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One-pot synthesis of 5-norbornene-2,3-dicarboxylic anhydride with high *exo/endo* ratio in a microreactor under high temperature and appropriate pressure

Hao Li [b], Xue Liu [b], Yang Xiao [c,*], Kun Cao [a,b,*]

[a] State Key Laboratory of Chemical Engineering, College of Chemical and Biological Engineering, Zhejiang University, Hangzhou 310058, China
[b] Institute of Polymerization and Polymer Engineering, Zhejiang University, Hangzhou 310058, China
[c] Institute for Micromanufacturing and Department of Chemical Engineering, Louisiana Tech University, 505 Tech Drive, Ruston, LA 71272, USA

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ABSTRACT

5-Norbornene-*exo*-2,3-dicarboxylic anhydride (*exo*-NDA), widely used in the synthesis of medicine and pesticide, was primarily obtained through the subsequent thermal isomerization of 5-norbornene-*endo*-2,3-dicarboxylic anhydride (*endo*-NDA) synthesized from cyclopentadiene (CPD) and maleic anhydride (MAH). Herein, density functional theory (DFT) was employed to elucidate the transition states and reaction pathways of different configurations. The *endo*-path exhibited a lower energy barrier, and the *exo*-isomer demonstrates greater structural stability. It was found that both high temperature and solvent polarity influenced the generation of NDA with different configurations. Due to considering solubility of MAH, an acetone/ethylbenzene mixed solvent was chosen for the reaction instead. According to the DFT calculations, we developed continuous-flow microreactor for high-efficiency one-pot synthesis of the isomers with *exo/endo* ratio of up to 1.19:1 as well as almost 100 % conversion and 98 % selectivity just in 2 min at 260 °C and 4 MPa, which CPD was generated in situ to participate in a series of Diels-Alder reactions instead of dicyclopentadiene as raw material existed at room temperature. Moreover, excessive or insufficient pressure in the reaction system should elevate byproduct formation, resulting in a decrease in reaction selectivity, as could prolonged residence time.

1. Introduction

As an important organic intermediate, *cis*-5-norbornene-*exo*-2,3-dicarboxylic anhydride (*exo*-NDA), is widely used in the synthesis of medicine and pesticide. For instance, *cis*-5-norbornene-*exo*-2,3-diimide synthesized by the one-step conversion of *exo*-NDA is the essential intermediate for the synthesis of a series of antipsychotics including lurasidone hydrochloride [1–4], tandospirone citrate [5,6] etc. In addition, the *exo*-NDA have significant advantages in the synthesis of the functional monomers and the corresponding polymers [7–9]. Synthesis of norbornene dicarboxylic anhydride from cyclopentadiene (CPD) and maleic anhydride (MAH) via the Diels-Alder reaction is a classical cycloaddition reaction. It can produce four stereocenters regionally and stereoselectivity in one synthetic step. The Diels-Alder reaction is considered one of the most effective tools to produce cyclic compounds in synthetic organic chemistry. Although the reaction process is relatively simple, CPD remains highly reactive at room temperature and is prone to spontaneously form dimer-dicyclopentadiene (DCPD). Therefore, it must be prepared beforehand by thermal decomposition of DCPD during the simultaneous separation of the CPD by fractional distillation, and needs to be refrigerated for near term use. It should be noted that only about 2/3 of DCPD could cleave into CPD, and the rest might form oligomers which need to be cleaved to higher temperatures [10]. This has proven to be inefficient and arduous.

Huertas et al. [11] induced the cleavage of DCPD into CPD through high temperature (206 °C) without solvent, which rapidly reacted in-situ with MAH to obtain a mixture of *cis*-5-norbornene-2,3-dicarboxylic anhydride with *endo/exo* ratio of 95:5 in 22 min. At the same time, high temperature also induced the formation of thermodynamically stable *exo*-type products, which increased the proportion of *exo*-isomer in the mixed products. Taylor et al. [12] also used DCPD to react with MAH at 185 °C. After extending the reaction time to 1 h, the yield was 46 % and the *endo/exo* ratio *cis*-5-norbornene-2,3-dicarboxylic anhydride could reach 4:1. Although the results of these reactions are good, there are

* Corresponding authors.
E-mail addresses: yxiao@latech.edu (Y. Xiao), kcao@che.zju.edu.cn (K. Cao).

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some problems with solvent-free reactions. Robinson et al. [13] cleaved DCPD, dissolved in the mixed solvent of acetone and ethyl acetate, in a nuclear magnetic tube at 190 °C to generate CPD, and used high temperature to promote the instantaneous reaction of CPD and MAH. In the reaction time of 10 min, the conversion exceeded 95 %, and the *exo*-isomer selectivity could be up to 20 %.

