Hydrolysis Kinetics of 2-Cyanopyridine, 3-Cyanopyridine, and 4-Cyanopyridine in High-Temperature Water

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ABSTRACT: We report herein the kinetic studies on hydrolysis of three cyanopyridines in high-temperature water. 3-Cyanopyridine, 4-cyanopyridine and 2-cyanopyridine underwent consecutive hydrolysis to the corresponding pyridinecarboxamides and picolinic acids. Further decarboxylation to pyridine was observed for 2-cyanopyridine hydrolysis. Experiments at different initial reactant concentrations revealed that these compounds exhibited the first-order kinetics. Experiments at different temperatures showed that the first-order rate constants displayed an Arrhenius behavior with activation energies of 74.3, 40.3, and 83.7 kJ mol^{-1} for 3-cyanopyridine, 4-cyanopyridine, 2-cyanopyridine, respectively. The activation energies obtained for 3-pyridinecarboxamide, 4-pyridinecarboxamide and 2-pyridinecarboxamide hydrolysis are 80.1, 32.7, and 70.5 kJ mol^{-1}, respectively. The effect of substituent position on activation energies for cyanopyridine and pyridinecarboxamide hydrolysis is ortho $\approx$ meta $>$ para. © 2012 Wiley Periodicals, Inc. Int J Chem Kinet 1–8, 2012

INTRODUCTION

High-temperature water (HTW), defined as liquid water above 180°C, is a green medium for chemical reactions. Compared with water at room temperature, HTW features lower dielectric constant, better solubility for small organic compounds, and higher ion product. All of these properties are temperature dependent and can be manipulated to optimize the reaction environment [1]. Therefore, HTW can support ionic, polar nonionic, and free-radical reactions. The relative rates of these different classes of reactions can be very sensitive to the reaction conditions. The state-sensitive nature of the solvent properties can give rise to marked temperature and density effects on the reaction kinetics, as observed experimentally for numerous reactions in HTW [2].

Nitriles were focused on because of their existence in industrial waste streams and in the product spectra from the reaction of aliphatic NO_2 containing

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compounds in HTW [3]. A better understanding of the behavior of nitriles in HTW would assist the attempts to use HTW for waste cleanup. In addition, hydrolysis of nitriles is one of the best approaches to prepare amides or carboxylic acids. Traditionally, hydrolysis of nitriles to the corresponding amides or carboxylic acids is carried out in water with a strong acid or base catalyst [4–6]. These base- or acid-catalyzed reactions have certain disadvantages such as undesired by-products, salt yield from additional neutralization, and environmental pollutions. HTW provides a green strategy without strong acid or base catalyst for amide or carboxylic acid production. Hence, it is important to understand the kinetics and mechanisms for the hydrolysis of nitriles in HTW.

There is a modest body of literature on hydrolysis of various kinds of nitriles in HTW, but it centers primarily on aromatic nitriles, aliphatic nitriles, and dinitriles [3,7–13]. The literature on hydrolysis of heterocyclic nitriles in HTW is much more sparse. The kinetics of 3-cyanopyridine was investigated in our previous article [14]. The activation energies for the hydrolysis of 3-cyanopyridine and 3-pyridinecarboxamide were obtained. However, the kinetics of the consecutive hydrolysis of 3-cyanopyridine in our previous work required additional experiments using 3-pyridinecarboxamide as a reactant, which is time consuming and needs to be improved. Moreover, the position of the nitrile substituent will probably affect the reaction activity of cyanopyridine. The research on the position effect will help us to have a better understanding on the hydrolysis of heterocyclic nitriles in HTW.

In this article, to further advance understanding of hydrothermal hydrolysis of heterocyclic nitrile, three compounds were selected for study: 3-cyanopyridine, 4-cyanopyridine, and 2-cyanopyridine. These compounds are the N-heterocyclic analogs of benzonitrile, and each compound has a nitrile substituent attached to 3-, 4-, and 2-carbon, respectively. These compounds can be used to examine effect of the heterocyclic N atom and nitrile substituent position on the nitrile hydrolysis. Figure 1 shows the reaction pathways for hydrolysis of the three cyanopyridines (2-picolinic acid can be subsequently decarboxylated). The model on the consecutive reactions is established without additional experiments using pyridinecarboxamide or picolinic acid as a reactant, and the activation energies for each reaction are obtained. The results provide insight into the effect of substituent position and heterocyclic N on hydrolysis of heterocyclic nitriles and amides.

