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Reaction mechanism of the green synthesis of glutaric acid†

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In this study, the reaction mechanism underlying the green synthesis of glutaric acid was studied *via* joint test technology. Density functional theory calculations were used to verify the mechanism. Quantitative analysis of glutaric acid *via* infrared spectroscopy and HPLC was established. The linear correlation between the two methods was good, from 0.01 to 0.25 g mL⁻¹. The analysis results of the two methods were consistent as the reaction progressed.

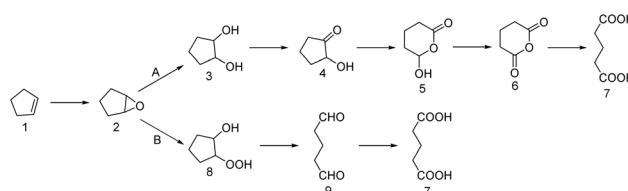
1. Introduction

The concept of Quality by Design (QbD)¹ has increased attention on process analytical technology (PAT).² PAT uses automated analytical instruments and chemometrics technologies,³ and it offers real-time analysis, data processing, condition optimization, and process feedback. The entire production process is under real-time monitoring, which can make production reasonable, reduce production costs, improve product quality, and reduce environmental pollution.^{4,5} Online spectroscopy is an advanced instrument and a component of process analysis technology. Commonly used instruments include online infrared (IR) spectroscopy and online Raman spectroscopy.^{6,7} IR spectroscopy is widely used in chemical, pharmaceutical, biological, food, and other fields^{8–12} because of its simplicity, fast analysis speed, and non-destructive characteristics. Online spectroscopy can measure the concentrations of reactants, intermediate products, and final products during the reaction process. It can also identify the best reaction time and obtain expected reaction products. Finally, it can be used to study the reaction mechanism by comparing the disappearance and absorption of the characteristic absorption peaks.^{13,14}

Glutaric acid is a colorless and needle-like crystalline solid. Glutaric acid and its derivatives are important fine chemical raw materials and intermediates with a wide range of applications in chemical, construction, medicine, agriculture, biology, and other fields.^{15–17} In recent years, the green process of preparing glutaric acid by oxidizing cyclopentene with hydrogen peroxide has attracted much attention.^{18–22} It uses environmentally friendly, inexpensive, and easily available hydrogen peroxide to replace the

traditional high-polluting oxidants that fundamentally eliminates pollution sources. Research on the reaction mechanism of the green synthesis of glutaric acid remains controversial. The reaction mechanism has the following two pathways (Scheme 1): K. Sato²³ detected intermediates 2, 3, and 4 by GC in the synthesis of adipic acid. Separate experiments showed that these intermediates are oxidized to glutaric acid under similar reaction conditions, and thus path A was proposed. During the synthesis of glutaraldehyde, Dai Weilin²⁴ *et al.* purified the clean intermediate 8 by flash column chromatography and characterized it by ¹H NMR, MS, and IR. The reaction process was further studied by GC, and epoxycyclopentane 2 was found to be quickly transformed into intermediate 8 that was then gradually transformed into glutaraldehyde 9. Therefore, reaction path B was proposed. During the synthesis of glutaric acid, Chen Hui²⁵ used GC to study the reaction process and detected intermediates 3, 9, and glutaric acid 7. The absence of intermediate 8 indicated that intermediate 8 was unstable. However, these data do not prove that path A does not exist; thus, it is speculated that both pathways may exist. Most research on the reaction mechanisms of green synthesis in glutaric acid is *via* offline GC analysis; there is no spectroscopic study on glutaric acid synthesis to date. Here, we studied the reaction mechanism of the green synthesis of glutaric acid *via* joint testing technology.

Studying the reaction mechanism of the green synthesis process of glutaric acid can help improve the selectivity of the



Scheme 1 Reaction mechanism path of green synthesis of glutaric acid.