These researchers used high-temperature/microwave cracking of DCPD to generate CPD in-situ to participate in the reaction, which improved the reaction efficiency. At the same time, the configuration change from *endo*-isomer to *exo*-isomer was induced by high temperature. Craig [14] showed that the *endo*-isomer was transformed into a mixture rich in *exo*-isomer by heating it at 190 °C for 1.5 h. Similar results were obtained when the *endo*-isomer was heated at high temperatures in decalin [15,16], *o*-dichlorobenzene [17] and toluene [18]. Welch et al [19] carried out the isomerization experiment of *endo*-NDA in a microchannel. Under different system temperatures (180–260 °C) and residence times (0.2–10 min), the formation of the *exo*-isomer increased with prolonged reaction times, up to an equilibrium ratio of about 1.8:1 under 230 °C. With the help of the high-efficiency heat transfer characteristics of the microchannel reactor, the reaction system could be unaffected by the boiling point of the solvent, so that the content of *exo*-isomer optimized by the thermodynamics was increased. On the other hand, the high-efficiency mass transfer in the microreactor under supercritical state can increase the collision probability of MAH and CPD generated by in-situ pyrolysis, reducing the formation of polycyclic by-products.

A lot of theoretical work has been devoted to the analysis of Diels-Alder reaction mechanism to explain the observed differences in *endo*/exo selectivity. The most widely accepted is the empirical *endo*-type rule (maximum accumulation of unsaturation) proposed by Alder and Stein [20]. Hoffmann and Woodward [21,22] used orbital symmetry and correlation diagram to explain the empirical rule. They proposed that the attractive secondary orbital interactions (SOI) between p-orbitals not directly involved in the formation of new sigma bonds was the fundamental reason for the *endo*-isomer selectivity. The concept of SOI was often cited to explain the stereoselectivity in various cycloaddition reactions based on frontier orbital theory [23–26]. However, the SOI theory based on simple basis is not as effective as expected. Sakata and Fujimoto [27] studied the reason for the *endo*-isomer selectivity of Diels-Alder reaction between CPD and MAH by density function theory (DFT). The results indicated that the C=O bond in MAH would repulse the carbon bridge, leading to the *endo*-isomer selectivity of the product. Many researchers have also calculated the structure of the product and the difficulty of the reaction between CPD and MAH by DFT. Larrañaga and Cózar [28] studied the influence of different α-substituents on the isomerization selectivity of Diels-Alder reaction. The presence of methyl in the α-site of electron withdrawing group could increase the formation trend of *exo*-isomers, but also increase the activation barrier and reduce the reaction rate. The initial reaction complexes transform towards the formation of energetic cycloadducts through a coordinated but slightly asynchronous transition structure. Meir [29] used DFT to calculate the internal reaction coordinates of the reaction between CPD and MAH under an external electric field (EEF). The results showed that the existence of the EEF would affect the activation barrier, which can lead to a catalytic or inhibitory effect. The catalytic effect could be equivalent to rate enhancements by 4–6 orders of magnitude. Simply flipping the EEF direction has the opposite effect, and the EEF acts as an inhibitor. In addition, the EEF also has influenced on the selectivity of *endo/exo* isomers.

In this work, in-situ CPD was utilized to react with MAH in a microchannel reactor to avoid the safety problems related to the use and storage of CPD. The Diels-Alder reaction of CPD and MAH was carried out in high temperature and pressure microchannel. High temperatures can induce the formation of *exo*-isomer and improve the reaction rate which promotes the completion of the reaction in a short time effectively. By adjusting the residence time, the products with different *endo/exo* ratios can be obtained. On the other hand, DFT was used to reveal the reaction process and transition state structure of different configurations. The proportion of isomers in the mixed products at high temperatures was predicted according to the calculated thermodynamic data. Based on the prediction, the *exo*-isomer selectivity was optimized, and the reaction degree was further regulated.

2. Experimental procedures

2.1. Materials

Dicyclopentadiene, with purity of 97 %, was provided by TCI (Shanghai). Ethylbenzene, with purity of 99.5 %, was provided by Macklin. Acetone, with purity of 99.7 %, was provided by Sinopharm Chemical Reagen. Maleic anhydride, with purity of 99 %, was provided by Aladdin. All chemicals were used directly without further purification.

