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# Bio-inspired Water-Driven Catalytic Enantioselective Protonation

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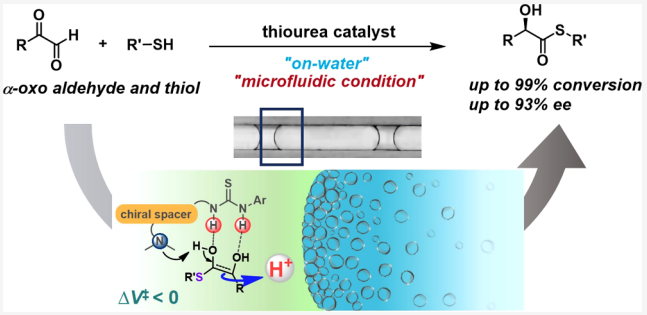
**ABSTRACT:** Catalytic enantioselective protonation of a prochiral carbanion in water is a common transformation in biological systems, but has been beyond the capability of synthetic chemists since unusually rapid movement of a proton in water leads to uncontrolled racemic protonation. Herein we show a crucial role of water, which enables a highly enantioselective glyoxalase I-mimic catalytic isomerization of hemithioacetals which proceeds via enantioselective protonation of an ene-diol intermediate. The use of on-water condition turns on this otherwise extremely unreactive catalytic reaction as a result of the strengthened hydrogen bonds of water molecules near the hydrophobic reaction mixture. Furthermore, under on-water conditions, especially under biphasic microfluidic on-water conditions, access of bulk water into the enantio-determining transition state is efficiently blocked, consequently enabling the enantioselective introduction of a highly ungovernable proton to a transient enediol intermediate, which mimics the action of enzymes.




## INTRODUCTION

Catalytic enantioselective protonation of a prochiral carbanion such as an enolate derivative[1] in water is a common transformation in biological systems to generate molecules with single handedness,[1a,2] but its application in synthetic chemistry has been a formidable challenge. The abnormally high mobility of the proton in water,[3] along with its relative lightness and small size,[4] renders enantioselective protonation in water extremely difficult as unusually fast proton diffusion in water, which occurs by stepwise hopping of a proton to a water molecule within a time frame of roughly 1−2 ps (i.e., by the so-called Grotthuss mechanism[3]), leads to uncontrolled racemic protonation. Therefore, governing the movement of protons within a catalytically active site in an enantioselective manner is extremely challenging.[5] To prevent the racemic protonation pathway and thus to achieve successful enantioselective protonation in water, it is essential to block the access of bulk water into catalytic sites, as is done by enzymes.

Among enzymes capable of catalyzing enantioselective protonations (e.g., decarboxylase,[2a] esterase,[2a] triose phosphate isomerase,[2b,c] glyoxalase,[2d−f] etc.), glyoxalase I in particular plays a critical role in the enzymatic defense against glycation by catalyzing the enantioselective isomerization of hemithioacetals, which form spontaneously between highly toxic α-keto aldehydes (e.g., methylglyoxal) and glutathione (GSH), to (*S*)-α-hydroxyacylglutathione derivatives.[2d−f] Inspired by the mechanism employed by natural glyoxalase I, we recently developed a highly efficient artificial enzyme model that mimics natural glyoxalase I.[6] In anhydrous organic solvents, this biomimetic glyoxalase I system showed exceptional enantioselectivity for a broad range of substrates. However, as noted, enantioselective introduction of a highly ungovernable proton to transient enediol intermediates in an aqueous environment remains extremely challenging. We were interested therefore in addressing this challenge by developing a biomimetic glyoxalase I-like system with which highly enantioselective catalysis could be achieved in water.

