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THE DECARBOXYLATION AND THERMAL STABILITY OF *p*-AMINOSALICYLIC ACID AND ITS SALTS

MAREK WESOŁOWSKI
Institute of Chemistry and Analytics, Medical Academy, Gdańsk (Poland)
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ABSTRACT

A survey has been given of the mechanism and kinetics of decarboxylation and thermal stability of *p*-aminosalicylic acid and its sodium and calcium salts in the solid state and solutions.

INTRODUCTION

p-Aminosalicyclic acid (PAS) and its sodium, potassium and calcium salts are fundamental preparations in the combined treatment of most cases of tuberculosis. In spite of the small toxicity of PAS, it should be admitted only in a very pure chemical form to the therapy, in particular free of its decarboxylation product, *m*-aminophenol (MAP). MAP provides a contamination responsible for a series of toxicity symptoms, such as hard hemolytic anaemia, connected with brucise. It is particularly important in view of the fact that during the ordinary treatment, the administered quantities of PAS amount to at least 1200 g, at a daily dose[1] of 10–16 g.

Because of the foregoing reasons, it has been decided to survey research works on decarboxylation of PAS, the mechanism and kinetics of decarboxylation as well as thermal stability of PAS and its salts in the solid state and in solutions.

1. STABILITY OF PAS AND ITS SALTS IN THE SOLID STATE

PAS is a white or almost white crystalline powder with a melting point of 140 °C. In a technical scale it is manufactured as a pale-cream microcrystalline powder of 97–99% purity, melting at 139–141 °C. Some authors[2–4] report an m.p. of 137 °C. PAS heated in a capillary[5] at a rate of 3 °C min^{-1}, melts at about 147 °C. Other authors report 150–151 °C as a m.p. of white crystalline PAS powder[6]. These discrepancies concerning the m.p. of PAS and N-n-butyl-PAS promoted Dobrowsky to determine a relationship between the m.p. of the compound itself as well as of its mixtures and the heating rates (Fig. 1)[7]. The observed phenomenon was explained as due to changes taking place in the crystal lattice during melting and decarboxylation of compounds. The kinetic equation:

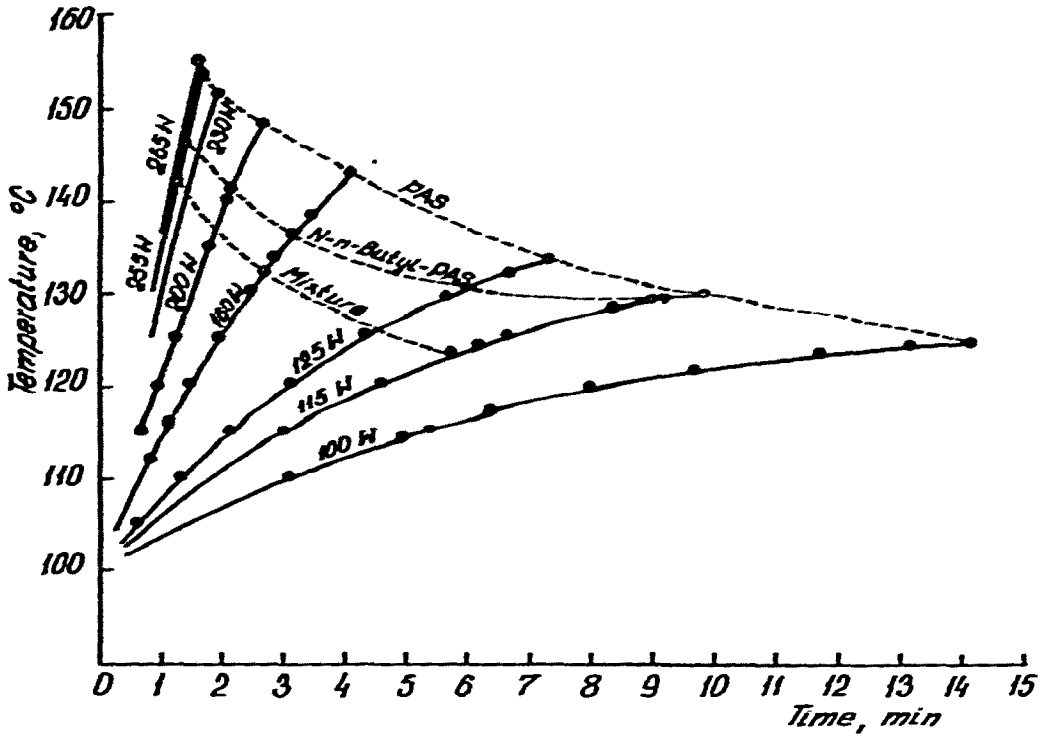


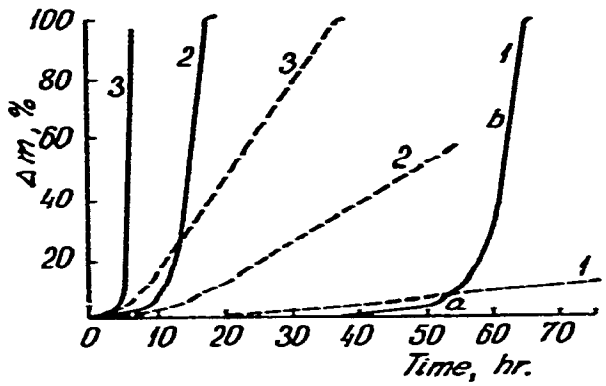
Fig. 1. Plot of melting points versus heating rates for PAS and N-n-butyl-PAS as well as their mixture. ⊖ = decomposition point; ● = measuring point; and w = heating current strength.

$$\log t^* = \frac{E}{2.30R} \cdot \frac{1}{T} + \log 2.30 + \text{loglog} \frac{N}{(N - n^*)}$$

$$K_1 = 6960 \qquad K_2 = -14.97$$

was derived where t^* is time required for melting and decarboxylation of PAS, T is absolute temperature of the heating bath, E is the energy of the crystal lattice and the term $N/N - n^*$ is a ratio of destroyed (n) and primary (N) centres of the crystal lattice. From this equation, the K_1 and K_2 constants were determined for PAS crystals. Moreover, it was shown that time required for melting and for complete decarboxylation of PAS was essentially the same at a constant bath temperature, irrespective of whether the heating was continuous or interrupted[8]. The m.p. of PAS is accompanied by decarboxylation and is not a good criterion of purity and identity of the compound.

Some authors[16, 40] report that the decarboxylation of PAS begins at about 110°C and continues up to 150°C. Decarboxylation of PAS was defined as so-called "type I reaction" in which a compound gives upon decomposition one molecule of a solid product and one molecule of a gaseous product[9]. Thus mean decarboxylation is governed by the nucleation kinetic theory. The decarboxylation of PAS is a topochemical and autocatalytic process displaying an induction period, followed by a



Temp. °C	Induction period hr.*	Acceleration period hr.*
59	above 200	—
74	59.0	6.0
78	12.2	4.5
90	5.0	1.7

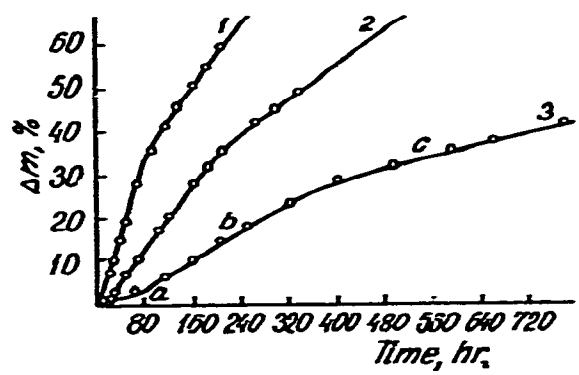
*for PAS alone

Fig. 2. Percentage of weight losses as a function of time of the thermal decarboxylation of PAS (continuous line), and its mixture with MAP (3–5%) (dashed line), in the solid state at ambient pressure and temperatures 1 = 74°C; 2 = 78°C and 3 = 90°C. a = Induction period and b = acceleration period of the decarboxylation.

