Correlation of Dielectric Constant and Solubilizing Properties of Tetramethyldicarboxamides

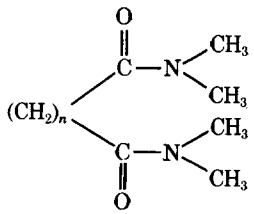
T. REBAGAY and P. DeLUCA ˣ

Abstract □ The dielectric constants of aqueous solutions of four tetramethyldicarboxamides (tetramethylpimelamide, tetramethylsuberamide, tetramethylazelamide, and tetramethylsebacamide) were measured at 25°. The values obtained were utilized in assessing the solubility behavior patterns of glutethimide, a semipolar, water-insoluble drug in these amide–water systems. At equimolar concentrations of water-rich amide solutions, the solubilizing power paralleled the chain length of the amides. The higher homologs appeared to favor more extensive solvation, as shown by the lower dielectric constants of their resulting solutions. Deviation in solubilizing action between the odd-carbon amides and the even-carbon amides, however, was exhibited at higher amide concentrations. The two odd-carbon amides, tetramethylpimelamide and tetramethylazelamide, showed consistently greater solubilizing action. This phenomenon was attributed to the greater association tendencies of the odd-carbon amides with water, which effectively reduced self-associations of glutethimide.

Keyphrases □ Dielectric constants—aqueous solutions of various tetramethyldicarboxamides, correlated with solubilizing properties □ Solubilizing properties—aqueous solutions of various tetramethyldicarboxamides, correlated with dielectric constants □ Tetramethyldicarboxamides—aqueous solutions, dielectric constants correlated with solubilizing properties □ Glutethimide—solubility assessed using dielectric constants of aqueous solutions of various tetramethyldicarboxamides

Substituted carboxamides exhibit potential as solubilizing agents for hydrophobic molecules (1). The solvent properties of amides are attributed in part to the strong dipole of the amide function and to the good electron-donating properties of the carbonyl group. Recent studies on a series of tetramethyl-substituted dicarboxamides possessing Structure I (n = 5–8) revealed that these amides show strong association tendencies in very dilute solutions and suggested that further aggregation of associated amide molecules leads to micellization (2).

A stronger amide–water interaction has been suggested for the odd-carbon amides of the homologous series, tetramethylpimelamide and tetramethylazelamide, using partial molal volume and viscosity behavior patterns (3). A minimum in the partial molal volume and a maximum in viscosity were observed at definite integral mole fractions for the odd-carbon homologs. Such behavior was not observed for the even-carbon amides, tetramethylsuberamide and tetramethylsebacamide. The stronger amide–water association for the odd-carbon amides could lead to greater disruption of the structure of the surrounding water molecules.



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The extent of water structure disruption can be reflected in the dielectric constant of the resulting solution. The change in dielectric constant may then be used as a measure of the degree of interaction of a particular amide with water. In general, such interactions could lead to the formation of ordered molecular aggregates of varying sizes that are made up of statistically preferred arrangements of different molecular species, either as hydrates or complexes (4).

The enhanced solubility of various substances as a function of dielectric constants has been reported (5–8). It is believed that solubility can be correlated with the dielectric constant when the solvent or solvent mixture exhibits similar bonding characteristics as the substance of interest. Correlation also can be obtained by using compounds belonging to the same homologous series, either alone or in combination as solvent blends (9).

To gain further knowledge of the tetramethyldicarboxamides as solubilizing agents for poorly soluble drugs, the dielectric constants of aqueous solutions of these amides were measured. The values obtained were then utilized in assessing the solubility behavior patterns of glutethimide, a semipolar, water-insoluble drug. Since the amides differ only in the number of methylene units in the hydrocarbon chain, the effect of chain length on the dielectric solubility profile of glutethimide was assessed.

