J. Chem. Eng. Data **1991**, *36*, 52-54

Stability Constant of the Calcium–Citrate(3–) Ion Pair Complex

Raj P. Singh,* Yaw D. Yeboah, Ernesto R. Pambid, and Pascal Debayle

Central Analytical and Materials Characterization Laboratories, Metrology, Standard and Materials Division, The Research Institute, King Fahd University of Petroleum and Minerals, Dhahran 31261, Saudi Arabia

By measuring the change in potential caused by the addition of sodium citrate to the solutions containing calcium and sodium chlorides, the stability constants (K) of the calcium–citrate(3–) ion pair were determined at ionic strengths 0.02–0.17 mol L^{-1} and temperatures 18–45 °C. No significant effect of temperature was observed on the values of the stability constants from 18 to 45 °C as the values of K occurred between 6.8 × 10^4 and 7.1 × 10^4 L mol^{-1} in this temperature range. The K value at 7.0 × 10^4 L mol^{-1} was also found in good agreement with the 7.16 × 10^4 L mol^{-1} obtained by calcium oxalate monohydrate solubility measurements. Thermodynamic functions, $\Delta G°$, $\Delta H°$, $\Delta S°$, and $\Delta C_p°$, for the Ca^{2+}–Cit^{3-} ion pair association reaction were calculated by the use of a van't Hoff isochore and the values of the thermodynamic stability constant of the ion pair complex at different temperatures. These results indicated that, similar to other calcium ion pair complexes, the calcium–citrate(3–) ion pair complex is also entropically stabilized. The ion pair association reaction was almost thermoneutral in the temperature range 18–45 °C, as $\Delta H°$ values were $<\pm 1$ kcal mol^{-1}.

Introduction

The calcium–citrate(3–), hereafter $CaCit^-$, ion pair is one of the important ion pairs used in the speciation calculations of urine (*1*). An accurate value of the stability constant for this ion pair is also required for the speciation of the synthetic solutions of crystal growth experiments, where citrate is studied as a growth inhibitor (*2–5*), in order to separate the effects due to calcium citrate complexing and those reflecting adsorption of citrate at the mineral surface.

Although the stability constant of $CaCit^-$ ion pair has been reported in the literature from different methods (*6–12*), the unusually large difference, 4.4 × 10^4 to 10.0 × 10^4 L mol^{-1} at 25 °C and 5.1 × 10^4 to 9.0 × 10^4 L mol^{-1} at 37 °C (values were corrected for ionic strength), between the reported values prompted us to redetermine its value. Since the stability constant values reported at 25 and 37 °C lie in the same range, the effect of temperature on the stability constant was also studied.

Experimental Section

Reagents. Doubly distilled, deionized water (Nanopure II) was used to prepare solutions. Stock solutions of calcium chloride (Merck), trisodium citrate (Fluka, AG), and sodium chloride (Merck) were prepared from analytical reagent grade chemicals. Analyses of sodium in sodium citrate and chloride in calcium chloride were made by ion chromatography (Dionex 2021i ion chromatograph) in order to know the exact concentrations of their stock solutions.

Measurements. A Radiometer F2112 calcium selectrode in combination with silver/silver chloride (Fisher Scientific) reference electrode was used for the free calcium measurements on a Fisher Accumet Selective Ion Analyzer Model 750. Titrations were made in Pyrex double-walled vessels in magnetically stirred solutions. Volumes of 200 mL of calcium chloride in the presence of different concentrations of sodium chloride (used for ionic strength adjustment) were titrated with 1.0-mL aliquots of 0.1 mol L^{-1} trisodium citrate by using automatic burets (Mettler DL40RC Memotitrator). The pH of the working solution was kept above 8.0 at which citrate will be fully ionized.