In biological transformation processes, water plays several roles, acting as a solvent, as a reactant molecule, or as a reaction regulator (or reaction enforcer).[7] Therefore, understanding the role of water is of fundamental importance for designing catalytic reaction systems to mimic the action of enzymes in nature as well as to achieve high reaction rates and (stereo)selectivities. Thus, in recent years, mimicking water-mediated enzymatic reactions has been the focus in the chemistry community.[8] In particular, "on-water"[9] catalysis has recently received considerable attention due to its effectiveness.[10] On-water catalysis enables enforced hydrophobic interactions between catalysts and substrates as a result of hydrophobic hydration effects,[11] consequently increasing reaction rates. According to recent spectroscopic and theoretical studies, the origin of the hydrophobic hydration effect is the strengthened H-bond network of water molecules

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near hydrophobic solutes.[12] Our recent studies have shown that the "hydrophobic amplification"[13] achieved under on-water conditions even enabled discovery of new catalytic reactions of otherwise completely unreactive substrates.[14] Furthermore, and more interestingly, we also demonstrated that water can function as a chirality amplifier in asymmetric catalytic reactions.[15] However, the positive effect of water on enantioselectivity is not a general rule. Rather, in many cases, the introduction of water as a reaction medium in asymmetric catalysis negatively influences enantioselectivity, because of its capacity for disrupting hydrogen bonds at catalytic sites.

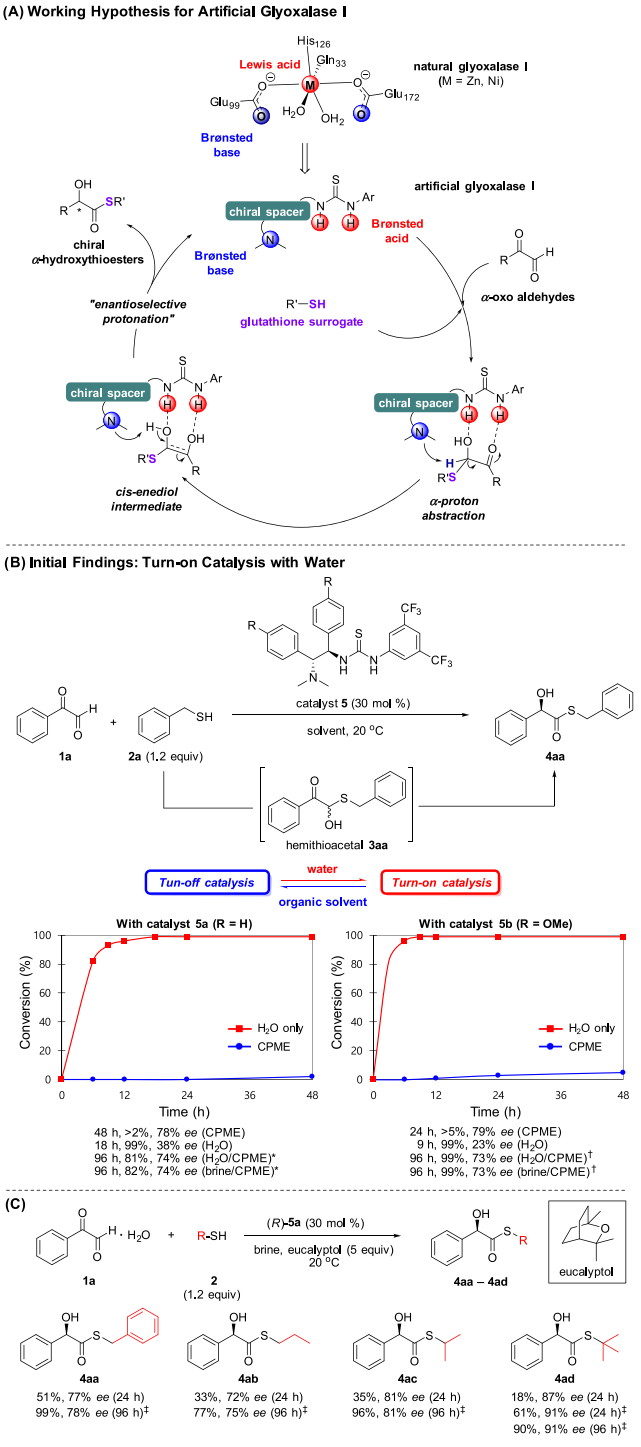
Here we report that, despite the abnormally high mobility of the proton in water, water can be an exceptionally efficient reaction medium for catalytic enantioselective protonation reaction. By employing "on-water" conditions, highly enantioselective organocatalytic glyoxalase I-mimicking isomerization of spontaneously formed hemithioacetal adducts between diverse $\alpha$-oxoaldehydes and thiols has been achieved, affording enantioenriched $\alpha$-hydroxy thioesters. The same reactions are almost impossible to conduct in organic solvents. Furthermore, we also demonstrated that the on-water approach, especially when employing a biphasic microfluidic approach, can be an efficient tool to limit access of bulk water into transition states, enabling successful enantioselective control of proton transfer.