EXPERIMENTAL

Materials

3-Cyanopyridine (99%) was obtained from Shanghai Bangcheng Chemical Co., Ltd. (Shanghai, People's Republic of China). 4-Cyanopyridine (99%), 2-cyanopyridine (99%), and 4-pyridinecarboxamide (98%) were obtained from ACROS Organics (Geel, Belgium). 3-Pyridinecarboxamide (99.5%) and 3-picolinic acid (99.5%) were obtained from Chengdu Kelong Chemical Co., Ltd. (Sichuan, People's Republic of China). 2-Pyridinecarboxamide (99%) was obtained from TCI Chemical Co., Ltd. (Shanghai, People's Republic of China). 4-Picolinic acid (99%) was obtained from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, People's Republic of China). 2-Picolinic acid (99%) was obtained from J & K Chemical, Ltd. (Beijing, People's Republic of China). They are all of analytical reagent grade and were used as received. Deionized water was prepared in-house.

Reactors

The reactor is made up of 316-L stainless steel, which mainly consists of a high-pressure autoclave (500-mL volume), a plunger pump, a mechanical impeller, and a sampling line. The schematic diagram is available in our previous publication [15]. The sampling line includes a high-pressure valve and a cooler. The apparatus exhibits the following capabilities: temperature up to 320°C, pressure up to 20 MPa, good temperature control of ±1°C and on-line sampling. The reactor and furnace were made by Dalian Kemao Experimental Equipment Co., Ltd. (Liaoning, People's Republic of China).

Experimental Procedure

The reactor was degassed with a vacuum pump and then filled with high-purity nitrogen. Three hundred milliliter of degassed deionized water was added to the reactor through the valve by using a plunger pump. After the temperature inside the reactor had reached the desired reaction temperature, 60 mL reactant solution

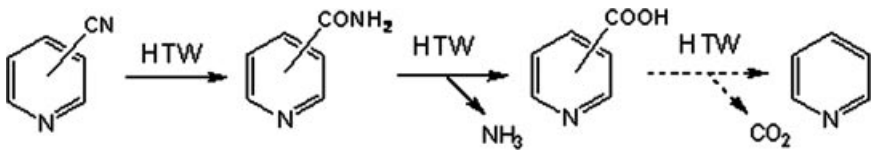

Figure 1 Reaction pathway for hydrolysis of cyanopyridines.

(in water) was quickly injected by the plunger pump through the valve and the line was rinsed with 20 mL of deionized water. After adding this material, the reactor returned to the reaction temperature within a few minutes. The system pressure was maintained at 8 MPa by high-pressure nitrogen from a cylinder. Finally, samples were collected at certain reaction times. The reaction mixture was constantly agitated at 400 rpm using a mechanical impeller throughout the duration of the reaction.

Sampling and Analysis

Two to three milliliter samples were collected after 1–2 mL of solution had first been vented to purge the sample line. The liquid sample was quantitatively analyzed by HPLC (Agilent 1100; Santa Clara, CA, USA) with a UV detector by an external reference method. The HPLC column was KNAUER-C_{18} (4 mm ID × 250 mm) (Berlin, Germany). For 3-cyanopyridine, the mobile phase was 5 g/L of H_3PO_4 solution:methanol:acetonitrile = 47:50:3 flowing at 0.6 mL/min; the column temperature was 35°C; the injection volume was 5 μL; and the microwave length of detector was 210 nm. For 4-cyanopyridine, the mobile phase was 3 g/L of H_3PO_4 solution:methanol:acetonitrile = 70:15:15 flowing at 0.6 mL/min; the column temperature was 35°C; the injection volume was 5 μL; and the microwave length of the detector was 268 nm. For 2-cyanopyridine, the mobile phase was 5 g/L of H_3PO_4 and 2 g/L triethylamine solution:methanol:acetonitrile = 75:20:5 flowing at 0.4 mL/min; the column temperature was 35°C; the injection volume was 10 μL; and the microwave length of the detector was 268 nm. Peaks were identified by comparison of their retention times with those of standard solutions of pure compounds, and identities were confirmed by GC/MS (Agilent 6890/5973).

