THE HYDROLYSIS OF ACETYLSALICYLIC ACID FROM AQUEOUS SUSPENSION*

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An investigation of the kinetics of the hydrolysis of acetylsalicylic acid from aqueous suspension is described. The net reaction is one of solution of the solid followed by hydrolysis in solution, so that the rate of reaction is dependent on the concentration of the saturated solution. Under conditions where the solubility of acetylsalicylic acid is small in comparison with the quantity in suspension, a zero order reaction results. The B.P.C. mixture is discussed.

The decomposition of acetylsalicylic acid solutions in water has been studied by several workers[1–6], who have shown that the compound is hydrolysed to form acetic and salicylic acids. The hydrolysis is a first order reaction, the net velocity being a function of the six possible reactions between the equilibria[7],

$$C_6H_4(OCOCH_3)COOH \rightleftharpoons C_6H_4(OCOCH_3)COO' + H^+$$
$$2\ H_2O \rightleftharpoons H_3O^+ \quad OH'$$

In consequence of this rapid hydrolysis from solution, the use of aqueous suspensions is preferred, although these too are known to decompose[8].

Examination of reactions between a suspended solid and its suspending medium requires a consideration of dissolution. The first measurements of dissolution were made by Noyes and Whitney[9], who observed the dissolution of benzoic acid and lead chloride respectively from a cylinder of the solid rotating in water. This was extended to chemical reaction by others[10,11], one of whom, Senter[12], said that the speed of the heterogeneous reaction depended on the rate of diffusion of the saturated solution from the solid, and the rate of the resulting homogenous chemical reaction. If either of these was appreciably slower than the other, its rate would determine that of the complete reaction. Under such conditions Senter[13] suggested that the effect of temperature on the reaction would indicate the relative rates, since the velocity of a chemical reaction is greatly influenced by temperature, an increase of 10° causing the rate of reaction to increase two or three fold, while the diffusion rises only 2·5 per cent per degree.

Experimental

A procedure introduced by Tsokalatos and Horsch[2] was used whereby the degree of hydrolysis was calculated from the increase in acidity of the system. Titrations were carried out with sodium hydroxide in the presence of ethanol, using phenol red as indicator.

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Effect of Temperature

Rates of hydrolysis of acetylsalicylic acid in mixture of acetylsalicylic acid B.P.C. were determined and compared at temperatures ranging from room temperature (approximately 20°) to 100°.

Decomposition at room temperature and at 34°. A quantity of mixture of acetylsalicylic acid B.P.C. stored in a glass stoppered bottle in a dark

TABLE I

HYDROLYSIS OF ACETYLSALICYLIC ACID SUSPENSIONS AT VARIOUS TEMPERATURES

Room Temperature		34°		50°		60°		70°		100°	
Time in days	Per cent $C_9H_8O_4$ remaining	Time in days	Per cent $C_9H_8O_4$ remaining	Time in hours	Per cent $C_9H_8O_4$ remaining	Time in hours	Per cent $C_9H_8O_4$ remaining	Time in hours	Per cent $C_9H_8O_4$ remaining	Time in minutes	Per cent $C_9H_8O_4$ remaining
4	98	7	93	1	99	1	93	1	91	15	85
7	96	15	87	2	98	2	90	2	81	30	71
13	95	21	78	3	96	3	89	3	73	45	62
19	93	29	76	4	94	4	85	4	65	60	52
26	93	36	66	5	92	5	82	5	59	75	42
47	89	43	60	6	92	6	75	6	54	90	36
62	89			7	91	7	71	7	47	120	19

cupboard (room temperature) and incubator (34°) was shaken daily, and sampled when required by removing approximately 5 g. in a tared weighing bottle.

Decomposition at 50°, 60°, *and* 70°. The reaction mixture was immersed in a constant temperature water bath and stirred continuously with a

TABLE II

RELATIVE VELOCITIES OF HYDROLYSIS OF MIXTURE OF ACETYLSALICYLIC ACID B.P.C. AT VARIOUS TEMPERATURES

Temperatures °C.	Mean velocity quotient (per 10°C.)
20 to 34	2·0
50 to 60	2·0
60 to 70	2·1
70 to 100	3·9
34 to 70	67

TABLE III

SOLUBILITY AND DISSOLUTION OF ACETYLSALICYLIC ACID

Temperature °C.	Solublility (percentage w/w)	Relative dissolution rate
20	0·33	1
34	0·50	1·5
50	1·0	3
60	1·5	4·5
70	3·3	10

mechanical stirrer. Approximately 5 ml. samples were withdrawn hourly into tared weighing bottles containing 15 ml. of cold water and weighed. The rapid cooling of the suspension thus, considerably retarded the rate of hydrolysis.

