Coordination Chemistry Reviews 417 (2020) 213337

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Recent advances in the aqueous chemistry of the calcium(II)-gluconate system – Equilibria, structure and composition of the complexes forming in neutral and in alkaline solutions

Bence Kutus [a,c], Xavier Gaona [b,*], Attila Pallagi [c], István Pálinkó [c], Marcus Altmaier [b], Pál Sipos [c,*]

[a] Department of Molecular Spectroscopy, Max Planck Institute for Polymer Research, D-55131 Mainz, Ackermannweg 10, Germany
[b] Institute for Nuclear Waste Disposal, Karlsruhe Institute of Technology, P.O. Box 3640, D-76021 Karlsruhe, Germany
[c] Institute of Chemistry, Material and Solution Structure Research Group, University of Szeged, H-6720 Szeged, Dóm tér 7, Hungary

ARTICLE INFO

Article history:
Received 31 January 2020
Received in revised form 22 March 2020
Accepted 6 April 2020

Keywords:
Gluconic acid
Gluconate
Calcium
Complex formation
Solution structure
Equilibrium constants and thermodynamics
Lactonization
Acid-base equilibria
Hyperalkaline solutions

ABSTRACT

Of the sugar carboxylates, D-gluconate is clearly the most significant representative: the world's annual production of this organic compound is estimated to be in the order of 10^5 tonnes. The reason of its mass production is due to its outstandingly broad range of practical (medical, pharmaceutical, industrial, *etc.*) applications. D-gluconate is a well-known and exceptionally popular complexing agent; accordingly, it has been the subject of a large number of coordination chemical research investigations. Its complexation properties are specially remarkable in alkaline to hyperalkaline pH conditions, where the deprotonation of one or more of its alcoholic OH groups provides a favourable frame for the formation of very stable chelate complexes with a large variety of metal cations. With the aim to show the state of the art of some relevant issues in the aqueous chemistry of the D-gluconate ion, the current paper focusses on the acid-base properties and calcium(II) complexation of the compound encompassing the entire experimentally available pH-range in water. The accessible literature on the deprotonation of carboxylic and alcoholic OH groups is collected and critically evaluated. The lactonization equilibria of D-gluconic acid are also scrutinized. The available data on the calcium complexes forming in neutral and in (hyper)alkaline solutions (both in terms of composition, formation constants and solution structure) are also discussed. Where feasible, some of these properties are compared with those of D-glucose and its derivatives as well as some less common sugar carboxylates, structurally related to D-gluconate, (*i.e.*, D-heptagluconate, L-gulonate and α-D-isosaccharinate). Special emphasis is laid on the relationship between complex stability and the type of metal-binding groups.

Contents

* Corresponding authors.
E-mail addresses: xavier.gaona@kit.edu (X. Gaona), sipos@chem.u-szeged.hu (P. Sipos).

https://doi.org/10.1016/j.ccr.2020.213337
0010-8545/

1. Introduction

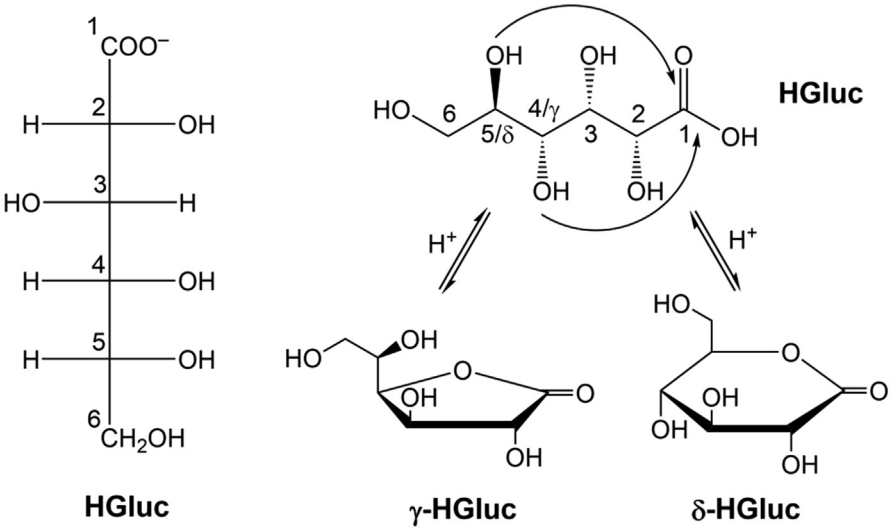
D-gluconic acid ((2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanoic acid, (HGluc, Scheme 1) is a polyhydroxy carboxylic acid with many applications in the food, pharmaceutical, dye, metal and cement industries, among others [1,2]. These applications are mostly related to its weak acidic character and the strong complexing capacity of its various deprotonated forms (including the D-gluconate anion, $Gluc^-$, and those containing alcoholate moieties, $GlucH_{-n}^{(n+1)-}$) forming under near-neutral to hyperalkaline (pH > 12) conditions. The enhanced stability of the gluconate complexes with respect to other monocarboxylic acids/salts is mainly due to the presence of alcoholic OH groups next to the carboxylate anchor group, giving rise to the formation of five-membered chelate rings. The chelate character of the gluconate complexes has been proposed in the literature for transition metals [1,3–10], lanthanides [11–14] and actinides [15–17], as well as for aluminium (III) [18–21], lead(II) [22,23] and calcium(II) [13,24–31], among others.

In the food and pharmaceutical industries, trace elements are often administered in the form of gluconate salts/complexes due to their ready absorption and appropriate tolerance by the body. Calcium(II) gluconate is used as a source of calcium for treating calcium deficiency by oral or intravenous treatment [2,32,33]. Iron(II/III) complexes with gluconate have been proposed as mediators for indirect electrochemical reduction of dyestuffs in textile dyeing processes ([34] and references therein). In this field, Bechtold and co-workers investigated the influence of Ca^{2+} ions on the redox chemistry of the Fe(III)/Fe(II) couple in the presence of $Gluc^-$. The study was motivated by the expected formation of binary (Ca(II)/gluconate) and ternary (Ca(II)/Fe(III)/gluconate) complexes altering the mediator properties of Fe(II/III) gluconate aqueous species, especially under alkaline conditions [35,36]. Note that the formation of similar type of ternary complexes with aldarate ligands (polyhydroxy dicarboxylates) was observed at basic pH for the systems Ca(II)/Al(III)/aldarate [37] and Ca(II)/B(III)/aldarate [38], respectively.

As for the metal industry, gluconate is commonly used in the galvanic deposition of nickel–cobalt onto aluminium, in the baths required for preparing surface plating of nickel, tin and zinc [1,39–41], but also as cleansing agent removing calcareous and rust deposits from metals or other surfaces (*e.g.*, galvanized iron, stainless steel, glass, among others) [1,2,42]. In many of these applications, gluconate is dissolved in very alkaline solutions. This combination benefits from the caustic nature of the solution and the ability of gluconate to solubilize calcium, magnesium and iron salts at high pH.

Sodium gluconate is widely used in the cement industry as an additive retarding the curing process. Gluconate-bearing cementitious materials retain a very high workability and plasticity, despite using a reduced content of water, and show increased stability upon setting [2,43–46]. The presence of gluconate in cement and concrete, and the planned use of these materials in some of the concepts for nuclear waste disposal (*i.e.*, repositories for low- and intermediate-level waste, L/ILW) have also brought awareness during the last two decades upon the complexation of gluconate with radionuclides and the potential mobilization of these complexes from the repository into the biosphere. Several studies have confirmed the strong complexation of gluconate with actinides (An) and fission products [47–57]. For An(III) and An(IV), these complexes are further stabilized in the presence of calcium, where the formation of ternary Ca(II)/An(III/IV) gluconate species has been proposed for Nd(III)/Cm(III) [58] and Th(IV) [59].

An accurate and complete knowledge of the thermodynamic properties of gluconate aqueous species and solid compounds arises as very useful in most of the gluconate applications summarized above. In spite of this, there is no recent comprehensive thermodynamic evaluation of the gluconate system available in the



Scheme 1. Chemical formula of D-gluconic acid (HGluc), as well its five- (γ-HGluc) and six-membered (δ-HGluc) lactones. Additionally, the nucleophilic attack of the OH group being the initial step in the acid-catalyzed lactonization is indicated.

literature. Sawyer reviewed all the literature published on gluconate until December 1963 and summarized the resulting thermodynamic data, although no critical evaluation of the original experimental studies was conducted by the author [1].

In similar terms, the last release of the NIST Standard Reference Database 46 in 2004 provided a very comprehensive compilation of thermodynamic data of gluconate (among many other organic ligands) and its complexes with many metal cations [60]. In the context of nuclear waste disposal, it is also noteworthy the work performed within the thermochemical database (TDB) project of the Nuclear Energy Agency (NEA). The 9th volume of this series was dedicated to the critical evaluation of the thermodynamic data available on the complexation of organic ligands with radionuclides relevant in nuclear waste disposal [61]. Although HGluc was not evaluated in this volume of the NEA–TDB, the review conducted on α-D-isosaccharinic acid ((2*S*,4*S*)-2,4,5-trihydroxy-2-(hydroxymethyl)pentanoic acid, HIsa, close analogue of HGluc) provides a very detailed overview of the type of complexes and stability expected for the former ligand.

Generally speaking, considerable knowledge has been accumulated on the coordination chemistry, that is: the structure and equilibria of complexes comprising polyhydroxy carboxylates and alkaline earth metal ions (in particular Ca^{2+}), forming in aqueous solutions of 2 < pH < 10 [13,24–27,29,62–70]. The interactions in this pH range involve weak chelation of the metal ion by the OH and COO^- functionalities, where the carboxylate moiety acts as anchor group. Usually, the formation constants of these simple, mononuclear 1:1, or in some cases 1:2 type stepwise calcium complexes are low. This situation changes dramatically under hyperalkaline conditions. In solutions of pH > 12, Ca^{2+} forms bi- and trinuclear complexes with $Gluc^-$ [26,28,30] as well as with a range of sugar carboxylate type ligands structurally related to $Gluc^-$ (*e.g.,* with D-heptagluconate and L-gulonate [30,71], but not with D-isosaccharinate [72]). These polynuclear Ca-complexes are of surprisingly high stability, so much so, that in solutions pH > 12, Ca^{2+} will be predominantly present in the form of complexes like $Ca_2L_2H_{-4}^{-2}$ (or $Ca_2LH_{-3}^{0}$) and $Ca_3L_2H_{-4}^{0}$ (besides, the minor species $CaLH_{-1}^{0}$ is formed to a minor extent). It is also noticeable that quite a few of these multinuclear species are charge-neutral.

The present work aims at providing a comprehensive review of the literature available for the aqueous solutions containing gluconate, calcium ions and supporting electrolytes (from dilute to highly saline) and encompassing the entire experimentally available pH-range (from acidic to hyperalkaine), from the perspective of solution thermodynamics and coordination chemistry. An attempt will be made to summarize the literature findings relating to the protonation (both carboxylate and alcoholate), lactonization and Ca(II) complexation of gluconate (Scheme 1). For the latter, close-to-neutral and hyperalkaline systems will be discussed separately. The structure of the complexes (both in the solution and in the solid state), when there are data available for them, will also be discussed. Also, the complexation properties of some gluconate-related ligands will be briefly assessed.

2. Deprotonation and lactonization equilibria of HGluc

2.1. General aspects and experimental methods

The protonation reaction of $Gluc^-$ and the corresponding equilibrium constants, ${K_p}^0$ and K_p, can be defined by the following equations:

$$Gluc^- + H^+ \rightleftharpoons HGluc \tag{1}$$

$${K_p}^0 = \frac{a_{HGluc}}{a_{Gluc^-} \cdot a_{H^+}} = \frac{\gamma_{HGluc}[HGluc]c^{\varnothing}}{\gamma_{Gluc^-}[Gluc^-] \cdot \gamma_{H^+}[H^+]} \tag{2}$$

$$K_p = {K_p}^0 \cdot \frac{\gamma_{Gluc^-} \cdot \gamma_{H^+}}{\gamma_{HGluc}} = \frac{[HGluc]c^{\varnothing}}{[Gluc^-][H^+]} \tag{3}$$

where ${K_p}^0$ is the thermodynamic protonation constant, referring to infinite dilution, expressed in terms of dimensionless activities (a), while K_p is the conditional protonation constant, expressed in terms of equilibrium molar concentrations (brackets) and $c^{\varnothing}$ is the standard molar concentration (1 mol·dm^{-3} or M). The activities and molar concentrations of a given species are connected via the so-called activity coefficients (γ). As for K_p, the term "conditional" means that the constant is valid only under the experimental conditions used for its determination (*i.e.*, a given ionic strength (I) and type of background electrolyte) [61]. In practice, it is desirable to keep the γ coefficients constant to avoid the variation of K_p throughout the measurement. Having these constants determined, ${K_p}^0$ is obtained by extrapolating them to infinite dilution ($I \rightarrow 0$).

The protonation equilibrium (Eq. (1)) has been widely investigated in the literature. Potentiometric techniques have been largely preferred to quantify this equilibrium, often in combination with polarimetric and coulometric methods. Recently, the use of NMR (^{1}H and ^{13}C) has gained relevance to study this system, especially in view of the ability of this technique to provide accurate speciation information based on the variation of the chemical shifts in the ^{1}H and ^{13}C NMR spectra of $Gluc^-$ and HGluc molecules. A relevant limitation of the technique is the high detection limit (at least millimolar range), imposing the use of relatively high gluconate concentrations in the experiment. In turn, this can affect the properties of the matrix solution and needs to be taken into account in the interpretation of the data.

Like other polyhydroxy carboxylic acids, such as HIsa and HGul, HGluc undergoes acid-catalyzed dehydration resulting in a formation of a 5- or 6-membered cyclic ester or lactone, γ-HGluc or δ-HGluc [73–82].

$$HGluc \rightleftharpoons \gamma\text{-}HGluc + H_2O \tag{4}$$

$${K_\gamma}^0 = \frac{a_{\gamma\text{-}HGluc} \cdot a_w}{a_{HGluc}} = \frac{\gamma_{\gamma\text{-}HGluc}[\gamma\text{-}HGluc] \cdot a_w}{\gamma_{HGluc}[HGluc]} \tag{5}$$

$$K_\gamma = {K_\gamma}^0 \cdot \frac{\gamma_{HGluc}}{\gamma_{\gamma\text{-}HGluc} \cdot a_w} = \frac{[\gamma\text{-}HGluc]}{[HGluc]} \tag{6}$$

$$HGluc \rightleftharpoons \delta\text{-}HGluc + H_2O \tag{7}$$

$${K_\delta}^0 = \frac{a_{\delta\text{-}HGluc} \cdot a_w}{a_{HGluc}} = \frac{\gamma_{\delta\text{-}HGluc}[\delta\text{-}HGluc] \cdot a_w}{\gamma_{HGluc}[HGluc]} \tag{8}$$

$$K_\delta = {K_\delta}^0 \cdot \frac{\gamma_{HGluc}}{\gamma_{\delta\text{-}HGluc} \cdot a_w} = \frac{[\delta\text{-}HGluc]}{[HGluc]} \tag{9}$$

where $K^0_{\gamma/\delta}$ and $K_{\gamma/\delta}$ are the lactonization constants at infinite dilution and at finite ionic strengths, respectively; a_w represents the activity of water. It is important to note that as in the case of K_p, $K_{\gamma/\delta}$ is expressed in terms molar concentrations; hence, their actual value depend on the ionic strength and the type of the inert electrolyte used [61].

Because the formation of a lactone involves the reorganization of the gluconic acid molecule, lactonization is a much slower process compared to the deprotonation of HGluc to form $Gluc^-$. Both lactones can form (Scheme 1), although several studies have indicated that the formation of δ-HGluc is kinetically favoured, at least under acidic conditions.

Due to the coupling of the protonation (Eq. (1)) and lactonization (Eqs. (4) and (7)) reactions, an adequate knowledge of the latter is necessary for the determination of log K_p. If sufficient time is allowed for both reactions to achieve equilibrium (typically ranging from hours to days, depending on the pH), and speciation techniques permit the quantification of protonation and lactonization processes, both log K_p and log $K_{\gamma/\delta}$ can be evaluated simultaneously. However, if equilibria are achieved but the experimental techniques do not allow distinguishing between HGluc and γ/δ-HGluc, an "apparent" protonation constant (log $K_{p,app}$) is determined according to the overall reaction:

$$Gluc^- + H^+ \rightleftharpoons HGluc^* \quad (10)$$

$$K_{p,app} = \frac{[HGluc^*]c^{\varnothing}}{[Gluc^-][H^+]} = \frac{([HGluc] + [\gamma\text{-HGluc}] + [\delta\text{-HGluc}])c^{\varnothing}}{[Gluc^-][H^+]} \quad (11)$$

where HGluc* represents all species (HGluc and γ/δ-HGluc) that are formed when the protonation of $Gluc^-$ takes place. Combining Eqs. (3), (6) and (9), the following relationship can be deduced:

$$\log K_{app} = \log K_p + \log(1 + K_\gamma + K_\delta) \quad (12)$$

Eq. (12) indicates that log $K_{p,app}$ > log K_p in all cases. In many of the available studies assessing protonation and lactonization reactions simultaneously (see Section 2.2), log K_p was determined from log $K_{p,app}$ and log $K_{\gamma/\delta}$. With this approach, the underestimation of the latter results in an overestimation of log K_p. Such an issue has been identified in several of the reviewed experimental studies, where the time considered in the experiment was insufficient to reach the equilibrium between HGluc and γ/δ-HGluc, especially in view of the very slow kinetics for the formation/hydrolysis of γ-HGluc (see Mitchell and Duke [75]). Motivated by the desire to describe the system under non-equilibrium conditions, too, several studies aimed at studying the time-dependence of the lactonization processes, utilizing polarimetry, coulometry, high-performance liquid chromatography or electrospray ionization mass spectrometry [74,75,77,78,81]. Since the reaction rates of the forward (lactone formation) and backward (lactone hydrolysis) are equal in equilibrium, the following relationship holds:

$$K_\gamma = \frac{k_{1,\gamma}}{k_{-1,\gamma}}; K_\delta = \frac{k_{1,\delta}}{k_{-1,\delta}} \quad (13)$$

where $k_{1,\gamma}$ and $k_{1,\delta}$ (s^{-1}) are the rate coefficients for lactone formation, and $k_{-1,\gamma}$ and $k_{-1,\delta}$ (s^{-1}) are those for lactone hydrolysis. In most cases, $k_{-1,\delta}$ was determined for the fast hydrolysis of δ-HGluc. Given that K_δ is known from independent measurements, $k_{1,\delta}$ can be calculated.

On the other hand, the slow lactonization kinetics as compared to the rapid protonation represents an advantage for the determination of log K_p when approaching the system with fast titrations, starting from alkaline conditions. This approach allows for the study of the thermodynamic equilibrium between HGluc and $Gluc^-$ without generating significant amounts of γ/δ-HGluc, and thus provides more accurate values of log K_p at the cost of disregarding the quantification of log $K_{\gamma/\delta}$.

Furthermore, the accurate determination of log K_p is indispensable when studying complex formation reactions under acidic conditions. Since both H^+ and the metal ion compete for the COO^- group of $Gluc^-$, the protonation and complexation reactions are not independent from each other. Consequently, using an inaccurate value of log K_p yields an inaccurate binding constant for Ca^{2+}, too.

