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Decarboxylation of tetrafluorophthalic acid in NH_3-enriched high temperature liquid water

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ABSTRACT

2,3,4,5-Tetrafluorobenzoic acid is an important pharmaceutical intermediate. A green technology for the decarboxylation of tetrafluorophthalic acid to 2,3,4,5-tetrafluorobenzoic acid in NH_3-enriched high temperature liquid water (HTLW) was developed. Tetrafluorophthalic acid could undergo the decarboxylation with the catalysis of NH_3 to 2,3,4,5-tetrafluorobenzoic acid in HTLW. A conversion of 98.1% and selectivity of 96.5% were achieved at 453.15 K for 1.5 h with an ammonia concentration of 13.4 mmol/L. The effects of ammonia concentration, initial concentration of reactant and reaction temperature were then investigated and correlated using a derivated equation. The results indicated that adequate addition of ammonia could adjust the pH of the reaction medium into 2.2–2.4, where the dominant form of the decarboxylation is the monovalent anion. Moreover, the kinetic data at different temperatures were fitted by a first-order equation, and the rate constants at each temperature and an activation energy of 190 kJ/mol were obtained.

1. Introduction

2,3,4,5-tetrafluorobenzoic acid is an important organic fluoride, primarily used for preparation of antibacterial agents of fluoroquinolone [1,2], such as lomefloxacin, sparfloxacin, levofloxacin, rufloxacin, etc. [3–5]. The antibacterial agents have many advantages including broad antimicrobial spectrum, strong and fast antimicrobial effects and few side-effects [6,7]. In global market of total antibacterial agents, quinolone ranked at third place followed by cephalosporin class and penicillin drugs. Additionally, the 2,3,4,5-tetrafluorobenzoic acid can be also used in preparation of conductive materials, organooxotin clusters and so on [8,9].

In the preparation of 2,3,4,5-tetrafluorobenzoic acid through decarboxylation, high boiling organic amine, such as tri-*n*-butylamine, was commonly used as solvent [10]. Transition metals, such as Cu [11], Ag [12] and Pd [13], were often employed as the catalyst for the decarboxylation of aromatic carboxylic acids. In literature, the protodecarboxylation was not affected by the copper source, but significantly facilitated by the presence of bipyridine ligands at the copper and the use of aromatic amines as solvent [14,15], indicating the medium plays an important role in the decarboxylation of aromatic carboxylic acids. High temperature liquid water (HTLW) is one of commonly environmentally benign mediums [16], which has a low dielectric constant thereby increasing its solubility for some organic compounds. In addition, the use of HTLW also eliminates the consumption of organic solvents and acid/base solution. However, problems associated with using the HTLW include necessity for high reaction temperatures because of low reaction rates and abundance of byproducts because of poor selectivity [17].

Given the capability of ammonia in enhancing reaction rates and its recyclability by post-reaction heating, herein we proposed using a solvent system by adding the ammonia to the HTLW to accelerate the decarboxylation rate of tetrafluorophthalic acid. The decarboxylation of carboxylic acids is subject to general base catalysis [18]. The behavior of tetrafluorophthalic acid decarboxylation was studied. The effects of ammonia concentration, initial concentration of reactant and reaction temperature were then investigated. The kinetic data at different temperatures were fitted by a first-order equation, and the rate constants at each temperature and an activation energy were obtained. Eventually, the effects of ammonia concentration, initial concentration of reactant and temperature on the decarboxylation of tetrafluorophthalic acid were described quantitatively using an equation.

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2. Experimental

2.1. Materials

Tetrafluorophthalic acid (≥98.5%) was purchased from Shanghai Kaisai Chemical Co. Ltd. 2,3,4,5-tetrafluorobenzoic acid (≥99.0%) was purchased from Shanghai Kangtuo Chemical Co. Ltd. Ammonia solution and ethanol (analytical reagent grade) were obtained from Hangzhou Chemical Reagent Co, Ltd. All chemicals were used as received. Deionized water was made in the laboratory.

