

SYNTHESES WITH STABLE ISOTOPES: ACETIC-1-<sup>13</sup>C,  
-2-<sup>13</sup>C, -<sup>13</sup>C<sub>2</sub>, AND -<sup>12</sup>C<sub>2</sub> ACIDS.

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Received on August 29, 1975

SUMMARY

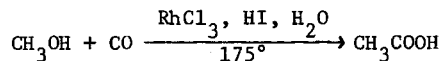
*Rhodium-catalyzed carbonylation of methanol at mild temperature and pressure has been developed for small- and large-scale preparations of the carbon isotope isomers of acetic acid.*

INTRODUCTION

Large quantities of acetic acid at high carbon-13 concentration were required for a program demonstrating the lack of adverse biological effects from incorporation of the isotope into biological systems (1) and the usefulness of stable isotopes for clinical diagnostic applications (2,3), in addition to its uses as a general synthetic intermediate. From consideration of the chemical form of the enriched isotope (carbon-<sup>13</sup>C monoxide) available from the production facility (4) and the scale of the preparations, the synthetic route to acetic acid chosen as most efficacious was that involving carbonylation of methanol (5,6).

Various methods have been utilized for preparing labeled acetic acids (7); some of these which are quite efficient for small-scale syntheses (e.g., with carbon-14) become rather impractical on a larger scale which is often encountered with the stable isotopes. For example, our initial preparation of acetic-1-<sup>13</sup>C

acid was carried out on a molar scale via the Grignard reaction utilizing a closed system which allowed admission of carbon-<sup>13</sup>C dioxide from a small cylinder to excess Grignard reagent at reduced pressure and temperature. The reaction went smoothly and in good yield; however, isolation and purification on this scale are somewhat tedious. Industrial production of acetic acid has long utilized catalytic methods and carbon monoxide; the rhodium-catalyzed carbonylation of methanol utilizing hydriodic acid as a promoter (5,6) appeared particularly attractive for isotopic syntheses. It was investigated and found to produce acetic acid in very good yield which could be readily isolated and purified. Further, it is applicable to both small- and large-scale preparations and to all the carbon isotope isomers of this important synthetic intermediate. Additionally, with certain limitations, other labeled carboxylic acids can be prepared from the appropriate alcohol.



#### RESULTS AND DISCUSSION

As illustrated in Fig. 1, the reaction proceeds smoothly after reaching the desired temperature, and its progress is readily followed by the decrease in pressure. The exothermic nature of the reaction is apparent in the large-scale preparations with the internal temperature rising above the set-point of the thermocouple-controlled electric furnace. Following completion of the reaction, as evidenced by no further pressure drop, and cooling of the autoclave to room temperature, the residual pressure is that expected from the methane contained in the starting material and the small excess of carbon monoxide. In the preparation of the methyl-labeled isomer, a large excess of carbon monoxide can be used which eliminates the production of methyl acetate; for the carboxyl- and double-labeled isomers, however, there has to be a compromise between the amount of carbon monoxide used and quantity of methyl acetates produced. The latter, if not desired for other uses, can be saponified to recover the components or, more simply, incorporated as starting material in a subsequent reaction.

Smaller scale reactions (for example, with a few tenths mole in a 300-cm<sup>3</sup>

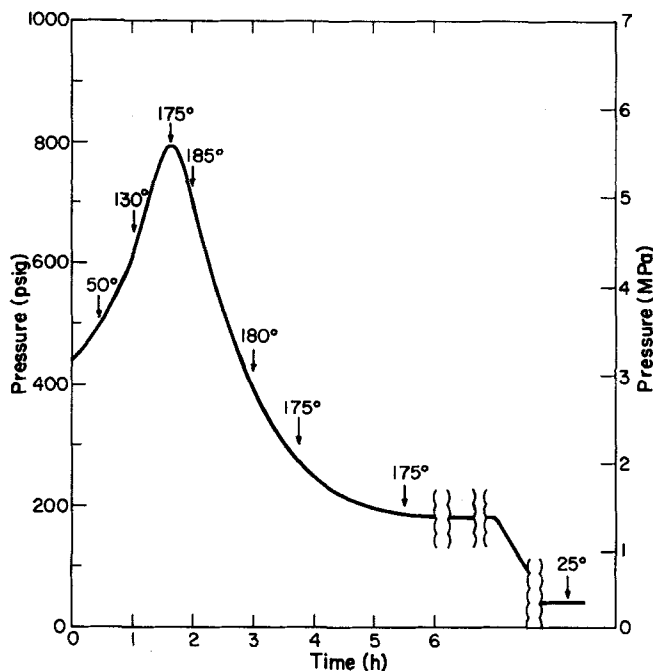


Fig. 1. Rhodium-catalyzed carbonylation of methanol-<sup>13</sup>C with carbon-<sup>13</sup>C monoxide.

