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Cryo-EM structures of atomic surfaces and host-guest chemistry in metal-organic frameworks

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Abstract

Host-guest interactions govern the chemistry of a broad range of functional materials, but direct imaging using conventional transmission electron microscopy (TEM) has not been possible. This problem is exacerbated in metal-organic framework (MOF) materials, which are easily damaged by the electron beam. Here, we use cryogenic-electron microscopy (cryo-EM) to stabilize the host-guest structure and resolve the atomic surface of zeolitic imidazolate framework (ZIF-8) and its interaction with guest CO₂ molecules. We image step-edge sites on the ZIF-8 surface that provides insight to its growth behavior. Furthermore, we observe two distinct binding sites for CO₂ within the ZIF-8 pore, which are predicted by density functional theory (DFT) to be energetically favorable. This CO₂ insertion induces an apparent ~3% lattice expansion along the <002> and

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Author contributions

Yuzhang Li, and Y.C. conceived the idea and designed the experiments. Yuzhang Li, Yanbin Li, H.W., and G.C. established the cryo-plunging methodologies. Yuzhang Li, K.W., and Y.T. synthesized the ZIF-8 particles. Yuzhang Li, Yanbin Li, G.H.W. and W.Z. performed the cryo-EM experiments. W.Z. processed the CTF-corrected images. R.V. simulated the TEM images according to experimental imaging conditions. W.H., and H.W. conducted other electron microscopy characterizations at room temperature. Yuzhang Li, K.W., W.Z., R.S., W.C. and Y.C. interpreted the results and co-wrote the paper. All authors discussed the results and commented on the manuscript.

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Competing financial interests

The authors declare no competing financial interests.

<011> directions of the ZIF-8 unit cell. The ability to stabilize and preserve host-guest chemistry opens a rich materials space for scientific exploration and discovery using cryo-EM.

Metal-organic frameworks (MOFs) are a large class of highly porous materials¹⁻³ whose chemistry and crystalline structure can be tuned for potential applications in gas storage⁴⁻⁶, separations⁷, and catalysis⁸. Interactions between the host framework and guest molecule are central to such applications but are poorly understood at the molecular level. Although transmission electron microscopy (TEM) has been used to study the empty MOF framework⁹⁻¹⁴, imaging sub-nanometer guest insertion within the MOFs is still challenging. Of note, a recent study successfully imaged guest single-molecule magnets via TEM, but at relatively low dosage and large molecular size (> 1 nm)¹⁴. The weak bonding between the guest molecule and framework is easily damaged even under low electron doses^{15,16}. Furthermore, guest molecules are likely to desorb from MOF pores under the high vacuum condition ($\sim 10^{-6}$ mbar) of the TEM at room temperature (supplementary text). Therefore, current studies rely on ensemble measurements using X-ray/neutron diffraction^{17,18}, nuclear magnetic resonance¹⁹, or theoretical simulations²⁰. However, the structural information obtained by these methods is averaged over bulk particles. Direct observations of individual MOF particles and their interaction with subnanometer guest species at high spatial resolution have not been possible.

Recently, cryogenic-electron microscopy (cryo-EM) was shown to be a powerful tool beyond structural biology. For instance, reactive lithium battery materials have been successfully stabilized for imaging and spectroscopy²¹⁻²⁵. Such cryogenic condition may also reduce radiation damage to the MOF framework (supplementary text). However, cryo-EM procedures developed for biological or battery materials are not necessarily compatible with MOFs. Here, we establish a new cryo-EM protocol to reveal atomic host-guest structures within MOFs, demonstrating that these entities, held together by weak interactions, can be preserved for high-resolution imaging at cryogenic condition (Fig. 1). As an example of this general approach, we investigate the surface structure of a zeolitic imidazolate framework (ZIF-8) and its host-guest chemistry with CO₂ molecules, with potential implications for both carbon capture and gas separations²⁶.

ZIF-8 is a body-centered cubic crystal that has a sodalite topology (space group $I\bar{4}3m$). The ZIF-8 particles (~ 100 nm in diameter) synthesized in this study (fig. S2) are confirmed to be highly crystalline via X-ray diffraction (XRD; fig. S1). Diffraction contrast from the ZIF-8 particles observed in low-magnification TEM images (Fig. 2a) further suggests a crystalline specimen. However, the bonding between the inorganic metal centers (Zn²⁺) and the organic linkers (2-methylimidazole) of the ZIF-8 framework is extremely sensitive to high electron doses. After exposure to ~ 50 e⁻/Å² at room temperature, the ZIF-8 particle quickly becomes amorphized, as indicated by both the high-resolution TEM (HRTEM) image (Fig. 2b) and its fast Fourier transform (FFT; Fig. 2b inset). Indeed, previous studies^{12,13} have shown that MOF materials quickly lose their crystallinity with an accumulated electron dose of only ~ 10 -20 e⁻/Å², with ZIF-8 becoming completely amorphous after 70 e⁻/Å² at room temperature. Consequently, any existing host-guest structure would be difficult to identify from the amorphized particle. To overcome these challenges, we established a flash-freezing

protocol modified from cryo-EM methodologies used in structural biology²⁷ to preserve the MOFs at their operating environment (e.g. empty or filled) for high-resolution imaging. First, the as-synthesized ZIF-8 particles were dispersed onto a carbon support TEM grid and vacuum-dried to remove all solvent from the ZIF-8 pore space. Samples were then directly plunged into liquid nitrogen while maintaining vacuum or kept in a 1 bar pressure CO₂ environment (Fig. 1a, methods). This freezing process prevents any air exposure and kinetically inhibits CO₂ desorption from the ZIF-8, preserving the host-guest interactions that were present at room temperature.

