

# Esterification of 2,6-pyridinedicarboxylic acid with n-butanol catalyzed by heteropoly acid $H_3PW_{12}O_{40}$ or its Ce(III) salt

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## Abstract

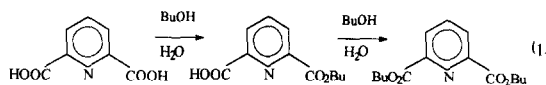
The liquid-phase esterification of 2,6-pyridinedicarboxylic acid (PA) with n-BuOH is efficiently catalyzed by heteropoly acid  $H_3PW_{12}O_{40}$  as a homogeneous catalyst and by its insoluble acidic Ce(III) salt,  $Ce_{0.87}H_{0.4}PW_{12}O_{40}$ , as a heterogeneous catalyst, yielding 100% of PA dibutyl ester. The Ce(III) salt has a lower activity than  $H_3PW_{12}O_{40}$  but can be easily recovered and re-used. Insoluble  $NH_4^+$ ,  $K^+$  and  $Cs^+$  salts also exhibit moderate activities. The activity of the salts decreases in the series:  $Ce_{0.87}H_{0.4}PW_{12}O_{40} \gg Cs_{2.5}H_{0.5}PW_{12}O_{40} \sim Cs_3PW_{12}O_{40} \sim Cs_2HPW_{12}O_{40} \sim (NH_4)_3PW_{12}O_{40} > K_3PW_{12}O_{40}$ .

**Keywords:** Cerium; Esterification; Heteropoly acid; Pyridinedicarboxylic acid; Tungsten

## 1. Introduction

Heteropoly acids (HPA) are efficient catalysts for organic synthesis [1–3]. Such reactions are often carried out in the liquid phase, e.g. in aqueous or polar organic solvents where HPAs are readily soluble. This makes catalyst recovery difficult. Thus the development of insoluble HPA catalysts is generally desirable for the operating under heterogeneous conditions. So far, a water-insoluble acidic cesium 12-tungstophosphate,  $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ , has been applied as a very efficient solid acid catalyst for liquid-phase reactions [2]. HPAs supported on certain activated carbons exhibit extraordinary stability towards leaching HPA from the carrier in aqueous and oxygenated organic solvents; they also show a rather high catalytic activity, e.g. in esterification [4,5].

This paper reports on the use of heteropoly acid  $H_3PW_{12}O_{40}$  and its insoluble salts, particularly an acidic Ce(III) 12-tungstophosphate,  $Ce_{0.87}H_{0.4}PW_{12}O_{40}$  (CePW), as, respectively, homogeneous and heterogeneous catalysts for liquid-phase esterification of 2,6-pyridinedicarboxylic acid (PA) with n-butanol, which is a step in the synthesis of pharmaceuticals [6].



It should be noted that HPAs, which are easily deactivated by N-bases, e.g. amines or pyridines, usually fail to catalyze organonitrogen compound conversions. But PA can be subjected to HPA catalysis since its N-basicity is substantially reduced by two neighboring carboxyl groups.

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## 2. Experimental

### 2.1. Materials

Chemical grade  $\text{H}_3\text{PW}_{12}\text{O}_{40} \cdot 19\text{H}_2\text{O}$  was recrystallized from water. Chemical grade  $\text{K}_3\text{PW}_{12}\text{O}_{40}$  and  $(\text{NH}_4)_3\text{PW}_{12}\text{O}_{40}$  were used without purification.  $\text{Cs}_{3-x}\text{H}_x\text{PW}_{12}\text{O}_{40}$  ( $x=0, 0.5$  and  $1.0$ ) were prepared by the interaction of  $\text{Cs}_2\text{CO}_3$  with  $\text{H}_3\text{PW}_{12}\text{O}_{40}$  [7]. The BET surface areas of  $\text{Cs}_{2.5}\text{H}_{0.5}\text{PW}_{12}\text{O}_{40}$  and  $\text{Cs}_3\text{PW}_{12}\text{O}_{40}$  were 92 and  $163 \text{ m}^2 \text{ g}^{-1}$ , respectively. Prior to use, all the catalysts were pre-treated in vacuo at  $250^\circ\text{C}$  for 2 h unless otherwise stated. 99% PA and chemical grade n-butanol were used without purification.

