ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D



# Facile preparation of N-alkyl-2-pyrrolidones in a continuous-flow microreactor

Feng Zhou, Boyu Zhang, Hongchen Liu, Zhenghui Wen, Kejun Wang, and Guangwen Chen

*Org. Process Res. Dev.*, **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.7b00392 • Publication Date (Web): 08 Mar 2018



## Just Accepted



ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

# Facile preparation of N-alkyl-2-pyrrolidones in a continuous-flow microreactor

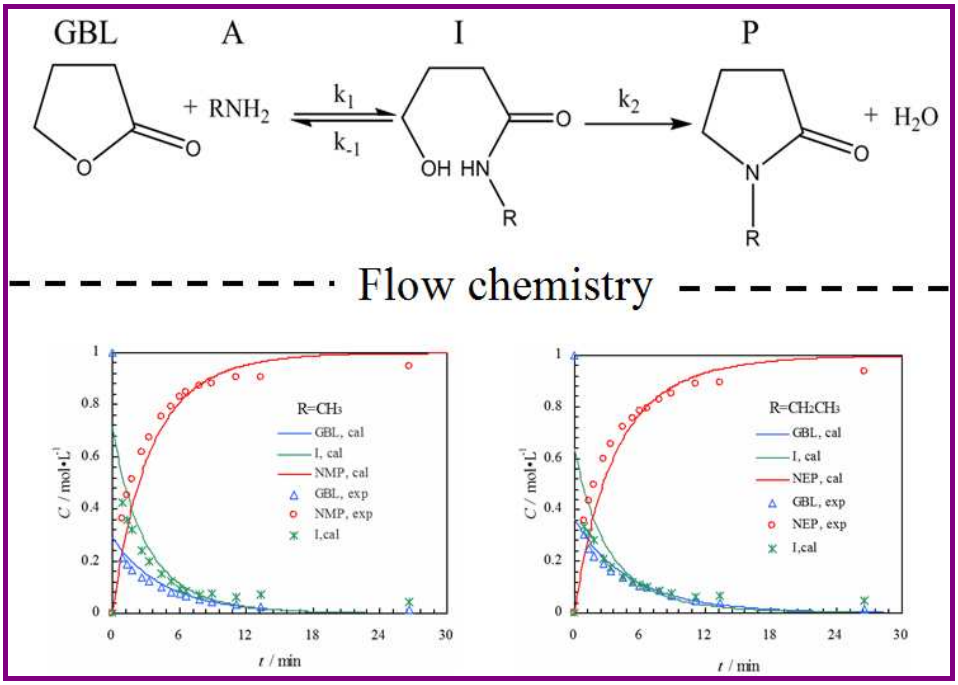
*Feng Zhou[1,2], Boyu Zhang[1], Hongchen Liu[1,2], Zhenghui Wen[1,2], Kejun Wang[1,2], Guangwen Chen[1*]*

[1] Dalian National Laboratory for Clean Energy, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China.

[2] University of Chinese Academy of Sciences, Beijing 100049, China.

* G.W. Chen. E-mails: gwchen@dicp.ac.cn.

**TABLE OF CONTENTS**



**ABSTRACT**

N-alkyl-2-pyrrolidones have been widely used in the petrochemical industry, agricultural chemical industry, for electronic materials, etc. The distinct advantages of using N-alkyl-2-pyrrolidones as solvents or reaction media make them particularly important. A continuous-flow microreactor was exploited for the preparation of N-methyl-2-pyrrolidone (NMP)/N-ethyl-2-pyrrolidone (NEP) in a highly controlled and safe manner; thus, its use improved the efficiency of the process. Various conditions (temperature, residence time, molar ratio of amine to γ-butyrolactone (GBL), GBL concentration, water content and presence of $H_3BO_3$ catalyst) were investigated to improve the synthesis of NMP/NEP. A microreactor was employed for the conversion of GBL to NMP and NEP, and the yields were up to 94.7 % for NMP and 93.9 % for NEP under the optimized conditions. Furthermore, a kinetic model, based on the reaction mechanism, was proposed to guide the design and optimization of the synthesis of NMP/NEP.

**Keywords:** microreactor, kinetic, γ-butyrolactone, N-alkyl-2-pyrrolidone, NMP, NEP

## INTRODUCTION

Thanks to the fundamental work by W. Reppe[1] on acetylene chemistry, pyrrolidones became industrially available and have been widely applied in the petrochemical industry, the agricultural chemical industry, electronic materials, etc.[1-3] In the above applications, N-alkyl-2-pyrrolidones are important solvents, extractants and reaction media. Among N-alkyl-2-pyrrolidones, NMP and NEP are the most versatile industrial solvents due to their unique properties, such as superior solubility, chemical stability, and low volatility.[1,3] Therefore, investigations into the syntheses of NMP and NEP are of great significance from an industrial perspective.

The many practical applications of NMP/NEP in industry have inspired increasing research interest in their syntheses, and various attempts have been made to make the preparation of NMP/NEP less expensive, greener and more efficient.[1-10] In general, there are two main methods for synthesizing NMP/NEP on an industrial scale. One is the catalytic hydrogenation of maleic anhydride, maleic acid or succinic acid with the corresponding primary amine in the presence of a catalyst. Many attempts focusing on developing more effective hydrogenation catalysts have been conducted to optimize this method.[4,5] The second, which involves the condensation of γ-butyrolactone (GBL) with the corresponding primary amine with or without a catalyst, is preferred in industry over the first method. Therefore, much more attention has been focused on improving this synthetic method.[3,6,9,10] For example, Reppe proposed an industrial process, in which both methylamine and GBL served as starting materials in the presence of a dehydrating catalyst, and this method produced NMP in 85~90% yield.[10] Microwave irradiation, a promising strategy for improving these methods, was introduced into the synthesis of NMP/NEP. The work of Jumbam and co-workers showed that a satisfactory yield of NMP could be obtained using highly active copper powder as the catalyst in conjunction with microwave irradiation.[8] Khatri et al. developed a process of reacting a dicarboxylic acid or corresponding anhydride with methylamine by heating via microwave irradiation to obtain an N-methyl imide and then converted the imide to NMP in a second step. Compared to the conventional heating, the reaction time was drastically reduced, and an 85~93 % yield of NMP was achieved.[2]

Although the aforementioned developed processes for the preparation of NMP/NEP have achieved some successes, a few obvious disadvantages including excessively high reaction

temperatures and pressures, long reaction times and safety risks still exist in the processes. These drawbacks would greatly limit the application of these modified synthetic processes from both economic and reaction performance perspectives. The rapid developments in flow chemistry in recent years[11-13] have inspired us to consider utilizing microreactors as effective tools to avoid the existing problems since microreactors possess significant advantages in terms of heat and mass transfer,[14-18] ease of manipulating reaction conditions,[19, 20] productivity,[21] efficiency[22, 23] and safety.[24, 25] Although the industrial syntheses of NMP/NEP have been developed over several decades, the behavior of this reaction system has not been sufficiently explored. Since the behaviors are apt to deviate substantially from the expected reaction conditions once converted to a batch process, exploring the details of the reaction behavior and overcoming the drawbacks in batch-mode when using microreactors are necessary to improve upon the conventional NMP/NEP preparation processes. Moreover, due to the ease of pressurizing microreactors, the boiling point limit can be readily eliminated. Hence, the reaction system can be kept in a superheated status using a safe and simple procedure and operated in an extended temperature range.