In the following Section, all log K_p and log $K_{\gamma/\delta}$ constants as well as the $k_{1,\gamma/\delta}$ and $k_{-1,\gamma/\delta}$ rate coefficients reported in the literature are listed in Tables 1 and 2, respectively. Furthermore, the meanings of the different terms of pH used throughout this work are the following: pH will be used when it is discussed in a general context, pH_c is referred to as –log ($[H^+]/c^{\varnothing}$), while pH_{obs} means the experimentally observed value, recorded directly from the pH meter. The latter differs from pH_c, when the calibration and the measurements are performed at different ionic strengths and/or in different medium. Namely, these parameters affect the activity of H^+ and the liquid junction potential of the electrode, hence pH_{obs} [61].

2.2. Review of available thermodynamic data for the system γ/δ-HGluc/HGluc/Gluc⁻

The pioneering work in the field was reported by Cannan and Kibrick [62], who studied the complex formation between $Gluc^-$ (among other carboxylates) and Zn^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+} as well as Ba^{2+} in acidic medium. The authors determined also log K_p in

Table 1
Conditional protonation constants (log K_p, Eq. (3)) reported in the literature, organized by increasing background electrolyte concentration. The data correspond to t = 25 °C unless indicated differently. Where reported, triple standard errors are included in parentheses.

Background electrolyte	log K_p	Reference	Method[a]
$I \rightarrow 0$	3.85[c]	Mitchell and Duke [75]	POL/POT
$I \rightarrow 0$	3.77(6)[d]	Pocker and Green [77]	POL/POT
$I \rightarrow 0$	3.92(10)[c]	Zubiaur et al. [79]	POT
0.015 M KCl	3.86	Heinz [83][f]	POT
0.1 M NaCl	3.46(6)[e]	Best et al. [19][e]	POT
0.1 M $NaClO_4$	3.50(9)	Gajda et al. [10]	POT
0.1 M $NaClO_4$	3.70(1)	Zubiaur et al. [79]	POT
0.1 M $NaClO_4$	3.47(2)	Giroux et al. [11]	POT
0.1 M $NaNO_3$	3.40(3)	Escandar and Sala [7][f]	POT
0.1 M KNO_3	3.439(3)	Motekaitis and Martell [18]	POT
0.1 M KNO_3	3.66	Bechtold et al. [35][f]	POT
0.1 M NaGluc/HGluc	3.30(6)	Zhang et al. [81][f]	^{13}C NMR/POT
0.15 M $NaClO_4$	3.57	Roos and Williams [84][f]	POT
0.2 M KCl	3.56	Cannan and Kibrick [62][f]	POT
0.2 M KCl	3.36(2)	Lakatos et al. [20]	POT
0.5 M $NaClO_4$	3.60(2)	Zubiaur et al. [79]	POT
0.5 M KNO_3	3.56(9)	Blomqvist and Still [6]	POT
1 M NaCl	3.23(3)	Pallagi et al. [25]	^{1}H NMR/POT
1 M NaCl	3.24(3)	Pallagi et al. [25]	^{13}C NMR/POT
1 M NaCl	3.35(1)	Kutus et al. [14]	POT/UV-vis
1 M NaCl	3.37(3)	Kutus et al. [82]	POT
1 M NaCl	3.26(6)	Kutus et al. [82]	POL/POT
1 M $NaClO_4$	3.63(1)	Zubiaur et al. [79]	POT
1 M $NaClO_4$	3.48(18)	Coccioli and Vicedomini [85]	POT
1 M $NaClO_4$	3.30(10)	Zhang et al. [16]	^{13}C NMR/POT
2 M $NaClO_4$	3.71(2)	Zubiaur et al. [79]	POT
3 M $NaClO_4$	3.85(1)	Zubiaur et al. [79]	POT
4 M NaCl	3.73(5)	Kutus et al. [31]	POT
[b]	3.70(5)	Sawyer and Bagger [74]	POL/POT

[a] NMR = nuclear magnetic resonance spectroscopy, POL = polarimetry, POT = potentiometry applying glass electrode (except for Ref. [62], where H_2-Pt electrode was used), UV-vis: spectrophotometry.
[b] Measurements were performed in pure lactone solutions or in solutions with several different buffers (sodium formate/formic acid, potassium hydrogen phthalate) and concentrations (0.05–0.89 M). The log K_p is given as the average of values obtained in different samples
[c] Thermodynamic protonation constant (log K_p^0, Eq. (2)), obtained by extrapolating data for log K_p to infinite dilution.
[d] Thermodynamic protonation constant (log K_p^0, Eq. (2)), obtained experimentally.
[e] Suggested to be log $K_{p,app}$ instead of log K_p by the authors of Ref. [19].
[f] The temperature was not indicated in Refs. [62] and [83]. The temperature was 20 °C in Refs. [7] and [35], 22 °C in Ref. [81] and 37 °C in Ref.[84]

Table 2
Kinetic rate coefficients of formation ($k_{1,\gamma/\delta}$) and hydrolysis ($k_{-1,\gamma/\delta}$) of γ- and δ-HGluc (Eq. (13)), respectively, and conditional equilibrium constants for the lactonization of HGluc (log $K_{\gamma/\delta}$, Eqs. (6) and (9)); organized by increasing background electrolyte concentration. The data correspond to t = 25 °C unless indicated differently. Where reported, triple standard errors are included in parentheses.

Reaction	Bacground electrolyte	$k_{1,\gamma/\delta}$ / s^{-1}	$k_{-1,\gamma/\delta}$ / s^{-1}	log $K_{\gamma/\delta}$	Reference	Method[a]
HGluc ⇌ γ-HGluc + H_2O	0.8 M NaCl			−0.68(3)	Kutus et al. [82]	^{13}C NMR
	[b]	$k_1^{\gamma} + k_{-1}^{\gamma} = 4.3\cdot10^{-4}$ [H^+]		−0.59(6)	Mitchell and Duke [75]	POL/POT
	[c]			−0.62[c]	Felty [76]	GC
HGluc ⇌ δ-HGluc + H_2O	$I \rightarrow 0$			−0.95[g]	Pocker and Green [77]	POL/POT
	$I \rightarrow 0$			−0.81(9)[h]	Zubiaur et al. [79]	POT
	≈ 0.01 M[d]	$3.807\cdot10^{-5}$[d]	$1.730\cdot10^{-4}$[d]	−0.66[d]	Combes and Birch [78]	POL
	0.05 M NaGluc[e]	$3.2\cdot10^{-5}$[e]	$1.1\cdot10^{-4}$[e]		Zhang et al. [81]	ESI-MS/^{13}C NMR/POT
	0.1 M $NaClO_4$			−0.91(6)	Zubiaur et al. [79]	POT
	0.1 M $NaClO_4$			−0.54(12)[e]	Zhang et al. [81]	^{13}C NMR/POT
	0.5 M $NaClO_4$			−0.93(10)	Zubiaur et al. [79]	POT
	0.8 M NaCl			−0.65(1)	Kutus et al. [82]	^{13}C NMR
	1 M $NaClO_4$			−1.15(6)	Zubiaur et al. [79]	POT
	2 M $NaClO_4$			−1.35(12)	Zubiaur et al. [79]	POT
	3 M $NaClO_4$			−1.90(33)	Zubiaur et al. [79]	POT
	[f]	$2.3\cdot10^{-5}$[f]	$1.78\cdot10^{-4}$[f]	−0.89[f]	Sawyer and Bagger [74]	COUL/POL/POT
	[b]	$k_1^{\delta} + k_{-1}^{\delta} = 5.5\cdot10^{-2}$ [H^+]		−0.73(3)	Mitchell and Duke [75]	POL/POT
	[b]	$k_1^{\delta} = 4.7\cdot10^{-2}$ [H^+] + $4\cdot10^{3}$ [OH^-] + $2.5\cdot10^{-4}$		−0.73(3)	Mitchell and Duke [75]	POL/POT
	[c]			−0.67[c]	Felty [76]	GC

[a] COUL = coulometry, ESI-MS: electrospray ionization mass spectrometry, GC = gas chromatography using flame ionization detector, NMR = nuclear magnetic resonance spectroscopy, POL = polarimetry, POT = potentiometry applying glass electrode.
[b] Measurements were performed with several concentrations of lactone (up to 0.2 M), HCl (up to 0.1 M) and NaCl (up to 0.3 M).
[c] Measurements were performed with several concentrations of lactone (up to 0.7–0.9 M). The log $K_{\gamma/\delta}$ constants are given as the average of values obtained in different samples.
[d] Refers to a solution containing ≈ 0.02 M HGluc and ≈ 0.01 M δ-HGluc, at pH_c ≈ 2.4. The log K_{δ} was calculated in this work from the $k_{1,\delta}$ and $k_{-1,\delta}$ rate coefficients. The temperature was 20 °C.
[e] pH_c ≈ 5.0. The $k_{1,\delta}$ coefficient was calculated internally from K_{δ} and $k_{-1,\delta}$, respectively. The temperature was 22 °C.
[f] Measurements were performed with several concentrations of pure or half-neutralized lactone (up to 0.2 M). The $k_{1,\delta}$ coefficient was calculated internally from K_{δ} and $k_{-1,\delta}$, respectively. The $k_{-1,\delta}$ coefficient is the average of those obtained by COUL as well as POL.
[g] Thermodynamic lactonization constant (log K_{δ}^{0}, Eq. (8)), obtained experimentally.
[h] Thermodynamic lactonization constant (log K_{δ}^{0}, Eq. (8)), obtained by extrapolating data for log K_{δ} to infinite dilution.

Table 3
Specific rotations of the two lactones of gluconic acid, γ-HGluc and δ-HGluc and those of the open-chain forms, HGluc and $Gluc^-$ as reported by various authors. These values were determined in the temperature range of 20–25 °C. Where reported, triple standard errors are included in parentheses.

γ-HGluc	δ-HGluc	HGluc	$Gluc^-$	Reference
–	+66.0°	+5.40°	+12.0°	Sawyer and Bagger [74]
+72.0°	+80.0°	−3.8°	+15.7°	Mitchell and Duke [75]
–	+66.3°	+5.80°	+15.0°	Pocker and Green [77]
–	–	−5.11°	–	Combes and Birch [78]
–	–	−5.7(8)°	+13.0(3)°	Kutus et al. [82]

0.2 M KCl for all the carboxylic acids under investigation. The titrations were conducted from acidic to alkaline conditions using NaOH as titrant. In the case of gluconate and despite working within the pH_c range 3–4.5, the authors did not consider the lactone formation in their data evaluation. Furthermore, the description of further relevant experimental details (*e.g.*, the length of the potentiometric titration) is missing in the paper. The value of log K_p reported by the authors is considered in this review to be higher than the real protonation constant.

Heinz [83] performed potentiometric titrations with HGluc (among other carboxylic acids) in the absence and presence of Ca^{2+}. The titrations were carried out in the pH_c range of 3–6, using 0.015 M KCl as background electrolyte. Although the length of the measurement was not indicated in the paper, the titration from acidic to alkaline conditions likely promoted the presence of relevant amounts of lactones in the system. Since the lactonization was not considered, the log K_p reported by Heinz is presumably overestimated.

Sawyer and Bagger [74] carried out a very comprehensive study on the lactone-acid-salt equilibria of HGluc combining polarimetric, potentiometric and coulometric methods. In the first step, the authors equilibrated the aqueous solutions of pure and half-neutralized δ-HGluc for 72 h, and determined the "apparent" dissociation constant (= −log $K_{p,app}$) by measuring the pH_c. In the second step, the authors measured the optical rotation of lactone samples of different concentrations, equilibrated again for 72 h. The pH_c values ranged between 2.36 and 3.96 and were set using organic buffers of different concentrations. Using the molar rotation of δ-HGluc, HGluc and $Gluc^-$ (also discussed in this review, see Table 3) and considering the value of −log $K_{p,app}$, the authors were able to determine log K_p and log K_{δ}.

The rate of δ-HGluc hydrolysis was also quantified by polarimetry and coulometry with and without the use of organic pH buffers, respectively. Significantly divergent rate constants were determined depending on the pH_c, as well as on the buffer and experimental method used. Despite the comprehensiveness of this study, the log K_p and log K_{δ} data reported by the authors are considered inaccurate due to the insufficient equilibration time considered in the experiment (see Mitchell and Duke [75]) and the limitations in the calibration/measurement of molar rotations (see Combes and Birch [78] and Table 3).

Mitchell and Duke [75] studied the equilibrium and kinetics of γ-HGluc and δ-HGluc hydrolysis using a combination of polarimetric and potentiometric techniques. The authors employed 0.1 M HCl and several pH buffers of different concentration to set the pH_c in the polarimetric characterization of the lactone hydrolysis.

The authors calculated log $K_{p,app}$ as well as log K_γ and log K_δ at different ionic strengths, which allowed them to obtain log K_p. They found that only log K_p depends on the ionic strength, and they extrapolated their data to determine the thermodynamic constant at infinite dilution. The specific rotations reported by the authors for δ-HGluc, HGluc and $Gluc^-$ differ significantly from those reported in Sawyer and Bagger [74] (Table 3). In contrast to Sawyer and Bagger, the authors observed that γ-HGluc becomes relevant after sufficiently long equilibration times, and concluded that a contact time of 72 h (as considered by Sawyer and Bagger) was insufficient to attain thermodynamic equilibrium within the system γ/δ-HGluc/HGluc. The authors also observed that $k_{-1,\delta}$ is strongly dependent on $[H^+]$ and $[OH^-]$, and thus different contact times are required for the equilibration of the system at different pH_c. Also, the authors suggested the lactone hydrolysis to take place *via* an uncatalyzed, an acid- and a base-catalyzed pathway, respectively.

Felty [76] studied the lactonization equilibria of numerous aldonic acids, including HGluc. To separate the free acid and the two lactones as well as to determine their concentrations, GC analyses were carried out for the *O*-trimethylsilylated derivatives. The results obtained at 25 °C agree very well with those of Mitchell and Duke [75] and Kutus et al. [82], respectively. Extending the temperature range from 0 to 45 °C, valuable insights into the thermodynamics of lactonization were gained. Namely, that the lactone formation reaction is endothermic (*i.e.*, it becomes more favorable with increasing temperature) and accompanied by an increase in the entropy. Being lactonization *de facto* a dehydration process explains the positive enthalpy change. Furthermore, the overall number of molecules increases during the reaction, yielding positive entropy. It can also be concluded from these thermodynamic parameters that the formation of γ/δ-HGluc is enthalpy-driven.

Pocker and Green [77] investigated the hydrolysis of δ-HGluc by means of polarimetry, potentiometry and spectrophotometry. Contrary to Mitchell and Duke [75], the authors determined specific rotations for δ-HGluc, HGluc and $Gluc^-$ to be very similar to those reported by Sawyer and Bagger. The samples were equilibrated for 72 h before the reading of the optical rotation. Similarly to the case of Sawyer and Bagger [74], log K_p and log K_δ data reported by the authors are considered inaccurate due to the insufficient equilibration time considered in the experiment and the limitations in the calibration/measurement of molar rotations (see Combes and Birch [78] and Table 3). The authors also evaluated the kinetics of δ-HGluc hydrolysis, and concluded that the overall pseudo-first-order rate constant includes an uncatalyzed (zeroth order) component. Additionally, $k_{-1,\delta}$ is a function of $[H^+]$ and $[OH^-]$, but also of the type and concentration of the pH buffer in solution. Consequently, the hydrolysis of δ-HGluc takes place *via* general acid/base catalysis, in line with previous findings of Sawyer and Bagger [74] as well as Mitchell and Duke [75].

Roos and Williams [84] conducted a series of potentiometric experiments to assess the acid-base properties of citric, folic, gluconic and succinic acid and the corresponding complexation with Mn, Zn and Fe. All experiments were performed in 0.15 M $NaClO_4$ at 37 °C. The log K_p reported by the authors is also included in Table 1, although acknowledging the relevant differences expected with respect to thermodynamic functions derived at t = 25 °C.

Coccioli and Vicedomini [85] studied the protonation of $Gluc^-$ and the complex formation with Pb(II) by a series of potentiometric titrations in the pH_c range of 1.5–5, using 1.0 M $NaClO_4$ as inert electrolyte. No account of the equilibration time allowed for each titration point was provided by the authors. Coccioli and Vicedomini acknowledged the possible formation of γ-HGluc and/or δ-HGluc under more acidic conditions, and therefore disregarded all experimental points with $pH_c \leq 3.5$ in the fitting process to determine log K_p. Remarkable quantities of lactone (5–15%) are expected to co-exist with HGluc at $pH_c \leq 4.5$, especially if titration has been initiated from the acidic range. Consequently, the log K_p reported by Coccioli and Vicedomini is likely an overestimation of the protonation constant.

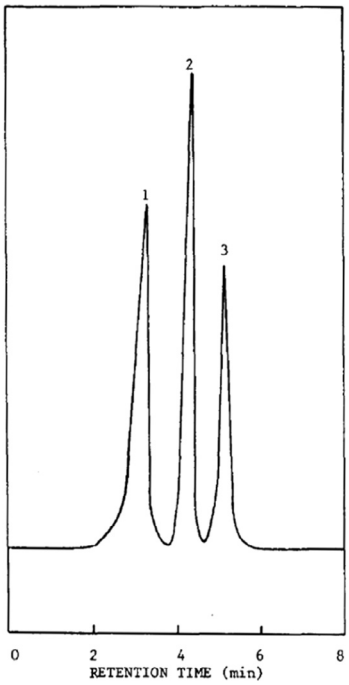


Fig. 1. HPLC analysis of (1) D-gluconic acid and its (2) γ- and (3) δ-lactones. Column: Dextropak; t = 20 °C; eluent: water. Reproduced with permission [78], Copyright 1988 Elsevier.

Motekaitis and Martell [18] investigated the complexes of Al(III) with hydroxycarboxylic acids by means of potentiometric titrations. The authors also assessed the log K_p of the carboxylic acids studied. In both cases, 0.1 M KNO_3 and KOH were used as background electrolyte and titrant solution, respectively. Titrations were performed within $2 \leq pH_c \leq 11$, but no information on the equilibration time allowed for each titration point was provided in the paper. In the case of HGluc, the possible formation of γ/δ-HGluc was not considered in the interpretation of the acid-base equilibrium. Provided that the titration of gluconate accomplished from acidic to alkaline conditions, significant quantities of lactone are to be expected below pH_c = 4.5.

Blomqvist and Still [6] assessed the complexation of Cu(II) and Cd(II) with $Gluc^-$, and complemented their study with the determination of log K_p. Potentiometric titrations were performed with KOH at t = 25 °C, using 0.5 M KNO_3 as background electrolyte. The concentration of H^+ was calculated from the pH readings using the relationship $pH_c = pH_{obs} - 0.14$. Although expected at $pH_c \leq 4.5$, the possible formation of γ/δ-HGluc was not considered in the calculations of log K_p. Neither pH_c range nor length of the titrations were reported in the manuscript. The log K_p value determined by the authors (Table 1) is likely to be overestimated due to the contribution of the lactonization reaction.

