tically significant, and no explanation can be offered for these results.

The size of inoculum and storage time (within the limitations of the experiment) were less significant factors. Storage conditions appeared to be the most significant factor.

Numerous variables were inherent in the study, and the data are inconclusive. Future studies may provide data to explain the differences in survival rates of *S. aureus* on solid dosage forms.

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Physical–Chemical Properties of Substituted Amides in Aqueous Solution and Evaluation of Their Potential Use as Solubilizing Agents

PATRICK P. DeLUCA▲, LEON LACHMAN*, and HANS G. SCHROEDER

Abstract □ The tetramethyl-substituted amides of pimelamide, suberamide, azelamide, and sebacamide markedly enhance the solubility of glutethimide in aqueous solution. Partition studies, surface tension measurements, and light-scattering measurements strongly suggest that the amides are associating at infinitely dilute concentrations and further aggregation of these associated molecules occurs with the possible formation of micelles at concentrations slightly higher than that observed for surfactants. The CMC's were identified at 0.41, 0.20, 0.031, and 0.11 *M* for pimelamide, suberamide, azelamide, and sebacamide, respectively. The solubility of glutethimide was increased significantly above the critical concentrations and, from the nature of the solubility curves, a micellar type of solubilization appears to be dominant.

Keyphrases □ Amides, tetramethyl substituted—partitioning, surface tension, and light-scattering measurements in aqueous solution, potential solubilizing agents (solubilization of glutethimide) □ Pimelamide, tetramethyl, as potential solubilizing agent—partitioning, surface tension, and light-scattering measurements in aqueous solution, solubilization of glutethimide □ Suberamide, tetramethyl, as potential solubilizing agent—partitioning, surface tension, and light-scattering measurements in aqueous solution, solubilization of glutethimide □ Azelamide, tetramethyl, as potential solubilizing agent—partitioning, surface tension, and light-scattering measurements in aqueous solution, solubilization of glutethimide □ Sebacamide, tetramethyl, as potential solubilizing agent—partitioning, surface tension, and light-scattering measurements in aqueous solution, solubilization of glutethimide □ Solubilizing agents, potential—tetramethyl-substituted amides □ Glutethimide solubility—effect of tetramethyl-substituted amides

The formulation of a suitable dosage form for administration *via* the oral, parenteral, and topical routes is often a problem with drugs that have only limited water solubility. For oral administration, a solution would preclude the requirement for dissolution as in the case of suspensions or solid dosage forms and facilitate passage of the drug across the lipid membrane. For topical preparations, a homogeneous system would facilitate percutaneous absorption; for parenteral administration, a solution is generally desirable, especially *via* the intravenous route.

Nonaqueous solvents are often combined with water to dissolve a sparingly soluble drug even for injectable preparations (1), and the solvent selected must be free of toxic and irritating effects and not give rise to pharmacological responses. Two-component solvent systems

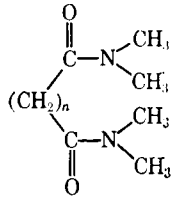
and hydrotropic agents have been employed and, more recently, surfactants have been used extensively.

The subject of micellar solubilization was dealt with thoroughly in two recent reviews by Mulley (2) and Swarbrick (3); and while hydrotropic solubilization (4) has received less attention, the literature on this type of solubilization has increased. Hydrotropes differ from surface-active agents in that they presumably do not possess surface activity or do not form micelles at low concentrations. Monosubstituted and disubstituted α-hydroxy acid amides, which are effective solubilizers, have been classified as hydrotropes.

N,N-Dimethylacetamide has been employed in the preparation of many dosage forms containing poorly soluble drugs (5). Specifically, the solubilities of tetracycline and oxytetracycline have been increased in nonaqueous systems by the addition of *N,N*-dimethylacetamide (6) and other amides of β-hydroxybutyric acid, succinic acid, adipic acid, tartaric acid, glycolic acid, and salicylic acid (7). A comprehensive study of the solubility of a number of drugs in acid amide solutions was undertaken by Samejima (8). The increase in solubility of the drugs studied was of relatively low order.

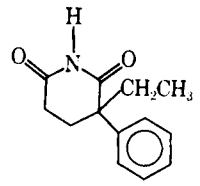
The excellent solvent properties of amides can be attributed in part to the strong dipole of the amide function and to the good electron-donating properties of the carbonyl group. Kostenbauder and Higuchi (9, 10) studied the molecular complexing tendencies of *N,N,N',N'*-tetramethylphthalamide series and some lower dicarboxylic acid amides and found increased solubility for chloramphenicol and *p*-hydroxybenzoic acid derivatives.

In light of these findings and on the basis of preliminary data for *N,N*-dimethylacetamide, *N*-methylpyrrolidone, and *N*-methylacetamide as solubilizing agents for poorly soluble drugs[1], it was felt that the higher homologs of *N,N,N',N'*-tetramethyl-substituted dicarboxylic acid amides were worthy of study. The general structure for the compounds selected is shown here. Hereafter these compounds will be referred to periodically simply as "amides."



pimelamide: $n = 5$
suberamide: $n = 6$
azelamide: $n = 7$
sebacamide: $n = 8$

The higher homologs were preferred because the inductive effect of the terminal amide groups upon each other would be negligible beyond succinamide where the functional groups are separated by three or more methylene groups. This type of structure would provide two, essentially independent, electron-donating groups



glutethimide

on a single molecule. Alkylation of the nitrogen groups was necessary to increase the solubility of the amides.

In this investigation, the properties of the amides in aqueous solution were studied and the potential solubilizing action of the amides was evaluated. Since the carbonyl group of an amide is a good electron donor, attraction for electron-accepting groups exists. Compounds possessing acidic hydrogen(s) such as alcohols, phenols, amines, xanthines, sulfonamides, and barbiturates should interact with the substituted amides. Glutethimide (2-ethyl-2-phenylglutarimide) is soluble to the extent of only 1 mg./ml. in water and it was selected for study.