Hastelloy pressure vessel heated in an oil bath) have been carried out using the same proportions of reagents with results essentially identical to those from the multimolar-scale preparation given below. The exact amount of water in the mixture has not appeared to be critical; it has usually been present in approximately the same molar quantity as the alcohol, since this is the ratio obtained in preparation of methanol-<sup>13</sup>C by hydrogenation of carbon-<sup>13</sup>C dioxide (8). No difference in catalytic activity was observed between anhydrous rhodium trichloride or the trihydrate, and since these were quite effective, other rhodium compounds or ligands (e.g., triphenylphosphine) were not investigated. Owing to the corrosive nature of rhodium carbonyl compounds (the active catalyst formed during the reaction), the pressure vessels must be of material more resistant than stainless steel (e.g., Hastelloy C). Use of potassium iodide as a promoter in place of hydriodic acid offered little advantage in decreasing the amount of iodide in the crude product, and the reaction rate was considerably lower.

Distillation of the reaction mixture gives an aqueous solution of the crude products contaminated with hydrogen iodide and iodine. The amount of the latter

materials is much less than that added initially; the remainder is in the black, solid residue which also contains carbon but has not been further characterized. Purification of the acetic acid is by redistillation following addition of phosphorous acid to reduce the iodine and silver sulfate to immobilize the iodide. For certain applications, the aqueous solution of acetic acid thus obtained is quite satisfactory (e.g., for preparing sodium acetate or as a biological substrate). However, other uses require the anhydrous material; we have found dehydration with magnesium sulfate to be effective and more convenient than other methods tried (e.g., azeotropic distillation with chloroform or regeneration of the acid from the sodium salt).

The proton magnetic resonance (pmr) spectrum of the methyl protons of acetic- $^{13}\text{C}_2$  acid at 100 mol %  $^{13}\text{C}$  would consist of four lines of equal intensity (an  $A_3XY$  spin system) produced by splitting the resonance at  $\delta$  1.8 by the two carbon-13 atoms. At lower carbon-13 concentrations, additional peaks corresponding to  $A_3X$  and  $A_3Y$  spin systems are present. By taking appropriate sums and

TABLE 1 -- Infrared Absorption of Acetic Acid Isotope Isomers<sup>a</sup>

$^{12}\text{CH}_3$ $^{12}\text{COOH}$	<u>Maxima (<math>\text{cm}^{-1}</math>)</u>		
	$\text{CH}_3$ $^{13}\text{COOH}$	$^{13}\text{CH}_3$ $\text{COOH}$	$^{13}\text{CH}_3$ $^{13}\text{COOH}$
1720	1680	1720	1680
1415	1395	1410	1395
1295	1275	1295	1275
1010	1010	1000	1000

<sup>a</sup> $^{13}\text{C}$  at ca. 90 mol %;  $^{12}\text{C}$  at ca. 99.999 mol %.

ratios of the heights of the peaks, the carbon-13 concentration at each individual position can be determined. For example, analysis of the spectrum shown in Fig. 2 gave 74 mol %  $^{13}\text{C}$  in the methyl group and 90 mol %  $^{13}\text{C}$  in the carboxyl group, values which are in excellent agreement with those expected from the synthesis which started with methanol and carbon monoxide at 73 and 90 mol %  $^{13}\text{C}$ , respectively. Some infrared spectral comparisons are given in Table 1.

