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Hydrolysis of Acetylsalicylsalicylic Acid and Salicylsalicylic Acid in Aqueous Solution[1)]

HISAKAZU SUNADA,*,[a] KATSUHIDE IBA,[b] SHUICHI OGAWA,[b] EITARO ARAKAWA,[b] TETSUKO MASUYAMA,[a] KATSUMI HARA,[a] and AKINOBU OTSUKA[a]

Faculty of Pharmacy, Meijo University,[a] Yagoto-Urayama, Tenpaku-cho, Tenpaku-ku, Nagoya 468, Japan and Chemical Research and Development Division, General Laboratories, Arakawa-Chotaro & Co.,[b] Kusakabe-Hananoki-cho, Inazawa, Aichi 492, Japan

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The hydrolysis of acetylsalicylsalicylic acid and salicylsalicylic acid in aqueous solutions of ionic strength 0.5 were investigated at various pH by means of a high performance liquid chromatographic method. The degradation of acetylsalicylsalicylic acid is considered to be a complex reaction in which parallel and consecutive reactions are involved; that is, acetylsalicylsalicylic acid may degrade through two pathways to form acetylsalicylic acid and salicylsalicylic acid, and subsequently, both compounds may be converted to salicylic acid. The overall degradation of acetylsalicylsalicylic acid obeyed pseudo-first-order kinetics. The pH–rate profiles for the reactions were determined by monitoring the degradation products.

Keywords——aspirin; acetylsalicylsalicylic acid; salicylsalicylic acid; salicylic acid; HPLC; hydrolysis; pH–rate profile

Since Edwards[2,3)] studied the hydrolysis of aspirin (ASA) in aqueous solution in 1950, the kinetics and mechanisms of the degradation of aspirin not only in solutions but also in the solid state have been studied by numerous investigators.

In recent years, four salicylate derivatives, acetylsalicylic anhydride, *cis*-disalicylide, acetylsalicylsalicylic acid (ASSA) and salicylsalicylic acid (SSA) have been detected as impurities in commercial aspirin.[4-11)] It was reported that these compounds produce undesirable side effects,[12-16)] so that it is important to know the stability of these compounds in aqueous solutions.

The purpose of this investigation was to achieve a detailed interpretation of the kinetics and mechanisms of degradation of these contaminants in aqueous solutions.

Experimental

Materials——ASA was obtained from Mitsui Pharm. Inc., and SSA from Yoshitomi Pharm. Ind., Co., Ltd. Salicylic acid (SA) and other chemicals used here were of the highest grade commercially available. ASSA was prepared as follows: 150 g of SSA (0.58 mol) was added dropwise to 175 ml of acetic anhydride with stirring and dissolved at 80 °C. After 20 min, about 100 drops of conc. sulfuric acid were added to the mixture and the whole was allowed to stand for 40 min at a constant temperature of 80 °C. After cooling to room temperature the reaction mixture was poured into ice obtained from 1 l of water in a beaker, and then filtered. The product was recrystallized from 67% (v/v) MeOH in H_2O. The crystals (mp 162—167 °C) were recrystallized from MeOH to give 147 g of colorless prismatic crystals (mp 165—168 °C, 84% yield).

High Performance Liquid Chromatography (HPLC)——The concentrations of ASSA, SSA, ASA and SA were determined by ultraviolet (UV) absorption measurement using a Twincle apparatus (JASCO) with a Lichrosorb RP-18 Column ($\phi = 4.6 \times 250$ mm) connected with a Uvidec 100-III ultraviolet detector (JASCO) set at 240 nm. Samples

were eluted with a mobile phase consisting of MeOH–H_2O (55 : 45). The flow rate was 1.6 ml/min, according to the procedure described in the literature[17] (benzoic acid as an internal standard).

Degradation Studies——1) Preparation of Sample Solution:[18] Stock solutions were prepared by dissolving the samples in buffer solutions of various pH (ionic strength $\mu=0.5$) at 40 °C, and diluted to the concentration of 3×10^{-4} mol/l. Sample solutions above pH 9 were prepared by dissolving the sample powder in buffer solutions, followed quickly by filtration with a membrane filter having a pore size of 0.45 μm. Hydrochloric acid (pH 0.5—2), acetate buffer solution (pH 2.5—6) and phosphate buffer solution (pH 7—11) were employed.

