# Kinetics of Degradation of Cinnarizine in Aqueous Solution[1]

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The kinetics of the degradation of cinnarizine in aqueous solution at various pH values and four different temperatures were investigated. The degradation of cinnarizine was observed as a pseudo first-order reaction. By determining the degradation rate of cinnarizine at various pH values, it was found that the degradation rate of cinnarizine increased with decreasing pH within the range from pH 3.0 to 1.0. The rate remained unchanged at below pH 1.2, and cinnarizine was stable at above pH 3.0. The pseudo first-order rate constants in aqueous solution (pH 1.20) at 60, 70, 80 and 90 °C were $1.85 \times 10^{-5}$, $1.05 \times 10^{-4}$, $4.07 \times 10^{-4}$ and $1.94 \times 10^{-3}$ min$^{-1}$, respectively. The activation energy of degradation in aqueous solution (pH 1.20) was calculated to be 36.8 kcal/mol from an Arrhenius plot.

Keywords——cinnarizine; stability; degradation; kinetics; Arrhenius plot; activation energy

Cinnarizine (CN), a cerebral blood flow improver, is widely used orally for treatment of cerebral apoplexy, cerebral arteriosclerosis and post traumatic cerebral symptoms. In a previous study,[2] an investigation was carried out with the aim of improving the dissolution characteristics of CN, and it was found that the dissolution rare of CN as the inclusion complex was about 30 times or more larger than that of intact CN. Further, new and efficient procedures (the neutralization method and spray-drying method[3]) were developed to prepare CN–$\beta$-cyclodextrin (CD) inclusion complex on a manufacturing scale. In the above method, it was necessary to dissolve CN in acidic solution. However, the stability of CN in acidic solution has not been investigated. CN (the chemical structure is shown in Chart 1) can be classified as a member of the benzhydryl amine group of antihistamines. The degradation of homochlorcyclizine (HCC), one of the benzhydryl group, in acidic solution has been reported.[4] Further, diphenhydramine (having a benzhydryl group, like CN), one of the antihistamines of the benzhydryl ether group, is also known to degrade in acidic solution.[5] From the above reports, the degradation of CN in acidic solution seemed likely. Therefore, an investigation was carried out on the kinetics of degradation of CN in acidic solution, the effect of pH on the degradation and the activation energy. The results are presented here.
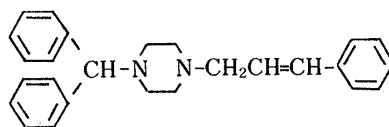
CH-N N-CH$_2$CH=CH-

Chart 1. Structure of Cinnarizine

### Experimental

**Materials**——CN was obtained from Eisai Co., Ltd. and other chemicals were of reagent grade. Deionized water was used in all experiments.

**Kinetic Measurement of Degradation of CN**——CN was dissolved in buffers to make a $1.63 \times 10^{-3}$ M solution. The pH values of 0.2 M sodium acetate–HCl solution used for measurement of the rate–pH profile of the degradation of CN were as follows; pH 0.4, 1.2, 1.7, 2.0, 2.2, 2.4, 2.8, 3.0, 3.8. The pH value of these buffer solutions was checked before and after the reaction, and were unchanged. The ionic strength of these buffer solutions was adjusted to 0.7 with NaCl. The first fluid for the disintegration test in the Japanese Pharmacopoeia X (pH 1.20) was used as the buffer solution for the estimation of the activation energy. A 5 ml aliquot of the buffer solution containing $1.63 \times 10^{-3}$ M CN was placed in a 10 ml glass ampule, which was sealed and kept in a controlled-temperature oven (Yamato Scientific Co., Ltd., Tokyo, Japan) at 60, 70, 80 or 90 °C with 0.1 °C precision. Ampules were withdrawn at appropriate intervals and cooled to room temperature. Then 10 ml of 10% hydrochloric acid and 15 ml of chloroform were added to 3 ml of the solution taken from the ampule. The mixture was shaken and the absorbance at 295 nm of the organic layer was measured. The degradation product (showing absorption at 295 nm) was not extracted. The amount of CN that remained in the solution was calculated by using a calibration curve prepared in advance.

### Results and Discussion

#### Kinetic Study

Nogami and Horioka,[5] and Nakano[4] reported that the degradations of diphenhydramine and HCC were first-order type processes. In the case of CN, the degradation reaction was also expected to be a first-order type process.

Figure 1 shows the relationship between residual CN (percent) on a logarithmic scale and time for the degradation of CN at various pH values. Each plot in Fig. 1 is linear. This result indicates that the degradation reaction of CN within the range of pH 0.4 to 3.0 is an apparent first-order reaction.

