Ionic Equilibria in Mixed Solvents: Formation of Calcium Lactate

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The ionization constants of lactic acid and the formation constants of calcium(II) lactate in methanol–water, ethanol–water, and glucose–water mixed solvent systems have been determined potentiometrically at four temperatures. An empirical equation correlating the formation constants of calcium(II) lactate in mixed solvents and in water has been derived by using a curve fitting technqiue. It was found that the formation constant is a function of a linear combination of the reciprocals of the bulk dielectric constants, and the equation has the same general form as Born's equation for the ionic processes in a dielectric medium. The experimental data suggest that primary process of coordination is via the attachment of two carboxylate groups of two lactate anions; the hydroxide groups are attached to the metal subsequent to the primary process, and the overall process of formation of calcium(II) lactate is endothermic.

It is frequently necessary to study the thermodynamics of reversible ionic equilibria in organic–water mixed solvent systems as many such processes of interest cannot be studied in a purely aqueous system (that is dilute aqueous solution of the members of the equilibrium only) because of the solubility, hydrolysis, and several other problems associated with water as the solvent (*18*). During the last 10 years there has been vigorous research activity in this area, and interest therein is still continuing (*11*). In such studies, an infinitely dilute solution in the solvent used is sometimes arbitrarily taken as the reference state. While the equilibrium constant of a reversible system determined in a particular solvent may be of considerable practical importance, the value of such a constant cannot be readily compared with the equilibrium constant of a similar reversible system determined in another solvent. Therefore, it would be extremely useful if there were a method for converting the equilibrium constant of a given reversible system determined in a particular solvent to the corresponding value in some other reference solvent, say water. The complexities of rigorous theory (*10*) as well as the difficulties of experiment in developing such a method are quite formidable. Taking an empirical approach to the problem, instead of struggling with an unmanageable theory, seems more reasonable to us. The foregoing statement must not be construed as an argument against the theory; in fact, a rigorous theory is essential for the comprehension of thermodynamics of ionic equilibria in mixed solvents. Empiricism is an operational approach, and the present work should be viewed in that light.

Sen and Adcock (*17*) were able to derive empirically from experimental data an equation correlating the ionization constants of 13 monocarboxylic acids in a large number of water–organic mixed solvents to the bulk dielectric constants of the mixed solvents and their components. When the bulk dielectric constant of the mixed solvent is equal to or higher than 40, the equation takes the form,

$$\mathrm{p}K_\mathrm{i}^* = \mathrm{p}K_\mathrm{i} + \beta\left(\frac{1}{\epsilon^*} - \frac{1}{\epsilon'}\right) \qquad (1)$$

in which K_i^* = ionization constant of the acid at zero ionic strength in the mixed solvent, K_i = ionization constant of the acid at zero ionic strength in water, ϵ^* and ϵ' are some linear combinations of the bulk dielectric constants of the two pure solvents and the mixed solvent, respectively, and β is the slope of the plot of experimental $\mathrm{p}K_\mathrm{i}^*$ vs. $(1/\epsilon^* - 1/\epsilon')$ (*4*). The significant feature of eq 1 is its striking similarity to Born's equation (*6*) derived from a purely electrostatic model for the ionization of acids or ionic systems. The results of Sen and Adcock's studies prompted us to extend the investigation to include the metal ion complexes. For a number of reasons, we selected the Ca(II)–lactic acid system as the first system to study. First, the calcium(II) ion has a closed-shell electronic configuration, and the assumption that the first-order interaction between the Ca^{2+} ion and the lactate anion is primarily Coulombic is valid. Secondly, calcium lactate is a biologically important system due to the fact that calcium is dispersed in the human body as calcium lactate. Therefore, the study of the thermodynamics of its formation may yield information of biological interest.

It should be realized that all interactions in solution are between solvated species. All equilibrium constants (e.g., the ionization constants of the acids, the formation constants of the complexes) refer to corresponding chemical equilibria among the solvated species. We have used the phrase "thermodynamic equilibrium constant" only to imply the value of the equilibrium constant of a particular process among the solvated species at zero ionic strength. Even with this restricted definition, there are a number of experimental problems which are difficult to overcome.

Experimental Section

Cells, Bridge, Electrodes, and Constant Temperature Bath. Electrolytic cells of the type

$$\mathrm{Pt,\ H_2}(P,\ \mathrm{atm})|\mathrm{HA}\ (m),\ \mathrm{organic\ solvent}\ (x),\ \mathrm{water}\ (y)||\mathrm{KCl\ (saturated)}|\mathrm{Hg_2Cl_2{-}Hg} \qquad (\mathrm{I})$$

were employed in all experimental determinations of the ionization constant of latic acid. The molarities of the acid used were 0.005, 0.01, 0.05, 0.10, and 0.20. The electrolytic cells of the type

$$\mathrm{Pt,\ H_2}(P,\ \mathrm{atm})|\mathrm{HA}\ (m_1),\ \mathrm{M(NO_3)_2}\ (m_2),\ \mathrm{NaNO_3}(m_3),\ \mathrm{HNO_3}\ (m_4),\ \mathrm{organic\ solvent}\ (x),\ \mathrm{water}\ (y)||\mathrm{KCl\ (saturated)}|\mathrm{Hg_2Cl_2{-}Hg} \qquad (\mathrm{II})$$

were used for the determination of the formation constants of a lactic acid complex of Ca(II).