2) Kinetic Procedures: Arbitrary amounts of sample solutions were taken into a tube with a stopper and incubated in a water bath thermostated at 40 ± 0.1 °C. At appropriate intervals, a small portion of sample solution was taken and analyzed by means of HPLC. To prevent degradation after sampling, sample solutions of pH 10 or above were added to conc. hydrochloric acid solution. The pH values of solutions were checked before and after reaction.

3) Computer Analysis: Rate constants were calculated on an FM-11 computer (Fujitu Co., Ltd.) using the nonlinear least-squares method, with errors of less than −400 in terms of AIC values, so fundamental errors in rate constants can be neglected.

Results and Discussion

The overall degradation pathway of ASSA may be described in terms of parallel and consecutive reactions, as shown in Chart 1, where k_1 and k_4 are rate constants for the

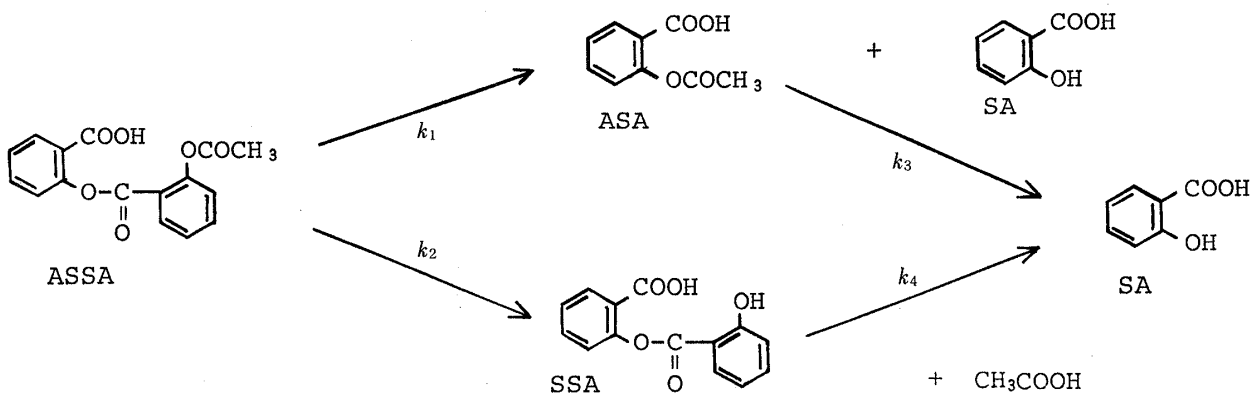

Chart 1

deacetylsalicylation reaction and k_2 and k_3 for the deacetylation reaction. The rates of each reaction may be described as follows.

$$-\frac{d[ASSA]}{dt}=(k_1+k_2)[ASSA] \tag{1}$$

$$\frac{d[ASA]}{dt}=k_1[ASSA]-k_3[ASA] \tag{2}$$

$$\frac{d[SSA]}{dt}=k_2[ASSA]-k_4[SSA] \tag{3}$$

$$\frac{d[SA]}{dt}=k_1[ASSA]+k_3[ASA]+2k_4[SSA] \tag{4}$$

The integration of these equations gives the concentration of each species at time t.

$$[ASSA]=[ASSA]_0\, e^{-(k_1+k_2)t} \tag{5}$$

$$[ASA]=\frac{k_1}{k_3-(k_1+k_2)}[ASSA]_0(e^{-(k_1+k_2)t}-e^{-k_3t}) \tag{6}$$

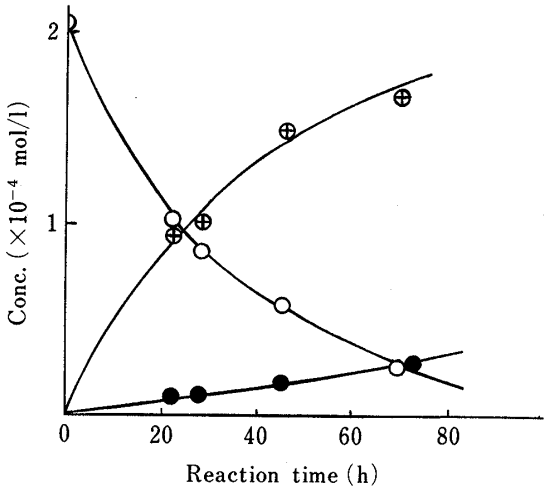

Fig. 1. Time Courses for ASSA and Its Degradation Products at pH 1.04 (40 °C, $\mu=0.5$)

