

Operando Nuclear Magnetic Resonance (NMR) Studies of a Trickle-bed Reactor Using D - T_2 Correlations

Amy Sparks^a, Lynn Gladden^a, Colin Brennan^b, and Mick Mantle^{a*}

Abstract: Catalytic conversions in fine-chemical and pharmaceutical production are increasingly performed in trickle-bed reactors. Optimisation of these processes is usually based on end of pipe measurement made at specific residence times. This process is both time-consuming and the data sometimes challenging to interpret. In the present work, *operando* nuclear magnetic resonance (NMR) techniques both at the scale of the whole bed (global) and spatially resolved within the bed (local) are used to gain new insights into the catalytic conversion process under reaction conditions. Spatially resolved spectroscopic and diffusion- T_2 -relaxation (D - T_2) methods interrogate local differences in chemical conversion and selectivity, and mass transport (molecular self-diffusion) respectively, thereby providing valuable information for process simulation models. This capability is demonstrated using the continuous flow three phase (gas-liquid-solid) hydrogenation of benzonitrile over a fixed bed of 0.5 wt% Pd/Al₂O₃ catalyst pellets yielding toluene and benzylamine. Global ¹H spectroscopic and D - T_2 were used to monitor chemical conversion and the approach to steady state; these were subsequently followed by spatially resolved ¹H spectra and spatially resolved D - T_2 correlations to examine the local differences in axial conversion and selectivity of the catalyst bed packing. At steady-state a global conversion of 63% was achieved with 65% and 25% selectivity to benzylamine and toluene respectively. Heterogeneities in the local (axial) conversion and selectivity differed by 31% along the total catalyst bed length. These techniques should be applicable to many three-phase heterogeneous catalytic systems provided that the T_2 relaxation time of the reactants and products is not prohibitively small.

Keywords: *In situ* measurement · Nuclear magnetic resonance · NMR correlations · Trickle bed reactor



Amy Sparks completed her PhD in Chemical Engineering at the University of Cambridge in the department of Chemical Engineering and Biotechnology. Her PhD research focused on the capabilities of NMR to track complex heterogeneous reactions under *operando* conditions.

1. Introduction

Trickle-bed reactors (TBRs) are extensively used in the fine-chemical and pharmaceutical industries and offer advantages over other three-phase batch reactor configurations, such as simplicity in operation, high catalyst loading per unit volume, and low operating costs.^[1,2] Ideally, the operating conditions for TBRs should be tailored to the desired results. This is usually carried out incrementally, which is often a time-consuming and costly process, and simulated models often lack experimental data for support. Performance is usually investigated by end of pipe measurement at specific residence times followed by varying the residence time. This is achieved either by change in bed length or flow rate both of which are time consuming and introduce variables that can impact scale dependant parameters such as in bed mixing.^[3,4] Therefore, a direct measurement with the ability to understand how local chemical conversion and catalytic processes vary with properties, *e.g.* flow rate, pressure, temperature, is key to development and successful scaling of such processes.

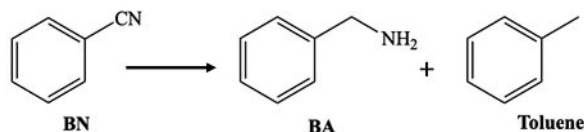
Nuclear magnetic resonance (NMR) is well suited to probe these systems as it is a non-invasive technique and can provide information on a range of length scales.^[5–7] *In situ* monitoring of TBRs using conventional ¹H spectroscopy is often difficult because magnetic susceptibility variations associated with the different materials present within the bed (solid catalyst, gas, and liquid reagents) give rise to broad, overlapping lineshapes in the ¹H spectra. To alleviate the difficulties with ¹H NMR methods of 3-phase systems some studies have instead focused on NMR active nuclei with a wider chemical shift range. For example, Zheng *et al.* used the ¹³C distortionless enhancement by polarisation transfer (DEPT) NMR technique to study the hydrogenation of octene in a packed bed reactor containing a 0.3 wt% Pd/Al₂O₃ catalyst pellets.^[8] Akpa *et al.* used volume selective ¹³C spectroscopy (VOSY) to study the competitive etherification and hydration reactions of 2-methyl-2-butene in reactor packed with an ion-exchange resin.^[9] This paper reports how ¹H Diffusion- T_2 -relaxation correlation (D - T_2) NMR based methods can be exploited to overcome the difficulties of magnetic susceptibility^[10,11] to track a reaction in a TBR under *operando* conditions. Benzonitrile (BN) hydrogenation to the desired product, benzylamine (BA), and undesired product, toluene, was used as a model system, as shown in Scheme 1. Primary amines are key intermediates for final products in a range of chemical industries, and the catalytic hydrogenation of nitriles is considered a favourable route for their production.^[10,11] Different supported metal catalysts can be used for this conversion depending upon the substrates including Raney Ni and

