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Influence of water-soluble pillararene hosts on Kemp elimination†

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Since pillar[5]arene was first discovered in 2008, it has developed into a multifunctional supramolecular host. Its application covers many fields from drug delivery and chemical sensing to the construction of molecular machines, and so on. Supramolecular catalysis based on pillar[*n*]arenes is one of the hot research topics that has emerged in recent years. In this paper, we have synthesized two water-soluble pillar[5]arenes with peripheral rims bearing opposite charges and investigated their influence on Kemp elimination reaction of 1,2-phenylisoxazole derivatives. It is found that both hosts have a moderate rate acceleration effect on the reaction, and the positively charged host H1 has a greater impact on the reaction rate than the negatively charged host H2.

1 Introduction

Enzymes are powerful and efficient catalysts that can promote the rapid progress of chemical reactions in organisms and maintain the normal operation of the body with high substrate specificity and selectivity.¹ These properties of enzymes have prompted chemists to search for artificial supramolecular hosts that can mimic these functions. Since the concept of supramolecular chemistry was proposed in the 1980s,² myriads of artificial supramolecular hosts have been synthesized, such as crown ethers,³ cyclodextrins,⁴ calixarenes,⁵ cucurbiturils,⁶ pillararenes,⁷ deep cavity cavitands,⁸ and self-assembled metal-organic cages.^{9,10} These hosts can accommodate guests that are complementary to their shape and sizes through various non-covalent interactions. Encapsulated guests often behave distinctly compared to the free state.¹¹ Therefore, their reactivity would be greatly influenced and modulated by supramolecular hosts.

So far, many unique reactions catalyzed or mediated by supramolecular hosts have been reported,^{12–15} and the utilization of well-defined nanospace to generate new chemical reactions or obtain novel products has been achieved. There are several strategies that have been frequently employed in modulating chemical reactivities, *e.g.* stabilization of transition state, destabilization of ground state, substrate preorganization, local concentration enrichment, desolvation, extra catalytic site incorporation.^{16,17} Chemists have been versed in performing chemical reactions using these approaches.¹⁸

Nevertheless, it remains challenging to approach the efficiency and complicity of natural enzymes.¹⁹

Pillar[*n*]arenes, which were first introduced in 2008 by Ogoshi group,⁷ have been developed into a versatile supramolecular host. Pillar[*n*]arenes can recognize guest molecules selectively in organic solvents, due to the possession of an electron-rich cavity and the combination of various noncovalent interactions such as dipole–dipole, C–H⋯π, π–π interactions.^{20–22} Owing to the easy synthesis and excellent binding performance of pillar[*n*]arenes, researchers have discovered their applications ranging from drug delivery,²³ chemical sensing²⁴ to molecular machines.²⁵ Catalysis by pillar[*n*]arenes is also one of the hot research topics, which emerged in the last few years.^{26,27} One of advantages of pillar[*n*]arenes is their tubular structures which allow for reactant ingress and product egress.²⁸ However, the key is to control the guest exchange dynamic that favours the product formation. So far, there are very limited reports investigating the cavity of pillar[*n*]arene in influencing chemical reactions in aqueous media. Moreover, not only catalysis was achieved,²⁹ but also in some cases, inhibitions were observed for the reaction occurred inside the pillararene cavity.^{30–32}

Herein, we report the effects of two oppositely charged water-soluble pillar[5]arene hosts^{33,34} on Kemp elimination reaction of 1,2-phenylisoxazole derivatives (Scheme 1). Previously, Michael Ward³⁵ and co-workers investigated the effect of water-soluble metal-organic cages [Co₈L₁₂]¹⁶⁺ on Kemp elimination reaction, and their results showed that the existence of cage has a huge rate acceleration ($k_{\text{cat}}/k_{\text{uncat}} = 2 \times 10^5$) on the reaction. We assume the hydrophobic cavity of pillar[5]arene will have similar effect on this reaction. It was found that our two hosts bearing opposite charges on their rims have influenced the reaction rate to different extent. The charged host can generate an electrostatic potential field (EPF) under the coulombic