Product yields were calculated as the number of moles of product recovered divided by the initial number of moles of cyanopyridine loaded into the reactor. The mole balances were calculated as the total number of moles of products and cyanopyridine recovered divided by the initial number of moles of cyanopyridine loaded into the reactor.

RESULTS AND DISCUSSION

Effect of Concentration on Hydrolysis of Cyanopyridine

Figure 2 shows the effect of initial concentration on the hydrolysis of 4-cyanopyridine at 220°C. The reaction pressure was maintained at 8 MPa. The concentrations of 4-cyanopyridine were 0.5, 0.75, 1.0, 1.5, and 2.0 g/L. The conversion rates were similar at different concentrations, which signal first-order kinetics for the hydrolysis reactions. Similar results were obtained for effect of concentration on 3-cyanopyridine and 2-cyanopyridine hydrolysis.

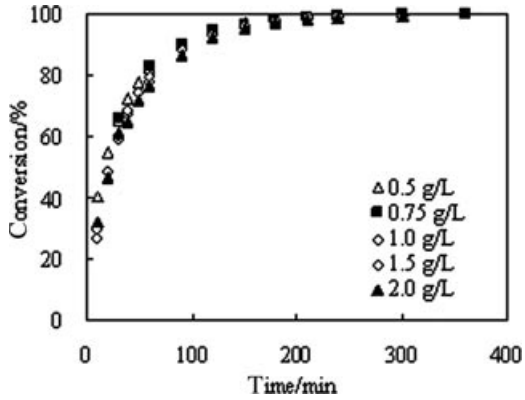

Figure 2 Temporal variation of 4-cyanopyridine conversions at 220°C and different initial concentrations.

Effect of Temperature on Hydrolysis of 3-Cyanopyridine

Figure 3 shows the effect of temperature on the hydrolysis of 3-cyanopyridine. The reactions were carried out at temperatures of 210, 220, 230, 240, and 250°C and an initial 3-cyanopyridine concentration of 0.5 g/L. The reaction pressure was 8 MPa. Nearly complete conversion of 3-cyanopyridine occurred after about 150 min at 250°C. At 210°C, on the other hand, the conversion was only 86% after 240 min. 3-Pyridinecarboxamide and 3-picolinic acid were the only products observed. The yield variation of 3-pyridinecarboxamide shows a clear trend of an intermediate product: at the beginning; it increased with the elapsing of the reaction time, then decreased after reaching a maxima. The maximum yield at each temperature was 70–80%. The yield of 3-picolinic acid always increased with the elapsing of the reaction time at each temperature. The curves in Fig. 3 are calculated from the first order consecutive reaction model and will be described later in this article. The mole balances at each temperature are shown in Fig. 3d. The mole balance was always around 95–105%.

Effect of Temperature on Hydrolysis of 4-Cyanopyridine

Figure 4 shows the effect of temperature on the hydrolysis of 4-cyanopyridine. The reactions were conducted at 190, 205, 220, 235, and 250°C and an initial 4-cyanopyridine concentration of 0.5 g/L. The reaction pressure was 8 MPa. At 250°C, 3-cyanopyridine was

