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REVIEW

Evaluation of Equilibrium Constants for Deprotonation and Lactonisation of α -D-Isosaccharinic Acid

Dhanpat Rai^a and Akira Kitamura^{b*}

^a *Rai Enviro-Chem, LLC, PO Box 784, Yachats, Oregon, USA;*

^b *Sector of Decommissioning and Radioactive Waste Management, Japan Atomic Energy Agency, 4-33 Muramatsu, Tokai, Naka, Ibaraki 319-1194, Japan*

A great deal of disagreement exists in the literature regarding the intrinsic deprotonation and lactonisation constants of α -D-isosaccharinic acid (ISA). Based on a combination of nuclear magnetic resonance (NMR) and interpretations using the specific ion interaction theory (SIT) of extensive experimental $\text{Ca}(\text{ISA})_2(\text{cr})$ solubility data involving α -D-isosaccharinic acid, the reliable value of $\log_{10} K^\circ$ for $[\text{HISA}(\text{aq}) \rightleftharpoons \text{ISA}^- + \text{H}^+]$ is -3.27 ± 0.01 and for $[\text{HISA}(\text{aq}) \rightleftharpoons \text{ISL}(\alpha\text{-D-isosaccharinate-1,4-lactone})(\text{aq}) + \text{H}_2\text{O}]$ is 0.49 ± 0.09 . These data also provide $\log_{10} K^\circ$ of -3.76 ± 0.09 for the reaction $[\text{ISL}(\text{aq}) + \text{H}_2\text{O} \rightleftharpoons \text{ISA}^- + \text{H}^+]$ and -3.88 ± 0.09 for the composite reaction $[\text{HISA}(\text{aq}) + \text{ISL}(\text{aq}) \rightleftharpoons \text{ISA}^- + \text{H}^+]$. Reinterpretation of extensive $\text{Ca}(\text{ISA})_2(\text{cr})$ solubility data using the SIT activity coefficient model provides $\log_{10} K^\circ$ of -6.40 ± 0.09 for $[\text{Ca}(\text{ISA})_2(\text{cr}) \rightleftharpoons \text{Ca}^{2+} + 2(\text{ISA})^-]$ and of 1.70 ± 0.09 for $[\text{Ca}^{2+} + \text{ISA}^- \rightleftharpoons \text{CaISA}^+]$ which are consistent with all of the available values.

*solubility; acidity constant; deprotonation constant; lactonisation constant;
isosaccharinate; thermodynamics; isosaccharinic acid*

*Corresponding author. Email: kitamura.akira@jaea.go.jp

1. Introduction

Isosaccharinic acid (HISA) has three different forms (alpha, beta, and xylo)¹. Each of these forms produces a related cyclic molecule, a lactone (ISL) in which the isosaccharinic acid loses a water molecule. HISA is a cellulose degradation product [1-4] and is known to form strong complexes with many elements (e. g., Th, U, Np, Pu, and Am) of interest in nuclear wastes (e. g., [3,5-9]). Significant quantities of HISA may be produced by degradation of cellulose in low level nuclear waste (LLW) repositories [1] so HISA-mediated mobilization of radionuclides from LLW is of potential environmental concern. The lactonisation reaction of ISA is coupled with the protonation and affects the speciation of ISA and the determination of the protonation constant in acidic solutions [10]. Therefore reliable values for acidity and lactonisation constants of HISA and values for HISA complexes of radionuclides are required to predict the environmental impacts of HISA that may be produced in LLW repositories. The focus of this article is a critical review of deprotonation and lactonisation constants of α -isosaccharinic acid because it is one of the most important degradation products of cellulose [10, 11] and by far the greatest amount of thermodynamic data are available for this compound. The chemical structures of α -HISA and its lactonisation product (α -D-isosaccharinate-1,4-lactone) are shown in Figure 1.

<Figure 1>

The α -HISA is known by many names [(2S, 4S)-2,4,5-Trihydroxy-2-(hydroxymethyl) pentanoic acid; 3-Deoxy-2-C-(hydroxymethyl)-D-erythro-pentonic acid; D-gluco-isosaccharinic acid; α -D-isosaccharinic acid; isosaccharinic acid;

¹ In this paper, unless otherwise identified, all references to isosaccharinate or isosaccharinic acid are for the alpha form. Where alpha = (2S,4S)-2,4,5-trihydroxy-2-(hydroxymethyl) pentanoic acid; beta = (2R,4S)-2,4,5-trihydroxy-2-(hydroxymethyl) pentanoic acid; and xylo = 3-deoxy-2-C-hydroxymethyl-D,L-tetronic acid.

α -D-glucoisosaccharinic acid; α -glucoisosaccharinic acid; α -isosaccharinic acid] [12]. A large number of investigators using several different experimental techniques (potentiometric, ^{13}C NMR, and electrophoresis) have reported values for acidity (Eq. 1) [7, 13-18] and lactonisation (transformation of α -D-isosaccharinic acid to α -D-isosaccharinate-1,4-lactone) (Eq. 2) [5, 13, 19] constants. The reported $\log_{10} K^\circ$ values for acidity constants (Eq. 1) for α -D-isosaccharinic acid vary from -3.27 to -4.04 (**Tables 1 and 2**). The $\log_{10} K^\circ$ values for lactonisation constants (Eq. 2) vary from 0.37 to 0.84 (Table 2).

<Table 1>

<Table 2>



A large amount of the currently available data related to the acidity and lactonisation constants of α -D-isosaccharinic acid was reviewed by Hummel et al. [10]. Hummel et al. [10] correctly criticized the literature data obtained by methodology other than NMR in that 1) it is not possible to determine individual intrinsic values for both the acidity and lactonisation constants by these methods, 2) most of the values reported in the literature are somewhere between intrinsic and composite protonation constants, and 3) it is only possible to estimate the value for the composite constant² (Eq. 3),.



² By substituting the values of $\text{ISL}(\text{aq})$ in terms of K_L^0 and of $(\text{ISA}^- + \text{H}^+)$ in terms of K_a^0 , where K_a^0 is the equilibrium constant for the reaction in Eq. 1 and K_L^0 for the reaction in Eq. 2, and rearranging, it can be shown that the $\log_{10} K^0 = \log_{10} K_a^0 - \log_{10} (1 + K_L^0)$ for the reaction in Eq. 3.

Because of the difficulties involved in determining accurate values for these individual constants, Hummel et al. [10] only recommended a $\log K^\circ$ value of $-(4.00 \pm 0.5)$ for the composite constant (Eq. 3) but with a large degree of uncertainty. Recently, Brown et al. [13] based on the same literature data (Table 1) reviewed by Hummel et al. [10] have elected to recommend intrinsic $\log K^\circ$ value of -4.04 ± 0.06 for the deprotonation constant (Eq. 1) and of 0.80 ± 0.02 for the lactonisation constant (Eq. 2) in direct disagreement with the conclusions reached by Hummel et al. [10]. It is clear from the above discussion that there is a large degree of uncertainty in the literature regarding the equilibrium constants for reactions in Eq. 1-3. The objective of this study is to critically evaluate the data previously reviewed by Hummel et al. [10] in conjunction with the α -HISA data not reviewed by Hummel et al. and the data for beta- and xylo-isosaccharinic acids to recommend intrinsic acidity and lactonisation constants for α -HISA.

