Validating Quantitative Hyperpolarised Reaction Monitoring on a Benchtop NMR Spectrometer

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1 Introduction

Benchtop NMR spectrometers (1 – 2 T) have several advantages for reaction monitoring applications.[1] However, moving to low-field carries additional experimental limitations.[2]
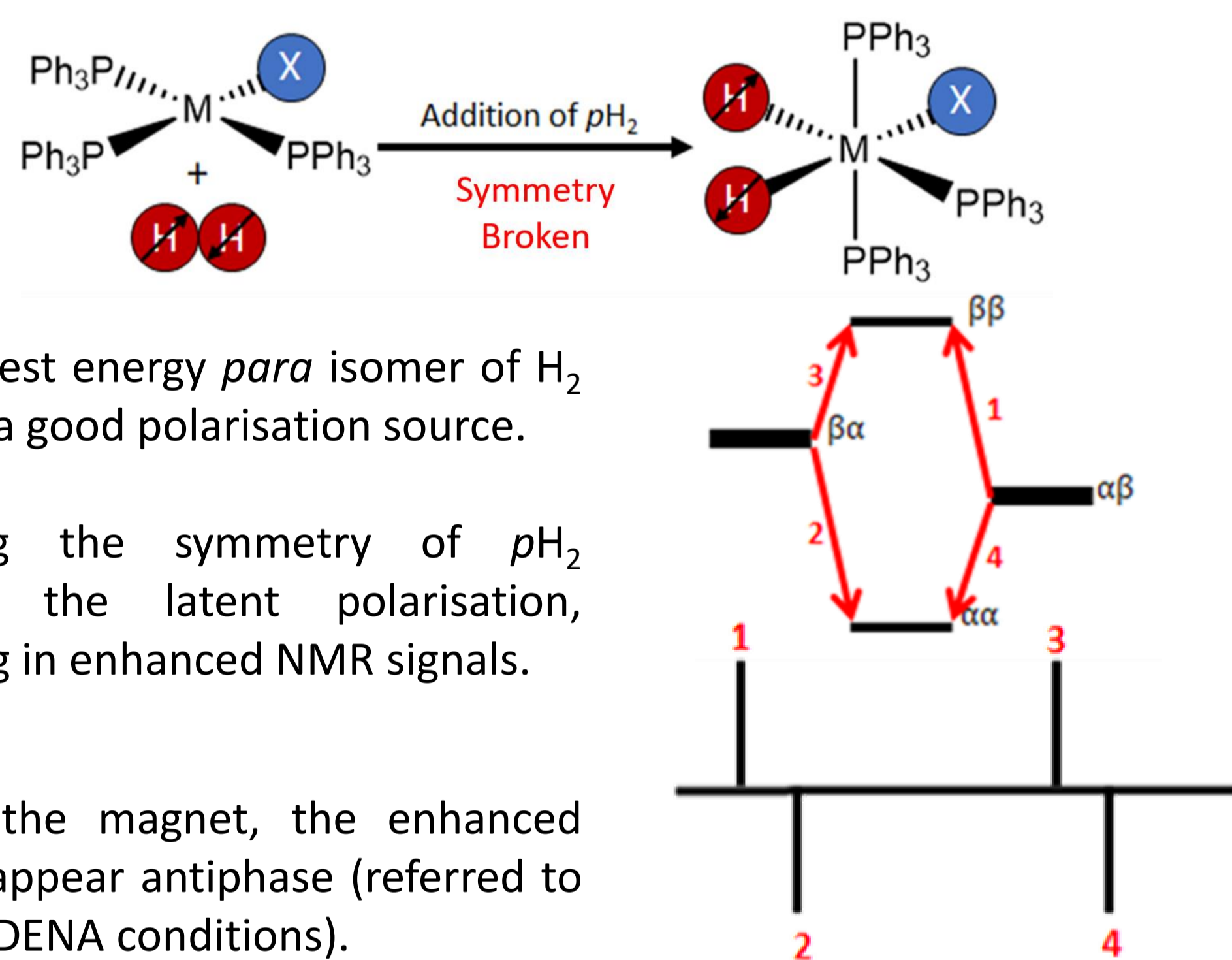
- Highly accessible: More affordable and customisable.
- Compact: Easier incorporation with reaction monitoring.
- Independently locked: Allows for use of *protio* solvents.

- Reduced sensitivity: [1]H population difference of 3 ppm.
- Compressed δ scale: 1 ppm is equivalent to 43 Hz.
- Temperature stabilised: Fixed 28.5 °C internal temperature.

These limitations must be overcome whilst also ensuring that the kinetic data obtained is both quantitative and reproducible.

2 Hyperpolarisation Through PHIP

The inherent insensitivity of low-field NMR is addressed through application of the PHIP hyperpolarisation technique to produce a non-Boltzmann nuclear spin distribution:[3]

- The lowest energy *para* isomer of H_2 (pH_2) is a good polarisation source.

- Breaking the symmetry of pH_2 unlocks the latent polarisation, resulting in enhanced NMR signals.

- Within the magnet, the enhanced signals appear antiphase (referred to as PASADENA conditions).

7 Conclusions and Future Work

Conclusions

1. A procedure for low-field reaction monitoring has been developed and employed.
2. Reproducible and valid kinetic parameters were obtained for a model system.