The lines were calculated from Eqs. 5, 7 and 8 using $k_1=1.05\times10^{-1}\,d^{-1}$, $k_2=6.90\times10^{-1}\,d^{-1}$, $k_3=1.21\ d^{-1}$ and $k_4=2.22\times10^{-2}\,d^{-1}$. ○, ASSA; ⊕, SSA; ●, SA.

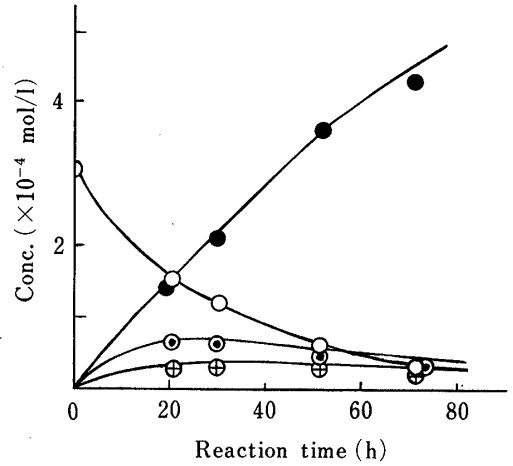

Fig. 2. Time Courses for ASSA and Its Degradation Products at pH 6.80 (40 °C, $\mu=0.5$)

The lines were calculated from Eqs. 5, 6, 7 and 8 using $k_1=5.58\times10^{-1}\,d^{-1}$, $k_2=1.88\times10^{-1}\,d^{-1}$, $k_3=1.18\,d^{-1}$ and $k_4=5.54\times10^{-1}\,d^{-1}$. ○, ASSA; ⊙, ASA; ⊕, SSA; ●, SA.

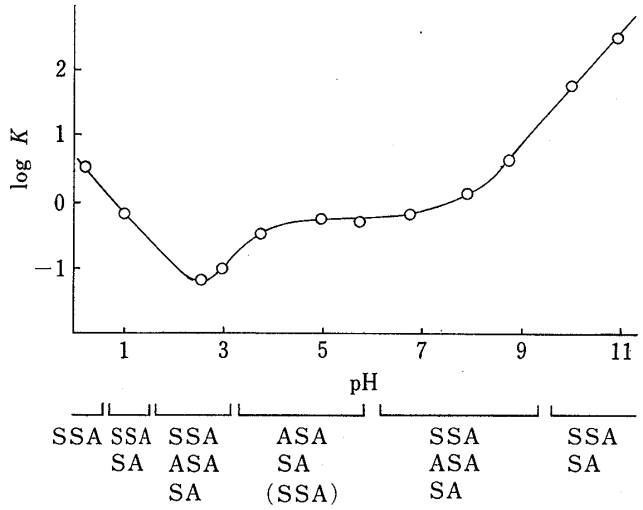

Fig. 3. pH–Rate Profile for Hydrolysis of ASSA in Buffer Solutions at 40 °C ($\mu=0.5$)

(SSA) means trace amounts.