2.2. Reactors

A batch reactor made of 316L stainless steel tubing with a volume of about 13.5 mL was used for the decarboxylation of tetrafluorophthalic acid. The reactor was composed of three parts: tube, stopper, and cap. The tube had an internal diameter of 12 mm, which was sealed by a stopper with a diameter of 13.8 mm. A cap was used to fix the tube and stopper. The reactor was heated by a steel box furnace which is capable of heating 12 reactors simultaneously. The furnace had a temperature deviation within ±2 K.

2.3. Experimental procedure

A certain amount of tetrafluorophthalic acid and 8 mL of ammonia solution with a certain concentration were added to the reactor. After being sealed, the reactor was put into the furnace, which had been preheated to the reaction temperature. We obtained the heating curve at the temperature of 453.15 K before our experiments. The heating curve showed the temperature of the liquid phase could get stable within 20 min and the temperature inside was 2 K lower than outside, so the temperature of furnace was set 2 K higher than the reaction temperature. After the reaction, the reactor was removed from the furnace and quenched in water. The sample was then collected from the quenched reactor.

2.4. Sampling and analysis

The post-reaction solution was discharged into a 50 mL volumetric flask. The reactor was then washed for three times with ethanol which was subsequently added to the flask as well. The liquid in the flask was analyzed by HPLC (Agilent1100) with a UV detector at 215 nm. The HPLC column was phenomenex Gemini C18 (250 mm × 4.6 mm, 5 μm). The mobile phase was 0.05 mol/L of NaH_2PO_4 (pH 3.5 adjusted by H_3PO_4): methanol at a volume ratio of 40:60. The mobile phase was prepared as follows: NaH_2PO_4 was dissolved in deionized water at a concentration of 0.05 mol/L, and then the pH value of this solution was adjusted to 3.5 using dilute phosphoric acid and pH indicator. The solution of NaH_2PO_4 was mixed with methanol at a volume ratio of 40:60 as the mobile phase. The column temperature was 308.15 K. The injection volume was 2 μL. Peaks were identified by matching their retention time with those of standard solutions of pure compounds.

3. Result and discussion

3.1. Effect of concentration of ammonia on decarboxylation of tetrafluorophthalic acid

Fig. 1 shows the effect of ammonia concentration on the decarboxylation of tetrafluorophthalic acid. The standard deviations in Fig. 1 were determined from three replicate experiments. The reactions were performed at tetrafluorophthalic acid concentrations of 10, 20, 30 and 40 mmol/L under 453.15 K for 1 h. The results showed that 2,3,4,5-tetrafluorobenzoic acid was the only product detected. The concentration of ammonia appeared to have a significant effect on the decarboxylation of tetrafluorophthalic acid. With the increase of ammonia loading, the conversion of tetrafluorophthalic acid firstly increased and then significantly decreased. The selectivities to 2,3,4,5-tetrafluorobenzoic acid were mostly higher than 90%. It indicates that an adequate amount of ammonia can significantly improve the rate of decarboxylation. The role of ammonia for the decarboxylation will be discussed later.

