

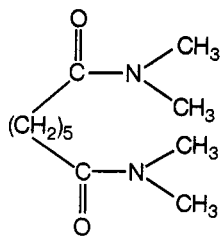
The Dielectric Constant and Dipole Moment of *N,N,N',N'*-Tetramethylpimelamide at 25 °C

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The dielectric constants of pure *N,N,N',N'*-tetramethylpimelamide and its aqueous solutions were measured at 25 °C and 1 MHz. The values obtained were utilized in the calculations of the dipole moment of the compound using Buckingham's theory for pure liquids as well as polar solutes dissolved in polar solvents. The values for the dielectric constant and dipole moment of the pure liquid amide were 37.6 dielectric units and 8.6 D, respectively. The solution dipole moment of 9.5 D was higher than that of the pure liquid and the difference may be attributed to molecular aggregation in the pure liquid state.

The replacement of water by nonaqueous solvents as a means of both stabilizing drugs against hydrolysis and enhancing the solubility of hydrophobic molecules is often employed in pharmacy. Nonaqueous solvents are often combined with water to dissolve a sparingly soluble drug even for injectable preparations (17). Two component solvent systems have been employed and more recently surface active agents have been used extensively.

The solubility of a solute in a solvent is the result of several factors, one of which is the dielectric characteristic of the solvent. *N,N,N',N'*-Tetramethylpimelamide (TMPA), an organic liquid miscible with water in all proportions at 25 °C, exhibits good potential as a solubilizer for poorly soluble drugs (5). The solvent properties of this amide can be attributed to the strong dipole of the amide group and to the good electron donating properties of the carbonyl group. Its water-solubilizing moiety (amide groups) can enter into dipole-dipole interaction with polar water molecules while its hydrocarbon portion can interact with hydrophobic solutes. Such interactions can help overcome the intermolecular forces (self-association) among solute molecules resulting in greater solubility.



The viscosities and partial molal volumes of aqueous solutions of tetramethylpimelamide have been reported recently (6). In continuing efforts to study its physicochemical properties, it was considered desirable to measure its dielectric constant and from the measured value calculate the dipole moment. These dielectric properties may provide useful information concerning its geometric structure and solubilizing action.

Experimental Section

N,N,N',N'-Tetramethylpimelamide was prepared according to a previous procedure (5). The synthesis involved the conversion of pimelic acid (Eastman Kodak Co., Rochester, N.Y.) to pimeloyl chloride by treatment with excess thionyl chloride (Fisher Scientific Co., Fairlawn, N.J.). Pimeloyl chloride was then treated with dimethylamine (Aldrich Chemical Co., Milwaukee,

Wis.) in alkaline media at 5 °C. The product formed was extracted with methylene chloride (Spectranalyzed, Fisher Scientific Co., Fairlawn, N.J.) and washed with distilled water. The extract was dried over anhydrous magnesium sulfate (Fisher Scientific Co.) clarified by filtration and stripped of methylene chloride in vacuo. The extraction, washing, drying, and stripping steps were repeated and the residual oil was subjected to two successive fractional distillation at 0.5 mmHg pressure. The middle fraction which had a boiling point of 157–158 °C at 0.5 mmHg (density at 25 °C, 1.0205 g/ml, and viscosity at 25 °C, 24.1 cP) was determined for purity by vapor phase chromatography (Model 1740-10 Varian gas chromatograph) and checked by differential scanning calorimetry (DSC-1B Perkin-Elmer) and by CHN analysis (Model 185 Hawlett Packard Analyser). Its purity was 99.5%.

Capacitance measurements were made with a General Radio Type 821-A Twin-T impedance measuring circuit (General Radio Co., Cambridge, Mass.). Radiofrequency current was supplied by a General Radio Type 1001-A standard signal generator and a Hallicrafters S-108 multiband communication receiver (Hallicrafters, Inc., Chicago, Ill.) was used as a null point detector. The design and use of this bridge have been thoroughly discussed by Gormley (8) and Hovermale (9).