Cryogenic temperature is known to reduce radiation damage induced by the electron beam^{15,28}. In our cryo-EM imaging experiment, we keep the specimen at $-170\text{ }^{\circ}\text{C}$ and expose it to different cumulative electron doses to determine its radiation damage sensitivity (fig. S7). We use a magnification corresponding to a pixel size of $0.68\text{ }\text{\AA}$ by $0.68\text{ }\text{\AA}$ to facilitate imaging at atomic resolution. In addition, a direct-detection electron-counting camera has a high quantum efficiency to enable acquisition of images with high signal-to-noise at all frequencies and a high frame rate to allow recording of multiple frames per specimen area followed by subsequent frame alignment to minimize beam-induced drift²⁹.

Figure 2c is a typical cryo-EM image of a ZIF-8 particle that was held under vacuum before flash-freezing. When viewed along the $\langle 111 \rangle$ zone axis, the ZIF-8 rhombic dodecahedral particle is hexagonal (dashed white lines) with well-defined $\{011\}$ edge planes joined by sharp vertices (fig. S3). Furthermore, the crystalline structure of the ZIF-8 particle is clearly preserved. Under low dose and low temperature conditions, the ZIF-8 structure shows structure information down to $1.86\text{ }\text{\AA}$ as evidenced by the FFT of this image (Fig. 2d, bottom), exceeding previously reported resolutions of ZIF-8. A simulated TEM image (Fig. 2d inset) also shows good agreement with the raw image. Even after exposure to $25\text{ e}^{-}/\text{\AA}^2$ that would ordinarily result in significant damage to the framework, ZIF-8 remains pristine at low temperatures (Fig. 2d). When the number of frames taken and the cumulative exposure are increased (Fig. 2e, f), ZIF-8 shows only partial loss of crystallinity after $90\text{ e}^{-}/\text{\AA}^2$ at low temperature, while the same specimen becomes fully amorphous after exposure of $50\text{ e}^{-}/\text{\AA}^2$ at room temperature (Fig. 2b). Quantitatively, the plot of normalized intensity in the FFT as a function of cumulative electron exposure (fig. S7) demonstrates that high-resolution information ($3\text{ }\text{\AA}$) is still retained after $90\text{ e}^{-}/\text{\AA}^2$. These experiments and the corresponding raw, unprocessed images (fig. S5) establish the increased stability of ZIF-8 using cryo-EM, allowing further exploration into its surface atomic structure and host-guest chemistry.

The atomic surfaces of materials often provide insight into their growth mechanism. In particular, the shape and size uniformity of ZIF-8 particles has been attributed to the formation of surface steps^{30,31}. Unfortunately, surface structures and their possible defects are more sensitive than the bulk to the electron beam, making atomic-resolution imaging difficult even at low electron doses¹². To preserve and study such surface structures immediately after growth, the as-synthesized ZIF-8 particles were flash-frozen and imaged without vacuum-drying (methods). Using $\sim 7\text{ e}^{-}/\text{\AA}^2$ cumulative electron dose, we have made a number of structure feature observations which were previously not seen at room temperature. Figure 3a is a denoised³² cryo-EM image of ZIF-8 after synthesis, which

(simplified as red spheres) projected along the $\langle 111 \rangle$. The simulated structure (Fig. 4g) matches well with the CTF-corrected cryo-EM image (Fig. 4e), providing strong evidence that CO₂ molecules are successfully preserved within the framework at cryogenic conditions and can be directly imaged using cryo-EM.

