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# Interaction between Pyrazine- or Pyridine-monocarboxamide and Sodium Hydroxy-carboxylate in Aqueous Solution.[*2] II.[*3]

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In the preceding paper,[*3] it was shown spectrophotometrically that pyrazinamide forms 1:1 molecular complex with sodium hydroxy-carboxylates, such as sodium *p*-aminosalicylate and sodium salicylate in aqueous solution, increasing its solubility. The present work is on the molecular complex formation of pyrazine- and pyridine-monocarboxamides with sodium *p*-aminosalicylate or sodium salicylate, whose equilibrium constants and values for heat of formation were calculated from measuring the values for heat of solution.

It was observed by the measurement of the values for heat of solution of amides in aqueous solutions of sodium *p*-aminosalicylate and sodium salicylate that the values for heat of solution decrease in proportion to the concentration of sodium hydroxy-carboxylate present. This decrease of the values for heat of solution was more than that might be caused by differences in concentration of the resultant solutions.

Assuming that this decrease in the values of heat of solution is due to the heat of complex formation of amide with sodium hydroxy-carboxylate, following equations were derived.

The reaction of amide ($A$) with sodium hydroxy-carboxylate ($O$) in aqueous solution may be represented by

$$A+O \rightleftharpoons AO \qquad (1)$$

Then

$$\frac{[A][O]}{[AO]}=K \qquad (2)$$

where $K$ is the equilibrium constant of reaction (1), and $[A]$, $[O]$, and $[AO]$ are the concentrations of free amide, sodium hydroxy-carboxylate, and the resulting complex, respectively.

Let $\Delta H_0$ and $\Delta H_1$ be the heat of solution of amide in water and in aqueous solution of sodium hydroxy-carboxylate, respectively; then $\Delta H_0 > \Delta H_1$ and $\Delta H_1$ decreases in proportion to the concentration of sodium hydroxy-carboxylate. If this difference $\Delta H_a$ is due to the complex formation,

$$\Delta H_a=\Delta H_0-\Delta H_1=\epsilon[AO] \qquad (3)$$

where $\epsilon$ is a constant, which signifies the heat of formation of one mole of the complex.

As the experiment in this study was conducted at exceedingly high concentrations of sodium hydroxy-carboxylate compared to those of the amide,

$$O \fallingdotseq [O] \qquad (4)$$

As to the amide,

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*2 Presented at the 80th Annual Meeting of the Pharmaceutical Society of Japan in Tokyo, April, 1960.

*3 Part I. H. Negoro, *et al.* : This Bulletin, **7**, 91 (1959). The title of Part I will be changed to the above title.

$$A=[A]+[AO] \quad (5)$$

where $A$ and $O$ are the quantities of the components added.

From equations (2), (3), (4), and (5), equation (6) is obtained.

$$K/\epsilon+O/\epsilon=AO/\Delta H_d \quad (6)$$

If $AO/\Delta H_d$ is plotted against $O$, a straight line should be obtained, from whose slope and intercept, the values of $K$ and $\epsilon$ can be respectively derived.

## Results and Discussions

The heat of solution of amides and sodium hydroxy-carboxylates in the solutions of various concentrations of sodium hydroxy-carboxylates is summarized in Table I. As the

Table I. Heats of Solution of Amides and Sodium Hydroxy-carboxylate in Aqueous Solutions of Sodium Hydroxy-carboxylates (joule/2 g., at 30°±0.005°)

| Soln. ($M$) of Na-PAS | Solute* added | | | | | Soln. ($M$) of Na-SAL | Solute* added | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Na-PAS | PZA | PA | NA | INA | | Na-SAL | PZA | PA | NA | INA |
| 0 | 285 | 380 | 332 | 306 | 312 | 0 | 145 | 380 | 332 | 306 | 312 |
| 0.237 | 285 | 328 | 293 | 267 | 254 | 0.312 | — | 318 | 296 | 258 | 269 |
| 0.474 | 270 | 275 | 264 | 233 | 219 | 0.625 | — | 279 | 270 | 228 | 232 |
| 0.711 | 259 | 254 | 244 | 200 | 208 | 0.938 | — | 265 | 268 | 206 | 215 |
| 0.948 | 248 | 223 | 226 | 180 | 185 | 1.25 | — | 242 | 253 | 189 | 191 |
| 1.422 | — | 212 | 229 | 161 | 167 | 1.88 | — | 218 | 228 | 161 | 166 |

* Na-PAS, sodium $p$-aminosalicylate; Na-SAL, sodium salicylate; PZA, pyrazinamide; PA, picolinamide; INA, isonicotinamide; NA, nicotinamide.

heat of solution of sodium $p$-aminosalicylate has little relation to the concentration of the aqueous solution of sodium $p$-aminosalicylate compared to those of amides, it may be concluded that the variation in the heat of solution of amides with the concentrations of sodium hydroxycarboxylates in solution results from interaction between the amide and sodium hydroxy-carboxylates.