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experiment and can lead to higher yields. It can also explain the danger of the reaction process, improve the reaction, increase safety, and reduce economic losses.²⁶ This work used the synthetic method proposed by Chen Hui (Scheme 2).²⁵ Tungstic acid is the catalyst, and cyclopentene is directly oxidized by hydrogen peroxide to produce glutaric acid. The method does not use organic solvents or phase transfer catalysts. It is environmentally friendly, has good cost-effectiveness, and conforms to the concepts of green development.²⁷

This article uses joint testing technology to explore the reaction mechanism of the green synthesis process of glutaric acid. We used real-time monitoring of the change in each component of the reaction process through online IR and online Raman spectroscopy. This was combined with HPLC offline analysis at various time points. Gaussian calculation methods were used to verify the synthesis mechanism of glutaric acid. We then established a quantitative analysis method for infrared spectroscopy and HPLC, conducted quantitative analysis, and compared the glutaric acid data between methods.

2. Reagents and instrumentation

2.1 Chemical reagents

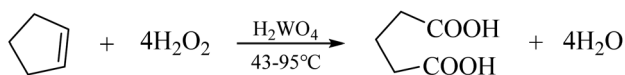
Hydrogen peroxide (50 wt%), glutaraldehyde, 25% aqueous solution (BR), tungstic acid (AR), cyclohexene (AR), adipic acid (AR), methanol (AR), potassium dihydrogen phosphate (AR), and phosphoric acid (AR) were purchased from Sinopharm Chemical Reagent Co., Ltd.; cyclopentene (purity 98%, Shanghai Aladdin Biochemical Technology Co., Ltd.), 1,2-epoxycyclopentane (purity 98%), and glutaric acid (98% purity) were purchased from Shanghai Macleans Biochemical Technology Co., Ltd., water (ultra-pure water). All reagents were used without further purification.

2.2 Instruments

Online IR (ReactIR 702L, Mettler Toledo); online Raman (ReactRaman 785, Mettler Toledo); HPLC (UltiMate 3000, Thermo Scientific); fully automated synthesis reactor (EasyMax 102, Mettler Toledo); 1/100 000 electronic balance (SQP, Sartorius); ultrasonic oscillator (AS3120, Autoscience).

2.3 HPLC detection method

Chromatographic column: Thermo Synchronis C18 (250 mm × 4.6 mm (id), 5 μm); mobile phase: 0.01 mol L⁻¹ potassium dihydrogen phosphate aqueous solution (phosphoric acid adjusted to pH 2–3)–acetonitrile (volume ratio 70 : 30); column temperature: 30 °C; flow rate: 1.0 mL min⁻¹; detection wavelength: 209 nm; injection volume: 1.0 μL.



Scheme 2 Preparation of glutaric acid through catalytic oxidation of cyclopentene with hydrogen peroxide.

2.4 Calculation method

All calculations used Gaussian 16 program with density functional theory (DFT) at the level of m062x/6-31g(d). This step optimized and analyzed the frequency of reactants, transition states, intermediates, and products.

2.5 Configuration of standard solution

Glutaric acid (accurate to 0.1 mg) was placed in a 50 mL volumetric flask and dissolved in water to accurately determine the volume. We then configured these as 0.01, 0.05, 0.10, 0.15, 0.20, and 0.25 g mL⁻¹.

2.6 Green synthesis process of glutaric acid

Hydrogen peroxide (52.80 g; 0.7760 mol) and tungstic acid (1.00 g; 0.004 mol) were used as a primer. This was stirred at 43 °C for 0.5 h, and cyclopentene (12.26 g; 0.1764 mol) was added dropwise for 1 hour and then incubated for 2 h. The temperature was then increased to 95 °C for three hours, and the temperature was held constant for 5 hours.

3. Results and discussion

3.1 Reaction mechanism through online spectroscopy

3.1.1 Identification of reaction characteristic peaks. Online spectroscopy technology was used to study the reaction mechanism by comparing the disappearance speed of the significant absorption peak of the reactants and the generation speed of the significant absorption peak of the product. This helped determine whether there is an active intermediate in the reaction process.²⁸ The system uses water as the solvent during the process of green synthesis of glutaric acid, which will greatly affect the IR detection results. The Raman spectroscopy method can avoid the influence of water, but the polarity of the system will greatly affect the Raman data. Therefore, the combination of IR and Raman not only avoids these effects but also makes the detection results more comprehensive.²⁹

