

Relationship of Composition of Nonaqueous Binary Solvent Systems and Dielectric Constant

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Abstract □ Five nonaqueous binary solvent systems are described. Each system is composed of a polar and a nonpolar component, both of which are inert and do not exhibit leveling effects. The dielectric constant of each system is related to the composition of the polar component expressed as mole fraction, percent weight by weight and volume by volume. Consequently, it is possible to prepare a solvent mixture with a specific dielectric constant within the range of values of dielectric constant provided by the system. The formulas relating dielectric constant to the particular expression of the composition of the polar component are reported.

Keyphrases □ Nonaqueous binary solvent systems—relationship between composition of polar component and dielectric constant, equation □ Dielectric constant of nonaqueous binary solvent system—relationship to composition of polar component, equation □ Solvent systems, nonaqueous binary—relationship between composition of polar component and dielectric constant, equation

The literature on nonaqueous titrimetry has expanded considerably over the last 3 decades. Solvents and their merits, solvent-solute interactions, titrants and their advantages, electrode systems, and different combinations of electrodes have been studied extensively, and these and similar topics were reviewed (1). The scope of nonaqueous solvent chemistry, the role of the solvent in chemical reactions, and related topics were discussed (2), and a thorough treatment of the electronic theory of acids and bases, acidic and basic radicals, neutralization, displacement, and acid and base catalysis was presented (3). Kolthoff and Bruckenstein (4) considered acid-base strength and equilibria in nonaqueous solutions.

Excellent reviews of the literature on nonaqueous titrimetry (5-8) and on its use in pharmacy (9) were presented. Theory, titrants and their standardization, solvents, and applications in general and in pharmaceutical analysis were covered (9). In all, wherever nonaqueous solvents are discussed the importance of the dielectric constant of the solvent is also emphasized and qualitative inferences are usually given. However, a rigid quantitative relationship is seldom indicated. In fact, in potentiometric titrations in nonaqueous media as well as any other scientific study where such media are employed and where the dielectric constant of the medium is of im-

portance, a binary solvent system that is well defined in terms of the dielectric constant and the corresponding composition should be useful.

THEORETICAL

When assuming an ideal mixture of two solvents, one nonpolar (referred to as Solvent 1) and the other polar (referred to as Solvent 2) where there is no change in the volume of the two solvents upon mixing and the effect of electrical forces of surrounding molecules on each other is negligible, the following terms can be defined:

M_1 = gram molecular weight of Solvent 1

M_2 = gram molecular weight of Solvent 2

n_1 = moles of Solvent 1

n_2 = moles of Solvent 2

X_1 = mole fraction of Solvent 1 in the mixture of the two solvents

X_2 = mole fraction of Solvent 2 in the mixture of the two solvents

\bar{V}_1 = molar volume of pure Solvent 1 = M_1/ρ_1 , in which ρ designates density

\bar{V}_2 = molar volume of pure Solvent 2 = M_2/ρ_2 , in which ρ designates density

\bar{P}_1 = molar polarization of pure Solvent 1

\bar{P}_2 = molar polarization of pure Solvent 2

P_m = total molar polarization of solvent mixture

$P_m = X_1\bar{P}_1 + X_2\bar{P}_2$

M_m = weight of 1 mole of mixture

$M_m = (n_1M_1 + n_2M_2)/(n_1 + n_2) = [(n_1M_1)/(n_1 + n_2)] + [(n_2M_2)/(n_1 + n_2)]$

$M_m = X_1M_1 + X_2M_2$

V_m = volume of 1 mole of mixture

$V_m = (n_1\bar{V}_1 + n_2\bar{V}_2)/(n_1 + n_2) = [(n_1\bar{V}_1)/(n_1 + n_2)] + [(n_2\bar{V}_2)/(n_1 + n_2)]$

$V_m = X_1\bar{V}_1 + X_2\bar{V}_2$

$\rho_m = (X_1M_1 + X_2M_2)/(X_1\bar{V}_1 + X_2\bar{V}_2)$, with ρ_m = (weight of 1 mole of mixture)/(volume of 1 mole of mixture)

Debye (10) reasoned that $P_m = X_1\bar{P}_1 + X_2\bar{P}_2$ and \bar{P}_1 is constant. \bar{P}_2 is considered constant here based on the assumptions of ideality of the mixture of the two solvents; however, it is not constant in real mixtures.

