

Continuous-Flow Fabry-Pérot Cavity for Enhanced Catalysis via Cooperative Vibrational Strong Coupling

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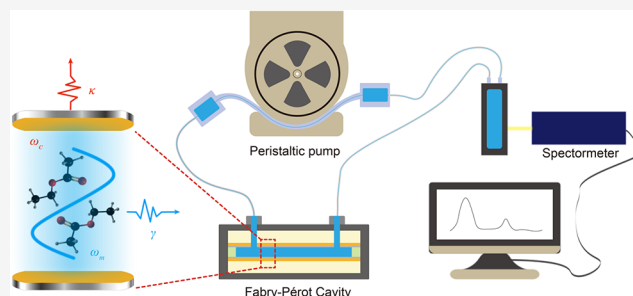
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Supporting Information

ABSTRACT: Polaritonic chemistry, which manipulates chemical and material properties using hybrid light–matter states formed by placing reactants in a vibration-tuned Fabry–Pérot (FP) cavity, has attracted significant interest. However, traditional FP cavities face challenges, such as restricted storage space and difficulties in sampling. In this work, a continuous-flow FP cavity coupled with real-time spectroscopy monitoring was constructed, and a demonstration of the flow-speed retention effect and the effect of placing cavities in series was investigated. The hydrolysis rate of 4-nitrophenyl octanoate (PNPO) was significantly increased under the cooperative vibrational strong coupling (VSC) effect between the reactant and solvent molecules. The VSC catalytic effect markedly reduced the reaction enthalpy of activation, implying that the hybrid light–matter states lowered the energy barrier of the transition state. The conversion rate of the PNPO hydrolysis reaction increases nonlinearly with an increase in the residence time. This work offers a new design rationale for reactors utilizing VSC in chemical production, demonstrating its great potential for industrial applications.

KEYWORDS: polaritonic chemistry, vibrational strong coupling, Fabry–Pérot cavity, hydrolysis dynamics, cavity catalysis



The formation of hybrid light-matter states can be achieved through the strategic confinement of reactant molecules within a vibration-tuned Fabry–Pérot (FP) optical cavity.¹¹ This configuration enables the realization of a VSC system by precisely tuning the cavity mode resonance to match specific covalent bond vibrations of the encapsulated molecules. Such resonance induces the emergence of vibro-polaritonic modes through coherent energy exchange, thereby fundamentally altering the chemical reaction landscape.¹² A paradigm-shifting demonstration by the Ebbesen group revealed that VSC could manipulate the potential energy surface governing the spiropyran–merocyanine photoisomerization reaction.⁷ This seminal work spurred extensive research into VSC-mediated chemical transformations, such as silyl deprotection processes,¹³ solvolytic reactions,¹⁴ Prins cyclization,¹¹ and exchange reactions.¹⁵ Our group has found that VSC can significantly enhance the efficacy of enzymatic ATP hydrolysis, signifying the potential to extend polaritonic chemistry into the field of biomedicine.¹⁶ Our subsequent exploration of aqueous-phase biochemical systems under VSC has found that VSC can

INTRODUCTION

Resonance, a ubiquitous physical phenomenon, arises when the vibrational frequencies of two systems are identical or similar, facilitating the transfer of energy between them and resulting in an amplification of their amplitudes.^{1,2} Specifically, in a system consisting of molecules and a resonator, resonant coupling between them can also be achieved by adjusting the cavity mode of the resonator to couple with the vibrational frequencies of the covalent bonds within the molecules (Figure 1a).³ When the coupling strength g of the system exceeds the average of the homogeneous decay rates of the molecules γ and the cavity with photon rate κ , that is $g > (\gamma + \kappa)/2$, the system transitions into a vibrational strong coupling (VSC) state.⁴ Furthermore, the vibrational coupling induces molecular polarization, generating two new polarized states: the upper polariton state (P+) and the lower polariton state (P-).⁵ Correspondingly, the spectral signature of this phenomenon is the emergence of two new split peaks, as illustrated in Figure 1b.⁶ The energy difference between these two states is defined as the Rabi splitting energy ($\hbar\omega_R$) (Figure 1c), which can also be referred to as the vacuum Rabi splitting energy, given that the vibrational coupling can still occur in the absence of real photon induction, even in the dark.⁷ This generation of hybrid light-matter states is termed polaritonic chemistry and has garnered extensive attention due to its capacity to manipulate the chemistry and material properties at the molecular level by altering molecular vibration patterns.^{8–10}