The cells were made of Pyrex glass with approximate dimensions of 8.5 cm diameter, and 8.5 cm height. Each cell was fitted with a stopper with openings for introducing a saturated calomel electrode (SCE), the hydrogen electrode, H_2 inlet tube, the microburet, and an all-glass stirrer.

The emf measurements were taken by means of a Leeds and Northrup K-3 Type universal potentiometer calibrated against an Eppley Unsaturated-Type Weston standard cell. Null detection readings were obtained by using a 0.004 μa mm^{-1} Rubicon galvanometer. The SCE used was a Corning No. 476002 Calomel reference electrode. The hydrogen electrodes were prepared from Sargent No. 5-30505 platinum foil electrodes by platinizing them according to Bates (*2*). The finished electrodes were intercompared, and those which did not agree within ±0.1 mV of each other were discarded.

A Sargent Thermonitor constant temperature control, along with a Sargent water bath cooler, provided temperature settings

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[†] Taken partly from the Ph.D. dissertation of J.J.G.

of 15, 25, 35, and 40 °C of the constant temperature bath with a precision of ±0.1 °C.

Chemicals and Solutions. All aqueous solutions were prepared by using double distilled water of conductivity ~3.3 × 10^{-6} mho cm^{-1}. Commercial reagent grade absolute methanol and ethanol were found to be chromatographically pure and were used without further purification. Anhydrous *d*-glucose, $[\alpha]^{20}_{D}$ +52.5 ± 0.5, purchased from Nutritional Biochemical Corporation was used without further purification. The lactic acid was purified according to the method of Borsook, Huffman, and Liu (*4*). All other chemicals used were of analytical reagent grade.

$Ca(NO_3)_2$ (0.010 15 M) stock solution was prepared from calcium nitrate and was rendered 1 × 10^{-4} M with respect to HNO_3. The stock solution was standardized according to standard procedure.

Mixed Solvents. The methanol-water and ethanol-water mixed solvents used contained 90, 80, 70, 50, 30, 20, and 10 wt % of the organic component. The glucose-water mixed solvents used were 0.01, 0.05, and 0.1 *m* with respect to glucose; however, in reporting data, solvent compositions were expressed as weight percent using appropriate density data. All solutions used in potentiometric determinations of the pK_i's of the acid and the log K_f's of the complexes were prepared volumetrically from the various stock solutions, solvents, and distilled water.

Emf Readings. The hydrogen gas used was Matheson Ultrapure hydrogen which was further purified by passing it through a deoxo catalytic purifier. Prior to introducing into the cell, the purified gas was passed through a bubbler containing the solvent used in the cell and maintained at the cell temperature. After initial purging, the hydrogen flow rate at the hydrogen electrode was maintained at three to four bubbles per second. It took about 3-4 h for the cell to reach initial equilibrium.

Titrations. For the data points needed for the constructions of the degree of formation curve (*3*, *16*), titration of a pair of nearly identical solutions was necessary (*10*). The first solution always contained 0.400 mequiv (0.036 g) of lactic acid, 0.050 mequiv of the metal ion, and an appropriate volume of the standard solution of $NaNO_3$ for adjusting for ionic strength to appropriate values (0.025, 0.050, 0.075, 0.100). The final volume was adjusted to 100 mL by adding appropriate solvent to give the desired composition. The second solution of a pair was prepared as above except that the metal salt solution was substituted with distilled water. The titrating base (NaOH) was prepared in appropriate solvent and added in increments of 0.5 mL to the titrant contained in the cell; the emf reading was taken after the equilibration of both temperature and the emf. The contribution to ionic strength due to the addition of NaOH was neglected. Computation of the concentration of unbound lactate anion from the two titrations is quite straight forward (*5*).

Data, Calculations, and Results. All computations and graph plottings were performed by using an IBM 360 computer and employing appropriate programs.