Close inspection of a single ZIF-8 unit cell reveals several key features of the host material during guest insertion. In the empty ZIF-8 pore (Fig. 4c), there are three areas of density (circled in blue) just inside the edges of the unit cell. This contrast likely comes from the three organic imidazolate linkers that protrude into the pore space, forming the 6-ring windows that connect each individual pore. Interestingly, these moieties are not observed in ZIF-8 unit cells after CO₂ loading (Fig. 4f), suggesting that the imidazolate linkers can rotate out of view to open the narrow 6-ring window (3.4 Å) for CO₂ (3.3 Å kinetic diameter) adsorption and diffusion throughout the framework. These results support previous descriptions of a “gate opening” phenomenon in ZIF-8, which explain how molecules larger than the 6-ring window (e.g. N₂ 3.6 Å kinetic diameter) can be accommodated into ZIF-8 pores via linker rotation^{37–40}. Although it is generally accepted that flexibility of the 6-ring windows occurs at various loading conditions, the ZIF-8 pore cavity itself is largely thought to remain rigid upon CO₂ insertion at ambient pressures. Surprisingly, we discover a 3% expansion of the $\langle 011 \rangle$ lattice repeat during CO₂ loading at atmospheric pressure. Figure 4h plots the integrated pixel intensities for the empty and CO₂-filled ZIF-8 unit cells along the $\langle 011 \rangle$ direction. The $\langle 011 \rangle$ lattice spacing for the empty ZIF-8 averaged over 10 unit cells is measured to be 12.04 Å (fig. S10), which matches well with the experimental value of 12.03 Å from XRD measurement³⁷. The precision in this TEM lattice measurement is approximately 0.07 Å (methods). After CO₂ loading, the ZIF-8 $\langle 011 \rangle$ lattice expands to 12.34 Å (fig. S11). Though lattice expansions of this magnitude (~3%) are possible for ZIF-8 (ref. 41), they have predominantly been observed at high pressure loadings (~10⁴ bar) of non-interacting gas molecules (e.g. N₂, O₂, Ar). However, the CO₂ still induces a similar unit cell expansion at much lower pressure (~1 bar CO₂ loading) in our experiments. This observation implies a strong interaction between CO₂ and the ZIF-8 framework, which further suggests ZIF-8 might be a promising carbon capture material.

To reinforce our results, it is important to investigate the host-guest structures along more than one zone axis. Projected in the $\langle 001 \rangle$ direction, the rhombic dodecahedral ZIF-8 particle appears as a square (Fig. 5a, 5d). With CTF-correction to address the contrast inversion issue mentioned above, the cryo-EM images of empty (Fig. 5b) and CO₂-filled (Fig. 5e) ZIF-8 can be more easily interpreted. Contrast is strongest for the Zn clusters, which are located at the bright square spots. These clusters are connected by the imidazolate linkers that are visible as lines of white contrast. When viewed along the $\langle 001 \rangle$ direction (Fig. 5c), ZIF-8 displays two structurally distinct pore cavities: one is located at the vertex of the Zn cluster (circled in green) and the second is adjacent to the square edge of the Zn cluster (boxed in orange). Both cavities do not appear to contain any density in the empty ZIF-8 (Fig. 5c). Upon CO₂ adsorption, bright contrast can be observed in the center of the 4-ring window (Fig. 5f). Interestingly, this appears only in the pore cavity located at the vertex of the Zn cluster and not the cavity at the Zn cluster edge. Although adsorption at the center of these particular 4-ring windows is different from the CO₂ binding location observed along

the $\langle 111 \rangle$ direction, DFT calculations show that CO₂ binding centered around the 4-ring window is also energetically favorable³⁶. The simulated ZIF-8 structure with the predicted CO₂ adsorption site (Fig. 5g) closely resembles the cryo-EM image (Fig. 5f), indicating that more than one adsorption site exists. Furthermore, the lattice expansion observed for the $\langle 011 \rangle$ direction is also present along the $\langle 002 \rangle$ direction (Fig. 5h). Whereas an 8.56 Å $\langle 002 \rangle$ lattice spacing is measured for the empty ZIF-8 (fig. S12), the $\langle 002 \rangle$ expands 3% to 8.78 Å after CO₂ insertion (fig. S13). The similar unit cell expansion and additional adsorption sites revealed here demonstrate the increased information gained by simply observing the particles along different crystallographic directions. To identify possible adsorption sites beyond the two observed here, a full tomographic tilt series of a single ZIF-8 particle can now be enabled by the additional stability afforded by cryo-EM.