2. Discussion

2.1. Difficulties involved in determining intrinsic constants

In terms of transformation, the rates for $\text{HISA(aq)}/\text{ISA}^-$ are extremely rapid but $\text{HISA(aq)}/\text{ISL(aq)}$ are relatively slow [10]. Both of these transformations occur in the acidic region and within a rather narrow pH range. Therefore the methods (such as potentiometric and electrophoresis) that 1) use rather short equilibration periods, and 2) cannot simultaneously quantify different species [HISA(aq) , ISA^- , and ISL(aq)] are not suited for determining values for both intrinsic constants. This is why Hummel et al. [10] concluded that the values previously reported (Table 1) are either composite constants or are something between composite and intrinsic constants.

2.2. A reliable approach to determining intrinsic constants

2.2.1. General Approach

Because the transformation rates of HISA(aq)/ISA⁻ are extremely rapid, ¹³C NMR is best suited for determining the value of the acidity constant (Eq. 1). Lactonisation is a relatively slow process and thus rates of HISA(aq) conversion to ISL depend on the equilibration period and are most likely also influenced by several other factors such as pH and HISA(aq) concentration. Long equilibration periods are required to guarantee that the lactonisation process has proceeded to equilibrium at a given pH value. Solubility studies, in contrast to other methods (i.e., potentiometry and electrophoresis), have the advantage that long equilibration periods can be achieved. Therefore solubility studies involving HISA(aq) in the acidic region with long equilibration periods in conjunction with deprotonation constants from NMR studies can be used to reliably determine the value of the lactonisation constant (Eq. 2). The ideal solubility study for this purpose must have the following attributes: 1) the solid phase used should be crystalline, rather than amorphous³, with rapid precipitation/dissolution kinetics, 2) the study should be conducted in the acidic region (pH < 5) with several data points per pH unit, 3) the cation of the solid phase should not: a) make strong complexes with ISA⁻ or if it does then the reliable complexation constant values should be available, and b) form strong complexes with hydroxide in the low pH region, and 4) the equilibration period should be relatively long. Among the solid phases (ThO₂(am), NpO₂(am), PuO₂(am), Fe(OH)₃(am) and Ca(ISA)₂ [3, 5, 6, 9, 20-22] for which solubility data in the presence of ISA are available, the only ones that meet all of the above criteria for ideal solubility study are the Ca(ISA)₂(cr) studies by Rai et al. [5, 23].

2.2.2. Specific Approach

The available ¹³C NMR data for different forms of isosaccharinic acid (i.e., alpha, beta, and xylo) will be reviewed to select a reliable value for the acidity constant of HISA(aq) (Eq.

³ An amorphous solid is not ideal because its chemical potential may vary depending on several different factors such as method of preparation, aging, and presence of impurities.

1). The available $\text{Ca}(\text{ISA})_2(\text{cr})$ solubility data will be reviewed. The low pH solubility data for relatively long equilibration periods [23] will be reinterpreted using the SIT fitting code (NONLINT-SIT [24]). The model input will include the experimental solubility data, the reliable value of the deprotonation constant as mentioned above, and the appropriate SIT ion-interaction parameters (**Table 3**). The fitting code will be used to determine the value for the lactonisation constant. The NONLINT-SIT will also be used to predict total Ca and ISA concentrations in equilibrium with $\text{Ca}(\text{ISA})_2(\text{cr})$ using the acidity and lactonisation constants as inputs from recently published data [13] to determine whether these constants are consistent with the extensive solubility data, the available reliable values of solubility product for $\text{Ca}(\text{ISA})_2(\text{cr})$, and the complexation constant for CaISA^+ (Table 4).

<Table 3>

2.3. Evaluation of intrinsic constants

2.3.1. Acidity constant of α -HISA(aq)

Cho et al. [18] determined a deprotonation constant of α -HISA(aq) by ^{13}C NMR studies. The NMR spectra show chemical and structural transformations as a function of pH. Cho et al. [18] used pH-dependent six ^{13}C ISA NMR lines to show that the most acidic proton is the one associated with the carboxylate group, and they reported an average $\log_{10} K^\circ$ of -3.27 ± 0.01 based on relatively dilute solutions of sodium salt. They reported a $\log_{10} K^\circ$ value of -3.36 ± 0.02 when they used Ca salt instead of Na salt. Calcium is known to form a weak complex with ISA^- (**Table 4**), and Cho et al. [18] did not consider the presence of this complex in calculating their value for the calcium salt. Although the difference in the values based on the Na and Ca salts is small, it is consistent with the presence of a weak CaISA^+ complex, and that difference most likely results from the presence of Ca complex. Therefore, we recommend $\log_{10} K^\circ$ of -3.27 ± 0.01 for Eq. 1. No other NMR-based values for

α -HISA(aq) are available. However, based on ^{13}C NMR studies with calcium salt (0.075 m) of β -gluco-isosaccharinic acid, Shaw et al. [25] report a $\log_{10} K$ value of -3.61 ± 0.03 for the deprotonation constant of β -HISA(aq). It is difficult to convert this value to zero ionic strength because of the possible complexation of isosaccharinate with Ca. Shaw et al. [25] did not account for Ca complexes and therefore the actual value most likely is higher than the value they report. Based on ^{13}C NMR studies, Almond et al. [26] report a $\log_{10} K$ value of -3.00 ± 0.05 for deprotonation constant of X-HISA(aq) (xylo isosaccharinic acid) in solutions with an ionic strength of 0.151 m. Using the SIT model we estimated⁴ a $\log_{10} K^\circ$ value of -3.26 ± 0.05 for X-HISA(aq) based on the data reported in Almond et al. [26]; this value is essentially identical to the value reported by Cho et al. [18] for α -HISA(aq). It is clear from the above discussion that the value we recommend for α -HISA(aq) is reasonable.

<Table 4>

Recently Brown et al. [13], based on the review of literature data, recommended a $\log_{10} K^\circ$ value of -4.04 ± 0.06 for the intrinsic deprotonation constant of α -HISA(aq) (Eq. 1). The value Brown et al. [13] recommend is too low for several reasons. 1) It is considerably lower than the intrinsic constant value (-3.27 ± 0.01) based on NMR data with which it is possible to reliably quantify, based on ^{13}C signals, both the HISA and ISA^- concentrations. It is not possible to quantify the individual ISA species by the methods used in the studies upon which Brown et al.'s [13] calculations are based. 2) Brown et al. [13] had no new data since the review by Hummel et al. [10] who state that the reported values are either composite constants or are something between composite and intrinsic constants. Therefore Brown et al. [13] could not possibly have arrived at an intrinsic constant based on these data. 3) The

⁴ Assuming the Na salt and that $\epsilon(\text{Na}^+, \text{ISA}^-) = -0.07$ [10]

value Brown et al. [13] recommend is completely at odds with the well established extensive $\text{Ca}(\text{ISA})_2(\text{cr})$ solubility data⁵, discussed later in this article.