rapid period (Fig. 2)[10, 11]. The rate of decarboxylation in the second period is 3- to 4-fold greater than that during the induction period. The decarboxylation at ambient temperature is characterized by a very long induction period, while an increase in temperature accelerates both steps, the induction period being reduced. The energy of activation of the rapid period of decarboxylation was calculated from a slope of a straight line for the first-order kinetic data and amounted to 20.5 kcal mol^{-1} within 70–100°C. The reaction is accelerated by water and MAP and the rate of decarboxylation is independent of the initial carbon dioxide pressure. In the carbon dioxide pressure range up to 760 mm of Hg the equilibrium in the system:

$$PAS \rightleftharpoons MAP + CO_2$$

was not reached. Some authors have suggested the existence of a third period of decarboxylation which was defined as a decay period (Fig. 3)[12, 13]. The accelerated



Temp. °C	Induction period hr.	t max. hr.
70	38	360
75	18	170
80	8	71

Fig. 3. Percentage of weight losses as a function of time of the thermal decarboxylation of PAS in the solid state at ambient pressure without moisture content at temperatures 1 = 80°C; 2 = 75°; and 3 = 70°C. a = Induction period; b = acceleration period; and c = decay period of the decarboxylation.

period of decarboxylation can be described by a kinetic equation:

$$\frac{dx}{dt} = k_a = \frac{x}{t - \tau}$$

where x is percentage of PAS decarboxylation at time t, τ is time of persistence of induction period and k_a is rate constant of the acceleration period of decarboxylation. The decay period was described by the kinetic equation:

$$\frac{dx}{dt} = k_d = \frac{x - x_{max}}{t - t_{max}}$$

where x_{max} is the percentage of PAS decarboxylation at t_{max}, which is the time when the reaction reaches the greatest velocity and k_d is the rate constant of the decay period of decarboxylation. A typical sigmoidal curve reported for PAS decarboxylation was, moreover, dependent on pressure and particle size of PAS crystals. Moisture has been found to affect largely the decarboxylation kinetics of PAS. Other reactions than the first-order kinetics reactions can be induced by the effect of sorbed moisture at a thin layer on the surface of PAS[9]. Moreover, sunlight induced PAS decarboxylation at an insignificant degree[39].

Dehydration of PAS–Na · $2H_2O$ was investigated by thermobalance. The process begins at 50°C, followed by an acceleration step beginning at 60°C, and the dehydration is completed at 83°C[14]. PAS–Na appears to be stable up to about 150°C[40]. The crystalline PAS–Na hydrate was considered to be a complex compound, whose conversion into an anhydrous form was thermodynamically inhomogeneous[15]. A transition point at 110°C was determined by heating PAS–Na · $2H_2O$ under a layer of paraffin oil. Anhydrous PAS–Na decomposes at 164–165°C, leaving quantitatively PAS–Na_2, which decomposes completely over the range 270–1000°C (Fig. 4)[16].