Combes and Birch [78] conducted a very comprehensive study on the hydrolysis of δ-HGluc using HPLC (Fig. 1), optical rotation and conductometry. As previously indicated by Pocker and Green [77], Combes and Birch confirmed the strong impact of the background electrolyte on the optical properties of gluconate and its derivatives. Hence, the specific rotation of HGluc in pure water was quantified as –5.11°, in contrast to the values of Sawyer and Bagger [74] as well as Pocker and Green [77], but in agreement with the one reported by Mitchell and Duke [75] as well as Kutus

et al. [82] (Table 3). This indicates that previous publications [74,77] using higher specific rotation of HGluc likely overestimated its concentration, thereby overestimating log K_p and underestimating log K_δ. The authors were able to quantify $k_{1,\delta}$ and $k_{-1,\delta}$ for the δ-lactonization of HGluc (*via* polarimetry), and also demonstrated that 140 h are not sufficient to reach the equilibrium of the formation of γ-HGluc.

Escandar and Sala [7] studied the dissociation constant of HGluc and its complexes with Cu(II) by potentiometry. Experiments were performed at t = 20 °C using 0.10 M $NaNO_3$ as background electrolyte. Both solid NaGluc and δ-HGluc were used as initial source of gluconate, dissolved in standard base and back-titrated by stepwise addition of standard acid. Both titration curves led to similar results (Table 1). The back-titration approach is considered to provide reliable log K_p due to the minimization of the presence of lactone in the aqueous solution.

Best et al. [19] assessed the acid-base properties of gluconate (among other hydroxycarboxylic acids) and its complexation with Al(III) using a series of potentiometric titrations in 0.1 M NaCl. δ-HGluc was chosen as initial source of gluconate in the experiments. The authors indicated that 3 to 4 h were necessary for the equilibration of some titration points, although no exact reference is provided to the case of gluconate. Best and co-workers did not specify either whether HCl or NaOH were used as titrating solutions, although the good agreement with other studies suggests that a back-titration with HCl was performed. Due to the use of δ-HGluc as source of gluconate, the authors indicated that log $K_{p,app}$ rather than log K_p was obtained from their experimental data.

Gajda et al. [10] investigated the role of hydroxy groups in the coordination chemistry of polyhydroxy carboxylic acids, including HGluc. Using potentiometric titrations at t = 25 °C and I = 0.1 M $NaClO_4$, the authors determined the log K_p of $Gluc^-$. In the case of aldonic acids (such as HGluc), a back-titration with $HClO_4$ starting from alkaline pH was used to avoid the error caused by lactonization.

Zubiaur et al. [79] studied the equilibrium δ-HGluc/HGluc/$Gluc^-$ by means of potentiometric titrations. The authors conducted their experiments in 0.1 M $\leq I \leq$ 3.0 M $NaClO_4$. All titrations were performed from acidic to alkaline conditions, starting in all cases from δ-HGluc. The authors observed strong kinetic effect on the pH readings within 3.8 $\leq pH_c \leq$ 6.5, and consequently allowed an equilibration time of 4 h for each titration step and thus approximately 2 weeks for each titration series. The authors, however, did not use any speciation technique to identify the different gluconate species in solution, but they assumed the lactonization reaction to be the formation δ-HGluc and they fitted their potentiometric data optimizing log K_p and log K_δ at different ionic strengths. This approach allowed them to obtain the thermodynamic constants by extrapolating the conditional constants to zero ionic strength.

Giroux et al. [11] combined potentiometry, UV–vis spectrophotometry, circular dichroism experiments as well as ^1H and ^{13}C NMR to assess the acid-base properties of $Gluc^-$ and its complexes with Pr(III). Experiments were performed in 0.1 M $NaClO_4$ at t = 25 °C *via* performing potentiometric titrations under acidic to alkaline conditions. A fast initial acidification of the starting gluconate solution and the optimization of the titration speed (to avoid lactone formation and allow a good stabilization of the measurements) were considered to minimize the interference caused by lactonization. The log K_p reported in this publication is in good agreement with other potentiometric studies conducted by back-titration, indicating that the authors probably succeeded in minimizing the amount of γ/δ-HGluc in their experiments.

Bechtold et al. [35] studied the stability of Ca(II)/Fe(III) gluconate complexes and their electrochemical properties by a series of potentiometric titrations. As a first step in the study, the authors determined the acidity constant of HGluc in the absence of calcium (II) and iron(III). Experiments were performed at t = 20 °C in 0.1 M KNO_3 as background electrolyte. Titrations were conducted within $2 \leq pH_c \leq 11.6$ using a back-titration approach with 0.1 M HNO_3. Considering the overall short duration of one measurement (~1 h), the log K_p determined in this work is realistic.

Zhang et al. [16] studied the protonation of gluconate and its complexation with Np(V) in acidic to near neutral pH conditions using potentiometric titrations and UV–vis spectrophotometry. Experiments were performed in 1.0 M $NaClO_4$ at t = 25 °C. Fast potentiometric back-titrations (60 s per titration point) were conducted at $3 \leq pH_c \leq 6$ with $HClO_4$ (Fig. 2). This approach was aimed at minimizing the impact of lactonization on the determination of log K_p.

Zhang et al. [81] investigated the lactonization and deprotonation of HGluc using ^{13}C NMR, potentiometric titrations and ESI–MS techniques. ^{13}C NMR measurements were performed to assess the equilibrium described in Eq. (1). All samples were prepared in D_2O, whereas DNO_3 and NaOD were used to adjust the pH. All solutions were prepared as 0.1 M NaGluc and let equilibrate for 3 days. Provided the very slow kinetics of the lactonization/hydrolysis reactions, the lactone ^{13}C NMR peaks (both for γ-HGluc and δ-HGluc) appear separately from those of HGluc/$Gluc^-$. Furthermore, the peak positions of the lactones are pH-independent. Consequently, given the pH_c is known, log K_p can be deduced from the variations of the chemical shifts of HGluc/$Gluc^-$, regardless of the amount of lactones formed. This property renders NMR spectroscopy to be an important tool to study acid-base equilibria without the interference of the lactonization.

Independent batch samples of different pH_c and at constant concentration of NaGluc (0.05 M) were prepared in 0.1 M $NaClO_4$ and let equilibrate for at least 3 days. The concentration of the hydrogen ion in each solution was measured with a combination pH electrode, and the resulting log $K_{p,app}$ apparent data were fitted taking log K_p determined by ^{13}C NMR into consideration. This approach made the determination of log K_δ possible, however, a discrepancy has been identified affecting the estimation of log K_δ, which was quantified using log K_p and log $K_{p,app}$ determined in

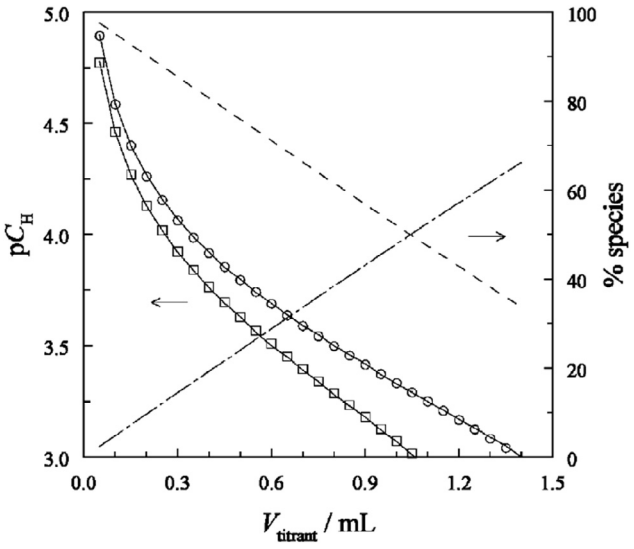


Fig. 2. Potentiometric titrations of the protonation of gluconate at t = 25 °C and I = 1.0 M $NaClO_4$. Titrant: 0.9893 M $HClO_4$. Symbols represent the experimental data (titration I (o): $[NaGluc]_T$ = 0.025 M, V_0 = 41 mL and II (□): ($[NaGluc]_T$ = 0.048 M, V_0 = 42 mL), while solid lines stand for the fitted values of $pC_H = -\log([H^+]/c^o)$. The dashed and dotted-dash line represent the % of $Gluc^-$ and HGluc calculated for titration II. Reproduced with permission [16], Copyright 2006 de Gruyter.

different background electrolytes of the same ionic strength (0.1 M NaGluc and $NaClO_4$).

In the final step, Zhang and co-workers determined the rate coefficient of the δ-lactonization of HGluc ($k_{1,\delta}$) by ESI–MS (Fig. 3). Based on Eq. (13) and using the value of log K_δ determined by potentiometry, the authors were also able to calculate the rate constant of the lactone hydrolysis ($k_{-1,\delta}$).

Lakatos and co-workers [20] reported on the complexation of $Gluc^-$ with Al(III) in the pH_c range of 2–10 at t = 25 °C and I = 0.2 M KCl. They calculated log K_p by conducting potentiometric titrations starting from acidic pH. To avoid lactonization, the samples were acidified just before the measurements. Additionally, the pH_c was always kept higher than 2, hence, the rate of lactonization / lactone hydrolysis processes was expected to be markedly slower than that of protonation / deprotonation reactions.

Pallagi et al. [25] studied the acid-base properties of gluconate and its complexation with Ca^{2+} using ^1H, ^{13}C and ^{43}Ca NMR. Experiments were performed in 1.0 M NaCl–NaGluc mixtures, with 0.2 M NaGluc in most of the cases. D_2O was present in all samples in a concentration of 20% v/v. The pH of the mixture solution was calculated as $pH_{mixt} = pH_{obs} + 0.08$, considering that pD = pH + 0.40, independently of the ionic strength. It is noteworthy that pH_{mixt} is not equal to pH_c as it was recorded in solutions of I = 1 M, while the electrode was calibrated with dilute buffer solutions. The protonation constant of $Gluc^-$ was obtained from the variations of the ^1H and ^{13}C NMR chemical shifts upon decreasing the pH_{mixt} from ~6.6 to ~1.8. As in the case of Zhang et al. [81], Pallagi and co-workers observed the development of additional lactone peaks in the ^{13}C NMR spectra upon decreasing the pH_{mixt} below ~3.8.

Kutus et al. [14] studied the complexation of gluconate with neodymium(III) at $2 \leq pH_c \leq 8$ using a combination of experimental methods (spectrophotometry, potentiometry, freezing point depression, conductometry and NMR spectroscopy). Because of the pH_c range considered for the study of the complexation, the authors determined the protonation constant of $Gluc^-$, too, by fitting the potentiometric and photometric data simultaneously. Titrations were performed with HCl and started from weakly alkaline conditions to minimize the impact of lactonization, while in the case of photometric measurements, the spectra were recorded directly after sample preparation.

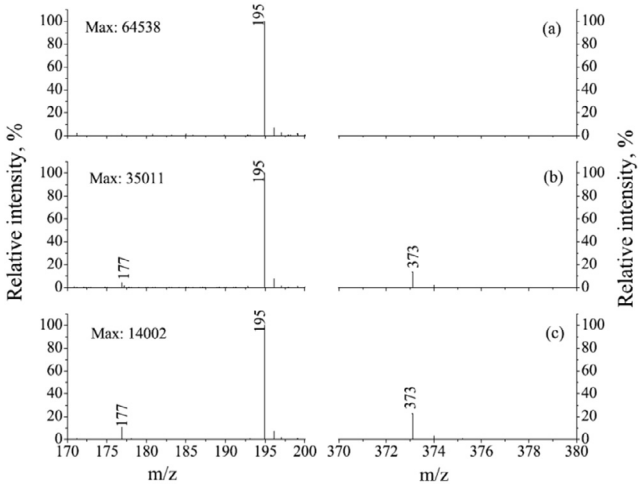


Fig. 3. Mass spectra of acidified gluconate samples at $[NaGluc]_T$ = 0.05 M and at different $pC_H = -\log([H^+]/c^o)$ values: (a) 0.0% acidification and pC_H = 6.2; (b) 50% acidification and pC_H = 4.3; (c) 100% acidification and pC_H = 3.3. m/z = 175: lactone anion with deprotonated hydroxyl group; m/z = 373: lactone adducted by gluconate. Reproduced with permission [81], Copyright 2007 Springer Verlag.

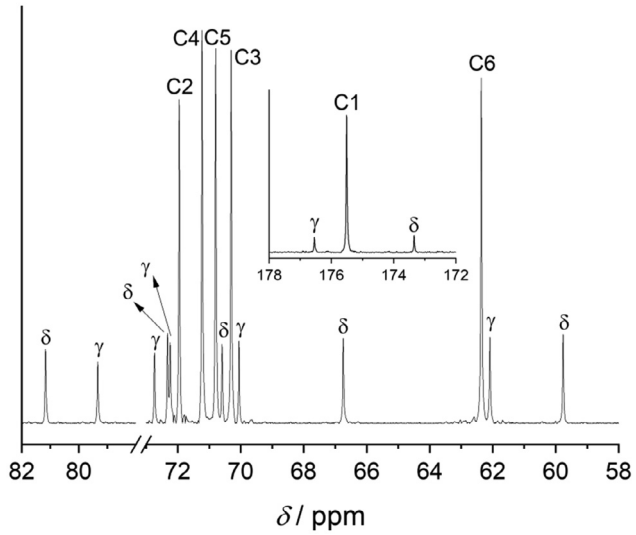


Fig. 4. ^{13}C NMR spectra of HGluc (C1–C6) and its γ- and δ-lactones. Experimental conditions: t = 25 °C, I = 0.8 M (NaCl), 20 %V/V D_2O; $[NaGluc]_T$ = 0.320 M, $[HCl]_T$ = 0.369 M. The figure has been replotted based on the data of Ref. [82].

Kutus and co-workers performed a comparative study on the protonation and lactonization of HGul and HGluc using various experimental methods [82]. Fast potentiometric titrations and polarimetric measurements were used for the quantification of the protonation equilibria. Based on their polarimetric measurements, the authors reported the specific rotation of HGluc in 1.0 M NaCl as –(5.7 ± 0.8)°. This value agrees well with the specific rotation reported by Combes and Birch [78] in pure water (–5.11°).

Additionally, the pH-dependence of the specific rotation of the $HGluc/Gluc^-$ system was used to calculate log K_p. As opposed to the potentiometric titrations, the pH_{obs} (measured together with the optical rotation) is not equal to pH_c, as in the case of Pallagi et al. [25]. Thus, the difference between pH_{obs} and pH_c is a plausible explanation for the discrepancy between log K_p(POL) and log K_p(POT) (Table 1). The latter was chosen as the real protonation constant by the authors and within experimental error, it is identical with the one obtained by the same group at I = 1 M NaCl [14].

Furthermore, ^{13}C NMR spectroscopy was used to distinguish between the two lactones and to determine log K_δ and log K_γ (Fig. 4). The values reported in this work are in good agreement with those from Refs. [75,76,78,81]. Furthermore, they clearly show that the lactones are formed to the same extent. Using log K_p(POT) as well as the two lactonization constants, the value of 3.53 is obtained as log $K_{p,app}$, which is higher by 0.16 than log K_p(POT). This difference sets an upper limit to which extent the log K_p can be overestimated at I = 1 M NaCl by neglecting lactonization equilibria.

Kutus et al. [31] reported on the complexation of gluconate with Mg^{2+} ions in the pH_c range of 2–13 studied by potentiometry, infrared, ^1H and ^{13}C spectroscopies. As for the pH_c measurements, fast titrations were performed at t = 25 °C and I = 4 M using NaCl as background electrolyte. Using the data obtained in the acidic range, the authors deduced log K_p.

In summary, a plethora of data regarding the protonation of gluconate and the lactonization of gluconic acid have accumulated over the past five decades. It is apparent from the magnitude of the lactonization constants that under strongly acidic conditions, the formation of γ- and δ-lactones has to be taken into account for a proper thermodynamic description of gluconate-containing

systems. Resolving the parallel (de)protonation, γ- and δ-lactone formation (or reverse hydrolysis) processes is possible with careful experimentation as well as with the combination of various experimental means, including NMR spectroscopy. As for the lactonization kinetics, the formation δ-HGluc is much faster. Despite this, the formation constants of γ- and δ-HGluc are essentially the same (within their reported uncertainties), indicating that (*via* Eq. (13)) the hydrolysis of the γ-isomer is much slower. The higher stability of the five-membered ring is in line with the observaation made for the diastereomeric L-gulonic acid γ-lactone [82].

3. Ca(II) complexation of $Gluc^-$ in neutral solutions

3.1. Formation and stability of $CaGluc^+$ and $CaGluc_2^0$ complexes and some of their analogues in near-neutral to slightly alkaline conditions

Carbohydrates and their derivatives (*e.g.,* aldoses, ketoses, sugar alcohols) interact weakly with calcium as well as with other alkaline earth metal ions. This is due to the relatively low electron density of the oxygen donor atoms, present in hydroxy, formyl and oxo groups, which are not strong competitors of the H_2O molecules bound to the metal ion. Consequently, the complexes, which are formed in weakly acidic to weakly alkaline solutions are of low stability and are of almost exclusively 1:1 stoichiometry [86].

As for Ca(II) complexes, these features lead to difficulties in the quantitative characterization of complexation equilibria with conventional methods (such as potentiometry, spectrophotometry, conductometry and calorimetry). First, the use of high metal and ligand concentrations is required. Second, such complexes are not detectable by UV–vis. A further complication is associated with the simultaneous formation of conformational isomers in these aqueous solutions. That is, when the association reactions between Ca^{2+} ions and carbohydrate derivatives are studied, only the average variations are detectable, hence, only the macroscopic equilibrium constants can be determined.

Molecular properties, such as electron density, optical activity or X-ray absorption can also be utilized when studying solution equilibria and structure. Polarimetry and NMR spectroscopy have been proven to be useful to extract complex formation constants. Furthermore, given the different conformers are long-lived enough on the NMR timescale, their metal-binding processes can be quantified independently. As for solution structure, various methods, such as NMR, X-ray absoprtion fine structure (EXAFS), infrared and Raman spectroscopies can be applied to identify the metal-binding sites of the ligands as well as to provide additional structural information (*e.g.,* bond lengths and angles, coordination numbers). The two vibrational spectroscopies are also essential, together with X-ray diffraction, to characterize the coordination compounds in the solid phase. Additionally, in the past few decades, structure optimization employing quantum chemistry emerged as an important tool to elucidate the nature of such metal–ligand interactions.

To separate the effects of different functional groups on the complex stability and solution structure, first gluconate-related compounds having only OH groups are discussed. Due to the weak binding ability of the OH moieties, the stability of the Ca(II) complexes forming with D-glucose and sugar alcohols heavily depends on the steric arrangement of these groups, as identified by Angyal and others [87–96]. In general, the favorable arrangement of at least three OH groups is desirable for complexation both for cyclic and open-chain ligands. For ring structures, the most stable structures are a) six-membered / pyranose rings having three non-adjacent OH groups in *triaxial* (*ax-ax-ax*) arrangement or b) three adjacent OH groups in *axial-equatorial-axial* (*ax-eq-ax*) sequence or c) five-membered / furanose rings with OH functions with the same *ax-eq-ax* motif (Scheme 2a–c). Acyclic polyols, whose OH groups are situated on the same side of the plane (*threo-threo*), exhibit stronger binding than those having *erythro-threo* or *erythro-erythro* arrangement (Scheme 2d–f). Accordingly, the order of complex stability is expected to be *ax-ax-ax* (six-membered) > *ax-eq-ax* (six-membered) > *ax-eq-ax* (five membered) as well as *threo-threo* > *erythro-threo* > *erythro-erythro*.

