

THE PREPARATION OF CHLORAL-1,2-¹⁴C HYDRATE

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SUMMARY

Chloral-1,2-¹⁴C hydrate was prepared by direct chlorination of labeled acetaldehyde in an overall 47% radiochemical yield. The reaction was carried out without a catalyst by heating at one temperature in a single stage reaction. No lower chloroacetaldehydes were detected.

Key Words: Chloral, Chlorination

INTRODUCTION

The comprehensive review of chloral chemistry⁽¹⁾ prompts us to communicate a preparation of labeled chloral hydrate. This material was required in tissue residue studies in our animal health program.

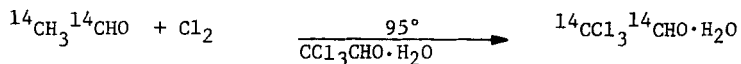
The synthesis of chloral-1-¹⁴C hydrate prepared by chlorination of ethanol-1-¹⁴C has been reported in the literature⁽²⁾ Following this method, we obtained chloral with a purity of 85-90%; the major impurities were chloral alcoholate and dichloroacetaldehyde. Modification of this procedure failed to increase the purity.

The chlorination of acetaldehyde was explored using procedures generally more suitable to large scale.^(3,4,5,6) Initial experiments gave mixtures of mono-, di- and trichloroacetaldehydes, plus large amounts of polymerization products. However, further adaptation, when applied to a 'hot run' gave chloral-1,2-¹⁴C hydrate from acetaldehyde-1,2-¹⁴C in 47% radiochemical yield. The product had a 99% radiochemical purity and a

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specific activity 7.49 mCi/mM.



DISCUSSION AND RESULTS

The reaction was carried out in the apparatus shown in Figure 1. The reaction vessel (R) containing carrier chloral hydrate and water was immersed in a 95° oil bath, with magnetic stirring (M). Chlorine was bubbled into the reactor through inlet tube B at such a rate that a slow reflux was maintained at the bottom of the dry-ice condenser A. Primary cooling was achieved by an ethylene glycol-water mixture circulated through condenser C by a refrigerated circulating bath.

Labeled acetaldehyde was transferred into trap T on a vacuum manifold and connected to gas inlet tube D by an 18/9 ball-socket joint. The labeled acetaldehyde⁽⁷⁾ was then transferred into the reaction vessel with a slow stream of nitrogen introduced through inlet N. Outlet E was connected to a scavenger trap containing dry-ice.

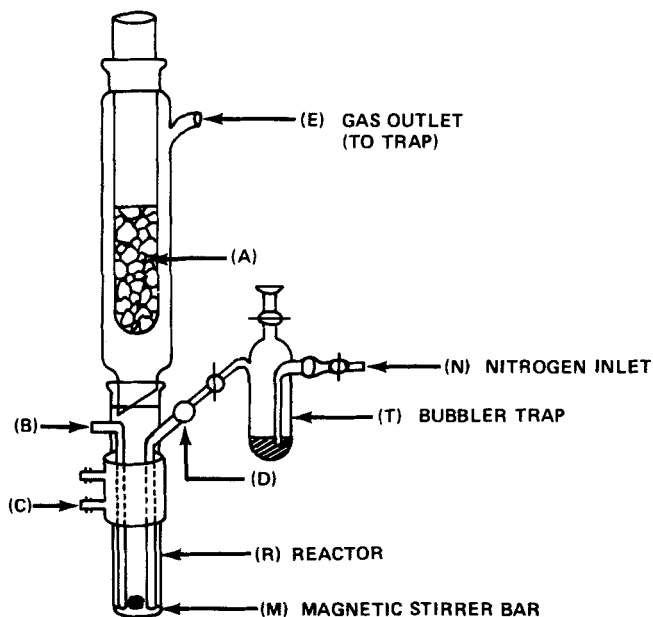


Figure 1. Apparatus for Chlorination of Acetaldehyde.

The use of the condenser C close to the reactor is essential to contain the volatile reactants and chloral hydrate in the reactor. Periodically, this condenser was warmed with steam to melt down the condensed product. A slow rate of addition of acetaldehyde-1,2-¹⁴C was essential to reduce the amount of polymerization by-product. The initial presence of unlabeled chloral hydrate in the reactor also diminished polymerization. It appeared that if the reaction mixture contained less than 50-60% chloral hydrate, polymerization increased. The polymeric by-product, removed during reaction work up, was quantitated throughout the reaction by thin layer chromatography ($R_f=0.0$, See Experimental).

EXPERIMENTAL

Gas chromatographs were taken on a Hewlett Packard chromatograph, model 5711, equipped with a 9'x2 mm column packed with 25% OV-17 on 80/100 mesh Chromosorb W.

Conditions: 60 ml/min. helium flow at 80 psi; 230°C injection port; 270°C hydrogen flame detector; 110°C oven. A Barber-Colman, series 5000 radio-activity exit monitor was connected to the gas exit by means of a splitter.

Radioscans were taken on a Varian-Berthold scanner, model 6000-10.

Conditions: Chart speed 10"/hr.; time const 10'; slit width 1 mm.

