

Hydrolysis of Cephaneone in SDS/*n*-C₅H₁₁OH/H₂O System

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The hydrolysis of cephanone in SDS micelle and SDS/*n*-C₅H₁₁OH/H₂O O/W microemulsion was studied through Uv-vis absorption spectroscopy. The change of pH value in the hydrolysis of cephanone was determined. The result shows that pH value decreases in the process of the hydrolysis, and that the SDS micelle and SDS/*n*-C₅H₁₁OH/H₂O O/W microemulsion accelerate the hydrolysis of cephanone compared with water.

Keywords cephanone, hydrolysis, SDS, micelle, O/W microemulsion, accelerate

Introduction

Micelle solution composed of surfactants can affect, adjust and control many chemical reactions according to its effects of local concentration, polarity, charge, microviscosity, electrostatics, etc.^{1,2} Recently, it has aroused much attention to conduct chemical reactions using microemulsion as microreactor.³⁻⁷ The effect of micelle on the chemical reaction stems from its static electricity and hydrophobicity. Usually, cationic surfactant can catalyze the reaction between nucleophile and neutral molecule, while anionic surfactant suspends this reaction.

Cephanone, which can inhibit the synthesis of mucopeptide of cell walls of gram-positive bacteria, is a β -lactam compound with high medicinal value.⁸⁻¹⁰ However, there have been hardly any reports on the stability of cephanone in the microemulsion. The hydrolysis of cephanone in SDS micelle and SDS/*n*-C₅H₁₁OH/H₂O O/W microemulsion has been studied in the present paper. The result shows that compared with water, SDS micelle and SDS/*n*-C₅H₁₁OH/H₂O O/W microemulsion accelerate the hydrolysis of cephanone.

Experimental

Materials

Cephanone (The Pharmaceutical Factory of Chongqing, 1000000 units), *n*-pentanol (*n*-C₅H₁₁OH, Aldrich, 99 + %), pyrene (Aldrich, 99%), sodium dodecyl sulfate (SDS, Sigma, chemical purity) was recrystallized twice in ethanol before use. Water used was dis-

tilled twice.

Measurement of the hydrolytic curve

On account of the similarity between the structure of cephanone and that of penicillin G potassium salt, the mechanism of the hydrolysis of cephanone is inferred as Scheme 1 according to that of penicillin G potassium salt.¹¹

It can be seen from Scheme 1 that the mid-product **B** of the hydrolysis of cephanone can be further hydrolyzed into the final product **D** in strong acidic media, or into the final product **C** in weak acidic or basic media. Cephanone and its final product **C** and **D** have no absorption above 300 nm, the mid-product **B** has an absorption around 320 nm (Fig. 1), while the other reagents have no absorption above 280 nm. Thus, the absorbance values (**A**) around 320 nm can be used to quantitatively indicate the relative content of product **B**. The dynamic hydrolysis curves were obtained by plotting absorbance value *A* versus time *t* at (50 ± 0.1) °C. The concentration of cephanone was 0.1% (*w*). The UV-vis absorption spectra were recorded on a UV-240 ultraviolet spectrometer (Shimadzu Co.).

Determination of pH value

The pH value in different systems containing 0.1% cephanone was determined by using a pHS-25 acidimeter (Shanghai Rex Instrument Factory) at (50 ± 0.1) °C.

Results and discussion

Hydrolysis of cephanone in water

Curve a in Fig. 2 shows the variation of the absorbance value (*A*) of the mid-product **B** in water with time *t*. It can be seen from this figure that the concentration of the mid-product **B** remains almost constant during the initial stage (*t* < 150 min). Then it rises abruptly and reaches its maximum at about 710 min. When *t* is over 710 min, it decreases gradually. Curve b in Fig. 2 shows that the pH value in water increases slightly in the initial

