Decarboxylation of p-Aminosalicylic Acid in the Solid State

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The decarboxylation reaction of p-aminosalicylic acid in the solid state has been demonstrated to be dependent on temperature, moisture, pressure, and particle size. Typical curves are given which indicate environmental influence on the degradation reaction. A possible gross mechanism is offered which analyzes the sigmoidal-type per cent decomposition *versus* time curve obtained with dry, atmospheric, thermal degradation of p-aminosalicylic acid. A set of equations which describes the kinetic data is given. Using these equations, the various rate constants have been determined.

THERE HAS BEEN only a limited number of degradation studies of organic compounds in the solid state reported (1–3). The available information, with few exceptions, is sketchy and inconclusive with respect to effects of various environmental conditions. p-Aminosalicylic acid decarboxylates into m-aminophenol and carbon dioxide in solution as well as in the solid state (4). The solution kinetics of this reaction have been reported elsewhere (5–7). The decomposition reaction of p-aminosalicylic acid in the solid state possesses pharmaceutical interest, yet it has been interpreted only vaguely (8).

The effects of such environmental conditions as temperature, moisture, pressure, particle size, and past history of solids as they relate to the decarboxylation of solid p-aminosalicylic acid as well as the influence of the decomposition product are reported.

THEORY

Most real crystals are imperfect. Investigators of mechanical properties of solids have shown that no macroscopic specimen ever exhibits the theoretical strength of a perfect crystal. This has led to the recognition that some of the imperfections are dislocations (9). Observation of solids has suggested that the nucleation of a new phase may, under certain conditions, occur not homogeneously but in the neighborhood of dislocations which may be distributed uniformly throughout the crystal. The nucleation of new phases occurs when local fluctuations in the energy of the crystal are sufficient to provide the necessary activation energy. The nuclei are formed at definite localized spots where the activation is least for structure-sensitive nucleation. The number of nuclei formed in a given time thus will depend upon the number of potential nucleus-forming sites which are generally associated with some type of lattice imperfection.

Solid reactions have been classified conveniently according to the shape of the per cent decomposition *versus* time curves obtained on thermal decomposition, for which there are three main types (10) as shown in Fig. 1. For the first case, (a) the most rapid rate of reaction occurs at the beginning of the decomposition. This is typical of the decomposition of solids where nuclei of the new phase are rapidly formed and where there is almost instantaneous coverage of the surface with a film of the solid product. In the second case, (b), there is an apparent induction period due to a slow rate of production of nuclei which is followed by the rapid acceleration period and terminated by the decay period. Under favorable conditions, the rate of production of nuclei is sufficiently low for them to grow to sizes which can be examined by visual methods. For the third case, (c), the initial stage may be represented by a small amount of gas evolution extending over a relatively long period of time. This is followed by the acceleration of the reaction as in the second-type curve. Where melting occurs during the decomposition, the form of the curve may not correspond with any of the above types.

If decomposition occurs in the solid phase without partial melting, owing to molecular volume changes, it may be assumed that the formation of product molecules induces strain in the crystal which further cracks, forming fresh surfaces upon which decomposition can occur. A theory based on this premise was proposed by Prout and Tompkins (11) to explain their observations on the decomposition of potassium permanganate and has been extended to organic solids by Vaughan and Phillips (3). The latter workers describe the sites of nucleation as regions where decomposition is favored, that is, where the reaction occurs with a low activation energy (12). Garner (12) has reported that the surface array of product molecules has a different unit cell from that of the original substance, and this sets up strains on the crystal surface that are relieved by the formation of cracks. He states that at the mouth of these cracks, a reaction will be favored by lattice imperfections and will spread down the crevices into the crystal. Decomposition on these surfaces produces additional and further cracking. Thus a type of chain branching process develops and occasionally these reacting surfaces will interfere with one another to break the chain. Prout and Tompkins (11) also stated that the
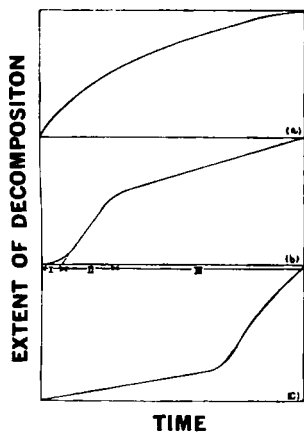
Fig. 1.—Graphic representation of three main types of decomposition – time curves in solid-state reactions; (I) induction period, (II) acceleration period (k_a), (III) decay period (k_d), which refer to case b.

