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Crystal interface evolution is monitored by super-resolution technique during the growth of small MOF crystals into larger ones, in solution. The reaction orders for metal ion and organic linker are determined by isolation method and found to be independent from the corresponding MOF chemical formulas. This leads to the proposal of a new mechanism for MOF growth, involving the assembling and fragmentation of secondary building units, followed by fragment accumulation in a reversible transition layer at the interface of the MOF crystal.
Determining factors in the growth of MOF single crystals unveiled by \textit{in situ} interface imaging

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SUMMARY
We trace the evolution of crystal interface during the solvothermal synthesis of metal-organic frameworks (MOFs) in flow cell by \textit{in situ} dark-field microscope. Precise measurement of the growth rate at specific crystal facets allows for the extraction of the key determining factors for the crystal growth of five typical MOFs, i.e., Cu-MOF-74 (1D), Co-ZIF, Cu-MOF-2-BDC, Cu-MOF-2-NDC (2D), and HKUST-1 (3D). Rather than strongly correlating to the corresponding chemical formulas, the compositional organic linker and metal ion play vital but separate roles for different MOFs, giving insight into the crystal growth mechanism. Moreover, upon interruption, retreat and recovery of the crystal interface are observed, unveiling the influence from interface to MOF crystal growth. This also leads to the discovery of a transition layer that mediates the linkage of molecular building blocks to form MOF single crystals at the interface.

INTRODUCTION
The behavior of crystal interface is always intriguing, not only because it is the frontier for various substance exchange and chemical reactions but also due to its dynamic nature, where the composition and structure evolve over time.1–4 Such variety and dynamics make it extremely challenging to characterize crystal interface, especially in a liquid environment.5 In this study, we use a dark-field microscope (DFM) to trace the evolution of metal-organic framework (MOF) crystal interface during their solvothermal synthesis (Scheme 1); attempting to understand the behavior of MOF crystal interface in solution, we investigated (1) the linkage and dissociation of the building blocks, (2) the activity at specific crystal facets, and (3) the evolution of crystal facets during crystal growth. A super-line localization method was developed for the quantitative measurement of crystal facet progression in correlation with the metal ion, organic linker, and the reaction temperature. Based on this quantitative analysis, kinetic parameters of crystal growth, including reaction orders and activation energy, were derived for MOFs with different structures and crystal shapes. The determining factors for the interface evolution of MOF crystals are also discussed, providing new insight into their growth mechanism and guidance for their industrial production.

MOFs, a fast-developing class of network crystals, are chosen here as an ideal subject for the \textit{in situ} crystal interface study. These frameworks, formed by the coordination of organic linkers to metal ions, offer molecularly defined pore spaces within which matter can be manipulated and controlled, exhibiting excellent storage, separation, and conversion properties.6–11 Different from molecular crystals,12 ionic
crystals,13,14 and metals,15 the formation of MOFs not only involve the geometry of the molecular building blocks but also the directionality imparted by the coordination bonds.6,7,16 Efforts have been made to depict the nucleation stage for the generation of MOF crystals,17,18 as well as how organic linkers dissociate from the bulk crystal.19 Here, we focus on the crystal interface evolution stage after the nucleation and formation of crystals in visible size, where small MOF crystals with defined shapes and facets grow into larger sizes, to obtain kinetic knowledge of MOF growth (Figure S6). Five MOFs with representative crystal shapes and various unit cells are investigated, i.e., Cu-MOF-74, one-dimensional (1D) and rod shaped with a formula of \([\text{C}_6\text{H}_2\text{O}_2\text{(COO)}_2]_n\text{Cu}_2n;20\) Co-ZIF, \([\text{C}_7\text{H}_5\text{N}_2]_n\text{Co}_n;21\) Cu-MOF-2-BDC (BDC: terephthalic acid), \([\text{C}_6\text{H}_4\text{(COO)}_2]_n\text{Cu}_n;22\) Cu-MOF-2-NDC (NDC: naphthalene-1,4-dicarboxylic acid), \([\text{C}_6\text{H}_2\text{(C}_4\text{H}_4\text{(COO)}_2)]_n\text{Cu}_n;23\) two-dimensional (2D) and square shaped; and HKUST-1, \([\text{C}_8\text{H}_3\text{(COO)}_3]_2n\text{Cu}_3n;24\) three-dimensional (3D) and octahedron shaped.24

Differences are found in the determining factors for the growth of these MOFs. For all MOFs, the reaction temperature is important for their crystal size expansion, as reflected in the activation energy. Separate influence is determined from the compositional metal ions and organic linkers, revealed by the apparent reaction orders. The values are found to be inconsistent with the ratio of metal ion to organic linker in the formula of the corresponding MOF. This is in stark contrast to the prevailing view that these molecular building blocks are correlated during MOF growth.25,26

A previous attempt successfully investigated the separate roles of metal ions and organic linkers by their alternative introduction, using layer-by-layer synthesis.27 In
this study, these building blocks were mixed in the same solution, under conditions commonly applied to the solvothermal synthesis of MOFs. A control variable method was used to extract the impact from each building block, with the other conditions fixed. Different reaction orders for metal ions and linkers were observed in the growth of different types of MOFs, providing an experimental basis for the discussion of a mechanism for MOF crystal growth. A new mechanism is proposed for the growth of Cu-MOF-2-BDC and -NDC crystals, which involves the assembling and fragmentation of secondary building units (SBUs), followed by the accumulation of the fragments at the crystal interface. It is also interesting that unprecedented negative reaction orders for organic linkers were identified in the case of HKUST-1 and Cu-MOF-74.

Furthermore, the use of flow cell in this study allows for real-time pausing and resuming of the growth reaction. A retreat and recovery of MOF crystal interface are observed upon interruption to interface evolution of Cu-MOF-2-NDC. This can be associated with the linkage and dissociation of the molecular building blocks, where a reversible transition layer is likely to exist between the MOF crystal bulk and the solution environment. The thickness of the transition layer was measured, and it decreased as the crystal grew larger. Based on this observation, the critical size is estimated, at the point of which crystalline domain is formed as the core, marking the emergence of MOF crystal.

