# Preparation of Fully Deuterated Fatty Acids by Simple Method

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# ABSTRACT

An economical, simple, efficient system of deuterating saturated fatty acids at atmospheric pressure has been developed. Exchange is carried out between fatty acids and deuterium gas over palladium on charcoal catalyst at 195 C. The method was applied to even membered fatty acids containing from 6-14 carbon atoms. The method yielded perdeuterated fatty acids of high isotopic purity with no evidence of other reaction products.

# INTRODUCTION

Perdeutero fatty acids are in increasing demand for a variety of investigations. Preparation of perdeutero fatty acids from algae (1) or by some synthetic methods (2,3) is either expensive or inconvenient. Atkinson, et al., (4) reported palladium (Pd) catalyzed hydrogen exchange of several hydrocarbons at atmospheric pressure. Their method appeared simple enough and chemically plausible to apply to straight chain fatty acids. This article reports the results of a feasibility study. By an adaptation of the method of Atkinson, et al., (4) saturated straight chain fatty acids can be deuterated completely with relative simplicity and convenience.

# **EXPERIMENTAL PROCEDURES**

An Aerograph hydrogen generator, model A-650, was used to produce deuterium gas by the electrolysis of a 20% solution of KOD in  $D_2O$ . KOD solution was prepared by weighing and thinly slicing metallic potassium (Mallinckrodt, St. Louis, Mo.) on a piece of smooth ceramic tile in a nitrogen tent (Instruments for Research and Industry, Cheltenham, Pa.). The potassium slices in nitrogen atmosphere were washed free from kerosene with light petroleum ether and blotted with soft tissue paper. The potassium then was transferred to a shallow nickel dish on the shelf of a desiccator in the nitrogen tent. D<sub>2</sub>O (99<sup>+</sup>% D isotope) had been placed at the bottom of the same desiccator in a large dish (14 cm diameter). The desiccator was closed and provided with a pressure release device (Bunsen valve) to permit escape of the  $D_2$  reaction product. It took ca. 5 days for 50 g sliced potassium metal to be converted com-

pletely to a concentrated solution of KOD with 100 ml  $D_2O$ . The desiccator was stored in the nitrogen tent at room temperature during that period. The KOD solution was diluted with  $D_2O$  to give the desired (20%) concentration. The concentration was calculated from the wt of potassium metal and the volume of solution.

The deuterium gas generated was passed through a drying tower packed with granular anhydrous CaSO<sub>4</sub> before introduction into the reaction vessel. The gas flow rate was 35-40 ml/min. Pd on charcoal (5% or 10% Pd) (Matheson, Coleman, & Bell, Norwood, Ohio) was employed as catalyst. Catalyst (4 or 5 g) was added to 25 g caproic, caprylic, capric lauric, or myristic acid (Sigma grade, Sigma, St. Louis, Mo.) in a 50 ml Erlenmeyer flask. The reaction mixture: catalyst slurried in neat fatty acid, was stirred magnetically and heated in an oil bath (Fisher wax, mp 60 C) at 195 C ± 5 C. A cylindrical Pyrex container with a diameter of 8-9 cm, wrapped with heating tape (Electroflex, Heat, Bloomfield, Conn.) and insulted with a winding of asbestos strings, was adequate for an oil bath. An asbestos board was inserted between the oil bath and the magnetic stirrer to reduce heat loss and protect the magnetic stirrer. Temperature was controlled by a variable transformer between the mains and the heating tape. The reaction vessel was conntected to a water condenser and then (in series) to a chilled ethanol condenser (-30 C) to lower the rate of fatty acid loss by volatilization. Solid fatty acid was noticed in the alcohol cooled condenser when the cooling temperature was <-15 C. The alcohol chilled condenser was thawed once every 24 hr to drain out the condensed mixture of volatilized fatty acid and water. A series of fatty acids could be deuterated simultaneously, in series, to economize on the use of deuterium gas and to save time. Two dry ice-cooled cold fingers were used as traps between each fatty acid reaction mixture to safeguard against carry-over from one reaction mixture to the next. Glass joint apparatus with Teflon sleeves was used. Tight seals were required to prevent condensation of atmospheric water vapor in the system. The alcohol cooled condenser was designed with an outlet at the top for the deuterium gas to pass to the cold finger and also a trap with a needle valve at the bottom of the same condenser to drain out water condensed from moisture originally in the system. A Calrod (500 watt) heated tube filled with CuO, ar-



FIG. 1. Proton magnetic resonance (PMR) spectra of dodecanoic acid after varying times of deuteration. A-zero time; B-100 hr; C-194 hr. The spectra were obtained at 50 C under identical conditions of filter band width (4 Hz), radio frequency field (0.005 right, 0.02 left), sweep time (250 sec.), sweep width (250 Hz right, 1000 Hz left), and spectrum amplification (1.6 x 1 right, 1.0 x 10 left). Rel. Int. = relative intensity.

ranged according to Wiberg (5), was assembled to oxidize and recover the <sup>1</sup>H-diluted deuterium gas passing out of the last reaction vessel. However, the above mentioned arrangement often will not be necessary, because the consumption of heavy water was only ca. 100 ml in a 100 hr run.