rate of increase of potentially reactive molecules may be represented by

$$\frac{dn}{dt} = \frac{\alpha n}{\delta t} \quad \text{(Eq. 1)}$$

where n is the number of potentially reactive molecules existing at the time t, δt is the average time interval between production and decomposition and α is the probability of branching. They propose that branching proceeds unhindered initially since there are many centers from which branching can originate, but as the reaction progresses considerable interference will arise. Thus when a plane of product molecules reaches a surface, either internal or external, where decomposition has already occurred the reaction will cease. If β is the probability of interference then Eq. -1 becomes

$$\frac{dn}{dt} = (\alpha - \beta) \frac{n}{\delta t} \quad \text{(Eq. 2)}$$

EXPERIMENTAL

The powdered p-aminosalicylic acid of U.S.P. grade[1] used in this study was found to have an average particle size of 3.3 μ as determined by a Fisher "subsieve sizer." Whole crystals of p-aminosalicylic acid were prepared by recrystallization from absolute ethanol *in vacuo*. The approximate diameter of the latter was determined by means of U. S. Standard sieves, and was found to be between 40 and 80 mesh.

The powdered p-aminosalicylic acid used in this study proved to be stable if stored at room temperature under a dry atmosphere for a three-year period. However, during this time a slight darkening of the powder occurred, which was thought to be the result of slow oxidation.

The general procedure used in the kinetic studies was as follows. A series of 10-ml. Pyrex beakers, each containing exactly 300 mg. of p-aminosalicylic acid, were arranged in a desiccator previously brought to thermal equilibrium for 24 hours. The desiccator was placed in an automatically controlled oven set at the experimental temperature (70–80 $\pm$ 0.5°). At various intervals, samples were removed, dissolved in approximately 25 ml.

of ethanol and titrated with standard sodium hydroxide solution using phenolphthalein as the end point indicator. An alternate spectrophotometric method of analysis was developed to determine both p-aminosalicylic acid and m-aminophenol simultaneously using the wavelengths 300 mμ for p-aminosalicylic acid and 230 mμ for m-aminophenol. The molar absorbance index (a_M) was calculated to be 6.47 $\times$ 10³ L./mole/cm. for m-aminophenol at the wavelength 230 mμ, and 9.70 $\times$ 10³ L./mole/cm. and 8.58 $\times$ 10³ L./mole/cm. for p-aminosalicylic acid at the wavelengths 230 mμ and 300 mμ, respectively. Beer's law was obeyed with both substances over a range of 2 $\times$ 10⁻³ mg./ml. to 8 $\times$ 10⁻³ mg./ml. In all the degradation studies the reaction was followed through at least 50% decomposition.

Dry, Atmospheric Pressure Studies.—The powdered p-aminosalicylic acid was decomposed under atmospheric pressure, at elevated temperatures and in the absence of water vapor. The samples were stored at 70, 75, and 80°. The p-aminosalicylic acid powder was subjected to a degassing process using reduced pressure below 1 mm. for 24 hours, but thermal treatment showed no difference in the reaction velocity with the degassed or untreated p-aminosalicylic acid.

In an attempt to study the effect of particle size on the reaction, an investigation of the thermal degradation of large crystals of p-aminosalicylic acid (diameter not less than 0.177 mm. and not larger than 0.420 mm.) was conducted in a similar manner. The progress of the initial reaction was observed microscopically and photographed.

A study was undertaken using powdered p-aminosalicylic acid to determine whether or not the induction period of the degradation process was due to thermal diffusion. If thermal diffusion were the cause of any induction period, new delays in the progress of the reaction should be experienced after intermittent quenching and reheating of the powder. Thus samples were heated at 80°, quenched during the known induction period, acceleration period, and decay period by cooling to room temperature, and maintaining this temperature for at least 6 hours. The quenching periods were then followed by reheating to 80°.