Although glutethimide is a weak acid, having a pKa of approximately 11.8, it was felt that the hydrogen of the imide grouping would be sufficiently acidic to accept electrons. The tendency of the amides to associate or aggregate in aqueous solution was determined by partition studies and light-scattering measurements, and the surface activity of the amides was determined by surface tension measurements.

EXPERIMENTAL

Preparation of Amides[2]—The tetramethyl-substituted amides were prepared by reacting the corresponding acid chlorides with dimethylamine in alkaline media. Since only the azelaoyl and sebacoyl chlorides were commercially available, pimeloyl and suberoyl chlorides were prepared by reacting thionyl chloride with the dicarboxylic acids. Purification of the amides involved either vacuum distillation for the odd-carbon amides, pimelamide and azelamide, or recrystallization from acetone and hexane for the even-carbon amides, suberamide and sebacamide.

The purity of the amides was determined by vapor phase chromatography[3] and checked by differential scanning calorimetry[4] and elemental (C,H,N) analysis[5]. In all cases, the amides were found to be greater than 99% pure.

Solubility of Amides—The solubility of the amides was determined in distilled water at 30° in a constant-temperature water bath using the phase solubility technique (11). The amides were added to 20 ml. of distilled water in 30-ml. glass-stoppered bottles and agitated for 24 hr. The amide concentration in solution was determined by reaction with hydroxylamine (12); where excess amide was employed, the amount undissolved was weighed. The effect of added electrolyte on solubility was determined by adjusting the ionic strength of the solutions to 0.1 and 0.75 with potassium chloride.

Partitioning Studies—The amides were partitioned between organic and aqueous phases using chloroform–isooctane (12.5:87.5 v/v) as the organic phase and water as the aqueous phase. Twenty milliliters of the water phase of known amide concentration was placed in a special shaker tube (13), and 20 ml. of the organic phase was added. The tubes were agitated for 10 hr. at ambient condition at a rate of 1 c.p.m. The amount of amide partitioning into the organic phase was determined by GC employing the

[1] Solubilities of glutethimide, reserpine, griseofulvin, and hexestrol were increased in the presence of *N,N*-dimethylacetamide, *N*-methylpyrrolidone, and *N*-methylacetamide.

[2] The authors greatly appreciate the help of Dr. John Nelson, Ciba-Geigy Pharmaceutical Co., for developing the method of synthesizing the amides.

[3] Model 1740-10 Varian gas chromatograph.

[4] DSC-1B, Perkin-Elmer.

[5] Model 185, Hewlett-Packard analyzer.

Table I—Molar Solubility of *N,N,N',N'*-Tetramethyl-Substituted Amides

Compound	Distilled Water	—Potassium Chloride— 0.1 *M*	0.75 *M*
Tetramethylpimelamide	Mixes in all proportions	Mixes in all proportions	Mixes in all proportions
Tetramethylsuberamide	2.52	2.50	1.14
Tetramethylazelamide	3.90	3.85	3.72
Tetramethylsebacamide	0.527	0.344	0.170

following conditions: 1.25% OV-225 on Chromosorb G, 1.8-m. × 0.635-cm. (6-ft. × 0.25-in.) column, column temperature 225°, detector temperature 280°, and injector temperature 285°.

Surface Tension Measurements—Surface tension measurements were made with a surface tensiometer[6] employing a platinum–iridium ring. The measurements were made at ambient conditions using 10 ml. of solution contained in a 5.1 × 1.3-cm. (2 × 0.5-in.) Petri dish. The ring had a circumference of 6.060 cm. and was thoroughly rinsed with 95% alcohol and heated to incandescence in a bunsen flame between measurements. Readings were allowed to stabilize, and an average of three readings was recorded for each concentration. The effect of sodium chloride and urea on the surface tension measurements was determined by adding sodium chloride or urea to the amide solutions. No correction was made for volume changes with sodium chloride, but with urea it was necessary to account for the volume change to correct the amide concentration.

Light-Scattering Measurements—A photometer[7] was utilized for light-scattering measurements at a wavelength of 436 nm. While the instrument measures absolute turbidity, the calibration was checked periodically with a polystyrene fraction of known molecular weight (105,000). The scattering cell was a sinter-fused optical glass cell which permitted readings at angles of 0, 45, 90, and 135° to the direction of the transmitted beam. The method employed was essentially the same as that used by Brice *et al.* (14) for the determination of absolute turbidity. The scattering intensities at an angle of 90° were used to determine the absolute turbidity. The turbidity due to the solvent was subtracted from the total values, and the difference represented the excess turbidity. It was necessary to filter the solutions several times through a 0.45-μ cellulose ester membrane filter[8] and to allow sufficient time for stabilization of the readings to occur.

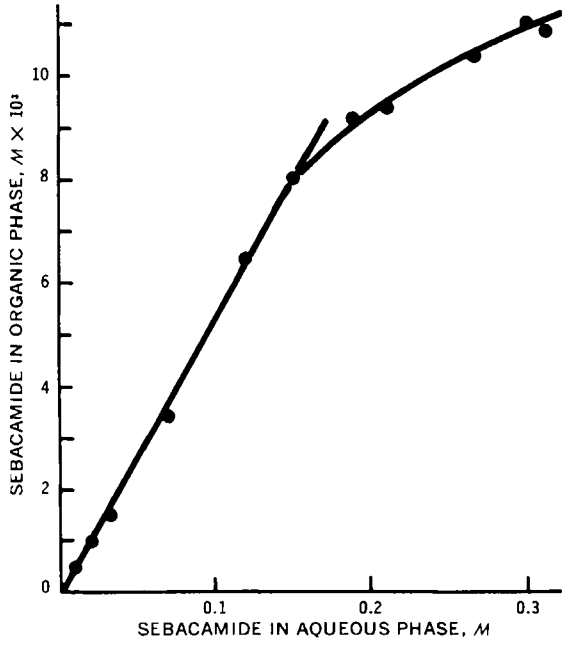


Figure 1—*Partitioning of tetramethylsebacamide between an organic phase of 12.5% chloroform in isooctane and an aqueous phase of water at room temperature.*