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Raney Co.^[12,13] In this work, Pd/Al₂O₃ catalyst was utilised for better NMR compatibility.



Scheme. 1. Hydrogenation of benzonitrile (BN) to benzylamine (BA) and toluene.

2. Experimental Methods

2.1 Materials Used

BN and H₂SO₄ were purchased from Alfa Aesar with 95% and 98% purity, respectively. CD₃OD was purchased from Goss Scientific with 99.8% purity. The reactant solution introduced in the reactor was prepared by the addition of BN in CD₃OD (0.35M), followed by dropwise addition of 1.4 eq. of H₂SO₄. 0.5 wt% Pd/Al₂O₃ was purchased from Alfa Aesar in the form of 2.5 mm diameter and 3.2 mm length cylinder pellets and were egg-shell type. BET analysis of the catalyst pellets yielded an average surface area of 102 ± 0.46 m²g⁻¹ and an average pore volume of 0.21 cm³g⁻¹. Metal dispersion and surface area, calculated from CO chemisorption isotherm measurements, were 23% and 5.2 m²g⁻¹ respectively.

2.2 Reactor Configuration and Operation

The reactor set-up is described in Fig. 1 and placed in the spectrometer as positioned in Fig. 2. 10 g of the catalyst pellets were loaded into a 25 mm I.D. and 29.5 cm height glass reactor to give a ~3.5 cm catalyst bed height. The catalyst was surrounded by 200 mm non-porous borosilicate glass beads to improve gas and liquid distribution and to centre the catalyst bed in the 7 cm length R.F. coil. Prior to packing the reactor, the glass beads and catalyst were dried at 120 °C. Once the reactor was packed, the system was sealed and purged with N₂ for 1h using a flow rate of 50 ml min⁻¹. The flow was then switched to H₂ to reduce the catalyst, which was maintained at the same flow rate for 1h. It was assumed these conditions were sufficient for reduction of Pd(II) to Pd(0) over the entire catalyst for two reasons: (1) visible observations of the reactor (outside the magnet) during reduction showed that there was no change in the physical colour of the catalyst pellets (from light grey to black) after 10 mins of reduction. (2) no difference in overall conversion at steady state was observed for a separate experiment when the catalyst pellets had been reduced for 0.5 hr. H₂ flow was then reduced to 20 ml min⁻¹ and the co-current liquid flow introduced until the catalyst bed was completely wetted (2 ml min⁻¹ flow rate for 10 mins). The liquid flow was then reduced to 0.3 ml min⁻¹. The wetting profile of the bed was monitored using 1D NMR spin echo imaging (details in the Supporting Information, S1) in the axial dimension and steady state NMR measurements (detailed below) were started once the total signal intensity was stable; *i.e.* when total ¹H signal intensity deviations were <6%.

To assess the relative contributions of ¹H NMR signal from inter- and intra- pellet liquids, the reactor was monitored using a multislice NMR imaging technique (see Supporting Information S2). Multislice spin-echo imaging shows that no ¹H signal is detected from the inter-pellet region. As the echo times, TE, of all NMR methods reported in section 2.3 were greater than that of the multislice spin-echo imaging sequence it can therefore be safely assumed that the ¹H NMR signal originates solely from the intraparticle liquid. The lack of detectable ¹H signal from the interparticle region of the bed is provisionally attributed to two factors: (i) interparticle liquid flowed in thin liquid films around