Decomposition at 100°. The same procedure was used as at 70°, the constant temperature being provided by a boiling water bath. Owing to the speed of the reaction, samples were withdrawn at 15 minute intervals, and as time did not permit duplicates, single determinations were made.

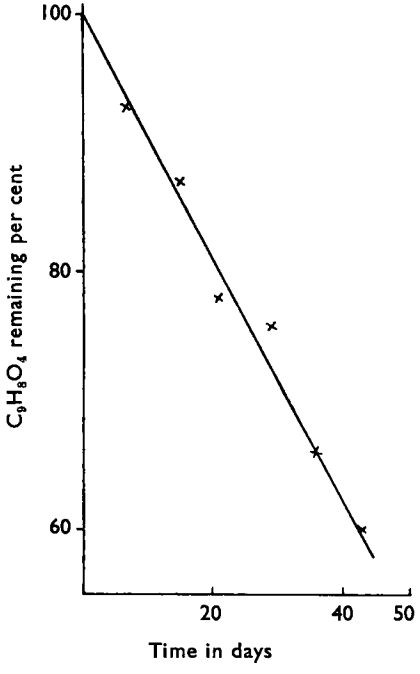

FIG. 1. Hydrolysis of mixture of acetylsalicylic acid at 34°.

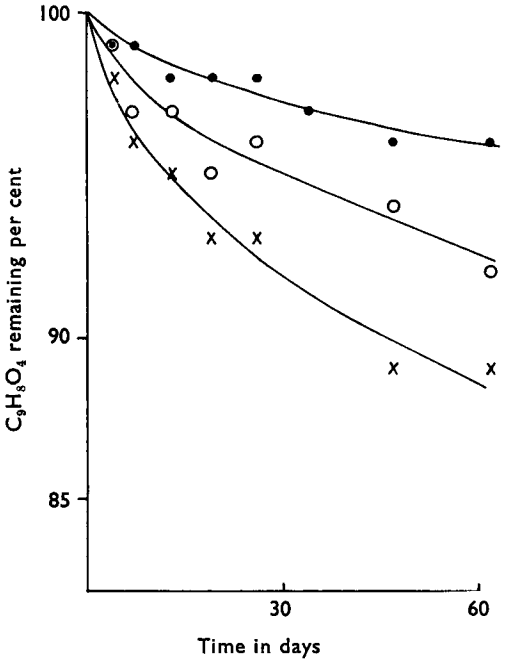

FIG. 2. Hydrolysis of acetylsalicylic acid suspensions at room temperature.

X Containing 3·3 per cent $C_9H_8O_4$ on preparation.
O ,, 6·5 ,, ,, ,, ,,
● ,, 13·0 ,, ,, ,, ,,

Results are summarised in Table I, and show the pronounced effect of temperature on the rate of reaction, 10 per cent hydrolysis occurring in only 15 minutes at 100°, and after 62 days at room temperature.

Effect of Concentration

Three suspensions were prepared, corresponding to mixture of acetylsalicylic acid B.P.C., and mixtures with double and quadruple the B.P.C. quantity of acetylsalicylic acid respectively. The preparations were stored in 500 ml. glass stoppered bottles in a dark cupboard, shaken daily, and the hydrolysis followed as before.

Three similar suspensions were also examined at 70°, and two suspensions, a single, and a double strength, at 100°.

Solubility Determinations

Solubilities were determined spectrophotometrically by a method described by Edwards[7].

Discussion

In order to compare the rates of hydrolysis at the various temperatures, graphs were plotted relating the percentage of undecomposed acetylsalicylic acid to time of reaction, and from these the percentage hydrolysis at selected times determined. Velocity quotients were calculated from this information as the relative increase in hydrolysis per 10° temperature rise. These values are shown in Table II. The anticipated diffusion velocity quotient for 10° would be $(0{\cdot}025 \times 10) + 1 = 1{\cdot}25$, which is less than the smallest of the experimental values. Further, although the two to three-fold increase for chemical reactions quoted by Senter is of the same order as most of the velocity quotients, it bears no comparison with the velocity quotient obtained between 34° and 70°. A clue to this very large figure was found in the observation that the suspensions became translucent at about 70°, indicating that the solubility of acetylsalicylic acid had increased with temperature, until at 70° all the acid in the mixture containing 3·3 per cent had dissolved. This is confirmed by the solubility figures, shown in Table III.