In this work, a continuous-flow microreactor was exploited to obtain an improved and more efficient process for preparing NMP/NEP. Various conditions (temperature, residence time, molar ratio of amine to GBL (M-ratio), GBL concentration, water content and presence of $H_3BO_3$ catalyst) were explored under continuous-flow conditions to elucidate the benefits of using a microreactor. A kinetic model was developed to guide the design and optimization of the synthesis of NMP/NEP.

## RESULTS AND DISCUSSION

### Viscosities of GBL/NMP/NEP in glycol

Conventionally, the preparation of NMP/NEP at high temperature must avoid the boiling point limitations of the raw materials by elevating the pressure, which allows the system to operate in the liquid phase. The introduction of glycol, a high-boiling solvent with good intersolubility with the raw materials, into the reaction system could greatly decrease the pressure required to overcome the boiling point limitations, thus making the operation safer. However, glycol is more viscous than many other solvents and the high viscosity could increase energy consumption by the

pump and even increase the risk of blockage. The viscosities of GBL, NMP and NEP in glycol were measured under various conditions (Figure 1).

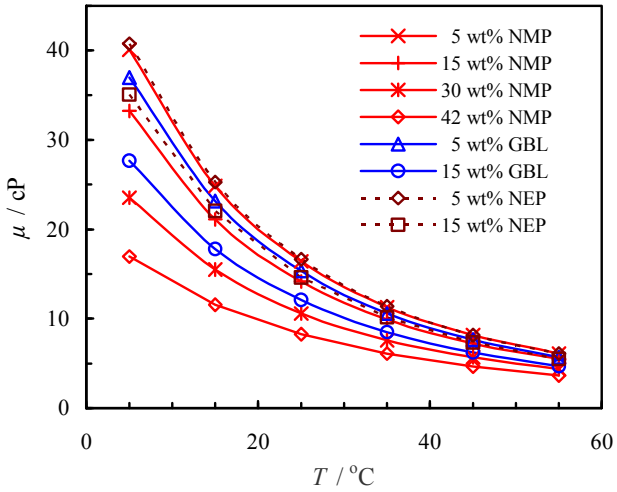
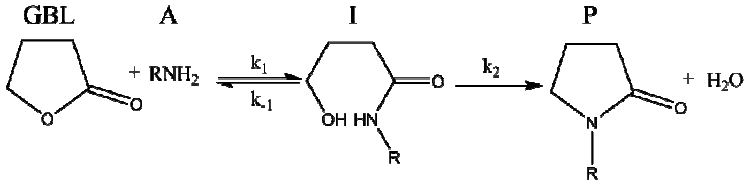



Figure 1. Viscosities of GBL/NMP/NEP in glycol at different temperatures

Both increasing the temperature (from 5 to 55 °C) and increasing the mass fraction of GBL/NMP/NEP in glycol decreased the viscosity and lowered the energy consumed in the delivery of the reagents in the synthesis of NMP/NEP. Moreover, decreasing the viscosity in the reaction system could also increase the rate of heat and mass transfer,[12] allowing the process to operate in a more controlled manner.

**Process optimization by a continuous-flow microreactor**

In both the continuous-flow microreactor and the batch reactor, the reaction between GBL with an amine consists primarily of the following two steps: GBL first reacts with the amine to generate the intermediate N-alkyl-4-hydroxybutyramide, and then the intermediate is cyclized to yield the anticipated product N-alkyl-2-pyrrolidone product with the concomitant elimination of a water molecule (Scheme 1).[8,9] Our efforts focused on a detailed exploration of various reaction conditions to clarify the synthesis of NMP/NEP in the continuous-flow microreactor.




Scheme 1

Considering that noncatalytic syntheses of NMP and NEP from GBL and the corresponding amine are commonly conducted at high temperatures and pressures,[3,9] the temperature in the 220~300 °C range were screened at 750 psi to elucidate the temperature dependence of the synthesis of NMP/NEP in a continuous-flow microreactor (Figure 2). The microreactor guaranteed the synthesis would be safer and more reliable than its batch counterparts, which are conducted under harsh conditions. Elevation of the temperature had a minor influence on GBL conversion (*X*) but caused a dramatic increase in the yield (*Y*) of NMP/NEP. As the temperature was increased from 220 °C to 300 °C, the GBL conversion increased by approximately 18 %, while the NMP/NEP yield increased by approximately 70 %. The sharp temperature dependence of the NMP/NEP yield clearly indicated the presence of a well-defined energy barrier in the conversion from the imide intermediate to NMP/NEP. Moreover, the GBL conversion for the preparation of NMP was slightly higher than that of GBL to NEP, which shows methylamine is more reactive than ethylamine.

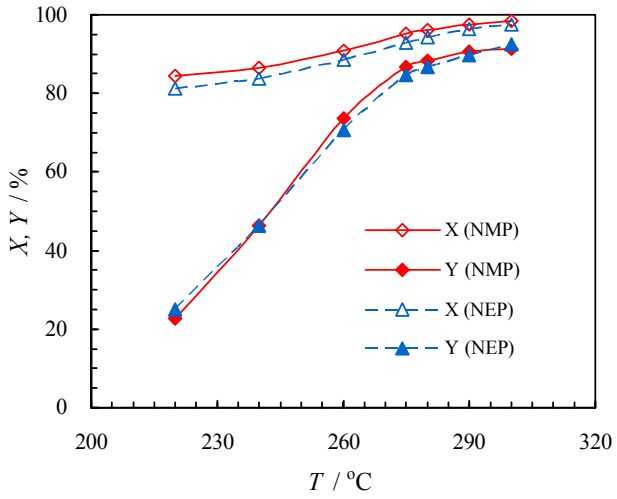



Figure 2. The temperature dependence of the preparation of NMP/NEP in a continuous-flow microreactor. Reaction conditions: reaction temperature 220~300 °C, residence time 13.3 min, GBL concentration 1.00 mol/L, and M-ratio 1.2.

Figure 3 shows the influence of the residence time on the GBL conversion and NMP/NEP yield. With increasing residence time, the GBL conversion and NMP/NEP yield initially increased and then plateaued. For example, 79 % GBL conversion (NEP) and 47 % NEP yield could be obtained in the initial 2.7 min, but in the next 23.9 min the GBL conversion (NEP) and NEP yield

increased by only 18 % and 44 % respectively. This result was mainly caused by the decrease in the GBL concentration with the increase of residence time, which resulted in the sharp decrease in reaction rate.

