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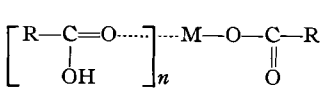
Research Articles

Complexation of Organic Acids and Bases with Their Salts in Aqueous Solution

By MICHAEL R. VALINOTI and SANFORD BOLTON

The solubilization of certain organic acids in aqueous solutions of their salts has been attributed to a complexation between the acid and anion species. In the present investigation solubility studies were used in an effort to ascertain the factors influencing such complexation and to determine the nature of the complexes formed. Benzoic acid, salicylic acid, *p*-hydroxy-, 2,4-dihydroxy-, 2,5-dihydroxy-, 2,6-dihydroxy-, and 3,4-dihydroxybenzoic acids, phenylacetic acid, adipic acid, barbituric acid, barbital, phenobarbital, and saccharin showed substantial increases in solubility in the presence of their sodium salts. Studies with atropine and procaine in solutions of their salts showed that similar complexes occurred in these systems. In some cases insoluble complexes were formed at high salt concentrations. Addition of hydroxyl groups to benzoic acid favors complexation. Quantitative evaluation of equilibrium constants could not be determined because of a concurrent salting out effect.

THE APPARENT increase in solubility of various organic acids in aqueous solutions of their alkali or alkaline earth metal salts has been attributed to the formation of an acid-anion complex (1–6). Ross and Morrison (1) have described solubility curves for various mandelic acid-metal mandelate systems and have noted the formation of complexes of acid-salt ratios of 1:1, 2:1, and 3:1. They proposed the following formula as the most favorable representation of the complex species



where n can be either 1, 2, or 3. Hoitsema (2) investigated the salicylic acid-sodium salicylate and hippuric acid-potassium hippurate systems

Received April 28, 1961, from the College of Pharmacy, University of Rhode Island, Kingston.
Accepted for publication June 23, 1961.
Presented to the Scientific Section, A. PH. A., Chicago meeting, April 1961.
Abstracted from part of a thesis submitted by Michael R. Valinoti in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

and isolated, in each case, 1:1 "double salt" complexes. Marshall and Cameron (3) noted the appearance of, and characterized, an insoluble complex in the succinic acid-potassium succinate system. Kolthoff and Bosch (4), in studies designed to determine the activity coefficient of benzoic acid in solutions of various salts, observed an increase in the solubility of benzoic acid in the presence of up to 1 *M* sodium benzoate. Higuchi and co-workers (5) have noted an insoluble benzoic acid-ammonium benzoate complex; and Ongley (6) has listed, without interpretation, the increase in solubility of benzoic, salicylic, and 2,6-dihydroxybenzoic acids in 1 *M* solutions of their salts.

It was the purpose of the present investigation to attempt to elucidate the prerequisite factors and the nature of the binding forces involved in this type of complex. Solubility studies with a number of model compounds were used to determine the extent of complexation. Benzoic acid, phenylacetic acid, and a group of hydroxybenzoic acids were selected to determine the effect of some structural features of aromatic acids on the degree of complexation. Systems containing suitable monocarboxylic, straight chain acids proved to be too difficult to analyze because of the formation of colloidal soap solutions by their salts. Therefore, the adipic acid-sodium adipate system was investigated as an example of complex formation by nonaromatic carboxylic acids. Since no similar studies involving noncarboxylic acids have been reported in the literature, saccharin, barbituric acid, barbital, and phenobarbital complexes were also investigated. Likewise, because of the absence of published work of an analogous nature concerning bases and their salts, atropine and procaine complexes are reported here.

EXPERIMENTAL

Reagents.—All chemicals used were of the highest purity commercially available. The purity of the acids and bases was checked by (*a*) melting point, (*b*) solubility analysis, and (*c*) titration with standard acid or base. Those compounds failing to meet these criteria were recrystallized, usually from hot water. The melting points of the acids and bases used are listed in Table I. Solutions of salts that were not readily available were prepared either directly by adding an equivalent of sodium hydroxide to the acid or by preparing solutions from pure salt which was obtained by evaporation of the above solutions in a flash evaporator. With the exception of disodium adipate, monosodium salts were used as complexing agents for all acids. Atropine sulfate and procaine hydrochloride, both U.S.P. grade, were used as complexing agents for the bases.

Procedure.—A solubility method, similar to that employed by Higuchi and Lach (7), was used to follow the course of complexation. In all cases, a constant excess of the solid acid or base was added to varying concentrations of the salt solution. To determine the solubilizing effect of salt beyond its saturation point, calculated amounts of salt were added to the saturated solution. Because the small changes in volume resulting from the solubilization of the excess salt during complex formation could not be determined accurately, values plotted beyond the salt saturation point are, of necessity, approximations.