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Scheme 1

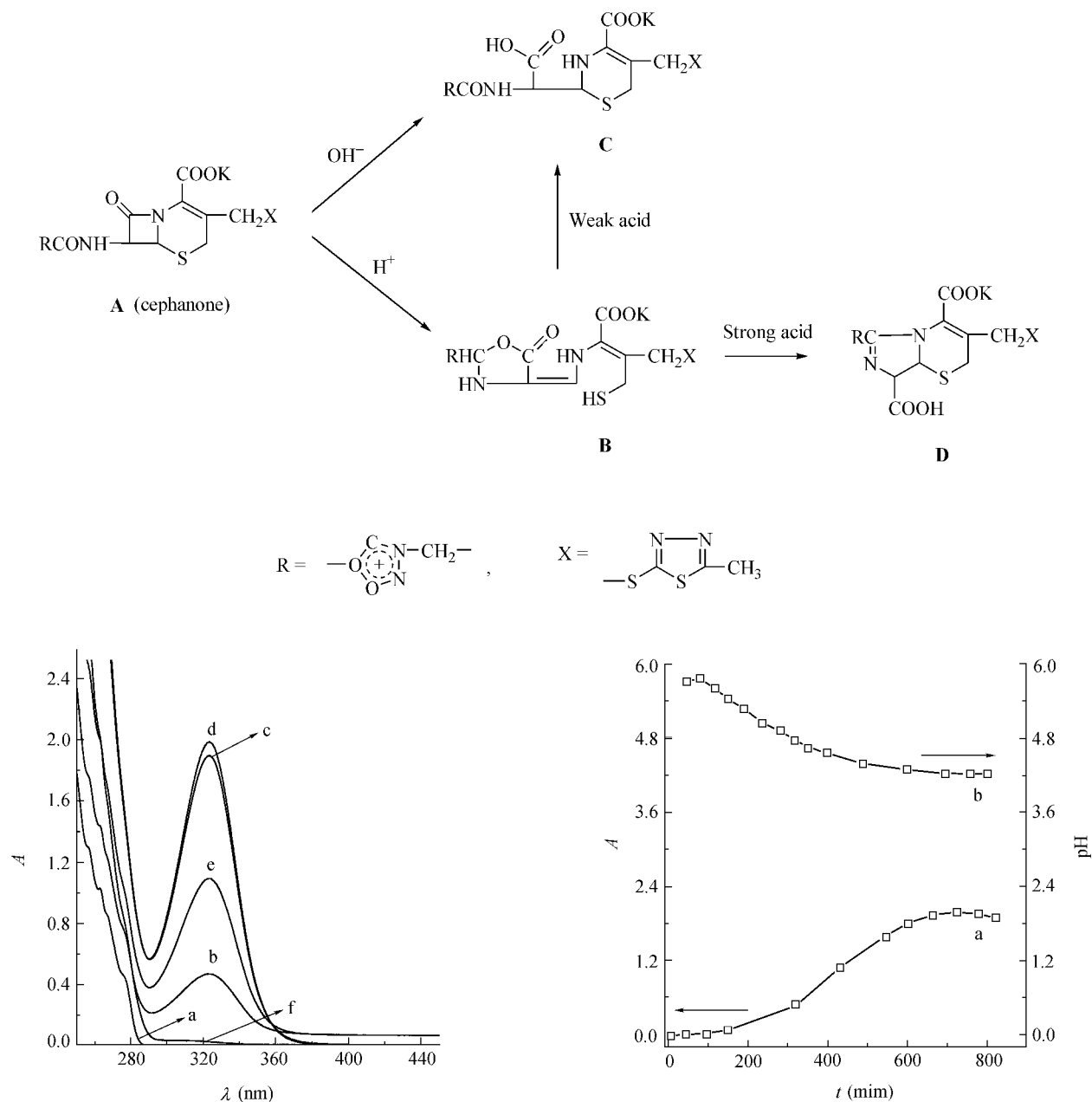


Fig. 1 Change of UV-vis spectra of cephanone aqueous solution with time t . Time : a , 4 min ; b , 318 min ; c , 432 min ; d , 723 min ; e , 821 min ; f , ∞ .

Fig. 2 Absorbance value A of the mid-product **B** and the pH value with time t in water (cephanone content = 0.1%).

stage , then it begins to decrease. The pH value drops to its minimum at about 700 min. When t is over 700 min , the pH value remains almost constant. Obviously , the time corresponding to the minimum pH value consists with that corresponding to the maximum concentration of the mid-product **B** in water. So the change of the pH value is related to the concentration of the mid-product **B**.

Cephanone can be hydrolyzed in water due to the attack of H^+ from water ionization. Thus , in the initial stage of the hydrolysis , the H^+ concentration decreases and the pH value increases. With the increasing concentration of the mid-product **B** , H^+ concentration increases

and the pH value decreases because of the larger dissociation constant of the group —SH in the mid-product **B**. After the pH value decreases to its minimum , on the one hand , the mid product **B** begins to hydrolyze further to produce the final product **C** (Scheme 1), which may make the pH value decrease ; on the other hand , the concentration of the mid-product **B** decreases gradually , which may make the $[\text{H}^+]$ from the ionization of the mid-product **B** decrease , so the pH value increases. The almost constant pH value when t is over 700 min in water indicates that the formation of the mid-product **B** and the transformation from the mid-product **B** to the final product

C are at equilibrium.