Solubility measurements were carried out by equilibrating approximately 20 mg of calcium oxalate monohydrate (BDH Chemical Co.) in 0.15 mol L^{-1} sodium chloride containing different concentrations (0.25–5.0 mmol L^{-1}) of trisodium citrate at 37 °C for over 50 h, to ensure complete equilibrium. After that, samples were filtered and diluted immediately to prevent any precipitation that could result due to the attainment of supersaturation with respect to calcium oxalate monohydrate at lower temperature. Diluted solutions were then analyzed for calcium and oxalate by using ion chromatography, and the solubility was calculated as the mean of four determinations.

Calculations

The apparent stability constant (K') of $CaCit^-$ ion pair can be expressed by

$$K' = [\mathrm{CaCit^-}]/f(\mathrm{Ca^{2+}})\,f(\mathrm{Cit^{3-}}) \qquad \text{(i)}$$

For the determination of K', $f(Ca^{2+})$ was calculated from the measured potential after each addition of citrate solution during the titration, and $b(Ca^{2+})$ was then determined by the subtraction of $f(Ca^{2+})$ from $t(Ca^{2+})$. In the above expressions f, b, and t represent free, bound, and total concentrations, respectively. By assuming that $[CaCit^-] = b(Ca^{2+}) = b(Cit^{3-})$ and that $f(Cit^{3-}) = t(Cit^{3-}) - b(Cit^{3-})$, the value of $f(Cit^{3-})$ was calculated.

Activity coefficients of mono-, di-, and trivalent ions were calculated by using the extended form of the Debye–Huckel equation as proposed by Davies (*13*):

$$-\log Y_Z = AZ_i^2[I^{1/2}/(1 + I^{1/2}) - 0.3I] \qquad \text{(ii)}$$

where A is the temperature-dependent Debye–Huckel constant. The corrections for the sodium–oxalate(2–) and calcium–oxalate(2–) ion pairs, required to determine the stability constant of $CaCit^-$ at 37 °C from solubility measurements, were made by using their respective stability constant values of 13.2 and 2746 L mol^{-1} at 37 °C (*1*, *14*). The values of stability constants of the $CaCit^-$ ion pair, determined from the solution containing sodium, chloride, calcium, and citrate ions, were corrected for the sodium–citrate(3–) ion pair by using its stability constant value of 8.5 L mol^{-1} at 25 °C. Since, the stability constant of the sodium–citrate(3–) ion pair was reported to be independent of temperature (*15*), the same value (at 25 °C) was used to correct the stability constants of the $CaCit^-$ ion pair determined at different temperatures.

As suggested in the literature (*16*, *17*), the thermodynamic functions for the standard change in free energy ($\Delta G°$), enthalpy ($\Delta H°$), entropy ($\Delta S°$), and heat capacity ($\Delta C_p°$) were calculated by using the following equations:

$$\Delta G° = -RT \ln K \qquad \text{(iii)}$$

$$\Delta C_p = A + BT \qquad \text{(iv)}$$

$$\Delta H°_T = \Delta H°_{T_0} + \int_{T_0}^{T} \Delta C_p \, dT \qquad \text{(v)}$$

$$\Delta S° = (\Delta H° - \Delta G°)/T \qquad \text{(vi)}$$

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* To whom correspondence should be addressed.

0021-9568/91/1736-0052$02.50/0

Table I. Typical Results of a Potentiometric Titration of Calcium against Citrate: Initial Concentration of NaCl = 0.15 M, Temperature = 37 °C, Average Ionic Strength = 0.154 mol L^{-1}