The effect of carbon dioxide pressure, over the solid acid, on the decarboxylation process rate has been investigated (8) at varied pressures (20–760 mm. Hg) which demonstrated no affect on the rate
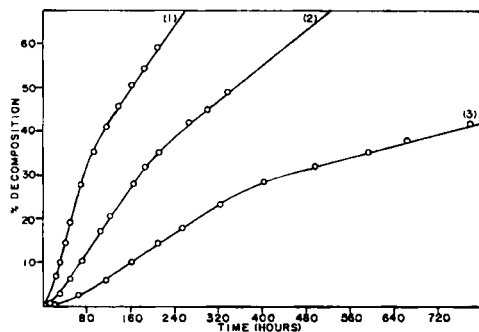

Fig. 2.—Per cent decomposition-time curves for the thermal decarboxylation reaction of p-aminosalicylic acid in dry, solid state at (1) 80°, (2) 75° and (3) 70°.
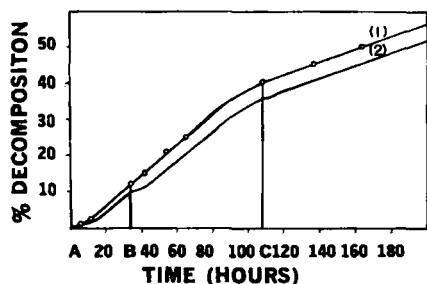
Fig. 3.—Comparison of actual data (O) with that of expected hypothetical curve were the decarboxylation of *p*-aminosalicylic acid at 80° to experience separate induction periods after quenching and subsequent heating at times *A*, *B*, and *C*.

or character of the decarboxylation process. In the present study the carbon dioxide pressure never was allowed to build up since samples were removed from the desiccator for analysis at approximately 24-hour intervals.

Dry, Reduced Pressure Study.—Since it was felt that the role of the solid product of decarboxylation, *m*-aminophenol, in the over-all reaction could be better understood if it were eliminated, the reaction was conducted at reduced pressure employing a vacuum oven. At a temperature of 80 ± 0.5° and approximately 10 mm. Hg pressure, the *m*-aminophenol readily sublimed. Under the same conditions, the *p*-aminosalicylic acid could not be detected in the sublimate. Spectrophotometric analysis of the reaction mixture demonstrated the absence of the decomposition product throughout the reaction.

Moist, Atmospheric Pressure Studies.—The effect of a constant humidity on the reaction was studied by placing samples of *p*-aminosalicylic acid over saturated solutions of appropriate inorganic salts to obtain aqueous tensions in the range between 30 and 80% absolute humidity (13). At higher humidities condensation took place and caused wetting of the powder. The desiccator containing the salt solution was allowed to equilibrate for 24 hours at the desired temperature before the samples were introduced. There appeared to be no weighable adsorption of water at 70° with an aqueous tension of 118.4 mm. Hg. If water was adsorbed by the powder, the possibility of solution kinetics would have been indicated.

Suspension Technique Study.—The utilization of a suspension technique proved useful in the solid-state decomposition study. After a screening of many vehicles, mineral oil was chosen because its inert properties eliminate interference with the reaction yet afford good heat transfer. The suspension was prepared by levigating *p*-aminosalicylic acid with mineral oil and a uniform dispersion was maintained with a power stirrer at constant speed. The reaction vessel, a Kjeldahl flask modified by the attachment of a side arm tube, allowed the withdrawal of samples for analysis without disturbing the reaction. The temperature was controlled by use of a circulating oil bath.

RESULTS

Dry, Atmospheric Pressure Studies.—The decarboxylation of *p*-aminosalicylic acid under the in-

fluence of atmospheric pressure, at elevated temperatures and in the absence of moisture is represented by the sigmoidal-type curves as given in Fig. 2. This typical per cent decomposition *versus* time curve consists of three parts that may be described as: (*a*) induction period; (*b*) acceleration period; (*c*) decay period (11). At a given temperature the induction period is found to occur only once in the thermal decarboxylation reaction. The per cent decomposition *versus* time curve represented by Fig. 3 (*1*) is the result of three consecutive heating and cooling periods at 80°. The samples were removed from the oven at the points A, B, and C and stored in a desiccator at room temperature for 6 or more hours. They were then replaced in the oven at 80° for further decomposition. If the induction period were dependent upon thermal diffusion then Fig. 3 (*2*) would be a hypothetical possibility for the per cent decomposition *versus* time curve. The existing difference in per cent decomposition at any time between Figs. 3 (*1*) and 3 (*2*) minimized the possibility of thermal diffusion since all points indicated in Fig. 3 (*1*) correspond within the limits of experimental error with those of uninterrupted runs made under the same experimental conditions. Haycock (10) describes this period as one due to the slow nuclei growth in the early stage of the reaction. The induction periods for the decarboxylation of *p*-aminosalicylic acid in a dry atmosphere decreased with increased heat intensity, and were found to be 38, 18, and 8 hours, for 70, 75, and 80°, respectively.

