1976

The Solubility of Calcium Oxalate as a Function of Dielectric Constant

Justina A. Molzon
University of Rhode Island

Recommended Citation

Molzon, Justina A., "The Solubility of Calcium Oxalate as a Function of Dielectric Constant" (1976). *Open Access Master's Theses.* Paper 210.
https://digitalcommons.uri.edu/theses/210

THE SOLUBILITY OF CALCIUM OXALATE AS A FUNCTION OF DIELECTRIC CONSTANT

BY

JUSTINA A. MOLZON

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE
IN
PHARMACY

UNIVERSITY OF RHODE ISLAND
1976

MASTER OF SCIENCE THESIS

OF

JUSTINA A. MOLZON

Approved:

Thesis Committee:

Major Professor Joan M. L

Anthony N. Paruta

Geo. E. Osborne

Charles I. Smith

A. A. Nickel

Dean of the Graduate School

UNIVERSITY OF RHODE ISLAND

1976

TABLE OF CONTENTS

ABSTRACT

The solubility of calcium oxalate monohydrate was determined via atomic absorption spectroscopy in a series of 1-alkanols and ethanol-water mixtures at 25°C., having known dielectric constants. It was found that solubility was linearly related to the dielectric constant of the 1-alkanols. In the ethanol-water mixtures, the solubility isotherm was curvilinear and on a dielectric constant basis an apparent break occurred in the isotherm, at a dielectric constant of sixty. This can be considered to be the point of ionization of divalent cations. The solubility isotherms in the cosolvent mixtures can be considered as repressive ionization phenomena.

LIST OF TABLES

FIGURES

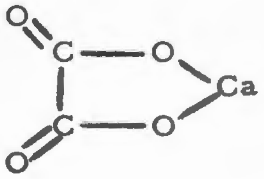
I. INTRODUCTION

This investigation involves the study of the solubility of calcium oxalate which, because of its very low aqueous solubility, is a major constituent of kidney stones. As this problem is directly related to the improvement of world living standards (1), the need to develop techniques to help dissolve and/or prevent these stones increases yearly. Any information related to the solubility phenomena of calcium oxalate should prove useful to the body of knowledge on this compound.

This inorganic compound is semipolar in nature, and the approach to the investigation was to develop a solubility isotherm by changing solvent polarity to mimic more closely the forces in the solute. A wide range of polarity can be obtained by using a variety of pure solvents or solvent mixtures having a broad spectrum of dielectric constants. This method yields a useful description of the solubility parameters of the compound under investigation.

II. CALCIUM OXALATE

The chemical formula for calcium oxalate is CaC_2O_4; it has a molecular weight of 128.10, in the dehydrated state. The structure considered to be most stable is:



It is considered to be relatively insoluble in both polar and nonpolar solvents. The Merck Index lists it as being practically insoluble in water or acetic acid. Only dilute solutions of strong acids, such as hydrochloric or nitric, will effect its solution (2).

Calcium oxalate may occur as either the mono-, di-, or trihydrate. Of these three forms, the monohydrate is the compound most commonly constituting kidney stones that are composed of a single chemical entity (3). It is also the least soluble, having a solubility product of 2.57×10^{-9} mole per liter at 25° C. (4). Further, the monohydrate is stable at temperatures above 0°C., while the other hydrates are unstable, giving off water of crystallization to revert to the more stable monohydrate (5). Both solubility and instability of calcium oxalate increases with increasing degrees of hydration (5). For example, at 0°C. the solubility of the trihydrate is found to be 1.25 times as soluble as the dihydrate, which in turn is 1.25 times as soluble as the monohydrate (5).

It should be pointed out that most of the literature concerning calcium oxalate focuses on its connection with renal stones. As a result, much of the information presented in this study has been extracted from reports pertaining to renal stone solubility, and this connection will frequently be mentioned.

III. CALCIUM OXALATE SOLUBILITY

The solubility of calcium oxalate has been studied under a variety of conditions. The approach taken by many authors is one related to the solubility of this compound in urine, where it is generally recognized that both calcium and oxalate are present in higher concentrations than can be obtained even in a saturated aqueous solution of calcium oxalate. This phenomenon, coupled with the basic aim to increase the solubility of calcium oxalate renal stones, has led to the design of many experiments which alter urinary components to study that effect upon calcium oxalate solubility.

Gretta Hammarsten, in 1929 (6), carried out one of the fundamental studies, applying the theory of Debye and Hückel to study the solubility of calcium oxalate in aqueous solutions of common urinary electrolytes. According to Debye and Hückel, the solubility of a salt is raised when the activity of the ions of the dissolved electrolytes, brought about by the interaction of the ions in solution, is decreased. These results could be interpreted mechanistically as a "salting-in" phenomenon.

Mathematically this concept, in terms of the activity coefficient of the ion under consideration (f_r), is as follows:

$$\text{Log } f_r = - \left[\frac{1.817}{(D \cdot T)\ 3/2} \ . \ 10^6 \right] . \ r^{2*} \sqrt{\mu}$$

where D signifies the dielectric constant of the water, T the temperature, r the ion whose solubility is being studied, with r^{2*} being the square of the valence of the ion and μ the ionic strength. From this expression it may be seen that log f_r becomes more negative as r and μ increases, and that f_r decreases with increasing charge and concentration of the ions of the solution. Further mathematical manipulation would demonstrate that these factors would cause an increase in the solubility product.

Hammarsten (6) found that the equations derived from this theory held only for very dilute solutions, since the experimentally determined solubilities of calcium oxalate in the various solutions did not follow those calculated from the given equations. Hence, she determined the effect of each salt on the solubility of calcium oxalate with the end result that calcium oxalate solubility was indeed increased by this "salting-in" effect.

It was found that sodium (either as the chloride or the dihydrogen phosphate), when present in a concentration comparable to urine, increased the solubility of calcium oxalate about three times. Potassium had a similar effect, but the addition of magnesium ions increased the solubility seven to eight times that found in water. Hammarsten explained this result suggesting the formation of a complex whereby a magnesium ion combines with two oxalate ions. When such a complex is formed, the ions as such disappear from the solution, and the solubility of calcium oxalate is increased.

Hammarsten also varied pH, and found that there was no significant increase in the solubility of calcium oxalate until the pH range exceeded that possible in normal human urine.

In 1938, Shehyn and Pall (7) studied the solubility of calcium oxalate in various salt solutions. They dealt with sodium sulfate, ammonium chloride, ammonium nitrate and ammonium sulfate, and related their findings to ionic strength. Ionic strength is defined as: $\frac{1}{2}\sum_{\mu} m_{\mu} e_{\mu}^{2}$ where m_{μ} is the molarity of the μ^{TH} ion, and e_{μ} is the charge of the μ^{TH} ion. Basically the rule regarding ionic strength states that the effect of the addition of a second salt on the solubility of a given, slightly soluble salt is the same for all salts and depends only on the ionic strength. Table 1 compares the solubilities of calcium oxalate for various ionic strengths of the second salt. As it can be seen, the agreement is fairly good.

In an attempt to determine the mechanisms playing a role in increasing the solubility of calcium oxalate in urine, Miller, Vermeulen and Moore (8) experimented in another series of pure solutions. They found that creatinine and hippuric acid had no effect in increasing solubility and that urea, sodium sulfate and sodium dihydrogen phosphate all showed slight solubilizing action. Magnesium chloride produced a marked increase in oxalate solubility, thus confirming Hammarsten's observations on solubilizing by magnesium ions. Sodium chloride was quite effective, because of the relatively high concentrations used. Citric acid markedly increased the oxalate solubility because of its calcium complexing properties.

In 1965, Elliot and Eusebio (9) varied the concentrations of each of the principal urinary inorganic and organic components in simple salt solutions to study those effects on calcium oxalate solubility. Maximal increase in solubility was provided by magnesium ion and by citric, lactic and hippuric acids. A minor increase was provided by sodium, potassium ammonium and sulfate ions. No increase in solubility was brought about by urea or creatinine.

TABLE 1

SOLUBILITY OF CALCIUM OXALATE IN VARIOUS SALT SOLUTIONS, COMPARED AT THE SAME IONIC STRENGTHS @ 28°C.

Ionic Strength	mgs. of CaC_2O_4/1. solution				
	NH_4NO_3	NH_4Cl	$(NH_4)_2SO_4$	Na_2SO_4	NaCl
0.01	10.4	10.0	10.3	10.0	11.3
0.02	12.1	11.6	12.0	11.6	11.6
0.05	16.1	15.9	16.6	15.8	13.3
0.10	21.6	20.2	22.8	21.1	18.6
0.20	28.0	25.9	33.6	26.5	23.0

H. Shehyn and D. B. Pall, J. Phys. Colloid Chem., 44, 171 (1940).

In another study, Elliot and Eusebio (10) also studied the effect of urinary amino acids upon the solubility of calcium oxalate. However, no significant effect was established.

The work of Hammarsten and of Elliot and Eusebio has prompted the current concept of calcium oxalate solubility: calcium and oxalate combine to form an uncharged complex CaC_2O_4, of constant concentration when in equilibrium with solid calcium oxalate. Work by Finlayson, Roth and DuBois (11) takes issue with this concept; these authors state that calcium oxalate solubility cannot be explained by a single CaC_2O_4 complex at calcium-to-oxalate concentration ratios greater than ten. It was not their concern to alter the solubility of calcium oxalate however, but to expound on the current solubility theory. Nevertheless the data derived are of great interest in that they provide a much needed means of comparison for this investigation. Also, since the study was done in 1973, their methods of investigation were considered to be up to date and therefore used as a model.

IV. DIELECTRIC CONSTANT AND SOLUBILITY

Polarity differences between solutes and solvents reflect the solubility of a variety of substances. Solubility studies usually have involved homologous series, which in turn results in a change in polarity, physical properties and solubility characteristics.

Since many properties of a homologous series change according to a geometric progression (12), the plot of the logarithm of these properties against the carbon number of the nonpolar hydrocarbon chain is linear. This has allowed for the development of a variety of solubility theories which attempt to predict the points of maximum solute/solvent solubility.