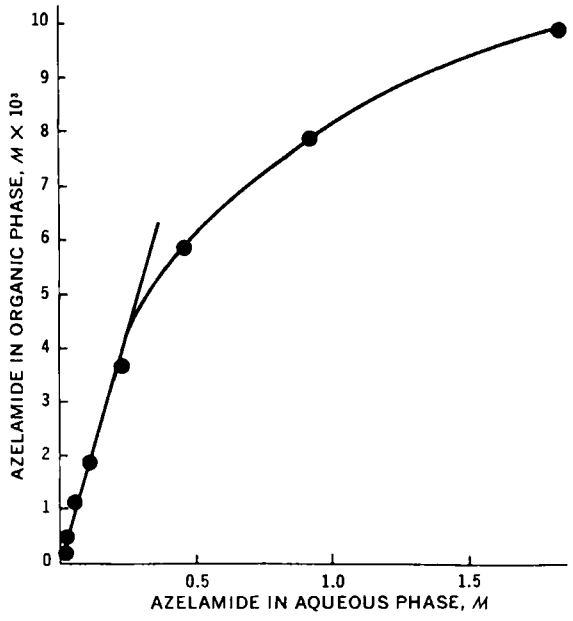


Figure 2—*Partitioning of tetramethylazelamide between an organic phase of 12.5% chloroform in isooctane and an aqueous phase of water at room temperature.*

The specific refractive index increments, *dn/dc*, were determined with a differential refractometer[9] at a temperature of 25° and a wavelength of 436 nm., using water as the solvent at five concentrations between 0 and 2.5%. Potassium chloride was used as a reference standard.

Solubilization of Glutethimide—Excess quantities of glutethimide[10], m.p. 84°, were placed into 30-ml. glass-stoppered bottles, and 20 ml. of solution of varying amide concentration was added. The bottles were tightly sealed and agitated in a constant-temperature water bath at 30° for at least 24 hr. until equilibration occurred. Equilibrium was determined by repetitive sampling, and it was found that 24 hr. of agitation was sufficient. The glutethimide concentration was determined spectrophotometrically using a spectrophotometer[11] with a recorder attachment at a wavelength of 257.6 nm. Anhydrous reagent methanol was used as the diluent for the drug samples.

RESULTS AND DISCUSSION

Aqueous Solubility—The tetramethyl-substituted amides were found to be extremely soluble in water. Table I lists the aqueous solubility values of the amides and the influence of ionic strength at a temperature of 30°. The solubility was not strictly a function of the chain length but was greater for the odd-carbon chain length amides. The C_5 compound, tetramethylpimelamide, is a liquid and mixes with water in all proportions. The C_7 compound, tetramethylazelamide, was soluble to the extent of 3.9 *M*.

The ionic strength of the solution appears to have a greater influence on the solubility of the even-carbon amides. At an ionic strength of 0.1, the solubility of tetramethylsuberamide was not altered; at an ionic strength of 0.75, the solubility was reduced by more than one-half. The solubility of tetramethylsebacamide was lowered by one-third at 0.1 and by two-thirds at 0.75. For the odd-carbon amides, tetramethylpimelamide and tetramethylazelamide, there was no apparent lowering of the solubility at either concentration of potassium chloride.

[6] DuNouy.
[7] Brice-Phoenix model 2000, Phoenix Precision Instrument Co., Philadelphia, Pa.
[8] Millipore Corp., Bedford, Mass.
[9] Brice-Phoenix model 430, Phoenix Precision Instrument Co., Philadelphia, Pa.
[10] 2-Ethyl-2-phenylglutarimide, supplied by the Ciba Pharmaceutical Co., Summit, N. J.
[11] Beckman DB.

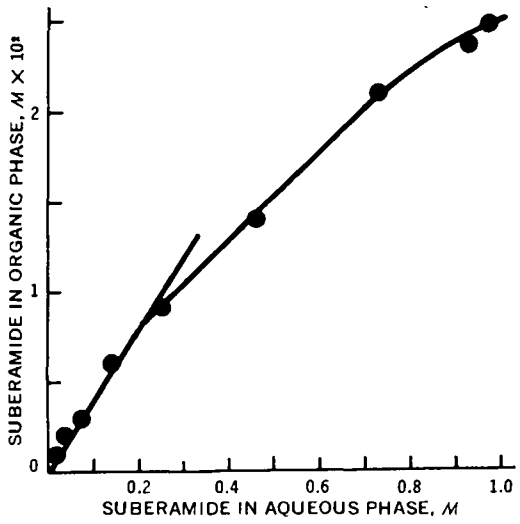


Figure 3—*Partitioning of tetramethylsuberamide between an organic phase of 12.5% chloroform in isooctane and an aqueous phase of water at room temperature.*

The salting-out effect of potassium chloride on the even-carbon amides indicates that solutions of these compounds might be less polar than the odd-carbon amides. However, to make a comparative assessment of polarity, dielectric constants of the amide solutions would have to be determined. Closer packing of the even-carbon chain has been demonstrated for dicarboxylic acids using X-ray analysis (15). Such behavior with the amides may give rise to a less polarizable compound, and the decrease in solubility of the even-carbon amides might be attributed to a preferential orientation of the polarizable water molecules around the ions of the added electrolyte.

Construction of molecular models shows that the odd-carbon amides favor a *cis*-configuration while the even-carbon compounds prefer a *trans*-orientation. The carbonyl groups for the odd-carbon amides are *cis* and in a parallel plane, while the nitrogen groups are *cis*-antiparallel; this type of orientation gives rise to a compound with a high dipole moment. The even-carbon amides have *trans*-antiparallel carbonyl groups and *trans*-parallel nitrogen groups; this symmetrical type of orientation results in a lower dipole and lower solubility.

Partition Studies—Partition isotherms for the amides are illustrated in Figs. 1–3. A linear relationship exists at low concentrations of the amides, but deviation from linearity occurs at higher concentrations, with more amide partitioning into the aqueous phase. Deviation of the partition isotherms at higher amide concentrations indicates increased association between amide molecules in aqueous solution. The break in the curve occurred at 0.15, approximately 0.25, and 0.22 *M* for sebacamide, azelamide, and suberamide, respectively.

