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Electronic Properties of N-Heteroaromatics. XVI.[1] Charge Transfer Properties of Pyrazolone Antipyretics. On the Complex Formation of Aminopyrine with Benzoic Acid and Salicylic Acid

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The anomalous phenomena with respect to solubility and coloration, which are observed when aminopyrine is combined with either benzoic acid or salicylic acid, have been studied by solubility method, refractometry, and spectrophotometry, and the following findings have been obtained from the experimental data: (1) a formation of charge-transfer complexes of 1:1 molar ratio between aminopyrine and either benzoic acid or salicylic acid were presumed, (2) from the comparative study of pyrazolone derivatives, it was concluded that 4-amino or 4-substituted amino moiety on the pyrazolone portions was found to be indispensable for the complex formation, and (3) as there were considerable differences between stability constants obtained by solubility method and those obtained from Benesi-Hildebrand plots, it was presumed that charge-transfer force might not be a sole driving force of the interaction.

It was known that unexpected phenomena occur when aminopyrine (4-dimethylamino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) is combined with either benzoic acid or salicylic acid.[3] Trituration gives liquefaction and the mixed substance has much higher solubility than that expected from each component. Furthermore, the mixed substance as well as the mixed solutions is colored in yellow. Regenbogen[4] made a study on the complex formation of aminopyrine with either benzoic acid or salicylic acid, making use of binary phase diagrams. According to the results, aminopyrine forms complexes of 1:1 and 2:3 molar ratios.

Although the depression of melting point caused by trituration may well be explained by Regenbogen's results, any study has not been undertaken on the anomalous solubility, as well as the coloring properties of the mixed solutions of both aminopyrine and benzoic acid derivatives. The aims of the present study is to investigate these phenomena through examinations of complexes formed between aminopyrine and either benzoic acid or salicylic acid in aqueous media.

Results and Discussion

Solubility of Benzoic Acid and Salicylic Acid in the Presence of Aminopyrine

In Fig. 1 is shown the effect of aminopyrine on the solubilities of benzoic acid or salicylic acid, indicating that both acids are solubilized by the addition of aminopyrine. The higher the temperature, the larger the solubilizing effect of aminopyrine. Even in the presence of an excess of benzoic acid derivatives, aminopyrine may not dissolve any more beyond the limit indicated by the arrow-2 signs in Fig. 1, suggesting that it might be the indication of saturation of complexes. In these ranges the color of the solutions is yellow and the indissolved phases which contain both aminopyrine and the acids turn into yellowish substances, being separated from aqueous phase.

1) Part XV: *Yakugaku Zasshi*, **87**, 1315 (1967).
2) Location: *Kita-4-bancho, Sendai.*
3) Z. Sugi and T. Nishioji, "Iyakuhin Haigo Kinki," Nankodo, Ltd., Tokyo, 1960, p. 97.
4) A. Regenbogen, *Chem. Zentr.*, **1918**, II, 625.

In explaining the solubility data (Table I and II), however, it should be taken into account that the change of apparent solubility of acids, Sa, might have been affected not only by solubilizing effect of aminopyrine, but also by the change of pH of solutions by the

