ACS Catalysis

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Dual-Surface Functionalization of Metal-Organic Frameworks for Enhancing the Catalytic Activity of *Candida antarctica* Lipase B in Polar Organic Media

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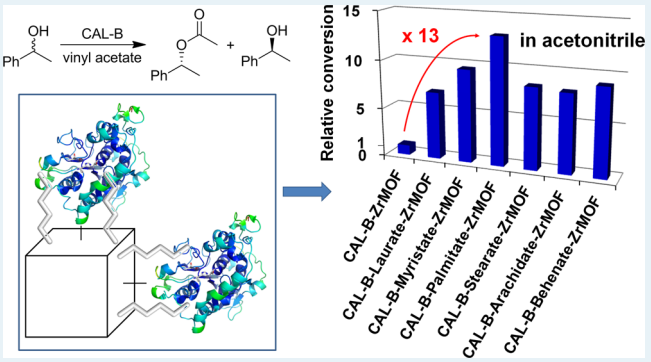
Supporting Information

ABSTRACT: One of the most attractive characteristics of metal organic frameworks (MOFs) is their diversity in use as functional materials, because their diversity means that the appropriate MOFs for the required applications can be readily generated from numerous elemental compounds. In addition, post-synthetic modifications of MOFs further expand their diversity. We describe a combined approach involving a typical post-synthetic modification and our previously reported surface modification to introduce multicompounds on MOFs. This method has been used to alter the local environments of a target biocatalyst and has enhanced the activity of the biocatalyst in polar organic media. It has been known that lipases are more active in nonpolar organic solvents than in polar ones. Hence, it can be hypothesized that surrounding lipase molecules with nonpolar compounds possibly increases the activity of lipases in polar organic solvents such as acetonitrile. A series of fatty acids (C12−C22) were conjugated with the amino groups of 2-amino-1,4-benzene dicarboxylate (NH_2−BDC) in UiO-66-NH_2 (ZrMOF) and then *Candida antarctica* lipase B (CAL-B) was covalently bonded to the pendent carboxylate groups on the surface of ZrMOF. The introduction of fatty acids around the covalently conjugated CAL-B molecules on ZrMOF improved the activity in acetonitrile by a factor of up to 13.



KEYWORDS: *bioconjugation, immobilization, lipase, metal organic frameworks, multifunctionalization, post-synthetic modification, surface modification*

Candida antarctica lipase B (CAL-B) is one of the most widely used biocatalysts in organic synthesis, because it is suitable as a catalyst in synthetic applications.[1,2] For example, CAL-B possesses high enantioselectivity for chiral secondary alcohols and high thermostability.[3] In addition, CAL-B exhibits high tolerance in various organic media.[4] The activity of CAL-B, however, varies according to the polarity of the organic media, which is similar to most other lipases.[5] For example, CAL-B exhibits its highest activity in nonpolar organic solvents, such as hexane and toluene, but exhibits lower activity in polar solvents, such as acetonitrile.[6] Although most lipases are less active in polar solvents, a polar solvent is often required, because of substrate solubility issues. Therefore, enhancing the activity of CAL-B in polar solvents improves the utilization of CAL-B in organic synthesis. The underlying reason why hydrolases, including CAL-B, exhibit lower activity in polar solvents has not been completely elucidated.[7] However, it can be hypothesized that the activity of CAL-B in polar media is possibly improved by surrounding the CAL-B molecules with nonpolar organic compounds. Covalent immobilization of CAL-B on supporting materials can separate all of the CAL-B molecules, and the introduction of nonpolar molecules onto the supporting materials can alter the local environments of the separated CAL-B molecules. For instance, Fernandez-Lafuente and co-workers reported the effect of the introduction of basic molecules on the lipase activity in aqueous media.[8] They used basic compounds as a blocking compound after the covalently immobilization of lipases using divinylsulfone on agarose. The introduction of the basic compounds presumably changes the local pH around lipase molecules and affects the activity of lipase. Herein, we explored the hypothesis by dual-surface functionalization of metal-organic frameworks (MOFs).