The formation of hybrid light-matter states can be achieved through the strategic confinement of reactant molecules within a vibration-tuned Fabry–Pérot (FP) optical cavity.¹¹ This configuration enables the realization of a VSC system by precisely tuning the cavity mode resonance to match specific covalent bond vibrations of the encapsulated molecules. Such resonance induces the emergence of vibro-polaritonic modes through coherent energy exchange, thereby fundamentally altering the chemical reaction landscape.¹² A paradigm-shifting demonstration by the Ebbesen group revealed that VSC could manipulate the potential energy surface governing the spiropyran–merocyanine photoisomerization reaction.⁷ This seminal work spurred extensive research into VSC-mediated chemical transformations, such as silyl deprotection processes,¹³ solvolytic reactions,¹⁴ Prins cyclization,¹¹ and exchange reactions.¹⁵ Our group has found that VSC can significantly enhance the efficacy of enzymatic ATP hydrolysis, signifying the potential to extend polaritonic chemistry into the field of biomedicine.¹⁶ Our subsequent exploration of aqueous-phase biochemical systems under VSC has found that VSC can

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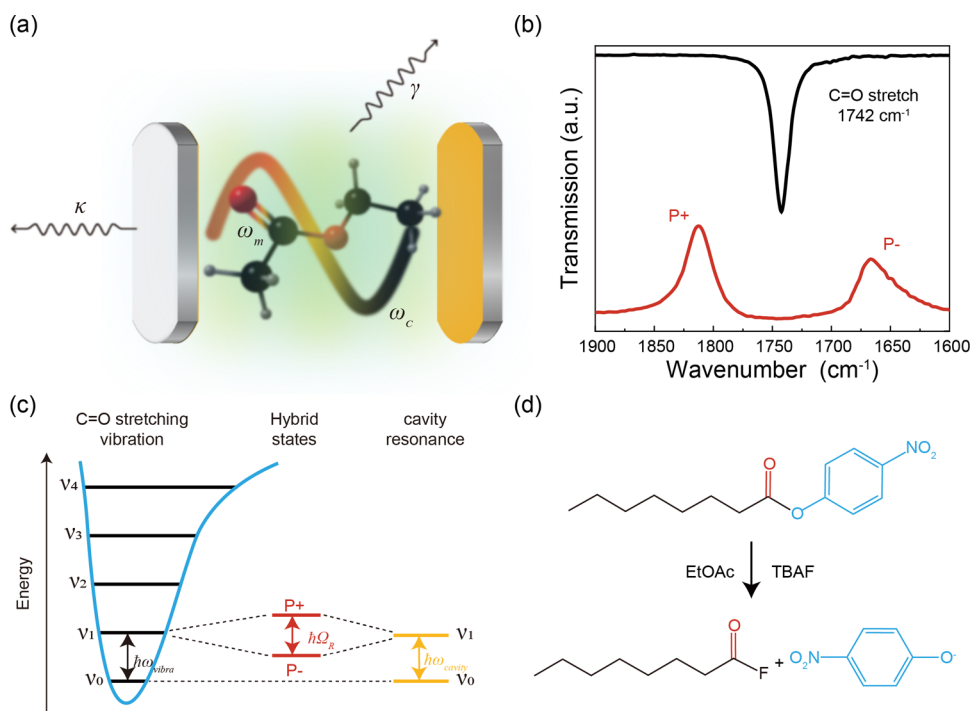


Figure 1. (a) Schematic illustration of the FP cavity of frequency ω_c coupling with the C=O stretching vibration of frequency ω_m , the cavity dissipation rate κ , and the average value of atomic excited state decay rate γ . (b) Polariton states P+ and P− formed by coupling the 3rd cavity mode with the C=O vibrational stretching mode (Cavity space length is approximately 6.28 μm). (c) Schematic illustration of the coupling of a molecular transition of energy $\hbar\omega_{\text{vibro}}$ and an FP cavity of energy $\hbar\omega_{\text{cavity}}$ generating hybrid states P+ and P− separated by Rabi splitting energy $\hbar\Omega_R$. (d) Hydrolysis of PNPO in ethyl acetate (EtOAc).

alter the melting temperature of DNA molecules, thereby facilitating nonspecific hybridization;^{17,18} enhance the catalytic efficiency of sucrase;¹⁹ facilitate base breaking; and achieve accurate DNA origami.²⁰ Some specific chemical bands, such as Si–C and Si–O bonds, can be selectively disrupted by precisely controlling the FP cavity modes.¹³ This technology enables us to actively determine which molecular bonds are broken,²¹ allowing for purposeful control over the reaction process and the promotion of specific product formation.²² Therefore, polaritonic chemistry presents a novel and efficient approach for the design and synthesis of new materials, considering its capability to not only alter the vibrational states of molecules but also impact electron distribution, ultimately modifying reaction pathways.

