Effect of pH and Citrate Ions on Adsorption of Benzoic Acid by Sulfamethazine

R. N. NASIPURI and SALEH A. H. KHALIL ˣ

Abstract □ The adsorption of benzoic acid on sulfamethazine particles was found to be pH dependent. At pH values above 4.2 (the pKa of benzoic acid), a gradual suppression of the adsorption occurred; at pH 4.9 and above, no adsorption was noted. The effect of sodium citrate on adsorption is attributable to pH and ionic strength effects. Citric acid had an insignificant effect on the adsorption. The role of pH and citrate ions on the dissolution of sulfamethazine in this system is discussed.

Keyphrases □ Benzoic acid—adsorption on sulfamethazine, pH and citrate-ion effects □ Sulfamethazine—benzoic acid adsorption, pH and citrate-ion effects □ Sulfonamides—adsorption of benzoic acid on sulfamethazine, pH and citrate-ion effects

The spoilage of the BPC mixture of sulfamethazine (sulfadimidine) for infants was attributable to possible adsorption of the preservative, benzoic acid, by the suspended sulfamethazine particles (1). The adsorption isotherm for benzoic acid on sulfamethazine and the suppressive effect of three hydrophilic polymers on the adsorption were studied (2). Both the equilibrium solubility and dissolution rate of sulfamethazine were remarkably inhibited due to saturation of the sulfonamide surface by adsorbed benzoic acid (3). The present article reports the effect of pH and citrate ions on the adsorption–dissolution relationship in the sulfamethazine–benzoic acid system.

EXPERIMENTAL

The materials used and the methods adopted were as previously reported (3). Adjustment of pH was made by the addition of a predetermined volume of either 0.05 *N* NaOH or 0.05 *N* HCl to the benzoic acid solution, and the pH value of the final system was checked[1]. In studying the effect of citrate ions, either sodium citrate[2] or citric acid[2] (both AR grade) was dissolved in the benzoic acid solution before the latter was added to sulfamethazine powder. All experiments were carried out at 24 ± 0.2°.

RESULTS AND DISCUSSION

Figure 1 shows the effect of citric acid and sodium citrate on the adsorption of 0.1 g % benzoic acid by sulfamethazine. In the concentration range studied, citric acid had no apparent effect on benzoic acid adsorption in systems containing varying concentrations of sulfamethazine. The incorporation of sodium citrate resulted in a gradual suppression of the adsorption, the effect being dependent on sodium citrate concentration. Complete suppression of adsorption was noted in the presence of about 1.7 mmoles/liter. The difference between the effect of citric acid and sodium citrate was attributable to changes in the pH of the system. The effect of pH on adsorption was, therefore, investigated. The results (Fig. 2) show that benzoic acid adsorption by sulfamethazine is pH dependent. An increase in pH value produced a suppression of adsorption, and almost complete suppression occurred at and above pH 4.9. No change in adsorption was observed at pH values below 3.1.

[1] Pye pH meter, model 291.
[2] BDH Chemicals Ltd., Poole, England.

Table I—Percentages of Benzoic Acid Adsorbed at Various pH Values with and without Sodium Citrate[a]

	Sulfamethazine Concentration, g %					
	0.1		0.2		0.4	
pH	I[b]	II[c]	I[b]	II[c]	I[b]	II[c]
3.5	35.8	30.6	63.1	48.2	76.4	73.8
3.8	36.0	28.1	60.8	40.3	56.5	54.0
4.0	34.6	26.8	47.9	35.1	48.3	45.3
4.2	34.2	24.3	36.9	29.0	39.1	36.1

[a] Initial concentration of benzoic acid = 0.1 g %. [b] I = with sodium citrate. [c] II = without sodium citrate.

The data plotted in Fig. 1 are similar to those of Fig. 2 in that adsorption was unchanged in systems containing citric acid (pH <3.1) while adsorption was suppressed in the presence of sodium citrate due to an increase in pH. That the role of sodium citrate on the adsorption is not solely due to pH effect is shown in Table I, where the percentages of benzoic acid adsorbed are shown for systems with and without citrate ions. At an identical pH value, the presence of citrate ions produced an increase in adsorption, possibly due to ionic strength effects. Changes in pH values affect both the degree of ionization of benzoic acid and the net charge on the sulfamethazine surface. Within the pH range of adsorption studied (pH 2.1–3.1, Fig. 2), sulfamethazine with an acidic pKa of 7.4 and a basic pKa of 2.2 (determined electrometrically at 24°) will be positively charged; the extent of ionization of the amino group is 55.7 and 11.2% at pH 2.1 and 3.1, respectively. Benzoic acid (pKa = 4.2), on the other hand, exists predominantly in the unionized form in the pH range of adsorption.

