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TRITIATION OF ORGANIC COMPOUNDS BY POLYMER-SUPPORTED BASE CATALYSTS

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SUMMARY

A range of organic compounds have been tritiated (and in some cases deuteriated) via hydrogen isotope exchange reactions using polymer supported base catalysts. The problem of poor thermal stability of some commercially available anion exchange resins, which limits their use as tritiation catalysts, has been overcome by the preparation of a more stable polymer supported pyridinium salt. The anion exchange resins are as effective at very high activities of tritiated water as they are at low and compounds containing nitro groups, which poison metal-catalysed exchange reactions, can be successfully labelled.

Key Words; Polymer supported base catalyst, hydrogen exchange, tritiation, ion exchange resins.

INTRODUCTION

In previous papers[1,2] we highlighted the potential and the advantages of using polymer supported acids, such as ion exchange resins, as catalysts in hydrogen isotope exchange reactions. The advantages demonstrated included, ease of separation of catalyst, facile isolation of tritiated products, and in some cases, unique selectivity in the regiospecificity of tritiation.

Bases, under homogeneous conditions have, if anything, been even more successful than acids in inducing hydrogen isotope exchange reactions[3,4]. In the present paper we explore the potential of using polymer supported bases, in the form of anionic exchange resins, to tritiate (and deuteriate) a

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range of organic compounds. The initial studies were concerned with the labeling of a number of model compounds using commercially available quaternary ammonium salts in their hydroxide form. Both gel form (low level of cross-linking) and macroreticular resins were employed. The same catalysts were then used to deuteriate two nitroaromatics that had previously been successfully tritiated[5,6] under aqueous alkali conditions, in order to compare the regiospecificities.

Subsequently, a polystyrene supported pyridinium hydroxide resin was synthesised in the hope that with its improved thermal stability, it could be employed to label some of the compounds which we had been unable to label initially. Finally, two compounds were chosen for tritiation with high specific activity tritiated water in order to see whether the catalysts continued to perform satisfactory with the much higher levels of radioactivity used.

RESULTS AND DISCUSSION

The properties of the polymer supported base catalysts, which were either purchased or synthesised, are given in Table 1. Although the maximum temperature at which the Amberlite 402 and Amberlyst A26 resins can be employed without decomposition is low and therefore restricts the range of compounds that can be labelled, the results in Tables 2 and 3 show that these encompass esters, ketones, hydrocarbons and nitroaromatics as well as the very weakly acidic dimethyl sulphoxide where, in effect, a highly basic medium has been created. The regiospecificity is never less than 100% and unlike a recently reported case[1], is the same as for the corresponding homogeneous labeling investigations. For the two nitro-aromatics, homogeneous labeling investigations [5,6] lead to the formation of intensely coloured purple or red solutions of σ complexes- in the present study the colour is confined to the surface of the catalyst.

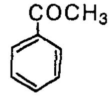
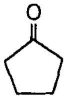
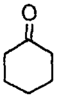
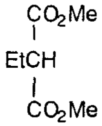
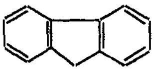
The number of compounds that could not be labelled (see footnote to Table 2) draws attention to the need to employ a more basic catalyst e.g. polymer supported organolithium reagents or the synthesis of a polymer supported base catalyst of high thermal stability. The present study is concerned with the latter approach. The extremely good thermal stability of pyridinium and related quaternary salts has

Table 1 Properties of Polymer Supported Base Catalysts

Catalyst	Polymer support	Type	Loading (dry,) (meq/g)	Cross-linking (%)	Decomposition Temperature (°C)[a]
Amberlite 402	PS-DVB	gel	4.3	6	60
Amberlyst A26	PS-DVB	macroreticular	4.4	>20	60
Resin I	PS-DVB	gel	2.0	1	>150[b]

[a]Refers to OH^- form [b]Ref 8

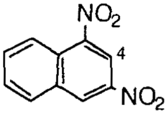
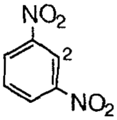
Table 2 Tritiation of model compounds by commercially available anion exchange resins[a]

Compound	Structure	Weight S/C[b] (mg)	Specific Activity (mCi /mmol)	^3H Chemical Shift (ppm)	NMR solvent	Position (Relative incorporation - %)
I		300/50[c]	11.50	2.55	$CDCl_3$	CH_3 (100)
II[d]		300/50	10.30	2.20	d_6-DMSO	α-CH_2 (100)
III[d]		300/54	11.40	2.24	d_6-DMSO	α-CH_2 (100)
IV	 $EtCH(CO_2Me)_2$	300/97[c]	9.30	3.48	d_6-DMSO	α-CH (100)
V	CH_3SOCH_3	300/100[c]	15.10	2.63	$CDCl_3$	CH_3 (100)
VI[e]		33/100	1.90	3.90	$CDCl_3$	CH_2 (100)