Hydrolysis of cephanone in SDS micelles

Fig. 3 is the partial diagram of SDS/*n*-C₅H₁₁OH/0.1% cephanone (aq). The systems studied in the present paper are in the O/W microemulsion region. Fig. 4 shows that in water and SDS micelle, the formation rates of the mid-product **B** are very slow within the first 100 min of the hydrolysis, and then increase faster. The formation rates of the mid-product **B** are similar in water and SDS micelle in the initial stage, but it is higher in SDS micelle than in water, at about 350 min when the mid-product **B** reaches its maximum concentration (710 min in water, Curve a in Fig. 4); and the dropping rate of the concentration of the mid-product **B** is higher in SDS micelle than in water. Thus, SDS micelle can promote the hydrolysis of

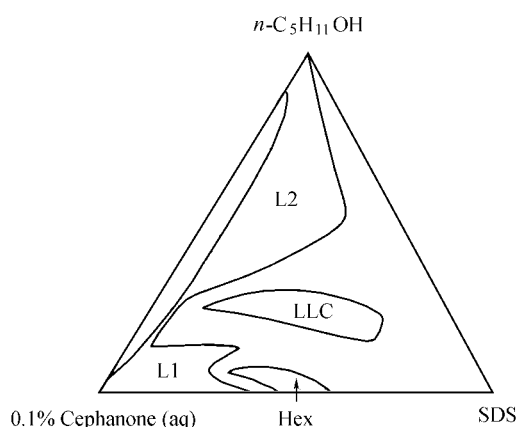


Fig. 3 Partial diagram of SDS/*n*-C₅H₁₁OH/0.1% cephanone (aq). L1, O/W region; L2, W/O region; LLC, lamellar liquid crystal region; Hex, hexagonal liquid crystal region.

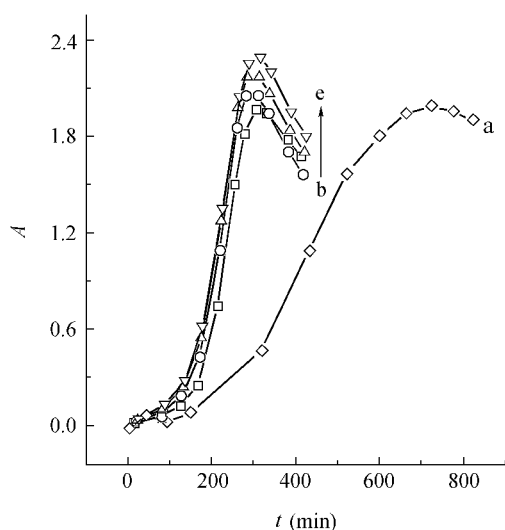


Fig. 4 Absorbance value *A* of the mid-product **B** with time *t* in SDS micelle (cephanone content = 0.1%). SDS content: a, 0%; b, 1%; c, 2%; d, 3%; e, 4%.

cephanone. It can also be seen that the hydrolysis rate of cephanone and the maximum concentration of the mid-product **B** increase slightly with the increasing SDS content, which shows that the stability of mid-product **B** is enhanced slightly at higher SDS content.

Fig. 5 shows that the pH value decreases steadily in SDS micelle, the decreasing rate of pH value is higher than that in water, and that it drops to its minimum at about 370 min. The time for pH value to reach its minimum consists with that for the mid-product **B** concentration to reach the maximum (Curve b in Fig. 4) in SDS micelle.

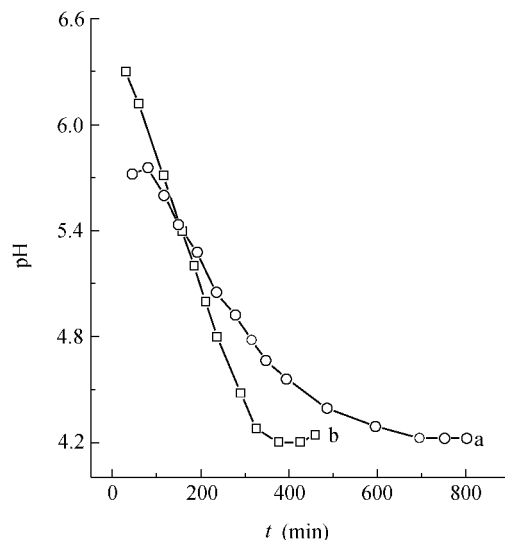


Fig. 5 Plots of the pH values of water (Curve a) and SDS micelle (Curve b, weight ratio of SDS:H₂O = 1:99) as a function of time *t* (cephanone content = 0.1%).