2.3.2. Lactonisation constant of α -HISA(aq)

As discussed earlier, extensive $\text{Ca}(\text{ISA})_2(\text{cr})$ solubility data sets [5, 21]⁶, I) as a function of pH (varying from 2.61 to 10.87), II) at a fixed CaCl_2 concentration of 0.036 mol.kg⁻¹ and as a function of pH (varying from 2.88 to 10.96), III) at a fixed pH value of approximately 8.0 and as a function of CaCl_2 molality (varying from 0.03 to 0.26), and IV) at a fixed pH value of approximately 8.2 and as a function of isosaccharinate molality (varying from 0.02 to 0.20), can be interpreted, especially the low pH data, in combination with HISA(aq) deprotonation constant selected above to obtain a reliable value for the lactonisation constant. Data sets I-III are from Rai et al. [23] and data set IV is from Rai et al. [5]. Four reasons are discussed in Section 2.2.1 as to why the $\text{Ca}(\text{ISA})_2(\text{cr})$ solubility data are best suited to determining the lactonisation constant. In addition, 1) the equilibration period with the other methods (potentiometric and electrophoresis) is relatively short, and 2) HISA(aq), ISA^- , and ISL are all present in various proportions in the low pH region and it is impossible to determine intrinsic constants without determining their specific concentrations simultaneously, a task impossible to complete because of the inherent inability of these methods to do so. With the intrinsic deprotonation constant value selected above, it is possible to precisely predict the concentrations of HISA(aq) and ISA^- at any given pH. Therefore the precise value for the lactonisation constant can be fitted from the low pH $\text{Ca}(\text{ISA})_2(\text{cr})$ solubility data, provided the reliability of the values for the solubility product of $\text{Ca}(\text{ISA})_2(\text{cr})$ and Ca-ISA complexes, which can also simultaneously be fitted along with the

⁵ The predicted concentrations using the deprotonation and lactonisation constants from Brown et al. [11] in combination with the reliable thermodynamic data for CA-ISA system are over an order of magnitude higher than the experimental concentrations.

⁶ The reanalyzed raw data from these publications are reproduced in supplemental data Tables A1-A4.

lactonisation constant, are independently verifiable. The reported [5, 19, 20] $\log_{10} K^\circ$ values for $\text{Ca}(\text{ISA})_2(\text{cr})$ solubility reaction (Eq. 4) determined with and without low pH data vary over a rather narrow range (-6.22 to -6.53) (Table 4). No new data have become available since these publications. Hummel et al. [10] reviewed all of these data and using the SIT model recommended an average $\log_{10} K^\circ$ value of -6.4 ± 0.2 for Eq. 4.



Calcium forms a weak complex with isosaccharinate. The reported [5, 27] $\log_{10} K^\circ$ values for the formation of CaISA^+ (Eq. 5) based on three different methods (solubility, potentiometric ion-selective-Ca electrode, and ion exchange) vary over a narrow range from about 1.5 to 1.8, and based on these data Hummel et al. [10] recommended an average value of 1.7 ± 0.3 (Table 4).



The original $\text{Ca}(\text{ISA})_2(\text{cr})$ solubility data [23] were interpreted by Rai et al. [5] using the Pitzer model. However, all of the available critically evaluated thermodynamic data for ISA reactions reviewed by Hummel et al. [10] have been interpreted using the SIT model [10]. Therefore for cross comparison purposes and to determine whether these average values recommended by Hummel et al. [10] are consistent with the extensive solubility data [5, 23], it is important that $\text{Ca}(\text{ISA})_2(\text{cr})$ solubility data also be interpreted using the SIT model. The NONLINT-SIT [24] was used for these interpretations. For these calculations we used $\text{Ca}(\text{ISA})_2(\text{cr})$ solubility data in combination with a $\log_{10} K^\circ$ value of -3.27 for Eq. 1 [18], -6.4 for Eq. 4 [10], 1.7 for Eq. 5 [10], the needed SIT ion-interaction parameters [$\epsilon(\text{Na}^+, \text{ISA}^-) = -0.07$ from Rai et al. [20] and $\epsilon(\text{Na}^+, \text{OH}^-) = 0.04$, $\epsilon(\text{Na}^+, \text{Cl}^-) = 0.03$, $\epsilon(\text{H}^+, \text{Cl}^-) = 0.12$, and

$\epsilon(\text{Ca}^{2+}, \text{Cl}^-) = 0.14$ from Hummel et al. [10]] (Table 3), and we fitted a $\log_{10} K^\circ$ of 0.49 ± 0.09 for the lactonisation constant (Eq. 2).

A very close agreement is observed between the experimental [5, 23] and the predicted total concentrations (based on the thermodynamic data developed in this study) in equilibrium with $\text{Ca}(\text{ISA})_2(\text{cr})$ for all four sets (Figures. 1-4). The close agreement between the experimental and predicted concentrations for the relatively high pH ($> \sim 5$) regions (Figures. 1-4), where complications from the $\text{HISA}(\text{aq})$ deprotonation and lactonisation is not a factor and the dominant species in this region are ISA^- , shows that Hummel et al.'s [10] recommended values for the solubility product (Eq. 4) and CaISA^+ complex are reliable and consistent with the solubility data reported in Rai et al. [5, 23]. Therefore, it seems reasonable that these values apply equally well to the low pH data. The increased total Ca concentration with the decrease in pH (Figures 2 and 3) is due to the decrease in ISA^- concentration caused by the conversion of ISA^- into $\text{HISA}(\text{aq})$ and $\text{ISL}(\text{aq})$. Because reliable thermodynamic data for all reactions with the exception of lactonisation of $\text{HISA}(\text{aq})$ are available, it therefore was possible to calculate a reliable value for the lactonisation constant (Eq. 2) from these data. The $\log_{10} K^\circ$ value for the lactonisation constant reported in the literature varies from 0.37 to 0.84 [5, 10, 18]. If we ignore the lower value, based on the same data as those reinterpreted in this study, the value we determined in this study is up to about 0.35 log units lower than the values reported previously (Table 2). Although the difference is not very large, the exact reasons for this difference are not known but most likely include the use of different values for deprotonation constants, and the inability of methods other than NMR to accurately quantify all individual species [especially $\text{HISA}(\text{aq})$ and ISA^- with a large ^{13}C shift of ISA^- lines as a function of pH]. The $\log_{10} K^\circ = 0.49 \pm 0.09$ for the lactonisation constant we determined is based on a reliable value for the intrinsic deprotonation constant determined by NMR, similar to the values reported by several other

authors (Table 2) and is consistent with all of the available $\text{Ca}(\text{ISA})_2(\text{cr})$ solubility data, which lends credence to the accuracy of the lactonisation constant determined in this study.

