Catalytic Active Hollow Fiber Membranes with an Enzyme-embedded MOF Coating

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Abstract: Enzymatic reactions have the potential to enable a greener production of chemicals and pharmaceuticals. Enzyme stability, -recycling, and the implementation into a continuous process are vital points for the commercial success of enzymatic reactions. Recent publications revealed the suitability of Metal-Organic Frameworks (MOFs) as an enzyme immobilization matrix, with increased physiochemical stability. However, the separation of these enzyme MOFs and the additional transport resistances are still challenging. We report for the first time the in-situ biomineralization of enzymes into MOF structures via interfacial crystallization. This method proves to be effective for the selective coating of porous polymeric hollow fibers in a straightforward one-step process. We produced well adhering and stable enzyme embedded MOF layers with high enzymatic activity. The fusion of the enzymatic active layer and the hollow fiber membrane enables the continuous enzymatic reaction by the combination of permeation and reaction. The results show the successful improvement of the enzymatic activity due to the convective transport of educts and products to the enzymatic active centers during permeation.

Introduction

Enzymatic reactions enable selective reactions under mild conditions such as low temperatures and aqueous environments, making them a promising alternative for more environmentally friendly synthesis in the (bio)chemical industry.[1] However, the limited enzymatic stability, the difficult separability of the product and the enzyme recycling pose a major challenge. To make a biotechnological process more favorable, these challenges must be addressed.

Enzyme immobilization on or in different carrier materials is a promising method to overcome these challenges.[2] Metal-Organic Frameworks (MOFs), which are three-dimensional nanoporous materials consisting of inorganic nodes and organic linkers, possess special properties that make them predestined for enzyme immobilization.[3–5] These include a precisely adjustable three-dimensional structure and a defined chemical microenvironment that counteracts enzyme denaturation.[6] Various MOFs have so far been successfully used for enzyme immobilization. The immobilization can be performed by post-synthetic adsorption/infiltration methods or in a single step during MOF synthesis.[7–12] In-situ biomineralization is a particularly interesting single-step method as it allows the immobilization of enzymes inside the MOF structure independent of the relationship between enzyme and pore size.[6,13–15] Mild reaction conditions during MOF synthesis are a requirement for successful in-situ biomineralization. Recent publications have successfully investigated a special subclass of MOFs, namely zeolite imidazolate frameworks (ZIFs), for the biomineralization of different enzymes, DNA and living cells.[16,17]

A Publications from 2015 describes the first successful in-situ biocrystallization in ZIF-8 crystals in a water-based system.[13] It has been shown that substrate affinity, enzyme activity, and stability to elevated temperature and organic solvents are increased by immobilization in ZIF-8 crystals, making this MOF class a promising material system. However, the recovery of the finely distributed MOF crystals after the enzymatic reaction poses a major challenge.[18]

A promising possibility to overcome these challenges is the immobilization of enzymatically active MOFs on porous synthetic membranes since enzymatic conversion and separation can take place in a single process step. In recent years, membranes have been successfully coated with pure MOF layers by various processes.[19,20] This made it possible to produce defect-free, uniform layers that are strongly intergrown with the membrane.[21–23] These membranes have so far been successfully used for gas separation and adsorption applications.[24–27]

However, so far, only two working groups have successfully modified a membrane with an enzyme- MOF layer. Zhang et al. deposited preformed ZIF-8 crystals, which were loaded with the enzyme carbonic anhydrase by adsorption on a modified flat sheet PAN membrane.[28] These MOF crystals serve as seeds for the crystallization of the subsequent in-situ growth of a defect-free ZIF-8 layer. The membrane showed an improved CO_2/N_2 selectivity of 9 to 165.5 compared to the enzyme-free membrane. A further publication from 2018 describes the modification of PAN ultrafiltration membranes in a complex multi-stage process with polyethyleneimines (PEI), metal-organic frameworks, lactase and polydopamine for the removal of micropollutants from wastewater.[29] However, this process does not produce interconnected MOF layers. Both so far described concepts rely on adsorptive enzyme binding to preformed MOF crystals, which can cause enzyme leaching and utilize time-consuming multi-step synthesis methods.[29] Furthermore, these publications do not demonstrate the modification of hollow fiber membrane, which are favorable since they allow an easier module design and a higher packing density.