The acceleration period of the decarboxylation reaction for the most part can be described simply by

$$\frac{dx}{dt} = k_a = \frac{x}{t - \tau} \qquad \text{(Eq. 3)}$$

where *x* is the per cent decomposition, τ is the induction period, *t* is the time where the decomposition is *x*, and k_a is the rate constant for the acceleration period.

The decay period follows the second inflection point, since after this point the rate-controlling factor becomes the number of unreacted nuclei which are produced at a constant rate. The equation for the decay period is

$$\frac{dx}{dt} = k_d = \frac{x - x_{max.}}{t - t_{max.}} \qquad \text{(Eq. 4)}$$

where $x_{max.}$ is the per cent decomposition at $t_{max.}$, $t_{max.}$ is the time at which the reaction reached maximum velocity (second inflection point), and *x* and *t* are the same as in Eq. 3. Similarly, Prout and Tompkins (11) derived separate equations for both the acceleration and decay periods having similar form but expressed the rate in terms of growth of active nuclei.

The least-mean-squares equation and the above equations were used to demonstrate the validity of the rate constants calculated. The acceleration and decay periods best fit an apparent zero-order reaction equation which indicates an independence of the rate of reaction on the fraction of *p*-aminosalicylic acid remaining. A study conducted with sample sizes of 75, 150, and 300 mg. of powdered *p*-aminosalicylic acid at 80° substantiated this by rendering a k_a value of 0.456 ± 0.046 mole% hr.$^{-1}$. The second inflection point, however, oc-
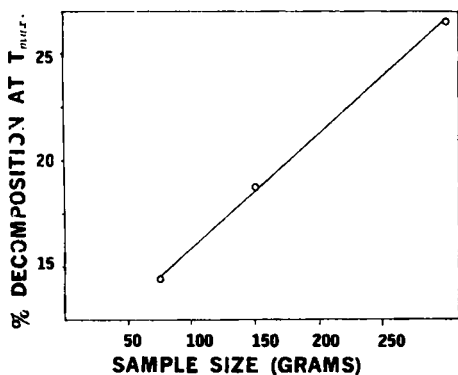
Fig. 4.—Relationship of the per cent decomposition at t_{max} versus the sample size for the decarboxylation of p-aminosalicylic at 80° under dry, atmospheric pressure.

TABLE I.—DATA OF THE DECARBOXYLATION REACTION OF DRY p-AMINOSALICYLIC ACID AT ATMOSPHERIC PRESSURE

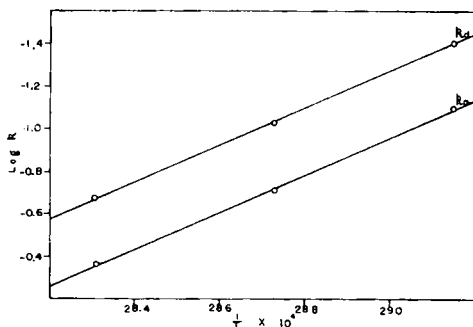| T, °C.	Induction Period (hr.)	$t_{max.}$ (hr.)	k_a (mole% hr.$^{-1}$)	k_d (mole% hr.$^{-1}$)
70	38	360	0.080 ± 0.004[a]	0.037 ± 0.002
75	18	170	0.195 ± 0.006[a]	0.094 ± 0.003
80	8	71	0.446 ± 0.011[b]	0.200 ± 0.005

[a] Average of two runs.   [b] Average of three runs.

Fig. 5.—Arrhenius plot for thermal degradation at a dry, atmospheric pressure.

curred at different degrees of decomposition with all three of the sample sizes. Analysis of the data indicated a linear relationship between the per cent decomposition at the second inflection point versus the sample size (Fig. 4). This suggested that the β value (Eq. 2) depends on the sample size.

Table I shows the effect of temperature on the induction period, $t_{max.}$ and the values of the acceleration period rate constant (k_a) and decay period rate constant (k_d). It was possible to reproduce the per cent decomposition versus time curves and calculate kinetic constants within acceptable limits.