2.2. Experiment device and operation procedure

The flow chart of the employed microreactor device was shown in Fig. 1. The device included two liquid feed sections, a preheating section, a mixing unit, a reaction section and a cooling section. The DCPD solution and MAH solution, prepared on the site, were fed through a constant P230/EPP010S liquid chromatography volume flow pump (Dalian Yilite Analytical Instruments, China). The pipes for the preheating section, the reaction section and the cooling section were VICI stainless steel microchannel (inner diameter was 500 μm, outer diameter was 1.588 mm, the length was 10 m). The preheating section was heated by an oil bath. After mixing the two materials through a Swagelok SS-1F0-3GC low dead zone T-joint, the reaction mixture was heated by gas chromatography column temperature box. The reaction residence time was adjusted by changing the flow rate of the two strands of material or the length of reaction section tube. The pressure in the reaction system was controlled by Swagelok KPB1S0A412P20000 back pressure valve with a range of 3–25 MPa. The inlet and outlet pressure values were measured by two Swagelok PTI-E-NG5000-19AO pressure sensors. Reaction products were detected on-line by gas chromatography with liquid samples taken at low temperature and pressure relief at the outlet, or by off-line gas chromatography-mass spectrometry (GC–MS) and conventional nuclear magnetic resonance (NMR) analysis of products' composition.

2.3. GC–MS/GC analysis

The products were determined by GC–MS analyses using Agilent 6890–5973 GC/MS spectrometer (Agilent, Co., U.S.A.) equipped with a 50-meter HP-1 column. The initial temperature of column was set at 70 ℃ and maintained for 2 min, after which the temperature was raised to 220 °C at a rate of 10 ℃/min, kept at constant temperature for 8 min, until the inlet temperature was 220 °C. The carrier gas flow rate was set to 0.5 mL/min and the shunt ratio was 100:1. A hydrogen flame ionization detector was used with a sampling volume of 0.5 μL. The setting conditions of MS: the interface temperature was 280 °C, the ion source temperature was 230 °C, and the fourth pole temperature was 150 °C. See (Fig. 2).

The product distribution was determined by GC 9790. A 50 m HP-1 column was assembled. The detection conditions were as follows: the pressure of nitrogen was 0.8 MPa, the pressure of hydrogen was 0.1 MPa, the pressure of air was 0.1 MPa, vaporization chamber temperature was 220 °C, and detector temperature was 220 °C. The temperature rising procedure was similar to the one employed for the GC–MS apparatus. A hydrogen flame ionization detector was used, and the injection volume was 0.5 μL.

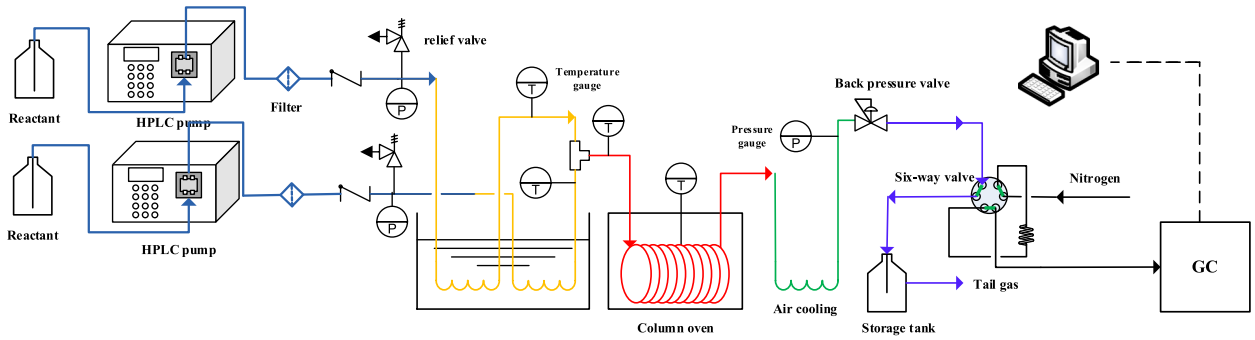


Fig. 1. Flow chart of NDA synthesis in the microreactor.

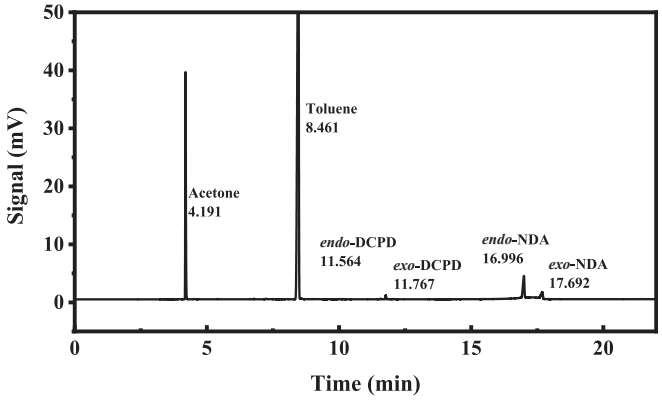


Fig. 2. Typical gas chromatogram for synthesis of NDA.