In this publication, we report for the first time the in-situ biomimetic mineralization of enzyme-containing ZIF-8 layers on a polymeric hollow fiber membrane (Polyethersulfone (PES)) by a single-step counter-diffusion process with two immiscible phases as illustrated in Figure 1. The described counter-diffusion process is inspired by the interfacial polymerization method, which is the established industrial manufacturing process for reverse osmosis membranes. Interfacial polymerization has proven to be suitable for polymerizing a thin enzymatic active pepsin layer onto a synthetic porous membrane.[30] These enzymatically active ultrathin pepsin membranes digest proteins and pass the products selectively ones their retention is low enough. This is represented by the slow kinetics in the order of hours. It would also be desirable to have access to enzymatically active membranes where single passage and short residence times of seconds results in the desired chemical conversion. Counter-diffusion processes have shown to produce defect-free, intergrown MOF films with controllable thickness without the need for further surface modification.[31] Most publications describe the counter diffusion process for inorganic membrane materials. Only a few publications describe the successful utilization of this method for the coating of polymeric flat sheet membranes[31–33] or even hollow fiber membranes.[34,35] However, this method has not been tested for the in-situ biomineralization of enzymes. Besides the proof of concept for this method to produce enzymatic active MOF layers, the transition from batch experiments to continuous enzymatic reaction shall be evaluated. For this purpose, the reaction mixture is permeated with different flowrates trough the coated hollow fiber membranes and the product concentration is monitored at the permeate outlet, to evaluate the coating stability and the influence of convective flow on the enzymatic activity.

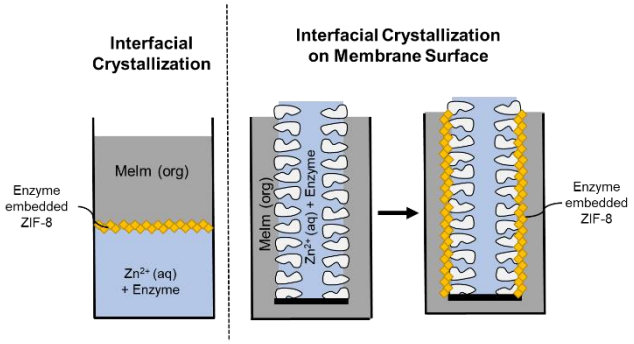

Figure 1. Schematic representation of the in-situ biomineralization of enzyme embedded MOF's via interfacial crystallization at a liquid-liquid interface (a), schematic representation of the interfacial crystallization of enzyme embedded MOFS on a hollow fiber membrane surface (b).

Results and Discussion

Interfacial crystallization of GOD@ZIF-8

Counter diffusion methods are well suited for the synthesis of MOF layers at the interface between two liquids with limited miscibility.[36–38] In recent publications, this concept shows promising results for the coating of porous membrane structures.[31,39] In this publication, the interfacial synthesis of ZIF-8 crystals with embedded glucose oxidase (GOD) should be performed at the interface between an organic (hexane + methanol + ethanol) 2-Methylimidazole and an aqueous Zinkacetate + GOD solution. The flavoprotein glucose oxidase catalyzes the oxidation of β-D-Glucose to D-gluconolactate and is a common model enzyme due to its high stability.[40,41] To evaluate the suitability of this method for the enzyme in-situ biomineralization concerning crystal morphology, enzyme inclusion, and enzymatic activity, the interfacial synthesis was performed in 3 mL vials (Figure 2 a). Immediately after overlaying the aqueous with the organic phase, the interface becomes turbid (Figure 1 a (left)), showing the spontaneous formation of ZIF-8 crystals at the interface. During the reaction time of three hours, more ZIF-8 is formed at the interface and partially starts to sediment (Figure 1 a (left)). Figure 1 c and d show the SEM images of the formed ZIF-8 and GOD@ZIF-8 crystals after three hours of reaction time. The SEM image of the pure ZIF-8 (Figure 2 c) shows a well intergrown layer composed of small (< 1µm) ZIF-8 crystals. In contrast to this, the morphology of the GOD@ZIF-8 layer (Figure 2 d) shows larger (1-3 µm) and more regular ZIF-8 crystals. The formation of larger crystals in the presence of proteins is also reported in literature and might be attributed to a local enrichment of metal ions and linkers arroud the proteins leading to facilitated crystallistzion of ZIF-8 around the proteins.[13] XDR analysis of the obtained MOF powders shows the characteristic peaks for ZIF-8 (see Support Information). Fluorescence microscopy images of the formed