For nonpolar liquids and dilute solutions of polar solutes in nonpolar solvents, Eq. 1 is available (11):

$$P_m = [(D - 1)/(D + 2)](M/\rho) \quad (\text{Eq. 1})$$

where P_m is the molar polarization. This quantity has the dimensions of volume and is really a molar polarizability. D is the dielectric constant, M is the gram molecular weight of the dielectric, and ρ is the density of the dielectric. The total molar polarization quantity, P_m , includes contributions from both the induced dipoles (induction effect) and the permanent dipoles (orientation

Table I—Best Values for Coefficients a , b , c , and d of $D_m = (aX_1 + bX_2)/(cX_1 + dX_2)$ Calculated by the Computer

Binary Solvent System	a	b	c	d
Benzene-acetonitrile	4.5840×10^{-3}	3.7530×10^{-2}	2.1153×10^{-3}	1.0000×10^{-3}
Benzene-nitromethane	4.5561×10^{-3}	3.5975×10^{-2}	2.2796×10^{-3}	1.0000×10^{-3}
Benzene-nitrobenzene	1.7589×10^{-2}	1.9965×10^{-1}	7.9076×10^{-3}	5.7292×10^{-3}
Benzene-acetone	1.6931×10^{-1}	9.9052×10^{-1}	7.7332×10^{-2}	4.7205×10^{-2}
Benzene-methyl isobutyl ketone	1.8045×10^{-1}	9.9064×10^{-1}	7.9600×10^{-2}	7.7053×10^{-2}

effect). If P_m , M , and ρ for a certain solvent or solvent mixture are known, the dielectric constant, D , can be calculated. Thus, D also has contributions from the induced dipoles and the permanent dipoles and as such can be used as a physical index representing the total intermolecular interactions in a solvent or solvent mixture.

From the formula $P_m = [(D - 1)/(D + 2)](M/\rho)$ and the fact that $V_m = M/\rho_m$, the following can be derived:

$$P_m = [(D_m - 1)/(D_m + 2)]V_m \quad (\text{Eq. 2})$$

where D_m is the dielectric constant of the mixture, and:

$$P_m D_m + 2P_m = V_m D_m - V_m \quad (\text{Eq. 2a})$$

$$D_m(P_m - V_m) = -2P_m - V_m \quad (\text{Eq. 2b})$$

$$D_m = (-2P_m - V_m)/(P_m - V_m) = (2P_m + V_m)/(V_m - P_m) \quad (\text{Eq. 2c})$$

$$V_m + 2P_m = X_1 \bar{V}_1 + X_2 \bar{V}_2 + 2X_1 \bar{P}_1 + 2X_2 \bar{P}_2 \quad (\text{Eq. 2d})$$

$$V_m + 2P_m = X_1(\bar{V}_1 + 2\bar{P}_1) + X_2(\bar{V}_2 + 2\bar{P}_2) \quad (\text{Eq. 2e})$$

$$V_m - P_m = X_1 \bar{V}_1 + X_2 \bar{V}_2 - X_1 \bar{P}_1 - X_2 \bar{P}_2 \quad (\text{Eq. 2f})$$

$$V_m - P_m = X_1(\bar{V}_1 - \bar{P}_1) + X_2(\bar{V}_2 - \bar{P}_2) \quad (\text{Eq. 2g})$$

$$D_m = [X_1(\bar{V}_1 + 2\bar{P}_1) + X_2(\bar{V}_2 + 2\bar{P}_2)]/[X_1(\bar{V}_1 - \bar{P}_1) + X_2(\bar{V}_2 - \bar{P}_2)] \quad (\text{Eq. 2h})$$