## RESULT AND DISCUSSION

**Bio-inspired Reaction Design and Initial Findings.** The glyoxalase I catalyzed isomerization of hemithioacetals proceeds via (i) activation of the hemithioacetals by metallic Lewis acids (Zn or Ni), (ii) deprotonation of the $\alpha$-proton by the basic catalytic site to form an enediol intermediate, and (iii) its enantioselective reprotonation, affording enantiopure $\alpha$-hydroxyacylglutathiones.[2d−f] We speculated that bifunctional thiourea organocatalysts would mimic this enzymatic process. The hydrogen-bond-chelating interaction between the acidic thiourea of the organocatalyst and two oxygen atoms of the hemithioacetals can enhance the electrophilicity of the carbonyl carbon atom of hemithioacetals, consequently increasing the acidity of the $\alpha$-proton. The basic amine moiety can further deprotonate the acidic $\alpha$-proton of the hemithioacetals, producing enediol intermediates which can then be enantioselectively reprotonated, producing enantioenriched $\alpha$-hydroxy esters (Scheme 1A).

To test our concept, bifunctional Takemoto-type catalysts **5** as artificial glyoxalase I mimics were examined for the isomerization of the hemithioacetal **3aa**, generated *in situ* from phenylglyoxal **1a** and benzylthiol **2a** as the GSH surrogate, affording $\alpha$-hydroxy thioester **4aa**. As shown in Scheme 1B, when reactions were performed in an organic solvent such as cyclopentyl methyl ether (CPME), almost no conversion was obtained even after 48 h. However, surprisingly, the use of water as reaction medium turned on this otherwise extremely unreactive catalytic reaction. Under on-water conditions, the reaction rate was remarkably accelerated presumably due to enforced hydrophobic interactions between catalysts and reactants and, thus, the reaction was completed within 9 h (using catalyst **5b**) or 18 h (using catalyst **5a**) (Scheme 1B). Although water enabled this biomimetic catalytic reaction, the *ee* values achieved in the absence of a hydrophobic cosolvent (i.e., only in water) were much lower than those obtained in CPME (Scheme 1B). It is probable that the interfacial hydrogen bonding activation of electrophile by bulk water molecules at the water-organic

**Scheme 1. Glyoxalase I-Mimicking Reaction Design and Initial Findings**[a]




[a](A) Plausible working hypothesis for the enantioselective isomerization of hemithioacetals catalyzed by bifunctional thiourea organocatalysts as an artificial glyoxalase I. (B) First observation of the hydrophobic amplification under on-water conditions. Conditions: phenyl glyoxal **1a** (0.1 mmol), benzyl thiol **2a** (0.12 mmol), and catalyst **5a** or **5b** (30 mol %) with 2 mL of reaction media at 20 °C. *5 equiv of CPME was added. †20 equiv of CPME was added (Tables S1 and S2). (C) Selected condition optimization. ‡10 equiv of R-SH and 10 equiv of eucalyptol were used.



