Effect of Urea on Solubility

Role of Water Structure

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The solubilities of benzoic and salicylic acid in aqueous urea, methylurea, and 1,3-dimethylurea solutions were studied. From a thermodynamic transfer model, the free energy, enthalpy, and entropy of solution were determined. By virtue of the fact that the solubilization process was nearly athermal and by the magnitude of the free energy and entropy values obtained, it was concluded that the enhanced solubilization of benzoic and salicylic acid in urea and alkylurea solutions did not involve complexation. The effect of urea on water structure and hydrophobic bonding was considered. By examination of the literature and analysis of the data obtained from this investigation it was proposed that urea, methylurea, and 1,3-dimethylurea solubilized benzoic and salicylic acids by "breaking up" water clusters surrounding the nonpolar molecule, increasing the entropy of the system, and producing a "driving" force for the solubilization. It was found that the alkyl substituted ureas, methyl- and 1,3-dimethylurea, produced a greater increase in solubility than urea, with 1,3-dimethylurea having the greater effect upon the solubility of the aromatic acids. It was noted that the urea and the alkylureas had the greatest solubilization effect on the more hydrophobic molecule, salicylic acid. A discussion of the solubilizing effect of urea on the aromatic acids is presented.

IT HAS BEEN reported that the presence of urea increases the water solubility of benzoic and the hydroxybenzoic acids (1, 2). Bolton (1) and Altwein *et al.* (2) studied the effect of urea on the solubilization of benzoic and salicylic acids. Altwein and co-workers (2) concluded that the interaction of urea with salicylic acid was a complex interaction but was definitely a "complexation" even though "urea possesses low complexing ability."

Bolton (1) termed the "interaction" of urea with salicylic and benzoic acids a complexation and calculated approximate stability constants (K_s), on the basis of a 1:1 interaction, of 0.2 for the urea–benzoic acid system and 0.3 for the urea–salicylic acid system.

These values are considerably lower than stability constant values of complexations which have been reported in the literature (3). Literature values have ranged from about $K_{1:1} = 2.0$ for salicylic acid and substituted amides to $K_{1:1} = 44$ for the complexation between salicylic acid and caffeine (3). Benzoic acid has yielded corresponding values for similar interactions (3).

The unusual thermodynamic data reported for urea–benzoic acid and urea–salicylic acid raises some doubt as to the mechanism of this solubilization. It was therefore of interest to consider the phenomenon in terms of the general properties of urea solutions. To appreciate fully the complex properties of aqueous solutions of urea, a discussion of water structure is in order.

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THEORETICAL ASPECTS

Water Structure and the Effect of Urea—Water, as ice, exists in an open structure consisting of tetrahedral hydrogen bonds between water molecules in three dimensions (4). When ice melts there still remains a high degree of hydrogen bonding in the resulting liquid. The hydrogen bonded water molecules take the form of "clusters" which are nearly spherical in shape (4). Therefore, there exist in liquid water two types of water molecules: (*a*) the free or unbonded water molecule; and (*b*) the clusters of hydrogen bonded water.

When nonpolar solutes dissolve in water, they increase the ordering of water molecules around them (5). It was from this model that the concept of "icebergs" or water molecule clusters, forming about nonpolar solutes, was evolved. Essentially, the nonpolar solute becomes associated with the tetrahedral water molecules and becomes its fifth neighbor through van der Waals interactions. The water cluster forms a partial cage around the hydrocarbon. Since there is greater stability in this penta-coordinated state, more molecules will occupy lower energy levels, promoting more hydrogen bonding and an ordering effect on the solvent (4). This process is known as *hydrophobic hydration* and is accompanied by a small decrease in enthalpy, a large decrease in entropy, and a resulting large positive free energy of the system.

An opposite effect is achieved when nonpolar moieties or residues associate in the presence of water. This phenomenon is termed *hydrophobic bonding*. The formation of the hydrophobic bond will involve a decrease in the ordering of the system since the "ice-like" regions between the nonpolar residues become partially melted as the residues come together. Therefore, there will be an increase in the entropy of the system, a small positive enthalpy, and a free energy of from -0.2 to -1.5 Kcal./mole. Hydrophobic bonding, from a mechanistic point of view, actually places a limitation on the solubility of nonpolar compounds in water. The hydrophobic interaction, which is "driven" by entropic contributions, would tend to "pull"

hydrocarbons out of solution, and is responsible for the low water solubility manifested by nonpolar compounds.