Notable among these is the Hildebrand and Scott solubility-parameter theory. Basically a thermodynamic description, the solubility parameter, δ, is a measure of intermolecular forces or cohesion between molecules and is defined as "the square root of the internal pressure." (13) Expressed mathematically the relationship is: $\delta = \left(\frac{\Delta H_v - RT}{V_1}\right)^{1/2}$

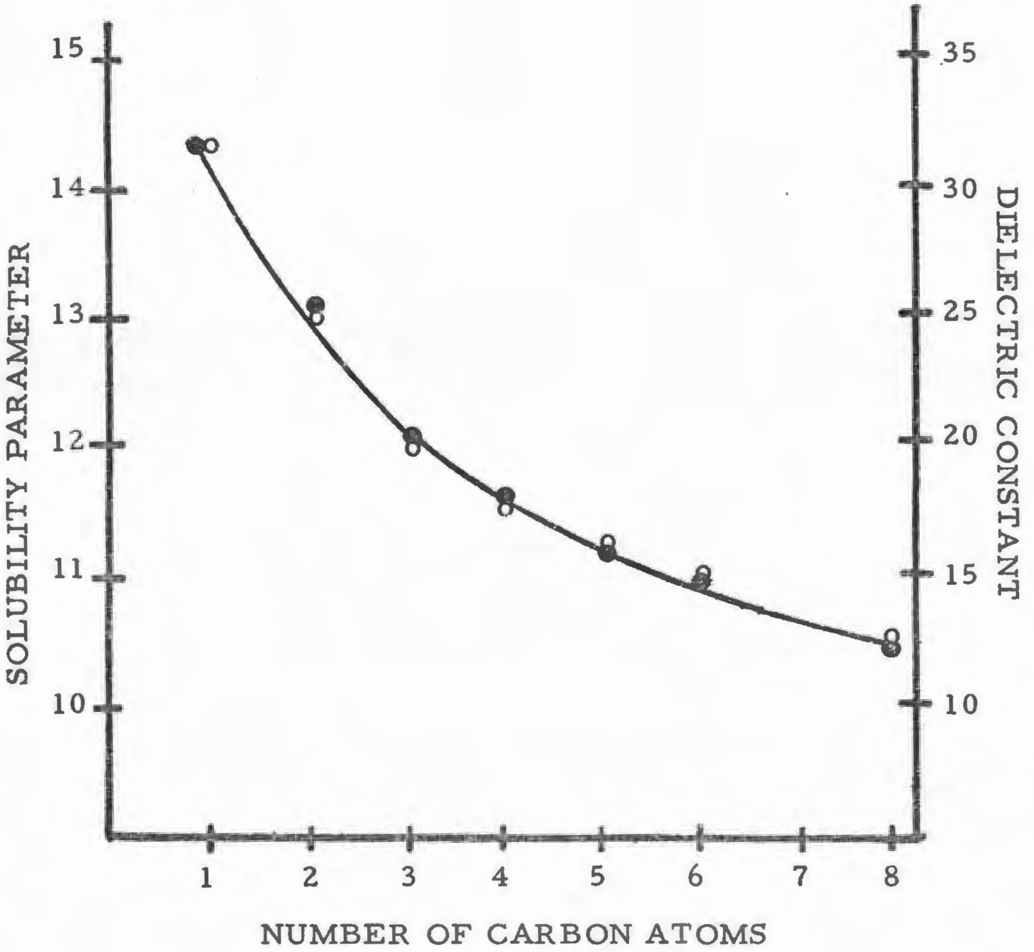


Figure 1. An Illustration of the Superimposition of Curves when Either the Solubility Parameter, o , or Dielectric Constant, ● , of a Series of N-Alkyl Alcohols is Plotted vs. the Number of Carbons.

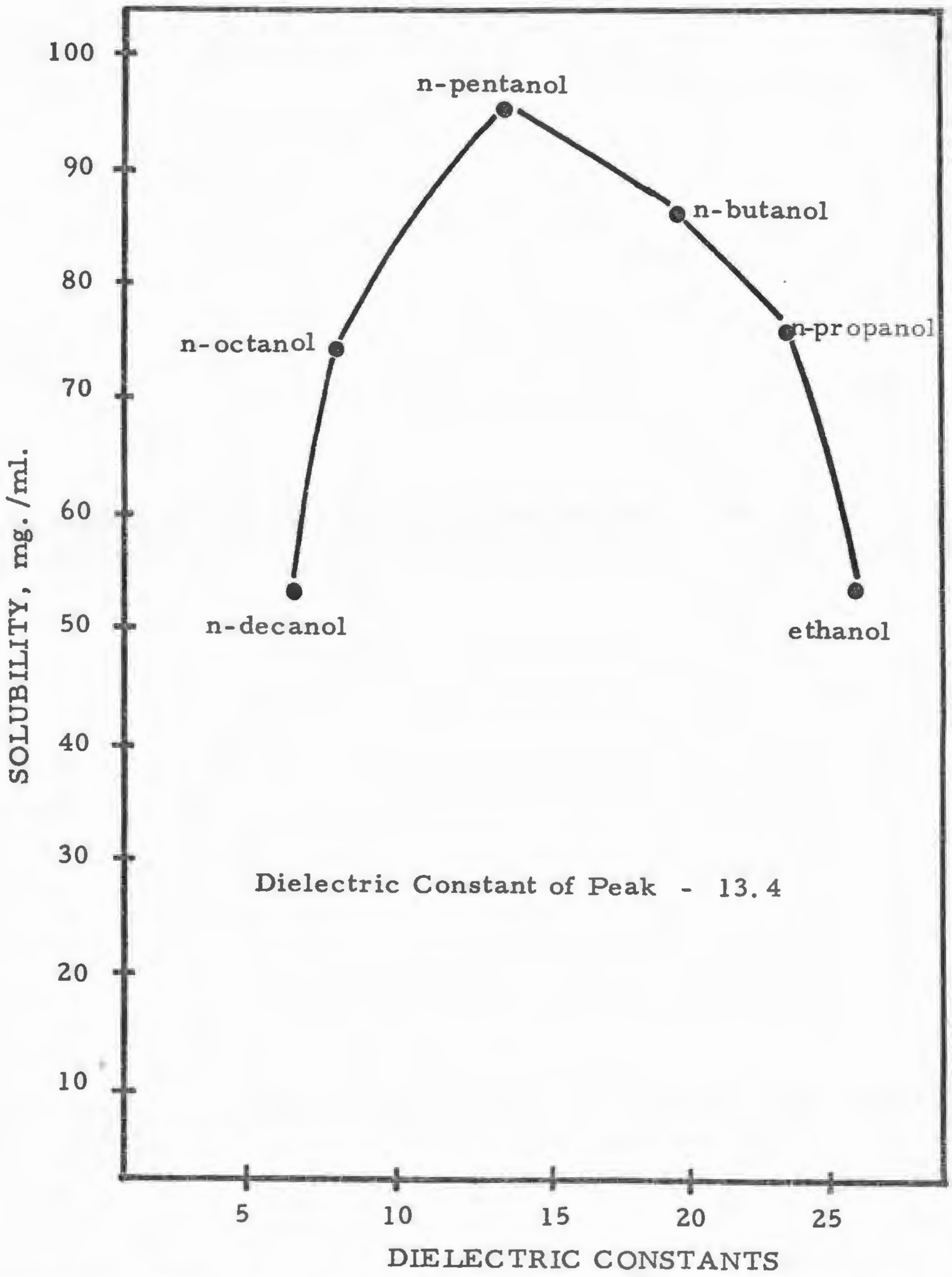


Figure 2. A Plot of the Solubility of Sodium Salicylate in mg./ml. at 25°C. vs. the Dielectric Constant of n-alkanols, which Illustrates the Phenomenon of Dielectric Requirement for a Metalo-Organic Compound.

where ΔH_v is the heat of vaporization and V_1 is the molar volume of the solute as a liquid at the desired temperature, R is the gas constant and T the absolute temperature. Highly polar substances have large solubility parameter values, and nonpolar solvents have low values.

A series of binary solvents of varying percentage strengths may be used to construct a system of solvents with dielectric constants that range between the values of the pure solvents. A solubility profile which delineates a smooth function of solubility with incremental values of dielectric constants may then be produced by determining the solubility of a compound in such solvent mixtures, as well as in each of the pure solvents.

The use of binary solvent systems makes it possible to obtain an expanded scale, which in turn permits the determination of the dielectric requirement of the compound (15). The dielectric requirement is the point of negligible polarity difference between solute and solvent; it is hence an indication of the compound's polarity. Graphically, it would appear as a peak in the solubility vs. dielectric constant curve. This may be seen in Fig. 2 (19).

The dielectric concept has been used to construct solubility profiles for several pharmaceuticals in binary mixtures (19, 20, 21, 22). Since calcium oxalate is similar in polarity to these compounds, it was felt that a study considering the effect of altering the dielectric constant upon the solubility of calcium oxalate would be fruitful.

Paruta et al. (14) have shown that the solubility parameter is also a linear function of the dielectric constant, ϵ . The relationship is: $\delta = 0.2\epsilon + 7.5$

Several investigators have used dielectric constants rather than solubility parameters to investigate the solubility of various solutes (15, 16, 17).

The dielectric constant of a solvent is its "charge separating" capability. In other words the dielectric constant is responsible for the dissociation of dissolved electrolytes. Paruta, et al., recognized a basic relationship between solubility and this aspect of many solvents, citing the correlation between decreasing solubility and decreasing dielectric constant. A clear example of this concept is shown in Figure 1 (14).

This relationship is supported by that shown in Coulomb's law where the dielectric constant is inversely related to the force separating two charged particles (18).

$$\text{FORCE} = \frac{q1\ q2}{\epsilon\ r^2}$$

where q and q are the net charges on the particles and ϵ is the dielectric constant of the medium in which the charges exist.

Also the Born equation relates the solubility of a weakly ionized, relatively insoluble salt to the dielectric constant:

$$\text{Log}\ \frac{S_1}{S_2} = \frac{e^2}{(2.303)2rkT}\left(\frac{1}{D_2} - \frac{1}{D_1}\right)$$

where S_1 and S_2 are the molar solubilities at the respective dielectric constants D_1 and D_2. The charge on an electron is taken in e. s. u., is an effective ion radius, k is Boltzman's constant, and T is the absolute temperature (19).

V. ANALYTICAL METHODS

The classical procedure for the determination of calcium in biologic fluids involves the precipitation of calcium as the oxalate, solution in sulfuric acid, and titration of the oxalate with potassium permanganate. However this procedure has inherent problems. The solutions of oxalate must be heated during titration and in dilute solutions the end point is unreliable (23).

A newer method which uses cerate oxidimetry avoids these problems (24). The principle of this method is to precipitate calcium as the oxalate salt and then oxidize it with ammonium hexanitratocerate. The excess cerate is then titrated with ferrous ion, using ortho-phenanthroline as an oxidation-reduction indicator. The only problem with this method is that the chemicals are difficult to obtain.