Future Work

1. Assessment of the wider applicability of the approach and the limitations, especially for faster reacting systems.
2. Extension of this approach to photochemical systems.

8 References

[1] E. Danieli, J. Perlo, A. L. L. Duchateau, G. K. M. Verzijl, V. M. Litvinov, B. Blümich and F. Casanova, *ChemPhysChem*, **2014**, 15, 3060 – 3066.
[2] M. V. S. Elipe and R. R. Milburn, *Magn. Reson. Chem.*, **2016**, 54, 437 – 443.
[3] S. B. Duckett and R. E. Mewis, Acc. Chem. Res., 2012, 45, 1247 – 1257.
[4] P. B. Chock and J. Halpern, *J. Am. Chem. Soc.*, **1966**, 88, 3511–3514.
[5] J. A. Aguilar, P. I. P. Elliot, J. López-S., R. W. Adams and S. B. Duckett, *Chem. Commun.*, **2007**, 1183–1185.
[6] C. Ammann, P. Meier and A. E. Merbach , *J. Magn. Reson.,*, **1982**, 46, 319–321.

3 Monitoring a PHIP-Hyperpolarised Reaction

To explore PHIP-enhanced reaction monitoring, the addition of H_2 to Vaska's complex was the ideal candidate:

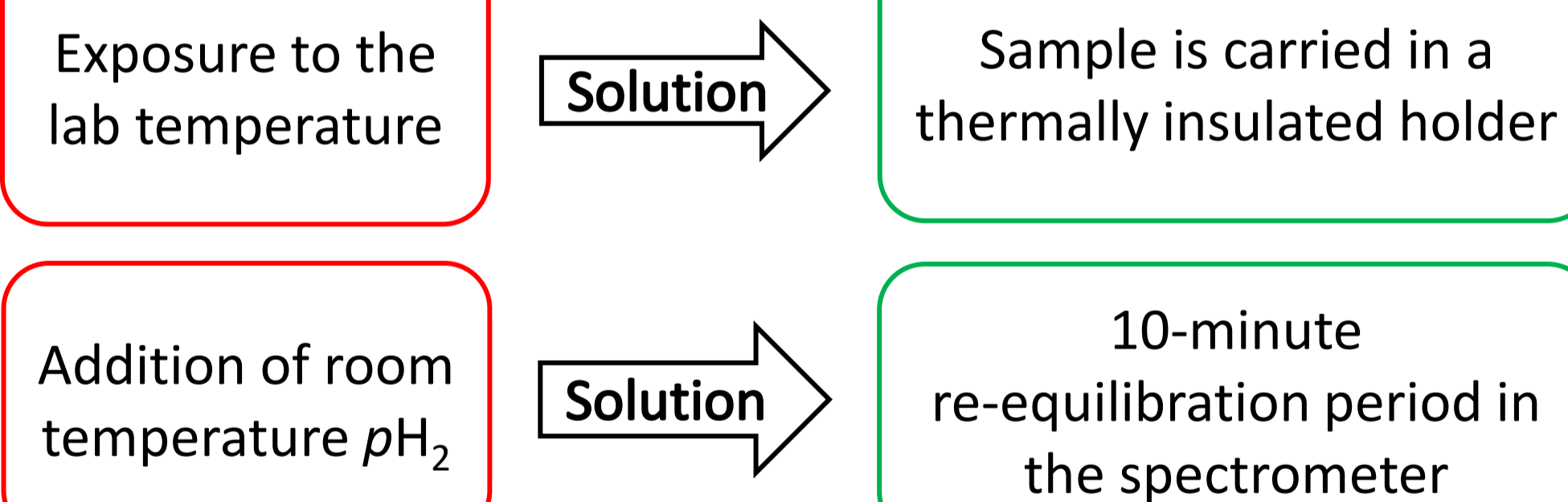- Irreversible at 28.5 °C.
- Simple kinetics.
- Easy to introduce pH_2.
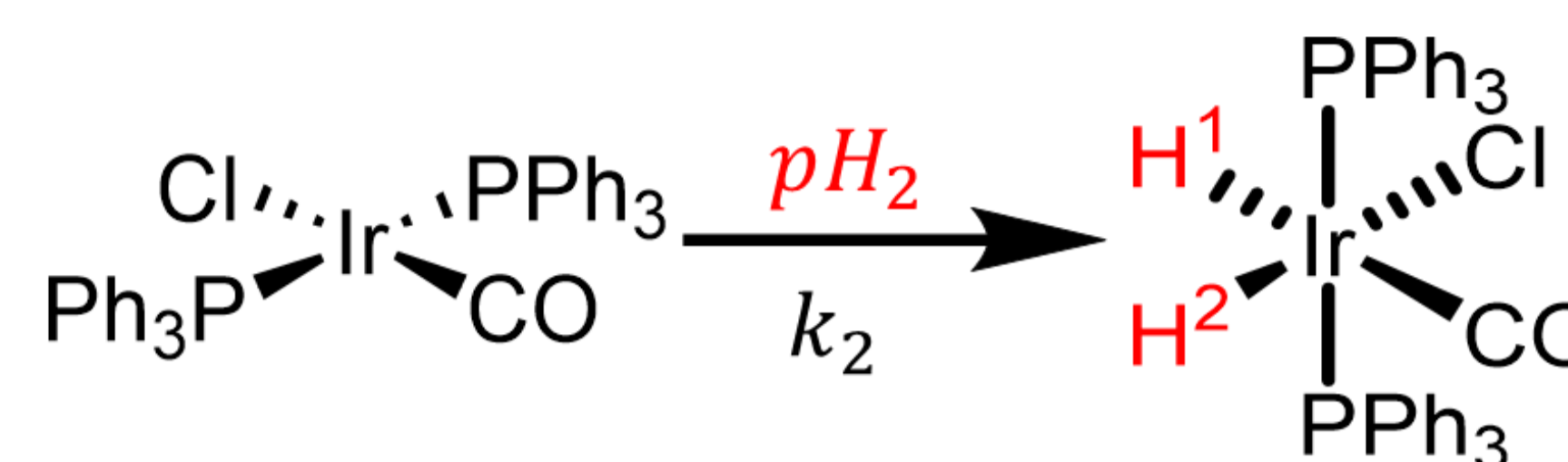
The reaction was monitored using the change in the integral of the hydride peaks at 5 second intervals:

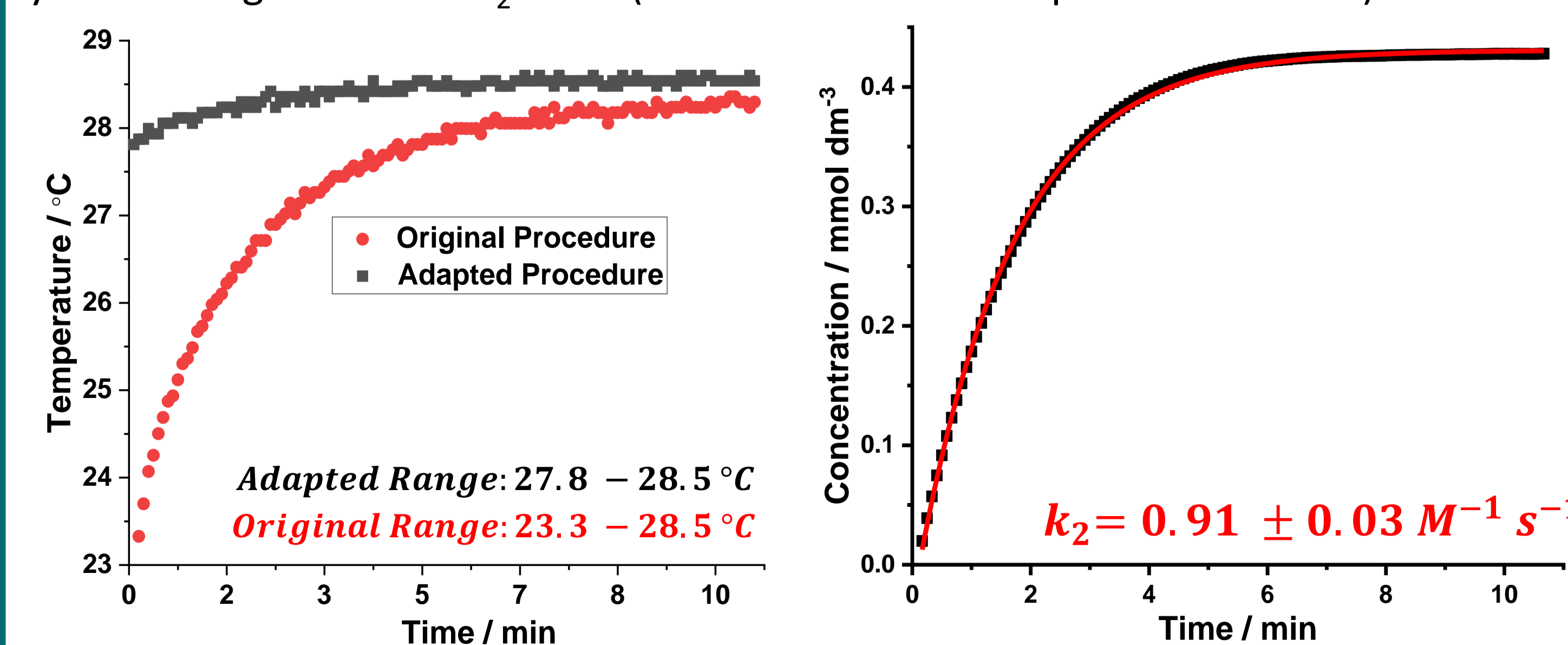| H^1	H^2
δ = -7.4 ppm	δ = -18.2 ppm
$J_{H-P(cis)}$ = 17.6 Hz	$J_{H-P(cis)}$ = 14.1 Hz
J_{HH} = 4.6 Hz	J_{HH} = 4.6 Hz
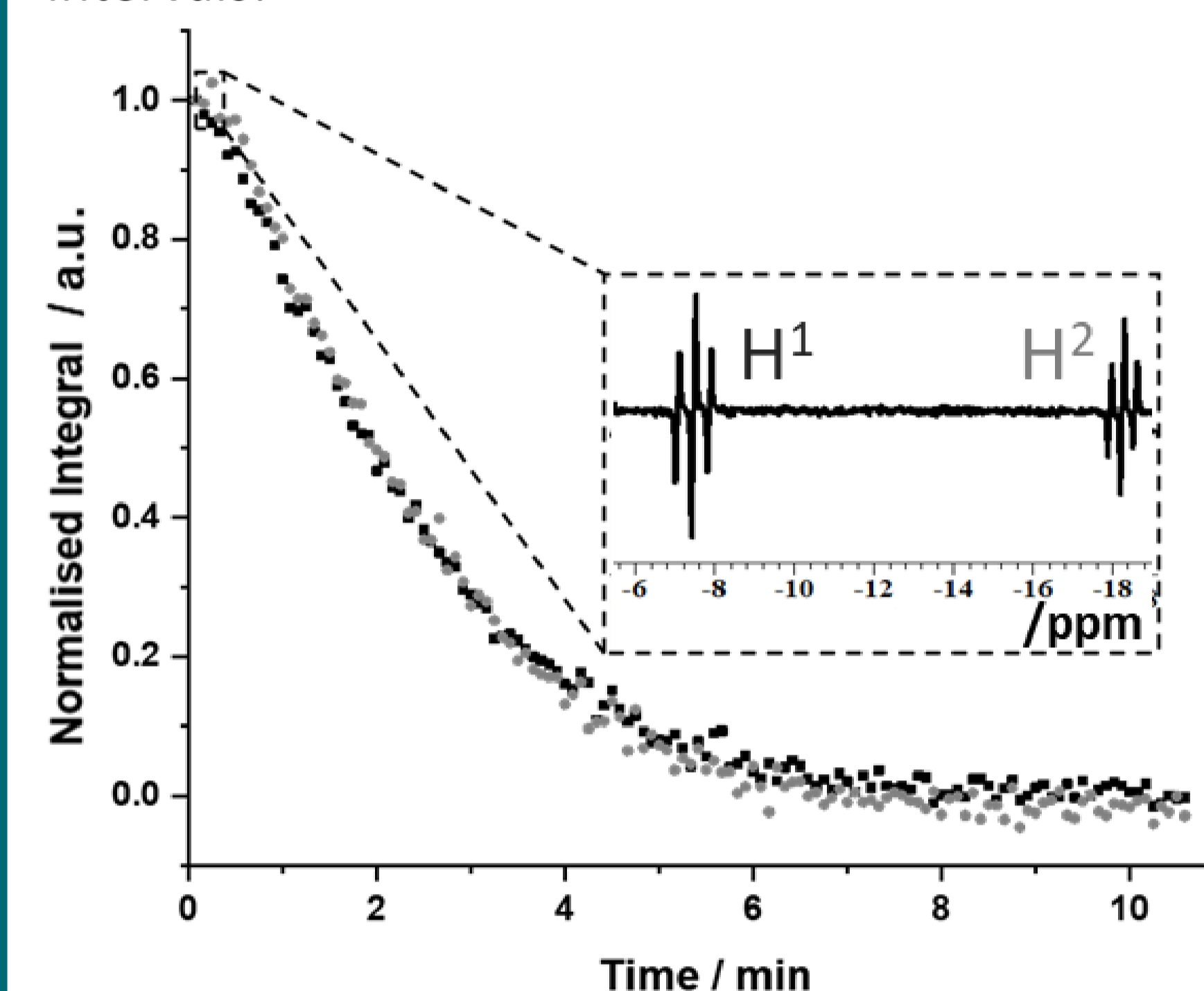
5 Temperature Studies