Let:

$$\bar{V}_1 + 2\bar{P}_1 = a \quad (\text{Eq. 3a})$$

$$\bar{V}_2 + 2\bar{P}_2 = b \quad (\text{Eq. 3b})$$

$$\bar{V}_1 - \bar{P}_1 = c \quad (\text{Eq. 3c})$$

$$\bar{V}_2 - \bar{P}_2 = d \quad (\text{Eq. 3d})$$

Then for an ideal binary solvent system:

$$D_m = (aX_1 + bX_2)/(cX_1 + dX_2) \quad (\text{Eq. 4})$$

The D_m values measured for a series of binary solvent systems of a nonpolar and a polar solvent can be used to find the best values of a , b , c , and d with the aid of a computer. Once these values are found, the entire composition of the binary solvent system and the corresponding dielectric constant can be represented by this formula.

EXPERIMENTAL

Selection of Solvent Systems—After studying and evaluating the dielectric constant, the acidity and/or basicity, the autoionization, the leveling effect, the chemical reactivity, and the toxicity of a large number of solvents, the following were selected as the polar components of the five binary solvent systems to be investigated: acetonitrile, nitromethane, nitrobenzene, acetone, and methyl isobutyl ketone. Benzene was selected as the nonpolar component in the following solvent systems: benzene-acetonitrile, benzene-nitromethane, benzene-nitrobenzene, benzene-acetone, and benzene-methyl isobutyl ketone. All reagents were of the highest purity grades available, and they were used without further purification and/or drying.

Preparation of Solvent Mixtures—Mixtures of the polar solvent in benzene were prepared in 100-ml volumetric flasks. The flask was weighed and the calculated volume of polar solvent was pipetted into the volumetric flask. The weight of the flask and the solvent was determined, and benzene was added to the mark. The final weight was then determined. This procedure permitted

calculation of the weight by weight and volume by volume percentages of the polar component. The mole fractions of the nonpolar component and the polar component were also calculated. All measurements were performed at a constant room temperature of $25 \pm 1^\circ$.

Determination of Dielectric Constant of Solvent Mixtures—

The Heterodyne-Beat method was employed for determining the dielectric constant, D , of each mixture. This method permitted the determination of values on solutions having low conductance. The procedure and apparatus used in these experiments were previously described (12).

After 1 hr of warm-up, the cell beaker and the plates of the variable capacitor were rinsed with pure benzene and pure acetone and dried in a stream of air. The cell beaker was then introduced into the variable capacitor, the top of the variable capacitor was replaced, and the whole unit, with the plate-columns of the variable capacitor separated (position a), was carefully introduced into the constant-temperature (25°) water bath. Fifteen minutes was allowed for temperature equilibration, and then the instrument was adjusted to indicate a constant frequency of the variable oscillator (by maintaining a circle on the oscilloscope). The precision air capacitor was read at this point. The variable capacitor plate-columns were then brought together (position b). The capacitance of the precision air capacitor was changed by rotating the dial, and the reading was taken when a stable circle appeared on the oscilloscope again. The difference between the two readings of the two positions ($b - a$) was designated as ΔC . At the beginning of the experiment, the ΔC was determined with just the dry, empty, cell beaker in place. This ΔC was designated as ΔC_{air} . The desired solvent mixture was introduced next and the measured ΔC was designated as ΔC_{liq} . The dielectric constant of that particular binary solvent sample was then calculated from $D = (\Delta C_{\text{liq}})/(\Delta C_{\text{air}})$. Each ΔC determination was repeated at least six times. The amount of solution in the beaker was always more than enough to cover the plates of the capacitor completely. The capacitor was handled with care to avoid any damage to the plates and potential change in ΔC .