In collective VSC, the coupling strength is proportional to the square root of the molecular concentration, and a high concentration favors VSC.²³ However, this approach is not applicable to chemical reactions involving low concentrations. Surprisingly, cavity catalysis can also be achieved via cooperative vibrational strong coupling, occurring when the solvent and reactant molecules have overlapping vibrational bands and the solvent concentration is sufficiently high for strong coupling with the cavity mode.²⁴ By leveraging the cooperative coupling effect of solvent molecules, the requirement for high solute concentrations in the VSC can be circumvented, expanding the scope of polaritonic chemistry experiments. Lather et al. observed that the cooperative vibrational strong coupling between the solvent water molecules and pepsin in the FP cavity altered the proton transfer process, resulting in a reduction of the reaction activation energy.²⁵ Subsequently, they reported that the cavity-catalyzed solvolysis rate of *para*-nitrophenyl acetate was

increased by an order of magnitude under the cooperative VSC effect of the reactant and solvent molecules.¹⁴ However, Garrett et al. reported that the influence of VSC on catalysis can be ignored, underscoring the necessity for deeper exploration of critical factors and mechanistic principles governing the cavity-modified reaction rate.²⁶ Francesco et al. recently reported that the solvolysis kinetics of *para*-nitrophenyl acetate can be accelerated by 2.7 times using nonlocal metasurfaces, maintaining surface lattice resonance without requiring surface parallelism as in FP cavities.²⁷ Therefore, investigating chemical reaction systems in the FP cavity, incorporating the cooperative coupling effect, and elucidating the underlying cooperative mechanisms are of significant importance.

The cavity spacing of the FP resonator needs to be precisely tuned to match the specific vibrational stretching mode of the molecules within the cavity to achieve VSC. Owing to the multimodal competition effect, it is advisable to keep the FP cavity spacing within 30 μm .²⁸ Furthermore, a smaller cavity spacing correlates with a lower order of the cavity mode, leading to a more pronounced cavity catalysis effect. Therefore, the traditional static FP cavities, with their highly limited volume, often restrict the reaction liquid to mere microliters, posing substantial challenges for reaction monitoring, product recovery, and subsequent processing. In this work, we constructed a continuous-flow FP cavity integrated with spectroscopy monitoring. This system not only enables real-time monitoring of reactions but also drastically expands the reaction liquid volume while preserving the cavity catalytic effect. In this continuous-flow system, the cavity-catalyzed solvolysis of PNPO under the cooperative coupling effect between the solvent ethyl acetate and the reactant was

