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^{3}H N.M.R. STUDIES OF TRITIATION OF AROMATICS BY BORON TRIBROMIDE AND ALUMINIUM CHLORIDE CATALYSED TRITIATED WATER EXCHANGE

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The use of Lewis acid type catalyst systems as very rapid techniques for the deuteriation and tritiation of aromatic [1-3] and some aliphatic [4] compounds is of considerable interest for the production of labelled compounds. The methods utilise (i) C_6D_6 (or C_6H_5T) as the isotope source[1], or (ii) a trace of high specific activity tritiated water as the isotope source and also co-catalyst[2]. The latter procedure is not applicable to deuteriation since inadequate isotope levels are obtained. The distinction between the two procedures (i) and (ii) have been discussed in detail elsewhere[3].

Generally, the alkylaluminium halides have been described as the most effective of this type of catalyst but a number of other halides, such as $SbCl_5$, $NbCl_5$, $AlCl_3$, BBr_3, likewise catalyse the hydrogen isotope exchange[3]. Besides the considerable advantages of speed and experimental simplicity possessed by these labelling methods when compared with conventional heterogeneous[5] and homogeneous[6] metal exchange techniques, these procedures do not suffer from the same problems of side reactions, such as the production of biphenyl from benzene as experienced in heterogeneous platinum catalysed methods[7]. The problem of poor reproducibility observed in early deuterium exchange work with these Lewis acid catalysts[1] has been overcome by control of the water or HCl co-catalyst present in the exchange system[3]. Some substituent migration has been observed to accompany the exchange in a few polysubstituted aromatics[8].

Because of the speed with which equilibrium is attained in the methylaluminium chloride exchange systems with C_6D_6, detailed studies of the orientation of incorporated deuterium in organic products and the relative rates of exchange of various aromatic compounds have not been reported. Furthermore the absence of a satisfactory procedure for determining tritium orientation in a molecule precluded an adequate study of this aspect of the tritiated water labelling method. Indirect evidence suggests that tritiation of alkylbenzenes occurs randomly within the aromatic centre and is confined to the aromatic protons[3].

We now report the application of recently developed ^{3}H n.m.r. spectroscopy to a study of the tritium distribution within some aromatic molecules labelled by the Lewis acid technique together with a brief study of the relative exchange rate with C_6D_6 of a number of aromatics catalysed by aluminum chloride. The results show that exchange can follow normal electrophilic substitution patterns and may not necessarily be confined to the aromatic protons within an alkyl aromatic as previously suggested. ^{3}H n.m.r. has recently been used to demonstrate the pattern of tritiation of *alkanes* by an equivalent exchange procedure[9].

Table 1

TRITIATION OF SUBSTITUTED AROMATICS[a]

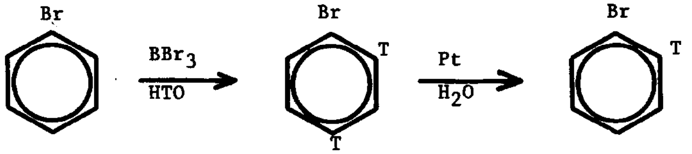
Compound	Catalyst	Activity (Ci.mole^{-1})	Percentage of Incorporated Tritium per site (position and %)				
Toluene	BBr_3	62	ortho 30,	meta <10,	para 40,	CH_3 <3	
Isopropylbenzene	BBr_3	345	ortho 18,	meta 5,	para 19,	CH 16,	CH_3 6
Bromobenzene	BBr_3	18	ortho 26,	meta <3,	para 47		
Naphthalene	BBr_3	40	α 38,	β 12			
Bromobenzene	$EtAlCl_2$	25	ortho 19,	meta 18,	para 25		
Bromobenzene	Pt	19	ortho <2,	meta 33,	para 33		

a. Reaction conditions: 0.1 ml organic, 0.05 g catalyst mixed and 0.05 ml HTO (5Ci.ml^{-1}) added. Tube sealed and held 70° for 12 hours.