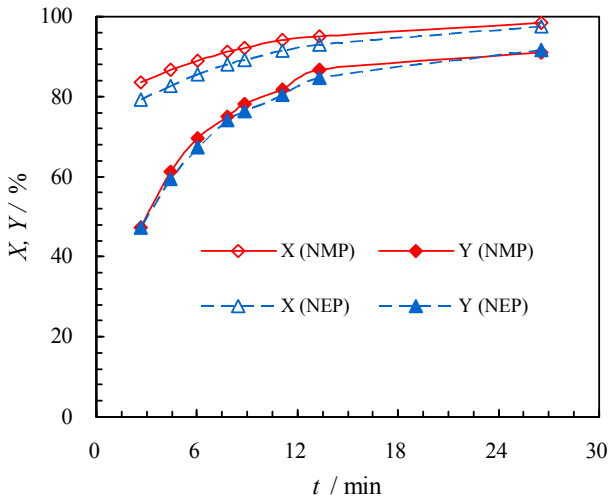



Figure 3. Investigation of residence time dependence of the synthesis of NMP/NEP in a continuous-flow microreactor. Reaction conditions: reaction temperature 275 °C, residence time 0~26.6 min, GBL concentration 1.00 mol/L, and M-ratio 1.2.

Methylamine and ethylamine in the experiments were used as aqueous solutions, thus it was necessary to investigate the effect of the water content ($W_C$) on the reaction. In our experiments, elevating the $W_C$ had no significant impact on either the conversion of GBL or the yield of NMP/NEP; the examined $W_C$ range was 5.65 ~ 8.43 mol/L for the synthesis of NMP and 1.39 ~ 8.43 mol/L for the synthesis of NEP (Figure 4). The GBL conversion and NMP/NEP yield remained constant with slight fluctuations, indicating that the reaction rate for the conversion from imide to NMP/NEP was far greater than that of the reverse process.

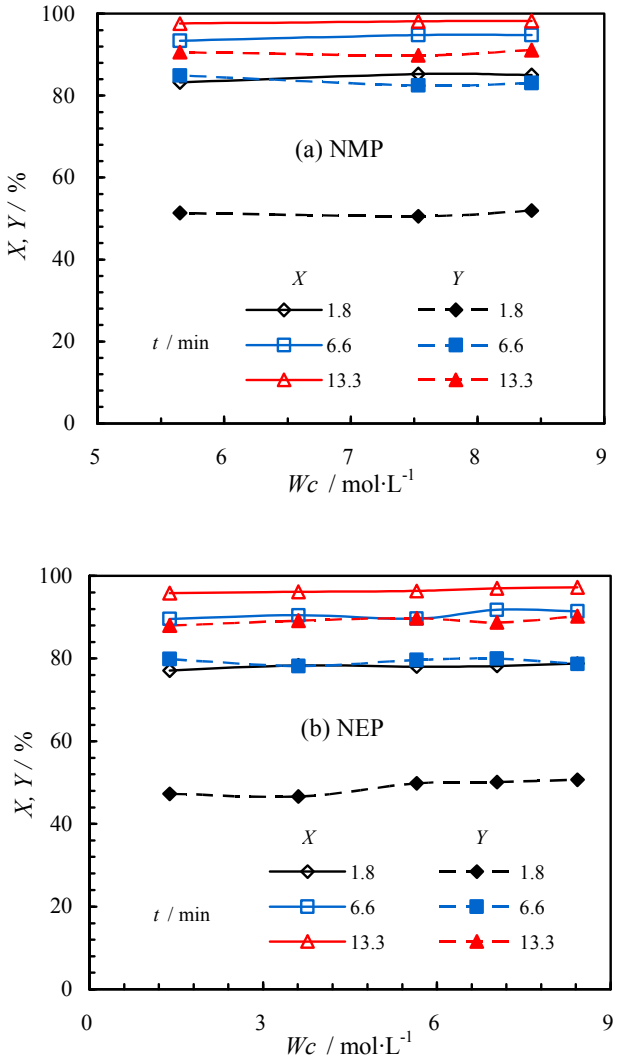


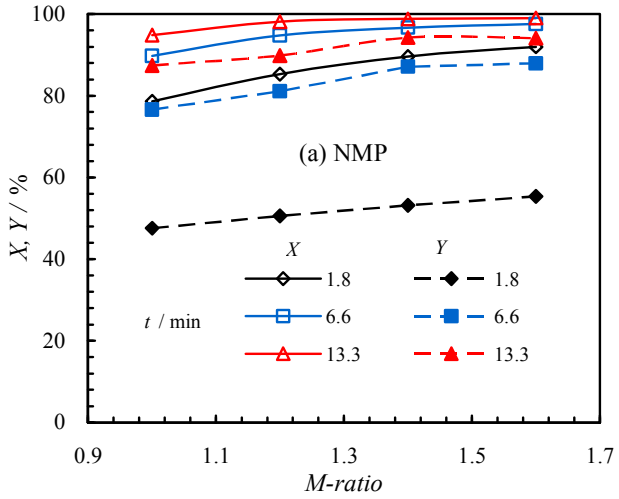

Figure 4. The effects of the $W_C$ on the syntheses of (a) NMP and (b) NEP under continuous-flow conditions. Reaction conditions: reaction temperature 290 °C, residence time 0~13.3 min, GBL concentration 1.00 mol/L, and M-ratio 1.2.

The screening of the M-ratio in the range 1.0~1.6 range at various residence times showed that the condensation of the amine with GBL was not sensitive to an increase in the M-ratio; only slight increases in the GBL conversion and the yield of NMP/NEP were observed then the M-ratio was increased from 1.0 to 1.6 (Figure 5). A slight excess of amine (e.g., M-ratio 1.2) was adequate for the preparation of NMP/NEP.

The GBL concentration was varied at various temperatures to elucidate the influence of GBL concentration on the reaction performance (Figure 6). Increasing the GBL concentration

noticeably increased both the GBL conversion and NMP/NEP yield, which was consistent with our expectations. A high GBL concentration could also lead to a high space-time yield. Nevertheless, an excessively high concentration of GBL could increase the risk of system instability due to the low boiling points of the amine and water.

Considering that a previous study found that a small amount of $H_3BO_3$ was beneficial for forming amides from carboxylic acids and amines,[26] the influence of the catalyst ($H_3BO_3$) on the synthesis of NMP/NEP under continuous-flow conditions was explored (Figure 7). As shown in the figure, the addition of $H_3BO_3$ did not cause a dramatic improvement in the reaction performance, and only a slight increase in the GBL conversion was obtained. This result might be because the acceleration of the reaction rate caused by the addition of $H_3BO_3$ was masked by the effect of the increased reaction temperature. Therefore, the addition of $H_3BO_3$ under continuous-flow conditions was deprecated to make the process be more environmentally friendly.



