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Salt Effects in Aqueous Solutions of Urea

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Abstract ☐ It is suggested, when working with drug–urea–water systems, that more than passing consideration be given to the effect or effects produced by addition of a fourth component, as, for example, when an acid is used to adjust pH. Data are cited which indicate that these effects are measurable and often predictable. Solubility data for methyl salicylate and methyl benzoate are given as functions of varying acid, salt, and urea concentrations. These data represent the equilibrium solubilities of the esters in the various systems at 30°. The solubilities were obtained by sampling and subsequent determination of the ester concentration using UV spectrophotometry. A mathematical model was derived which permits a quantitative evaluation of salt effects in urea solutions. The theoretical calculations, based on this model, were found to be in good agreement with the experimental values observed for neutral and pH 1 solutions of methyl salicylate and methyl benzoate in urea. Extension of these findings to an earlier investigation indicates that significant error in interpretation of solubility in urea may result if these salt effects are disregarded.

Keyphrases ☐ Urea aqueous solutions—salt effects ☐ Methyl salicylate and benzoate solubility—urea–water mixture ☐ Electrolyte, HCl concentration effects—methyl salicylate and benzoate solubility ☐ UV spectrophotometry—analysis

The introduction of a fourth component into a urea–drug–water system will produce changes in both the physical and chemical properties of the system. Understandably, the inclination is to disregard or minimize the resultant effects, especially when the rationale of the investigation appears to be unaltered by doing so. However, it is imperative that some quantitative estimate be obtained before following this premise, since the magnitude of these effects may be large enough to require reassessment of the object of the experiment.

Work on systems involving urea–water mixtures are particularly prone to questionable assumptions. For example, during their study of the solubility of salicylic acid in urea solutions, various authors (1–3) sought to preclude ionization of the salicylic acid by making the solutions pH 1 with strong acid. In two instances, the workers made the solutions 0.1 *N* in H^+. Taking note of observed irregularities in this matter, however, Feldman and Gibaldi (1) were careful to adjust the pH of each solution to 1. These two different procedures result in systems that are not equivalent, a fact that may have been responsible for the differences in observations and conclusions. The strong acid which was added in these studies is certain to exhibit a characteristic influence on the solubility of any additional solutes. Whether this influence is significant and measurable in multicomponent mixtures of urea, water, drug, and salt is typical of the problem which should concern the investigator.

Wetlaufer *et al.* (4) demonstrated that salt effects do exist in urea solutions. These workers found that the solubility of skatole in aqueous urea–sodium chloride solutions was measurably less than in solutions of the same urea concentration but containing no sodium chloride. Additionally, it was estimated that this "salting out" approximated that observed when the solubility of skatole in water and in water–sodium chloride solution was compared. Thus, it would seem that the salt effects are not only measurable but also are relatively independent of the urea concentration. In that event, one is in a favorable position to quantify similar effects in urea solutions in general.

THEORETICAL CONSIDERATIONS

The phenomena of "salting in" and "salting out" have been described empirically by the Setschenow equation (5):

$$\log S^\circ/S = KC \qquad \text{(Eq. 1)}$$

where S° and S are the molar solubilities of a nonelectrolyte in pure water and in a solution containing C moles/l. of electrolyte, respectively. The symbol, K, is an empirical salt parameter, which is characteristic of both the electrolyte and nonelectrolyte species.

For the case of low nonelectrolyte concentration, it can be assumed that the interactions between the molecules of nonelectrolyte are minimal and may be disregarded (6). Equation 1 then becomes

$$\log S°/S = kC \qquad \text{(Eq. 2)}$$

where k is a salt parameter of considerably less complexity than K. Because of the relatively low solubilities of the drugs involved in the present study, as well as the availability of pertinent salt parameters in this form, it is convenient to use k rather than K. Mention is made of the more complex term, K, to emphasize the need for consideration of an alternative when the solubility of the drug or nonelectrolyte is proportionately greater.

The salt parameter, k, is often referred to as the "salting-out" constant. This may be misleading since the inference is that all electrolytes reduce the solubility of nonelectrolyte or drug species. Such is not the case. Referring to Eq. 2, it is seen that k is a salting-out constant if positive, but it becomes a salting-in constant if negative. Long and McDevit (6) compiled data which show that the magnitude and algebraic sign of k are determined by the nature of the electrolyte and nonelectrolyte. For solutions of benzoic acid, the salt constant is positive when the electrolyte is composed of small ions, and it becomes increasingly negative as the size of the ions increases. For example, in sodium chloride, $k = +0.18$; while in tetraethylammonium iodide, $k = -0.63$. On replacing benzoic acid with salicylic acid, the same constants decrease by approximately 0.01.