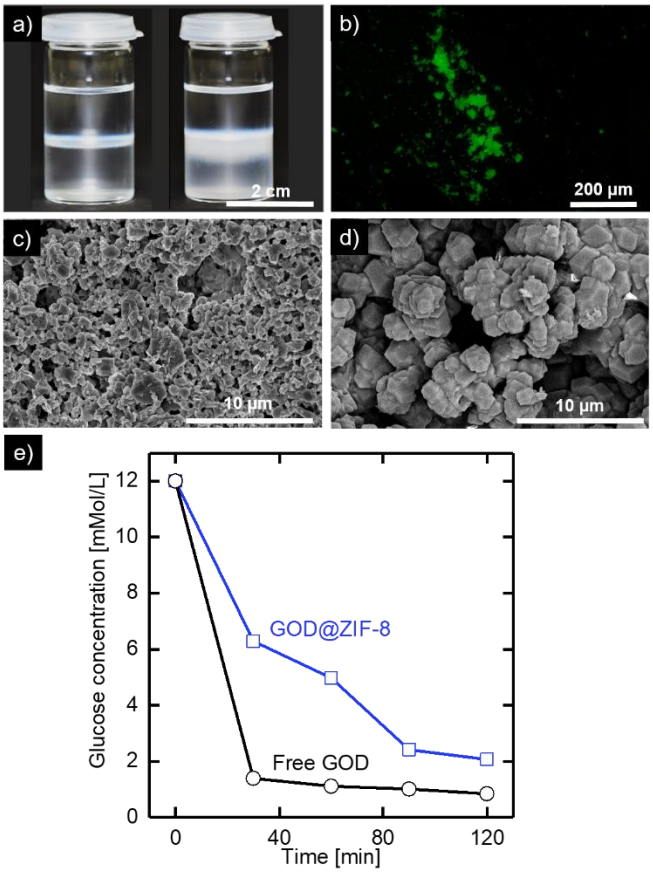

Figure 2. In-situ biomineralization of GOD@ZIF-8 at the liquid-liquid interface between an aqueous MeIm and an organic (Hexane + MeOH + EtOH) ZnAc solution (a), fluorescence microscopy image of GOD@ZIF-8 crystals synthesized with NCS-fluorescein labeled GOD (b), SEM micrographs of ZIF-8-layers without added GOD (c), SEM micrographs of ZIF-8- films with 2 mg/mL GOD in the aqueous phase (d), enzymatic activity test of GOD@ZIF-8 crystals and free GOD in PBS buffer with 12 mM glucose (e).

ZIF-8 crystals (Figure 2 b) show an evenly distributed fluorescence of the ZIF-8 crystals revealing the successful enzyme immobilization. In addition to labeling experiments, the enzyme encapsulation efficiency was determined via a colorimetric bicinchoninic acid (BCA) protein assay. During the interfacial crystallization, the encapsulation efficiency is 25%.
Figure 2 e shows the enzymatic activity test of the synthesized GOD@ZIF-8 crystals and the free enzyme performed in PBS buffer with 12 mM glucose at 37°C. The glucose concentration decreases from 12 mM to 6 mM within the first 30 minutes and reaches nearly full conversion (2 mM) of glucose after 2 hours, showing the successful immobilization of active enzyme. The steady but not linear glucose conversion can be explained by the decrease in substrate concentration. The immobilized enzyme shows reduced enzymatic activity in comparison to the free enzyme. This decreased activity may be caused by the restricted transport of products and educts to the active centers or a partial denaturation during the immobilization procedure.