EXPERIMENTAL

Materials—The tetramethyl-substituted dicarboxamides were prepared according to a previously reported procedure (2). The purity of the amides was determined by vapor phase chromatography, and the conductivity of aqueous amide solutions was checked by the method described previously (10).

Apparatus for Capacitance Measurements—An impedance bridge assembly[1] was used in conjunction with two-terminal parallel plate cells for capacitance measurements at 1 MHz. Similar cells with platinum electrodes are structurally satisfactory[2] and convenient for measuring low conducting liquids (11, 12). The ends of the external leads to the cell electrodes were fitted with special adapters so that the cell, which was suspended in an oil bath during measurements, could be easily attached to the bridge by a shielded coaxial cable having a dual banana plug connection at each end.

The principal aspects for determining the cell constants and for calculating dielectric constants were described previously (13, 14). The standard media used in the determination of cell constants were air and water, which have dielectric constants of 1.0005 and 78.304 (15), respectively, at 25°.

The temperature for the dielectric constant determinations was controlled to within ±0.05° using a constant-temperature bath[3] filled with light paraffin oil. Readings from the bath thermometer, with 0.1° subdivisions, were compared with those from an NBS-calibrated thermometer; appropriate corrections were applied.

[1] Twin-T, General Radio Co., Cambridge, Mass.

[2] Measurements of the dielectric constant of water were made at 5° intervals in the 25–55° range to check the calibrations of the cells and the experimental procedure in general. No variations in the cell constants were observed, indicating that the cell configuration remained constant.

[3] Model H-1, Cannon Instrument Co., State College, Pa.

Table I—Dielectric Constants of Tetramethyldicarboxamides–Water Systems in Relation to Solubility of Glutethimide

Substituted Amide				Glutethimide	
Molarity	Weight Percent	Mole Fraction × 100	Dielectric Constant	Solubility, $M \times 10^3$	Relative Solubility, S/S_0
		Tetramethylpimelamide			
0.0			78.3	4.60	1.00
0.04	1.71	0.146	78.0	5.20	1.13
0.10	2.95	0.255	77.8	6.06	1.32
0.25	6.04	0.537	77.2	8.23	1.79
0.4	9.14	0.838	76.6	11.3	2.46
1.0	21.51	2.25	73.6	29.1	6.33
2.0	42.13	5.76	66.9	103.4	22.5
2.8	58.63	10.64	60.1	318.	69.1
3.0	62.75	12.40	58.2	399.	86.7
3.9	81.31	26.76	48.5[a]	1343.	292.0
4.76	100.00	100.	37.6		
		Tetramethylsuberamide			
0.0	0.0	0	78.3	4.6	1.00
0.04	1.04	0.083	78.0	4.6	1.00
0.10	2.38	0.192	77.6	4.6	1.00
0.25	5.73	0.477	76.4	4.7	1.02
0.40	9.08	0.781	75.1	11.9	2.59
0.50	11.31	0.995	74.3	16.6	3.61
1.00	22.48	2.24	69.8[a]	34.5	7.5
2.00	44.80	6.01	59.7[a]	138.0	30.0
2.40	53.73	8.39	55.2[a]	330.0	71.7
		Tetramethylazelamide			
0.0	0.0	0	78.3	4.60	1.00
0.04	0.99	0.074	78.1	4.85	1.05
0.10	2.43	0.185	77.6	5.70	1.24
0.25	6.03	0.474	76.4	7.5	1.63
0.5	12.04	1.006	74.4	18.0	3.91
1.00	24.05	2.30	70.1	39.5	8.59
2.00	48.08	6.44	60.3	230	50.0
3.00	72.10	16.10	49.2	700	152
3.90	93.72	52.57	38.0[a]	1472	320
		Tetramethylsebacamide			
0.0	0.0	0	78.3	4.60	1.00
0.04	1.03	0.073	77.9	4.60	1.00
0.10	2.57	0.185	77.5	4.60	1.00
0.25	6.42	0.486	76.1	8.56	1.86
0.40	10.16	0.788	74.7	17.6	3.83
0.50	12.82	1.022	73.8[a]	22.2	4.83

[a] Value calculated from Eq. 1.