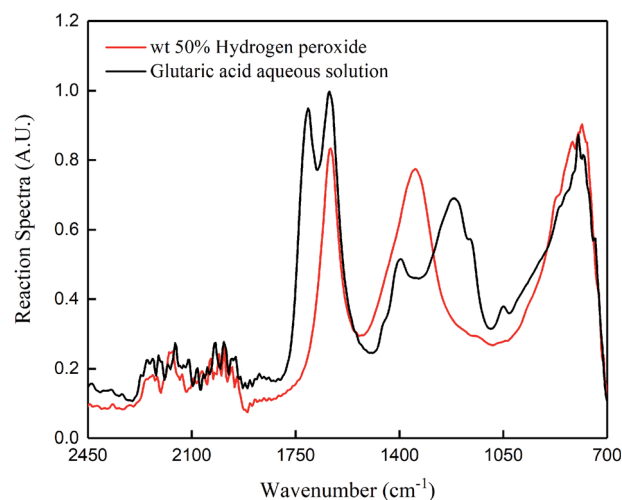


Fig. 1 Standard infrared spectra of glutaric acid and hydrogen peroxide solutions.

Fig. 1 shows the standard spectrum obtained by online IR scanning of 50% hydrogen peroxide and glutaric acid aqueous solution. We observed the changes in the glutaric acid based on the peak at 1707 cm^{-1} ($\text{C}=\text{O}$ stretching vibration). Fig. 2 shows the standard spectrum obtained by online Raman scanning of 50% hydrogen peroxide and cyclopentene based on the peaks at 1614 cm^{-1} ($\text{C}=\text{C}$ stretching vibration) and 876 cm^{-1} ($\text{O}-\text{O}$ stretching vibration) to observe the change in cyclopentene and hydrogen peroxide.

3.1.2 Spectral analysis results and discussion. Real-time monitoring of the reaction process of green synthesis of glutaric acid was done *via* online spectroscopy technology. Fig. 3 shows the changing trend of each component during the reaction. On addition of cyclopentene, a peak at 1614 cm^{-1} (attributable to the $\text{C}=\text{C}$ stretching vibration in cyclopentene) was detected by online Raman. This quickly increased to the maximum. The peak quickly disappeared after addition of cyclopentene. At the same time, online IR spectroscopy detected a peak at 1083 cm^{-1} ($\text{C}-\text{O}$ stretching vibration). This increased rapidly until it plateaued. The peak gradually decreased until it disappeared as the temperature rises. The peak at 1707 cm^{-1} (attributable to the $\text{C}=\text{O}$ stretching vibration in glutaric acid) was detected by online IR spectroscopy, and it gradually rises and plateaus.

Fig. 4 displays a three-dimensional spectrum obtained by online IR spectroscopy during the reaction process, which shows the changes in each component during the reaction process in more detail and more intuitively. The figure shows the peaks at 1083 cm^{-1} , 1037 cm^{-1} ($\text{C}-\text{O}$ stretching vibration), and 965 cm^{-1} ($\text{O}-\text{O}$ asymmetric stretching vibration). These then disappear at the end of the reaction. The trend in the change is also consistent: we speculated that these changes are the characteristic absorption peaks of the same intermediate, which is consistent with the IR spectrum of intermediate **8**.²⁴ Concurrently, we show that intermediate **8** is relatively stable in the system in contrast to prior work.²⁵

The results show that cyclopentene is first oxidized to produce intermediate **8**, which is relatively stable at low temperatures. As the temperature rises, intermediate **8** is

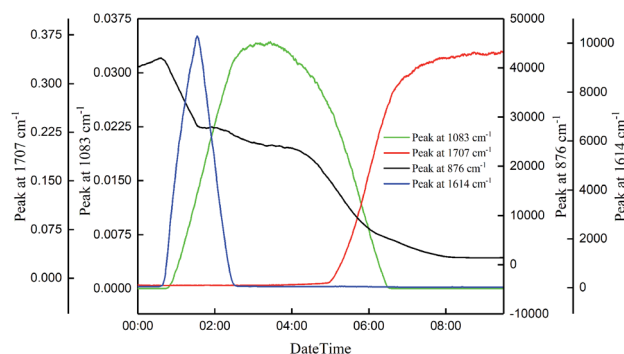


Fig. 3 Variation trend diagram of each component during the green synthesis of glutaric acid.

gradually converted into glutaric acid according to path B described in Scheme 1.

