

A CONTINUOUS SYNTHESIS METHOD OF HYDROXYLMETHYL PHOSPHONATES USING THE MICROFLUIDIC REACTOR

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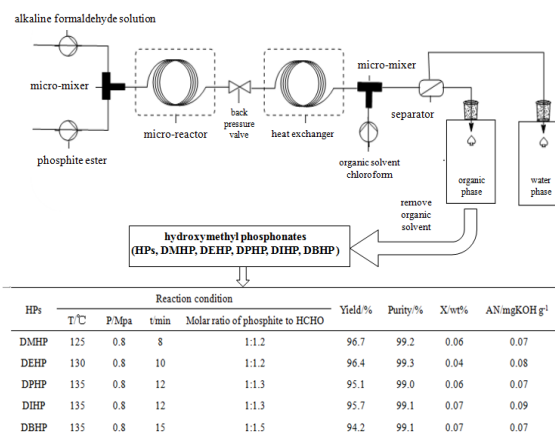
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Hydroxymethyl phosphonates (HPs) are important organic chemical raw materials and intermediates. HPs are generally synthesized by phosphite esters and formaldehyde using the conventional organic synthesis device. It shows the disadvantages of strong heat-release and more by-products for the reaction, and high acid number (AN), low yield and low purity for the product. We have designed a microfluidic reactor to synthesize HPs that can overcome above mentioned disadvantages. During the microfluidic reaction process, a series of reaction conditions can be controlled precisely. According to adopt the optimal reaction conditions, five HPs were obtained with low AN (<0.15 mg KOH/g), high yield (>94%) and high purity (>99%). The designed microfluidic reactor can reduce labor cost, save equipment area, and cut down the amount of wastewater. The synthesis process can also realize continuous production and scale-up production with no amplification effect.



INTRODUCTION

Hydroxymethyl phosphonates (HPs) are important organic chemical raw materials and intermediates, widely used in medicine,¹⁻³ pesticide,^{4,5} fine chemical industry for production of organic phosphoric acid corrosion inhibitors, plastic auxiliaries, dye additives, lubricant additives, adhesives and flame retardants.⁶⁻⁹ For example, dimethyl hydroxymethyl

phosphonate (DMHP) was used for synthesis of herbicide glyphosate.⁴ Diethyl hydroxymethyl phosphonate (DEHP) was used to synthesize tenofovir dipivoxil and adefovir dipivoxil as anti-HIV and anti-HBV drugs.^{10,11} HPs were mainly prepared by hydroxymethylation reaction using phosphite esters and formaldehyde (HCHO) as the starting materials. Under the traditional synthetic technology in the conventional reactor, the molar ratio of raw materials (phosphite ester

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and HCHO) ranged from 1:1.0 to 1:1.3, reaction temperature ranged from 100 °C to 120 °C, reaction pressure ranged from 3 kPa to 5 kPa, and reaction time ranged from 1h to 5 h.¹²⁻¹⁴ Because the reaction was extremely exothermic, the targeted HPs exhibited significantly increased byproducts with high acid value (AN), in turn, led to low purity and low yield.¹⁵⁻¹⁹ Stowell *et al.*²⁰ studied the preparation of HPs with paraformaldehyde and dialkyl phosphite/trialkyl phosphite as raw materials in the presence of triethylamine catalyst. The results indicated that the products showed high AN in the range of 2.6 mg KOH g⁻¹ and 3.5 mg KOH g⁻¹. Wang *et al.*¹² studied the preparation of HPs to reduce the side reactions according to drop feeding or batch feeding to regulate the feeding amount in the presence of polar organic solvent. The results showed that the method got the yield of higher than 90%, the purity of more than 98.9%, the AN of less than 0.2 mg KOH g⁻¹ and the water content of lower than 0.08 wt%. However, this method was not suitable for large-scale continuous industry production due to the limitation of drop feeding or batch feeding.¹²