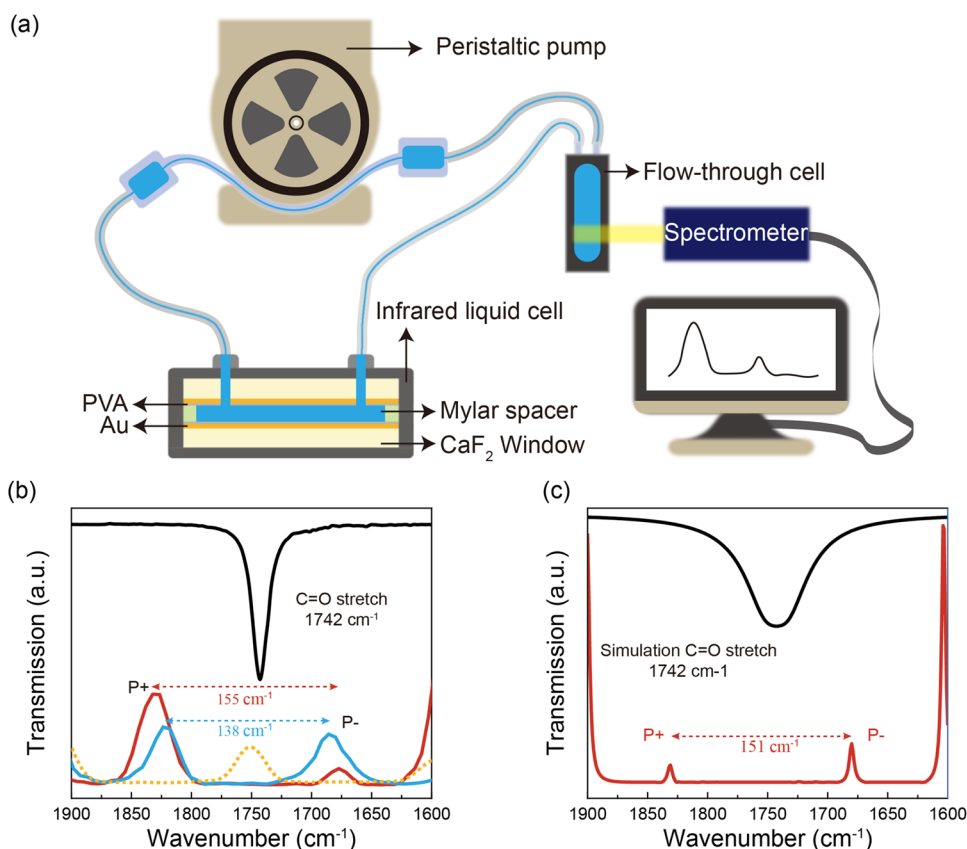


Figure 2. (a) Schematic diagram of a continuous-flow FP cavity by assembling a coupled system comprising a peristaltic pump, FP cavity, and UV–vis spectrophotometer. (b) IR transmission spectra of FP cavity on VSC with C=O stretching mode, neat EtOAc (red trace), 4 mM PNPO in EtOAc (blue trace), 4 mM PNPO in hexane (orange dotted trace). (c) Simulated IR transmission spectra of the C=O stretching mode and polaritonic states P+ and P– formed by coupling to the 11th cavity mode.

investigated (Figure 1d). The mechanisms underlying the cooperative coupling effect and cavity catalysis were systematically explored through a thermodynamic analysis. Additionally, the demonstration of the flow-speed retention effect and the effect of placing cavities in series was also investigated.

EXPERIMENTAL SECTION

Construction of the Continuous-Flow FP System. The FP cavity was assembled from an infrared liquid cell, CaF₂ windows, and Mylar spacers, according to our previous publications (the physical image is shown in Figure S1).^{6,16,18–20,28,29} The continuous-flow reaction and detection system was assembled from an FP cavity, a peristaltic pump (LabVI-II, SHENCHEN), and an ultraviolet–visible (UV–vis) spectrophotometer (Cary 3500 UV–vis Engine, Agilent Technologies), as shown in Figure S1. A flow-through cell was carefully positioned within the UV–vis spectrophotometer for real-time detection of the concentration of PNPO hydrolysis products at 350–500 nm. The FP cavity was connected to the flow-through cell through a capillary rubber tube, and the flow rate of the reaction liquid was controlled via the peristaltic pump. All of the tubing and connectors utilized in this system were supplied by Nanjing Runze Fluid Control Equipment Co., Ltd.

Here, we constructed a continuous-flow FP cavity by assembling a coupled system comprising a peristaltic pump, FP cavity, and UV–vis spectrophotometer, as illustrated in Figure 2a. In this system, the reaction liquid within the FP

cavity was pumped into a flow-through cell, enabling real-time monitoring of concentration fluctuations to track the reaction progress. This system is capable of expanding the reaction liquid volume from 8 μ L to approximately 2 mL, addressing the challenge of product sampling and analysis. The FP cavity consists of two sputtered gold reflective mirrors with transparent CaF₂ windows, and the spacing between the gold surfaces is controlled by a Mylar film spacer. To verify the influence of VSC on the PNPO hydrolysis reaction in the continuous-flow FP cavity, we designed control experiments, including non-cavity and off-resonance scenarios. The non-cavity experiments were carried out in an FP cavity consisting of one CaF₂ window without sputtered gold coating and another sputtered gold mirror. The off-resonance experiments were performed in the FP cavity, where the cavity mode was absolutely detuned from resonance by adjusting the cavity spacing. It is worth emphasizing that in order to strictly limit the influence of the CaF₂ window and gold surfaces on the reaction solution, we have spin-coated PVA on each window piece.

After PNPO and TBAF were mixed in a centrifuge tube, the inlet tubing of the peristaltic pump was rapidly inserted into the tube, and the reaction solution was pumped into the flow cell and tubing system at a flow rate of 2.7 mL/min. Subsequently, the FP cavity was connected, and the flow rate was adjusted to 1.35 mL/min for the slow infusion of the reaction solution. When the entire tubing system was completely filled with the reaction solution, the inlet line was closed and the flow rate was reduced to the circulation mode.

