of saturated solution. These were evaporated to dryness by sweeping dried air over them at room temperature. Two weighed 0.1-g. samples of acetanilide in corresponding amounts of water were also so treated. When constant weight of ±0.2 mg. was secured over a period of forty-eight hours, the two samples of known weight each retained about 0.6 mg. of water. This correction was applied proportionately to the weights of the residues from the two solution samples. The solubility values thus obtained were 0.6400 and 0.6371% acetanilide, a satisfactory check for the value at 25° shown in Table II.

TABLE II

SOLUBILITY OF ACETANILIDE

Temp.,[a] °C.	Sol., wt. %
0.00	0.3598
10.13	.4414
20.00	.5612
25.00	.6390
30.00	.7285
40.00	.9737
50.00	1.326
60.00	1.857
70.00	2.676

[a] Regulation ±0.05°, except at 70° where it was ±0.10°.

The results are given in Table II and are plotted in Fig. 1. For comparison, the data of Schoorl and de Weerd[4] are also plotted. The maximum average deviation of the mean obtained in the measurements was 0.3%. For all cases this was equal to or smaller than the possible variation due to temperature fluctuation. It is thought that the measurements are accurate to ±0.3%.

These determinations have been made as the preliminary to a study of the effect of electrolytes on the solubility of acetanilide. This work is now in progress.

Summary

The solubility of acetanilide in water has been determined from 0 to 70°.

DAVIDSON, NORTH CAROLINA RECEIVED APRIL 18, 1945

[CONTRIBUTION FROM THE CONTROL LABORATORY OF GELATIN PRODUCTS CORP., AND THE DEPARTMENT OF CHEMISTRY, WAYNE UNIVERSITY, DETROIT, MICHIGAN]

A Study of the Binary System Nicotinamide–Ascorbic Acid[1,1a]

BY CECIL W. BAILEY,[2] J. RUSSELL BRIGHT[2] AND JOSEPH J. JASPER[3]

Certain difficulties were encountered in the production of vitamin capsules in which the contents were mixtures containing varying amounts of nicotinamide and vitamin C (ascorbic acid). It has been shown that vitamin C forms salts with numerous metallic ions and with organic bases, *e. g.*, with the cinchona alkaloids,[4] quinine, quinidine, hydroquinine and hydroquinidine. The purpose of the present study was to ascertain by means of a temperature–composition diagram whether or not a reaction takes place in the system nicotinamide–ascorbic acid. Similar measurements were made using nicotinic acid in place of nicotinamide, in order to elucidate on the type of linkage involved.

Experimental

Preparation of Mixtures.—Pure nicotinamide (m. p. 129–131°) and pure ascorbic acid (m. p. 188–190°) were dissolved in absolute methyl alcohol in separate beakers and then mixed. The alcohol was removed by evaporation to dryness on a steam-bath. All resulting mixtures were dried *in vacuo* over phosphoric oxide for 168 hours and stored in a desiccator over the same desiccant.

The yellow molecular addition compound of nicotinamide and vitamin C was also prepared in the dry state by mixing equimolecular quantities of the two components in a ball mill. The product was identical with that prepared in solution. This addition compound is insoluble in acetone, ether, and petroleum ether; very slightly soluble in benzene, carbon tetrachloride, and chloroform; slightly soluble in ethylene dichloride; and soluble in alcohol, aniline, diethylene glycol, propylene glycol, and water. The solubility relations of the compound are noticeably different in comparison to the corresponding behavior of the separate components. For example, nicotinamide is moderately soluble in acetone but insoluble in diethylene glycol. Ascorbic acid is quite insoluble in aniline, diethylene glycol, and propylene glycol. Similarly, mixtures of nicotinic acid and ascorbic acid were prepared from alcoholic solutions.

Melting points on the various mixtures were determined in small open capillary tubes using a Thiele tube containing sulfuric acid which was kept stirred. Two Anschütz thermometers were used, one with a range of 90–150° and the other with a range of 145–200°.