Membrane Coating with GOD@ZIF-8

The promising concept of GOD@ZIF-8 crystallization at a liquid-liquid interface is applied as a coating process to generate an enzyme-containing ZIF-8 layer on top of commercially available PES 200 polymeric hollow fiber membranes. For the membrane coating step, the membrane pores and the membrane lumen is filled with a GOD containing aqueous Zink acetate solution and subsequently placed into the organic phase containing the organic linker. After a reaction time of 3 hours, GOD@ZIF-8 functionalized membranes are obtained. The coating morphology was investigated by scanning electron microscopy. Figure 3 shows the respective SEM micrographs of the uncoated (a, c) and the GOD@ZIF-8 coated membrane (b, d).
The cross-section images (Figure 3 a-b) show the successful deposition of a crystalline MOF layer on the membrane shell side. These images prove the suitability of the counter diffusion process for the in-situ biomineralization of GOD onto a hollow fiber surface. The layer has a thickness of 8 µm and consists of intergrown large MOF crystals with a size between 1-3 µm. The MOF layer penetrates to some extent into the porous membrane matrix indicating a layer growth predominantly from the organic to the aqueous phase wetting the polymer support. In literature, enzyme-free MOF layers with a thickness of 8.8 micrometers and 10-25 micrometers were synthesized on polymeric membranes by the counter diffusion concept.[34,35] The top view SEM micrographs (Figure 3 c-d) show a compact GOD@ZIF-8 layer composed out of small intergrown crystals, covering the entire membrane surface.
To evaluate the biomineralization of GOD inside the MOF coating, the protein content inside the MOF layer is analyzed via a colorimetric BCA protein assay in a triple determination. The measured protein content on the membrane was 29±3 µg/cm^2, showing the successful biomineralization.
The enzymatic activity of the GOD@ZIF-8 coated membranes was analyzed by incubation of coated membrane pieces (3 cm (1.89 cm^2)) in a 12 mM glucose solution at 37°C. The decrease in glucose concentration is measured at regular time intervals. Figure 3 e shows the corresponding data. Each data point is the average value of three independent measurements. To identify the glucose conversion caused by adsorbed enzymes on the membrane surface, a bare PES was exposed to the same coating and cleaning procedure but without the addition of the organic crosslinker during the in-situ biomineralization. This reference membrane leads to an initial decrease in glucose concentration from 12 mM to 11 mM, which can be attributed to dilution effects caused by absorbed water in the membrane. After this initial decrease, the reference membrane shows no enzymatic activity, indicating that GOD does not significantly adsorb on the membrane surface since both have a negative surface charge at a neutral pH.[42,43]