CePW was prepared by the interaction of  $\text{H}_3\text{PW}_{12}\text{O}_{40}$  with Ce(III) chloride in aqueous solution acidified with HCl.  $\text{H}_3\text{PW}_{12}\text{O}_{40} \cdot 19\text{H}_2\text{O}$  (3.0 mmol) was dissolved in 20 ml of water, and 2.0 ml of 10% aqueous HCl was added to the solution. To this solution was added dropwise  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (2.7 mmol) in 2.0 ml of 10% aqueous HCl with stirring. The resulting solution was gently evaporated to dryness to quantitatively afford a solid residue. The latter was dried in vacuo at  $250^\circ\text{C}$  for 2 h. The product was an anhydrous white powder. Anal. Calcd for  $\text{Ce}_{0.87}\text{H}_{0.4}\text{PW}_{12}\text{O}_{40}$ : Ce, 4.06; P, 1.03; H, 0.013.

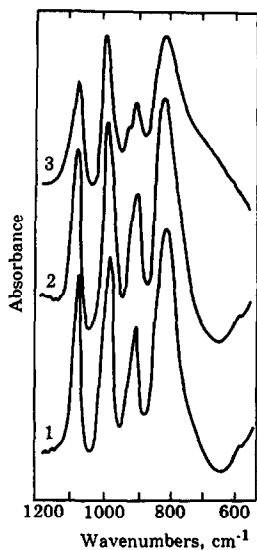


Fig. 1. IR spectra of CePW pre-treated at various temperatures for 2 h: (1) –  $250^\circ\text{C}$ , (2) –  $300^\circ\text{C}$ , (3) –  $350^\circ\text{C}$ .



Fig. 2.  $^{31}\text{P}$  NMR spectra of CePW at room temperature: (1) – 5 wt% aqueous solution, pH 2.5–3.0, (2) – saturated solution in n-BuOH ( $0.15 \text{ g l}^{-1}$ ), (3) – MAS spectrum for solid CePW pre-treated at  $250^\circ\text{C}$  for 2 h, (4) – MAS spectrum for solid CePW recovered after reaction (dried in vacuo at  $50^\circ\text{C}$ ).

Found: Ce, 4.06; P, 1.08; H (by difference), 0.013. No chloride ions was present ( $\text{AgNO}_3$ ). Acidic protons in CePW were also determined by pyridine adsorption (see below). The Keggin structure of the CePW heteropolyanion was confirmed by IR and  $^{31}\text{P}$  magic angle spinning (MAS) NMR. IR (KBr): 1087, 980, 900, 805  $\text{cm}^{-1}$  (Fig. 1);  $^{31}\text{P}$  MAS NMR:  $-15.2 \text{ ppm}$  (Fig. 2). These results are in good agreement with reported data [8,9].

### 2.2. Esterification of PA

The esterification of PA was carried out in a glass reaction vessel equipped with a stirrer and a

Dean–Stark trap. The reactor was charged with PA and n-butanol ( $[PA]/[n-BuOH] = 1:30$  mol/mol) and heated to reflux ( $118^\circ\text{C}$ ). The reaction was started by adding the catalyst. The water that formed in the reaction was removed by azeotroping with butanol. Aliquots of the reaction mixture were taken in appropriate time intervals, diluted with acetone and analyzed by TLC: Silufol UV-254 plates, eluent EtOH (96%): $\text{NH}_3$  (25%): $\text{H}_2\text{O} = 25:4:3$ ,  $R_f = 0.36; 0.70; 0.82$  for PA, PA butyl ester and PA dibutyl ester, respectively. The amount of the products was determined by TLC/UV–Vis (a Specord M40 instrument,  $\lambda = 267$  nm).