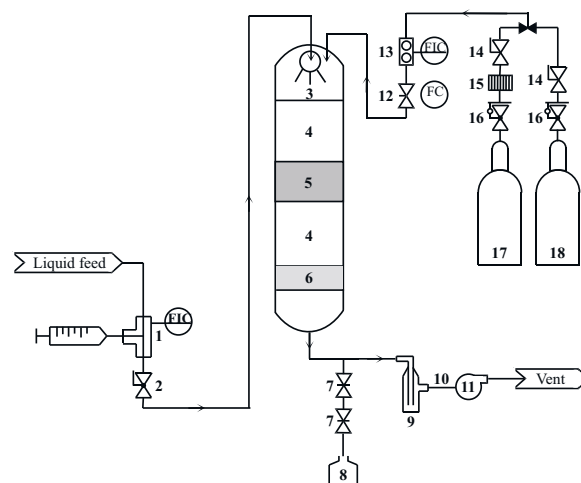


Fig. 1. Schematic of the laboratory-scale TBR. The numbered components are as follows: 1. Syringe pump, 2. Quarter-turn valve, 3. Liquid distributor, 4. Borosilicate glass beads, 5. Catalyst bed, 6. Glass frit filter, 7. Needle valve, 8. Sampling container, 9. Glass bubbler, 10. Exhaustion duct, 11. Exhaustion fan, 12. Metering valve, 13. Gas flowmeter, 14. Shut-off plug valve, 15. Flash-back arrestor, 16. Pressure regulator, 17. H₂ gas cylinder, 18. N₂ gas cylinder.

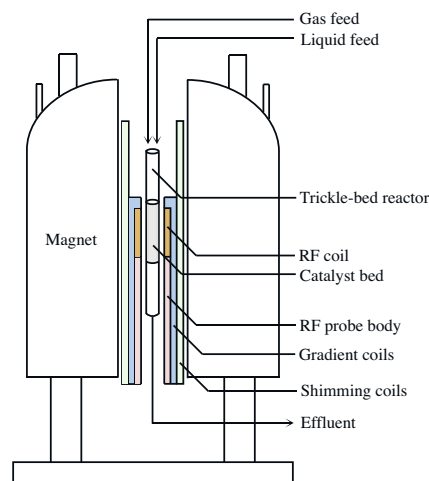


Fig. 2. Schematic diagram of the laboratory-scale reactor set-up inside the 7.05T superconducting magnet.

the 200 mm borosilicate glass beads; (ii) the T_2 relaxation time of this liquid is sufficiently fast relative to the echo time of all NMR experiments as not to be detectable.

2.3 NMR Methods

This section details the NMR methods used to acquire *ex situ*, global and local measurements. Details of the pulse sequences are provided in the Supporting Information (S3 & S4).

2.3.1 Bulk ¹H NMR Spectroscopy

A bulk/pure liquid ¹H spectrum from the reactor outlet was measured with a standard pulse-acquire sequence in a 5 mm NMR tube in a Bruker BioSpin WB DMX 300 spectrometer operating at a ¹H frequency of 300.13 MHz. This spectrometer consisted of a 7.05 T vertical superconducting magnet and an 8 mm ¹H/²H I.D. radiofrequency coil with a 90° pulse length of 15 μs.

2.3.2 Operando Global and Local Reactor Measurements

All *operando* reactor measurements were conducted in a Bruker Avance III SWB 300 MHz spectrometer with a 66 mm I.D.,

equipped with a 7.05 T vertical superconducting magnet. Measurements were taken using a 40 mm long dual resonance birdcage coil, tuned to a ^1H resonance of 300.89 MHz and used a 90° pulse length of 21 ms. Three types of experiments were performed: (i) The 13-Interval Alternating Pulsed Field Gradient Stimulated Echo combined with Periodic Refocusing of J -Evolution by Coherence Transfer (APGSTE-PROJECT)^[14,15] was used to acquire the global D - T_2 distributions; (ii) phase-encoded APGSTE-PROJECT was used for local D - T_2 distributions; and (iii) standard 1D chemical shift imaging (CSI)^[16] was used to acquire local ^1H spectra. Acquisition times for (i), (ii), and (iii) were 23 mins, 12 h, and 10 mins, respectively. For (iii), the number of k -space points was restricted to 8, which gave a balance between adequate SNR and acquisition time. Data acquisition times for (iii) were limited by the financial costs associated with prolonged continuous flow of reactant and deuterated solvent. All recycle times were based on T_1 - T_2 relaxation data and were set as $5 \times T_1$ of the longest T_1 in the system. Details of the characterisation of species in mixtures under non-reactive conditions is reported in the Supporting Information (S3), and part of the characterisation is shown in Fig. 3.

