Dielectric Constants of Solid–Liquid and Liquid–Liquid Systems as a Function of Composition

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Abstract □ The dielectric constant of a solid substance in the dissolved state may be found by using a solvent with a dielectric constant that remains invariable when the solid substance is dissolved. The slope values obtained from dielectric constant *versus* concentration plots of the solid substance in two solvents with different dielectric constants are extrapolated or interpolated. The dielectric constant of a solid substance in the dissolved state also can be found directly from the dielectric constants of solutions of the solid in one solvent at two concentrations. The dielectric constants are converted to polarizations, and the two values allow calculations of the polarizations of the solvent and solute separately. From the polarization of the solute, one can calculate its dielectric constant (in dissolved state). Such a procedure is correct only if the dielectric constant is concentration independent.

Keyphrases □ Dielectric constants—solid–liquid and liquid–liquid systems, as a function of composition, polarizations, monoethyl ether, diethylene glycol, propylene glycol, methylparaben □ Solid–liquid systems—dielectric constants determined as a function of composition □ Liquid–liquid systems—dielectric constants determined as a function of composition

Figure 1—*Dielectric constant of monoethyl ether of diethylene glycol with various amounts of propylene glycol (Table I). These values are expressed as volume fractions (●) and weight fractions (O).*

Dielectric constants (ϵ) are used in pharmaceutics for a variety of correlations, particularly concerning solubility (1–5) and hydrophobic–lyophobic balance (6, 7). Since binary or larger component number systems are frequently involved in basic investigations in pharmaceutics, the behavior of ϵ as a function of composition is important.

In a binary system, ϵ is a function of the content (x) of one of the components (A or B). For two pure liquids, A and B, one can introduce the respective dielectric constants ϵ_A and ϵ_B and can estimate the dielectric constant, ϵ, of a mixture of the two *via* a weight-averaging formula:

$$\epsilon = x_A \epsilon_A + x_B \epsilon_B \qquad (Eq. 1)$$
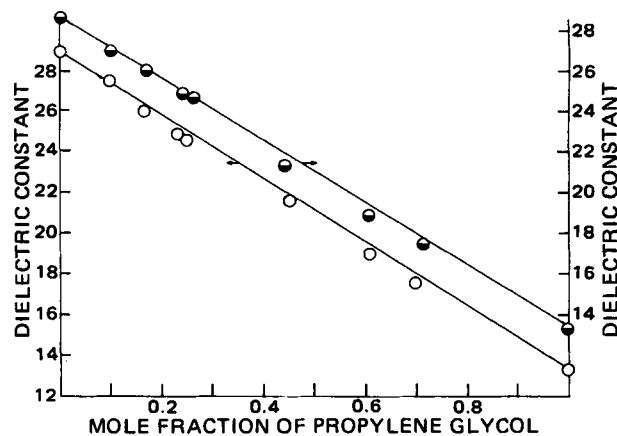
Whether x should be a volume or a weight fraction has been discussed previously (7, 8) and will be addressed in a subsequent article.

If one component (A) is a solid, then Eq. 1 cannot be used directly unless one knows ϵ_A in a dissolved state (ϵ_A'). Thus, there is a need for establishing ϵ_A' for substances that are solid at room temperature (or other temperatures of investigation). This requirement is particularly important (9) if one evaluates macroscopic properties (*e.g.*, hydrophile–lipophile balance) for a series of compounds where one or more are solid and the remainder liquid at room temperature. In such a case, one would be forced to work at temperatures above the melting point of the highest melting substance in the series, and this can introduce other problems, both experimental and theoretical.

This article deals with two methods of obtaining ϵ^l for a substance that is solid at the temperature of investigation.

EXPERIMENTAL

Materials—Analytical grade materials were used as received. As shown in Table I, various dielectric constants were obtained by mixing
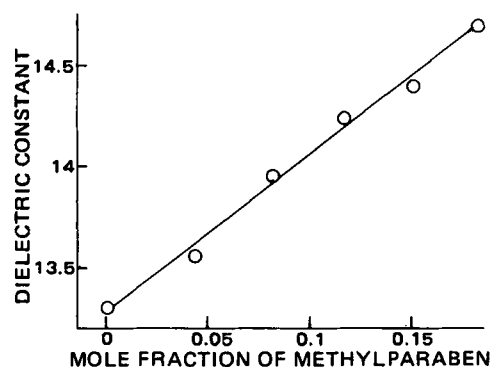
the monoethyl ether of diethylene glycol[1] with either propylene glycol or water in various proportions. Other dielectric constants were obtained by use of other solvents (as a check for solvent nonspecificity)—*viz.*, polyethylene glycol 400[2], triethylene glycol[3], and mixed mono- and diglycerides of saturated C_{16-18} fatty acids[4]. Methylparaben USP[5] was used as the solute.