At this point it is apparent that the solubility of a sparingly soluble drug varies in a regular fashion with the concentration of added electrolyte. Furthermore, the magnitude of the solubility of the drug in electrolyte solution relative to that in pure water is indicative of the nature of the electrolyte. One might now ask whether a similar rationalization is possible when the solvent is a urea–water mixture. In this regard, findings of Wetlaufer *et al.* (4) hold some promise. On substitution into Eq. 2, their data yield a value of $k = 0.13$ for the solubility of skatole in pure water relative to that in a 0.15 M NaCl solution. This compares favorably with $k = 0.18$, obtained for the solubility of skatole in a 7 M urea solution relative to that in a solution of the same urea concentration but 0.15 M in sodium chloride as well. These results suggest that the solubilizing of the urea and the salting out of the sodium chloride may be additive effects.

PRESENT INVESTIGATION

An extension of these findings was undertaken in the present investigation. The solubility of methyl salicylate and of methyl benzoate was studied as a function of varying urea and hydrochloric acid concentrations in an attempt to identify and estimate the effect of added electrolyte on the solubility of these esters in urea–water mixtures. The work presupposes the establishment of two criteria upon which subsequent interpretations are dependent. First, the salt parameter, k, is a characteristic of a particular electrolyte, at least in the case where the solutes are electrolytes of similar structure. Second, the salt parameter is relatively independent of the urea concentration.

EXPERIMENTAL

The solubilities of methyl salicylate and methyl benzoate were studied as a function of urea concentration in both neutral solutions and solutions adjusted to pH 1. In addition, the solubility of methyl salicylate was studied as a function of urea concentration in solutions containing sodium chloride. The experimental uncertainty was estimated to be 1%.

Materials—Urea, reagent grade;[1] methyl salicylate, Eastman grade;[2] methyl benzoate, reagent grade;[3] hydrochloric acid, Baker analyzed reagent;[1] sodium chloride, reagent grade;[1] and methanol, absolute,[1] were used without further purification in this investigation.

Method—The neutral urea solutions, ranging in concentration from 0 to 5 M, were prepared in 25-ml. volumetric flasks by dissolving the appropriate amount of urea in distilled, deionized water and diluting to volume. The acidic urea solutions, also ranging in concentration from 0 to 5 M, required additional precautions. The desired amount of urea was placed in a 25-ml. beaker and dissolved in a minimum of water. Then, by using a Corning model 10 pH meter, the solution was adjusted to pH 1 with concentrated hydrochloric acid. Enough water and acid were added to bring the volume of the solution to approximately 22–23 ml. The solution was transferred to a 25-ml. volumetric flask, where the volume of the solution was adjusted to the mark using 1-ml. portions of a 0.1 N hydrochloric acid solution, each of which had previously been used to rinse the original beaker. A final check of the resulting solvent system showed no measurable change from pH 1. All urea solutions were prepared on the day of their use.

Each 25-ml. sample of urea solution was transferred to a 50-ml. glass-stoppered flask. One milliliter of the methyl ester was introduced using a pipet. This quantity assured ample excess. The flask and contents were then placed in a shaker bath, thermostated at 30 ± 0.2°, and allowed to equilibrate for 24 hr.

After the equilibration period, three 1-ml. samples of the clear supernatant were withdrawn from each flask by pipet. The pipets were equipped with a simple, cotton prefilter to exclude extraneous material and were preheated to ensure the continuous solubility of the ester within the sample. The samples were subsequently diluted to an appropriate volume, using a 1:10 water–methanol solvent mixture. The absorbance at 306 mμ for methyl salicylate or at 272 mμ for methyl benzoate was obtained with a Beckman DB-G spectrophotometer. The ester concentration was then obtained from a Beer's law plot. It had previously been determined that neither the acid nor the urea offered interference with the spectral measurements.

