

- (6) G. J. G. Parry and D. G. Ferry, *J. Chromatogr.*, **128**, 166 (1976).
(7) J. P. Cano, J. Catalin, *et al.*, *Eur. J. Toxicol. Environ. Hyg.*, **9**, 213 (1976).
(8) W. R. Dixon, R. L. Young, R. Ning, and A. Liebman, *J. Pharm. Sci.*, **66**, 235 (1977).
(9) A. Kobiela-Krzyzanowska, *Pharmazie*, **31**, 649 (1976).

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Solubility of Calcium Oxalate in 1-Alkanols and Ethanol-Water Mixtures

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Abstract □ Solubility profiles for calcium oxalate were determined in pure 1-alkanols and ethanol-water mixtures at 20°. The magnitude of solubility in the aliphatic alcohols was highest in methanol and decreased in a nonlinear fashion as the dielectric constant decreased, going to *n*-decanol. In ethanol-water mixtures, the solubility increased nonlinearly with water content or increasing dielectric constants. The work factor for these systems was also calculated and, as expected, a "mirror image" to the solubility profiles was evidenced. In the mixed solvent system, a dramatic change in the magnitude of solubility occurred after a dielectric constant value of about 60, indicating ionic association or ion-pairs below this value. The Born relationship of solubility and ionic size was tested in the ethanol-water system, and the ionic size of the divalent species of about 2.27 Å agreed with the theoretical ionic size of about 2.4 Å. These results indicate that the water number of calcium is 8 or that a monolayer of dipoles surrounds this divalent cationic species.

Keyphrases □ Calcium oxalate—solubility in various 1-alkanols and ethanol-water mixtures □ Solubility—calcium oxalate in various 1-alkanols and ethanol-water mixtures

Calcium oxalate, a component of certain types of "body" stones, is a typical example of a metallo-organic substance whose solubility characteristics should be a major area of investigation. This study is an initial effort into determining these solubility profiles in a series of pure 1-alkanols and ethanol-water mixtures. Since calcium oxalate is highly insoluble, its solubility as a function of polarity would be determined by covering the range of polarity by various solvents and solvent mixtures. Additionally, the spectrum of polarity would be manifested by the dielectric constants of the solvent systems. Thus, the charge-separating ability of various solvents would be indicative of their effect on the ionization and subsequent dissociation of the solute measured by the solubility product of calcium oxalate.

BACKGROUND

Calcium oxalate is considered to be insoluble in both polar and non-polar solvents (1). It may occur as a mono-, di-, or trihydrate, with the monohydrate being the most stable form as well as the least soluble (2, 3). The monohydrate has a solubility product of 2.57×10^{-9} mole/liter at 25° (4).

In 1929, Hammarsten (5) studied the solubility of calcium oxalate, applying the Debye-Huckel theory of ion activity in the presence of urinary electrolytes. A "salting-in" increase in solubility was found by the use of sodium chloride, monobasic sodium phosphate, potassium

chloride, and magnesium chloride. Also, pH had no effect when varied over the usual physiological range.

Shehyn and Pall (6) studied the solubility of calcium oxalate as a function of the ionic strength of various salts. Other studies relating to solubility in salt solutions also were performed (7-9). Finlayson *et al.* (10) presented information on the complex set of equilibria of calcium oxalate in aqueous systems. An ionizable salt, sodium salicylate, was studied previously in mixed solvent systems of various types (11).

EXPERIMENTAL

Chemicals—Calcium oxalate¹, calcium chloride², methanol³, ethanol⁴, 1-propanol⁵, 1-butanol⁶, 1-pentanol⁷, 1-hexanol⁸, 1-octanol⁹, 1-decanol¹⁰, and distilled deionized water were used. The purity and anhydrous nature of the solvents were tested as previously described (11).

Equipment—A refractometer¹¹, a demineralizer¹², a centrifuge¹³, and an oscilloscope¹⁴ were used.