Our work here demonstrates the powerful utility for cryo-EM to preserve and image atomic MOF surface structures and guest molecules within its pore cavities. We revealed that ZIF-8 growth likely initiates at a step-edge surface site and discovered structural changes in ZIF-8 during CO₂ insertion. This study opens opportunities to further investigate such host-guest interactions to develop a complete picture of MOF adsorption kinetics at the single particle level. Using cryo-EM, the many applications of different MOFs with distinct guest molecules can be probed at the atomic level. New discoveries and findings will provide insight to their fundamental operation and shape future designs of these tunable materials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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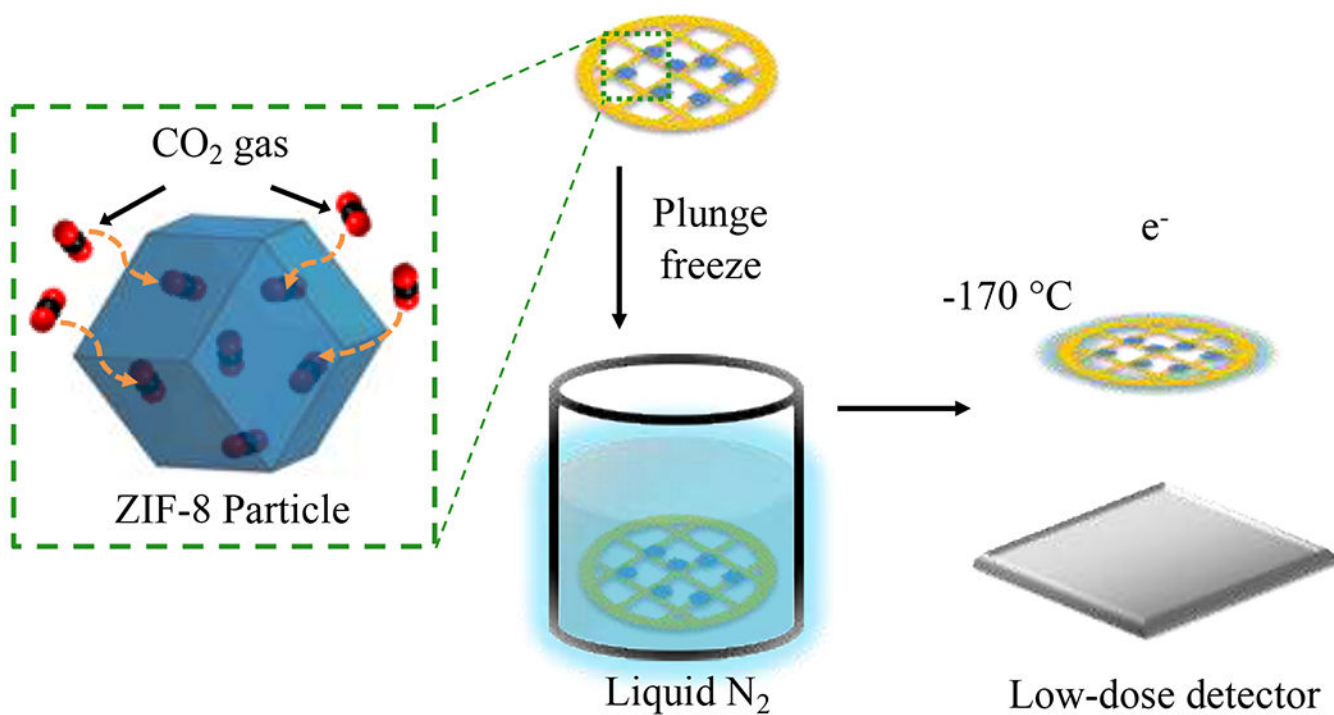


Figure 1 |. Preserving and stabilizing host-guest interactions using Cryo-EM.

Vacuum-dried ZIF-8 particles are exposed to CO₂ gas at ambient temperature and pressure after synthesis. In this environment, the particles are then plunge-frozen directly into liquid nitrogen to freeze in the host-guest structure and chemistry. Low-dose images are then recorded at cryogenic condition using a direct electron detector.