The cells used in conjunction with the bridge assembly were two-terminal parallel plate glass cells. The electrodes were made from concave platinum plates which were 3 cm in diameter and were 3 mm apart. The volume of the cells was approximately 30 ml. 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 Twin-T bridge by shielded coaxial cables (General Radio Type 274) having a dual banana plug connection at each end. The principal aspects for determining the cell constants and for calculating dielectric constants have been described previously (11, 18). Similar glass cells with platinum electrodes have been found to be structurally satisfactory and convenient to use for measurement on low-conducting liquids having high dielectric constants (1, 4, 10). All capacitance measurements were made at 1 MHz; residual inductance corrections were assumed to be negligible at this frequency (8). Scale corrections as supplied by the General Radio Corporation were made on all capacitance changes. The standard media used in the determination of cell constants were air and water which have dielectric constants of 1.0005 and 78.304 (12), respectively, at 25 °C.

The temperature for the dielectric constant determinations was controlled within ± 0.05 °C using a Cannon Model H-1 constant temperature bath (Cannon Instruments, Pa.) filled with light paraffin oil. The bath thermometer with 0.1 °C subdivisions was compared with an NBS-calibrated thermometer; appropriate corrections were applied.

All the amide-water solutions were prepared on a weight basis using high purity reverse osmosis water that was further purified by successive passage through a demineralizing unit (Corning Model LD-3, Corning Glass Works, Parkersburg, W.Va.) and a filter assembly containing a 0.2 μ m cellulose ester membrane filter (GSPW 02500, Millipore Corporation, Bedford, Mass.). Water treated in this manner had a specific conductivity of about 10^{-7} ohm $^{-1}$ cm $^{-1}$ and contained less than 250 particulates per liter (>2 μ m particle size) as measured by an au-

Table I. The Dielectric Constants and Other Related Properties of *N,N,N',N'*-Tetramethylpimelamide-Water Mixtures at 25 °C

Wt % amide	Mole fraction of amide	Density (g/ml)	Refractive index	Dielectric constant
3.55	0.0031	0.9970	1.3400	77.6
9.31	0.0086	1.0040	1.3495	76.3
22.60	0.0239	1.0102	1.3719	73.1
42.51	0.0585	1.0254	1.4059	66.8
100.00	1.000	1.0205	1.4862	37.6

tomatic particle counter (High Accuracy Products Corporation, Claremont, Calif.). The cells were cleaned with conductivity water and rinsed with distilled acetone. They were then blown dry with dry air before they were filled with the test solutions. The cells were placed on the constant temperature bath and allowed to equilibrate for at least 15 min before connection to the Twin-T bridge. Dielectric constants measured in this manner were reproducible within ± 0.1 dielectric unit at 25 °C.

Densities were obtained using pycnometers similar to those described by Sears and O'Brien (15) and refractive indices were measured using an Abbe refractometer at 25 °C.

Results and Discussion

Capacitance changes measured by the bridge are related to the dielectric constant by the equation

$$\Delta C = C_0 + \epsilon C_v \quad (1)$$

The experimental cell parameters, C_0 and C_v used were: $C_0 = 3.53$ pF, $C_v = 1.3472$ pF for cell I; $C_0 = 4.20$ pF, $C_v = 1.5146$ pF for cell II.

The dielectric constant, refractive index, and density data of the amide-water mixtures are given in Table I. The values reported are the averages of duplicate measurements. The precision was within 0.2% for dielectric constant and 0.02% for densities and refractive indices.

Figure 1 depicts the variation of the solution dielectric constant over the entire concentration range. It is evident from the curves that, at dilute concentrations, linear dependence is observed. However, at amide concentrations greater than 20% (2 mol %), a curvature is produced. The curvature may be assumed arbitrarily as due to the formation of molecular aggregates. This assumption is supported by light scattering studies (5) on this amide which showed a rapid increase in the number of aggregates with increasing concentration resembling the behavior of high polymer solutions. It is apparent that self-association produced the aggregates. This tendency for self-association is very likely to occur since the number of water molecules available for interaction with the amide dipole (either with the two unshared pairs of electrons on the carbonyl oxygen or on the dimethyl substituted nitrogen on each end of the amide) is reduced at high amide concentrations.

The dielectric constant of the pure liquid amide was found to be 37.6. Within experimental error, this value is the same as that reported for *N,N*-dimethylacetamide (14) and is not very different from that of *N,N*-dimethylformamide.