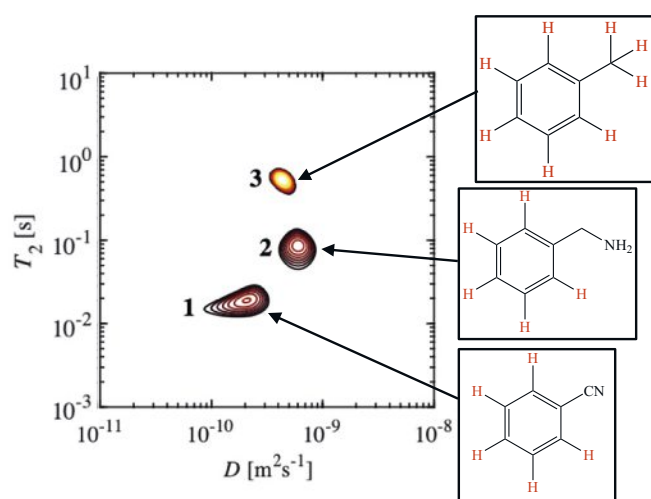


Fig. 3. The D - T_2 distributions for 1:1:1 imbibed mixture of BN, BA, and toluene, represented by peaks 1, 2, and 3, respectively. The protons in red correspond to peaks in the distribution.

2.4 Data Analysis

All D - T_2 data for reaction tracking were inverted using Tikhonov regularisation combined with generalised total variation (GCV) to locate the optimum smoothing parameter. Distributions were produced with 200×200 logarithmically spaced points. The peak integrals for each component were extracted within the distributions and adjusted post-processing to account for T_2 weighting during the echo times within the D - T_2 pulse sequence. Adjustments for T_1 weighting were not required as T_1 was found to be similar for the characterisations carried out with individual solutions of BN, BA, and toluene and in mixtures. The integrals were then normalised to the same measurement within the reactor under non-reactive conditions (*i.e.* without the catalyst reduction step) and this was taken as the measurement at $t=0$. This distribution is shown in Fig. 4j and was used to calculate the conversion and selectivity.

3. Results and Discussion

3.1 Global Measurements

Fig. 3 shows an example of a D - T_2 correlation plot taken for a model/phantom mixture of 1:1:1 BN:BA:Tol imbibed in the

catalyst pellets under non-reactive (*ex situ*) conditions. The species observed here are solely from intrapellet liquid. The main features of the plot show three peaks with a 5:5:8 integral ratio: (1) aromatic protons on BN, (2) aromatic protons on BA, and (3) aromatic and alkyl peaks on toluene. No evidence was seen for $-\text{NH}_2$ protons and it was assumed that this was due to the effect of the quadrupolar ^{14}N nucleus rendering the T_2 values of $-\text{NH}_2$ protons to be too small to be detected. Assignment of peaks was also supported with 1D and 2D T_1 , D , and T_2 measurements, as detailed in Supporting Info (S3).

The progression to steady-state was tracked using the global D - T_2 experiment, and the resulting distributions are shown in Fig. 4. The appearance of the D - T_2 plot at 338 mins is consistent with that presented in Fig. 3 and the small differences in diffusion and T_2 values and broader distributions were attributed to slight temperature changes in the reactor, different species compositions and different NMR spectrometers used. The quantity of toluene was unable to be reliably obtained from the first three time points at 23, 68, and 113 mins (Fig. 4a-c), likely due to a combination of its low concentration and proximity to the BA peak. Nonetheless, a clear trend in the peak integrals was observed: BN (1) decreased steadily, followed immediately by an increase in BA (2), and later an increase in toluene (3). Indeed, literature studies report an increase in the hydrogenolysis pathway forming toluene once an initial build-up of BA is observed.^[17–19] Steady state was reached around 300 mins, with a residence time of ~ 46 mins, based on the flow rate, mass of catalyst, and pore volume. The plateau before 100% conversion of BN was reached indicated the residence time was not sufficient for full conversion. Further work is required to study the presence of mass transfer limitations which may be influencing reactor performance at these operating conditions.