The association reaction between the Ca^{2+} ion and a sugar-type ligand (L) as well as the corresponding thermodynamic (β_{11}^0) and conditional (β_{11}) 1:1 stability constants are defined as

$$Ca^{2+} + L^{z-} \rightleftharpoons CaL^{(2-z)+} \tag{14}$$

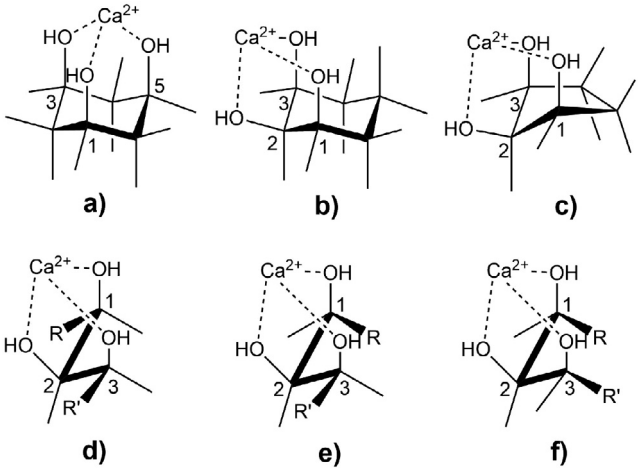
$$\beta_{11}{}^0 = \frac{a_{CaL^{(2-z)+}}}{a_{Ca^{2+}} \cdot a_{L^{z-}}} = \frac{\gamma_{CaL^{(2-z)+}}[CaL^{(2-z)+}]c^{\varnothing}}{\gamma_{Ca^{2+}}[Ca^{2+}] \cdot \gamma_{L^{z-}}[L^{z-}]} \tag{15}$$

$$\beta_{11} = \beta_{11}{}^0 \cdot \frac{\gamma_{Ca^{2+}} \cdot \gamma_{L^{z-}}}{\gamma_{CaL^{(2-z)+}}} = \frac{[CaL^{(2-z)+}]c^{\varnothing}}{[Ca^{2+}][L^{z-}]} \tag{16}$$

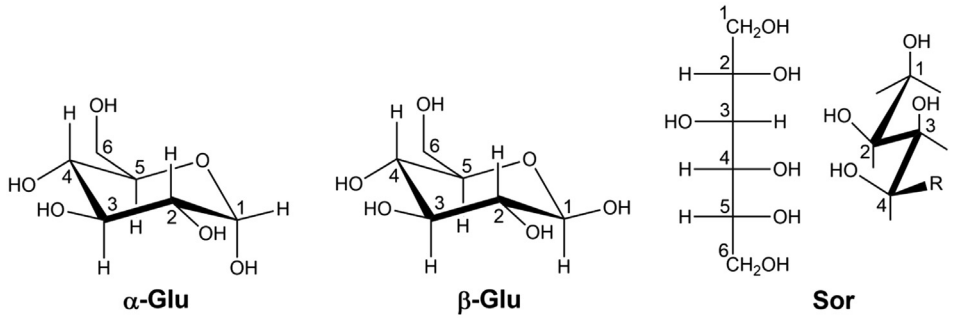
where a, γ denote activities and activity coefficients, brackets stand for molar concentrations of a given species in equilibrium and $c^{\varnothing}$ is the standard molar concentration (1 M).

As for D-glucose ((2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanal, Glu, Scheme 3), however, neither the α- nor the β-D-glucopyranose isomer (Scheme 3) has a favourable steric arrangement, thus, Glu is not able to form stable complexes with Ca^{2+}. Indeed, the log β_{11} constant could not be deduced from ^{1}H NMR spectroscopic [88], thin-layer chromatographic [97] and potentiometric (employing Ca^{2+}-ion selective electrode, Ca-ISE) [66,70,98] measurements. The value of log β_{11} was suggested to be smaller than –1 in Ref. [66] which agrees with the one (–1.12) obtained from conductometric experiments performed at 30 °C [99].

Contrary to the observations reported by Angyal [88], Pallagi and co-workers were able to determine the stability constant both for the α (log β_{11} = 0.18) and β (log β_{11} = 0.23) anomeric forms from the gradual upfield shift of the ^{13}C NMR peaks upon the addition of $CaCl_2$ at t = 25 °C [100]. These constants, however, should be considered with care. First, they were obtained by assuming that either the α- or the β-anomer is solely present, therefore they are



Scheme 2. Steric arrangements of the OH groups for calcium(II) complexation in the order of decreasing complex stability. For cyclic triols: a) 1,3,5-*ax-ax-ax* triol and b) 1,2,3-*ax-eq-ax* triol on a six-membered ring; c) 1,2,3-*ax-eq-ax* triol on a five-membered ring. For acyclic triols: d) *threo*-1,2-*threo*-2,3, e) *erythro*-1,2-*threo*-2,3 and f) *erythro*-1,2-*erythro*-2,3 sequences.



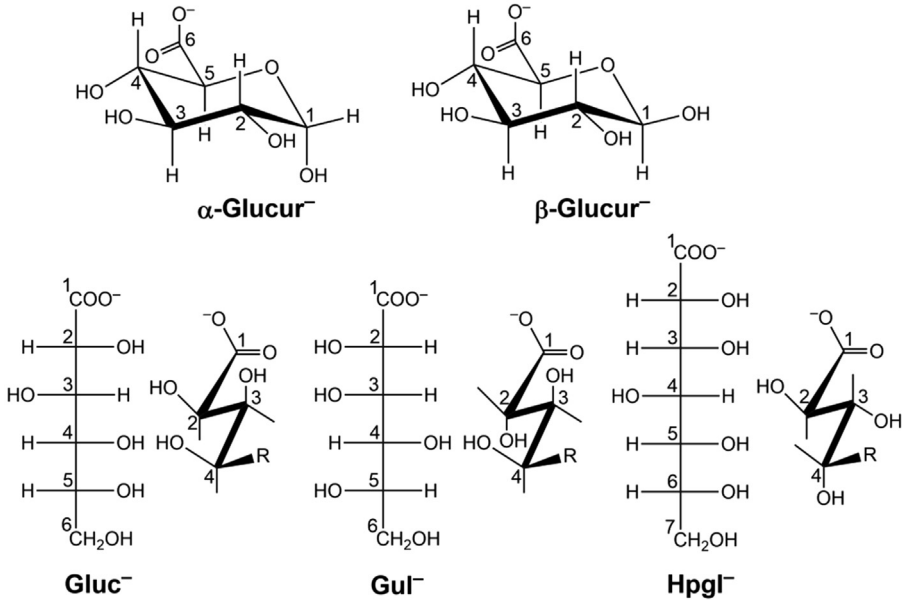
Scheme 3. Structural formulae of α-D-glucose (α-Glu), β-D-glucose (β-Glu) and D-sorbitol (Sor). "R" represents the C(5)HOH-C(6)H_2OH moiety.

upper estimates and refer to an average effect of the Ca(II) complexation on the ^{13}C chemical shifts. Second, although the ionic strength was adjusted to 1 M in each sample using NaCl, the ionic medium was replaced almost completely to $CaCl_2$ at the highest concentrations of Ca^{2+}. Considering this "medium effect", the constants obtained can be regarded as semi-quantitative estimates at best.

In the same work, insights into the structure of the $CaGlu^{2+}$ solution species have been gained as well. Based on the variation of the peak areas of the two isomers, the authors concluded that the relative weight of α-anomer increases upon metal ion-binding. Using the ^{1}H–^{43}Ca heteronuclear multiple quantum coherence (HMQC) two-dimensional NMR technique, the interaction between the Ca^{2+} ion and the C(1)OH group (adjacent to the ethereal oxygen) was revealed for both anomers. On the other hand, molecular modeling performed at the HF/6–31G(d,p) level suggested the additional coordination of the ethereal oxygen as well as C(6)OH. In conclusion, the binding of Ca^{2+} is likely to take place to a small extent in aqueous solutions; however, the formation constant is too low rendering its quantitative determination to be difficult.

Stronger complex formation was reported for D-sorbitol ((2*S*,3*R*,4*R*,5*R*)-hexane-1,2,3,4,5,6-hexol, Sor, Scheme 3), which can be obtained by reducing the formyl group of D-glucose. Moulik and Khan [99] performed conductometric experiments at 30 °C in very dilute solutions ($[CaCl_2]_T$ = 0.002 M), yielding log β_{11} = –0.79. Kieboom et al. [95] combined solubility experiments with potentiometry, which yielded log β_{11} = 0.18 (t = 25 °C, in the absence of background electrolyte). By the same methodology, Mäkinen and Söderling [96] obtained log β_{11} = –0.09 (t = 25 °C, also in the absence of background electrolyte), while Haas reported log β_{11} = –0.52 (t = 25 °C, I = 0.7 M KNO_3) [66] by means of Ca-ISE titrations. Using the same method and also varying the concentration of Sor (0.097–0.387 M), Kutus and co-workers [70] determined a significantly higher value for log β_{11} (0.04, t = 25 °C, I = 1 M NaCl). Beattie and Kelso [101] carried out ^{13}C NMR experiments, from which they deduced log β_{11} = –0.22 (t = 36 °C). Despite the different temperature, this value is significantly lower than the one was obtained (log β_{11} = 0.20, t = 25 °C) by Pallagi et al. [100], using the same technique.

Similarly to D-glucose, it can be stated that the extent of association is small, thus, the actual value of the formation constant is very sensitive to the experimental method, the ionic strength and the concentrations of the metal ion / ligand applied. The majority of the literature data [70,84,95,96,100,101], however, is consistent with the average value of 0.0 ± 0.3 for log β_{11}. Additionally, comparing the results obtained for Glu and Sor, it can be stated that the second forms more stable complexes with the Ca^{2+} ion.



Scheme 4. Structural formulae of α-D-glucuronate (α-Glucur$^-$), β-D-glucuronate (β-Glucur–), D-gluconate (Gluc$^-$), L-gulonate (Gul$^-$) and D-heptagluconate (Hgpl$^-$). "R" represents the C(5)HOH-C(6)H_2OH (Gluc$^-$, Gul$^-$), or the C(5)HOH-C(6)HOH-C(7)H_2OH (Hpgl$^-$) moiety.

This can be explained by the favorable *threo-threo* arrangement of Sor (Schemes 2 and 3) and by the flexibility of this ligand. That is, the large number of coexisting conformations results in more favored reactions in view of entropy.

As for the structure of the $CaSor^{2+}$ complex, the metal-binding sites were proposed to be the C(1)OH, C(2)OH, C(4)OH and C(6)OH groups, based on the long-range couplings observed in the $^{1}H–^{43}Ca$ HMQC spectrum [100]. Conversely, C(3)OH should be the coordinating group due to the *threo*-2,3-OH motif. Owing to the very broad ^{1}H peaks, however, the peak assignment was not obvious. Based on the assignment of the ^{1}H NMR peaks reported previously [102], the most probable binding sites are, indeed, the C(1)OH, C(2)OH and the C(3)OH groups, while the fourth one can be either the C(4)OH or C(6)OH.

Expectedly, introduction of a negatively charged anchoring group (*e.g.* carboxylate) into the ligand will result in the formation of complex(es) with significantly higher stability. Oxidizing the terminal CH_2OH group of D-glucose, the D-glucuronic acid or its deprotonated form, the D-glucuronate ion ((2*S*,3*S*,4*S*,5*R*)-2,3,4,5-tetrahydroxy-6-oxohexanoate, $Glucur^{-}$, Scheme 4) can be obtained. Due to the presence of the CHO group, $Glucur^{-}$ is known to exist in α and β pyranose forms. Since this ligand provides an interplay between structural rigidity and strong binding affinity, studying its Ca(II) complexation is useful to understand which factor has stronger impact on complex stability.

Gould and Ranking [103] performed a comprehensive study on the distribution between the α- and β-anomeric forms with and without Ca^{2+}, combining potentiometry and polarimetry. Similarly to Glu, β-$Glucur^{-}$ is the dominant epimer in metal-free solutions, while α-$Glucur^{-}$ is probably the more preferred isomer for Ca^{2+}-binding. This can be deduced from the equilibrium ratio of [Ca(β-Glucur]/[Ca(α-Glucur] = 0.94, as well as from the log $\beta_{11}(\alpha)$ = 1.57 and log $\beta_{11}(\beta)$ = 1.45 constants determined (the temperature and ionic strength were not indicated in this work). The preference for α-$Glucur^{-}$ was further corroborated by IR measurements for the solid $Ca(Glucur)_2$ salt [104].

Concerning the rest of literature, no distinction was made between the complexation of the α- and β-isomers, hence, only the macroscopic formation constant was determined. Makridou et al. [105] obtained log β_{11} as 1.49 (t = 25 °C, I = 1 M $NaClO_4$) by means of potentiometric measurements using a glass electrode. Despite the different ionic strength, this value is considerably higher than those obtained by Ca-ISE titrations. The log β_{11} was found to be 1.03 (t = 25 °C, I = 0.7 M KNO_3) by Haas [66], which agrees well with the one was deduced by van Duin and co-workers [38] (log β_{11} = 1.1, t = 25 °C, I = 0.1 M KCl). A somewhat

Table 4
Conditional formation constants (log β_{1q}, Eq. (16)) of the $CaL_q^{(2-q)+}$ complexes, where L denotes D-gluconate ($Gluc^{-}$) or D-heptagluconate ($Hpgl^{-}$) or L-gulonate (Gul^{-}); organized by the reaction and increasing background electrolyte concentration. Data correspond to t = 25 °C unless indicated differently. Where reported, triple standard errors are included in parentheses.

Reaction	Background electrolyte	log β_{1q}	Reference	Method[a]
$Ca^{2+} + Gluc^{-} \rightleftharpoons CaGluc^{+}$	$I \rightarrow 0$	1.7(3)[c]	Pallagi et al. [25]	^{13}C NMR
	$I \rightarrow 0$	1.94[d]	Vavrusova et al. [27]	SOL/POT/TITR
	$I \rightarrow 0$	1.72(21)[d]	Skibsted and Kilde [65]	GLE POT
	$I \rightarrow 0$	1.89(30)[d]	Skibsted and Kilde [65]	ISE POT
	$I \rightarrow 0$	1.70[e]	Vercammen [67]	
	0.1 M KCl	1.6	van Duin et al. [38]	ISE POT
	0.15 M NaCl	1.28	Stumpff and McGuigan [69]	ISE POT
	0.16 M NaCl	1.22	Schubert and Lindenbaum [63]	IEX
	0.2 M NaCl	1.49(12)	Vavrusova et al. [68]	ISE POT
	0.2 M KCl	1.21	Cannan and Kibrick [62][i]	H_2-Pt POT
	0.5 M NaCl	1.05(30)	Masone and Vicedomini [33]	ISE POT
	0.7 M KNO_3	1.31	Haas [66]	ISE POT
	1 M NaCl	0.70(5)[f]	this work	H_2-Pt POT
	1 M NaCl	1.02(3)	Pallagi et al. [25]	^{13}C NMR
	1 M NaCl	1.15(27)	Vavrusova et al. [68]	SOL/POT/TITR
	1 M NaCl	1.08(4)	Kutus et al. [70]	ISE POT
	1 M $NaClO_4$	1.21(5)	Zhang et al. [13]	GLE POT
	[b]	1.36	Kieboom et al. [95]	SOL/POT/TITR
$Ca^{2+} + 2\ Gluc^{-} \rightleftharpoons CaGluc_2^0$	0.5 M NaCl	1.88(24)	Masone and Vicedomini [33]	ISE POT
	1 M NaCl	1.65(9)	Kutus et al. [70]	ISE POT
$Ca^{2+} + Hpgl^{-} \rightleftharpoons CaHpgl^{+}$	1 M NaCl	1.00(4)	Kutus et al. [70]	ISE POT
	1 M NaCl	0.85	Pallagi et al. [71]	^{13}C NMR
	1 M NaCl	1.21(12)	Pallagi et al. [71]	ISE POT
$Ca^{2+} + 2\ Hpgl^{-} \rightleftharpoons CaHpgl_2^0$	1 M NaCl	1.61(7)	Kutus et al. [70]	ISE POT
$Ca^{2+} + Gul^{-} \rightleftharpoons CaGul^{+}$	0.1 M KCl	1.6[g]	van Duin et al. [38]	ISE POT
	1 M NaCl	0.88(5)	Kutus et al. [107]	ISE POT
	1 M NaCl	1.09(1)[h]	Kutus et al. [107]	^{1}H NMR
	1 M NaCl	1.12(3)[h]	Kutus et al. [107]	$^{1}H/^{13}C$ NMR
$Ca^{2+} + 2\ Gul^{-} \rightleftharpoons CaGul_2^0$	1 M NaCl	1.51(9)	Kutus et al. [107]	ISE POT

[a] GLE/H_2-Pt/ISE POT = potentiometry applying glass, hydrogen or Ca^{2+}-ion selective electrode (Ca-ISE); IEX = ion-exchange with isotope detection; NMR = nuclear magnetic resonance spectroscopy; SOL/TITR/POT = solubility determination *via* Ca-ISE or EDTA titration.
[b] Measurements were performed with ligand concentrations of 0.2–0.8 M.
[c] Thermodynamic formation constant (log β_{11}^0, Eq. (15)), calculated by extrapolating from the data for log β_{11} obtained at I = 1 M and 2–4 M (not shown), and from those of Refs. [33], [63] and [66].
[d] Thermodynamic formation constant (log β_{11}^0, Eq. (15)), obtained by extrapolating data for log β_{11} to infinite dilution.
[e] Thermodynamic formation constant (log β_{11}^0, Eq. (15)), calculated from the data for log β_{11}, reported in Ref. [63].
[f] This constant has been recalculated in this work from the one reported in Ref. [26], assuming the formation of the $Ca_2Gluc_2H_{-4}^0$ complex [28]; for discussion, see Section 4.2.
[g] Data correspond to D-gulonate.
[h] Obtained by fitting only the ^{1}H chemical shifts or the ^{1}H and ^{13}C chemical shifts simultaneously as a function of $CaCl_2$ concentration.
[i] The temperature is not indicated.

lower constant was determined by Kutus and co-workers [70] (log β_{11} = 0.80, t = 25 °C, I = 1 M NaCl), which is consistent with the higher ionic strength employed. Although there is a considerable uncertainty in the formation constant, it can be safely deduced that log β_{11}(CaGlucur$^+$) is higher not only than log β_{11}(CaGlu^{2+}) but also than log β_{11}(CaSor^{2+}). Consequently, the presence of a strong binding group overcomes the destabilizing effect caused by the rigid structure (CaGlucur$^+$ *vs.* CaSor^{2+}).

D-gluconate exhibits both enhanced metal ion-binding and flexibility, also possesses the favorable *threo-threo* configuration adjacent to the COO$^-$ group (Schemes 1 and 4). Regarding the Ca(II) complexation equilibria of Gluc$^-$, a great body of research has been devoted to determine the stoichiometry of the Ca(II) complex as well as to quantify its binding strength. Under near-neutral to slightly alkaline pH conditions, the complex formation takes place between Ca^{2+} and Gluc$^-$, mainly (in fact, almost exclusively) 1:1, although the formation of the 1:2 complex was also detected at very high [Gluc$^-$]$_T$/[Ca^{2+}]$_T$ ratios.