Based on the trend of safety, cleanliness, efficiency and sustainability in the 21st century chemical industry, flow chemistry developed rapidly. The flow reactor has its own advantages according to continuously pump reactive materials and reagents for mixture and reaction

under the controllable conditions.²¹⁻²³ The reaction can be much more faster, because the reactants can be diffused and mixed in a few seconds, and the reaction temperature can be higher than the solvent's boiling point. The reaction can be much more cleaner, since the reactants can be rapidly heated or cooled so as to precisely control the temperature with high specific surface area and volume ratio. The reaction can be much more safer owe to quite fewer amount of dangerous intermediates and reaction heat generated in the reactor per unit time. What's more, the reaction can be more selective because of the advantages of fast, clean and safe in the continuous flow reactor.

In this study, HPs were first attempted to be synthesized by the microfluidic reactor. Synthesis route and the targeted HPs are showed in Fig. 1. The synthesis of the targeted HPs by the microfluidic reactor had overcome the disadvantages of strong heat-release and more by-product for the reaction and high AN, low yield and purity for the product. It also showed the advantages of simple operation, controllable reaction conditions, reduce labor cost, save equipment area. The synthesis method can reduce the amount of wastewater which can promote much more green environmental protection. Moreover, the synthesis process can be continuous, and also be amplified by parallel connection with no amplification effect.

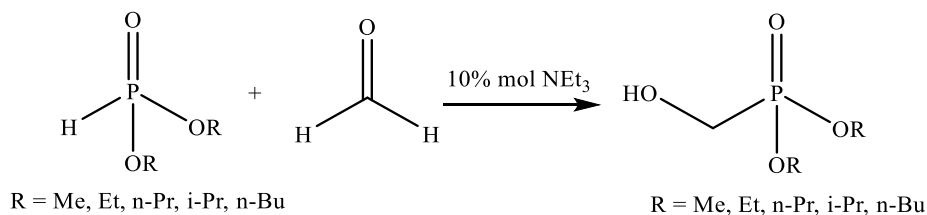


Fig. 1 – Synthesis route and the five targeted HPs (dimethyl hydroxymethyl phosphonate (DMHP), diethyl hydroxymethyl phosphonate (DEHP), dipropyl hydroxymethyl phosphonate (DPHP), diisopropyl hydroxymethyl phosphonate (DIHP), dibutyl hydroxymethyl phosphonate (DBHP)).

RESULTS AND DISCUSSION

Taking the synthesis of DMHP as a sample, the influences of the molar ratio of raw materials (phosphite ester and HCHO), reaction temperature (T) and reaction time (t) on the yield of the product were studied. The detailed influences were shown in Fig. 2. Seen from Fig. 2A, the higher the molar ratio of raw material, the higher the reaction yield. That is, the more excessive HCHO can promote

the positive completion of the reaction. When the molar ratio exceeded 1:1.2, excess formaldehyde had relatively not significant influence on the yield with the range from 96.5% to 96.7%. Considering the factor of energy consumption, so the optimal molar ratio of 1:1.2 was determined. In Fig. 2B, the yield increased significantly at the temperature range between 120 °C and 145 °C. When the reaction temperature was 125 °C, the yield reached the highest (96.6%). Therefore, the optimal reaction temperature was determined to be 125 °C.

As shown in Fig. 2C, the higher the reaction time, the higher the reaction yield. That is, the more longer reaction time can promote the completion of the reaction. When the reaction time exceeded 8 min, longer time had relatively not significant

influence on the yield with the range from 95.0% to 96.6%. Considering the energy consumption and possible side reactions under the condition of long reaction time, the optimal reaction time of 8 min was determined.