The potential of the hydrogen electrode of the cell

$$\mathrm{Pt,\ H_2}(P,\ \mathrm{atm})|\mathrm{H}(a_{\mathrm{H^+}}),\ \mathrm{L^-}(a_{\mathrm{L^-}}),\ \mathrm{organic}\ (x),\ \mathrm{H_2O}\ (y)||\mathrm{KCl\ (sat)}|\mathrm{Hg_2Cl_2\text{-}Hg} \qquad \mathrm{(III)}$$

is given by

$$E_{H_2} = E_{\mathrm{measd}} - E_{\mathrm{SCE}} - E_j^{\mathrm{m}} \qquad (2)$$

where the symbols have their usual significance. From the Nernst equation

$$E_{H_2} = \frac{2.303RT}{F} \log \frac{a_{\mathrm{H^+}}}{P_{H_2}{}^{1/2}} \qquad (3)$$

which, when corrected to unit pressure, reduces to

$$E_{\mathrm{corr}} = E_{H_2} + \frac{2.303RT}{2F} \log \frac{760}{P_{H_2}} \qquad (4)$$

Substitution for E_{H_2} from eq 2 gives

$$E_{\mathrm{corr}} = E_{\mathrm{measd}} - (E_{\mathrm{SCE}} + E_j^{\mathrm{m}}) + \frac{2.303RT}{2F} \log \frac{760}{P_{H_2}} \qquad (5)$$

Consideration of eq 3 under the standard condition of unit pressure and substitution of eq 4 leads to

$$\mathrm{pH} = \frac{E_{\mathrm{corr}}F}{2.303RT} \qquad (6)$$

In the current studies, a saturated calomel electrode in conjunction with a hydrogen electrode was used to measure E_{measd} from which E_{corr} and the pH of the medium were calculated using eq 5 and 6. The values of E_{corr} and hence the values of pH are not corrected for the liquid junction potential E_j^{m}. The values of the liquid junction potential for mixed solvents are practically nonexistent in the literature; on the basis of the limited number of values of liquid junction potential in aqueous medium available in the literature (*5*), we believe that the error in E_{corr} due to the neglect of E_j^{m} may not exceed 1%. An error of this magnitude will introduce an error of less than 0.2 pH units in the pH computation. In the foregoing discussion, it has been tacitly assumed that the reference state is that of unit fugacity of the hydrogen gas and unit activity coefficient of the solvated hydrogen ion.

It is of interest to note here that the difference in the pH measured by means of the cell III under standard conditions and that measured by means of an identical cell with pure water only as the solvent and also under standard conditions is a measure of the primary medium effect (*13*). With reference to the two standard cells mentioned above, the primary medium effect can be given by a precise expression by

$$\frac{2.303RT}{F}\mathrm{pH}_{(\mathrm{R})} - \frac{2.303RT}{F}\mathrm{pH}_{(\mathrm{x})} = (E_{\mathrm{H^+(R)}} - E_{\mathrm{H^+(x)}}) + (E_j^{\mathrm{w}} + E_j^{\mathrm{m}}) \qquad (7)$$

in which the first parenthetic term on the right-hand side is the primary medium effect. The subscripts (R) and (x) refer to pure water and to mixed solvent medium, respectively. Therefore, the left-hand side is also a measure of the primary medium effect except for the correction due to the liquid junction potentials of the two cells.

P_{H_2} of eq 5 was calculated from the relation

$$P_{H_2} = P_{\mathrm{bar}} - (P_{\mathrm{s}} + P_{\mathrm{w}}) + \frac{0.4h}{13.6} \qquad (8)$$

in which P_{bar} is the barometric pressure, P_{s} and P_{w} are the partial pressures of the organic component and water, and *h* is the average depth of the hydrogen jet during the titration. Vapor pressures of methanol and ethanol calculated using Schlessinger's equation (*15*) were converted to partial pressures using Raoult's law. The vapor pressures of pure water were obtained from Bates (*2*).

The ionization constant, pK_i^*, of lactic acid was determined from a series of single measurements of hydrogen ion (solvated) concentration of lactic acid solutions of different concentrations (0.005, 0.01, 0.05, 0.1, and 0.2 M) using the cell I. Since the hydrogen ion data were calculated from emf measurement employing a hydrogen electrode, it was assumed that such hydrogen ion datum closely represented the mean activity of the hydrogen ion in the solution. Consequently, pK_i^* was calculated using the relation

$$pK_i^* = 2\mathrm{pH} + \log([\mathrm{HA}] - 10^{-\mathrm{pH}}) \qquad (9)$$

assuming unit activity coefficient for the uncharged species HA. The mean pK_i^* was calculated from the five values of pK_i^* after rejecting any deviant, and these are reported as experimental pK_i^* in Table I. The pK_i values of lactic acid in pure aqueous medium were calculated by using Martin and Tartar's (*12*) temperature (*t*) dependent equation

Table I. Ionization Constants of Lactic Acid [a]

