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Kinetics and Mechanism of Degradation of Chlorphenesin Carbamate in Strongly Acidic Aqueous Solutions[1)]

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The kinetics and mechanism of the degradation of chlorphenesin carbamate (α-CPC) in various strongly acidic aqueous solutions were studied at 40 to 60 °C.

The degradation of α-CPC obeyed pseudo first-order kinetics. The rate law of the degradation could be explained in terms of specific acid-catalyzed hydrolysis. From the analysis of the Arrhenius plot of the degradation, which was linear, the apparent activation energy and the apparent entropy at 50 °C of the degradation reaction were calculated to be 21.8 kcal·mol^{-1} and −21.3 cal·deg^{-1}·mol^{-1}, respectively.

Chlorphenesin was detected as the acidic degradation product of α-CPC. The degradation mechanism in a strongly acidic aqueous solution was different from that in the strongly alkaline aqueous solution obtained previously and was shown to involve the removal of the carbamoyl group by hydrogen ion catalysis without isomerization.

Keywords——chlorphenesin carbamate; skeletal muscle relaxant; kinetics; hydrolysis; strongly acidic aqueous solution

In a previous report,[2)] we showed that the degradation mechanism of chlorphenesin carbamate (α-CPC) in an alkaline environment involved isomerization, equilibrium and degradation. In this study, we investigated whether the degradation mechanism in a strongly acidic environment was the same as that in the strongly alkaline environment, and we also examined the degradation kinetics.

Experimental

Materials——α-CPC, chlorphenesin-2-carbamate (β-CPC, the isomer of α-CPC) and chlorphenesin (CP) were kindly supplied by the manufacturer (Upjohn Company, U.S.A.) and were used without further purification. All other chemicals used were of reagent grade.

Acidic Solutions——Acidic solutions of 0.1, 0.5 and 1 N hydrochloric acid were prepared, and were standardized by using sodium carbonate (standard reagent) according to JP IX before each use.

Kinetics of the Degradation of α-CPC in Strongly Acidic Aqueous Solutions——About 0.025 g of α-CPC was dissolved in 100 ml each of various acidic aqueous solutions. Solutions thus obtained were placed in glass ampoules (10 ml). After being sealed, the ampoules were stored at the desired reaction temperatures (40 °C for studying the effect of acidic concentration and 50 and 60 °C for the measurement of activation energy). The final concentration of α-CPC was 1 mM. To examine the degradation mechanism of α-CPC, the degradation kinetics of β-CPC were simultaneously examined at a concentration of 0.5 mM (because of its low solubility in water). At suitable intervals, samples were withdrawn, cooled on ice and assayed for α-CPC, β-CPC and CP by the high performance liquid chromatography (HPLC) method described previously.[2)] However, 5 N hydrochloric acid was not added to stop the reaction because the samples were already very acidic.