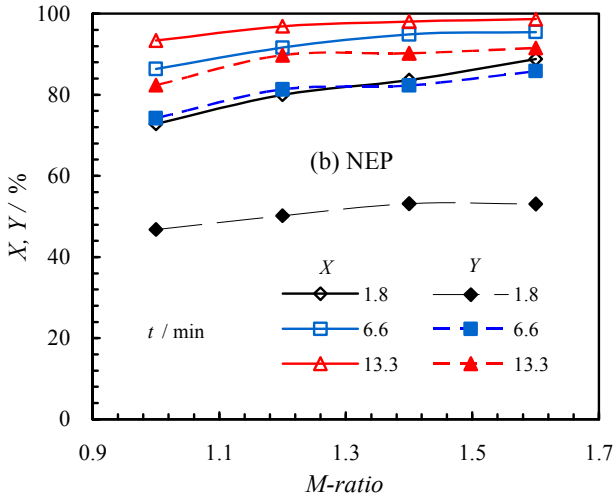
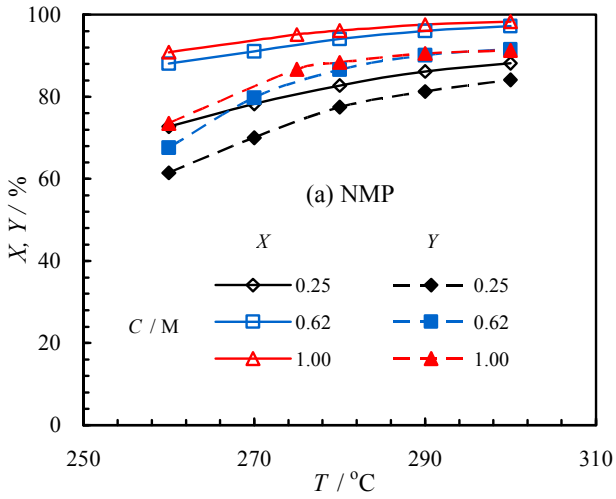



Figure 5. Screening of the M-ratio for the syntheses of (a) NMP and (b) NEP under continuous-flow conditions. Reaction conditions: reaction temperature 290 °C, residence time 0~13.3 min, GBL concentration 1.00 mol/L, and M-ratio 1.0~1.6.



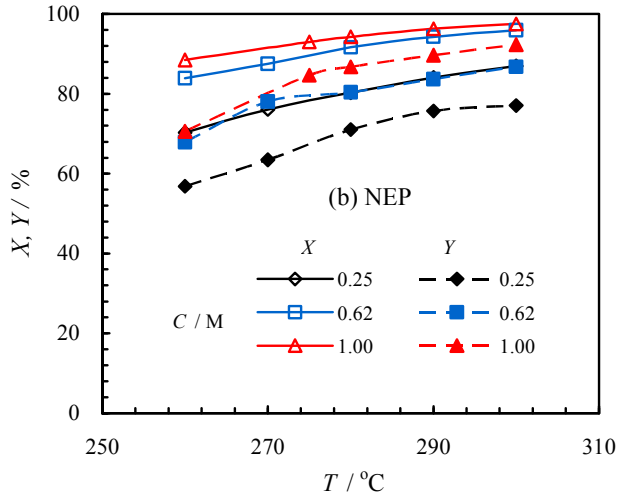
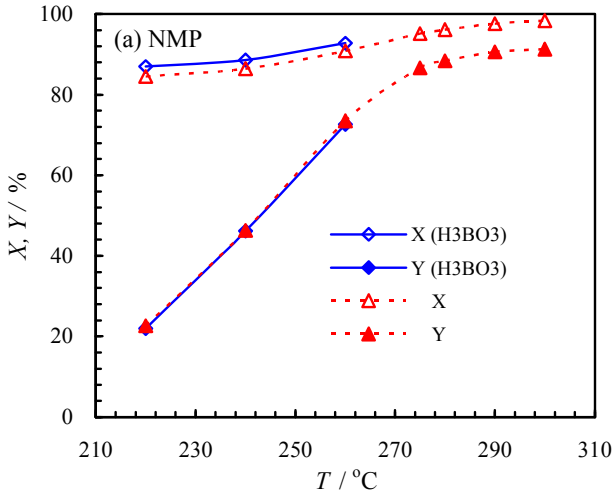



Figure 6. Influence of the GBL concentration on the syntheses of (a) NMP and (b) NEP under continuous-flow conditions. Reaction conditions: reaction temperature 260~300 °C, residence time 13.3 min, GBL concentration 0.25~1.00 mol/L, and M-ratio 1.2.



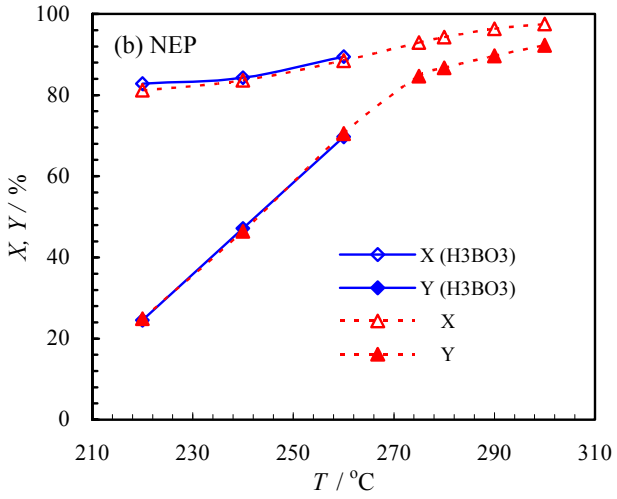



Figure 7. The influence of the catalyst ($H_3BO_3$) on the syntheses of (a) NMP and (b) NEP under continuous-flow conditions. Reaction conditions: reaction temperature 220~300 °C, residence time 13.3 min, GBL concentration 1.00 mol/L, M-ratio 1.2, and $H_3BO_3$: 2.4 % ( mole fraction based on GBL).