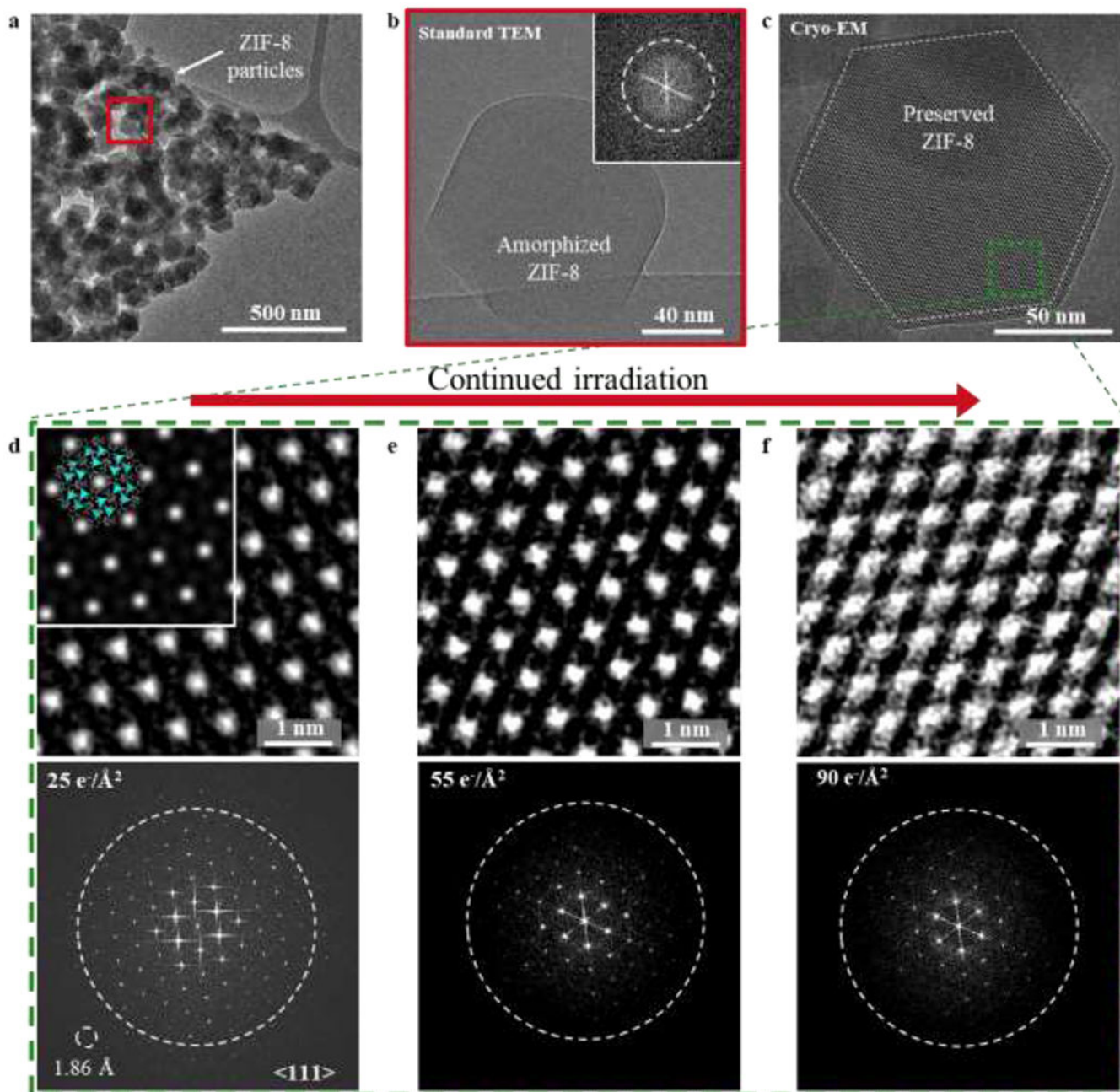


Figure 2 | Electron irradiation of ZIF-8 at cryogenic temperatures.

a, TEM image of ZIF-8 particles taken at room temperature with electron dose rate $2 \text{ e}^-/\text{\AA}^2/\text{s}$ for $\sim 1\text{s}$. Diffraction contrast suggests sample is crystalline. **b**, HRTEM image of red boxed region from (a). After accumulated electron dose of $\sim 50 \text{ e}^-/\text{\AA}^2$, ZIF-8 becomes completely amorphous. Inset: corresponding FFT showing no crystallinity in the sample. **c**, Cryo-EM image of ZIF-8 (outlined by dashed white line) taken along the $\langle 111 \rangle$ direction at $-170 \text{ }^\circ\text{C}$ with electron dose rate of $\sim 4.5 \text{ e}^-/\text{\AA}^2/\text{s}$ for 1.5s. At 225 nm underfocus, bright spots in the ZIF-8 lattice correspond to empty pore space. **d**, **e**, **f**, Magnified images of green boxed region from (c) exposed to electron doses of $25 \text{ e}^-/\text{\AA}^2$ (**d**), $50 \text{ e}^-/\text{\AA}^2$ (**e**), and $90 \text{ e}^-/\text{\AA}^2$ (**f**)

with corresponding FFT pattern below. The dashed circle on the FFT represents an information transfer of 2.5 Å. Information transfer of 1.86 Å is possible, as indicated by the reflection circled in **(d)**. Inset of **(d)**: The ZIF-8 atomic structure is overlaid onto the simulated TEM image, which is calculated using 225 nm underfocus and 100 nm sample thickness. The simulated image matches reasonably well with the experimental cryo-EM image.