The refractometer was used to check the purity of the solvents, and the oscilloscope was used to determine dielectric constants.

Procedure—A rotating apparatus holding screw-capped glass vials was filled with the appropriate solvent or solvent mixture and rotated at 40 rpm in the presence of excess calcium oxalate. The temperature was maintained at 20° by a temperature control unit¹⁵. Samples were withdrawn with pipets through a glass wool wrap after equilibration for 24 hr. The samples were centrifuged at 1000 rpm for 10 min because of the fine nature of particles, and a clear supernate at 20° was drawn for analysis on an atomic absorption spectrophotometer¹⁶.

The samples were analyzed from previously determined calibration curves with known concentrations of calcium as calcium chloride in the appropriate solvents or solvent mixtures. These measurements were made with a calcium vapor lamp at the 4227-Å absorption line for gaseous calcium atoms at a source current of 12 μamp using an acetylene-air mixture.

For the pure solvents and up to about 40% water in the mixed solvent system, 12 samples were analyzed. At higher water concentrations to pure water, eight samples were tested for calcium concentration. These results

¹ Lot 762198, certified powder, J. T. Baker Chemical Co.

² Lot XGZ, anhydrous, Mallinckrodt Chemical Works.

³ Lot VMN, anhydrous, spectrophotometric grade, Mallinckrodt Chemical Works.

⁴ Absolute, U.S. Industrial Chemical Co.

⁵ Lot 35592, "Baker Analyzed," J. T. Baker Chemical Co.

⁶ Lot TDY, analytical reagent, Mallinckrodt Chemical Works.

⁷ Lot 776291, certified, U.S. Industrial Chemical Co.

⁸ Lot H1330, Aldrich Chemical Co.

⁹ Lot 22, Mallinckrodt Chemical Works.

¹⁰ Lot 17, Matheson, Coleman and Bell.

¹¹ Abbe-3, Bausch & Lomb Optical Co.

¹² Bantam model BD-1, Barnstead Still and Sterilizer Co.

¹³ Damon/IEC Division, Damon Corp.

¹⁴ Chemical model V, E. H. Sargent and Co.

¹⁵ Temprol 150, Precision Scientific Co.

¹⁶ Model 3D3, Perkin-Elmer Corp.

Table I—Solubility of Calcium Oxalate in Various Notations at 20° as a Function of the Dielectric Constants and Work Factors of the Aliphatic Alcohols Listed

Alcohol	Dielectric Constant ^a	Work ^b , ergs × 10 ¹²	Average Calcium Concentration, ppm	Calcium Concentration × 10 ⁵ , moles/liter	Solubility Product, K _{sp} , × 10 ¹⁰ , moles/liter
Methanol	32.6	1.2	0.064	0.045	0.00203
Ethanol	24.4	1.6	0.052	0.037	0.00134
1-Propanol	20.2	1.9	0.040	0.028	0.00079
1-Butanol	17.2	2.2	0.033	0.023	0.00054
1-Pentanol	14.9	2.6	0.029	0.020	0.00042
1-Hexanol	13.4	3.1	0.025	0.018	0.00031
1-Octanol	9.9	3.9	0.023	0.016	0.00026
1-Decanol	8.0	4.8	0.017	0.012	0.00014

^a Determined by oscillometric method. ^b Calculated from $W = 2e_1e_2/\epsilon r$.

Table II—Solubility of Calcium Oxalate in Various Notations at 20° as a Function of the Dielectric Constants and Work Factors of the Relative Concentration of Ethanol-Water Mixtures