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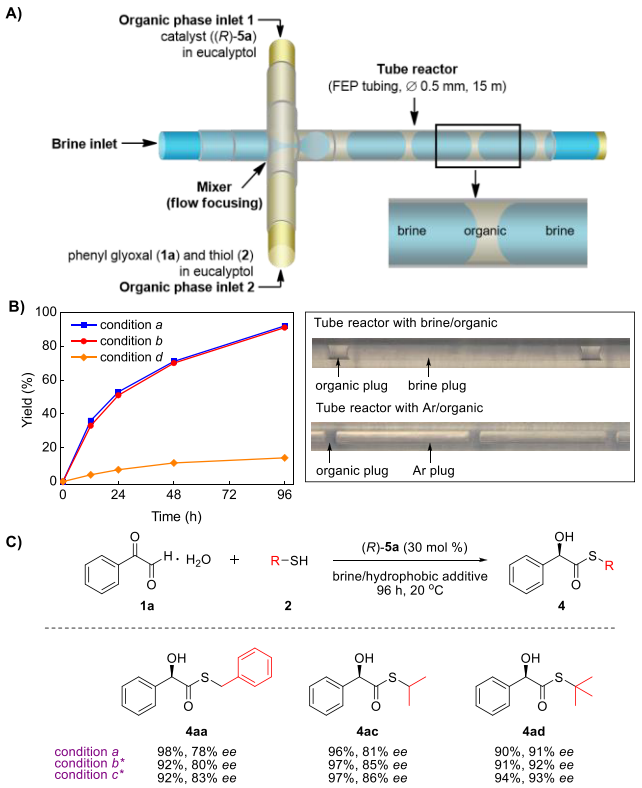
phase boundary (i.e., the non-enantioselective on-water catalytic effect) can negatively influence enantioselectivity.[10e,16] Therefore, to achieve successful enantioselective catalysis in water, it is important to suppress the hydrogen bonding interactions of water molecules at the enantio-determining step. The use of a hydrophobic cosolvent represents one of the simplest means of achieving this end; the hydrophobic cosolvent shields the transition state from contact with water.[14]

To our delight, the addition of CPME as a hydrophobic cosolvent additive yielded markedly enhanced enantioselectivity. For example, using catalyst **5a**, the enantioselectivity was increased from 38% *ee* to 74% *ee* by adding 5 equiv of CPME (Scheme 1B). With these encouraging results, a number of hydrophobic cosolvents were further screened using **5a** as catalyst, and it was found that eucalyptol, a natural cyclic ether and a monoterpenoid, proved optimal with respect to both chemical yield and enantioselectivity of the desired product (Scheme 1C and Supporting Information, Table S1). Using eucalyptol as a hydrophobic cosolvent, we then evaluated the effect of thiol structures on reaction rate and enantioselectivity. Regardless of the degree of substitution, alkyl thiols were found to serve as general GSH surrogates in terms of enantioselectivity (Scheme 1C and Supporting Information, Figure S1). Notably, the enantioselectivity of alkyl thiols increases with the steric bulkiness of the substituent. Thus, a significant enhancement in enantioselectivity was observed when the substituent was changed from a primary to a tertiary alkyl group (from 77% to 87% *ee*). However, when tertiary butyl thiol was used, the reaction rate decreased dramatically due to the steric effect (only 18% conversion after 24 h) (Scheme 1C). The problem of low conversion was easily addressed by increasing the molar ratio of thiols. With 10 equiv of thiols, the reaction could be completed after 4 days and, moreover, increased *ee* values were obtained (for example, an *ee* of **4ad** from 87% to 91%) (Supporting Information, Table S2).

