



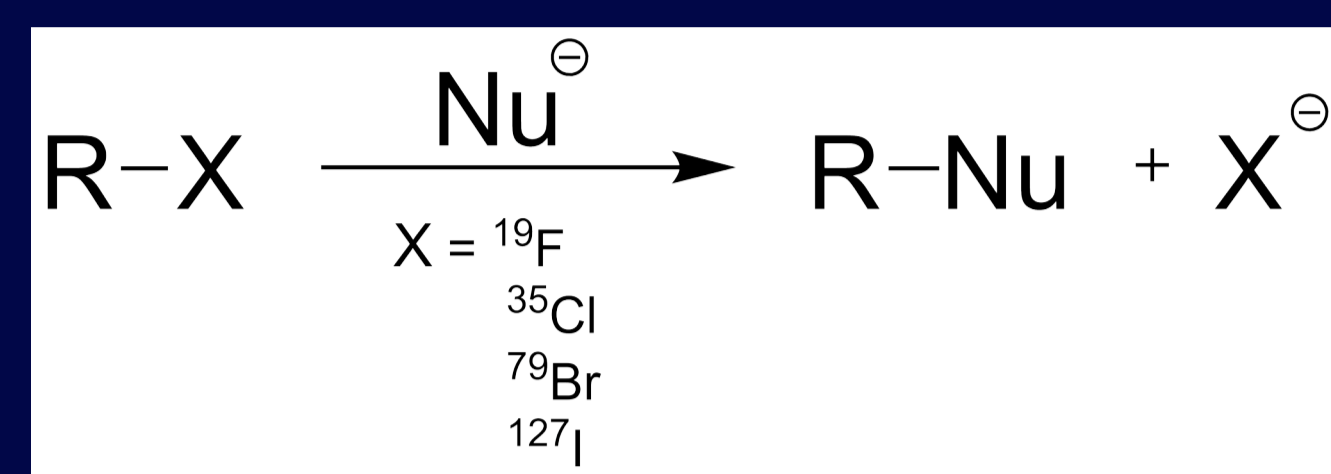
Halide NMR Spectroscopy for Following Reaction Kinetics



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Introduction

The inevitable release of halide ions during certain chemical and biochemical processes involving substitution or elimination, provides the basis of a simple and direct NMR method for monitoring the course and kinetics of these reactions (Scheme 1).¹⁻³



Scheme 1

Each of the halide nuclei has at least one NMR active isotope - ${}^{19}\text{F}$, ${}^{35}\text{Cl}$ and ${}^{37}\text{Cl}$, ${}^{79}\text{Br}$ and ${}^{81}\text{Br}$, and ${}^{127}\text{I}$ - which are NMR active, and which may, in principle, be readily exploited for the purpose of following reaction kinetics, particularly in systems where other monitoring methods, including ${}^1\text{H}$ NMR spectroscopy, are contra-indicated. Such is the case for ionic liquids, which may possess a very rich ${}^1\text{H}$ NMR profile or are completely unsuitable for GC analysis.¹

We have been uncovering the advantages and limitations of this approach to monitoring reaction pathways and rates using the following nuclei and reactions: e.g. ${}^{19}\text{F}$ and $\text{S}_{\text{N}}\text{Ar}$ substitution of aromatic fluorides; e.g. ${}^{35}\text{Cl}$, and the solvolysis of aliphatic chlorides^{1,2} with alcohols; e.g. ${}^{79}\text{Br}$, and a Heck palladium-catalysed cross-coupling of an aromatic bromide³ with an olefin; e.g. ${}^{127}\text{I}$, and the Menschutkin reaction involving the alkylation of pyridines.

Results

${}^{19}\text{F}$ NMR Spectroscopy

Isotope	Spin	Natural abundance, %	Magnetogyric ratio, $\text{g}/10^7 \text{ rad s}^{-1} \text{ T}^{-1}$	Relative sensitivity
${}^{19}\text{F}$	1/2	100	25.1	0.834

