Interaction of Urea and Thiourea with Benzoic and Salicylic Acids

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Urea forms soluble complexes of low stability with benzoic acid in water, methanol, and dioxane. With salicylic acid, urea forms insoluble interaction products which can be isolated from the above solvents. On the basis of these results a procedure for the separation of salicylic acid from benzoic-salicylic acid mixtures is described. Thiourea forms only soluble complexes of low stability. The difference in the extent of interaction in the different solvent systems is explained on the basis of competing solute-solvent interactions, which can be translated into terms of solute solubilities.

ALTHOUGH in recent years much work has been reported on the formation of molecular complexes in pharmaceutical systems, the complexing agents used have often been toxic or medicinally potent substances. The desirability of investigating the complexing properties of nontoxic or less potent compounds is apparent. In the present study, urea, a comparatively innocuous drug, has been examined as a possible complexing agent.

Clathrates, or inclusion compounds of urea, have found useful application in the separation of closely related hydrocarbons (1–4) and mixtures of structurally related fatty acids (5, 6). Inasmuch as these urea inclusion complexes usually involve very small molecules such as CO_2 and H_2O_2 or straight chain hydrocarbons and their derivatives, it became of interest to study the interaction of urea solutions with more complex molecules where clathrate formation is not possible. Evidence of nonclathrate complexes of urea and pharmaceutically important substances has appeared in the literature. For example, aqueous solubilities of terramycin (7) and benzocaine (8) were shown to be increased in the presence of urea. Solid tetracycline-urea complexes have been prepared which have improved stability and solubility properties over the uncomplexed drug (9–11). Complexes of sulfonamides (12), wool fat alcohols (13, 14), quinoxaline (15), detergents (16–18), and barbituric acid derivatives (19) with urea have also been described.

In this report the interactions of urea and thiourea (chosen for purposes of comparison) with benzoic and salicylic acids have been followed by means of solubility studies. The high affinity of urea for water resulted in a low complexing tendency in this solvent. (See References 7 and 8.) Therefore, two nonaqueous solvents, methanol and dioxane, were also used. Although, in general, the degree of interaction was small in all cases, definite complexes were found. The difference of the solubility characteristics of the urea–benzoic acid and urea–salicylic acid complexes in the nonaqueous solvents suggested a possible separation procedure of salicylic acid from benzoic-salicylic acid mixtures. One approach to such a separation is described.

EXPERIMENTAL

Solubility Studies

A. Aqueous Solutions.—The interactions in aqueous solution were followed by determining acid solubility as a function of urea (thiourea) concentration. Excess benzoic (0.25 Gm.) and salicylic (0.625 Gm.) acids were equilibrated with 10 ml. of solutions of varying urea and thiourea concentrations by rotating the mixtures in capped vials for 18 hours in a constant temperature water bath at 30 ± 0.1°. All solutions were made 0.1*N* with H_2SO_4 to prevent dissociation of the acid species. The amount of acid in solution was determined concurrently by two methods: (*a*) titration of a clear aliquot with standardized NaOH solution; and (*b*) spectrophotometric examinations utilizing the peak for benzoic acid at 274 mμ and salicylic acid at 302.5 mμ.

B. Nonaqueous Solutions.—The interactions in methanol and dioxane were followed by determining acid solubility as a function of urea (thiourea) concentration and urea (thiourea) solubility as a function of acid concentration. Approximately 3 ml. of solution was equilibrated as in *A* for at least 24 hours in vials equipped with polyethylene-lined caps. The amounts of reagent in excess during the solubility studies are tabulated in Table I.

The mixtures were analyzed as follows. One milliliter of a clear aliquot was pipeted into a tared 10-ml. beaker, and the solvent was removed by evaporation with the aid of gentle heat. The residue was weighed and acid content was determined by titration with a standardized NaOH solution. The urea content could then be determined by difference. (Since the solutions often contained large concentrations of reactants, it was very difficult to measure total solution volume accurately. This presented no problem when only soluble interaction species were formed, as the method of analysis gave

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TABLE I.—COMPONENTS IN NONAQUEOUS SYSTEMS

