Exploiting in-situ NMR to monitor the formation of a metal-organic framework

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Abstract

The formation processes of metal-organic frameworks are becoming more widely researched using in-situ techniques, although there remains a scarcity of NMR studies in this field. In this work, the synthesis of framework MFM-500(Ni) has been investigated using an in-situ NMR strategy that provides information on the time-evolution of the reaction and crystallization process. In our in-situ NMR study of MFM-500(Ni) formation, liquid-phase 1H NMR data recorded as a function of time at fixed temperatures (between 60 and 100 °C) afford qualitative information on the solution-phase processes and quantitative information on the kinetics of crystallization, allowing the activation energies for nucleation (61.4 ± 9.7 kJ mol⁻¹) and growth (72.9 ± 8.6 kJ mol⁻¹) to be determined. Ex-situ small-angle X-ray scattering studies (at 80 °C) provide complementary nanoscale information on the rapid self-assembly prior to MOF crystallization and in-situ powder X-ray diffraction confirms that the only crystalline phase present during the reaction (at 90 °C) is phase-pure MFM-500(Ni). This work demonstrates that in-situ NMR experiments can shed new light on MOF formation, opening up the technique to providing better understanding of their crystallisation mechanisms.

Introduction

Metal-organic framework (MOF) materials are widely studied and have many applications in areas ranging from gas storage and separation¹–³ to catalysis⁴ and chemical sensors.⁵–⁷ However, mechanistic aspects of MOF formation remain relatively understudied, with the majority of structural information obtained post hoc. Van Vleet et al. have reviewed the application of in-situ techniques to monitor nucleation and growth of MOFs,⁸ including X-ray diffraction⁹,¹⁰ and other X-ray scattering techniques,¹¹–¹³ while Cheetham et al. have described progress over the past 20 years in understanding the parameters that control
crystallization of MOFs in solution.\textsuperscript{14} Although pre-nucleation and pre-equilibrium species have been shown to play a critical role in MOF formation reactions,\textsuperscript{15} the majority of studies have focused on nucleation and subsequent crystal growth.

In the last few years, Wu and co-workers have shown that it is possible to gain high-quality structural information from in-situ synchrotron XRD measurements on a range of reactions, providing significant new insights into the time evolution of post-nucleation stages of MOF crystallization.\textsuperscript{16–19} Another example of this approach by Polyzoidis \textit{et al.} detailed the formation of ZIF-8,\textsuperscript{20} while Zahn \textit{et al.} used in-situ energy dispersive X-ray diffraction to study the coordination-modulated formation of zirconium fumarate MOFs.\textsuperscript{21} Recently, X-ray scattering techniques have been combined with computational studies to determine the factors that control the nucleation and growth parameters in the polymerisation of 2D covalent organic frameworks (COFs).\textsuperscript{22}

Microscopy techniques, including liquid cell transmission electron microscopy (LCTEM)\textsuperscript{23} and atomic force microscopy (AFM),\textsuperscript{24,25} have also become popular in investigating crystal growth mechanisms. These techniques can be extremely useful in combination with spectroscopic methods and X-ray scattering experiments, allowing multiple length scales of the MOF crystallization process to be probed.

To date, however, NMR spectroscopy has not been widely used to study the evolution of MOF syntheses. Nevertheless, solid-state NMR is a valuable technique for characterization of various aspects of MOF materials post-synthesis,\textsuperscript{26,27} including host-guest interactions, framework motion, and guest diffusion.\textsuperscript{28,29} Examples include the use of $^{129}$Xe NMR to identify interactions between frameworks and adsorbed guest molecules in an activated sample of UMCM-1,\textsuperscript{30} and studies of the diffusion of CO$_2$ guest molecules within the pores of MOF-74-Mg.\textsuperscript{31,32} Notably, these methods all report the post-synthetic behaviour of MOFs.