Another relatively new method makes use of a specific ion electrode (25). Similar in appearance to a standard glass electrode, specific ion electrodes measure the single ion activity of an ion in solution. The major disadvantage of this method is that it is not adaptable to use with organic solvents.

The method of choice in this study was atomic absorption spectroscopy, which was also used by Finlay, Roth and DuBois (11). It is based on the ability of atoms to absorb radiation at definite, characteristic wavelengths. Besides being a convenient and neat method of analysis, it can detect calcium in amounts as little as one part per billion.

Atomic absorption spectroscopy is based on the theory that neutral atoms in the gaseous state absorb radiant energy by means of electronic transitions of the outermost electrons within the atomic structure. As radiant energy is focused on the gaseous atoms, some energy at particular wavelengths is absorbed by the neutral atoms, raising their energy levels to excited states. The absorption spectrum of a particular element is characteristic of that element. Consequently, this procedure may be used as a qualitative test. If the quantity of the energy which is absorbed is determined, this procedure becomes a quantitative analytical technique (26, 27).

For quantitative work the atomic absorption spectroscopy apparatus is used as follows: A flame is produced using nitrous oxide or acetylene as fuels; oxidants are used in various concentrations, depending on the temperature of the flame needed to vaporize the sample. The sample solution is aspirated directly into the "carburetor" as a fine mist and intimately mixed with the fuel and oxidant. This mixture is then fed into the burner where the fuel is oxidized and the sample is vaporized. A hollow cathode ray tube is aimed at a particular region of the flame. The cathode tube and burner are aligned with the monochromator and the detector to assure maximum sensitivity. The monochromator is set at the wavelength of the energy to be measured. A variable slit in the system increases the sensitivity. A meter calibrated in arbitrary units is incorporated in the electronics of the system to measure the quantity of energy absorbed by the neutral atoms. This meter can be calibrated using known standards so that an unknown solution can be quantitatively measured.

The major instrumental differences between atomic and solution absorption instruments lie in the radiation source (the hollow cathode ray tube) and the sample container. The whole system is dependent on the principles behind the hollow cathode ray tube. Atomic absorption lines are very narrow and thus create a measurement problem not encountered with solution absorption apparatus. No ordinary monochromator is capable of yielding a band of radiation as narrow as these absorption peaks, so in order to follow Beer's law, some means of narrowing the band width with respect to the width of the absorption peak had to be developed. The hollow cathode ray tube provided a solution to this problem.

These tubes are constructed of the metal to be analysed. As a result, a source of radiation is available which emits a line of the same wavelength as that to be used for the absorption analysis. For example, if the 4227 Å absorption line of calcium is chosen for the analysis of that element, a calcium vapor lamp can be used as a source. In such a lamp, gaseous calcium atoms are excited by an electrical discharge; the excited atoms then emit characteristic radiation as they return to lower energy levels. A part of the emitted radiation will have exactly the same wavelength as the resonance absorption lines. Thus, for example, calcium atoms that have been excited will emit 4227 Å lines. With a properly designed source, the emission lines will have band widths that are significantly narrower than the absorption band widths, and the absorption bands will be discernible. Now Beer's law will apply and a linear relationship between absorbance and concentration will be present.

VI. EXPERIMENTAL

EQUIPMENT

A rotating apparatus holding twenty-eight screw-capped glass vials of twenty milliter volume was set to cycle at forty revolutions per minute. The rotation of the vials caused the solute to traverse the full length of the vial twice per revolution, providing a means of agitation of the contents. This apparatus was immersed in a fifteen-gallon circulating[1] water bath maintained at 25.0 ± .5°C. by a Temptrol 150 unit.[2]

The assay procedure employed: a Perkin-Elmer atomic absorption spectrophotometer, Model 303[3]; Mettler type H8[4] analytical balance; a Sargent Chemical Oscillometer, Model V[5];

---

[1] Sargent Heater and Circulator for Thermostatic Baths, E. H. Sargent and Co., Chicago, Ill.

[2] Precision Scientific Company, Chicago, Illinois.

[3] Perkin-Elmer, Norwalk, Conn.

[4] Will Scientific, Inc., Rochester, N. Y.

[5] E. H. Sargent and Company, Chicago, Illinois.

Abee-3L Refractometer[1]; Bantam Demineralizer, Model BD-1[2]; and an IEC HT[3] centrifuge. The data were computed with a Hewlett Packard Model 10 calculator[4] and 98262A calculator plotter.[5]

CHEMICALS

The chemicals used for this study were as follows:

Calcium Oxalate, Certified Powder, Lot 762198[6]

Calcium Chloride, Anhydrous, Analytical Reagent, Lot XGZ[7]

Methyl Alcohol Anhydrous, Spectrophotometric Grade Solvent, Lot VMN[7]

Absolute Ethyl Alcohol, U.S.P.-N.F., Reagent Quality[8]

---

[1] Bausch and Lomb Optical Company, Rochester, N.Y.

[2] Barnstead Still and Sterilizer Co., Boston, Mass.

[3] Damon/IEC Division Damon Corp., Needham Hts., Mass.

[4] Hewlett-Packard Calculator Products Div., Loveland, Col.

[5] Hewlett-Packard Calculator Products Div., Loveland, Col.

[6] Fisher Scientific Company

[7] Mallinckrodt Chemical Works

[8] U.S. Industrial Chemicals Company

1-Propanol, "Baker Analyzed" Reagent, Lot 35592[1]

1-Butanol, Analytical Reagent, Lot TDY[2]

1-Pentanol, Certified, Lot 776291[3]

1-Hexanol, Lot Hi330[4]

1-Octanol, OR^{tm}, Lot 22[2]

1-Decanol, Lot 17[5]

Certified Benzene, 99 Mol % Pure (Thiophene Free)
Lot 793869[3]

Certified Acetone, 99 Mol % Pure, Lot 792702[3]

---

[1] J. T. Baker Chemical Company

[2] Mallinckrodt Chemical Works

[3] Fisher Scientific Company

[4] Aldrich Chemical Company, Inc.

[5] Matheson, Coleman and Bell

DISSOLUTION PROCEDURES

Approximately ten to twenty milliter volumes of each solvent mixture were placed in vials along with excess calcium oxalate. The vials were rotated in the water bath for twenty-four hours, a period found to be adequate for equilibrium (11). The vials were removed from the water bath, set upright, and allowed to settle. Due to the very fine nature of the suspended material, it was necessary to centrifuge the vials containing the more viscous solvents at 1000 r. p. m. for ten minutes. Sample aliquots were then withdrawn from the supernatant using pipets tipped with glass wool. Three sample vials were run for each solvent system and each solubility determination represents the average value from at least three runs for each sample.

ESTABLISHMENT OF PURITY

The purity of the alcohols was verified by means of refractive index and dielectric constant measurements.

Refractive Index - Benzene, 99% mole free, was used to check the accuracy of the Abee-3L Refractometer. An experimental value of 1.4986 compared with the literature value of 1.4979 (28). Refractive index values at 25°C. for the various alcohols tested are presented in Table 2.

Dielectric Constant - The procedure used was the same as that described for the determination of dielectric constant for the experimental solvent mixture. Water contamination is an important consideration with methanol, ethanol and propanol, since they are very hygroscopic. Further, any water present as a contaminant would strongly influence the solubility properties of the alcohol under consideration. The dielectric constant, which is sensitive to water contamination, may therefore be used as a purity index. Dielectric constants for the various alcohols tested are presented in Table 3, and strongly agree with literature values, thus indicating no water contamination.

TABLE 2

REFRACTIVE INDEX VALUES FOR VARIOUS ALCOHOLS AT 25°C.

ALCOHOL	EXPERIMENTAL VALUE	LITERATURE VALUE
Methanol	1.3274	1.3266[a](25°)
Ethanol	1.3597	1.3594[a](25°)
1-Propanol	1.3837	1.3835[a](25°)
1-Butanol	1.3980	1.3992[a](25°)
1-Pentanol	1.4087	1.4080[a](25°)
1-Hexanol	1.4180	1.4178[b](20°)
1-Octanol	1.4278	1.4275[a](25°)
1-Decanol	1.4359	1.4366[b](20°)

[a] A. Weissberger and E. Proskauer, Organic Solvents, 2nd ed., Interscience Publishers, Inc., New York, 1955.

[b] Handbook of Chemistry and Physics, 49th ed., The Chemical Rubber Co., Cleveland, 1968.

TABLE 3

DIELECTRIC CONSTANT VALUES FOR VARIOUS ALCOHOLS AT 25°C.

ALCOHOL	EXPERIMENTAL VALUE	LITERATURE[a] VALUE
Methanol	32.6	32.63
Ethanol	24.4	24.30
1-Propanol	20.2	20.1
1-Butanol	17.2	17.1
1-Pentanol	14.9	13.9
1-Hexanol	12.4	13.3
1-Octanol	9.9	9.86[b]
1-Decanol	8.0	7.93[b]

[a] "Table of Dielectric Constants of Pure Liquids", U. S. Dept. of Commerce, NBS Circular 514.

[b] Calculated from literature value at 20° and temperature coefficients to adjust value to 25°.

PREPARATION OF SOLVENT MIXTURES

In order to provide for the construction of a solubility profile in terms of dielectric constant, solvent mixtures with predictable dielectric constants were used. The series of alcohols from methanol to decanol, excepting heptanol and nonanol, provided a range of dielectric constants from approximately 32 to 8. This scale was expanded to a range of 24 to 80 by the use of ethanol-water mixtures, varied in ten percent (V/V) increments. Since the dielectric constants of solvent mixtures are given in the literature (29) in terms of W/W, the V/V mixtures were converted to their corresponding W/W values and their dielectric constants extrapolated. These data may be found in Table 4 and their relationship is described in Figure 3.

TABLE 4

A SUMMARY OF THE DIELECTRIC CONSTANTS FOR THE ETHANOL-WATER MIXTURES USED IN THIS STUDY.

