Applying Splitting Patterns in ^1H NMR to Evaluate a Reaction Mechanism

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Abstract

This experiment provides second semester organic chemistry students with direct experience preparing and running an NMR sample, to experimentally confirm a reaction mechanism and to strengthen the students' ability to interpret splitting patterns with ^1H -NMR spectra. This experiment makes use of the reduction of a ketone, 3-hydroxyacetophenone, to an alcohol, 3-hydroxy-1-phenylethanol using sodium borohydride (NaBH_4) or sodium borodeuteride (NaBD_4). Each pair of students performs a reduction reaction with either protonated or deuterated conditions. Pairs of students then combine into groups of 4 to compare spectral data. Students observe the change in the splitting pattern caused by deuterium incorporation into the alcohol product and confirm the reaction mechanism.

Introduction

Deuterium labelling experiments are often utilized as an analytical and research tool. There are numerous examples of research articles that make use of deuterium transfers experiments to explore reaction mechanisms, probe stereochemistry and explore reaction kinetics. The technique has application in many specialties of chemistry including drug development and protein biochemistry. However, it is usually not emphasized at the undergraduate level.

In this experiment, students perform a reduction of 3-hydroxyacetophenone using either NaBH_4 or NaBD_4 , compare the NMR spectra of the products, locate the hydrogen from the reducing agent on the product and explore how deuterium incorporation into the product changes the spin-spin splitting pattern of the product. The product, 3-hydroxy-1-phenyl ethanol, is a solid at room temperature making purification simple, quick and efficient, representing a significant improvement on similar experiments that generate liquid products.

Scheme 1. In the first step, hydride ($:\text{H}^-$) detaches from BH_4^- and attacks the carbonyl carbon. Pi-electrons simultaneously move onto oxygen to form the alkoxide ion. In the second step, the non-bonding electrons on oxygen pick up a proton from solvent as the ion is neutralized with acid.

Experimental Overview

The reduction mechanism proceeds in two steps (Scheme 1): In the first step, hydride ($:\text{H}^-$) detaches from BH_4^- and attacks the carbonyl carbon. Pi-electrons simultaneously move onto oxygen to form the alkoxide ion. In the second step, the non-bonding electrons on oxygen pick up a proton from solvent as the ion is neutralized with acid.

Pairs of students perform the reaction shown in Scheme 2. The instructor then pairs two groups. One group has the protonated NaBH_4 and the second group has the deuterated NaBD_4 . Deuterium requires different operating conditions for NMR and is therefore silent under the condition of ^1H -NMR. The coupling constants for proton-deuterium splitting are very small. When H and D are on adjacent carbons, the H-D coupling is negligible. When deuterium is present in the sample, it will not show up on the spectrum and will not split its neighbouring protons.

At this point, students propose a mechanism for the reaction with the understanding that hydrogen originates from NaBH_4 and appears on the same carbon as the alcohol. The hydrogen that originates from hydride presents as a quartet when split by the 3 neighbouring protons and the three neighbouring protons on the methyl present as a doublet when split by their single neighbour (Figure 1A).

Scheme 2. The reduction of 3-hydroxyacetophenone with NaBH_4 .

Results

As shown in Figure 2, when NaBH_4 is used, the NMR spectrum of the product contains a quartet and doublet. When the reaction is carried out with NaBD_4 , the NMR spectrum of the product shows no signal for deuterium and the neighbouring (methyl) protons present as a singlet. The aromatic peaks remain the same in both sets of spectra.

The disappearance of the peak at 4.81 ppm proves that hydride (or deuteride) originating from NaBH_4 (or NaBD_4) attacks the carbonyl as shown in Scheme 1. Since all other components of the experiment are protonated, the hydride must originate from NaBH_4 .

In the laboratory report, students are asked to reflect on previously learned interpretation skills, correlate the effect of deuterium on spin-spin splitting and make a judgment to determine how deuterium incorporation affects the spin-spin splitting of neighboring protons.

Figure 1. A. When the hydride originates from NaBH_4 , the peak presents as a quartet when split by the 3 neighbouring protons. The 3 methyl protons present as a doublet when split by their single neighbour. B. If deuterium is incorporated into the final product, the peak from deuterium is silent and its neighbour, the methyl protons, are no longer split.

Discussion

This experiment gives second semester organic chemistry laboratory student's hands-on experience with NMR. It reinforces concepts of chemical shift and spin-spin splitting learned in lecture and introduces deuterium transfer as a tool to deduce a reaction mechanism. The reaction utilizes a ketone whose product remains a solid at room temperature, making for a quicker and more successful isolation of the product. This allows much greater student success in carrying out the experiment and more time can be spent on the NMR interpretation and mechanistic aspects of this experiment.

Figure 2. A. NMR results show a quartet (4.81 ppm) and doublet (1.42 ppm) when NaBH_4 is used. B. There is no signal for deuterium and neighbouring (methyl) protons present as a singlet (1.42 ppm) when NaBD_4 is used. The aromatic peaks remain the same.

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