Wt % organic	t = 15 °C pK_i^* Exptl	t = 15 °C pK_i^* Calcd	t = 25 °C pK_i^* Exptl	t = 25 °C pK_i^* Calcd	t = 35 °C pK_i^* Exptl	t = 35 °C pK_i^* Calcd	t = 40 °C pK_i^* Exptl	t = 40 °C pK_i^* Calcd
				Methanol–Water Medium				
10.00	4.02	3.95	3.82	3.95	3.56	3.96	3.19	3.97
20.00	4.17	4.05	3.93	4.06	3.74	4.08	3.58	4.10
30.00	4.38	4.18	4.16	4.19	4.20	4.22	3.83	4.25
50.00	4.44	4.47	4.54	4.51	4.52	4.57	3.97	4.61
70.00	4.82	4.92	5.30	5.00	4.90	5.09	4.12	5.16
80.00	5.21	5.22	5.24	5.32	5.39	5.43	4.73	5.50
90.00	5.52	5.58	5.52	5.69	5.86	5.82	5.52	5.92
				Ethanol–Water Medium				
10.00	3.71	3.97	3.69	3.98	3.28	3.99	3.16	4.00
20.00	3.93	4.11	3.82	4.12	3.55	4.14	3.41	4.15
30.00	4.01	4.27	4.20	4.29	3.46	4.33	4.14	4.35
50.00	4.58	4.72	4.65	4.78	4.66	4.85	4.47	4.88
70.00	5.22	5.38	5.58	5.49	5.40	5.62	5.27	5.67
80.00	5.80	5.83	6.3	5.99	5.39	6.15	6.35	6.25
90.00	6.27	6.41	6.47	6.60	6.05	6.80	7.43	6.91
				Glucose–Water Medium				
0.0018	3.91	3.90	3.67	3.90	3.47	3.91	3.37	3.92
0.0089	3.74	3.88	3.47	3.88	3.48	3.89	3.68	3.90
0.0177	3.98	3.86	3.88	3.86	3.83	3.86	3.77	3.87

[a] In pure water pK_i ranges from 3.86 to 3.87 between 15 and 40 °C.

Table II. Formation Constants of Calcium Lactate [a]

Wt % organic	t = 15 °C Log K_1^* Exptl	t = 15 °C Log K_1^* Calcd	t = 15 °C Log K_2^* Exptl	t = 15 °C Log K_2^* Calcd	t = 25 °C Log K_1^* Exptl	t = 25 °C Log K_1^* Calcd	t = 25 °C Log K_2^* Exptl	t = 25 °C Log K_2^* Calcd	t = 35 °C Log K_1^* Exptl	t = 35 °C Log K_1^* Calcd	t = 35 °C Log K_2^* Exptl	t = 35 °C Log K_2^* Calcd	t = 40 °C Log K_1^* Exptl	t = 40 °C Log K_1^* Calcd	t = 40 °C Log K_2^* Exptl	t = 40 °C Log K_2^* Calcd
								Methanol–Water Medium								
10.00	1.59	1.58	1.17	1.16	1.72	1.70	1.30	1.28	1.93	1.91	1.43	1.41	2.12	2.10	1.63	1.61
20.00	1.78	1.75	1.36	1.33	1.92	1.89	1.50	1.47	2.14	2.11	1.64	1.61	2.34	2.30	1.85	1.81
30.00	2.00	1.94	1.58	1.52	2.15	2.09	1.73	1.67	2.39	2.33	1.89	1.83	2.60	2.53	2.11	2.04
50.00	2.51	2.41	2.09	1.99	2.71	2.60	2.29	2.18	2.99	2.88	2.49	2.38	3.23	3.11	2.74	2.62
70.00	3.29	3.12	2.87	2.70	3.55	3.36	3.13	2.94	3.90	3.70	3.40	3.20	4.18	3.97	3.69	3.48
80.00	3.83	3.60	3.41	3.18	4.12	3.88	3.70	3.46	4.49	4.23	3.99	3.73	4.80	4.52	4.31	4.03
90.00	4.45	4.16	4.03	3.74	4.77	4.46	4.35	4.04	5.17	4.85	4.67	4.35	5.52	5.18	5.03	4.69
								Ethanol–Water Medium								
10.00	1.64	1.62	1.22	1.20	1.77	1.75	1.35	1.33	1.98	1.96	1.48	1.46	2.16	2.14	1.67	1.65
20.00	1.87	1.83	1.45	1.41	2.02	1.98	1.60	1.56	2.25	2.20	1.75	1.70	2.43	2.39	1.94	1.90
30.00	2.16	2.09	1.74	1.67	2.32	2.25	1.90	1.83	2.57	2.50	2.07	2.00	2.77	2.69	2.28	2.20
50.00	2.94	2.80	2.52	2.38	3.17	3.02	2.75	2.60	3.48	3.32	2.98	2.82	3.70	3.54	3.21	3.05
70.00	4.09	3.84	3.67	3.42	4.41	4.14	3.99	3.72	4.83	4.54	4.33	4.04	5.09	4.79	4.60	4.30
80.00	4.89	4.57	4.47	4.15	5.29	4.93	4.87	4.51	5.76	5.38	5.26	4.88	6.11	5.71	5.62	5.22
90.00	5.91	5.48	5.49	5.06	6.36	5.90	5.94	5.48	6.90	6.41	6.40	5.91	7.26	6.75	6.77	6.26
								Glucose–Water Medium								
0.18	1.442	1.442	1.022	1.022	1.561	1.561	1.141	1.141	1.763	1.763	1.263	1.263	1.944	1.944	1.454	1.454
0.89	1.447	1.446	1.027	1.026	1.567	1.566	1.147	1.146	1.769	1.768	1.269	1.268	1.951	1.950	1.461	1.460
1.77	1.454	1.453	1.034	1.033	1.574	1.573	1.154	1.153	1.777	1.775	1.277	1.275	1.958	1.957	1.468	1.467