It is widely held that urea has the ability to reduce hydrophobic bonding (5–7). This effect has been ascribed to the unusual capacity of urea for "breaking up" the icebergs in liquid water. Urea becomes associated with the structured water by hydrogen bonding and takes an active part in the formation of a more open "lattice" structure (8). The increase in entropy gained by "disruption" of water structure by urea makes the association of nonpolar molecules by hydrophobic bonding thermodynamically less favorable, and there is an increase in water solubility of the nonpolar compound.

Mukerjee and Ghosh (6) have shown that urea effectively reduces the degree of self-association of methylene blue in aqueous solution, thereby increasing its water solubility. Katayama *et al.* (9) showed the effect of urea on the aqueous solubility of a series of azo-dyes. They noted that urea had a more pronounced effect on the solubility of those compounds having the larger "hydrophobic surface."

Abu-Hamdiyyah (8) proposed that urea participated in the formation of "mixed" clusters in aqueous solution. The "mixed" clusters were found to be less thermally stable than pure water clusters, indicating a higher enthalpy in the aqueous urea solutions and an entropic driving force for the spontaneous transfer of nonpolar solutes from pure water to aqueous urea solutions (10). The increase in entropy was attributed to the "increase in the number of available cavities or interstices for the solute molecules in aqueous urea solutions."

Abu-Hamdiyyah (8) also predicted, on the basis of the above conclusions, the effect of alkyl-substituted ureas on the strength of the hydrophobic bond. He stated that (*a*) an alkylurea derivative would have a decreased ability to hydrogen bond with water compared to the ability of urea itself, thereby decreasing the ability of the urea derivative to participate in cluster formation, and (*b*) the alkyl groups themselves could only be accommodated in the cavities produced in the aqueous solution, resulting in a decrease in the number of cavities available for the nonpolar compound. He concluded that alkyl substituted ureas would have a minimal effect on hydrophobic bonding as compared to urea.

Thermodynamic Considerations—When considering the process where a compound is transferred from water to urea solution, the following equation may be written (5, 9):

compd. in water (mole fraction N_0) $\rightarrow$
compd. in urea solution (mole fraction N) (Eq. 1)

The ratio of the mole fractions N/N_0, may be considered as a partitioning ratio since it involves the distribution of the compound between two phases, the water phase and the urea solution phase.

In this case the free energy of partitioning (ΔF) may be determined from the following expression (9):

$$\Delta F = -2.3\,RT \log (N/N_0) \qquad \text{(Eq. 2)}$$

The enthalpy of partitioning (ΔH) can be determined from the following relationship, which represents a modification of the van't Hoff equation (9, 11):

$$\frac{d \ln (N/N_0)}{dT} = \frac{\Delta H}{RT^2} \qquad \text{(Eq. 3)}$$

Rearranging to solve for ΔH;

$$\Delta H = -2.3R\,[d \log (N/N_0)/d(1/T)] \qquad \text{(Eq. 4)}$$

From this equation it can be seen that a plot of log (N/N_0) *versus* $1/T$ for each urea concentration would result in a straight line with a slope equal to $-\Delta H/2.3R$, providing ΔH remains reasonably constant over the temperature range studied. The change in entropy (ΔS) associated with this process can be determined by use of the following equation (9):

$$\Delta S = \frac{\Delta H - \Delta F}{T} \qquad \text{(Eq. 5)}$$

EXPERIMENTAL

Materials—The benzoic acid (m.p. 122°), salicylic acid (m.p. 159°), and urea (m.p. 132°) used in this study were Fisher certified reagent grade. Methylurea (m.p. 101°) and 1,3-dimethylurea (m.p. 107°) were obtained from Eastman Kodak. The purity of each drug was determined by melting point analysis and determination of ultraviolet spectra.

Assay Procedures—Beer's law plots were obtained for benzoic and salicylic acid by diluting aliquot portions of standard solutions of each drug with 0.1 *N* HCl–anhydrous methanol (1:10) solution.

