25/02/2022

NMR Spectroscopy

1. Fundamental aspects of NMR spectroscopy

   a. Consider a sample in an NMR spectrometer with magnetic field B_0. For the protons (^{1}H) in this sample, there are two spin states of interest – α (aligned with B_0) and β (aligned against B_0). The relative populations of the two spin states (N_α and N_β) are described by a Boltzmann distribution. Calculate N_α-N_β, assuming that the sample is at room temperature in a 400 MHz instrument.

   b. Generally speaking, ^{13}C NMR is a less sensitive technique than ^{1}H NMR. Explain why this is the case and describe how sensitivity issues with ^{13}C NMR are overcome.

   c. NMR spectra for quadrupolar nuclei can be quite poor. Paramagnetic compounds tend to give even worse spectra, even for spin-½ nuclei. Why are these kinds of spectrum generally of low quality?

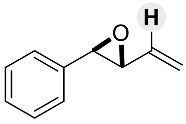
   d. Modern NMR spectroscopy is almost exclusively Fourier-transform NMR (FT-NMR). Briefly explain what the Fourier transformation does.

   e. For quantitative NMR (qNMR), it is generally advisable to measure the relaxation time (T_1) for all nuclei of interest, and then set the delay time for your experiments as 5xT_1 for the longest T_1 value. Why is this delay time suggested?

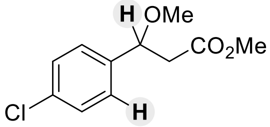
   f. Why might it be beneficial to change the spectral width (SW) and offset (O1P) parameters when running an NMR experiment?

2. Structural and stereochemical assignment

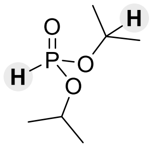
   a. Estimate all coupling constants for the protons indicated below.



1

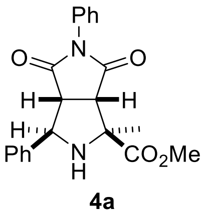


2

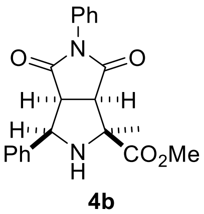


3

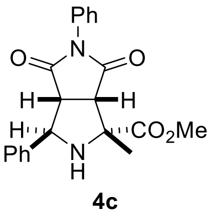
   b. Consider the three diastereoisomers shown below. Which of these compounds matches the data provided?



4a



4b

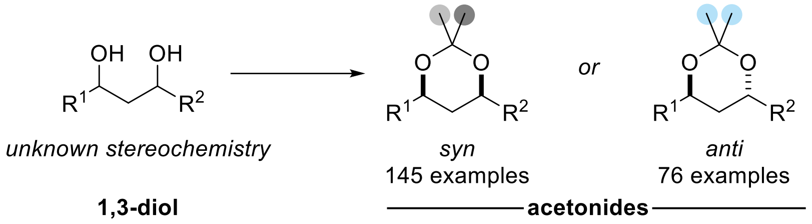


4c

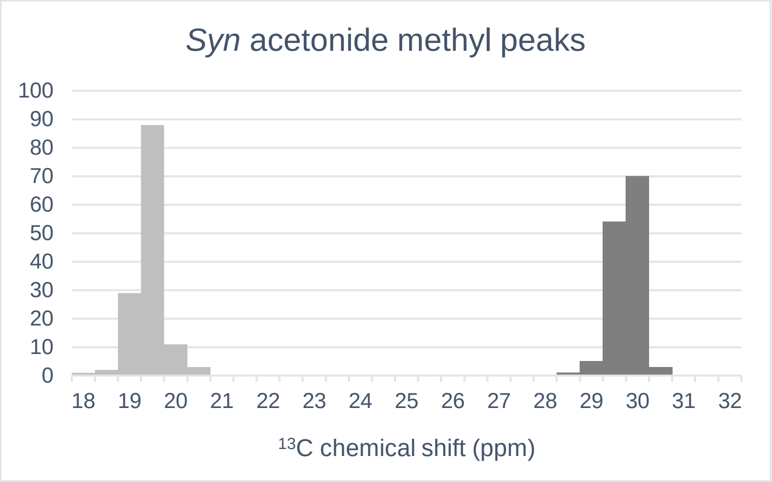
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.18 (m, 8H), 7.01-6.98 (m, 2H), 4.81 (d, *J* = 9.1 Hz, 1H), 3.80 (s, 3H), 3.61 (dd, *J* = 9.1, 7.7 Hz, 1H), 3.37 (d, *J* = 7.6 Hz, 1H), 2.59 (br s, 1H), 1.58 (s, 3H).