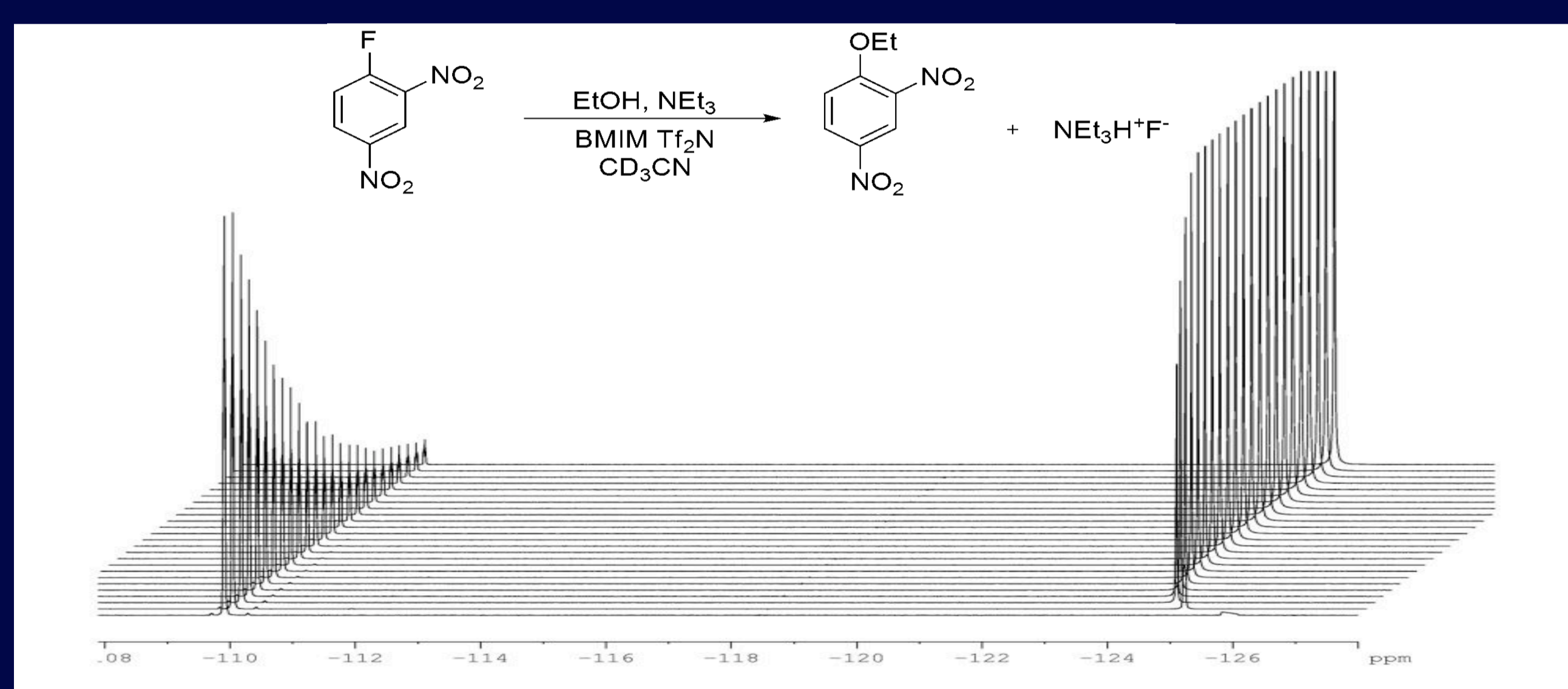


Figure 1. ${}^{19}\text{F}$ NMR spectra of the fluoride substitution reaction, showing the disappearance of the starting 2,4-dinitrofluorobenzene (-109.5 ppm), and the appearance of F^- (-124.5 ppm).

${}^{35}\text{Cl}$ NMR Spectroscopy

Isotope	Spin	Natural abundance, %	Magnetogyric ratio, $\text{g}/10^7 \text{ rad s}^{-1} \text{ T}^{-1}$	Relative sensitivity
${}^{35}\text{Cl}$	3/2	75.78	2.62	0.00358