Absorbance was determined by means of a Beckman DB recording spectrophotometer at the 272 mμ peak for benzoic acid and the 304 mμ peak for salicylic acid. Absorbance *versus* concentration plots were then constructed, and the slope was determined by the method of least squares.

Possible interference with the assay procedure was determined by adding various quantities of 3 *M* urea or urea derivative to known concentrations of each drug. No shifts in absorbance maxima and no alterations in absorbance values were noted.

Solubility Determinations—Initial solubility studies were conducted according to the methods of Altwein *et al.* (2). After encountering significant experimental difficulties, which are discussed in a subsequent section of this report, the following methodology was adopted.

The quantity of urea, methylurea, or 1,3-dimethylurea needed to produce a given volume of 3 *M* solution was carefully weighed out on a Mettler balance (model H15). The urea was then dissolved in a minimum amount of water. The pH of the solution was adjusted to pH 1 with concentrated HCl to suppress ionization of the acid species. All pH measurements were recorded by means of a Beckman Zeromatic pH meter. The solution was then transferred to a suitable volumetric flask and brought to volume with 0.1 *N* HCl.

Solutions of urea or urea derivative ranging from 0 to 3 *M*, at half-molar intervals, were prepared in 25-mm. screw cap culture tubes, by adding an appropriate amount of 3 *M* urea solution and sufficient 0.1 *N* HCl to bring the total volume to 10 ml.

A sufficient amount of drug (benzoic acid, 0.5 Gm.; salicylic acid, 0.6 Gm.) was added to each tube to insure an excess at equilibrium. The

mouth of each tube was covered with aluminum foil and capped to prevent evaporation.

The samples were equilibrated in a Metabolyte water bath shaker[1] at temperatures of 30°, 33°, 40°, and 45° and in a Gyrotory incubator shaker model G-25[1] at 37° for periods not less than 12 or more than 18 hr. Equilibrium was determined by repetitive sampling.

Before the tubes were to be sampled, the shaker was turned off to allow the excess solid material to settle. The liquid was then filtered through a Millipore[2] filter (0.45 μ pore size) to insure that no solid particles were present in the sample. To eliminate any variation due to a temperature differential, the filtration and sampling equipment were maintained at the same temperature as that of the equilibrium study.

One milliliter of sample was withdrawn from the filtrate and was diluted to 10 ml. with acidified methanol (1 ml. 0.1 *N* HCl to 100 ml. anhydrous methanol). All subsequent dilutions were made with 0.1 *N* HCl–acidified methanol (1:10). The absorbance of each solution was determined and the drug concentration was calculated from the absorbance values by use of the Beer's law plots.

RESULTS AND DISCUSSION

The initial solubility studies, using the method of Altwein *et al.* (2), involved equilibrating the drug in stock solutions of urea prepared in 0.1 *N* HCl. However, this approach led to a number of unusual findings. The pH values of 1 to 5 *M* urea solutions prepared in this manner were then checked to determine whether a substantial difference in pH existed between samples. Values ranged from pH 1.45 in 1 *M* urea to pH 2.40 at a 5 *M* urea concentration. The increase in pH of 0.1 *N* HCl solution as a function of urea concentration is apparently due to the presence of impurities in the urea, since urea itself is too weak a base to produce these effects. Bull *et al.* (12) have reported that even recrystallized urea contains small amounts of ammonium cyanate present in sufficient quantity to elevate the pH of HCl solutions. The effect of increasing pH on the solubility of benzoic and salicylic acids is quite significant in view of the fact that the greater the degree of ionization, the greater the solubility.

The procedures described under *Experimental* were adopted to overcome these difficulties. At each urea concentration, sufficient HCl was added to insure that essentially all the benzoic or salicylic acid in solution existed in the undissociated form. Under these experimental conditions little degradation of urea will occur (13). In addition, the ionic strength of these solutions was sufficiently high so that the small ionic contamination in the urea sample should have little effect on the solubility data.

