Applications of a Polymer-supported Acid Catalyst to Tritiation Studies: Implications Concerning Reaction Mechanisms

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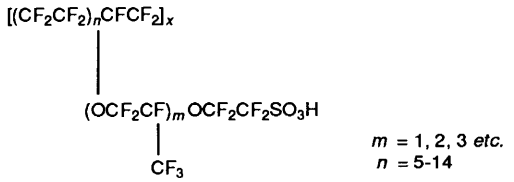
Application of ^3H NMR spectroscopy to the determination of the regiospecificity of acid-catalysed hydrogen–tritium exchange of a number of heterocyclic and aromatic compounds under homogeneous (trifluoromethanesulphonic acid) and corresponding heterogeneous conditions (Nafion) serves to highlight different mechanistic features and the advantages of using the latter kind of catalyst for the preparation of tritiated compounds.

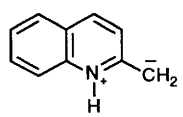
As the realisation dawns that polymer-supported catalysts offer many advantages over their homogeneous counterparts, notably improved yields, ease of recovery, simplified work-up, improved selectivity and mild reaction conditions, their use is becoming more widespread.[1] Here we illustrate their application in one of the more demanding and, as yet relatively unexplored, areas,[2,3] namely in the preparation of radioactive (in our case tritiated) compounds.

Acid-catalysed hydrogen isotope exchange is one of the most widely used methods of preparing tritiated compounds[4] and as triflic (trifluoromethanesulphonic) acid is one of the strongest acids known (H_0 *ca.* −14.6) the availability of its heterogeneous counterpart, Nafion resin **1**, provides an excellent opportunity of assessing its potential in this area. Furthermore the availability of ^3H NMR spectroscopy[5] to delineate the pattern of labelling under both homogeneous and heterogeneous conditions provides a unique opportunity of comparing the reaction mechanisms that pertain in these circumstances. A number of heterocyclic as well as aromatic compounds, both activated and deactivated, were chosen as substrates and the results obtained are summarized in Table 1.

Different regiospecificities imply that different mechanisms are operative and that these are related to the acidity. Previous studies[6] of acid-catalysed hydrogen isotope exchange of quinoline at elevated temperatures (182–245 °C) in D_2SO_4 (covering the acidity range from pH 0.5 to D_0 −9) show that only the 5, 6 and 8 positions undergo exchange, with the C-8(H) being the most reactive. These results are similar to



1, Nafion

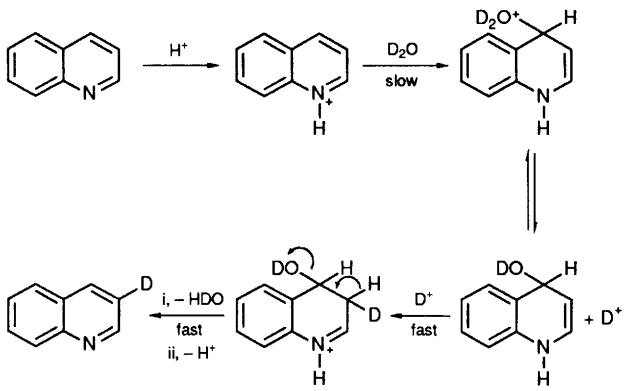


2, Ylide intermediate

Table 1 Tritiation of heterocyclic and aromatic compounds under homogeneous (triflic acid) and heterogeneous (Nafion NR50 beads) conditions