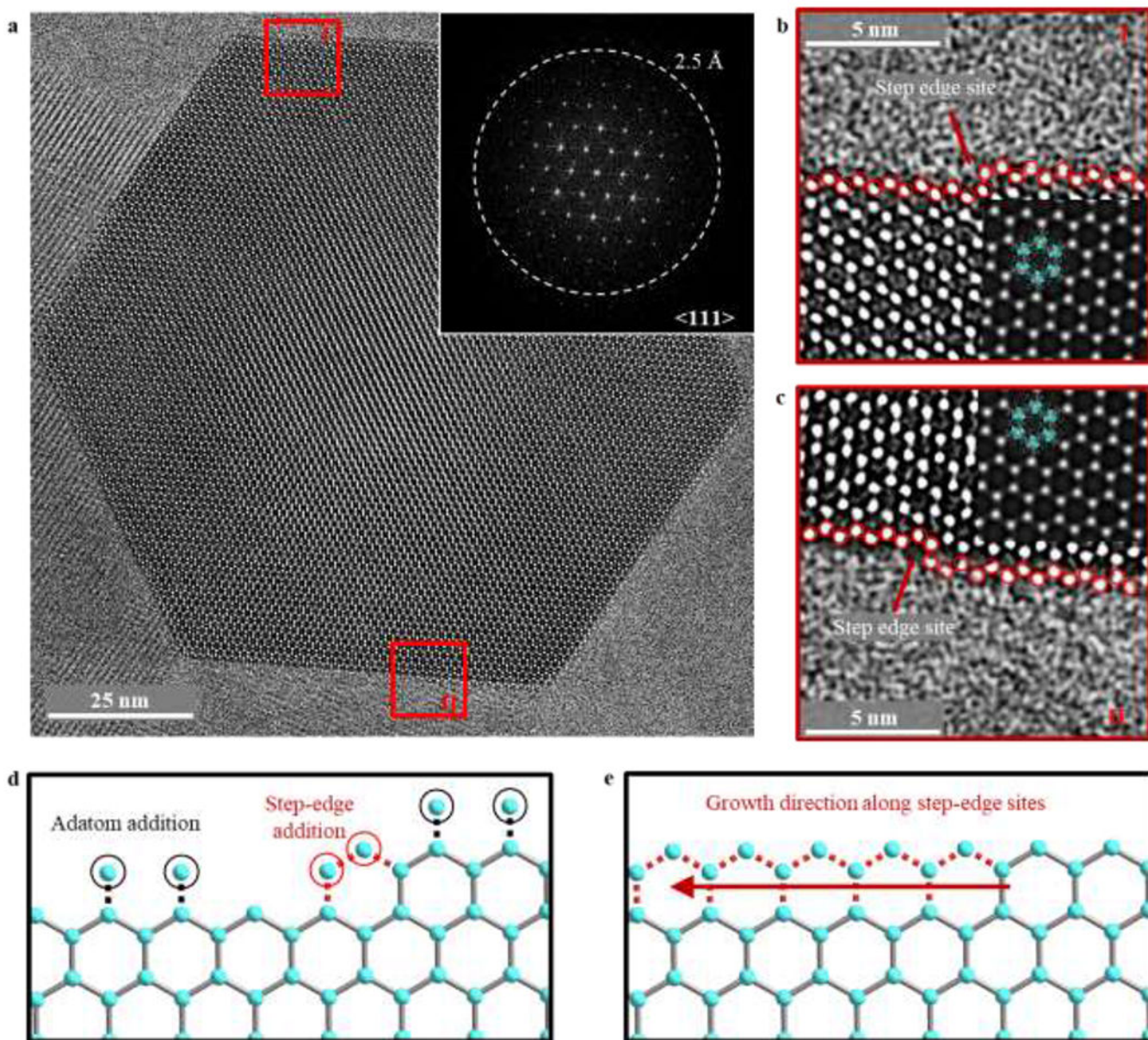


Figure 3 | Atomic surface and step-edge sites of ZIF-8 particles.

a, Denoised cryo-EM image of ZIF-8 after synthesis (not vacuum-dried) taken at 250 nm overfocus with electron dose rate of $\sim 4.5 \text{ e}^-/\text{\AA}^2/\text{s}$ for 1.5s. Bright spots correspond to Zn clusters. Inset: corresponding FFT pattern. White dashed circle represents information transfer of 2.5 Å. **b, c**, Magnified images of region I (**b**) and region II (**c**) boxed in red from (**a**). The ZIF-8 atomic structure is overlaid onto a simulated TEM image in the second inset, which is calculated using 250 nm overfocus and 100 nm sample thickness. The simulated TEM image matches well with the experimental cryo-EM image. The Zn clusters on the surface are double-coordinated and are outlined in red circles. A step-edge site is observed in both (**b**) and (**c**), indicated by the red arrow. **d**, Schematic of possible surface additions of Zn clusters during ZIF-8 growth. Whereas adatom addition (circled in black) would result in single-coordinated Zn clusters, addition at the step-edge site (circled in red) would result in

double-coordinated Zn clusters. **e**, Schematic of ZIF-8 growth initiated at the step-edge site, which is thermodynamically more favorable.