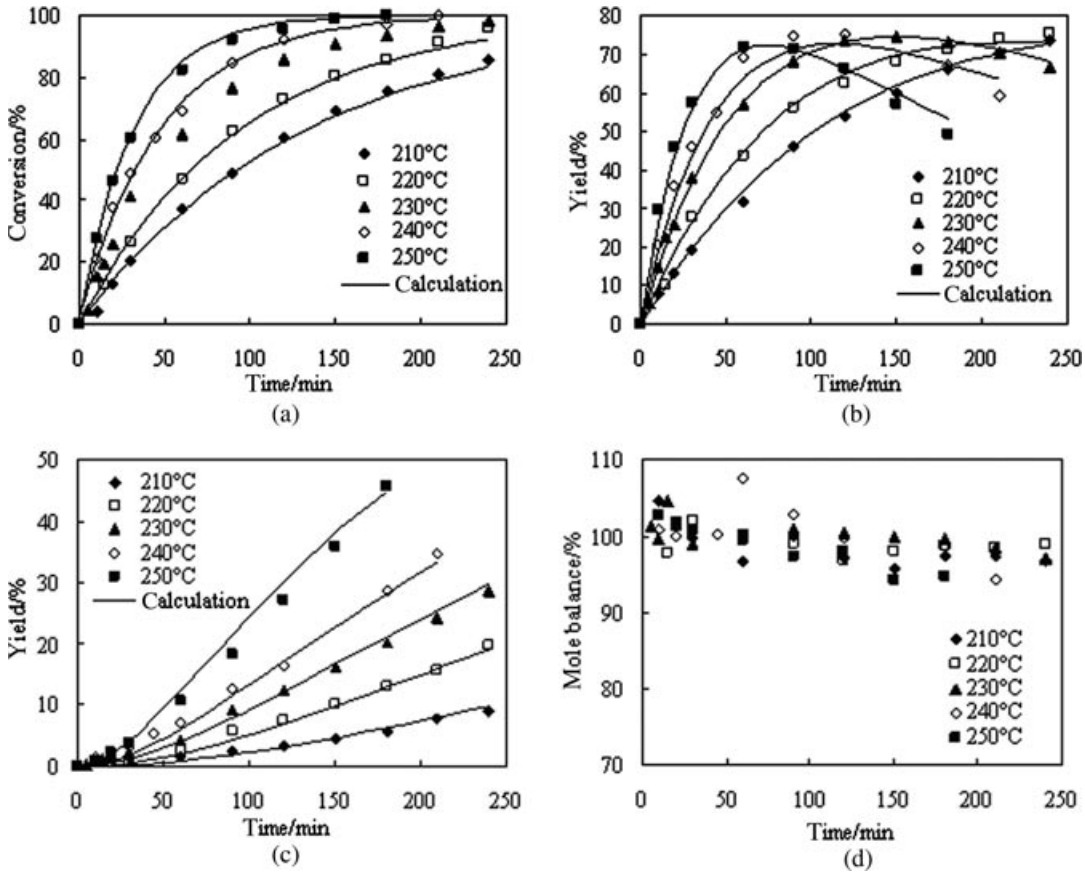

Figure 3 Temporal variation of 3-cyanopyridine conversion, yields to 3-pyridinecarboxamide and 3-picolinic acid, and mole balance at different temperatures: (a) conversion of 3-cyanopyridine, (b) yield of 3-pyridinecarboxamide, (c) yield of 3-picolinic acid, and (d) mole balance.

nearly consumed within 90 min and the conversion was 78% at 190°C for 90 min. The effect of temperature on 3-cyanopyridine seems not to be very significant. 4-Pyridinecarboxamide and 4-picolinic acid were the only products observed. Their yields at each temperature are shown in Figs. 4b and 4c. Same as in 3-pyridinecarboxamide, the yield variation of 4-pyridinecarboxamide shows a clear trend of the intermediate product. The maximum yield at each temperature was about 65%. The yield of 4-picolinic acid always increased with elapsing of the reaction time at each temperature. The smooth curves were again obtained from a first-order kinetic model that will be discussed in the next section. The mole balances at each temperature are shown in Fig. 4d. The mole balance was always around 90–105%.

Effect of Temperature on Hydrolysis of 2-Cyanopyridine

Figure 5 shows the effect of temperature on the hydrolysis of 2-cyanopyridine. The reactions were conducted at 210, 220, 230, 240, and 250°C and an initial 2-cyanopyridine concentration of 0.5 g/L. The reaction pressure was 8 MPa. Nearly complete conversion of 4-cyanopyridine occurred after about 30 min at 250°C. At 210°C, on the other hand, the conversion was only 88% after 90 min. Differing from the products of 3-cyanopyridine and 4-cyanopyridine, pyridine was observed as a product besides 2-pyridinecarboxamide and 2-picolinic acid, which suggests decarboxylation occurred in the reaction system. The yield variation of 2-pyridinecarboxamide also shows a clear trend of the intermediate product. The maximum yield at each temperature was around 80%. The yield of 2-picolinic acid was relatively low. Eleven percent was the highest yield achieved for 2-picolinic acid within 90 min. The yield of pyridine kept increasing with elapsing of the reaction time at each temperature. The smooth curves were again obtained from a first-order kinetics model that will be discussed in the next section. The mole balances at each temperature are shown in Fig. 5e. Most of them were around 90–110%. Some points for the mole balance at 240 and 250°C were