The values of protonation and lactonisation constants determined in this study provide $\log_{10} K^0$ of -3.88 ± 0.09 for the composite reaction (Eq. 3) as compared to the value (-4.0 ± 0.5) recommended by Hummel et al. [10]. The value we determined is much more precise than the Hummel et al.'s value, but the average values are very similar and the value in Hummel et al. is based on a large number of literature data which lends additional support to the accuracy of the protonation and lactonisation constants determined in this study.

Recently, Brown et al. [13] have proposed intrinsic $\log_{10} K^0$ values for deprotonation (-4.04 ± 0.06 , Eq. 1) and lactonisation (0.80 ± 0.02 , Eq. 2) constants. It is important to determine whether the Brown et al.'s [13] values are consistent with the extensive experimental and thermodynamic data for the $\text{Ca}(\text{ISA})_2$ system. To perform this test, we used the NONLINT-SIT model and well-established values for Ca - ISA system reactions (Eqs. 4 and 5) (proposed by Hummel et al. [10] and verified in this study) (Table 4) and appropriate ion-interaction parameters (Table 3) along with the values for reactions (Eqs. 1 and 2) reported by Brown et al. [13] (Tables 1 and 2) to predict the concentrations of Ca and ISA as a function of pH and in equilibrium with $\text{Ca}(\text{ISA})_2(\text{cr})$. These predicted Ca and ISA concentrations as a function of pH for the low pH set (Set I) are compared to experimental data reported by Rai et al. [23] (**Figure 6**). It is expected that if the values for reactions (Eq. 1 and 2) are correct, there should be a close agreement between the experimental and predicted concentrations in the entire pH range including the $\text{pH} < \sim 4$ region and not just in the high pH region where $\text{HISA}(\text{aq})$ and $\text{ISL}(\text{aq})$ are unimportant. A large disagreement between the predicted and experimental Ca and ISA concentrations as a function of pH in the

relatively low pH region ($\text{pH} < \sim 4$)⁷ clearly shows that the values for reactions (Eqs. 1 and 2) as proposed by Brown et al. [13] cannot possibly be correct. **One of the major reasons for disagreement between our results and those presented in Brown et al. [13] is due to the value of the protonation constant. If we surmise that the value Brown et al. [13] select from the literature data for the protonation constant is instead for the composite constant, as concluded by Hummel et al. [10] from the same literature data, the major differences will be reconciled.**

<Figure 2>

<Figure 3>

<Figure 4>

<Figure 5>

<Figure 6>

2.4. Summary of data selection

In summary, the $\log_{10} K^\circ$ values for intrinsic deprotonation (Eq. 1) and lactonisation (Eq.2) constants that we recommend based in this review are -3.27 ± 0.01 and 0.49 ± 0.09 , respectively, and these values are 1) consistent with the extensive Ca-ISA system data reported by several authors [5, 21-23, 27, 28] and Hummel et al.'s [10] recommended values based on their critical review of these data using the SIT model, and 2) similar to the values Rai et al. [5] determined based on the interpretation of Ca-ISA system data using the Pitzer model. The average values for the solubility product for $\text{Ca}(\text{ISA})_2(\text{cr})$ and formation of CaISA^+ recommended by Hummel et al. [10] have been verified in this study. Calculations based on extensive Ca-ISA system data also provide improved uncertainty values in the $\log_{10} K^\circ$ for the reactions in Eq. 4 and 5 (-6.4 ± 0.09 and 1.7 ± 0.09 , respectively).

⁷ The same conclusion is reached by plotting the experimental and predicted concentrations for Set II, the graph is not included in this presentation.

3. Conclusion

Our critical review has provided reliable $\log K^\circ$ values for the reactions $[\text{HISA}(\text{aq}) \rightleftharpoons \text{ISA}^- + \text{H}^+]$, $[\text{HISA}(\text{aq}) \rightleftharpoons \text{ISL}(\text{aq}) + \text{H}_2\text{O}]$, $[\text{ISL}(\text{aq}) + \text{H}_2\text{O} \rightleftharpoons \text{ISA}^- + \text{H}^+]$, and $[\text{HISA}(\text{aq}) + \text{ISL}(\text{aq}) \rightleftharpoons \text{ISA}^- + \text{H}^+]$. Strong evidence is presented as to why the values recently proposed by Brown et al. [13] for the above reactions are unreliable. Reinterpretation of extensive $\text{Ca}(\text{ISA})_2(\text{cr})$ solubility data using the SIT model provides $\log K^\circ$ values for $[\text{Ca}(\text{ISA})_2(\text{cr}) \rightleftharpoons \text{Ca}^{2+} + 2(\text{ISA})^-]$ and $[\text{Ca}^{2+} + \text{ISA}^- \rightleftharpoons \text{CaISA}^+]$, the values that are consistent with the average of all of the available values recommended by Hummel et al. [10]

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Figure captions

Figure 1. The chemical structures of α -HISA (a) and its lactonisation product (α -D-isosaccharinate-1,4-lactone) (b) (after [10])

Figure 2. Experimental [23] and predicted (NONLINT-SIT model) concentrations of Ca and ISA as a function of pH for samples equilibrated with $\text{Ca}(\text{ISA})_2(\text{cr})$ for 75 days. Predictions based on the thermodynamic data reported in Table 3 and corresponding to “this study” data reported in Tables 2 and 4. Lines represent predicted concentrations: Heavy solid lines represent total concentrations of either Ca or ISA and other lines concentrations of different species as marked.

Figure 3. Experimental [23] and predicted (NONLINT-SIT model) concentrations of Ca and ISA as a function of pH for samples equilibrated in $0.036 \text{ mol.kg}^{-1}$ CaCl_2 solutions with $\text{Ca}(\text{ISA})_2(\text{cr})$ for 8 days. Predictions based on the thermodynamic data reported in Table 3 and corresponding to “this study” data reported in Tables 2 and 4. Lines represent predicted concentrations: Heavy solid lines represent total concentrations of either Ca or ISA and other lines concentrations of different species as marked.

Figure 4. Experimental [5] and predicted (NONLINT-SIT model) concentrations of Ca as a function of ISA concentration from solutions equilibrated with $\text{Ca}(\text{ISA})_2(\text{cr})$ at pH ~ 8.3 for 48 days. Predictions based on the thermodynamic data reported in Table 3 and corresponding to “this study” data reported in Tables 2 and 4. Lines represent predicted concentrations: Heavy solid lines represent total concentrations of either Ca or ISA and other lines concentrations of different species as marked.

