Boric Acid in the Aqueous Carboxylation of m-Aminophenol to p-Aminosalicylic Acid[1]

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The formation of p-aminosalicylic acid (PAS) in the aqueous modification of the Kolbe-Schmitt process is shown to be an equilibrium. Boric acid when added to the reaction mixture increases the yield of PAS. Presumably boric acid chelates the PAS formed in the reaction and thus displaces the equilibrium toward greater conversion of m-aminophenol to PAS. Additionally, boric acid strikingly suppresses the formation of the dicarboxylated by-product, 4-amino-6-hydroxyisophthalic acid. How boric acid exerts this latter effect is not known. Several possibilities are discussed.

Numerous papers have described an aqueous modification of the Kolbe-Schmitt process for the synthesis of p-aminosalicylic acid (PAS).[2-6] The yields claimed in most instances are modest and run ca. 60% of theory. This apparent yield usually includes a variable amount of the dicarboxylated product, 4-amino-6-hydroxyisophthalic acid.[7,8] When this is eliminated and the concomitant process losses are taken, the yield of purified PAS frequently is not greater than 40% of theory.

As detailed in a previous publication, the addition of boric acid to the carboxylation reaction mixture definitely increases the yield of PAS and, further, the crude product contains much less of the dicarboxylated by-product.[9] This paper will be limited to an investigation into the nature of the reaction.

The extent of conversion of m-aminophenol to PAS was determined by two methods. In one of these the reaction mixture was analyzed directly from its ultraviolet spectrum. The details of this method are given in the experimental section. The other method was simply that of direct isolation.

The spectrum method was used because of the great speed with which it can be applied; however, it has serious limitations. Fundamentally it depends on the assumption that m-aminophenol and PAS are the only materials in the reaction mixture which absorb above 250 mμ. Since this condition is never met exactly and various by-products are usually formed, frequent checks of the validity of results are necessary. In practice, although there is some difference in their spectra, the method works

to give useful relative data on the combined yield of PAS and its carboxylated derivatives. Where the yield of dicarboxylated acid is low, as in the boric process, the conversion figures by the spectrum method approach the actual PAS yield.

The "equilibrium" nature of the aqueous carboxylation reaction is suggested by the steady-state condition reached in curve 1 of Fig. 1, where the course of a typical "nonboric" reaction is shown. Consistent with this interpretation lowering the concentration of one reactant (bicarbonate) lowered the extent of conversion (curve 2, Fig. 1).
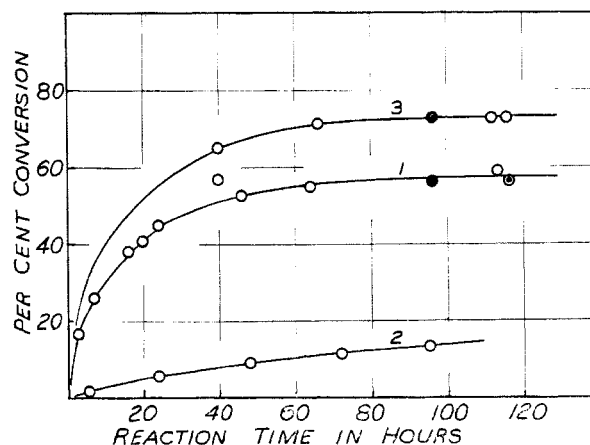

Fig. 1. Carboxylation of m-aminophenol to mixtures of PAS plus 4-amino-6-hydroxyisophthalic acid: conversion determined by spectrum method

Curve 1. Concentrated reaction mixture
Curve 2. Dilute reaction mixture
Curve 3. Concentrated reaction mixture with boric acid added
O   Starting with m-aminophenol
⊙   Starting with PAS
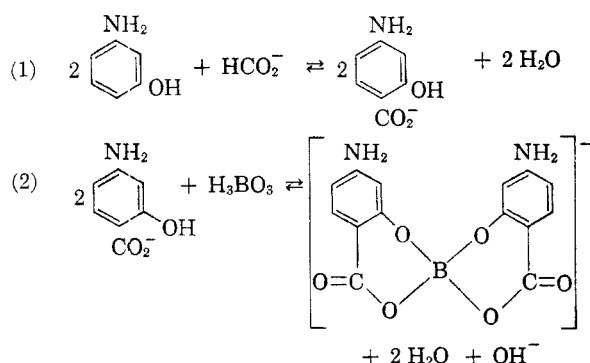●   Yield of "mixed acids" determined by direct isolation