Each drug was equilibrated with urea and methylurea at 30°, 37°, and 45° and with 1,3-dimethylurea at 30°. The N/N_0 ratios were determined from the base solubility of each drug (N_0) and the corresponding solubility in urea (N) solution. The solubility curves in mg./ml. of drug *versus* molarity of urea for each drug and urea derivative at the temperatures studied are represented by Figs. 1–4. Solubility data are also tabulated in Tables I and II. It can be seen from the graphs that the solubility of benzoic and salicylic acid is a linear function of urea concentration. The plots of solubility of drug *versus* moles of urea derivative for methylurea show curvature. Similar plots were observed for 1,3-dimethylurea at 30°. In each case the solubility of both drugs is increased significantly

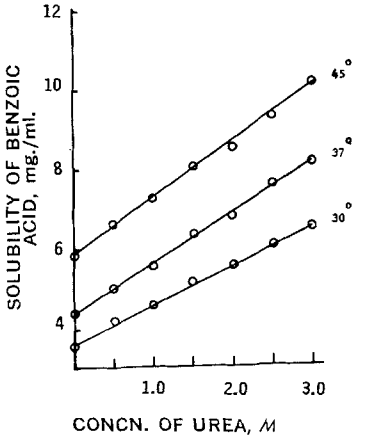

Fig. 1—Solubility of benzoic acid as a function of urea concentration.

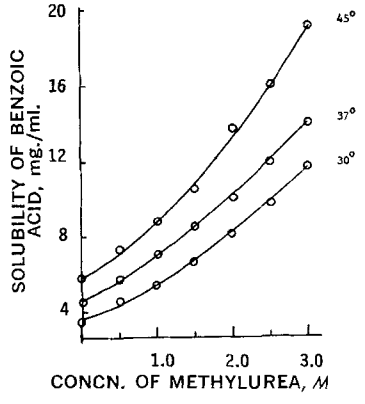

Fig 2—Solubility of benzoic acid as a function of methylurea concentration.

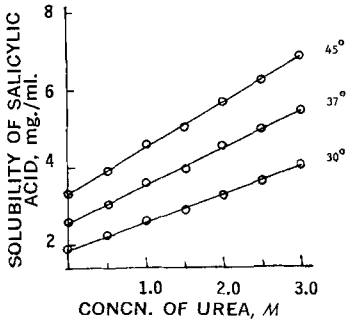

Fig. 3—Solubility of salicylic acid as a function of urea concentration.

[1] New Brunswick Scientific Corp., New Brunswick, N. J.
[2] Millipore Filter Corp., Bedford, Mass.

by the addition of urea or urea derivative to the aqueous solutions. For each drug the order of effectiveness of the urea derivatives as solubilizers decreased in the following manner: 1,3-dimethylurea > methylurea > urea. Comparative solubility plots of benzoic and salicylic acid at 30° as a function of urea derivative are presented in Figs. 5 and 6.

To determine the enthalpic contribution to the dissolution process, log N/N_0 values of salicylic and benzoic acid for each concentration of urea and methylurea between 0.5 and 3.0 M were plotted *versus* $1/T$. The slope of each plot was determined by the method of least squares and the ΔH calculated. The change in enthalpy was found to be exceedingly small, in the order of ±100 cal. The random nature of the results, however, prevented a definitive statement as to whether the process was endothermic, exothermic, or athermal. The variation in ΔH from concentration to concentration showed no trend and appeared to involve a random error.

In an attempt to refine the data, solubility determinations of each drug were carried out in 2 M solutions of urea and methylurea at 33° and 41°,

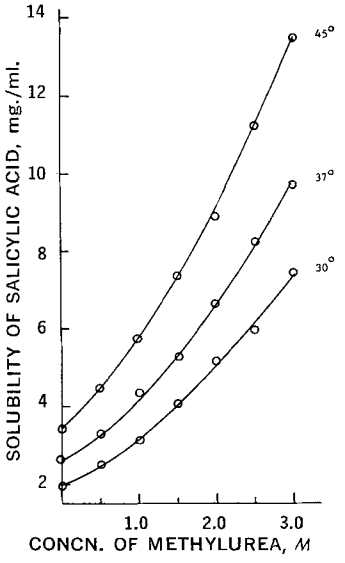

Fig. 4—Solubility of salicylic acid as a function of methylurea concentration.