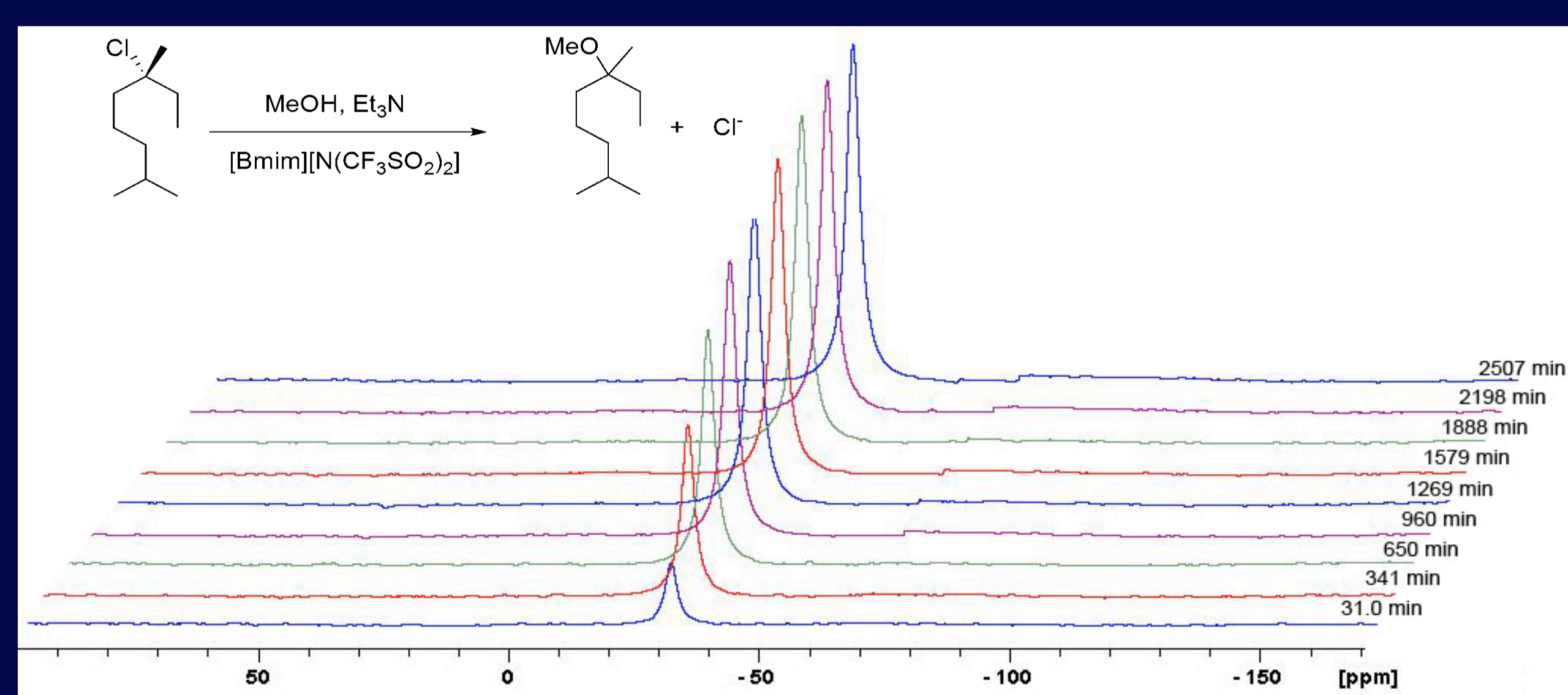


Figure 2. ${}^{35}\text{Cl}$ NMR time course of chloride anion release from methanolysis of alkyl chloride as shown in reaction scheme.

Results (cont.)

${}^{79}\text{Br}$ NMR Spectroscopy

Isotope	Spin	Natural abundance, %	Magnetogyric ratio, $\text{g}/10^7 \text{ rad s}^{-1} \text{ T}^{-1}$	Relative sensitivity
${}^{79}\text{Br}$	5/2	50.69	6.72	0.0403