3.2 HPLC analysis results and discussion

Samples were taken every 0.5 h and analyzed by HPLC (Fig. 5). When the dropwise cyclopentene addition is over, the response value of intermediate **8** reaches its highest value, and there is basically no change during the heat-preservation process. The response value of the intermediate gradually decreases as the temperature rises, and glutaraldehyde **9** is produced concurrently. After 5.5 hours, glutaric acid **7** appeared in sampling analysis, and the response value of glutaric acid **7** gradually increased as the reaction proceeded. The response value of glutaric acid was constant after 8 hours of reaction.

3.3 Reaction mechanism

The combination of online spectroscopy and HPLC showed that cyclopentene **1** is oxidized to intermediate **8** and then intermediate **8** is converted to glutaraldehyde **9**. Finally, glutaraldehyde **9** is oxidized to produce glutaric acid **7** (Scheme 3). The reaction mechanism is basically the same as the path B reported in Scheme 1. The difference is that intermediate **8** is relatively stable.

3.4 Theoretical calculation and verification

We also used Gaussian to perform theoretical calculations on the reaction process and evaluate the reaction pathway by comparing

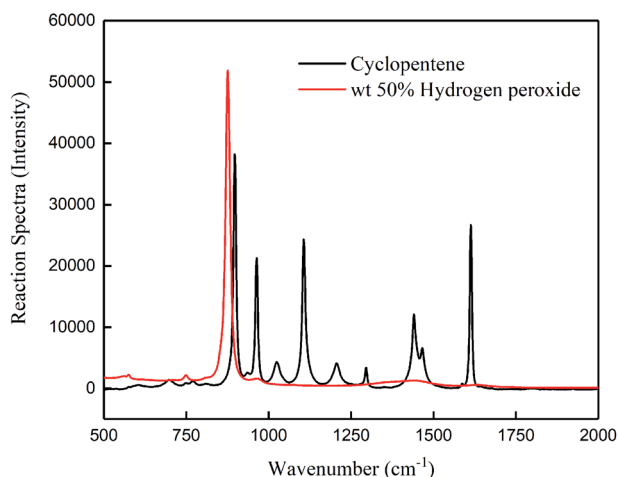


Fig. 2 Standard Raman spectra of cyclopentene and hydrogen peroxide solutions.

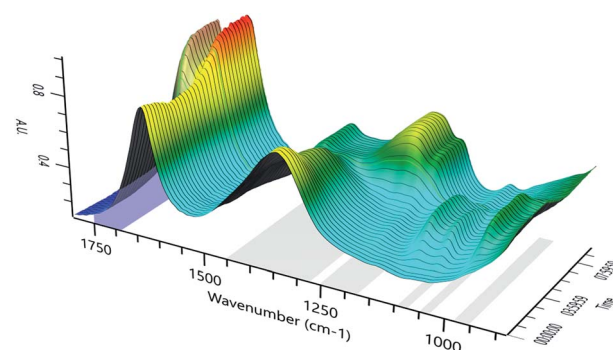


Fig. 4 Three-dimensional plots of the reaction process obtained by online infrared spectroscopy.



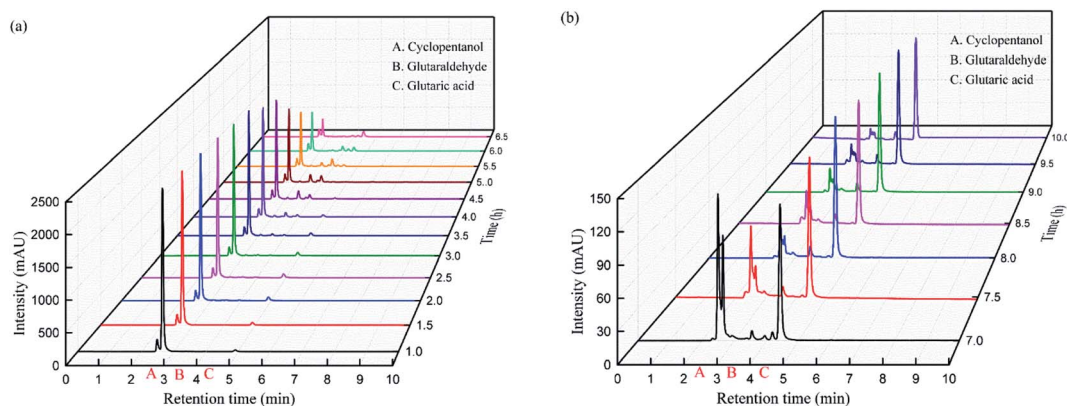
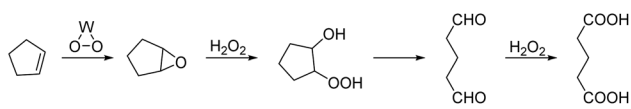


Fig. 5 HPLC results of the green synthesis of glutaric acid. (a) 1.0 to 6.5 hours. (b) 7.0 to 10.0 hours.