An attempt was made to determine the dielectric constants of higher homologues of the series,

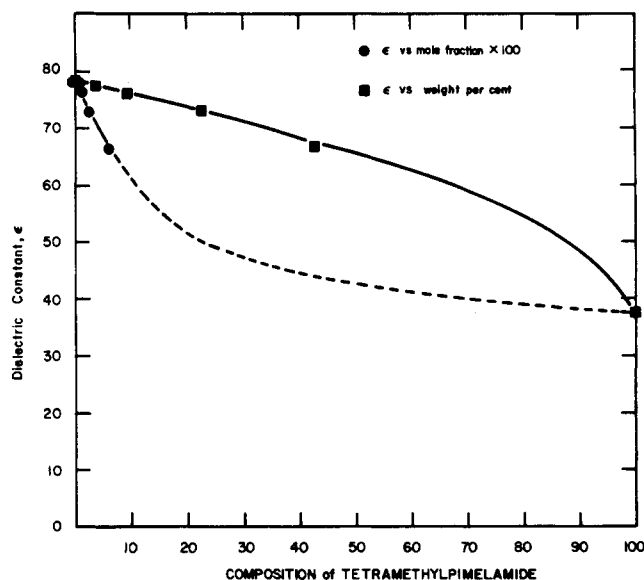
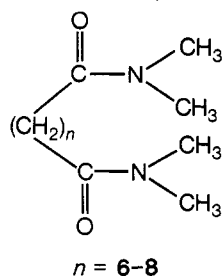


Figure 1. Dielectric constant vs. composition of *N,N,N',N'*-tetramethylpimelamide.

by heating the amides (purity, >99%) to their melting points (88–90 °C). The melted amides were highly conductive preventing capacitance measurements at 1 MHz. Additionally, it was noted that slight dissociation took place and any value reported under such conditions would be unreliable.

Having obtained values of the dielectric constants of the pure liquid amide and its aqueous solutions, the dipole moment can then be calculated. The model chosen for this compound was that of Buckingham (2, 3) which treats the solute molecule as an ellipsoid uniformly polarized in a principal direction surrounded by a homogeneous and continuous medium whose dielectric constant is equal to that of the bulk of the solution. His equation for the orientation polarization of pure liquids, σP_1 , is given by eq 2 and the orientation polarization of the solute, σP_2 , is indicated in eq 3.

$$\sigma P_1 = \frac{4\pi N \mu_1^2}{9kT} = \frac{(\epsilon_1 - n_1^2)[\epsilon_1 + (n_1^2 - \epsilon_1)A_1]^2}{\epsilon_1(2\epsilon_1 + n_1^2)[1 + (n_1^2 - 1)A_1]^2} \frac{M_1}{\rho_1} \quad (2)$$

$$\sigma P_2 = \frac{4\pi N \mu_2^2}{9kT} = \frac{1}{X_2} \left[\frac{\epsilon_{12} + (n_2^2 - \epsilon_{12})A_2}{1 + (n_2^2 - 1)A_2} \right]^2 \times \left[\frac{(\epsilon_{12} - n_{12}^2)(X_1 M_1 + X_2 M_2)}{\epsilon_{12}(2\epsilon_{12} + n_{12}^2)\rho_{12}} - X_1(\sigma P_1) \left(\frac{1 + (n_1^2 - 1)A_1}{\epsilon_{12} + (n_1^2 - \epsilon_{12})} \right)^2 \right] \quad (3)$$

The shape factor A for the amide was determined from its axial ratio, b/a , following the method of Westheimer and Kirkwood (19) and referring to the graphs of Osborn (13). An A value of 0.21 was calculated using a prolate spheroid with its b/a equal to 0.59. σP_2 at infinite dilution was calculated by means of a least-squares computer program.

The computation of the dipole moments from Buckingham's theory is carried out as in his paper and also that of Edward, Farrell, and Job (7). The value of the dipole moment calculated by the Kirkwood (16) equation

$$\mu_2 = (0.01281 \times 10^{-18}) \times \left[\frac{TM_2}{\rho_2} \left(\frac{\{\epsilon_2 - 1\}\{2\epsilon_2 + 1\}}{9\epsilon_2} - \frac{n_2^2 - 1}{n_2^2 + 2} \right) \right]^{1/2} \quad (4)$$

is included for comparative purposes.