**Condition Optimization Using Biphasic Microfluidic Conditions.** As described, the use of a hydrophobic cosolvent was pivotal in achieving high enantioselectivity; this is ascribed to the "spatial separation" of water from the transition state. Nevertheless, under stirred conditions, it is difficult to perfectly suppress the negative interfacial hydrogen bonding interaction between the aqueous phase and organic reactants, since new organic-water interfaces are constantly regenerated as a result of stirring. We hypothesized that this problem could be addressed by employing a biphasic microfluidic system, where precisely defined micron-sized monodisperse water and organic plugs could easily be generated in a tube reactor.[15,17] Under static conditions in a tube reactor, new organic-water interfaces cannot be recreated during the reaction and, thus, the interfacial surface area must be incomparably smaller than the interfacial surface area generated with stirring, consequently minimizing the contact area between bulk water molecules and the transition state. Furthermore, the diffusion process of protons in water might be influenced by the confinement effect.[18] According to recent studies using polarization-resolved femtosecond infrared transient absorption spectroscopy, in nanosized confined water droplets, the diffusion rate of protons is significantly slower than that in bulk water.[18] Considering all these assumptions, catalytic isomerization of the hemithioacetal **3aa**, spontaneously generated from **1a** and **2a**, was performed as a model reaction in a biphasic microfluidic system (eucalyptol/brine).

This system was set using a cross-junction meeting of controlled flows of brine and organic solutions containing the organic reactants (**1a** and **2a**) and catalyst **5a**. The reaction mixture was injected into the system using a syringe pump. A series of droplets of different sizes were created in the hydrophobic tubing (fluorinated ethylene propylene, FEP, inner diameter (ø) = 500 $\mu$m, length = 15 m) by adjusting the flow rate ratio ($Q_w/Q_o$) between the aqueous and organic phases (Scheme 2A). After the tube was filled with the reaction

**Scheme 2. Microfluidic Experiments**[a]




[a](A) Biphasic microfluidic system for isomerization of hemithioacetal **3a**. Conditions: phenyl glyoxal **1a** (0.1 mmol), benzyl thiol **2a** (1 mmol), catalyst **5a** (30 mol %), and eucalyptol (10 equiv): plugs form at the junction between eucalyptol solution containing the reagents (organic phase) and an aqueous phase (brine). Plugs then travel down the FEP tubing where the reaction occurs. (B) Reaction profiles under different conditions. (C) Effect of biphasic microfluidic conditions on enantioselectivity. Conditions: (a) magnetic stirring (1150 rpm), brine (2 mL), eucalyptol (10 equiv), 20 °C. (b) Microfluidic condition ($Q_o$:$Q_w$ = 6:120 $\mu$L/min) in ø = 500 $\mu$m FEP tubing, 20 °C. (c) microfluidic condition ($Q_o$:$Q_w$ = 6:120 $\mu$L/min) in ø = 500 $\mu$m FEP tubing, 20 °C, 150 psi BPR. *The isolated yields could not be determined since the total amount of organic reaction mixture in the micro-tube was too small to determine the correct yield. Thus, we determined the conversions using $^1$H NMR integration instead of isolation yields.