It is suggested, therefore, that the adsorption process involves the unionized form of benzoic acid since no adsorption was noted at pH values above 4.9. Clarke and Armstrong (4) found that, in the adsorption of benzoic acid on kaolin, the negatively charged anion was adsorbed on the clay. As shown in Figs. 1 and 2, benzoic acid adsorption was not altered in the 2.1–3.1 pH range in spite of the change in the ionization of the amino group from 55.7 to 11.2%. Sulfadiazine, sulfathiazole, and sulfapyridine also did not adsorb benzoic acid to any significant extent.

From the foregoing, it is assumed that the adsorption of benzoic acid by sulfamethazine is of a physical type and probably in-

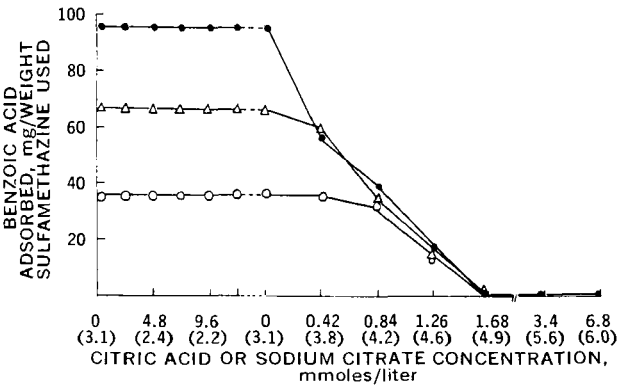

Figure 1—*Effect of citric acid and sodium citrate on the adsorption of 0.1 g % benzoic acid by sulfamethazine. The concentrations of sulfamethazine in the system (g %) were: ○, 0.1; △, 0.2; and ●, 0.3, 0.4, 4, and 10. Figures in parentheses are the pH values of the systems.*

Table II—Effect of Sodium Citrate on Benzoic Acid Adsorption and Sulfamethazine Solubility[a]

Sodium Citrate Concentration, mmoles/liter	Sulfamethazine Concentration, g %							
	Benzoic Acid Adsorbed, mg %				Sulfamethazine Solubility, mg %			
	0.1	0.2	4	10	0.1	0.2	4	10
0	36.4	67.6	95.6	95.8	4.4	4.8	39.8	40.4
0.42	36.0	60.8	54.5	60.7	7.2	30.8	40.3	40.3
0.84	34.2	36.9	39.3	38.8	21.9	36.2	40.6	39.4
1.68	1.3	1.4	1.1	3.1	39.6	39.8	39.6	40.1
3.36	1.1	0	0	0	40.3	40.4	40.5	40.6
5.04	0	0	0	0	40.1	39.7	39.9	39.4
6.72	0	0	0	0	39.8	40.3	39.7	39.8

[a] Initial concentration of benzoic acid = 0.1 g %.

Table III—Effect of Citric Acid on Benzoic Acid Adsorption and Sulfamethazine Solubility[a]

Citric Acid Concentration, mmoles/liter	Sulfamethazine Concentration, g %							
	Benzoic Acid Adsorbed, mg %				Sulfamethazine Solubility, mg %			
	0.1	0.2	4	10	0.1	0.2	4	10
0	36.8	68.1	95.8	96.1	4.6	4.9	40.3	39.6
0.6	36.4	67.7	95.6	94.8	4.1	5.2	46.1	45.8
1.2	36.2	67.2	96.1	95.8	4.3	6.4	50.3	52.1
2.4	35.9	66.9	95.5	96.2	6.6	6.8	56.9	55.9
4.8	36.2	68.1	95.8	94.8	7.0	7.0	65.1	66.4
7.9	36.1	67.9	93.9	95.1	7.3	6.9	73.1	74.0
9.6	36.1	66.8	94.7	95.8	7.8	7.6	80.7	81.3
12.0	35.8	67.4	95.1	96.3	8.1	8.0	84.1	85.5

[a] Initial concentration of benzoic acid = 0.1 g %.

volves the unionized form of the acid and the dimethylpyrimidine moiety of the sulfonamide.

In the concentration range of 0.1–0.3 g % sulfamethazine, benzoic acid adsorption was proportional to the amount of sulfamethazine in the system. At pH 3.1, benzoic acid (0.1 g % initial concentration) was adsorbed to the extent of about 34 mg/0.1 g sulfonamide (or 0.76 mmole/mmole). This constant value represents the "saturation" of the sulfonamide surface by the adsorbed benzoic acid. At and above 0.3 g % sulfamethazine, the amount of benzoic acid adsorbed was constant, approaching about 96 mg.