In recent years, there has been progress in the development of techniques to monitor the time-evolution of crystallization of organic materials from solution using in-situ NMR spectroscopy,\textsuperscript{33} both by the application of solid-state NMR measurements\textsuperscript{34,35} and by combined liquid-state and solid-state NMR measurements\textsuperscript{36,37} (the "CLASSIC" NMR technique). The CLASSIC NMR strategy, in particular, yields information simultaneously on the time-dependent changes that occur in the liquid phase (e.g., changes in molecular aggregation and speciation) and in the solid phase (e.g., changes in the polymorphic identity of the solid phase.
and the amount of solid produced) during crystallization from solution. In such experiments, the use of a high-field solid-state NMR spectrometer is essential to allow monitoring of both the liquid phase and the solid phase (we note that, if a traditional liquid-state NMR spectrometer were used to record liquid-state NMR data in a crystallizing system, the formation of the solid product would render shimming impossible to maintain). In addition to the application of these in-situ NMR strategies to study organic crystallization systems, they are also a potentially powerful approach to gain new insights into MOF formation processes, including the nature of the initial liquid-phase reaction system and mechanistic aspects of the formation of the solid product.

Herein, we exploit this type of in-situ NMR methodology (carried out using a high-field solid-state NMR spectrometer) to monitor the time-dependent changes that occur in a reaction system during MOF formation. The proton-conducting nickel-phosphonate MOF material MFM-500(Ni), first synthesized by Pili et al., was chosen for this study as it provides the opportunity to measure both $^1$H and $^{31}$P NMR spectra and as the metal sites in the MOF material are non-paramagnetic. By studying the MOF synthesis at several fixed temperatures, we demonstrate that quantitative kinetic information on the crystallization of MFM-500(Ni) can be obtained, particularly from the in-situ liquid-phase $^1$H NMR data. Small-angle X-ray scattering and in-situ X-ray diffraction measurements provide complementary insight to the mechanism deduced by NMR, and reveal that formation of the crystalline MOF is likely preceded by the aggregation of linker into cylindrical stacks in solution.

**Experimental**

For our in-situ NMR study of the synthesis of MFM-500(Ni), we simplified the previously reported synthesis by using only water and DMF as the solvent mixture (both of which were deuterated for the NMR measurements) and using increased concentrations of the reactants nickel nitrate [1.14 M] and 1,3,5-benzene-tri-p-phenylphosphonic acid (BTPPA) [0.57 M] (Scheme 1). Laboratory syntheses (see SI for details) and in-situ NMR syntheses were carried out using different total volumes but identical concentrations and reactant ratios. In the in-situ NMR experiments, the reaction solution (20 μL) was inserted into an NMR rotor and heated to the reaction temperature within the NMR spectrometer, with the experiment carried out at each of the following (fixed) temperatures: 60, 70, 80, 90, 100 °C. We note that the accessible temperature range of such experiments are limited by (i) the upper temperature limit of the NMR probe (<120 °C in our experiments) and (ii) pressure build-up in the sealed zirconia.
rotor. The \textit{in-situ} NMR strategy was implemented by recording a cycle of three different types of NMR measurement: (a) direct-excitation \textsuperscript{1}H NMR (to give the \textsuperscript{1}H NMR spectrum of the liquid phase), (b) direct-excitation \textsuperscript{31}P NMR spectra \textit{without} \textsuperscript{1}H decoupling (to give the \textsuperscript{31}P NMR spectrum of the liquid phase) and (c) direct-excitation \textsuperscript{31}P NMR spectra \textit{with} \textsuperscript{1}H decoupling (to give a \textsuperscript{31}P NMR spectrum containing contributions from both liquid and solid phases). This sequence of measurements was repeated throughout the duration of the experiment. The time to record one sequence of the three spectra was 7.1 min, representing the time-resolution of monitoring the MOF formation process in the \textit{in-situ} NMR experiment. The total duration of the experiment at each temperature was established from laboratory control experiments, and ranged from 4 - 36 hr. For all NMR measurements, the MAS frequency was 12 kHz, the recycle delay was 3 s, and 90° pulses were used with nutation frequencies of 56 kHz (\textsuperscript{1}H) and 42 kHz (\textsuperscript{31}P). For \textsuperscript{1}H NMR and \textsuperscript{31}P NMR measurements without \textsuperscript{1}H decoupling, the acquisition comprised 4 scans. For \textsuperscript{31}P NMR measurements with \textsuperscript{1}H decoupling, the acquisition comprised 128 scans and \textsuperscript{1}H decoupling was carried out using SPINAL-64\textsuperscript{40} at a nutation frequency of 56 kHz. More details of the experimental procedures are reported in Supporting Information.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme1.png}
\caption{Adapted synthesis of MFM-500(Ni), in which 1,3,5-benzene-tri-\textit{p}-phenyl phosphonic acid (BTPPA) and Ni(NO\textsubscript{3})\textsubscript{2}·6H\textsubscript{2}O were reacted in deuterated solvent (D\textsubscript{2}O/d\textsubscript{7}-DMF) at the following temperatures: 60, 70, 80, 90, 100 °C. Laboratory-scale product is shown in the vial and BTPPA linker dimer pairs in the crystal structure are shown right (see Figure S7 for more detail of the crystal structure).}
\end{figure}