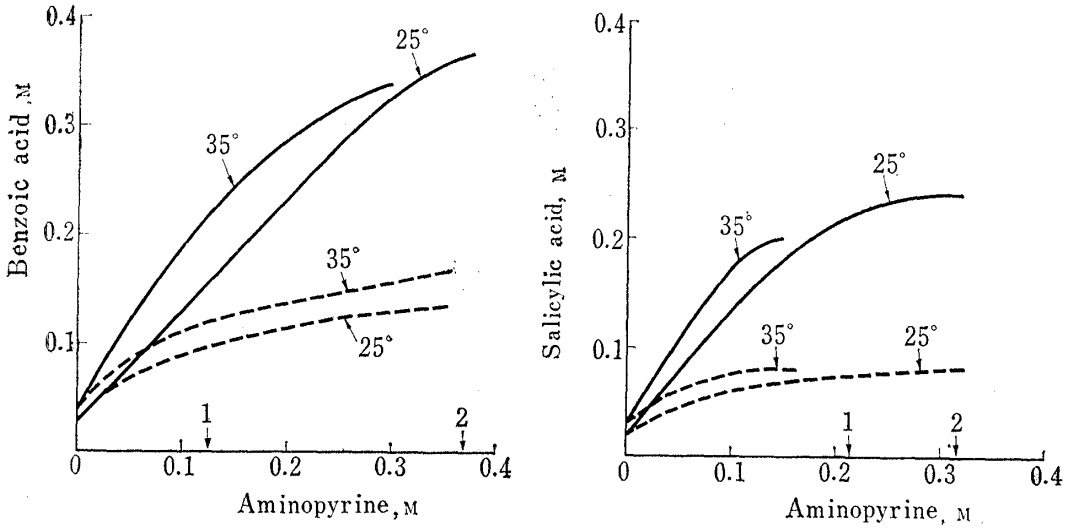

Fig. 1. Solubilization of Benzoic Acid and Salicylic Acid by Aminopyrine
Solid line: Solubility curve of acid in the presence of aminopyrine
Dotted line: Calculated solubility values of acid at found pH
1: Solubility of aminopyrine in water at 25°
2: Found solubility of aminopyrine in the mixed systems at 25°

TABLE I. Interaction between Aminopyrine and Benzoic Acid in Water

Aminopyrine added ($\times 10^{-2}$M)	(A_t) ($\times 10^{-2}$M)	(S_a) ($\times 10^{-2}$M)	pH found	(S_H) ($\times 10^{-2}$M)	$(S_a)-(S_H)$ ($\times 10^{-2}$M)	$(A_t)-(C)$ ($\times 10^{-2}$M)	K_S
			at 25°				
0.00		2.90	2.82				
4.00	3.99	7.18	4.16	5.90	1.28	2.71	8.01
6.00	5.97	8.68	4.30	6.88	1.80	4.17	6.22
12.0	12.0	13.7	4.42	8.52	5.24	6.88	9.09
16.0	15.2	18.8	4.60	11.5	7.25	8.75	7.18
22.0	21.9	23.0	4.62	12.0	11.1	10.9	8.43
24.0	24.0	24.7	4.65	12.3	12.4	11.6	8.67
28.0	27.9	28.3	4.71	14.0	14.3	13.7	7.36
32.0	32.0	30.0	4.72	14.3	15.7	16.3	6.73
34.0	34.1	32.1	4.73	14.4	17.7	16.4	7.53
36.0	35.8	34.1	4.73	14.5	19.7	16.5	8.40
38.0	37.1	35.8	4.73	14.5	20.5	16.6	8.54
42.0	38.4	35.7	4.73	14.6	20.8	17.5	8.15
46.0	38.4	36.4	4.74	14.9	21.5	16.9	8.41
			at 35°				
0.00		4.01	2.96				
5.00	5.00	12.9	4.26	9.51	3.45	1.55	23.5
10.0	10.2	19.5	4.43	12.3	7.22	2.98	19.7
15.0	14.3	24.2	4.52	14.3	9.96	4.34	15.9
17.5	17.0	25.8	4.54	14.8	11.1	5.90	12.8
20.0	19.1	29.3	4.55	15.0	14.3	4.76	20.3
22.5	21.8	30.4	4.56	15.3	15.2	6.60	15.2
25.0	23.1	32.4	4.57	15.5	16.9	6.20	17.6
27.5	25.2	32.4	4.57	15.5	16.9	8.30	13.2
30.0	25.2	32.4	4.57	15.5	16.9	8.30	13.2

Table II. Interaction between Aminopyrine and Salicylic Acid in Water

Aminopyrine added ($\times 10^{-2}$M)	(A_t) ($\times 10^{-2}$M)	(S_a) ($\times 10^{-2}$M)	pH found	(S_H) ($\times 10^{-2}$M)	(S_a)−(S_H) ($\times 10^{-2}$M)	(A_t)−(C) ($\times 10^{-2}$M)	K_s
			at 25°				
0.00		1.68	2.50				
4.00	3.98	5.39	3.31	3.95	1.44	2.54	28.7
6.00	5.89	7.53	3.41	4.63	2.90	2.99	20.1
8.00	8.03	10.3	3.55	5.91	4.39	3.64	20.6
10.0	10.1	11.4	3.57	6.04	5.36	4.74	19.1
14.0	14.2	15.8	3.64	6.95	8.83	5.37	23.1
16.0	15.9	17.9	3.65	6.96	10.9	5.00	30.1
18.0	17.8	19.7	3.67	7.52	12.2	5.60	28.1
20.0	19.7	21.9	3.68	7.80	14.2	5.50	31.0
22.5	22.6	23.8	3.70	8.11	15.7	6.90	31.0
25.0	23.6	25.2	3.72	8.22	16.9	6.70	31.1
27.5	24.1	25.3	3.73	8.22	17.1	7.00	31.0
30.0	24.2	25.4	3.73	8.22	17.2	7.00	31.1
40.0	24.2	25.4	3.73	8.22	17.2	7.00	29.7
			at 35°				
0.00		2.39	2.43				
5.00	4.94	8.03	3.21	4.99	3.04	1.90	32.1
7.50	17.5	10.1	3.31	5.80	4.24	3.26	22.2
10.0	10.2	13.8	3.36	6.28	7.54	2.66	45.9
12.5	12.6	15.8	3.38	6.59	9.23	3.37	41.6
15.0	14.6	18.9	3.43	7.05	11.9	2.70	62.9
17.5	15.9	19.1	3.44	7.16	12.0	3.90	43.3
20.0	16.3	19.7	3.45	7.29	12.4	3.90	43.6
22.5	16.3	19.7	3.45	7.29	12.4	3.90	43.6
30.0	16.3	19.7	3.45	7.29	12.4	3.90	43.6