V/V % H_2O	W/W % H_2O	DIELECTRIC CONSTANT
0	0.0	24.3
10	12.19	29.6
20	23.80	34.3
30	34.88	39.7
40	45.45	46.0
50	55.50	52.3
60	65.20	58.5
70	74.50	64.0
80	83.30	69.3
90	91.80	74.1
100	100.00	78.5

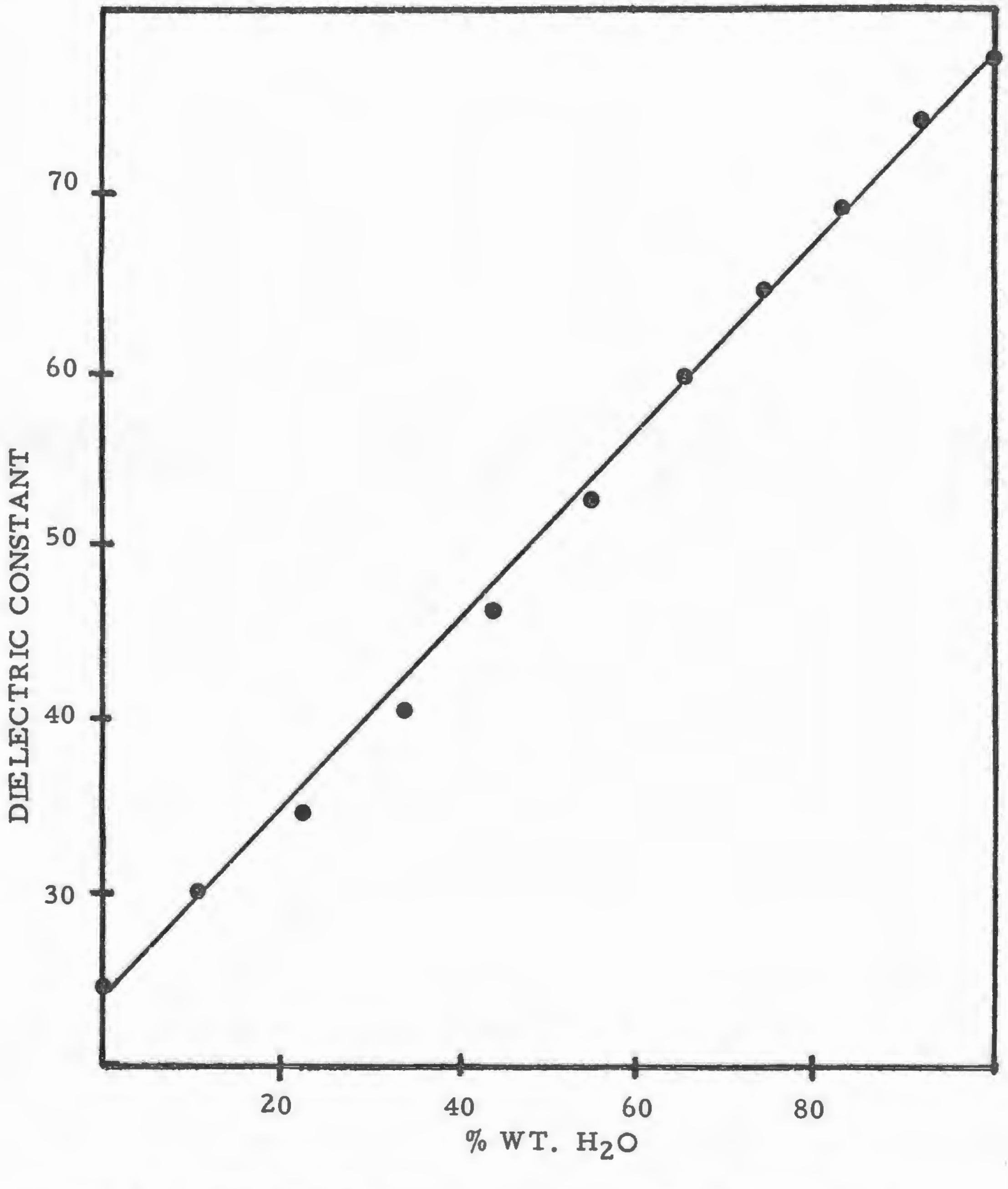


Figure 3. A Plot of the Dielectric Constants at 25°C. as a Function of Composition, Expressed as W/W Percent Water.

THE MEASUREMENT OF DIELECTRIC CONSTANT

A Model V Sargent Oscillometer was used to measure the dielectric constants of the various solvents and solvent mixtures. The instrument was warmed for at least twenty-four hours prior to use. The sample holder, a glass cell, was washed, rinsed with deionized water, and dried in an oven at 150°C. prior to use. When readings were made, the clean dry cell was first placed in the cell holder to obtain a zero adjustment of the instrument. After the test solvent was placed in the cell, three readings were taken, and then the cell was emptied and rinsed three times with the solvent to be next tested. To increase the reproducibility of the readings, the cell was filled to the same level for each measurement and placed in the cell holder in the same geometric position.

Since this method is a relative one because the oscillometer does not yield a direct reading of the dielectric constant, the instrument must be calibrated with solvents of known dielectric constant. Mixtures of ethyl alcohol and deionized water along with 99 mol % pure benzene and acetone were used as standards.

The dielectric constants and temperature coefficients for the standard liquids are given in the literature (30).

The data from several readouts made possible the generation of a graph of readout vs. dielectric constant. The readouts from the solvents being tested were then plotted against this standard curve and the corresponding dielectric constant was determined. These data may be found in Tables 5 and 6 and Figure 4.

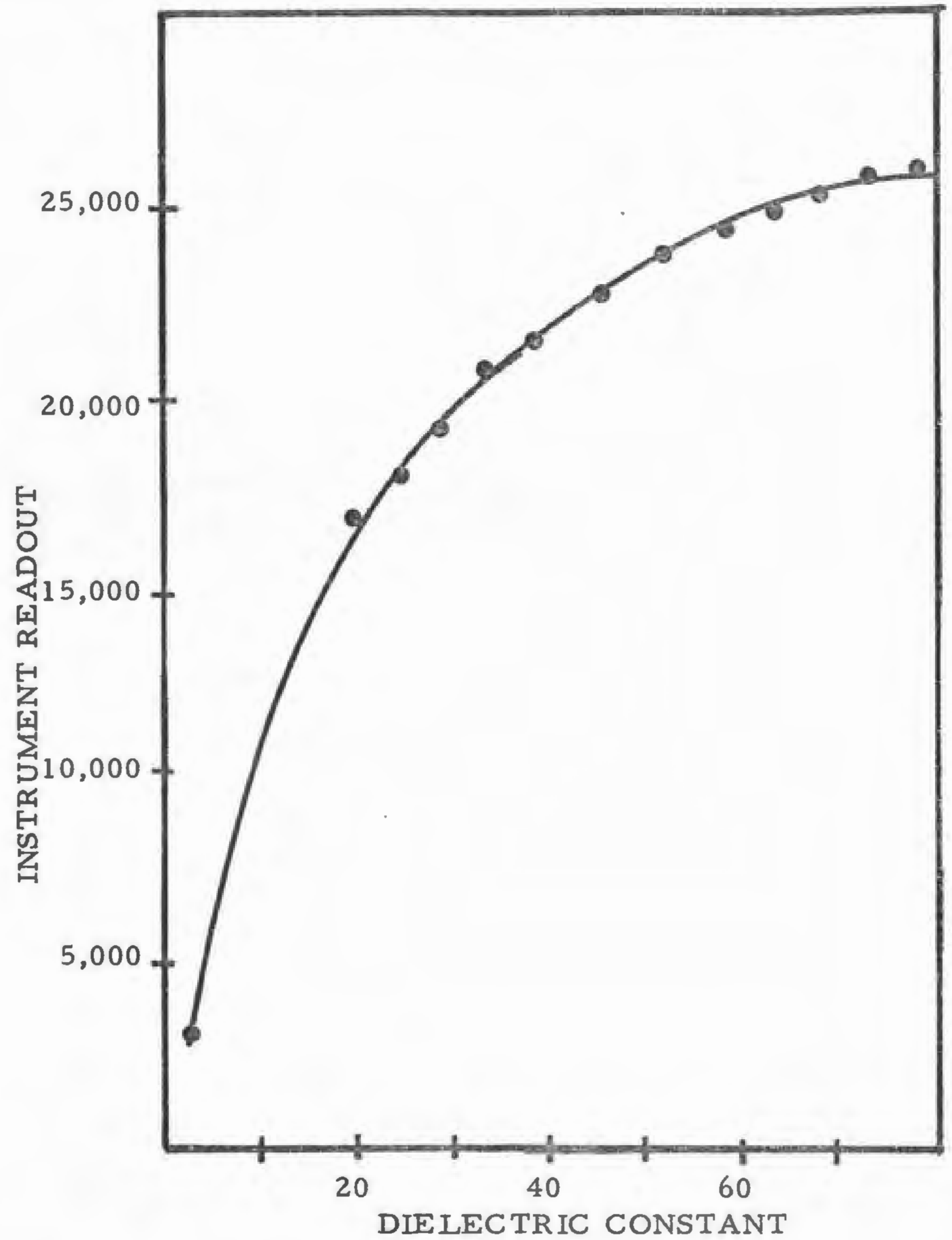


Figure 4. A Plot of the Calibration Curve Obtained on the Model V Sargent Oscillometer with Respect to Instrument Readings vs. Known Dielectric Constants of Pure Solvents and Solvent Mixtures.

TABLE 5

A SUMMARY OF THE INSTRUMENT READINGS FOR V/V PERCENT ETHANOL-WATER MIXTURES AND THE CORRESPONDING DIELECTRIC CONSTANT IN CALIBRATION OF THE SARGENT CHEMICAL OSCILLOMETER, MODEL V, AT 25°C.

V/V % H_2O	INSTRUMENT READING	DIELECTRIC CONSTANT
0	17708.8	24.3
10	18885.33	29.6
20	20552.4	34.3
30	21667.0	39.7
40	22739.33	46.0
50	23598.66	52.3
60	24379.0	58.5
70	24953.66	64.0
80	25386.33	69.3
90	25756.66	74.1
100	26077.66	78.5

TABLE 6

THE DETERMINED DIELECTRIC CONSTANTS FOR N-ALCOHOLS AT 25°C.

ALCOHOL	INSTRUMENT READING	DIELECTRIC CONSTANT
Methanol	20188.33	32.6
Ethanol	17708.8	24.4
1-Propanol	16310.25	20.2
1-Butanol	14994.0	17.2
1-Pentanol	13714.66	14.9
1-Hexanol	12300.5	12.4
1-Octanol	10563.25	9.9
1-Decanol	9133.33	8.0

ASSAY PROCEDURE

The samples were analyzed for calcium using a Perkin-Elmer atomic absorption spectrophotometer, Model 303. Measurements were made at a wavelength of 4227 Å and a slit setting of 4. The visible range was used and the source current was set at 12 ma. A scale setting of 1 or 3 was used, depending upon the concentration of calcium present. An air flow rate of 9 flowrater units was employed. Before the start of each series of analyses, the fuel (acetylene) flow rate was adjusted to compensate for the various solvents. This value was usually 8 flowrater units.