The steady state, once reached, remains constant as demanded by an equilibrium reaction. In the last cited example (curve 2, Fig. 1) the limiting conversion (not shown in curve) of 21.6% reached after 335 hr. continued and after 440 hr. had changed only slightly (22.5%). A final criterion pointing to the reaction being an equilibrium is that the same final steady state is reached starting with

(1) Presented before the Medicinal Division of the American Chemical Society at Miami, Fla., April 1957.

(2) German Patent 50835, issued 1890.

(3) J. T. Sheehan, J. Am. Chem. Soc., 70, 1665 (1948).

(4) H. Erlenmeyer, B. Prijs, E. Sorkin, and E. Suter, Helv. Chim. Acta, 31, 988 (1948).

(5) F. Wesseley, K. Benedict, and H. Benger, Monatsh., 79, 185 (1948).

(6) D. J. Drain, D. D. Martin, B. W. Mitchell, D. E. Seymour, and F. S. Spring, J. Chem. Soc., 1498 (1949).

(7) H. C. Beyerman and G. L. G. Wielaert, Rec. trav. chim., 71, 1213 (1952).

(8) L. Doub, J. A. Schaefer, and C. T. Walker, Abstracts of Papers, 118th Meeting American Chemical Society, 1950.

(9) L. Doub, U. S. Patent 2,540,104 (issued 1951).

PAS in a suitably compensated reaction mixture instead of *m*-aminophenol.

The yields presented in Fig. 1 were calculated by the spectrum method and suffer the limitation of that method. In general, these yield figures determined thus approximate to the total crude yield as determined by direct isolation experiments. Two points determined by direct isolation are plotted in Fig. 1 for comparison. Determined by either method these, yield figures often include large amounts of dicarboxylated product. This is particularly true of yields determined after the steady state is reached. Indeed, all of our experience suggests that the dicarboxylated product is produced more slowly than is PAS and much of the time equilibrium in the nonboric process represents the slow production of this by-product.

The effect of adding boric acid to the reaction mixture is illustrated in curve 3, Fig. 1. As is evident by comparison with the otherwise identical run of curve 1, the over-all time course of the reaction is not greatly changed. The principal apparent effect is to raise the extent of steady state conversion. The gain in yield at the steady state effected in this particular example is approximately 12%. However, since much less of the dicarboxylated product is produced in the presence of boric acid than in its absence (especially for the prolonged reaction times shown here), the above yield gain reflects an even greater PAS yield differential. It is worth noting that the reaction mixture corresponding to curve 3 was selected arbitrarily. With a more concentrated reaction mixture under external carbon dioxide pressure even higher PAS yields are realized in the boric process.[9,10]

Except that it ignores the production of dicarboxylated product, the scheme of (1) and (2) is adequate to explain the data presented here. The chelate structure is assumed from that postulated by Boeseken for borosalicylate ion.[11]

$$\text{(1)} \quad 2 \underset{\text{OH}}{\overset{\text{NH}_2}{\bigcirc}} + HCO_2^- \rightleftarrows 2 \underset{\overset{|}{CO_2^-}}{\overset{\text{NH}_2}{\underset{\text{OH}}{\bigcirc}}} + 2H_2O$$

$$\text{(2)} \quad 2 \underset{\underset{CO_2^-}{\bigcirc}}{\overset{\text{NH}_2}{\bigcirc}}_{\text{OH}} + H_3BO_3 \rightleftarrows \left[\begin{array}{c} \text{chelate structure} \end{array} \right]^- + 2H_2O + OH^-$$

The aqueous carboxylation is formulated as an equilibrium in (1). This equilibrium is displaced toward completion by the removal of PAS to form the boric chelate in (2). This, then, is the explanation of the increased yield attained in the boric process.

