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Short Research Article

Investigations of isotope scrambling during the deuterodechlorination of *ortho*-chloroacetanilide†

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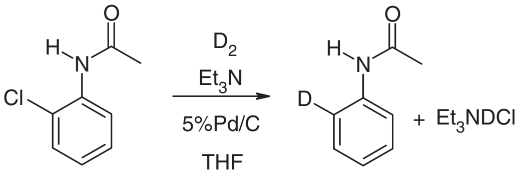
Introduction

The dehalogenation of haloaromatics is a facile and common approach to labelling organic compounds with hydrogen isotopes. However, the dehalogenation of haloaromatics frequently yields low atom% abundance due to isotopic scrambling at the labelled site. The behaviour is particularly acute with chloroaromatics. A few studies have attempted to investigate the parameters controlling this behaviour but usually with only partial success.[1a–c] Recently the observation of a large deuterium isotopic effect in ortho-deuterated anilides[2] provided a simple method with which to study this scrambling by ^{1}H-NMR.

Results and discussion

The model reaction chosen was the deuterodechlorination of *ortho*-chloroacetanilide (Scheme 1).



Scheme 1

Initial screening of a range of palladium catalysts for maximum isotopic labelling (still only ca. 80%D in the best case) whilst maintaining a deficiency of D_2 gas defined the test reaction: *ortho*-chloroacetanilide (0.5 mmol), 5% palladium on carbon paste (Aldrich 26,670-7, 30 mg) and triethylamine (100 µl) in THF (2 ml) with D_2 (0.36 mmol) at ambient temperature and pressure.

In common with previous work the current (extensive) studies failed to identify all the processes involved in this complex scrambling process. However some interesting observations were made and useful conclusions can be drawn.

N-deuteration of the substrate showed that the scrambling probably did not arise from the amide NH. Perhaps surprisingly, addition of D_2O to the system showed only a small increase in %D in the product, whilst addition of H_2O showed no obvious decrease. Addition of drying agents or use of newly dried solvent had no effect. ^{2}H-NMR studies, using excess D_2, showed the formation of exchangeable[3] deuteron signals with time (these corresponded to amide ND and HOD/Et_3NDCl resonances only: there was no detectable labelling of the solvent or triethylamine α- or β-protons)[‡] but the rate was slow compared with the dehalogenation reaction and, significantly, was unrelated to the %D of the *o*-deuteroacetanilide product, which proved essentially constant from the earliest sampling point (1 h, 18% reaction) to the completion of the dehalogenation reaction at (5 h, 100% reaction). However, very significant decreases in %D (43 and

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49%) were observed when delays of 7 and 18 h were introduced before the addition of the substrate, or if the rate of the dehalogenation was decreased by addition of 0.004 mol/mol of iodobenzene (a catalyst poison for dehalogenation, reduction from 80%D to 21%D). In these cases the competing H_2O/D_2 isotope equilibration could well have been the dominant process leading to the very low %D achieved. Given the known[3b] fractionation of H_2 isotopomers on Pd it is possible that even minor H/D exchange processes could lead to an over-representation of the key (i.e. reactive) HD or H_2 on the catalyst and hence to scrambling in the product.

Studies are continuing. However, in view of our results it would seem advisable to: (a) avoid methanol as solvent; (b) ensure that the rate of any target dechlorination reaction is maximized before finally resorting to the labelling step; (c) ensure that the substrate is present in the reaction before the addition of the isotopic hydrogen to avoid dilution via scrambling with adventitious water; (see footnote ‡);[3] (d) be aware of the profound effect on isotopic incorporation of poisoning by iodoaromatics or intramolecular iodine substituents.

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