In SDS micelle, at the initial stage of the hydrolysis, the hydrolysis rate of cephanone existing at the surface of micelle is higher than that in water due to the higher concentration of proton adsorbed at the surface of the micelles. On one hand, the concentration of the mid-product **B** increases, which leads to the increase of acidity and the lower of pH value. On the other hand, those H⁺ from water ionization attacks cephanone molecule to form hydrolysis product making the acidity decrease and the pH value increase. In SDS micelle, the proton concentration is much higher at the surface of the micelle, so the former effect on the pH value is greater and the apparent pH value decreases at the initial stage. The location of cephanone can be confirmed by the experiment of distribution constant¹² (Fig. 6). The distribution constant of cephanone between micellar and aqueous phase is 7.1, which shows that there exists an intermolecular interaction between cephanone and SDS.

From the above results, it can be seen that SDS micelle can promote the hydrolysis of cephanone. Since the pH values are less than 7 and the variation patterns of the pH value are similar in water and in SDS micelle, the mechanism of the hydrolysis of cephanone are the same in SDS micelle and in water. Cephanone can be ionized into

cephanone⁻ and K⁺ in the aqueous solution, and its polar groups (carboxyl, carbonyl and amino group) are easily attacked by proton, which leads to the rupture of β -lactam ring (Scheme 1). The above mention follows that the promoting effect of SDS on hydrolysis of cephanone may be related to the charge character of SDS and the interaction between cephanone and SDS. In SDS micelle, the hydrophilic group SO₄⁻ in SDS molecule repels cephanone⁻ group adsorbed in the surface of the micelle and increases the charge density of the polar groups in cephanone molecule, which enhances the hydrolysis of cephanone. On the other hand, H⁺ can be adsorbed at the surface of SDS micelle, which increases the contact of H⁺ with cephanone molecules at the surface of micelle. Thus, the hydrolysis of cephanone is enhanced.

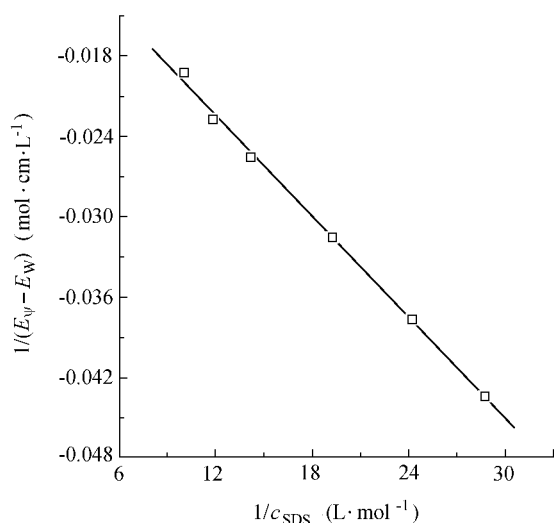


Fig. 6 Plot of $(E_{\Psi} - E_w)^{-1}$ vs. c_{SDS}^{-1} .

The effect of SDS on the hydrolysis of cephanone can also be confirmed by the initial pH value of the hydrolysis of cephanone (Fig. 5). It can also be seen that in water and in SDS micelle, the changing tendencies of pH values are similar but the initial pH values are different. The initial pH values are 5.7 in water and 6.2 in SDS micelle. It is obvious that the surface of the micelle of anionic surfactant SDS adsorbs positive ion H⁺, which makes the proton concentration lower in water continuous phase and the pH value higher. The initial pH value represents the initial concentration of OH⁻ in the solution. There is an exclusive effect between OH⁻ and cephanone, which can make the negative charge density of cephanone higher and the hydrolysis of cephanone occur more easily. The higher initial pH value in SDS micelle than that in water means that SDS can accelerate the hydrolysis of cephanone.