\textbf{Results and discussion}

We focus initially on the liquid-state \textsuperscript{1}H NMR spectra recorded in our \textit{in-situ} NMR studies, as they show well-defined evolution of several distinct resonances throughout the MOF.
formation process and provide more detailed information than the $^{31}$P NMR spectra (which are discussed below). Figure 1a-e shows (as intensity contour plots) the time-evolution of the liquid-state $^1$H NMR spectrum at each temperature; three individual spectra from the beginning, middle and end of each experiment are also shown. At each temperature, the $^1$H NMR spectrum contains resonances in the range 7 – 8 ppm due to aromatic $^1$H environments (denoted $H_a$, $H_b$ and $H_c$) in the linker, assigned in Figure 1f (see section S2, Figure S1 for NMR peak assignments). All three $^1$H signals in this range shift non-monotonically as a function of time during the reaction, initially to lower ppm and then to higher ppm (Figure S2).

Figure 1. Intensity contour plots of the $^1$H NMR spectra recorded as a function of time in the *in-situ* NMR study of MFM-500(Ni) synthesis, and individual spectra selected at specific times (indicated by horizontal dashed lines in the contour plots), at (a) 60 °C, (b) 70 °C, (c) 80 °C, (d) 90 °C and (e) 100 °C. Assignments of the three peaks due to aromatic $^1$H environments (denoted $H_a$, $H_b$ and $H_c$) in the BTPPA linker are shown in (f). The spectra are shown without normalization.
To better understand the shifts of these \(^1\)H signals, \(^1\)H NMR spectra were measured for solutions containing just the BTPPA linker at room temperature in both \(d_6\)-DMSO and in the reaction solvent mixture (\(D_2O/d_7\)-DMF) (Figures S4 and S5 respectively), and also in the reaction solvent mixture at the temperatures used in the \textit{in-situ} NMR study (Figure S6). At room temperature in \(d_6\)-DMSO, the \(^1\)H NMR peaks are sharp and well-resolved (Figure S4), but in the \(D_2O/d_7\)-DMF mixture (Figure S5) they are broader. Significantly, the peak due to \(^1\)H environments (\(H_d\)) in the central aromatic ring of the linker is at lower ppm relative to the other aromatic peaks (\(H_b\) and \(H_c\)), consistent with aggregation of the linker in the reaction solution. This interpretation is supported by the variable temperature \(^1\)H NMR spectra of the linker in the reaction solvent mixture (Figure S6); as temperature is increased, the peaks become increasingly well-resolved and shift to higher ppm, consistent with greater thermally-promoted disaggregation of the linker. Using this information, shifts in the peaks observed in our \textit{in-situ} \(^1\)H NMR spectra are tentatively assigned to a combination of deprotonation, aggregation and subsequent metal-complexation of the BTPPA linker. Significantly, these processes are not observable by simply monitoring nucleation and crystal growth by the other methods outlined in the Introduction above. The intensities of the \(^1\)H NMR peaks for the linker remain reasonably constant until nucleation and product precipitation begin, as discussed further below.

At each temperature, there is also a broad peak in the \textit{in-situ} \(^1\)H NMR spectra, initially at ~6.5 ppm but then shifting gradually towards ~4.5 ppm and becoming sharper over the course of the reaction. The evolution of this peak is ascribed to a change in the solvent mixture during the reaction, resulting from liberation of (non-deuterated) water molecules from the nickel coordination sphere, which ultimately constitute a significant proportion of the final solvent, with simultaneous H/D exchange. At the end of the reaction, the nominal solvent ratio \(d_7\)-DMF:D\(_2\)O:H\(_2\)O is approximately 4:3:1 (v/v/v).