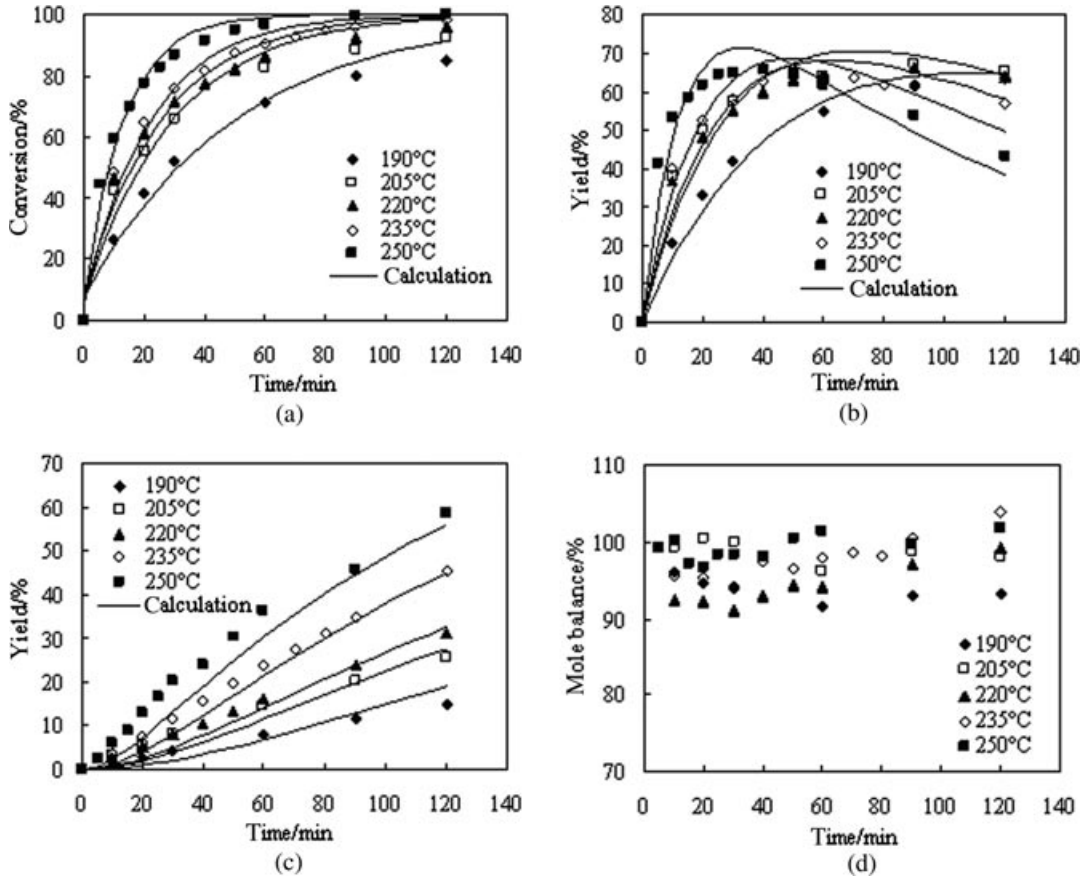

Figure 4 Temporal variation of 4-cyanopyridine conversion, yields to 4-pyridinecarboxamide and 4-picolinic acid, and mole balance at different temperatures: (a) conversion of 4-cyanopyridine, (b) yield of 4-pyridinecarboxamide, (c) yield of 4-picolinic acid, and (d) mole balance.

below 90%, which was probably due to the experimental errors.