The work involving sodium chloride was handled in the same manner. Again, it was found that the salt offered no spectral interference.

pH of Urea–Water–HCl Mixtures—A 50-ml. sample of 8.0 M urea was transferred, by pipet, to a 100-ml. beaker which had been suspended in a bath thermostated at 30.0°. Electrodes from a Corning model 10 pH meter were then positioned so that contact was made with the urea solution in the beaker. Constant boiling hydrochloric acid, 20.248% by weight, was introduced in a stepwise fashion from a 50-ml. buret. The quantities of acid required for the mixture to reach pH values of 3.0, 2.5, 2.0, 1.5, and 1.0 were re-

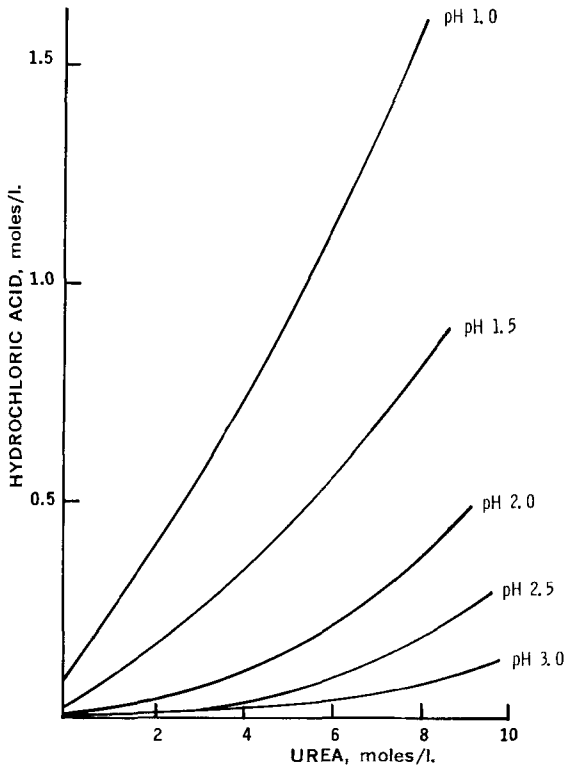

Figure 1—*pH of aqueous solutions containing both urea and hydrochloric acid.*

[1] Baker Chemical Co., Phillipsburg, N. J.
[2] Eastman Organic Chemicals, Rochester, N. Y.
[3] Fisher Scientific Co., Pittsburgh, Pa.

Table I—Solubility of Methyl Salicylate in 1.5 *M* Sodium Chloride Solutions of Varying Urea Concentration at 30°

Urea Concentration, *M*	Solubility, mg./ml.	Salt Parameter, *k*
0	0.46	0.20
3	0.90	0.18
4	1.06	0.18
5	1.29	0.16

corded. The molar concentration of urea and of HCl at each of these pH values was calculated by assuming ideal additivity of the volumes of mixture and added titrant. The entire procedure was repeated for 1.0, 4.0, and 6.0 *M* urea solutions.

RESULTS AND DISCUSSION

This work may be viewed as the result of three successive determinations, each of which was dependent upon the preceding. Initially, it was necessary to establish the fact that a characteristic salt effect was identifiable and would yield quantitative results in solutions of varying urea concentration. The solubility of methyl salicylate in solutions of urea and sodium chloride was studied for this purpose. A parameter was then derived that represented the salt effects influencing the solubility of methyl salicylate in solutions of urea and hydrochloric acid. Finally, predictions based on the proposed model were compared with the experimental values observed for the solubility of methyl benzoate, also in solutions of urea and hydrochloric acid.

Methyl Salicylate–Urea–Sodium Chloride—The existence of measurable and predictable salt effects was verified by determining the solubility of methyl salicylate in solutions that were 1.5 *M* in sodium chloride but which contained varying concentrations of urea. This high concentration of sodium chloride represents an upper limit of the ionic strength in the hydrochloric acid–urea solutions shown in Fig. 1. At the same time, it provides data which may serve as an indication of the limit to which meaningful quantitative relationships may be extended.

Table I gives the observed solubility of methyl salicylate in aqueous systems of the indicated composition, as well as the salt

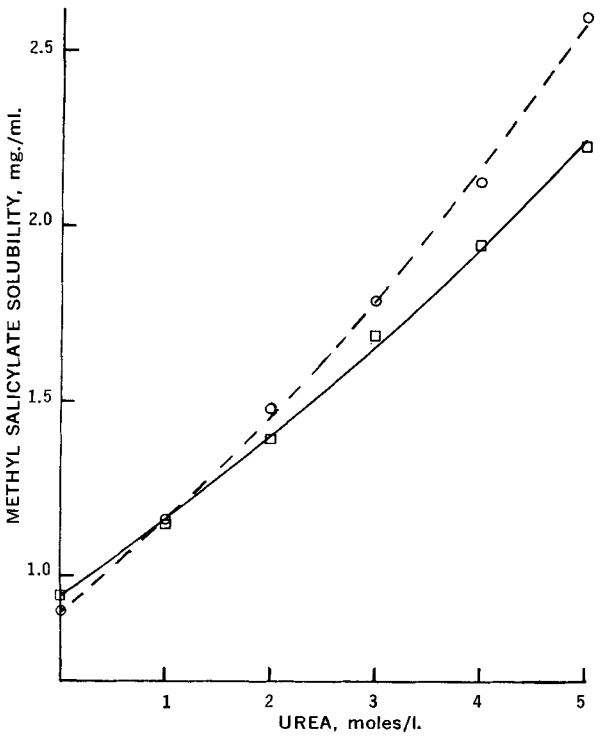

Figure 2—*Solubility of methyl salicylate in solutions of urea. Key: □, experimental points determined in neutral media; ○, experimental points determined at pH 1; ——, plot of Eq. 5; and - - -, plot of Eq. 6.*