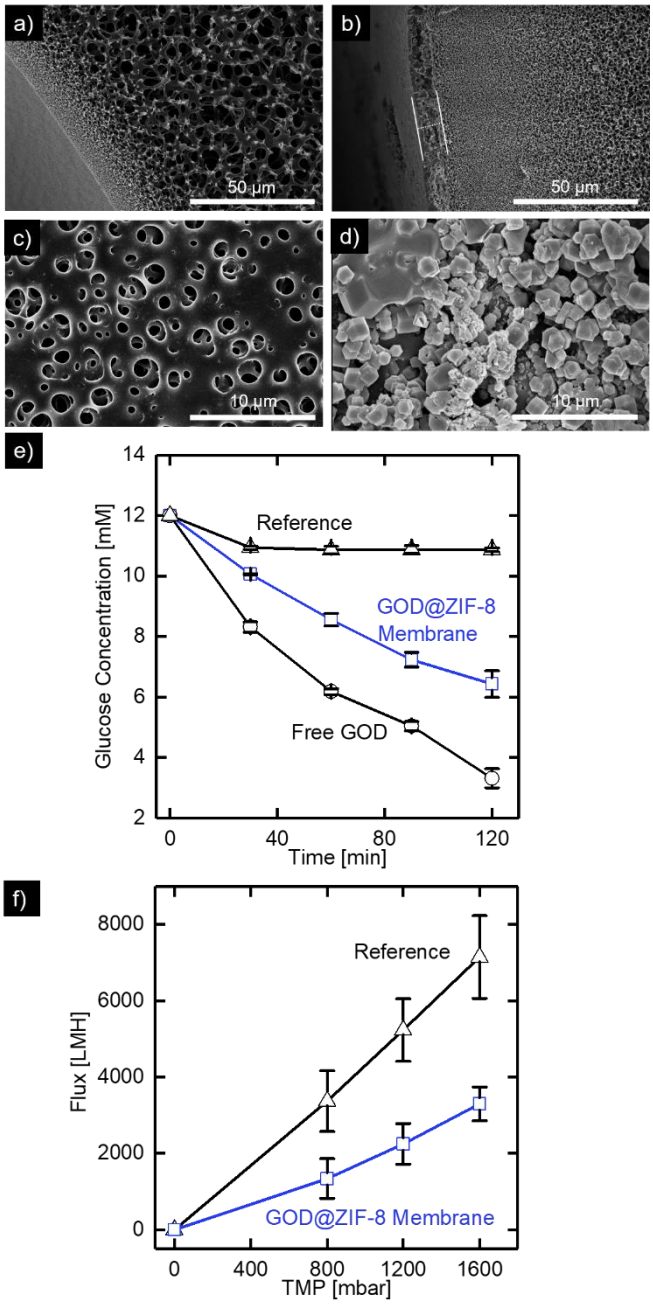

Figure 3. SEM micrographs of an uncoated PES hollow fiber membrane (a,c) and a PES hollow fiber membrane coated with a GOD@ZIF-8 layer via interfacial crystallization (b,d), enzymatic activity of a GOD@ZIF-8 coated membrane (e). Pure water flux measurement performed with DI water under constant pressure conditions in dead-end mode during inside out permeation for an uncoated (black) and GOD @ ZIF coated membrane (blue) (f). All error bars represent the standard deviation based on three independent measurements of three different membranes.

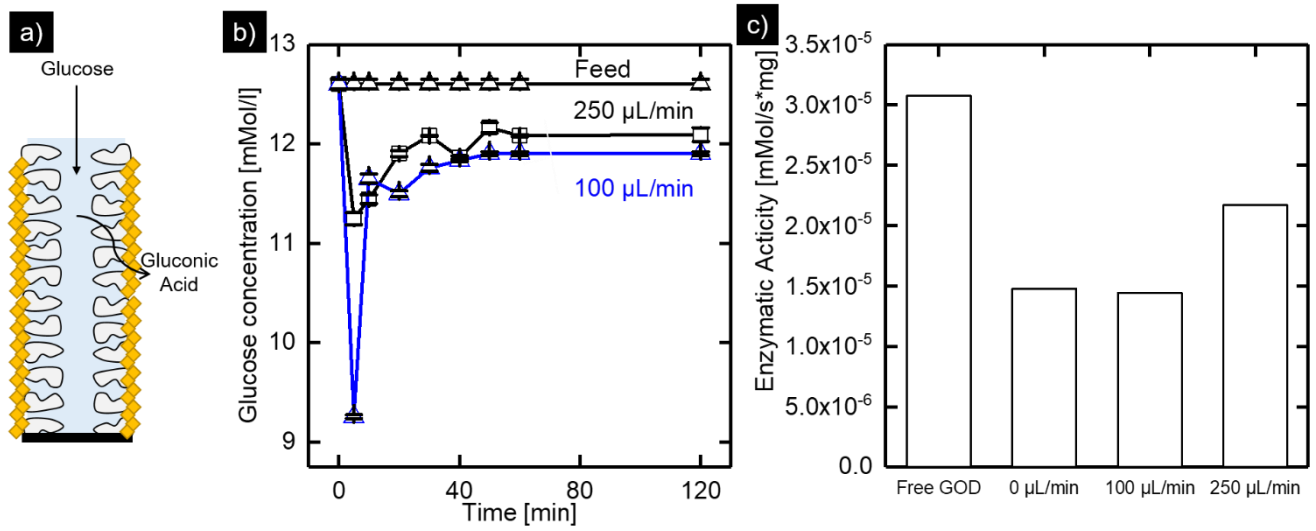

Figure 4. Schematic representation of the continuous enzymatic conversion of glucose on a GOD @ ZIF 8 Membrane (a), concentration profiles of glucose for different flowrates (b), comparison of the calculated conversion rates (c).