Due to variability in absorbance vs. concentration curves, it was necessary to prepare a series of standard solutions for each solvent. This variability may be seen in Figure 5. A solute series consisted of the following concentrations of calcium (expressed in ppm): 0.1, 0.25, 0.5, 0.75, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 10.0, 15.0, and 20.0. This allowed the establishment of a set of standard curves, from which the values of the unknowns could be read. Each unknown was read three times to establish continuity of data, and three unknowns were run for each solvent.

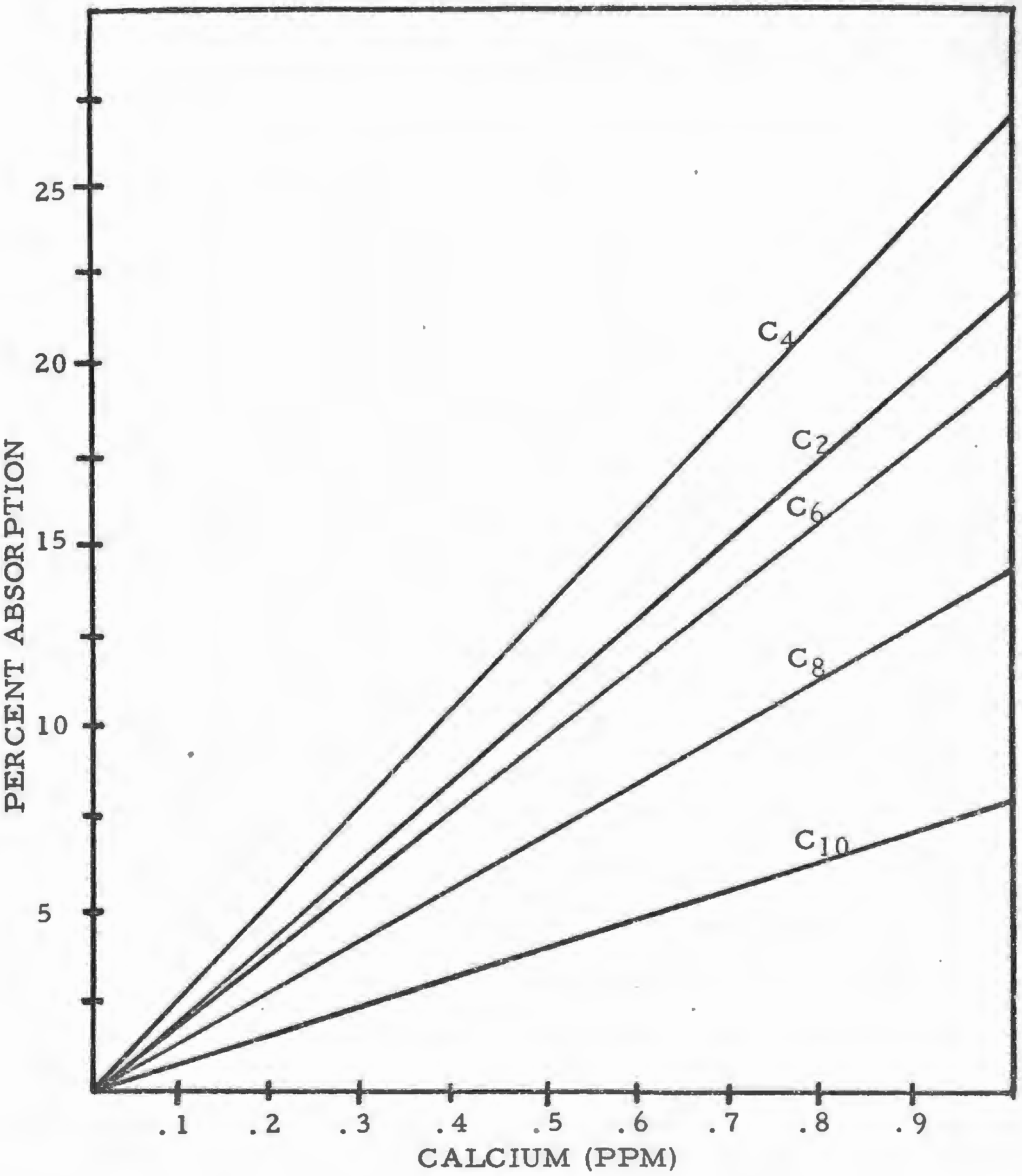


Figure 5. A Plot of Percent Absorption vs. Concentration for Standard Solutions of Calcium (in n-alcohols), Expressed in Parts Per Million.

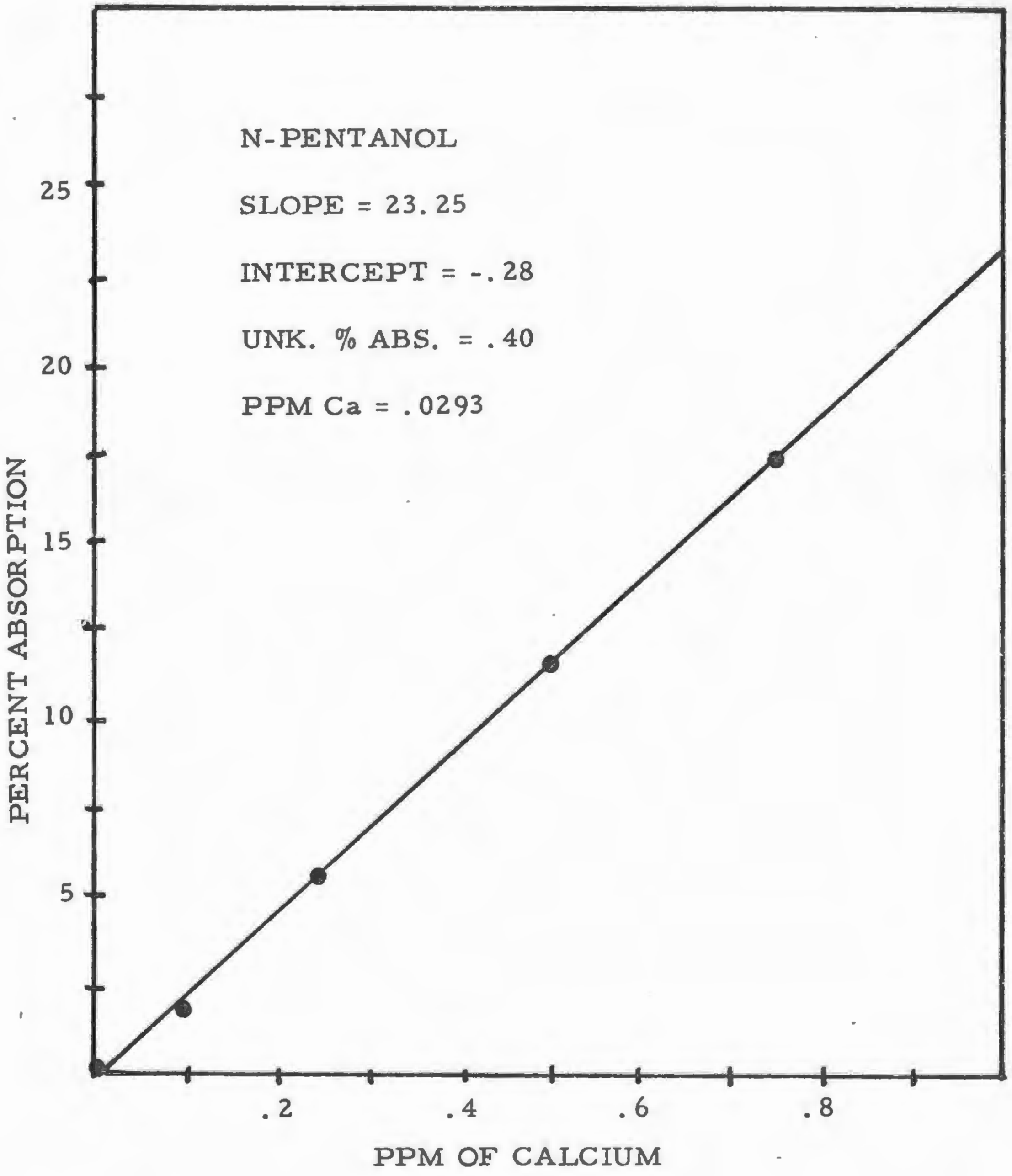


Figure 6. A Representative Determination of the Calcium Concentration in Unknowns of n-alcohols at 25°C. Expressed in Parts Per Million.

TABLE 7

A SUMMARY OF THE SLOPES AND INTERCEPTS OBTAINED FROM THE STANDARD CURVES FROM ATOMIC ABSORPTION SPECTROSCOPY. THE LAST TWO COLUMNS GIVE THE PERCENT ABSORPTION FOR THE UNKNOWNS AND THE CONCENTRATION OF CALCIUM EXPRESSED AS PPM.

ALCOHOL	SLOPE	INTERCEPT	UNK. % ABS.	PPM Ca
Methanol	22.57	0.0514	1.80	0.064
Ethanol	22.0	0.02	1.30	0.052
1-Propanol	23.84	-0.813	0.40	0.047
1-Butanol	27.07	-0.25	0.55	0.033
1-Pentanol	23.25	-0.28	0.40	0.029
1-Hexanol	19.80	0.00	0.50	0.025
1-Octanol	14.60	0.094	0.36	0.023
1-Decanol	9.00	0.00	0.10	0.017

It was not necessary to prepare a series of standard solutions for each of the binary solvent mixtures, since a preliminary study showed little variability between absorbance vs. concentration curves. This is illustrated in Figure 7. As a result, standards were made for 0%, 20%, 50%, 80% and 100% V/V concentrations of ethanol/water mixtures. The unknowns were then determined by using the closest standard curve, in terms of concentration.

The standards for each solvent were made by initially preparing 1000 ppm of calcium samples by dissolving 0.277 gram of calcium chloride in sufficient deionized water to yield 100 milliters of solution. The series of standards was then obtained by appropriate dilutions of the concentrate.

The 100% standards consisted of 1.0, 2.0, 3.0, 4.0, and 5.0 ppm of calcium.

The 80% standards consisted of 1.0, 3.0, 5.0, and 6.0 ppm of calcium.

The 50% standards consisted of 0.25, 0.5, 0.75 and 1.0 ppm of calcium.

The 20% standards consisted of 0.25, 0.5, 0.75, and 1.0 ppm of calcium.

The 0% standards consisted of 0.25, 0.5, 0.75 and 1.0 ppm of calcium.

