Multi-Nuclear, High-pressure, Operando FlowNMR Spectroscopic Study of Rh/PPh₃ - Catalysed Hydroformylation of 1-Hexene

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Supplementary information

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Experimental

Materials and methods:

Unless stated otherwise, all manipulations were carried out under an inert atmosphere of argon using standard Schlenk line techniques. 1-hexene was purchased from Acros Organics, stirred over potassium overnight followed by a fractional distillation under argon over the same metal. Triphenylphosphine, [Rh(acac)(CO)$_2$] and 1,3,5-trimethoxybenzene were purchased in the highest purity available and used without further purification. Toluene was freshly distilled from sodium under argon before every use. Carbon monoxide (99.99 %) and hydrogen (99.95 %) gases were supplied by BOC.

The hydroformylation of 1-hexene was carried out in a Büchi Miniclave pressure reactor made of glass and stainless-steel lid connected to the flow NMR apparatus via 1/16” Swagelok connections. A micro-annular gear pump (mzr-6355 from HNP Mikrosysteme GmbH) was used to circulate the reaction mixture through the 1/16” polyetheretherketone (PEEK, Upchurch Scientific) tubing with 0.76 mm i.d. connected to an InsightMR flow tube (Bruker) placed in the probe of the spectrometer. The inner volume the flow system was approximately 6.4 mL.

NMR spectra were recorded on a Bruker 500 MHz Advance II$^{+}$ Ultrashield equipped with a nitrogen-cooled BBO Prodigy CryoProbe. $^1$H NMR chemical shifts are referenced against TMS (99.5 % purity in CDCl$_3$) and $^{31}$P NMR shifts are referenced to 85% H$_3$PO$_4$. The reaction monitoring software used was InsightMR, and data processing was performed with TopSpin 4.0.6 and DynamicCenter 2.5.6.
Caution: carbon monoxide is a colourless, odourless, flammable and highly toxic gas – experiments should only be conducted in the presence of a calibrated CO sensor.

The FlowNMR apparatus was flushed with laboratory grade toluene and then purged with argon for at least 10 minutes to remove traces of air and moisture. Triphenylphosphine (see table below), dicarbonyl(acetylacetonato)rhodium(I) (12.90 mg, 0.05 mmol) and 1,3,5-trimethoxybenzene (33.64 mg, 2 mmol) were added to the pressure glass vessel together with a teflon-coated stir bar followed by sealing of the autoclave with all tubing attached (see Figure S1). The system was leak-checked, vacuum-argon cycled three times at room temperature and then kept under argon. The inlet of the flow tube was then moved into a separate Schlenk flask that contained dry toluene under argon, and the outlet to the waste bottle. Dry toluene was then pumped through the flow tube for 5 minutes to leave the transfer lines, pump and flow tube filled with dry solvent (6.4 mL). Thereafter, both flow tube ends were reconnected to the reactor which was topped up with dry toluene (15 mL) and 1-hexene (84.16 mg, 1.25 mL, 10 mmol) against a flow of argon. The NMR tube and tip were then inserted into the spectrometer, stirring started and the reaction mixture was pumped through the system at 4 mL/min once all solids had fully dissolved. The reactor, heat exchanger and NMR probe were heated to 50 °C, and once the temperature had stabilised throughout the system the NMR spectrometer lock was turned off, shimmed on $^1$H peaks and tuned to proton and phosphorus. Spectra of the reagents were recorded both statically and at 4 mL/min. Acquisition parameters for interleaved $^1$H, selectively excited $^1$H and $^{31}$P{$^1$H} NMR measurements were entered (details below) and the sequence commenced to start the FlowNMR reaction monitoring. After acquisition of at least one sequence of measurements the autoclave was firstly pressurised with 6 bar H$_2$ followed by other 6 bar of CO to start the reaction. At the end of the reaction additional calibration spectra with and without flow were recorded before all heating was switched off, the flow stopped and the reactor carefully vented into the fumehood. An aliquot of the reaction mixture was taken by syringe and analysed by GC-FID/MS to confirm $^1$H NMR spectral assignments.
| \([\text{PPh}_3]/[\text{Rh}]\) | \(\text{PPh}_3\) loadings                |
|-----------------|---------------------------------------|
| 0               | -                                     |
| 1               | 13.12 mg, 0.05 mmol                   |
| 3               | 39.35 mg, 0.15 mmol                   |
| 6               | 78.69 mg, 0.3 mmol                    |
| 10              | 131.15 mg, 0.5 mmol                   |
| 20              | 262.30 mg, 1 mmol                     |