TABLE I—SOLUBILITY OF BENZOIC ACID AS A FUNCTION OF UREA CONCENTRATION AND TEMPERATURE

	Solubility of Benzoic Acid, mg./ml.		
	30°	37°	45°
Urea, *M*			
0.0	3.56	4.41	5.83
0.5	4.23	5.10	6.66
1.0	4.61	5.63	7.31
1.5	5.25	6.45	8.16
2.0	5.67	6.93	8.63
2.5	6.22	7.75	9.46
3.0	6.60	8.35	10.35
Methylurea, *M*			
0.0	3.56	4.41	5.83
0.5	4.51	5.74	7.34
1.0	5.50	7.11	8.81
1.5	6.83	8.47	10.50
2.0	8.20	10.21	13.66
2.5	9.80	12.02	16.19
3.0	11.85	14.35	19.26
1,3-Dimethylurea, *M*			
0.0	3.56	...	...
0.5	4.95	...	...
1.0	7.37	...	...
1.5	9.72	...	...
2.0	12.32	...	...
2.5	15.56	...	...
3.0	19.01	...	...

TABLE II—SOLUBILITY OF SALICYLIC ACID AS A FUNCTION OF UREA CONCENTRATION AND TEMPERATURE

	Solubility of Salicylic Acid, mg./ml.		
	30°	37°	45°
Urea, *M*			
0.0	1.97	2.62	3.40
0.5	2.27	3.05	3.87
1.0	2.61	3.60	4.51
1.5	2.86	3.96	5.03
2.0	3.32	4.46	5.74
2.5	3.68	4.94	6.35
3.0	4.03	5.57	6.92
Methylurea, *M*			
0.0	1.97	2.62	3.40
0.5	2.52	3.35	4.46
1.0	3.14	4.39	5.75
1.5	4.03	5.25	7.39
2.0	5.17	6.64	8.92
2.5	5.96	8.24	11.21
3.0	7.42	9.74	13.46
1,3-Dimethylurea, *M*			
0.0	1.97	...	...
0.5	2.97	...	...
1.0	4.04	...	...
1.5	5.61	...	...
2.0	7.33	...	...
2.5	9.71	...	...
3.0	12.53	...	..

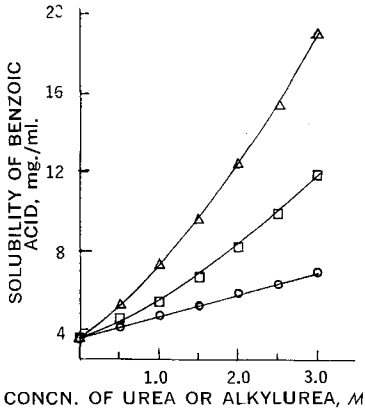

Fig. 5—Effect of urea, methylurea, and 1,3-dimethylurea on solubility of benzoic acid at 30°. Key: Δ,1,3-dimethylurea; □, methylurea; ○, urea.

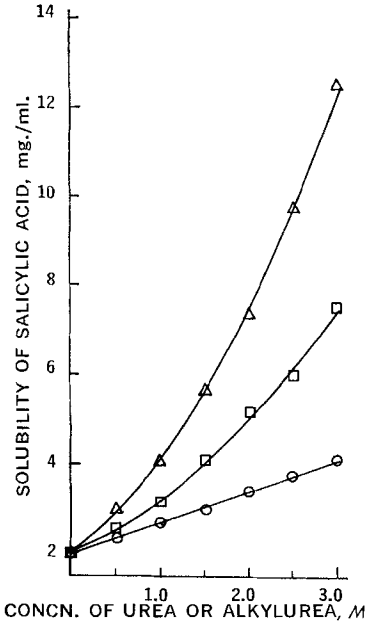

Fig. 6—Effect of urea, methylurea, and 1,3-dimethylurea on solubility of salicylic acid at 30°. Key: Δ, 1,3-dimethylurea; □, methylurea; O, urea.

and in 2 *M* 1,3-dimethylurea at 33°, 37°, 41°, and 45°. It was anticipated that a total of five temperature data points for each drug in each urea solution would clarify the extent of enthalpic contribution. Unfortunately, this was not the case. The ΔH values closely approximated zero, but the degree of inherent error prevented assignment of a positive or negative sign to the enthalpic component.