[a] Log K_1 and log K_2 in pure water (*14*): at 15 °C, 1.44, 1.02; at 25 °C, 1.56, 1.14; at 35 °C, 1.76, 1.26; at 40 °C, 1.94, 1.45.

$$pK_i = 3.857 + (5.00 \times 10^{-5})(t - 22.5)^2 \qquad (10)$$

derived from conductance data. Harned and Embree (*9*) also proposed a similar temperature dependent equation for pK_i's of the monoprotic acids in general. The pK_i values calculated by using eq 10 were then converted to corresponding pK_i^* values in the mixed solvent using eq 1 proposed by Sen and Adcock (*17*), and these are reported as calculated pK_i^* in Table I. The mean value of β = 120, with a standard deviation of 16 obtained by Sen and Adcock for 13 acids (*18*) was used in theoretical computation of pK_i^* of lactic acid in various mixed solvents. The bulk dielectric constants of the mixed solvents containing methanol or ethanol were obtained from Åkerlöf (*1*), and those for the glucose solutions were acquired by using Furth's data (*7*).

Progressive formation of the lactate complexes in mixed solvents with titration by the base was followed potentiometrically according to the procedure originally developed by Calvin and Wilson (*5*). The values of the step formation constants K_1^* and K_2^* were obtained by interpolation from the degree of formation curves (*16*). The experimental values of log K_1^* and log K_2^* were plotted against $\mu^{1/2}$ for each temperature; log K_1^* and K_2^* values at zero ionic strength reported in Table II as experimental log K_1^* and K_2^* were obtained by extrapolation from these plots. The calculated log K_1^* and log K_2^* were computed from the equation

Table III. Average Formation Constants of Calcium Lactate

Wt % organic	t = 15 °C Log K_{av}^* Exptl	t = 15 °C Log K_{av}^* Calcd	t = 25 °C Log K_{av}^* Exptl	t = 25 °C Log K_{av}^* Calcd	t = 35 °C Log K_{av}^* Exptl	t = 35 °C Log K_{av}^* Calcd	t = 40 °C Log K_{av}^* Exptl	t = 40 °C Log K_{av}^* Calcd
			Methanol-Water Medium					
10.00	1.38	1.37	1.51	1.49	1.68	1.66	1.87	1.85
20.00	1.57	1.54	1.71	1.66	1.89	1.96	2.09	2.05
30.00	1.79	1.73	1.94	1.88	2.14	2.08	2.35	2.28
50.00	2.30	2.20	2.50	2.39	2.74	2.63	2.98	2.86
70.00	3.08	2.91	3.34	3.15	3.65	3.45	3.93	3.72
80.00	3.62	3.39	3.91	3.67	4.24	3.98	4.55	5.27
90.00	4.24	3.95	4.56	4.25	4.92	4.60	5.27	4.93
			Ethanol-Water Medium					
10.00	1.43	1.41	1.56	1.54	1.73	1.71	1.91	1.89
20.00	1.66	1.62	1.81	1.77	2.00	1.95	2.18	2.14
30.00	1.95	1.88	2.11	2.04	2.32	2.25	2.52	2.44
50.00	2.73	2.59	2.96	2.81	3.23	3.07	3.45	3.29
70.00	3.88	3.63	4.20	3.93	4.58	4.29	4.84	4.54
80.00	4.68	4.36	5.08	4.72	5.51	5.13	5.86	5.46
90.00	5.70	5.27	6.15	5.69	6.65	6.16	7.01	6.50
			Glucose-Water Medium					
0.0018	1.232	1.232	1.351	1.351	1.513	1.513	1.699	1.699
0.0089	1.237	1.236	1.357	1.356	1.519	1.518	1.706	1.705
0.0177	1.244	1.243	1.364	1.363	1.527	1.525	1.713	1.712