System	Wt. of Component in Excess, Gm.
Salicylic acid–urea–methanol	Salicylic acid–1.35 urea–0.70
Salicylic acid–urea–dioxane	Salicylic acid–1.40 urea–0.20
Benzoic acid–urea–methanol	Benzoic acid–2.0 urea–1.0
Benzoic acid–urea–dioxane	Benzoic acid–2.0 urea–0.15
Salicylic acid–thiourea–methanol	Salicylic acid–2.0 thiourea–0.40
Salicylic acid–thiourea–dioxane	Salicylic acid–2.0 thiourea–0.75
Benzoic acid–thiourea–methanol	Benzoic acid–2.0 thiourea–0.40
Benzoic acid–thiourea–dioxane	Benzoic acid–2.0 thiourea–0.75

molar concentrations directly; i.e., the concentration of complexing agent added equalled the concentration found in solution. The points on the graphs after the appearance of an insoluble species are approximations, since changes in solution volume during the precipitation process could not be determined.)

RESULTS

Interaction Studies

A. Aqueous Solution.—Figure 1 illustrates the effect of urea and thiourea on the solubilities of benzoic and salicylic acids in water. Only in the case of the salicylic acid–urea interaction did an insoluble interaction product appear before urea or thiourea saturation. Along the first plateau region of this curve an insoluble species appeared; along the immediately following descending portion the precipitate showed acid-urea ratios between 1–1 and 2–1. Calculation of the acid-urea ratio from the phase diagram according to Higuchi and Lach (20) suggested formation of a 1–1 complex which could not be reconciled with the analysis of the insoluble phase in this region of the curve. The form of the following portion of the curve suggested that a new insoluble species was being formed, and analysis of the precipitate in this region corresponded to a 1–1 complex. After this plateau region the apparent solubility of acid increased slowly, although the insoluble phase still consisted of a 1–1 species. The high concentrations of urea at the latter portions of the curve undoubtedly were at least partially responsible for the unusual solubility pattern of the acid and no effort was made to rationalize the curve in this region.

Because of the high concentrations of complexing agent used and the uncertainty of the nature of the interaction products, stability constants for the interactions were not calculated. It is apparent by inspection of Fig. 1, however, that the stability of salicylic acid complexes were stronger than the benzoic acid complexes, and the thiourea complexes were stronger than the urea complexes.

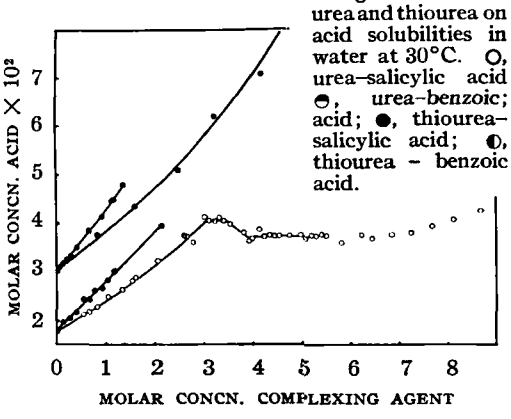

Fig. 1.—Effect of urea and thiourea on acid solubilities in water at 30°C. ○, urea–salicylic acid ◒, urea–benzoic; acid; ●, thiourea–salicylic acid; ◐, thiourea – benzoic acid.

B. Nonaqueous Solutions.—Figures 2, 3, and 4 illustrate the results obtained in methanol and dioxane. Figure 2 shows the effect of urea on the acid solubilities in these solvents. Thiourea showed no complexing tendencies under these conditions; these data are not included in the plot. The solubilities of the acids decreased slightly in the presence of thiourea. A slight decrease or lack of change of acid solubility did not necessarily indicate a lack of interaction in these systems. At the high solute concentrations used in these studies, if no interaction takes place between the solutes, we might expect a competition for solvent molecules and a resultant substantial decrease in solubility. In fact, this mutual "squeezing out" of the solute molecules probably occurred to some extent in most of the systems in this study. Urea formed a 1–1 insoluble complex with salicylic acid in both methanol and dioxane. The final plateau regions in these curves indicate saturation with respect to urea as well as complex and the systems are invariant. The plateaus formed in the benzoic acid–urea systems were due to urea saturation; only soluble species were formed in these systems. It is apparent that urea complexed more strongly with benzoic acid in dioxane than methanol.