***Experimental and kinetic modeling investigation***

To investigate the kinetics of the synthesis of N-alkyl-2-pyrrolidone, a reasonable kinetic model should be first established based on the reaction mechanism (Scheme 1). Since as previously discussed, the $W_C$ had no significant impact on the reaction performance, the reverse reaction from NMP/NEP to intermediate was not considered in the kinetic modeling. Accordingly, a kinetic model was proposed that involved the reactants (GBL and alkylamine (**A**)) combining in a reversible way to form an intermediate (**I**), and then **I** further dehydrated to generate the N-alkyl-2-pyrrolidone (**P**). Based on the results of the investigations conducted under the above reaction conditions, the dehydration step was the rate-determination step, and $k_1+k_{-1}>>k_2$. Therefore, a pre-equilibrium between GBL, **A** and **I** could be established and the reaction rate from **I** to **P** was too slow to affect the maintenance of the pre-equilibrium (Hypothesis 1).[27,28] Thus, the equilibrium constant, $K$, of GBL, **A** and **I** can be described by Equation (1).

$$K = \frac{c_1}{c_{\mathrm{GBL}} c_{\mathrm{A}}} = \frac{k_1}{k_{-1}} \quad (1)$$

The rate of the formation of **P** was derived as follows:

$$\frac{\mathrm{d}c_{\mathbf{P}}}{\mathrm{d}t} = k_2 c_{\mathbf{I}} = k_2 K c_{\mathrm{GBL}} c_{\mathbf{A}} \tag{2}$$

where $k_i$ was the rate constant for reaction $i$. According to the Arrhenius equation and the van't Hoff equation, $k_i$ and $K$ can be described by Equations (3) and (4).

$$\ln k_i(T) = -\frac{E_i}{RT} + \ln A_i \tag{3}$$

$$\ln K(T) = -\frac{\Delta H^{\phi}}{RT} + \frac{\Delta S^{\phi}}{R} \tag{4}$$

In the above equations, $A_i$ and $E_i$ denote pre-exponential factor and activation energy ($\mathrm{kJ \cdot mol^{-1}}$), respectively, $R$ is the universal gas constant (8.314 $\mathrm{J \cdot mol^{-1} \cdot K^{-1}}$), $T$ is the absolute temperature (K), $\Delta H^{\Phi}$ represents the standard molar enthalpy change ($\mathrm{kJ \cdot mol^{-1}}$) and $\Delta S^{\Phi}$ the standard molar entropy change ($\mathrm{J \cdot mol^{-1} \cdot K^{-1}}$).

To determine the changes in the concentrations of the reagents over time, the kinetic experiments were performed in the continuous-flow microreactor at 260, 275 and 290 °C with the concentration of GBL and amine being 1.0 $\mathrm{mol \cdot L^{-1}}$ and 1.2 $\mathrm{mol \cdot L^{-1}}$, respectively. Figure 8 shows the experimental data from the given conditions, and the remaining data are given in the Supporting Information (Figure S1). High selectivity for NMP/NEP was achieved when the residence time was increased to 26.6 min at 290 °C. Meanwhile, a 94.7 % yield of NMP (Figure 8(a)) and 93.9 % yield of NEP (Figure 8(b)) could be achieved within 26.6 min at 290 $^{\mathrm{o}}$C. Therefore, intermediate **I** can be considered as the sole byproduct in the reaction (Hypothesis 2). Then, the concentration of **I** can be calculated by mass balance.

According to Scheme 1, the consumption of **A** and GBL was equivalent, so the concentrations of the reaction species can be described as follows:

$$c_{\mathbf{A}} = c_{\mathrm{GBL}} + c_{\mathbf{A}0} - c_{\mathrm{GBL0}} \tag{5}$$

where $c_{\mathbf{A}0}$ and $c_{\mathrm{GBL0}}$ are the initial concentrations of **A** and GBL, respectively.

Substituting Equation (5) into Equation (1), the **I** concentration can be written as the following:

$$c_{\mathbf{I}} = K c_{\mathrm{GBL}}^2 + K c_{\mathrm{GBL}} c_{\mathbf{A}0} - K c_{\mathrm{GBL}} c_{\mathrm{GBL0}} \tag{6}$$

Based on the mass balance, the concentration of **P** can be expressed as Equation (7).

$$c_{\mathbf{P}} = c_{\mathrm{GBL}0} - c_{\mathrm{GBL}} - c_{\mathbf{I}} \tag{7}$$

Combining Equations (6) and (7), the concentration of **P** can be written as Equation (8).

$$c_{\mathbf{P}} = c_{\mathrm{GBL}0} - (Kc_{\mathbf{A}0} - Kc_{\mathrm{GBL}0} + 1)c_{\mathrm{GBL}} - Kc_{\mathrm{GBL}}^2 \tag{8}$$

Substituting Equations (5) and (8) into Equation (2) gives the following:

$$\frac{\mathrm{d}c_{\mathrm{GBL}}}{\mathrm{d}t} = -\frac{k_2 Kc_{\mathrm{GBL}}(c_{\mathrm{GBL}} + c_{\mathbf{A}0} - c_{\mathrm{GBL}0})}{2Kc_{\mathrm{GBL}} + Kc_{\mathbf{A}0} - Kc_{\mathrm{GBL}0} + 1} \tag{9}$$

To fit the equation, the initial equilibrium concentration of GBL should be obtained according to Equation (1). The relationship between the initial equilibrium concentration of **A**, **I** and GBL ($c^*_{\mathbf{A}0}, c^*_{\mathbf{I}0}$ and $c^*_{\mathrm{GBL}0}$) can be expressed as the following:

$$c^*_{\mathbf{A}0} = c^*_{\mathrm{GBL}0} + c_{\mathbf{A}0} - c_{\mathrm{GBL}0} \tag{10}$$

$$c^*_{\mathbf{I}0} = c_{\mathrm{GBL}0} - c^*_{\mathrm{GBL}0} \tag{11}$$

Combining Equations (1), (10) and (11), the initial equilibrium concentration of GBL can be calculated from Equation (12).

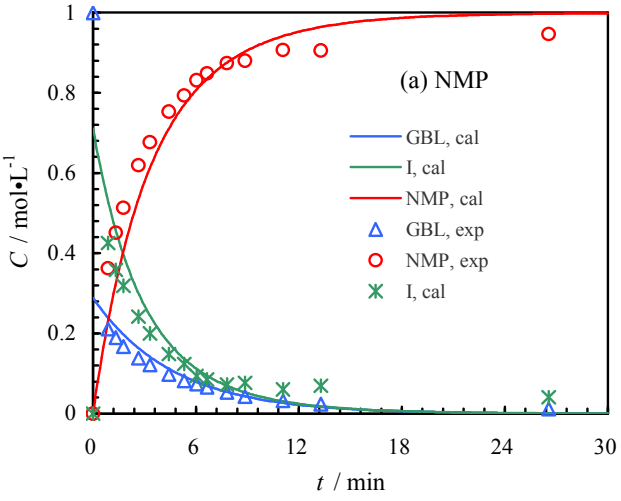
$$c^*_{\mathrm{GBL}0} = \frac{Kc_{\mathrm{GBL}0} - Kc_{\mathbf{A}0} - 1 + \sqrt{(Kc_{\mathbf{A}0} - Kc_{\mathrm{GBL}0} + 1)^2 + 4Kc_{\mathbf{A}0}}}{2K} \tag{12}$$