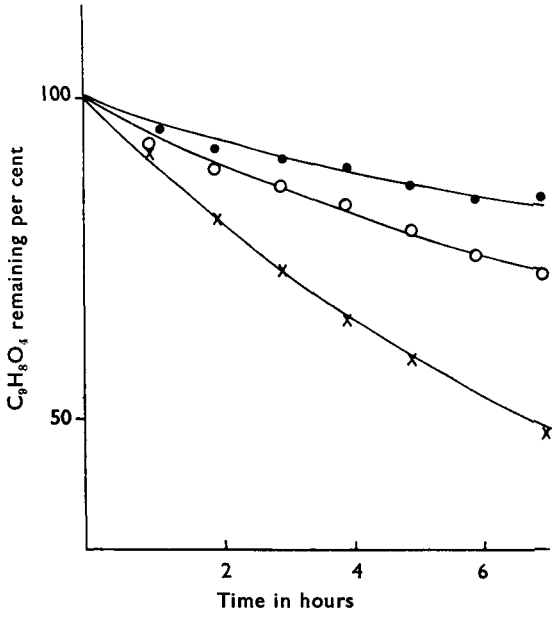

Fig. 3. Hydrolysis of acetylsalicylic acid suspensions at 70°.

X Containing 3·4 per cent $C_9H_8O_4$ on preparation.
O " 6·9 " " " "
● " 12·9 " " " "

The Noyes Whitney equation:—

$$\frac{dc}{dt} = k(c_s - c)$$

where c is the concentration of the continuous phase, and C_s that of the saturated solution, predicts that the rate of dissolution increases with solubility. Relative rates of dissolution, calculated when t and c are zero, are given in Table III, and indicate that increase in dissolution alone cannot be responsible for the high velocity quotients.

Figure 1 shows the curve of concentration against time for the hydrolysis at 34°. It is a straight line, which indicates that the rate of hydrolysis is independent of the quantity of acetylsalicylic acid in suspension, or in

other words, is of zero order. This suggests that the reaction at 34° is in two parts, (*a*) solution of acetylsalicylic acid, followed by, (*b*) decomposition of the acetylsalicylic acid in solution. As the acid in solution decomposes, more dissolves, so that the rate of hydrolysis depends on the strength of the saturated solution. The hydrolysis of the suspension is therefore slow because the acetylsalicylic acid in solution only, is subject to hydrolysis. Since the solubility is constant the rate of hydrolysis is independent of the total quantity of acetylsalicylic acid, and the reaction is zero order. In the light of this mechanism, the marked increase of reaction rate with temperature is not surprising.

If the reaction is zero order, the more concentrated a suspension the smaller would be the proportion of acetylsalicylic acid hydrolysed, so that the stability of such suspensions should increase with concentration. By comparing the rates of hydrolysis of suspensions of different strengths, the zero order reaction can be verified, and more stable preparations of acetylsalicylic acid formulated.

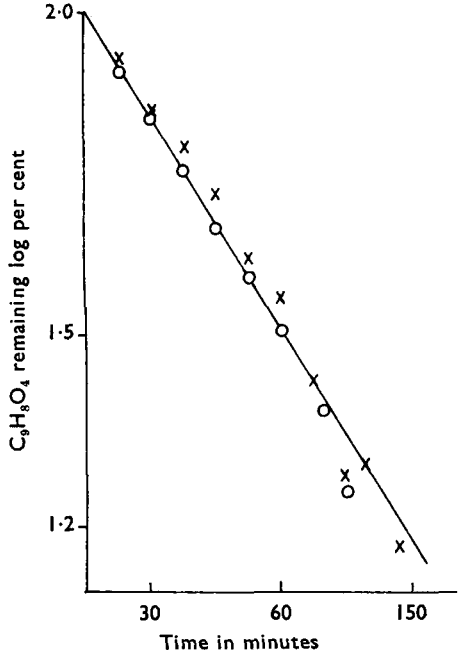

FIG. 4. Hydrolysis of acetylsalicylic acid suspensions at 100°.
X Containing 3·3 per cent $C_9H_8O_4$ on preparation.
O " 6·9 " " "

The rates of hydrolysis of suspensions containing 3·3, 6·5, and 13·0 per cent of acetylsalicylic acid at room temperature are shown in Figure 2. There was a definite increase in stability with concentration, at every stage of the determination the degree of hydrolysis was in the same order as the concentrations, and after 62 days storage the percentages of unchanged acetylsalicylic acid were 90, 94 and 97 per cent respectively, relative rates of hydrolysis being 10:6:3.