Figure 5. Experimental [23] and predicted (NONLINT-SIT model) concentrations of ISA as a function of CaCl_2 concentration from solutions equilibrated with $\text{Ca}(\text{ISA})_2(\text{cr})$ at

pH ~8.0. Predictions based on the thermodynamic data reported in Table 3 and corresponding to “this study” data reported in Tables 2 and 4. Lines represent predicted concentrations: Heavy solid lines represent total concentrations of either Ca or ISA and other lines concentrations of different species as marked. (Note: The original authors [23], based on Pitzer modeling, had erroneously concluded that these data support the formation of $\text{Ca}(\text{ISA})_2(\text{aq})$. As shown in this figure these data are very well interpreted with the model selected in this study).

Figure 6. Experimental [23] and predicted (NONLINT-SIT model) concentrations of Ca and ISA as a function of pH for samples equilibrated with $\text{Ca}(\text{ISA})_2(\text{cr})$ for 75 days. Predictions based on the thermodynamic data reported in Table 3 and corresponding to “this study” data reported in Tables 4 in combination with deprotonation and lactonisation constant values for $\text{HISA}(\text{aq})$ from Brown et al. [13] (Tables 1 and 2). Lines represent predicted concentrations: Heavy solid lines represent total concentrations of either Ca or ISA and other lines concentrations of different species as marked.

Table 1. Intrinsic deprotonation constants (see footnote “d”) of α -D-isosaccharinic acid [HISA(aq) \rightleftharpoons ISA⁻ + H⁺] proposed by various authors based on methods other than NMR

Method ^a	I	$\log_{10} K$	$\log_{10} K^{\circ}$	Reference
pot	0.01	-3.75	-3.84 ^b	[14]
pot	0.1	-3.83	-4.04 ^b	[14]
em	0.0015	-4.02	$\sim -4.02^b$	[15]
em	0.002	-4.05	$\sim -4.05^b$	[15]
em	0		-3.87	[16]
pot	0		-3.98	[16]
pot	1.00	-3.78 ± 0.05	-4.12 ^b	[17]
pot		-3.65 ± 0.05	-3.97 ± 1.0^c	[7]
Review	0		-4.04 ± 0.06^d	[13]

^a pot = potentiometry, em = electromigration, NMR = Nuclear Magnetic Resonance
^b Estimated by us using the SIT model for the proposed reaction. Also see footnote “d”.
^c Calculated by Hummel et al. [10] to zero ionic strength from the concentration constant reported by the authors
^d Calculated based on the data reported in this table and assuming that the proposed reaction is correct. The very same data Hummel et al. [10] concluded do not represent intrinsic constants as the reaction in the title of this table portrays but represents either a composite constant for the reaction (HISA(aq) + ISL(aq) \rightleftharpoons ISA⁻ + H⁺) or something between an intrinsic constant and a composite constant. **We conclude from our study that the values reported in this Table are consistent with the extensive data we analyzed only if the values are for the composite constant rather than for the intrinsic constant (see text for details).**

Table 2. Intrinsic deprotonation and lactonisation constants of alpha-, beta-, and xylo-isosaccharinic acids

Reaction	$\log_{10} K^\circ$	Reference	Comments ^a
$\text{HISA}(\text{aq}) \rightleftharpoons \text{ISA}^- + \text{H}^+$	-3.27 ± 0.01	[18]	NMR, Na(α -ISA)
	-3.36 ± 0.02	[18]	NMR, Ca(α -ISA) ₂
	-3.26 ± 0.05^b	[26]	NMR, X-ISA
	-3.61 ± 0.03^c	[25]	NMR, β -ISA
	-3.27 ± 0.01	This study	α -ISA
$\text{HISA}(\text{aq}) \rightleftharpoons \text{ISL}(\text{aq}) + \text{H}_2\text{O}$	0.37 ± 0.07	[5]	Sol, α -ISA, Pit
	0.34^d	[26]	NMR, X-ISA, pH 1.97
	0.51^d	[26]	NMR, X-ISA, pH 1.27
	0.71^d	[26]	NMR, X-ISA, pH 1.09
	0.84 ± 0.19^d	[19]	Chr, α -ISA
	0.80 ± 0.02^d	[13]	Chr, α -ISA
	$< 0.8^e$	[18]	NMR, α -ISA
	0.49 ± 0.09	This study	Sol, α -ISA, SIT
$\text{ISL}(\text{aq}) + \text{H}_2\text{O} = \text{ISA}^- + \text{H}^+$	-4.84 ± 0.07	[13]	Review, α -ISA
	-3.78 ± 0.19^f	[26]	NMR, X-ISA
	-3.76 ± 0.09	This study	α -ISA

^a NMR = nuclear magnetic resonance, Sol = solubility, Chr = ion chromatography
^b Calculated by us using the SIT model from $\log_{10} K = -(3.00 \pm 0.05)$ in 0.151 molal ionic strength solutions reported by the authors; see text for details.
^c This value is a concentration constant determined in 0.0075 molal Ca(β -ISA)₂ solutions as the authors report. However, from the other information provided by the authors, it appears that the ionic strength of the solutions should be 0.075 molal. For this reason and because the authors did not consider the formation of Ca(β -ISA)⁺ complex, it is difficult to precisely calculate the value for the thermodynamic equilibrium constant.
^d Concentration constants reported by the authors. Because of the lack of charge on any of the species involved in the reaction, concentration constants can be assumed to be identical to the thermodynamic constants.
^e Calculated by Dr. Cho, the senior author of the quoted reference (personal communication with Dr. Cho, October 2014). Calculations based on a limited data and the values varied from -0.3 to 8. The calculated values show pH dependence as noted in this table for X-ISA values. The values increase with the decrease in pH.
^f Calculated by us from the data in the quoted reference.

Table 3. SIT ion-interaction parameters used in this study to interpret the $\text{Ca}(\text{ISA})_2(\text{cr})$ solubility data (all values from [10] unless otherwise noted)

Species	ε ($\text{kg}\cdot\text{mol}^{-1}$)
Na^+ , ISA^-	-0.07^{a}
Na^+ , OH^-	0.04
Na^+ , Cl^-	0.03
H^+ , Cl^-	0.12
Ca^{2+} , Cl^-	0.14
^a From Rai et al. [20]	

Table 4. Thermodynamic data for the Ca-(α -ISA) system

Reaction	$\log_{10} K^\circ$	Reference	Comments ^a
$\text{Ca(ISA)}_2(\text{cr}) \rightleftharpoons \text{Ca}^{2+} + 2 \text{ISA}^-$	-6.53 ± 0.02	[21] ^b	Sol, pH 6.5 to 8.7
	-6.36 ± 0.10	[22]	Sol, pH 12 to 12.8
	-6.26 ± 0.07	[5]	Sol, pH 2.61 to 11, Pitzer
	-6.4 ± 0.2	[10]	Review, SIT
	-6.4 ± 0.09	This study	Review, Sol, pH 2.61 to 11, SIT
$\text{Ca}^{2+} + \text{ISA}^- \rightleftharpoons \text{CaISA}^+$	1.70	[22]	pH 12 to 12.8
	1.44 ± 0.07	[5]	Sol, pH 2.61 to 11, Pitzer
	1.8 ± 0.1	[27]	Ix, pH ~6.0
	1.78 ± 0.04	[27]	Pot, ise-Ca, pH ~6.2
	1.7 ± 0.3	[10]	Review, SIT
	1.70 ± 0.09	This study	Sol, pH 2.61 -11, SIT

^a Sol = solubility, Ix = ion exchange, pot = potentiometry

^b This value is based on the data presented in this paper and further calculations by van Loon et al. [27] to include the contribution of CaISA^+ to the solubility; van Loon et al. [21] report a value of -6.22 ± 0.03 without the inclusion of CaISA^+ in their analyses.