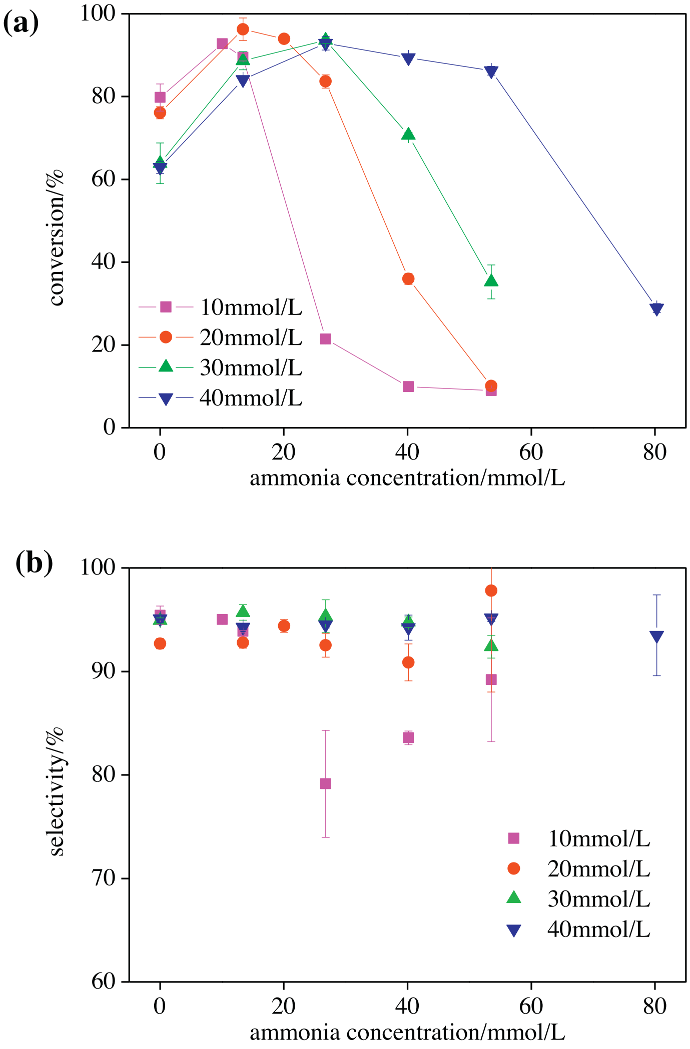


Fig. 1. Effect of ammonia concentration on the decarboxylation of tetrafluorophthalic acid at 453.15 K. The concentrations of tetrafluorophthalic acid are 10, 20, 30 and 40 mmol/L, respectively.

3.2. Effect of reactant initial concentration on decarboxylation of tetrafluorophthalic acid

Fig. 2 shows the effect of initial concentration on the decarboxylation of tetrafluorophthalic acid. The reactions were performed using 13.4 mmol/L ammonia solution, which was the optimized ammonia concentration based on Fig. 1. Four concentrations of tetrafluorophthalic acid (10, 20, 30 and 40 mmol/L) were used and the reaction temperature was 443.15 K. The conversion rate of tetrafluorophthalic acid slowed with the increase of reactant initial concentration. It suggests that the ammonia concentration of 13.4 mmol/L was not suitable for high reactant concentration and the reaction was not sufficiently accelerated. As shown in Fig. 2b, the selectivity to 2,3,4,5-tetrafluorobenzoic acid at different reactant concentrations was maintained no less than 90%.