The plot of the logarithms of k_a and k_d against $1/T$ gave two straight lines (Fig. 5) with almost identical slopes, yielding activation energies of 41.0 and 40.9 kcal./mole, respectively. This showed that the reaction at each stage was the same even though the intercept changed.

The photographs[2] of p-aminosalicylic acid crys-

tals point out that cracking and splintering occurs during the early stages of the solid-state reaction [Figs. 6(a) and 6(b)]. The fractures occurred at points of irregularity in the crystal. The more perfect the crystal, the greater was the amount of time needed for fracturing to be initiated. It can be seen from Fig. 6(a) that the cracking took place at a point of irregularity in the crystal. The fractured crystal had to be mechanically moved into the field of the microscope since fracturing apparently occurred with an explosive force. This was probably due to a release of carbon dioxide from the decarboxylation reaction. As the reaction progressed, the subsequent cracking followed more quickly, and with the approach of the acceleration period the disintegration rate markedly increased. The fracturing process of the p-aminosalicylic acid crystals led to a velocity rate greater than that of the powdered p-aminosalicylic acid during the acceleration period. The rate of degradation of the crystals is compared in Fig. 7 with that of the powdered p-aminosalicylic acid exposed to the same conditions. In comparing the two curves for powdered and larger crystalline p-aminosalicylic acid it can be seen that the induction period was longer, the acceleration period had less duration and greater velocity in the case of the larger crystalline state than the powdered form. These results may be explained
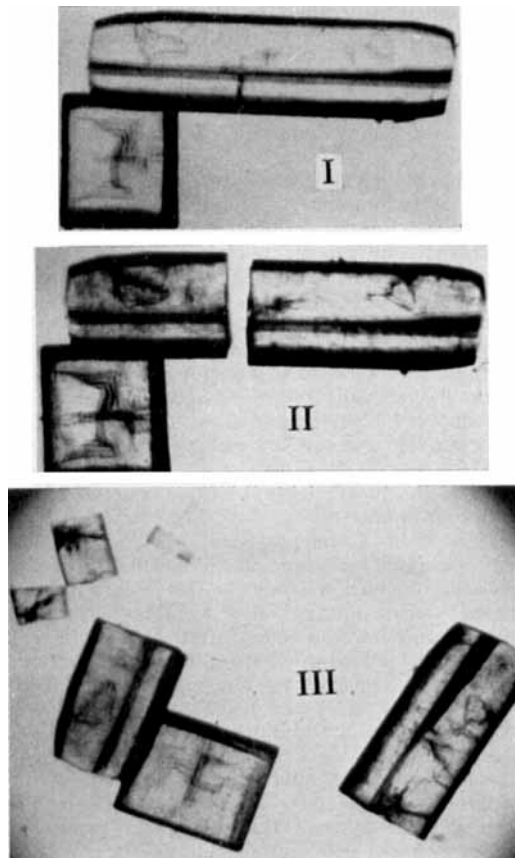

Fig. 6a.—Illustration of the cracking process experienced by whole crystals of p-aminosalicylic acid in the early stages of thermal decomposition at 80°; (I) before exposure, (II) after 7-hr. exposure, (III) after 9-hr. exposure.
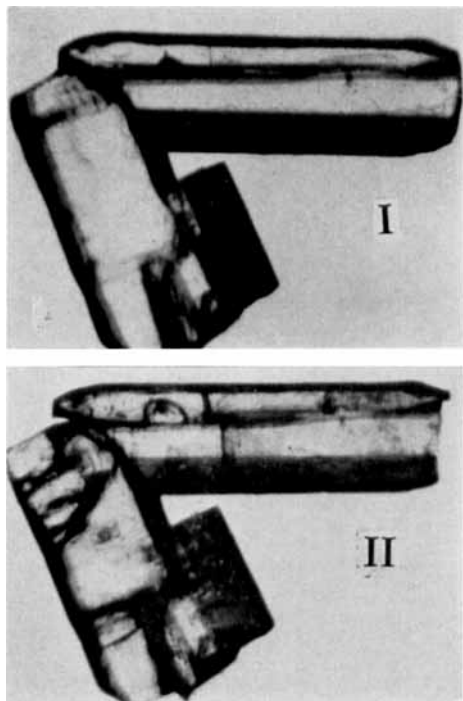
Fig. 6b.—Illustration of the cracking process experienced by whole crystals of *p*-aminosalicylic acid in the early stages of thermal decomposition at 80°; (I) before exposure, (II) after 7-hr. exposure.