pH	$t(Ca^{2+})$, mmol L^{-1}	$t(Cit^{3-})$, mmol L^{-1}	$f(Ca^{2+})$ Ca–ISE	$f(Ca^{2+})$ calcd	$b(Ca^{2+})$, mmol L^{-1}	$[NaCit^{2-}]$, mmol L^{-1}	$f'(Cit^{3-})$, mmol L^{-1}	$f''(Cit^{3-})$, mmol L^{-1}	K', L mol^{-1}	K_0, L mol^{-1}	K, L mol^{-1}
8.285	2.4515	0.4660	2.1034	2.0925	0.3481	0.01948	0.1179	0.09842	1404	43 685	52 320
8.141	2.4396	0.9275	1.7423	1.7557	0.6953	0.0444	0.2322	0.1878	1719	53 486	66 119
8.09	2.4279	1.3846	1.4323	1.4595	0.9956	0.07611	0.389	0.3129	1787	55 602	69 124
8.036	2.4163	1.8373	1.1687	1.2083	1.2476	0.1153	0.5897	0.4744	1810	56 318	70 016
8.018	2.4048	2.2857	0.9536	1.0028	1.4512	0.1622	0.8345	0.6723	1824	56 753	70 432
8.01	2.3934	2.730	0.7780	0.8395	1.6154	0.2162	1.1146	0.8984	1863	57 967	71 912
8.02	2.3821	3.1698	0.6542	0.7118	1.7279	0.2759	1.4419	1.166	1832	57 002	70 482
8.023	2.3709	3.6056	0.5585	0.6124	1.8124	0.3401	1.7932	1.4531	1810	56 318	69 487
8.041	2.3598	4.0374	0.4804	0.5344	1.8794	0.4075	2.158	1.7505	1813	56 411	69 538
8.049	2.3488	4.4651	0.4163	0.4726	1.9325	0.4771	2.5326	2.0555	1833	57 033	70 269
								mean[b]	1822	56 691	70 158
								std dev	22	684	861
								%RSD	1.2	1.2	1.2

[a] $f'(Cit^{3-})$ = free citrate concentration without $NaCit^{2-}$ correction; $f''(Cit^{3-})$ = free citrate concentration with $NaCit^{2-}$ correction; K' = conditional $CaCit^-$ ion pair stability constant; K_0 = $CaCit^-$ ion pair stability constant after ionic strength correction; K = thermodynamic stability constant of the $CaCit^-$ ion pair (after ionic strength and $NaCit^{2-}$ ion pair correction). [b] Mean of last eight numbers.

Table II. Stability Constants of the $CaCit^-$ Ion Pair as Determined by a Calcium Ion Selective Electrode at 37 °C with Use of Equation 1

av ionic strength, mol L^{-1}	K' (mean + SD), L mol^{-1}	K_0, L mol^{-1}		K, L mol^{-1}
0.170	1 720 ± 30[a]	55 900		69 900
0.154	1 850 ± 81[b]	57 600		70 900
0.056	4 860 ± 42	60 700		68 600
0.0198	12 100 ± 600	66 600		70 900
			mean	70 000
			std dev	1 100
			%RSD	1.6

[a] Mean value based on three experiments. [b] Mean value based on four experiments.

By integration of eq v and substitutions from eqs iii and iv, we finally get

$$\ln K = [(\ln T/T_0 + (T^{-1} - T_0^{-1})T_0)/R]A + [((T - T_0) + (T^{-1} - T_0^{-1})T_0^2)/2R]B + C + [(T^{-1} - T_0^{-1})/R]D \quad \text{(vii)}$$

In eqs iii–vii, K is the stability constant of $CaCit^-$ ion pair, R is the gas constant, T is the temperature in Kelvin, T_0 is 298 K, A and B are constants, $C = \ln K_{T_0}$ and $D = -\Delta H°_{T_0}$. The values of A, B, C, and D were determined as 5.2275, −0.1254, 11.1753, and 12.9760, respectively.

Results and Discussion

The results of a typical titration of calcium ions against citrate ions, carried out at 37 °C, are reported in Table I. In all the titrations the first two data points were excluded from the mean value of the stability constant. The small values of the percent relative standard deviations (<1.5%) clearly reveal the excellent reproducibility of the method.