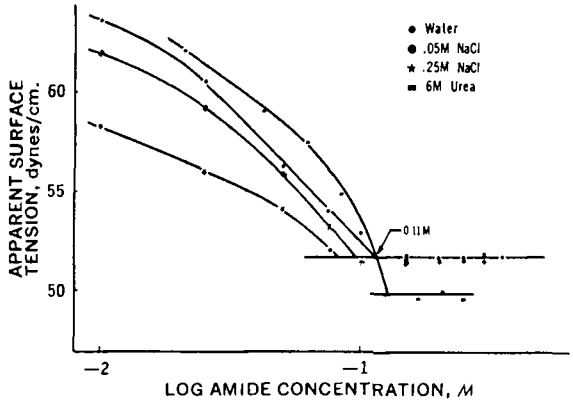


Figure 4—*Apparent surface tension as a function of tetramethylsebacamide concentration in water, 0.05* M *NaCl, 0.25* M *NaCl, and 6* M *urea.*

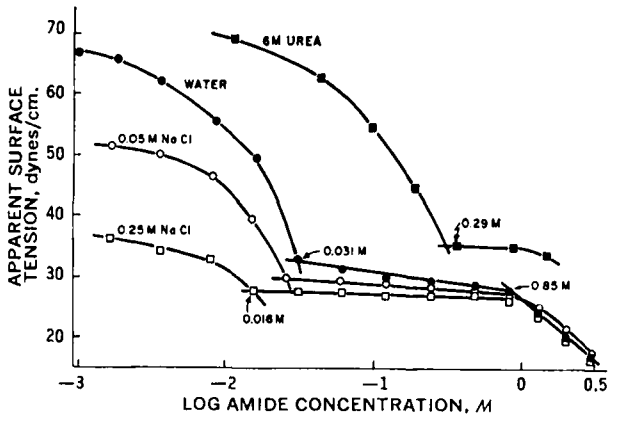


Figure 5—*Apparent surface tension as a function of tetramethylazelamide concentration in water, 0.05* M *NaCl, 0.25* M *NaCl, and 6* M *urea.*

Surface Tension Measurements—The results of the surface tension measurements are represented in Figs. 4–7 as plots of apparent surface tension *versus* the logarithm of the molar concentration. The curves show that the amides possess surface activity and that a critical concentration is associated with each amide.

For sebacamide, the break in the surface tension curve (Fig. 4) occurred at approximately 0.11 *M*. The addition of electrolyte suppressed the critical concentration only slightly. This effect is consistent with the findings of previous workers who studied the effect of electrolytes on nonionic association colloids (16–19) and found a decrease in the CMC.

Urea was included in the surface tension studies because of its ability to disaggregate nonpolar units within a molecule by weakening hydrophobic bonding (20, 21). Aside from the occurrence of a slight lowering of surface tension at the critical concentration, 6 *M* urea had no significant effect on the measurements. Due to the limited solubility of sebacamide, it was not possible to follow the surface tension beyond 0.5 *M* amide.

For azelamide, the break in the surface tension curve (Fig. 5) occurred at 0.031 *M*. In the presence of electrolyte, the surface tension was lowered and the break in the curve occurred at slightly lower concentrations. Urea at 6 *M* concentration had a profound effect on the surface tension, delaying the lowering and shifting the break in the curve to a concentration 10-fold higher than that in water. A second break in the surface tension curve was observed at a concentration of approximately 0.85 *M* amide, and a further lowering of the surface tension occurred with an increase in amide concentration. Much research has been done on the properties of

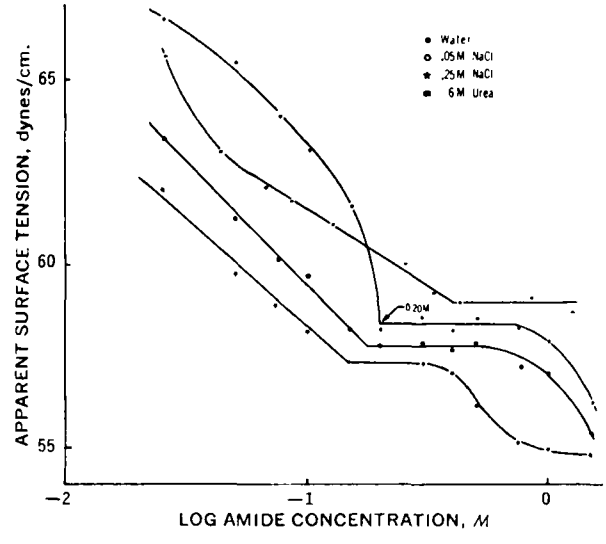


Figure 6—*Apparent surface tension as a function of tetramethylsuberamide concentration in water, 0.05* M *NaCl, 0.25* M *NaCl, and 6* M *urea.*

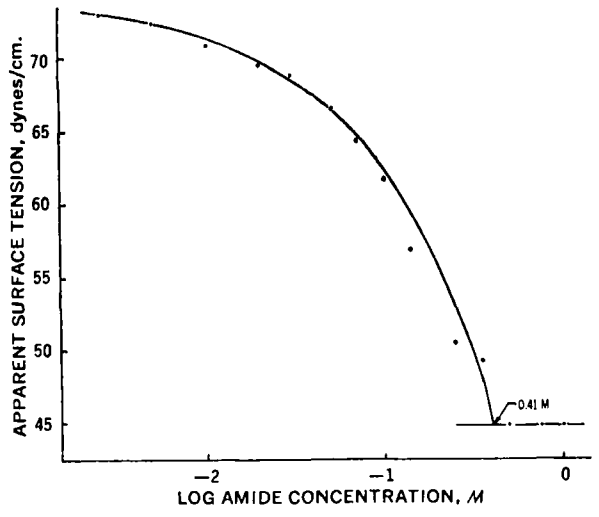


Figure 7—*Apparent surface tension as a function of tetramethylpimelamide concentration in water.*

surfactant solutions above the CMC, and several workers have identified a second CMC (22–24). While little has been done to explain this phenomenon, it has been postulated that an increase in size and asymmetry was associated or responsible for the second CMC.