To corroborate the \textit{in-situ} \(^1\)H NMR results, laboratory control experiments were carried out on a larger scale in which reaction solutions of identical concentration and reactant ratio were heated in screw-top vials at 60, 70, 80, 90 and 100 °C. For the experiment at 80 °C, \(^1\)H NMR and \(^{31}\)P\{\(^1\)H\} NMR spectra were recorded \textit{ex-situ} for samples extracted periodically from the reaction solution, showing good agreement with the \textit{in-situ} NMR results (Figure S8). In the
laboratory-control experiment at each temperature, the reaction occurred on a similar timescale to the corresponding in-situ NMR experiment. Both sets of experiments produced a green crystalline material, which was shown by powder XRD to be phase-pure MFM-500(Ni) (Figure S9). In both the in-situ NMR experiments and the laboratory-control experiments at all temperatures studied, this material was the only crystalline product observed.

We now consider the $^{31}$P NMR spectra recorded (with and without $^1$H decoupling) in the in-situ NMR study. Figure 2a shows an intensity contour plot of the in-situ $^{31}$P NMR spectra recorded without $^1$H decoupling (giving liquid-phase $^{31}$P NMR data) as a function of time during the MOF synthesis at 60 °C (and the first spectrum recorded in this experiment is shown in Figure S10). At this temperature, a single, broad peak is observed, and distinct $^{31}$P resonances from different linker environments are not resolved. The intensity of the signal decreases over the course of the experiment, consistent with loss of the linker from the solution phase. The intensity drops markedly from ca. 9 hr (Figure 2b) and continues to decay until ca. 20 hr, comparable to the behaviour observed in the in-situ $^1$H NMR data at 60 °C (see Figure 3).

The in-situ $^{31}$P NMR spectra recorded with $^1$H decoupling (which contain contributions from both liquid and solid phases) are uninformative regarding the formation of solid MFM-500(Ni) as the signal in these spectra remains broad and weak throughout the MOF formation process, possibly as a result of tuning/arcing problems experienced during measurement of these spectra. The first spectrum of this type recorded in the in-situ NMR study at 60 °C is shown in Figure S10. At higher temperatures, the in-situ $^{31}$P NMR spectra recorded with $^1$H decoupling are also uninformative due to the broadness of the peaks and weakness of the signal. For comparison, the solid-state $^{31}$P NMR spectrum for a powder sample of MFM-500(Ni) prepared ex situ, recorded under analogous conditions to the in-situ $^{31}$P NMR spectra with $^1$H decoupling, is shown in Figure S11.
Figure 2. (a) Intensity contour plot showing the time-dependence of the in-situ $^{31}$P NMR spectrum (recorded without $^1$H decoupling) at 60 °C, representing the liquid-state $^{31}$P NMR signal. (b) Intensity vs. time plot for the liquid-state $^{31}$P NMR signal.

To analyse the formation of solid material during the syntheses, an in-situ study of the reaction at 90 °C was carried out on beamline I12 at Diamond Light Source,\textsuperscript{41} recording the evolution of the powder XRD pattern as a function of time. An induction period of ca. 80 min is observed prior to formation of crystalline material of sufficient particle size to be observed by X-ray diffraction. The powder XRD data confirm that the first crystalline phase that appears is MFM-500(Ni), with no other crystalline phases observed at any stage of the reaction (Figure S12). Furthermore, the initial rise in the amount of MOF present is consistent with the rate of loss of the $^1$H NMR signal due to the BTPPA linker (Figure 3). Unfortunately, the reaction kinetics could not be reliably determined from the powder XRD data as the high concentration of the reaction solution (used to mimic the conditions in our in-situ NMR study) resulted in rapid formation of clumps of crystallites which tended to drop unpredictably out of the measurement region in the sample tube, leading to irregular drops in signal intensity (Figure S13). Instead, a quantitative kinetic analysis of the MOF formation process based on the results from our in-situ $^1$H NMR study is presented below; in this regard, we emphasize that a distinct advantage of the in-situ NMR approach is that the data are measured for the whole sample volume throughout the experiment. The slightly longer induction time for product formation in the in-situ powder XRD experiment can be attributed to the need to form crystalline particles of sufficient size to observe sharp peaks in the powder XRD data. In order to characterize the formation of smaller particulates that are potentially invisible to the powder XRD measurements, ex-situ studies of MFM-500(Ni) formation were carried out using small-angle X-ray scattering (SAXS).

