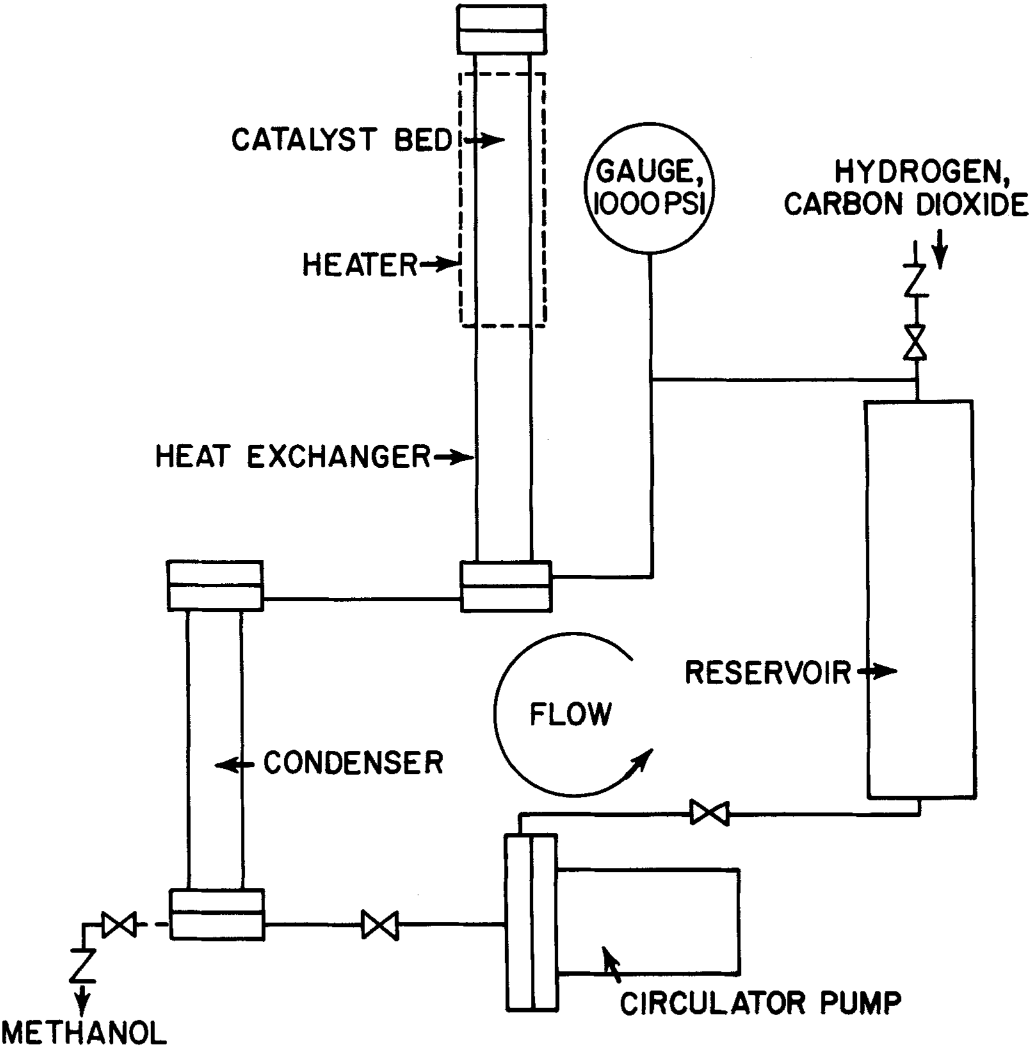


Fig. 1. Large-scale methanol synthesis apparatus

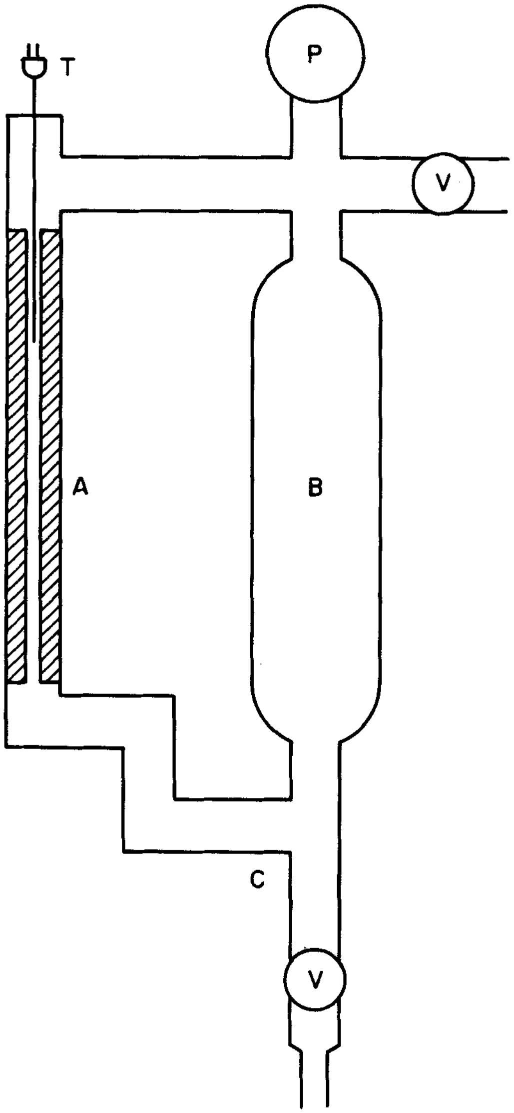


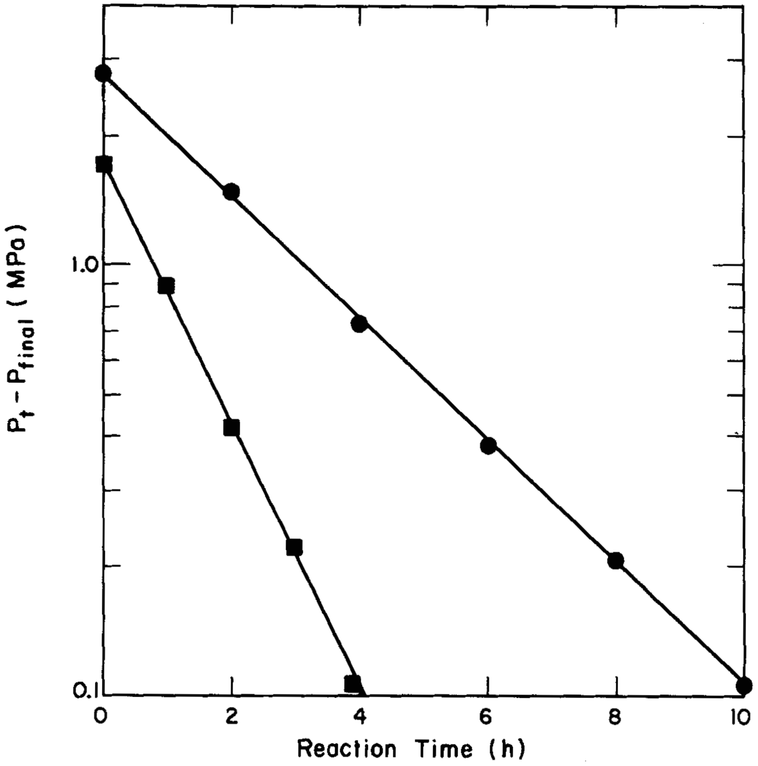
Fig. 2. Small-scale methanol synthesis apparatus

(A) catalyst chamber, 8 mm i.d. by 20 cm with 3-mm i.d. cylindrical cavity, ca. 8 cm^3 (6 g) of catalyst, heated by 250-watt electrical heating tape
(B) reservoir, 300 cm^3 stainless steel cylinder
(C) condenser region
(P) pressure gauge, 0 to 1000 psi
(T) thermocouple, 1/16 in. o.d.
(V) valves

rate is approximately a tenth mole per day. Construction is entirely of stainless steel tubing and fittings -- no machining operations were required. Circulation of the reactants is through thermal convection, heating of the catalyst chamber by electrical heating tape, and condensation of product by immersion of the lower portion of the apparatus in an ice bath. It was found necessary to incorporate a 3-mm diameter hole (copper screen) through the catalyst bed (6 g) to obtain adequate circulation. When the carbon dioxide is available at low pressure or through generation from carbonate, cryogenic pumping can be used to effect the desired pressurization by condensing the carbon dioxide with liquid nitrogen in 0.5-in. diameter tubing attached by a T-fitting to the inlet line.