Molecular Weight Determinations.—The usual Beckmann apparatus was used to make freezing point measurements. Cryoscopic determination of the molecular weight of the nicotinamide–ascorbic acid compound using distilled water as the solvent gave 180.0, 165.6 and 147.3; theoretical 298.12. Cryoscopic determination using aniline as the solvent gave discordant results, namely, 46.77, 62.01, 63.76, 49.54, 43.29 and 40.90. Ebullioscopic determination of the molecular weight by the method of Menzies and Wright[5] using absolute ethyl alcohol as the solvent gave 176.2, 171.4 and 166.8.

Results

Experimental data for the nicotinamide–ascorbic acid system are presented in Table I and Fig. 1. These data show the formation of a 1,1-

(1) Original manuscript received November 10, 1943.

(1a) Presented before the Symposium on Molecular Addition Compounds of the Division of Physical and Inorganic Chemistry at the Pittsburgh meeting of the American Chemical Society, September, 1943.

(2) Gelatin Products Corporation, Detroit, Michigan.

(3) Wayne University, Detroit, Michigan.

(4) Swiss Patents 208,852 and 214,108; British Patent 533,480.

(5) A. W. C. Menzies and S. L. Wright, THIS JOURNAL, 43, 2314 (1921).

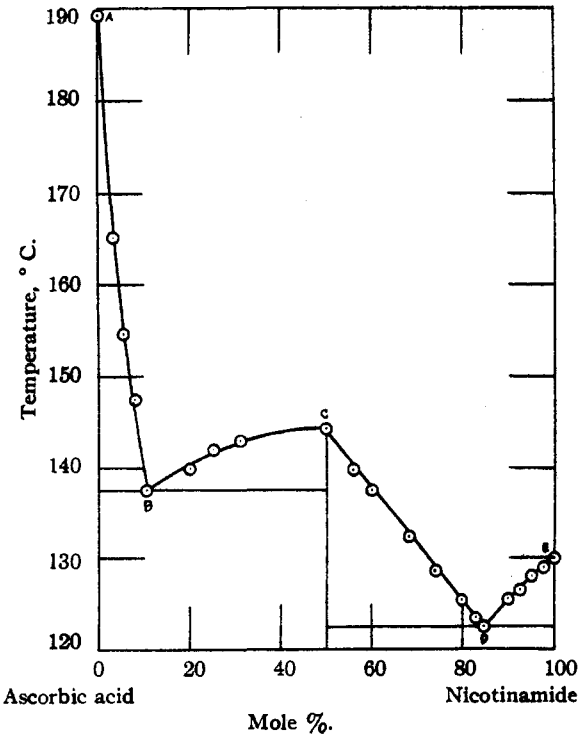

Fig. 1.—Temperature–composition diagram of the system nicotinamide–ascorbic acid.

addition compound, $C_5H_4NCONH_2{=}C_6H_8O_6$, with a melting point of 143.5 to 145.5° (uncor.) with decomposition. Eutectics occur at 87.0 mole % and 13.0 mole % ascorbic acid.

TABLE I

Mole %, ascorbic acid	M. p. range,[a] °C., uncor.	
100.00	188.0–190.0 dec.	AB—solid ascorbic acid, saturated solution, vapor
97.50	165.0–167.5 dec.	
95.00	154.0–156.0 dec.	
92.50	147.0–149.0 dec.	
88.88	136.0–139.0 dec.	
		B—eutectic: solid ascorbic acid, solid addition compound, saturated solution, vapor
80.00	139.0–141.0 dec.	BCD—solid addition compound, saturated solution, vapor
75.00	141.0–143.0 dec.	
66.66	142.0–145.0 dec.	
50.00	143.5–145.5 dec.	
45.00	138.0–142.0 dec.	
40.00	136.0–139.0 dec.	
33.33	131.0–134.0	
25.00	125.0–132.0	
20.00	124.0–127.0	
16.66	122.0–124.0	
		D—eutectic: solid nicotinamide, solid addition compound, saturated solution, vapor
12.50	121.0–123.0	DE—solid nicotinamide, saturated solution, vapor
10.00	124.0–125.5	
7.50	125.0–126.0	
5.00	126.0–128.0	
2.50	127.0–129.0	
Nicotinamide	129.0–131.0	

[a] The center of the range was used to plot Fig. 1.