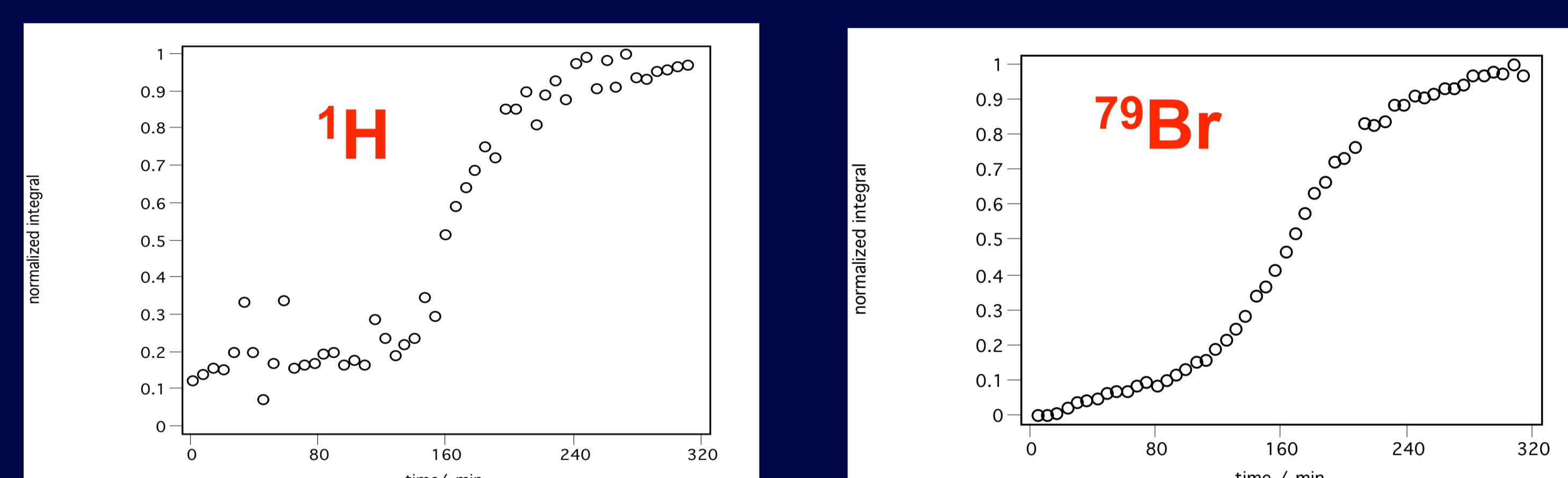
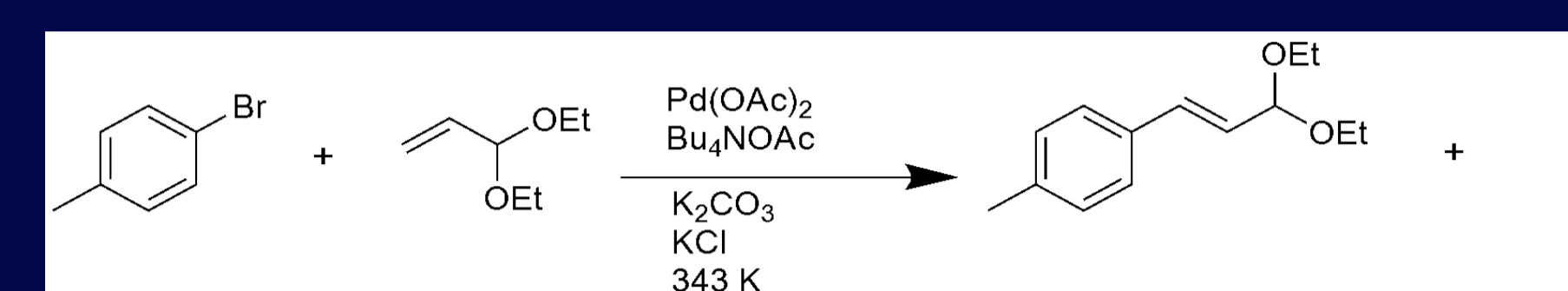


Figure 3. Comparison of integrals from ${}^1\text{H}$ and ${}^{79}\text{Br}$ interleaved NMR spectra following the Heck reaction. Note the greater precision for the data from ${}^{79}\text{Br}$.

${}^{127}\text{I}$ NMR Spectroscopy

Isotope	Spin	Natural abundance, %	Magnetogyric ratio, $\text{g}/10^7 \text{ rad s}^{-1} \text{ T}^{-1}$	Relative sensitivity
${}^{127}\text{I}$	5/2	100	5.35	0.093