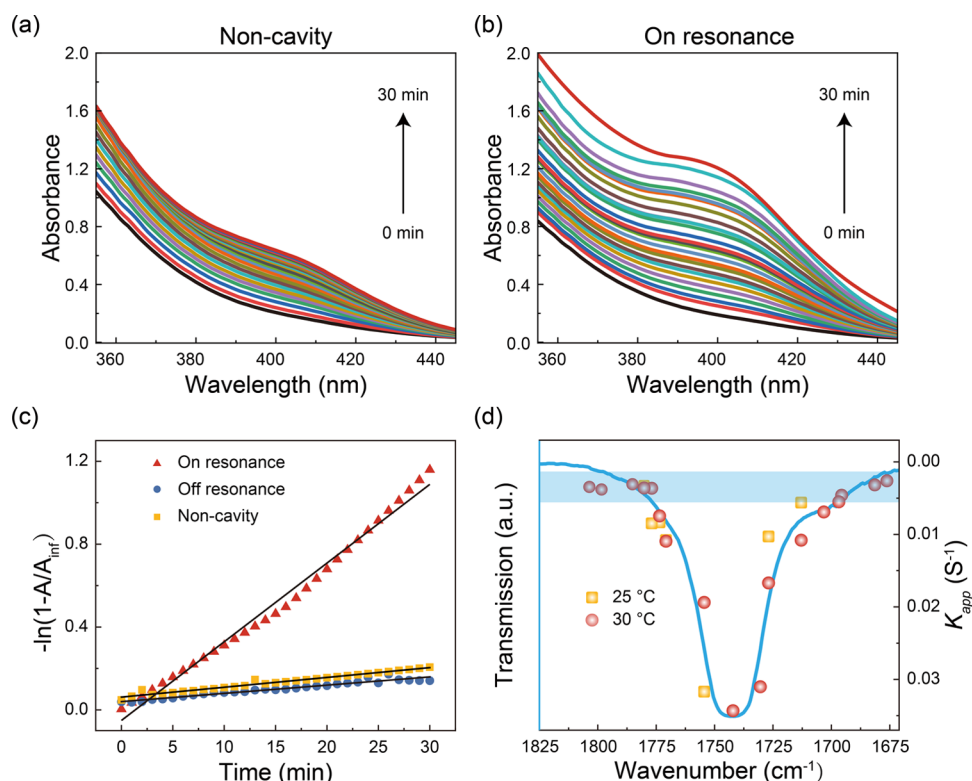


Figure 3. (a, b) Absorption spectra showing the evolution of the PNP⁻ product in 30 min for the non-cavity and on-resonance cavity, respectively. (c) First-order apparent kinetic traces for non-cavity, on-resonance cavity, and off-resonance cavity. (d) The variation of the apparent rate constant with the coupling degree between the cavity mode and the C=O stretching mode.

Owing to the operational time variation across experiments, real-time spectral monitoring was initiated 2 min after mixing the reaction solution, with the solution continuously circulating under a peristaltic pump drive during monitoring. The FP cavity and tubing were fastened with specialized clamps to ensure airtightness. The circulation system was thoroughly rinsed with EtOAc before and after each experiment to remove residual reagents. Particular attention was paid to maintaining the fluidity and airtightness of the liquid cell: the former directly influenced the pressure balance between the pump inlet and outlet during circulation, while the latter prevented reaction solution volatilization, both critical factors for ensuring experimental reproducibility.

RESULTS AND DISCUSSION

To investigate chemical reactions catalyzed by VSC under a cooperative coupling effect, we selected the hydrolysis of PNPO as the model reaction, as depicted in Figure 1d. The PNPO can undergo hydrolysis in EtOAc solvent, facilitated by the alkaline environment provided by tetrabutylammonium fluoride (TBAF). The Fourier transform infrared (FT-IR) spectra (Figure S2) revealed that neat EtOAc, PNPO, and the PNPO reaction mixture all displayed a characteristic peak at 1742 cm⁻¹ corresponding to the C=O stretching vibration, with the exception of the catalyst TBAF. This indicates that the FP cavity-catalyzed hydrolysis may proceed through the cooperative coupling between EtOAc and PNPO, sharing the same C=O stretching mode, while the catalyst TBAF does not participate in this cooperative coupling process.