In contrast to this, the GOD@ZIF-8 coated membrane shows a continuously decreasing glucose concentration. Within two hours, 5.5 mM glucose is converted, and the concentration decreases nearly linear over time. This proves the successful immobilization of active GOD within the MOF layer on the membrane shell side. Additionally, the small error bars demonstrate a reproducible membrane coating method. Reference experiments with the free enzyme show the activity loss caused by the immobilization. For this purpose, the glucose conversion by 50 µg free GOD, which is the measured amount of enzyme in the ZIF-8 coating, is monitored. The free enzyme shows higher activity and converts 9 mM glucose in two hours. The decreased activity of the immobilized enzyme can be caused by mass transport limitations or by changes in the enzyme structure. However, the results demonstrate the successful coating of a commercial polymeric hollow fiber with an enzymatic active MOF layer.

Continuous enzymatic reaction inside a membrane module

To evaluate the influence of the GOD@ZIF-8 coating on the membrane performance, the pure water permeability of a coated GOD@ZIF-8 membrane and a reference membrane was investigated. Figure 3 f depicts the results of the pure water flux measurements for an uncoated PES 200 reference membrane and a coated PES 200 membrane. All experiments were performed in dead-end mode via inside out permeation. Each data point represents the mean value of three independent measurements, while the respective error bars depict the standard deviation. For the reference membrane, the error bar is in the range of 15%. The coated membrane shows similar error bars indicating a reproducible coating method. For both membranes, the flux increases linear with increasing transmembrane pressure (TMP), indicating a stable layer. If the layer would not stable during inside out permeation, parts of the coating can delaminate from the membrane, changing the membrane resistance and leading to a nonlinear flux increase. In comparison to the uncoated membrane, the permeability of the coated membrane decreases by 54%. The reason for the decreased permeability is the additional transport resistance due to the ZIF-8 layer and partial pore blocking.

However, the results show that the MOF layer is not entirely dense, allowing the permeation of water, which is an essential prerequisite for a continuous enzymatic reaction in a liquid phase. For the investigation of the continuous enzymatic conversion of glucose, coated membranes (85 mm membrane length) were mounted into tubular dead-end modules with a total module volume of 3.4 mL (see Figure S3). Fresh glucose solution with a concentration of 12.6 mM/l is pumped at a constant flow rate into the membrane lumen channel, permeating thought the membrane wall, and passing the enzymatic active GOD@ZIF-8 layer were glucose is converted to gluconic acid (see Figure 4 a). The glucose concentration at the module outlet was measured for different flow rates over a time period of 120 minutes after the module is filled with glucose solution. Figure 4 b shows the resulting concentration profiles of the feed and the permeate for a feed flow rate of 250 µl/min, and 100 µl/min. For both flowrates, an increased glucose conversion is detected in the first 5 minutes. This low glucose concentration can be caused by initial dilution of the feed solution by water adsorbed in the membrane porosity. After this initial high glucose conversion, the permeate concentration approaches a constant value for the experiment duration. For a flowrate of 250 µl/min (residence time of ≈ 816 sec), a permeate concentration of 12.1 mM/l is reached. For a decreased flow rate of 100 µl/min (residence time of ≈ 2040 sec), the permeate glucose concentration decreases to 11.9 mM/l, which can be explained by the longer residence time. This constant glucose conversion over the entire experiment time shows that no significant enzyme leaching occurs, highlighting the coating stability for operation under continuous flow.