For the CaGluc$^+$ aqueous species, the thermodynamic association constant, log β^0_{11}, was found to be in the range of 1.7–1.9 [25,27,65,67] when extrapolating the experimental data to zero ionic strength. These constants are listed in Table 4. Conversely, the log β^0_{11} values obtained for the Ca^{2+} complexes of monocarboxylate compounds is about one order of magnitude lower [106]. This is most probably due to the absence of alcoholic OH groups on the ligand, which rules out the possibility of the formation of chelate structures.

At finite ionic strengths, a plethora of data for the formation constant have been published applying various experimental methods. The values of log β_{11} vary in the range of 0.70–1.36 and were obtained from potentiometric titrations employing platinized platinum hydrogen [26,66], glass [13] and Ca^{2+} ion-selective electrode [33,38,66,68–70,95], ion-exchange [63] and ^{13}C NMR spectroscopic [25] measurements. All these constants are presented in Table 4.

Contrary to the CaGlu^{2+}, CaSor^{2+} and CaGlucur$^+$ complexes, there is a lower uncertainty in the stability constants for the CaGluc$^+$ species, given that the ionic strength is the same (or very similar). By way of example, the log β_{11} varies between 1.08 and 1.21 at I = 1 M, corresponding to NaCl [25,68,70] or NaClO$_4$ [70]. The only exception is the value of 0.37 [26], which has been recalculated to be 0.70 in this work (see Section 4.2). Still, this value is probably underestimated, since it was obtained from potentiometric titrations applying a platinum electrode, which is less sensitive to this pH-independent complexation reaction than a Ca^{2+} ion-selective electrode.

For sugar carboxylates that are closely structurally-related to Gluc$^-$ (Scheme 4), that are L-gulonate ((2*S*,3*S*,4*R*,5*S*)-2,3,4,5,6-penta hydroxyhexanoate, Gul$^-$) and D-heptagluconate (2*R*,3*R*,4*R*,5*S*,6*R*)-2,3,4,5,6,7-hexahydroxyheptanoate, Hpgl$^-$), log β_{11} was obtained from Ca-ISE as well as ^{1}H and ^{13}C NMR experiments (Table 4) [38,70,71,107]. The equilibrium constants regarding the 1:1 complexes are very similar to that of CaGluc$^+$ owing to structural similarities. Although the Gul$^-$ and Hpgl$^-$ ligands are lacking the favorable *threo-threo* configuration (Schemes 1 and 4), this appears to be outweighed by the flexibility of the ligand and by the presence of identical metal ion-binding groups (particularly the COO$^-$).

Based on the majority of literature data, it can be concluded that the stability of the 1:1 complexes follows the order of Gluc$^-$ ≈ Gul$^-$ ≈ Hpgl$^-$ > Glucur$^-$ ≫ Sor ≫ Glu, which reflects the crucial role of COO$^-$ (Gluc$^-$ *vs.* Sor as well as Glucur$^-$ *vs.* Glu) and ligand flexibility (Gluc$^-$ *vs.* Glucur$^-$ as well as Sor *vs.* Glu) on the binding strength.

At higher [Gluc$^-$]$_T$/[Ca^{2+}]$_T$ ratios, the formation of the 1:2 calcium complex, CaGluc$_2^0$, was claimed to be observed first by polarimetric measurements performed by Sipes [64]. Later, Ca-ISE potentiometric measurements carried out by Masone and Vicedomini [33] yielded log β_{12} = 1.88 (t = 25 °C, I = 0.5 M NaCl). Additionally, further Ca-ISE [69] and ^{13}C NMR [25] measurements implied its formation, though, the variations were too small preventing a quantitative evaluation.

A recent study by Kutus et al. [70] was aimed at clarifying whether the formation of the CaGluc$_2^0$ complex really takes place and attempts were made to accurately determine its formation constant. The same research group carried out analogous measurements with Gul$^-$ [107] and Hpgl$^-$ [70].

During the potentiometric titrations using Ca-ISE (*e.g.*, the Ca^{2+}-Gluc$^-$ system, Fig. 5), the observed cell potentials were found to shift towards smaller [Ca^{2+}] values to a much higher extent than those observed with uncharged ligands, like Glu and Sor [70,84]. Moreover, the titration curves obtained for Gluc$^-$ containing

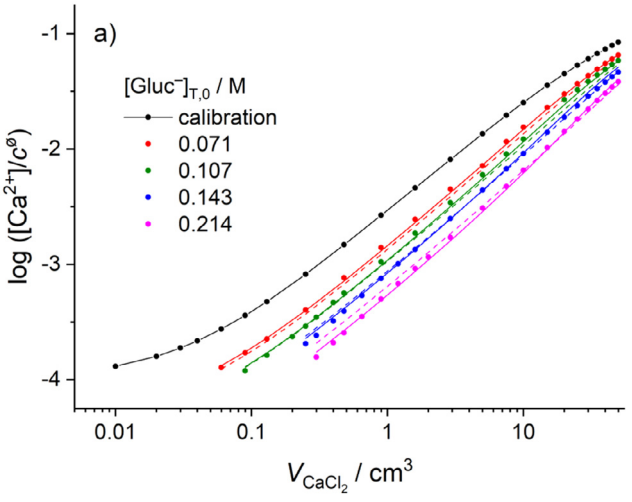


Fig. 5. Ca-ISE titration curves in the Ca(II)/Gluc$^-$ system; y axis: logarithm of the concentration of free Ca^{2+}, x axis: added volume of the titrant $CaCl_2$. Experimental conditions: t = (25.0 ± 0.1) °C, I = 1 M (NaCl), V_0 = 70 cm^3; [$CaCl_2$]$_{T,0}$ = 10^{-4} M. The initial total concentrations of the ligand are shown in the legend. The concentration of the titrant $CaCl_2$ was 0.201 M. Symbols refer to the measured data; lines were calculated by assuming the formation of the CaGluc$^+$ complex (dashed), or both the CaGluc$^+$ and CaGluc$_2^0$ complexes (solid). The figure has been replotted based on the data of Ref. [70].

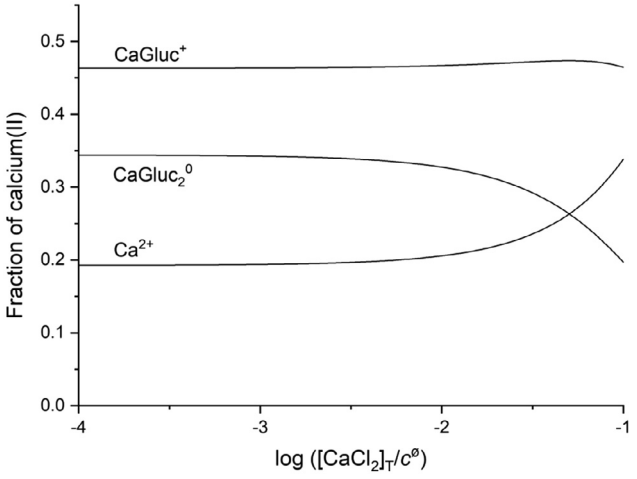


Fig. 6. Distribution diagram of Ca(II) containing species in the Ca(II)/Gluc$^-$ system; y axis: fraction of a given species relative to the concentration of $CaCl_2$, [$CaCl_2$]$_T$. The calculations correspond to t = 25 °C, I = 1 M (NaCl) and [NaGluc]$_T$ = 0.200 M.

systems were found to be essentially identical to those measured for $Hpgl^-$ and Gul^- containing solutions. Accordingly, the stability constants for the complexes of $Gluc^-$, Gul^- and $Hpgl^-$ with calcium(II) are (not surprisingly) similar.

The results of the calculations assuming solely the formation of the $CaGluc^+$ species are depicted as dashed lines in Fig. 5. The log β_{11} constant obtained (1.23, not shown in Table 4) [70] agrees reasonably well with other values obtained *via* Ca-ISE titrations [13,25,33,63,66] especially if one considers the different ionic strength applied.

It is obvious, however, that there are systematic deviations between the observed and calculated data (even for the points falling in the linear section of the calibration curve), when only the formation of the 1:1 complex is assumed. (The same observations were made for the titration curves of the other two ligands, Gul^- and $Hpgl^-$, too). Thus, in the next step, formation of the 1:2 complex (CaL_2^0) was also considered:

$$Ca^{2+} + 2L^- \rightleftharpoons CaL_2{}^0 \tag{17}$$

$$\beta_{12} = \frac{[CaL_2{}^0]c^{\varnothing}}{[Ca^{2+}][L^-]^2} \tag{18}$$

Including the 1:2 complex, the abovementioned errors practically disappear (demonstrated by the solid lines in Fig. 4). Thus, this model was accepted in this study and the corresponding computed stability products for the 1:1 and 1:2 complexes are presented in Table 4. The Ca(II) concentration distribution diagram calculated for the Ca^{2+}-$Gluc^-$ system (Fig. 6) attests that the formation of the 1:2 species exceeds 30% of $[CaCl_2]_T$ at high ligand to metal ratios and similar values were computed for the other two ligands (Gul^- and $Hpgl^-$) as well.

Regarding $CaGluc_2^0$, the value obtained in this work for log β_{12} is commensurate with that reported previously [33] and the difference can be accounted for the various ionic strength applied (0.5 M NaCl in Ref. [33] *vs.* 1 M NaCl in Ref. [70]). In conclusion, this hitherto uncertain species was proposed by different experimental methods [25,33,64,69,70] therefore its existence can be postulated. In light of these findings and structural similarity, the formation of $CaHpgl_2^0$ and $CaGul_2^0$ is not surprising (see their formation constants in Table 4).

3.2. The structure of the complexes forming in or crystallized from neutral solutions

The association of alkaline metal ions is known to affect the optical activity of the interacting ligand [108]. The optical rotation of such solutions (exemplified in Fig. 7) gradually decreases with increasing calcium concentration indicating that upon complexation, the optically active complexes formed have a specific rotation smaller than that of the uncomplexed anion. Although the direction of this variation is well-defined, its magnitude (0.5° for $Gluc^-$) is rather small, despite that about 75% of $Gluc^-$ is bound in the two complexes at the highest $CaCl_2$ concentration (calculated from the formation constants listed in Table 4). In conclusion, the specific rotations of the free ligand and that of the complexes are only slightly different entailing that accurate determination of the formation constants *via* polarimetry is not possible.

On the other hand, the experimental optical rotations (Fig. 7) could be fitted well by using the formation constants of $CaGluc^+$ and $CaGluc_2^0$ obtained from Ca-ISE titrations (Table 4) [109]. This calculation indeed yielded specific rotations being not very much different for the complexed and uncomplexed forms of gluconate. Polarimetric measurements resulted in the same outcome for heptagluconate and gulonate, too. (The specific rotations are listed in Table 5.) In conclusion, the formation of the 1:1 and especially the 1:2 complexes affects the equilibrium conformation of $Gluc^-$ to a minor extent.

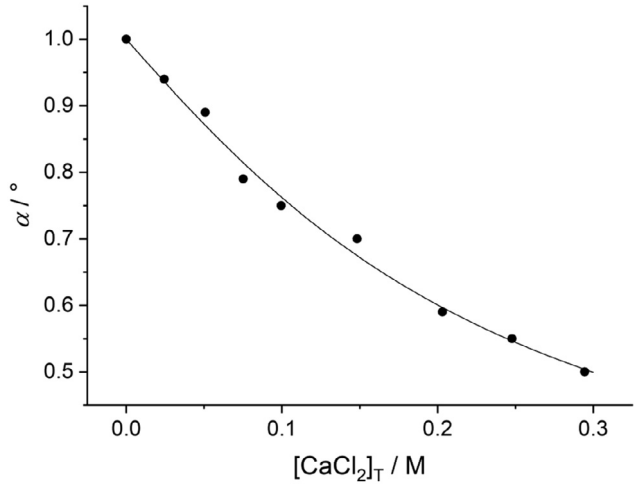


Fig. 7. Optical rotation of $Gluc^-$ (α) as a function of $CaCl_2$ concentration, $[CaCl_2]_T$. Experimental conditions: t = (25 ± 2) °C and I = 1 M (NaCl); a) $[Gluc^-]_T$ = 0.200 M, $[Ca^{2+}]_T$ = 0–0.295 M. Symbols refer to the measured data; the solid line was calculated by assuming the formation of the $CaGluc^+$ and $CaGluc_2^0$ complexes with formation constants reported in Ref. [70].

Regarding the structure of the $CaGluc^+$ solution species, the coordination of the COO^-, C(2)OH and C(4)OH (originally interpreted as C(3)OH) was suggested on the basis of the variation of ^{13}C NMR chemical shifts [24]. In a recent publication, the ^1H–^{43}Ca HMQC NMR measurement (Fig. 8) attested the coordination of C(2)OH and C(3)OH groups [25]. The authors suggested the simultaneous formation of linkage isomers in which either the C(2)OH or both C(2)OH and C(3)OH functions act as binding sites. Quantum chemical calculations suggested that the second is more stable, which can be elucidated that in this isomer, two five-membered chelates are formed, while only one (six-membered) chelate is present in the first structure. It has to be noted that $Gluc^-$ has the *threo*-2,3-*threo*-3,4-triol sequence, therefore the Ca(II) chelation by C(2)OH, C(3)OH and maybe C(4)OH is preferred.

From recent quantum chemical calculations by Bugris et al. [29] (taking implicit and explicit solvent effects into account), it was demonstrated that the most stable structure of the aqueous $CaGluc^+$ complex involved the binding of the O1, O2 and O3 oxygen atoms. For the lowest-energy structure (Fig. 9), the Ca^{2+} ion is bound to one oxygen of the COO^- group and also coordinated by the C(3)OH moiety, yielding the coordination number of 6. When the Ca^{2+} is assumed to be bound to the COO^- and C(2)OH groups, the free energy of this isomer is only 3.4 kJ·mol^{-1} higher than that of the previous one. This difference is not significant considering that the energy of thermal motion is 2.48 kJ·mol^{-1} at 25 °C. This finding supports the previous assumption of Pallagi et al. [25], namely, the co-existence of these two isomers. Furthermore, in both isomers, $Gluc^-$ acts as a bidentate ligand, and several

Table 5
Specific rotations of the free ligand, L^-, and its calcium(II) complexes, CaL^+ and CaL_2^0, where L^- denotes D-gluconate ($Gluc^-$), D-heptagluconate ($Hpgl^-$) and L-gulonate (Gul^-). The data are taken from Kutus [109] and correspond to t = (23 ± 2) °C; triple standard errors are included in parentheses.

Ligand (L^-)	L^-	CaL^+	CaL_2^0
$Gluc^-$	+12.8°	+1.5(1.8)°	+9.4(3.5)°
$Hpgl^-$	+6.1°	+1.7(1.4)°	+3.8(2.4)°
Gul^-	−12.8°	−1.0(3.0)°	−13.0(4.5)°

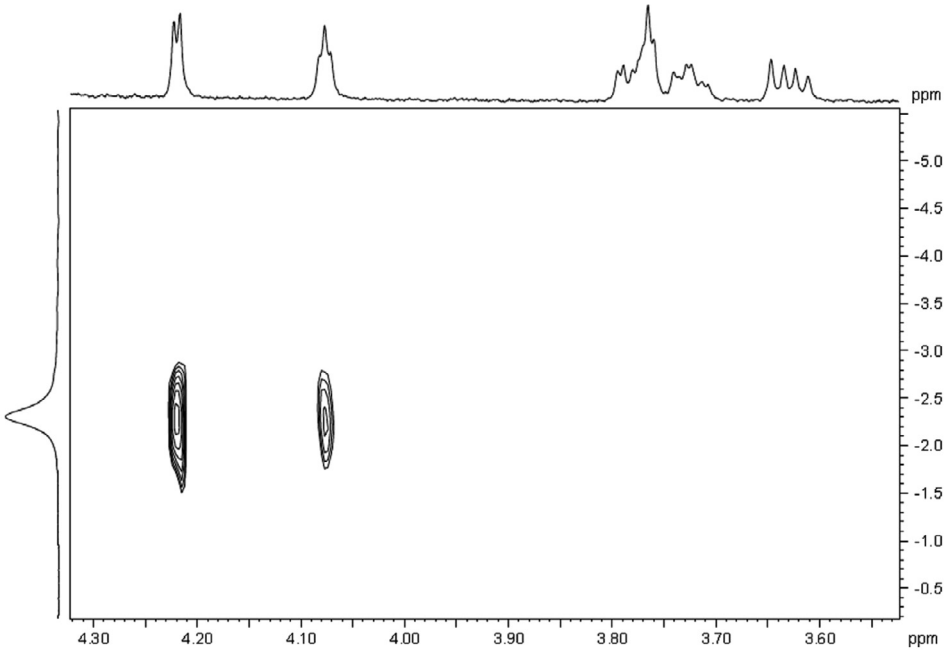


Fig. 8. The 2D ^{1}H–^{43}Ca HMQC spectrum (^{1}H: x, ^{43}Ca: y axis) of the solution containing 0.2 M $CaCl_2$ and 0.2 M NaGluc. The peaks of H(C2) and H(C3) are seen around 4.24 and 4.08 ppm, respectively. Reproduced with permission [25] Copyright 2010 Elsevier.

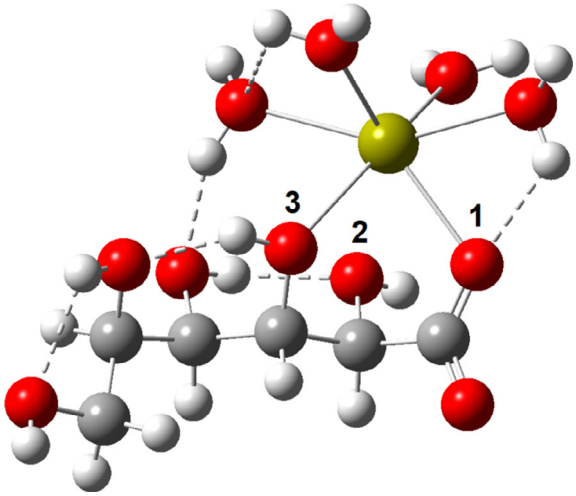


Fig. 9. The optimized model structure of the lowest-energy $CaGluc^{+}$ complex. Calculations were performed at B3LYP level applying the 6–311++g(d,p) basis set. Implicit solvent effects were taken into account utilizing the polarizable continuum model. Solid or dashed lines represent the Ca–O interactions or the hydrogen bonds. The picture was prepared on the basis of the data published in Ref. [29].

intramolecular hydrogen bonds contribute to the stabilization of the overall structure.

In the case of $Hpgl^{-}$, two-dimensional ^{1}H–^{43}Ca NMR measurements revealed the probable coordination of all the three OH functions [71] inferring the coexistence of coordination isomers. The Ca(II) ion, on the other hand, is bound to four heptagluconate anions acting as bidentate ligands and to a water molecule in the $CaHgpl_2{\cdot}4H_2O$ single crystal [110]. The carboxylate group binds Ca^{2+} in a monodentate manner, in line with the findings for the $CaGluc^{+}$ aqueous complex [25,29].