Volume Percent of Water	Dielectric Constant ^a	Work ^a , ergs × 10 ¹²	Average Calcium Concentration, ppm	Calcium Concentration × 10 ⁵ , moles/liter	Solubility Product, K _{sp} , × 10 ¹⁰ , moles/liter
0	24.4	1.6	0.05	0.035	0.0012
10	29.3	1.3	0.06	0.042	0.0018
20	34.3	1.1	0.15	0.106	0.0110
30	39.7	0.97	0.24	0.169	0.028
40	46.0	0.83	0.43	0.303	0.092
50	52.3	0.73	0.65	0.458	0.209
60	58.3	0.66	0.87	0.613	0.375
70	64.0	0.60	1.40	0.986	0.972
80	69.3	0.55	2.43	1.71	2.93
90	74.1	0.52	3.90	2.75	7.54
100	78.5	0.49	5.33	3.75	14.08

^a See Table I.

were averaged for each solvent and solvent mixture, and the variation in replicate samples was about 0.001-0.005 ppm of calcium. The larger variations were found at low concentrations, leading to an error of about 10%. The smaller variations occurred for relatively higher concentrations, with errors of about 1-2 and <0.1% at calcium concentrations of about 0.1 and about 1 ppm or above, respectively.

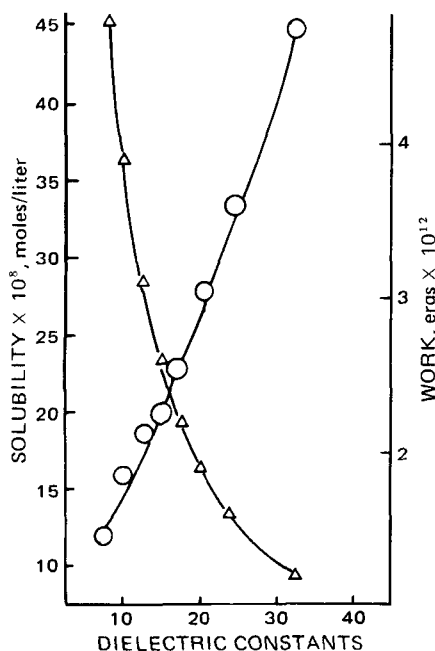


Figure 1—Plot of the solubility at 20° of calcium oxalate, in moles per liter (O), and the work factor, in ergs (Δ), as a function of the dielectric constant of the 1-alkanols.

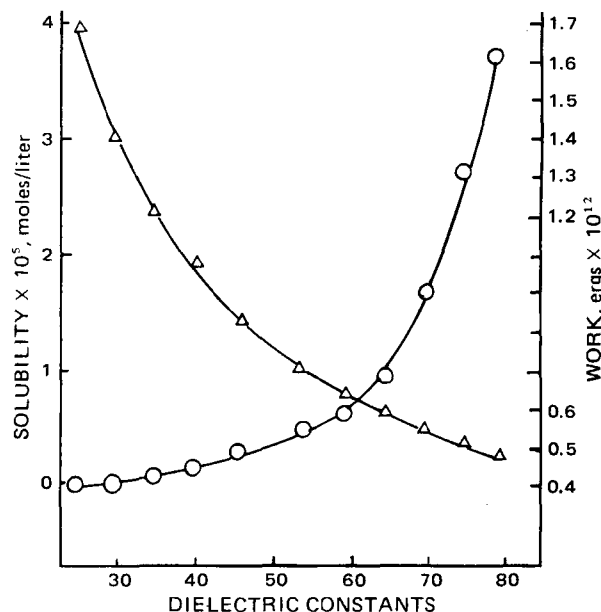


Figure 2—Plot of the solubility at 20° of calcium oxalate, in moles per liter (O), and the work factor, in ergs (Δ), as a function of the dielectric constants of ethanol-water mixtures.

RESULTS AND DISCUSSION

The experimentally determined solubilities of this solute, expressed in various concentration notations at 20° in the 1-alkanols and ethanol-water mixtures, are given in Tables I and II. The dielectric constants and work factors are also listed. The solubility in these cases increased with increasing dielectric constants and decreasing work factors. For the pure alcohols, the solubility increased in a nonlinear fashion from 1-decanol to methanol. Similarly, the solubility in ethanol-water mixtures also increased with increasing water content. This result indicates an enhancement of dissociation with increasing dielectric constants, as expected from Coulomb's law.