The mixtures, in duplicate, were placed in stoppered glass vials and rotated in a water bath at 30 ± 0.1° for at least 3 hours. In the base systems the shaking time was kept to a minimum to minimize hydrolytic decomposition.

In general, a 5-ml. sample of filtrate was withdrawn by means of a pipet fitted with a piece of rubber tubing plugged with cotton. The majority of the sodium salts were very soluble in water and, consequently, their solutions became very viscous as the saturation point was approached. This condition and the presence of large amounts of solid acid, complex, or salt in the system made withdrawal of accurate aliquots unfeasible in some instances. As a consequence, the solubility analyses were carried

TABLE I.—SOLUBILITY CHARACTERISTICS AND INTERACTIONS OF SOME ORGANIC ACIDS AND BASES WITH THEIR SALTS

Compound	M.P., °C.	Solubility Compound, Mole/L. × 10^2	Solubility Salt, Mole/L.	Apparent K_1, L./Mole	Insoluble[a] Complex
Benzoic acid	122	3.07	2.98	0.5	none
Salicylic acid	158	1.88	4.3	0.9	1:1
p-Hydroxybenzoic acid	215–216	5.71	2.6	0.7	1:1, 1:2
2,4-Dihydroxybenzoic acid	225 decompn.	4.87	0.60	2.2	none
3,4-Dihydroxybenzoic acid	201–202 decompn.	11.4	0.85	0.9	1:1
2,5-Dihydroxybenzoic acid	204–206 decompn.	17.4	1.45	2.8	1:1
2,6-Dihydroxybenzoic acid	164–167 decompn.	7.54	1.60	1.6	none
Phenylacetic acid	76–77	14.7	3.00	1.2	none
Adipic acid	152–154	19.6	2.00	7.5[b]	2:1
Saccharin	224–226	1.95	3.00	1.9	none
Barbituric acid	247–250 decompn.	11.1	0.10	0.9	1:1
Barbital	188–191	4.38	0.90	0.5	none
Phenobarbital	172–176	0.612	2.65	1.0	1:4
Atropine	116–117	1.00	1.03	13.	none
Procaine	59–61	1.92	2.80	4.8	none

[a] Ratios given are for acid:salt. [b] Calculated on basis of 2:1 complex.

out to a point of salt concentration beyond which the results were believed to be inaccurate.

The clear aliquot was titrated potentiometrically with standard sodium hydroxide or hydrochloric acid, unless the titration was readily amenable to the use of phenolphthalein. Barbital and phenobarbital, which were titrated potentiometrically, required the prior addition of ethanol to the aqueous solutions in order to yield a clearly discernible end point. For a number of compounds, in concentrated salt solutions, the end point could not be clearly detected. In these cases, to eliminate most of the salt, the aqueous aliquot was first extracted with ether (chloroform was used in the case of atropine), the organic solvent evaporated, and the residual acid or base titrated as before. Preliminary determination of known concentrations of the acids and bases in concentrated solutions of their salts substantiated the accuracy of the above method.

The acid:salt ratios of the insoluble complexes were determined by analyzing the precipitates in the appropriate containers for acid content.

RESULTS

Benzoic and Monohydroxybenzoic Acids.—Figure 1 illustrates the results obtained for benzoic, salicylic, and *p*-hydroxybenzoic acids. The benzoic acid curve, up to 1 *M* sodium benzoate, parallels the previously reported data of Kolthoff and Bosch (4) whose study was made at 25°. No insoluble complex is formed in this system; the plateau region at high salt concentration indicates that the solution, in this range, is saturated with respect to salt. Salicylic acid shows a significantly greater complexing tendency than benzoic acid. The decrease in acid solubility, observed at low salt concentrations, is probably a salting out effect, a result also observed by Hoitsema (2). The termination of the sharply ascending curve is caused by the appearance of an insoluble complex containing acid and salt in a 1:1 ratio. Further addition of salt results in depletion of acid in solution as more complex is precipitated (7). *p*-Hydroxybenzoic acid, like benzoic acid, shows no initial decrease in solubility. A 1:1 complex precipitated along the first plateau region on this curve. The shape of the terminal portion of the curve and the analysis of the solid phase in that region strongly suggest the formation of a new insoluble species containing acid and salt in a ratio of 1:2.