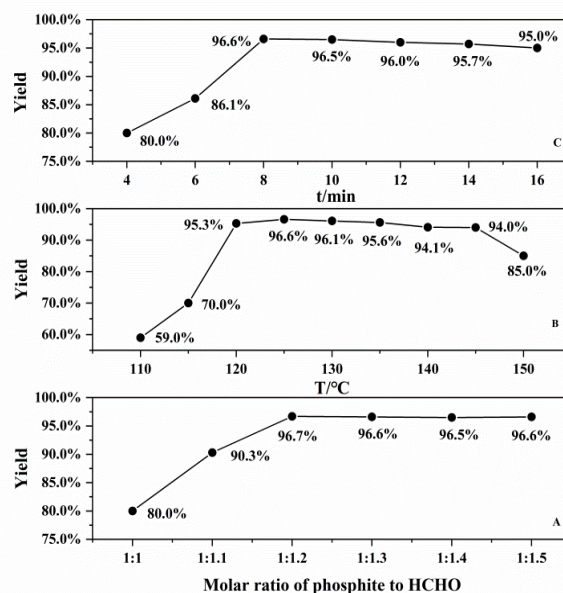


Fig. 2 – Influences of reaction conditions for the synthesis of DMHP using the microfluidic reactor.

Under the optimal conditions of molar ratio of raw material, reaction temperature and reaction time, DMHP was synthesized with good yield (96.7%) and purity (99.2%), and low water content (0.06 wt %) and AN (0.07 mg KOH g⁻¹). The detailed synthesis condition and product information were listed in Table 1. According to the study process of the synthesis of DMHP, the optimal conditions for the synthesis of DEHP, DPHP, DIHP and DBHP were determined. Also, under the corresponding optimal conditions, these HPs were synthesized. As listed in Table 1, for the five HPs, the synthesis yields were up to 94% (ranged from 94.2% to 96.7%), the purities were more than 99% (ranged from 99.0% to 99.3%), the

ANs were lower than 0.15 mg KOH g⁻¹ (ranged from 0.07 mg KOH g⁻¹ to 0.09 mg KOH g⁻¹), and the water contents were less than 0.08wt% (ranged from 0.04 wt% to 0.07 wt%). By calculating, the corresponding productivity of DMHP, DEHP, DIHP, DPHP and DBHP was 2.64 kg·d⁻¹, 2.06 kg·d⁻¹, 1.69 kg·d⁻¹, 1.68 kg·d⁻¹, and 1.28 kg·d⁻¹ respectively. The experimental results showed that the microfluidic reactor presented the advantages with controllable reaction conditions. Compared to the conventional reactor, the reaction time of the microfluidic reactor was greatly shortened. The AN value was significantly reduced. And the yield and the purity of the targeted HPs were effectively increased.

Table 1

Synthesis condition and product information of the five targeted HPs

HPs	Reaction condition	Yield/%	Purity/%	X/wt%	AN/mgKOH g ⁻¹
DMHP	125 0.8 8 1:1.2	96.7	99.2	0.06	0.07
DEHP	130 0.8 10 1:1.2	96.4	99.3	0.04	0.08
DPHP	135 0.8 12 1:1.3	95.1	99.0	0.06	0.07
DIHP	135 0.8 12 1:1.3	95.7	99.1	0.07	0.09
DBHP	135 0.8 15 1:1.5	94.2	99.1	0.07	0.07

EXPERIMENTAL

Materials

Chemicals of triethylamine ((C₂H₅)₃N, AR), 37% formaldehyde solution (HCHO, AR), trichloromethane (CHCl₃, AR), dimethyl phosphite ((CH₃O)₂PHO, AR), diethyl phosphite ((C₂H₅O)₂PHO, AR), dipropyl phosphite ((C₃H₇O)₂PHO, AR), diisopropyl phosphite ((C₃H₇O)₂PHO, AR), dibutyl phosphite ((C₄H₉O)₂PHO, AR) for synthesis of the targeted compounds were obtained from Merck Chemicals (Shanghai) Co., Ltd., China. Standard substances of the five HPs (DMHP, DEHP, DPHP, DIHP and DBHP) for identification of the targeted compounds were obtained from Sinopharm Chemical Reagent Co., Ltd., China.

Chemicals of methanol (CH₃OH, AR), Karl-Fischer reagent (KFR-C06, CP) for determination of the water content of the targeted compounds were obtained from Tianjin Siyou Fine Chemical Product Co., Ltd., China.