3.2 Local Measurements

Details of the pulse sequences and NMR parameters used for local (spatially resolved) measurements are given in Supporting Information (S4). Fig. 5 shows the D - T_2 distributions as a function of spatial position along the axial z -dimension at steady state (>400 mins) from a separate study with a fresh catalyst packing but performed under the same operating conditions as the global measurements shown in Fig. 4. The results in Fig. 5 show that hydrogenation of BN to BA was dominant at the top of the reactor, whilst hydrogenolysis to toluene occurred mostly at the bottom of the bed. This indicated that longer residence times of the liquid in contact with the catalyst promoted the undesirable formation of toluene. From the plot of chemical species versus axial position (Fig. 5f), chemical species versus residence time can be extracted, in effect obtaining the full kinetic information from one experiment. The average residence time within each slice was 6, 17, 29, and 40 mins, respectively, as the axial position increases. From these initial experiments qualitatively the system is following the expected $\text{A} \rightarrow \text{B} \rightarrow \text{C}$ pathway with first order loss of BN, a typical intermediate profile for BA and zero order formation of toluene.^[19]

^1H chemical shift imaging (CSI) is an NMR technique that adds spatial information to conventional NMR spectra (see Supporting Information S4). In this study, this method was used to acquire 64 equally spaced NMR spectra, each corresponding to a spatial location in the reactor. Of these 64, 12 corresponded to the active catalyst region. Fig. 6a shows ^1H spectra extracted from three spatial positions along the reactor: within the glass beads (-1 cm); at the centre of the active catalyst region (0 cm); and at the bottom of the active catalyst region (3.5 cm). Each spectrum contained the peak corresponding to solvent hydroxyl protons at ~ 5.8 ppm and aromatic resonances at ~ 7.8 ppm. No clear peaks were observed in the alkyl region at -1 cm, which was expected as no products were formed in this glass bead only area. However, at 0 and 3.5 cm the alkyl resonances were present, indicating the formation of toluene.

