A CONVENIENT SYNTHESIS OF ETHYL-^{14}C-ISOCYANATE

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Alkylisocyanates react with several functional groups on proteins,[1,2] have been employed as active-site-specific reagents for serine proteases[3] and yeast alcohol dehydrogenase[4] and inhibit red-cell sickling.[5,6] A need for ethyl-^{14}C-isocyanate labeled at the isocyanate carbon atom for cellular studies at this university provided the impetus for its synthesis from sodium propionate-1-^{14}C. Starting labeled sodium propionate was chosen because of its availability and low cost and the ease with which it can be converted to ethylisocyanate through use of a modified Curtius[7] reaction. Further, owing to the physical properties of the reactants and expected by-products (sodium propionate, sodium azide, sodium chloride) facile purification of the isocyanate was allowed. Thus far the reaction conditions have not been optimized; there is evidence of an appreciable quantity of undistilled ethylisocyanate in the quenched pot residue. Even so the overall distilled yield of final compound ranged between 55-67%.

Starting sodium propionate-1-^{14}C* was dissolved in a 1 to 4 mixture of propionic acid and dry diglyme. The resulting solution was added to a large excess of propionyl chloride and allowed to equilibrate for 48 hours at 25°. Since we subsequently observed a nearly 1 to 1 incorporation of ^{14}C into the ethylisocyanate it would appear that essentially all ^{14}C label originally presumed to be present as propionic anhydride was equilibrated into the propionyl chloride. It is well known that a volatile acid chloride can be prepared from a mixed anhydride using benzoyl chloride.[8] The radiolabel in the formed propionic anhydride is similarly expected to be incorporated into the large

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excess of propionyl chloride; this equilibration likely is catalyzed by the HCl produced during anhydride formation.

The equilibrated acid chloride mixture was added dropwise to a stirred suspension of excess finely powdered sodium azide at 70° in diglyme over one and one-half hours. Radiolabeled ethylisocyanate was removed by concurrent distillation into a receiver held at -78°. A slow rate of addition was maintained to prevent foaming due to the evolution of nitrogen during the reaction. Through this method 21.9 μCi/mM of propionyl chloride solution derived from 1 mCi of sodium propionate-1-^{14}C (53 mCi/mM) was converted to 2.24g of ethylisocyanate having a specific activity of 19.2 μCi/mM.

Experimental

All solvents used were dried and distilled. Radioactivity was measured using a Packard Tricarb Model 3375 liquid scintillation spectrometer. Radiochemical purity was determined using the diethylurea derivative of the formed ethylisocyanate by thin layer chromatography using two solvent systems (tetrahydrofuran and 95% ethanol). Radioactivity on the thin layer chromatographs was monitored with a Baird-Atomic Beta Camera Model 6000. For proof of structure, NMR spectra were recorded using a Varian A-60-A spectrometer; IR spectra were recorded using a Perkin Elmer Model 257.

Preparation of the Propionyl-1-^{14}C Chloride Solution.-A solution of sodium propionate-^{14}C (1 mCi, 53 mCi/mM) dissolved in propionic acid (0.1ml) and dry diglyme (0.4ml) was added to propionyl chloride (5.0ml, 57.2mM). The resulting solution was stoppered and kept at 25° for 48 hours.

Ethyl-^{14}C-isocyanate.-The prepared propionyl chloride solution was added dropwise with stirring to 10ml of dry diglyme containing finely powdered sodium azide (14g., 216mMol) at 70° during 1 1/2 hours in an atmosphere of dry argon. After accumulation of sufficient ethylisocyanate concomitant distillation occurs and the distillate was collected at -78°. After the addition was complete the reaction mixture was stirred at 70° for an additional 1/2 hour. Subsequently, the oil bath was heated to 140° to obtain an additional

fraction of radiolabeled ethylisocyanate. Subsequent quenching of the pot residue with aqueous KOH afforded an appreciable quantity of labeled diethylurea. The yield of distilled ethyl-^{14}C-isocyanate based on starting propionyl chloride was 2.24g(55%)(19.2 μCi/mM).

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