All measurements were made at 25° , and the values reported were the averages of at least six trials. The data from two replicates were pooled. Each replicate represented an entire experimental determination of D for all of the benzene-polar component mixtures of the individual binary solvent system from low D to the highest D measurable by the instrument. The pooled data were fed to a computer¹ to determine the best-fitting polynomial that would express D as a function of the percent weight by weight or volume by volume of the polar component of the binary solvent system, and the best values were determined for the coefficients a , b , c , and d in Eq. 4.

RESULTS AND DISCUSSION

The solvents used in nonaqueous titrimetry vary widely in their properties: the dielectric constant, the acidity and/or basicity, the autoionization, the leveling effect, the chemical reactivity, and the toxicity. Certain solvents are used for the titration of acids or bases but generally not both. Some inert solvents have been used for titration of both acids and bases. The solvents selected as the polar component of the binary solvent systems are inert and do not present any leveling effects. They also provide a varied range of dielectric constants and chemical structures. Ac-

¹ IBM 360/44 computer running under HASP and OS.

Table II— D_m Expressed as a Polynomial Function of Percent Weight by Weight (in Grams) of the Polar Component of the Binary Solvent System in 100.00 g of Total Mixture

Benzene-acetonitrile:
 $D_m = 2.28880 + 0.29719588W + 0.84850605 \times 10^{-3}W^2 - 0.94192253 \times 10^{-6}W^3 - 0.20513955 \times 10^{-7}W^4$

Benzene-nitromethane:
 $D_m = 2.24461 + 0.20290456W - 0.18107903 \times 10^{-2}W^2 + 0.70412945 \times 10^{-4}W^3 - 0.38935198 \times 10^{-6}W^4$

Benzene-nitrobenzene:
 $D_m = 2.29464 + 0.14154240W + 0.11201036 \times 10^{-2}W^2 - 0.26201666 \times 10^{-5}W^3 + 0.97894765 \times 10^{-7}W^4$

Benzene-acetone:
 $D_m = 2.27947 + 0.14625993W + 0.24731895 \times 10^{-3}W^2 + 0.52095944 \times 10^{-5}W^3 - 0.37250925 \times 10^{-7}W^4$

Benzene-methyl isobutyl ketone:
 $D_m = 2.27923 + 0.77094202 \times 10^{-1}W + 0.32896261 \times 10^{-3}W^2 - 0.16212037 \times 10^{-5}W^3 + 0.12050527 \times 10^{-7}W^4$

Table III— D_m Expressed as a Polynomial Function of Percent Volume by Volume (in Milliliters) of the Polar Component of the Binary Solvent System in 100.00 ml of Total Mixture

Benzene-acetonitrile:
 $D_m = 2.28849 + 0.26297646V + 0.91613647 \times 10^{-3}V^2 + 0.30119845 \times 10^{-6}V^3 - 0.32592511 \times 10^{-7}V^4$

Benzene-nitromethane:
 $D_m = 2.23619 + 0.25477603V - 0.23317571 \times 10^{-2}V^2 + 0.86627173 \times 10^{-4}V^3 - 0.55120893 \times 10^{-6}V^4$

Benzene-nitrobenzene:
 $D_m = 2.29588 + 0.19525744V + 0.10431213 \times 10^{-2}V^2 - 0.98546458 \times 10^{-6}V^3 + 0.35515077 \times 10^{-7}V^4$

Benzene-acetone:
 $D_m = 2.27430 + 0.13201515V + 0.29015152 \times 10^{-3}V^2 + 0.55827506 \times 10^{-5}V^3 - 0.30885781 \times 10^{-7}V^4$