The significance of the calcium salt of D-gluconic acid has already been mentioned. Therefore it is somewhat surprising that the crystal structure of $CaGluc_2{\cdot}H_2O(s)$ has been determined and published only recently [29]. The reason for this may be that slow cooling of an aqueous solution yields fine needles that are unsuitable for single crystal X-ray diffraction studies. The hanging drop vapour diffusion method however resulted in almost isometric single crystals with the size of approximately 0.05 mm × 0.02 mm × 0.01 mm. The $CaGluc_2{\cdot}H_2O$ crystallizes in orthorhombic system, forming coordination polymers (Fig. 10). The coordination number of the Ca^{2+} ion was found to be nine, considered to be surprisingly high compared to the majority of other Ca(II) containing structures [111], (*e.g.*, it was found to be 7 in the lactobionate complex of Ca(II), where the metal ion is coordinated to the gluconate part of the lactobionate ion [112]). Furthermore, the coordination polyhedron of Ca^{2+} is that of a distorted triaugmented triangular prism. Similarly to $Hpgl^{-}$ [110], bidentate coordination of the carboxylate ion was not discernible. Conversely, two of these groups act as a bridging ligand by binding two metal ions simultaneously, in a monodentate manner (Fig. 10). Such coordination motic has been deduced from the infrared analysis of the solid $CaGluc_2$ salt [24].

4. Acid-base equilibria and Ca(II) complexation of $Gluc^{-}$ in alkaline solutions

Alkaline conditions are of paramount relevance in the field of the coordination chemical interactions between calcium(II) and gluconate ions. As it was already mentioned, the underground repositories for the deposition of low- and intermediate-level radioactive waste are of general importance due to safety reasons. As repositories make frequent use of cement-based materials, alkaline pore water may form by incidental water intrusion [113–115]. Gluconate, being an additive to Portland cement [2,43–46], is likely to be present in these systems [53]. The ability of $Gluc^{-}$ to bind metal ions (as it will be shown below) becomes more pronounced in these alkaline systems, therefore the quantitative description of complexation processes between $Gluc^{-}$ and the constituents of concrete, *e.g.*, calcium(II) ions is of particular interest.

Furthermore, $Gluc^{-}$ was proposed to be the model compound of different organic substances (*e.g.*, humic substances) that might be present in strongly caustic Bayer liquors [116,117]. It has also been

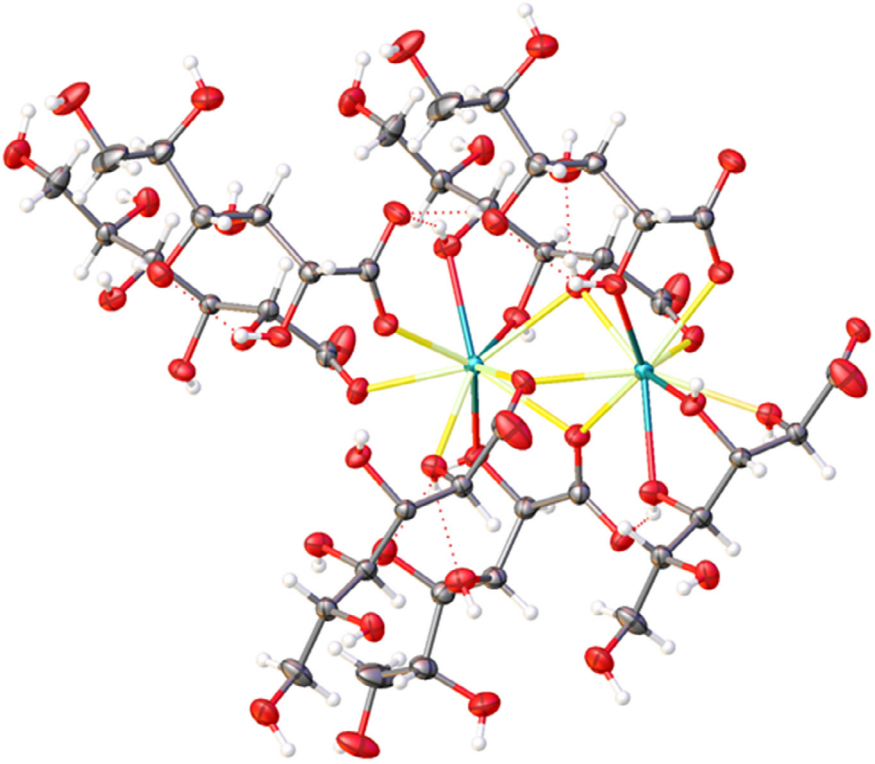


Fig. 10. The dinuclear segment of a polymeric chain in the 100 K single crystal structure of $CaGluc_2 \cdot H_2O$ single crystal with the bridging bonds highlighted. The picture was prepared on the basis of the data published in Ref. [29].

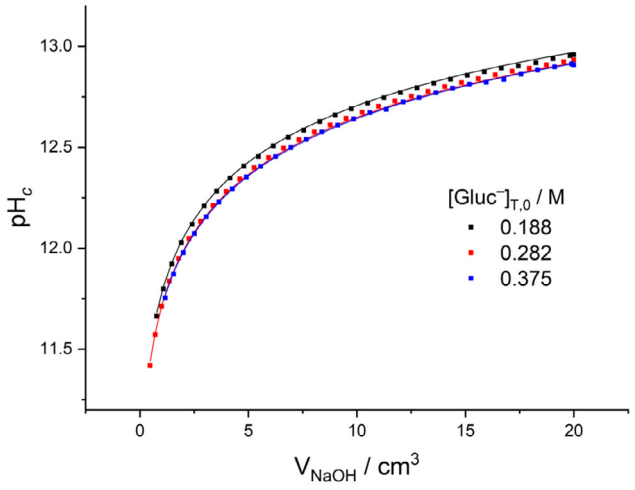


Fig. 11. H_2-Pt electrode potentiometric titration curves of the $Gluc^-/OH^-$ system; y axis: $pH_c = -\log([H^+]/c^\varnothing)$, x axis: added volume of the titrant NaOH. Experimental conditions: t = (25.0 ± 0.1) °C, I = 1 M (NaCl), V_0 = 80 cm^3 (black and blue) or 85 cm^3 (red); $[NaOH]_{T,0} = 10^{-3}$ M. The initial total concentrations of NaGluc are shown in the legend. The concentration of the titrant NaOH was 0.927 M. Symbols refer to the measured data; solid lines were calculated by assuming the formation of the $GlucH_{-1}^-$ species. The figure has been replotted based on the data of Ref. [26].

reported, that the solubility of $Ca(OH)_2(s)$ (used for NaOH recovery) is severely affected by a range of complexing ligands, in particular $Gluc^-$ [116–118].

The enhanced complexing ability of $Gluc^-$ is certainly associated with the involvement of alcoholate (O^-) moieties in the metal ion-binding (beside that of the COO^- group). First, we summarize our current knowledge on the acid-base properties of the alcoholic hydroxy groups of $Gluc^-$. For comparison, data for some hydroxycarboxylates closely related to $Gluc^-$ are also discussed.

4.1. Deprotonation of the alcoholic OH of $Gluc^-$ in strongly alkaline medium

Alcohols are weak acids, and for the acid dissociation reaction the acid dissociation constant log K_a is –15.5 and –16.0 for methanol and ethanol, respectively [119]. The acidity of simple hydroxycarboxylates are usually similar to these values or even smaller [120,121]. For statistical reasons, polyhydroxy carboxylates are stronger acids, since each additional OH group decrease the pK_a with 0.3 logarithmic unit [122].

The conditional acid dissociation constant, K_a, for a hydroxycarboxylate anion, L^-, in general can be expressed as:

$$L^- \rightleftharpoons LH_{-1}^{2-} + H^+ \tag{19}$$

$$K_a = \frac{1}{K_p} \cdot \frac{[LH_{-1}^{2-}]c^\varnothing}{[L^-][H^+]} \tag{20}$$

where K_p is the protonation constant of AH_{-1}^{2-} and $c^\varnothing$ again stands for the standard molar concentration, 1 mol·dm^{-3} or M. To demonstrate how the acidity of $Gluc^-$ changes in the presence of Ca^{2+} under alkaline conditions, the log K_a instead of log K_p will be discussed in this Section.

Most probably due to experimental challenges, only a few data are available in the literature for the log K_a of $Gluc^-$. The available methods for determining K_a are limited to potentiometry using H_2-Pt electrode or NMR titrations. As it can be seen, potentiometric effects caused by alcohol deprotonation (Fig. 11) may reach $pH_c \approx 0.2$ units (≈ 12 mV), which is (using careful experimentation) readily and accurately measurable and expected to provide reliable values for log K_a values. The values discussed in this Section are listed in Table 6.

In the first report on the deprotonation of $Gluc^-$ to form $GlucH_{-1}^{2-}$, a probably unrealistic log K_a (–11.18, t = 37 °C and I = 0.15 M

Table 6
Conditional deprotonation constants (log K_a, Eq. (20)) for D-gluconate ($Gluc^-$), D-heptagluconate ($Hpgl^-$), L-gulonate (Gul^-) and a-D-Isosaccharinate (Isa^-), organized by the reaction and background electrolyte concentration. Data correspond to t = 25 °C unless indicated differently. Where reported, triple standard errors are included in parentheses.

Reaction	Background electrolyte	log K_a	Reference	Method[a]
$Gluc^- \rightleftharpoons GlucH_{-1}^{2-} + H^+$	0.1 M $NaClO_4$	−13(1)	Zhang et al. [81][b]	^{13}C NMR
	0.15 M NaCl	−11.18	Roos and Williams [84][b]	GLE POT
	1 M NaCl	−13.68(3)	Pallagi et al. [26]	H_2-Pt POT
	1 M $NaClO_4$	−13.66(24)	Coccioli and Vicedomini [23]	H_2-Pt POT
	4 M NaCl	−14.08(3)	Buckó et al. [28]	H_2-Pt POT
	4 M NaCl	−13.90(3)	Buckó et al. [28]	^{13}C NMR
	4 M NaCl	−13.32(3)	Buckó et al. [28][c]	H_2-Pt POT
	4 M NaCl	−12.65(2)	Buckó et al. [28][d]	H_2-Pt POT
	4 M NaCl	−13.92(6)	Kutus et al. [31]	GLE POT
$GlucH_{-1}^{2-} \rightleftharpoons GlucH_{-2}^{3-} + H^+$	1 M $NaClO_4$	−14.02(30)	Coccioli and Vicedomini [23]	H_2-Pt POT
	4 M NaCl	−14.72(5)	Buckó et al. [28]	H_2-Pt POT
$Hpgl^- \rightleftharpoons HpglH_{-1}^{2-} + H^+$	1 M NaCl	−13.41(2)	Pallagi et al. [71]	H_2-Pt POT
$Gul^- \rightleftharpoons GulH_{-1}^{2-} + H^+$	1 M NaCl	−13.72(2)	Kutus et al. [30]	H_2-Pt POT
	1 M NaCl	−13.75(3)	Kutus et al. [30]	^{13}C NMR
$Isa^- \rightleftharpoons IsaH_{-1}^{2-} + H^+$	1 M NaCl	−14.5(3)	Dudás et al. [72]	^{13}C NMR

[a] GLE/H_2-Pt/ISE POT = potentiometry applying glass, hydrogen or Ca^{2+}-ion selective electrode (Ca-ISE); NMR = nuclear magnetic resonance spectroscopy.
[b] The temperature was 22 °C in Ref. [81] and 37 °C in Ref. [84].
[c] Data corresponds to 50 °C.
[d] Data corresponds to 75 °C.

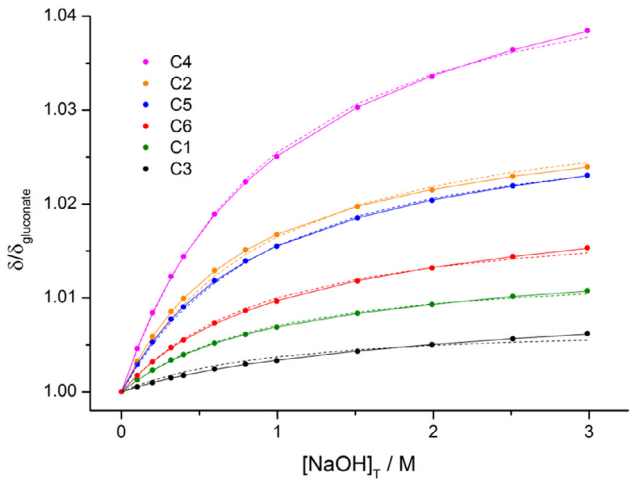


Fig. 12. Observed (symbols) and calculated (lines) ^{13}C NMR chemical shifts of gluconate-containing species as a function of $[NaOH]_T$. Experimental conditions: t = 25 °C, I = 4 M (NaCl); $[NaGluc]_T$ = 0.200 M, $[NaOH]_T$ = 0–2.989 M. The calculations were performed by fitting the first (dashed line) or the first and second (solid line) deprotonation constants of $Gluc^-$. For better visualization, the chemical shifts were normalized to those of 0.200 M NaGluc. The assignment of the nuclei (legend) is the same as in Schemes 1 and 4. Reproduced with permission [28], Copyright 2019 Elsevier.

$NaClO_4$) was published by Roos and Williams, who used glass electrode [84]. Combining this method with ^{13}C NMR, a value of −13 ± 1 (t = 22 °C, I = 0.1 M $NaClO_4$) was proposed by Zhang and coworkers [81]. The considerably high uncertainty of log K_a is reasonable in light of that pH_c measurements were limited to < 13, due to the poor performance of the glass electrode at such high pH_c. Hence, the authors observed only partial deprotonation of $Gluc^-$ and their value can be regarded as a semi-quantitative estimation.

Employing H_2-Pt electrode, known to be more accurate for pH measurements in alkaline solutions, similar values of log K_a (t = 25 °C, I = 1 M) were reported by two different groups [23,26]. Coccioli and Vicedomini [23] also concluded that $GlucH_{-1}^{2-}$ can be further deprotonated, yielding $GlucH_{-2}^{3-}$ (t = 25 °C, I = 1 M $NaClO_4$). In a recent study, Buckó et al. [28] conducted H_2-Pt potentiometric and ^{13}C NMR studies at t = 25 °C and I = 4 M (using NaCl as inert electrolyte). The log K_a deduced from the titrations is in excellent agreement with the one obtained by Kutus et al. [31] under identical experimental conditions, using however glass electrode.

As for the NMR experiments, inclusion of the two-fold deprotonated $Gluc^-$ was necessary to obtain an acceptable fit for the ^{13}C chemical shifts (see the dashed and solid lines in Fig. 12). This finding confirms that of Coccioli and Vicedomini [23], whose value is however higher by 0.7 logarithmic units. This discrepancy can be attributed to the difference in the ionic strength as well as to the different methods employed. In case of H_2-Pt potentiometric titrations in Ref. [28], the ratio of $[NaOH]_T/[NaGluc]_T$ was limited to lower values as compared to the ^{13}C NMR experiments. Consequently, the formation of the $GlucH_{-2}^{3-}$ was not observed by this technique.

The log K_a for $GlucH_{-1}^{-}$ was also determined at t = 50 and 75 °C (Table 6) by Buckó et al. [28]. The temperature-dependent constants thus obtained allowed the calculation of the enthalpy and entropy changes of deprotonation applying the van't Hoff equation (ΔH = 57 kJ mol^{-1} and ΔS = −79 J·mol^{-1} K^{-1}).

With regard to hydroxycarboxylates closely related to $Gluc^-$, log K_a was reported to be −13.41 for $Hpgl^-$, determined by H_2-Pt potentiometric measurements (t = 25 °C, I = 1 M NaCl) [71]. The higher acidity of $Hpgl^-$ can be explained by the statistical effect of the higher number of OH functions [122]. With regard to the deprotonation of Gul^-, H_2-Pt electrode and ^{13}C NMR studies (t = 25 °C, I = 1 M) yielded log K_a = −13.72 and −13.75, respectively [30]. The latter values are practically identical to those found for $Gluc^-$ under identical experimental conditions. Contrary to this, the log K_a value for Isa^- (at t = 25 °C, I = 1 M NaCl) was found to be almost one order of magnitude lower from ^{13}C NMR measurements [72], which indicate that Isa^- is significantly weaker acid than $Gluc^-$. These observations (and others, see Section 4.2) led to the conclusion, that "caution should be exercised when using gluconate as a thermodynamic model for isosaccharinate" [123].

4.2. Formation of complexes between Ca(II) and $Gluc^-$ under alkaline conditions

When the pH of a solution, containing Ca^{2+}-ions in a concentration of around 0.1 M, is raised to pH ≈ 13, the formation of a large amount of $Ca(OH)_2$(s) (portlandite) precipitate can be observed. Addition of NaGluc (in excess relative to Ca^{2+}) to this precipitate was found to result in instantaneous dissolution of the solid. This simple test-tube experiment served as the starting point for studying interactions between Ca(II) and gluconate in alkaline solutions.

Upon deprotonation of the OH group, an alcoholate (O^-) is formed, which (due to its increased basicity) is a much more effective binding site for bi-, tri- and tetravalent metal ions, than the OH moiety. Metal ions (*i.e.*, Ca^{2+}), in turn, facilitate the deprotonation of the OH groups and the parallel complex formation. In other words, Ca^{2+} decreases the pK_a of the ligand, that is, increases the acidity of the alcohol group, since it is a strong competitor of H^+ for the O^- moiety. This process is the well-known metal-ion-induced (or promoted) ligand deprotonation.

For metal-ion polyhydroxy carboxylate complexes, van Duin et al. proposed a generalized scheme [124]. According to this, at first the deprotonation of the COOH group takes place, which is followed by the dissociation of the neighboring α-OH group. Finally, a further H^+ is displaced from another (not necessarily the β-) OH functional group, resulting in the coordination of the metal ion by a diolate moiety. It was predicted that for alkaline earth metal ions, the OH deprotonation occurs in solutions of pH ≥ 10.

Ca(II)-complexes forming *via* ligand deprotonation have higher stability, as the Ca(II)-alcoholate interactions are plausibly stronger than those with OH. In some early works, it was already stated that with increasing pH, the calcium sequestering capacity is enhanced in alkaline solutions containing $Gluc^-$ and $Hpgl^-$ [125].

For calcium complexation, the general complexation reactions and the corresponding β_{pq-r} conditional stability products can be expressed as:

$$pCa^{2+} + qL^- \rightleftharpoons Ca_pL_qH_{-r}^{(2p-q-r)+} + rH^+ \quad (21)$$

$$\beta_{pq-r} = \frac{[Ca_pL_qH_{-r}^{(2p-q-r)+}]}{[Ca^{2+}]^p[L^-]^q(c^\varnothing)^{1+r-p-q}} \quad (22)$$

where L^- stands for polyhydroxy carboxylate anions.

Sipes [64] in his Ph.D. thesis observed the displacement of the alcoholic proton from the $CaGluc^+$ complex in the pH range of 10–11, using polarimetry. In the same work, the formation of a Ca(II) gluconate complex of 2:1 metal:ligand stoichiometry was invoked at higher pH.

The interactions between calcium ions and $Gluc^-$ at high pH were studied in detail in the work of Pallagi et al. [26]. Systematic pH-potentiometric measurements (Fig. 13) using the H_2-Pt electrode revealed the simultaneous formation of both mono- and polynuclear complexes containing calcium ion(s) and deprotonated $Gluc^-$ molecule(s). When only the plausible $CaGlucH^0_{-1}$ species was included in the speciation model, the experimentally observed cell potential values were not correctly reproduced. The very pronounced dependence of the titration curves on the metal ion concentration (Fig. 13) already strongly indicated the possible formation of polynuclear complex(es). This is not unprecedented, as the removal of protons from hydroxycarboxylates and the simultaneous formation of remarkably stable polynuclear complexes were reported for other metal ions, *e.g.*, for Cu(II) [3,7,10].