Hydrolysis of cephanone in SDS/*n*-C₅H₁₁OH/H₂O O/W microemulsion

Fig. 7 shows the change of the concentration of the mid-product B with *n*-C₅H₁₁OH content in SDS/*n*-C₅H₁₁OH/H₂O O/W

microemulsion at a constant weight ratio of SDS/H₂O = 1:99. It can be seen that the hydrolysis rate decreases with increasing *n*-C₅H₁₁OH content. In O/W microemulsion when the *n*-C₅H₁₁OH content increases, cosurfactant *n*-C₅H₁₁OH participates in the forming of micelle and causes the volume of the O/W microemulsion droplets to increase, which enables the surface of O/W microemulsion droplets to adsorb more cephanone molecules, so the content of cephanone in water continuous phase decreases, and then the hydrolysis rate is decreased; at the same time, the charge density on the surface of microemulsion droplet decreases, H⁺ concentration at the surface of microemulsion droplets is decreased, and then the hydrolysis of cephanone existing at the surface of microemulsion droplets is decreased, too. So the hydrolysis of cephanone is decreased with the increase of *n*-C₅H₁₁OH content.

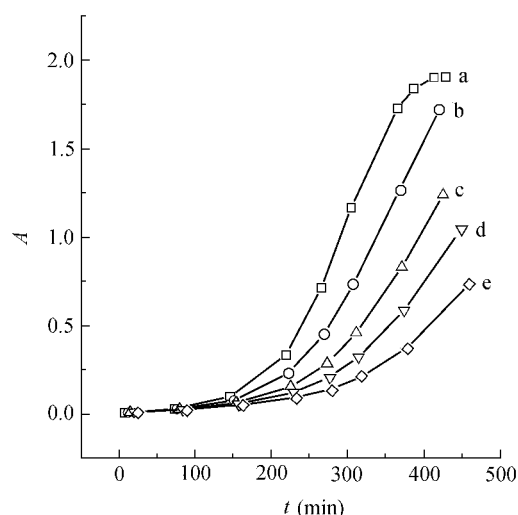


Fig. 7 Plots of the absorbance value *A* of the mid-product B as a function of time *t* in SDS/H₂O/*n*-C₅H₁₁OH/O/W microemulsion with different *n*-C₅H₁₁OH content (weight ratio of SDS:H₂O = 1:99, cephanone content = 0.1%). *n*-C₅H₁₁OH content: a, 0.5%; b, 1.0%; c, 1.5%; d, 2.0%; e, 2.5%.

Fig. 8 shows that at the constant weight ratio of *n*-C₅H₁₁OH:H₂O = 2:98 in SDS/*n*-C₅H₁₁OH/H₂O O/W microemulsion system, the hydrolysis rate of cephanone increases with SDS content. It is obvious that with increasing SDS content, the charge density at the surface of O/W microemulsion droplet increases and the charge repulsion between SDS and cephanone is enhanced, which leads to the increase of the negative charge density of carbonyl in cephanone molecule and the attack of electrophile on cephanone. So the hydrolysis of cephanone is enhanced.

It can be seen that the hydrolysis of cephanone in O/W microemulsion (Curve b in Fig. 8) is slower than that in micelle (Curve b in Fig. 4) with the same SDS concentration. This result may be due to the fact that the existing

of cosurfactant $n\text{-C}_5\text{H}_{11}\text{OH}$ in the interphase of SDS micelle lowers the negative charge density of O/W microemulsion droplets, which decreases the concentration of H^+ adsorbed at the surface of O/W microemulsion droplets. Thus, the hydrolysis of cephanone adsorbed at the surface of O/W microemulsion droplets decreases and so does the apparent hydrolysis rate of cephanone.

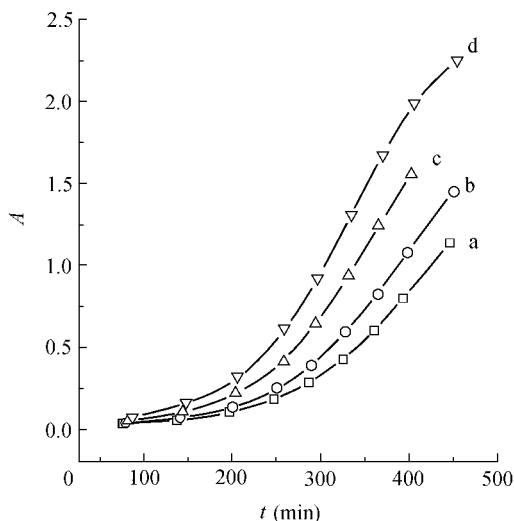


Fig. 8 Plots of the absorbance value A of the mid-product **B** as a function of time t in SDS/ H_2O / $n\text{-C}_5\text{H}_{11}\text{OH}$ O/W microemulsion with different SDS content (weight ratio of $n\text{-C}_5\text{H}_{11}\text{OH} : \text{H}_2\text{O} = 2 : 98$, cephanone content = 0.1%). SDS content : a, 0.5% ; b, 1.0% ; c, 2.0% ; d, 3.0%.