3. Results and discussion

3.1. Density functional theory

In the synthesis process of NDA, due to the influence of the stereoselectivity of Diels-Alder cycloaddition, there are two compounds with different configurations generated. The generation pathways of different configurations are undoubtedly of great interest. Fig. 3 (a) and (b) show the energy profiles in the IRC under different paths and the key geometric configuration details under different structures. Compared with the *endo*-isomer, the *exo*-isomer has a slightly higher energy barrier (almost 0.9 kcal·mol^{-1}), which makes them non preferentially selective in kinetics. Moreover, the *retro*-Diels-Alder reaction of *exo*-isomer need to overcome energy barrier of 35.7 kcal·mol^{-1}. Under high-temperature conditions, the cumulative amount of the *exo*-isomer increases, leading to a higher proportion.

MAH has strong polarity, and the polar solvent environment may affect the isomerization reaction pathway. Fig. 3 (c) summarizes the effects of different solvents on the energy barrier and product stability under different paths. It can be seen that the polarity of the solvent has direct influence on energy barrier. Using chloroform as a solvent can reduce the energy barrier of the *endo*-path to 13.8 kcal·mol^{-1}, which is 4 kcal·mol^{-1} less than that of the *exo*-path, which is not conducive to the formation of *exo*-isomer. In contrast, using acetone as a solvent could effectively reduce the energy barrier of *exo*-path from 18.0 kcal·mol^{-1} to 16.4 kcal·mol^{-1}, and the energy barrier of the *endo*-path from 15.9 kcal·mol^{-1} to 15.4 kcal·mol^{-1}, which is not only conducive to the formation of the *exo*-isomer, but could also promote the reaction, and shorten the required reaction time.

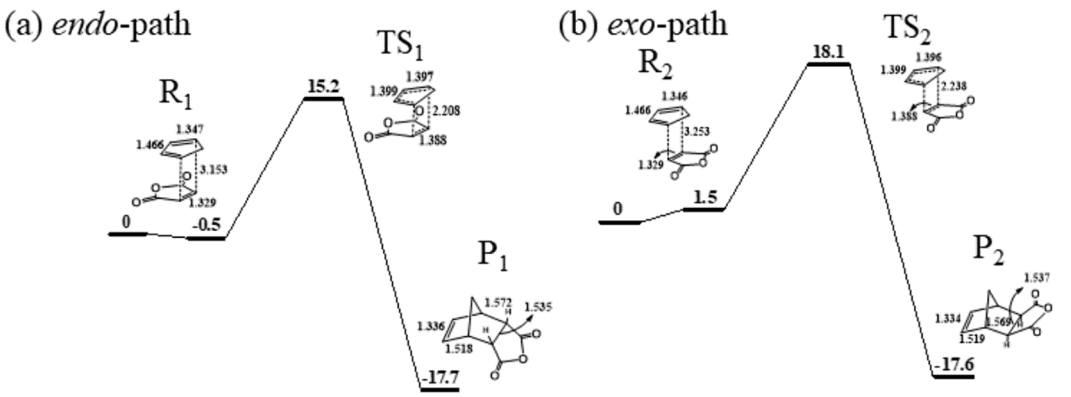
According to the relationship between the Boltzmann distribution and relative free energy, the theoretical proportions of different configurations of NDA under different temperatures and different solvents are calculated. The calculation results are shown in Fig. 3 (d). The electrostatic interaction between polar solvents and MAH is stronger, and the solvent effect becomes more pronounced, compared to non-polar solvents. In the range of 200–300 °C, the proportion of *exo*-NDA under solvent-free conditions is higher than that in solvent environments. This may be due to the enhanced molecular thermal motion under high temperature conditions, and the stronger thermodynamic stability of *exo*-NDA compared to *endo*-NDA, resulting in a larger calculated ratio. In the polar solvents, the electrostatic interaction between polar solvent molecules and the anhydride structure helps to stabilize the molecular structure. Under these conditions, the activation energy barrier of the *endo*-pathway is lower, resulting in a higher proportion of *endo*-NDA than under solvent-free condition. With reaction temperature increasing, the proportion of *exo*-isomer gradually approaches the theoretical ratio determined by the activation energy barrier of the reaction. When the molecular thermal motion is intense enough, the effects of temperature could be negligeable, leading to a 1:1 ratio of isomers.