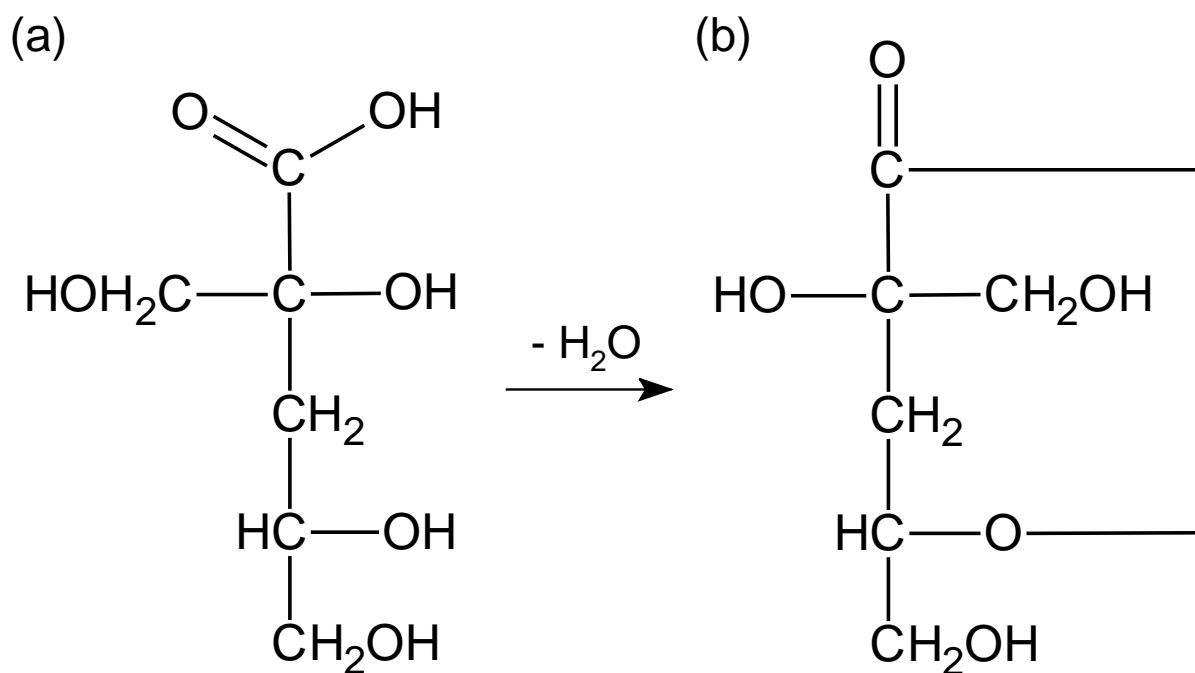


Figure 1.

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Evaluation of Equilibrium Constants for Deprotonation and Lactonisation of α -D-Isosaccharinic Acid