Essentially quantitative yields of methanol are produced in both types of apparatus. Over an approximately three-year period, ca. 7 kg methanol has been produced in some 50 preparations in the large-scale equipment. Representative kinetics are shown in Fig. 3 for synthesis of methanol-^{13}C in the large-scale apparatus and for methanol-^{13}C-d_4 in the small unit. Excess (ca. 25%) hydrogen (deuterium) was ordinarily used, with the carbon dioxide being added first. In the small apparatus this order of addition usually resulted in a slow initial rate, probably related to initiation of convective circulation. When the carbon dioxide was added after the deuterium, a temperature rise was evident on addition of the carbon dioxide, and a normal rate of reaction was immediately established.

Proton resonance spectroscopy (pmr) can be effectively used for determination of carbon-13 concentration in methanol-^{13}C [i.e., the ratio of the area of



(-■-) for synthesis of methanol-^{13}C in the large-scale apparatus and
(-●-) methanol-^{13}C-d_4 in the small-scale apparatus

Fig. 3. Carbon dioxide hydrogenation pressure kinetics

the methyl-^{12}C peak at δ 3.35 to the sum of the areas of the doublet at 70.5 Hz on either side (due to ^{13}C-H coupling) is the ^{12}C/^{13}C ratio]. Although such an isotope analysis cannot be directly obtained by carbon-13 nuclear magnetic resonance (cmr), cmr was very effective in confirming that the products from the methanol-^{12}C syntheses contained less than 10 ppm methanol-^{13}C and, therefore, that the starting carbon-^{12}C dioxide was indeed greater than 99.999 atom percent carbon-12. Combustion of the product to carbon dioxide and mass spectrometric analysis for carbon-13 are unreliable at this level. Some physical properties and infrared spectral data are given in Table I.

TABLE I. Properties of Methanol Isotope Isomers

	$^{12}CH_3OH$	$^{13}CH_3OH$	$^{13}CD_3OD$
Specific gravity	1.0000	1.0310	1.1660
n_D^{22}	1.3278	1.3276	1.3286
Ir, cm^{-1}	3700	3700	2730
	3000	3000	2210
	2890	2890	2090
			1105
	1340	1340	1280
	1050	1040	990
	1025	1005	970
	1005	981	950

EXPERIMENTAL

Materials and Methods--Carbon-^{13}C dioxide (ca. 90 atom % ^{13}C) and carbon-^{12}C dioxide (ca. 99.999 atom % ^{12}C) were produced by the Los Alamos Scientific Laboratory Stable Isotopes Separation Facility of Group CNC-4. Infrared spectra were measured in the vapor phase on a Perkin-Elmer Model 710. Pmr spectra were taken on a Perkin-Elmer-Hitachi Model R-24 with sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal reference. Gas chromatographic analyses were carried out with a Varian Model EP90 using 1/8-in. by 10-ft columns of Porpaq-Q (120/150) and FFAP on Chrom W (20%, 60/80) in series at a column temperature of 170° and helium flow of 0.6 cm^3/sec; retention times: water, 3.1 min; methanol, 3.7 min. Specific gravities were determined at 21° by weighing the products in a pycnometer of ca. 5 cm^3 volume and are given relative to the carbon-12 isomer. Mass spectrometric analyses for carbon-13 of the carbon dioxide obtained from combustion of methanol were carried out on a CEC-620 mass spectrometer. The Van Slyke-Folch type wet combustions were performed in a glass apparatus [10] in which the sample (a few mg) was first frozen in liquid nitrogen, the apparatus was evacuated to around 10 Pa (0.1 Torr), and the oxidation was carried out in the usual manner. The carbon dioxide was condensed in a side arm with liquid nitrogen and then, by replacing the liquid nitrogen with Dry Ice, distilled into an evacuated mass spectrometry bulb.