by reference to the cracking process which imposed sites of reaction different from that induced by grinding. In other words, the cracking process supplies numerous new potential sites for degradation by continually cracking and fracturing, whereas the powdered *p*-aminosalicylic acid, as observed microscopically, did not appear to be further fractured. The fracturing process occurring with crystalline *p*-aminosalicylic acid was brought about either by uneven heating of the crystals or by a release of carbon dioxide generated from the decarboxylation reaction. It is felt that the apparent lack of fracturing experienced by the powdered *p*-aminosalicylic acid can be clarified on the grounds that uniform heating of the particles should be possible and also that the particles have been endowed, from past history, with numerous cracks and crevices for the release of any carbon dioxide formed.

After the second inflection point of the per cent decomposition *versus* time curve the particles, from the crystals, appeared to be of uniform size and shape, and did not appear to undergo any further change during the subsequent decay period. The duration of the acceleration period seemed to be dependent on the particle size and the physical means used in obtaining this size.

Dry Atmosphere, Reduced Pressure Study.— When the reaction was conducted under reduced pressure it was found that the induction period was maintained but without incidence of a second inflection point (Fig. 8). The rate of reaction at this reduced pressure (approximately 10 mm. Hg) increased the degradation by a multiple of 4.4. To

establish the composition of the sublimate from the reaction, a "cold-finger" apparatus was utilized. The solidified vapor was shown to be *m*-aminophenol by infrared analysis and by melting point determination. This study was primarily pursued to eliminate the possibility that *p*-aminosalicylic acid also sublimed under these conditions. However, the possibility exists that *p*-aminosalicylic acid vaporizes and decomposes before it condenses to yield the same results. This point could not be resolved experimentally. Spectrophotometric analysis of the reaction mixture demonstrated the absence of decomposition product throughout the reaction. Hence, there was no accumulation of *m*-aminophenol on the surface of the *p*-aminosalicylic acid as occurs under dry, atmospheric pressure.

Moist, Atmospheric Pressure Studies.—Figures 9 and 10 represent the typical curves for the thermal decarboxylation of *p*-aminosalicylic acid in a moist atmosphere. The results of this series of experiments showed that (*a*) the induction period was greatly diminished at the lower temperature employed; (*b*) a more rapid velocity than in the dry state was evident; (*c*) once again no second point of inflection was noted. Analysis of the samples for *m*-aminophenol showed that this by-product must have been removed during the progress of the reaction by a process similar to steam distillation in the moist atmosphere.
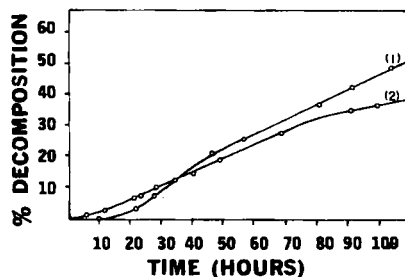

Fig. 7.—Per cent decomposition-time curves for the decarboxylation reaction of *p*-aminosalicylic acid in the dry, solid state at 80°; (*1*) whole crystals, 40/80 sieve size, (*2*) ground crystals, *ca.* 3.3 μ.
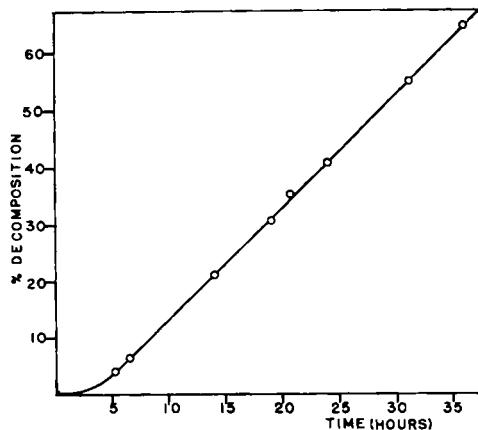