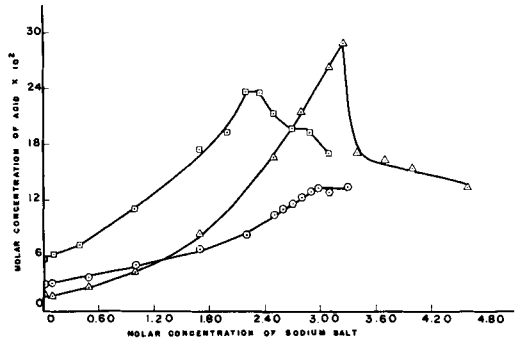


Fig. 1.—Apparent solubilization of benzoic ⊙, salicylic △, and *p*-hydroxybenzoic ▣ acids by their sodium salts in water at 30°.

Dihydroxybenzoic Acids.—Figures 2 and 3 show the results of the dihydroxybenzoic acid interactions studied. Among these acids, only the 2,6-dihydroxy derivative shows an initial decrease in solubility. This acid and 2,4-dihydroxybenzoic acid form soluble complexes only. Analysis of these curves according to a method suggested by Higuchi and Lach (7) indicated formation of 1:1 complexes. In both the 3,4-dihydroxy and 2,5-dihydroxybenzoic acids, precipitation of a 1:1 complex occurs after an initial increase in the apparent solubility of the acid.

Phenylacetic and Adipic Acids.—Figure 4 shows the interaction of phenylacetic and adipic acids with their respective sodium salts. In the phenylacetic acid system, a salting out effect is apparent at low salt concentrations, as evidenced by the appearance in the solubility curve of an initial flattened portion followed by an abrupt rise. Adipic acid forms an insoluble complex with its sodium salt. Analysis of the precipitate on the descending portion of the curve was indicative of an insoluble species containing acid to salt in a 2:1 ratio. At the terminal segment of the curve, the solution is saturated with salt and the solid phase consists of insoluble complex plus salt.

Noncarboxylic Acids.—Figure 5 shows the results obtained for saccharin. A pronounced initial decrease in acid solubility is noted, followed by solubilization up to the salt saturation point. Further addition of salt along the plateau region failed to precipitate a complex species.

Figure 6 illustrates the varied behavior of barbituric acid and its derivatives. The barbituric acid-barbiturate complex is the least soluble of all

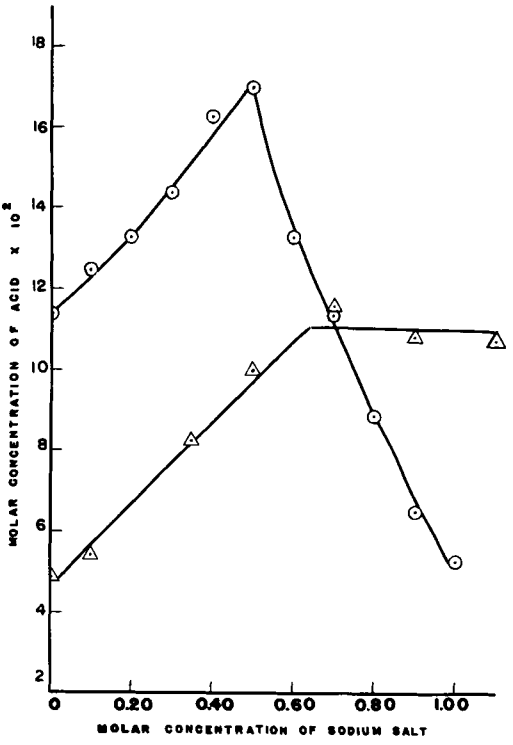


Fig. 2.—Apparent solubilization of 2,4-dihydroxybenzoic △ and 3,4-dihydroxybenzoic ⊙ acids by their sodium salts in water at 30°.