The timescale of the reaction at 90 °C, investigated by in-situ powder XRD, was too fast for reliable SAXS measurements at this temperature. Instead, the reaction was carried out in
the laboratory at 80 °C and SAXS data were recorded ex situ on samples extracted from the solution during the first 4 hr of the reaction. Data analysis (Figures S14 and S15) shows the initial formation and growth of core-shell cylindrical particles, elongation of which accelerates at around 135 min. This observation is consistent with the period corresponding to the significant decrease in the intensity of the linker protons in the in-situ 1H NMR experiment from ca. 2.5 hr onwards (Figure 3). These data support the concept of pre-aggregation of the linkers in the reaction solution, as observed in the variable-temperature 1H NMR spectra of the linker described above (Figures S4, S5 and S6), with metal ions bridging these aggregates to form core-shell cylinders that grow throughout the initial period (see Section S16 of SI for more details). Furthermore, the crystal structure of MFM-500(Ni) contains ligand "dimers" in a staggered conformation with respect to the three arms of each linker around the central phenyl ring, which are then eclipsed to the next pair of dimers in the ligand "stack" along the c-axis, all of which are bridged by columns of metal ions (Figure S7). We propose that the cylindrical structures suggested by the SAXS experiment may be the precursors for these stacks (Figure S16).

We now focus on establishing quantitative information on the reaction kinetics from analysis of the time-dependence of the peak intensities in the in-situ liquid-state 1H NMR spectra (Figure 1a-e). At each of the five reaction temperatures, the decrease in peak intensities as a function of time for the three aromatic 1H resonances of the BTPPA linker (Hₐ, Hₐ and Hₐ) was successfully fitted using the two-stage model of Gualtieri. All peaks in each 1H NMR spectrum were fitted to Lorentzian lineshapes, with the five overlapping peaks at higher chemical shift fitted simultaneously (an example is shown Figure S3). Each Lorentzian was defined by chemical shift, linewidth and intensity, with polynomial functions used to fit the baseline of the spectrum. From such fitting of the 1H NMR spectra, the time-dependent intensities for the three linker peaks were established. These intensities were then normalized by scaling the values so that the highest intensity for each peak was set to unity (Figure 3).

The Gualtieri model for nucleation and growth was used to fit our experimental data of peak intensities as a function of time (recalling that our measurements probe the decrease in peak intensities due to loss of the BTPPA reactant from the solution phase) using the following equation for the relative intensity of each peak as a function of time:

\[
I_{rel}(t,k_n,k_g,b,n) = 1 - \left( \frac{1 - \exp(-(k_n t)^n)}{1 + \exp(-(t - k_n^{-1})b^{-1})} \right)
\]
In this expression, $k_n$ is the rate constant for nucleation, $b$ is proportional to the standard deviation of the mean nucleation time ($1/k_n$), $k_g$ is the rate constant for crystal growth and $n$ denotes the dimensionality of the growth process. At a given temperature, the time-dependence of all three peak intensities was fitted simultaneously using this model giving a single set of values of $k_n, k_g$ and $b$, with only a scaling factor ($s_j$) varied independently for each peak (labelled $j = 1, 2, 3$). Thus, the intensity of peak $j$ at temperature $T$ and time $t$ is given by:

$$I^{(j)}(t, s_j, k_n^{(T)}, k_g^{(T)}, b^{(T)}) = s_j I_{rel}(t, k_n^{(T)}, k_g^{(T)}, b^{(T)}, n)$$

Consequently, the fitting of the data at each temperature involved only six fitted parameters: $s_1, s_2, s_3, k_n, k_g$ and $b$. At each temperature, the fitting process was carried out for different (fixed) values of the parameter $n$ (with $n = 1, 2$ or $3$). In all cases, the best fits were obtained using $n = 1$. The values of $k_n, k_g$ and $b$ obtained from the fitting process at each temperature are given in Table S1 (see section S5 of SI).
Figure 3. Intensity vs time plots for the three aromatic peaks of the BTPPA linker obtained from the *in-situ* $^1$H NMR data, together with the fits obtained using the Gualtieri model (*red lines*). Oscillations in the peak intensities in the first ~8 hr of the experiment at 60 °C were caused by variations in the probe tuning.