RESULTS AND DISCUSSION
Tracing the growth interface of MOF single crystal by in situ DFM
The evolution of MOF growth interface was traced in situ by DFM. Unlike atomically precise methods, such as electron microscopes and atomic force microscopes (AFMs) that were usually required to obtain insight at the molecular level, optical methods are rarely applied to the study of crystal growth owing to their limited spatial resolution. Here, we demonstrate that accessible, facile, and nondestructive optical methods, such as DFM, are also suitable for the in situ study of crystal interface, where an appropriate setup was designed (Scheme 1; Figure S7). In this regard, three aspects are critical for the accuracy of the measurement: (1) the use of flow cell, (2) specific optic geometry of the DFM, and (3) precise temperature control. These three aspects were demonstrated in the visualization of Cu-MOF-2-NDC crystal growth interfaces as an example (Figure 1).

First, a flow cell was designed to provide a stable concentration of metal ions and organic linkers during the period of MOF crystal growth (Scheme 1A; Figures S8, S9, and S75). Based on multiple trials, an appropriate flow rate was chosen (Figure S72) to minimize the difference in molecular diffusion coefficient for metal ions and linkers (Figure S73), and to avoid concentration change of these molecular building blocks as they were consumed along the crystal growth process in traditional closed systems. Slip boundary conditions and shear stress might exist in the flow cell, but these have little influence on MOF crystal growth in this study, based on fluid flow simulations and experimental results (Figure S74–S77). With the precise control of flow rate, the progression profile of MOF crystal interface was kept linear against time, making it much easier to extract the contributions from metal ions and organic linkers. This flow cell design is also different from microfluidic systems for the synthesis of MOFs by microdroplet flow (MF) reaction, where the resulting MOF crystals keep on moving as carried by the liquid flow. Here, the majority of MOF single crystals remained stationary during the entire growth process (Figure S74), with their positions being accurately calibrated by inert Au...
Figure 1. Progression profile of MOF crystal interface obtained using super-resolution technique

(A) The simultaneous tracing of several individual Cu-MOF-2-NDC single crystals in a sequence of DFM images selected from 61,200 frames collected along their growth; scale bars represent 20 μm.

(B) The sequence of DFM images for four representative MOF single crystals marked in Figure 1A; a gray background is applied in the images of crystal 4 to avoid interference from other crystals in the same view; scale bars represent 2 μm.

(C and D) Visualization (C) and identification (D) of the interface position for the no. 3 single crystal in (B) by super-resolution technique; scale bars represent 5 μm.

(E) Growth curves of each single crystal obtained by combining the progression of crystal interface at four crystal edges of the square shape. Continuous and systematic variation of synthetic condition is induced along the crystal growth. Insert is a residual distribution of a typical section from the growth curve and a residual histogram corresponding to the residual distribution with a FWHM of 4.1 nm, representing the trace resolution of super-resolution technique used in this study.
nanoparticles as position markers under the same camera view (Figure S28). This allows for real-time tracing of specific crystal interface for every crystal in the same batch.

Second, the growth of multiple individual MOF crystals in the same view (200 x 200 μm) was tracked simultaneously by in situ DFM camera (Figures 1A and 1B), with a frame rate of 20 Hz through a period that varied from 1,680 to 3,060 s to give a typical total frame of 61,200 for the analysis (Figures 1A and 1B). Conical incident light was used to illuminate the MOF crystals in DFM camera (Schemes 1B and 1C; Figures 1A, 1B, and S7). The optic geometry of the microscope kept the reflected and refracted light away from the camera, leaving the crystal center dark in the DFM image, while only the scattering light at the edges of each crystal was captured by the camera in the microscope, outlining the crystal interface (Schemes 1B and 1C; Figure S7). This unique feature of DFM allows for focusing on the crystal interface at specific crystal facet throughout the crystal growth process, which is different from classic bright-field optical microscope where the areas of crystal body and interface are usually obscured. The selective highlighting of the crystal interface combined with the super-resolution technique provide accurate positional information of the crystal edges with a typical trace resolution of 4.1 nm (Figures 1C–1E and S35). The reliability of our data is based on an accurate statistical analysis taking into account the subtle difference in the individual crystal’s local chemical environment (Figures 2 and 3). It is worth noting that both the positional information of the crystal and the movement of the crystal facet are accurately measured for each individual crystal in the same batch, where multiple crystals are growing simultaneously. This is distinct from the diffraction methods such as X-ray, where the crystal size is averaged out from multiple crystals without knowing the specific position of each crystal in the solution.

Last but not least, the temperature of the flow cell was precisely controlled by the power of the electrical heating mantle placed beneath the flow cell and was calibrated by an infrared camera (Schemes 1A and 1B; Figure S8). This avoided the potential influence from heating of the solution by incident light (Figure S36). The use of a temperature control system here guarantees a stable reaction temperature, ranging from room temperature to 90 °C, during the crystal growth process, which is critical for the linearity of the progression profiles of crystal facets. This entire optic setup was applied to monitor the growth of all five MOFs in this study, demonstrating the universality of the DFM platform to study crystal growth (Figures S10–S14).

Prior to the image processing, other structure characterizations such as scanning electron microscope (SEM) and X-ray diffraction were performed on these MOFs (Figures S15–S24). The detailed morphologies of the crystal facets are shown in SEM images, in good accordance with the crystal interface outlined in DFM images (Figures 1B, 3D–3F, and S15–S19). Sharp peaks were observed in the powder X-ray diffraction (PXRD) patterns of these MOFs, confirming their crystallinity and phase purity (Figures S20–S24). The crystal facets of Cu-MOF-2-NDC were indexed by single-crystal X-ray diffraction analysis of the square-shaped crystal. Most of the crystals observed in the camera view were laying on the (001) facet, and the crystal interface moved along [010] and [100] directions extending the edges of the square (Figure S25).