Since the transport of educts and products to the active enzyme sites is expected to have a significant impact on the enzymatic conversion rate, the experiments performed under constant flow conditions are expected to show an increased conversion rate in comparison to experiments without flow. To determine the influence of mass transport limitations on the enzymatic conversion of glucose, the conversion rates of the batch and the

continuous process were compared. To achieve the comparability of these two processes, the conversion rate in the batch process was determined, taking into account the concentration change from Figure 3 e during the first 30 minutes (assuming linear degradation), the volume of the glucose solution, and the enzyme mass according to Equation 1. For the determination of the conversion rate for the continuous process, we analyzed the concentration difference between feed and permeate ($\Delta C_{Glucose}$), the residence time in the module (τ), the module volume (V_{Module}) and the enzyme mass (m_{GOD}) according to Equation 2.

$$\frac{\Delta C_{Glucose} \cdot V_{Solution}}{\Delta t \cdot m_{GOD}} = conversion\ rate\ \left[\frac{mMol}{\mu g \cdot s}\right] \quad (1)$$

$$\frac{\Delta C_{Glucose} \cdot V_{Module}}{\tau \cdot m_{GOD}} = conversion\ rate\ \left[\frac{mMol}{\mu g \cdot s}\right] \quad (2)$$

Figure 4 c depicts the calculated conversion rates of the free enzyme, the batch- and the continuous reaction. The free enzyme serves as a benchmark to determine the influence of immobilization on enzyme activity. The free enzyme shows the highest conversion rate of $3.1 \cdot 10^{-5}$ mMol/s·mg. The enzyme immobilized on the membrane shows a reduced enzymatic activity by 50% in the batch experiment. Diffusion limitation due to encapsulation or a partial change in the enzyme structure during the immobilization procedure can cause a decrease in enzyme activity. Active transport of educts to the enzymatic active centers by permeation poses a promising way to overcome the diffusion limitation. During the continuous enzymatic reaction in the membrane module at a low flow rate of 100 µL/min, an enzymatic activity corresponding to the batch experiment is reached. When the flow rate is increased to 250 µL/min, the enzymatic activity increases by a factor of 50% to $2.2 \cdot 10^{-5}$ mMol/s·mg compared to the batch reaction. This improved enzymatic activity emphasizes the importance of the active transport of educts and products to the enzymatic active centers. These results demonstrate the suitability of GOD@ZIF-8 membranes for continuous enzymatic reactions showing high stability and improved enzymatic activity.

Conclusion

In the present study, we presented the coating of a PES hollow fiber membrane with an enzyme-embedded ZIF-8 layer by a single-step interfacial biomineralization method. The technique yielded well adhering uniform and intergrown ZIF-8 layers on the membrane shell side. Due to its simplicity, the technique enables the large scale production of coated membranes. Enzyme quantification measurements and activity tests revealed the successful immobilization of active GOD. For the first time, polymeric hollow fiber membranes are successfully coated with permeable enzyme embedded MOF layers via an interfacial biomineralization method. The coated membranes represent an enzyme membrane reactor capable of converting the substrate during permeation. We could show that the convective transport of educts and products during permeation increases the enzymatic activity by 50% when applying high feed flow rates. During the experiments, no loss in activity over time was detectable, highlighting the coating stability and emphasizing the applicability of these composite membranes for continuous enzymatic reactions. The work highlights the potential of interfacial crystallization of enzyme embedded MOFs onto porous synthetic membranes for efficient membrane bioreactors. The presented method can be transferred to other enzymes and membranes as long as the membrane is permeable for the enzyme and the MOF precursors.

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Keywords: metal-organic framework • hollow fiber membranes • in-situ biomimetic mineralization • enzyme immobilization • bioreactor

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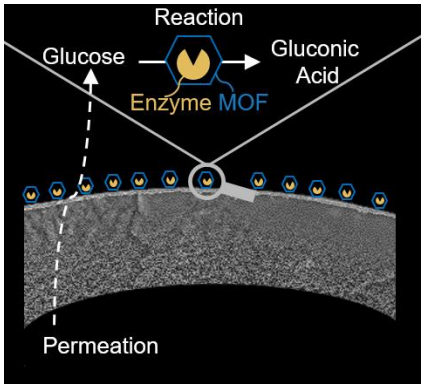

We report for the first time the successful in-situ biomineralization of an enzyme-containing MOF layer on a polymeric hollow fiber in a facile one-step process. The interconnection between an enzymatic active layer and a porous membrane proves to overcome stability drawbacks, removes the need for MOF separation and leads to increased enzyme activity due to the improved mass transport by permeation.