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Kemp elimination reaction of 1,2-phenylisoxazole derivatives. In the spectra of free **G1**, the absorption peak of **G1** is around 280 nm. When the reaction started, a new absorption peak corresponding to **P1** appeared at 325 nm. As time goes by, the absorption peak of **G1** gradually decreased and the **P1**'s gradually increased (Fig. S12†). After that, the positively charged host **H1** and the negatively charged host **H2** were added separately, and their corresponding UV-Vis spectra were obtained (Fig. S13 and S14†). Preliminary results showed that not only the presence or the absence but also the kind of the hosts affected the speed of the reaction. After accurate data fitting by eqn (2), three kinetic curves and corresponding rate constants were obtained (Fig. S18–S20†), which showed that the hosts could accelerate the reaction rate of **G1** by 5.8 ($k_{\text{H1-G1}}/k_{\text{free G1}}$) and 2.9 ($k_{\text{H2-G1}}/k_{\text{free G1}}$) times, respectively (Fig. 1). The results of **G2** were similar to that of **G1**. In the spectra of **G2**, the absorption peak of **P2** is at 378 nm. Due to the poor solubility of **G2**, the reaction curve of free **G2** cannot be well fitted to obtain specific rate constant (Fig. S21†). But it is certain that in the presence of the hosts, the rate acceleration caused by **H1** is 4 times ($k_{\text{H1-G2}}/k_{\text{H2-G2}}$) faster than that of **H2** (Fig. S22 and S23†). The above results indicate that the presence of the host can indeed speed up the reaction rate, and the positively charged host **H1** is more efficient than the negatively charged **H2**.

In addition to UV-Vis, ^1H NMR was also used to track the above reactions. 10 equiv. NaOH solution was added in the UV-Vis experiments, but since the concentrations of the host and guest were increased to 1×10^{-3} M in ^1H NMR experiments, the corresponding concentration of NaOH increased to 1×10^{-2} M. This concentration in ^1H NMR was so high that the reaction proceeded too fast to be recorded by ^1H NMR. Therefore, the concentration of NaOH was reduced to 2 equivalents. In the process of **G1**, the proton signals of **G1** gradually disappeared and the peaks of **P1** gradually appeared (Fig. S9–S11†). The specified two peaks (the peaks of **G1** (7.82 ppm) and **P1** (6.56 ppm)) were integrated in the ^1H NMR spectra to obtain the corresponding reaction yields. Further data processing gave a yield–time curve and further fitted three kinetic curves (Fig. S24–S26†). It was

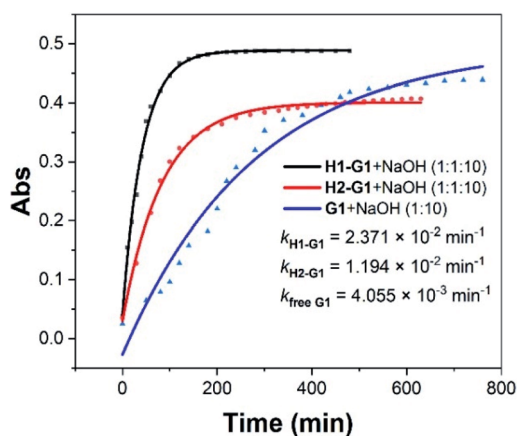


Fig. 1 Kinetic curves for the UV-Vis experiments of **G1** with 10 equiv. of NaOH in the presence and absence of the water-soluble pillar[5] arene hosts **H1** and **H2**.