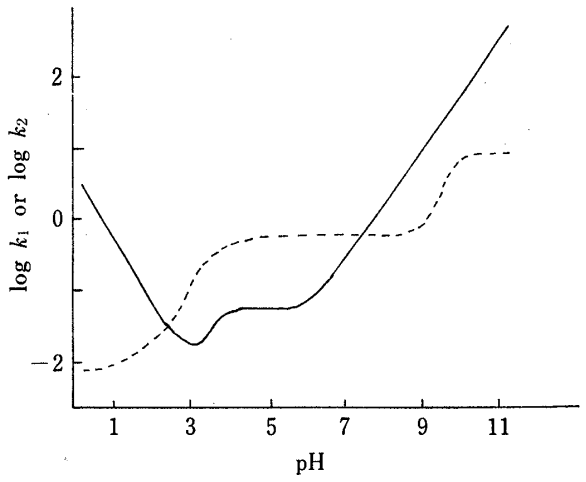

Fig. 4. pH–log k_1 and k_2 Profiles at 40 °C

----, k_1; ——, k_2.

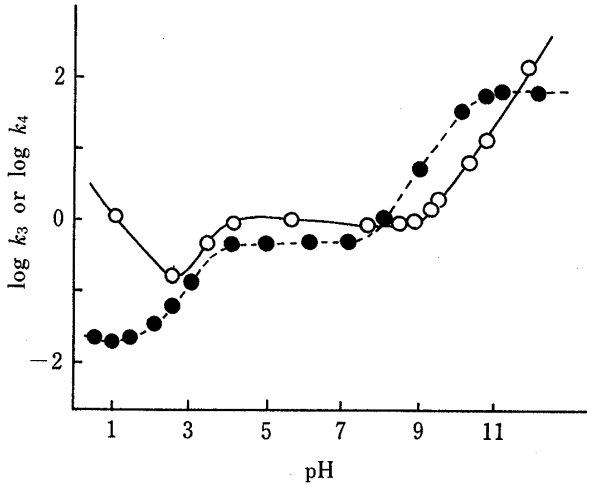

Fig. 5. pH–log k_3 and k_4 Profiles at 40 °C

——, k_3; ○, experimental value for ASA. ----, k_4; ●, experimental value for SSA.

$$[\mathrm{SSA}]=\frac{k_2}{k_4-(k_1+k_2)}[\mathrm{ASSA}]_0(e^{-(k_1+k_2)t}-e^{-k_4t}) \tag{7}$$

$$[\mathrm{SA}]=2[\mathrm{ASSA}]_0-\frac{k_1}{(k_1+k_2)}[\mathrm{ASSA}]_0e^{-(k_1+k_2)t}$$

$$-\frac{k_1}{(k_1+k_2)(k_3-k_1-k_2)}[\mathrm{ASSA}]_0(k_3e^{-(k_1+k_2)t}-(k_1+k_2)e^{-k_3t})$$

$$-\frac{2k_2}{(k_1+k_2)(k_4-k_1-k_2)}[\mathrm{ASSA}]_0\,(k_4e^{-(k_1+k_2)t}-(k_1+k_2)e^{-k_4t}) \tag{8}$$

The HPLC method was employed to follow the degradation process of ASSA at various pH. Figures 1 and 2 show typical time courses for ASSA and its degradation products.

The overall degradation of ASSA was found to be a pseudo-first-order reaction over the whole range of pH in the present study. The pseudo-first-order rate constant K, which corresponds to k_1+k_2 in Eq. 1, can be obtained from the slope of a linear plot of the logarithm of the remaining concentration of ASSA against time.

Figure 3 shows the log K–pH profile for ASSA degradation at 40 °C and an ionic strength of 0.5. The main hydrolysis products in each pH range are shown under the figure.

The rate constants k_1, k_2, k_3 and k_4 at various pH were calculated from Eqs. 5, 6, 7 and 8 by means of a computer using the t time course data for ASSA and its degradation products. The pH–log k_1, k_2, k_3 and k_4 profiles are shown in Figs. 4 and 5 by solid or dotted lines.

The degradation studies on SSA and ASA were carried out in separate experiments. The pseudo-first-order rate constants obtained are plotted on Fig. 5 as open circles (ASA) and closed circles (SSA). They are in good agreement with the calculated values.

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References and Notes

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18) Preliminary measurements were made on buffer solutions ranging in ionic strength from 0.04 to 0.5, and at total buffer concentration from 0.01 to 0.15. No significant effect of ionic strength or total buffer concentration was observed. All the kinetic studies were carried out at ionic strength 0.5. The ionic strength was adjusted by the addition of potassium chloride.