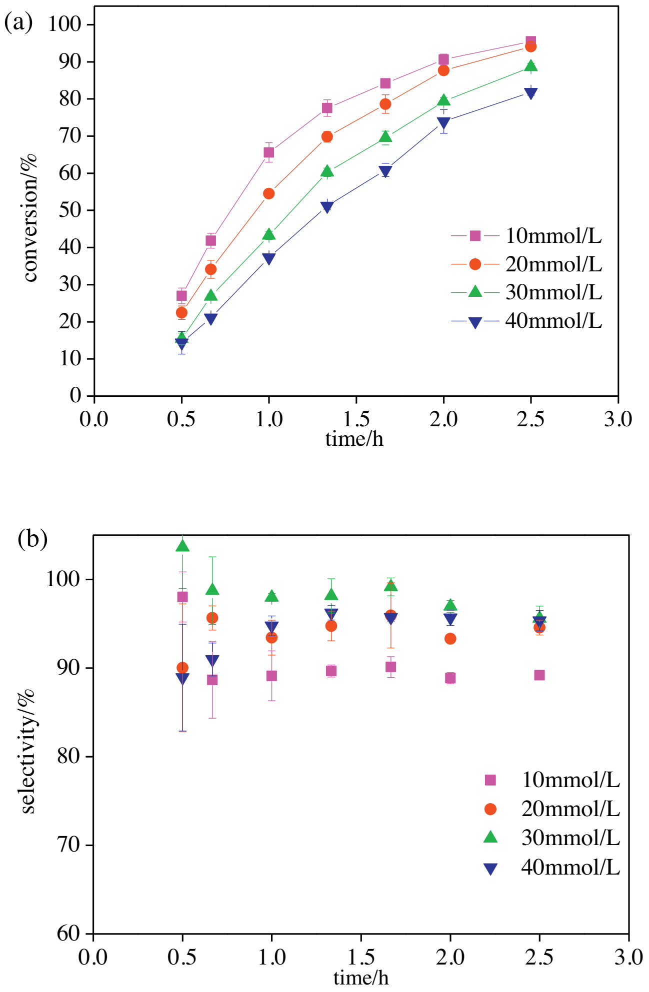


Fig. 2. Effect of initial reactant concentration on the decarboxylation of tetrafluorophthalic acid at 443.15 K. The concentrations of tetrafluorophthalic acid are 10, 20, 30 and 40 mmol/L, respectively.

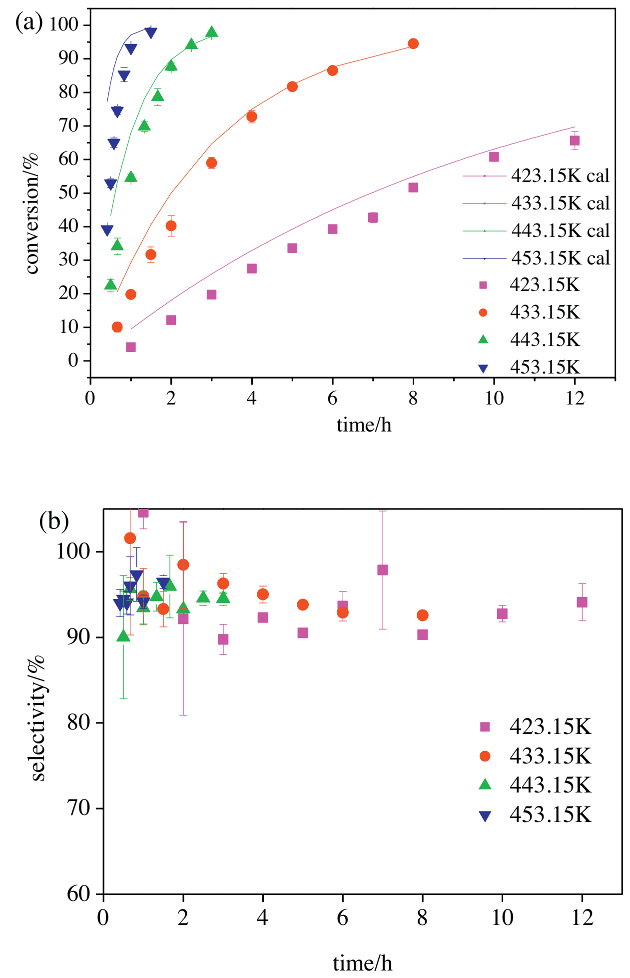


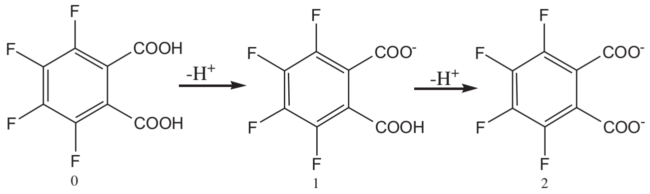
Fig. 3. Effect of temperature on the decarboxylation of tetrafluorophthalic acid. The reaction temperatures are 423.15, 433.15, 443.15 and 453.15 K, respectively.

3.3. Effect of temperature on decarboxylation of tetrafluorophthalic acid

Fig. 3 shows the effect of temperature on the decarboxylation of tetrafluorophthalic acid. The reactions were carried out at temperatures of 423.15, 433.15, 443.15, and 453.15 K with an ammonia concentration of 13.4 mmol/L and an initial reactant concentration of 20 mmol/L. High reaction temperature significantly accelerated the decarboxylation rate of tetrafluorophthalic acid. Nearly complete conversion occurred after about 90 min at 453.15 K. The conversion at 423.15 K, however, was only about 65% after 12 h reaction.