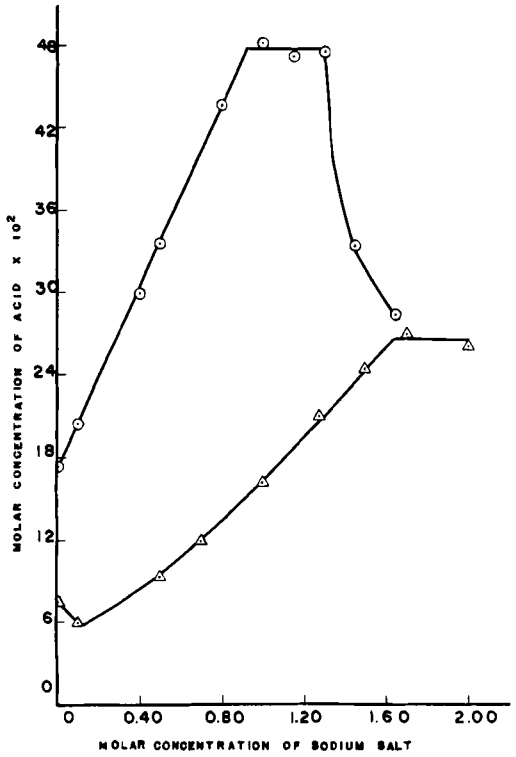


Fig. 3.—Apparent solubilization of 2,5-dihydroxybenzoic ⊙ and 2,6-dihydroxybenzoic △ acids by their sodium salts in water at 30°.

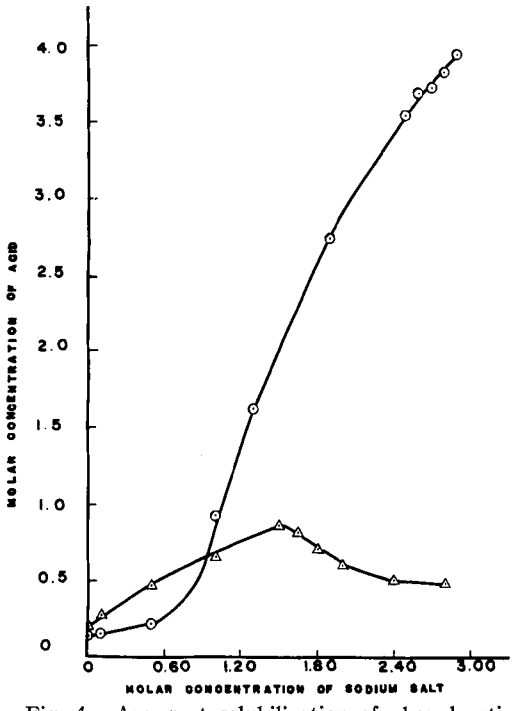


Fig. 4.—Apparent solubilization of phenylacetic ⊙ and adipic △ acids by their sodium salts in water at 30°.

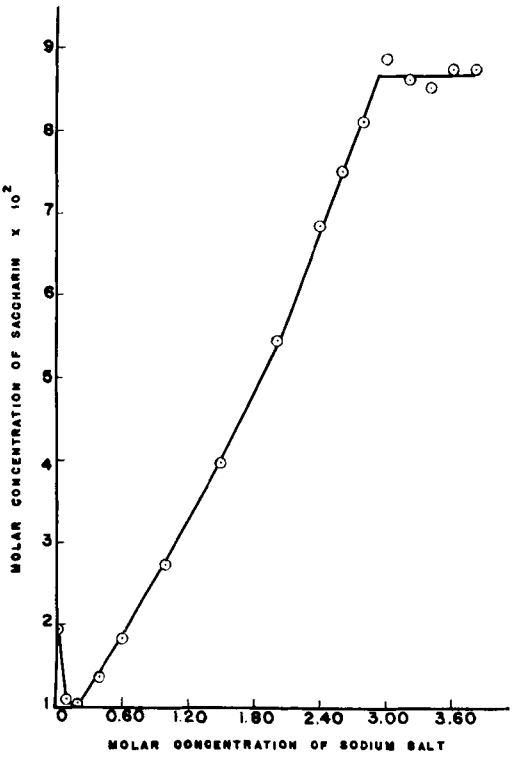


Fig. 5.—Apparent solubilization of saccharin by sodium saccharin in water at 30°.

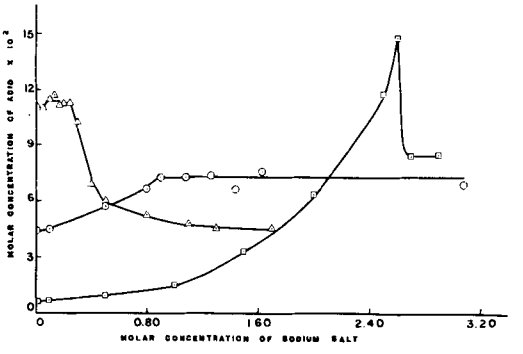


Fig. 6.—Apparent solubilization of barbituric acid △, barbital ⊙, and phenobarbital ◻ by their sodium salts in water at 30°.

complexes noted in this study. After an initial decrease, a small increase in acid solubility is observed, followed by the appearance of a 1:1 complex. Again, along the terminal portion of the curve, the system is saturated with salt and is invariant. Barbital is solubilized up to the salt saturation point, and no insoluble complex is formed. In the case of phenobarbital, the relatively small increase in solubility at low salt concentrations may indicate a salting out effect, somewhat masked by complex formation (similar to the phenylacetic acid system). With increasing salt concentration, however, solubilization increases rapidly. The insoluble complex which appeared at high salt concentration corresponded closely to an acid:salt ratio of 1:4.