Benzene-methyl isobutyl ketone:
 $D_m = 2.27783 + 0.69132964 \times 10^{-1}V + 0.40893065 \times 10^{-3}V^2 - 0.22678710 \times 10^{-5}V^3 + 0.18502331 \times 10^{-7}V^4$

ording to Kucharsky and Safarik (1), a wide range of potential measurements is also possible in most of these solvents. The lack of leveling effect and the inertness of the solvents were judged to be the two most important factors. Benzene is also an inert non-leveling solvent of very low dielectric constant and, therefore, a good choice for the nonpolar component of the binary solvent system. Thus, a mixture of benzene and any one of the polar components would in effect act more as a nonreactive medium in which the acid molecules may be dispersed and suspended as monomer, dimer, trimer, and/or higher polymolecular aggregates. The degree of the intramolecular aggregation of the acid molecules depends on the polarity (dielectric constant) of the particular solvent mixture and the possibility of the acid and/or the solvent molecules forming intra- and/or intermolecular hydrogen bonding. One can safely assume that the effect and extent of polarity and intermolecular attractions among the solvent molecules themselves can be summarized and included in the dielectric constant. Thus, the dielectric constant of the solvent system is an important physical constant for characterizing the particular solvent mixture.

Selection of binary solvent systems of a polar component and a nonpolar component provides the investigator with a range of available dielectric constants (limited by those of the pure components) out of which it is possible to select a mixture with definite composition and resultant dielectric constant. When media of varying dielectric constants are needed, this approach is more versatile and effective than using pure solvents of different dielectric constants, since in the latter case the solvent molecular structure differs with every new dielectric constant used. In the former case the molecular species of the solvent system are the same and only their ratio varies with the different dielectric constant values employed. Furthermore, it is virtually impossible to find solvents that cover a range of dielectric constants with a regular incremental increase of dielectric constant as those of, for example, the benzene-acetonitrile solvent system ($D = 5, 10, 15, 20, 25, 30, \text{ and } 35$).

Binary solvent systems have been used to advantage in non-aqueous titrimetry. In such cases, the acidity or basicity of the polar component and the resulting leveling effect may be undesirable factors. Even in cases where binary mixtures of inert solvents are used, the composition of the mixture most suitable for titrations is selected empirically. However, a systematic study of a binary solvent system could result in the determination of the exact composition of the binary solvent system (of two inert non-leveling solvents) most suitable for the titrations.

Mixtures of the five binary solvent systems (benzene-acetonitrile, benzene-nitromethane, benzene-nitrobenzene, benzene-acetone, and benzene-methyl isobutyl ketone) were prepared and the D_m was measured. The computer running under HASP and OS used the pooled data (the two replicates together for each binary solvent system) and determined the best values for the coefficients $a, b, c,$ and d (Table I). The same computer facilities de-

termined the polynomial functions that would fit the data best when the dielectric constant was expressed as a function of the percent weight by weight (Table II) and volume by volume (Table III) of the polar component. These tables give the final form of the polynomial for each of the five binary solvent systems. From these polynomials, one can provide the calculated values of D_m for percent values (weight by weight or volume by volume increasing in increments of 5, for example) of the polar component of the binary solvent system. An enlarged graph of these values accurately plotted enables the investigator to read the composition of the binary solvent system (in percent weight by weight or volume by volume) corresponding to the D_m value desired and make up the solvent mixture of a definite dielectric constant by the gravimetric or volumetric methods. The polynomial functions are reported using W to represent the percent weight by weight of grams of polar component in 100.00 g of total mixture and V to represent the percent volume by volume of milliliters of polar component in 100.00 ml of total mixture.

The calculations were first performed by the computer on each replicate separately. The comparison of the results indicated that the differences between the replicates were minor and of no significance. The data for the two replicates of each binary solvent system were then pooled to produce the final results reported here.