Table II—Solubility of Methyl Salicylate and Methyl Benzoate in Solutions of Urea at 30°

Ester	Molar Concentration of Urea 0	1	2	3	4	5
	Ester Solubility, mg./ml.					
Methyl salicylate (neutral media)	0.95	1.15	1.39	1.69	1.95	2.23
Methyl salicylate (pH 1)	0.88	1.16	1.48	1.79	2.13	2.60
Methyl benzoate (neutral media)	2.42	2.90	3.34	3.75	4.30	4.88
Methyl benzoate (pH 1)	2.16	2.68	3.20	3.90	4.62	5.42

parameters for sodium chloride in each system. The latter were calculated according to Eq. 2 by comparing the solubilities of the ester in solutions of like urea concentration.

Thus, for example,

$$\log \frac{\text{solubility of drug in 5 } M \text{ urea}}{\text{solubility of drug in 5 } M \text{ urea} + 1.5 \text{ } M \text{ NaCl}} = kC \quad \text{(Eq. 3)}$$

where the denominator of the log term is the solubility of methyl salicylate in the urea–salt solutions as given in Table I. The numerator is the solubility of methyl salicylate in solutions of urea alone and may be found in Table II. The salt concentration, *C*, is 1.5 in all cases.

The results shown in Table I establish the criteria necessary for continued effort on the overall problem. The salt parameter for sodium chloride in these solutions agrees well with the value cited earlier (6) with regard to the effect of this salt on the aqueous solubility of salicylic acid. In view of the high concentration of salt used in the present work, the agreement is excellent. Additionally, the parameter is in fair agreement with the value calculated in connection with the solubility of skatole (1). This is as expected, since skatole bears some structural resemblance to methyl salicylate. Furthermore, the salt parameter appears to be only slightly dependent on the urea concentration. Presumably, even this small dependence will vanish at lower salt concentrations, where the change in sodium chloride activity with urea concentration decreases (7).

From the foregoing, it must be concluded that the solubility of a drug in urea–water systems containing electrolyte relative to that in electrolyte-free solutions may be approximated in a quantitative fashion. This, in turn, assumes prior knowledge of the sign and magnitude of the salt parameter and a realization that the predictions are less valid at high salt and high urea concentrations. The effects under consideration are not those by which urea–solute or urea–solvent interactions alter drug solubility, but are simply those which are presumed to result from the presence of electrolyte species.

Methyl Salicylate–Urea–Hydrochloric Acid—In contrast to the work already discussed, the solubility of methyl salicylate in urea solutions at pH 1 presents an interesting complication. Unlike the obviously consistent and predictable effect produced by adding sodium chloride, Fig. 2 suggests the salt effect of hydrochloric acid is strongly dependent on the urea concentration. In the absence of urea, hydrochloric acid salts out the ester. Then, as the urea concentration is increased, a salting in appears, which offsets the initial effect and soon predominates. As seen from Fig. 1, the concentration of hydrochloric acid is increasing along with that of the urea. This suggests the possiblity of a relationship between the increasing salt effect and the increasing acid concentration. However, a direct correlation seems impractical since hydrochloric acid characteristically salts out benzoic acid derivatives (6), and the addition of more acid should further decrease the solubility of the methyl salicylate. The answer to this paradox rests with observations that these solutions may contain another species in addition to the obvious components.

Consider, first, the fact that the solubility of methyl salicylate increases with additional acid and urea. In terms of the earlier discussion, this phenomenon results when the ions of the added electrolyte are large. Although one might regard the hydronium ion and its associated waters of hydration as being large, an explanation of the enhanced solubility on the basis of additional hydrochloric acid is out of the question. The results of this investigation, as well as those cited from other workers, have shown that this acid definitely salts out the ester.