addition of the base. Solubility of weak acid at a given hydrogen ion concentration, (S_H), could be controlled simply by hydrogen ion concentration, (H^+), and dissociation constants of the acid, K.

$$(S_H)=(S_0)\left\{1+\frac{K}{(H^+)}\right\} \qquad (1)$$

(S_H) in equation (1) stands for the solubility of unionized species of the acid, which can be calculated from the solubility of the acids and hydrogen ion concentration of the solution. The values of (S_H) were found to be 2.76×10^{-2}M (25°) and 3.72×10^{-2}M (35°) for benzoic acid, and 1.76×10^{-2}M (25°) and 1.78×10^{-2}M (35°) for salicylic acid. The values of K were obtained spectrophotometrically to be 7.95×10^{-5} (25°) and 8.51×10^{-5} (35°) for benzoic acid, 1.00×10^{-3} (25°) and 1.05×10^{-3} (35°) for salicylic acid. Calculated solubilities at the respective pH are shown in Fig. 1 by dotted lines, which could be regarded as the concentrations of free acids. The differences between the solubility values found and calculated may be attributable to net increase of solubility due to the presence of aminopyrine. Since, as shown latter from the results of refractometric and spectrophotometric examinations, the soluble complexes are consisted of equimolar aminopyrine and the acids, concentration of complex, (C), could be estimated to be equal to (S_a)−(S_H), and consequently the stability constants of the complex, Ks, could be calculated by equation (2),

$$K_S=\frac{(\text{complex})}{(\text{free aminopyrine})\,(\text{free acid})}=\frac{(S_a)-(S_H)}{(At)-(C)\times(S_H)} \qquad (2)$$

where (A_t) stands for the concentration of aminopyrine found in solution. K_s values thus obtained are shown in Tables I and II. The average K_s values and thermodynamic data, namely changes of free energy, ΔF, enthalpy, ΔH, and entropy, ΔS, are summarized in Table

Table III. Thermodynamic Data for the Interaction of Aminopyrine with Acids, obtained from Solubility Data

Interactants	Temp.	K_S (average)	ΔF cal/mole	ΔH cal/mole	ΔS (e.u.)
Aminopyrine–Benzoic acid	25	7.79	−1,220	13,400	49.2
	35	16.8	−1,750		49.2
Aminopyrine–Salicylic acid	25	27.5	1,950	7,710	32.4
	35	42.2	2,280		32.0