Determination of Dielectric Constant—The solutions were prepared without volume adjustment, equilibrated thermally in a thermostatic bath at 25°, and brought to volume with solvent. After their densities were determined (to allow concentration conversions), the solutions were placed in the cell of a Q-meter[6] to measure dielectric constants. The cell was thermostated at 25 ± 0.1°, and the dielectric constant was determined at 1340 kHz. The apparatus was equipped with a "powder cell," which, in a similar fashion, allows measurement of the dielectric constant of a solid.

Determinations were made at nine different concentrations in each

Figure 2—*Effect of mole fraction of methylparaben on the dielectric constant in solutions in monoethyl ether of diethylene glycol.*

[1] Gattefosse, SFPA, St. Priest, France.
[2] Hoechst Chemical Co., Hoechst, West Germany.
[3] Rhone-Poulenc Chemical Co., Paris, France.
[4] Labrasol Solvent, Gattefoss, SPFA, St. Priest, France.
[5] Merck & Co., Rahway, N.J.
[6] Q-metre Ferisol T 803 A, Geffroy et Cie, Paul-Vaillant-Couturier, 78 Trappes, France.

Table I—Solvents Used in Mixtures for Dielectric Constant Measurements

Solvent	Solvent A	Solvent B	Volume Fraction	Mole Fraction	Weight Fraction	Dielectric Constant, 25°
1	Monoethyl ether of diethylene glycol	—	1.0	1.0	1.0	13.3
2	Monoethyl ether of diethylene glycol	Propylene glycol	0.715	0.928	0.709	17.6
3	Monoethyl ether of diethylene glycol	Propylene glycol	0.617	0.899	0.606	18.9
4	Monoethyl ether of diethylene glycol	Propylene glycol	0.454	0.321	0.443	21.3
5	Monoethyl ether of diethylene glycol	Propylene glycol	0.240	0.144	0.231	24.9
6	Monoethyl ether of diethylene glycol	Propylene glycol	0.170	0.100	0.163	26.1
7	Monoethyl ether of diethylene glycol	Propylene glycol	0.100	0.050	0.096	27.5
8	—	Propylene glycol	0.000	0.000	0.000	28.5
9	Monoethyl ether of diethylene glycol	Water	0.909	0.571	0.908	20.8
10	Monoethyl ether of diethylene glycol	Water	0.869	0.471	0.868	23.9
11	Monoethyl ether of diethylene glycol	Water	0.823	0.386	0.821	26.6
12	Monoethyl ether of diethylene glycol	Water	0.792	0.337	0.791	29.6
13	Polyethylene glycol 400	—	1.00	1.00	1.00	14.0
14	Triethylene glycol	—	1.00	1.00	1.00	23.5
15	Mono- and diglycerides of saturated C_{16-18} fatty acids	—	1.00	1.00	1.00	9.9

of the 15 solvents listed in Table I. Measurement of the dielectric constant of solid methylparaben also was carried out by measuring the dielectric constant of a suspension in a mixture of chloroform and the monoethyl ether of diethylene glycol[1] having a density matching that of methylparaben. This was done to minimize settling during the dielectric constant determination.
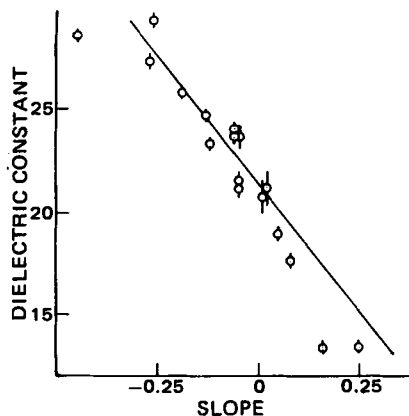
RESULTS AND DISCUSSION

A typical set of dielectric constants plotted *versus* composition of a liquid–liquid binary mixture is shown in Fig. 1. Plotting is carried out as a function of both weight and volume fractions. The line shown is not a least-squares fit line but connects the terminal experimental points, This line shows that all of the experimental points lie on one side of the chord, indicating that there is some curvature in either case. If one includes x = 0, this curvature becomes more evident.