Figure 2 shows the relationship between residual CN (percent) on a logarithmic scale and time for the degradation of CN at four different temperatures, 60, 70, 80 and 90 °C, in pH 1.20
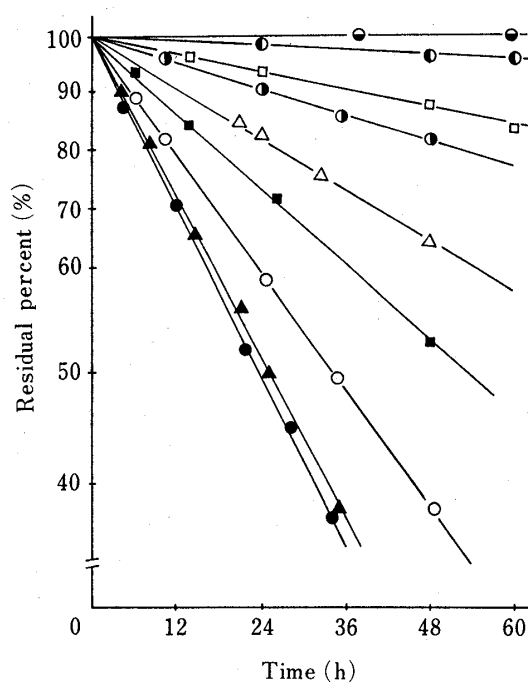


Fig. 1.  First-Order Plots for the Degradation of CN in Buffer Solutions of pH 0.4—3.8 at 80 °C

●, pH 0.4; ▲, pH 1.2; ○, pH 1.7; ■, pH 2.0; △, pH 2.2; ◑, pH 2.4; □, pH 2.8; ◐, pH 3.0; ◒, pH 3.8.
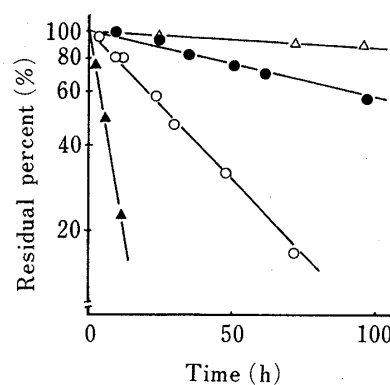


Fig. 2.  First-Order Plots for the Degradation of CN in Aqueous Solution of pH 1.20

△, 60 °C; ●, 70 °C; ○, 80 °C; ▲, 90 °C.

TABLE I. Apparent First-Order Rate Constants for the Degradation of CN at 80 °C

| pH | $k$ (min$^{-1}$) |
|---|---|
| 0.4 | $4.82 \times 10^{-4}$ |
| 1.2 | $4.65 \times 10^{-4}$ |
| 1.7 | $3.31 \times 10^{-4}$ |
| 2.0 | $2.23 \times 10^{-4}$ |
| 2.2 | $1.55 \times 10^{-4}$ |
| 2.4 | $7.61 \times 10^{-5}$ |
| 2.8 | $5.13 \times 10^{-5}$ |
| 3.0 | $1.37 \times 10^{-5}$ |
| 3.8 | 0 |

TABLE II. Effect of Temperature on the Rate Constant of the Apparent First-Order Degradation of CN in Aqueous Solution of pH 1.20

| °C | $k$ (min$^{-1}$) |
|---|---|
| 60 | $1.85 \times 10^{-5}$ |
| 70 | $1.05 \times 10^{-4}$ |
| 80 | $4.07 \times 10^{-4}$ |
| 90 | $1.94 \times 10^{-3}$ |

buffer solution. Each plot in Fig. 2 is linear, indicating that the degradation reaction of CN in the range of 60 to 90 °C in pH 1.20 buffer solution is an apparent first-order reaction. The results shown in Figs. 1 and 2 indicate that the assumption that the reaction is first-order is reasonable, and it is considered that the degradation of CN in acidic solution is similar to that of diphenhydramine or HCC.

The apparent first-order rate constant, $k$, was calculated from the slope of each straight line shown in Figs. 1 and 2. The results are shown in Tables I and II.

**Effect of pH on the Degradation Rate of CN in Aqueous Solution**

Figure 3 shows the relationship between rate constants ($k$) and pH on the basis of the data shown in Table I. The degradation rate of CN increased with decreasing pH from 3.0 to 1.0. Below pH 1.2, the degradation rate of CN remained unchanged and CN was stable at above pH 3.0. The rate-pH profile of CN shown in Fig. 3 is similar in pattern to that of HCC. In the case of HCC, the reaction rate–pH profile was explained as follows;[4] in the aqueous solution of HCC·2HCl there is the following equilibrium: $HCC^{2+} \rightleftharpoons HCC^{+} + H^{+}$, where $HCC^{+}$ and $HCC^{2+}$ represent uni- and bivalent HCC ions, respectively. The apparent rate constant, $k$, of the degradation of HCC·2HCl varies with the mole fraction $F$ of $HCC^{2+}$ according to $k = k'F$, where $k'$ is the rate constant of the degradation of $HCC^{2+}$. This indicates that of the two ionic species of HCC, only $HCC^{2+}$ is susceptible to degradation, which starts with the cleavage of the bond between the $p$-chlorobenzhydryl group and the nitrogen atom.