The effect of pH on the dissolution of sulfamethazine in the presence of 0.1 g % benzoic acid is plotted in Fig. 3. The dissolution plot of the sulfonamide in the absence of benzoic acid is shown for comparison. Depending on the sulfamethazine content in the system, the pH produced either an increase or a decrease in the equilibrium solubility of sulfamethazine. As previously reported (3), when the sulfonamide surface becomes saturated with the adsorbed benzoic acid, inhibition of sulfamethazine dissolution occurs. This is shown in Fig. 3 in systems containing 0.1 and 0.2 g % sulfamethazine. In the pH range where no change in adsorption occurred (pH 2.1–3.1), the equilibrium solubility ranged between 4.2 and 8.1 mg %. These values are to be compared with 39.8 and 84.6 mg % in systems having pH 3.1 and 2.1, respectively, but in these systems the adsorbed benzoic acid did not saturate the surface. At pH values higher than 4.2, the equilibrium solubility of all systems studied reached almost a constant value of about 40 mg %, since no adsorption occurred (Figs. 2 and 3).

The effect of sodium citrate and citric acid on sulfamethazine solubility in the presence of benzoic acid can be attributed to pH effect and adsorption of benzoic acid. Table II correlates, as a function of sodium citrate concentration, the amount of benzoic acid adsorbed and the equilibrium solubility of sulfamethazine. The suppression of benzoic acid adsorption restored the inhibited sulfamethazine solubility to the equilibrium value of about 40 mg %. In systems containing citric acid, the effect of pH on sulfa-

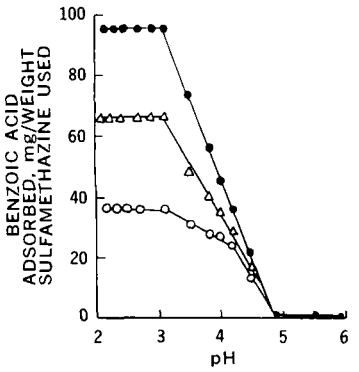

Figure 2—*Effect of pH on the adsorption of 0.1 g % benzoic acid by sulfamethazine. The concentrations of sulfamethazine in the system (g %) were: ○, 0.1; △, 0.2; and ●, 0.3, 0.4, 4, and 10.*

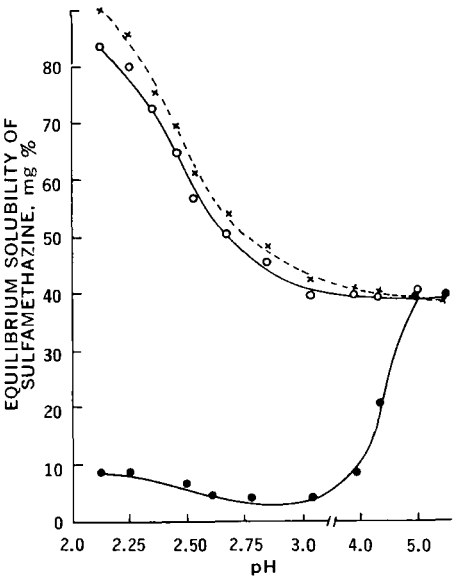

Figure 3—*Effect of pH on the equilibrium solubility of sulfamethazine in the presence of 0.1 g % benzoic acid. The concentrations of sulfamethazine in the system (g %) were: ●, 0.1 and 0.2; and ○, 4 and 10 (×, solubilities in the absence of benzoic acid).*

methazine solubility was dependent on the sulfonamide content in the system (Table III). At low sulfamethazine concentrations (0.1 and 0.2 g %), citric acid did not significantly increase the lowered sulfamethazine solubility because of the saturation of the surface by the adsorbed benzoic acid. At higher sulfamethazine concentrations (4 and 10 g %), citric acid increased the equilibrium solubility by virtue of its effect on lowering the pH.

In conclusion, the effect of electrolytes such as sodium citrate on adsorption should be interpreted not only on the basis of changing the dielectric constant of the system (5) but also on the possible effect of the electrolyte on the system pH. This may alter the ionization of electrolytic adsorbates and the charge characteristics of the adsorbent.

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[x] To whom inquiries should be directed. Present address: Department of Pharmacy and Pharmacology, Faculty of Medicine and Pharmacy, University of Benin, Benin City, Nigeria.