After all the standards and unknowns were analyzed, plots of percent absorption vs. concentration yielded a linear relationship, indicating that the Beer-Lambert relation held. The unknowns were then determined in terms of ppm of calcium present, by reading them directly from the graph. This method is illustrated in Figure 7. It was not felt necessary to convert these values into the corresponding amount of calcium oxalate monohydrate, since a relationship was being defined.

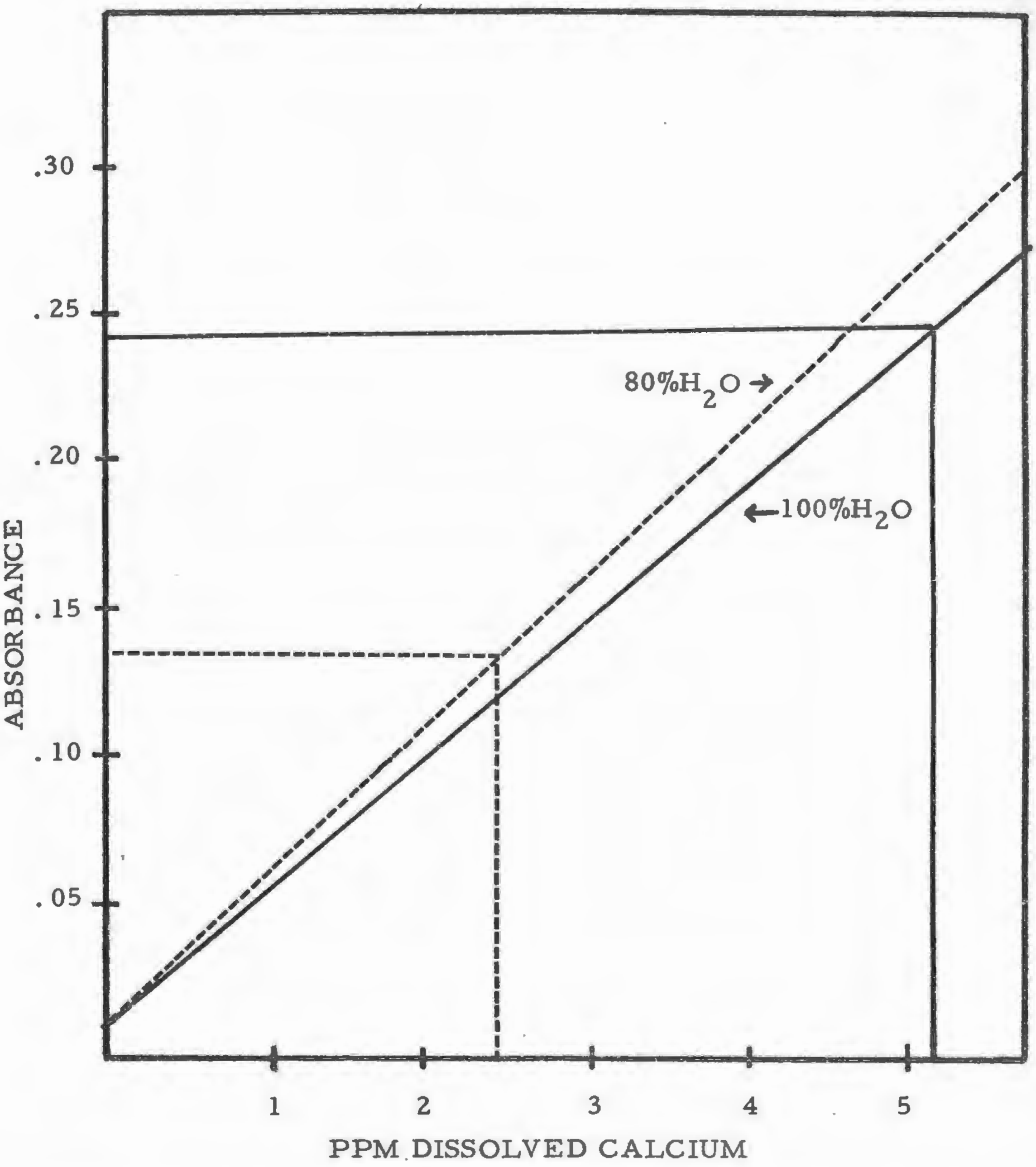


Figure 7. An Illustration of the Determination of the Calcium Concentrations in Unknowns of V/V Percent Ethanol-Water Mixtures at 25°C., Expressed as Parts Per Million.

VII. RESULTS AND DISCUSSION

The solubility of calcium oxalate in parts per million was determined in a series of 1-alkanols at 25°C. The alkanols encompass a relatively wide variation of polarity which, because it is directly related both to carbon number and dielectric constant, permits the interchange of these values in graphic presentation of results, as convenience and/or clarity dictate.

In Figure 8, the experimentally determined solubility of calcium oxalate is shown versus the carbon number of the alkanols used in this study. This information is also tabulated in Table 8. The values shown are average values of solubility in replicate samples. In all cases at least six samples were assayed, and in many cases nine to twelve replicate determinations were made. As can be seen, the solubility decreases in non-linear fashion with increasing carbon number, results which could be expected because of the diminishing non-polarity of the solvents used. It would, no doubt, be expected that 1-heptanol and 1-nonanol would fit into this observed non-linear curve, since the experimentally determined points for the alcohols close to these in polarity or carbon number were plotted.

TABLE 8

A SUMMARY OF THE SOLUBILITY OF CALCIUM OXALATE, EXPRESSED IN PPM, AT 25°C. AS A FUNCTION OF THE DIELECTRIC CONSTANT OF THE N-ALCOHOLS USED IN THIS STUDY.

ALCOHOL	DIELECTRIC CONSTANT	PPM CALCIUM
Methanol	32.6	0.064
Ethanol	24.4	0.0522
1-Propanol	20.2	0.047
1-Butanol	17.2	0.0325
1-Pentanol	14.9	0.0293
1-Hexanol	12.4	0.0252
1-Octanol	9.9	0.0225
1-Decanol	8.0	0.017

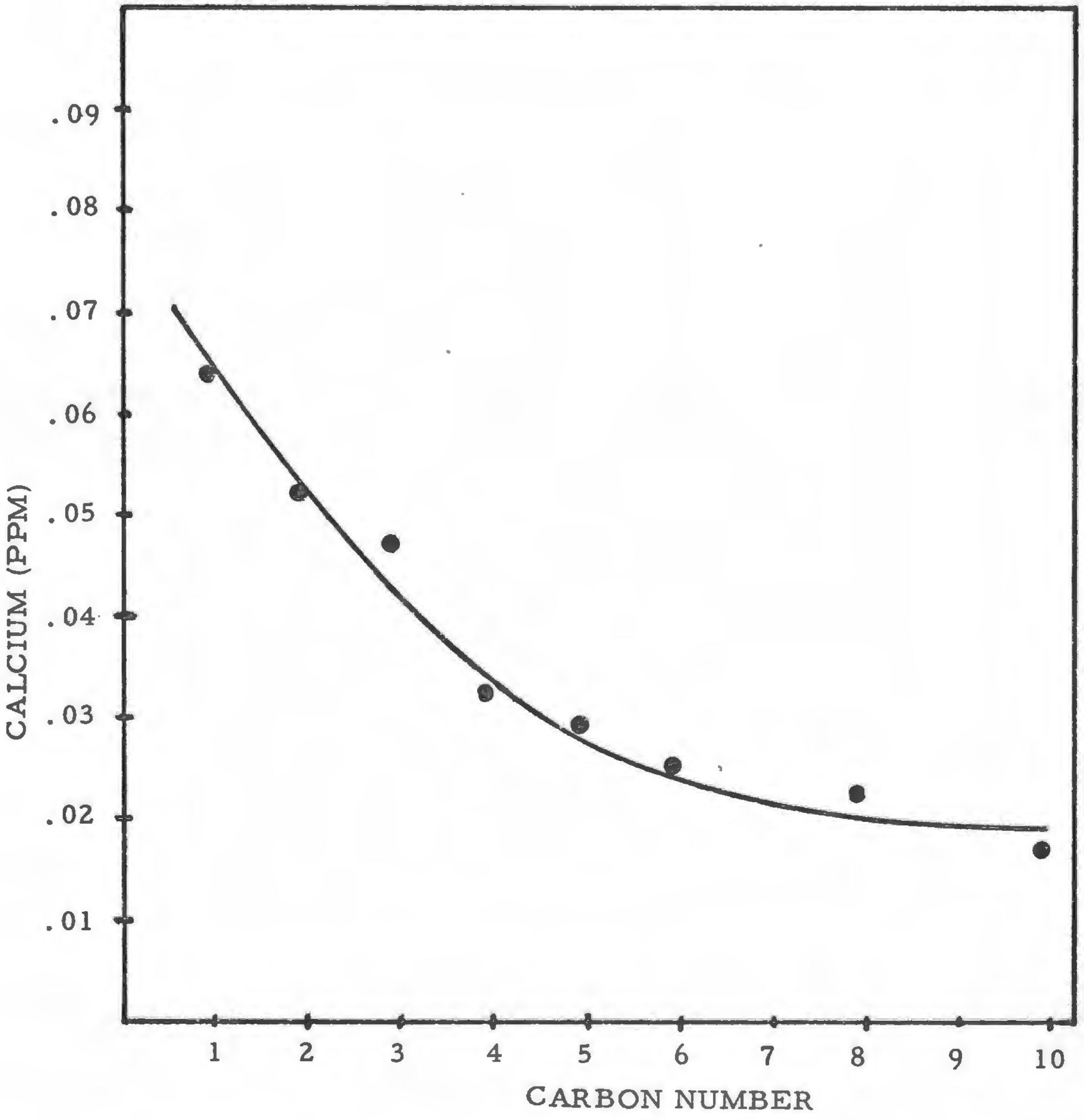


Figure 8. A Plot of the Solubility of Calcium Oxalate at 25°C. Expressed in Parts Per Million as a Function of the Carbon Number of the n-alkanols Used in this Study.