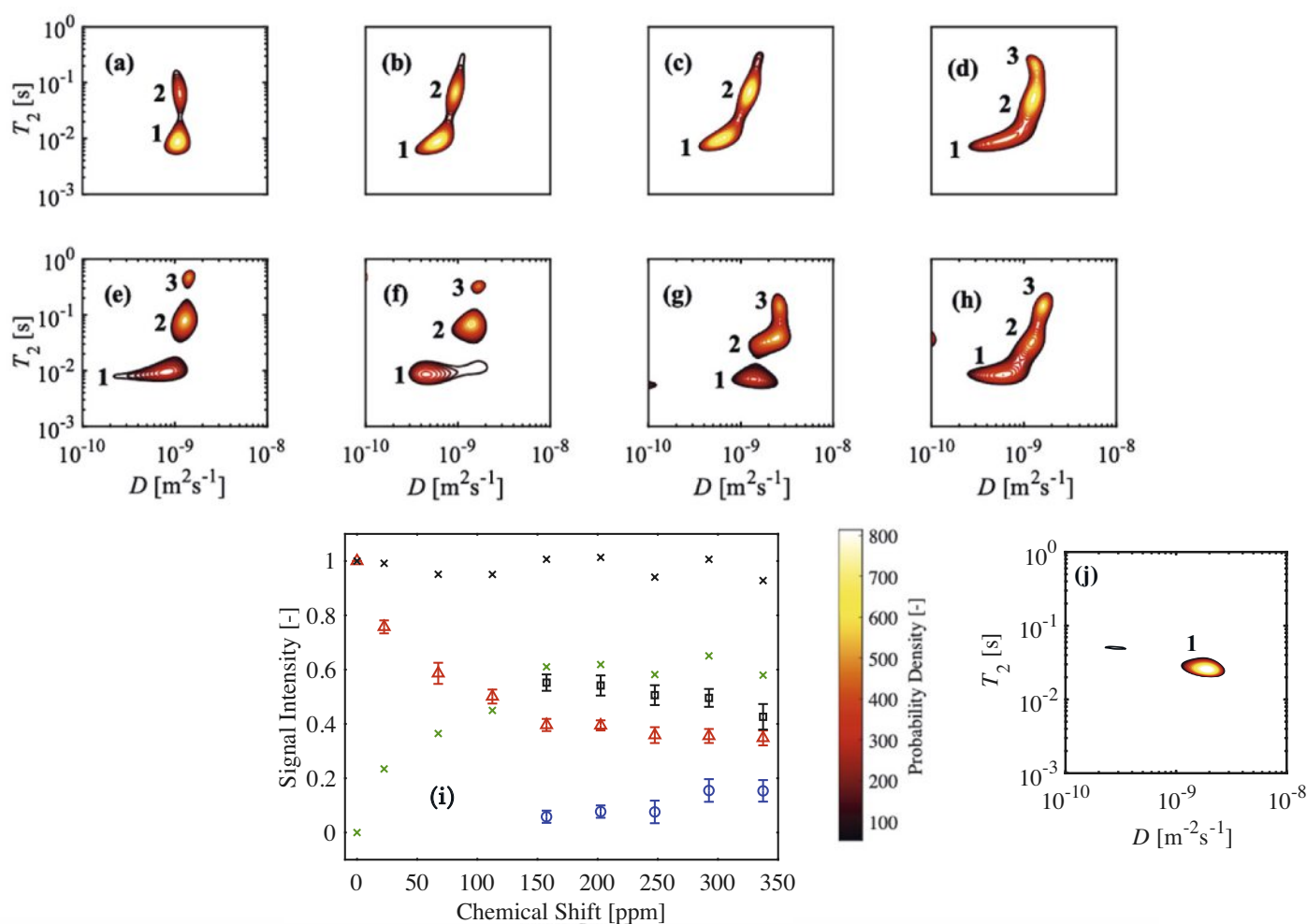


Fig. 4. The global D - T_2 distributions generated using Tikhonov regularisation during TBR start-up of BN hydrogenation as a function of time on stream. The datasets correspond to reaction at times (a) 23, (b) 68, (c) 113, (d) 156, (e) 203, (f) 248, (g) 293, and (h) 338 mins. Times are the mid-point of the data acquisition time and (j) BN (Δ), BA ($\square$), and toluene ($\circ$) are represented by peaks 1, 2, and 3, respectively. The total products ($\times$) and mass balance ($\times$) are shown. The peak integrals extracted from the D - T_2 distributions (a)-(h), relative to the BN integral from distribution (j) under non-reactive conditions at time 0. Error bars are the standard error multiplied by the students' T-distribution from two repeat experiments.