mixture, the flows of brine and organic solutions were stopped, and the outlet of the tube was then sealed with paraffin film. The static biphasic plugs were then kept inside the tubing for 96 h at 20 °C, without any shaking. Gratifyingly, the reactions proceeded smoothly even in the static droplets. The reaction profile in the static droplets is almost the same as that observed under the conventional stirring condition (Scheme 2B) (see Supporting Information, Table S3, for additional experimental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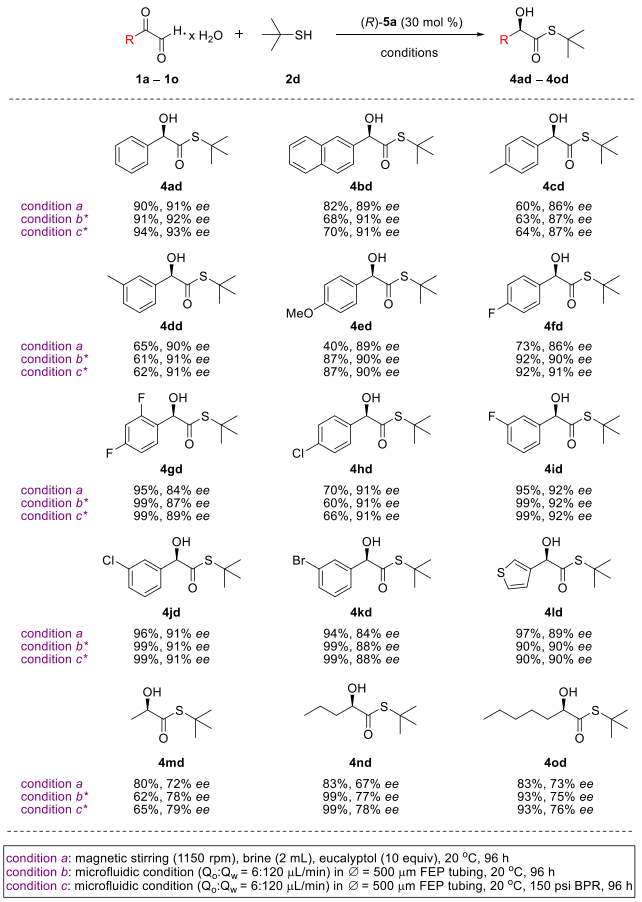
results regarding the effect of droplet size on the catalytic results). However, the same reaction proceeded extremely sluggishly when the organic plugs were generated by injecting argon gas instead of water into the tube reactor, further confirming the crucial role of on-water conditions for the observed rate acceleration (Scheme 2B). Furthermore, as per our expectations, the microfluidic on-water conditions created consistently higher *ee* values than those obtained under stirring conditions (Scheme 2C). Notably, the pressure within the microfluidic system which was controlled using a back pressure regulator (BPR) (ca. 10 bar) resulted in an additional increase in *ee* values (Scheme 2C). One plausible explanation for this slight, but noticeable, increase in enantioselectivity under pressure is increased water viscosity (i.e., decreased proton mobility) with rising pressure.[19] All the above-mentioned results strongly indicate that the microfluidic on-water condition perfectly limits the access of bulk water to the transition state.

**Substrate Scope of Water-Driven Enantioselective Protonation.** Next, substrate generality was investigated using both microfluidic and batch reactors. For all aromatic, heteroaromatic, and aliphatic substrates **1a**−**1o** tested in this study, a dramatic increase in reaction rate was observed under both on-water and static biphasic microfluidic conditions compared with those obtained in a homogeneous organic solvent. Thus, all aromatic α-oxoaldehydes **1a**−**1k** examined in this study smoothly underwent the reaction, producing the corresponding (*R*)-α-hydroxy thioesters **4ad**−**4kd** in high yields with good to excellent enantioselectivities. Heteroaromatic glyoxal **1l** was also smoothly converted into the desired product **4ld** with high enantioselectivity. Furthermore, highly toxic methylglyoxal **1m** and other alkyl glyoxals **1n**−**1o** were also smoothly converted into the corresponding α-hydroxy thioesters **4md**, **4nd**, and **4od**, respectively, albeit with moderate enantioselectivity. For all substrate classes, as anticipated, the microfluidic on-water system gave noticeably higher enantioselectivities than those obtained with on-water batch conditions (condition *a* vs conditions *b* and *c* in Scheme 3). Here again, in some cases (e.g., for **4ad**, **4fd**, **4gd**, **4md**, **4nd**, and **4od**), additional increases in enantioselectivity were achieved by increasing pressure within the microfluidic system (condition *b* vs *c* in Scheme 3). Considering these results in sum, the use of biphasic microfluidic systems could provide a solution for the intrinsic problem of the introduction of water as a solvent in asymmetric catalysis in which water can interfere with the catalysis.