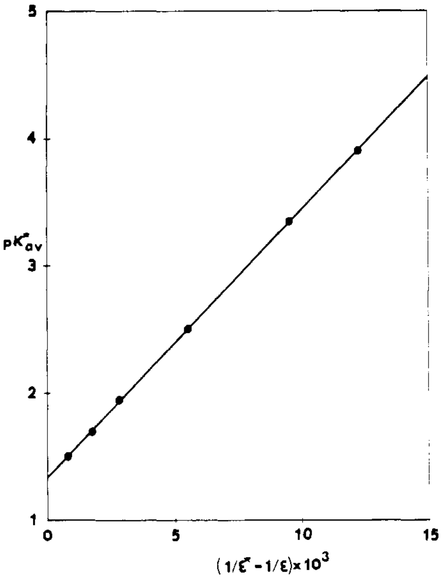

Figure 1. Plot of pK_{av}^* vs. $(1/\epsilon^* - 1/\epsilon) \times 10^3$ for the methanol-water system at 25 °C.

$$\log K_i^* = \log K_i + \beta\left(\frac{1}{\epsilon^*} - \frac{1}{\epsilon}\right) \tag{11}$$

in which K_i^* is the step formation constant at zero ionic strength in mixed solvent, K_i is the corresponding step formation constant in pure water (*8*), ϵ^* is the bulk dielectric constant of the mixed solvent, and ϵ is the bulk dielectric constant of water. The experimental log K_{av}^* at zero ionic strength and at various temperatures reported in Table III were obtained by extrapolation of experimental log K_{av}^* ($K_{av}^* = (K_1^* K_2^*)^{1/2}$) vs. $\mu^{1/2}$ plots. In passing it may be noted that agreement between the log K_{av}^* obtained by extrapolation and that obtained by computation using the corresponding values of log K_1^* and log K_2^* from Table II is excellent. This is to be expected; however, this proves the self-consistency of the computational technique used. The calculated log K_{av}^* was computed using eq 11 in which K_i^* and K_i were respectively replaced by K_{av}^* and K_{av}. This K_{av} was obtained from literature (*8*) values of K_1 and K_2. The value of β was 190 for methanol-water systems, 192 for ethanol-water systems, and 185 for glucose-water systems, and denotes the slopes of the three respective plots of pK_{av}^* vs. $(1/\epsilon^* - 1/\epsilon)$ (cf. Figures 1-3).

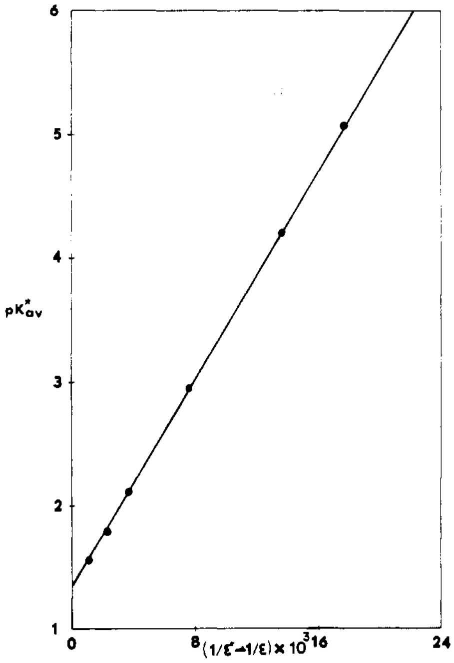

Figure 2. Plot of pK_{av}^* vs. $(1/\epsilon^* - 1/\epsilon) \times 10^3$ for the ethanol-water system at 25 °C.

Discussion and Results

The primary objective of this study was to obtain a function that would correlate the formation constants K_1^*, K_2^*, and K_{av}^* (defined earlier) in a mixed solvent to the formation constants K_1, K_2, and K_{av} in pure water. It was reasonable to assume that an equation similar to that obtained by Sen and Adcock (*17*) for the case of monoprotic acids may be applicable also in the case of metal lactate complexes because a metal complex may be viewed as a weak acid in which the proton has been replaced by a metal ion. This assumption should be especially valid in the

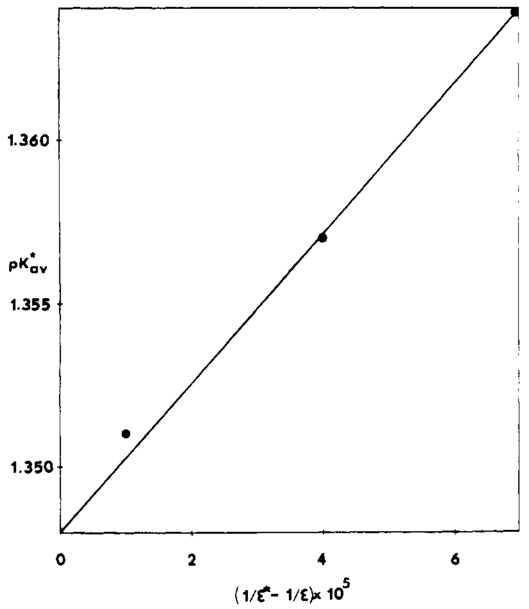

Figure 3. Plot of pK_{av}^* vs. $(1/\epsilon^* - 1/\epsilon) \times 10^5$ for the glucose–water system at 25 °C.

case of Ca^{2+} ion for the reasons outlined in the introductory section.

