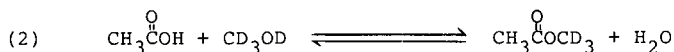
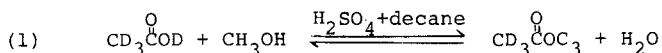


## A SIMPLE PREPARATION OF THE ISOTOPICALLY SUBSTITUTED METHYL ACETATES

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While undergraduates are taught that preparing esters is a straight forward matter, the synthesis of small quantities of volatile esters is often not easy.

Several years ago, Dr. Merez in this Department developed a partition method<sup>1</sup> for shifting the equilibrium in the Fischer esterification procedure. His strategy was to mix equimolar amounts of alcohol and ester in an inert organic solvent and treat this mixture with concentrated sulfuric acid. The sulfuric acid sequesters the water produced in the reaction and drives the reaction to completion.



We were in need of the specifically deuterated methyl acetates shown above. Methanol-d<sub>4</sub> is clearly the least expensive source of the methyl-d<sub>3</sub> ester function. Similarly, acetic acid-d<sub>4</sub> is the least expensive source of acetate-d<sub>3</sub>. The two-phase partition method seemed ideally suited to our needs. The two unanswered questions were: Does H<sub>2</sub>SO<sub>4</sub> catalyze H/D exchange of the enolizable acetate protons? Can methyl acetate be isolated pure in high yield?

Methyl acetate can indeed be isolated in high yield by bulb-to-bulb distillation from decane. Furthermore, isotope

exchange is not significant under these conditions: While initial experiments used  $D_2SO_4$  as catalyst, its failure to cause exchange in  $CH_3CO_2CD_3$  suggests that  $H_2SO_4$  would work as well.

Other isotopically substituted forms of acetic acid and methanol are now available<sup>2</sup>. We suggest that the approach described here is the method of choice for the synthesis of labelled methyl and acetate esters.<sup>3,4</sup>

#### EXPERIMENTAL

Methyl acetate- $d_6$ . Equimolar quantities of acetic acid- $d_4$  [ 0.96 gm, 0.015 mole; 99.5 atom %, Merck, Sharp and Dohme] and methanol- $d_4$  [ 0.54 gm, 0.015 mole; 99.5 atom %, Stohler Isotope Chemicals] were dissolved in 5 ml of decane in a 10 ml round bottom flask stirred magnetically. A catalytic amount (0.10 ml) of  $D_2SO_4$  [99.5 atom % D, Merck, Sharp and Dohme] was added. Separation to two phases occurred. The course of the reaction was monitored by observing the decrease in the volume of the lower acid layer. One hour at room temperature was sufficient to effect completion of the reaction. The organic layer was separated. It was washed successively with 1 ml portions of phosphate buffer (0.5M, pH 6.5), water, and saturated sodium chloride. It was dried over magnesium sulfate.

The ester was removed from the decane by bulb-to-bulb distillation. This involved attaching the flask containing the methylacetate in decane, and a clean, dry receiver, to two outlets of a small vacuum line. The former flask was frozen in liquid nitrogen and the line evacuated to 20-30 Torr. The dewar of liquid nitrogen was then moved to cool the receiver. The former flask was warmed to 40° with stirring. Care was

necessary in warming the flask to prevent frothing. The product methyl acetate-d<sub>4</sub> weighed 0.96 gm, 80% yield.

By glc (10'x 1/8" 10% DEGS on Chrom W 100/120 mesh), the methyl acetate contained less than 1% decane and no other chemical impurities. By mass spectrometry it contained less than 1% of the corresponding d<sub>5</sub> species.

Acetic-d<sub>3</sub>-acid methyl ester. Acetic acid-d<sub>4</sub> [1.00 gm, 0.016 mole] was mixed with an equimolar amount of methanol and treated with 0.10 ml D<sub>2</sub>SO<sub>4</sub> as above. The yield of acetic-d<sub>3</sub>-acid methyl ester was 1.01 gm, 82%. Both its chemical purity (glc) and isotopic purity (mass spectrometry) were greater than 99%.

Acetic acid methyl-d<sub>3</sub> ester. As above, 0.54 gm methanol-d<sub>4</sub> was mixed in decane with an equimolar amount of acetic acid, freshly distilled from acetic anhydride. D<sub>2</sub>SO<sub>4</sub> was used as the catalyst. The ester was obtained as above in 78% yield. The absence of detectable excess deuterium in the d<sub>3</sub> ester indicates that H/D exchange is not significant under these conditions.

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