Figure 1 shows a plot of calcium solubility, expressed in moles per liter, versus the dielectric constants of the aliphatic alcohols. A nonlinear isothermal solubility profile is evidenced, which is the mirror image of the calculated work factors in these alcohols (also plotted in Fig. 1).

In Fig. 2, calcium solubility in moles per liter is plotted in the same manner for the ethanol-water mixtures; the same characteristics were observed. The solubility increased with increasing water content; at a dielectric constant of about 60, there was a dramatic increase in solubility disproportionate with water concentration.

This portion of the solubility isotherm was approximately linear and was supported by the work of Larson and Hunt (12), which states that

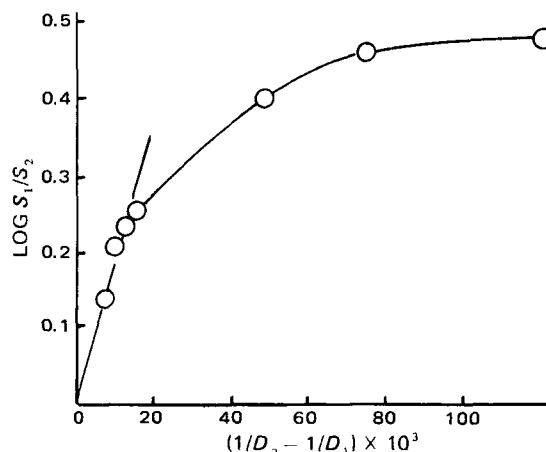


Figure 3—Plot of the log of the solubility ratio for calcium oxalate at 20° as a function of the reciprocals of the dielectric constants of the ethanol-water mixtures.

divalent ionic species are associated below this dielectric constant value. The decreasing solubility with increasing nonpolarity suggests increasing association of the calcium and oxalate moieties as a partially dissociated ion-pair. These ion-pairs would be strongly associated at lower dielectric constants, resulting in diminished solubility, with the association decreasing in strength as the dielectric constant of the medium increased.

Since the data were available, the Born theory (13) could be tested for validity in predicting the average ion radius once solubilities had been determined in two solvents of varying dielectric constants. These calculations were given previously (11) and are summarized here. In Fig. 3, $\log S_1/S_2$ for calcium oxalate is plotted versus the reciprocal of the difference in dielectric constants in the ethanol-water mixtures.

A straight-line relationship is observed at water concentrations of 60% (v/v) to pure water. The slope of this line has a value of 53. From this slope, an average ion radius of 2.27 Å was calculated.

The theoretical ionic radius for calcium and oxalate could be obtained from ionic radii and water numbers. The calcium ion possesses a water number of 8-12, and the oxalate ion has a water number of 2. The radius for the oxalate anion was about 2.4 Å. For calcium with a water number of 8, indicating a monolayer of water dipoles, the average ion radius was also 2.4 Å. With a water number of 12, a bimolecular layer of water dipoles is present and the radius was 3.6 Å.

The good agreement of the average ion radius from theoretical consideration of 2.4 Å and the experimentally determined value of 2.27 Å supports the use of the Born expression and suggests that the calcium ion in these binary systems possesses a water number of 8.