Further analysis of the data indicated that the method used for determining ΔH values was considerably more sensitive than the experimental procedures. The following illustration may serve to clarify the problem. Assume that the N/N_0 ratios for a particular experimental condition at 30° and 45° were 1.50 and 1.53, respectively. Further assuming that the N/N_0 ratio is really constant, these data would be in error to the extent of 1.5%. However, when the N/N_0 ratios are converted to logarithms the error is increased to approximately 4.5%. The 1.5% deviation (which is a reasonable approximation of experimental error) and the corresponding 4.5% deviation in the log of N/N_0 yields a ΔH of approximately −255 cal./mole, rather than zero.

The failure to refine the data by no means negates the value of determining the thermodynamic parameter, albeit an approximation. The methods employed were sufficiently sensitive to permit the conclusion that the enthalpic component was indeed small, certainly no greater than ±100 cal., and to a first approximation considered as zero.

The type of complexation most frequently described in the pharmaceutical literature involves the formation of a hydrogen bond (11). The enthalpy for the formation of a hydrogen bond is between 3 and 5 Kcal./mole (14), well above the small ΔH's noted in this investigation. Furthermore, it has been reported (15) that the strength of the hydrogen bond formed by urea molecules is of the same order of magnitude as those bonds formed by water. Therefore, even if urea formed hydrogen bonds with the benzoic or salicylic acid molecule, the strength of the bond would be about the same as the hydrogen bond formed between water and the drug molecule, and there should be no significant increase in solubility of the drug in aqueous urea solutions.

The free energies (ΔF) for the solubilization process have also been computed and are reported in Tables III and IV. They are small negative values similar to values reported by Katayama (9) and others (10, 15), who have solubilized nonpolar solutes in urea solutions. The negative sign is indicative of the spontaneity of the process.

Bolton (1), relying on complexation theory to explain the interaction of urea and salicylic acid, calculated apparent stability constants for the process. The magnitude of these constants, however, would yield a positive ΔF indicating a nonspontaneous process, which is clearly not the case. Moreover, the free energy values obtained in this investigation also tend to rule out a complexation mechanism in that the ΔF values of complexation are usually in the 2–5 Kcal./mole range (3, 16).

Since salicylic acid and benzoic acid do not appear to be solubilized by urea *via* a complexation mechanism, the possibility remains that urea is in some way "disrupting" water structure and thereby bringing about an increase in the solubility of the aromatic acids.

The solubility of benzoic and salicylic acid in water is due largely to the presence of polar groups on the aromatic ring. Water can solvate the benzoic or salicylic acid molecule through dipole interaction forces, particularly hydrogen bond formation. Thus, benzoic acid has a higher water solubility than salicylic acid. The latter, by forming intramolecular hydrogen bonds, presents a more "hydrophobic surface" to the solvent. When benzoic or salicylic acid is placed in water two interactions are possible.

The first possibility is that there is an interaction between the polar group on the aromatic nucleus and the water clusters. This hydrogen bonding between the polar group on the acid molecule and the water clusters would tend to break the clusters of hydrogen bonded water molecules and replace them partially with hydrogen bonds between the polar portion of the aromatic acid and the free water molecules. This interaction would tend to increase the solubility of the drug molecule through the negative ΔH values produced by hydrogen bond formation and the positive ΔS values brought about by the break up of water clusters.

The second possible point of interaction is between the nonpolar or hydrophobic portion of the drug molecule and the water clusters. The interaction comes about through van der Waal's forces and results in a hydrophobic hydration of the nonpolar molecule. An interaction of this type would tend to be a limiting factor in the solubility of the compound because of the large negative entropies and positive free energies which result. As noted previously, extensive hydrophobic hydration produces a situation where hydrophobic bonding between drug molecules and the resulting limitation on solubility would be energetically favored.