From the data given in Table I, $\Delta H_d$ and $AO/\Delta H_d$ were calculated, and the latter were plotted against $O$ as shown in Fig. 1. Equation (6) is found to be almost valid in each case.

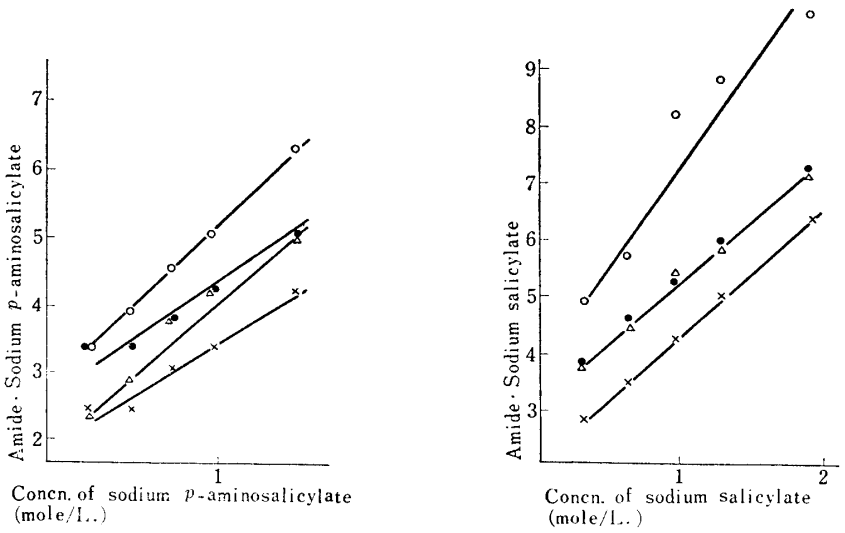


Fig. 1. A Plot of $A\cdot O/\Delta H_d$ against Concentration of Sodium Hydroxy-carboxylate
-○-○- PA -•-•- NA -△-△- INA -x-x- PZA

Table II. Equilibrium Constant ($K$) and Heat of Formation ($\epsilon$) (measured calorimetrically, at 30°±0.005°)

| Solute added | Solution of Na-PAS | | Na-SAL | |
|---|---|---|---|---|
| | $K$(mole/L.) | $\epsilon$(joule/mole) | $K$(mole/L.) | $\epsilon$(joule/mole) |
| PA | 1.23 ±0.16 | 4408±132 | 1.15±0.4 | 2929±457 |
| NA | 0.935±0.32 | 4449±552 | 1.32±0.15 | 4464±204 |
| INA | 0.69 ±0.09 | 3959±355 | 1.36±0.28 | 4571±379 |
| PZA | 0.63 ±0.23 | 4545±942 | 0.86±0.07 | 4357±216 |
| | 1.05* | | 0.94* | |

* Obtained spectrophotometrically in previous work*3 (at 25 ).

Using this equation, the equilibrium constants ($K$) and the heats of formation ($\epsilon$) were calculated and are given in Table II. Comparing these values of pyrazinamide with corresponding values obtained by spectrophotometry reported in the preceding paper,*3 and taking the experimental errors and the difference in temperature at which experiments were made into account, they may be judged to coincide with each other.

The considerably small heats of complex formation of these amides with sodium hydroxy-carboxylates suggest that these complexes are formed by other than hydrogen bonding and this may be supported by the fact that the coloring of pyrazinamide–sodium *p*-aminosalicylate complex solution has little relationship to temperature; further investigation will be made about this.

## Experimental

**Material**—Pyrazinamide, nicotinamide, sodium *p*-aminosalicylate, and sodium salicylate were all commercial products (pure crystals of Sankyo Co., Ltd.), and isonicotinamide and picolinamide were purified by recrystallization, as mentioned elsewhere.[1]

**Apparatus**—Same as described in the previous paper.[1]

**Procedure**—Aqueous solution of sodium hydroxy-carboxylates was prepared in various concentrations of 5, 10, 15, 20, and 30 w/v%.

The heats of solution of amides and hydroxy-carboxylates (2 g. or 1 g.) in $H_2O$ or aqueous solutions of sodium hydroxy-carboxylate (300 cc. each) were measured at 30°±0.005°, at least in duplicate.

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## Summary

Molecular complex formation between pyrazine- or pyridine-monocarboxamides and sodium *p*-aminosalicylate or sodium salicylate in aqueous solution was studied by measuring the heats of solution values. Assuming 1:1 complex formation, the equilibrium constant ($K$) and the heat of formation ($\epsilon$) were calculated.

Comparing these values for pyrazinamide with corresponding values obtained spectrophotometrically and reported in the preceding paper, and taking the experimental errors and the difference in temperature at which experiments were made into account, they may be judged to coincide with each other.

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1) Part IV. H. Negoro, *et al.* : Yakugaku Zasshi, **80**, 1184 (1960).