**MOF crystal growth rate obtained by super-resolution technique**

The growth rate for a MOF crystal was derived from the progression profile of its crystal edges. The distance between each crystal edge and the body center was monitored as a function of time (Figures 1C, 1D, and S27), using the square-shaped
Cu-MOF-2-NDC crystal as an example. Since only the crystal interface was highlighted in each DFM image (Figures 1B and 1C), the precise location of the crystal edge could be determined, applying Gaussian fitting based on the corresponding contour map (Figures 1C, 1D, and S27), and marked as the position of the resulting peak. This is termed super-line localization, a super-resolution technique similar to the typically super-point localization used for the tracking of a single molecule and nanoparticle in a solution.38–40 The intensity of the peak, reflecting the brightness of the crystal edge in the DFM image, might be related to the thicknesses of...
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the crystals, due to the good accordance with the increase in the height profile of MOFs along the [001] direction in their ex situ AFM images taken at areas identical to the DFM images (Figure S26). However, the increase in thickness did not affect the accurate tracing of the crystal edge, since it was perpendicular to the evolution plane of the crystal edges along [010] and [100] directions highlighted in the DFM camera.

The evolution of crystal edges was accurately traced by applying super-resolution technique, where adjacent 10 frames were merged (accumulated over 0.5 s) to give high-quality images, albeit of a relatively low pixel resolution, 400 nm. The progression profiles of four edges in the same crystal were converged to one crystal growth profile (Figures 1E, S29, and S30), where the subtle drift of the entire crystal along the growth process was corrected. These allowed for achieving a typical trace resolution of 4.1 nm, with precision at unit cell level (Figures 1E and S35). When the temperature and the concentrations of metals and organic linkers were fixed in the flow cell, a linear relationship was observed between edge extension ($D_l$) and reaction time ($t$) (Figure 1E). Since the increase in the crystal thickness ([001] direction) was negligible in comparison with the crystal size extension along [010] and [100] directions (Figure S38), the crystal growth rate ($r$) can be represented by the edge extension ($D_l$) in the square plan, consistent with the analysis applied to a molecular single crystal. Therefore, the slope of the crystal growth profile gave the crystal growth rate ($r$), dividing edge extension ($D_l$) by the reaction time ($D_t$) (Figure 1E):

$$r = \frac{D_l}{D_t}$$

(Equation 1)

The initial point of the crystal growth profile, $t_0$, was chosen when there was a sufficient amount of crystals reaching suitable sizes (1–2 μm) with their crystal interfaces visible (Figures 1A and 1B). This allowed us to only focus on the evolution of crystal interface at the stage of crystal size extension, rather than at the nucleation stage, at the very beginning, where the crystal interface was not distinguishable from the body in DFM images.

Growth profiles of four Cu-MOF-2-NDC single crystals in the same camera view exhibited similar growth rates, 1.26 ± 0.06 nm·s⁻¹ (Figure 1E). The difference in their crystal sizes, possibly originating from their different nucleation times, did not influence their growth rates; thus, the kinetics of MOF crystal growth was independent from the crystal size during the test period of 1,800 s. The uniformity in their growth rates also demonstrated the precision in temperature control and the advantage of using flow cell. These crystals were always in contact with fresh reactant solution of constant concentration (Figures S8 and S9), minimizing the difference in local chemical environment at crystal interface of various crystals.

During the growth process, the feed solution was flushed twice, breaking the growth profile into three sections, reflected in the small steep steps at 422.45 and 851.55 s (Figure 1E). In this test, a solution with an identical composition was used, where all three sections exhibited an identical growth rate for each crystal, showing that the
mechanic change in solution did not affect the crystal growth rate. In the test of other MOF crystals with different morphologies, linear growth was also observed (Figures S31–S34). These tests paved the way for the study on crystal growth kinetics.

It is worth noting that the subtle difference in growth rates among individual crystals was clearly observed here. This valuable information on crystals is largely missing in space-averaged characterizations, such as X-ray diffraction and light scattering. We found that the growth rate of MOF crystal was slightly affected when there were other crystals nearby (Figure S41). The unambiguous identification of these crystals in the DFM image allowed us to exclude them from the statistical analysis.

**Metal ion as the determining factor for MOF crystal growth**

Kinetic parameters, such as apparent reaction order and activation energy, are critical to unveil the determining factors for MOF crystal growth. Systematic variation of the reaction conditions was introduced in the flow cell by changing the reaction temperature and feed solution with different concentrations of metal ion or organic linker during the continuous growth of MOF crystals. The reaction orders of metals and organic linkers were obtained by isolation method, where the concentration of one component was varied systematically with all other conditions fixed. The values of reaction orders were not restricted to integer numbers here and were therefore closely reflecting the actual reaction kinetics. We noted that the reaction orders for molecular building blocks were successfully obtained for the growth of extended covalent networks of a different kind, covalent-organic frameworks, but a different method, known as the integration method, was applied. In those attempts, the experimental growth curves were fitted with existing models of integer reaction order to give an overall estimation, whereas the separate role of each building block remained unknown. The isolation method used here does not rely on any existing model, where the reaction order can be non-integer, and the impact from each molecular building block is also given.

In the case of Cu-MOF-2-NDC, feedstock solutions of Cu$^{2+}$ concentrations in the range of 0.015, 0.025, 0.035, 0.045, and 0.055 mol·L$^{-1}$ were added sequentially into the flow cell (Figure 2A), each for a duration of 408.6 s corresponding to 8,172 frames. During the switching, the flow cell was flushed with the new feedstock shortly (30 s) with a much higher flow rate (2,000 μL·min$^{-1}$, 100 times that of the experimental rate used for crystal growth, 20 μL·min$^{-1}$) to achieve steady concentration prior to recording (Figure S8). Each section of MOF crystal growth at a specific Cu$^{2+}$ concentration exhibited a nearly linear curve with a unique slope, based on which the growth rate during this section was obtained. As the Cu$^{2+}$ concentration increased gradually, faster growth rate was observed. The log values of these growth rates were plotted against the log values of their Cu$^{2+}$ concentrations, where a linear fitting was performed with the satisfactory regression (Figures 2D and S46). The slope of the resulting line was the apparent reaction order of Cu$^{2+}$ ($m$) for this MOF crystal.