Table II. The Calculated Dipole Moment of *N,N,N',N'*-Tetramethylpimelamide at 25 °C

Theoretical treatment	Dipole moment (D)
Kirkwood	9.0
Buckingham (pure liquid)	8.6
Buckingham (solution)	9.5

Table II shows the calculated dipole moments. The μ values obtained using Buckingham's equations for pure liquid and polar solute in polar solvent are in good agreement with the Kirkwood equation. The μ value from the Buckingham equation for pure liquid is slightly lower than that obtained from the Kirkwood equation for pure liquid. The solution dipole moment is about 10% higher than the pure liquid value of the Buckingham equation. The discrepancy observed between the pure liquid moment and the solution dipole moment may be due to molecular aggregation in the pure liquid state.

The moment of the amide molecule is the resultant of the moments of the two C=O, two C—N, and four N—CH₃ bonds with the expectation that the long CH₂ chain would have little effect on the moment. The structure of the amide also indicates that it can be regarded as consisting of two halves, each containing four dipoles.

The dipole moment of *N,N*-dimethylacetamide (14) is 3.96. From the calculated dipole moment of *N,N,N',N'*-tetramethylpimelamide, the molecule seems to be equivalent to two *N,N*-dimethylacetamide molecules forming a linear dimer. The two amide groups appear to be oriented as nearly as possible in the same direction with respect to the molecular axis. This type of orientation could give maximum moment to the molecule. The fairly long methylene chain to which the amide groups are terminally attached seems to be flexible enabling the amide groups to orient independently of each other. Parallel alignment of the carbonyl groups in the same direction best fits the calculated dipole moment in this study.

Nomenclature

oP = orientation polarization

μ = dipole moment

ϵ = dielectric constant

N = Avogadro's number

k = Boltzmann's constant

T = absolute temperature

n = refractive index

ρ = density

A = shape factor

M = molecular weight

a = major semiaxis

b = minor semiaxis

X = mole fraction

ΔC = measured change in capacitance

C_0 = invariant capacitance within the leads and bridge

C_v = cell constant which depends upon the geometrical dimensions of the cell

Subscript

1 = liquid or solvent

2 = solute

12 = solution

Literature Cited

- (1) Akerlof, G. A., *J. Am. Chem. Soc.*, **54**, 4125 (1932).
- (2) Buckingham, A. D., *Aust. J. Chem.*, **6**, 93 (1953).
- (3) Buckingham, A. D., *Aust. J. Chem.*, **6**, 323 (1953).
- (4) Coates, G. E., Coates, J. E., *J. Chem. Soc.*, 77 (1944).
- (5) DeLuca, P. P., Lachman, L., Schroeder, H., *J. Pharm. Sci.*, **62**, 1320 (1973).
- (6) DeLuca, P. P., Rebagay, T. V., *J. Phys. Chem.*, **79**, 2493 (1975).
- (7) Edward, J. T., Farrell, P. G., Job, J. L., *J. Phys. Chem.*, **77**, 2191 (1973).
- (8) Gormley, J. F., Ph.D. Dissertation, University of Kentucky, Lexington, Kentucky, 1952.
- (9) Hovermale, R. A., Ph.D. Dissertation, University of Kentucky, Lexington, Ky., 1958.
- (10) Kempa, R., Lee, W. H., *J. Chem. Soc.*, 1936 (1958).
- (11) Leader, G. R., *J. Am. Chem. Soc.*, **73**, 856 (1951).
- (12) Maimberg, C. G., Maryott, A. A., *J. Res. Natl. Bur. Stand.*, **56**, 1 (1956).
- (13) Osborn, J. A., *Phys. Rev.*, **67**, 351 (1945).
- (14) Purcell, W. P., Singer, J. A., *J. Phys. Chem.*, **71**, 4316 (1967).
- (15) Sears, P. G., O'Brien, W. C., *J. Chem. Eng. Data*, **13**, 112 (1968).
- (16) Smyth, C. P., "Dielectric Behavior and Structure", McGraw-Hill, New York, N.Y., 1955.
- (17) Spiegel, A. J., Noseworthy, M. M., *J. Pharm. Sci.*, **52**, 917 (1963).
- (18) Vaughn, J. W., Sears, P. G., *J. Phys. Chem.*, **62**, 183 (1958).
- (19) Westheimer, F. H., Kirkwood, J. G., *J. Chem. Phys.*, **6**, 513 (1938).

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