3.4. Kinetics on decarboxylation of tetrafluorophthalic acid

Our previous work indicated that the decarboxylation of pentafluorobenzoic and quinolinic acid exhibited a first order kinetics [16]. Thus, we fitted the data of conversion of tetrafluorophthalic acid versus reaction time at each temperature by Origin (Version 7). The calculated decarboxylation rate constants were determined as 0.0959 ± 0.0024, 0.378 ± 0.007, 1.39 ± 0.06, 3.28 ± 0.14 h^{-1} at 423.15, 433.15, 443.15, and 453.15 K, respectively. The curves in Fig. 3 show that the yield profiles calculated by the first-order model well represented the experimental data at all temperatures. The uncertainties shown are the standard deviations in the rate constants as determined by the parameter estimation software. The rate constants at each temperature were fitted by the Arrhenius equation. The Arrhenius parameters, as determined from unweighted linear regression of ln k vs. 1000/T, are $E_a = 190 \pm 11$ kJ mol^{-1}, and $A = 10^{22.5 \pm 1.3}$ h^{-1}.



Scheme 1. Dissociation process for tetrafluorophthalic acid.

3.5. Mechanism on decarboxylation of tetrafluorophthalic acid

Fig. 1 shows a significant effect of the ammonia concentration in solution on the decarboxylation of tetrafluorophthalic acid. Additionally, Fig. 2 shows that the initial concentration of reactant remarkably impacted the reaction in the presence of ammonia. As commonly known, the dissociation process for dibasic acid undergoes step by step as shown in Scheme 1. The distribution fraction of the three forms in an aqueous phase strongly depends on its pH value which is dictated by the concentration of acidic reactant and the amount of added ammonia into solution. For better

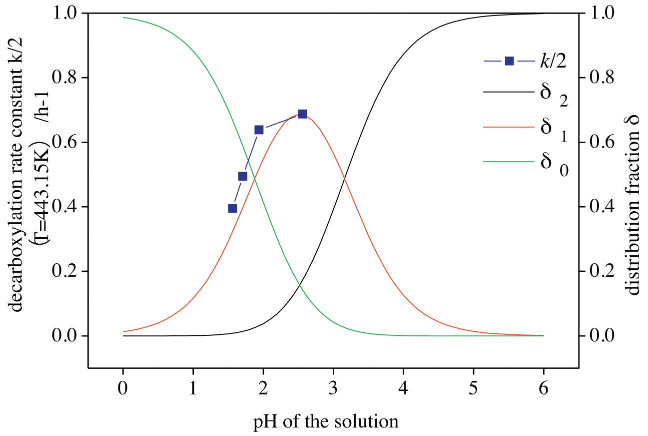


Fig. 4. Decarboxylation rate constant (at 453.15 K) and distribution fraction of various species from tetrafluorophthalic acid at different pH value. δ_0 is the distribution fraction of $H_2C_8O_4F_4$. δ_1 is the distribution fraction of $HC_8O_4F_4^-$. δ_2 is the distribution fraction of $C_8O_4F_4^{2-}$.

Table 1
Rate constant for the decarboxylation of tetrafluorophthalic acid at different pH value.

Initial concentration of reactant/mmol/L	pH	k/h^{-1}
10	2.558	1.3743 ± 0.0281
20	1.94	1.2766 ± 0.0467
30	1.706	0.9897 ± 0.0350
40	1.56	0.7908 ± 0.0325

understanding of the chemistry and mechanism for the decarboxylation reaction in the ammonia-enriched aqueous phase, the pH value of the reaction solution was measured and correlated with the rate constants of the decarboxylation reaction. As shown in Fig. 4, the rate constant of the decarboxylation reaction increased significantly with the increase of pH value.

