

Penicillin G as Electrolyte and Colloidal Electrolyte¹

By J. W. MCBAIN, HARRIETTE HUFF² AND A. P. BRADY²

There is disagreement concerning the state of aggregation of penicillin salts in aqueous solution. On the basis of surface tension and ultramicroscopic observations, Hauser, Phillips and Phillips³ have reported sodium benzyl penicillinate (penicillin G) as a colloidal electrolyte. On the other hand, Kumler and Alpen⁴ concluded from conductivity and surface tension measurements that both potassium and sodium salts of penicillin G are only molecularly dispersed in water. Since neither of those lines of evidence is conclusive, it seemed worth while to make other types of measurement on the solutions to decide between these opposing views. This note presents measurements of the conductivity, surface tension, freezing points, and dye solubilization at various concentrations of aqueous solutions; showing that sodium penicillin G above 0.25 m. is indeed a colloidal electrolyte, but that in lesser concentration it is an ordinary electrolyte. The authors^{3,4} referred to were dealing with dilute solutions such as 0.017 mole/liter or 0.6%.

Experimental

Crystalline sodium penicillin G was kindly furnished by Bristol Laboratories, Inc., of Syracuse, New York, and according to their analysis was 96.9% G with the remainder being F, dihydro F, and K.

The conductivity was measured at 2000 cycles in an oil thermostat at $25 \pm 0.005^\circ$ with a Dike-Jones type bridge using an oscillograph to detect the balance point. The conductivity water was about 0.8×10^{-6} mho.

The crystalline penicillin and its solutions were stored in a refrigerator. With the exception of the solubilization measurements, all determinations were made with solutions less than six hours old and with less than half an hour at room temperature.

Results and Discussion

The results are given in Table I and plotted in Figs. 1 and 2. The freezing point results are expressed in terms of g , the practical osmotic coefficient, the ratio of the lowering to the ideal lowering for a uni-univalent salt. Figure 1 also includes the results of solubilization measurements both with water and with isotonic salt solution as solvents. Both freezing point and solubiliza-

(1) This work was carried out under a contract between the Office of Naval Research and Stanford Research Institute, under the supervision of Professor J. W. McBain.

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(3) E. A. Hauser, J. W. Phillips, and R. G. Phillips, 22nd National Colloid Symposium, Cambridge 1948; *Science*, **106**, 616 (1947); also E. A. Hauser, American Chem. Soc. Meeting, Portland, September, 1948.

(4) W. D. Kumler and E. L. Alpen, Pacific Division Amer. Assoc. Adv. Sci., Berkeley, June, 1948; *Science*, **107**, 567 (1948).

TABLE I

OSMOTIC COEFFICIENT AT 0° AND EQUIVALENT CONDUCTIVITY AND SURFACE TENSION OF SODIUM PENICILLIN G SOLUTIONS AT 25°

Molal	Concentration Equiv./liter	Osmotic coefficient, g .	Equivalent conductivity
0.602	0.526	0.625	36.5
.318	.294	.852	43.2
.173	.1652	.924	50.0
.0968	.0942	.950	53.5

tion show that sodium penicillin G aggregates in concentrated solution, but the critical concentration of 0.25 m. (8.26% G) is so high that it is of little interest biologically. Solubilization experiments in the presence of isotonic salt solution

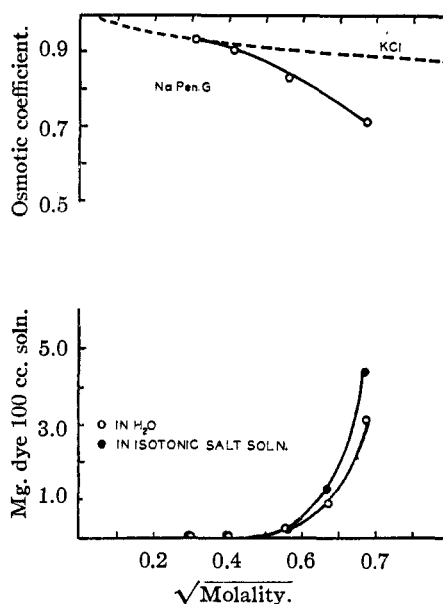


Fig. 1.—The osmotic coefficient g of sodium penicillin G as compared with that of potassium chloride; also its solubilizing power in water and in isotonic salt solution (0.9% NaCl).

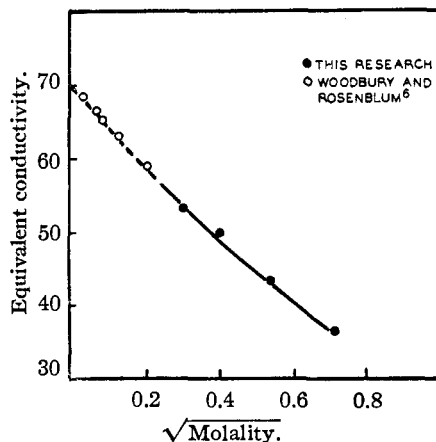


Fig. 2.—The equivalent conductivity of sodium penicillin G.

show little effect upon critical concentration. The equivalent conductivity curve shows no break or a very doubtful one at the critical concentration, as expected for this type of polycyclic compound. Bile salts and sodium abietate, both shown to be colloidal electrolytes by freezing point measurements, give no break in the conductivity curve.^{5,6} The conductivity curve determined here ties in satisfactorily with the data given by Woodbury and Rosenblum,⁷ converted from 30 to 25° by assuming that the salt has the same temperature coefficient as that of the sodium ion.