Chemicals of potassium hydrogen phthalate (C₈H₅KO₄, PT), toluene (C₆H₅CH₃, AR), isopropanol (C₃H₇OH, AR) and potassium hydroxide (KOH, AR) for determination of the acid number (AN) of the targeted compounds were obtained from Tianjin Siyou Fine Chemical Product Co., Ltd., China.

Experimental instruments

For the microfluidic reactor, analytical liquid chromatography pump (NP7010C) was used as the feed pump which was obtained from Zhejiang Harbor Technology Co., Ltd., China. Micro-mixer (P-713) was obtained from IDEX Corporation, the United States. The micro-reactor, which was a void tubular reactor made of polytetrafluoroethylene with the inner diameter of 0.5–1 mm and the volume of 20 mL, was obtained from IDEX Corporation, the United States. Back pressure valve (BP-10) was obtained from Zaiput Flow Technologies, the United States. The heat exchanger, which

was a void tubular reactor made of stainless steel with the inner diameter of 0.5–1 mm and the volume of 20 mL, was obtained from IDEX Corporation, the United States. Liquid-liquid separator (SEP-10) was obtained from Zaiput Flow Technologies, the United States.

The purity of the targeted compounds was detected by an Agilent 7890 gas chromatograph (GC) equipped with a fused silica capillary column (DB-1, 30 m length × 0.25 mm inner diameter × 0.25 μm film thickness) and a flame ionization detector.

For determination of the water content of the targeted compound, electronic balance (ML204A/2) and trace moisture tester (V20) were obtained from Mettler-Toledo Instruments (Shanghai) Co., Ltd., China.

For determination of the AN of the targeted compounds, electronic balance (ML204A/2) was obtained from Mettler-Toledo Instruments (Shanghai) Co., Ltd., China. Automatic Potentiometric Titrator (702) was obtained from Metrohm china Limited.

The microfluidic reactor

The microfluidic reactor was designed for synthesis of the HPs with phosphite esters and formaldehyde as the starting materials, and NEt₃ as catalyst. The specific experimental device is shown in Fig. 3. Micro-mixer 3 was set up for mixing starting materials with the two analytical liquid chromatography pump 1 and 2. The micro-reactor 4 was connected with micro-mixer 3. Followed micro-reactor 4, back pressure valve 5 was used for adjusting the pressure of reaction solution. Micro-mixer 7 was set up for mixing reaction materials with analytical liquid chromatography pump 8. Between the back pressure valve 5 and micro-mixer 7, heat exchanger 6 was set for cooling reaction solution with ice-water bath. Followed the micro-mixer 7, liquid-liquid separator 9 was connected with container 10 for collecting organic phase and container 11 for collecting water phase.

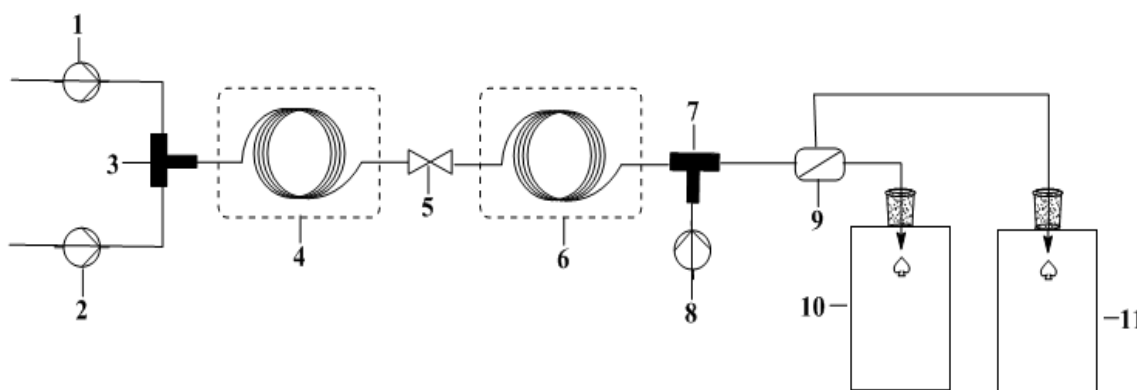


Fig. 3 – Process schematic of the synthesis of the HPs using the microfluidic reactor:

1 – feed pump, 2 – feed pump, 3 – micro-mixer, 4 – micro-reactor, 5 – back pressure valve, 6 – heat exchanger, 7 – micro-mixer, 8 – feed pump, 9 – liquid-liquid separator, 10 – container for organic phase, 11 – container for water phase).