The basicity of the ring nitrogen (electron-pair donating power) is shown by the data of Table II

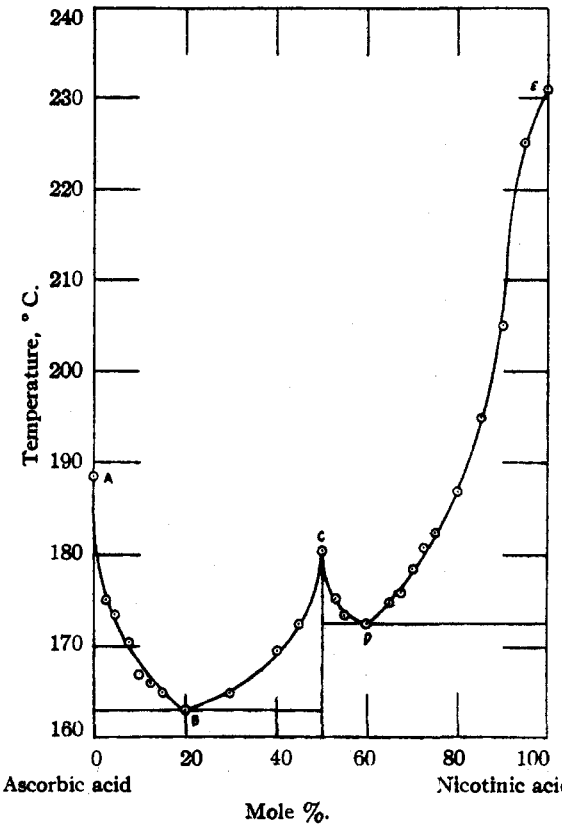

Fig. 2.—Temperature–composition diagram of the system nicotinic acid–ascorbic acid.

and Fig. 2, which indicate the formation of a 1,1 compound, nicotinic acid–ascorbic acid, $C_5H_4NCOOH{=}C_6H_8O_6$, with a melting point of approximately 181°.

TABLE II

Mole %, ascorbic acid	M. p. range,[a] °C., uncor.	
100.0	187.0–190.0	AB—solid ascorbic acid, saturated solution, vapor
97.5	172.0–178.0	
95.0	172.0–175.0	
92.5	169.0–172.0	
90.0	164.0–170.0	
87.5	163.0–169.0	
85.0	163.0–167.0	
80.0	160.0–166.0	B—eutectic: solid ascorbic acid, solid addition compound, saturated solution, vapor

TABLE II (*Concluded*)

Mole % ascorbic acid	M. p. range,[a] °C., uncor.	
70.0	163.0–167.0	BCD—solid addition compound saturated solution, vapor
60.0	166.0–173.0	
55.0	169.0–176.0	
50.0	179.0–182.0	
47.5	172.0–178.0	
45.0	172.0–175.0	
40.0	169.0–176.0	D—eutectic: solid nicotinic acid, solid addition compound, saturated solution, vapor
35.0	172.0–178.0	DE—solid nicotinic acid, saturated solution, vapor
32.5	174.0–178.0	
30.0	176.0–181.0	
27.5	179.0–183.0	
25.0	181.0–184.0	
20.0	184.0–190.0	
15.0	193.0–197.0	
10.0	202.0–208.0	
5.0	224.0–227.0	
Nicotinic acid	230.0–232.0	

[a] The center of the range was used to plot Fig. 2.

