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TRITIUM LABELLING OF ALKANES USING ORGANOALUMINIUM DIHALIDE CATALYSTS

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Recently a rapid and simple technique for the tritiation of various types of aromatic and olefinic compounds using organometallic halides as catalysts was described in detail.[1] The procedure involved the addition of ethylaluminium chloride, or one of a number of similar Lewis acid type halides, to the organic compound followed by a few microlites of high specific activity tritiated water (5 Ci g^{-1}). Labelling of most aromatic compounds and a number of alkenes was complete within a few minutes at room temperature. With these aromatic and olefinic compounds no significant byproduct formation accompanied the labelling except for a few polysubstituted aromatics such as the dibromobenzenes where some substituent migration was observed.[2]

The results previously discussed[1,3] implied that the technique was not satisfactory for the labelling of saturated hydrocarbons. We now report that recent detailed studies of the tritiation of a variety of alkanes show the technique to be applicable to many alkanes, in particular those containing tertiary carbon atoms, only a slight modification in reaction conditions (time and temperature) being necessary in some instances.

The use of relatively drastic conditions such as concentrated D_2SO_4 for the deuteration of tertiary alkanes, and liquid DBr/$AlBr_3$ for the deuteration of both straight and branched chain alkanes is well known.[4] Such deuteration procedures can be adapted for tritium labelling and are in contrast to the present tritiation technique where conditions are relatively mild, and the degree of tritium incorporation into the organic compound is frequently high. The trace amounts of high specific activity impurities of the type produced by the metal catalysed labelling procedure[5] are also not encountered.

The results of the tritiation of a number of compounds representative of various types of alkane are listed in the table. In each case ethylaluminium chloride (0.15 mmole) was added under a dry nitrogen atmosphere to the alkane (3.5 mmole) followed by high specific activity tritiated water (12.5 mCi, 5Ci ml^{-1}). The sealed sample was either stored at room temperature, or 96°. Samples were analysed by means of a gas chromatograph coupled to a radiation detector.

Labelling of both cyclic and non-cyclic alkanes was observed in every case where the molecule contained at least one hydrogen atom attached to a tertiary carbon atom. In general the degree of tritium incorporation was considerably enhanced by elevation of the reaction temperature to 96°. In contrast, of the alkanes studied, not one possessing only primary and secondary hydrogen atoms showed any significant tritiation at either room temperature or 96° (see footnote to table). The conclusion that the presence of a tertiary hydrogen atom is necessary if an alkane is to be labelled by this procedure is in accord with the ease of hydrogen exchange observed when alkanes are treated with strong acids.[4]

In most instances when labelling of the alkane occurred, some skeletal isomerisation to yield labelled byproduct was also observed. In the case of a substance which forms a particularly stable carbonium ion, such as 2,3-dimethylbutane, the degree of isomerisation was very low, and the small degree (5%) of active byproduct produced was thought to be due to the presence in the starting material of traces of alkenes which have been shown to label very readily by this technique.[1] With 3-methylpentane substantial conversion to either 2-methylpentane or 2,3-dimethylbutane, both of which form more stable carbonium ions, occurred. Likewise, considerable isomerisation of the dimethylcyclohexanes to a variety of isomers was observed. In such cases the degree of isomerisation was considerably greater at 96° than at room temperature with the result that, while the degree of tritiation of the parent compound was lower at room temperature the radio-chemical purity of the product was usually higher. In general it was possible to isolate pure labelled parent compound by gas chromatography and, in some instances, isolation of an isomerised product which possessed high specific activity was also possible, thus constituting a route to an otherwise unavailable labelled compound.

The results clearly show that the simple tritiation technique described is applicable beyond the aromatic and unsaturated systems previously studied, although reaction times greater than the few minutes required for aromatics[1] are necessary (footnote (d) in table). The observation that alkanes with tertiary hydrogen atoms may be labelled suggests the technique may be applicable to the labelling of more complicated molecules than have been used here, such as the ring systems of cholestane and saturated steroids. Investigations in this direction are continuing.

TABLE. Tritiation of Alkanes Using $EtAlCl_2/HTO$ [a]

Compound[c]	Activity of Compound[b]				Principal Active Byproducts
	70 hr at 23°		65 hr at 96°		
	$mCi\ mole^{-1}$	% Activity in Parent	$mCi\ mole^{-1}$	% Activity in Parent	
3-methylpentane[d]	150	21	790	38	2-methylpentane or 2,3-dimethylbutane
2,3-dimethylpentane[d]	410	44	1060	51	2,2,3-trimethylbutane
2,3-dimethylbutane	<20	-	1870	95	low molecular weight hydrocarbons
methylcyclohexane	<20	-	1440	88	low molecular weight hydrocarbons
ethylcyclohexane	<20	-	830	66	dimethylcyclohexanes
trans-1,2-dimethylcyclohexane	60	35	740	43	trans-1,4- and cis-1,2-dimethylcyclohexanes
cis-1,3-dimethylcyclohexane	270	83	770	68	trans-1,2-, cis-1,4-, cis-1,2-dimethylcyclohexanes
trans-1,3-dimethylcyclohexane	50	84	1400	65	trans-1,2-, cis-1,4-, cis-1,2-, cis-1,3-dimethylcyclohexanes
trans-1,4-dimethylcyclohexane	290	71	1000	65	trans-1,2-, cis-1,4-, cis-1,2-dimethylcyclohexanes

[a] Reagents: Organic compounds (3.5 mmoles), $EtAlCl_2$ (0.15 mmoles), HTO (0.14 mmoles, 12.5 mCi, 5 Ci g^{-1})

[b] A specific activity of 1000 mCi $mole^{-1}$ corresponds to 28% of available tritium

[c] In addition to the compounds listed the following alkanes showed no labelling at room temperature or 96°: n-hexane, n-heptane, 2,2-dimethylbutane, 3,3-dimethylpentane, cyclohexane, 1,1-dimethylcyclohexane

[d] Negligible labelling of 3-methylpentane and 2,3-dimethylpentane was observed after 3 minutes at room temperature.

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