Dielectric Constant Determination—All amide–water solutions were prepared on a weight basis, with the necessary weight in vacuum corrections applied[4]. The cells were cleaned with distilled conductivity water and rinsed with acetone. They were then blown dry with air before they were filled with the test solutions. The cells were placed in the constant-temperature bath and allowed to equilibrate for at least 15 min.

RESULTS AND DISCUSSION

The dielectric constant data for the amide–water systems are given in Table I. Plotting the solution dielectric constant *versus* concentration for the amides resulted in a linear relationship only at dilute concentrations (Fig. 1). At concentrations greater than 20% amide, a curvature was produced. The curvature may be assumed arbitrarily as due to molecular associations resulting in the formation of molecular aggregates. Molecular association with water is likely to occur with the two unshared pairs of electrons on the carbonyl oxygen or on the sterically more obstructed lone pair of electrons on the dimethyl-substituted nitrogen on each end of the amide molecule. This assumption is supported by light-scattering studies on these amides, which showed a rapid increase in the number of aggregates with increasing concentration, resembling the behavior of high polymer solutions (2).

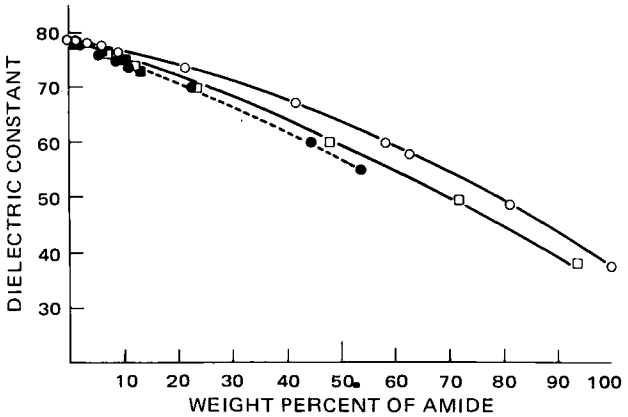

Figure 1—*Dielectric constant* versus *composition of tetramethyldicarboxamides. Key:* ○, *tetramethylpimelamide;* ●, *tetramethylsuberamide;* □, *tetramethylazelamide; and* ■, *tetramethylsebacamide.*

An equation[5] of the type:

$$\epsilon = a + bx + cx^2 \qquad \text{(Eq. 1)}$$

where ϵ is the solution dielectric constant, x is the concentration, and a, b, and c are constants, describes the behavior of the solution dielectric constant. The constants for each amide are obtained through fitting the mean experimental ϵ values to Eq. 1, using a nonlinear least-squares program of the type described by Wentworth (16). Some ϵ values of the even-carbon amides listed in Table I are calculated with Eq. 1.

The solubility data of glutethimide in the different amide–water systems are listed in Table I, and solubility profiles are depicted in Fig. 2. The solubility patterns showed an almost exponential rise with a decreasing solution dielectric constant. This finding may imply more effective hydration of the glutethimide molecules as the concentration increases and the formation of various hydrates having their own solubility characteristics.

A clearer illustration of the phenomenon occurring at the water-rich region (high ϵ) is depicted in Fig. 3*a*. The solubility ratios, S/S_0 (S refers to the solubility of glutethimide in the amide–water mixture, and S_0 is its solubility in water), are plotted as a function of the dielectric constant. Below a certain amide concentration, the solubility ratios remained almost constant, indicating that addition of small amounts of amides did not significantly change the solubility pattern.