Results and Discussion

Figure 1A shows the chromatogram of CP(1), α-CPC(2) and β-CPC(3) in a standard

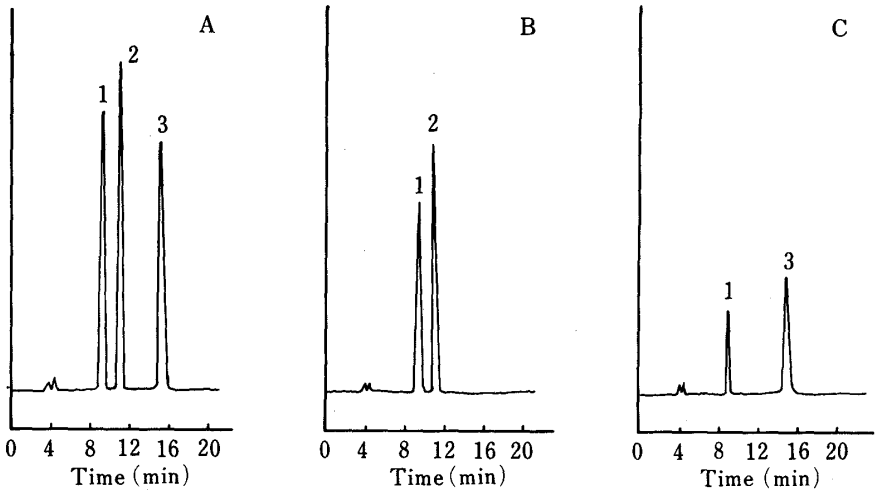

Fig. 1. Chromatograms of α-CPC, β-CPC and Their Degradation Products

A, standard solution; B, reaction solution of α-CPC in 0.532 N HCl at 60 °C after 192 h; C, reaction solution of β-CPC in 0.532 N HCl at 60 °C after 65 h; 1, CP; 2, α-CPC; 3, β-CPC.

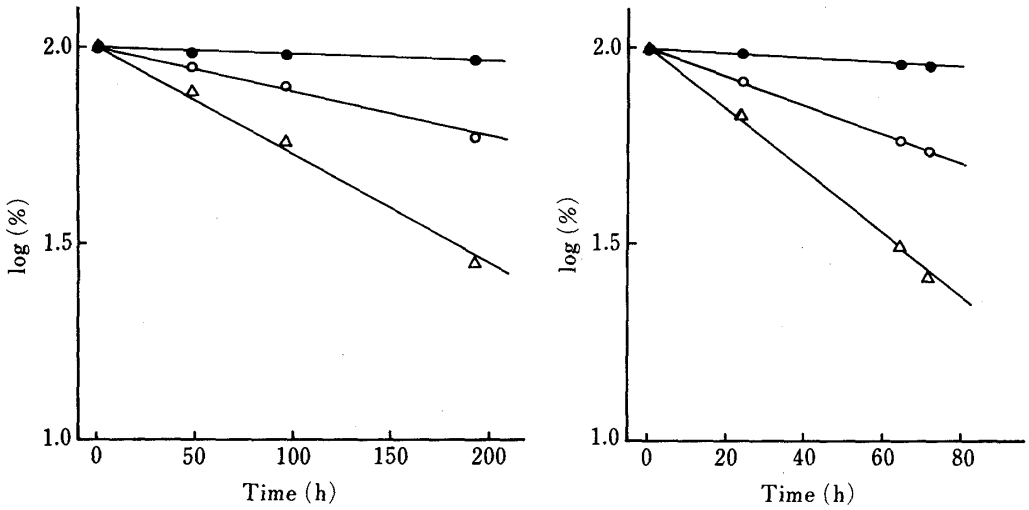

Fig. 2. Time Courses of the Degradation of α-CPC and β-CPC in Various HCl Solutions at 60 °C

A, degradation of α-CPC; B, degradation of β-CPC; ●, 0.107 N HCl; ○, 0.532 N HCl; △, 1.06 N HCl.

solution. Figure 1B shows the chromatogram of the degraded solution in 0.532 N HCl at 60 °C after 192 h. The degradation of α-CPC yielded a single product. To examine the degradation mechanism of α-CPC, β-CPC was degraded under the same conditions as α-CPC, as shown in Fig. 1C. The degradation of β-CPC gave a single degradation product, which had a retention time identical with that of the degradation product of α-CPC, and of CP(1) of the standard solution. β-CPC, an isomeric degradation product, was not observed in a strongly acidic aqueous solution (Fig. 1). In the strongly alkaline aqueous solution, the degradation of α-CPC involved isomerization and degradation. Therefore, in strongly acidic aqueous solutions, the isomerization was considered to be inhibited by hydrogen ions.

Figure 2 shows the time courses of the decrease of α-CPC and β-CPC in various concentrations of hydrochloric acid. The degradations of α-CPC and β-CPC obeyed pseudo-first order kinetics in all cases.