REFERENCES

- (1) "The Merck Index," 7th ed., Merck & Co., Rahway, N.J., 1960, p. 196.
- (2) E. L. Prien and E. L. Prien, Jr., *Am. J. Med.*, **45**, 659 (1968).
- (3) G. Hammarsten, in "Etiologic Factors in Renal Lithiasis," A. J. Butt, Ed., Charles C Thomas, Springfield, Ill., 1956, pp. 89-94.
- (4) "Handbook of Chemistry and Physics," 49th ed., Chemical Rubber Co., Cleveland, Ohio, 1968, p. B-307.
- (5) G. Hammarsten, *C. R. Trav. Lab. Carlsberg*, **17**, 1 (1929).
- (6) H. Shehyn and D. B. Pall, *J. Phys. Colloid Chem.*, **44**, 166 (1940).
- (7) G. H. Miller, C. W. Vermeulen, and J. D. Moore, *J. Urol.*, **79**, 607 (1958).
- (8) J. S. Elliot and E. Eusebio, *Invest. Urol.*, **3**, 72 (1965).
- (9) *Ibid.*, **2**, 428 (1965).
- (10) B. Finlayson, R. Roth, and L. DuBois, in "Urinary Calculi," International Symposium on Renal Stone Research, Madrid, Spain, 1972, pp. 1-7.
- (11) A. N. Paruta and J. W. Mauger, *J. Pharm. Sci.*, **60**, 432 (1971).
- (12) R. C. Larson and H. Hunt, *J. Phys. Chem.*, **43**, 417 (1939).
- (13) M. Born, *Z. Phys.*, **1**, 45 (1920).

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Pyrrole, Furan, and Thiophene Oxamates as Potential Antiallergy Agents

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Abstract □ Nine heterocyclic oxamic acid derivatives were synthesized and tested in the rat passive cutaneous anaphylactic assay as potential antiallergy agents. Some compounds also were tested for their effects on cholesterol-lipoprotein levels and for diuretic, antidiabetic, and antifertility activities in rats.

Keyphrases □ Heterocyclic oxamates, various—synthesized, evaluated as antiallergy agents □ Oxamates, various heterocyclic—synthesized, evaluated as antiallergy agents □ Antiallergy agents, potential—various heterocyclic oxamates evaluated □ Structure-activity relationships—various heterocyclic oxamates evaluated as antiallergy agents

Some years ago, several heterocyclic oxamates (IIa-IIIi, Table I) were synthesized (Scheme I) as possible precursors for various indole isosteres. Although these efforts proved unsuccessful, routine screening¹ of these new compounds in the rat passive cutaneous anaphylaxis (PCA) assay as potential antiallergy agents (1-3) showed some significant activity (*viz.*, IIa, Table II) (4). Subsequently, the activity (parenterally) was shown to reside in the free acid (5). Antiallergic activity associated with novel oxamic acids was noted recently (6-13), and Sellstedt *et al.* (14) described structure-activity relationships between the oxamates and cromolyn sodium, "the only compound on the market that prophylactically inhibits the liberation

of the mediators of allergic reactions initiated by antibody-antigen interactions" (14).

In addition to the evaluation for antiallergic activity, pharmacological test data were obtained for diuretic activity in fasted rats (IIa-IIc, IIe-IIIi, and III) (15) and antidiabetic activity in rats (IIb, IIc, IIe, IIh, and III) (16). No significant activity was observed. In an antifertility test (17), IIh administered subcutaneously to three female rats (10 mg/day) prevented conception in all animals, and the compound was considered active by the criteria of this test. In the modified procedure of Tinsho *et al.* (18) for effect on cholesterol-lipoprotein levels in rats, IIa lowered both serum cholesterol (T/C = 0.67) and serum lipoprotein (T/C = 0.63) fractions significantly at 50 mg/kg po. However, IIa was inactive in preventing experimental thrombosis.

EXPERIMENTAL²

The amino-substituted heterocycles, Ia-Ij, were prepared by the procedure of Gewald and coworkers (19-21). 2-Amino-5-ethoxycarbon-

² Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. NMR spectra were determined on a Hitachi Perkin-Elmer R 20A high-resolution NMR spectrometer, using tetramethylsilane as the internal reference. IR spectra were determined on a Perkin-Elmer 237B grating spectrophotometer, using the potassium bromide technique. UV spectra were determined in methanol solution with a Perkin-Elmer 202 UV-visible spectrophotometer. Elemental analyses were determined by Atlantic Microlab, Atlanta, Ga. TLC was performed on Eastman chromatogram sheets, type 6060 (silica gel).

* From The Upjohn Co.'s biological evaluation program.