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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 noncovalent 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 complicacy 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 sensing[24] 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 Ward[35] and co-workers investigated the effect of water-soluble metal–organic cages $[Co_8L_{12}]^{16+}$ on Kemp elimination reaction, and their results showed that the existence of cage has a huge rate acceleration ($k_{cat}/k_{uncat} = 2 \times 10^5$) 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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interaction to control the chemical reaction, which has been considered and applied by external electric field or high concentrated ionic aggregates.[36,37] The same is true for our two hosts, which will also generate EPF and affect the reactions of the encapsulated guests.

2 Experimental

2.1 Materials

All solvents and reagents used in this study are chemically pure. 1,4-Diethoxy benzene was purchased from Tokyo Chemical Industry Co. Ltd., polyformaldehyde and ammonium hydroxide solution were purchased from Shanghai Titan Scientific Co. Ltd (China), ethyl bromoacetate, triphenylphosphine, carbon tetrabromide and *s*-trioxane were purchased from the Saen Chemical Technology (Shanghai) Co. Ltd, boron tribromide and boron trifluoride diethyl etherate were purchased from Shanghai Macklin Biochemical Co. Ltd. Guests **G1** and **G2** were purchased from Aladdin Chemical Reagent Co. Ltd (Shanghai, China) and Bide Pharmatech Ltd (Shanghai). All solvents were purchased from Shanghai Titan Scientific Co. Ltd (China) and used directly without further purification. Hosts **H1** and **H2** were synthesized according to the reported procedures.[33,34]

2.2 Binding affinity measurements

Binding constants were measured by ^{1}H NMR titrations with a Bruker Avance 400 MHz spectrometer and ITC experiments by a GE MicroCal iTC200. In the ^{1}H NMR experiments, guest concentration was maintained to be 5×10^{-4} M, and then different equivalents of host were added successively. With the addition of host, the signal peaks of guest shifted upfield. The addition was stopped when the peaks of guest no longer shifted. Fitting of the data was performed using Origin 2021 according to the following equation:

$$\Delta\delta = (\Delta\delta_\infty/[G]_0)\,(0.5[H]_0 + 0.5([G]_0 + 1/K_a) - (0.5([H]_0{}^2 + (2[H]_0(1/K_a - [G]_0)) + (1/K_a + [G]_0)^2)^{0.5})) \quad (1)$$

where $\Delta\delta$ is the chemical shift changes of H_1 in **G1**, $\Delta\delta_\infty$ is the chemical shift changes when **G1** is completely complexed, $[G]_0$ is the fixed initial concentration of **G1**, and $[H]_0$ is the varying concentrations of the host. In the ITC experiments, the guest concentration (5×10^{-4} M) was kept constant, and then a total volume of 25 μL hosts (5×10^{-3} M) were injected in 25 aliquots.

2.3 Kinetic measurements

UV-Vis spectroscopy by a Shimadzu UV 1780 UV-Vis Spectrophotometer was employed for the kinetic measurements of Kemp elimination reaction. During the tests, host concentrations were maintained to be 1×10^{-4} M in a 3 mL cuvette, and then 10 μL of guest (3×10^{-2} M) was added to keep the molar ratio of host-guest at 1 : 1. Subsequently, 10 equiv. NaOH solution was added to the above mixture to initiate the reaction. The absorption peaks of products **P1** and **P2** appear at 325 nm and 378 nm, respectively, and the tests were stopped when the absorption of the product was no longer enhanced. In the control experiments of free guests, the guest concentration was also kept to be 1×10^{-4} M. Fitting of the data was performed using Origin 2021 mono-exponential growth function,

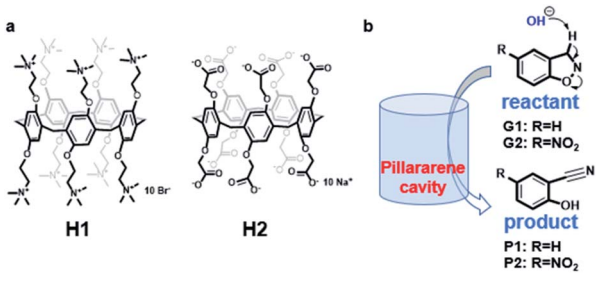
$$y = A_1 \times \exp(-x/t_1) + y_0 \quad (2)$$

where y is the absorption or yield of product and x is corresponding time. The rate constant k is the inverse of the life time t_1.