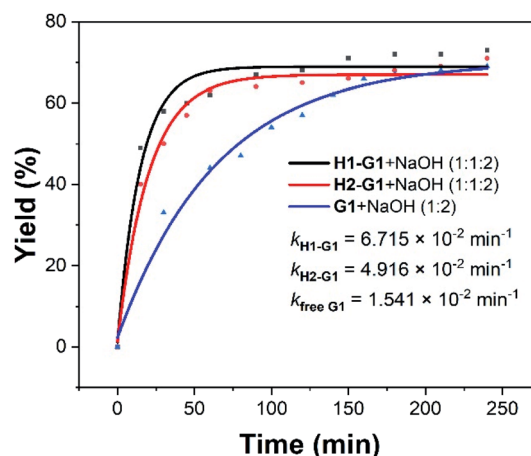


Fig. 2 Kinetic curves for the ^1H NMR experiments of **G1** with 2 equiv. of NaOH in the presence and absence of the water-soluble pillar[5] arene hosts **H1** and **H2**.

found that the presence of hosts accelerated the reaction rate by 4.4 ($k_{\text{H1-G1}}/k_{\text{free G1}}$) and 3.2 ($k_{\text{H2-G1}}/k_{\text{free G1}}$) times (Fig. 2). These results were consistent with that obtained by UV-Vis. Due to the poor solubility of **G2** in water, no reliable data was obtained in the ^1H NMR experiments.

The mechanism on how the pillar[5]arene hosts influence the rate of Kemp elimination reaction is proposed. Due to the poor water-solubility of substrates **G1** and **G2**, the reaction rate of the guest in aqueous solution is relatively slow. However, they can be enclosed in the cavity of water-soluble pillararene through hydrophobic interaction in the presence of supramolecular host, which increases the solubility of the reactants, hence the reaction rate will be increased. In addition, the reaction in this paper is a type of E2 elimination reaction, which involves a negatively charged transition state (TS). The EPF generated by the positive **H1** can stabilize the negatively charged TS and reduce activation energy of the reaction. Moreover, the high positive charge in **H1** results in accumulation of hydroxide ions around the host surface, affording a very high local concentration of anionic OH^- close to the bound

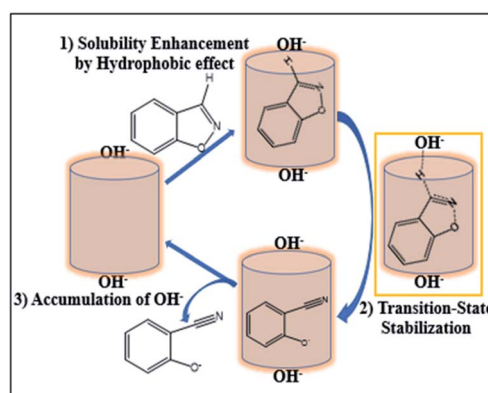


Fig. 3 Proposed possible mechanism of the Kemp elimination reaction in the presence of water-soluble pillararene hosts.



guest in the cavity. Although the EPF of **H2** cannot stabilize the TS, it can remove negatively charged products through electrostatic repulsion, thus playing a catalytic role (Fig. 3).

4 Conclusions

In summary, Kemp elimination reaction of 1,2-phenylisoxazole derivatives in aqueous phase was investigated using two water-soluble pillar[5]arenes with different rim charges. Our results by UV-Vis and ^1H NMR showed that the positively charged host **H1** brought a roughly 6-fold rate acceleration to the reaction, and the negatively charged host **H2** would also accelerate the reaction but not as fast as **H1**. Although pillararene hosts didn't give a significant rate acceleration on Kemp elimination in this case, our studies in this article provides an example for the use of pillararene cavity to modulate chemical reactions, and expands the functions and applications of pillararenes. Our laboratory is also actively seeking other reactions that can be catalyzed by pillararenes with greater extent.

Author contributions

Q. Liu performed the experiments and wrote the original draft. X. Tian, Y. Shen and X. Huang completed partial synthesis of the hosts. K. Wang and X. Hu designed and supervised the project. All authors reviewed and revised the manuscript.

Conflicts of interest

There are no conflicts to declare.

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