Chloral-1,2-¹⁴C Hydrate.

The reaction vessel R was charged with water (1.5 ml) and carrier chloral hydrate (1.5g, 9.06 mM) and then immersed in an oil bath heated at 95°. Chlorine gas was bubbled through the solution until a slow reflux was obtained. Acetaldehyde-1,2-¹⁴C (0.500 g, 11.36 mM; 227 mCi, 20 mCi/mM) was vacuum transferred into the bubbler trap T which was clamped to the reaction apparatus. A slow stream of nitrogen carried the acetaldehyde-1,2-¹⁴C into the reaction over 5 hours. Carrier acetaldehyde (0.200 g, 4.54 mM) was added to the bubbler trap and this was transferred to the reaction in the same manner. After a total of 9 hours the dry-ice cold finger was replaced with a water condenser and the reaction was heated (95°) for an additional 15 hours. Chlorine was continuously bubbled through the

reaction during this time. Periodically, chloral hydrate which collected on condenser C was melted down into the reaction mixture by passing steam through C.

The mixture was cooled and neutralized with saturated sodium bicarbonate solution and continuously extracted with diethylether for 20 hours. The ether was dried over magnesium sulfate and removed by distillation. The residual chloral hydrate (2.37 g, 58%) had a specific activity of 7.49 mCi/mM (107.3 mCi). The chemical purity was 99% as determined by gas chromatography. The chromatography of the product is shown in Figure 2 and that of a reference mixture of mono-, di- and trichloroacetaldehyde is shown in Figure 3.

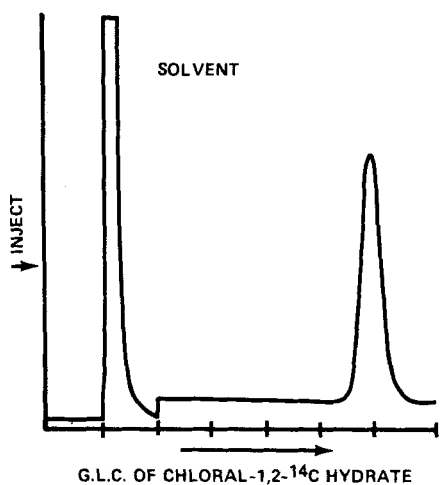


Figure 2.

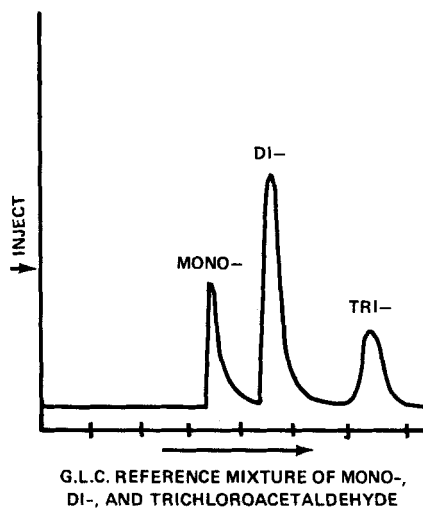


Figure 3.

By use of a radioactivity exit monitor the radiochemical purity was determined as 99%. The radioscan of a silica gel GF plate eluted with ether:ethyl acetate (50:50) showed the product to be homogenous ($R_f=0.5$). Polymeric by-products if present, appear at the origin ($R_f=0.0$) in this system.

The radioscan is shown in Figure 4.

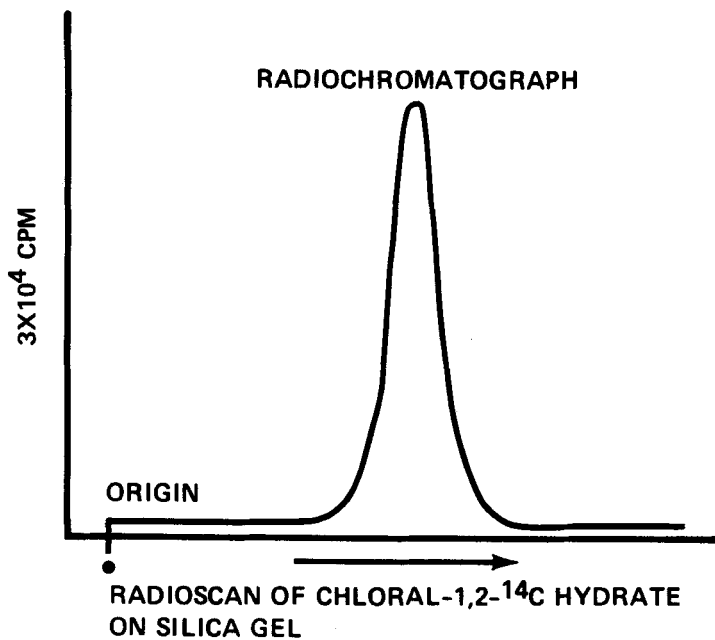


Figure 4. Radiochromatograph of Chloral-1,2-¹⁴C on Silica GF (ether:ethyl acetate (50:50)).

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