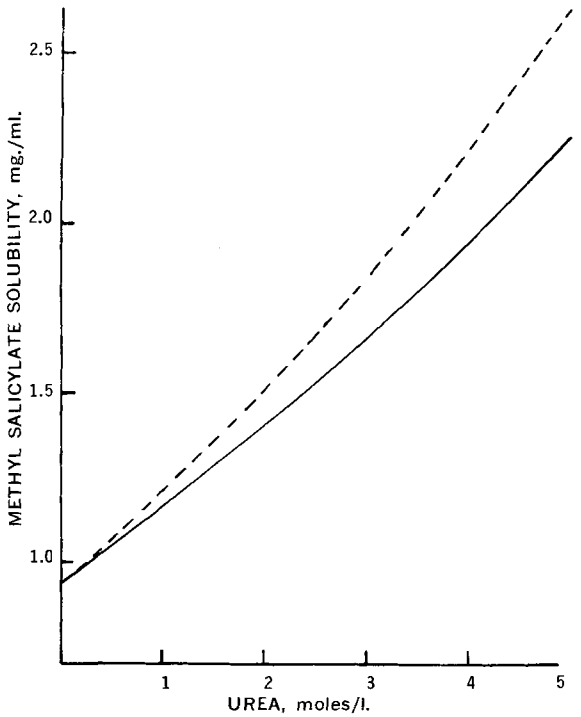

Figure 3—*Solubility of methyl salicylate in solutions of urea adjusted so as to exclude the salting out of the hydrochloric acid. Key:* ——, *plot of Eq. 5; and* - - -, *plot of Eq. 7.*

Second, the activity of the hydrochloric acid is drastically reduced in urea solutions, as implied from Fig. 1. Of the explanations for this particular phenomenon, the formation of some proton–urea complex seems the more feasible at the present time. Thus, Bull *et al.* (8) studied the conductance of hydrochloric acid in aqueous solutions of urea. Their findings suggest the existence of an electrolyte species that is considerably less mobile, and presumably bulkier, than the proton. This view has been supported by spectral (9) and dilatometric (10) evidence, as well. In essence, these workers have described an electrolyte species which is capable of salting in.

By assuming this interaction to be a fact, it becomes possible to rationalize the conditions that account for the observed ester solubilities in acid media. For example, consider an aqueous solution saturated with respect to methyl salicylate at pH 1. The concentration of ester in this solution is approximately 0.05 mg./ml. less than it would be in neutral media because of the salting out caused by the nearly 0.1 *M* concentration of hydrochloric acid. If this solution is made 5 *M* in urea, Fig. 1 shows that the hydrochloric acid concentration must be increased to 0.90 *M* to maintain the pH at 1. At the same time, the concentration of methyl salicylate increases to 2.60 mg./ml. Since the pH is 1, the activity of the hydrochloric acid must, likewise, remain at 0.1 *M*, as in the original solution. As a result, the new solution is 0.8 *M* in a species which is not contributing to the acidity *per se*. This is the quantity of hydrochloric acid that has interacted with the urea to form the larger, salting-in species. In that event, the concentration of unreacted or pure urea has decreased to 4.2 *M*. Thus, the final solution may be described as being 0.1 *M* in acid, 4.2 *M* in urea, and 0.8 *M* in the complex and containing 2.60 mg./ml. of methyl salicylate.

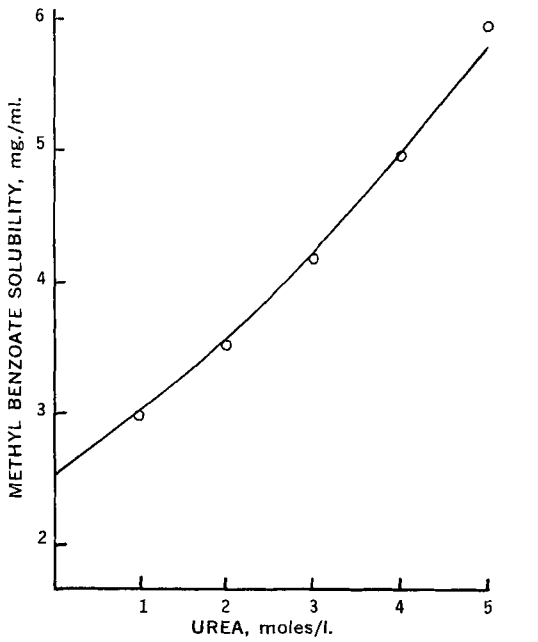

Figure 4—*Solubility of methyl benzoate in solutions of urea containing the hydrochloric acid–urea complex. Key:* O, *values calculated according to Eq. 2; and* ——, *plot of Eq. 11.*

The use of the term "complex" to define the acid–urea interaction product does not necessarily imply that the authors advocate complex formation in the customary sense. The exact nature of the interaction is uncertain and open to conjecture. Use of the term is simply an expediency, which will be employed throughout the remainder of this report. Additionally, it appears that the authors have tacitly assumed a relatively simple relationship between the observed pH values and the corresponding concentrations of the electrolytes in each solution. Unfortunately, such a relationship is inaccurate. However, since the final conclusion is unaffected by this assumption, it was decided to utilize this approach to simplify the discussion.