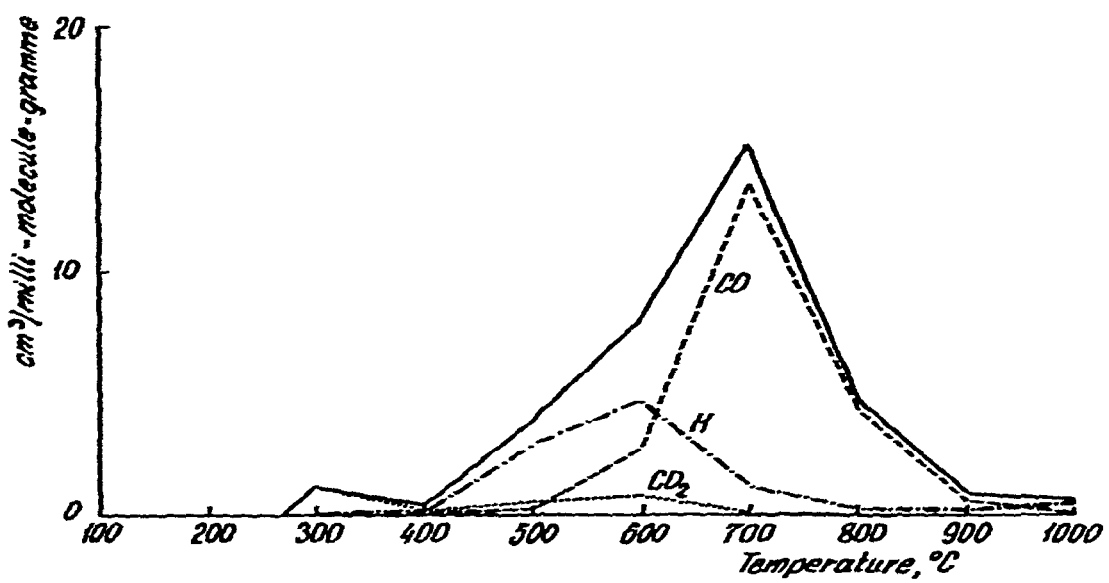


Fig. 4. Volume of volatilizing gaseous products: carbon dioxide, carbon oxide and hydrogen formed by the thermal decomposition of PAS–Na.

The residue provides 11.2% of the original amount of PAS–Na. The dehydration of PAS–Ca · $7H_2O$ begins at 50°C and is considerably accelerated at 120°C[14]. PAS–Ca · $2H_2O$, forming up to 160°C, is a final product of dehydration. Total decomposition takes place above 175°C. According to Utsumi et al.[17], PAS–Ca · $6H_2O$ loses its crystalline water completely at ambient temperature. Anhydrous PAS–Ca is able to absorb moisture from the environment to form an intermediate modification which after a long period is converted to PAS–Ca · $6H_2O$. This was confirmed by the X-ray diffraction pattern. The phenomenon is disadvantageous, since the anhydrous compound is characterized by a smaller density and volume. These facts suggest that tablets formed from the anhydrous compound slowly absorb water and gradually change to give PAS–Ca · $6H_2O$, resulting in the volume increase of crystals and promotion of tablets disintegration. The DTA curve of PAS–Na over the range 20–600°C was also shown[18, 19].

2. STABILITY OF PAS AND ITS SALTS IN SOLUTION

PAS is difficultly soluble in water giving a saturated solution with a pH of about 3.5, which undergoes decarboxylation[2–4, 6]. The kinetics of the decarboxylation of PAS and some 4- and 5-substituted derivatives of salicylic acid (SA) over the range 90–230°C in a quinoline solution satisfy the first-order kinetic equation[20]. All substituents, except for the H_2N–, HO– and H_5C_2O– ones, have almost no effect on the decarboxylation rate of SA. A deviation from Hammett's equation, describing a logarithmic relationship between ionization constants and rate constants of decarboxylation of the above three derivatives was explained on the assumption that the compounds had the first kind of substituents, characterized by large negative δ constants. These were responsible for the appearance of a positive mezomeric effect by negative charge of aromatic carbon atoms, thus activating the *o*- and *p*-positions for the electrophilic substitution. The substituents have been shown to affect individual steps of decarboxylation. Generally, the mechanism of PAS decarboxylation can be suggested by assuming three steps involving a preliminary ionization of the carboxyl group, followed by proton attachment to the negative charge of the aromatic carbon atom of the anion so formed and then the loss of carbon dioxide. In studies on the kinetics of decarboxylation of PAS at 20°C in dilute hydrochloric acid and acetate buffer, its absorption bonds at 265 and 300 nm were utilized (Fig. 5)[21, 22]. By spectrophotometric and potentiometric methods, the ionization constants of PAS were determined:

$$K_0 = \frac{[HA][H^+]}{[H_2A^+]} = 1.66 \cdot 10^{-2} \pm 12\%$$

$$K_1 = \frac{[A^-][H^+]}{[HA]} = 2.32 \cdot 10^{-4} \pm 2\%$$

The decarboxylation of PAS occurs by two different mechanisms: as a monomolecular

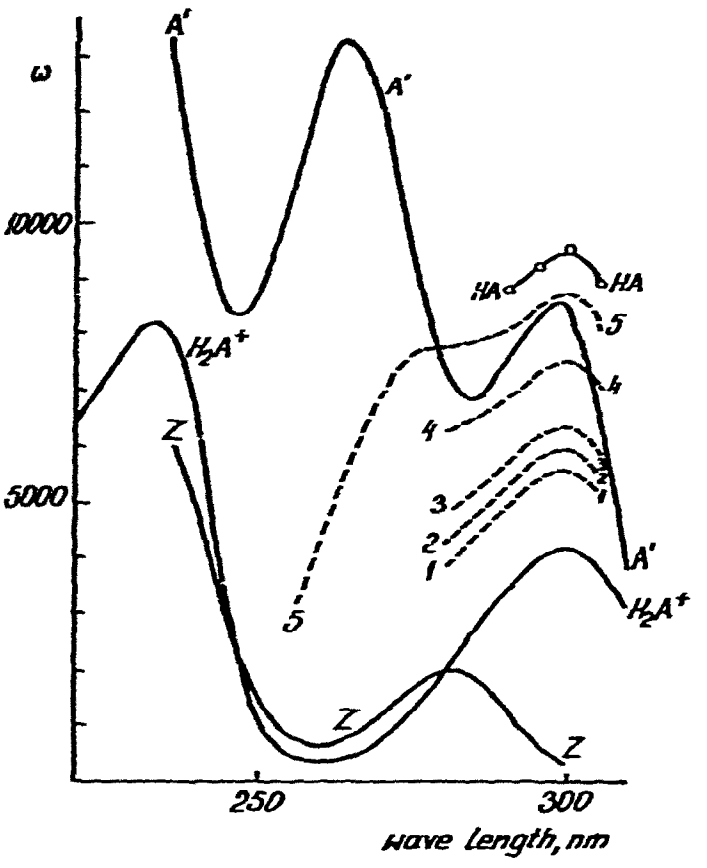


Fig. 5. UV-spectrum of PAS solutions. A' = 3 · 10⁻³N NaOH; H_2A^+ = 2N HCl; 1 = 4 · 10⁻²N HCl; 2 = 3 · 10⁻²N HCl; 3 = 2 · 10⁻²N HCl; 4 = 1 · 10⁻²N HCl; 5 = 2.5 · 10⁻³N HCl; HA = non-dissociated PAS; Z = MAP.

reaction of electrophilic substitution (S_E 1) and as a bimolecular reaction of the electrophile substitution (S_E 2). The S_E 1 reaction is pseudo-first-order one. However, in the S_E 2 reaction an activated complex is formed and for this reason it is the second-order reaction. The rate of decarboxylation is thus a sum of overall rates of both reactions:

$$-\frac{dc}{dt} = \frac{k_{HA}}{K_1}[A^-][H^+] + \frac{k_{H_2A^+}}{K_0}[HA][H^+]$$

where dc/dt is total rate of PAS decarboxylation and k_{HA} and $k_{H_2A^+}$ are decarboxylation rate constants of PAS and of PAS ammonium cation, respectively (Fig. 6). The rate constant, $k_{H_2A^+}$, is 10-fold smaller than k_{HA}, owing to the inhibiting effect of the NH_3^+-group which is formed as the pH of solution is lowered. In a similar manner, the kinetics of decarboxylation of the H_2N-, HO- and H_3OC-substituted SA was described[22, 23]. The reaction takes place in hydrochloric acid solutions over the range 20–85°C. It could be demonstrated whether attachment of proton and liberation