The surface tension of these solutions is fairly low, but relatively independent of concentration and may easily result from small amounts of impurities.

(5) J. W. McBain and S. A. Johnston, *Proc. Roy. Soc. (London)*, **191A**, 129 (1942).

(6) I. M. Kolthoff and W. F. Johnson, *J. Phys. Chem.*, **50**, 446 (1946).

(7) D. T. Woodbury and C. Rosenblum, *J. Biol. Chem.*, **171**, 447 (1947).

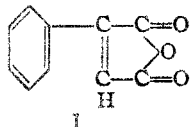
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A Preparation of Phenylmaleic Anhydride

BY LEONARD E. MILLER, HARLOW B. STALEY AND D. J. MANN

Although phenylmaleic anhydride (I) was first isolated in low yield as a by-product in the synthesis of phenylmalic acid by the reaction of phenylsuccinic acid with bromine and phosphorus tribromide,¹ no satisfactory procedure for the preparation of (I) has been reported.



I

When phenylsuccinic anhydride is permitted to react with N-bromosuccinimide in the presence of a catalytic amount of benzoyl peroxide, phenylmaleic anhydride can be isolated in 57-64% yield.

The use of N-bromosuccinimide as a dehydrogenating agent for several hydroaromatic compounds has been reported recently by Barnes.²

Experimental³

Phenylsuccinic anhydride,⁴ m. p. 53-54°, was prepared in 78-84% yield from phenylsuccinic acid.⁵

Into a 500-ml., two-necked flask, equipped with a mechanical Hershberg stirrer (made of nichrome wire) and a condenser fitted with a drying tube, were placed 17.8 g. (0.1 mole) of N-bromosuccinimide, 8.8 g. (0.05 mole) of phenylsuccinic anhydride, 200 ml. of carbon tetrachloride

and 0.1 g. of benzoyl peroxide. The reaction mixture was heated under reflux with stirring for twenty-four hours, during which time the solution became bromine-red in color and a precipitate of succinimide formed. After the mixture was cooled to room temperature, the insoluble succinimide was separated on a filter and washed with several portions of hot benzene until the washes no longer gave a positive Baeyer test with potassium permanganate (about 150 ml. of benzene were required). When cool, the combined benzene and carbon tetrachloride solutions deposited an additional small quantity of succinimide which was separated. The clear solution was concentrated by distillation to a volume of 30 ml. and was then placed in a refrigerator for two hours. The crystals of phenylmaleic anhydride which formed were separated and recrystallized from dry acetone-petroleum ether (high boiling); yield 2.1-2.3 g., m. p. 119-120° (reported, 119-119.5°⁶).

After the evaporation of the carbon tetrachloride filtrate to dryness under reduced pressure (water pump) in a two-bulb distillation apparatus, the residue was distilled under reduced pressure (1.0 mm.). At 60-70° a few drops of a yellow liquid were collected; this forerun was discarded. At 130-145° a yellow solid was collected. This material was recrystallized twice from dry acetone-petroleum ether (high boiling) (Norite) to give 2.1-2.3 g. of phenylmaleic anhydride, m. p. 119-120°. From the combined recrystallization filtrates, 0.8-1.0 g. of equally pure product was isolated. The total yield was 5.0-5.6 g. (57-64%).

The percentage yield was slightly lower (53-57%) when four times these amounts were used.

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Displacement-chlorination of Dimethylamino-propanol-2

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The reaction of methanesulfonyl chloride with dimethylaminopropanol-2 in an inert solvent was found to give rise to the *o*-mesylate hydrochloride (II) admixed to a greater or lesser extent with the hydrochloride of the propanolamine (I). The *o*-mesylate hydrochloride (II) could be obtained directly and in pure condition by conducting the reaction in a solvent mixture consisting of equal parts of chloroform and acetone.

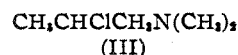
The *o*-mesylate hydrochloride was titrated with one equivalent of alkali and was converted thereby to the free ester base, characterized as its picrate. When heated above its melting point for a short time the *o*-mesylate hydrochloride was converted smoothly by internal displacement into dimethylamino-2-chloropropane (III). The latter was isolated and identified as its picrate.



(I)



(II)



(III)

Experimental

Dimethylaminopropanol-2 *o*-Mesylate Hydrochloride.—To a stirred solution of 10.5 g. of dimethylaminopropanol-2 in 25 cc. of chloroform at 0° was added portion-wise a solution of 12.5 g. of methanesulfonyl chloride in 25 cc. of chloroform. The homogeneous solution was treated with

(1) Alexander, *Ann.*, **258**, 67 (1890).

(2) Barnes, *This Journal*, **70**, 145 (1948).

(3) All m. p.'s and b. p.'s are uncorrected.

(4) Verkade and Hartman, *Rec. trav. chim.*, **52**, 945 (1933).

(5) "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley & Sons, Inc., New York, N. Y., 1941, p. 451.