In order to compare our value of the $CaCit^-$ stability constant with the values reported in the literature, the K' values were corrected for ionic strength and reported as K_0 in Table I. A mean value of K_0 at 5.7 × 10^4 L mol^{-1} is quite comparable with 6.0 × 10^4 L mol^{-1}, used by Werness et al. (1) in the speciation of urine. However, the $f(Ca^{2+})$ value, calculated by using K_0 at 6.0 × 10^4 L mol^{-1}, were found substantially higher than $f(Ca^{2+})$ values measured by a calcium ion selective electrode (ISE) (columns 4 and 5, Table I; $p < 0.005$). This means that the K_0 value at 5.7 × 10^4 L mol^{-1} is somewhat lower than the correct value of the thermodynamic stability constant of the $CaCit^-$ ion pair.

It seems that the lower value of K_0 may have resulted due to the presence of sodium ions (0.15 mol L^{-1}) in the medium, which have bound a substantial amount of citrate ions as the sodium-citrate(3−) (column 7, Table I) ion pair. Therefore, a true value of the thermodynamic stability constant can only be obtained by correcting K' for both ionic strength and the sodium-citrate(3−) ion pair. Accordingly, the K_0 values were further corrected for the sodium-citrate(3−) ion pair reported as K in the last column of Table I. An excellent agreement ($p > 0.2$) between $f(Ca^{2+})$ calculated, using K of the $CaCit^-$ ion pair at 7.0 × 10^4 L mol^{-1}, and measured values (ISE) revealed the accuracy of the mean K value at 7.0 × 10^4 L mol^{-1}.

Table II shows the value of the $CaCit^-$ stability constants determined from calcium and citrate titrations carried out at different ionic strengths. An obvious increase in the K' value with a decrease in ionic strength is clearly seen in column 2 of

Table III. Stability Constants of the $CaCit^-$ Ion Pair at Different Temperatures and a Comparison between Various Literature Values

method	temp, °C	ionic strength mol L^{-1}	K, mol^{-1}	K_0, L mol^{-1}	K, L mol^{-1}	ref
amalgam electrode	25	0.15 NaCl	1480	44 400	54 000	6
ion exchange	25	0.16 NaCl	1430	45 000	56 300	7
Ca electrode	25	0.10 $NaClO_4$	4660	100 100	117 100	8
Ca electrode	25	0.10 NaCl	2630	56 300	67 600	9
Ca electrode	25	0.154 NaCl	1820	56 700	69 700	this work
frog heart	37	0.154 NaCl	1660	51 600	63 500	10
calcium carbonate solubility	37	0.15 NaCl	2040	61 300	75 400	10
Ca electrode	37	0.10	4270	89 430	107 300	11
pH filtration	37	0.15 NaCl	1880	56 400	69 400	12
Ca electrode	37	0.154 NaCl	1850	57 600	70 800	this work
calcium oxalate solubility	37	0.15 NaCl	1940	58 200	71 600	this work
Ca electrode	18	0.154 NaCl	1860	58 000	71 300	this work
Ca electrode	45	0.154 NaCl	1780	55 300	68 000	this work

Table IV. Thermodynamic Parameters of Calcium–Citrate(3–) Association at Different Temperatures

temp, K	ln K^a	$-\Delta G°$, kcal mol^{-1}	$\Delta H°$, kcal mol^{-1}	$\Delta S°$, cal deg^{-1} mol^{-1}	$\Delta C_p°$, cal deg^{-1} mol^{-1}
291	11.174 65	6.46	0.21	22.92	−31.25
298	11.151 96	6.60	−0.013	22.12	−32.13
310	11.167 61	6.88	−0.41	20.89	−33.63
318	11.127 26	7.03	−0.68	19.97	−34.63

[a] K is in units of L mol^{-1}.

Table II. A marked difference among the K_0 values (obtained after correcting K' for ionic strength only) again emphasized the importance of taking into account the $NaCit^{2-}$ ion pair correction, when calculating the thermodynamic stability constant (K) for the $CaCit^-$ ion pair from solutions containing calcium, sodium, and citrate ions. This indeed is the case, since, after additional correction of the $NaCit^{2-}$ ion pair, all the K_0 values (obtained from different ionic strengths) changed to the values close to 7.0×10^4 L mol^{-1} (%RSD = 1.6%, last column of Table II).