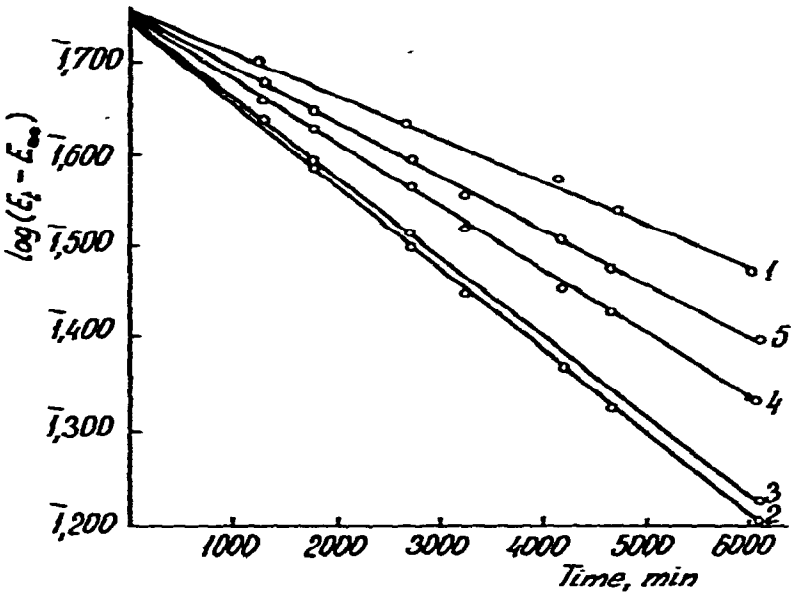


Fig. 6. Kinetics equation $k = (1/t)\ln[(E_0 - E_\infty)/(E_t - E_\infty)]$ curves for dilution hydrochloric acid solutions of PAS at $[H^+]$. $1 = 3 \cdot 10^{-2}$; $2 = 1.6 \cdot 10^{-3}$; $3 = 1.2 \cdot 10^{-3}$ and $4 = 3.92 \cdot 10^{-4}$ as well as for acetate buffer at $[H^+]$; $5 = 3.2 \cdot 10^{-4}$.

of carbon dioxide occurred simultaneously or via an intermediate state involving a proton attached to the carbon atom of the aromatic ring. In the bimolecular reaction, the rate constant of decarboxylation increases and the activation energy decreases with increasing electron-donating power of a substituent. The decarboxylation rate of PAS at 30°C, as compared with other aromatic amino acids, strongly decreases with increasing hydrochloric acid concentration[24]. The rate decrease was caused by a change in the mechanism from the rate determining carbon atom protonation (σ-complex formation) to rate determining elimination of CO_2 or CO_2H^+ from the corresponding σ-complex intermediate, X or HX^+, respectively. A quantitative estimation of these findings was given on the basis of the Hammett acidity function, H_0, providing a proper means of expressing acidity of strong acid, because rates of decarboxylation were measured in 0.1–4.0 N hydrochloric acid solutions. Introduction of the CH_3CONH–substituent of smaller negative σ value in the *p*-position of SA, in contrast to the H_2N–substituent, affects markedly the PAS decarboxylation[25]. N-acetyl-PAS was shown to be more stable than PAS. It did not decarboxylate in solution above pH 3.1 over 12 days. Below pH 3.1 a slow decarboxylation was observed, probably due to decarboxylation of PAS, set free by hydrolysis of the amide linkage in N-acetyl-PAS. Moreover, at pH 2.1 about 8% N-acetyl-PAS decarboxylated within 12 days, whilst PAS was decarboxylated in about 23% during the first day at the same pH value. The first-kind substituent $(CH_3)_2N$– with a significantly greater negative σ value, in contrast to the H_2N–substituent, substituted in the *p*-position of SA, promoted markedly the decarboxylation of PAS[26]. On the basis study of $(CH_3)_2N$–