3 Results and discussion

Binding experiments between the host **H1** and guest **G1** were followed using ^{1}H NMR spectroscopy in D_2O solution. First, we kept the total concentration of **G1** and **H1** at 6 mM, and measured the job's plot by changing their molar ratio. With the increase of **H1** content, upfield shifts of the proton peaks of **G1** appeared, which signified that there is host-guest interaction between them and indicated the formation of a 1 : 1 inclusion complex (Fig. S1 and S2†). Next, the binding constant between **H1** and **G1** was obtained through ^{1}H NMR titrations. The peaks of **G1** shifted upfield in the titration experiment between **H1** and **G1**. Fitting the data by eqn (1) gave the binding constant as 51 M^{-1} (Fig. S3 and S4†). Similarly, the binding constant between **H2** and **G1** was calculated to be 24 M^{-1} (Fig. S5 and S6†). Meanwhile, ITC was used to test the binding between the hosts and **G1**, and the values of binding constant are 698 M^{-1} (**H1–G1**) and 641 M^{-1} (**H2–G1**), respectively (Fig. S27 and S28†). There is an order of magnitude difference in binding constants measured by ^{1}H NMR and ITC, which is attributed to the fact that heat of dilution and assembly process may also occur during the ITC experiments. Overall, the binding of the Kemp elimination substrate **G1** with the water-soluble pillar[5]arene is not strong, which is mainly caused by the lack of charges on the substrate; the neutral guest can tumble freely within the tubular cavity of pillar[5]arene. In terms of **G2**, similar binding mode was observed upon mixing it with **H1** and **H2** in 1 : 1 ratio (Fig. S7 and S8†).

Although weak binding between the above hosts and guests were observed, we assume the charge difference on the rims will still influence the rate of Kemp elimination. Ultraviolet-Visible (UV-Vis) spectroscopy is a common method for quantitatively studying compounds in solution, and we used it to study the



Scheme 1 (a) Structure of the pillar[5]arene hosts; (b) illustration of the Kemp elimination reaction within the pillar[5]arene cavity.

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 ($k_{\mathbf{H1-G1}}/k_{\text{free G1}}$) and 2.9 ($k_{\mathbf{H2-G1}}/k_{\text{free G1}}$) 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 ($k_{\mathbf{H1-G2}}/k_{\mathbf{H2-G2}}$) 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, ^{1}H 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 ^{1}H NMR experiments, the corresponding concentration of NaOH increased to 1×10^{-2} M. This concentration in ^{1}H NMR was so high that the reaction proceeded too fast to be recorded by ^{1}H 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 ^{1}H 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 found that the presence of hosts accelerated the reaction rate by 4.4 ($k_{\mathbf{H1-G1}}/k_{\text{free G1}}$) and 3.2 ($k_{\mathbf{H2-G1}}/k_{\text{free G1}}$) 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 ^{1}H NMR experiments.

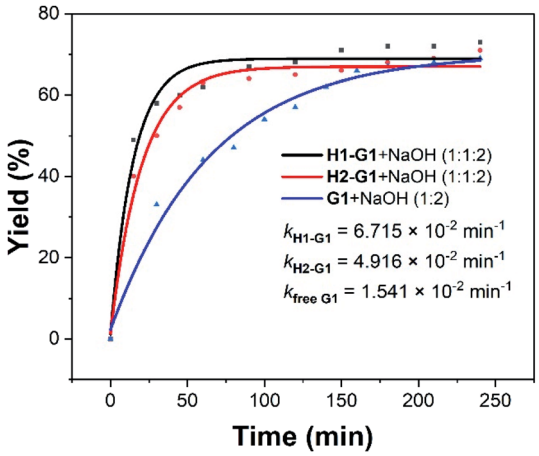


Fig. 2 Kinetic curves for the ^{1}H NMR experiments of G1 with 2 equiv. of NaOH in the presence and absence of the water-soluble pillar[5]arene hosts H1 and H2.