MOFs have garnered much more attention in the last few decades.[9] One attractive characteristic of MOFs is their large void volume. In addition, another fascinating characteristic of MOFs is their diversity. MOFs can be prepared from numerous elemental compounds, organic linker compounds and metal ions. The diversity of MOFs makes them employed for various applications. For instance, they have been used in catalysis, gas storage, and separation systems.[10] Recently, post-synthetic modification has been shown to introduce additional organic

Received: November 13, 2016
Revised: December 5, 2016
Published: December 12, 2016

DOI: 10.1021/acscatal.6b03222
ACS Catal. 2017, 7, 438−442

groups into MOFs, which has expanded their diversity.[11] Post-synthetic modification uses an intact functional group, such as the amino group of 2-amino-1,4-benzene dicarboxylic acid (NH_2−BDC), in the organic linker compound to react with a compound after synthesis of an MOF. Besides, our research group has proposed another approach for the modification of the surface of MOFs and described the conjugation of biomolecules onto MOFs.[12] While conventional post-synthetic modifications have focused on using a particular functional group as a reactive site to introduce the second functional group in the linker compound, we focused on the surface modification of MOFs without using such specific organic linkers. The linker organic compounds or metal ions on the surface of an MOF do not bind to each other and therefore remain intact pendent groups. The unreacted functional groups of organic linker compounds on the surface of MOFs can be activated and used to introduce other compounds onto MOFs. We have demonstrated that biomolecules can be conjugated to various structural MOFs and are also functionally active. In response to the findings of our previous study, we hypothesized that the combination of typical post-synthetic modification and our approach would allow multifunctionalization of the surface of MOFs (Figure 1a). Such multifunctionalization may allow control over the environment of a particular molecule that is surrounded by other compounds (Figure 1b).

We explored our hypothesis using UiO-66-NH_2 (ZrMOF), which is composed of Zr(IV) and 2-amino-1,4-benzene dicarboxylate (NH_2−BDC). The NH_2−BDC amino group remains intact during the synthesis of ZrMOF and can be modified through post-synthetic modification. In addition, the surface pendent carboxylate group on the ZrMOF also serves as a reaction center to bind biomolecules, as we have previously shown.[12] Furthermore, ZrMOF is stable in water, which is an important property, with respect to the conjugation of biomolecules onto MOFs, because the modification process occurs in an aqueous system, because of the solubility issues with the biomolecules.

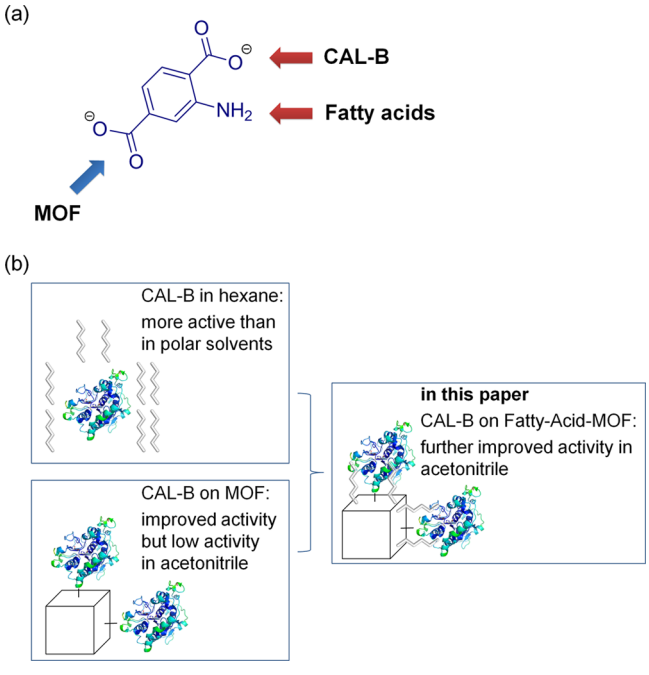


Figure 1. (a) 2-Amino-1,4-benzene dicarboxylic acid (NH_2−BDC). NH_2−BDC possesses two functional groups. The amino and pendent carboxyl groups can be used for the decoration of both fatty acids and biomolecules. (b) Systemic diagram for the dual-surface modification of MOFs. Immobilization of CAL-B can improve its activity, but its activity decreases in polar media. Providing a nonpolar local environment for CAL-B can increase its activity in polar organic media. CAL-B represents *Candida antarctica* lipase B.