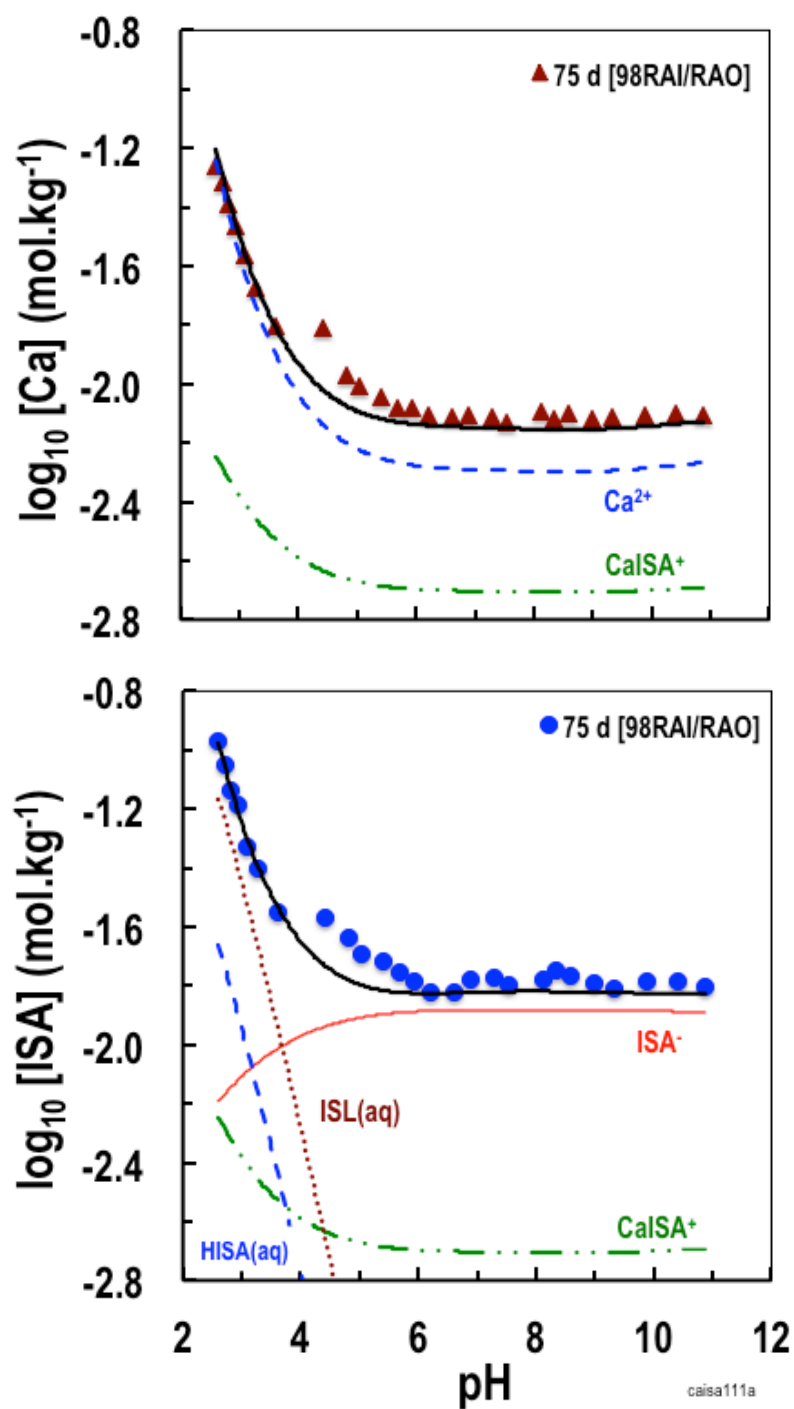
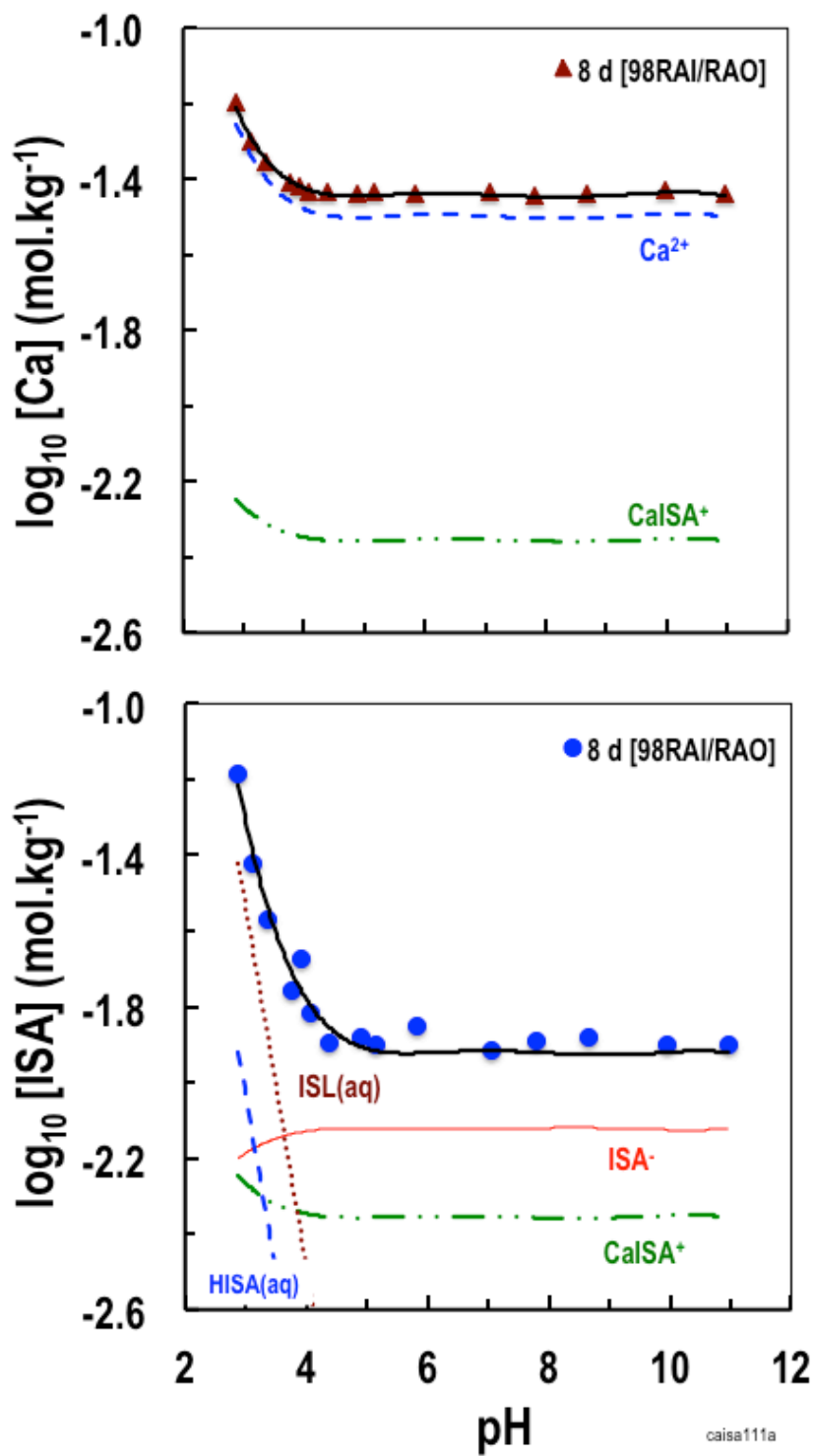


Figure 2.

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Evaluation of Equilibrium Constants for Deprotonation and Lactonisation of α -D-Isosaccharinic Acid



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Figure 3

Dhanpat Rai and Akira Kitamura

Evaluation of Equilibrium Constants for Deprotonation and Lactonisation of α -D-Isosaccharinic Acid

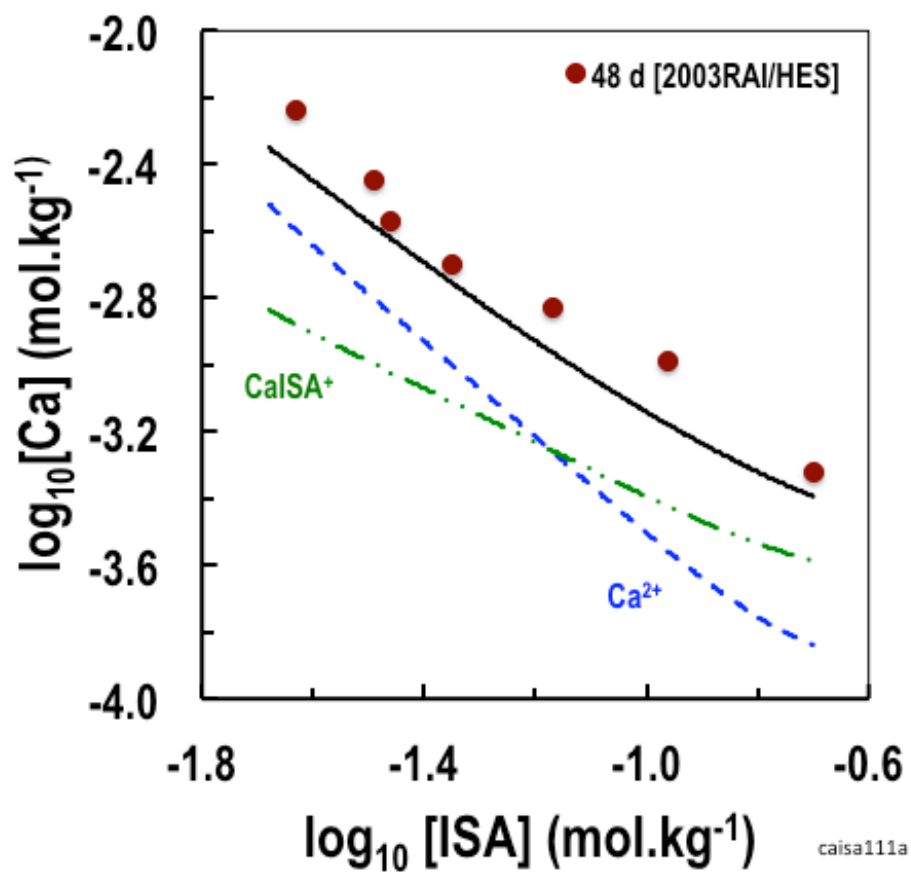


Figure 4.