### 2.3. Techniques

IR spectra were recorded on a Specord IR-75 spectrometer in KBr pellets. 161.677 MHz solution  $^{31}\text{P}$  NMR spectra were obtained on a MSL-400 Bruker spectrometer in the frequency range of 10 kHz, pulse duration 12  $\mu\text{s}$ , delay between pulses 30 s and accumulation number 500. 121.46 MHz  $^{31}\text{P}$  MAS NMR spectra of solid samples were measured on a CXP-300 Bruker spectrometer in the frequency range of 50 kHz, pulse duration 10  $\mu\text{s}$ , delay between pulses 90 s, accumulation number 12–28, spin rate 4 kHz. 85%  $\text{H}_3\text{PO}_4$  was used as an external reference.

The amount of proton sites in CePW was determined by IR spectroscopy of adsorbed pyridine (UR-20 spectrometer). CePW pellets were pre-treated in oxygen at  $300^\circ\text{C}$  for 2 h. Pyridine was adsorbed at  $150^\circ\text{C}$  for 15 min, the sample was then evacuated at  $150^\circ\text{C}$  for 30 min, and the IR spectra were taken. The amount of pyridinium ions was determined from the integral intensity of the spectral band at  $1540\text{ cm}^{-1}$ , using the extinction of  $3.0 \pm 0.5\text{ cm}^2\text{ }\mu\text{mol}^{-1}$  [10]. The error of the measurement was about 25%.

## 3. Results and discussion

### 3.1. Characterization of CePW

CePW has been prepared by the interaction of  $\text{H}_3\text{PW}_{12}\text{O}_{40}$  with  $\text{CeCl}_3$  in aqueous solution in the

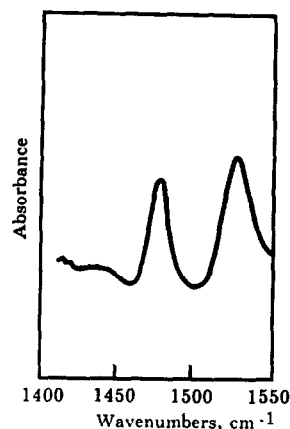


Fig. 3. IR spectrum of pyridine adsorbed on CePW.

presence of HCl. The acidification is necessary in order to avoid the decomposition of the Keggin heteropolyanion. CePW is thermally stable at least up to  $300^\circ\text{C}$ , which is confirmed by IR (Fig. 1). In the IR spectrum of the sample pre-treated at  $350^\circ\text{C}$ , the bands at  $700$  and  $910\text{ cm}^{-1}$  are observed. Since these bands are absent at lower pre-treatment temperatures, it may be indicative of the decomposition of the CePW at  $350^\circ\text{C}$ .

The presence of acidic protons in CePW has been confirmed by IR spectroscopy of adsorbed pyridine. The IR spectrum of pyridine adsorbed on CePW (Fig. 3) exhibits well-known bands of the pyridinium ion at  $1480$  and  $1540\text{ cm}^{-1}$  [10]. It is noteworthy that the band at  $1450\text{ cm}^{-1}$  assigned to pyridine adsorbed on Lewis sites [10] is practically not observed. The same spectrum was obtained for pyridine on  $\text{H}_3\text{PMo}_{12}\text{O}_{40}$  [11]. The amount of proton sites in CePW calculated from the intensity of the  $1540\text{ cm}^{-1}$  band was  $58\text{ }\mu\text{mol g}^{-1}$ . This value is about a half of that found from chemical analysis. Some of the proton sites in CePW were probably inaccessible for pyridine molecules under the adsorption conditions used.