Temperature gradients during the reaction could skew the kinetic parameters obtained. Two main sources of temperature loss were identified:

Exposure to the lab temperature → **Solution** → Sample is carried in a thermally insulated holder

Addition of room temperature pH_2 → **Solution** → 10-minute re-equilibration period in the spectrometer

This adapted experimental protocol resulted in a reduced temperature gradient[6] and yielded a higher overall k_2 value (that still lies within experimental error):

Adapted Range: $27.8 - 28.5 °C$
Original Range: $23.3 - 28.5 °C$

$k_2 = 0.91 \pm 0.03 \ M^{-1} \ s^{-1}$

Outline of Experimental Method

1. Shake + Transfer

2 mg [IrCl(CO)(PPh$_3$)$_2$]
4 bar pH_2 (>99%)
0.6 mL C$_6$D$_6$

2. Monitor + Process

3. Integrate + Analyse Kinetics

4 Probing the Validity of Kinetic Parameters

The actual rate of product formation can be determined from the accumulation of the integrated signal over time:
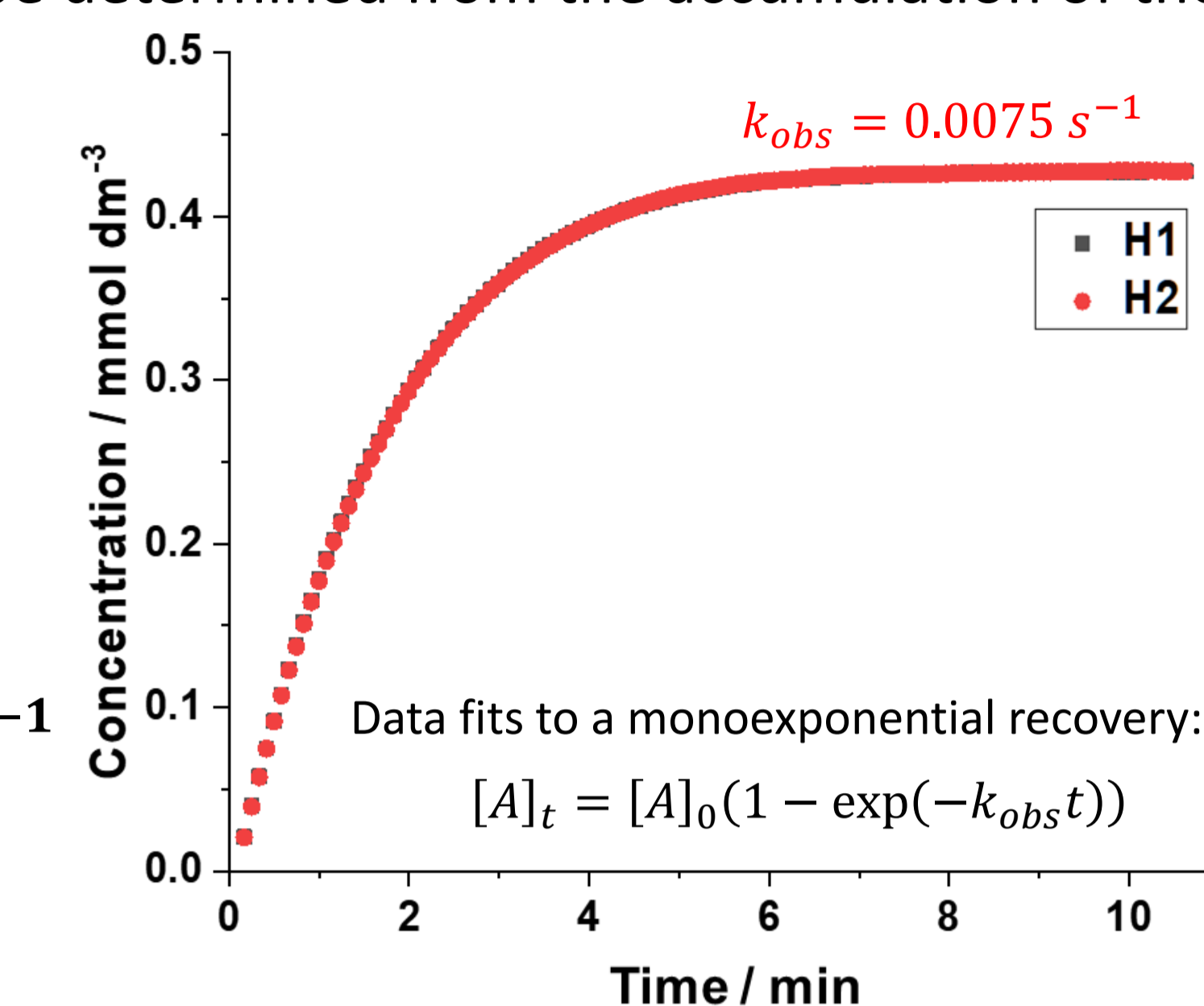
$$rate = k_{obs}[Vaska]$$

$$where \ k_{obs} = k_2[pH_2]$$
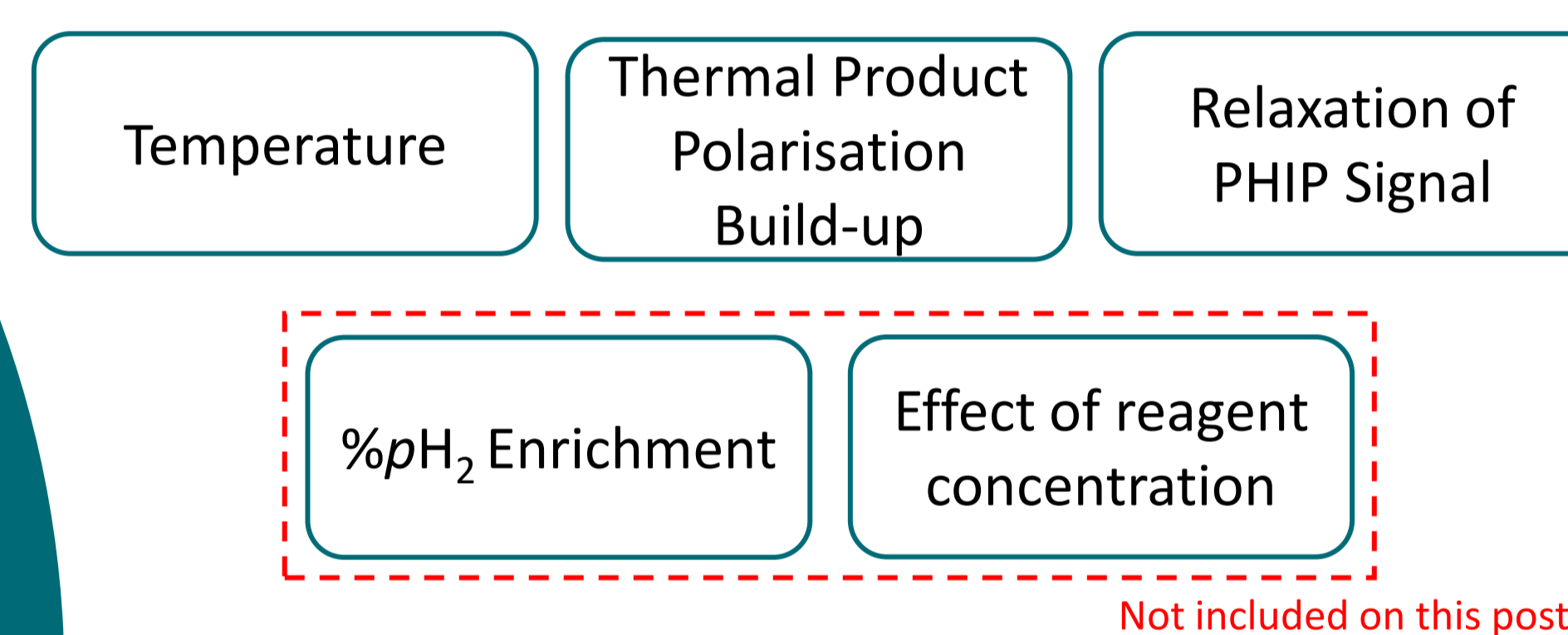
$$k_2 = \frac{k_{obs}}{[pH_2]^*}$$