In order to estimate the distribution fraction of the three forms in the aqueous phase, the dissociation constants of tetrafluorophthalic acid were determined by potentiometric titration [19] at room temperature using an ionic background of 0.1 mol/L of KNO_3. The values were obtained as $pK_{a1} = 1.88 \pm 0.15$ and $pK_{a2} = 3.16 \pm 0.02$. The relationship between distribution fraction for the three forms and pH value of the solution are shown in Fig. 4. By comparing the rate constant of the decarboxylation with the distribution fraction of the monovalent anion form, it was suggested that the rate constant increased significantly with the increase of the amount of monovalent anion form. These observations and results indicated that the decarboxylation rate of tetrafluorophthalic acid was determined by the amount of monovalent anion form. The distribution fraction of the monovalent anion form over pH value of the solution was calculated using the following equation.

$$\delta_1 = \frac{[HC_8O_4F_4^-]}{c} = \frac{K_{a_1}10^{-pH}}{\left(10^{-pH}\right)^2 + 10^{-pH}K_{a_1} + K_{a_1}K_{a_2}} \quad (1)$$

where δ_1 is the distribution fraction of the monovalent anion form ($HC_8O_4F_4^-$), c is the total concentration of tetrafluorophthalic acid and $[HC_8O_4F_4^-]$ is the concentration of the monovalent anion form.

As such, an assumption was made that the rate constant of the decarboxylation was linearly relevant to the amount of monovalent anion form in the reaction medium. The linear equation fitted by the data in Table 1 can be expressed as

$$k(T = 443.15\text{K}) = 0.3357 + 1.6054\delta_1 \quad (2)$$

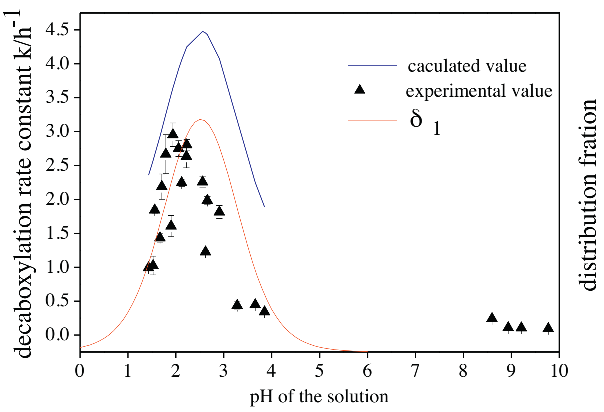


Fig. 5. Experimental and calculated decarboxylation rate constant at 453.15 K and distribution fraction of different forms from tetrafluorophthalic acid at different pH value. δ_1 is the distribution fraction of $HC_8O_4F_4^-$.

Then the following equation can be obtained by combining Eqs. (1) and (2).

$$k(T = 443.15\text{K}) = \frac{1.6054K_{a_1}10^{-pH}}{\left(10^{-pH}\right)^2 + 10^{-pH}K_{a_1} + K_{a_1}K_{a_2}} + 0.3357 \quad (3)$$

According to the data in Fig. 3, we used a first-order rate equation to fit conversion versus time at each temperature (in Section 3.4). The result shows that the conversion rate of tetrafluorophthalic acid fits a first-order equation, based on which rate constants and apparent activation energy for the decarboxylation were obtained. The Arrhenius equation for the decarboxylation rate constant (k(T)) can be expressed as