Additional experiments were conducted to explore the effects of reaction temperature, system pressure and residence time on the generation of MAH with different configurations. Based on the DFT calculations, the generation rules of different isomers were explored to predict the proportion of isomers. Of note, while acetone as a solvent is more conductive to the synthesis of *exo*-isomer in a short timeframe, due to considering solubility and safety concerns, an acetone/ethylbenzene mixed solvent is a better choice for the reaction instead.

3.2. One-pot synthesis process of exo-isomer

The source of diene required for synthesizing NDA is from DCPD. During the reaction process, DCPD needs to first generate CPD in situ through the reverse Diels-Alder reaction, and then undergo a Diels-Alder reaction with MAH. The reaction temperature can not only affect the thermal cracking process of DCPD, but also affect the reaction pathway between CPD and MAH, generating NDA with different configurations. The system pressure was kept at 4 MPa, the residence time was 1 min, the mass fraction of MAH in the mixed solution (the mixed solvent of acetone and ethylbenzene, in which the mass ratio of acetone to ethylbenzene was 3:7, same below) was 10.2 wt%, and the molar ratio of MAH to DCPD was 1.02:0.5. The comparative experiments were carried out at different temperatures in the microchannel reactor, and the reaction results were shown in Fig. 4. When the temperature is higher than 240 °C, the conversion of DCPD is more than 95 %. The increase of temperature can promote the pyrolysis of DCPD while promoting the main reaction, so that more CPD is generated in situ to participate in the reactions, and the conversion is further increased. However, the increase of CPD concentration can also promote the reaction between CPD and DCPD, that is, simultaneously promote the side reaction, which leads to the decrease of selectivity.

The Diels-Alder reaction of CPD with MAH is affected by the energy barrier, and the *endo*-isomer products are preferentially generated under the kinetic control, while the *exo*-isomer products are



(c) Energy barriers

Solvent	Path	ΔG(kcal·mol^{-1}) TS	P
solvent-free	*endo*	15.9	-18.3
	exo	18.0	-18.7
o-dichlorobenzene	*endo*	15.7	-17.2
	exo	16.9	-18.8
dichloromethane	*endo*	15.6	-17.5
	exo	17.9	-18.1
chloroform	*endo*	13.8	-19.1
	exo	17.8	-18.3
ethylacetate	*endo*	15.8	-17.3
	exo	16.7	-19.1
acetone	*endo*	15.4	-17.4
	exo	16.4	-19.0

*Polar: acetone > ethylacetate > chloroform >dichloromethane > *o*-dichlorobenzene

(d) conformational ratio

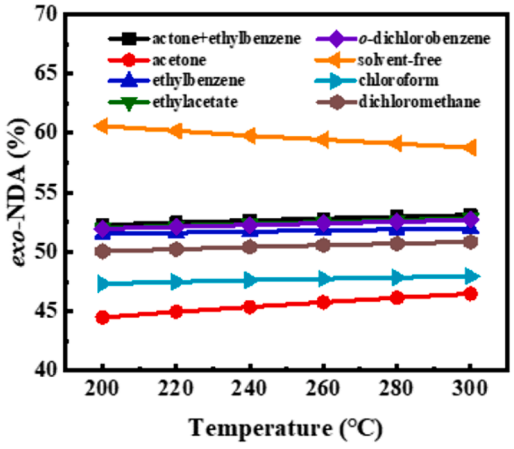


Fig. 3. M06-2X-GD3/6–311++G(d,p)//M06-2X-GD3/6-311G(d,p) SMD energy [kcal·mol^{-1}] profile for the Diels-Alder reaction of NDA for (a) the *endo*-path, and (b) the *exo*-path. (c) Energy barriers for the endo and exo pathways for the Diels-Alder reaction of cyclopentadiene and maleic anhydride at different solvents. (d) Effects of temperature and solvents on conformational ratio.

thermodynamically controlled. Therefore, increasing the reaction temperature is conducive to the formation of *exo*-isomer and the transformation of *endo*-isomer to *exo*-isomer. A similar conclusion can be obtained from Fig. 3 (d). At 200 °C, the ratio of *exo/endo* is 0.12:1. With the increase of temperature, the content of *endo*-isomer products first increases and then decreases, and the content of *exo*-isomer products keeps an upward trend. High temperature can promote the transformation of the *endo*-isomer to the *exo*-isomer. At 260 °C, the ratio of *exo/endo* increases to 0.96:1, which is less than the theoretical equilibrium distribution ratio (1.11:1). When the residence time is extended, the ratio can approach the theoretical value. Considering the side reaction, although it can greatly promote the formation of *exo*-isomer products at higher temperature, the selectivity of the reaction might be reduced. At the same time, the precipitation and adhesion of oligomers generated by multi-step cycloaddition reactions of CPD may cause the blockage of the microchannel, so a reaction temperature in the range of 240–260 °C is more appropriate.