CePW is readily soluble in water. With no mineral acid added, the Keggin anion of CePW has been found to hydrolyze to the lacunary anion  $\text{PW}_{11}\text{O}_{39}^{7-}$  ( $\text{PW}_{11}$ ). The aqueous solution, initially colorless, turned yellow, which may be explained by the formation of complexes between  $\text{Ce}^{3+}$  and  $\text{PW}_{11}$ . The complexes  $\text{PW}_{11}\text{Ce}^{3+}$  and  $(\text{PW}_{11})_2\text{Ce}^{3+}$  have been described elsewhere

Table 1  
Esterification of 2,6-pyridine dicarboxylic acid with n-BuOH catalyzed by  $H_3PW_{12}O_{40}$  or its salts

Catalyst <sup>a</sup> (%)	Time h	Composition, wt%		
		PA	BE	DBE
$H_3PW_{12}O_{40}$ (1.0)	1.5	2	8	90
	3.0	0	0	100
$H_3PW_{12}O_{40} \cdot 19H_2O$ <sup>b</sup> (3.7)	6.0	2	6	92
$H_3PW_{12}O_{40} \cdot 19H_2O$ <sup>b</sup> (5.4)	6.0	0	0	100
$H_2SO_4$ (1.0)	1.5	0	7	93
	3.0	0	0	100
$Ce_{0.87}H_{0.4}PW_{12}O_{40}$ (5.4)	2.5	2	8	90
	3.0	0	0	100
KU-2-8 (6.6)	24	0	6	94
$(NH_4)_3PW_{12}O_{40}$ (5.4)	6.0	55	34	11
$K_3PW_{12}O_{40}$ (5.4)	6.0	65	28	7
$Cs_3PW_{12}O_{40}$ (5.4)	6.0	40	30	30
$Cs_2HWP_{12}O_{40}$ (5.4)	6.0	49	40	11
$Cs_{2.5}H_{0.5}PW_{12}O_{40}$ (5.4)	6.0	30	25	45

[PA]/[n-BuOH] = 1/30 mol/mol, 118°C.

<sup>a</sup> The catalysts were pre-treated in vacuo at 250°C for 2 h. The amount of catalyst based on the total reaction mixture is given in parentheses.

<sup>b</sup> The HPA hydrate was used without pre-treatment.

[12,13]. They are unstable in acidic solution and decompose at pH < 1 to form saturated species [12]. The decomposition of Keggin structure and the formation of the  $PW_{11}$  complexes is evidenced by <sup>31</sup>P NMR (Fig. 2, spectrum 1). In the <sup>31</sup>P spectrum, there is no line at -15 ppm characteristic of the  $PW_{12}O_{40}^{3-}$  anion [8]; instead there are lines at -14.0 and -19.5 ppm, which may be assigned to  $PW_{11}$  complexes with  $Ce^{3+}$  [13]. A group of small peaks around 12 ppm may be attributed to

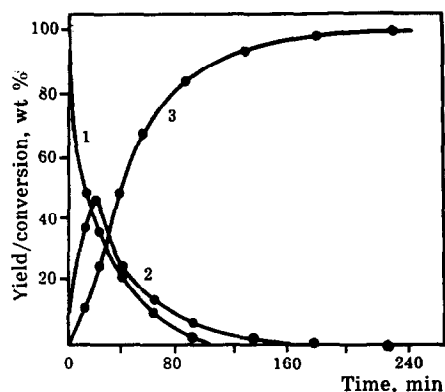


Fig. 4. Esterification of PA with n-BuOH catalyzed by  $H_3PW_{12}O_{40}$  (1.0 wt%) at 118°C: (1) – PA, (2) – BE, (3) – DBE.

unsaturated species, e.g.  $PW_{11}$ ,  $P_2W_{17}$  and  $P_2W_{21}$  [8].

In oxygenated organic solvents, CePW is scarcely soluble, the Keggin structure being retained. For instance, in n-butanol the retention of Keggin structure of CePW is supported by observing the line at -15.2 ppm in <sup>31</sup>P NMR spectrum (Fig. 2). Below is given our estimation of solubilities ( $g\ l^{-1}$ ) of CePW (pre-treated at 250°C for 2 h) in some organic solvents at room temperature:

Solvent	Solubility CePW $g\ l^{-1}$
MeOH	13
EtOH (96%)	10
n-BuOH	0.15
t-BuOH	0.03
1,4-Dioxane	0.02
Acetone	1.1

In solvents such as BuOH and dioxane, the solubility of CePW is very low. Thus, CePW may be used as a solid acid catalyst in such media.