Equation 11 was obtained by a curve fitting technique from plots of $\log K_1^*$, $\log K_2^*$, or $\log K_{av}^*$ vs. $(1/\epsilon^* - 1/\epsilon)$, in which ϵ^* was the bulk dielectric constant of the mixed solvent, and ϵ was the bulk dielectric constant of water. Straight line plots (computer plotted) were obtained in each case with slopes β equal to 190 for methanol–water systems, 192 for ethanol–water systems, and 185 for glucose–water systems, for all four temperatures at which measurements were made. We believe that the agreements between experimental values of pK_i^*, $\log K_1^*$, and $\log K_2^*$ and the corresponding calculated values reported in Table I, II, and III are excellent, especially when their discrepancies are compared with the discrepancies of the published equilibrium constants for various systems (*18*). Since the plots were all linear (and parallel when solvent components were the same), and the intercept was always pK_{av}, or $\log K_1$ or $\log K_2$ (depending upon the plot), and since the fundamental variable was a linear combination of the reciprocals of the bulk dielectric constants, it was reasonable to assume that it should be possible to parametrize the plots for different solvents in such a way as to represent the correlation of K_{av} and K_{av}^* (and also of K_1 and K_1^*, K_2 and K_2^*) by one general equation regardless of the solvent components. After examining several trial plots, the appropriate variable turned out to be $(1/\epsilon^{**} - 1/\epsilon'')$ in which $\epsilon^{**} = \epsilon^* + (\epsilon - \epsilon\text{org})$, and $\epsilon'' = (2\epsilon - \epsilon\text{org})$, and the general correlating equation was found to be

$$\log K_{av}^* = \log K_{av} + \beta(1/\epsilon^{**} - 1/\epsilon'') \qquad (12)$$

in which the computed β was 204. The fact that a single β value correlates K_{av} and K_{av}^*, K_1 and K_1^*, K_2 and K_2^* (dependent on solvent if eq 11 is used) implies that the ratio K_1/K_2, or K_1^*/K_2^* is determined primarily by the statistical factors (*8*, *9*). However, this may not be true of all complexes.

Equations 11 and 12 have the same general form as the equation

$$\ln K_1 = \ln K_2 + \left(\frac{Ne^2}{2RTa} \cdot Z_+ \cdot Z_-\right)(1/\epsilon_1 - 1/\epsilon_2) \qquad (13)$$

(the symbols have their usual significance) derived from Born's electrostatic model (*5*). It follows from the foregoing discussion that $\log K_{av}^*$ (also $\log K_1^*$, or $\log K_2^*$) is a function of $(1/\epsilon^{**} - 1/\epsilon'')$ only, regardless of the actual composition of the mixed solvent, and consequently eq 12 represents the function sought.

In regions of very low dielectric constants of the solvents, the plots of $\log K_{av}^*$ (or $\log K_1^*$, $\log K_2^*$) vs. $(1/\epsilon^{**} - 1/\epsilon'')$ curve upwards, and an additional exponential term is required for writing the appropriate analytical function. It is reasonable to assume that in solvents of low dielectric constant, second and higher order forces (Coulombic and perhaps non-Coulombic) make significant contributions toward stabilizing the complex (formation of ill-defined associated species also should not be ruled out), and Born's electrostatic model is no longer adequate. For the linear portion of the graph (that is, in solvents of bulk dielectric constant 40 or higher) eq 12 is good; therefore, the first-order Coulombic forces predominate in stabilizing the complex, and Born's model is a sufficiently adequate description of ionic complex formation. Nevertheless, ab initio calculations