Scheme 3 Reaction mechanism of green synthesis of glutaric acid.

the energy required to form a transition state during the reaction process.^{30–34} The difference in reaction mechanism is mainly in the ring-opening reaction of 1,2-epoxide; thus, only the calculation of the process is performed. The acidic ring-opening reaction mechanism of 1,2-epoxide is shown in Scheme 4.³⁵ Under these acidic conditions, the oxygen atom is protonated and positively charged in the epoxide; the nucleophile attacks the adjacent carbon atom to cause a S_N2 (ref. 36) reaction.

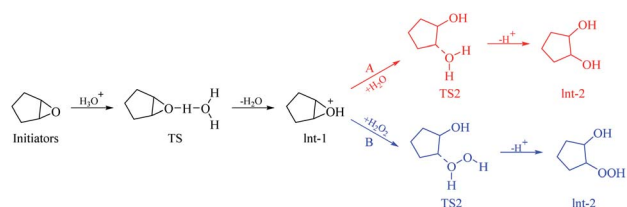
The calculation results of the acidic ring-opening reaction of 1,2-epoxide during the synthesis of glutaric acid is shown in Fig. 6. The calculated activation free energy is $11.97 \text{ kcal mol}^{-1}$ in pathway A of the TS2 transition state. The calculated activation free energy of $11.38 \text{ kcal mol}^{-1}$ is lower than that from route B. The results show that pathway B has a lower reaction energy barrier than pathway A and is more likely. The calculated results are consistent with the experimental results.

3.5 Quantitative analysis

3.5.1 Standard curve by online IR spectroscopy and HPLC. Yield is an important parameter in the chemical production process. The glutaric acid product was quantitatively analyzed by HPLC and online infrared spectroscopy. Fig. 7 shows the

standard curve of glutaric acid. The HPLC results show that the mass concentration of the glutaric acid standard solution is in the range of $0.01\text{--}0.25 \text{ g mL}^{-1}$ with good linear correlation. The linear equation is $y = 327.45454x - 0.24943$, $R^2 = 0.9998$. The mass concentration of the glutaric acid standard solution obtained *via* online IR spectroscopy is in the range of $0.05\text{--}0.25 \text{ g mL}^{-1}$ with good linear correlation. The linear equation is $y = 117.092x - 2.1788$, $R^2 = 0.9991$.

3.5.2 Process quantitative analysis. The change of glutaric acid concentration was analyzed by offline HPLC and online IR spectroscopy to monitor the reaction rate (Fig. 8). Before 8 h of reaction, the concentration of glutaric acid obtained by online IR spectroscopy was higher than that obtained by HPLC. This is due to the influence of glutaraldehyde as measured at 1707 cm^{-1} ($\text{C}=\text{O}$ stretching vibration) of the product glutaric acid. During the gradual conversion of glutaraldehyde to glutaric acid, the concentration of glutaric acid obtained by online IR spectroscopy is increasingly consistent with the concentration of glutaric acid obtained by HPLC. Until glutaraldehyde is



Scheme 4 Ring-opening reaction mechanism of 1,2-epoxide under acidic conditions.