*Taken to be 0.012 M using literature solubility data.
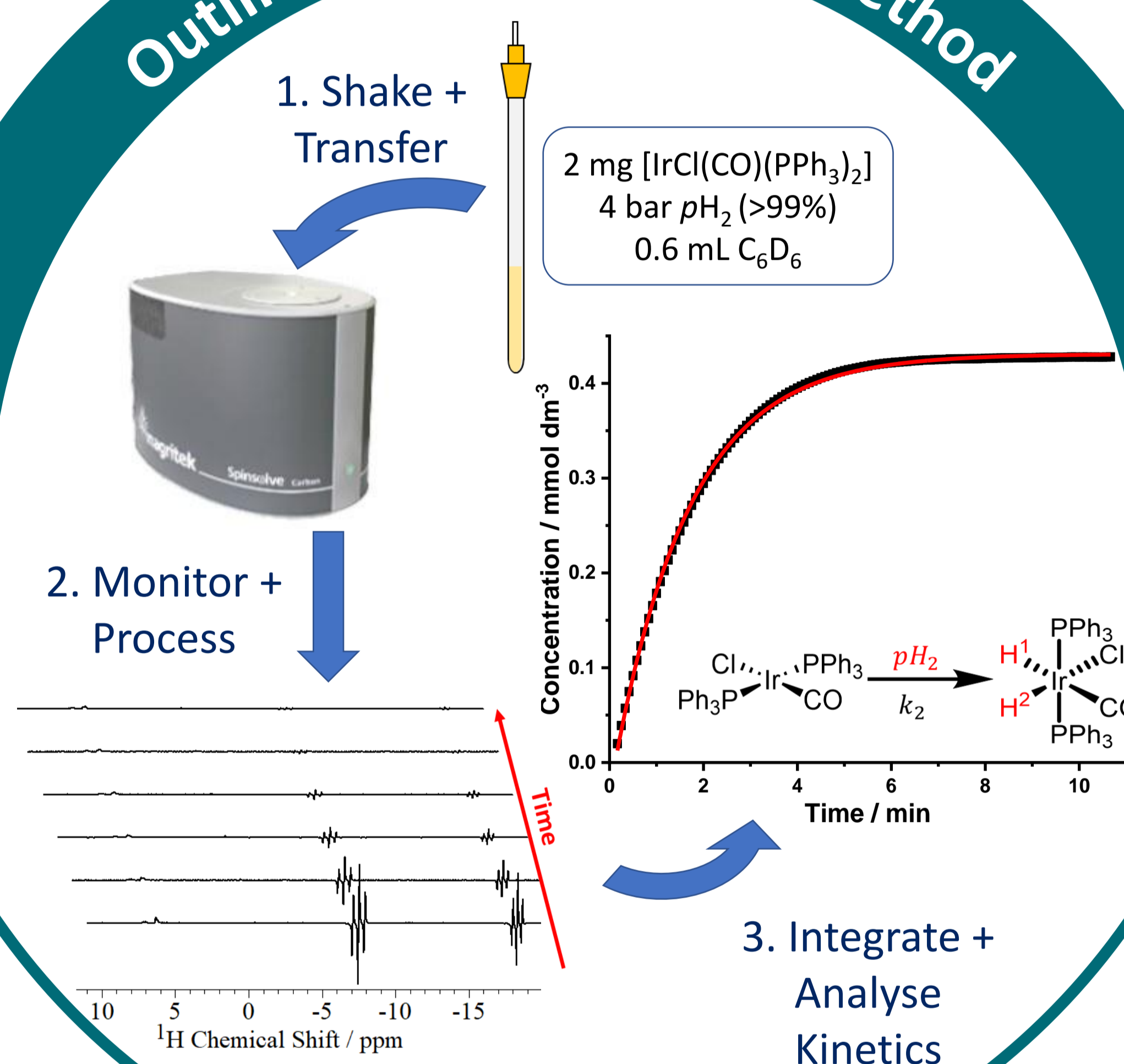
$$k_2(28.5 \ °C) = (0.850 \pm 0.011) \ M^{-1} \ s^{-1}$$