The deuteration process was monitored by proton magnetic resonance (PMR) (Varian A-60D analytical NMR instrument) analysis. Samples were taken for analysis periodically with pasteur pipettes and Büchner filtered using extremely retentive filter paper (Carl Schliecher and Schuell, no. 576). Fatty acids that were solid at room temperature were Büchner filtered in an oven at temperatures 5-10 C above their mp, and the PMR measurements on these samples were taken at 70 C.

IR spectra were obtained from thin films of the neat acids with a Perkin-Elmer 2373 spectrometer.

Mass spectroscopy was carried out with a Hitachi RMU6D mass spectrometer.

Gas liquid chromatography (GLC) was carried out on methyl esters of the acids, employing a Hewlett-Packard research chromatograph 5750, and 10% diethyleneglycol succinate on



FIG. 2. Mass spectrum of exhaustively deuterated (194 hr) dodecanoic acid, obtained at 70 eV. Rel. Int. = relative intensity.

80-100 mesh Chromosorb W-BP. The methyl esters were prepared by the methanol- $BF_3$  method of Morrison and Smith (6).

## **RESULTS AND DISCUSSION**

The exchange of deuterium for hydrogen on the fatty acids takes several days for virtual completion under these conditions, but the reaction requires little attention once initiated. Different parts of the fatty acid molecule exchange at different rates. Figure 1 shows, as an example, how the PMR spectrum of dodecanoic acid changed progressively with deuteration. The peak at 6.2 ppm represents the -COOH proton. Of all the features of the original spectrum, this peak disappeared most rapidly on deuteration. The relative contributions of the different methylene protons also are seen to have changed after 100 hr (compare the top and middle curves).

The neutralization equivalent of caproic acid before deuteration was found to be 119 (Theory: 116). After deuteration, a neutralization equivalent of 135 was found (theory: 128). There is no indication here of appreciable reduction of the acid.

The major peaks in the GLC of the perdeutero esters were retarded in comparison with the perhydro esters. We saw no significant change in the chemical composition of the samples following complete deuteration.

IR spectra of the acids were obtained before and after deuteration. For example, the IR spectrum of deuterated caproic acid (neat) showed absorption bands of medium intensity at 1054, 1085, 1298, and 2100 cm<sup>-1</sup>; strong bands at 1357, 1710, and 2215 cm<sup>-1</sup>; a broad band of medium intensity at 2535 cm<sup>-1</sup>; and broad bands of low intensity at 2910 and 3425 cm<sup>-1</sup>. The following bands, apparent in perhydro caproic acid, were absent in the perdeutero compound: 935, 1105, 1235, 1280, 1412 (present but very weak), 1466, 2855, 2865, 2930, 2960 cm<sup>-1</sup>. Also absent in the perdeutero caproic acid spectrum was the broad absorption envelope from 3000-330 cm<sup>-1</sup>. The IR spectra observed were consistent with those reported by Jones (7) for perhydro and perdeutero fatty acids.

The mass spectra obtained for the perdeuterated fatty acids are exemplified by the fragmentation pattern of exhaustively deuterated dodecanoic acid shown in Figure 2. The pattern is qualitatively similar to that obtained from the perhydro-dodecanoic, with mass replacements of <sup>1</sup>H by <sup>2</sup>H in the fragments.

Caprylic and myristic acids were deuterated to the extent of  $\geq 95\%$  in 113 hr under the above conditions, starting with 24 g perhydro acids and 4 g 10% Pd on charcoal. The uncorrected yields of deuterated acids were 65% and 75%, respectively. We attribute losses to volatilization over the exchange period, withdrawal of samples for analysis, and mechanical losses in filtration. There were no obvious nonmechanical losses. In limited comparisons, the catalyst containing 10% Pd appeared to be more effective than that containing 5% Pd.

A higher temperature and a higher catalyst concentration might be expected to speed the exchange process. However, the practical temperature limit for this bath fluid was  $\sim 195$  C based upon volatility. The amount of Pd-charcoal catalyst is limited by the requirement of maintaining a reaction slurry sufficiently fluid that effective stirring can be achieved. Effective stirring is essential, since there exists the ultimate in heterogeneity: a three phase system composed of liquid fatty acid, solid catalyst, and gaseous D<sub>2</sub>.

In summary, we have shown that Pd cata-

lyzed deuteration of fatty acids occurs under preparatively feasible conditions. Since a similar method already has been shown effective for deuteration of hydrocarbons, the present procedure may be applicable for deuteration of additional classes of organic compounds.

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