Each MOF single crystal was traced separately to provide a unique value of reaction order. Multiple parallel experiments were performed under identical conditions, generating data of multiple (typically 36–75) individual crystals. Similar results were obtained to provide sufficient samples for statistical analysis, thus giving a profile of reaction orders (Figure S47). The peak position of the Gaussian fitting represented the reaction order of 1.09 for Cu$^{2+}$ (Figure 2G). A narrow full width at half maximum (FWHM) was observed in the Gaussian distribution histogram, demonstrating the accuracy of the statistical analysis, where the subtle difference
in the apparent reaction orders between different crystals might originate from their structure features and local chemical environments during the growth process. This allows for the unveiling of apparent reaction order of metal ion independently and accurately for the crystal growth of a MOF. This previously unknown aspect also reveals that the apparent reaction orders for different MOF single crystals are not the same, and not necessarily integers.

Furthermore, this *in situ* interface imaging method was also applied to study the apparent reaction orders for other MOFs, including 1D MOF with rod shape, Cu-MOF-74 (Figures 3A, 3G, and S42); 2D MOFs with square shape, Co-ZIF (Figure S49) and Cu-MOF-2-BDC (Figures 3B, 3H, and S44); and 3D MOF with octahedron shape, HKUST-1 (Figures 3C, 3I, and S51). In the case of Cu-MOF-2-BDC, isoreticular to Cu-MOF-2-NDC, the apparent reaction orders for Cu$^{2+}$ was 0.81, in the same ballpark of those for Cu-MOF-2-NDC, indicating similar reaction kinetics. In the case of HKUST-1, the apparent reaction order for Cu$^{2+}$ was 1.10, close to that of Cu-MOF-2-NDC, 1.09, and Cu-MOF-2-BDC, 0.81 (Figure 3I). All three MOFs were composed of Cu$^{2+}$ paddle-wheel-shaped SBUs (Figures 3B, 3C, and S5), unveiling a possible correlation between the reaction order and the type of SBU.

**Organic linker as the determining factor for MOF crystal growth**

The apparent reaction order for the organic linker ($n$) was also obtained, by systematic variation of the linker concentration, while fixing the temperature and concentration of metal ions (Figures 2H, 3J–3L, S43, S45, S48, S50, and S52). In the case of Cu-MOF-2-NDC and Cu-MOF-2-BDC with isoreticular crystal structure, the reaction orders for NDC and BDC linkers were determined as 0.49 and 0.43, respectively (Figures 2H, 3K, S45, and S48). Such proximity in apparent reaction orders indicated that the growth mechanism is similar for these two 2D MOFs with almost the same crystal structure. The reaction orders of metal ion and organic linker of another MOF with a 2D-layered structure, Co-ZIF, were also measured, as 2.92 and 2.12, respectively, which were distinctively different from those of Cu-MOF-2-NDC and Cu-MOF-2-BDC (Figures S49 and S50). Such difference might originate from the types of SBUs as well as the organic linkers (Figures S2–S4). Nevertheless, both the reaction orders of metal ion and organic linker were positive for all three MOFs with a 2D structure, indicating that both constituents are the determining factors for their crystal growth.

The reaction order of organic linker, however, was not always positive. In the study of HKUST-1 with a 3D morphology, an apparent negative reaction order of the tri-topic organic linker BTC (trimesic acid), –1.14, was observed. This does not mean that the crystal stopped growing or even dissolved upon the addition of BTC linker (Figures 3L and S52) but rather that when a higher concentration of BTC was introduced into the flow cell, the MOF crystals grew slower. This is counterintuitive to the Le Châtelier’s principle where an increase in the amount of starting materials will push the reaction toward the products. This is also different from the prevailing view that both metal ions and organic linkers are responsible for driving crystal formation. In order to double check whether this was an experimental error, more than three parallel experiments were performed, yielding the same negative reaction order (Figure S53). In addition, experiments were performed with gradually decreasing concentration of linkers (Figure S54), instead of the increasing sequence (Figures 3L and S52). Still, a negative reaction order was observed. Both experiments confirm that an increase in the concentration of organic linkers will lead to a slowdown of crystal growth in the case of HKUST-1. It is worth noting that the SBU for HKUST-1 is identical to that in
Cu-MOF-2-NDC and Cu-MOF-2-BDC, and the reaction orders of the Cu$^{2+}$ ion are in the same ballpark (Figures 2G, 3B, 3C, 3H, and 3I).

The growth of another Cu MOF, Cu-MOF-74 with a 1D pore structure, was also studied. A positive reaction order, 0.34, was observed for Cu$^{2+}$, whereas the apparent reaction order for organic linker DHTP (2,5-dihydroxyterephthalic acid) was found slightly negative (~0.14) (Figures 3G, 3J, S42, and S43). The absolute value of the reaction order of organic linker for this 1D MOF was relatively small, indicating that the growth of this MOF is less sensitive to the concentration of DHTP linker. This might be related to the shape of 1D SBU in Cu-MOF-74 (Figures 3A and S1), where the formation of Cu containing SBUs is driving the growth of the MOF. In fact, the crystal is also needle shaped, propagating along the c axis, which is the same direction of SBU extension.

All these results show that the metal ion and organic linker play separate roles in the crystal growth of MOFs, different from the prevailing view that these components are generally correlated. With the knowledge of reaction orders, the rate constant can be derived for each MOF single crystal, which is in good accordance with the experimental result (Figure S46B; Table S8; supplemental information).

For MOFs with different structures, compositions, and morphologies, the determining factors for their crystal growth vary (Table S7). Here, for three MOFs with a 2D-layered structure, i.e., Cu-MOF-2-NDC, Cu-MOF-2-BDC, and Co-ZIF, both metal ions and organic linkers are responsible for their crystal growth; for MOFs with a 1D pore structure, Cu-MOF-74, the metal ion favors the extension of SBUs and hence the development of a needle-shaped crystal. As for the MOF with a 3D structure, HKUST-1, the organic linker slowed down the growth rate, whereas the metal ion accelerated the crystal growth. For all five MOFs, the values of apparent reaction orders for metal ions and organic linkers are different from the ratio in the corresponding MOFs, further demonstrating the independent role of these constituents in MOF crystal growth.