When one component is a solid, linearity is retained, as in the case studied here (Fig. 2). These plots cannot be made over the entire concentration range because of the limiting solubility. Good linearity of such plots was observed with all solvents in Table I, the correlation coefficients being above 0.98 for all plots with six to nine data points. Therefore, one can write for the dielectric constant of the solution (ϵ):

$$\epsilon = \gamma N_A + \zeta \qquad \text{(Eq. 2)}$$

where N_A is mole fraction of methylparaben and where the slope, γ, and the intercept, ζ, are functions of the solvent used, *i.e.*, are functions of the solvent dielectric constant, ϵ_B.

With a solvent for which $\gamma = 0$, addition of methylparaben to the solvent will not change the dielectric constant, and the dielectric constant of the solvent and solute will be identical. If such a procedure is adopted, the dielectric constant of methylparaben in the dissolved state, ϵ'_A, can be found as the value of ϵ_B where γ becomes zero. The least-squares fit values of γ (slopes) from the solvents in Table I are shown in Fig. 3 as a function of the solvent dielectric constant. This plot is linear, and the least squares fit of the line is given by $\epsilon_B = -20.75\gamma + 21.0$. The ordinate intercept occurs at 21.0 ± 0.6. At this dielectric constant, the solution will have a dielectric constant that is concentration independent.

For accuracy, it should be noted that the rationale for weighted averaging (Eq. 1) is based on polarizations, P (10), rather than on dielectric constants. Polarizations of molecules in the condensed states are usually determined in the following fashion. The substance (with a molecular weight of M_A) is dissolved in a solvent of molecular weight M_B. The mole fractions of the solute and solvent are N_A and N_B, respectively. The dielectric constant, ϵ, of this binary mixture is then measured. This procedure allows calculation of the composite polarization, P:

$$P = \frac{\epsilon - 1}{\epsilon + 2} \frac{N_A M_A + N_B M_B}{\rho} \qquad \text{(Eq. 3)}$$

where ρ is the mixture density. The composite polarization is assumed to be related to the individual polarizations, P_A and P_B (8), by the relation:

$$P = N_A P_A + N_B P_B = (P_A - P_B)N_A + P_B \qquad \text{(Eq. 4)}$$

since:

$$N_A + N_B = 1 \qquad \text{(Eq. 5)}$$

If ϵ is not composition dependent, then Eqs. 3 and 4 can be combined to:

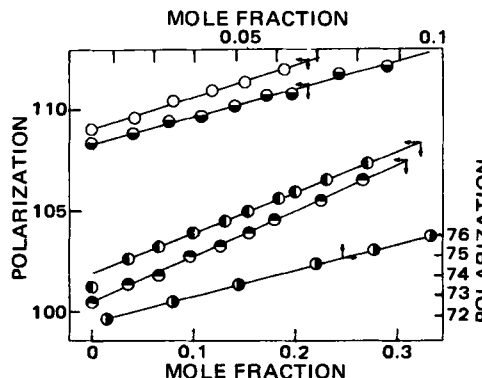$$P = \frac{Q}{\rho} (N_A M_A + N_B M_B) = N_A P_A + N_B P_B \qquad \text{(Eq. 6)}$$

where $Q = (\epsilon - 1)/(\epsilon + 2)$. Equation 6 has the unique solution:

$$P_A = QM_A/\rho \qquad \text{(Eq. 7a)}$$

and:

$$P_B = QM_B/\rho \qquad \text{(Eq. 7b)}$$

allowing direct evaluation of P_A from ϵ. If ϵ is concentration dependent, then the direct transition from Eq. 5 to Eq. 7a is not necessarily valid. For this reason, the dielectric constant of methylparaben in various solvent mixtures was determined. When conversions to polarization values are carried out according to Eq. 3, plots such as Fig. 4 result and Eq. 4 is

Figure 3—*Slopes, γ, of data plotted according to Eq. 2 as the abscissa with the dielectric constant of the pure solvent, ϵ_B, as the ordinate.*

Figure 4—*Effect of mole fraction of methylparaben on polarization observed in solvents of dielectric constants: 13.4 (○, Solvent 1), 20.8 (◑, Solvent 9), 23.9 (◐, Solvent 10), 27.5 (◔, Solvent 7), and 29.6 (◓, Solvent 12). The solvent numbers correspond to designations in Table I.*

Table II—Slopes and Intercepts of Graphs Plotted According to Eq. 4 for Methylparaben