Previous studies on these amides (2) suggested the formation of micelles at very dilute concentrations of the amides. Critical micelle concentrations (CMC) were reported to be at 0.41, 0.20, 0.031, and 0.11 M for the pimelamide, suberamide, azelamide, and sebacamide, respectively. A sudden change in the solubility pattern was also observed, which may correspond to the CMC of the amide micelle or any mixed micelles arising from the addition of glutethimide. At the micellar region, it is believed that micellization removes the alkyl or nonpolar groups of the amides from the aqueous to nonaqueous environment, producing a high density of hydrophilic groups at the micellar surface and resulting in the hydrophobic solvation of nonpolar moieties (3).

The micellar interior behaves in the same way as an organic phase in a two-immiscible phase system in which water is one phase. It is

[4] Weight in vacuum corrections applied using:

$$M_{vac} = M_{air} + \frac{K(M_{air})}{1000}$$

where M_{vac} is the weight of the object in vacuum, M_{air} is the observed weight in air, and K is a correction factor related to the density of the object ("Handbook of Chemistry and Physics," 47th ed., R. C. Weast and S. M. Selby, Eds., Chemical Rubber Co., Cleveland, Ohio, 1966, p. D-75).

[5] An equally applicable alternative expression is:

$$\epsilon_{12} = \epsilon_1 + KW_2 + K_1W_1W_2$$

where ϵ_{12} and ϵ_1 are the dielectric constants of the mixture and water, respectively; K and K_1 are constants; and W_1 and W_2 refer to the weight fractions of the water and amide, respectively.

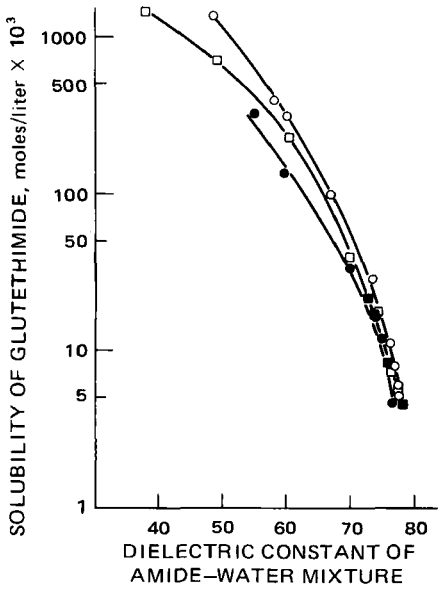

Figure 2—*Solubility of glutethimide in relation to the solution dielectric constant of amide–water mixtures. Key:* O, *tetramethylpimelamide;* ●, *tetramethylsuberamide;* □, *tetramethylazelamide; and* ■, *tetramethylsebacamide.*

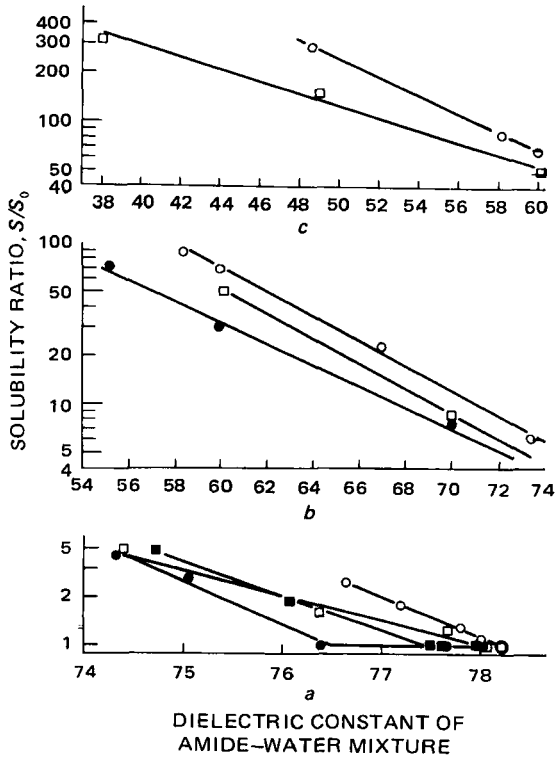

Figure 3—*Solubility ratios of glutethimide* versus *dielectric constants of amide–water mixtures. Key:* a, *water-rich mixtures;* b, *moderate amide concentrations;* c, *amide-rich mixtures;* O, *tetramethylpimelamide;* ●, *tetramethylsuberamide;* □, *tetramethylazelamide; and* ■, *tetramethylsebacamide.*