The comparative rates of hydrolysis of similar suspensions at 70°, shown in Figure 3, gave the same picture, but at 100° the rates of hydrolysis of the two suspensions were identical, and the hydrolysis curves superimposable (Fig. 4).

In the hydrolysis at room temperature and at 70° the percentage hydrolysis in a given time depends on, and is approximately proportional to the concentration of the suspension. The hydrolysis curves for the determinations at room temperature do not follow the straight line of the

zero order reaction, but the plot of log concentration against time showed that the reaction is also not first order at any concentration.

At 70° the hydrolysis curves show less curvature than at room temperature, and approach the straight line of the zero order reaction as the concentration is increased. In the log concentration against time curves in Figure 5, the 3·4 per cent suspension follows a straight line, indicating

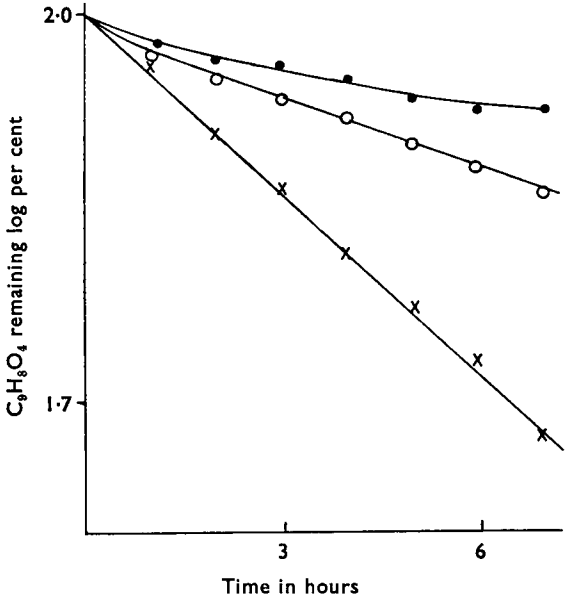

FIG. 5. Hydrolysis of acetylsalicylic acid suspensions at 70°.

X containing 3·4 per cent $C_9H_8O_4$ on preparation.
O " 6·9 " " " "
● " 12·9 " " " "

that the reaction is first order. Most of the reaction with the 6·9 per cent suspension behaves in the same way, while the 12·9 per cent suspension exhibits a definite curve. The curves in the figure suggest the presence of a first order reaction, but with the more concentrated suspension this is less marked. The inference however confirms that the solubility of acetylsalicylic acid at 70° lies below 6·9 per cent, that the 3·4 per cent suspension decomposes unimolecularly, and that as the quantity of acetylsalicylic acid in suspension increases above 3·4 per cent, the effect of the first order reaction becomes less in relation to the zero order reaction of solution followed by hydrolysis.

The behaviour of the reaction at 100° was typically first order, so that concentration had no effect on the progress of the reaction.

The aim of this work has been to determine in what way acetylsalicylic acid hydrolyses from aqueous suspension, why the suspension is more stable than the solution, and what steps can be taken to further stabilise the suspension.

It was intended that the work be comparative and not quantitative. To give absolute figures for hydrolysis rates, particle size and degree of agitation would have to be defined. These conditions were standardised in as much as the same sample of acetylsalicylic acid was used throughout, together with the same stirrer running at the same speed, but neither property was measured.

The rate of hydrolysis has been studied with several samples of mixture of acetylsalicylic acid B.P.C., mainly as control in storage tests on other suspensions, and the degree of hydrolysis has varied from 1 to 4 per cent after 7 days at room temperature. Similarly, 3 to 5 per cent and 5 to 6 per cent were found to have hydrolysed after 14 and 21 days respectively. The limit test of the British Pharmacopoeia allows a maximum of 0·05 per cent of salicylic acid in acetylsalicylic acid, and 0·15 per cent in the tablets, so that the mixture would cease to comply with these requirements after less than one day's storage.

Temperature has been shown to have marked effect on the rate of hydrolysis, a rise from 20° to 34° resulting in a one-and-a-half to twofold increase. It is therefore important that the mixture be kept in a cool place.

As the rate of hydrolysis is inversely proportional to concentration, a suspension containing four times the quantity of acetylsalicylic acid as the official mixture will hydrolyse only a quarter as much in a given time. By increasing the concentration of the acid in the B.P.C. mixture fourfold the stability can be increased to the same extent and the mixture would lose less than 1 per cent of its potency in one week.

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