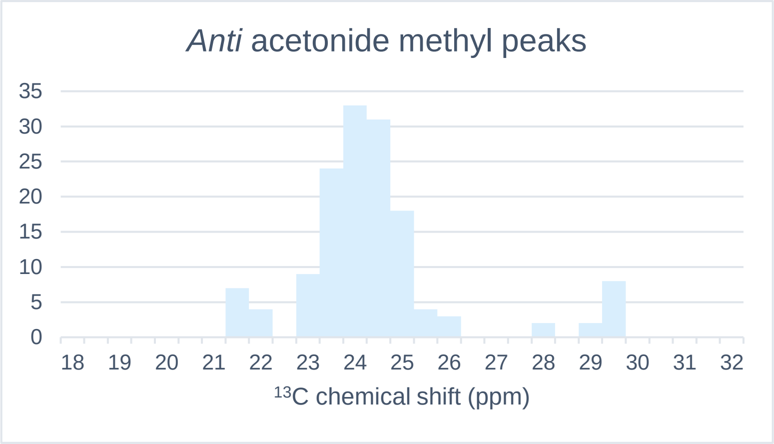
NOESY interactions: 4.81, 3.61 (5%)
3.61, 3.37 (8%)
3.37, 1.58 (6%)

   c. The 1,3-diol motif is present in a wide variety of natural products, and is frequently protected as the corresponding acetonide for ease of purification and characterisation. Using a database of ^{13}C NMR spectra for acetonides reported in the literature (see overleaf), the Rychnovsky group have shown that the relative stereochemistry of an acetonide (*syn* or *anti*) can be determined using the ^{13}C chemical shifts corresponding to the methyl groups (highlighted).



J. Org. Chem., **1993**, *58*, 3511

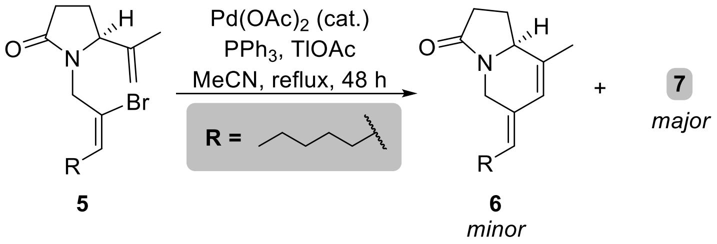




i. Explain how this data can be used to assign the relative stereochemistry for a given acetonide.

ii. Suggest why the distributions of chemical shifts differ for *syn* and *anti* acetonides.

d. Consider the palladium-catalysed reaction shown overleaf. The desired Heck product, **6**, was a minor component of the reaction mixture. Identify the major product, **7**, from the NMR data provided. Propose a mechanism for the formation of **7** (N.B., TlOAc is believed to act as a bromide scavenger, and was added to the reaction mixture to facilitate elimination).



^{1}H NMR (500 MHz, CDCl$_3$): δ 5.43 (dt, *J* = 15.5, 6.6 Hz, 1H), 5.32 (d, *J* = 15.5 Hz, 1H), 3.93 (t, *J* = 7.2 Hz, 1H), 3.72 (d, *J* = 11.4 Hz, 1H), 3.11 (d, *J* = 11.4 Hz, 1H), 2.62 (m, 1H), 2.38 (ddd, *J* = 16.9, 10.0, 2.1 Hz, 1H), 2.18 (m, 1H), 2.03 (m, 2H), 1.74 (m, 1H), 1.31-1.22 (m, 6H), 1.09 (s, 3H), 0.87 (t, *J* = 6.9 Hz, 3H), 0.56 (d, *J* = 5.9 Hz, 1H), 0.46 (d, *J* = 5.9 Hz, 1H).

