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Exchange Reactions between Hydrogen Gas and Hydroxyl Groups. A Convenient Preparation of Tritium-labeled Water¹

BY C. GARDNER SWAIN AND A. JERRY KRESGE

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The exchange reactions between deuterium gas and methanol or water catalyzed by platinum have been found to proceed at a convenient rate at room temperature and to be limited to exchange of hydroxylic hydrogen. Use of this reaction to label water with tritium provides a superior method for preparing tritiated water. An extension to the preparation of tritiated alcohols is suggested.

Tritium is in many respects a better label for organic molecules than carbon-14. It is supplied by the Atomic Energy Commission as carrier-free gas (T_2) with 2.6 curies per ml. (S.T.P.), a molar activity 900 times that of isotopically pure $C^{14}O_2$. It is expected to be always several hundred times cheaper per curie than carbon-14.² The health hazard is considerably less with T than with C^{14} .³ Moreover, recent advances in instrumentation⁴ and assaying techniques⁵ have largely removed the difficulties in precise determination of tritium which hampered its early use.

Before these advantages of tritium can be utilized, however, simple and efficient methods of incorporating this isotope into organic compounds must be devised. In this paper we report the results of our investigations concerning the synthesis of deuteriated methanol and deuteriated and tritiated water by catalytic exchange.

Methanol.—Catalytic exchange of deuterium gas with methanol had been accomplished at least once before we began this work: Okamoto reported that only the hydroxylic hydrogen exchanged when methanol was stirred with platinum-black at 0° .⁶ His evidence, however, did not exclude completely the possibility of a relatively minor incorporation of deuterium in the methyl group at 0° . The extent of any exchange on carbon might be considerably increased at 25 – 30° . Since the position of labeling in tritiated methanol is often very important, we decided to examine more closely the selectivity of this exchange.

In our preliminary experiments at room temperature, light methanol was stirred with 5% of its weight of platinum oxide in the presence of deuterium gas. Exchanged methanol was then recovered from the reaction mixture by vacuum transfer into a trap from which samples were removed for deuterium analysis. Infrared absorption was used to detect deuterium on both oxygen and carbon and to distinguish between the two. The spectrum of methanol from run 1 (Table I) measured in matched

cells against light methanol showed a new absorption at 2400 cm.^{-1} , which is the expected position for OD stretching (ν_7) in both CH_3OD and CH_2DOD ,⁷ and another new but much weaker band at 2180 cm.^{-1} , which is the expected position for CD stretching (ν_2) in CH_2DOD .⁷ Material from a second experiment in which the ratio of deuterium

TABLE I

EXCHANGE OF METHANOL WITH DEUTERIUM GAS OVER PLATINUM CATALYST AT 25°

Run	MeOH, mmoles	D_2 , mmoles	Time, hours
1	50	1.1	15
2	10	13	15
3	10	13	72

gas to methanol was raised by a factor of about 50 corroborated that exchange was occurring in the hydroxyl group: it showed a much stronger OD absorption at 2400 – 2500 cm.^{-1} and an approximately corresponding increase in the absorption at 2180 cm.^{-1} . The latter band, however, was still very weak. In a third experiment, exposure time was increased by a factor of five. No difference could be detected in the spectrum of the product: The OD absorption neither decreased nor did the other band increase. Relative intensities of the OH and OD absorption of a sample of methanol from run 2 measured as a thin film between sodium chloride plates indicated that the deuterium content of the OH group was approximately 84%, which is more consistent with the value of 72% calculated assuming exchange in only the OH group than with the value of 36% calculated assuming exchange for all four hydrogens of methanol.⁸ The

$$\epsilon_{OH}/\epsilon_{OD} = (\nu_{OH})^2/(\nu_{OD})^2 \cong 2$$

$$c_{OD}/c_{OH} = [\log(I/I_0)_{OD}/\log(I/I_0)_{OH}] \cdot [\epsilon_{OH}/\epsilon_{OD}] = [\log 0.33/\log 0.66] 2 = 5.3$$

3,5-dinitrobenzoate of a sample of methanol from run 3 then was prepared; its infrared spectrum showed no absorption whatever in the CD stretching region and proved to be identical with the spectrum of a sample of authentic methyl 3,5-dinitrobenzoate. Finally, some methanol-*d* was prepared by exchanging light methanol with deuterium oxide using *p*-toluenesulfonic acid as catalyst. Its infrared spectrum also showed the weak band at 2180 cm.^{-1} and proved to be identical in all

(1) This work was supported in part by the research program of the Atomic Energy Commission under Contract No. AT(30-1)-905.