Results summarised in Table 1 show the distribution of tritium in representative substituted aromatics labelled by the addition of BBr_3 followed by high specific activity tritiated water (50 µl, 5 Ci/ml) to the compound. Details of the procedure have been published[3]. Samples were allowed to stand overnight at 70° before analysis by radio-gaschromatography and ^{3}H n.m.r. (64 MHz Bruker WP60). For comparison purposes, a typical result with $EtAlCl_2$ and one with heterogeneous Pt catalysis is included.

In every aromatic nucleus where exchange is induced by BBr_3 the tritium is directed to those positions favoured in electrophilic substitution of the same molecules. This is in marked contrast to results with $EtAlCl_2$ where, in accord with previous predictions[3], labelling within the aromatic nucleus appears to be random. This observation, together with the considerable evidence[10] that charge transfer complexes exist between benzene and aluminium halides, indicates that exchange may occur while the aromatic is π-bonded to the metal atom. When this charge transfer is particularly strong, as in the case of $EtAlCl_2$ with an aromatic, the preference for ortho and para attack is no longer prevalent. It is necessary to utilise a more moderate catalyst, such as BBr_3, to achieve high specificity.

The pattern of the tritium within the aromatic nucleus also contrasts markedly with that typical of heterogeneous platinum exchange. The use of ^{3}H n.m.r. analysis of bromobenzene exchanged for 45 hours at 170° over platinum metal (conditions normally regarded as severe for heterogeneous platinum) demonstrates very clearly the extreme de-activation of ortho positions (Table 1) attributed to steric effects [11]. No tritium was detectable in the ortho position. Clearly the combined use of Pt exchange and BBr_3 exchange renders specific labelling within such a molecule a possibility.



The extent to which labelling in the side chain accompanies aromatic exchange in the presence of BBr_3 is more complex. Results to date, of which two examples are included in Table 1, toluene and isopropylbenzene, suggest that alkyl exchange is substantial where a tertiary hydrogen atom exists in the alkyl chain. This is analogous to the result published for alkanes themselves where it was demonstrated[4] that a tertiary hydrogen was necessary to obtain labelling with $EtAlCl_2$ and ^3H n.m.r. showed all positions within such an alkane contained tritium[9].

In support of the contention that exchange catalysed by Lewis acid type halides can show a pattern analogous to electrophilic substitution are the relative reactivities for exchange between a variety of aromatics and C_6D_6 catalysed by $AlCl_3$, summarised in Table 2. While the exchange was very fast and approaching equilibrium and thus not amenable to an orientation study by n.m.r. the overall pattern is that to be expected in an acid exchange system. Thus, for example, progressive substitution of halogen within the aromatic nucleus renders it increasingly unreactive.

Table 2

EXCHANGE OF AROMATICS WITH C_6D_6 CATALYSED BY $AlCl_3$[a]

Compound	Time (min.)	%D in aromatic positions[b]	No. of H Exchangeable[c]
Ethylbenzene	5	36	5
Chlorobenzene	30	26	5
Bromobenzene	30	14	5
Mesitylene	10	15	3
Biphenyl	40	40	10
3-methyldiphenyl	60	42	9
α,α,α-trifluorotuluene	120	nil	-
1,3,4-trichlorobenzene	120	nil	-

a. Reaction Conditions: organic 0.05 ml, C_6D_6 0.2 ml, $AlCl_3$ 35 mg, mixture held at room temperature.

b. Equilibrium %D assuming aromatic exchange only is 80% (approx.).

c. As shown by mass spec. distribution of D at equilibrium.

The results quoted demonstrate the considerable significance of ^3H n.m.r. in hydrogen isotope exchange studies, particularly the ability to measure accurate isotope levels in individual positions unresolved in proton n.m.r. spectra, by virtue of the fact that proton-decoupled spectra of tritium labelled molecules consist of sharp singlets[12]. Furthermore, the results quoted show that Lewis acid type labelling systems are capable of a higher degree of specificity and control by the experimenter than previously suggested.

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