NMR-based *in situ* mixing device:

Unravelling the mechanism of phase-transfer catalysed reactions

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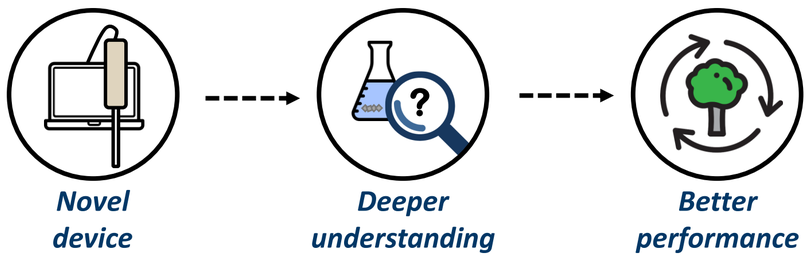
I. Project overview

Phase-transfer catalysis, PTC, is extensively used in preparation of **life-saving drugs** and other industrial manufacturing processes as a **greener** and **more sustainable** strategy.[1]

Investigation of PTC is challenging and there is **no method** that allows ***in situ* analysis** of PTC via nuclear magnetic resonance spectroscopy (NMR).

The aim of the project is to develop an **NMR-based mixing system** that allows *in situ* analysis of PTC, to promote its understanding and applications, and lead to a greener future.



II. What is PTC?

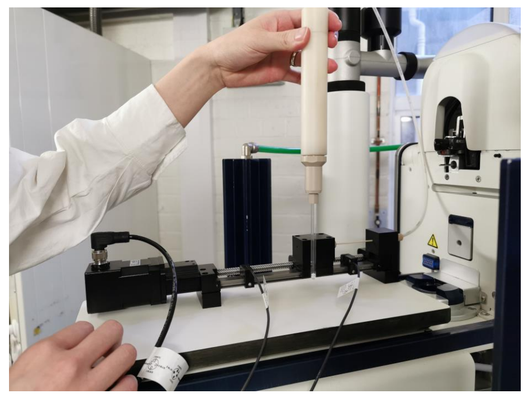
PTC enormously enhances the speed of reaction by bringing chemicals from **different phases** (e.g. solid and liquid) into proximity --- it acts like a detergent for dissolving grease into water.

The PTC market is projected to grow from **£682.3 million** in 2018 to **£998.9 million** by 2026.[2]

However, the nature of PTC means it requires **continuous mixing**, which seems an easy requirement but is **incompatible** with many analytical techniques, including NMR.

What we need is to **install a mixer into the NMR.**

Mixing device



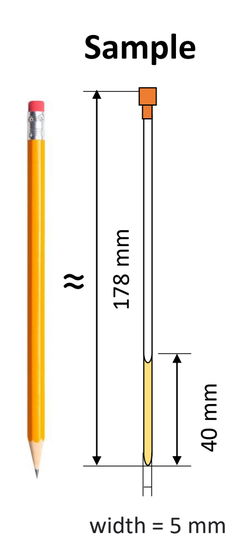
III. Why NMR?

NMR provides more structural data than any other spectroscopy method.

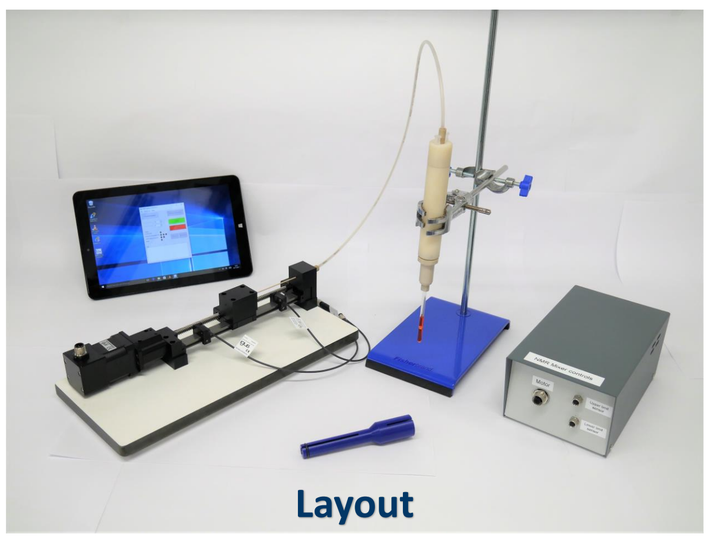
It has the advantages of being non-destructive, and allows simple sample preparation, and rapid data acquisition.