Further, Nakano reported that the $F$-pH profile calculated from $pK_{a2}$ follows the same pattern as the rate–pH profile of HCC.[4]

It can thus be assumed that the degradation of CN in aqueous solution occurs only on $CN^{2+}$ ion, and that the apparent rate constant, $k$, of the degradation of CN varies with $F$ of $CN^{2+}$. The value of $k'$, which is the degradation rate of the $CN^{2+}$ ion, is assumed to be $4.82 \times 10^{-4}$ min$^{-1}$ at 80 °C. This value is about 3.6 times larger than $k'$ of HCC and suggests that CN is more unstable than HCC. $pK_{a2}$ of CN has not been reported, but can be deduced from the rate–pH profile of CN. It is about 1.95.

**Effect of Temperature on the Degradation Rate of CN**

The apparent first-order rate constants for the degradation of CN at four different temperatures in pH 1.20 buffer solution are shown in Table II. The rate constant ($k$) at 60 °C was found to be $1.85 \times 10^{-5}$ min$^{-1}$. This value, which is fairly small, suggested a slow reaction. However, the rate constant at 90 °C was $1.94 \times 10^{-3}$ min$^{-1}$. This value is 100 times larger than that at 60 °C. The above results indicate that the degradation rate of CN increases
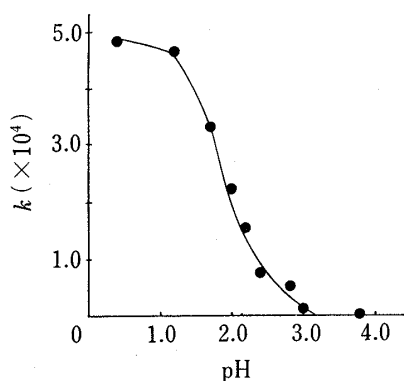
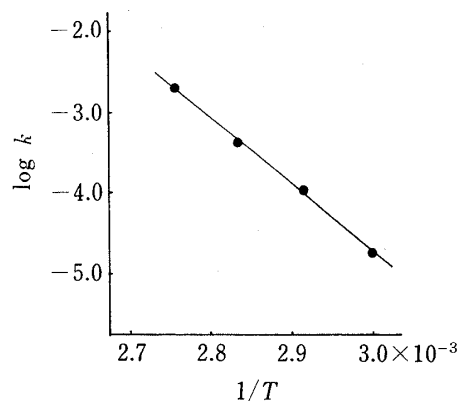Fig. 3.  Rate–pH Profile for the Degradation of CN in the Buffer Solution at 80 °C

Fig. 4.  Arrhenius Plot Based on the Rate Constants Measured at pH 1.20

remarkably with increasing temperature.

Figure 4 shows an Arrhenius plot of the rate constant on the basis of the data shown in Table II. The plot is linear, and the activation energy of the reaction at pH 1.20 was calculated to be 36.8 kcal/mol, which is larger than that of diphenhydramine, 23.9 kcal/mol,[5] and as large as that of HCC, 38.8 kcal/mol.[4] As the activation energy of CN was fairly large, it can be concluded that the degradation of CN does not occur readily in acidic solution at low temperature.

As described above, CN is degraded in aqueous solution at below pH 3.0 and the reaction is apparently first-order. The degradation rate of CN increased with decreasing pH or increasing temperature, but CN solution seemed to be fairly stable at room temperature. These results indicate that the process of dissolving CN in acidic solution when preparing CN–$\beta$-CD complex by means of the neutralization method and spray-drying method[3] should not present any serious problem.

## References and Notes

1) A part of this work was presented at the 104th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, March 1984.
2) T. Tokumura, H. Ueda, Y. Tsushima, M. Kasai, M. Kayano, I. Amada and T. Nagai, Chem. Pharm. Bull., **32**, 4179 (1984).
3) T. Tokumura, Y. Tsushima, K. Tatsuishi, M. Kayano, Y. Machida and T. Nagai, Yakuzaigaku, **45**, 1 (1985).
4) K. Nakano, Yakugaku Zasshi, **88**, 259 (1968).
5) H. Nogami and M. Horioka, Yakugaku Zasshi, **81**, 79 (1961).