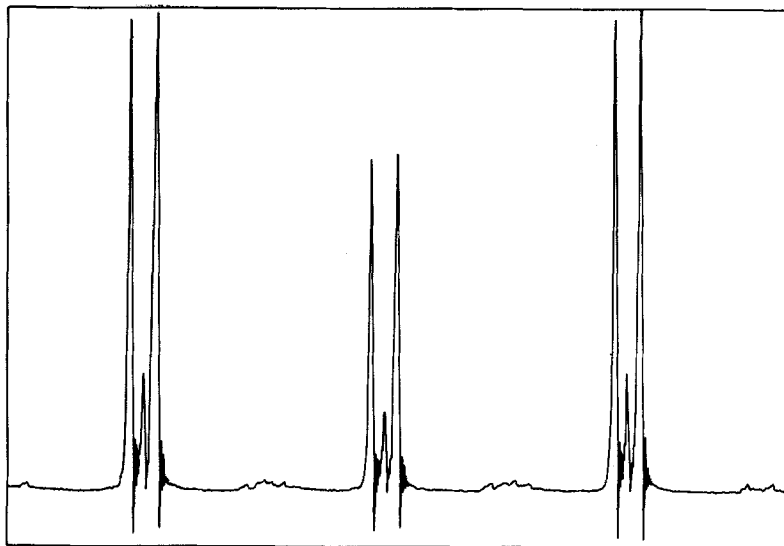


Fig. 2. Nuclear magnetic resonance spectrum of the methyl protons in acetic-<sup>13</sup>C<sub>2</sub> acid; 73 mol % <sup>13</sup>C at C-2, 90 mol % <sup>13</sup>C at C-1;  $\delta$  1.8,  $J_{CH} = 130$  Hz,  $J_{CCH} = 7$  Hz.

#### EXPERIMENTAL

Materials and Methods—Carbon-<sup>13</sup>C monoxide (ca. 90 mol % <sup>13</sup>C) and carbon-<sup>12</sup>C monoxide (ca. 99.999 mol % <sup>12</sup>C) were produced by the Los Alamos Scientific Laboratory Stable Isotopes Separation Facility of Group CNC-4. Methanol-<sup>13</sup>C and methanol-<sup>12</sup>C were prepared as previously reported (8). Infrared spectra were obtained from a liquid film on a Perkin-Elmer Model 710 spectrophotometer and are reported to the nearest 5 cm<sup>-1</sup>. Pmr spectra were taken on a Perkin-Elmer-Hitachi Model R-24. Gas chromatographic analyses were carried out with a Varian Model EP90 using 1/8-in. by 10-ft columns of Porpaq-P (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<sup>3</sup>/sec; retention times: water, 3.1 min; methanol, 3.7 min; methyl acetate, 7.1 min; acetic acid, 11.1 min. Mass spectrometric analyses for carbon-13 of the carbon dioxide obtained from combustion (8) were carried out in a CEC-620 mass spectrometer.

Acetic-<sup>13</sup>C<sub>2</sub> Acid—Methanol-<sup>13</sup>C (143 g, 4.36 mol, 91.3 mol % <sup>13</sup>C), water (120 g), rhodium trichloride (1.0 g, 0.005 mol), and 57% hydriodic acid (25 cm<sup>3</sup>) were placed in a 1-gal (U. S.), magnetically stirred autoclave of Hastelloy C

alloy. Carbon- $^{13}\text{C}$  monoxide (3.14 MPa, 440 psig, 4.47 mol, 91.6 mol %  $^{13}\text{C}$ , containing 6.1% methane<sup>\*</sup>) was added by cryogenic pumping utilizing a 300-cm<sup>3</sup> stainless steel cylinder and liquid nitrogen. The autoclave was electrically heated to 175° over a period of about 2 h and the pressure reached a maximum of 5.55 MPa (790 psig); the pressure decreased over the next 3 h to a constant value of 1.34 MPa (180 psig). After cooling to room temperature, the residual pressure (ca. 0.4 MPa, 40 psig) was vented through a Dry Ice trap, and the autoclave and trap contents were transferred to a distillation flask with several rinses of water. Following total distillation at ca. 50 kPa (400 Torr), the solution was redistilled at atmospheric pressure after addition of 5 cm<sup>3</sup> of 30% phosphorous acid and 5 g of silver sulfate. The forerun contained methyl- $^{13}\text{C}$  acetate- $^{13}\text{C}_2$  (8 g, 0.1 mol) [pmr:  $\delta$  3.4 ( $\text{CH}_3\text{O}-$ ,  $J_{\text{CH}} = 148$  Hz,  $J_{\text{COCH}} = 4$  Hz), 1.8 ( $\text{CH}_3\text{CO}-$ ,  $J_{\text{CH}} = 130$  Hz,  $J_{\text{CCH}} = 7$  Hz)], acetic- $^{13}\text{C}_2$  acid (12 g, 0.2 mol), and water (25 g), and the product fraction consisted of acetic- $^{13}\text{C}_2$  acid (243 g, 3.9 mol, 90% of theory) [pmr: Fig. 2] and water (135 g). Anhydrous acetic acid was obtained by treating the mixture with magnesium sulfate (1.25 g/g water), filtering and washing the hydrated solid with dichloromethane, and distilling the solution.

#### ACKNOWLEDGMENTS

The technical assistance of Mr. T. G. Sanchez is gratefully acknowledged. This work was performed under the auspices of the U. S. Energy Research and Development Administration.

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\* Methane (a by-product of the isotope enrichment processes) is inert to the reaction conditions.

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