**Impact from reaction temperature on MOF growth**

In addition to the study of reaction orders, the other critical aspects of MOF crystal growth kinetics, the activation energies ($E_a$), were also assessed (Figure 2C, 2F, 2I, 3M–3O, and S55–S59). For all five MOFs, as the reaction temperature increased gradually, the growth rates became faster in the flow cell, when the concentrations of metal ion and organic linker were fixed (Figure 2C). Based on the Arrhenius equation, systematical and sequential variation of the reaction temperatures revealed the accurate activation energies for Cu-MOF-74, Cu-MOF-2-BDC, Cu-MOF-2-NDC, Co-ZIF, and HKUST-1 as 115.6, 59.9, 82.1, 73.6, and 71.3 kJ·mol$^{-1}$, respectively (Table S9). These values were a result of the collective and statistical analysis of 32–163 crystals, where the activation energy of each individual crystal was obtained separately (Figures 2I, 3M–3O, and S55–S59). This is different from the activation energies obtained based on an average size of multiple crystals in the solution.31,42

The study of determining factors provides valuable guidance for the production of MOFs. The growth rates of 1D, 2D, and 3D MOFs can be accelerated by 1.7–5.6 times through adjusting the reactant concentration and reaction temperature. In the case of Cu-MOF-74, a rapid growth of single crystal was achieved at the rate of 10.2 nm·s$^{-1}$ at 68.7°C, with Cu$^{2+}$ and linker concentrations of 0.10 and 0.02 mol·L$^{-1}$, respectively, which is among the fastest crystal growth rate for MOF production (Table S10). Moreover, the acceleration of crystal growth was also verified in a closed system for Cu-MOF-2-NDC, where the growth rate of crystal was...
effectively increased by rational application of the corresponding determining factors (Figure S60). This acceleration matched well with the theoretical growth rate calculated from the experimental results of apparent reaction orders for metal ions and organic linkers, demonstrating the potential application of these factors in the precise control of crystal size and growth rate for the industrial production of MOFs.

Reversible transition layer at the crystal interface
Beyond the impact from the external solution environment, including the concentration of building blocks and the reaction temperature, is there any other factor influencing the crystal growth of MOFs? With this question in mind, we tested the dynamic behavior of the crystal interface by pausing and resuming the crystal growth during the solvothermal synthesis of Cu-MOF-2-NDC with fixed temperature (Figure 4A). Specifically, the crystal growth was paused, after linear growth for 300 s, by introducing bare solvent without metal ions or organic linkers at the same flow rate of 20 μL·min⁻¹, for the following 300 s, until the position of the crystal interface became steady. It was then resumed by switching back to the original reaction solution to give a new linear growth curve starting from 700 to 1,050 s (Figures 4A and S61). Such interruption was induced 4 times during a continuous test of 3,200 s in total.

Two important observations were made. First, the crystal interface quickly retreated right after the environment was switched to bare solvent, lasting about 50 s for every interruption (Figures 4B and 4C). The retreat of the interface is unexpected, with an obvious movement of position ranging from 10 to 40 nm, which is way beyond the trace resolution of 4.1 nm. Such retreat of the interface was observed at all four edges of the square-shaped single crystal simultaneously, ruling out the possible drift of the entire crystal (Figure S61). Even when the crystal growth was stopped, the interface would remain roughly at the same position, rather than moving backward to the crystal center. The retreat of the interface indicates that the interface is dynamic, in stark contrast to the stable crystal bulk. Different from direct attachment in classic models, the molecular building blocks, metal ions and linkers, do not directly become part of the highly ordered MOF unit cell at the interface. Instead, they are likely to form a dynamic transition layer with less ordering, which mediates the crystal growth.

The other observation was also unexpected. Here, the growth rate slowed down to 1.80, 1.53, 1.39, and 1.21 nm·s⁻¹ after the 1st, 2nd, 3rd, and 4th interruption, respectively (Figures 4D and S63), compared with the observations for unaltered crystal growth rate without interruption (Figure 1E). This infers that the transition layer is another factor to influence the growth of MOF crystals. When it is interrupted, the local composition and/or the structure of the transition layer might change; thus, the growth continuum is broken at the crystal interface. Notably, the influence from the transition layer is relatively small in comparison with that from the environmental factors, such as the concentration of metal ions and organic linkers, as shown in the experiments with systematic variation of their concentrations after crystal growth interruption (Figures S65 and S66). The overall trend in the change of crystal growth rate is still dominated by these environmental factors (Figures S67–S69).

Nonetheless, with the high trace resolution offered by this interface imaging method, the influence from the possible transition layer was still visible in all interruption experiments (Figures 4A, 4B, and S63). These observations were not accidental; they occurred to each crystal in the batch and in every repeated experiment.
Results from additional experiments also ruled out the possibility of systematic artifact (Figures S65 and S66). The accuracy in trace resolution allowed us to analyze the retreat distance (Figure 4B) of the crystal interface quantitatively, which might provide valuable information to estimate the thickness of the possible existing transition layer. Regardless of the sequence of change in concentration of the reaction solution, a similar trend was observed (Figures S65 and S66). The retreat distance of the interface was the longest after the first interruption, when the crystal size was small, and this distance became shorter after each following interruption, as the crystal became larger. This trend was also in good accordance with the tests in which identical solution concentration was applied after each interruption.