The activation volume of the Diels-Alder cycloaddition reaction between MAH and CPD is negative, so the change of pressure can affect the reaction rate. The impact result is shown in Fig. 5. The pressure had little effect on the conversion percentage. Under low pressure, there are two phases (gas–liquid) present in the microchannel reactor. Due to the difference of acetone content between the two phases, there may be the problem of uneven material distribution (MAH is more likely to dissolve in the solvent with larger polarity, DCPD is more likely to dissolve in the phase with larger ethylbenzene content), which reduces the probability of collision reaction between MAH and CPD generated in situ. The side reaction of CPD and DCPD is larger, which leads to the decrease of selectivity. With the increase of pressure, the gas phase disappears and there is only one phase in the microchannel reactor. The CPD generated in situ can be captured by MAH in time, which reduces the collision reaction probability with DCPD and increases the reaction selectivity. The pyrolysis of DCPD may be affected slightly with the further increase of pressure, but the conversion rate is not affected much. On the other hand, because the reactions of CPD with MAH or DCPD are reactions with negative activation volume, both are enhanced synchronously, resulting in the decrease of reaction selectivity. At the same time, the increase of pressure may restrict the rotation of intramolecular bonds, which then affect the configuration transformation. Therefore, it is best to control the reaction pressure to the extent that the gas phase disappears in the microchannel.

In the microchannel reactor, the main reaction processes include the pyrolysis of DCPD, the Diels-Alder reaction of MAH and CPD, and the configuration conversion of NDA. The configuration conversion of NDA plays a decisive role in the content of *exo*-isomer products. Fig. 6 shows the effect of residence time on the experimental results. When the reaction is carried out for 0.25 min under 260 °C, the conversion rate can exceed 90 %, and the raw material is nearly consumed in about 0.5 min. There was no significant change in the selectivity within 2 min. The pyrolysis of DCPD and the Diels-Alder reaction of MAH and CPD were mainly completed in a short time in the early stage of the reaction. With the increase of residence time, the products of *endo*-isomer controlled by kinetics gradually changed to *exo*-isomer controlled by thermodynamics. When the reaction time is 2 min, the ratio of *exo/endo* can reach