From these potentiometric titrations, the best chemical model included the following species: $CaGluc^+$, $CaGlucH^0_{-1}$, $Ca_2GlucH^0_{-3}$ and $Ca_3Gluc_2H^0_{-4}$, in addition to the monohydroxido complex of Ca(II), namely, $CaOH^+$ [126]. Recently, it was found that the solution equilibrium of Ca(II) is dominated by the $Ca(OH)^0_2$ aqueous complex in ligand-free solutions (hence, $CaOH^+$ is a minor species) [127]. Furthermore, recent calculations revealed that $Ca_2GlucH^0_{-3}$ can be replaced by $Ca_2Gluc_2H^{2-}_{-4}$ (yielding the same fitting quality), which was shown to form in a broad temperature range (see below) [28]. Although, the 2:1:–3 and 2:2:–4 species are apparently not easily distinguishable under the experimental conditions in Ref. [26], here the model consisting of $CaGluc^+$, $CaGlucH^0_{-1}$, $Ca_2Gluc_2H_{-4}^{2-}$ and $Ca_3Gluc_2H^0_{-4}$ is chosen. Accordingly, the original dataset were reevaluated using this speciation model and the formation constants of $CaOH^+$ and $Ca(OH)^0_2$ [127]; the corresponding stability products are shown in Table 7.

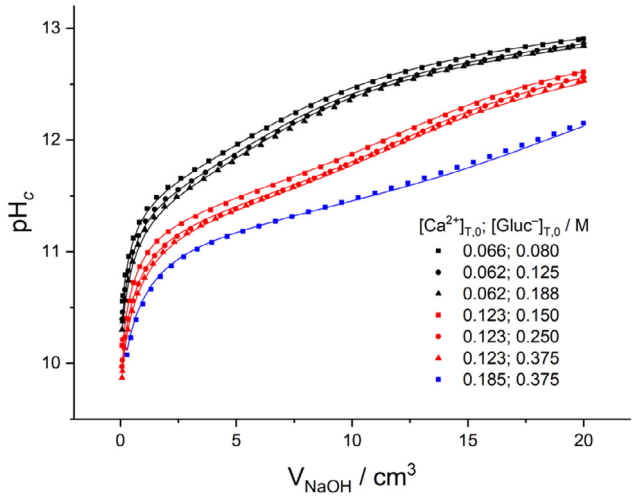


Fig. 13. H_2-Pt electrode potentiometric titration curves of the Ca(II)/$Gluc^-$/OH^- system; y axis: $pH_c = -\log([H^+]/c^\varnothing)$, x axis: added volume of the titrant NaOH. Experimental conditions: t = (25.0 ± 0.1) °C, I = 1 M (NaCl), V_0 = 80 cm^3, except for the first titration (black squares); $[NaOH]_{T,0} = 10^{-3}$ M. The initial total concentrations of $CaCl_2$ and NaGluc are shown in the legend. The concentration of the titrant NaOH was 1.026 M. Symbols refer to the measured data; simulations were performed based on the chemical model including the $Ca_2Gluc_2H^{2-}_{-4}$ species. See Section 4.2 as well as Table 7 for discussion. The figure has been replotted based on the data of Ref. [26].

In addition to potentiometric titrations, the existence of the bi- and trinuclear gluconate-containing species was supported by freezing point depression, ESI-MS and EXAFS measurements as well as by conductometry (proving the formation of charge neutral complexes) [26]. A representative species distribution diagram for this system is shown in Fig. 14.

As for the $CaGlucH^0_{-1}$ aqueous species, the metal-ion-induced ligand deprotonation can be quantified as well. The deprotonation of $Gluc^-$ in the $CaGluc^+$ complex is defined by the following reaction:

$$CaGluc^+ \rightleftharpoons CaGlucH_{-1}{}^0 + H^+ \quad (23)$$

while the corresponding deprotonation constant, K_{11-1}, can be deduced from log β_{11} (Eq. (16)) and log β_{11-1} (Eq. (22)):

$$K_{11-1} = \frac{[CaGlucH_{-1}{}^0][H^+]}{[CaGluc^+]c^\varnothing} = \frac{\beta_{11-1}}{\beta_{11}} \quad (24)$$

Using log β_{11} = 1.08 (Table 4) and log β_{11-1} = −10.76 (Table 7), log K_{11-1} is −11.84. That is, the pK_a of the bound $Gluc^-$ (11.84) is approximately lower by two orders of magnitude than the pK_a of the free ligand (13.68, see Table 6). This clearly shows that the formation of an alcoholate group is significantly facilitated by an already bound Ca^{2+}. The driving force of this reaction is (1) the very strong interaction between the Ca^{2+} ion and the O^- moiety and (2) the concurrent formation of a stable chelate structure.

Furthermore, the direct binding of $GlucH^{2-}_{-1}$ to Ca^{2+} can also be characterized:

$$Ca^{2+} + GlucH_{-1}{}^{2-} \rightleftharpoons CaGlucH_{-1}{}^0 \quad (25)$$

$$K_{11} = \frac{[CaGlucH_{-1}{}^0]c^\varnothing}{[Ca^{2+}][Gluc^-]} = \frac{\beta_{11-1}}{K_a} \quad (26)$$

From log K_a = −13.68 (Eq. (20), Table 6), and log β_{11-1} = −10.76 (Eq. (22), Table 7), log K_{11} is found to be 2.74, indicating that deprotonation of the OH moiety results in roughly two orders of magni-

Table 7
Conditional stability products (log β_{pq-r}, with triple standard errors) of the $Ca_pL_qH_{-r}^{(2p-q-r)+}$ complexes, where L^- denotes D-gluconate ($Gluc^-$), D-heptagluconate ($Hpgl^-$) and L-gulonate (Gul^-); organized by the reaction and increasing background electrolyte concentration. Literature sources are shown beneath the acronyms of each ligand. Data correspond to t = 25 °C unless indicated differently.

Reaction	Background electrolyte	$Gluc^-$	$Hpgl^-$	Gul^-
$Ca^{2+} + L^- + H_2O \rightleftharpoons CaLH^0_{-1} + H^+$	1 M NaCl	−10.76(3)[a]	−10.65(5)[b] [30]	
	4 M NaCl	−11.73(3) [28]		
	4 M NaCl	−11.17(3)[c] [28]		
	4 M NaCl	−10.59(3)[d] [28]		
$2\ Ca^{2+} + 2\ L^- + 4\ H_2O \rightleftharpoons Ca_2L_2H^{2-}_{-4} + 4\ H^+$	1 M NaCl	−44.99(8)[a]		
	4 M NaCl	−46.54(3) [28]		
	4 M NaCl	−44.21(5)[c] [28]		
	4 M NaCl	−41.91(3)[d] [28]		
$3\ Ca^{2+} + 2\ L^- + 3\ H_2O \rightleftharpoons Ca_3L_2H^{+}_{-3} + 3\ H^+$	1 M NaCl			−30.46(4) [30]
	4 M NaCl		−31.39(3) [128]	
$3\ Ca^{2+} + 2\ L^- + 4\ H_2O \rightleftharpoons Ca_3L_2H^{0}_{-4} + 4\ H^+$	1 M NaCl	−41.89(8)[a]	−41.64(9)[b] [30]	−42.66(4) [30]
	4 M NaCl	−43.80(3) [28]		
	4 M NaCl	−41.23(2)[c] [28]		
	4 M NaCl	−38.95(3)[d] [28]		

[a] The constants were recalculated in this work by replacing the $Ca_2GlucH^0_{-3}$ complex (not shown) to the $Ca_2Gluc_2H^{2-}_{-4}$ one in the original model, reported in Ref. [26]. Additionally, the formation constants of $CaOH^+$ and $Ca(OH)^0_2$ solution species reported in Ref. [127] were used during fitting.
[b] The constants reported in Ref. [71] were recalculated in Ref. [30] by using the formation constants of $CaOH^+$ and $Ca(OH)^0_2$ solution species, reported in Ref. [127].
[c] Data corresponds to 50 °C.
[d] Data corresponds to 75 °C.

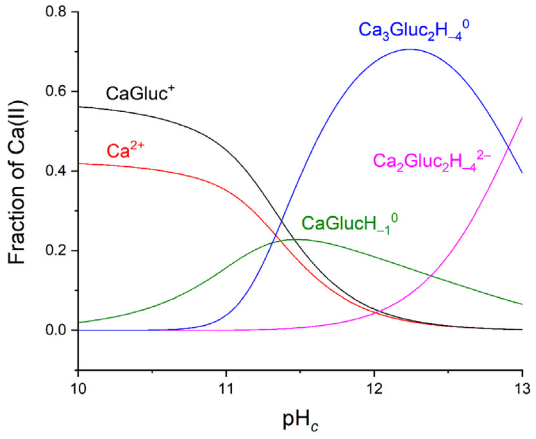


Fig. 14. Distribution diagram of Ca(II) containing species in the Ca(II)/$Gluc^-$/OH^- system; y axis: fraction of a given species relative to the concentration of $CaCl_2$, $[CaCl_2]_T$, x axis: $pH_c = -\log [H^+]/c^\ominus$). The calculations correspond to t = 25 °C, I = 1 M (NaCl) and $[CaCl_2]_T$ = 0.185 M as well as $[NaGluc]_T$ = 0.375 M and based on the chemical model including the $Ca_2Gluc_2H^{2-}_{-4}$ species. See Section 4.2 as well as Table 7 for discussion.

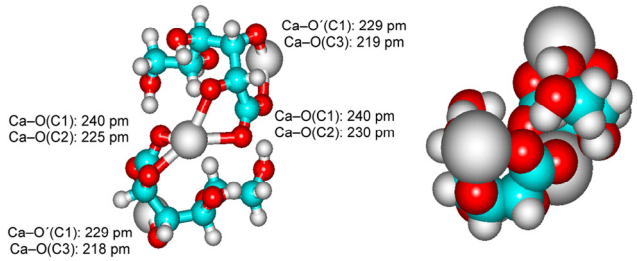


Fig. 15. Optimized geometry of the $Ca_3Gluc_2H^0_{-4}$ complex (ball-and-stick and space-filling models). The corresponding metal–ligand bond length are indicated. Reproduced with permission [26] Copyright 2014 The American Chemical Society.

tude increase in the stability of the complex species formed, relative to that containing hydroxyl group (that is $CaGluc^+$, for which log β_{11} = 1.08, see Table 4)). Beside $Gluc^-$, the formation constants of further 1:1:−1 Ca-sugar carboxylate complexes were determined, and all of these were found to be formed in the alkaline pH-range. In an early work, Makridou et al. [105] reported the formation constant of log β_{11-1} = −10.40 for the mononuclear Ca-complex of D-glucuronate. In more recent studies, the formation constants of $CaHpglH^0_{-1}$ (log β_{11-1} = −10.35 [71]) and the $CaIsaH^0_{-1}$ (log β_{11-1} = −11.36 [72]) were determined at t = 25 °C and I = 1 M NaCl.

$Gluc^-$ was proven to form polynuclear Ca-complexes in alkaline solutions at elevated temperatures, too. In the recent work of Buckó et al. [28], the formation constants of the $CaGlucH^0_{-1}$, $Ca_2Gluc_2H^0_{-4}$ and $Ca_3Gluc_2H^0_{-4}$ species were determined in the temperature range of 25–75 °C at 4 M NaCl ionic strength. Additionally, it was found that $Ca_2Gluc_2H^{2-}_{-4}$ can be substituted by its monomer, $CaGlucH^-_{-2}$ at 25 and 50 °C. Based on this finding, the authors proposed that the latter species undergoes dimerization, than the forming $Ca_2Gluc_2H^{2-}_{-4}$ abstracts one Ca^{2+}, yielding the main 3:2:−4 complex. Furthermore, the authors found that the abstraction of a Ca^{2+} ion by the 2:2:−4 complex is accompanied by $\Delta H \approx 0$.

The formation of polynuclear calcium complexes similar to those with gluconate both in terms of composition and stability, were also observed in alkaline solutions containing sugar carboxylates that are structurally closely related to $Gluc^-$. In alkaline solutions containing calcium(II) ions and $Hpgl^-$, the formation of $Ca_3Hpgl_2H^0_{-4}$ was observed by Pallagi et al. [71]. In analogous solutions containing Gul^-, the existence of the $Ca_3Gul_2H^0_{-4}$ and $Ca_3Gul_2H^+_{-3}$ were concluded from potentiometric titrations by Kutus et al. [30]. Both studies were performed at t = 25 °C and I = 1 M, employing NaCl as background electrolyte. Remarkably, at significantly higher ionic strength (4 M NaCl), beside the $Ca_3Hpgl_2H^0_{-4}$ complex, the $Ca_3Hpgl_2H^+_{-3}$ species was also found to be formed [128], analogous to the case of Gul^-. (The respective stability products are also listed in Table 7.) It is also important to note, that polynuclear calcium(II) complexes were not detected in alkaline solutions containing Isa^- [72], confirming again that the analogy between $Gluc^-$ and Isa^- should be handled with caution [123].

From these observations, the following general picture emerges. In hyperalkaline (pH > 12) aqueous solutions, Ca^{2+} ions form unusual solution complexes with certain (but not all) carbohydrates containing carboxylate and alcohol(ate) donor groups. These polynuclear (bi- or trinuclear) solution species are of surprisingly high stability, for example, the polynuclear complexes of gulonate ($Ca_3Gul_2H^0_{-4}$ and $Ca_3Gul_2H^+_{-3}$) are so stable, that the formation of

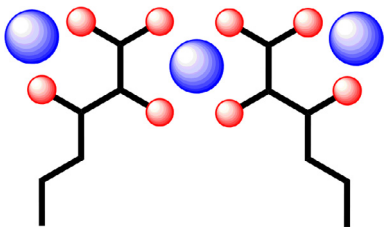


Fig. 16. Schematic structure of the short-chain polynuclear complex built up of Ca^{2+} ions (blue circles) and $GlucH^{3}_{-2}$ ions (the coordinating oxygens of which are represented by red circles).

the plausible mononuclear $CaGulH^{0}_{-1}$ complex cannot be experimentally detected in the ligand concentration range considered in the available experimental studies [30].

4.3. The structure of the complexes forming in alkaline solutions

The coordination sites of $Gluc^-$ in the bi- and three nuclear Ca-complexes were found to be the COO^-, C(2)-O^- and C(3)-O^- groups. This was proven by Ca(II) concentration- and temperature-dependent ^1H NMR spectra [26]. The structure of the $Ca_3Gluc_2H^{0}_{-4}$ complex was optimized by quantum chemical calculations at the HF/6–31(d,p) level (the structure is displayed in Fig. 15). Accordingly, the central Ca^{2+} is bound by one oxygen of each carboxylate and by the two C(2)-O^- groups, establishing two five-membered chelate rings. The other two metal ions are coordinated by the other oxygen of the COO^- and by the C(3)-O^- moieties, thereby forming six-membered chelate structures. As a result, each carboxylate acts as a bridging ligand between two (chemically non-equivalent) metal ions.

The prerequisite structural motif which makes the gluconate ion capable of forming these polynuclear complexes is the ability of the carboxylate group to act as a bridging ligand and, at the same time, the presence and contribution of the two adjacent alcoholate moieties (*i.e.,* C(2)-O^- and C(3)-O^-). In the mononuclear $CaGlucH^{0}_{-1}$complex, just like for the parent $CaGluc^+$ species, the formation and coexistence of the two binding isomers can be inferred with the five- or the six-membered chelate structure. This makes possible the simultaneous binding of two calcium ions from the opposite directions to the same gluconate molecule. The formation of the complex, however, does not end at this point as the uncoordinated sides of the calcium ions are still available for binding to the next gluconate unit. Ultimately, this results in the formation of "Ca-L-Ca-L-Ca" type short chains as schematically represented in Fig. 16.

The relative positions of the alcoholate functionalities determine their availability for complexation and seem to be the key. For gluconate, it makes possible to bind two calcium ions simultaneously by C(2)-O^- and C(3)-O^- with the carboxylate as bridge. For Isa^-, this was found not to be the case. The C(2)-O^- does but the C(6)–OH (situated on the carbon atom second from the carboxylate group) does not participate in the Ca^{2+} binding, as it was proven by ^{13}C NMR measurements (that is, the ^{13}C NMR signal of C6 remained unchanged upon Ca^{2+} complexation in strongly alkaline solutions). This is suspected to be the structural reason why Isa^- does not form polynuclear complexes with calcium ions. On this basis, it was suggested that the readily available gluconate is not a good model compound of isosaccharinate, both in terms of structure and stability [72].

The structures of the $Ca_3Hpgl_2H^{0}_{-4}$ and $Ca_3Gul_2H^{0}_{-4}$ have been recently scrutinized by Kutus et al. [30]. Initially, from temperature-dependent ^1H NMR spectra, it was suggested [71] that the in this type of complex, the binding sites in $Gluc^-$ and $Hpgl^-$ are identical (that is, COO^-, C(2)-O^- and C(3)-O^- groups.) However, more detailed ^1H NMR measurements proved that the coordination sites of $Hpgl^-$ seem to be same as those of Gul^-, *i.e.*, COO^-, C(2)-O^- and C(4)-O^- groups (as the H2 peak is shifted downfield, while the H4 peak is shifted upfield for both ligands upon Ca^{2+} complexation). This leads to the conclusion that the analogy in the binding sites stems from the similarity of the arrangement of the OH groups.

Although Gul^- and $Hpgl^-$ differ in their relative configuration, the C(2)–OH and C(3)–OH groups are in *erythro*, while the C(3)–OH and C(4)–OH groups are in *threo* position in both anions. It is striking that in $Gluc^-$ the C(2)–OH and C(3)–OH groups are in *threo* position. It seems therefore likely that the *threo* or *erythro* configuration accounts for the differences in the coordination mode of $Gluc^-$ and Gul^-/$Hpgl^-$. In other words, after the formation of the ^-OOC–C(2)-O^- binding moiety, the steric arrangement (or spacing) of the C(3)–OH group relative to that of C(2)–OH determines whether the C(3)–OH or the C(4)–OH group will be coordinated to the Ca^{2+} ion. These results are in accordance with the rules proposed by Angyal et al. for sugar alcohols [94], *i.e.,* in neutral medium the complex formed *threo*-1,2-*threo*-2,3 triol is more stable than that with *threo*-1,2-*erythro*-2,3 triol. For sugar carboxylates, both the C(2)–OH and C(3)–OH groups can participate in the Ca^{2+} ion coordination in *threo-threo* case ($Gluc^-$), while the C(2)–OH and C(4)–OH groups are preferred in *threo-erythro* arrangement (Gul^- and $Hpgl^-$). From these observations it can be concluded that configuration plays crucial role in the formation of deprotonated Ca(II) complexes. These statements may hold for other metal complexes of carbohydrate derivatives, too.

5. Summary

The thermodynamic and structural characterization of the Ca^{2+}/ $Gluc^-$/ H_2O system emerges as a multifold and scientifically challenging exercise. In acidic solutions, the carboxyl deprotonation and lactonization takes place in parallel. Under (hyper)alkaline conditions the formation of one or more alcoholate groups on gluconate gives rise to the formation of a variety of monomeric and polynuclear Ca^{2+} complexes.

Acidic and neutral medium With careful experimentation and applying various experimental methods simultaneously, it proved to be possible to separate the experimental effects caused by carboxyl deprotonation and lactonization, and to accurately characterize the underlying multiple chemical equilibria and kinetic processes. The subtleties of the lactonization of gluconic acid have been revealed in great detail, including the separate evaluation of the formation of γ- and δ-lactones.