Preparation of Catalyst--A solution of 868 g (2.94 mol) copper nitrate trihydrate, 312 g (0.35 mol) zinc nitrate hexahydrate, and 140 g (1.05 mol) chromium nitrate nonahydrate in 10 dm^3 water was added with vigorous stirring to a solution of 547 g sodium carbonate in 10 dm^3 of water at 85°. The precipitate was filtered, washed thoroughly with water, extruded into small rod sections (ca. 2-mm diameter), and air-dried in an oven while the temperature was slowly increased to around 250°. The pellets were transferred to the catalyst section of the synthesis apparatus which was evacuated, brought to 0.8 MPa (100 psig) with helium, and heated to 230°. With the catalyst bed heaters shut off, hydrogen was added in 7-kPa (1-psig) increments while the temperature was held within a 10° range. The catalyst (which contained copper, zinc, and chromium in a ratio of about 7:2:1) was then ready for production of methanol; the odor of methylamine(s) ordinarily could be detected in the first few runs, apparently owing to some of the catalyst being incompletely reduced.

Synthesis of Methanol-^{13}C (Large-Scale Apparatus)--To the apparatus (Fig. 1), containing 2.75 MPa (385 psig) pressure of residual hydrogen, was added 0.88 MPa (128 psig, 206 g, 6.59 mol) of carbon-^{13}C dioxide (91.3 atom % ^{13}C), followed by 0.88 MPa of hydrogen [total of 3.63 MPa (512 psig), 26.3 mol]. The condenser cooling water, catalyst heater (thermostat at ca. 225°), and circulation pump were turned on. Within about a half hour the catalyst bed reached operating temperature, and the pressure began to decrease (Fig. 3). After the pressure had dropped to the final value of 0.88 MPa, the product was slowly withdrawn through the valve at the bottom of the condenser into a chilled receiver to give 330 g (98.4% yield) of 50 mole percent (by gas chromatography) methanol in water. Preliminary separation of methanol from the water was accomplished by fractionation at atmospheric pressure. Anhydrous methanol was obtained by bulb-to-bulb vacuum transfer from molecular sieve (3A, 10 g per g of water): pmr (neat) δ 3.35 (d, $^{J}13_{C-H}$ = 141 Hz).

Synthesis of Methanol-^{12}C (Large-Scale Apparatus)--Carbon-^{12}C dioxide (containing less than 10 ppm carbon-^{13}C dioxide) was hydrogenated by the procedure given above, except that these reactions were carried out in a different (but identical) apparatus dedicated solely to carbon-12. Cmr analysis* of the methanol-^{12}C showed that it contained less than 8 ppm methanol-^{13}C.

Synthesis of Methanol-^{13}C-d_4 (Small-Scale Apparatus)--The small-scale hydrogenation apparatus (Fig. 2) was charged with 6 g of the Cu-Zn-Cr catalyst, and the catalyst was reduced with deuterium gas as described previously. In a typical reaction with the catalyst bed (A) heated to 220° and the condensation region (C) cooled in ice water, deuterium was added to a pressure of 3.14 MPa (440 psig, 0.44 mol). A slight decrease (ca. 10°) in the temperature of the catalyst bed was noticed after the deuterium addition. Carbon-^{13}C dioxide [ca. 90 atom % ^{13}C, 0.69 MPa (100 psig), 4.49 g, 0.10 mol] was added; the temperature of the catalyst bed increased to 225-230°. After 24 h with the temperature of the catalyst bed being maintained at approximately 220°, the pressure had fallen by 2.76 MPa (400 psig). The valve (V) on the condensation trap (C) was partially opened, and the liquid was drained from the trap. The apparatus was then repressured to a total pressure of ca. 4 MPa with three parts deuterium and one part carbon dioxide.

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*Personal communication, Dr. N. A. Matwiyoff, Inorganic Chemistry Group (CNC-4), this Laboratory.

The methanol-^{13}C-d_4-deuterium oxide mixtures from several runs, which contained a small amount of uncharacterized water-insoluble material, were combined and washed with 5 ml of xylene. The xylene layer was washed with deuterium oxide (2 x 2 cm^3), and the combined methanol-^{13}C-d_4-deuterium oxide layers were distilled through an 8-cm fractionating column. The yield of methanol in this mixture averaged ca. 95% from carbon dioxide. The methanol-^{13}C-d_4-deuterium oxide mixture was generally used as such in subsequent reactions but could be distilled from molecular sieve with essentially quantitative recovery to produce anhydrous methanol-^{13}C-d_4.

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