Fig. 8.—A per cent decomposition time curve for the decarboxylation of *p*-aminosalicylic acid under dry atmosphere and reduced pressure (*ca.* 10 mm.) at 80°.
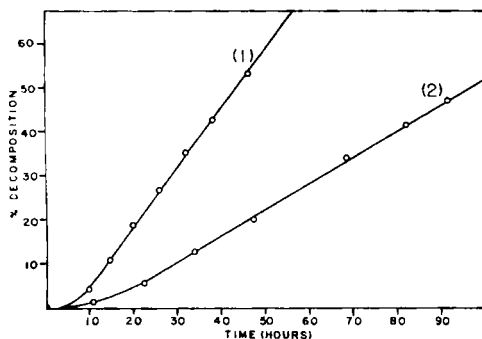
Fig. 9.—Per cent decomposition-time curves for the decarboxylation of *p*-aminosalicylic acid in a moist atmosphere at 80°; aqueous tension, (*1*) 181.0, (*2*) 8.13 mm. Hg.

The activation energy was reduced considerably from that obtained under dry, atmospheric conditions; however, it remained constant at all the aqueous tensions employed (Table II). The activation energy for the decarboxylation of *p*-aminosalicylic acid in aqueous solution was reported (5) as 19.4 Kcal./mole as compared to 29.5 Kcal./mole for the reaction under moist atmospheric conditions. The 10 Kcal. difference between solution kinetics and a saturated solution on the surface of a solid perhaps could be assigned to a complex of the heats of solution, dissolution, and sublimation.

A plot of the velocity constants *versus* the aqueous tension (Fig. 11) was linear, indicating that the mechanism of the reaction remained unchanged when the humidity was varied.

If one extrapolates Fig. 11 to zero pressure the velocity constant is very close to zero. Therefore, at constant temperature, if we double the vapor pressure of water the velocity constant is doubled. Zero-order solution kinetics seemed to be indicative of this relationship since the solubility of the *p*-aminosalicylic acid in the adsorbed moisture appeared to be a function of the aqueous tension over the sample. However, if we attempted to analyze,

$$\frac{d(\text{PAS})}{dt} = k_1 (\text{PAS}) = k_0$$

where k_1 (1.986 hr.$^{-1}$) is the first-order rate constant for an aqueous soluton (5) and k_0 (0.003 hr.$^{-1}$) is the zero-order rate constant for a saturated solution on the surface, then the concentration of *p*-aminosalicylic acid in solution required to equate k_1 with reference to k_0 would be 0.0015 mole of acid. The total sample size of *p*-aminosalicylic acid (0.00196 mole) would require that approximately 80% of the solid acid be in solution for the above relationship to exist. If one considers the slow rates of dissolution and diffusion in a stagnant system, it appears presumptuous to substantiate purely solution kinetics.

Table II indicates the effect of humidity on the induction period, the *k* values and apparent activation energy.

Suspension Technique Study.—The per cent decomposition *versus* time curve obtained for the decarboxylation of *p*-aminosalicylic acid in suspension is shown in Fig. 12. It is characterized by the typical induction period followed by the reaction
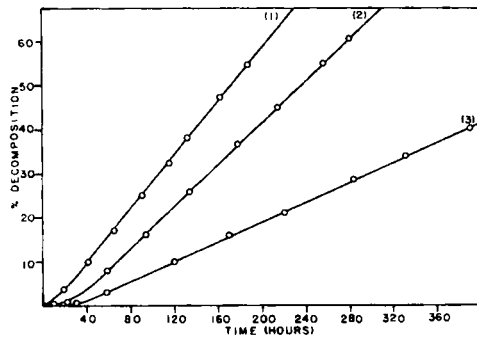

Fig. 10.—Per cent decomposition-time curves for the decarboxylation of *p*-aminosalicylic acid in a moist atmosphere at 70°; aqueous tension, (*1*) 144.0, (*2*) 118.4, (*3*) 52.3 mm. Hg.

TABLE II.—DATA OF THE DECARBOXYLATION REACTION OF *p*-AMINOSALICYLIC ACID UNDER MOIST, ATMOSPHERIC PRESSURE CONDITIONS

T, °C.	Aqueous Tension (mm. Hg)	Induction Period (hr.)	k, mole% hr.$^{-1}$[a]	Apparent Activation Energy, Kcal./mole
70	52.3	34	0.113 ± 0.005	29.3
70	118.4	26	0.245 ± 0.006	29.8
70	144.0	8	0.305 ± 0.003	29.3
80	81.3	7	0.600 ± 0.012	29.6
80	181.0	5	1.310 ± 0.023	29.5

[a] Average of two runs.

without incidence of a second inflection point. During the reaction a solid material collected in the neck of the reaction vessel; analysis proved it to be *m*-aminophenol. The mineral oil, therefore, provided a medium which facilitated the removal of *m*-aminophenol from the surface of the *p*-aminosalicylic acid.