Salt Parameter for the Complex—A straightforward calculation of a salt parameter for the complex was precluded by the presence of a second salt, namely, the "unreacted" hydrochloric acid. This situation is simplified considerably if the data are adjusted so as to exclude the salting-out effect of the hydrochloric acid. An attempt was made to quantify this effect, using the data of both the methyl salicylate and methyl benzoate solubilities at pH 1. The adjustments proved to be unduly complicated; in view of the associated experimental uncertainties, the attempt was abandoned in favor of a more direct but approximate procedure. Since the activity of the acid is presumed to be constant by virtue of maintaining the pH at 1, and in view of the findings with regard to the initial study on the salt effects at constant sodium chloride concentration, it was assumed that the salting-out effect of the hydrochloric acid was the same over the entire range of urea concentrations studied. Thus, in equation form, the assumption was

$$\log S^\circ/S^* = \text{constant} \qquad \text{(Eq. 4)}$$

where S° is the solubility of ester in neutral media; and S^* is the solubility of ester in a hypothetical solution containing water, urea, and the acidic form of the hydrochloric acid only. The error introduced is minimized by the fact that the salting-out effect is, in addition, relatively small. Using a parameter of 0.1 (4), the constant in Eq. 4 becomes 0.01. This particular value is not derivable from the present data, but it does reflect the magnitude of the effect.

The actual adjustment is illustrated in Fig. 3. The dashed curve in Fig. 2, which represents the solubilities of methyl salicylate at pH 1, has been shifted upward so that its intercept now corresponds with that of the solid curve, representing the solubilities in neutral media. In effect, this cancels the salting out of the "acidic" hydrochloric acid.

The use of empirical equations presents a more quantitative view of the procedure. Equations 5 and 6 are the result of a least-squares treatment of the data in Table II and represent the solubilities of methyl salicylate, S, as functions of urea concentration, U, in neutral media and at pH 1, respectively.

$$S = 0.94 + 0.211\,U + 0.010\,U^2 \qquad \text{(Eq. 5)}$$

$$S = 0.89 + 0.247\,U + 0.018\,U^2 \qquad \text{(Eq. 6)}$$

If the curve is shifted upward, Eq. 6 becomes

$$S = 0.94 + 0.247\,U + 0.018\,U^2 \qquad \text{(Eq. 7)}$$

and, to a good approximation, represents the solubility of methyl salicylate in urea solutions that contain the acid–urea complex only.

The salt parameter for the complex may be determined by using the appropriate values obtained from Eqs. 5 and 7 and Fig. 1. The variables used in Eq. 2 are defined as: S = the solubility of methyl salicylate in a solution containing U moles/l. of urea and C moles/l. of the complex; C = the molar concentration of the complex, found by subtracting 0.1 M from the concentration of hydrochloric acid in a U M urea solution at pH 1; and $S°$ = the solubility of methyl salicylate in neutral media containing U' moles/l. of unreacted urea, where $U' = (U - C)$.

As an example, consider the solubility of methyl salicylate in 5 M urea at pH 1. It was shown earlier that this solution, while 5 M in total urea, is only 4.20 M in unreacted urea. Substitution of the latter value in Eq. 5 gives $S° = 2.01$ mg./ml. Using 5 M in Eq. 7, one finds $S = 2.63$ mg./ml. Since the solution is presumably 0.80 M in the complex, Eq. 2 becomes

$$\log 2.01/2.63 = 0.80\,k \qquad \text{(Eq. 8)}$$

A similar treatment also was applied to solutions 1, 2, 3, and 4 M in urea. The pertinent data are listed in Table III. Subsequently, a value of $k = -0.160$ was determined from the slope of a log $S°/S$ *versus* C plot.