As shown in Table S1, the fitted parameters at 60, 70, 80 and 90 °C show the expected trends of increasing rate constants for nucleation ($k_n$) and growth ($k_g$) as temperature is increased, as well as a decrease in the standard deviation in the mean nucleation time ($b$) as temperature is increased. The probability distributions for nucleation as a function of time, determined from the kinetic parameters, are shown in Figure 4(a) (see Section S5 of SI) and
also exhibit the expected variation with temperature. The kinetic parameters determined at 60, 70, 80 and 90 °C are found to exhibit Arrhenius behaviour (Figures 4(b), 4(c)), allowing the activation energies for the nucleation and growth of MFM-500(Ni) to be determined as 

\[ E_{(n)}^{(a)} = 61.4 \pm 9.7 \text{ kJ mol}^{-1} \] and \[ E_{(g)}^{(a)} = 72.9 \pm 8.6 \text{ kJ mol}^{-1} \], respectively. These values are comparable to the activation energies of other single-phase forming reactions at similar temperatures determined using diffraction-based approaches.\(^{43-47}\) We note that the rate constant for growth \((k_g)\) determined at 100 °C is slightly lower than at 90 °C and clearly represents an outlier in the Arrhenius plot for the growth kinetics (Figure 4c); for this reason, the results at 100 °C were omitted from the calculation of activation energies.\(^{48}\)

![Figure 4](image)

**Figure 4.** (a) The nucleation probability distribution for MFM-500(Ni) formation, obtained by fitting the *in-situ* \(^1\)H NMR data to a Gualtieri model at each temperature studied. Arrhenius plots for (b) nucleation and (c) growth of MFM-500(Ni) using the values of \(k_n\) and \(k_g\), respectively, determined from our *in-situ* \(^1\)H NMR data. In each case, the best-fit line was calculated using the data points for 60, 70, 80 and 90 °C, as discussed in the text.

**Conclusions**

In summary, we have demonstrated the successful application of *in-situ* NMR methodology to monitor the formation of MFM-500(Ni), yielding information on the time-evolution of the liquid phase prior to and during MOF formation. In particular, monitoring the time-dependent changes in \(^1\)H signal intensities allow activation parameters to be determined for the nucleation and crystal growth processes. This method extends the scope and capability of *in-situ* monitoring of MOF synthases, most significantly with regard to early-stage processes in the liquid phase, offering the possibility to gain new information that is typically unattainable by X-ray scattering techniques. On the other hand, *ex-situ* SAXS and *in-situ* powder XRD provide complementary and confirmatory information on the MOF growth process in the present study, showing that formation of cylindrical linker-based aggregates precedes the
appearance of crystalline MFM-500(Ni). Further MOF syntheses are currently under investigation by the in-situ NMR method, which can readily be extended to interrogate other NMR-active nuclei.

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Conflicts of interest

There are no conflicts to declare.

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The fact that the fitted value of $k_g$ at 100 °C is out of line with those determined at lower temperatures merits further investigation. The peak shifts in the $^1$H NMR spectra as a function of time at 100 °C are consistent with those observed at lower temperatures, albeit occurring on a shorter timescale, and no other products are observed either from NMR or powder XRD data, suggesting that the low value of $k_g$ is unlikely to be due to an alternative reaction mechanism. We note that, in the experiment at 100 °C, the loss of the linker from the solution did not reach completion by the end of the experiment (see Figure 3). This fact may contribute to unreliability in the determination of $k_g$, which is significantly influenced by the behaviour of the data in later stages of the experiment. Unfortunately, we were unable to repeat the experiment at 100 °C due to the limited time available at the NMR facility used for this work.