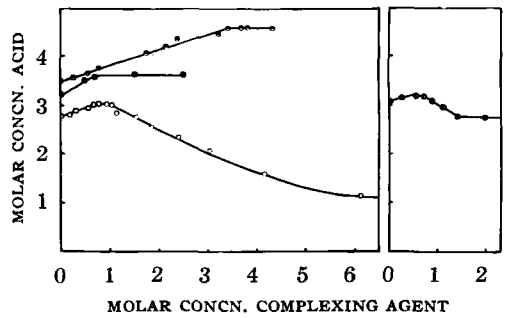

Fig. 2.—Effect of urea on acid solubilities in methanol and dioxane at 30°C. ○, urea–salicylic acid–methanol; ◒, urea–benzoic acid–methanol; ◐, urea–salicylic acid–dioxane; ●, urea–benzoic acid–dioxane.

The effect of the acids on urea and thiourea solubility in dioxane and methanol is shown in Figs. 3 and 4. These studies further establish the nature of the interactions, especially those in dioxane where urea and thiourea solubilities were comparatively small. The low interaction tendency of thiourea in methanol was confirmed. However, in dioxane, the solubility of thiourea was increased

to a small extent in the presence of the acids; salicylic acid proved to be the slightly stronger complexing agent (Fig. 4). Also the comparatively strong interaction of urea with the acids in dioxane is clearly illustrated in Fig. 4. Again, the final invariant regions in these curves are caused by saturation of the system by complexing agent.

Comparison of the extent of interaction, somewhat obscure in most cases in the acid-saturated system (Fig. 2), can be made from examination of Figs. 3 and 4. The urea–salicylic acid complex was stronger in dioxane than methanol and the urea–salicylic acid complex was stronger than the urea–benzoic acid complex in dioxane.

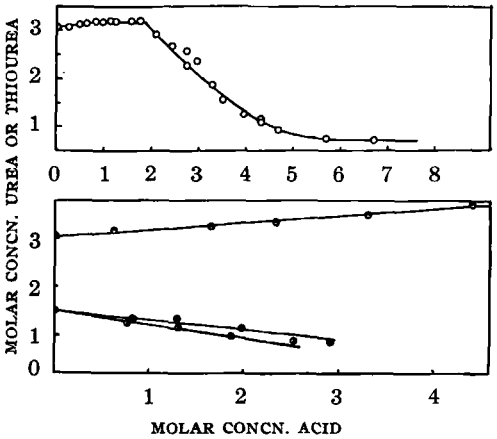

Fig. 3.—Effect of acid on urea and thiourea solubilities in methanol at 30°C. ○, urea–salicylic acid; ◓, urea–benzoic acid; ◑, thiourea–salicylic acid; ●, thiourea–benzoic acid.

Separation of Salicylic Acid from Salicylic-Benzoic Acid Mixtures

A procedure for a separation of salicylic acid from mixtures with benzoic acid was designed based on the low solubility of the urea–salicylic acid complex compared to the urea–benzoic acid complex in methanol. Methanol, rather than dioxane, was chosen as the solvent for the procedure because the low solubility of urea in dioxane reduced the amount of salicylic acid which it can precipitate. (The system, urea–salicylic acid–dioxane, became invariant due to urea saturation with almost 3*M* salicylic acid in solution, while the invariance point in methanol left only 1*M* salicylic acid in solution. See Fig. 2. Also, because of the greater solubility of urea in methanol, urea solubilized benzoic acid more in methanol than in dioxane.

The method of separation was as follows. One gram of a mixture of salicylic and benzoic acids was shaken with 1 ml. of methanol and $^2/_3$ Gm. of urea for approximately 1 hour at 30°. The resultant precipitate was filtered and sucked dry under

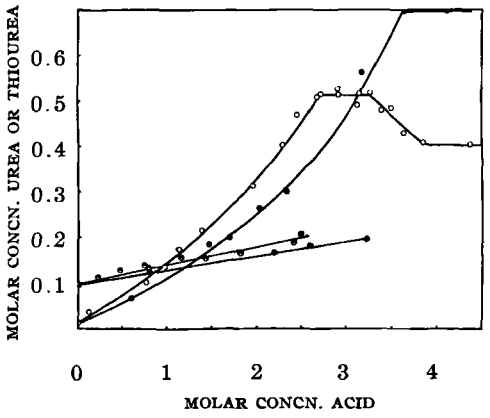

Fig. 4.—Effect of acid on urea and thiourea solubilities in dioxane at 30°C. ○, urea–salicylic acid; ●, urea–benzoic acid; ◓, thiourea–salicylic acid; ◐, thiourea–benzoic acid.

vacuum. The dried precipitate was weighed and mixed with 15 ml. of water per 2 Gm. of precipitate. This slurry was stirred with a magnetic stirrer for 5–7 minutes to dissolve the urea, and the remaining solid was collected in a sintered-glass funnel and dried. The salicylic acid content of this residue was assayed by measuring the color produced with ferric chloride using a Bausch and Lomb spectronic 20 colorimeter (21). Further salicylic acid purity can be achieved by repeating the process. (See Table II.)