Table S1. Amounts of \(\text{PPh}_3\) charged within the autoclave reactor for each flow run reaction with different number of ligand equivalents.
Flow tube inlet
Flow tube outlet
Pressure reader
H₂ connection
CO connection
Schlenk line connection
Liquid addition port
Figure S1. Autoclave used for the Rh-catalysed hydroformylation of 1-hexene. CO, H₂ and both flow tube parts are shown connected to the reactor lid.
**Analysis**

**FlowNMR acquisition parameters:**

$^1$H, selectively excited $^1$H, and $^{31}$P{$^1$H} NMR experiments were interleaved in each cycle and continuously executed every 5 minutes until the end of the reaction.

$^1$H NMR (zg30):
- NS = 16 s
- D1 = 1 s
- RG = 9
- O1P = 4.7 ppm
- SW = 40 ppm
- Expt = 42 s

Selective excitation $^1$H NMR (seldpfgse_calc.ptg):
- NS = 32 s
- D1 = 1 s
- RG = 203
- O1P = -5 ppm
- SW = 20 ppm
- CNST 21 = -8 ppm
- CNST 55 = 5 ppm
- Expt = 1 min 37 s

$^{31}$P{$^1$H} NMR (zgpg):
- NS = 160 s
- D1 = 0.5 s
- RG = 203
- O1P = 50 ppm
- SW = 400 ppm
- Expt = 2 min 27 s
Static calibration spectra were recorded with the same parameters but with longer D1 that were changed for every experiment as follows:

- $^1$H NMR spectra $\Rightarrow$ D1 = 60 s
- Selective excitation $^1$H NMR spectra $\Rightarrow$ D1 = 10 s
- $^{31}$P$^{(1)}$H NMR spectra $\Rightarrow$ D1 = 90 s

**GC analyses:**

GC-FID/MS analyses were carried out on a Shimadzu GCMS-QP2020 ultra NCI with a non-polar BPX5 column (30 m x 0.25 mm x 0.25 μm) using pentane as solvent to prepare samples and electron ionization for MS mode. Split ratio was 10:1, column pressure 320.5 kPa, column flow = 3.14 mL/min, injector temperature 250 °C, FID temperature 250 °C with argon. The initial oven temperature was 50 °C, then hold for 3 minutes, ramp at 3 °C /min to 120 °C, ramp at 20 °C /min to 250 °C, then hold for 3 minutes.

Analyte retention times were: 1-hexene (1.55 min), 2-hexene (1.60 min), 3-hexene (1.60 min), toluene (2.94 min), 2-methylhexanal (4.56 min), $n$-heptanal (5.53 min), 1,3,5-trimethoxybenzene (20.94 min), triphenylphosphine (26.33 min). A sample chromatogram is shown in Figure S2. The same methods as for FID separation were used in GC-MS(EI) mode: 1-hexene (m/z = 56 [M]$^+$, 100 %), 2-hexene (m/z = 55 [M]$^+$, 100 %), 3-hexene (m/z = 56 [M]$^+$, 100 %), 2-methylhexanal (m/z = 58 [M]$^+$, 100 %), $n$-heptanal (m/z = 70 [M]$^+$, 100 %), 1,3,5-trimethoxybenzene (m/z = 168 [M]$^+$, 100 %), triphenylphosphine (m/z = 262 [M]$^+$, 100 %). Mass fragmentation spectra are shown in Figures S3-S9.