Therefore, the degree of solubility of benzoic or

TABLE III—THERMODYNAMIC PARAMETERS FOR SALICYLIC ACID IN UREA SOLUTIONS

	ΔF, cal./mole 30°	37°	45°	ΔH, cal./mole	ΔS (e.u.)
Urea, *M*					
0.5	− 85	− 76	− 83		+0.3
1.0	− 173	−195	−181		+0.6
1.5	− 225	−255	−249	≅ 0	+0.8
2.0	− 318	−329	−333		+1.1
2.5	− 385	−394	−391		+1.3
3.0	− 435	−460	−453		+1.4
Methylurea, *M*					
0.5	− 149	−153	−172		+0.5
1.0	− 281	−318	−333		+1.0
1.5	− 435	−429	−492	≅ 0	+1.4
2.0	− 583	−575	−612		+1.9
2.5	− 671	−711	−759		+2.3
3.0	− 803	−814	−876		+2.7
1,3-Dimethylurea, *M*					
0.5	− 249	...	...		+0.8
1.0	− 436	...	...		+1.4
1.5	− 634	...	...	≅ 0	+2.1
2.0	− 795	...	...		+2.6
2.5	− 966	...	...		+3.2
3.0	−1120	...	...		+3.7

TABLE IV—THERMODYNAMIC PARAMETERS FOR BENZOIC ACID IN UREA SOLUTIONS

	ΔF, cal./mole 30°	37°	45°	ΔH, cal./mole	ΔS (e.u.)
Urea, *M*					
0.5	− 105	− 92	− 83		+0.4
1.0	− 159	−133	−126		+0.5
1.5	− 237	−234	−214	≅ 0	+0.8
2.0	− 281	−279	−249		+0.9
2.5	− 339	−350	−307		+1.1
3.0	− 372	−394	−366		+1.2
Methylurea, *M*					
0.5	− 145	−162	−147		+0.5
1.0	− 265	−295	−262		+0.9
1.5	− 395	−404	−405	≅ 0	+1.3
2.0	− 504	−521	−540		+1.7
2.5	− 612	−622	−650		+2.0
3.0	− 728	−730	−759		+2.4
1,3-Dimethylurea, *M*					
0.5	− 199	...	...		+0.7
1.0	− 440	...	...		+1.5
1.5	− 608	...	...	≅ 0	+2.0
2.0	− 751	...	...		+2.5
2.5	− 893	...	...		+3.0
3.0	−1014	...	...		+3.4

salicylic acid in pure water would depend upon the relative magnitudes of the hydrophobic surface of each molecule. Since salicylic acid, by virtue of its intramolecular bonding, has the larger hydrophobic surface and can, therefore, demonstrate self-interaction to a greater extent by hydrophobic bonding, it should (based on the above consideration) have a lower water solubility than benzoic acid. This is, of course, the case.

Since urea effectively breaks up the clusters of hydrogen bonded water molecules in aqueous solution resulting in an increase in the entropy of the system, there would be less entropy to be gained by the hydrophobic bonding between the relatively nonpolar benzoic or salicylic acid molecules. Since formation of the hydrophobic bond has been decreased, there is a resulting increase in water solubility of the drug molecule.

If this mechanism is correct, then urea should have a greater effect upon the more hydrophobic molecule. A comparison of N/N_0 values reveals that salicylic acid, the more hydrophobic molecule, is solubilized by urea to a greater extent than the less hydrophobic benzoic acid molecule.

The effect of the alkyl substituted ureas, methylurea and 1,3-dimethylurea, on the solubility of benzoic and salicylic acid raises a number of interesting considerations. Based on Abu-Hamdiyyah's theory (8), the substituted ureas should have less of an effect on hydrophobic bonding than unsubstituted urea. This, in turn, would result in less solubilization of drug molecules by the alkylurea derivatives. The results of this study clearly show the opposite effect. Methylurea and 1,3-dimethylurea were more effective in solubilizing benzoic and salicyclic acid than urea, with 1,3-dimethylurea having the greatest effect. The values of log N/N_0 for 2 *M* 1,3-dimethylurea with both aromatic acids at various temperatures showed that ΔH was extremely small but slightly positive, and ΔF was negative (approximately −700 to −900 cal./mole). These values indicate the solubility increase was entropic in origin as was the case with unsubstituted urea.

These findings, however, should not be construed as a criticism of Abu-Hamdiyyah's model because the present experimental system is different from the system considered in the model. Considering the basicity of urea, and particularly the alkyl ureas, it is reasonable to conclude that at pH 1, there is present significant amounts of the conjugate acids of the ureas. While there exists a likelihood that these solutions have the same structure as aqueous solutions of nonionic ureas, this fact is yet to be experimentally demonstrated.

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