The FP cavity was turned to the 11th optical mode (with a cavity spacing of approximately 23 μm) that couples with the C=O stretching vibration, thereby ensuring strong coupling

while also providing adequate space for the reaction liquid. The 11th mode of the FP cavity strongly couples to the C=O stretching vibration of neat EtOAc, generating two new P+ and P− peaks at 1832 and 1677 cm⁻¹, respectively (Figures 2b and S3). These peaks display a Rabi splitting of 155 cm⁻¹, corresponding to a 4.4% change in transition energy, which is consistent with the theoretical simulation results (Rabi splitting of 151 cm⁻¹, Figure 2c, and the detailed simulation was described in the Supporting Information). Analogously, in the 4 mM PNPO reaction mixture, the Rabi splitting also reached 138 cm⁻¹, with a 3.9% change in the transition energy. In contrast, in the 4 mM PNPO solution in hexane, no significant Rabi splitting was observed due to the low concentration, which was insufficient for coupling with the FP cavity. These findings confirm the occurrence of a cooperative VSC effect between EtOAc and PNPO, mediated by the overlapping C=O stretching mode. It is hypothesized that the cooperative VSC of EtOAc may alter the reaction pathway of PNPO and subsequently affect its bond-dissociation energy.³⁰

One of the hydrolysis products of PNPO is *para*-nitro phenoxide (PNP⁻), which exhibits a characteristic absorption peak at around 405 nm. Therefore, the formation of PNP⁻ can be monitored by using a UV–vis spectrophotometer, providing direct access to the relative concentration of the product and thus facilitating the detection of the progress of the hydrolysis reaction. As shown in Figure 3a, the real-time monitoring results of the hydrolysis reaction of PNPO in the non-cavity display that the absorption peak of the product PNP⁻ at 405 nm gradually rises within 30 min. A similar phenomenon was observed in our constructed continuous-flow FP system, in which the cavity was tuned to strongly couple with the C=O

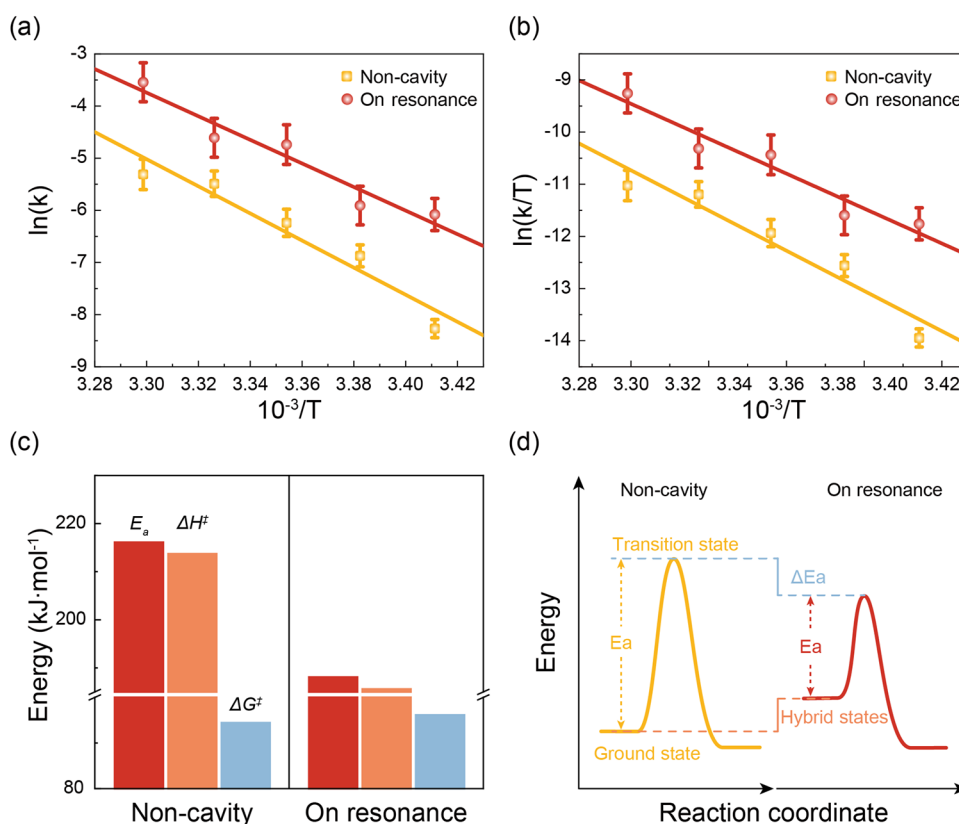


Figure 4. (a) Arrhenius plot and (b) Eyring plot for reaction in a resonance cavity and non-cavity. The full line is the corresponding linear fitting. (c) Data comparison between non-cavity and on resonance of E_a , $\Delta H^\ddagger$, and $\Delta G^\ddagger$. (d) Schematic diagram of the cavity catalysis mechanism.