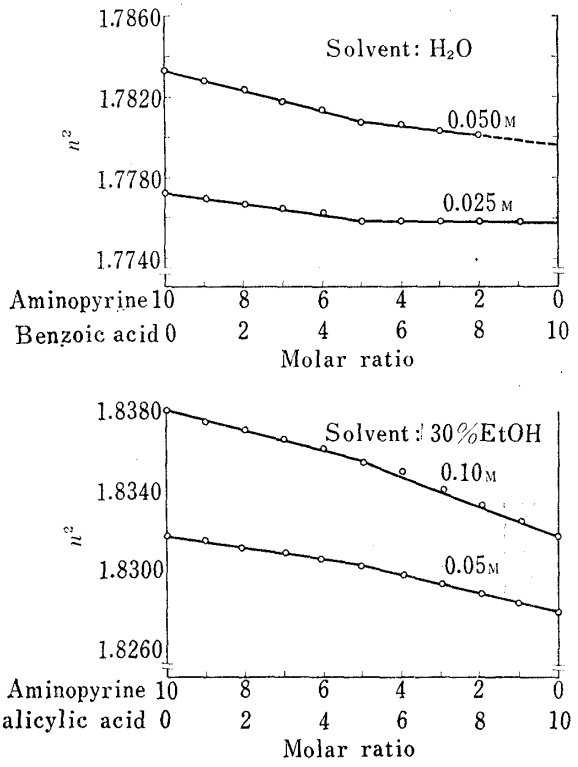

Fig. 2. Refraction of Serial Mixtures of Aminopyrine and Acids at 25°

III. These data indicate that the reaction of the complex formation is considered to be endothermic. It is noteworthy that ΔH and ΔS values are considerably large.

Refraction of Aqueous Mixtures of Aminopyrine with Benzoic Acid and Salicylic Acid

In Fig. 2 is shown a relationship between molar ratio and square of refractive indexes in aqueous mixtures of aminopyrine and the acids, indicating that aminopyrine forms 1:1 complexes with both benzoic acid and salicylic acid, respectively. Owing to the low solubility of benzoic acid, the 0.05M curve of the serial mixtures of aminopyrine and benzoic acid could not be completed at a higher concentration range of the acid. 30 per cent ethanol was used as a solvent for the mixtures of aminopyrine and salicylic acid.

Spectrophotometoric Properties of Complexes formed between Aminopyrine and the Acids in Aqueous Solution

In Fig. 3 is shown spectra of the mixed aqueous solutions of aminopyrine with either benzoic acid or salicylic acid. The differences of the spectra between mixed solutions and aminopyrine are shown in dotted lines.Spectra of the mixtures are quite characteristic. At 25°, new absorption maxima appeared at 377 mμ and 360 mμ in the spectra of aminopyrine-benzoic acid system and aminopyrine–salicylic acid system, respectively. At 35° these maxima shifted about 4 mμ toward blue and the color became more intensive. Color intensity was affected considerbly by pH of the solutions and the absorption maximum shifted toward blue with an increasing polarity of solvent. These facts could be taken as an indication that the colored products or complexes are susceptible to influences of environmental conditions. The appearance of the new broad bands in the near ultraviolet region seems to suggest charge–transfer type interactions between aminopyrine and benzoic acid derivatives, wherein the former acts as an electron–donor and the latter as an electron–acceptor.

By applying the above mentioned data to equation (3) of Benesi–Hildebrand

$$\frac{(B)\cdot l}{\Delta D}=\frac{1}{K_B\cdot\varepsilon\cdot(A)}+\frac{1}{\varepsilon} \qquad (3)$$

5) H.A. Benesi and J.H. Hildebrand, *J. Am. Chem. Soc.*, **71**, 2073 (1949).

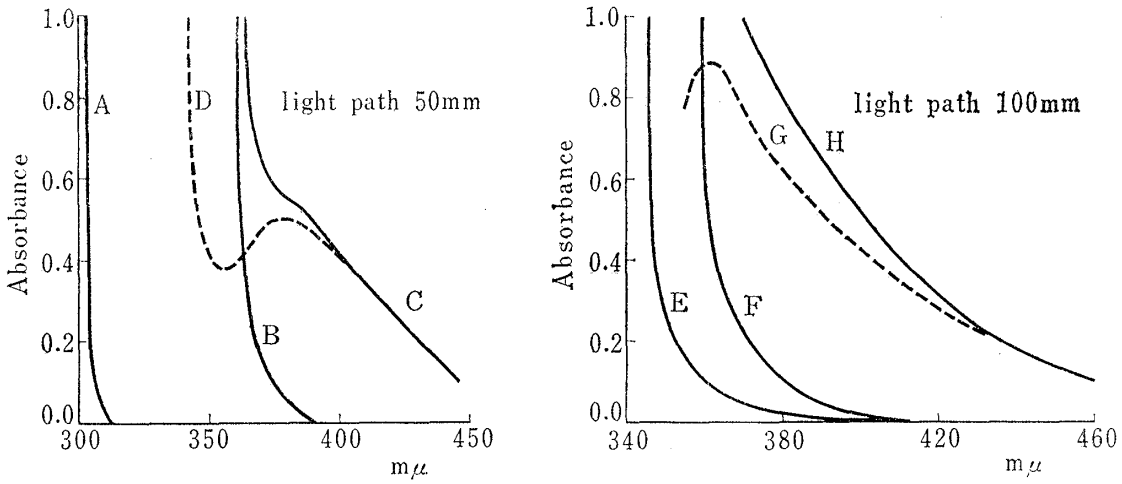

Fig. 3. Absorption Spectra of Mixtures of Aminopyrine and Acids
A: Benzoic acid (0.02M) B: Aminopyrine (0.25M) C: Benzoic acid (0.02M)+Aminopyrine (0.25M)
D: C when B was used as reference E: Salicylic acid (0.02M) F: Aminopyrine (0.25M)
G: Salicylic acid (0.02M)+Aminopyrine (0.25M) H: G when F was used as reference