The equilibrium constant, *K*, was first determined by Equation (1) based on the experimental data (Figure 9). As shown in the figure, Hypothesis 1 caused the red points within 3 min, which is a significant deviation from the kinetic model, while Hypothesis 2 caused the red points beyond 8 min. For example, methylamine was more reactive than ethylamine in the preparation of NMP/NEP, which should cause a smaller deviation from Hypothesis 1. For this reason, the red points within 3 min that significantly deviated from the kinetic model also appeared in the kinetic model of NEP. All the red points were excluded in the determination of *K*. The corresponding fitted *K* values at different temperatures are listed in Table 1. According to these results, increasing the reaction decreased the value of *K*, indicating that the forward reactions from GBL to **I** were exothermic. Afterwards, $k_2$ for NMP/NEP was obtained according to Equation (9) by fitting experimental data, and the applied initial concentrations were the initial equilibrium concentrations of GBL. The fitted rate constant $k_2$ values at different temperatures are listed in Table 1.

The fitted $K$ and $k_2$ values at different temperatures were employed to construct a van't Hoff plot and an Arrhenius plot (Figure 10) according to Equations (3) and (4), respectively. The reaction enthalpy ($\Delta H^{\Phi}$) and entropy ($\Delta S^{\Phi}$) for the van't Hoff correlation and the activation energy ($E_2$) and pre-exponential factor ($A_2$) for the Arrhenius correlation could be obtained from the slope and intercept, respectively. The results are given in Table 2.

Based on the obtained kinetic parameters, the corresponding equilibrium constants, $K$, and rate constants, $k_2$, of the kinetic model at 260, 275 and 290 °C were calculated. Then, the kinetic model was applied to calculate the reagent concentrations versus residence time for NMP/NEP (Figures 8 and S1, solid lines). As shown in the figures, the calculated values were in good agreement with the experimental values. The deviation between the measured and calculated results was mainly due to the hypotheses employed in the kinetic model.

The kinetic model was applied to predict the conversion of GBL and yield of NMP/NEP at different initial GBL concentrations and reaction temperatures to investigate the validity of the model. The values predicted by the above kinetic model were compared with the observed experimental data as shown in Figure 11. The model represents the data reasonably well, with ±10 % errors, which confirmed that it can effectively guide the preparation of NMP/NEP. In addition to NMP and NEP, the other N-alkyl-2-pyrrolidones including N-octyl-2-pyrrolidone, N-dodecyl-2-pyrrolidone and N-(2-hydroxyethyl)-2-pyrrolidone are of practical application value.[1] The kinetic model proposed in this paper could be well applied to their syntheses processes if the reactions are well consistent with the hypotheses adopted in this kinetic model.



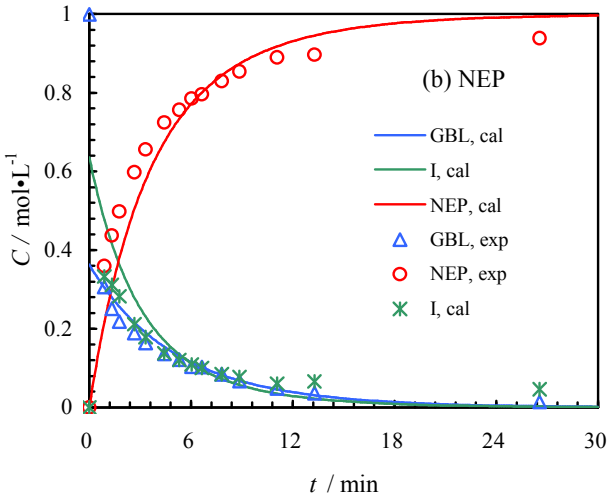



Figure 8. Comparison of measured and calculated concentrations versus residence time at different temperatures for (a) NMP and (b) NEP. Reaction conditions: reaction temperature 290 °C, residence time 0~26.6 min, GBL concentration 1.00 mol/L, and M-ratio 1.2.

Table 1. Equilibrium constants, $K$, and kinetic rate constants, $k_2$, for the syntheses of NMP and NEP

| Temperature | $K$ (NMP) | $K$ (NEP) | $k_2$ (NMP) | $k_2$ (NEP) |
|---|---|---|---|---|
| °C | L·mol$^{-1}$ | L·mol$^{-1}$ | min$^{-1}$ | min$^{-1}$ |
| 260 | 7.12 | 4.86 | 0.152 | 0.132 |
| 275 | 5.92 | 3.87 | 0.261 | 0.226 |
| 290 | 5.05 | 3.10 | 0.425 | 0.456 |

Table 2. van't Hoff and Arrhenius parameters determined from the current work

| Category | van't Hoff | | Arrhenius | |
|---|---|---|---|---|
| | $\Delta H^{\Phi}$ | $\Delta S^{\Phi}$ | $E_2$ | $A_2$ |
| | kJ·mol$^{-1}$ | J·mol$^{-1}$·K$^{-1}$ | kJ·mol$^{-1}$ | |
| NMP | -28.60 | -37.34 | 85.58 | $3.70\times10^{7}$ |
| NEP | -37.41 | -57.01 | 102.74 | $1.49\times10^{9}$ |

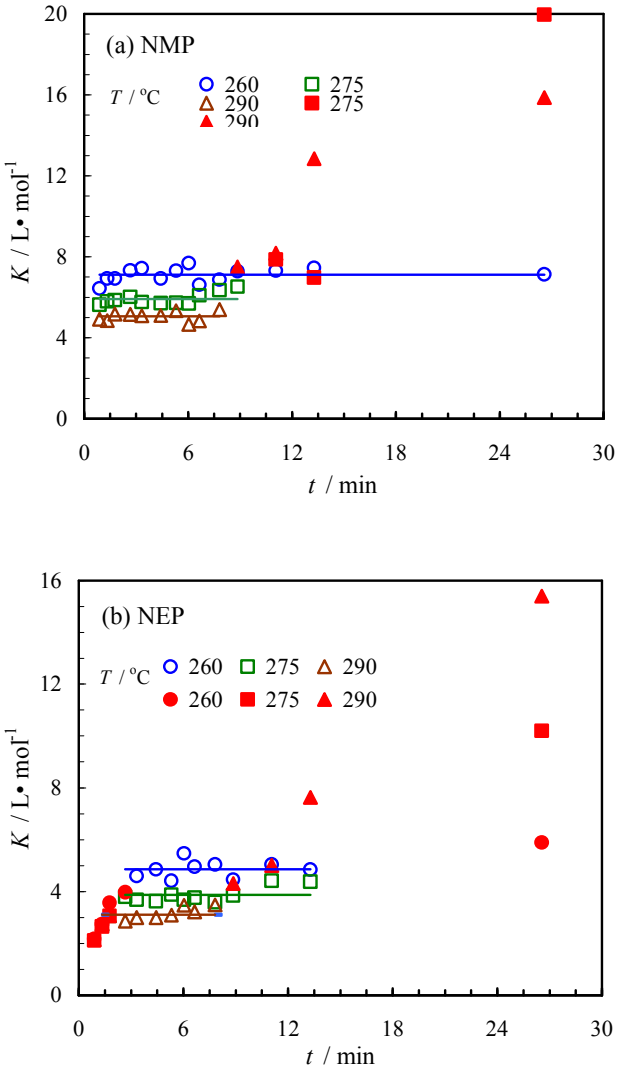



Figure 9. Estimated equilibrium constants, *K*, from the kinetic model for (a) NMP and (b) NEP at different temperatures