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

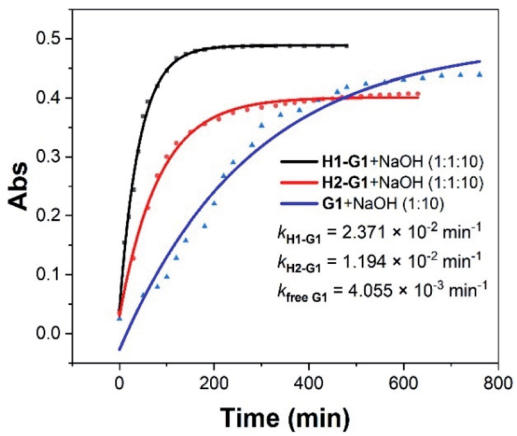


Fig. 1 Kinetic curves for the UV-Vis experiments of G1 with 10 equiv. of NaOH in the presence and absence of the water-soluble pillar[5]arene hosts H1 and H2.

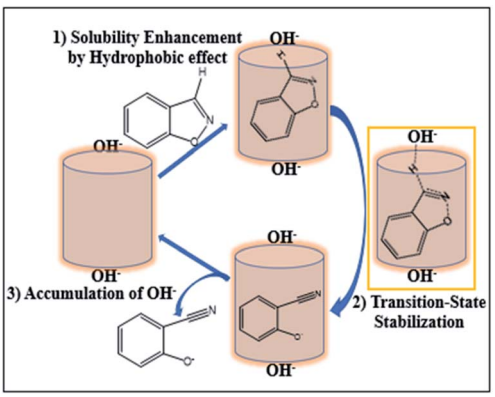


Fig. 3 Proposed possible mechanism of the Kemp elimination reaction in the presence of water-soluble pillararene hosts.

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 ^{1}H 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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Notes and references