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interruption (Figures 4F, S63, and S64). Therefore, a correlation emerges between the retreat distance of the interface ($D_H$) and the size of the crystal, represented by the distance from crystal center to the edge ($l$), which is one half of the edge length ($a$) in a square-shaped crystal (Figures 4F and S70). This infers that the influence from the transition layer becomes smaller as the crystal size becomes larger, where the ordering of the building blocks in the crystal bulk is strengthened and reflected in the increased crystallinity. Furthermore, a quantitative linear fitting was performed between the interface retreat thickness ($D_H$) and the size of the crystal ($l$) (Figure 4F), giving the critical size for the emergence of crystalline domain for the MOF crystal. In the case of Cu-MOF-2-NDC, the crystal size is estimated to be 150 nm. This observation is in good accordance with the existence of the amorphous cluster before the emergence of crystalline domain in the growth of other MOFs, and the value of critical size here is also in the same ballpark to the size of the amorphous cluster in a previous study.  

**Linkage and dissociation of molecular building blocks at MOF crystal interface**

The above new knowledge is directly obtained from experiments, which provides a solid base for the discussion on the behavior of molecular building blocks at the crystal interface during MOF growth. Both the retreat and recovery of the interface upon interruption (Figure 4A), as well as the negative apparent reaction order for organic linkers BTC (Figure 3L), indicate that the conversion from molecular building blocks to crystal bulk is not an elementary reaction. Although there are only limited examples of elementary reactions, the multi-step nature of MOF crystal growth is confirmed here, which is distinctively different from that of the molecular crystal or metal salt with relatively simple components.  

A reversible surface coordination process is likely to take place during MOF growth, in the transition layer described here, at the crystal interface. Such transition layer is active for substance and energy exchange with the outer environment and also responsible for the regulation of building blocks to form highly ordered crystal bulk (Figure S71). This reversible surface coordination process involves the accumulation of growth unit and the dissociation of the crystal bulk (Figure S71). The molecular building blocks, not yet mature to become a solid part of the crystal, can still be dissociated from the transition layer, once the feedstock solution is removed and switched to bare solvent (Figures 4A and S63). Upon switching back to the original growth solution, where new building blocks are supplied from the environment, a new balance is established at the crystal interface to sustain the crystal growth (Figure S71). This phenomenon also reflected the difference between the transition layer and the crystalline core in regard to their solubility in pure solvent; whereas the transition layer can be dissolved, the crystalline core remains almost unaltered in the flow of pure solvent. However, this feature is not exactly the same as the dissolution behavior of classic ionic solids as described by Madelung energy. The underlying reason is similar though, where the binding energy between the linker and metal containing building blocks in the crystalline core is much higher than that in the transition layer.

The existence of a reversible transition layer provides a reasonable explanation for both the crystal growth interruption and the negative reaction order. The rate of accumulation for metal ion and organic linker to form growth units and the rate of their dissociation from the crystal bulk can be separately tuned by reaction conditions, since these might involve two different steps in the crystal growth process (Figure S71). When the accumulation is faster than dissociation, the crystal interface advances forward as reflected in the increase of the crystal size (Figure S71).
Otherwise, the crystal interface moves backward as the building blocks are dissociated from the transition layer, reflected in the interface retreats (Figures 4A and S62B). Further experiments were also performed where the reactant solutions were flowed at higher rates to wash the crystal interface (200 μL·min⁻¹ as shown in Figure S62A). The crystal interfaces extended continuously as expected, rather than the growth interruption. It is worth noting that the retreat and recovery of the interface are only observed when the crystal growth is interrupted by washing with pure solvent. In the continuous growth of crystal, without interruption, such a reversible transition layer might also exist. It provides a steady equilibrium for the size extension of the MOF single crystal (Figure 1E), instead of reversing the movement of the interface. In the case of HKUST-1, as the concentration of BTC linker increases gradually, the rate of building block dissociation might be accelerated more than the rate of accumulation; thus, the crystal growth is slowed down, manifested in an apparent negative reaction.

**Possible multi-step growth mechanism for Cu-MOF-2-BDC and -NDC**

The apparent reaction orders accurately measured also allow us to consider the possible reaction mechanism. Here, we use Cu-MOF-2 as an example for discussion. If the growth mechanism were a classic monomer-by-monomer addition (Figure 5A), where the metal (Cu²⁺) and linker (L, L = BDC or NDC) were added to the MOF interface in an alternating manner, the ratio between the corresponding apparent reaction order would have been 1:1, according to the MOF formula, depending on how many pairs of metal ions and linkers are connected at the same time. However, the experimental values were 1 and 0.5 for Cu²⁺ and organic linker, respectively, ruling out such possibility. Another possible mechanism involves the formation of a cluster of Cu₂L₄, corresponding to the underlying SBU for Cu-MOF-2.²² ²¹ It was well established that the SBU, coordination complex of linkers with metal ions in the center, was critical for the design of MOFs,²² ²³ as well as the nucleation process of MOF growth.²² ²³ Is it possible that the metal ion and linker coordinate to form Cu₂L₄, followed by its accumulation at the MOF crystal interface (Figure 5B)? If this were the case, the apparent reaction orders would have been 2 for Cu²⁺ and 1 for organic linkers for Cu-MOF-2, still different from the experimental data. Thus, it was unlikely that the paddle-wheel-shaped Cu₂L₄ SBU aligned directly at crystal growth interface during MOF growth process.

The analysis of the above two possibilities encouraged us to further propose a third mechanism (Figure 5C). This involves both the formation and fragmentation of Cu₂L₄ SBU, where a new species with a smaller size, CuL₂, functions as the growth unit for the formation of Cu-MOF-2 single crystal. Specifically, in step I, Cu²⁺ and linker L quickly form Cu₂L₄ SBU as a critical intermediate. This is followed by its division into a smaller species, CuL₂ (step II), where a fast equilibrium is achieved. Then, CuL₂ combines with Cu²⁺ to join the transition layer at the MOF crystal interface (step III) and gradually converts into crystalline bulk as the rate-determining step for MOF growth. The reaction orders of Cu²⁺ and linker L derived from this mechanism are 1.0 and 0.5, respectively, well matched with the corresponding apparent reaction orders obtained in the experiments for both Cu-MOF-2-BDC and Cu-MOF-2-NDC (Figures 2G, 2H, 3H, and 3K). In this mechanism, fast equilibrium approximation is applied, which requires k₂ to be much smaller than k₁ and k₋₁, therefore a large amount of CuL₂ species will accumulate in the growth solution. This is in good accordance with the relatively high abundance of CuL₂ species observed in the mass spectroscopy analysis of the growth solution of Cu-MOF-2 in a previous report.²²
**Figure 5. Possible reaction mechanisms for the growth of Cu-MOF-2 single crystal**