Isolation of Myricadiol, Myricitrin, Taraxerol, and Taraxerone from *Myrica cerifera* L. Root Bark

B. D. PAUL, G. SUBBA RAO*, and GOVIND J. KAPADIA[x]

Abstract □ Isolation and identification of three triterpenes, myricadiol, taraxerol, and taraxerone, and a flavonoid glycoside, myricitrin, from the root bark of *Myrica cerifera* L. are reported.

Keyphrases □ Myricadiol—isolation and identification from *Myrica cerifera* root bark □ Myricitrin—isolation and identification from *Myrica cerifera* root bark □ Taraxerol—isolation and identification from *Myrica cerifera* root bark □ Taraxerone—isolation and identification from *Myrica cerifera* root bark □ *Myrica cerifera* L.—isolation and identification of three triterpenes and one flavonoid glycoside

"Bayberry bark" (myrtle wax or southern bayberry), the dried root bark of *Myrica cerifera* L. (Myricaceae), is known to exhibit astringent, emetic, and antipyretic activities when administered orally (1, 2). In medical practice, it has been used externally as a stimulant for indolent ulcers (1). Recently, the aqueous extracts and the tannin fractions of *Acacia villosa, Krameria ixina,* and *K. triandra* were prepared, bioassayed, and found to be tumorigenic in rats (3, 4). In a continuation of these studies, the authors isolated tannins of *M. cerifera* L. root bark and leaves and are currently examining them for carcinogenicity. The present paper describes the identification of four crystalline nontannin compounds isolated during the fractionation of tannins from the root bark of *M. cerifera.*

EXPERIMENTAL

Isolation of Triterpenes—The powdered root bark[1] of *M. cerifera* (1 kg) was extracted with 3 liters of petroleum ether (bp 38–47°) in a continuous extractor for 24 hr. The defatted bark powder was then similarly extracted with benzene (3 liters) for 24 hr. The benzene extract was concentrated (~25 ml) and chromatographed on a column (2.5 cm i.d. × 30 cm) of neutral alumina[2] (40 g). The following sequence of solvents with increasing polarity was used for elution: petroleum ether (1 liter), petroleum ether–benzene (2:1 mixture, 1 liter; 1:1 mixture, 1 liter), benzene (1 liter), and benzene–chloroform (2:1 mixture, 1.5 liters).

Taraxerone (I)—The petroleum ether–benzene (2:1) eluant of the alumina column was evaporated to dryness, and the residue was crystallized from petroleum ether–benzene to yield 280 mg of taraxerone, mp 238–239° [lit. (5) mp 242–244°]; mass spectrum: m/e 424 (M^+), 409 ($M - CH_3$), and 300 ($M - C_9H_{16}$). The IR and mass spectra of the isolated compound were identical to those of reference taraxerone. The melting point of the reference compound remained unchanged when mixed with the plant isolate.

Taraxerol (II)—Removal of the solvents from the petroleum ether–benzene (1:1) eluant of the alumina column and crystallization of the resulting residue from methanol yielded 141 mg of taraxerol, mp 282–283° [lit. (5) mp 282–283°]; mass spectrum: m/e 426 (M^+), 411 ($M - CH_3$), and 302 ($M - C_9H_{16}$). It formed a monoacetate derivative (IV), mp 302° [lit. (5) mp 304–305°]; mass spectrum: m/e 468 (M^+), 453 ($M - CH_3$), 408 ($M - HOCOCH_3$), and 344 ($M - C_9H_{16}$). The IR and mass spectra of both the isolated alcohol and its acetate derivative were identical to those of reference taraxerol and its acetate, respectively. The melting points of both reference compounds were unaltered when admixed with the respective plant products from *M. cerifera.*

Myricadiol (III)—The benzene–chloroform (2:1) eluant of the alumina column deposited a semicrystalline precipitate when left overnight at room temperature. The precipitate was crystallized from hot alcohol (95%) to afford 450 mg of myricadiol, mp 267–268° [lit. (6) mp 273–274°]; mass spectrum: m/e 442 (M^+), 427 ($M - CH_3$), and 302 ($M - C_9H_{16}O$). Acetylation of the isolated compound with acetic anhydride–pyridine gave a diacetate (V), mp 254° [lit. (6) mp 256.5°]; mass spectrum: m/e 526 (M^+), 511 ($M - CH_3$), 466 ($M - HOCOCH_3$), and 344 ($M - C_{11}H_{18}O_2$). The IR

[1] *The plant material* used was collected in South Carolina and provided by Dr. J. F. Morton, Morton Collectanea, University of Miami, Coral Gables, Fla.

[2] Brockmann activity I, 80–200 mesh, Fisher Scientific Co.