where (A), (B), l, ΔD, K_B and ε stand for concentration of aminopyrine, concentration of acids, cell length, increment of absorbancy, stability constants and molar extinction coefficient of complexes, respectively, linear relationship were obtained between reciprocal increment of absorbancy and reciprocal concentration of aminopyrine as shown in Fig. 4.

This could be taken as indications of complexes of 1:1 molar ratio. Stability constants of the complexes, computed from the slopes and intercepts of the Benesi-Hildebrand plots, and thermodynamic data of the complex formation reactions obtained spectrophotometrically, are summarized in Table IV.

While the ΔH and ΔS values in Table IV are resembling closely to those obtained from solubility data (Table III), K_B values are considerably smaller than K_S values. As mentioned in several papers,[6-8] it may be said that while K_S comes from the sum of all driving

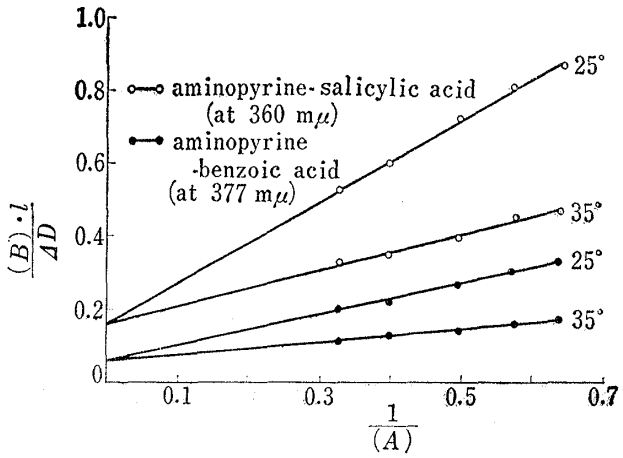

Fig. 4. Benesi-Hildebrand Plots for the Mixtures of Aminopyrine and Acids

Table IV. Thermodynamic Data for the Interaction of Aminopyrine with Acids, obtained from Benesi-Hildebrand Plots

Interactants	Temp.	K_B	ε	ΔF cal/mole	ΔH cal/mole	ΔS (e.u.)
Aminopyrine-Benzoic acid (377 mμ)	25	0.91	25.0	55.6	12,900	43.4
	35	1.87	25.0	−381		43.4
Aminopyrine-Salicylic acid (360 mμ)	25	1.57	6.67	−266	13,000	44.4
	35	3.23	6.67	−713		44.4

6) D.A. Wadke and D.E. Guttman, *J. Pharm. Sci.*, **54**, 1293 (1965).
7) D. Ross and M. Bassin, *J. Am. Chem. Soc.*, **76**, 69 (1954).
8) K.A. Connors and J.A. Molica, *J. Pharm. Sci.*, **55**, 772 (1966).

forces which participate in the complex formation, K_B gives measure for charge-transfer interaction only.

So that the differences of these stability constants may indicate that the mode of the complex formation cannot be ascribed solely to charge-transfer force, and the other types of driving forces such as hydrogen bonding and ionic bonding may be possibly involved in the reaction of the complex formation.

Interaction of Antipyrine and Its Derivatives with Acids

In order to examine a possible role of dimethylamino group of aminopyrine in the complex formation, the same experiments were carried out with antipyrine (2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) and 4-isopropyl-, 4-bromo-, and 4-aminoantipyrine.

Since there is no appreciable differences between the found solubilities of benzoic acid derivatives in the presence of antipyrine and the solubility values of the acids calculated by equation (1)(Table V), it is evident that solubilization of the acid did not take place in the presence of antipyrine. Far from being solubilized, in the presence of an excess of benzoic acid, the solubility of antipyrine decreased markedly.