**Physical Origin of Water-Driven Catalysis.** It is reasonable to assume that, under "on-water" catalytic conditions, water molecules around hydrophobic reactants would form stronger hydrogen bonds than in the bulk, as observed with a purely hydrophobic small molecule like methane.[12b] This enhanced hydrogen bonding could then pressurize the hydrophobic reactants in water cages. Thus, chemical reactions with a negative volume of activation, $\Delta V^{\ddagger}$ (i.e., when the difference in the volume of the transition state and the starting materials is <0), could be accelerated under "on-water" conditions.[20] However, experimental proof for strengthened hydrogen bonds of water molecules under on-water catalytic conditions has never been reported.

IR spectroscopy is a powerful tool for determining the relative strengths of hydrogen bonds between water molecules near hydrophobic solutes.[12a,b] Frequencies of O-H or O-D stretching mode ($\nu_{OH}$ or $\nu_{OD}$) in vibrational spectroscopy can

**Scheme 3. Substrate Generality of Water-Induced Hydrophobic Amplification in the Enantioselective Isomerization of Hemithioacetals**[a]




[a]*The isolated yields could not be determined since the total amount of organic reaction mixture in the micro-tube was too small to determine the correct yield. Thus, we determined the conversions using $^1$H NMR integration instead of isolation yields.

be used as a reliable and sensitive H-bond strength marker. A downshift (red shift) of the $\nu_{OH}$ or $\nu_{OD}$ stretching mode, relative to the reference spectrum of bulk water, should indicate enhanced H-bond strength. Therefore, to determine whether enhanced hydrogen bond strengths of water molecules occur under the present on-water conditions, the O-D stretching band spectra of isotopically diluted HDO molecules were recorded in the absence and in the presence of the hydrophobic reaction mixture. The spectrum of $\nu_{OD}$ of HDO molecules perturbed by the reaction mixture was obtained by applying the double-subtraction procedure[12b,21] to remove contributions from $H_2O$ and HDO in the bulk to IR spectra (see Supporting Information, Figure S2). As shown from the resulting O-D spectrum that is perturbed only by the reaction mixture (Figure 1A), a remarkable red shift of $\nu_{OD}$ ($\Delta\nu_{OD}$) of about 60 $cm^{-1}$ was observed. This result strongly indicates that the hydrogen bonds of water molecules in the first hydration shell of the hydrophobic reaction mixture under on-water conditions also become significantly enhanced relative to bulk water. To the best of our knowledge, this is the first spectroscopic evidence for the strengthened hydrogen bonds of water molecules near hydrophobic reactants under on-water catalytic conditions.



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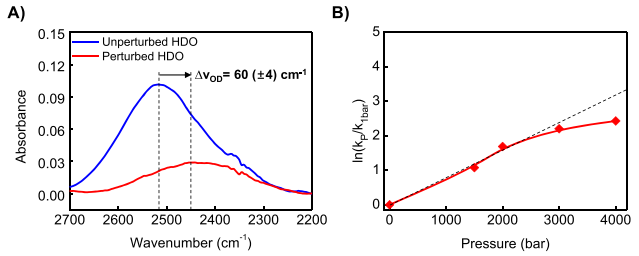


**Figure 1.** Mechanism study for elucidating origin of the acceleration effect of on-water condition. (A) Spectra of the $\nu_{OD}$ of the HDO molecules under on-water conditions (blue line, HDO solution in $H_2O$ (20 °C, 1 bar); red line, HDO molecules perturbed by the reaction mixture (eucalyptol (0.059 M), **1a** (0.2 equiv), **2d** (1 equiv), (*R*)-**5a** (0.06 equiv), and a mixture of 1.4% (v/v) $D_2O$ in $H_2O$ (2 mL)). (B) Determination of activation volume according to the equation $\ln(k_P/k_{1\ bar}) = -(\Delta\Delta V^{\ddagger}/RT)(P-1) + C$ ($k_{rel}$ = 1.0 (1 bar), $k_{rel}$ = 2.93 (1.5 kbar), $k_{rel}$ = 5.40 (2 kbar), $k_{rel}$ = 9.05 (3 kbar), $k_{rel}$ = 11.33 (4 kbar) (Table S4).