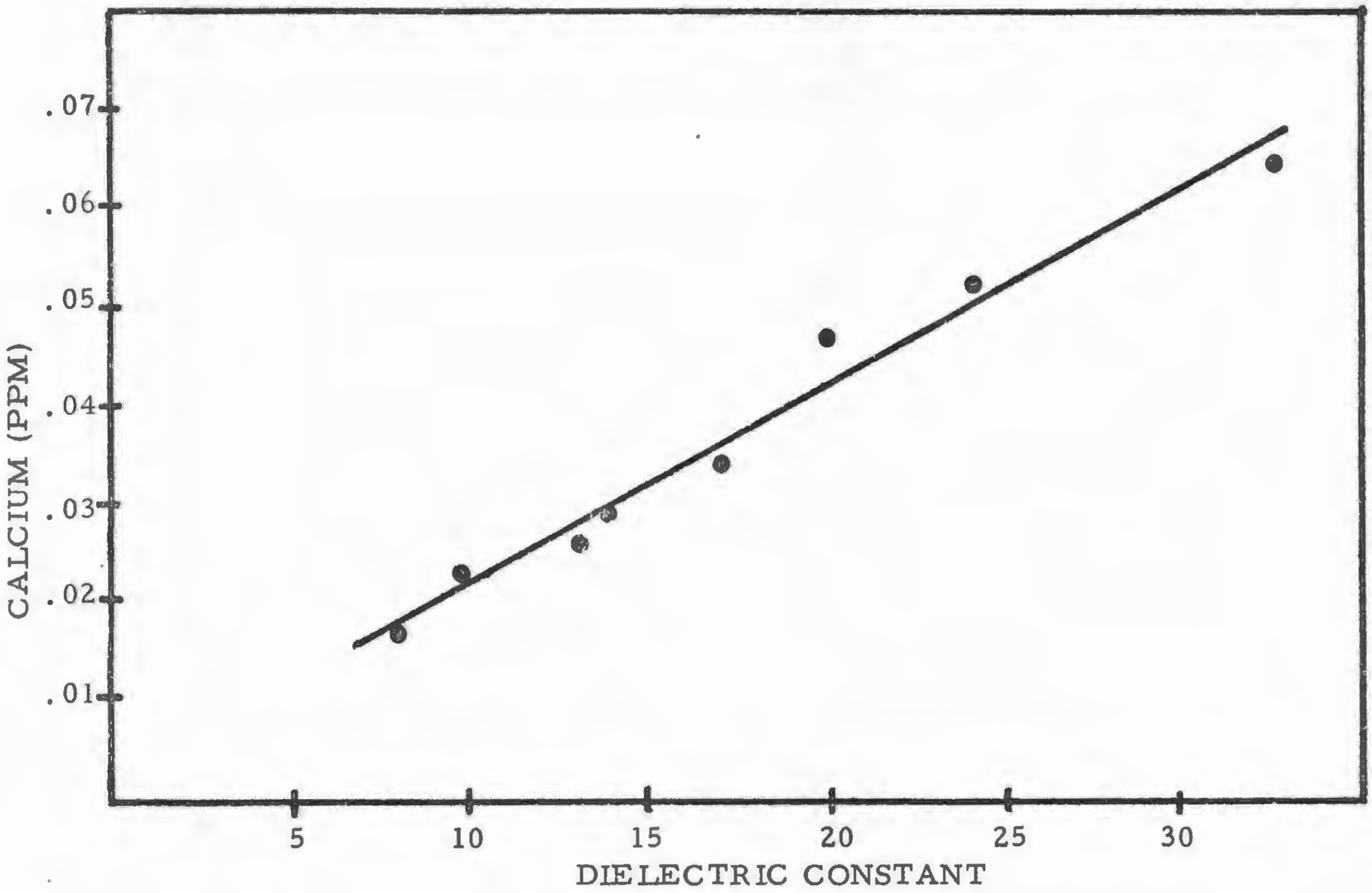


Figure 9. A Plot of the Solubility of Calcium Oxalate at 25°C. Expressed in Parts Per Million as a Function of the Dielectric Constant of the Series of n-alkanols Used in this Study.

In Figure 9, where the solubility of calcium oxalate in parts per million *versus* the dielectric constant of the 1-alkanols is shown, an approximately linear relationship is observed. In this case, a slope can be determined which will yield a relationship of solubility per dielectric unit. As determined by a least-squares method of analysis, the slope has a value of 1.986×10^{-3} per dielectric unit ($r^2 = .971$). This very interesting phenomenon of linear relationship of solubility to dielectric constant of very diverse nonelectrolytes has been previously found for other systems (19).

In order to determine the variation of solubility with composition of a binary solvent system, the solubility of calcium oxalate was also determined in ethanol-water systems. This allowed for the incremental variation of both polarity and dielectric constant; the range of dielectric constants was approximately twenty-four to seventy-eight. These experimental values are given in Table 9 and were determined in the same manner as that of the pure solvent scan.

In Figure 10, where the solubility of calcium oxalate in parts per million *versus* the percent volume/volume of water is shown, the solubility is seen to vary in a non-linear fashion, possessing low solubility in zero percent water (pure ethanol) and increasing to a maximum solubility of approximately five parts per million in one hundred percent water.

When plotted against a dielectric constant scale, the solubility isotherm in Figure 11 is of course similar to variation of concentration on a volume/volume basis. However, the curve is limited to a narrower spectrum of variation. The curve is also non-linear, rising exponentially. It might be possible that the solubility of calcium oxalate, from these isotherms, over narrow ranges of composition of dielectric constant, possesses linear segments at relatively high water content or relatively high ethanol content. Up to approximately sixty percent volume/volume of water, a linear segment can be identified from these isotherms; its slope is 1.40×10^{-2} / % V/V H_2O (r^2 =.925). Another linear segment occurs from sixty to one hundred percent volume/volume of water. This segment is more easily recognized on a dielectric constant plot. This segment possesses a slope of 1.95×10^{-1} / ϵ unit (r^2 = .810). At values intermittent between these, nonlinearity occurs.

The consideration of the magnitude of solubility of a substance such as calcium oxalate is predicated upon its ability to dissociate and ionize in polar and semipolar solvent systems, whether the solvents be pure or mixed systems.

The curves generated in the determination of calcium oxalate solubility versus the changing polarity of the pure solvent or mixed solvent, in reality indicate suppressive ionization phenomena. There can be no doubt that in the case of this very insoluble inorganic compound, these effects are related to the charge-separating ability or capacity of the solvents or solvent mixtures. A modification of Coulomb's law indicates a reciprocal relationship between solubility and dielectric constant, whereby the greater the dielectric constant of the media, the less the force required to separate the ions. This means that the capacity of these semipolar solvents to induce the separation of charge is continuously diminished with diminishing dielectric constant.

Often the presence of a semipolar solvent enhances the ionization phenomena of a compound. However, in the case of calcium oxalate, the types of solubility isotherms obtained are more appropriately related to the dissociative phenomena of this weak electrolyte, thus implying the separation of charge over a sufficient distance so that these ions act independently.

TABLE 9

A SUMMARY OF THE SOLUBILITY OF CALCIUM OXALATE, EXPRESSED IN PPM, AT 25°C. AS A FUNCTION OF THE DIELECTRIC CONSTANT IN A SERIES OF ETHANOL-WATER MIXTURES.

VOL. % H_2O	DIELECTRIC CONSTANT	PPM CALCIUM
0	24.3	0.0522
10	29.3	0.05
20	34.3	0.15
30	39.7	0.24
40	46.0	0.426
50	52.3	0.65
60	58.3	0.866
70	64.0	1.4
80	69.3	2.13
90	74.1	2.53
100	78.5	5.33

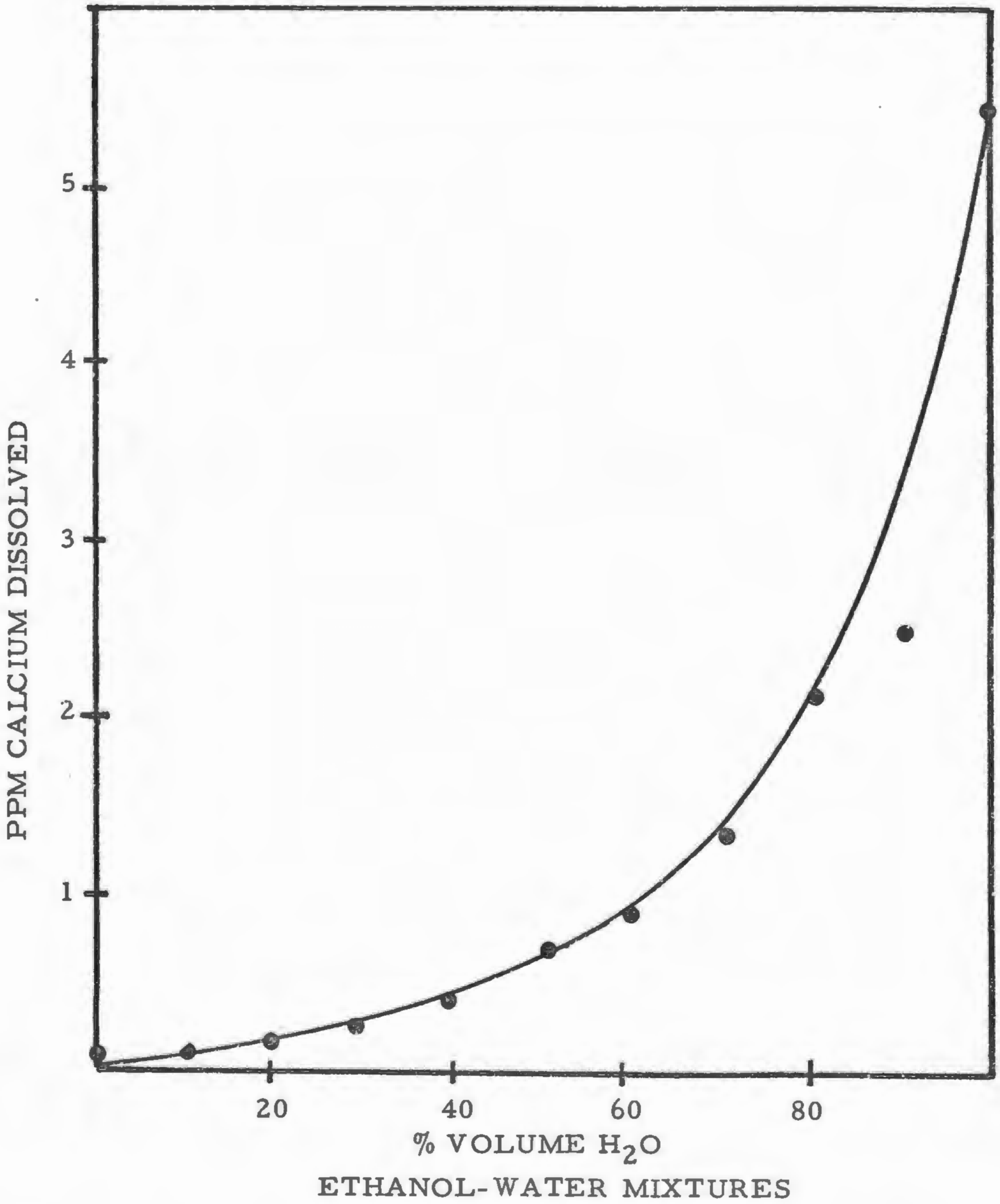


Figure 10. A Plot of the Solubility of Calcium Oxalate at 25°C. Expressed in Parts Per Million as a Function of V/V Percent Ethanol-Water Mixtures.