Kinetics of Hydrolysis

Figure 1 shows the reaction pathways for the three cyanopyridines. 3-Cyanopyridine and 4-cyanopyridine underwent consecutive hydrolysis in HTW. The rate equation for each reaction was assumed to be first order in the concentration (C) of each species in the reaction. The mole balance equations for each of the species are as follows:

$$-\frac{dC_A}{dt} = k_1 C_A \tag{1}$$

$$\frac{dC_B}{dt} = k_1 C_A - k_2 C_B \tag{2}$$

$$-\frac{dC_C}{dt} = k_2 C_B \tag{3}$$

where C_A refers to the concentration of cyanopyridines, C_B is the concentration of amides, and C_C is the concentration of carboxylic acids. k_1 is the rate constant for cyanopyridine hydrolysis to amide, k_2 is the rate constant for amide hydrolysis to carboxylic acid.

For 2-cyanopyridine, the equations for the consumption of 2-cyanopyridine and production of 2-pyridinecarboxamide are the same as Eqs. (1) and (2). The equations for the production of 2-picolinic acid and pyridine are as follows:

$$-\frac{dC_C}{dt} = k_2 C_B - k_3 C_C \tag{4}$$

$$-\frac{dC_D}{dt} = k_3 C_C \tag{5}$$

where C_D is the concentration of pyridine and k_3 is the rate constant for 2-picolinic acid decarboxylation.

We compiled the above equations into Scientist from MicroMath (Scientist Software, St. Louis, MO, USA) and fitted the concentrations for each of the species versus time data at each temperature. The software solved the governing differential equations for a