Acknowledgment.—The authors wish to acknowledge the fact that Mrs. Laurene Paterson Opferman, formerly of the Research Laboratory of Gelatin Products Corporation, first discovered that a reaction occurred between nicotinamide and ascorbic acid, and first made the reaction product.

Summary

1. Temperature–concentration data are presented for the system nicotinamide–ascorbic acid, and tentatively for the system nicotinic acid–ascorbic acid.

2. It has been shown that nicotinamide reacts with vitamin C to give a yellow[6] reaction product $C_6H_4NCONH_2{=}C_6H_8O_6$, m. p. 143.5 to 145.5° (uncor.).

3. Evidence is presented to show that the linkage is between the ring nitrogen and the "acceptor" molecule.

4. Molecular weight determinations indicate dissociation in solution.

(6) Subsequent to the original presentation of this paper, it has been shown by T. H. Milhorat in *Proc. Soc. Exp. Biol. Med.*, **55**, 52 (1944), that ascorbic acid reacts with nicotinamide and nicotinic acid with the production of a yellow color.

DETROIT, MICHIGAN RECEIVED APRIL 25, 1945

[CONTRIBUTION FROM THE AMERICAN CYANAMID COMPANY]

The Effects of Variations of *p*H on the Ultraviolet Absorption Spectra of Some Sulfonamides

BY E. J. ROBINSON AND L. F. PEKRUL

That the ultraviolet absorption maxima of some sulfonamides differ both in position and intensity, depending upon whether the compounds are in alkaline or acid solution, has been shown in several recent publications.[1] No one, to our knowledge, has carried out a thorough investigation of these changes in relation to *p*H, although data from such studies are essential before one can apply the ultraviolet method to the qualitative and quantitative analyses of these drugs.

Stenstrom and collaborators[2] noted that both the positions and the intensities of the ultraviolet absorption maxima of phenol and tyrosine in aqueous media changed with *p*H. The same observation was made by Flexser, Hammett and Dingwall[3] on a series of weak acids and bases. Both groups of investigators interpreted these variations as resulting from changes in the ion: molecule ratio, and used the data in calculating the dissociation constants of the compounds studied.

(1) Böhme and Wagner, *Arch. Pharm.*, **280**, 255 (1942); Kumler and Strait, THIS JOURNAL, **65**, 2349 (1943); Bell, Bone and Roblin, *ibid.*, **66**, 847 (1944); Vandenbelt and Doub, *ibid.*, **66**, 1633 (1944).

(2) Stenstrom and Reinhardt, *J. Phys. Chem.*, **29**, 1477 (1925); Stenstrom and Goldsmith, *ibid.*, **30**, 1683 (1926).

(3) Flexser, Hammett and Dingwall, THIS JOURNAL, **57**, 2103 1935).

The experiments reported in this communication are the outgrowth of an attempt made several years ago to apply ultraviolet absorption spectroscopy to the analysis of mixtures of sulfonamides in biological fluids.

Experimental

Stock aqueous solutions of the drugs were made up from material recrystallized twice from 50% ethyl alcohol. Samples for spectrophotometry were prepared by suitably diluting aliquots of the stock solutions with buffers of the desired *p*H. In each case an equal volume of water similarly diluted with buffer served as a blank. The *p*H determinations were made on the final buffered drug solutions using a Beckman Glass Electrode *p*H Meter. In the more alkaline solutions the special high *p*H glass electrode was used and the proper ion correction applied to the reading.

All absorption measurements were made at room temperature using a Beckman Photoelectric Spectrophotometer, Model DU. From plots of % transmission *versus* wave length, the positions of the absorption maxima were located to the nearest 10 Å. The values of the molecular extinction coefficients at the desired wave lengths were calculated in the usual way.

With these compounds we have found that, at a given *p*H, the position and intensity of any maximum is constant regardless of the buffer combination used as solvent. The same is true if the desired *p*H is attained simply by the addition of acid or alkali to the unbuffered drug solution.