(2) W. F. Libby, *Chem. Eng. News*, **35**, No. 20, 19 (May 20, 1957). Current prices per curie are \$2 for T_2 , \$22,000 for C^{14} .

(3) R. F. Barker, *Isotopics*, **6**, No. 1, 10 (1956).

(4) Tracerlab Catalog D, Tracerlab, Inc., Boston, Mass., 1956, p. 76.

(5) C. A. Ziegler, D. J. Chleck and J. Brinkerhoff, *Anal. Chem.*, **29**, 1774 (1957); C. G. Swain, V. P. Kreiter and W. A. Sheppard, *ibid.*, **27**, 1157 (1955); K. E. Wilzbach, L. Kaplan and W. G. Brown, *Science*, **118**, 522 (1953).

(6) G. Okamoto, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **31**, 211 (1937).

(7) E. F. Barker and G. Bosschieter, *J. Chem. Phys.*, **6**, 563 (1938).

(8) This calculation was based on the assumption that the extinction coefficients are related as the square of the frequencies (*cf.* E. B. Wilson, Jr., J. C. Decius and P. C. Cross, "Molecular Vibrations," McGraw-Hill Book Co., Inc., New York, N. Y., 1955, p. 191).

respects with the infrared spectrum of methanol obtained in runs 2 and 3. The weak absorption at 2180 cm.^{-1} , then, cannot be a CD stretching vibration; it is more likely the harmonic of some other methanol vibration, perhaps the CO stretching (ν_5) which occurs at 1034 and 1040 cm.^{-1} in CH_3OD .⁹

Gas-liquid chromatographic analysis (silicone oil on firebrick) of a sample of methanol from run 2 showed that the material was homogeneous. The platinum-catalyzed reaction at room temperature, therefore, consists of exchange on oxygen alone and very probably involves no other reaction.

The reaction between methanol and deuterium over platinum was next studied at higher temperatures to determine whether exchange on carbon could occur. Since it already had been shown that the hydroxylic hydrogen of methanol exchanges with hydrogen gas on platinum, methanol-*d* rather than light methanol was used in these experiments. The hydroxyl group served as an "internal" source of deuterium gas. This, in turn, permitted use of a smaller actual gas to liquid volume ratio and a correspondingly smaller reaction vessel. Spreading of catalyst and methanol over glass walls was thus held to a minimum.

In two experiments, one at 95° and one at 240° (Table II), the infrared spectrum of the recovered methanol (10% in CCl_4 solution) was identical with that of the starting material. No isomerization had occurred and, therefore, no exchange on carbon.

TABLE II
CATALYTIC REACTION OF METHANOL-*d*

Run	Catalyst species	Wt. cat., mg.	MeOD, mmoles	Temp., °C.	Time, hours
4	Pt	35	25	95	24
5	Pt	35	25	240	19
14	Ni	100	12 ^a	25-30	70
11	Ni	60	12	25-30	24
12	Ni	300	12	25-30	24
17	Ni	100	12	200	24
16	None	..	12	300	24

^a Used MeQH and 13 mmoles of D_2 gas.

The reaction between methanol and deuterium using Raney nickel as catalyst was studied as well. A preliminary run using light methanol and deuterium gas showed that nickel, like platinum, effected exchange in the hydroxyl group but not on carbon. A number of subsequent runs were then performed using methanol-*d* in a manner similar to that described above for platinum. Temperatures as high as 200° failed to produce any exchange on carbon.

Finally, a sample of methanol-*d* was heated to 300° without catalyst. The product was identical with starting material by infrared spectrum.

Water.—Exchange between water and deuterium gas over platinum was studied in a manner similar to that described for methanol. Deuterium analyses were accomplished by refractive index measure-

(9) These values are for the gas phase and, strictly speaking, should be corrected for association in the liquid before a comparison with the 2180 cm.^{-1} absorption is made.

ment.¹⁰ The data in Table III show that exchange is essentially complete in twelve hours.

TABLE III
EXCHANGE OF 0.50 ML. OF WATER WITH 300 ML. OF DEUTERIUM GAS (S.T.P.) OVER 25 MG. OF PLATINUM CATALYST AT 25°

Run	Time, hours	% D in H_2O^a
7	1	2
9	12	30
10	50	28
6	120	30

^a Calcd. at equilibrium: 32%.