(A) Monomer-by-monomer addition mechanism. 

\[
\text{Cu}^{2+} + L \xrightarrow{k_1} \text{MOF (CuL)}^* \\
\frac{d(\text{CuL})^*}{dt} = k_{L}[\text{Cu}^{2+}]
\]

or

\[
2 \text{Cu}^{2+} + 2L \xrightarrow{k_1} \text{MOF (Cu}_2\text{L}_2)^* \\
\frac{d(\text{Cu}_2\text{L}_2)^*}{dt} = k_{L}[\text{Cu}^{2+}]^2
\]

(B) Mechanism involves the formation and direct accumulation of Cu\text{L}_4 SBU. 

(L) \text{Cu}_2\text{L}_4 + 2\text{Cu}^{2+} \xrightarrow{k_1} \text{MOF (Cu}_4\text{L}_4)^* \\
\frac{d(\text{Cu}_4\text{L}_4)^*}{dt} = k_{[\text{Cu}_2\text{L}_4]}[\text{Cu}^{2+}]^2 = k_{L}[\text{Cu}^{2+}]^2
\]

(C) Mechanism involves the formation of Cu\text{L}_4 SBU and its fragmentation into Cu\text{L}_2. The organic linker is represented by gray rod, whereas the species of one and two Cu\text{L}_2 are represented by blue hemisphere and spheres, respectively. The details of the representation are illustrated at the very bottom.

* The chemical formula of Cu-MOF-2 is Cu\text{L}_n, which can also be noted as Cu\text{L}_m\text{SBU}, n as integer, for the convenience to describe in different mechanism. The conversion between d(Cu\text{L}_m) and d(Cu\text{L}) is d(Cu\text{L}_m) = 1/n d(Cu\text{L}), with the reaction order unaffected.
If this mechanism proves to be a major possibility, Cu$_2$L$_4$ SBU plays a structural directing role, consistent with previous studies of MOF growth at the nucleation stage, but it is the fragmentation product, CuL$_2$, that functions as the important species bridging the formation of SBU and the growth of MOF. Given all of the above, we note that there might be other possible explanations or mechanisms for MOF crystal growth. The proposed mechanism merely provides an example of how the results obtained in this study could be used as new experimental guidelines for continuing exploration in this field.

Conclusions

Here, we show that optical methods can be used to study crystal growth in a solution with a trace resolution of several nanometers. The DFMs combined with super-resolution techniques are well suited for the study of interface evolution for a complex crystal, MOF, and this might also be used to investigate other important crystals in solution. Identifying and quantifying the determining factors for MOF growth, including the apparent reaction orders of metal ions and organic linkers and the activation energy, provides new guidelines for the industrial production of MOFs and a new understanding of MOF growth at molecular level.

It is also shown that the crystal growth of MOFs is not an elementary reaction. A multi-step process is likely to exist involving the accumulation of the building blocks and their dissociation from the crystal in separate steps. In addition to the classic environmental factors, the crystal interface itself will also influence crystal growth, manifested in its retreat and recovery at the possible transition layer. The existence of a reversible transition layer is likely to mediate the crystal formation process as well as the dissociation of the crystal, offering the dynamics in the crystal growth of MOFs. This study depicts an alternative way of describing the evolution of crystal interface, compared with existing models.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Hexiang Deng (hdeng@whu.edu.cn).

Materials availability

This study did not generate new materials.

Data and code availability

Data relating to the materials, methods, experimental procedures, mathematical models and other characterization are available in the supplemental information. All other data are available from the authors upon reasonable request.

DFM platform

The in situ interface imaging of MOF single crystals in solution was performed on Olympus IX71 DFM platforms. The DFM configuration is composed of white light source, condenser lens, home-designed flow cell, heating ring, objective lens, and electron-multiplying charge coupled device (EMCCD) camera placed beneath the sample (Scheme 1A; Figure S7). The individual MOF single crystals were illuminated with molecular structures, where the solvents and counter anions coordinated to Cu$^{2+}$, as well as possible charges of the motifs, are omitted for clarity. The steps involving the formation of species in the growth solution are represented by orange arrows, and their accumulation at the crystal interface is marked by blue arrows. The light blue and orange backgrounds represent the crystalline bulk and transition layer of MOF, respectively.

Figure 5. Continued

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by Cold White Collimated LED (MCWH2-C1) lamp source for Olympus BX & IX focused through an Olympus U-DCD0.92-0.8 dark-field condenser. The scattering light signal from the crystal interface was collected by a 40X NA0.60 air objective and followed by the detection using an ANDOR Ixon unknown date-897D-CS0-#BV EMCCD camera operated with a frame rate of 50 ms to generate a movie. The images in the movies were processed by super-resolution technique to trace the interface location for each MOF single crystal along its growth form small crystal to large one. The growth kinetic parameters of each individual MOF crystal were obtained by quantitative analysis. Constant bright spots from gold nanoparticles in DFM images were used as markers for the correction of the inevitable image drift with nanometer accuracy.