Methyl Benzoate–Urea–Hydrochloric Acid—The basic premise of this paper may now be tested by using the salt parameter for the complex to predict analagous effects on the solubility of other nonelectrolyte solutes. The methyl benzoate solubility data, given in Table II, were used for this purpose. In neutral media and at pH 1, respectively, these data may be represented as

$$S = 2.52 + 0.295\,U + 0.038\,U^2 \qquad \text{(Eq. 9)}$$

$$S = 2.16 + 0.457\,U + 0.039\,U^2 \qquad \text{(Eq. 10)}$$

On shifting the intercept, as is done with the data on methyl salicylate to exclude the salting out of the acidic hydrochloric acid, Eq. 10 becomes

$$S = 2.52 + 0.457\,U + 0.039\,U^2 \qquad \text{(Eq. 11)}$$

If the proposed method is correct, it should be possible to calculate solubility data at pH 1, given data in neutral media and the necessary parameters for Eq. 2. In a like manner, the data in neutral media may be determined from those at pH 1. As an example, assume that the solubilities of methyl benzoate in neutral urea solutions are known and that the data at pH 1 are desired. The procedure is to (*a*) calculate the product k C, using the value $k = -0.160$ and the appropriate C; (*b*) determine $S°$, using the corresponding U' and Eq. 9; and (*c*) calculate S, using Eq. 2. For purposes of illustration, it is convenient to use the values for C and U' given in Table III. Thus, at $U' = 4.20$, $S°$ is found to be 4.43 mg./ml. and C is 0.80. On substitution, Eq. 2 becomes

$$\log 4.43/S = (-0.160)\,(0.80) \qquad \text{(Eq. 12)}$$

from which the solubility of methyl benzoate in a 5 M urea solution at pH 1, S, is calculated to be 5.95 mg./ml. Five such values were derived and are indicated by circles in Fig. 4. For comparison, the figure includes a curve representing Eq. 11. The agreement is excellent and attests to the validity of the proposed concepts.

An interesting situation becomes evident when these findings are extended to an earlier investigation reported by Feldman and Gibaldi (1). These workers determined the thermodynamic changes associated with the solution of salicylic and benzoic acids in urea solutions at pH 1. Their results are based on a direct application of solubility data, without regard for the salting-in effects suggested in the present study. As such, the calculated free energy changes are probably too high, and actually represent a composite of the salting-in and urea–water effects. By way of comparison, the parameters previously outlined indicate that the free energy values derived by Feldman and Gibaldi for their 3 M urea systems should be reduced by 110 cal./mole. In turn, this would require an adjustment of the observed entropy changes. On the average, these alterations would represent approximately 25% of the reported values.

pH of Urea–Water Solutions—Figure 1 is a composite of the results obtained by titrating various urea solutions with concentrated hydrochloric acid, according to the procedure outlined in the *Experimental* section. The data at pH 1 were used in the present investigation. The additional values are included for informational purposes only. It is not presumed that this figure represents other than a good approximation. The observations are similar to those described by Bull *et al.* (8), except that the current data were obtained for much higher acid concentrations.

Table III—Data Employed in Calculation of the Salt Parameter, k

Total Urea, M (U)	Complexed Urea, M (C)	Free Urea, M (U')	Solubility of Methyl Salicylate, mg./ml.: Complex-Free Solution ($S°$)	Solubility of Methyl Salicylate, mg./ml.: In Presence of Complex (S)	$-\log S°/S$
1	0.16	0.84	1.13	1.21	0.030
2	0.31	1.69	1.33	1.50	0.052
3	0.47	2.53	1.54	1.84	0.077
4	0.63	3.37	1.76	2.22	0.102
5	0.80	4.20	2.01	2.63	0.118

A problem in interpretation arises with the realization that these are not actually pH values. With a change in solvent from water to a urea–water mixture, the term pH loses its meaning, and there is no assurance that a pH meter is indicating hydrogen-ion activity. As a result, there are additional uncertainties in the assumptions made earlier with regard to the concentration of "free" or uncomplexed HCl. None of these uncertainties, however, greatly affects the findings of this investigation.

The determination of actual hydrogen-ion activities is beyond the scope of the present work. Nevertheless it is still possible to estimate the effect of changing solvents by using a modification of the Born equation (11). On substituting the appropriate dielectric constants, one finds that a 1-mv. change in potential may be expected on transferring a 1–1 electrolyte of given activity from water to a solvent having the dielectric constant of a 5 M urea solution. This is, admittedly, an oversimplification of a complex problem, but the treatment should convey the magnitude of the effect. In relation to the practice of equating pH and concentration, the effect would seem to be negligible.