ZrMOF was synthesized from $ZrCl_4$ and NH_2−BDC with an equivalent molar amount of water, according to previously described methods in the literature.[15] The average diameter of the particles was ∼200 nm (Figure 2a). The sized particles are suitable to reduce the mass-transfer limitations, compared to micrometer-sized beads.[16] Six fatty acids (C12, C14, C16, C18, C20, and C22, described in Table 1) were then conjugated to the intact ZrMOF amino group through amide-bond formation. The fatty acids were first activated by *N*,*N*′-diisopropyl carbodiimide (DIC), which is one of the peptide coupling reagents, and then were reacted with ZrMOF. Scanning electron microscopy (SEM) analyses exhibited that the morphology of the fatty-acid-conjugated ZrMOF was not altered (Figure 2a). In addition, powder X-ray diffraction (PXRD) patterns and infrared (IR) analyses demonstrated that the crystallinity and characteristic peaks of ZrMOF were conserved after fatty-acid conjugation (see Figure 2c, as well as Figure S1a in the Supporting Information). Fatty-acid conjugation was confirmed by electrospray ionization−mass spectrometry (ESI-MS) and nuclear magnetic resonance (NMR) analyses of the samples released from the ZrMOF digestion by hydrofluoric acid (HF). ESI-MS analyses clearly supported the fatty-acid conjugation by showing the pseudo-molecular ions ($M\text{-}H^-$) of the fatty-acid-conjugated NH_2−BDC (Figure S2 in the Supporting Information). However, the NMR spectra showed a mixture of the characteristic peaks of fatty-acid-conjugated NH_2−BDC and unreacted NH_2−BDC (see Figure 3). This indicates that not all of the free amino groups of ZrMOF were conjugated to fatty acids. Presumably, the fatty acids are too large to enter the ZrMOF, so the amino groups on the surface are the only ones that are modified.

The pendent carboxylate groups on the surface of the fatty-acid-conjugated ZrMOFs were then activated by DIC in dichloromethane (DCM). After the DCI-activated fatty-acid-conjugated ZrMOFs were sequentially washed with DCM, acetone, and water, the ZrMOFs were reacted with CAL-B in an aqueous buffer. To compare the effects of the fatty acids on the activity of CAL-B, CAL-B-conjugated ZrMOF without conjugated fatty acids was also prepared using the same procedure. In addition, ZrMOF without activation by DCI was also treated with CAL-B to determine whether CAL-B is physically absorbed by the fatty-acid-conjugated ZrMOF. The process for the CAL-B conjugation also did not alter the morphology, XRD patterns, or IR spectra of ZrMOF (see Figures 2b and 2c, as well as Figure S1b in the Supporting Information). The amount of the conjugated CAL-B on ZrMOFs was almost the same for all cases, and was measured as 3.3 mg of CAL-B per 1 g of fatty-acid-ZrMOF.

After the conjugation of CAL-B on the MOFs, the hydrolysis activity of the CAL-B-conjugated MOFs was measured whether the activity of the conjugated CAL-B on ZrMOFs still remains. The reaction was conducted by mixing (±)-1-phenylethyl acetate and the CAL-B-conjugated MOFs in BES buffer (5 mM, pH 7.2). ZrMOF without the conjugation of CAL-B does not show any hydrolysis activity, while the conjugated CAL-B on ZrMOFs was still functionally active (see Figure S3 in the