SUMMARY

This investigation was initiated, planned, and performed to study some binary solvent systems that are inert and, therefore, do not present the leveling effect and the related problems. Five binary solvent systems were selected. Each was composed of benzene and a polar component with dielectric constant values ranging from 2.29 for pure benzene to 12.80 (pure methyl isobutyl ketone), 20.97 (pure acetone), 34.82 (pure nitrobenzene), 35.90 (pure nitromethane), and 37.5 (pure acetonitrile). Several mixtures of each binary solvent system were prepared and their dielectric constants were measured. The data from measurements of the dielectric constant, D_m , of the different mixtures of each binary solvent system were pooled (two replicates), and the best fitting curve for the data was obtained using a computer. Two curves were obtained for each system: one representing D_m as a function of the percent volume by volume and the other representing D_m as a function of the percent weight by weight of the polar component. From these two curves, it is possible to calculate how much of the polar component and benzene should be combined to produce a mixture having the desired dielectric constant.

Furthermore, a formula was derived to express the dielectric constant of the mixture as a function of the mole fractions of benzene (X_1) and the polar component (X_2). The same computer facility was used to determine the best value of each coefficient of the formula. Thus, five sets of coefficients were obtained. The five

binary solvent systems are completely defined in this manner. The calculated D_m values of the particular binary solvent system can be plotted (on a large graph) against the percent volume by volume and weight by weight of the polar component of the system. It is possible, then, to select and prepare any mixture of the binary solvent system having a definite dielectric constant.

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Pharmacokinetics of Pentazocine in the Rhesus Monkey

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Abstract □ The time course of pentazocine concentration was followed in the plasma and cerebrums of individual monkeys by obtaining serial samples of both tissues after intravenous administration of tritiated drug. Plasma concentrations of pentazocine were also followed in a monkey after portal vein infusion. A three-compartment open-system model adequately fits the observed plasma data. The use of the constants derived from that model to predict the time course of pentazocine concentration in the brain results in a good fit with the observed cerebral concentrations. As expected, portal vein infusion caused a reduction in the area below the plasma concentration-time curves and in the percentage of pentazocine excreted in the urine. The relative proportions of known metabolites and their conjugates in urine were determined.

Keyphrases □ Pentazocine—pharmacokinetics, correlation between plasma and brain concentrations, rhesus monkey □ Pharmacokinetics—pentazocine, correlation between plasma and brain concentrations, rhesus monkey □ Plasma concentration, pentazocine—correlated with brain concentration, rhesus monkey □ Brain concentration, pentazocine—correlated with plasma concentration, rhesus monkey

Pentazocine, unlike morphine and a number of its surrogates, is present in brain tissues in much higher concentration than it is in the corresponding plasma after parenteral administration to cats (1), monkeys (2), mice (3), and rats (4). Brain plasma concentration ratios were found to be relatively constant in the rat (4) and rhesus monkey (2) but not as constant in the mouse (3). Pentazocine concentrations in the cerebrum, cerebellum, thalamus, midbrain, pons, and medulla of the rhesus monkey were similar at various times after administration of 0.5 mg/kg im of the drug (2). In addition, only pentazocine, not any of its

metabolites, was found in the brain after parenteral administration of tritiated pentazocine or of nonradioactive pentazocine (1-4), implying that the analgesic activity of pentazocine resides in the parent compound and not in its metabolites. In man, peak analgesia after intravenous administration occurred at a time approximately coincident with the apparent end of the distributive phase of the plasma concentration-time curve (5). After intramuscular administration, peak analgesia coincided approximately with the end of the absorption phase (5). Similar results were found in the rat (6) but not in the mouse (3).

The purpose of the reported experiments was to demonstrate that a kinetic model based on the plasma concentration-time curve could be used successfully to predict pentazocine kinetics in another tissue, especially the brain, and, therefore, that any physiological response that could be correlated with plasma pentazocine concentrations could also be correlated with brain pentazocine concentrations.

The rhesus monkey was used because the metabolism of pentazocine has been studied more thoroughly in this species than in others and is known to be similar to that in man. Moreover, its brain is sufficiently large to permit the removal of multiple samples of cerebral tissue.

EXPERIMENTAL

Chemicals—Pentazocine [1,2,3,4,5,6 - hexahydro - *cis* - 6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol] and pentazocine labeled with tritium in the 4-position were pre-