### 3.2. Esterification of 2,6-pyridinedicarboxylic acid

We have found that anhydrous  $H_3PW_{12}O_{40}$  (1 wt%) is the efficient homogeneous catalyst for the esterification of PA with n-butanol, yielding 100% of PA dibutyl ester (DBE) (118°C, 3 h) (Table 1). Per equal catalyst weight,  $H_3PW_{12}O_{40}$  is almost as effective as sulfuric acid, but per equal amount of protons, HPA is one order of magnitude more active than  $H_2SO_4$ . This is in agreement with the relative acid strengths of the two acids [1]. The hydrate  $H_3PW_{12}O_{40} \cdot 19H_2O$  has a lower activity compared to anhydrous HPA because water inhibits the reaction.

Fig. 4 shows the kinetic curves for the reaction (1) in the presence of HPA. As expected, the reaction is a consecutive process, with PA butyl ester (BE) as an intermediate product being formed.

CePW effectively catalyzes reaction (1), providing a 100% yield of DBE (5.4 wt%, 3 h). The reaction is likely to be a heterogeneous process for the following reasons: (1) CePW is visibly insoluble in the reaction mixture; and (2) the reaction practically stopped when the catalyst was filtered off. CePW is less active than the parent HPA but much more active than acidic ion-exchange resin KU-2-8, a conventional catalyst of reaction (1) [6]. The  $^{31}\text{P}$  MAS NMR spectrum for CePW recovered after the reaction (Fig. 2) shows that the structure of the catalyst was retained during the reaction.

The important advantage of CePW is that it can be easily recovered after reaction and re-used. Thus, we have carried out seven runs of the PA esterification with the same CePW sample (5.4 wt%). After each run the catalyst was filtered off, washed with fresh n-BuOH and re-used. A 100% yield of DBE was obtained in each run, although a gradual decrease in activity was observed probably due to the loss of the catalyst during filtration. For this reason, the period of time for the reaction to be completed was accordingly increased from 3 h in the first run to 6 h in the seventh run.

Water-insoluble salts  $\text{K}_3\text{PW}_{12}\text{O}_{40}$ ,  $(\text{NH}_4)_3\text{PW}_{12}\text{O}_{40}$  and  $\text{Cs}_{3-x}\text{H}_x\text{PW}_{12}\text{O}_{40}$  ( $x=0, 0.5, 1.0$ ), having high surface areas, are also moderately active in reaction (1) as heterogeneous catalysts. Even if these solids are prepared (by precipitation from aqueous solutions) to be stoichiometric, residual quantities of protons still remain, which are apparently responsible for the catalytic activity of these salts [14]. All these salts show the same activity within a factor of two and are substantially less active than CePW:

$$\text{Ce}_{0.87}\text{H}_{0.4}\text{PW}_{12}\text{O}_{40} \gg \text{Cs}_{2.5}\text{H}_{0.5}\text{PW}_{12}\text{O}_{40} \approx \text{Cs}_3\text{PW}_{12}\text{O}_{40} \approx \text{Cs}_2\text{HPW}_{12}\text{O}_{40} \approx$$

$(\text{NH}_4)_3\text{PW}_{12}\text{O}_{40} > \text{K}_3\text{PW}_{12}\text{O}_{40}$ . It has been shown that in certain reactions of non-polar molecules in hydrocarbon media  $\text{Cs}_{2.5}\text{H}_{0.5}\text{PW}_{12}\text{O}_{40}$  as solid acid catalyst exhibits very high activity, the highest in the series of salts  $\text{Cs}_{3-x}\text{H}_x\text{PW}_{12}\text{O}_{40}$ , sometimes even higher than the parent HPA [2,15]. However, in our polar system all  $\text{Cs}^+$  salts showed almost the same activity, lower than that of  $\text{H}_3\text{PW}_{12}\text{O}_{40}$ . This may be explained by the strong solvation of acid sites with polar solvent, leveling their acid strength.

The mechanism of CePW catalysis in reaction (1) is as yet unknown. In this case both Brønsted and Lewis ( $\text{Ce}^{3+}$ ) acid sites may be important.

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