1 T. Wang, X. Fan, C. Hou and J. Liu, *Curr. Opin. Struct. Biol.*, 2018, **51**, 19–27.
2 J.-M. Lehn, *Angew. Chem., Int. Ed.*, 1988, **27**, 89–112.
3 G. W. Gokel, W. M. Leevy and M. E. Weber, *Chem. Rev.*, 2004, **104**, 2723–2750.
4 Y.-M. Zhang, Y.-H. Liu and Y. Liu, *Adv. Mater.*, 2020, **32**, 1806158.
5 Y. Razuvayeva, R. Kashapov and L. Zakharova, *Supramol. Chem.*, 2020, **32**, 178–206.
6 R.-C. Mutihac, A. A. Bunaciu, H.-J. Buschmann and L. Mutihac, *J. Incl. Phenom. Macro.*, 2020, **98**, 137–148.
7 T. Ogoshi, S. Kanai, S. Fujinami, T.-A. Yamagishi and Y. Nakamoto, *J. Am. Chem. Soc.*, 2008, **130**, 5022–5023.
8 S. Mosca, Y. Yu and J. Rebek, *Nat. Protoc.*, 2016, **11**, 1371–1387.
9 Q.-F. Sun, J. Iwasa, D. Ogawa, Y. Ishido, S. Sato, T. Ozeki, Y. Sei, K. Yamaguchi and M. Fujita, *Science*, 2010, **328**, 1144–1147.
10 C. T. McTernan, T. K. Ronson and J. R. Nitschke, *J. Am. Chem. Soc.*, 2019, **141**, 6837–6842.
11 A. Galan and P. Ballester, *Chem. Soc. Rev.*, 2016, **45**, 1720–1737.
12 Y. Fang, J. A. Powell, E. Li, Q. Wang, Z. Perry, A. Kirchon, X. Yang, Z. Xiao, C. Zhu, L. Zhang, F. Huang and H.-C. Zhou, *Chem. Soc. Rev.*, 2019, **48**, 4707–4730.
13 G. Olivo, G. Capocasa, D. Del Giudice, O. Lanzalunga and S. Di Stefano, *Chem. Soc. Rev.*, 2021, **50**, 7681–7724.
14 C. Gaeta, P. La Manna, M. De Rosa, A. Soriente, C. Talotta and P. Neri, *ChemCatChem*, 2021, **13**, 1638–1658.
15 M. Petroselli, Y.-Q. Chen, J. J. Rebek and Y. Yu, *Green Synth. Catal.*, 2021, **2**, 123–130.
16 K. Wang, J. H. Jordan, X.-Y. Hu and L. Wang, *Angew. Chem., Int. Ed.*, 2020, **59**, 13712–13721.
17 W. Liu and J. F. Stoddart, *Chem*, 2021, **7**, 919–947.
18 B. Mitschke, M. Turberg and B. List, *Chem*, 2020, **6**, 2515–2532.
19 Z. Dong, Q. Luo and J. Liu, *Chem. Soc. Rev.*, 2012, **41**, 7890–7908.
20 C. Han, G. Yu, B. Zheng and F. Huang, *Org. Lett.*, 2012, **14**, 1712–1715.
21 N. L. Strutt, H. Zhang, M. A. Giesener, J. Lei and J. F. Stoddart, *Chem. Commun.*, 2012, **48**, 1647–1649.
22 X. Shu, S. Chen, J. Li, Z. Chen, L. Weng, X. Jia and C. Li, *Chem. Commun.*, 2012, **48**, 2967–2969.
23 G. Yu, W. Yu, Z. Mao, C. Gao and F. Huang, *Small*, 2015, **11**, 919–925.
24 P.-Y. Li, Y. Chen, C. H. Chen and Y. Liu, *Soft Matter*, 2019, **15**, 8197–8200.
25 C. Biagini, S. D. P. Fielden, D. A. Leigh, F. Schaufelberger, S. Di Stefano and D. Thomas, *Angew. Chem., Int. Ed.*, 2019, **58**, 9876–9880.
26 K. Wang, X. Tian, J. H. Jordan, K. Velmurugan, L. Wang and X.-Y. Hu, *Chin. Chem. Lett.*, 2021, DOI: 10.1016/j.cclet.2021.06.026.
27 K. Wang, J. H. Jordan, K. Velmurugan, X. Tian, M. Zuo, X.-Y. Hu and L. Wang, *Angew. Chem., Int. Ed.*, 2021, **60**, 9205–9214.
28 D. Zhang, J. Cheng, L. Wei, W. Song, L. Wang, H. Tang and D. Cao, *J. Phys. Chem. Lett.*, 2020, **11**, 2021–2026.
29 D. G. Liz, A. M. Manfredi, M. Medeiros, R. Montecinos, B. Gomez-Gonzalez, L. Garcia-Rio and F. Nome, *Chem. Commun.*, 2016, **52**, 3167–3170.
30 J.-C. Gui, Z.-Q. Yan, Y. Peng, J.-G. Yi, D.-Y. Zhou, D. Su, Z.-H. Zhong, G.-W. Gao, W.-H. Wu and C. Yang, *Chin. Chem. Lett.*, 2016, **27**, 1017–1021.
31 G. Yu, J. Zhou, J. Shen, G. Tang and F. Huang, *Chem. Sci.*, 2016, **7**, 4073–4078.
32 D. Xia, P. Wang and B. Shi, *Org. Biomol. Chem.*, 2017, **15**, 7618–7622.
33 T. Ogoshi, M. Hashizume, T.-A. Yamagishi and Y. Nakamoto, *Chem. Commun.*, 2010, **46**, 3708–3710.

34 Y. Ma, X. Ji, F. Xiang, X. Chi, C. Han, J. He, Z. Abliz, W. Chen and F. Huang, *Chem. Commun.*, 2011, **47**, 12340–12342.
35 W. Cullen, M. C. Misuraca, C. A. Hunter, N. H. Williams and M. D. Ward, *Nat. Chem.*, 2016, **8**, 231–236.
36 A. C. Aragones, N. L. Haworth, N. Darwish, S. Ciampi, N. J. Bloomfield, G. G. Wallace, I. Diez-Perez and M. L. Coote, *Nature*, 2016, **531**, 88–91.
37 Y. Pocker and R. F. Buchholz, *J. Am. Chem. Soc.*, 1970, **92**, 4033–4038.