While it would be desirable from the standpoint of establishing a more accurate value for the salt parameter, k, a precise knowledge of the "free" HCl concentration is unnecessary for the present purpose. In the final analysis, the term log $S°/S$ relates the ester solubilities in HCl–urea solutions. Through the relationship $S° = f(U—C)$, this term is found to be somewhat insensitive to variations in the concentration of uncomplexed acid. For example, a 25% error in "free" acid concentration produces only a 5% error in log $S°/S$ in 1 M urea. This is considerably smaller than the potential error if the salt effect is disregarded completely. In view of the results, it appears that the approximation, pH = "free" acid concentration, is reasonable. It is by no means precise. A more precise analysis will depend on a quantitative evaluation of the activity coefficients as a function of ionic strength and solvent composition.

CONCLUSION

It is well to emphasize that the model proposed in this paper is speculative. To indicate otherwise would presuppose intimate knowledge of a solvent system which is, to say the least, complex and little understood. The treatment, of necessity, is based on circumstantial evidence. However, the high degree of self-consistency within the model cannot be denied, and it would seem that any real judgment against it must await additional evidence. At this time, there appears to be little reason why a similar analysis cannot be applied to any aqueous urea solution, provided, of course, that the characteristic salt constant is known or determined.

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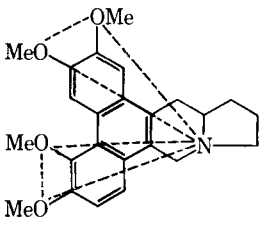
Common Receptor-Complement Feature among Some Antileukemic Compounds

KWANG-YUEN ZEE-CHENG and C. C. CHENG

Abstract □ A common structural feature was found among some nonalkylating antileukemic agents such as aminopterin, anthramycin, 5-azacytidine, bisketopiperazines, camptothecin, cytosine arabinoside, daunomycin, demecolcine, emetine, glutarimide antibiotics, harringtonine, 6-mercaptopurine riboside, methotrexate, sangivamycin, streptonigrin, tylocrebrine, tylophorine, vinblastine, and vincristine. This structural feature consists of a triangulation composed of one nitrogen and two oxygen atoms with rather definite interatomic distances. This structural characteristic may contribute to the *in vivo* binding to one of the pertinent receptor sites involved in leukemia geneses.

Keyphrases □ Antileukemic compounds—common receptor complement □ Structural similarity, antileukemic agents—triangular pattern, nitrogen, oxygen atoms □ Oxygen, nitrogen pattern, interatomic distances—antileukemic activity

In connection with structure–activity studies of various oncolytic agents, a common structural feature was noted among a number of antileukemic agents. The purpose of this paper is to present a preliminary account of this observation.



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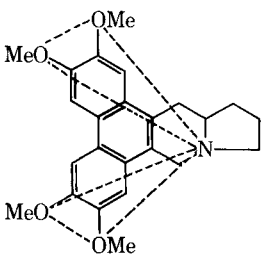

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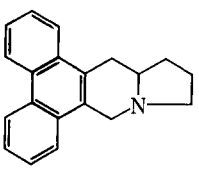

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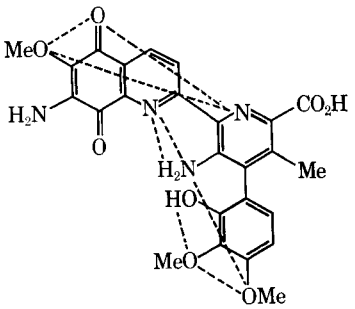

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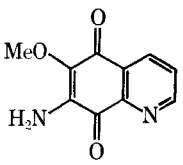
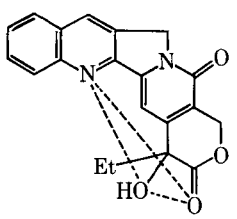


V

THEORETICAL

The tylophora alkaloids (1), tylocrebrine (I) and tylophorine (II), were found to possess antileukemic activity against leukemia L-1210 in mice (2). The nucleus of these alkaloids, phenanthro-[9,10:6′,7′]indolizidine (III) (3), however, is devoid of the activity (4) exhibited by the polysubstituted methoxy derivatives.

The antibiotic streptonigrin (IV), the structure of which contains an *o*-aminoquinone unit (5), exhibits a broad spectrum of inhibitory activity against a number of leukemias, lymphomas, carcinomas, and other tumor systems (6–13). Although the *o*-aminoquinone unit is also present (5) in two other types of antitumor antibiotics (mitomycin C and actinomycin D, for example), a synthetic compound, 7-amino-6-methoxy-5,8-quinolinedione (V) (14), which possesses a partial structure of this antibiotic in that it contains the *o*-aminoquinone unit, failed to retain the original antileukemic activity.[1]



VI

[1] Test results were provided by Dr. Harry B. Wood and Robert B. Ing of the Cancer Chemotherapy National Service Center, National Cancer Institute, U. S. Public Health Service.