How the formation of dicarboxylated acid fits into the scheme of (1) and (2) is not known. There are at least two possibilities. In the simplest of these PAS could be carboxylated directly to the isophthalic acid. In the other, *m*-aminophenol could first be carboxylated *para* to the hydroxyl group and this product, in turn, carboxylated to the substituted isophthalic acid. Both of these reaction sequences presumably would be reversible. That the formation of dicarboxylated product is suppressed in the boric acid process could be compatible with either scheme. In both, if the product isophthalic acid chelates less firmly with boric acid than does PAS its formation would be suppressed in favor of PAS. The second sequence would be particularly affected since it can be predicted that the initial *p*-hydroxy acid would not chelate with boric acid.

Several extensions of this reaction were attempted with no significant success. Carboxylation of *m*-aminophenol in the presence of an aluminum or an iron salt, both of which might chelate the product PAS of reaction I, gave no increase in yield. When *m*-aminophenol was replaced by either phenol or β-naphthol in these low temperature, aqueous reaction mixtures, with boric acid there was no more than a trace of carboxylation.

Yield determination by spectrum method. Concentrations of PAS and *m*-aminophenol in the reaction mixtures were determined by a modification of the standard two-component assay procedure.[12] The absorption curves of both compounds first were determined in 0.1N phosphate *p*H 7.0 buffer solution, and the coefficients of both at wave lengths 242 and 265 mμ selected for the assay readings. The maximum difference between absorptive intensity of the two compounds is at 265 mμ, while at 242 mμ the intensities are equal. This simplified calculations to some extent, without detracting significantly from the accuracy of the values obtained.

Absorption values at the selected wave lengths were read off the ultraviolet curves recorded at suitable dilution over a considerable range, rather than by spot readings only at the wave lengths. The contours of the curves gave general confirmation of the relative amounts of the components present.

In early experiments, parallel readings and determinations were obtained also after dilution of the reaction mixtures in 2N HCl, using absorptive constants measured for the compounds in this medium at 270 and 300 mμ. In all cases the calculated values corresponded closely with those obtained in the *p*H 7 buffer solution, and in later experiments the measurements in acid were discontinued.

Small scale experiments: product not isolated. A. A series of

(10) The particular data given here are reflected in our extensive experience with this process both on the laboratory and plant scale. The isolated yield of pure PAS under optimum conditions in the aqueous carboxylation reaction without boric acid runs 35–45% of theory, with boric acid it is upward of 60%.

(11) A. E. Martell and M. Calvin, *The Chemistry of the Metal Chelate Compounds*, Prentice-Hall, Inc., New York, N. Y., 1952, p. 48.

(12) M. G. Mellon, Editor, *Analytical Absorption Spectroscopy*, John Wiley & Sons, New York, N. Y., 1950, p. 374.

tubes was employed. Each tube contained 0.65 g. m-aminophenol, 3.0 g. potassium bicarbonate, and 5 ml. of water. In two tubes 0.91 g. PAS was substituted for the 0.65 g. m-aminophenol (MAP) to check the reversibility of the reaction. In some tubes (see table below), 0.74 g. boric acid was added. The tubes were sealed and heated in a water bath at 90° for the indicated time. The tubes were then removed, cooled, the seal was broken and the contents were diluted to 100 ml. This solution was assayed directly by the ultraviolet spectrum.

Starting with	Hours Heating	Boric Acid, G.	PAS Weight, G.	% Conversion
MAP	3	—	0.15	16.5
MAP	7	—	0.24	26
MAP	16	—	0.35	38
MAP	20	—	0.37	41
MAP	24	—	0.41	45
MAP	40	—	0.52	57
MAP	44	—	0.48	53
MAP	64	—	0.51	56
MAP	113	—	0.54	59
PAS	116	—	—	56
PAS	170	—	—	57
MAP	40	0.74	0.60	66
MAP	66	0.74	0.65	72
MAP	112	0.74	0.67	74
MAP	116	0.74	0.67	74

B. Ten and nine tenths grams of m-aminophenol (m.p. 121–122°) and 50 g. potassium bicarbonate were made up to 500 ml. with water. This was heated to and held at 90–91° while carbon dioxide was passed in at 3–4 bubbles per second. At intervals, samples were removed and the extent of conversion to PAS was determined by the spectrum method. The following results were obtained:

Reaction Time (Hr.)	PAS Formed (G.)	Extent of Conversion (%)
5.5	0.25	1.6
24	0.85	5.5
48	1.40	9.1
72	1.80	11.7
95	2.05	13.4

Larger scale experiments: (without boric acid) product isolated. Six hundred grams of potassium bicarbonate and 131 g. of m-aminophenol were suspended in 1 l. of water in an autoclave and heated at 90–95° under 35 lb. per sq. in. external dioxide pressure for 4 days. (This heating period exaggerates the production of decarboxylated product.) A sample of the reaction mixture taken after cooling was analyzed directly by the ultraviolet spectrum method; apparent yield 112 g., 61%.