It is highly desirable to use NMR for studying PTC.

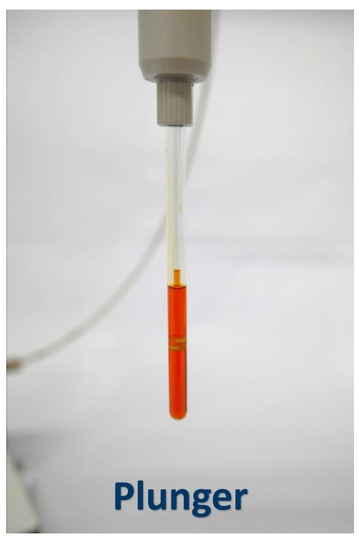
Conventionally, a lot of **manual processing** is required to overcome the inherent incompatibility, and the results can be **distorted**.



IV. NMR-based *in situ* mixing device



Layout



Plunger

- **Portable**

  The system can be removed when not in use, and the set-up takes less than 20 minutes.

- **Universal**

  The device is compatible with **any** NMR spectrometer.

- **Automated & Accurate**

  All experimental parameters can be accurately controlled by the in-house built software.

- **Efficient mixing**

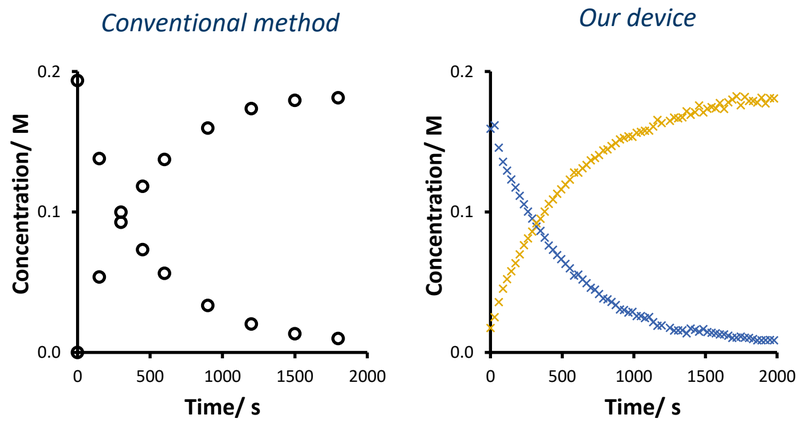
  12 designs of plunger tips were evaluated to find the optimum.

- **Safe**

  Non-magnetic and chemically-resistant materials are used.

V. Performance

We used our new device to investigate a PTC fluorination.[3]



With the new device:

- ✓ **90%** less reagents
- ✓ **10** times more data
- ✓ **Faster** analysis

It greatly speeds up our investigation, and allows us to propose a reaction mechanism, which could guide further improvement of current process.

VI. Outlook

We have designed and developed the **first** *in situ* phase-mixing system for NMR which allows **real-time automated** analysis of PTC. We have applied it to study a PTC fluorination and got excellent results.

We speculate that further development of the device will promote a deeper understanding of PTC processes in general and accelerate their industrial applications in various aspects.

We have an ongoing collaboration with TgK, a UK scientific engineering SME, to commercialise the device.

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References

1) J. Tan and N. Yasuda, *Org. Process Res. Dev.*, 2015, **19**, 1731–1746. 2) Verified market research, *Global Phase Transfer Catalyst Market Size By Type, By End User, By Geographic Scope and Forecast*, 2021. 3) G. Pupo, F. Ibba, D. M. H. Ascough, A. C. Vicini, P. Ricci, K. E. Christensen, L. Pfeifer, J. R. Morphy, J. M. Brown, R. S. Paton and V. Gouverneur, *Science*, 2018, **360**, 638–642.