DISCUSSION

The thermal decomposition of *p*-aminosalicylic acid is characterized by the typical sigmoidal curve which has been reported for other solid-state reactions (9, 14, 15). An induction period, the duration of which was governed by experimental conditions, was experienced with all the studies. The increased induction period with larger crystals was apparently due to a limited number of dislocations prior to cracking. In time the fracturing process supplied numerous irregular chips which further disintegrated, generating new points of dislocations. After this initial period the reaction velocity exceeded that of the powdered *p*-aminosalicylic acid exposed to the same conditions. It is felt that this phenomenon was due to the abundance of nuclei formed from the explosive fracturing of the crystals. After the second inflection point of the per cent decomposition *versus* time curve the particles appeared to be of uniform size, and did not undergo further change during the subsequent decay period. The extent and velocity of the acceleration period appeared to be both dependent on the surface area of the *p*-aminosalicylic acid, and whether the active sites arose from either a thermally induced cracking process or physical grinding.

The experiments involving various environments other than dry, atmospheric pressure all produced
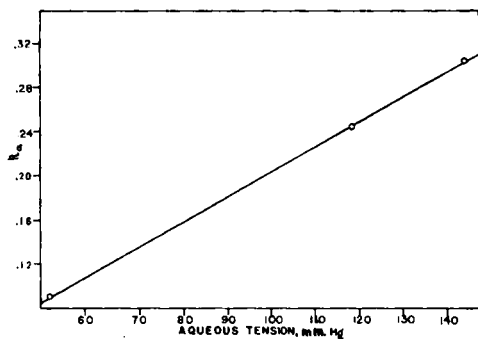
Fig. 11.—Relationship of velocity constant to the aqueous tension at 70°.

Fig. 12.—Per cent decomposition-time curve for the decarboxylation of *p*-aminosalicylic acid in a mineral oil suspension (*ca.* 0.1%) at 80°.

similar per cent decomposition *versus* time curves (Figs. 8–10, 12), which are characterized by the absence of a second inflection point. All have in common the removal of *m*-aminophenol from the reaction site. It appeared that the reduced pressure, moist atmosphere, and hot mineral oil function as transport media facilitating the removal of *m*-aminophenol from the surface of the *p*-aminosalicylic acid, which maintained the β value (Eq. 2) at a minimum. The second inflection point observed with dry, normal atmospheric conditions was brought about by an interference of the decomposition product which was eliminated under the other stated conditions. The removal of the decomposition product hastened the reaction velocity. The buildup of *m*-aminophenol on the surface of the *p*-aminosalicylic acid acted as a deterrent, decreasing the rate of reaction. Of course, decomposition must be considerable (25–30%) before the *m*-aminophenol causes a pronounced effect on the reaction rate (utilizing 300 mg. sample).

The experimental data obtained under moist atmospheric conditions were not thought sufficiently quantitative to analyze as purely solution kinetics; however, the possibility does exist. The fact that the decomposition product, *m*-aminophenol, was removed from the sample appeared to indicate that the moisture did aid in the transport of the *m*-aminophenol from the solid sample. Our findings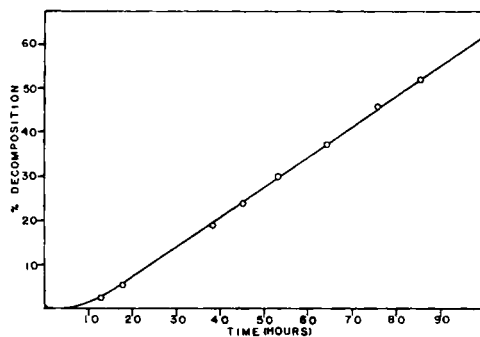 contradict the conclusion of a previous study (8) which suggests that water functions as a catalyst. In the same study (8), it was reported that *m*-aminophenol, physically incorporated with *p*-aminosalicylic acid, also caused a catalytic effect. The grinding method utilized for introducing *m*-aminophenol possibly created new cracks in the *p*-aminosalicylic acid crystals which may account for apparent changes in the reaction rate when the *m*-aminophenol was not included.

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