![Figure S2. Chromatogram obtained from the hydroformylation reaction mixture of 1-hexene.](image-url)
Figure S3. Mass spectrum fragmentation of 2-methylhexanal

Figure S4. Mass spectrum fragmentation of n-heptanal

Figure S5. Mass spectrum fragmentation of 1,3,5-trimethoxybenzene

Figure S6. Mass spectrum fragmentation of triphenylphosphine

Figure S7. Mass spectrum fragmentation of 1-hexene
Figure S8. Mass spectrum fragmentation of 2-hexene

Figure S9. Mass spectrum fragmentation of 3-hexene
Quantitative NMR acquisition

Correction factors

Flow effects resulting from different degrees of pre-magnetisation may be corrected for by comparing integral values from flow spectra with static reference measurements. A correction factor is then calculated for each peak comparing the integral at static and flow conditions and used for quantifying the data (Figure S10 and Table S2).

\[ CF = \frac{I_{\text{static}}}{I_{\text{flow}}} \]

\[ I_{\text{corrected}} = CF \times I \]

\[ C_{\text{compound}} = \frac{I_{\text{corrected}}}{N_{\text{internal standard}} \times N_{\text{compound}}} \times C_{\text{internal standard}} \]

Figure S10. Formulae used to calculate the concentrations of each compound during the reaction. I=peak integral, CF=correction factor, C=concentration and N=number of nuclei contributing to the peak.

Table S2. Correction factors obtained from \(^1\)H NMR spectra of the mixture of compounds present during hydroformylation of 1-hexene at 50 °C under 12 bar of syngas. Substrate and internal standard (1,3,5-trimethoxybenzene) could be calculated at the beginning and end of flow run whereas hydrogen and products were only calculated when the acquisition was stopped.

|          | 1-hexene (start) | 1-hexene (end) | TMB aromatic (start) | TMB aromatic (end) | TMB methyl (start) | TMB methyl (end) | 1-heptanal (end) | 2-methylhexanal (end) | Hydrogen (end) |
|----------|------------------|----------------|----------------------|-------------------|-------------------|-----------------|-----------------|----------------------|----------------|
| CF       | 4.54             | 4.29           | 2.56                 | 2.71              | 1.76              | 1.69            | 5.09            | 4.70                 | 1.13           |

Selectively excited \(^1\)H spectra were recorded at a much higher RG settings. Thus, to allow these experiments to be quantitative relative to other signals detected without selective excitation, a relative integral value (RIV) has to be calculated to account for the difference in receiver gains (Figure S11).
\[
RIV = \frac{I_{\text{hydride}} \times RG_{\text{normal}} \times RGCF}{RG_{\text{hydride}}}
\]

\[
[\text{Hydride}] = RIV \times \frac{C_{\text{internal standard}}}{I_{\text{internal standard}}} \times \frac{C_{\text{internal standard}}}{N_{\text{internal standard}}}
\]

Figure S11. Formulas used to calculate the concentrations of hydride species. I=peak integral, CF= correction factor, C= concentration and N=number of nuclei causing the peak.

**T<sub>1</sub> longitudinal relaxation time**

A fully quantitative NMR experiment requires a detection time of at least 5 times \(T_1\) relaxation time. The latter can vary with temperature, solvent, reaction mixture and concentration. We thus measured \(T_1\) for each \(^1\text{H}\) and \(^{31}\text{P}\ \{^1\text{H}\}\) NMR signal under our hydroformylation conditions. The \(D_1\) for static experiment was then chosen to be 5 times higher than the longest \(T_1\) found for each type of nuclei.