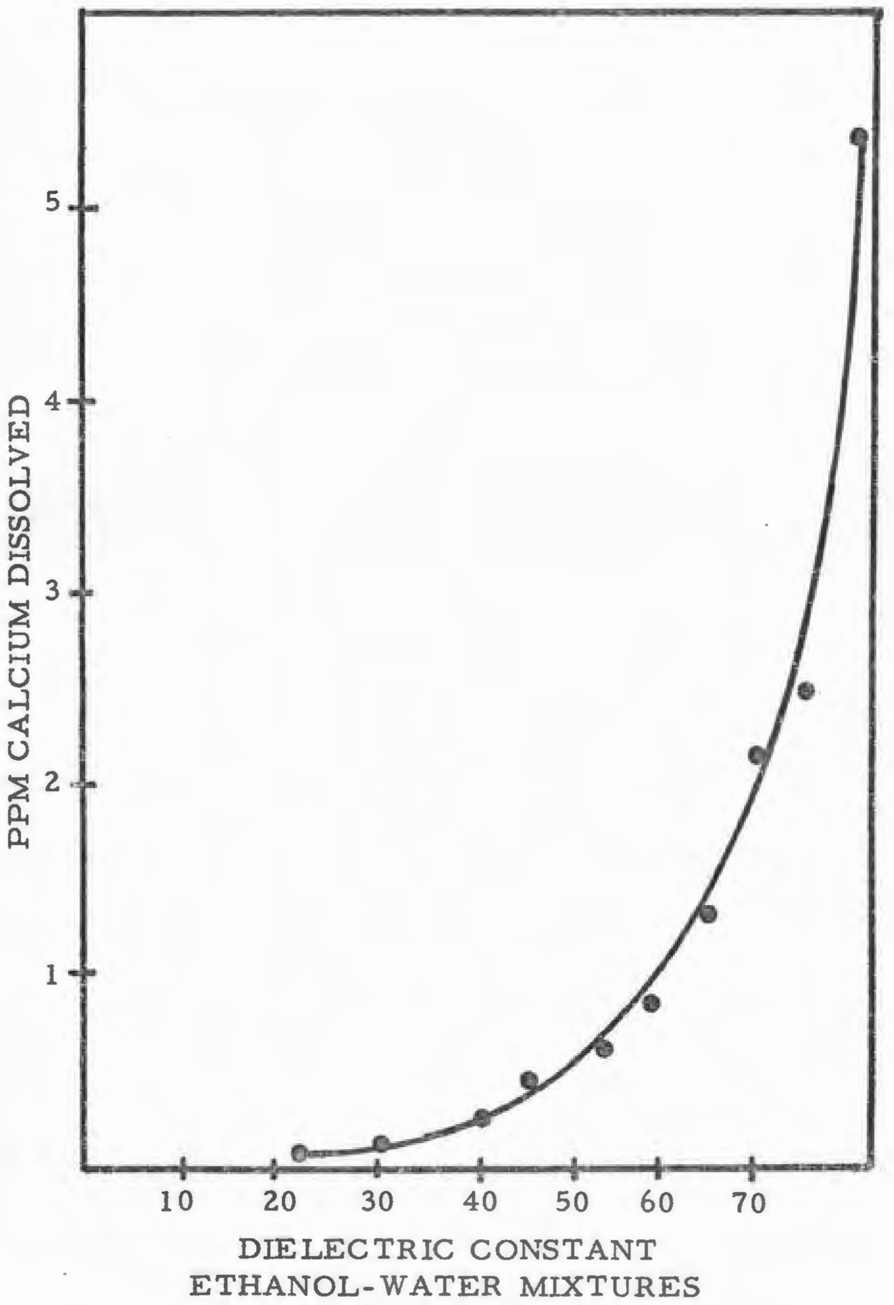


Figure 11. A Plot of the Solubility of Calcium Oxalate at 25°C. Expressed in Parts Per Million as a Function of the Dielectric Constant of Ethanol-Water Mixtures.

It has been stated (31) that in media of dielectric constant below sixty, divalent ions will be associated. Since calcium oxalate dissociates as shown,

$$CaC_2O_4 \longrightarrow Ca^{2+} + C_2O_4{}^{2-}$$

this may account for the sharp increase in slope at approximately the dielectric constant of sixty, where the calcium oxalate has a greater tendency to dissociate.

Since the solubility profile for calcium oxalate is a repressive ionization curve, the compound acts as if it were completely associated at low dielectric constant values. The decrease in dielectric constant with increasing nonpolar solvent concentration causes the solubility to decrease, since the work required to separate the charges becomes larger.

The curves obtained in this solubility profile reveal no peaks or shoulders, but generally rise continuously and asymptotically toward greatest solubility in pure water. Hence, a dielectric requirement is not indicated. However, assuming that water has the practical maximum polarity, the dielectric requirement in this case would be about eighty.

A consequence of these results related the rather poor solvating capacity of the solvent systems used. This indicates that the cohesional interactions of the solutes are the determinant of its aqueous, alcoholic and hydro-alcoholic solubility.

VIII. SUMMARY

1. The solubility of calcium oxalate monohydrate was determined at 25°C. in a series of 1-alkanols and ethanol-water mixtures, having known dielectric constants, via atomic absorption spectroscopy.

2. When solubility was plotted versus the dielectric constant of the 1-alkanols, a linear relationship was developed. This showed that solubility had fair parallelism to dielectric constant.

3. When the solubility was plotted versus the dielectric constant of the ethanol-water mixtures, a non-linear relationship resulted, with low solubility occurring in zero percent water (pure ethanol) and increasing solubility occurring until a maximum was reached in one hundred percent water.

4. The solubility isotherms in the ethanol-water mixtures can be considered as repressive ionization phenomena.

5. In the ethanol-water mixtures, the solubility isotherm was curvilinear and on a dielectric constant basis, an apparent

break occurred in the isotherm at a dielectric constant of sixty. This can be considered to be the point of ionization of divalent cations.

IX. REFERENCES

(1) Foreword to the compilation of papers presented at the Renal Stone Research Symposium, Leeds, England, 17-20 April, 1968.

(2) Merck Index, 7th ed., Merck and Co., Inc., Rahway, N.J., 1960, p. 196.

(3) E. L. Prien and E. L. Prien, Jr., Amer. J. Med., 45, 659 (1968).

(4) Handbook of Chemistry and Physics, 49th ed., The Chemical Rubber Co., Cleveland, 1968, p. B-307.

(5) G. Hammarsten, "On Calcium Oxalate Stones", in Etiologic Factors in Renal Lithiasis, ed. by A. J. Butt (Springfield, Ill.: Charles C. Thomas, 1956), pp. 89-94.

(6) G. Hammarsten, Compt. Rend. Trav. Lab. Carlsberg, 17, 1 (1929).

(7) H. Shehyn and D. B. Pall, J. Phys. Colloid. Chem., 44, 166 (1940).

(8) G. H. Miller, G. W. Vermeulen and J. D. Moore, Journ. of Urology, 79, 607 (1958).

(9) J. S. Elliot and E. Eusebio, Invest. Urology, 3, 72 (1965).

(10) J. S. Elliot and E. Eusebio, Invest. Urology, 2, 428 (1965).

(11) B. Finlayson, R. Roth and L. DuBois, "Calcium Oxalate Solubility Studies", in Urinary Calculi, Int. Sym. Renal Stone Res., Madrid, 1972 (Karger, Basel, 1973), pp. 1-7.

(12) J. Ferguson, J. Proc. Roy Soc. (Series B), 127, 397 (1939) cited by P. A. Schwartz, "Solubility of Aminobenzoate Esters" (M.S. Thesis, University of Rhode Island, 1972), p. 3.

(13) A. Martin, Physical Pharmacy, Lea and Febiger, Philadelphia, 1970, p. 302.

(14) A. N. Paruta, B. J. Sciarrone, and N. G. Lordi, J. Pharm. Sci., 53, 1349 (1964).

(15) N. G. Lordi, B. J. Sciarrone, T. J. Ambrosio and A. N. Paruta, J. Pharm. Sci., 53, 463 (1964).

(16) W. E. Moore, J. Pharm. Sci., 51, 391 (1962).

(17) W. G. Gorman and G. D. Hall, J. Pharm. Sci., 53, 1017 (1964).

(18) V. R. Williams and H. B. Williams, "Basic Physical Chemistry for the Life Sciences, W. H. Freeman and Co., San Francisco, 1973, p. 3.

(19) A. N. Paruta and J. W. Mauger, J. Pharm. Sci., 60, 432 (1971).

(20) A. N. Paruta, B. J. Sciarrone, and N. G. Lordi, J. Pharm. Sci., 53, 1349 (1964).

(21) A. N. Paruta and S. A. Irani, J. Pharm. Sci., 54, 1334 (1965).

(22) T. L. Breon and A. N. Paruta, J. Pharm. Sci., 59, 1306 (1970).

(23) P. L. Kirk and P. C. Tompkins, Ind. Eng. Chem. Anal. Ed., 13, 277 (1941).

(24) E. Y. Berger, Clin. Chem., 1, 249 (1955).

(25) Analytical Methods Guide, Orion Research Inc., Cambridge, Mass., 1975.

(26) D. A. Skoog and D. M. West, Principles of Instrumental Analysis, Holt, Rinehart and Winston, Inc., N. Y., 1971, pp. 115-130.

(27) J. Ramierez-Munoz, Atomic-Absorption Spectroscopy, Elsevier Publishing Co., N. Y., 1968.

(28) A. Weissberger and E. Proskauer, Organic Solvents, Interscience Publishers, Inc., N. Y., 1955.

(29) T. L. Breon, "Solubility of Several Barbiturates", (M. S. Thesis, University of Rhode Island, 1969), p. 28.

(30) P. Sherrick, G. Dowe, R. Karr, and E. Ewan, Manual of Chemical Oscillometry, E. H. Sargent and Co., Chicago, 1954.

(31) R. G. Larson and H. Hunt, J. Phys. Chem., 1939, 417.