felt that the glutethimide molecule is of a favorable size to penetrate or incorporate itself into the micelle, causing an increase in solubility. A globular type of micelle for the odd-carbon amides, while an open micelle shape that is configurationally constrained to accommodate more glutethimide molecules, may account for their higher solubility.

As depicted by Fig. 3*b*, with a moderate increase in amide concentrations beyond the micellar region, it is apparent that an environment favorable for the solubilization of glutethimide is created. The odd-carbon amides exhibited a minimum in partial molal volume in this region, and this phenomenon was attributed to maximum cooperation of water clusters in the amide environment with the amides to form "clathrate-like" structures (3). The amides aid in the solubilization of glutethimide by breaking up water clusters surrounding the glutethimide molecules and effectively reducing self-association of glutethimide.

As the environment of the glutethimide molecules becomes progressively reduced in dielectric constant (amide-rich region, Fig. 3*c*) a strong interaction between glutethimide molecules and water clusters persists. Viscosity data of the odd-carbon amide systems reveal a maximum in viscosity in this region (3). It was postulated that an amide-hydrate with an approximate 2:1 solvent–amide ratio was formed at the maximum in the viscosity curve. Formation of this hydrate involved further breakdown of more clusters of hydrogen-bonded water in the vicinity of the glutethimide molecules. The possibility of glutethimide–water associations through hydrophobic bonding is apparent.

SUMMARY AND CONCLUSIONS

Examination of the structures of the tetramethyldicarboxamides indicates that their solubilizing properties can be correlated with the length of the carbon chain to which the amide groups are terminally attached. When taking equimolar concentrations of the amides and noting their corresponding solution dielectric constants (Table I), the following trends are evident:

1. At the water-rich regions of the amide–water systems, just beyond the CMC, the solubilizing action of the amides varies slightly. The solubilizing power parallels the chain length of the amides. This result is to be expected, since the dielectric constants corresponding to equimolar concentrations decrease with the length of the chain. It appears that the higher homologs favor more extensive solvation by water, resulting in the lowering of the solution dielectric constant. Also, since the magnitude and direction of the resultant electrostatic field depend on the orientation of the amide molecules and/or molecular aggregates of varying sizes, it seems that the smaller the amide molecule or its aggregates, the more it can adjust its position to accommodate a variety of orientations favoring higher polarizations.

2. While there is a definite correlation between the dielectric constant and solubilizing properties, deviations occur at higher amide concentrations, indicating a more complex nature of their interactions with water. The two odd-carbon amides, tetramethylpimelamide and tetramethylazelamide, showed consistently greater solubilizing power relative to their even-carbon amide analog, tetramethylsuberamide, within the solubility range of the suberamide. The better solubilizing action of the odd-carbon amides may be attributed to their greater association tendencies with water clusters in the vicinity of the glutethimide molecules; self-associations of glutethimide molecules are effectively reduced, thus promoting solubility. However, the dielectric properties of these amides alone as the parameter for determining solubilizing action could not give a firm interpretation of the molecular events occurring because of the complexity of their association tendencies in aqueous solutions.