Figure 6 shows the surface tension curves for tetramethylsuberamide, with the initial break in the curve occurring at 0.2 *M* amide in water; the lowering of the surface tension with suberamide is not as pronounced as with the other amides. The surface tension was found to be stable up to approximately 0.9 *M*, where the second break in the curve occurred. Added electrolyte enhanced the lowering of the surface tension and caused the break in the curve to occur at slightly lower concentrations. Urea delayed the break in the curve.

In the surface tension curve for pimelamide (Fig. 7), the break in the curve occurred at approximately 0.41 *M* amide concentration. Because of the limited amount of pimelamide available, no attempt was made to study the effect of urea or electrolyte, but it is

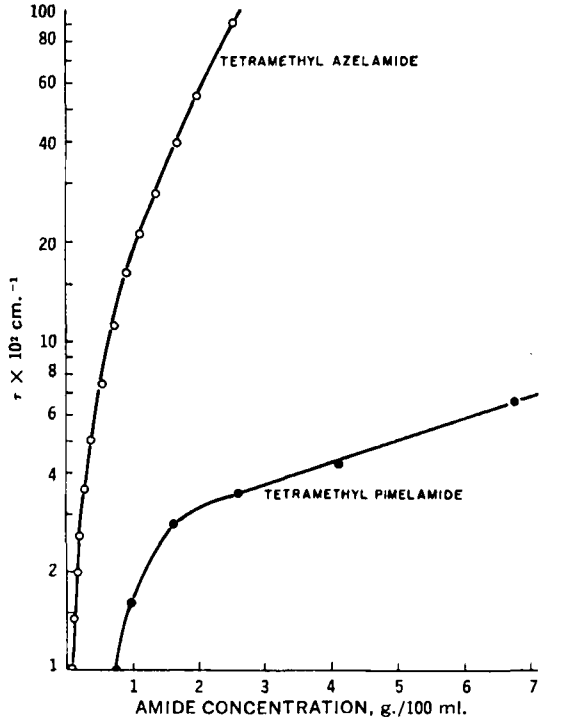


Figure 8—*Excess turbidity as a function of amide concentration for tetramethylazelamide and tetramethylpimelamide in water.*

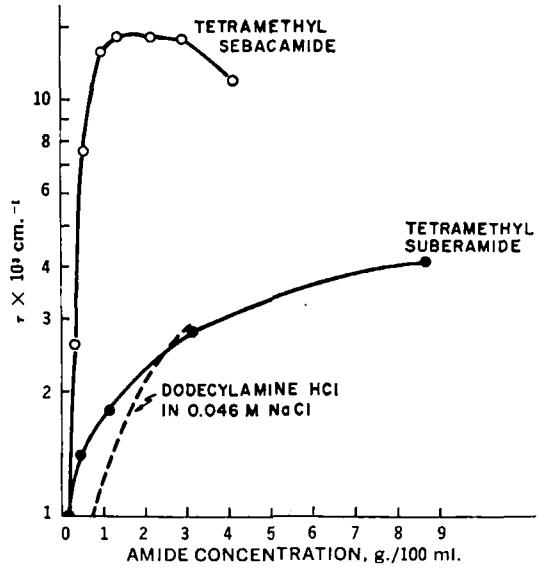


Figure 9—*Excess turbidity as a function of amide concentration for tetramethylsuberamide and tetramethylsebacamide in water. The dotted line is for dodecylamine hydrochloride in 0.046 M NaCl (27).*

believed that the effects would be the same as those observed for the other amides.

The surface tension lowering with the increase in amide concentration indicates that the amides have surface activity, and the break in the curve with a subsequent plateau suggests that saturation at the surface has been achieved in a manner closely resembling that for surfactants. Such behavior is well recognized for surfactant or detergent molecules; but to our knowledge, nothing has been reported on the possibility of a compound with two similar polar groups, one on each end of the molecule, such as the substituted dicarboxylic acid amides, behaving in this manner.

The apparent formation of micelles of the amides is not as spontaneous as one would expect for ionic surfactants. Additionally, it is suspected that some premicellar aggregation is occurring because of the necessity to "age" the solution to obtain stable surface tension readings. The effect of electrolyte in lowering the CMC has been well documented for ionic and nonionic surfactants. In addition to a simple dehydrating effect, Schick (18) postulated a salting-out effect for the lowering of CMC's by electrolytes.

Urea, by virtue of its two bonding centers on each molecule, undergoes hydrogen bonding with water; at high enough concentrations, it reduces the structure of water. This effect was studied with dodecylpyridinium salts (20), proteins (25), and alkyltrimethylammonium alkyl sulfates (21). As a result of the lowering of the interfacial energy between the hydrocarbon and water, the free energy differences between the hydrophobic groups and the water would be reduced and, therefore, the CMC would increase. Urea was found to have a profound effect with azelamide, elevating the CMC 10-fold, while with suberamide and sebacamide the CMC was increased only slightly.

Light-Scattering Measurements—To obtain estimates of weight average molecular weights of associated molecules and aggregates, *i.e.*, polymers and micelles, light-scattering measurements have been employed (26). Light scattering depends largely upon the microscopic heterogeneity of the solution due to fluctuations in concentration. The extent of these spontaneous fluctuations in concentration is a measure of the osmotic work; therefore, a relationship exists between the intensity of the scattered light and the osmotic pressure of the solution. Light scattering offers the advantage that the property being measured increases with an increase in molecular weight, whereas the reverse is true for osmotic pressure.

In Figs. 8 and 9, the excess turbidity at 90° of the amide solutions over that of water is plotted on a log scale as a function of amide concentration. The turbidity was found to increase rapidly from zero concentration in a manner resembling the behavior of high polymer solutions (27).