Table IV. Thermodynamics of Formation of Calcium Lactate

	t = 15 °C			t = 25 °C			t = 35 °C			t = 40 °C		
	$\Delta H°$, kcal mol^{-1}	$\Delta G°$, kcal mol^{-1}	$\Delta S°$, eu	$\Delta H°$, kcal mol^{-1}	$\Delta G°$, kcal mol^{-1}	$\Delta S°$, eu	$\Delta H°$, kcal mol^{-1}	$\Delta G°$, kcal mol^{-1}	$\Delta S°$, eu	$\Delta H°$, kcal mol^{-1}	$\Delta G°$, kcal mol^{-1}	$\Delta S°$, eu
Methanol–Water Medium												
10.00	8.18	−0.79	31.12	7.15	−0.89	26.97	7.15	−1.03	26.53	8.18	−1.17	29.83
20.00	8.67	−0.98	33.21	7.57	−1.01	28.78	7.57	−1.16	28.31	8.67	−1.30	31.85
30.00	9.33	−1.02	35.94	8.41	−1.15	32.06	8.41	−1.31	31.54	9.33	−1.47	34.48
50.00	11.31	−1.32	43.84	10.09	−1.48	38.81	10.09	−1.68	38.19	11.31	−1.86	42.06
70.00	14.12	−1.76	55.13	13.93	−1.98	50.35	13.03	−2.23	49.55	14.12	−2.45	52.92
80.00	15.44	−2.07	60.79	13.87	−2.32	54.30	13.87	−2.60	53.45	15.44	−2.83	58.37
90.00	17.10	−2.43	67.75	15.14	−2.70	59.83	15.14	−3.01	58.89	17.10	−3.28	65.07
Ethanol–Water Medium												
10.00	8.01	−0.82	30.64	7.15	−0.92	27.07	7.15	−1.06	26.63	8.01	−1.19	29.39
20.00	8.67	−0.95	33.39	7.99	−1.07	30.39	7.99	−1.22	29.90	8.67	−1.36	32.03
30.00	9.50	−1.12	36.83	8.83	−1.25	33.81	8.83	−1.42	33.26	9.58	−1.57	35.35
50.00	11.98	−1.56	46.98	11.35	−1.75	43.96	11.35	−1.98	43.26	11.98	−2.15	45.11
70.00	15.94	−2.22	63.02	15.98	−2.49	61.93	15.98	−2.80	60.95	15.94	−3.01	60.53
80.00	19.57	−2.68	77.23	18.98	−3.01	70.73	18.08	−3.37	69.62	19.57	−3.65	74.16
90.00	21.72	−3.26	86.70	21.92	−3.64	82.73	21.02	−4.07	81.43	21.72	−4.37	83.30
Glucose–Water Medium												
0.18	7.71	−0.71	29.22	6.81	−0.80	25.53	6.81	−0.93	25.11	7.71	−1.06	28.01
0.89	7.75	−0.71	29.34	6.81	−0.80	25.54	6.81	−0.93	25.12	7.75	−1.06	28.13
1.77	7.75	−0.71	29.36	6.85	−0.81	25.70	6.85	−0.94	25.27	7.75	−1.07	28.14

for the determination of the formation constants of a complex in different solvents may not be successful, because the model, although elegant, is primitive and it ignores numerous microscopic phenomena. However, with the accumulation of additional experimental data, it might be possible to classify the metal ions and the ligands on the basis of the β values, and to calculate the formation constant of a complex in a new solvent from the known β value and the known bulk dielectric constant of the new solvent (provided that the formation constant of the complex is known at least in another solvent). We believe that this hypothesis is worth testing.

It is worthwhile to investigate the structural and thermodynamic implications of the magnitude of K_1^* and K_2^* values of calcium(II) lactate. Both formation constants are of the same order of magnitude and are observed at pH's much too low for the ionization of the enolic proton to occur. In fact, lactic acid exhibits only one ionization constant. These facts suggest that the two formation constants (K_1^*, K_2^*, or K_1, K_2) correspond to the attachment of two ligands (lactate anions) through the same mechanism—i.e., via the carboxylate group. However, after the attachment of the carboxylate group to the metal, the hydroxide group is most conviently located to coordinate with the metal. Such coordination of the hydroxide group may not be strong; furthermore, there may be some strain due to the large size of the Ca^{2+} ion (0.99 Å), and consequently the overall process of formation of calcium(II) lactate may be endothermic, and entropy driven. This expectation is supported by the experimental data discussed in the next paragraph. The structure of calcium(II) lactate proposed here is also supported by Prout et al. (*14*) in their determination of the structure of copper(II) lactate by x-ray crystallography. They concluded that the lactate anion behaves as a bidentate ligand coordinating first via the carboxylate group, and then by the -OH group without the loss of its proton.

The enthalpy, entropy, and free energy of formation for the calcium(II) lactate complexes were computed from the temperature dependence of the formation constants of the complexes. These values are compiled in Table IV. A great deal of confidence may not be placed on the precision of the numerical values of ΔH° so tabulated, since ΔH° values are not too sensitive to changes in the values of K with respect to temperature. However, it may be concluded that the overall trend is reliable and the formation of calcium lactate is endothermic and is entropy driven. It may only be speculated that the formation of calcium lactate in biological fluids may be one of many temperature balancing processes.

Glossary

β	slope of the plot of log K_i^* (or log K_1, log K_2, log K_{av}) vs. some linear combination of reciprocals of bulk dielectric constants of the solvents; the numberical value of β depends upon the linear combination used; see text
ϵ^*, ϵ^{**}, ϵ''	stand for some linear combination of the bulk dielectric constants of the pure solvents; see text
K_i^*, K_1^*, K_2^*	extrapolated or calculated ionization constants or formation constants at zero ionic strength in the solvent
K_{av}^*	extrapolated or calculated average formation constants at zero ionic strength in the solvent

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