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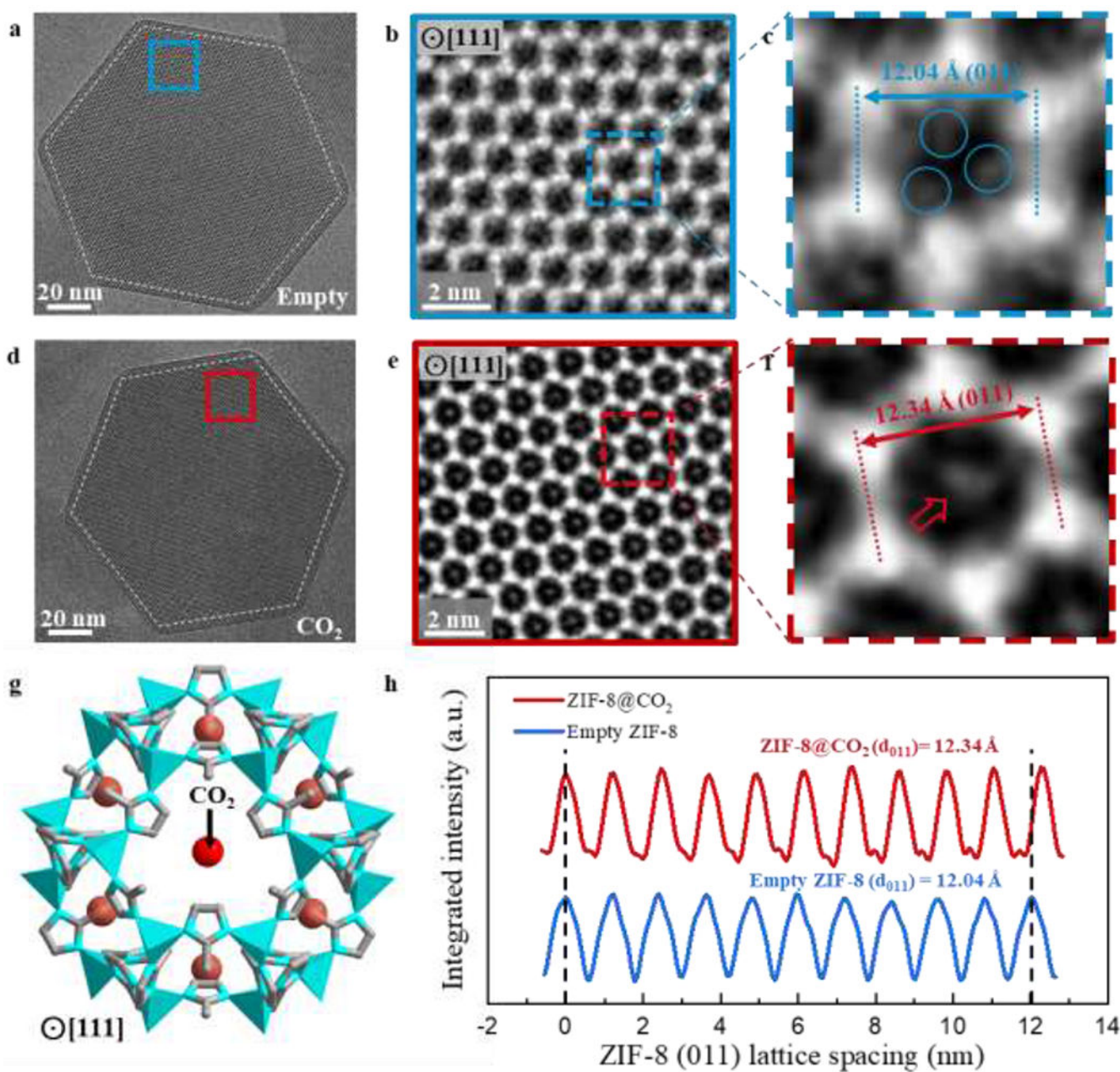


Figure 4 | Host-guest structures within ZIF-8 viewed along $\langle 111 \rangle$ projection.

a, Cryo-EM image of vacuum-dried, empty ZIF-8 (outlined by white dashed lines) taken with electron dose rate of $\sim 4.5 \text{ e}^-/\text{\AA}^2/\text{s}$ for 1.5s along the $\langle 111 \rangle$ projection. **b**, CTF-corrected denoised image of blue boxed region from (a). Bright regions correspond to mass density. **c**, Magnified image of a single ZIF-8 unit cell from (b). Density (circled in blue) near the interior edge of the unit cell may correspond to the organic imidazolate linkers. **d**, Cryo-EM image of CO₂-filled ZIF-8 particle (outlined by white dashed lines) taken with electron dose rate of $\sim 4.5 \text{ e}^-/\text{\AA}^2/\text{s}$ for 1.5s along the $\langle 111 \rangle$ projection. **e**, CTF-corrected denoised image of red boxed region from (d). Bright regions correspond to mass density. Contrast in the center of the 6-ring window is clearly observed for multiple unit cells. **f**,

Magnified image of a single ZIF-8 unit cell from (e). Density at the center of the unit cell (indicated by red arrow) likely corresponds to CO₂ adsorbed within ZIF-8. g, Simulated structure of ZIF-8 with DFT-predicted binding site of CO₂ (simplified as red spheres) along the <111> projection. This is consistent with the experimental cryo-EM image from (f). h, Integrated intensity of ZIF-8 plotted over 10 unit cells along the <011> direction, indicating a 3% lattice expansion when CO₂ is introduced to ZIF-8.