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Effects of Bis(2-ethylhexyl) Phthalate on Chromosomes of Human Leukocytes and Human Fetal Lung Cells

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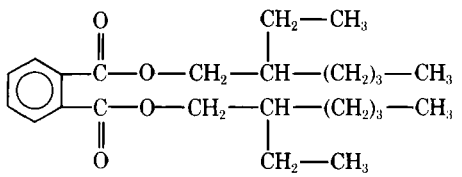
Abstract □ Blood from two male and two female donors was exposed at 37° for 4 hr to concentrations of 60.0, 6.0, 0.6, and 0.06 μg of a widely used plasticizer, bis(2-ethylhexyl) phthalate, per milliliter of blood. The bis(2-ethylhexyl) phthalate was solubilized with polysorbate 80. Appropriate polysorbate and nonpolysorbate controls also were established. Following the 4 hr of incubation, phytohemagglutinin was added and tissue cultures were established. In addition, human fetal lung cells were exposed in tissue culture to a medium containing 6.0 μg/ml of bis(2-ethylhexyl) phthalate in polysorbate 80 for 5 days. Similar controls also were established for these experiments. Analysis of chromosome preparations from all cultures obtained failed to show any increased evidence of isochromatid and chromatid breaks or gaps or abnormal forms at any studied concentration when compared to the control cultures. In addition, analysis of fetal lung cell preparations for aneuploidy failed to reveal any differences between cells from study and control cultures. This study involved a short-term exposure to bis(2-ethylhexyl) phthalate in various concentrations which did not cause damage in leukocytes or fetal lung cells.

Keyphrases □ Bis(2-ethylhexyl) phthalate—effect on chromosomes of human leukocytes and fetal lung cells □ Phthalate esters—bis(2-ethylhexyl) phthalate, effect on chromosomes of human leukocytes and fetal lung cells □ Chromosomes, human leukocyte and fetal lung cell—effect of incubation with bis(2-ethylhexyl) phthalate □ Toxicity, potential—bis(2-ethylhexyl) phthalate, effect on chromosomes of human leukocytes and fetal lung cells □ Plasticizers—bis(2-ethylhexyl) phthalate, effect on chromosomes of human leukocytes and fetal lung cells

Bis(2-ethylhexyl) phthalate (I) is a plasticizer used in the fabrication of polyvinyl chloride medical devices such as blood storage bags, blood administration assemblies, hemodialysis units, and cardiopulmonary bypass units, and it is one of the most widely used of the phthalate esters. In many instances, it represents 40% or more of the total weight of the finished plastic (1). Roll *et al.* (2) demonstrated by GLC techniques that



I

phthalate esters are found almost universally as contaminants on or in items such as laboratory glassware, laboratory chemicals, metal foils, rubber stoppers, and distilled water.

Trimble *et al.* (3) and Guess *et al.* (4, 5) were among the first to note that I leaches out of polyvinyl chloride in the presence of blood or certain other solvents. Since that time, several investigators quantitated the rate of leaching of I from various polyvinyl chloride devices under various conditions (6–10).

Jaeger and Rubin (11) first demonstrated the presence of I in various human tissues following transfusion of blood stored in polyvinyl chloride blood bags. Much research has since been performed to quantify the toxicogenic implications of phthlates in various organs and tissues. Petersen *et al.* (12) showed that I can be detected in liver, lung, and spleen of calves following exposure to cardiopulmonary procedures and in the same organs of humans exposed to prolonged renal hemodialysis.

Recent publications and reviews confirmed that I probably has a low order of acute toxicity (13–15). However, the long-range, subtle toxicogenic potential of this agent is becoming of paramount concern. Guess and coworkers (5, 16) were among the first to suggest potential hazards from long-term exposure of this agent. Observations of cells in tissue culture (19, 20), teratogenic effects (16, 17, 21–24), and effects on reproduction (12, 25) and related studies appear to substantiate this suggestion. While the data are not conclusive and there is incomplete agreement between laboratories, evidence suggests that I and/or its metabolites are toxic at the cellular level, that I interferes with normal reproductive patterns, and that lower molecular weight phthalate esters are teratogenic.

To evaluate possible mechanisms of toxicity and add a dimension to previous studies, human leukocytes and human fetal lung cells were exposed to I at various concentrations and their chromosomes were analyzed for possible changes.