The odd-carbon amides, azelamide and pimelamide, showed unusually high scattering intensities, and the values obtained for

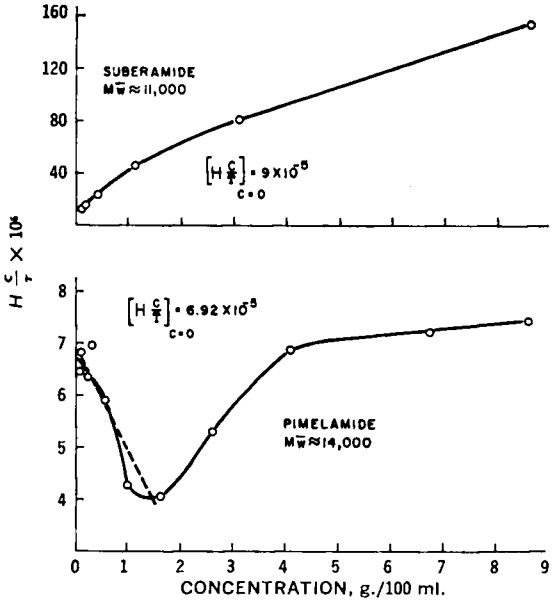


Figure 10—*Specific reciprocal turbidity as a function of amide concentration for tetramethylsuberamide and tetramethylpimelamide in water.*

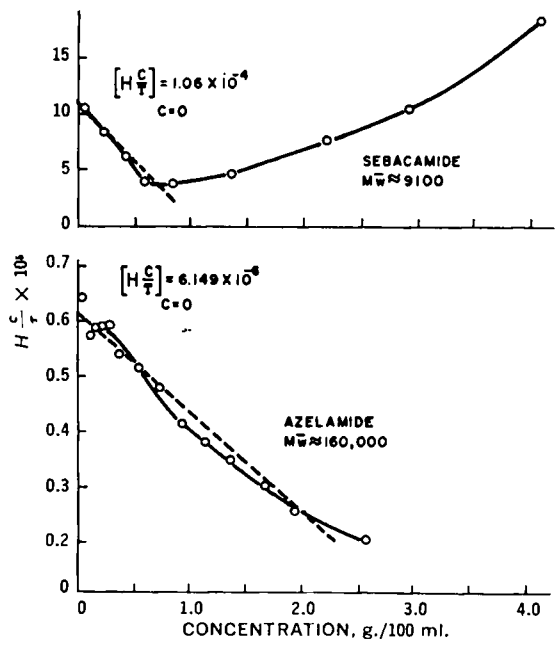


Figure 11—*Specific reciprocal turbidity as a function of amide concentration for tetramethylazelamide and tetramethylsebacamide in water.*

azelamide are in the order of at least 10 times those found for polymer solutions at similar concentrations. It was difficult to carry light-scattering measurements beyond 2 g./100 ml. because a high amount of scattering occurred at 0°. The turbidity of the pimelamide solution was lower than that for azelamide but was still higher than that found for most polymer solutions.

The intensity of scattering for the even-carbon amides was approximately one order of magnitude less than that for the previous odd-carbon amides. The turbidity of the sebacamide solution increased rapidly and reached a plateau at about 1.5 g./100 ml. Herrmann *et al.* (28), in their studies on the micellar properties of alkyl dimethylphosphine oxide solutions, observed maxima in the turbidity–concentration curves. The curve for suberamide closely resembles that found for polymers but is still of higher magnitude than that found for soap solutions above the CMC. The dotted line represents the curves for dodecylamine hydrochloride in 0.046 *M* sodium chloride solution above the CMC (26). It was not possible to plot the curves for the detergent in water on the graph since the turbidity reached a maximum value at approximately 0.3×10^{-3} cm.$^{-1}$. The influence of chain length on the turbidity is clearly evident for the even- and odd-carbon amides, with the higher homologs in each case showing greater scattering.

To determine average molecular weights from turbidity measurements, the refractive index increment must be determined since the refractive index of the solution is also a function of concentration. Debye (29) transformed Van't Hoff's law for high polymer solutions into the following equation:

$$H\frac{c}{\tau} = \frac{1}{MW} + 2Bc + \ldots \qquad \text{(Eq. 1)}$$

which, at high dilutions, would be a good linear approximation for the reciprocal specific turbidity as a function of concentration; τ is the experimentally measured excess turbidity of the solution, c is the concentration in grams per milliliter, and MW is the average molecular weight. The constant B depends on the solvent, and H can be calculated from refraction measurements using the following equation:

$$H = \frac{32\pi^3}{3}\frac{\eta_0^2}{N\lambda^4}\left(\frac{\eta - \eta_0}{c}\right)^2 \qquad \text{(Eq. 2)}$$

where η_0 and η are the refractive indexes of the solvent and solution, respectively; N is Avogadro's number (6.023×10^{23}); and λ is the wavelength of light employed for the light-scattering measurements. A plot of $H(c/\tau)$ *versus* concentration generally produces a straight line at low concentrations, where the Van't Hoff equation is valid. The intercept is equal to the reciprocal of the average molecular weight.

In Figs. 10 and 11, $H(c/\tau)$ is plotted as a function of the amide concentration. As shown in Fig. 10, the curve for pimelamide decreases, passes through a minimum, and then increases. Such nonideal behavior was reported by Robins and Thomas (24) for dodecylaminoethanol salts and by Herrmann *et al.* (28). Extrapolation of the data below 1 g./100 ml. using least-squares treatment results in an average molecular weight of approximately 14,000. For suberamide, the curve closely resembles that obtained for polymers and extrapolation of the data gives an average molecular weight of 11,000.

As shown in Fig. 11, the plot for azelamide has a negative slope with considerable fluctuations in the turbidity values at dilute concentration. The curve resembles that for bovine serum albumin in water (30), with the curvature and "scattering" of points at dilute concentrations considered to be routine occurrences and attributed to the activity of the solvent and various charge factors. The average molecular weight for azelamide appears to be in the range of 160,000.