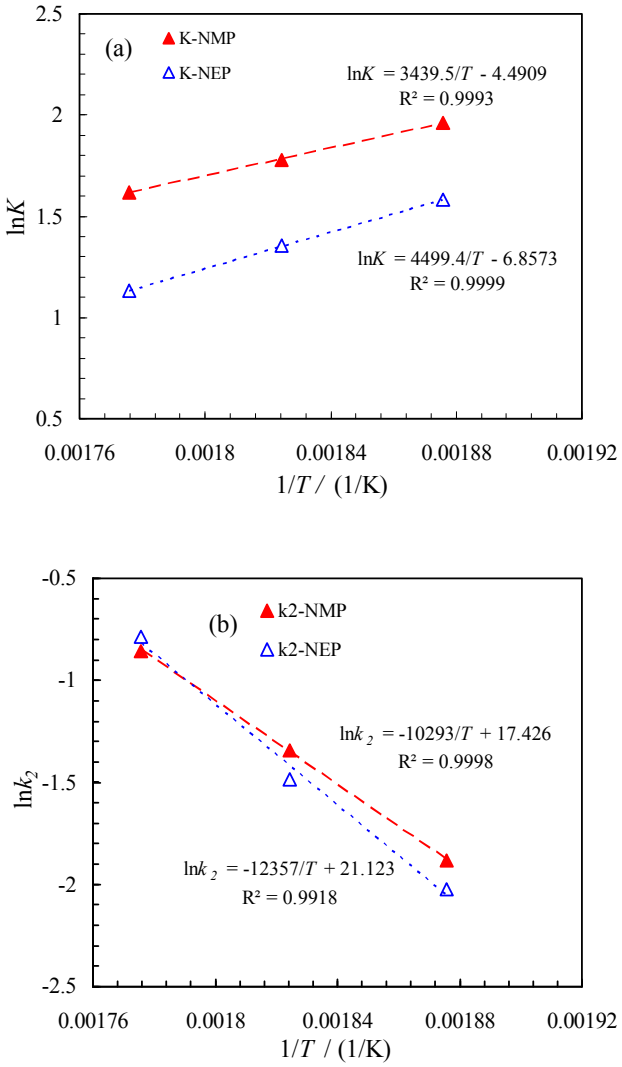



Figure 10. (a) van't Hoff correlation between the temperature and equilibrium constant, $K$; (b) Arrhenius correlation between the temperature and rate constant, $k_2$

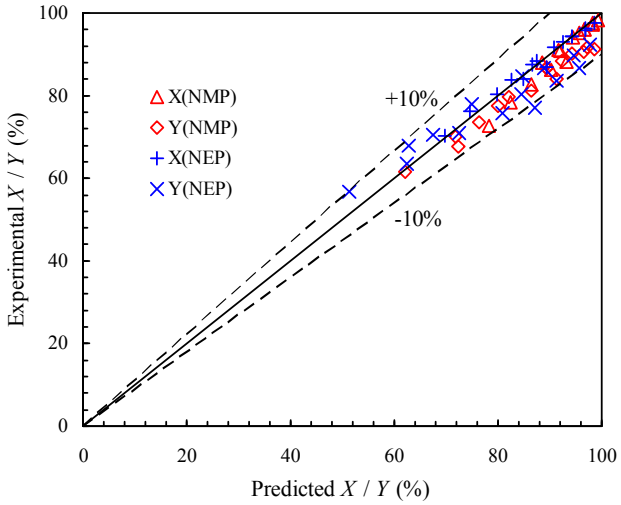



Figure 11. Comparison of experimental and predicted GBL conversion ($X$) and NMP/NEP yield ($Y$)

## CONCLUSION

A novel continuous-flow strategy was developed for the synthesis of NMP/NEP in a highly controlled and safe manner to improve the process efficiency. Various conditions (temperature, residence time, M-ratio, GBL concentration, $W_C$ and presence of $H_3BO_3$ catalyst) were explored under continuous-flow conditions to elucidate the synthesis of NMP/NEP. Up to 94.7 % yield of NMP and 93.9 % yield of NEP could be achieved in the continuous-flow microreactor with a GBL concentration of 1.00 mol·L$^{-1}$ and an amine concentration of 1.20 mol·L$^{-1}$ at 26.6 min and 290 °C. The preparation of NMP/NEP using microreactors could be easily applied to a larger scale reaction by simply numbering-up. In addition, the kinetic model, proposed based on the reaction mechanism were proved to be valid for guiding the design and optimization of the preparation of NMP/NEP.

## EXPERIMENTAL SECTION

All chemicals were purchased from commercial sources and were used without further purification. The contents of methylamine and ethylamine in their aqueous solutions were determined by titration. The viscosities were measured by a viscometer from Brookfield. Gas chromatography analyses were carried out on an Agilent 7890A gas chromatography. The conditions for gas chromatography were as follows: PEG-20 M column 30 m × 0.32 mm × 0.5 μm,

carrier gas: nitrogen, injection temperature: 260 °C, detector temperature: 270 °C, and oven temperature: 150 °C (1 min hold ) to 260 °C ( 20 °C / min, 1 min hold ).