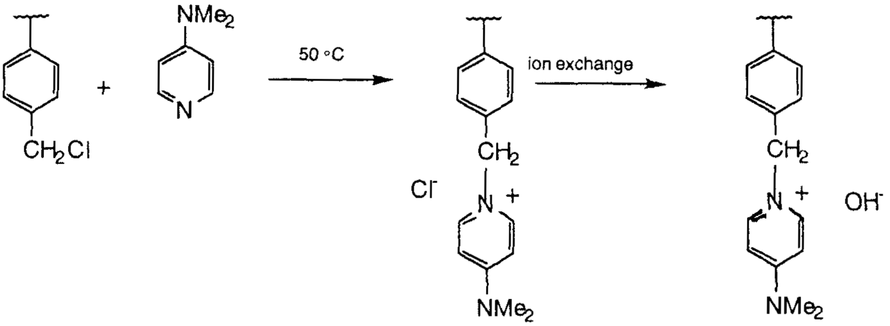
[a]All runs at 40°C/16h unless stated otherwise, with Amberlyst A26 as catalyst, using tritiated water of specific activity 3.4Ci cm^{-3}, $10^{-2}cm^3$) [b]S=substrate, C=catalyst [c]Amberlite 402 gave the same regiospecificities of labelling [d]25°C/24h [e]Reaction solvent 1,4-dioxane ($0.3cm^3$) [f]Following compounds did not label, triphenylmethane; 4-methylcatechol; 2-methylpyridine; 2-phenylpyridine; quinoline; pyridine-N-oxide; adipic acid.

led to their adaption as phase transfer catalysts[7] and recently Mulholland and coworkers[8] have used the hydroxide salts in nucleophilic reactions with ^{18}F at elevated temperatures. We therefore prepared a polystyrene bound pyridinium hydroxide moiety (Resin 1) by nucleophilic attack of 4-(dimethylamino)pyridine on a Merrifield resin (chloromethylated polystyrene) in accordance with the scheme:

Table 3 Deuteriation of Nitroaromatic compounds by Amberlyst A26[a]

Compound	Structure	Weight S/C[b] (mg)	Degree of Exchange (%)	^{2}H Chemical Shift (ppm)	Position (% Relative Incorporation)
VII[c]		21/100	53	9.02	4 (100)
VIII[c]		94/100	12	9.10	2 (100)

[a]Reaction conditions 40 °C/16h. In each case $0.1cm^3$ of D_2O were used. ^{1}H and ^{2}H n.m.r spectra were recorded in $CDCl_3$ and $CHCl_3$ respectively. Nitrobenzene and m-nitrobenzoic acid failed to undergo exchange [b]S=substrate, C=catalyst [c]Solvent : 1,4-dioxane ($0.5cm^3$)

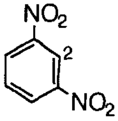
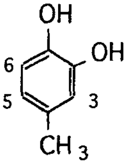
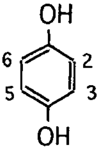
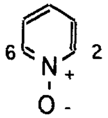


Resin 1

Scheme

This particular catalyst was able to tritiate a number of compounds (Table 4) such as phenols and pyridine-N-oxides that had failed to undergo exchange with either of the commercial anion exchange resins. These promising results suggest a more detailed investigation of its capability is warranted.

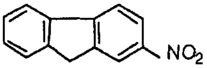
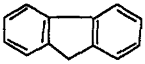
Table 4 Tritiation of Various Compounds using Resin 1 [a].

Compound	Structure	Weight S/C (mg)	T(°C)/h	Specific Activity (mCi/mmol)	^3H Chemical Shift (ppm)[b]	Position (% Relative Incorporation)
IX		160/100	100/18	1.5	8.81	2 (100)
X		105/100	100/18	3.9	6.63 6.46 6.68	3 (43) 5 (45) 6 (12)
XI		50/100	100/18	1.1	6.63	2,3,5,6 (100)
XII		76/100	120/120	1.7[c]	8.27	2,6 (100)

[a] All reactions conducted in solutions of the substrate in 1,4-dioxane ($0.5cm^3$) using tritiated water ($4Ci\ cm^3$, $10^{-2}cm^3$) Quinoline and baclofen failed to label [b] All n.m.rs recorded in d_6-DMSO [c] Using tritiated water of specific activity $20Ci\ cm^{-3}$, $2 \times 10^{-3}cm^3$.

Some catalysts are more susceptible to radiation damage than others and it is important that the findings at low specific activities can be repeated at higher levels. The findings in Table 5 confirm that this indeed is the case. For 2-nitrofluorene the specific activity of $5Ci\ mmol^{-1}$ was double that obtained when $AlCl_3$ was used as catalyst[9]. An attempt at transition metal catalysed exchange was unsuccessful, no doubt due to the poisoning effect of the nitro group. The specific activity in the case of fluorene itself was lower than for the nitro compound as the tritiated water had previously been used for the labeling of the latter. Finally, the two labelled products could be obtained at high radiochemical purity, a feature commented upon previously[2], and the amount of double labeling is consistent with the high specific activity of the tritiated water employed.