stretching mode (Figure 3b). In contrast, the peak intensity for the on-resonance cavity is much higher than that without the FP cavity at the same reaction time, which corresponds to a higher product concentration and a faster reaction rate. These results indicate that the PF cavity still exhibits cavity-catalyzed effects in the continuous-flow mode, significantly enhancing the hydrolysis rate of PNPO.

The pseudo-first-order kinetic traces were measured at conditions of cavity-on-resonance, cavity-off-resonance, and non-cavity, respectively, as shown in Figure 3c. Linear regression analysis was then conducted to obtain the apparent rate constant. The apparent rate constant (k^{non}) for the non-cavity condition was $0.47 \times 10^{-2} \text{ min}^{-1}$. Notably, the apparent rate constant (k^{on}) for the cavity-on-resonance condition increased by an order of magnitude to $3.80 \times 10^{-2} \text{ min}^{-1}$, demonstrating that the VSC exerts a significant catalytic effect on the hydrolysis reaction rate. In the control experiments, the apparent rate constant for the cavity-off-resonance condition ($k^{\text{off}} = 0.40 \times 10^{-2} \text{ min}^{-1}$) was found to be comparable to that observed in the non-cavity condition. This suggests that the contact between the gold film and the reaction liquid had little impact on the reaction rate, as Au merely served as a resonant element within the FP cavity and did not participate in the chemical reaction process. Figure 3d illustrates the variation of the apparent rate constant across different detuning levels. When the coupling degree of the FP cavity with the C=O stretching mode was changed from VSC to detuning, the corresponding apparent rate constant decreased from its maximum value to the constant observed in the non-cavity condition. Moreover, the dispersion curves (Figure S4) of the upper and lower polariton branches clearly exhibit an

anticrossing at the bare absorption peak when the incidence angle of the light is adjusted. This further confirms that the system can maintain VSC while keeping the normal incidence.

To elucidate the mechanism of PNPO hydrolysis catalyzed by VSC, the temperature dependence of the apparent rate constant under on-resonance and non-cavity conditions was measured to obtain the thermodynamic activation parameters. According to the Arrhenius eq (Figure 4a), the calculated activation energy (E_a) decreased from 216 to 188 kJ·mol⁻¹ under VSC. This numerical difference directly reflects the regulatory effect of VSC on the reaction kinetics, which may optimize the reaction path through polaron-mediated potential energy surface reconstruction.^{13,30} Furthermore, the enthalpy of activation ($\Delta H^\ddagger$), which was obtained from the Eyring eq (Figure 4b), decreased from 213.7 to 185.6 kJ·mol⁻¹ due to VSC, representing a 13.1% reduction (Figure 4c, the detailed calculation was described in the Supporting Information). This finding indicates a reduction in the energy required for the reactants to transform into the transition state (TS) under VSC. On the one hand, the reduction can be attributed to the cooperative VSC effect between the FP cavity mode and the overlapping C=O stretching mode of the solvent and reactants, leading to the formation of hybrid energy states, which effectively elevate the ground-state energy of the reactants, as illustrated in Figure 4d.³¹ On the other hand, the transition state becomes more polar under VSC, thus possessing a lower energy. Additionally, the VSC effect reduced the calculated entropy of activation ($\Delta S^\ddagger$) by 82 J·mol⁻¹·K⁻¹, reflecting the formation of a more stable solvent shell near the TS. The rigidity of the solvent cage leads to a reduction in the number of microscopic states of the system