DOI: 10.1021/acscatal.6b03222
ACS Catal. 2017, 7, 438−442

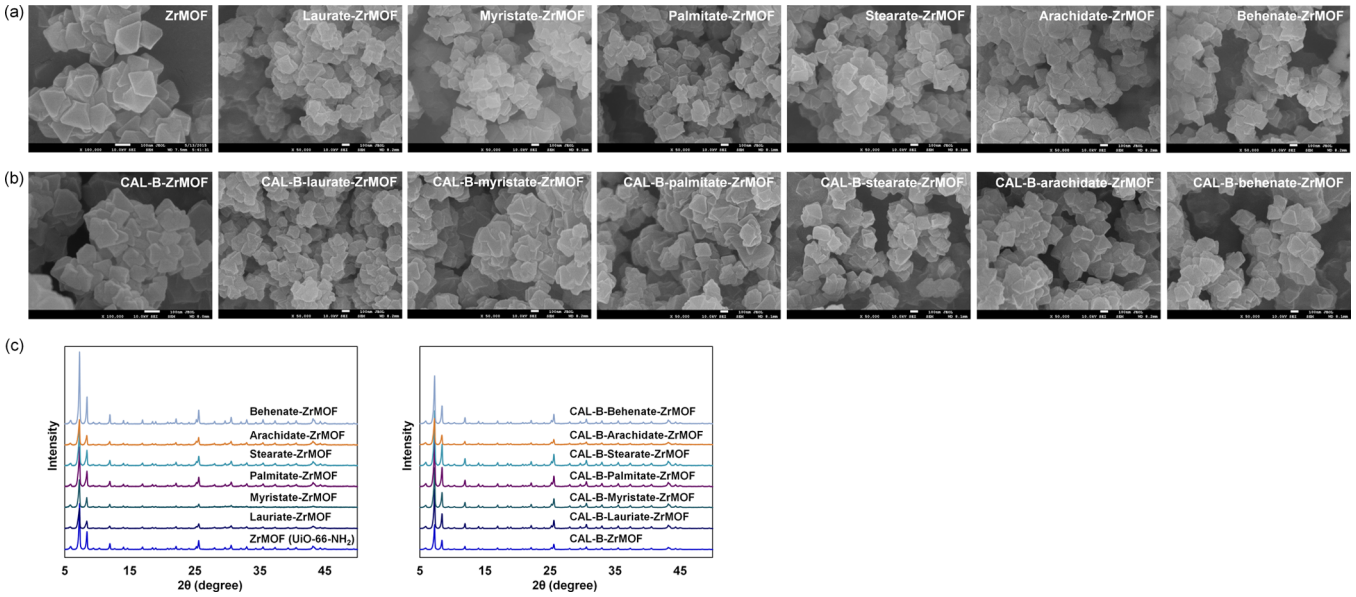
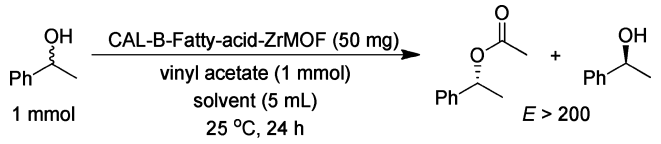


Figure 2. Scanning electron microscopy (SEM) images of the unmodified and modified ZrMOFs: (a) ZrMOF (UiO-66-NH_2) and fatty-acid-conjugated ZrMOFs and (b) CAL-B-conjugated ZrMOFs (the scale bars in the SEM images represent 100 nm). Powder X-ray diffraction (PXRD) analyses of the unmodified and modified ZrMOFs: (c) fatty-acid-conjugated ZrMOFs (left) and CAL-B-conjugated Zr-MOFs (right). (PXRD patterns are conserved in all cases.)

Table 1. Conversion of the Transesterification, As Catalyzed by CAL-B-Fatty-Acid-Conjugated ZrMOFs[a]