Table 5 High Specific Activity Tritiation of Fluorenes using Amberlyst 26[a]

Compound	Structure	Weight S/C[b] (mg)	T(°C)/h	Specific Activity (Ci/mmol)	^{3}H Chemical Shift (ppm)[c]	Position (% Relative incorporation)	RCP[d]
XIII		28/64	50/18	5.1[e] 4.8[f]	4.09 4.08	CHT (98) CT_2 (2)	84.4 (98.3)
VI		15/30	50/18	0.9[e]	3.89 3.86	CHT (>98) CT_2 (<2)	75.7 (99.1)

[a] Using tritiated water (ca. 12Ci, with a nominal specific activity of 1500Ci cm^{-3}). Reaction solvent was 1,4-dioxane-DMF (3:2, total 0.5cm^3) [b] S=substrate, C=catalyst [c] ^{3}H n.m.r spectra recorded in d_6-DMSO [d] Radiochemical purities of crude (and purified products) respectively [e] Determined from UV spectroscopy [f] Determined by mass spectrometry

EXPERIMENTAL

Commercially Available Anion Exchange Resins - Amberlyst A26 and Amberlite IRA 402 were obtained in their chloride form (Aldrich). Conversion to the hydroxide form was carried out by eluting one litre of 5% w/v NaOH per 100g resin down a column of the resin at a flow rate of 5cm^3min^{-1}, followed by distilled water until a neutral pH was obtained. The macroreticular resin was further washed with ethanol, diethyl ether and dried under vacuum at room temperature. Amberlite 402 was similarly dried, but in this this case no chemical wash was conducted. Attempts to eliminate all water from the polymers by storing at high vacuum in the presence of P_2O_5 led to both colour changes and a reduction in particle size, and so these resins were discarded.

Preparation of Resin 1 -Biobeads-SX1 of chloromethylated polystyrene (1.8% divinylbenzene, Bio-Rad Laboratories) were stirred in methanol for 15 minutes in order to allow the beads to swell. 4-(Dimethylamino)pyridine was added so that the pyridine and the chloromethyl functionality of the resin were in a 3:1 stoichiometric ratio, and the mixture was heated under reflux with stirring for 24 hours. The resultant solid was filtered off, washed with methanol and dried under vacuum at room temperature. The polymer contained 2.87% nitrogen and 3.48% ionizable chlorine corresponding to degrees of functionalisation of 82 and 79% respectively. Conversion to the hydroxide form was carried out in the same manner as that for the commercial resins.

Purification Of Substrates- Acetophenone, cyclopentanone, and cyclohexanone were distilled at atmospheric pressure and dimethyl sulphoxide at reduced pressure. Fluorene and triphenylmethane were recrystallised from chloroform-ethanol mixtures and the other compounds were used directly.

Hydrogen Isotope Exchange Reactions at Low Specific Activity - In a typical reaction, known amounts of substrate (see Tables), catalyst, solvent (if necessary) and tritiated water of the appropriate specific activity were introduced into a thick walled (5mm o/d) pyrex tube which was frozen, evacuated, flame sealed and placed in a thermostatted bath at the required temperature for a pre-determined time. On completion the tube was cooled, opened and the solution taken into diethyl ether (20cm^3) prior to washing with cold water (3 x 20cm^3) in order to remove the excess and labile tritium. The ethereal layer was then dried over magnesium sulphate, and the solvent removed by the use of a rotary evaporator to yield the crude labelled material.

Hydrogen Isotope Exchange Reactions at High Specific Activity -In this case tritium gas (which was stored in a uranium getter) was liberated by heating, and transferred to a small flask where it was reduced over platinium oxide to yield tritiated water. Known amounts of substrate, catalyst and solvent were introduced into a thick walled pyrex tube which was then cooled in liquid nitrogen, and attached to a vacuum line from where a known volume of high specific activity tritiated water was transferred. The subsequent procedure was similar to that used for the low specific activity tritiated water.

Analysis of Tritiated Products -The radioactivity was measured using a Beckmann LS 1801 Liquid Scintillation Counter, a 4% w/v solution of 2,5-diphenyloxazole in toluene being the scintillation cocktail. For the low level tritiations the specific activities were determined by counting aliquots of solutions containing known amounts of substrate. For the high level tritiations the concentrations were determined spectrophotometrically, or the specific activities were measured directly with the use of a Kratos MS25 Rf mass spectrometer operating in the electron impact mode at 70eV.

The radiochemical purities were determined (a) in the case of liquids by radio-gas chromatography (Carlo-Erba 4200 chromatograph equipped with a polarised ion chamber detector) and (b) in the case of solids by radio-thin layer chromatography (Le Croy 8013A TLC linear analyser). The regiospecificity of the labeling procedure was obtained via the ^2H and ^3H n.m.r spectra which were recorded on a Bruker AC300 FT Spectrometer operating at 46 and 320MHz respectively with broad band proton decoupling. ^1H n.m.r spectra were obtained at 300MHz.

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