The effect of acid concentration on the degradation of α-CPC was examined. pH was

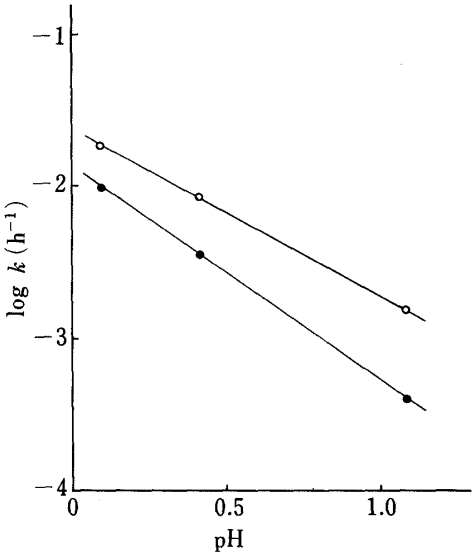

Fig. 3. Rate–pH Profile of the Degradation Rate Constants at 60 °C
●, α-CPC; ○, β-CPC.

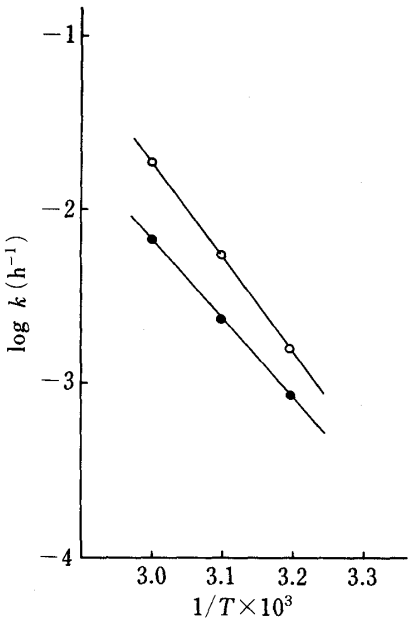

Fig. 4. Arrhenius Plots of the Rate Constants of the Degradation in 1.06 N HCl
●, α-CPC; ○, β-CPC.

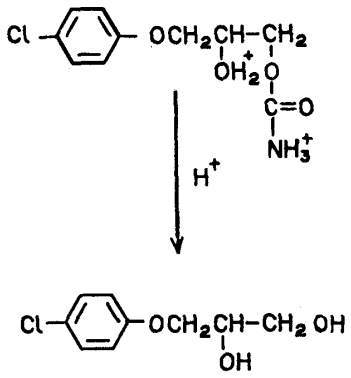

Chart 1. Proposed Degradation Mechanism of α-CPC in Strongly Acidic Aqueous Solutions

calculated taking into account the mean activity coefficient of a concentrated hydrochloric acid solution.[3]

Figure 3 shows the rate–pH profiles. In the case of β-CPC, the plot of the logarithm of the rate constants *versus* pH was linear with a slope of minus unity. However, in the case of α-CPC, it was linear with a smaller value than minus unity. It was considered that the apparent entropy of α-CPC was about 3 times smaller than that of β-CPC. This suggests that the degradation of α-CPC and β-CPC is dominated by specific acid catalysis. Judging from Figs. 1 and 2, the OH group and the amino group of α-CPC were protonated in strongly acidic aqueous solution as reported by Schmid and Voak.[4] The degradation mechanism of α-CPC in strongly acidic aqueous solutions is considered to be as shown in Chart 1. The protonated OH_2^+ group is inhibited from attacking the carbamoyl carbon nucleophilically. Therefore, the isomerization of α-CPC is considered not to take place in strongly acidic solutions, and the protonated α-CPC is degraded to CP by means of hydrogen ion catalysis. The degradation mechanism of β-CPC is considered to be the same as that of α-CPC.

The effect of temperature on the degradation of α-CPC and β-CPC was examined at 40 to

60 °C. The plots of the logarithm of rate constants *versus* the reciprocal of temperatures were linear. The apparent activation energies for α-CPC and β-CPC were calculated to be 21.8 and 26.0 kcal·mol^{-1}, respectively. Furthermore, the apparent entropies at 50 °C for the degradation of α-CPC and β-CPC were calculated to be −21.3 and −6.9 cal·deg^{-1}·mol^{-1}, respectively.

References and Notes

1) This paper forms Part II of "Studies on the Kinetics and Mechanism of Drug Degradation." This study was presented at the 100th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1980.
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3) T. Yamana, "Iyakuhinsokudoron," Nankodo, Tokyo, 1979, pp. 21—23.
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