			Reaction Conversion[b] (%)				
entry	enzyme	number of carbons of fatty acid	hexane (E_T^N = 0.009)	MTBE (E_T^N = 0.124)	THF (E_T^N = 0.207)	*t*-BuOH (E_T^N = 0.389)	acetonitrile (E_T^N = 0.460)
1	ZrMOF		n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]
2	CAL-B + palmitate-ZrMOF (without DCI activation)	C16	n.d.				n.d.[c]
3	CAL-B-ZrMOF		19 ± 1.2[d]	21	5.4	4.7	1.3 ± 0.3
4	laurate-CAL-B-ZrMOF	C12	18 ± 1.1	29	6.8	6.0	9.0 ± 2.6
5	myristate-CAL-B-ZrMOF	C14	14 ± 5.1	29	8.9	6.9	12.4 ± 2.2
6	palmitate-CAL-B-ZrMOF	C16	27 ± 3.7	35	8.8	9.9	17 ± 1.1
7	stearate-CAL-B-ZrMOF	C18	36 ± 4.3	24	7.0	8.8	10.9 ± 0.5
8	arachidate-CAL-B-ZrMOF	C20	41 ± 5.2	25	4.1	6.0	10.6 ± 1.4
9	behenate-CAL-B-ZrMOF	C22	46 ± 3.5	30	7.5	7.1	11.8 ± 0.1

[a]The maximum conversion is ~50%, because CAL-B possesses high enantioselectivity for (±)-1-phenylethyl alcohol (E > 200).[13] [b]E_T^N represents Reichardt's normalized polarity scale.[14] MTBE = *tert*-butylmethyl ether, THF = tetrahydrofuran, and *t*-BuOH = *tert*-butyl alcohol. [c]n.d. = not detected. [d]The errors are represented by standard deviations for at least three measurements; entries without errors are single measurements.

Supporting Information). It is noteworthy that the reactions catalyzed by the fatty-acid-conjugated ones exhibited higher conversion, by a factor of ~2.7, compared to the reaction by the solely CAL-B conjugated one.

To evaluate the effect of fatty-acid conjugation on the activity of CAL-B-conjugated ZrMOFs in organic media, we first measured the reaction conversions of the transesterification of (±)-1-phenylethyl alcohol in nonpolar organic solvents, including hexane and *t*-butylmethyl ether (MTBE) (see Table 1). The reaction was performed with (±)-1-phenylethyl alcohol (1 mmol) and vinyl acetate (1 mmol) at 25 °C for 24 h. For comparison, the activities of ZrMOF and palmitate-conjugated ZrMOF treated with CAL-B without DCI activation were also measured (entries 1 and 2 in Table 1). In both cases, no detectable activity was observed. These results indicate that ZrMOF does not have any catalytic activity in the reaction and that CAL-B does not physically bind to ZrMOF without DCI activation. In contrast, CAL-B-conjugated ZrMOF exhibited an ~20% conversion in hexane and MTBE. Although we did not expect that surrounding CAL-B with fatty acids would enhance its activity in nonpolar media, fatty-acid-conjugated ZrMOF exhibited higher reaction conversions in both hexane and MTBE. One possible explanation is that the conjugated fatty acids on ZrMOF orient in the direction of CAL-B binding. Because of the hydrophobicity of the surface of CAL-B,[17] hydrophobic interaction would be established between the fatty acids and the surface of CAL-B during the conjugation of CAL-B. In contrast, the substrate entrance of CAL-B lacks the

DOI: 10.1021/acscatal.6b03222
ACS Catal. 2017, 7, 438−442

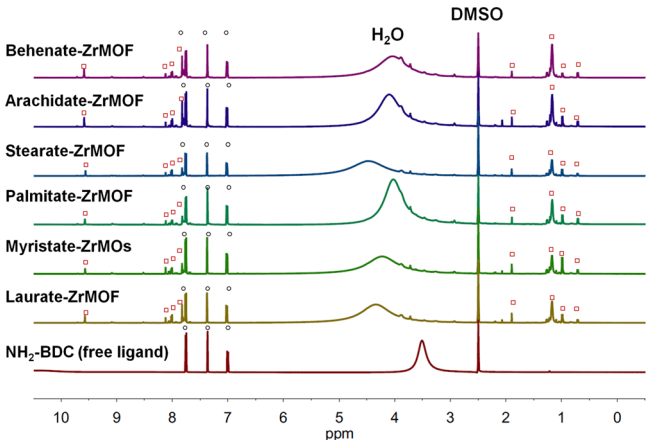


Figure 3. ^{1}H NMR spectra of the digested fatty-acid-conjugated ZrMOFs. Black circles indicate unmodified NH_2−BDC and red squares represent fatty-acid-conjugated NH_2−BDC released from the digested ZrMOFs.