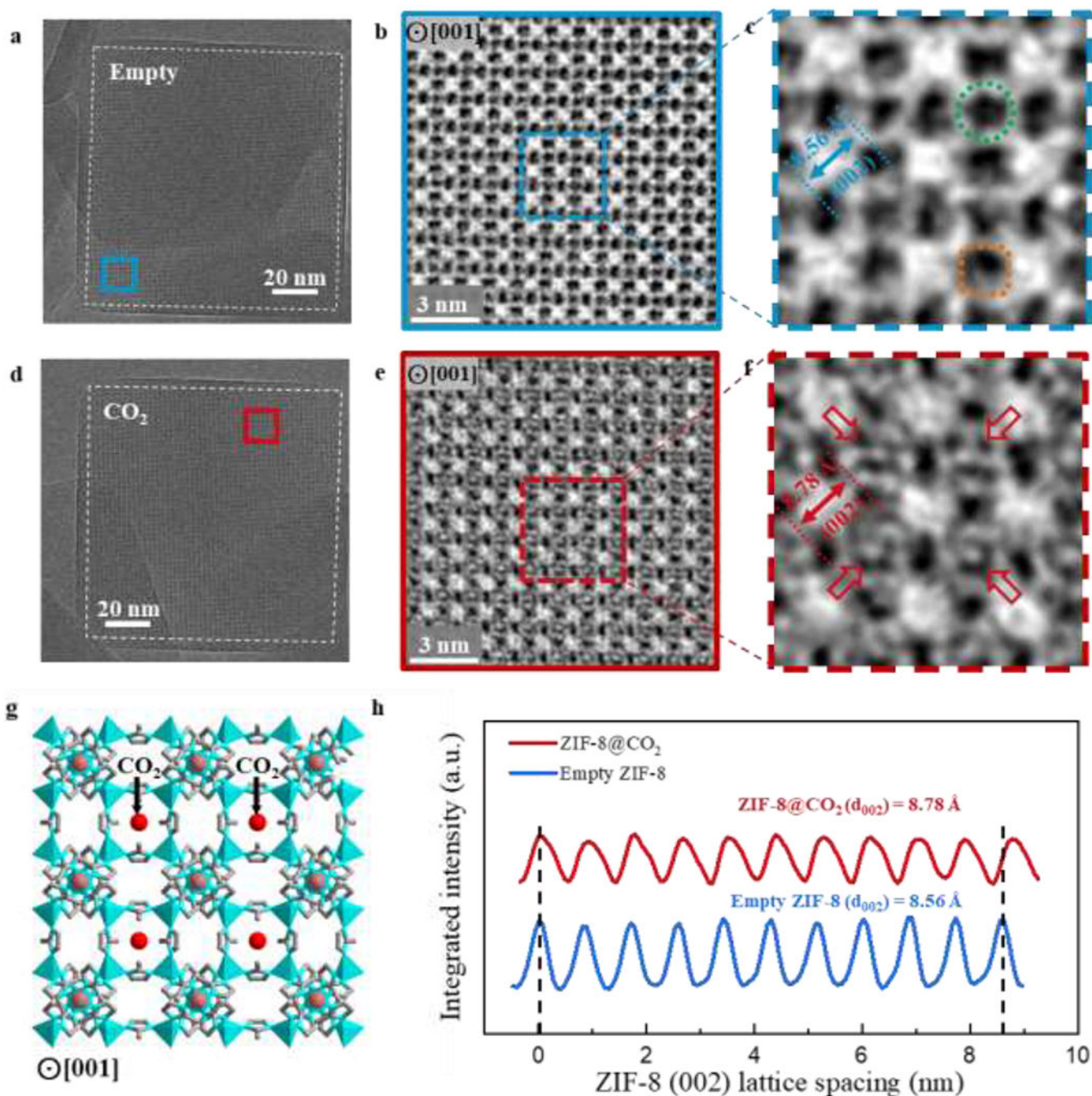


Figure 5 | Host-guest structures within ZIF-8 viewed along $\langle 001 \rangle$ projection.

a. Cryo-EM image of vacuum-dried, empty ZIF-8 (outlined by white dashed lines) taken with electron dose rate of $\sim 4.5 \text{ e}^-/\text{\AA}^2/\text{s}$ for 1.5s along the $\langle 001 \rangle$ projection. **b.** CTF-corrected denoised image of blue boxed region from (a). Bright regions correspond to mass density. **c.** Magnified image of ZIF-8 unit cells in blue box from (b). Green circle indicates pore cavity at the vertices of the Zn clusters. Orange square indicates pore cavity at the edges of the Zn clusters. **d.** Cryo-EM image of CO₂-filled ZIF-8 particle (outlined by white dashed lines) taken with electron dose rate of $\sim 4.5 \text{ e}^-/\text{\AA}^2/\text{s}$ for 1.5s along the $\langle 001 \rangle$

projection. **e**, CTF-corrected denoised image of red boxed region from (**d**). Bright regions correspond to mass density. Contrast near the center of the 4-ring window is clearly observed for multiple unit cells. **f**, Magnified image of ZIF-8 unit cells in red box from (**e**). Density near the center of the unit cell (indicated by red arrows) likely corresponds to CO₂ adsorbed within ZIF-8. Note that only the pore cavity at the vertices of the 4-ring window contain the density in the center. **g**, Simulated structure of ZIF-8 with DFT-predicted binding site of CO₂ (simplified as red spheres) along the $\langle 001 \rangle$ projection. This is consistent with the experimental cryo-EM image from (**f**). **h**, Integrated intensity of ZIF-8 plotted over 10 unit cells along the $\langle 002 \rangle$ direction, indicating a 3% lattice expansion when CO₂ is introduced to ZIF-8