Table S3. \(T_1\) values obtained for a mixture of compounds in protonated toluene under 6 bar of \(\text{H}_2\) and 50 °C.

| Longitudinal relaxation time \(T_1\) on \(^1\text{H}\) spectra (s) | n-heptanal (1) | PPh3=O (2) | PPh3 (3) | TMB aromatic (4) | 1-hexene terminal alkene (5) | 1-hexene internal alkene (6) | Hydrogen (7) | TMB methyl (8) |
|---|---|---|---|---|---|---|---|---|
| \(\text{n-heptanal}\) | 8.65 | 4.08 | 4.98 | 5.59 | 8.01 | 7.18 | 1.22 | 3.06 |
Figure S12. \( T_1 \) function found by \(^1\text{H} \) NMR for a mixture of compounds in protonated toluene under 6 bar of \( \text{H}_2 \) and 50 °C.
Table S4. \( T_1 \) values obtained by \( ^{31}P\{^1H\} \) NMR for a mixture of compounds in protonated toluene under 6 bar of \( H_2 \) and 50 °C.

| Longitudinal relaxation time \( T_1 \) on \( ^{31}P\{^1H\} \) (s) |
|---------------------------------------------------------------|
| \( PPh_3=O \) (1)                                             | \( PPh_3 \) (2) |
| 3.83                                                          | 17.1            |

Figure S13. \( T_1 \) function found by \( ^{31}P\{^1H\} \) NMR for a mixture of compounds in toluene under 6 bar of \( H_2 \) at 50 °C.
Catalysis

Reaction selectivity

Chemoselectivity towards hydroformylation is calculated as: \%
\text{=} \frac{([\text{n-heptanal}] + [2\text{-methylhexanal}])}{([\text{h-heptanal}] + [2\text{-methylhexanal}] + [2\text{- and 3-hexene}])} \times 100.

Linear-to-branched product ratio is calculated as: L:B = \frac{([\text{n-heptanal}])}{([2\text{-methylhexanal}])}.
Conversion is calculated as: \%
= 100 – \frac{([1\text{-hexene}])}{([1\text{-hexene}]_0)} \times 100.

Reaction kinetics

Reaction rate constants were calculated from the compound concentration profiles in the first 100 min of the reaction. Linear regressions in suitable regimes were used that did not necessarily span the same time intervals.

Table S5. Calculated reaction rate constant for each compound present in the reaction mixture of the hydroformylation reaction for six experiments loaded with same [Rh] = 2.5 mM, [1-hexene] = 500 mM and [TMB] = 100 mM and different [PPh_3]. The rate constants were calculated in the first 100 min of the reaction.

| \[\text{PPh}_3]/[\text{Rh}]=0 | \[\text{PPh}_3]/[\text{Rh}]=1 | \[\text{PPh}_3]/[\text{Rh}]=3 | \[\text{PPh}_3]/[\text{Rh}]=6 | \[\text{PPh}_3]/[\text{Rh}]=10 | \[\text{PPh}_3]/[\text{Rh}]=20 |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Consumption of 1-hexene \(k_{\text{obs}}\)=mM/min | 0.69 | 0.82 | 2.43 | 1.95 | 1.30 | 1.23 |
| Formation of n-heptanal \(k_{\text{obs}}\)=mM/min | 0.22 | 0.46 | 1.62 | 1.75 | 1.19 | 1.08 |
| Formation of 2-methylhexanal \(k_{\text{obs}}\)=mM/min | 0.09 | 0.2 | 0.51 | 0.58 | 0.39 | 0.33 |
| Formation of 2- and 3-hexene \(k_{\text{obs}}\)=mM/min | 0.53 | 0.37 | - | - | - | - |
NMR experiments

$^{31}$P and $^1$H DOSY NMR experiments were carried out to calculate the diffusion of various rhodium complexes. By comparison, this allowed us to derive whether these species were monomeric or dimeric.

*Figure S14. $^{31}$P DOSY diffusion curve of [RhH(CO)$_2$(PPh$_3$)$_2$] (A/B) in the presence of OPP$_3$ (3) and PPh$_3$ (4).*
Figure S15. $^1$H DOSY diffusion curve of [RhH(CO)$_2$(PPh$_3$)$_2$] (A/B).
In addition, $^1$H-$^{31}$P HMBC measurements were carried out to verify the correlation of some hydride and phosphorus peaks.
Figure S17. $^1$H–$^{31}$P HMBC spectrum of $[\text{RhH(CO)}_2(\text{PPh}_3)_2]$ and $[\text{RhH(CO)(PPh}_3)_3]$. 
Rh-complexes characterisation