Literature $k_2(28.5 \ °C)^4 = (0.86 \pm 0.03) \ M^{-1} \ s^{-1}$

$k_{obs} = 0.0075 \ s^{-1}$

Data fits to a monoexponential recovery:

$$[A]_t = [A]_0(1 - \exp(-k_{obs}t))$$

To ensure kinetic parameter reliability, several experimental parameters require assessment:

- Temperature
- Thermal Product Polarisation Build-up
- Relaxation of PHIP Signal
- %pH_2 Enrichment
- Effect of reagent concentration

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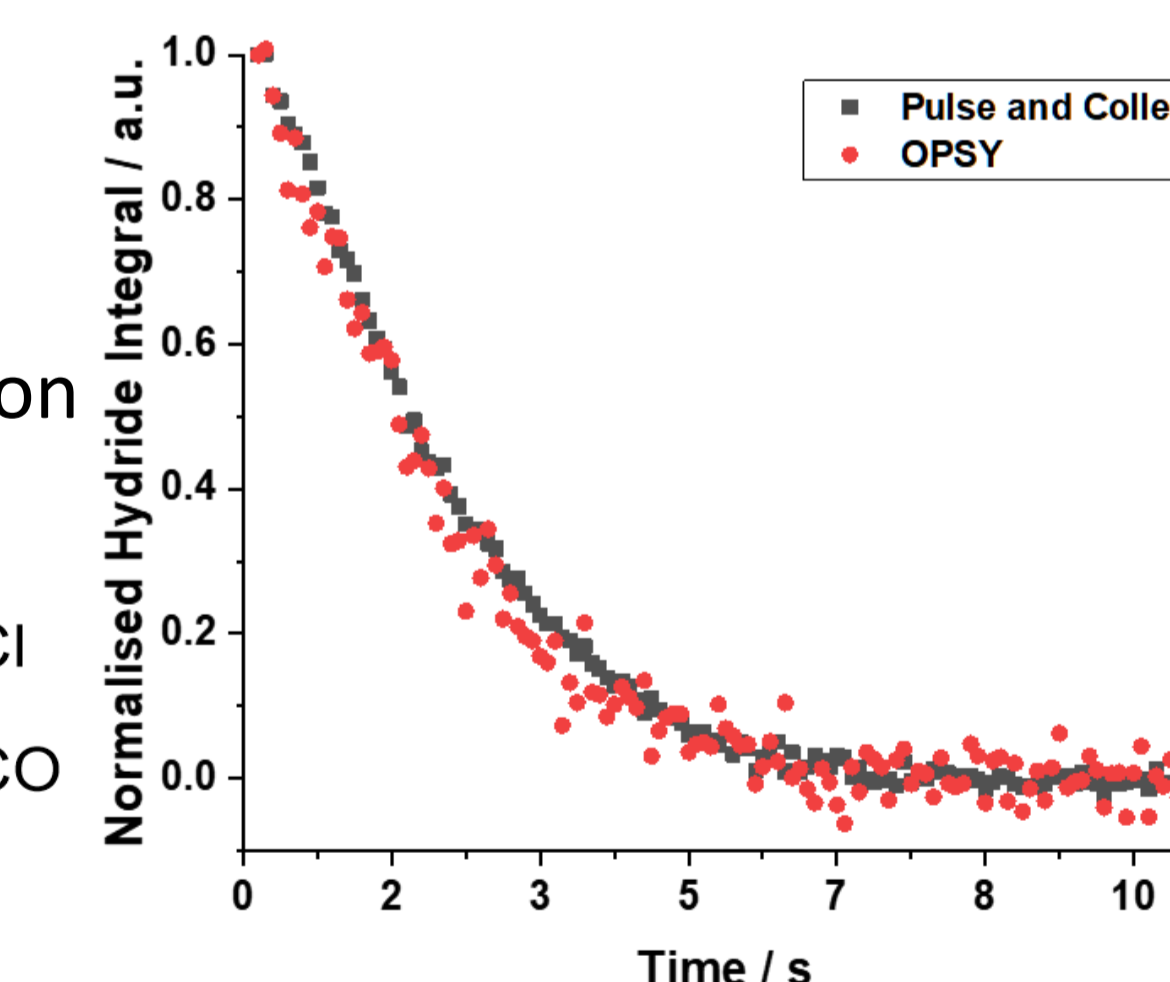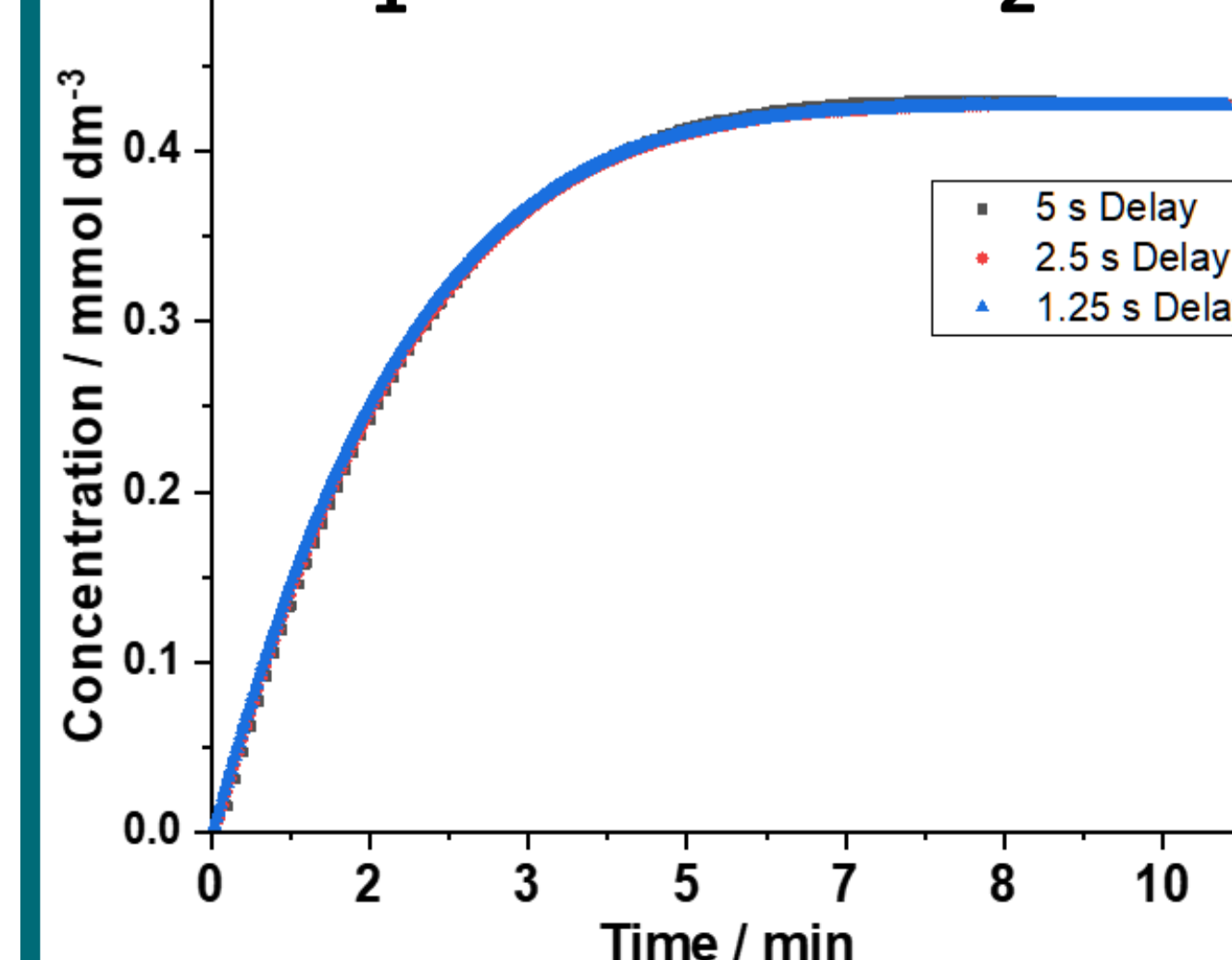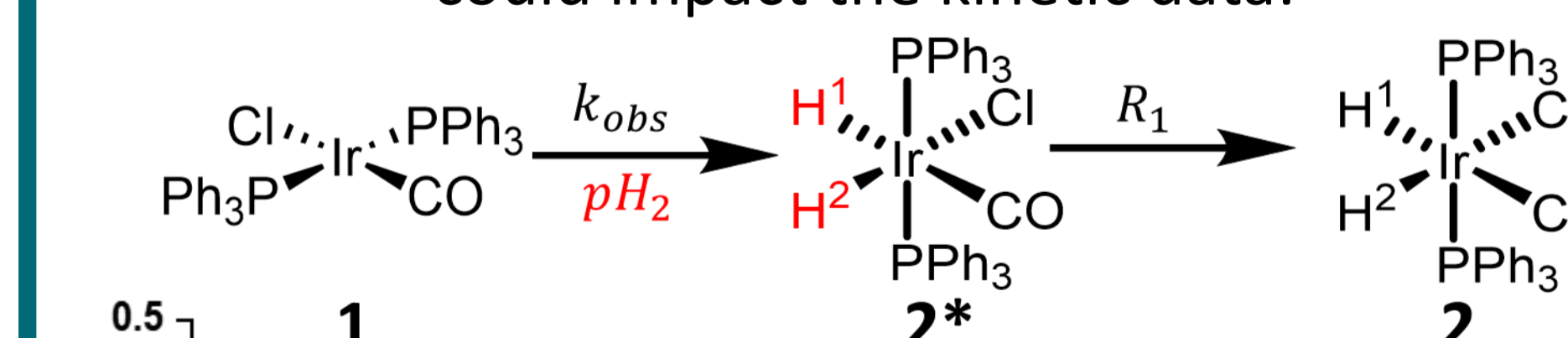
6 Polarisation Studies

Thermal Product Polarisation

NMR signals from the bulk product could skew the measured hydride integrals. OPSY experiments showed that this had a minimal impact on the signal decay.[5]

PHIP Signal Relaxation

PHIP signal relaxation prior to acquisition could impact the kinetic data:

The interplay between these parameters can be given as:

$$\frac{d[2^*]}{dt} = k_{obs}[1] - R_1[2^*]$$

If R_1 has a large effect, a variation of k_{obs} with experimental delay would be observed. Both simulations and experiments proved this to be a negligible effect.