The reaction mixture was cooled to 0° and after filtering from insoluble material, was acidified strongly with concentrated hydrochloric acid. The precipitate was filtered off and washed thoroughly with water. Yield after drying at 60°, 128 g. hydrochloride (56% yield). Conversion to free amino compound. The above hydrochloride was slurried in 200 ml. water (mechanical stirring) and dissolved by the slow addition of potassium bicarbonate. Water was added during this process making the final solution volume to 600

ml. This solution was decolorized by adding sodium hydrosulfite and filtering through charcoal. It was then acidified by the addition of 250 ml. dilute phosphoric acid (1 part water plus 1 part 85% phosphoric acid). The slurry was cooled to 0° and the product was filtered off and washed with cold water. The product after drying at 35° in vacuo, 89 g. (48% yield as PAS) dec. 160–162°, (rapid heating), is largely dicarboxylated compound.[10]

Anal. Nitrogen, found 7.93, 7.65, corresponds to approximately 65–70% dicarboxy compound. Neutral equivalent, found 113.9, corresponds to ca. 63% dicarboxy compound (contains only traces of phosphate, less than 0.6% determined colorimetrically). One gram dissolved in dilute bicarbonate was added to excess 6% nitric acid, a small amount of insoluble dicarboxy compound, m.p. 228–229° was filtered off.

Larger scale experiments: (with boric acid) product isolated. To a similar reaction mixture was added 148 g. of boric acid and the above experiment repeated up to the stage where the crude hydrochloride was isolated. The yield of PAS indicated by the spectrum method was 72.5%. The reaction mixture was first cooled strongly and filtered from insoluble material. The crude product was then isolated as in the previous experiment. This solid was dried and 25 g. (an 0.09 aliquot) was mixed for 10 min. with 50 ml. methanol containing 2 drops of saturated ethanolic hydrochloric acid. This treatment removes co-precipitated boric acid. The solid was filtered off and was washed with 25 ml. of methanol, then with 10 ml. of ether. Yield 15.0 g. crude hydrochloride (73.5% based on the starting m-aminophenol) which analyzed 92.5% pure by ultraviolet spectrum. A sample converted to the free amine as in the previous example was substantially pure p-aminosalicylic acid.[10]

Anal. Calcd. for $C_7H_7NO_3$: C, 9.15; neut. equiv., 153.1. Found: N, 9.12%; neut. equiv., 153.7, 154.8; decomposes when heated rapidly (in a bath preheated to 140°) sharply in the range 145–150° depending on the rate of heating.

Rate of production of dicarboxylated product (4-amino-6-hydroxyisophthalic acid). Reaction A was repeated double size in a small high pressure autoclave at 300 p.s.i. pressure of carbon dioxide. The reaction product was isolated as the hydrochloride as in the large scale runs. For analyses samples were converted to the free amine by the procedures described in the same experiment. The amount of 4-amino-6-hydroxy-isophthalic acid (dicarboxylated product) was estimated from the neutral equivalent. The results are summarized in the following table:

Reaction Time, Hr.	PAS Hydrochloride, G.	Yield, %	Neutral Equivalent of "Free Amine"	Estimated Content of Dicarboxylated Product
4	0.38	17	153.5	—
16	1.1	48	152.2	ca. 1%
64	1.3	58	145.0	ca. 10%

Unsuccessful application to phenol and to β-naphthol. Reaction mixtures similar to the above with boric acid were set up with phenol and the β-naphthol substituted for m-aminophenol. Where phenol was used two runs were made, each at 270 p.s.i. for 44 hr., one being held at 170° the other at 200°. The single run with β-naphthol was made at 125° overnight followed by heating at 195° for a total of 84 hr. The pressure was maintained near 800 p.s.i.

In all three cases the starting material was recovered nearly quantitatively, and no o-hydroxy acid could be isolated.

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