For sebacamide, extrapolation of the data below 1 g./100 ml. gives a molecular weight of 9100, which is similar to that for suberamide at infinite concentration. However, unlike suberamide, further association of aggregation appeared to occur as the concentration of sebacamide was increased. An initial negative slope was found, with a minimum in the curve occurring at approximately 0.8 g./100 ml. The results of the light-scattering measurements are listed in Table II.

The deviation from linearity of the light-scattering curves was discussed previously for polymers (27, 31, 32) and can be attributed to one or more of the following:

1. Interparticulate interference, giving rise to dissymmetry; *i.e.*, the ratio of the intensity scattered at two angles symmetrical about 90° (33).
2. A distribution of molecular weights, giving rise to depolarization (34); *i.e.*, the molecules are no longer isotropic.
3. The presence of an impurity.
4. Continued association of polymer molecules.
5. The equation is valid only at very dilute concentrations.

Dissymmetry became a problem above a concentration of 1.5–2.0 g./100 ml. Because of the disproportionate increase of scattering intensities at angles of 45 and 135° as the amide concentrations were increased, it was not possible to extend the light-scattering measurements to a concentration where the breaks in the apparent surface tension curves, partition isotherms, and glutethimide solubility profiles occurred.

Table II—Light-Scattering Results for Tetramethyl-Substituted Amides at 436 nm.

	dn/dc[a]	$\left[H\frac{c}{\tau}\right]_{c=0}$	$\overline{MW}$	N[b]
Pimelamide	0.162	6.9×10^{-5}	14,000	65
Suberamide	0.164	9.0×10^{-5}	11,000	48
Azelamide	0.164	6.2×10^{-6}	160,000	660
Sebacamide	0.137	1.1×10^{-4}	9,100	36

[a] Refractive index increment. [b] Number of monomers comprising the aggregate.

It was felt that, at the dilute concentrations, dissymmetry would be negligible and the depolarization caused by large molecules, a mixture of different molecular sizes, or concentration effects would not be significant. While it may not be possible to estimate average molecular weights by such treatment, the significance of the light-scattering data is that the amides appear to exist as associated molecules at very dilute solutions. To gain insight into the orientation and size of these aggregates, the influence of time, temperature, and electrolytes on the light-scattering measurements must be considered. Without such measurements, it is possible only to conjecture when trying to explain the light-scattering curves. The presence of maxima, minima, and curvature in the light-scattering curves was reported by several researchers (24, 28, 30, 32, 35). Robins and Thomas (24) showed that, for the iodide and nitrate salts of 2-dodecylaminoethanol, maxima in the curves occurred at a salt concentration of approximately 1.5% followed by a broad minimum at approximately 3% concentration. The hypothesis proposed for this behavior was that, at just above the CMC, the micelles were spherical in shape and the positive slope was due to solvent–solute interactions. At the inflection point in the curve, the micelles became more asymmetrical in shape and the negative slope was attributed to solute–solute interaction, *i.e.*, growth of the micelles. The increase in turbidity over this range was greater than the solute–solvent interaction effect and, consequently, the slope was negative. The upward curvature in the curves following the minima was believed to be due to a less rapid growth in the size of the micelles to the extent that the solute–solvent interaction had greater influence.

Curves for sebacamide, azelamide, and pimelamide show negative slopes, with the sebacamide and pimelamide curves exhibiting minima at approximately 1.0% concentration followed by an increase in the specific reciprocal turbidity function. On the basis of this hypothesis, it is possible that association of the amides continues to occur at dilute amide concentration due to strong solute–solute interaction. The inflection in the curve occurs when the solute–solvent interaction becomes greater than the affinity of the amide molecules to associate further.

No attempt was made in this study to correct for dissymmetry or depolarization, even though the data show that dissymmetry was occurring and became significant as the concentration of amide was increased. Consequently, the data in this study are subject to error, but this should be of a low order of magnitude at the dilute concentration. It is unlikely that this behavior can be attributed to the presence of an impurity since GC, thermal, and elemental analyses show the amides to be at least 99% pure.

Table III—Solubilization of Glutethimide with Tetramethyl-Substituted Amides at 30°

Amide Concentration, M	—Glutethimide Solubility ($M \times 10^3$) in Presence of— Pimelamide, $M \times 10^3$	Suberamide, $M \times 10^3$	Azelamide, $M \times 10^3$	Sebacamide, $M \times 10^3$
0.0[a]	4.60	4.60	4.60	4.60
0.04	5.20	4.60	4.85	4.60
0.10	6.06	4.60	5.70	4.60
0.25	8.23	4.70	7.50	8.56
0.40	11.3	11.9	—	17.62
0.50	—	16.6	18.0	22.22
1.0	29.1	34.5	39.5	
2.0	103.4	138.0	230.0	
2.4	—	330.0	—	
2.8	318		—	
3.0	399		700	
3.9	1343		1472	

[a] Solubility of 2-ethyl-2-phenylglutarimide in water (1.0 mg./ml.).

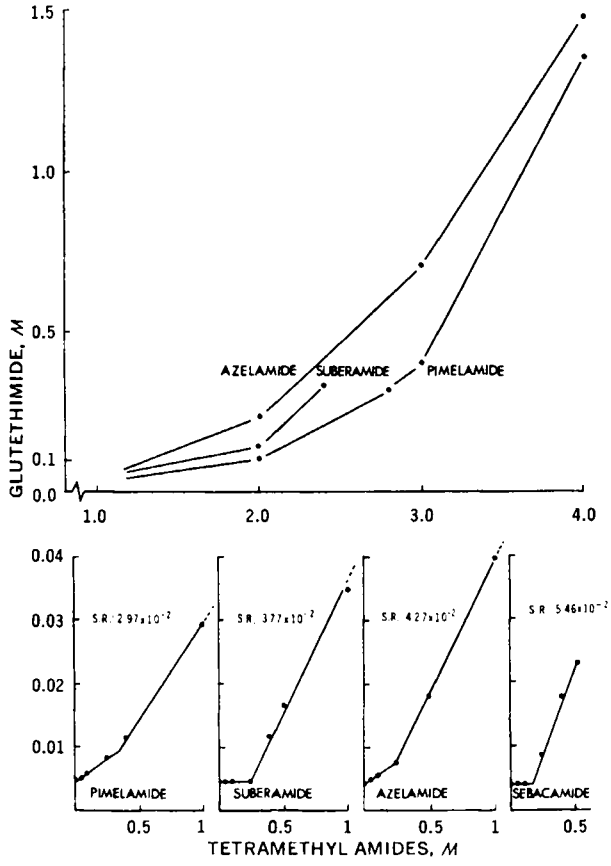


Figure 12—*Solubility curves for glutethimide with tetramethyl-substituted amides at 30°. Lower curves show the solubility over an amide concentration of 0–1* M, *and the upper curves show the solubility above 1* M.