Dielectric Constant, 25° [a]	R [b]	n [c]	Intercept	Slope	$P(1)$ at $N_A = 1$
17.6	0.985	8	98.8	27.7	121.4
18.9	1.000	8	94.8	26.8	121.5
21.3	1.000	8	88.4	32.6	121.0
23.5	0.998	9	106.1	16.8	122.8
21.3	1.000	7	78.6	42.7	121.3
28.5	1.000	5	51.7	69.7	121.4
23.5	0.986	8	117.6	3.33	120.9
13.3	0.994	7	109.2	15.3	124.5
23.9	1.000	9	101.7	21.0	122.7
20.8	0.998	9	108.4	13.8	122.2
29.6	0.999	9	100.5	22.7	123.2
24.9	0.999	6	73.6	48.3	122.0
26.1	1.000	5	71.4	49.8	121.2
27.5	1.000	5	69.4	51.5	120.7

[a] Solvents are listed in Table I. [b] Correlation coefficient. [c] Number of points from which the least-squares parameters were determined.

obeyed. The least-squares statistics for these lines are shown in Table II.

According to Eq. 4, if extrapolation is carried out to $N_A = 1$, a value is obtained for the polarization of the solute, i.e., $P_A = P(1)$, where the latter is the extrapolated value. These values are listed in Table II; even though the extrapolation is long, there is good agreement. By inserting

the average of these values (122.7), the density of methylparaben (1.09 g/cm³), and its molecular weight (152) into Eq. 7a, one obtains:

$$Q = \frac{\epsilon - 1}{\epsilon + 2} = P_A \rho / M_A = 1.09(122.7/152) = 0.88 \qquad (Eq. 8)$$

This equation gives $\epsilon = 21.8$, which coincides with the previously quoted value $\gamma = 21.0 \pm 0.6$. This value may rationally be denoted ϵ'_A, i.e., the dielectric constant of the methylparaben in the dissolved state. This result differs significantly from values obtained by using a solids cell in the Q-meter [ϵ_A (solid) = 2.70] and suspension techniques ($\epsilon = 5.8$).

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Acid Dissociation and Metal Complex Formation Constants of Penicillamine, Cysteine, and Antiarthritic Gold Complexes at Simulated Biological Conditions

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Abstract □ Ionization constants for acid functions of D-penicillamine, L-cysteine, thiomalic acid, and thioglucose were measured by pH titration at 37° and 0.15 M ionic strength. Chelate formation constants for these ligands with calcium(II), iron(III), and gold(I) were then determined under the same conditions chosen to approximate the *in vivo* situation. Only iron(III) formed both 1:1 and 1:2 chelates with D-penicillamine, L-cysteine, and thiomalate; calcium formed weak and gold strong 1:1 complexes with all ligands studied. Because of precipitate formation, the stability constants for the systems thioglucose-iron(III), D-penicillamine-gold(I), and L-cysteine-gold(I) had to be determined indirectly with thiomalic acid as the competing ligand. The *in vivo* fate of antiarthritic gold(I) compounds remained uncertain, but gold(I) chelates probably persist as such for extended periods.

Keyphrases □ Penicillamine—acid dissociation and metal complex formation constants with calcium(II), iron(III), and gold(I), simulated biological conditions □ Cysteine—acid dissociation and metal complex formation constants with calcium(II), iron(III), and gold(I), simulated biological conditions □ Thiomalic acid—acid dissociation and metal complex formation constants with calcium(II), iron(III), and gold(I), simulated biological conditions □ Thioglucose—acid dissociation and metal complex formation constants with calcium(II), iron(III), and gold(I), simulated biological conditions □ Gold complexes—stability constants of antiarthritic gold(I) complexes and penicillamine and cysteine, simulated biological conditions □ Iron(III) and calcium(II) complexes—with penicillamine, cysteine, thiomalic acid, and thioglucose, simulated biological conditions

D-Penicillamine (I), 3-mercapto-D-valine, is the accepted therapeutic agent for the treatment of Wilson's disease (1, 2) and cystinuria (3, 4). Compound I is also a well-known antidote in lead and mercury poisoning (5–7) and has been investigated as a protective agent against radiation (8). It has been approved for rheumatoid arthritis therapy (9) in several countries but not in the United States because of some potentially severe side reactions. However, I success rates in rheumatoid arthritis treatment

are at least as high as those with the established drugs aurothioglucose (II) and aurothiomalate (III), and dangerous toxic side effects can largely be avoided by careful monitoring of the patient's blood (10).

The mode of action of I in cystinuria is well understood—the mixed disulfide (IV) formed with cysteine (V) is more soluble than cystine (VI) (11). The therapeutic value in Wilson's disease as well as in the treatment of heavy metal poisoning results from its strong *in vivo* metal