Next, we performed kinetic measurement of the catalytic isomerization reaction of **3aa** at various pressures to determine the activation volume ($\Delta V^{\ddagger}$) and, thus, to shed light on the nature of the transition state of the reaction under the on-water system. All kinetic measurements under applied pressure (between 1 and 4 kbar) were carried out at 20 °C in $CH_2Cl_2$, monitoring the consumption of hemithioacetal **3aa** and the formation of hydroxyl thioester **4aa** by $^1$H NMR analysis. The reaction was significantly accelerated by pressure, showing an 11-fold rate increase from 1 bar to 4 kbar (see Supporting Information, Table S4). From these data, the activation volume was determined to be −19.4 mL/mol (Figure 1B).[20c,d] This study indicates that the transition state of our process is significantly more compact than the combinations of starting materials, confirming that the reaction must be accelerated under on-water conditions by strengthened H-bonds of water molecules near a hydrophobic reaction mixture (i.e., by hydrophobic hydration effect).

**Mechanistic Studies in Support of the Proposed Reaction Pathway.** Finally, to further elucidate the mechanism of the present biomimetic catalytic reaction, we carried out isotope experiments using 1-deuterated-phenylglyoxal. The isotope experiments clearly confirmed that, in a manner similar to natural glyoxalase I, the isomerization reaction proceeded with deprotonation of the $\alpha$-proton of hemithioacetal to form the enediol intermediate and subsequent enantioselective protonation.[2f,6] We exclude a direct 1,2-hydride shift reaction mechanism since no deuterium incorporation was observed at the $\alpha$-carbon position of the thioester group in the final product (see Supporting Information, Figure S3).[22] The observed primary kinetic isotope effect ($k_H/k_D$ > 5) further indicates that the deprotonation of the $\alpha$-proton of hemithioacetals providing the enediol is the rate-determining step (see Supporting Information, Figure S4). Moreover, the experimentally observed linear relationship between the catalyst *ee* and the product *ee* confirms that the reaction involves a single catalyst in the enantio-determining protonation step (see Supporting Information, Table S5).

## CONCLUSION

In summary, we provide a successful example of enantioselective protonation in water revealing how to govern the movement of a highly mobile proton in water in an enantioselective manner. Water enables highly enantioselective glyoxalase I-mimic catalytic isomerization of hemithioacetals generated in situ from glyoxals and thiols in the presence of bifunctional organocatalysts, a reaction which proceeds via enantioselective protonation of the *cis*-enediol intermediate. Under on-water conditions, the reaction rate was dramatically accelerated. By contrast, the same reactions were almost impossible to conduct in organic solvents. A remarkable red shift of the isotopically decoupled IR O-D stretching vibrations under on-water conditions and a negative volume of activation of the present reaction strongly suggest that this water-enabled catalysis stems from the strengthened hydrogen bonds of water molecules near the hydrophobic reaction mixture (i.e., hydrophobic hydration effect), which drives tight hydrophobic interactions between catalyst and reactants in confined water cages. Furthermore, under on-water conditions, especially under biphasic microfluidic conditions, access of bulk water to the enantio-determining transition state is efficiently blocked, consequently enabling the highly enantioselective introduction of a highly mobile proton to the transient enediol intermediate which mimics the action of enzymes. In most cases, the $\alpha$-hydroxy thioester products were obtained with over 90% enantiomeric excess. Thus, employing biphasic microfluidic systems could provide a solution for addressing the intrinsic problem of the introduction of water as a solvent in asymmetric catalysis, in which water can negatively interfere with the catalysis, lowering stereoselectivity. We also believe that our results may provide a potential starting point for designing more challenging biomimetic catalytic asymmetric reactions in which water helps regulate reaction rates and selectivity.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11815.

Experimental details, analytical data for all new compounds, and mechanistic experiments (PDF)

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### Author Contributions

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### Notes

The authors declare no competing financial interest.



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