However, the effect of $n\text{-C}_5\text{H}_{11}\text{OH}$ (Fig. 7) on the hydrolysis of cephanone is larger than that of SDS in the O/W microemulsion (Fig. 8) though the effects of SDS and $n\text{-C}_5\text{H}_{11}\text{OH}$ on the hydrolysis are reversed. This result indicates that the change of the number of O/W microemulsion droplets caused by the variation of SDS concentration is smaller than that of the charge density of the O/W microemulsion caused by the variation of $n\text{-C}_5\text{H}_{11}\text{OH}$ concentration.

To obtain the apparent reaction rate constant, the hydrolysis of cephanone is carried out in buffer solution with $\text{pH} = 3.56$. Thus, the mechanism of hydrolysis of cephanone shown in Scheme 1 can be simplified as the following consecutive reaction.



Where, **A** is cephanone, **B** is the mid-product and **C** is the final product, k_1 and k_2 are the first and the second apparent reaction rate constants, respectively.

According to the characteristics of consecutive reaction, the maximum concentration (y_m) and its corresponding time (t_m) of the mid-product **B** can be expressed as follows.¹³

$$t_m = \frac{\ln k_2 - \ln k_1}{k_2 - k_1} \quad (2)$$

$$y_m = c_A \left(\frac{k_1}{k_2} \right)^{\frac{k_2}{k_2 - k_1}} \quad (3)$$

Where c_A is the initial concentration of cephanone. So, k_1 and k_2 in different systems can be obtained from Fig. 9 by the formulas (2) and (3), and the result is shown in Table 1.

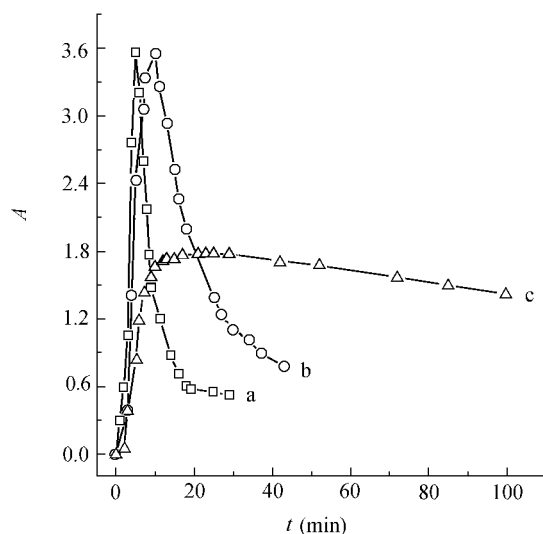


Fig. 9 Plots of the absorbance value A of the mid-product **B** as a function of time t in different systems with $\text{pH} = 3.56$ (cephanone content = 0.1%). Systems : a, SDS micelle (SDS content = 1.0%) ; b, SDS/ $n\text{-C}_5\text{H}_{11}\text{OH}$ / H_2O O/W microemulsion (SDS content = 1.0%, $n\text{-C}_5\text{H}_{11}\text{OH}$ content = 1.0%) ; c, water.

Table 1 Hydrolysis rate constants k_1 and k_2 of cephanone in different systems (cephanone content = 0.1%, $\text{pH} = 3.56$)

System	Water	SDS micelle ($c_{\text{SDS}} = 1.0\%$)	O/W microemulsion ($c_{\text{SDS}} = 1.0\%$, $c_{\text{OH}} = 1.0\%$)
k (min^{-1})	0.019	0.134	0.081
k (min^{-1})	0.083	0.287	0.122

It can be seen from Table 1 that the apparent hydrolysis rate constant of cephanone is larger in SDS micelle than in water, but it is smaller in the SDS/ $n\text{-C}_5\text{H}_{11}\text{OH}$ / H_2O O/W microemulsion than in SDS micelle at the fixed SDS content. Therefore, SDS can accelerate but $n\text{-C}_5\text{H}_{11}\text{OH}$ can inhibit the hydrolysis of cephanone, and it is accordant with the results shown in Fig. 7 and Fig. 8.

Conclusions

SDS can enhance, while $n\text{-C}_5\text{H}_{11}\text{OH}$ can inhibit the hydrolysis of cephanone. The effect of SDS on the hydroly-

ysis of cephanone is related to the electrostatic effect between SDS and cephanone.

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