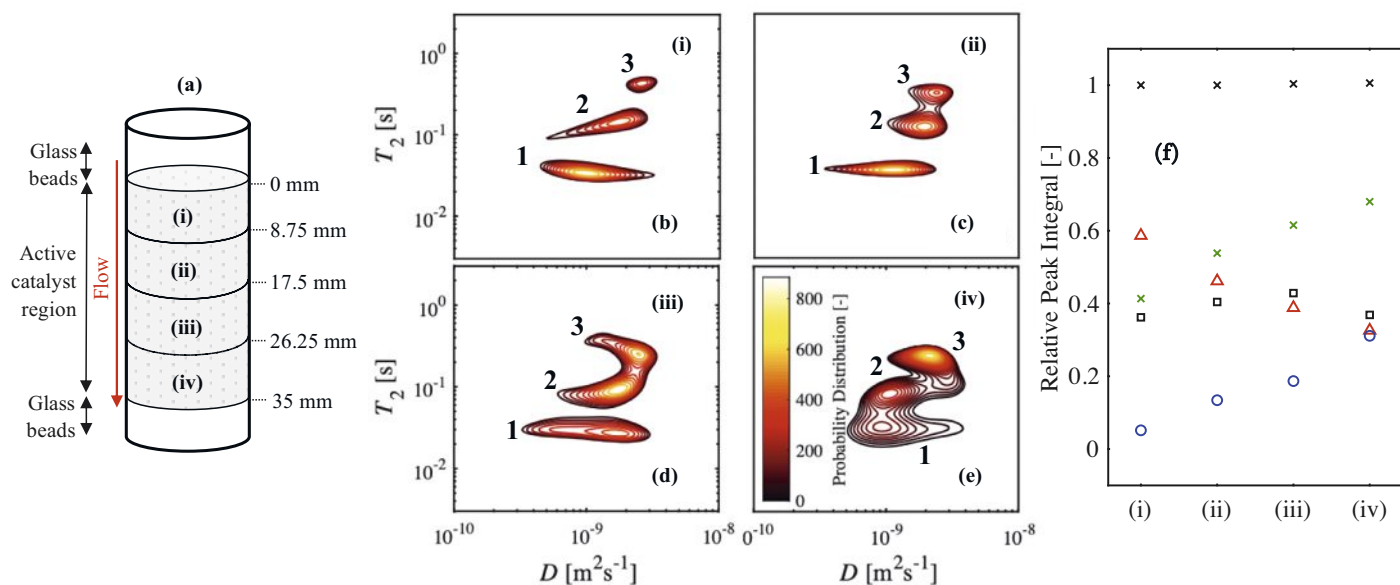


Fig. 5. (a) A schematic displaying the location of the axial D - T_2 distributions. (b-e) The local distributions acquired using the phase encoded D - T_2 technique at steady-state at positions (i) 0-8.75, (ii) 8.75-17.5, (iii) 17.5-26.25, and (iv) 26.25-35 mm respectively, where 0 mm is the top of the catalyst bed. (f) The corresponding relative peak integrals as a function of axial position for BN (Δ), BA ($\square$), and toluene ($\circ$), and are represented by peaks 1, 2, and 3, respectively. The total products ($\times$) and mass balance ($\times$) are shown.

Due to large ^1H spectral overlap (as a result of magnetic susceptibility broadening), accurate quantification of chemical composition was not possible, although the variation in chemical shift as a function of catalyst bed length was qualitatively assessed. Quantitative analysis through chemical shift may be possible with other NMR techniques, *e.g.* correlation spectroscopy (COSY), which rely on cross peaks arising from J -coupling and are independent of the line broadening caused by susceptibility differences.^[20] The chemical shift of the alkyl peak (the shoulder between ~ 3.5 ppm and 2.1 ppm) at each position was estimated, as shown in Fig. 6b, and indicates a sharp decrease in chemical shift at the top of the bed, followed by a steadier decrease towards the bottom of the reactor. The high quantities of toluene at lower points in the reactor were consistent with the results observed using the local D - T_2 measurements.

Fig. 7 shows the ^1H spectrum of a bulk liquid aliquot taken from the reactor outlet at steady state. Using the integral of the BN aromatic resonance, $\sim 68\%$ reactant conversion was calculated, whilst selectivity for BA and toluene was $\sim 41\%$ and $\sim 59\%$, respectively, estimated from the alkyl peak integrals. These values were close to those estimated from the D - T_2 correlation distribution integrals calculated for the bottom slice of the reactor (2.625–3.5 cm, Fig. 5e), with $\sim 67\%$ BN conversion, and 44% and 55 % selectivity for BA and toluene, respectively. This suggests that any reactant or product accumulation in the reactor was minimal.

4. Conclusions

This paper reports the first application of D - T_2 measurements to track *in situ* global and local intra-pellet chemical compositions in an operating TBR under ambient conditions. The relative global compositions of BN, BA, and toluene during BN hydrogenation were estimated to have reached steady state at around ~ 300 mins. Subsequently, local measurements were conducted to observe the variation in BN, BA, and toluene spatially in the axial direction of the reactor thus providing profiling and kinetic information from one experiment. Variation in the flow rate would allow a more established link between chemical composition, kinetics and hydrodynamics within the bed. A preference was shown for the hydrogenolysis pathway to form toluene at higher residence times, *e.g.* towards the reactor outlet. This study showed D - T_2 distributions demonstrate the ability to separate ^1H species (when ^1H spectral resolution is not possible due to magnetic susceptibility broadening) which enables quantitative compositions to be attained.