interaction, because no amino acids are present in the substrate entrance. Hence, the interaction presumably drives the substrate entrances to be arranged outward from the center of ZrMOFs, although the orientation is not finely controlled. Such orientation of CAL-B molecules may decrease the mass-transfer limitation of substrates and thus increases the reaction conversion, compared to the randomly orientated CAL-B.[18] Besides, the hydrophobic substrates are presumably absorbed to a greater degree on the hydrophobic surface of the fatty-acid conjugated ZrMOFs, in comparison with the naked ZrMOF. This may provide better contact between CAL-B and the substrates, and improve the reaction rates. The specific effects of fatty-acid conjugation were different in each solvent. In hexane, the longer fatty acids increased the conversion up to 2.4 fold (entry 9 in Table 1). In MTBE, the palmitate-CAL-B-ZrMOF provided the highest conversion (entry 6 in Table 1). In addition, we examined these reactions in two medium polar solvents (tetrahydrofuran (THF) and *tert*-butyl alcohol (*t*-BuOH)) and a polar solvent (acetonitrile). As expected, the fatty-acid conjugation provided an increased conversion in all three solvents. However, the improvements of the conversion in THF and *t*-BuOH are similar to those in hexane or MTBE (i.e., up to 2.1-fold). On the other hand, a dramatic effect of fatty-acid conjugation was obtained in the reaction with acetonitrile. The highest conversion was obtained from the CAL-B-palmitate-ZrMOF-catalyzed reaction in acetonitrile and was higher, by a factor of 13, than that obtained using CAL-B-ZrMOF as the catalyst. The reason is not clear at the current stage why the highest conversion was obtained in the CAL-B-palmitate-ZrMOF-catalyzed reaction over the reactions by the other fatty-acid conjugated ones. However, a certain balance between stabilization by hydrophobicity and mass-transfer limitations may account for the result. The hydrophobicity of fatty acids should be stronger, according to the increasing alkyl chain length, and may help more stabilization of CAL-B in polar media. In contrast, the fatty acids with longer chain lengths probably shield the CAL-B molecule more tightly, because of lesser flexibility in polar media. Such shielding effect by fatty acids that are too much longer presumably increases the mass-transfer limitations, and, as a consequence, the reaction rate decreases. Therefore, the maximum activity of CAL-B was obtained with the middle length fatty-acid conjugated one (i.e., CAL-B-palmitate-ZrMOF). In addition, it is noteworthy that the conversion in acetonitrile by CAL-B-palmitate-ZrMOF was comparable to that in hexane by CAL-B-ZrMOF. These results demonstrated that the introduction of hydrophobic molecules near CAL-B can alter the local environment and improve the activity of CAL-B.

In conclusion, we have successfully demonstrated dual functionalization of the surface of MOFs and used this strategy to alter the local environment of a biomolecule that was conjugated to an MOF. This approach resulted in enhancing the activity of CAL-B. Because of the number of combinations of organic linker compounds and metal ions, the possible combinations of MOFs are almost unlimited, but the organic linker compounds must be stable during the preparation process. The conjugation of thermally unstable biomolecules onto MOFs is able to expand the bioapplications for MOFs, including enzyme immobilization.[19] Moreover, the multi-functionalization of the surface of MOFs possibly provides various functionalities on the surface of MOFs and thus can be employed for a cascade catalytic system by combining a catalytic MOF and biocatalyst.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b03222.

Experimental details and Figures S1−S3 (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (No. 2010-0022069) and the Ministry of Science, ICT, and Future Planning (No. 2014R1A2A2A01004836).

■ DEDICATION

This paper is dedicated to Prof. Romas Kazlauskas for the occasion of his 60th birthday.

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DOI: 10.1021/acscatal.6b03222
ACS Catal. 2017, 7, 438−442