Table S6. $^1$H and $^{31}$P($^1$H) NMR data of the carbonyl ligands of various of [HRh(L)$_{2+x}$(CO)$_{2-x}$]$_x$ complexes.

| Complex                                      | $\delta$$_H$/ ppm | $\delta$$_P$/ ppm | $^1$J$_{RhP}$/ Hz |
|----------------------------------------------|--------------------|--------------------|-------------------|
| [RhH(CO)$_2$(PPh$_3$)$_2$] (A/B)              | -9.2               | 37.3               | 139.2             |
| [RhH(CO)(PPh$_3$)$_3$] (D)                   | -9.4               | 41.5               | 154.1             |
| [Rh(CO(CH$_2$)$_2$CH$_3$)(CO)$_3$(PPh$_3$)] (Q) | -                  | 27.7               | 71.8              |

Additional data

Flow NMR $^1$H Spectra

Figure S17. Flow $^1$H NMR spectra of hydroformylation of 1-hexene under our reaction conditions.
Figure S18. Flow $^1$H NMR spectra showing hydroformylation product formation of n-heptanal and 2-methylhexanal.

Figure S19. Flow $^1$H NMR spectra showing hydroformylation substrate consumption of 1-hexene.
Figure S20. Flow $^1$H NMR spectra showing dissolved hydrogen evolution during hydroformylation reaction.

Concentration profiles of hydroformylation reactions

Figure S21. Concentration profiles of hydroformylation reactions at 50 °C under 12 bar of syngas (1:1 H$_2$/CO) using [RhH(CO)$_2$(acac)] = 2.5 mM, [1-hexene] = 500 mM, [TMB] = 100 mM and [PPh$_3$] = 0 mM. [PPh$_3$]/[RhH(CO)$_2$(acac)] used is 0.
Figure S22. Concentration profiles of hydroformylation reactions at 50 °C under 12 bar of syngas (1:1 H₂/CO) using [RhH(CO)₂(acac)] = 2.5 mM, [1-hexene] = 500 mM, [TMB] = 100 mM and [PPh₃] = 2.5 mM. [PPh₃]/[RhH(CO)₂(acac)] used is 1.

Figure S23. Concentration profiles of hydroformylation reactions at 50 °C under 12 bar of syngas (1:1 H₂/CO) using [RhH(CO)₂(acac)] = 2.5 mM, [1-hexene] = 500 mM, [TMB] = 100 mM and [PPh₃] = 7.5 mM. [PPh₃]/[RhH(CO)₂(acac)] used is 3.
Figure S24. Concentration profiles of hydroformylation reactions at 50 °C under 12 bar of syngas (1:1 H\textsubscript{2}/CO) using [RhH(CO)(acac)] = 2.5 mM, [1-hexene] = 500 mM, [TMB] = 100 mM and [PPh\textsubscript{3}] = 15 mM. [PPh\textsubscript{3}] /[RhH(CO)(acac)] used is 6.

Figure S25. Concentration profiles of hydroformylation reactions at 50 °C under 12 bar of syngas (1:1 H\textsubscript{2}/CO) using [RhH(CO)(acac)] = 2.5 mM, [1-hexene] = 500 mM, [TMB] = 100 mM and [PPh\textsubscript{3}] = 25 mM. [PPh\textsubscript{3}] /[RhH(CO)(acac)] used is 10.
Figure S26. Concentration profiles of hydroformylation reactions at 50 °C under 12 bar of syngas (1:1 H₂/CO) using [RhH(CO)₂(acac)] = 2.5 mM, [1-hexene] = 500 mM, [TMB] = 100 mM and [PPh₃] = 50 mM. [PPh₃] /[RhH(CO)₂(acac)] used is 20.

References

1. A. M. R. Hall, J. C. Chouler, A. Codina, P. T. Gierth, J. P. Lowe and U. Hintermair, Catal. Sci. Technol., 2016, 6, 8406–8417.