Substrate	Conditions		Pattern of tritiation (rel. incorporation)	Conditions[b]		Pattern of tritiation (rel. incorporation)
	Homogeneous	*T*/°C, *t*/day		Heterogeneous	*T*/°C, *t*/day	
Quinoline	0.2 g + 1 ml[a]	90, 6	5 (25%) 8 (75%)	0.2 g + 20 mg[a]	140, 8	3 (100%)
	0.2 g + 1 ml[a]	140, 5	5 (39%) 8 (58%) 6 (3%)	—	—	
	0.2 g + 1 ml[a]	180, 9	5 (43%) 8 (51%) 6 (6%)	—	—	
6-Nitroquinoline	0.03 g + 1 ml[a]	140, 14	Very low incorporation	0.2 g + 20 mg[a]	180, 9	3 (100%)
4-Methylquinoline	0.3 g + 0.5 ml[a]	180, 4	3 (15%) 5 (21%) 6 (34%) 8 (30%)	0.3 g + 20 mg[a]	180, 4	Me (94%) 3 (4%) 2 (1%) 6 (1%)
4-Methylpyridine	0.2 g + 0.2 ml[a]	180, 4	Me (100%)	0.2 g + 20 mg[a]	180, 4	Me (100%)
2,4,6-Collidine	0.2 g + 0.2 ml[a]	140, 8	2,4,6-Me (100%)	0.2 g + 20 mg[a]	140, 5	2,4,6-Me (100%)
	0.2 g + 4 ml[a]	180, 5	3,5 (100%)	—	—	
Toluene	0.2 g + 5 ml[a]	25, 1	2,6 (29%) 3,5 (64%) 4 (6%)	0.4 g + 20 mg[a]	90, 2	2,6 (64%) 3,5 (6%) 4 (30%)
o-Toluidine	0.2 g + 0.5 ml[a]	100, 4	3 (19%) 4 (23%) 5,6 (58%)	0.2 g + 50 mg[a]	100, 4	3 (43%) 5 (57%)
Chlorobenzene	0.2 g + 0.5 ml[a]	90, 4	Decomposes	0.2 g + 20 mg[a]	180, 9	2,6 (35%) 3,5 (43%) 4 (22%)

[a] Catalyst. [b] Typically the substrate, catalyst and tritiated water (5 Ci ml^{-1}; 5–10 μl) were placed in a narrow thick-walled glass tube, cooled in liquid nitrogen and evacuated prior to sealing. On completion the cooled contents were extracted into diethyl ether. After washing to remove labile tritium, the solution was dried (anhydrous Na_2SO_4) and the solvents removed. The radioactivity of the substrate gave total incorporations in the range 0.1–10 mCi such that specific activities of the order of 1–10 mCi mmol^{-1} are obtained. ^{3}H NMR (^{1}H decoupled) spectra were obtained at 320 MHz, and the ^{1}H NMR spectra remained unchanged.



Scheme 1 Hydrogen exchange of quinoline at C-3 by covalent hydration

those obtained by us using triflic acid and are consistent with a mechanism that involves electrophilic attack on the conjugate acid. The same authors[6] found that at lower acidities (from pH 0.5 to H_0 −3) exchange of the 5, 6 and 8 hydrogens decreases whilst that of the 2 and 3 hydrogens increases. Isotopic incorporation at C-3 proceeds through covalent hydration and the specific tritiation witnessed using the Nafion catalyst indicates that this mechanism is operative under the heterogeneous conditions (Scheme 1).

Deactivated quinolines such as the 6-nitro compound are more readily labelled using the heterogeneous catalyst and methyl substituted quinolines are virtually specifically tritiated in the methyl group in contrast to the situation pertaining under homogeneous conditions where the pattern of labelling is similar to that observed with the parent compound. When exchange into the methyl position takes place under aqueous conditions, base-catalysed deprotonation *via* an ylide intermediate **2** is invoked.[7] The results therefore show that for the quinolines, mechanisms associated with the Nafion catalyst are different from those observed for triflic acid and are more in line with those experienced at lower acidities.

Although pyridine itself is difficult to label with both triflic acid and Nafion at 180 °C the pattern of labelling witnessed for methyl-substituted pyridines is the same for both catalysts, namely specific incorporation into the methyl groups(s). However, increasing the concentration of triflic acid at the expense of substrate can alter the regiospecificity and is consistent with earlier findings[8] on the deuteriation of collidine in D_2SO_4. The main advantage of the Nafion catalyst for these compounds is the ease with which the labelled substrates can be isolated, contrasting markedly with the difficulties experienced in isolating free bases from neutralised triflic acid.

Finally, for the three aromatic compounds investigated: (*i*) toluene is labelled in the ring by both catalysts; (*ii*) for *o*-toluidine the Nafion catalyst is more sensitive to substituent effects; and (*iii*) Nafion-induced exchange is possible for chlorobenzene whereas in triflic acid it decomposes at temperatures as low as 90 °C.

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