Synthesis of Tritiated Compounds.—Tritium-labeled water was prepared from carrier-free tritium gas by a method similar to those described above. Platinum generated *in situ* from platonic oxide was used in the preparation. It was found more convenient to use tritium as the reducing agent instead of the usual hydrogen; in this way tritiated water was formed by the oxidation of tritium as well as by exchange. Platonic oxide in excess of that required to oxidize all of the tritium gas was employed, and the course of the reaction was followed by noting the pressure of gas in the reaction chamber. This pressure proved to be a linear function of time during the oxidation and then leveled off at a steady final value (Fig. 1). The fact that the final pressure was no more than 5 mm. above the vapor pressure of water indicates that this reaction went almost to completion and that at least 95% of the reducing gas was consumed. The radioactive yield, however, was even higher than this because exchange occurred as well as oxidation. At the beginning of an experiment cold water usually was used in an amount 600 times the molar amount of tritium. Assuming a statistical distribution, at equilibrium, 600/601 of the tritium was incorporated in the water. Therefore the radioactive yield was 99.99%. This water had a molar activity of approx. 100 curies per mole. Less active water could, of course, be produced even more efficiently.

This process seems adaptable to the preparation of pure tritium oxide: carrier water can be dispensed with and the oxidation performed with dry platonic oxide.

The method seems superior to the existing preparations of tritiated water.¹¹ It is safe, requires the use of only simple apparatus and gives excellent radioactive yields.

We did not apply the method to the synthesis of tritium-labeled methanol, but the extension is obvious. Platonic oxide can first be reduced to platinum with ordinary hydrogen and the catalyst freed of resultant water by pumping. Use of this catalyst to effect exchange between methanol and tritium gas will then produce hydroxyl-labeled alcohol of any desired activity.

(10) C. N. Lewis and D. B. Lutten, Jr., *THIS JOURNAL*, **55**, 5051 (1933); R. H. Crist, G. M. Murphy and H. C. Drey, *ibid.*, **55**, 5060 (1933); *J. Chem. Phys.*, **2**, 112 (1934).

(11) E. M. Hodnett, C. F. Feldman and J. J. Flynn, Jr., *Experientia*, **12**, 96 (1957); R. F. Glascock, "Isotopic Gas Analysis for Biochemists," Academic Press, Inc., New York, N. Y., 1954, pp. 203, 206; E. J. Wilson, Atomic Energy Research Establishment Memorandum, Harwell, England, I/M 28 (July, 1953).

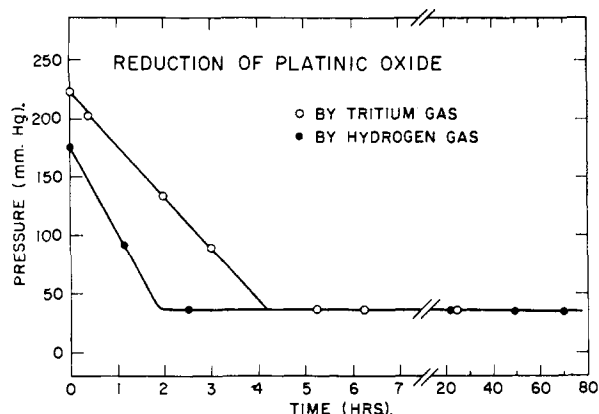


Fig. 1.—Kinetic data on formation of platinum catalyst at room temperature.

Experimental

Methanol.—Reagent grade methanol was dried by the method of Lund and Bjerrum.¹²

Methanol-*d*.—Twenty grams of deuterium oxide (99.5%, Stuart Oxygen Co.), 16 g. of methanol and a few crystals of *p*-toluenesulfonic acid were placed in the pot of a Holzman still.¹³ Methanol was then distilled off very slowly. Only the first 10 ml. was collected, over a 1° boiling range.

Platinic Oxide.—Platinum dioxide from Baker and Co., Inc., Newark, N. J. (brown powder, 83.93% PtO₂), was used without further purification.

Raney Nickel.—The catalyst was type W-2 made in the standard way.¹⁴

Exchange of Methanol with Deuterium.—Reactions at room temperature were carried out in a 250-ml. round-bottomed flask on the bottom of which a flat-bottomed, cylindrical well of approximately 1-ml. capacity had been blown. Methanol (0.40 ml.), platinic oxide (15 mg.) and a small, glass-enclosed magnetic stirring bar were placed in this well. The methanol was degassed, the space above was flushed once with deuterium, and the flask was filled to atmospheric pressure with deuterium. Reaction was begun by starting the magnetic stirrer.