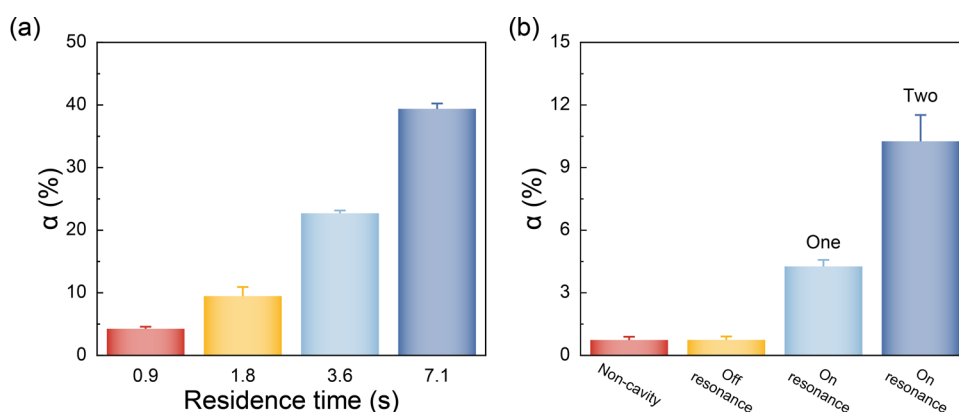


Figure 5. (a) Conversion rate (α) variation with different flow-speed residence times in one FP cavity under the VSC. (b) Conversion rates at different conditions: non-cavity, off-resonance cavity, one on-resonance cavity, and two on-resonance cavities.

and a decrease in the degree of disorder, directly manifested as a reduction in the activation entropy.³⁰ Under the combined effect, the Gibbs free energy ($\Delta G^\ddagger$) under the VSC decreased by 3.7 kJ·mol⁻¹. According to the transition state theory, the significant reduction of the activation enthalpy and the decrease of the activation entropy form the “activation entropy-enthalpy compensation” effect, ultimately promoting the decrease of the activation free energy and achieving the directional regulation of the reaction kinetic path, providing clear thermodynamic evidence for the VSC-modified chemical reaction system.

We regulated the fluid flow rate using the peristaltic pump to investigate the conversion yield of the PNPO hydrolysis reaction under various residence times within the FP cavity on VSC. Figure 5a shows that the conversion rate increases nonlinearly as the residence time increases. When the residence time is 7.1 s, the conversion rate of the hydrolysis reaction reaches up to 39.37%. Furthermore, under the same residence time, the conversion rate under VSC conditions (4.26%) was obviously higher than that under non-cavity (0.74%) and off-resonance cavity (0.74%) conditions. The conversion rate increased to 10.26% when the two FP cavities were connected in series (Figure 5b). These results indicate that the hydrolysis conversion yield of PNPO increases with prolonged exposure duration within the FP cavity or higher volumes of reactant solution confined in the cavity. Although the VSC effect is limited to the interior of the FP cavity, the continuous flow of liquid causes all reactants to periodically flow through this area. The implementation of continuous-flow mode leverages convective transport to enhance mass transfer efficiency beyond the diffusion-limited regime inherent in batch systems (static FP cavities). This manifests that the continuous-flow FP cavity, as a new type of catalytic reactor, has shown significant advantages and potential for application in chemical production.

CONCLUSIONS

In summary, through the use of a continuous-flow FP cavity coupled with real-time spectroscopy monitoring, the hydrolysis rate of PNPO was significantly enhanced by the cooperative VSC effect of the reactant and solvent molecules. The continuous-flow FP cavity not only retains the catalytic capability of a static FP cavity but also introduces a new type of chemical reactor, significantly addressing the limitations of traditional static FP cavities, such as restricted

reaction volume and difficulties in sampling. This design enables real-time spectroscopic monitoring while significantly expanding the reaction volume, bridging the connection between cavity catalysis-enhanced and scalable chemical processes, and providing a scientific and practical solution for the engineering application of vibrating polaron catalysis technology. The changes in thermodynamic activation parameters revealed that the activation energy barrier for the reactants to transform into the transition state under VSC has significantly decreased, optimizing the reaction path. VSC effectively compensates for the thermodynamic adverse factors caused by the reduction of activation entropy through the energy advantage generated by reducing the activation enthalpy, thereby achieving the directional regulation of the reaction kinetic path. We predict that the application of VSC technology will bring innovative advancements to traditional chemical synthesis, particularly in areas where precise control of the reaction conditions is essential, with profound implications for both chemical reaction engineering and the synthesis of new substances.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsphotonics.5c00417>.

Lab-made FP cavity and assembled reaction system (Figure S1); the IR transmission spectra of EtOAc, PNPO, TBAF, and reaction mixture (Figure S2); IR transmission spectra of FP cavity on VSC with C=O stretching mode (Figure S3); IR spectra of the FP cavity at the C=O stretching vibrational with different light paths (Figure S4); Fabry–Pérot optical model (Figure S5); and thermodynamics calculation and Simulation Section (PDF)

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Notes

The authors declare no competing financial interest.

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