An excellent agreement between the K value for the $CaCit^-$ ion pair at 7.0×10^4 L mol^{-1}, as determined by use of a calcium ion selective electrode, and the K value at 7.16×10^4 L mol^{-1} (%RSD = 2.9%, $n = 4$), as obtained from the solubility of calcium oxalate monohydrate in different sodium citrate solutions, further confirmed the accuracy of the results reported in the present studies. In Table III, we have summarized the results of the stability constants reported by different authors at 25 and 37 °C together with our results obtained at other temperatures. It can be seen from Table III that temperatures between 18 and 45 °C have almost no effect on the stability constant of the $CaCit^-$ ion pair.

The K value of the $CaCit^-$ ion pair at 7.0×10^4 L mol^{-1}, determined by calcium ion selective electrode in the present studies, also compared well with the value (6.9×10^4 L mol^{-1}) determined by Meyer (*12*) by potentiometric titrations. The K values determined by Hastings et al. (*10*) using a calcium carbonate solubility method at 37 °C and by Craggs et al. (*9*) using a calcium electrode at 25 °C are also, essentially, in the same range, as their K values differed only by 7.6% and 3.5%, respectively, from 7.0×10^4 L mol^{-1}. However, the results by other authors showed substantial deviations, maybe due to some experimental error in the methods used.

The calculated values of thermodynamic functions for the standard changes in free energy ($\Delta G°$), enthalpy ($\Delta H°$), entropy ($\Delta S°$), and heat capacity ($\Delta C_p°$), from use of eqs iii–vii and the K values in Table III, are reported in Table IV. The small values ($< \pm 1$ kcal mol^{-1}) of $\Delta H°$ indicates that the reaction $Ca^{2+} + Cit^{3-} \leftrightarrow CaCit^-$ is almost thermoneutral in the temperature range 18–45 °C. The $\Delta S°$ values reflected that the ion pair complex is entropically stabilized. The positive entropy change is indicative of the release of solvent molecules from the cospheres of free ions when association takes place, as reported for other ion-association reactions (*18–20*). The $\Delta S°$ values for the $CaCit^-$ ion pair complex are comparable to the $\Delta S°$ values reported (*15*) for the proton-association reaction $H^+ + HCit^{2-} \leftrightarrow H_2Cit^-$ ($K = \sim 60\,000$ L mol^{-1}). It seems that the $\Delta S°$ values for proton–citrate-association reactions are increased with the increase in the stability constant (K) of the proton–citrate ion pairs. Positive changes in entropy have also been reported for other calcium ion pair complexes (*21–23*) and normally, the $\Delta S°$ values are increased with the increase in the stability constant of the resulted ion pair. This, in turn, may reflect that the dehydration of ion-pair-forming ions is faster when the ion-association interaction is stronger.

In conclusion, on the basis of calcium ion selective measurements at different temperatures and ionic strengths, an accurate value of the stability constant of the $CaCit^-$ ion pair has been reported. The results have emphasized the importance of taking into account both the sodium–citrate(3–) ion pair and ionic strength correction when determining the thermodynamic stability constant of the $CaCit^-$ ion pair from solutions containing sodium, chloride, calcium, and citrate ions at physiological ionic strengths. The Ca^{2+}–Cit^{3-} ion pair association reaction was found to be nearly thermoneutral ($\Delta H° < \pm 1$ kcal mol^{-1}) with stability constants insensitive to temperature in the range 18–45 °C. In addition, through the calculation of $\Delta S°$ values, it was shown that the $CaCit^-$ ion pair is entropically stabilized, similar to other calcium ion pair complexes reported in the literature (*18*, *21–23*).

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Received for review November 16, 1989. Accepted July 2, 1990. This work is part of KFUPM/RI Project No. 15010, supported by the Research Institute of King Fahd University of Petroleum and Minerals.