Solubilization of Glutethimide—The data presented in Table III illustrate the influence of the substituted amides on the solubility of glutethimide. For the even-carbon amides below a concentration of 0.25 *M*, there appeared to be no significant increase in glutethimide solubility; with the odd-carbon amides, interaction did occur. However, a substantial increase in the solubility of the drug was not observed until above 0.4 *M* concentration of the amides. The increase in solubility of glutethimide parallels the increase in chain length of the amides but, because of the greater solubility of the odd-carbon amides, it is possible to attain higher levels of glutethimide with pimelamide and azelamide.

The data in Table III are represented graphically in Fig. 12, where the amount of glutethimide solubilized is plotted as a function of amide concentration. To permit the full range of glutethimide levels reached to be plotted on a single graph, the *y* axis is broken. The solubilization at low amide concentrations is shown by the lower curves for the four amides, while the upper curves depict what occurs at higher amide concentrations. With the possible exception of sebacamide, it is evident from the nonlinearity of the plots that glutethimide solubility is not directly proportional to the amide concentration over the entire solubility range. However, for all the amides there appears to be a linear relationship over an amide concentration of 0.2–1.0 *M*.

The solubilizing capacity of the amides for glutethimide is represented on the lower graphs by the saturation ratios, *i.e.*, moles of glutethimide per mole of amide, over the concentration range from the break in the curve up to 1.0 *M* amide. It was not possible to calculate saturation ratios above 1 *M* amide concentration due to the nonlinearity of the curves. Above 1 *M* amide concentration, the amount of glutethimide solubilized increased significantly with an increase in amide concentration. At 3.9 *M* azelamide, a concentration of 320 mg./ml. of glutethimide was attained, representing

a 320-fold increase from that in water; for pimelamide at the same concentration, 292 mg. of glutethimide was solubilized per milliliter.

The shape of the solubility curves suggests that two types of interactions are involved; one type occurs below some critical concentration of amide and a second, more pronounced interaction, predominates above the critical concentration. The interaction that occurs between glutethimide and azelamide and pimelamide prior to the break in the curve was found to be of low order. The fact that the even-carbon amides, sebacamide and suberamide, do not interact with glutethimide below the critical point might be attributed to either a preferred orientation of the odd-carbon amides or, as indicated by light-scattering data, the existence of larger aggregates for the odd-carbon amides giving rise to a greater hydrophobic center.

Of greater significance is the interaction with glutethimide occurring at higher amide concentrations. The nature of the interaction and the break in the surface tension curves suggest micelle formation with higher order complexes forming above the critical point. It appears that at higher amide concentrations, above 1.0 *M*, the drug may be participating in or influencing the aggregate structure or that further aggregation of the amides occurs which gives rise to larger or more densely oriented hydrophobic centers. In any event, the solubility of glutethimide in azelamide and suberamide was enhanced significantly at a concentration where the second break in the surface tension curves occurred.

Preliminary toxicity screening of the amides revealed that the toxicity by the intravenous route for pimelamide and suberamide was similar or slightly less than that for dimethylacetamide and *N*-methylacetamide, while azelamide and sebacamide appeared to be slightly more toxic. However, due to the existence of large associated molecules at low concentration, passage across the lipid membrane may be restricted and the amides may find application for solubilizing drugs for oral and topical administration. Absorption studies are presently being contemplated, but an oil–water partition study revealed that the oil–water partition coefficient is extremely low and both the toxicity and oil partitioning appear to increase with an increase in chain length. Further toxicity and tissue tolerance experimentation will be conducted.

SUMMARY AND CONCLUSIONS

The tetramethyl-substituted amides of sebacamide, azelamide, suberamide, and pimelamide appear to possess the potential of solubilizing hydrophobic molecules due to their strong association tendencies, as indicated by partitioning studies, surface tension measurements, light-scattering measurements, and solubility studies. The nature of the partition isotherms, surface tension curves, and solubility curves for glutethimide suggests the existence of aggregates or micelles of the amides, and possibly the solubilization of glutethimide can be attributed to a micellar type of interaction.

While it is conceivable, as indicated by surface tension measurements, that a micellar type of aggregation occurs at some critical concentration, the light-scattering measurements strongly suggest the existence of large associated molecules at very dilute concentrations. The scattering intensity was of a magnitude similar to that for polymer solutions, and the intensity increased significantly with an increase in amide concentration. The odd-carbon amides, azelamide and pimelamide, show greater light-scattering intensity, greater lowering of surface tension, and higher solubility in water than the even-carbon amides, suberamide and sebacamide. Additionally, unlike the solubility observed for the even-carbon amides, the solubility of the odd-carbon amides was not reduced by an increase in ionic strength and they interacted slightly with glutethimide at low concentration. The further lowering of surface tension following a plateau area in the surface tension curves for two of the amides, azelamide and suberamide, suggests either that the aggregates formed are surface active or that a reorientation at the surface is occurring.

If the amides are of a size that hinders penetration of semipermeable membranes, they may find application in drug delivery systems as implants as well as being used as dialysis solutions in cases of glutethimide intoxication. Considerably more work is needed to determine the potential value of the amides as solubilizing agents and vehicles in drug delivery systems.

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