PAS decarboxylation kinetics in aqueous solution, it was suggested that decarboxylation could only take place via the zwitterion state, i.e., an internal salt. At a pH value of the iso-electric point the zwitterion species was present to an extent of approximately 30%, much accelerating decarboxylation of $(CH_3)_2N$–PAS. It was concluded that the $(CH_3)_2NH^+$–group was more active than the NH_3^+– one in promoting decarboxylation of the –COOH group. The kinetics of PAS decarboxylation at 20°C in an aqueous solution can be characterized by the following equation, developed on the basis of the zwitterion theory:

$$-\frac{dc}{dt} = k^+[H_2A^+] + k^0[HA] + k^-[A^-]$$

where dc/dt is the rate of PAS decarboxylation, and k^+, k^0 and k^- are rate constants. The mechanism of PAS decarboxylation at 60 and 80°C was explained on the basis of a monomolecular reaction[27]. On the basis of the ionization constant values of the –COOH and H_2N– substituents of *p*-aminosalicylic, *p*-aminobenzoic and *o*-aminobenzoic acids, which were determined spectrophotometrically, the effect of conjugation of both substituents with the benzene ring and the effect of the intramolecular hydrogen bond on the ionization equilibrium were estimated[28]. The values were then employed for interpretation of the PAS decarboxylation constant in various solvents at different pH values and temperatures[29]. The difference in the first-order kinetic equation in organic solvents, in contrast to buffered solutions, was explained by variations in pH during PAS decarboxylation. A relationship between the logarithm of the rate constant of decarboxylation and of the pH value of solution shows a maximum at pH between the values pK_1 and pK_2, which correspond to the ionization constants of the H_2N– and –COOH groups, respectively. Studies of PAS decarboxylation in an aqueous solution show that the minimal rate of decarboxylation was obtained in a 0.5 M aqueous solution of PAS in the presence of 0.5 M acetate buffer[30]. In the presence of a potassium phosphate buffer over the range 50–60°C, almost no induction period in PAS decarboxylation was observed. Moreover, within the remaining temperature ranges considerable reduction of the induction periods was noted[31]. A sodium oxalate buffer induced appearance of two induction periods during PAS–Ca decarboxylation.

Investigations of the degree of PAS decarboxylation in solutions by a spectrophotometric method at various pH values, shows that acidic medium and higher temperatures accelerate decarboxylation of PAS. Even solutions stored at lower temperatures in a refrigerator were stable only for a limited period[32–34]. Ethanolic solutions of PAS were considerably more stable and did not decarboxylate at about 70°C but at the b.p.[35, 36]. PAS–Na, in contrast to PAS was decarboxylated in aqueous solution at a considerably lesser extent because the pH value of the PAS–Na solution falls within the range 7–8, thus protecting the salt from decarboxylation[37–41]. A 20% solution of PAS–Na was decarboxylated by about 2.5% during a three months storage, and when autoclaved at 115°C for 30 min the decarboxylation degree was close to 30%. It is not true that the contact with strong alkali accelerates decarboxyla-

tion of PAS solutions[3, 4, 6]. Colorimetric studies on the stability of medicinal sirups containing PAS–Na and PAS–Ca and various flavourings showed that decarboxylation of both compounds was faster in more acidic solutions and at higher temperatures[42, 43]. PAS–Na dissolved in a malt sirup was stable for several months[44]. Rate constants of PAS–Na and PAS–Ca decarboxylation at 37°C in artificial gastric and intestinal juices were estimated[45]. PAS–Na and PAS–Ca were decarboxylated, in 60–65 and 28%, respectively, in artificial gastric juice and in δ and 3.2% in artificial intestinal juice during 120 min.