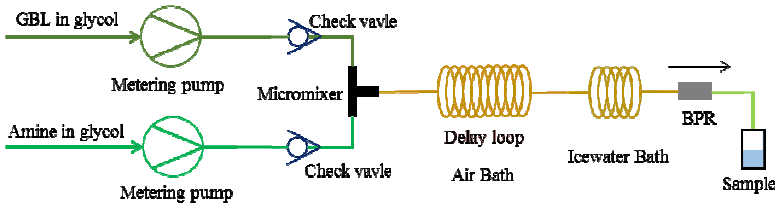



Figure 12 Schematic overview of the continuous-flow microreactor system for the preparation of NMP/NEP

A schematic overview of the continuous-flow microreactor system for the preparation of NMP/NEP is shown in Figure 12. In the experiments, both aqueous methylamine/ethylamine and GBL were dissolved in glycol and delivered into the system by metering pumps (Series II pump, Chrom. Tech. Inc., USA). The check valves were installed in the reaction system to prevent the reverse flow of the reactants. The mixing was performed in a stainless steel T-shaped mixer with a 1.2 mm diameter through-hole. The mixing time was in the order of hundreds of milliseconds,[29, 30] which was far less than the reaction time and thus could be neglected in the analysis. A stainless steel delay loop (internal diameter 0.6 mm) was directly connected to the micromixer to serve as the reactor channel for the synthesis of NMP/NEP. The whole delay loop was divided into two sections. One section was the reaction loop, which was 9.4 m long and was immersed in the air bath to control the reaction temperature. The other section was the termination loop, which was 0.5 m long and immersed in an ice water bath to quench the reaction. The reaction system was pressurized to 750 psi by a back-pressure valve to avoid the boiling point limitations. The residence time inside the reaction loop was accurately controlled by altering the flow velocity. Among all employed flow conditions, the Reynolds number for the reaction mixture in the delay loop was between 0.5 and 30, indicating laminar flow inside the microreactor. During the experiments, the quenched samples were collected for analysis after the system reached the steady state. All samples were analyzed by GC 7890A with an FID detector.

## AUTHOR INFORMATION

Corresponding Author

*E-mail address: gwchen@dicp.ac.cn

## NOTES

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

Authors would like to thank Hengqiang Li and Jiansheng Chu (engineers in our research group) for their help in the fabrication of microreactor and the building of experimental setup. We gratefully acknowledge the financial supports for this project from National Natural Science Foundation of China (Nos. U1608221, 21506205 and U1662124), DICP (ZZBS201706), the Youth Innovation Promotion Association CAS (No. 2017229) and the STS program of CAS.

## SUPPORTING INFORMATION

Supporting Information Available: Comparison of measured and calculated concentrations versus residence time at 260 and 275 °C for NMP/NEP.

## REFERENCES

[1] Harreus, A. L.; Backes, R.; Eichler, J. -O.; Feuerhake, R.; Jäkel, C.; Mahn, U.; Pinkos, R.; Vogelsang, R. *2-Pyrrolidone. In Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA, 2011.

[2] Khatri, P. K.; Jain, S. L.; etc. Process for microwave assisted synthesis of N-methyl pyrrolidone. Patent US 9090560, July 28, 2015.

[3] Schmidtke, H.; Versch, R.; etc. Process for continuously preparing N-ethyl-2-pyrrolidone (NEP). Patent US 7994350, August 9, 2011.

[4] Bergfeld, M.; Wiesgickl, G. Process for producing pyrrolidone and N-alkyl pyrrolidones. Patent US 5478950, December 26, 1995.

[5] Bergfeld, M.J.; Uihlein, K. Process for manufacturing 2-pyrrolidone or N-alkylpyrrolidones. Patent US 6008375, December 28, 1999.

[6] Bertola, A. Process for the production of N-methyl pyrrolidone. Patent US 6248902, June 19, 2001.

[7] Jiarong, Z.; Mao, H.; etc. Method for producing of ultra-clean and high-purity N-methyl

pyrrolidone, Patent US 8519157, August 27, 2013.

[8] Jumbam, N. D.; Phuthuma, L.; Ndebvu, R.; Ngarivhume, T. S. *Afr. J. Chem.* **2011**, *64*, 42-43.

[9] Yoon, Y. S.; Shin, H.K.; Kwak, B. S. *Catal. Commun.* **2002**, *3* (8), 349-355.

[10] Reppe, W. *Chem. Ing. Tech.* **1950**, *22*, 361-373.

[11] Wirth, T. *Microreactors in Organic Synthesis and Catalysis*; Wiley-VCH: Weinheim, 2008.

[12] Dietrich, T. *Microchemical Engineering in Practice*; John Wiley & Sons: Hoboken, NJ, 2011.

[13] Noël, T.; Su, Y. H.; Hessel V. *Beyond organometallic flow chemistry: The principles behind the use of continuous-flow reactors for synthesis. In Organometallic Flow Chemistry*; Springer International Publishing, 2015.

[14] Cao, H.S.; Chen, G.W.; Yuan, Q. *Ind. Eng. Chem. Res.* **2009**, *48* (9), 4535-4541.

[15] Chen, Y.Z.; Zhao, Y.C.; Han, M.; Ye, C.B.; Dang, M.H.; Chen, G.W. *Green Chem.* **2013**, *15* (1), 91-94.

[16] Chen, Y.Z.; Su, Y.H.; Jiao, F.J.; Chen, G.W. *RSC Adv.* **2012**, *2* (13), 5637-5644.

[17] Shen, J.N.; Zhao, Y.C.; Chen, G.W.; Yuan, Q. *Chin. J. Chem. Eng.* **2009**, *17* (3), 412-418.

[18] Wen, Z.H.; Jiao, F.J.; Yang, M.; Zhao, S.N.; Zhou, F.; Chen, G.W. *Org. Process Res. Dev.* **2017**, *21* (11), 1843-1850.

[19] Zaborenko, N.; Bedore, M.W.; Jamison, T.F.; Jensen, K.F. *Org. Process Res. Dev.* **2011**, *15* (1), 131-139.

[20] Laue, S.; Haverkamp, V.; Mleczko, L. *Org. Process Res. Dev.* **2016**, *20* (2), 480-486.

[21] Falss, S.; Tomaiuolo, G.; Perazzo, A.; Hodgson, P.; Yaseneva, P.; Zakrzewski, J.; Guido, S.; Lapkin, A.; Woodward, R.; Meadows, R.E. *Org. Process Res. Dev.* **2016**, *20* (2), 558-567.

[22] Newman, S. G.; Jensen, K. F. *Green Chem.* **2013**, *15* (6), 1456-1472.

[23] Wiles, C.; Watts, P. *Green Chem.* **2014**, *16* (1), 55-62.

[24] Ge, H.; Chen, G.W.; Yuan, Q.; Li H.Q. *Chem. Eng. J.* **2007**, *127* (1), 39-46.

[25] Ge, H.; Chen, G.W.; Yuan, Q.; Li H.Q. *Catal. Today.* **2005**, *110* (1), 171-178.

[26] Tang, P. *Org. Synth.*, **2005**, *81*, 262-272.

[27] Wright, M. R. *An Introduction to Chemical Kinetics*; John Wiley & Sons: Hoboken, NJ, 2004.

[28] Atkins, P.; Julio, P. *Atkins' Physical Chemistry(8th Eds)*; Oxford University Press: New York, 2006.

[29] Falk, L.; Commenge, J. -M. *Chem. Eng. Sci.* **2010**, *65* (1): 405-411.

[30] Falk, L.; Commenge, J. -M. *Characterization of Mixing and Segregation in Homogeneous Flow Systems. In Micro Process Engineering: A Comprehensive Handbook*; Wiley-VCH: Weinheim, 2008.