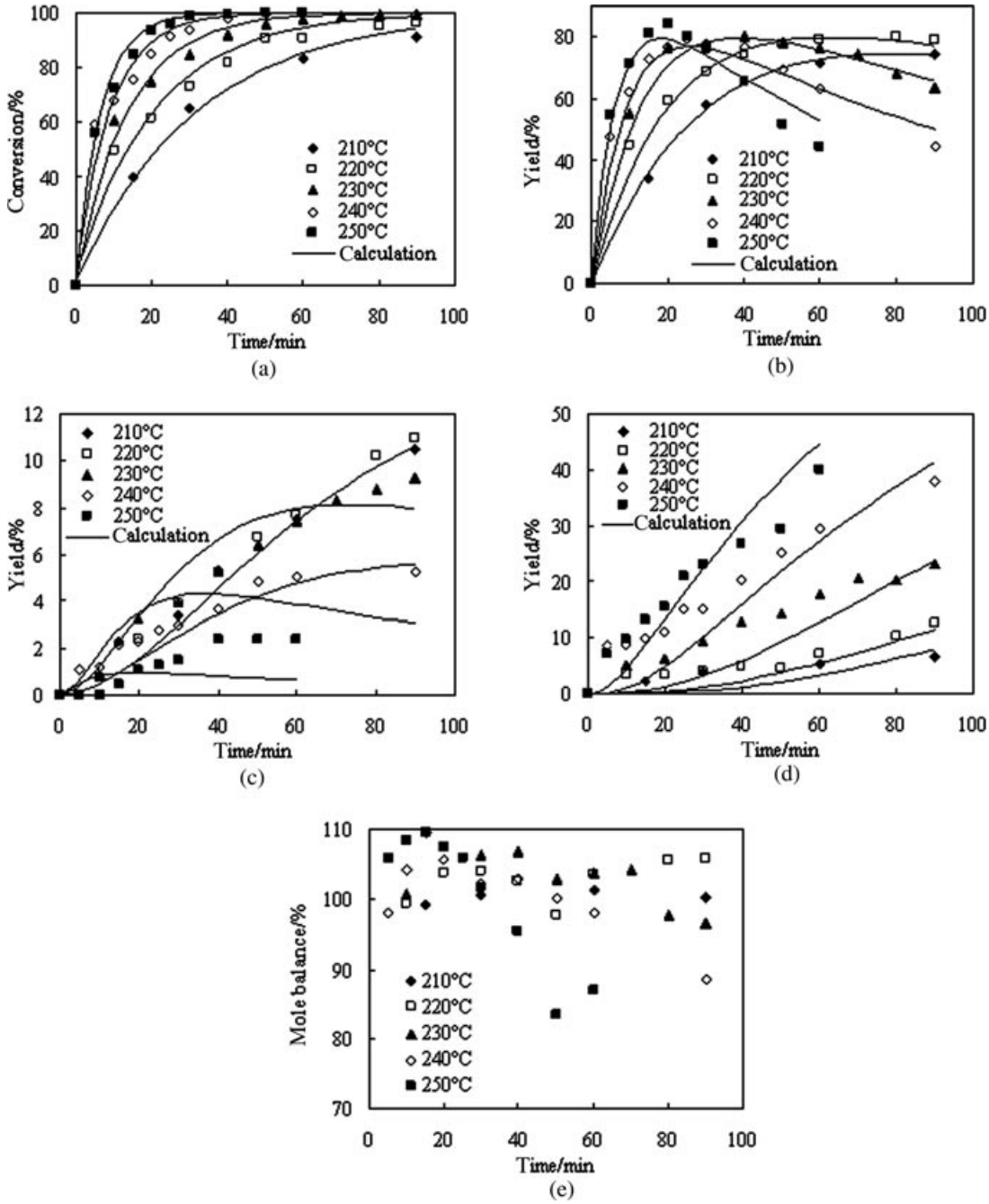

Figure 5 Temporal variation of 2-cyanopyridine conversion, yields to 2-pyridinecarboxamide, 2-picolinic acid and pyridine, and mole balance at different temperatures: (a) conversion of 2-cyanopyridine, (b) yield of 2-pyridinecarboxamide, (c) yield of 2-picolinic acid, (d) yield of pyridine, and (e) mole balance.

batch reactor and simultaneously estimated the value of the rate constant by minimizing the sum of the squared differences between the experimental and calculated concentration for each of the species.

The curves in Figs. 3–5 show that the reactant conversion and product yields calculated using the model reasonably represent the experimental data for most steps of consecutive hydrolysis of the three cyanopyridines at all temperatures. This data fitting provided estimates for the rate constants at each temperature. The results of this parameter estimation are presented in Table I. The uncertainties shown are the standard deviations in the rate constants as determined by the parameter estimation software. The standard deviations

Table I Hydrolysis (Decarboxylation) Rate Constants ($\times 10^{-3}$ min^{-1}) for Cyanopyridines, Pyridinecarboxamides, and Picolinic Acid

T (°C)	3-Cyanopyridine	3-Pyridinecarboxamide	4-Cyanopyridine	4-Pyridinecarboxamide	2-Cyanopyridine	2-Pyridinecarboxamide	2-Picolinic Acid
190			19.8 ± 0.9	3.2 ± 0.4			
205			33.9 ± 2.2	3.92 ± 0.37			
210	7.42 ± 0.08	0.837 ± 0.061			31.6 ± 0.8	3.58 ± 0.32	17.3 ± 4.0
220	10.6 ± 0.2	1.43 ± 0.07	38.2 ± 1.8	4.75 ± 0.41	47.8 ± 1.8	2.86 ± 0.39	37.9 ± 12.5
230	16.0 ± 1.4	2.00 ± 0.69			73.2 ± 3.3	5.17 ± 0.34	45.5 ± 7.3
235			45.8 ± 1.9	6.63 ± 0.31			
240	20.7 ± 1.5	2.6 ± 1.0			109 ± 6	7.90 ± 0.58	136 ± 49
250	31.2 ± 0.7	4.17 ± 0.11	76.4 ± 8.5	8.45 ± 0.49	152 ± 8	11.6 ± 0.6	95.6 ± 116.4
E_a (kJ/mol)	74.3 ± 2.7	80.1 ± 5.1	40.3 ± 5.9	32.7 ± 2.6	83.7 ± 1.4	70.5 ± 16.5	194 ± 41

of rate constants given in the table are all satisfactory except the values for 2-picolinic acid decarboxylation. Fortunately, we have focused on the consecutive hydrolysis of cyanopyridines.