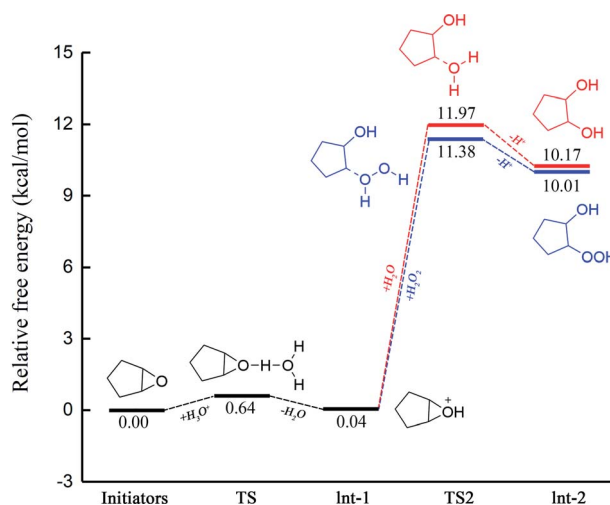


Fig. 6 Comparison of the free energy of the two reaction pathways of the ring-opening reaction of 1,2-epoxide in the green synthesis of glutaric acid.

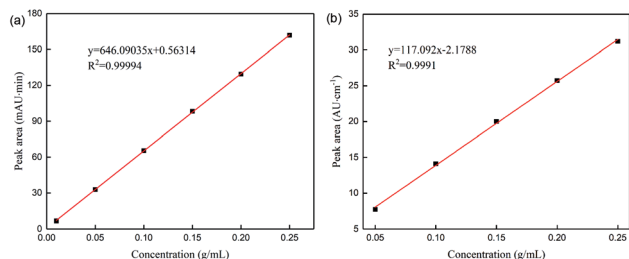


Fig. 7 Standard curve for the quantitative analysis of glutaric acid by (a) HPLC and (b) online infrared spectroscopy.

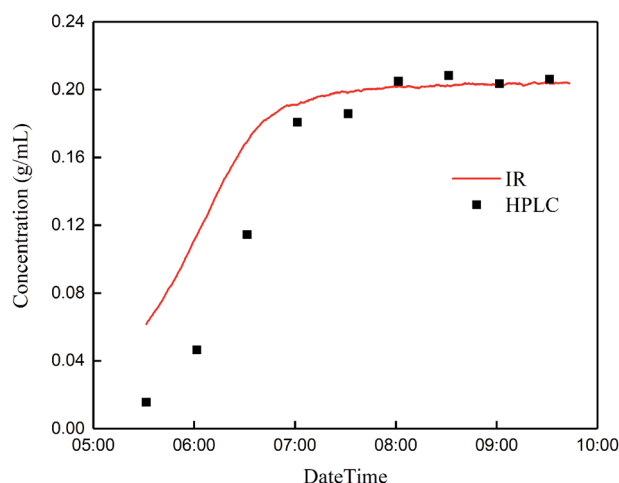


Fig. 8 Concentration of glutaric acid during the reaction.

completely converted to glutaric acid, the concentration of glutaric acid remains basically constant, and the results of the two methods are consistent.

4. Conclusions

We evaluated the reaction mechanism underlying the green synthesis of glutaric acid *via* online and offline analyses. Online spectroscopy and offline HPLC analyzed the concentration of each component during the reaction process. The reaction mechanism was found to follow route B. Gaussian calculations of the free energy change during the acidic ring-opening process of 1,2-epoxide were compared to the reaction energy barriers of different pathways. The results show that the reaction mechanism conformed to path B, which is consistent with the experimental results. Finally, a quantitative analysis method for IR spectroscopy of glutaric acid was established and verified and compared with HPLC. The linear correlation between the two methods was good from 0.01 to 0.25 g mL⁻¹. The concentration measured by online IR spectroscopy was higher than that measured by HPLC when the reaction was incomplete because of the influence of glutaraldehyde. The results from the two methods gradually became similar as the reaction proceeded.

In conclusion, online spectroscopic analysis technology can monitor changes in each component during the reaction

process in real-time. The results can show whether an active intermediate has been formed. Offline analysis technology and Gaussian calculations can further explore the reaction mechanism. In addition, online IR spectroscopy can be used for quantitative analysis and real-time monitoring of changes in concentration. This can eliminate the need for offline sampling.

Author contributions

Conceptualization: Chun-Sheng Cheng, Zhen-Yun Wei and Jie Hu; methodology: Xuan Liu, Xu Ming and Quan-Guo Li; resources: Chun-Sheng Cheng and Zhen-Yun Wei; writing (original draft preparation): Jie Hu; writing, review, and editing: Chun-Sheng Cheng and Zhen-Yun Wei.

Conflicts of interest

There are no conflicts to declare.

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