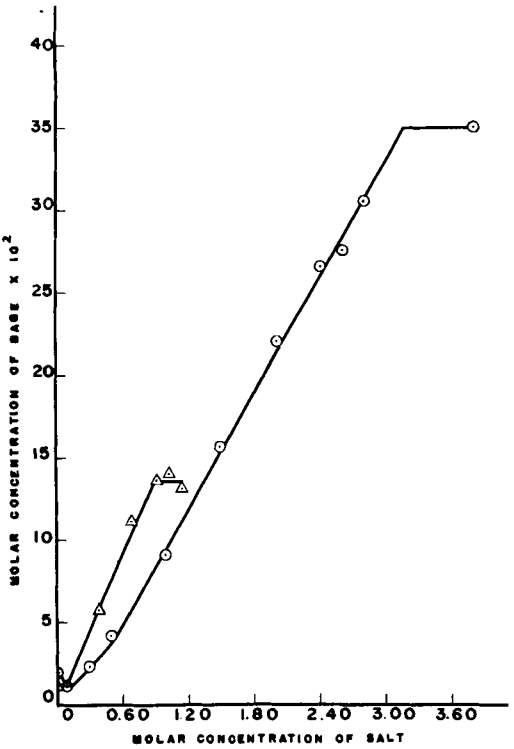


Fig. 7.—Apparent solubilization of atropine by atropine sulfate △ and procaine by procaine hydrochloride ⊙ in water at 30°.

Bases.—The complexation of atropine and procaine with their salts is shown in Fig. 7. The curves are similar in nature to those observed in the acid systems. In both of these cases no insoluble complex appears. In the procaine system, the observed increase in solubility of both the base and salt species due to complex formation indicated formation of a 1:1 complex (7).

DISCUSSION

The fact that complex formation in these systems is accompanied by an inseparable salting out effect renders accurate evaluation of stability constants impossible. Nevertheless, constants were approximated for 1:1 complexes, neglecting salting out effects. These constants were calculated, according to a previously reported method (7), from the initial portions of the curves where 1:1 complexation could be considered to be the predominant equilibrium. Although this approach, admittedly, yields only rough approximations, the results appeared to give a reasonable indication of the extent of complex formation (Table I). In any case the constants, thus calculated, give low values since salting out effects tend to obscure complexation effects.

The K_1 value for barbituric acid was approximated from the final invariant portion of the curve. In this region, the solution is saturated with both complex and salt. The solubility of the complex may be estimated from the initial rise in the solubility curve, and the solubility of the salt is known. The concentration of free acid in these solutions may be calculated as follows

(free acid) = (total acid in solution) − (complex)

and

$$K_1 = \frac{(\text{complex})}{(\text{free acid})\,(\text{free salt})}$$

Since physical properties, such as melting point and solubility, are measures of intermolecular forces and may give insights into complexation forces, these data are included in Table I.

In the series of benzoic acid and its hydroxy derivatives, there appears to be little or no correlation of complexing activity with the indicated physical properties. This fact suggests that the interaction is the result of an interplay of many factors. The solubility of the complexes formed also shows no obvious relation to any single property of these acids. The fact that the addition of hydroxy groups to the benzoic acid nucleus results in an increase in the degree of complexation suggests that binding may occur through hydrogen bonds as well as through the metal atom as previously suggested (1). It is of interest to note that the 2-substituted hydroxy acids showed the strongest complexation in all cases.

The limited, comparable data reported by Ross and Morrison (1) for mandelic acid indicates that at low salt concentrations this acid complexes more strongly with its sodium salt than does phenylacetic acid with its salt. The introduction of a hydroxyl group in mandelic acid may again be offered as an explanation of this difference.

Significant complexation occurred in the nonaromatic acid and the base systems; but the degree of binding, as well as the solubility of the complexes, again appeared to be nonselective.

The variety of complex systems tested indicates that interaction between organic acids or bases and their salts is a widespread phenomenon. There does not appear to be any overall structural requirements although, in a given class of compounds, certain structural variations are probably influential. Despite a wide range of melting points and solubilities of the acids, bases, and their salts, these factors alone do not seem to provide a basis for correlation with complexing activity.

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