NOESY interactions: 1.09*, 3.93 (8%)
1.09*, 5.32 (6%)
**selectively irradiated*

J. Chem. Soc. Perkin Trans. 1, **2000**, 1129

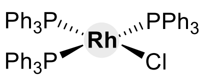
^{13}C NMR (75 MHz, CDCl$_3$): δ 175.9, 132.3, 127.5, 67.3, 58.2†, 35.1, 33.8, 33.4, 29.9, 24.1, 23.1, 17.2, 14.7, 14.6.**

†*peak mis-reported in paper - this value is estimated based on ChemDraw predictions*

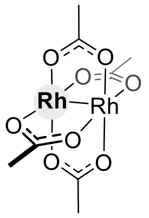
***two peaks appear to be missing - both estimated in the range of 30-32 ppm*

3. Mechanistic experiments

   a. Although ^{103}Rh is a spin-½ nucleus with 100% natural abundance, it has a very small gyromagnetic ratio and frequently displays very long relaxation times. Suggest a strategy for measuring the ^{103}Rh chemical shifts for each of the two complexes below.

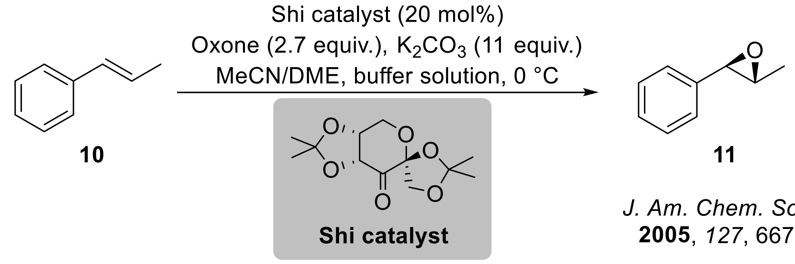


8
^{103}Rh δ = -1291 ppm (CD$_2$Cl$_2$)

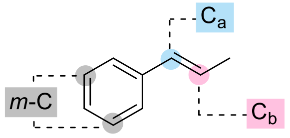


9
^{103}Rh δ = 7301 ppm (CD$_3$CN)

   b. The Shi epoxidation shown below was allowed to run to high conversion and quantitative ^{13}C NMR spectra were taken of the recovered starting material, **10**. Relative to the *meta*-carbons highlighted, the alkene carbons each integrated to give a value greater than 1. Explain this observation.



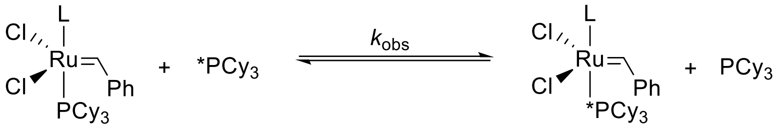
J. Am. Chem. Soc., **2005**, *127*, 6679

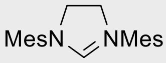


	integrations*		
conversion	*m*-C	C$_a$	C$_b$
83±1%	2.000	1.009	1.039
93±1%	2.000	1.016	1.052

**6-experiment average*

c. In order to understand the mechanism(s) by which Ru olefin metathesis catalysts operate, a series of ^{31}P NMR experiments were carried out (see below).



L	cat.	k_{obs}(80 °C) (s^{-1})	$\Delta S^{\ddagger}$ (e.u.)
PCy_3	**12a**	9.6 ± 0.2	12 ± 2
	**12b**	30 ± 2	13 ± 1

J. Am. Chem. Soc., **2001**, *123*, 6543

i. The rate of phosphine exchange was first examined using VT-NMR, and found to be slow even at 100 °C. What would you expect to observe for fast exchange?

ii. Measurement of the rate of phosphine exchange was achieved using magnetisation transfer (MT). Briefly explain how this can allow the exchange to be measured.

iii. By varying the temperature of the MT experiments, an Eyring plot was generated. From the Eyring analysis, the phosphine exchange was shown to have large positive $\Delta S^{\ddagger}$ values. What does this imply about the reaction mechanism?