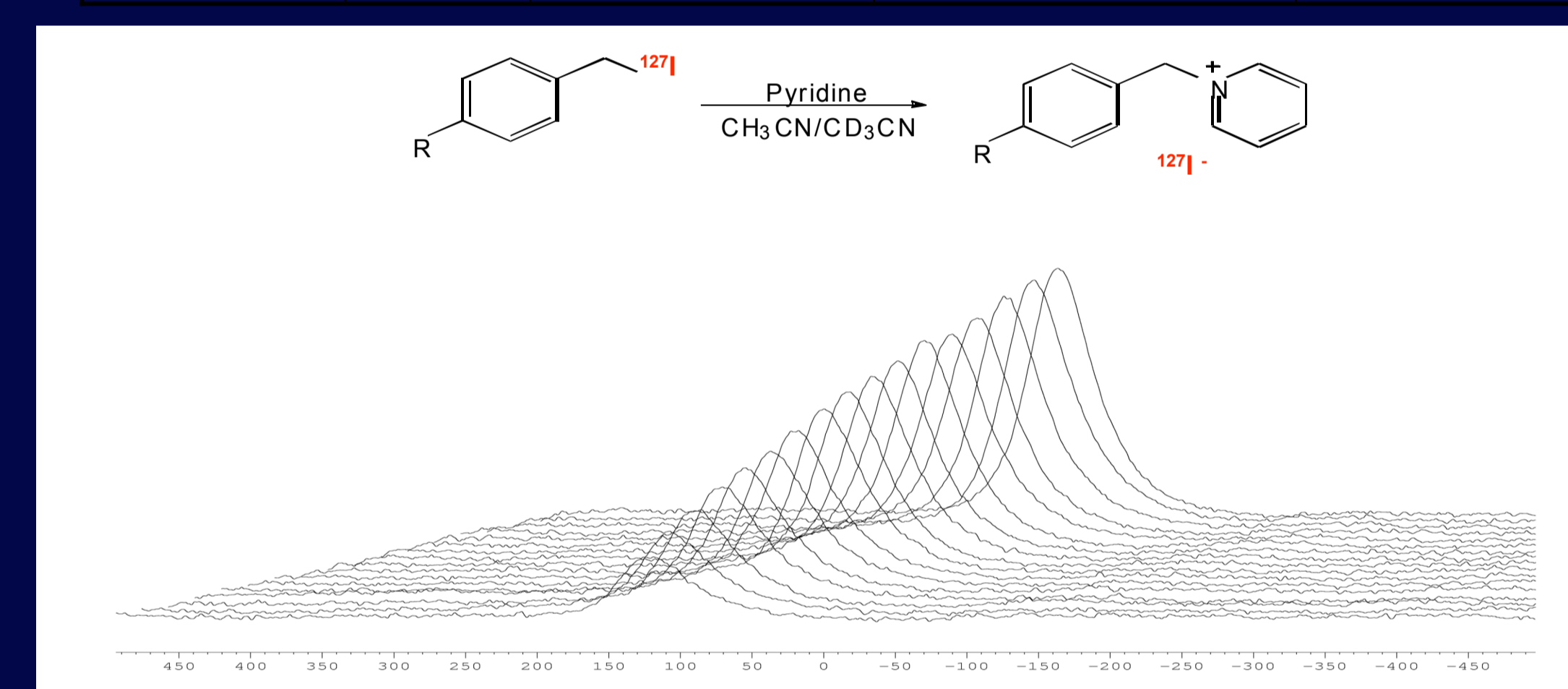


Figure 4. ${}^{127}\text{I}$ NMR spectra of time course for the Menschutkin reaction of pyridine with benzyl iodide in acetonitrile.

Conclusions

1. Each of the halide nuclei may be used to follow the progress of some simple organic reactions
2. ${}^{19}\text{F}$ is best because it's spin 1/2, high sensitivity, and both reactant and products can be observed in the same spectra without interference from other nuclei.
3. The others - ${}^{35}\text{Cl}$, ${}^{79}\text{Br}$ and ${}^{127}\text{I}$ - can clearly be used to monitor reactions as the anion is released into solution without interference from signals of other nuclei.
4. However, ${}^{35}\text{Cl}$, ${}^{79}\text{Br}$ and ${}^{127}\text{I}$ are, with increasing size, increasingly sensitive to their environment, and are subject to line broadening which may render them unobservable in certain solvents or linked to certain counter-cations.
5. ${}^{35}\text{Cl}$ can be observed in a broad range of solvents, and despite its lower sensitivity, can provide insight into the mechanism of a reaction.
6. ${}^{79}\text{Br}$ as Br^- has a higher sensitivity, but is invisible in solvents such as methanol, or viscous liquids such as butyl methyl imidazolium (ionic) liquids.
7. Similarly, ${}^{127}\text{I}$ as I^- is limited to situations where the solvent viscosity is low and the ion pairing does not increase relaxation.

References

1. Man, B. Y. M.; Hook, J. M.; Harper, J. B. *Tetrahedron Lett.* **2005**, 46, 7641-7645.
2. Yau, H. M.; Barnes, S. A.; Hook, J. M.; Youngs, T. G. A.; Croft, A. K.; Harper, J. B. *Chem. Commun.* **2008**, 30, 3576-3578.
3. Chan, S. J.; Howe, A. G.; Hook, J. M.; Harper, J. B. *Mag. Reson. Chem.* **2008**, accepted.