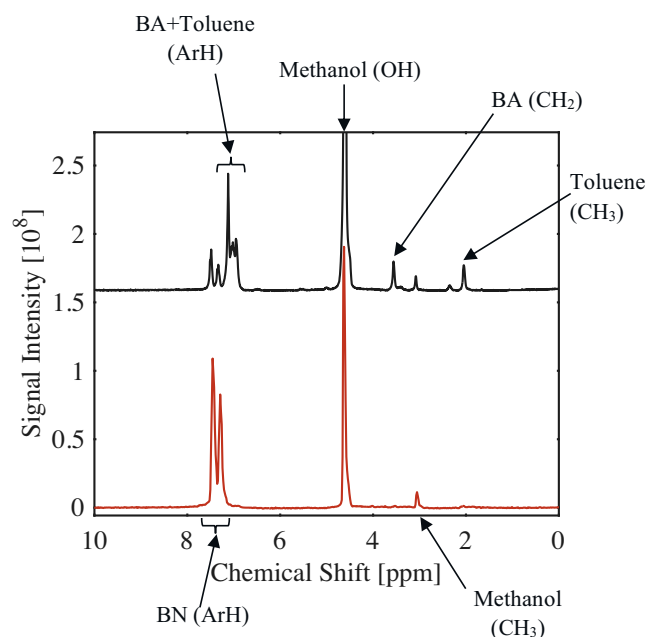


Fig. 7. A ^1H spectrum of the reactor outlet acquired under steady-state reactive conditions (–) and under non-reactive conditions (–).

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Supplementary Information

Supplementary information is available at <https://doi.org/10.2533/chimia.2024.129>.

Author Contributions

The authors confirm contribution to the paper as follows: study design: Amy Sparks, Mick Mantle, Colin Brennan, and Lynn Gladden; implementation and data collection: Amy Sparks; analysis: Amy Sparks; interpretation of results: Amy Sparks, Mick Mantle, Colin Brennan and Lynn Gladden; draft manuscript preparation: Amy Sparks. All authors reviewed the results and approved the final version of the manuscript.

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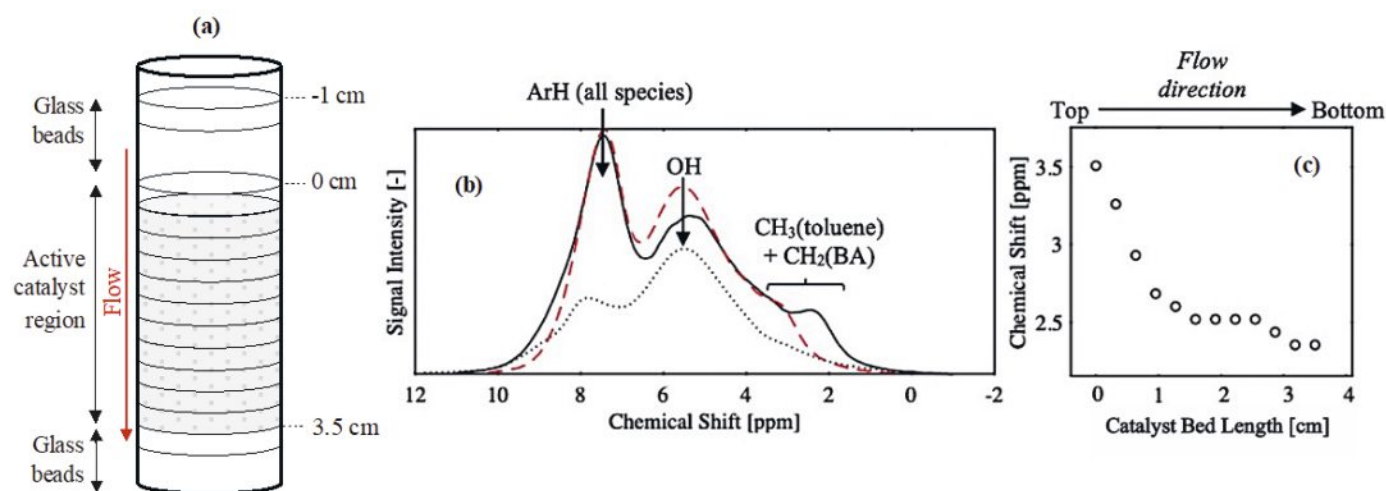


Fig. 6. (a) A schematic displaying the location of the (b) extracted CSI ^1H spectra from 1.6 mm slices in the reactor obtained at steady state, corresponding to -1 (····), 0 (---), and 3.5 (—) cm. 0 cm represents the top of the catalyst bed, therefore the measurement at -1 cm corresponds to the unreacted liquid surrounding the glass beads. (b) The approximate chemical shift of the alkyl peak as a function of catalyst bed length.

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