**In situ interface imaging for MOF crystal growth**

The flow cell was designed by parallel arrangement of two quartz slides with a distance of 0.32 mm sealed by AB glue, and it was placed between condenser lens and objective on DFM platform (Figure S8). The inlet and outlet of the liquid is using perfluoroalkoxy (PFA) tubes with an inter diameter of 0.5 mm. A suitable observation field in the eyepieces of the microscope was identified by adjusting the microscope focal distance. The inlet tube was connected to a vial containing stock solution of metal ions and organic linkers, while the outlet of flow cell was connected to the micro syringe pump to extract the solution and accurately control the growth rate. A steady rate of 20 μL·min⁻¹ was used during MOF growth, unless specified otherwise. It was worth noting that the extraction design here avoided potential cracking of flow cell caused by excessive pressure induced from injection. The temperature of the flow cell was precisely controlled by the power of electrical heating mental placed beneath the flow cell and further calibrated by infrared camera. The image view covered an area of 200 × 200 μm in the quartz flow cell, corresponding to 512 × 512 pixels in the DFM image. The EMCCD camera was started recording after the flow rate and reaction temperature were steady. The **in situ** imaging method on DFM platforms was suitable for MOFs with various dimensionalities, Cu-MOF-74, Cu-MOF-2-BDC, Cu-MOF-2-NDC, Co-ZIF and HKUST-1. When recording was finished, the flow cell was taken off from the DFM setup and opened carefully for **ex situ** characterizations.

**Kinetic study for the quantitative analysis of MOF crystal growth determining factors**

In the kinetic study of MOF growth by **in situ** interface imaging, one of the determining factors, concentration of metal ions and organic linkers, as well as temperature, was isolated and varied sequentially in a continuing test. In the case of Cu-MOF-2-NDC as an example, the detailed conditions were shown in Table S3, and the experimental procedures were described as follows. In the investigation of Cu²⁺ as the determining factor, the concentration of organic linkers (0.035 mol·L⁻¹) and temperature (50°C) were fixed, while the concentrations of Cu²⁺ were varied sequentially from low to high (0.015, 0.025, 0.035, 0.045, and 0.055 mol·L⁻¹). The stock solution with Cu²⁺ concentration of 0.015 mol·L⁻¹ was made by mixing the Cu²⁺ solution, prepared by dissolving 36.2 mg Cu(NO₃)₂·3H₂O in 3 mL mixed solvent, N, N-dimethylformamide (DMF), ethanol (EtOH) and methanol (MeOH) with volumetric ratio of 1:1:1, and a different solution of the organic linker, prepared by dissolving 45.4 mg NDC in 3 mL mixed solvent with identical ratio. The solutions of other concentrations were prepared in similar way. The starting time of crystal growth (t₀) was chosen when the square plated-shaped crystals visible in the observation field reached suitable sizes (1–2 μm). A DFM movie lasting 410 s was recorded. Then, the flow cell was flushed with the following solution in the sequence...
(Cu$^{2+}$: 0.025 mol·L$^{-1}$, linker: 0.035 mol·L$^{-1}$) for 30 s with a rate of 2,000 µL·min$^{-1}$ prior to a resumed recording. This was achieved by switching the inlet of the flow cell into new growth solution. In the new growth section, the flow rate was adjusted back to 20 µL·min$^{-1}$ for another 410 s. This continued for the rest of solutions in the sequence, and after the recording of the last section, the camera was stopped, and the heating device was turned off. The remaining solution in the flow cell was extracted out at a flow rate of 1 µL·min$^{-1}$ until empty. The investigation of the organic linker as determining factor was performed in similar way, where the concentration of Cu$^{2+}$ (0.025 mol·L$^{-1}$) and temperature (50°C) were fixed, while the concentrations of organic linker NDC were varied sequentially from low to high (0.010, 0.015, 0.025, 0.035, and 0.045 mol·L$^{-1}$). The impact from growth temperature was also assessed in the same way, where the concentrations of metal ions and organic linkers were kept constant (Cu$^{2+}$: 0.075 mol·L$^{-1}$, organic linkers: 0.075 mol·L$^{-1}$), while the growth temperature were varied sequentially from low to high (62.3°C, 65.4°C, 68.1°C, 69.4°C, and 71.8°C). Similar experimental procedures were applied for other MOFs with various dimensionalities, Cu-MOF-74, Cu-MOF-2-BDC, Co-ZIF, and HKUST-1. The detailed growth conditions were listed in Tables S1, S2, S5, and S6.

Dynamics of crystal interface upon crystal growth interruption
A stock solution with the concentrations of Cu$^{2+}$ ions, 0.075 mol·L$^{-1}$, and organic linker NDC, 0.050 mol·L$^{-1}$, was applied as the initial condition at a flow rate of 20 µL·min$^{-1}$, while the temperature was fixed at 50°C. Then, the feed solution was changed to bare solvent of DMF, EtOH, and MeOH with volumetric ratio of 1:1:1, without Cu ions or NDC linker, at 300 s from the starting time of crystal growth ($t_0$). Different from the flashing with the rate of 2,000 µL·min$^{-1}$ applied in the kinetic study, where the stock solution of the next concentration of metal ion and linkers were used by following the sequence, here, the bare solvent was used, and at the same flow rate to the prior section, 20 µL·min$^{-1}$, without flushing. The location change of the interface was traced for 300 s with the bare solvent in flow cell. Then, it was switched back to the original stock solution with the same concentration of Cu$^{2+}$ ions, 0.075 mol·L$^{-1}$, and organic linker NDC, 0.050 mol·L$^{-1}$, at the same flow rate for another 300 s. This alternating switching process was applied as the interruption induced to the crystal growth of Cu-MOF-2-NDC, 4 times in a continuous test. The detailed growth condition was listed in Table S4. Other interruption experiments were also performed using the same bare solution, but it was switch to stock solution of different concentration of metal ion and organic linker, either in a sequence of increasing or decreasing concentration.

Other experimental procedures and characterizations
Chemicals and detailed synthetic conditions, SEM, PXRD, crystal face indexing, AFM, and other experimental procedures are provided in the supplemental information.

SUPPLEMENTAL INFORMATION
Supplemental information can be found online at https://doi.org/10.1016/j.chempr.2022.03.006.

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AUTHOR CONTRIBUTIONS
H.D. and X.Z. conceived the idea and led the project. J.H., X.H., J.L., and M.L. conducted the experiments. R.M. and H.L. performed the fluid flow simulation. J.H., X.Z., and H.D. designed the experiments. J.H. and H.D. prepared the first version of the manuscript, and all authors contributed to the discussion on the results and the final version.

DECLARATION OF INTERESTS
The authors declare no competing interests.

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REFERENCES