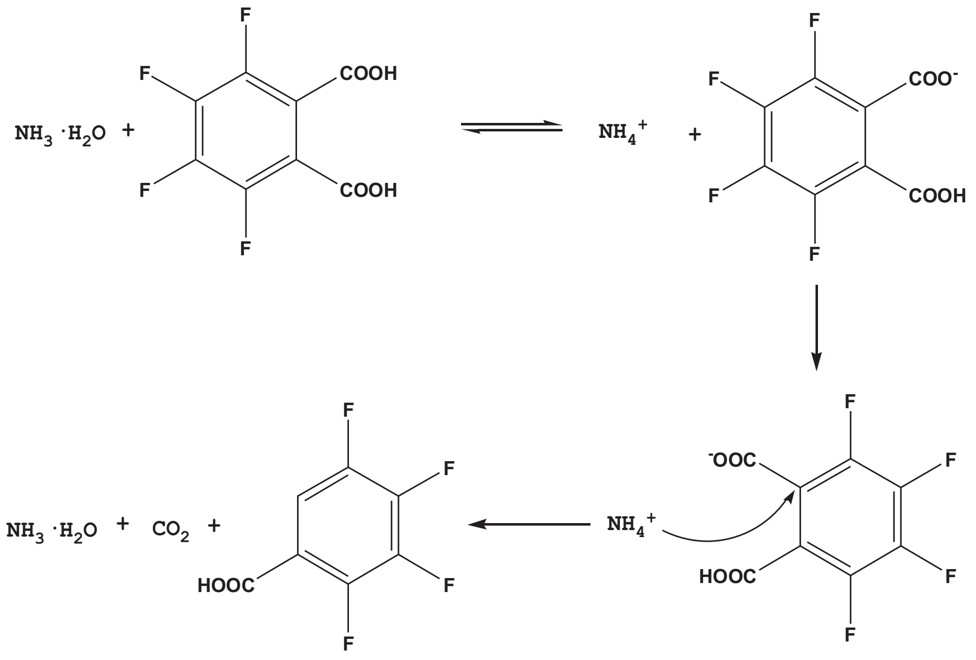
$$k(T) = k(T = 443.15\text{K})e^{\frac{E_a}{R}\left(\frac{1}{443.15} - \frac{1}{T}\right)} \quad (4)$$

Taken together, the effects of the ammonia concentration, initial concentration of reactant and temperature on the decarboxylation of tetrafluorophthalic acid can be expressed as the following equation

$$k(T) = \left(\frac{1.6054K_{a_1}10^{-pH}}{\left(10^{-pH}\right)^2 + 10^{-pH}K_{a_1} + K_{a_1}K_{a_2}} + 0.3357\right) e^{\frac{E_a}{R}\left(\frac{1}{443.15} - \frac{1}{T}\right)} \quad (5)$$

The rate constant of decarboxylation at 453.15 K was calculated by Eq. (5), and the results are shown in Fig. 5. Meanwhile, the distribution fraction of the monovalent anion form and the rate constants for decarboxylation obtained from experiments at 453.15 K are also shown in Fig. 5. These results suggested that the decarboxylation rate constants varied significantly with the distribution fraction of the monovalent anion form and the experimental data were directionally similar to the calculated values. The profile of calculated rate constant using the model approximately matches the experimental data. Generally, the experimental rate constant was lower than the calculated value, which might be derived from the differing dissociation constant for the tetrafluorophthalic acid at different temperatures and errors in estimating the experimental values using only one data set.

The mechanism for the decarboxylation of tetrafluorophthalic acid is proposed in Scheme 2, during which the ammonia plays a role in the proton transfer for the decarboxylation [10]. As pH value of the solution increases with the addition of ammonia, the protonated form losses protons and was subsequently converted to other forms. The decarboxylation can be remarkably promoted at an adequate pH range from 2.2–2.4, when the dominant form in the aqueous phase is the monovalent anion.



Scheme 2. Mechanism for the decarboxylation of tetrafluorophthalic acid.

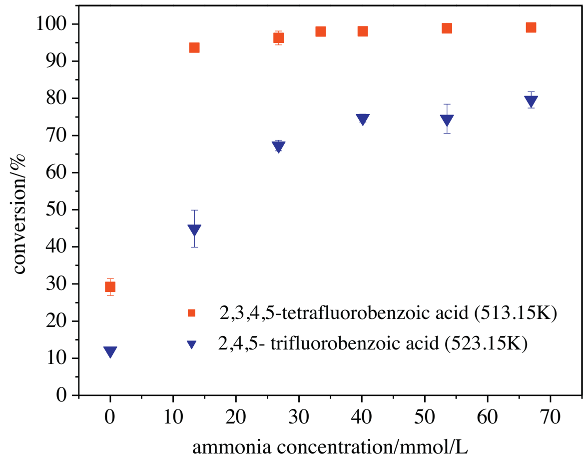


Fig. 6. Effect of ammonia concentration on the decarboxylation of 2,3,4,5-tetrafluorobenzoic acid (513.15 K, 1.5 h) and 2,4,5-trifluorobenzoic acid (523.15 K, 3 h).