Dhanpat Rai and Akira Kitamura

Evaluation of Equilibrium Constants for Deprotonation and Lactonisation of α -D-Isosaccharinic Acid

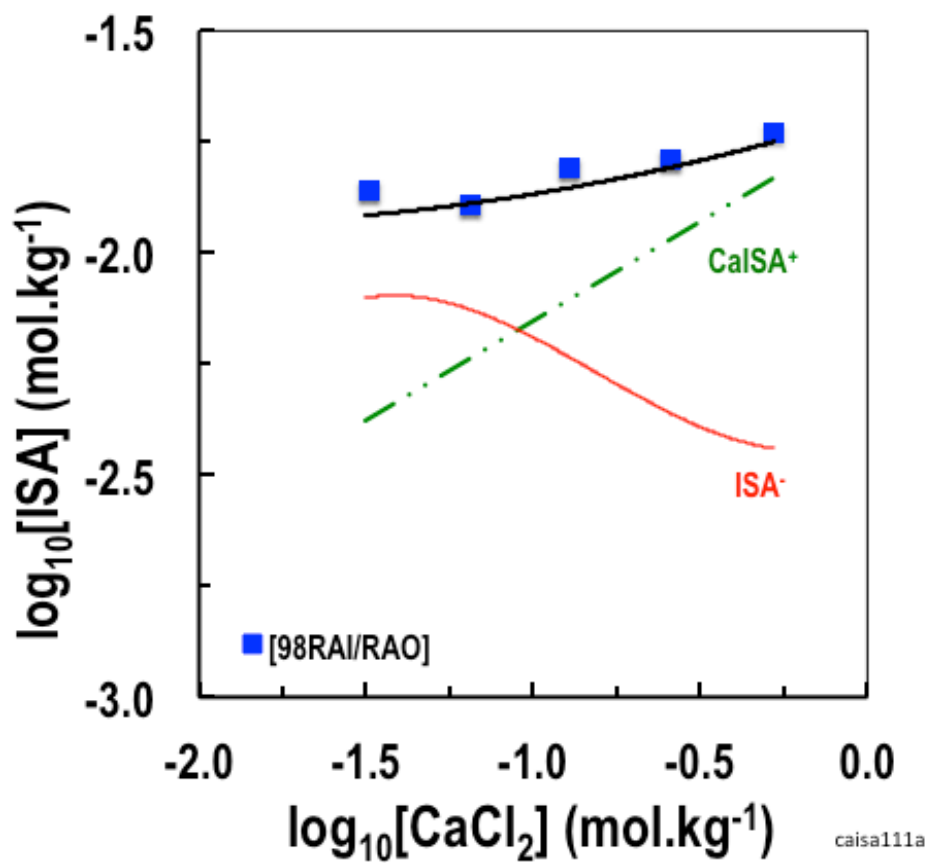


Figure 5.

Dhanpat Rai and Akira Kitamura

Evaluation of Equilibrium Constants for Deprotonation and Lactonisation of α -D-Isosaccharinic Acid

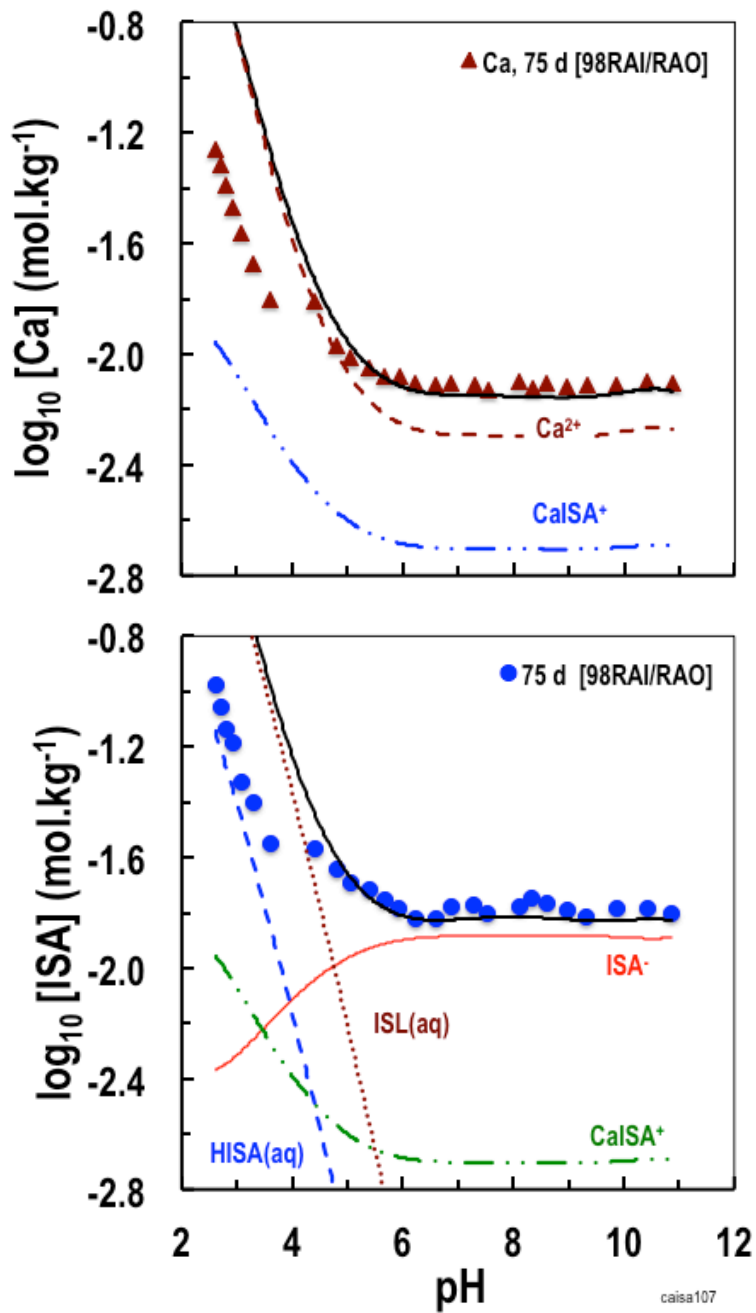


Figure 6.

Dhanpat Rai and Akira Kitamura

Evaluation of Equilibrium Constants for Deprotonation and Lactonisation of α -D-Isosaccharinic Acid