The variation of the rate constants with temperature followed the Arrhenius equation. The Arrhenius parameters were determined by linear regression of ln k versus $1/T$. The Arrhenuis parameters were A (min^{-1}) = $10^{5.90 \pm 0.28}$, E_a = 74.3 ± 2.7 kJ mol^{-1} for 3-cyanopyridine hydrolysis; A (min^{-1}) = $10^{5.61 \pm 0.53}$, E_a = 80.1 ± 5.1 kJ mol^{-1} for 3-pyridinecarboxamide hydrolysis; A (min^{-1}) = $10^{2.87 \pm 0.62}$, E_a = 40.3 ± 5.9 kJ mol^{-1} for 4-cyanopyridine hydrolysis; A (min^{-1}) = $10^{1.17 \pm 0.28}$, E_a = 32.7 ± 2.6 kJ mol^{-1} for 4-pyridinecarboxamide hydrolysis; A (min^{-1}) = $10^{7.55 \pm 0.15}$, E_a = 83.7 ± 1.4 kJ mol^{-1} for 2-cyanopyridine hydrolysis; A (min^{-1}) = $10^{5.06 \pm 1.72}$, E_a = 70.5 ± 16.5 kJ mol^{-1} for 2-pyridinecarboxamide hydrolysis; A (min^{-1}) = $10^{19.1 \pm 4.2}$, E_a = 194 ± 41 kJ mol^{-1} for 2-picolinic acid decarboxylation.

Effect of Substituent Position on Hydrolysis

At 300°C and 8.7 MPa pressure, benzonitrile can be almost consumed for 225 min [3]. Based on our results, complete consumption takes about 150, 90, and 30 min for 3-cyanopyridine, 4-cyanopyridine, and 2-cyanopyridine, respectively, at 250°C and 8 MPa pressure, which indicates that the heterocyclic N atom can lower the hydrothermal stability of benzonitrile. In Table I, the activation energies for 3-cyanopyridine and 2-cyanopyridine hydrolysis are quite similar, but much higher than the activation energy of 4-cyanopyridine hydrolysis. Similar results can be found in pyridinecarboxamide hydrolysis: The activation energies for 3-pyridinecarboxamide and 2-pyridinecarboxamide hydrolysis are similar, but much higher than the activation energy of 4-pyridinecarboxamide hydrolysis. The effect of substituent position on activation energies for cyanopyridine and pyridinecarboxamide hydrolysis is ortho ≈ meta > para. At 220°C, the rate constants of cyanopyridine hydrolysis have the sequence of ortho > para > meta, and the rate constant sequence for pyridinecarboxamide hydrolysis is para > ortho > meta. However, both the rate constants for ortho-cyanopyridine and pyridinecarboxamide are highest at 250°C, because of the high activation energy. Moreover, differing from 3-cyanopyridine and 4-cyanopyridine, the 2-cyanopyridine reaction system yielded a large amount of pyridine, which indicates not only orthocyanopyridine and pyridinecarboxamide have lower hydrothermal stability but also orthopicolinic acid does. It is probably caused by the short distance between the substituents and heterocyclic N atom. Overall, orthocyanopyridine, pyridinecarboxamide, and picolinic acid are more active than meta- and paraposition cyanopyridines, pyridinecarboxamides, and picolinic acids.

CONCLUSION

2-Cyanopyridine, 3-cyanopyridine and 4-cyanopyridine undergo consecutive hydrolysis on the timescale of hours in liquid water at temperatures around 200°C. For 3-cyanopyridine and 4-cyanopyridine, their corresponding pyridinecarboxamides and picolinic acids are products observed. 2-Cyanopyridine yielded 2-pyridinecarboxamide, 2-picolinic acid, and pyridine as the observed products. All cyanopyridines exhibited consecutive first-order kinetics. The activation energies were determined to be 74.3, 40.3, 83.7, 80.1, 32.7, and 70.5 kJ mol^{-1} for 3-cyanopyridine, 4-cyanopyridine, 2-cyanopyridine, 3-pyridinecarboxamide, 4-pyridinecarboxamide, and 2-pyridinecarboxamide hydrolysis, respectively. The effect of substituent position on activation energies for cyanopyridine and pyridinecarboxamide hydrolysis is ortho ≈ meta > para. Ortho-cyanopyridine,

pyridinecarboxamide, and picolinic acid are more active than meta- and paraposition cyanopyridines, pyridinecarboxamides, and picolinic acids.

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