Decarboxylation of PAS and its salts in aqueous solutions is important in the quantitative estimation of PAS. PAS solution was treated with an excess of 0.25 N solution of barium hydroxide and the excess was back-titrated acidimetrically[46, 47]. The results were in agreement to within 1% with a quantity of MAP assessed colorimetrically. Moreover, the alkalimetric titration is applicable to the determination of carbon dioxide distilled from an aqueous PAS solution heated below its b.p.[48]. Interference of atmospheric carbon dioxide was eliminated by pentane as a sealing liquid. A gasometric method of measuring carbon dioxide formed in a solution of PAS was also described[49].

The solubility curve of PAS–Na over the range -50 to $+50$ has an indicated inflection at 2°C[50]. A thermal balance method and measuring vapour pressure over the solution indicated that the liquid below 2°C was PAS–Na · $1.5H_2O$, a while above that temperature PAS–Na · $1.2H_2O$ occurred. PAS–Na · $1.2H_2O$ was completely dehydrated above 70°C. PAS was also studied by the RTA method under programmed temperature over the range 20–400°C (Fig. 7)[51]. Identification of

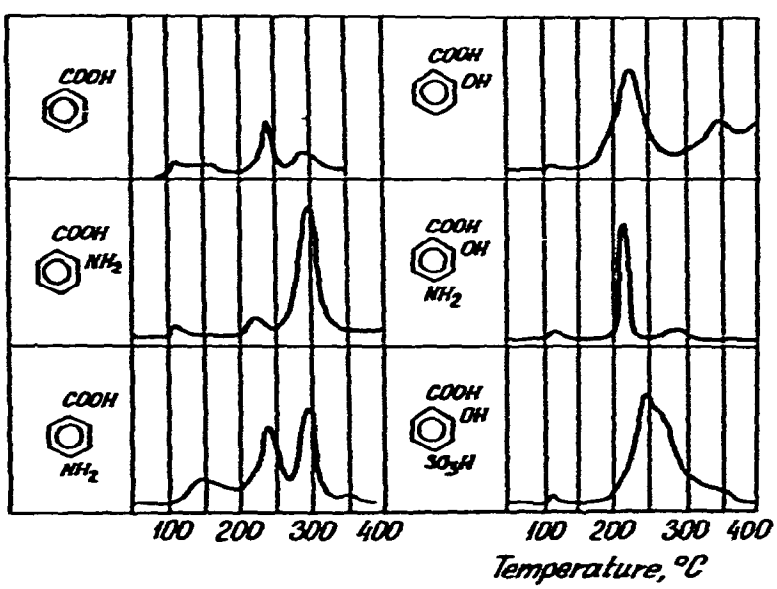


Fig. 7. Volume of volatilizing gaseous products formed by the thermal reaction of benzoic, *ortho*- and *para*-aminobenzoic, salicylic, *para*-amino and sulphosalicylic acids with alkaline cupric carbonate in quinoline solution.

decomposition products enabled identification of individual functional groups.

In connection with the problems discussed, it would be useful to pay attention to colour changes of solution accompanying PAS and PAS–Na decarboxylation[52—54]. The change of colour is associated with the decarboxylation, it is due to oxidation of MAP and to the presence of impurities[55, 49]. One of the major coloured oxidation products of MAP is 3,3'-dihydroxyazoxybenzene[56]. Ascending 2-dimensional paper chromatography of the red-brown photo-decomposition products of PAS showed the presence of 14 compounds, one of which was identified as MAP[57]. MAP and β-resorcilic acid were detected by thin-layer and paper chromatography[58]. Polymerized PAS and MAP were detected by infrared spectroscopy[59, 60, 39]. The criteria of purity and stability of PAS–Na solutions have been suggested by Krepinsky and Stiborova[61—65].

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