Table II shows the results of this separation for two acid mixtures. No effort was made to recover salicylic acid quantitatively, and the column headed *Ppt. Recovered* is merely for information. More quantitative yields could be obtained by repeating the process on the alcohol soluble portion.

DISCUSSION

As mentioned before, no effort was made to calculate equilibrium constants since the exact nature of the interactions was not known. However, in order to have a basis on which to compare the extent of interaction in the different systems, values were calculated according to Higuchi and Zuck (22) from the initial portions of the curves as if 1–1 complexation were occurring. Table III shows the results of these calculations.

The effect of solvent on the extent of interaction may be explained on the basis of competitive reactions between solute and solvent molecules, *i. e.*, the greater the interaction of the solutes with the solvent, the lower will be the complexing tendency between solute molecules. This effect can be translated in terms of solubility which is a measure of solute-solvent interaction forces. Since the solubilities of the two solutes should be a factor in deter-

TABLE II.—RECOVERY OF SALICYLIC ACID FROM BENZOIC ACID–SALICYLIC ACID MIXTURE

Acid Mixture, Wt. and Compn.	Ppt. Recovered, Wt. and Compn.	Wt. and Compn. of Ppt. Recovered (process repeated on Ppt. in Col. 2).
15 Gm.–33% salicylic acid–67% benzoic acid	2.4 Gm.–78% salicylic acid	1.5 Gm.–98.5% salicylic acid
20 Gm.–50% salicylic acid–50% benzoic acid	6 Gm.–98% salicylic acid	3.7 Gm. 99.5% salicylic acid

TABLE III.—APPARENT 1–1 STABILITY CONSTANTS

Solvent	Interacting Species	Approximate K_1 (Complex)/(Urea) (Acid)
Water	Urea–benzoic acid	0.2
	Urea–salicylic acid	0.3
	Thiourea–benzoic acid	0.33
	Thiourea–salicylic acid	0.55
Methanol	Urea–benzoic acid	0.12
	Urea–salicylic acid	0.15
	Thiourea–benzoic acid	—
	Thiourea–salicylic acid	—
Dioxane	Urea–benzoic acid	5
	Urea–salicylic acid	7
	Thiourea–benzoic acid	0.32
	Thiourea–salicylic acid	0.47

mining the magnitude of the interaction, it is well to know the solubilities of all the species involved. In the present studies, solubilities can be conveniently obtained from the figures, except for urea and thiourea in water, which are approximately 10 *M* and 2 *M*, respectively (23). It is apparent from these considerations that the degree of interaction seems to be directly related to the solubilities of the interacting species. The acid-urea interactions are strongest in dioxane > water > methanol. Considering that all species are extremely soluble in methanol, the small reactivity in this solvent would be expected. A further look at the dioxane and water systems reveals that in each solvent one component is very soluble, while one component is relatively insoluble; the acids are insoluble in water, while urea is insoluble in dioxane. A comparison of actual solubility values shows that the solubilities of both the insoluble and soluble components in water are greater than both values in dioxane. This, it seems, would account for the greater complexing tendency in dioxane. Exactly analogous considerations apply and hold for the thiourea interactions. It is interesting that the degree of interaction for thiourea is very similar in both water and dioxane and the products of thiourea and acid solubilities are also very close in both solvents.

Similar observations have been made by Marvel and Lemberger (24) and Gans and Higuchi (25). In both cases, differences in complexing tendencies in different solvents were attributed to competing solvent-solute interactions. Unfortunately, the solubilities of the complexing agents in the solvents studied were not determined and an analysis similar to the above one cannot be made.

The toxic nature of thiourea and its low complexing tendencies in these nonclathrate type systems suggest a limit to its possible usefulness. On the other hand, results presented here and past reports of urea complexes strongly recommend further investigation of urea as a complexing agent in pharmaceutical systems. Its low complexing tendency in water should be more than compensated by its high solubility and comparative nontoxicity.

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