Table V. Interaction of Antipyrine with Benzoic Acid and Salicylic Acid in Water at 25°

Antipyrine added ($\times 10^{-2}$M)	Benzoic Acid				Salicylic Acid			
	Antipyrine found ($\times 10^{-2}$M)	Benzoic acid found ($\times 10^{-2}$M)	(S_H) ($\times 10^{-2}$M)	pH found	Antipyrine found ($\times 10^{-2}$M)	Salicylic acid found ($\times 10^{-2}$M)	(S_H) ($\times 10^{-2}$M)	pH found
0.00		2.90		2.82		1.69		2.51
5.00	4.98	2.95	3.02	3.08	2.95	2.02	1.89	2.58
10.0	9.96	3.10	3.07	3.16	3.25	2.04	1.92	2.60
15.0	13.7	3.15	3.12	3.22	3.28	2.04	1.92	2.60
20.0	19.8	3.18	3.13	3.23	3.30	2.04	1.92	2.60
25.0	19.0	3.18	3.13	3.23	3.30	2.04	1.92	2.60
30.0	19.0	3.18	3.13	3.23	3.30	2.04	1.92	2.60
40.0	19.0	3.18	3.13	3.23	3.30	2.04	1.92	2.60

No changes were found in the solubility data of benzoic acid and salicylic acid even in the presence of either 4-isopropylantipyrine or 4-bromoantipyrine. Coloration was not observed in all the mixtures mentioned above.

However, it was found that net solubility of benzoic acid increased in the presence of 4-aminoantipyrine and that a new absorption band appeared in the vicinity of 420 mμ when both components were mixed in aqueous medium. Therefore, it may be said that 4-amino- or 4-substituted-amino group in the part of phenyl-substituted pyrazolones is necessary for the complex formation with benzoic acid derivatives.

Studies are in pursuit with a hope of obtaining more detailed informations about the interactions between aminopyrine and benzoic acid derivatives.

Experimental

Material——Aminopyrine, mp 108°(recrystallized from ligroin), antipyrine, mp 112°(ligroin), 4-bromoantipyrine, mp 117°(benzene), benzoic acid, mp 122°(H_2O), and salicylic acid, mp 157°(H_2O) were used. 4-Aminoantipyrine was synthesized according to Knorr, *et al.*[9] and recrystallized from ligroin-benzene, mp 108—109°. 4-Isopropylantipyrine, kindly supplied from by Nihon Shinyaku Co., Ltd., was recrystallized from benzene, mp 108—109°.

Measurements of Solubility——Weighed amount of the antipyretics, an excess of acids, and 25 ml of

9) L. Knorr and T. Geuther, *Ann.*, **293**, 56 (1895).

redistilled water were taken in a 100 ml flask. The flasks were stoppered and mounted on a thermostat of adjusted temperature and shaken for 48 hr. Test solutions were pipetted through a cotton filter, and analyzed for each component by the methods described below.

Determination of Solutes——Aminopyrine was extracted with alkalized dichloroethane and the acid components were extracted with acidified dichloroethane. Each component thus separated quantitatively from test solutions and the dichloroethane solutions were subjected to the analysis of aminopyrine, benzoic acid and salicylic acid, spectrophotometrically at the wavelengths of 275, 272, and 306 mμ, respectively. Separation of antipyrine and the acid components could not be achieved by simple extraction, because of partition of antipyrine into both organic and aqueous phases. Each component in the mixtures of antipyrine and either benzoic acid or salicylic acid were analyzed by simultaneous spectrophotometry at the two wavelengths. Test solutions were diluted with 1/15M phosphate buffer of pH 2.0 for the measurements and the differences of optical density of each component were found to be large enough. Wavelengths used were 260 and 274 mμ for the mixtures of antipyrine and benzoic acid, and 260 and 303 mμ for the mixtures of antipyrine and salicylic acid.

Refractometry——Abbe's refractometer of Shimadzu make was used, being maintained at $25\pm0.1°$. As it was found that about 24 hr were necessary for the equilibration to complete the complex formation reaction, measurements of refraction were carried out 24 hr after the preparation of mixed slutions.

Spectrophotometry of Yellow Mixtures——A Hitachi model EPS-3 recording spectrophotometer was used. To attain the complete equiliblium for coloration, 48 hr were maintained before the measurements.

Determination of Dissociation Constants——It was carried out spectrophotometrically according to Albert, *et al.*[10]

10) A. Albert and E.P. Serjeant, "Ionization Constants of Acid and Base," Methuen & Co., Ltd., London, and John Wiley & Sons, Inc., New York, 1962, p. 69.