Reaction was stopped after an appropriate interval and the methanol was distilled under vacuum into a trap cooled with liquid nitrogen. The distillate was then analyzed for deuterium by measuring its infrared spectrum in a Perkin-Elmer model 21 spectrophotometer, usually as a 10% CCl₄ solution.

Raney nickel-catalyzed exchanges were done in a similar fashion with the exception that the methanol under which the catalyst was stored and transferred was first distilled away. A known quantity of fresh methanol then was added to the dry catalyst by vacuum transfer.

High-temperature reactions were done in a sealed tube of about 5-ml. capacity made by constricting a thick-walled Pyrex test-tube. After placing the reactants in it, the tube was degassed and flushed with deuterium, sealed off under atmospheric pressure of deuterium, and packed with glass wool into a steel high-pressure hydrogenation vessel. After heating and shaking in a standard high-pressure hydrogenation apparatus for the appropriate time, the tube was cooled, opened and placed in a holder connected to a vacuum line. Methanol was distilled out in the usual fashion and analyzed.

Exchange of Water with Deuterium.—These reactions were done in a manner similar to that described above for methanol. Deuterium analyses were done by refractive index, making use of the fact that the refractive index of a

(12) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1941, p. 360; 1957, p. 289.

(13) C. W. Gould, Jr., G. Holzman and C. Niemann, *Anal. Chem.*, **20**, 361 (1948).

(14) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., p. 181.

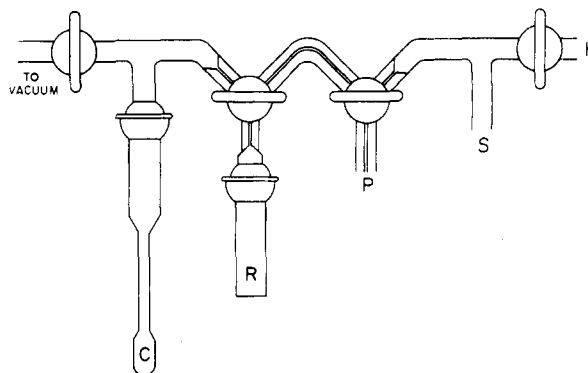


Fig. 2.—Apparatus for preparation of tritium-labeled water from tritium gas.

mixture of light and heavy water has been found to be linear with mole fraction.¹⁰ Lewis observed the relationship

$$\Delta n = -0.00449x$$

where Δn is the change in refractive index at 25° measured with white light and x is the mole fraction. Using an Abbe refractometer with prisms at $25 \pm 0.05^\circ$, we found the coefficient of x to be -0.0046 . Table IV summarizes analytical data for four runs.

TABLE IV

Sample	n_D^{25}	Mole % D
H ₂ O	1.3326	..
D ₂ O	1.3278	..
7	1.3325	2
9	1.3312	30
10	1.3313	28
6	1.3312	30

Preparation of Tritiated Water.—The apparatus used is shown in Fig. 2. Ordinary tank hydrogen used for flushing was introduced at H and a high vacuum line was attached at the other end. Tritium (5 curies, 1.93 ml., carrier-free, A. E. C., Oak Ridge) in a break-tip ampoule was sealed on at S; P led to a Toepler pump,¹⁵ which had a reference arm, with meter stick, below the Toepler bulb, fed at the bottom by a common movable leveling bulb of mercury, so that it also conveniently served as a manometer to follow the course of the reaction. Tubing between the two central stopcocks as well as at P was capillary; R had a capacity of about 5 ml. At the start of a run, water (1.00 ml.), platinic oxide (50 mg.) and a small, glass-enclosed magnetic stirring bar were placed in R. The water was degassed and the system was flushed several times with ordinary hydrogen. The system was then evacuated and closed off from the vacuum line. Tritium was transferred into R by means of the Toepler pump and reaction was begun by starting the stirrer. Pressure measurements were taken at appropriate intervals until a steady value was reached; stirring was then continued for 10–12 hours longer to ensure complete exchange. Figure 1 shows the pressure-time relationship for this run followed by reduction of the unchanged oxide with 5.0 ml. of light hydrogen. In the experiments with tritium the catalyst never changed color completely from the brown of the oxide to the black of the metal, indicating that an excess of oxide had been used.

When tritium incorporation was complete, residual gas was pumped off and the labeled water was transferred into one or more bulbs C which could be sealed off for storage. Liquid nitrogen or solid carbon dioxide was used to retain the water in R during evacuations and to condense it in traps C on warming R to room temperature.

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(15) R. F. Glascock, ref. 11, pp. 43, 170.