Synthesis process of HPs

According to process schematic shown in Fig. 3, the targeted HP was synthesized by alkaline formaldehyde solution and phosphite ester. Alkaline formaldehyde solution, having the 1:10 molar ratio of EtN₃ to HCHO, was pumped into micro-mixer 3 through feed pump 1. Phosphite ester was

pumped into micro-mixer 3 through feed pump 2. The mixed solution was infused into micro-reactor 4, and carried out hydroxymethylation reaction at a certain temperature and pressure for a certain time. Reaction solution was infused into heat exchanger 6 through back pressure valve 5 to cool down, and then infused into micro-mixer 7. At the same time, organic solvent chloroform was pumped into micro-mixer 7

by feed pump 8. After the micro-extraction in micro-mixer 7, the extract was infused into liquid-liquid separator 9 for phase separation. The organic phase in container 10 was removed organic solvent to obtain the targeted HP.

Determination methods

GC was used to detect the purity of the targeted HPs. The working information was as follows: the oven temperature started at 40°C and increased at 60°C min⁻¹ to 350°C. The hydrogen and air were the carrier gas with the flow rate of 30 mL min⁻¹ and 300 mL min⁻¹, respectively. The split ratio was 100:1 and the split flow rate was 80 mL min⁻¹. A 0.2 µL sample was injected for analysis. The concentration of the targeted HPs was determined by external standard method according to the corresponding standard substance. And the purity of the targeted HPs was gotten by calculation.

According to Chinese standard GB/T 6283- 2008 (Chemical products-determination of water Karl-fischer method (general method)), the water content of the targeted HP was determined. Setting the moisture tester to titration state, the mass (m_1 , mg) of water was detected by electronic balance and the used volume (V_1 , mL) of Karl-Fischer reagent was determined, then the titre (T , mg H₂O/mL) of Karl-Fischer reagent was calculated according to the Eq. (1). Setting the moisture tester to determination state, the mass (m_2 , mg) of the sample and the used volume (V_2 , mL) of Karl-Fischer reagent were detected following the same steps above, then the water content (X , %) of sample was calculated according to the Eq. (2).

$$T = \frac{m_1}{V_1} \quad (1)$$

$$X = \frac{V_2 \times T \times 100}{m_2} \quad (2)$$

AN of the targeted HP was determined by the Chinese standard GB/T 7304-2014 (Standard test method for acid number of petroleum products by potentiometric titration). The sample was weighed (m_s , g) and dissolved in titration solvent. Then it was titrated by the standard solution of potassium hydroxide-isopropanol (M_{KOH} , mol/mL) with corresponding alkaline buffer solution as titration endpoint. AN (calculated by KOH, mg g⁻¹) was calculated by the used volume (V_2 , mL) of KOH according to the Eq. (3).

$$AN = \frac{V_{AB} \times M_{\text{KOH}} \times 56.1}{m_s} \quad (3)$$

CONCLUSIONS

Aiming at the synthesis of HPs, the microfluidic reactor was first used to overcome the disadvantages of strong heat-release and more by-product for the reaction, and high AN, low yield and purity for the products. Under the corresponding optimal conditions, HPs were synthesized with low AN (<0.15 mg KOH/g), high yield (>94%) and high purity (>99%). The

results further confirm that the microfluidic reactor can provide relatively larger surface area for enhancing the transfer efficiency of heat and mass and thus achieve the high yield and high purity of the products. In addition, the synthetic device can reduce labor cost, save equipment area, and reduce the amount of waste water which can promote more green environmental protection. The synthesis process can be continuous, and also be amplified by parallel connection with no amplification effect. It will be a suitable for industrial application of scale-up production.

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