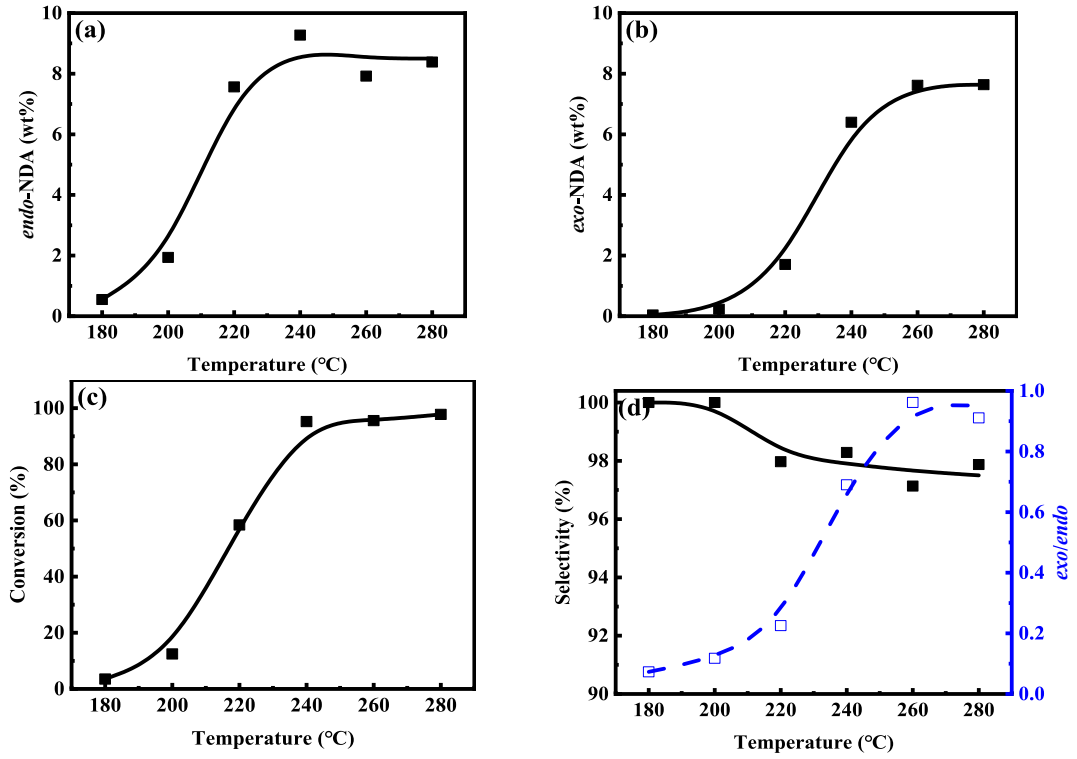


Fig. 4. Effects of reaction temperature on the Diels-Alder reaction (a) the proportion of *endo*-NDA in the sample solution, (b) the proportion of *exo*-NDA in the sample solution, (c) the conversion of DCPD, (d) the selectivity of NDA and *exo/endo* isomerization ratio.

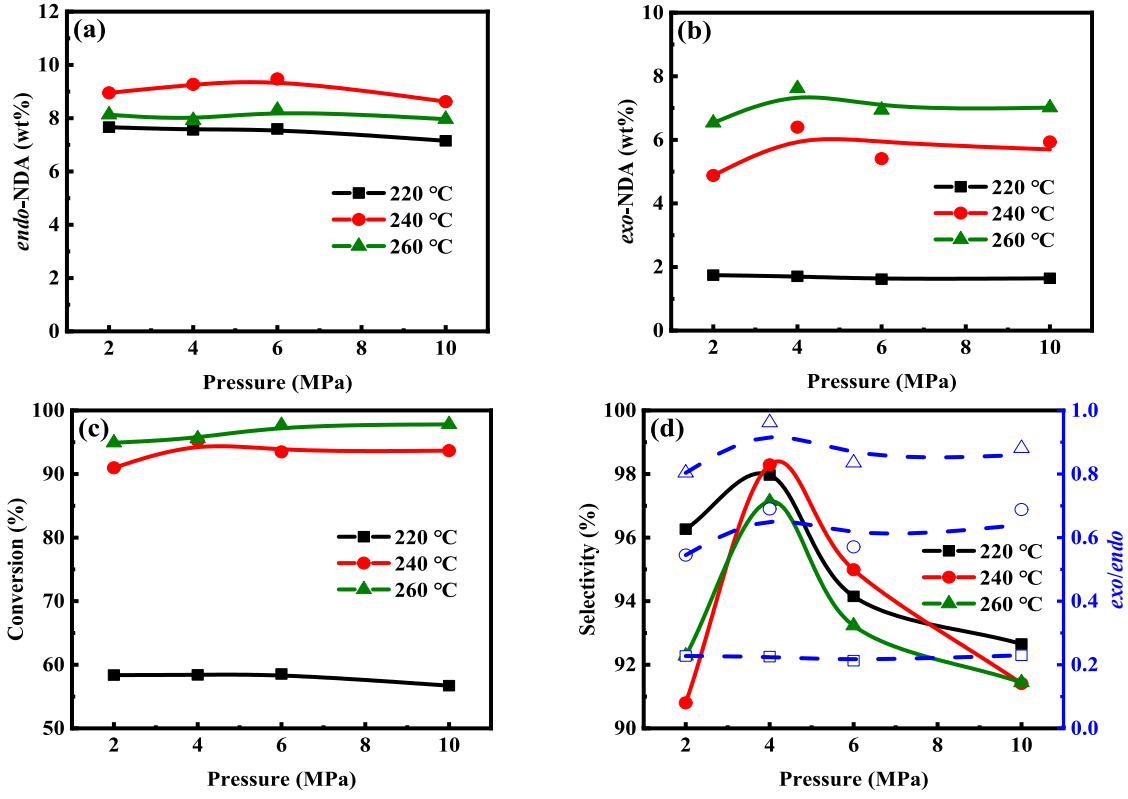


Fig. 5. Effects of system pressure on the Diels-Alder reaction (a) the proportion of *endo*-NDA in the sample solution, (b) the proportion of *exo*-NDA in the sample solution, (c) the conversion of DCPD, (d) the selectivity of NDA and *exo/endo* isomerization ratio.