3.6. Decarboxylation of multi-fluorobenzoic acids

The decarboxylation of 2,3,4,5-tetrafluorobenzoic acid and 2,4,5-trifluorobenzoic acid in NH_3-HTLW were investigated, and the results are shown in Fig. 6. The concentration of 2,3,4,5-tetrafluorobenzoic acid or 2,4,5-trifluorobenzoic acid was 30 mmol/L. 2,3,4,5-tetrafluorobenzoic acid was reacted in NH_3-HTLW at 513.15 K for 1.5 h, and 2,4,5-trifluorobenzoic acid was reacted in NH_3-HTLW at 523.15 for 3 h. The standard deviations in Fig. 6 were determined from three replicate experiments. Similar phenomenons were observed that the concentration of ammonia significantly impacted the decarboxylation of 2,3,4,5-tetrafluorobenzoic acid or 2,4,5-trifluorobenzoic acid. Without the addition of ammonia, the conversions of 2,3,4,5-tetrafluorobenzoic acid and 2,4,5-trifluorobenzoic acid were 29.2% and 12.1%, respectively. When 13.4 mmol/L of ammonia was added, the conversions of 2,3,4,5-tetrafluorobenzoic acid and 2,4,5-trifluorobenzoic acid increased to 93.6% and 44.9%, respectively. In addition, the conversion variations of 2,3,4,5-tetrafluorobenzoic acid and 2,4,5-trifluorobenzoic acid were different from that of tetrafluorophthalic acid. With the increase of ammonia loading, the decarboxylation conversions of 2,3,4,5-tetrafluorobenzoic acid and 2,4,5-trifluorobenzoic acid first increased and then kept stable, not similar with the variation trend of tetrafluorophthalic acid conversion. It attributed to that 2,3,4,5-tetrafluorobenzoic acid and 2,4,5-trifluorobenzoic acid are monocarboxylic acid but tetrafluorophthalic acid is dicarboxylic acid.

Through the preceding study and discussion, the variation of conversion is closely related to the distribution fraction of the monovalent anion form of multi-fluorobenzoic acids over pH value of the solution. Different monocarboxylic acids have different pK_a value, so they have different distribution fractions of the monovalent anion which can explain why different carboxylic acids have different optimal ammonia concentrations. When reaction substrate is dicarboxylic acid, as commonly known, the ease of the decarboxylation reactions depended upon the type of the substitution of the aromatic compound, fully ionized specie of tetrafluorophthalic acid is not favorable for the decarboxylation. As a result, the conversion of tetrafluorophthalic acid firstly increased and then significantly decreased with the increase of ammonia loading.

4. Conclusion

A green technology for the decarboxylation of tetrafluorophthalic acid to 2,3,4,5-tetrafluorobenzene in NH_3-enriched high temperature liquid water (HTLW) was developed. The decarboxylation of tetrafluorophthalic acid exhibited the first-order kinetics, and the activation energy was determined to be 190 $kJ\,mol^{-1}$. The addition of adequate amount of ammonia to the HTLW could significantly enhance the reaction rates and had no side effect on the selectivity to 2,3,4,5-tetrafluorobenzoic acid. The effects of ammonia concentration, initial reactant concentration and temperature on the decarboxylation of tetrafluorophthalic acid were correlated using an equation. The results indicated that adequate addition of ammonia could adjust the pH of the reaction medium into 2.2–2.4, where the dominant form of the decarboxylation is the monovalent anion. The pH values of the aqueous solution could impact the conversion of carboxylic acids by influencing their distribution fractions of the monovalent anion. Overall, ammonia plays a significant role in the proton transfer during the decarboxylation.

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