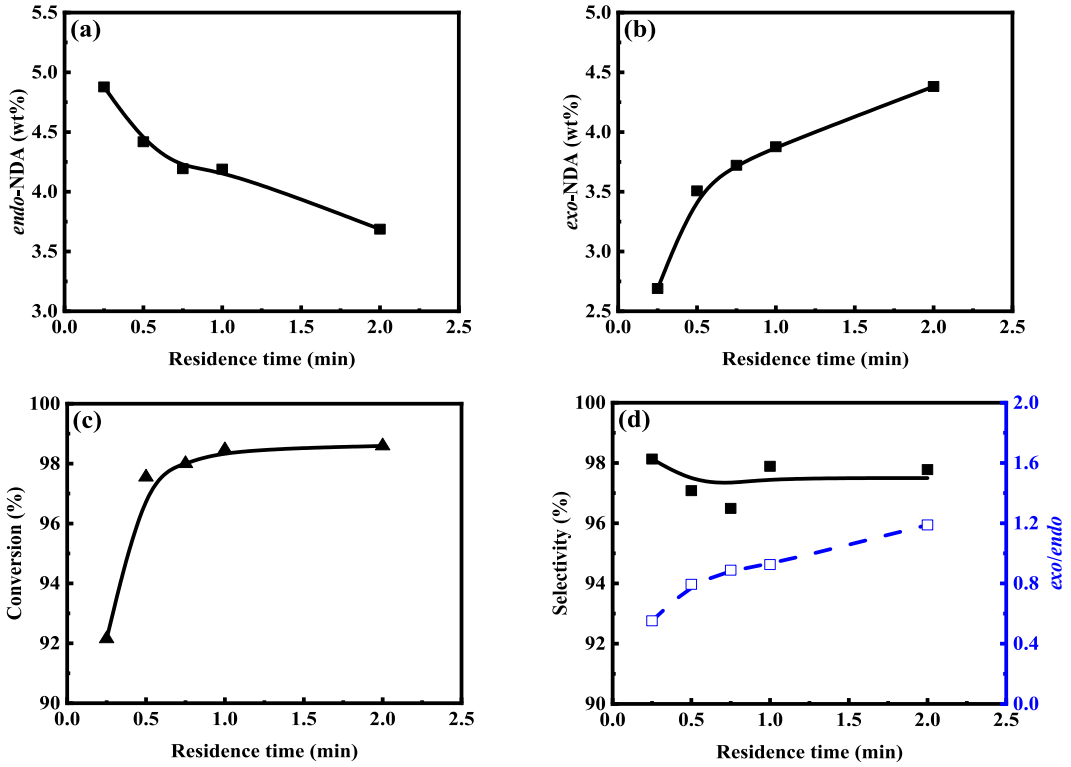


Fig. 6. Effect of residence time on the Diels-Alder reaction (a) the proportion of *endo*-NDA in the sample solution, (b) the proportion of *exo*-NDA in the sample solution, (c) the conversion of DCPD, (d) the selectivity of NDA and *exo/endo* isomerization ratio.

1.19:1, which is almost the same as the theoretical equilibrium distribution ratio (1.11:1). It can be considered that the reaction process in the microchannel reactor has reached equilibrium. It is worth noting that under the premise of the same length of microchannel, with the extension of residence time, the flow rate of fluid gradually slows down, resulting in the increase of the probability that the viscous by-products generated by the reaction adhere to the wall of microchannel, which can block the microchannel. Thus, the residence time should not be too long to avoid the possibility of blockages.

4. Conclusions

Synthesis of NDA from DCPD and MAH in a microchannel reactor was investigated. According to the DFT calculations, the transition state barrier of *exo*-path is higher than that of *endo*-path, leading to a preference for *endo*-isomer products. It is necessary to enhance the formation of *exo*-isomer products by increasing the temperature. In addition, solvent polarity also affects the diastereoselectivity of the reaction. High temperatures can promote the gradual transition of *endo*-NDA generated by kinetic control to *exo*-NDA favored under thermodynamic control. However, at sufficiently high temperature, the difference in energy barrier between the generation and decomposition of NDA in the two configurations could be ignored, resulting in similar proportion of the two isomers in the total product. Excessive or insufficient pressure in the reaction system can elevate byproduct formation, resulting in a decrease in reaction selectivity, as can prolonged residence time. Therefore, controlling system pressure such that the gas phase disappears in the microchannel and optimizing residence time are crucial. Through operational adjustments, the reaction could be carried out to completion within 2 min, the selectivity can reach 98 %, and the ratio of *exo/endo* can approach the equilibrium distribution ratio of the theoretical configuration, with a best case reaching 1.19:1 at 260 °C and 4 MPa.

CRediT authorship contribution statement

Hao Li: Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Xue Liu:** Investigation, Formal analysis, Conceptualization. **Yang Xiao:** Writing – review & editing. **Kun Cao:** Writing – review & editing, Resources, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cej.2024.155561.

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