It has been shown that in weakly acidic to alkaline conditions, calcium ions form both 1:1 and 1:2 complexes with gluconate, and that the formation of the 1:2 species is related to the flexibility of the organic ligand. Recently, the crystal structure of the solid $CaGluc_2{\cdot}H_2O$ has also been determined.

It has been experimentally demonstrated (and supported by quantum mechanical calculations), that in the $CaGluc^+$ solution species the calcium ions are simultaneously chelated by COO^-/ C(2)–OH and COO^-/C(3)–OH, and therefore the two binding isomers coexist in solution.

Alkaline (hyperalkaline) medium The acid dissociation constants of the alcoholic OH of gluconate and those of some structurally related ligands have been determined and were found to correlate with the stability of the calcium complex formed with the alcoholate functionality. Deprotonation of the OH group results in a *ca.* hundredfold increase in the stability of the corresponding solution species.

In (hyper)alkaline aqueous solutions, Ca^{2+} ions were found to form polynuclear solution species with gluconate as well as with

certain (but not all) structurally related sugar-carboxylates; the complexes identified are of remarkably high stability, predominantly bi- or trinuclear and quite a few (but not all) of them are charge-neutral; calcium ions are simultaneously bound to the COO^-/C(2)-O^- and COO^-/C(3)-O^- of the gluconate, giving rise to the formation of short Ca-L-Ca-L-Ca chains. Upon comparison with other sugar carboxylic acids, the COO^-/C(2)-O^- motif always participates in metal-binding, while the actual configuration is determines whether the second alcoholate binding site is the C(3)-O^- or the C(4)-O^- group.

6. Outlook

The thermodynamic description of the binary Ca(II)-gluconate system is considered to be essential in the development of thermodynamic models of more complex systems, *i.e.* ternary systems including different metals, lanthanides (Ln) and actinides (An) of the type Ca(II)/M(II/III/IV)/$Gluc^-$ with M = Ni(II), Fe(III), Al(III), Ln (III)/An(III), An(IV), *etc.* The current review demonstrates that several (but not all) building blocks are now available for constructing these models. In aqueous solutions (in particular in alkaline ones), when polyhydroxy carboxylate ions, Ca^{2+} and further tria- or tetravalent cations are simultaneously present, binary as well as high stability heteropolynuclear (or ternary) complexes of $Ca_nM_mL_p$ type are formed. It is possible that in aqueous solutions various binary complexes (both mono- and polynuclear) comprising Ca^{2+} and sugar carboxylates serve as precursors of these highly stable ternary species. Their formation, nature and stability is determined by the chemical properties of the ligand as well as by that of the metal ions. The knowledge of the chemical motifs determining the stability and the structure of these solution species (both binary and ternary) is a prerequisite for the construction of thermodynamic models describing the abundance and distribution of the contributing components among the various complex species forming. Albeit considerable efforts are currently being made to elucidate the thermodynamics, composition and structure of these heteropolynuclear species, our current knowledge on them is limited. Therefore, and especially in view of their manifold practical relevance (such as the thermodynamic modelling of the aqueous chemistry certain radioactive waste repositories, or understanding the fundamental aspects of certain industrial processes in, *e.g.,* alumina refining, corrosion inhibition or textile dyeing), the detailed study of such systems is warranted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was jointly supported by the European Union and the Hungarian Government through the GINOP-2.3.2-15-201600013 and the NKFIH K 124 265 Grants. B. K. is grateful for the TÁMOP 4.2.4.A/A2-ELMH-12-0086 and UNKP-17-3-IV-SZTE-9 Grants within the framework of the National/New National Talent Programs (Hungary). The contribution of X. G. and M. A. to this work was funded by the German Ministry of Economic Affairs and Energy (BMWi) within the framework of the GRAZ project with contract number 02E11415C. All these supports are highly appreciated.

References

[1] D.T. Sawyer, Chem. Rev. 64 (1964) 633–643.
[2] S. Ramachandran, P. Fontanille, A. Pandey, C. Larroche, Food Technol. Biotechnol. 44 (2006) 185–195.
[3] R.L. Pecsok, R.S. Juvet Jr., J. Am. Chem. Soc. 77 (1955) 202–206.
[4] R.L. Pecsok, J. Sandera, J. Am. Chem. Soc. 77 (1955) 1489–1494.
[5] R.L. Pecsok, J. Sandera, J. Am. Chem. Soc. 79 (1957) 4069–4071.
[6] K. Blomqvist, E.R. Still, Anal. Chem. 57 (1985) 749–752.
[7] G.M. Escandar, L.F. Sala, Can. J. Chem. 70 (1992) 2053–2057.
[8] G.M. Escandar, L.F. Sala, M.G. Sierra, Polyhedron 13 (1994) 143–150.
[9] G.M. Escandar, J.M. Salas Peregrin, M. Gonzalez Sierra, D. Martino, M. Santoro, A.A. Frutos, S.I. Garcia, G. Labadié, L.F. Sala, Polyhedron 15 (1996) 2251–2261.
[10] T. Gajda, B. Gyurcsik, T. Jakusch, K. Burger, B. Henry, J.J. Delpuech, Inorg. Chim. Acta 276 (1998) 130–140.
[11] S. Giroux, P. Rubini, B. Henry, S. Aury, Polyhedron 19 (2000) 1567–1574.
[12] S. Giroux, S. Aury, B. Henry, P. Rubini, Eur. J. Inorg. Chem. (2002) 1162–1168.
[13] Z. Zhang, B. Bottenus, S.B. Clark, G.X. Tian, P. Zanonato, L.F. Rao, J. Alloy Compd. 444 (2007) 470–476.
[14] B. Kutus, N. Varga, G. Peintler, A. Lupan, A.A.A. Attia, I. Pálinkó, P. Sipos, Dalton Trans. 46 (2017) 6049–6058.
[15] K.L. Nash, M. Borkowski, M. Hancock, I. Laszak, Sep. Sci. Technol. 40 (2005) 1497–1512.
[16] Z. Zhang, S.B. Clark, G. Tian, P.L. Zanonato, L. Rao, Radiochim. Acta 94 (2006) 531–536.
[17] Z. Zhang, G. Helms, S.B. Clark, G.X. Tian, P. Zanonato, L.F. Rao, Inorg. Chem. 48 (2009) 3814–3824.
[18] R.J. Motekaitis, A.E. Martell, Inorg. Chem. 23 (1984) 18–23.
[19] W.M. Best, J.M. Harrowfield, T.M. Shand, R.V. Stick, Aust. J. Chem. 47 (1994) 2023–2031.
[20] A. Lakatos, T. Kiss, R. Bertani, A. Venzo, V.B. di Marco, Polyhedron 27 (2008) 118–124.
[21] A. Pallagi, A.G. Tasi, G. Peintler, P. Forgo, I. Palinko, P. Sipos, Dalton Trans. 42 (2013) 13470–13476.
[22] R.L. Pecsok, R.S. Juvet Jr., J. Am. Chem. Soc. 78 (1956) 3967–3972.
[23] F. Coccioli, M. Vicedomini, J. Inorg. Nucl. Chem. 40 (1978) 2106–2110.
[24] H.A. Tajmir-Riahi, J. Inorg. Biochem. 39 (1990) 33–41.
[25] A. Pallagi, P. Sebők, P. Forgo, T. Jakusch, I. Pálinkó, P. Sipos, Carbohydr. Res. 345 (2010) 1856–1864.
[26] A. Pallagi, É. Bajnóczi, S. Canton, T. Bolin, G. Peintler, B. Kutus, Z. Kele, I. Pálinkó, P. Sipos, Environ. Sci. Technol. 48 (2014) 6604–6611.
[27] M. Vavrusova, R. Liang, L.H. Skibsted, J. Agric. Food Chem. 62 (2014) 5675–5681.
[28] Á. Buckó, B. Kutus, G. Peintler, I. Pálinkó, P. Sipos, Polyhedron 158 (2019) 117–124.
[29] V. Bugris, Cs. Dudás, B. Kutus, V. Harmat, K. Csankó, S. Brockhauser, I. Pálinkó, P. Turner, P. Sipos, Acta Crystallogr. B 74 (2018) 598–609.
[30] B. Kutus, Cs. Dudás, G. Peintler, I. Pálinkó, P. Sipos, Carbohydr. Res. 460 (2018) 34–40.
[31] B. Kutus, Cs. Dudás, E. Orbán, A. Lupan, A.A.A. Attia, I. Pálinkó, P. Sipos, G. Peintler, Inorg. Chem. 58 (2019) 6832–6844.
[32] B. Michael, D.W. Coyne, S. Fishbane, V. Folkert, R. Lynn, A.R. Nissenson, R. Agarwal, J.W. Eschbach, S.Z. Fadem, J.R. Trout, J. Strobos, D.G. Warnock, Kidney Int. 61 (2002) 1830–1839.
[33] M. Masone, M. Vicedomini, Ann. Chim. (Rome) 71 (1981) 517–523.
[34] T. Bechtold, E. Burtscher, G. Kühnel, O. Bobleter, J. Soc. Dyers Colour. 113 (1997) 135–144.
[35] T. Bechtold, E. Burtscher, A. Turcanu, J. Chem. Soc., Dalton Trans. (2002) 2683–2688.
[36] T. Bechtold, A. Turcanu, J. Appl. Electrochem. 34 (2004) 1221–1227.
[37] F.R. Venema, J.A. Peters, H. van Bekkum, Recl. Trav. Chim. Pays-Bas 112 (1993) 445–450.
[38] M. van Duin, J.A. Peters, A.P.G. Kieboom, H. van Bekkum, Carbohydr. Res. 162 (1987) 65–78.
[39] E.A.A. El Meguid, S.S.A. El Rehim, E.M. Moustafa, Thin Solid Films 443 (2003) 53–59.
[40] S.S.A. El Rehim, S.S. Refaey, G. Schwitzgebel, F. Tara, M.B. Saleh, J. Appl. Electrochem. 26 (1996) 413–418.
[41] G.O. Mallory, J.B. Hajdu, Electroless Plating: Fundamentals and Applications, American Electroplaters and Surface Finishers Society, Washington, WA, U.S., 1990.
[42] E.W. Flick, Advanced Cleaning Product Formulations, Noyes Publications, Westwood, NJ, U.S., 1994.
[43] N.B. Singh, Cem. Concr. Res. 6 (1976) 455–460.
[44] V.S. Ramachandran, M.S. Lowery, Thermochim. Acta 195 (1992) 373–387.
[45] C. Jolicoeur, M.A. Simard, Cem. Concr. Compos. 20 (1998) 87–101.
[46] H.F.W. Taylor, Cement Chemistry, 2nd Ed., Thomas Telford Publishing, London, UK, 1997.
[47] L.R. van Loon, M.A. Glaus, K. Vercammen, Acta Chem. Scand. 53 (1999) 235–240.
[48] E. Wieland, L.R. van Loon, Cementitious Near-field Sorption Database for Performance Assessment of an ILW Repository in Opalinus Clay, NAGRA Technical Report No. NTB 02–20, Wettingen, Switzerland, 2002.
[49] M.A. Glaus, L.R. van Loon, A Generic Procedure for the Assessment of the Effect of Concrete Admixtures on the Retention Behaviour of Cement for Radionuclides: Concept and Case Studies, PSI Report No, Paul Scherrer Institute, Villigen, Switzerland, 2004.
[50] P. Warwick, N. Evans, T. Hall, S. Vines, Radiochim. Acta 92 (2004) 897–902.
[51] J. Tits, E. Wieland, M.H. Bradbury, Appl. Geochem. 20 (2005) 2082–2096.

[52] I. Pointeau, D. Hainos, N. Coreau, P. Reiller, Waste Manage. 26 (2006) 733–740.
[53] X. Gaona, V. Montoya, E. Colàs, M. Grivé, L. Duro, J. Contam. Hydrol. 102 (2008) 217–227.
[54] N. Evans, R. Hallam, S. Aldridge, P. Warwick, N. Bryan, 1st Annual Workshop RECOSY, Forschungszentrum Karlsruhe GmbH, Karlsruhe, Germany, 2009.
[55] E. Colàs, M. Grivé, I. Rojo, L. Duro, Radiochim. Acta 99 (2011) 269–273.
[56] E. Colàs, M. Grivé, I. Rojo, J. Solution Chem. 42 (2013) 1545–1557.
[57] E. Colàs, M. Grivé, I. Rojo, L. Duro, J. Solution Chem. 42 (2013) 1680–1690.
[58] H. Rojo, X. Gaona, T. Rabung, M. Garcia-Gutierrez, T. Missana, M. Altmaier, Dalton Trans. in preparation.
[59] H. Rojo, J. Tits, X. Gaona, M. Garcia-Gutiérrez, T. Missana, E. Wieland, Radiochim. Acta 101 (2013) 133–138.
[60] Smith R.M., Martell A.E., NIST Critically Selected Stability Constants of Metal Complexes Database, NIST Standard Reference Database 46 (n.d.) 2004.
[61] W. Hummel, G. Anderegg, L. Rao, I. Puigdomènech, O. Tochiyama, Chemical Thermodynamics, Vol. 9. Chemical Thermodynamics of Compounds and Complexes of U, Np, Pu, Am, Tc, Se, Ni and Zr with, in: Selected Organic Ligands, Elsevier, North Holland, Amsterdam, The Netherlands, 2005.
[62] R.K. Cannan, A. Kibrick, J. Am. Chem. Soc. 60 (1938) 2314–2320.
[63] J. Schubert, A. Lindenbaum, J. Am. Chem. Soc. 74 (1952) 3529–3532.
[64] G.E. Sipes, Structure and Stability Constants of Boron, Calcium and Magnesium Gluconate Chelates from Optical Rotation and Computer Analysis Ph.D. Thesis, University of Illinois, Urbana, IL, U.S., 1969.
[65] L.H. Skibsted, G. Kilde, Dan. Tidsskr. Farm. 46 (1972) 41–46.
[66] J.W. Haas, Mar. Chem. 19 (1986) 299–304.
[67] K. Vercammen, Complexation of Calcium, Thorium and Europium by α-Isosaccharinic Acid under Alkaline Conditions Ph.D. Thesis, Swiss Federal Institute of Technology, Zurich, Switzerland, 2000.
[68] M. Vavrusova, M.B. Munk, L.H. Skibsted, J. Agr. Food Chem. 61 (2013) 8207–8214.
[69] F. Stumpff, J.A.S. McGuigan, Anal. Biochem. 459 (2014) 46–52.
[70] B. Kutus, D. Ozsvár, N. Varga, I. Pálinkó, P. Sipos, Dalton Trans. 46 (2017) 1065–1074.
[71] A. Pallagi, Z. Csendes, B. Kutus, E. Czeglédi, G. Peintler, P. Forgó, I. Pálinkó, P. Sipos, Dalton Trans. 42 (2013) 8460–8467.
[72] C. Dudás, B. Kutus, É. Böszörményi, G. Peintler, Z. Kele, I. Pálinkó, P. Sipos, Dalton Trans. 46 (2017) 13888–13896.
[73] P.A. Levene, H.S. Simms, J. Biol. Chem. 68 (1926) 737–749.
[74] D.T. Sawyer, J.B. Bagger, J. Am. Chem. Soc. 81 (1959) 5302–5306.
[75] R.E. Mitchell, F.R. Duke, Ann. NY. Acad. Sci. 172 (1970) 131–138.
[76] J.R. Felty, Thermodynamics of Aldonic Acids and Lactones, M.Sc. Thesis, Texas Tech University, Lubbock, TX, U.S, 1972.
[77] Y. Pocker, E. Green, J. Am. Chem. Soc. 95 (1973) 113–119.
[78] C.L. Combes, G.G. Birch, Food Chem. 27 (1988) 283–298.
[79] J. Zubiaur, R. Castano, N. Etxebarria, L.A. Fernandez, J.M. Madariaga, Talanta 45 (1998) 1007–1014.
[80] S. Ekberg, C. Ekberg, Y. Albinsson, J. Solution Chem. 33 (2004) 465–477.
[81] Z. Zhang, P. Gibson, S.B. Clark, G. Tian, P.L. Zanonato, L. Rao, J. Solution Chem. 36 (2007) 1187–1200.
[82] B. Kutus, G. Peintler, Á. Buckó, Zs. Balla, A. Lupan, A.A.A. Attia, I. Pálinkó, P. Sipos, Carbohydr. Res. 467 (2018) 14–22.
[83] E. Heinz, Biochem. Z. 321 (1951) 314–342.
[84] J.T.H. Roos, D.R. Williams, J. Inorg. Nucl. Chem. 39 (1977) 367–369.
[85] F. Coccioli, M. Vicedomini, J. Inorg. Nucl. Chem. 40 (1978) 2103–2105.
[86] B. Gyurcsik, L. Nagy, Coord. Chem. Rev. 203 (2000) 81–149.
[87] S.J. Angyal, K.P. Davies, J. Chem. Soc. D: Chem. Commun. (1970) 500–501.
[88] S.J. Angyal, Aust. J. Chem. 25 (1972) 1957–1966.
[89] S.J. Angyal, Pure Appl. Chem. 35 (1973) 131–146.
[90] S.J. Angyal, R.J. Hickman, Aust. J. Chem. 28 (1975) 1279–1287.
[91] S.J. Angyal, Chem. Soc. Rev. 9 (1980) 415–428.
[92] L.-G. Ekström, A. Olin, Acta Chem. Scand. A 31 (1977) 838–844.
[93] H. Lönnberg, A. Vesala, Carbohydr. Res. 78 (1980) 53–59.
[94] S.J. Angyal, D. Greeves, J.A. Mills, Aust. J. Chem. 27 (1974) 1447–1456.
[95] A.P.G. Kieboom, H.M.A. Buurmans, L.K. van Leeuwen, H.J. van Benschop, Recl. Trav. Chim. Pays-Bas. 98 (1979) 393–394.
[96] K.K. Mäkinen, E. Söderling, Calcif. Tissue Int. 36 (1984) 64–71.
[97] J. Briggs, P. Finch, M.C. Matulewicz, H. Weigel, Carbohydr. Res. 97 (1981) 181–188.
[98] J.-P. Morel, C. Lhermet, N. Morel-Desrosiers, J. Chem. Soc., Faraday Trans. 1 (84) (1988) 2567–2571.
[99] S.P. Moulik, D.P. Khan, Carbohydr. Res. 36 (1974) 147–157.
[100] A. Pallagi, Cs. Dudás, Z. Csendes, P. Forgó, I. Pálinkó, P. Sipos, J. Mol. Struct. 993 (2011) 336–340.
[101] J.K. Beattie, M.T. Kelso, Aust. J. Chem. 34 (1981) 2563–2568.
[102] R.E. Hoffman, T.J. Rutherford, B. Mulloy, D.B. Davies, Magn. Reson. Chem. 28 (1990) 458–464.
[103] R.O. Gould, A.F. Rankin, J. Chem. Soc. D: Chem. Commun. (1970) 489–490.
[104] H.-A. Tajmir Riahi, Carbohydr. Res. 122 (1983) 241–248.
[105] C. Makridou, M. Cromer-Morin, J.P. Scharff, Bull. Soc. Chim. Fr. 12 (1977) 59–63.
[106] P.G. Daniele, C. Foti, A. Gianguzza, E. Prenesti, S. Sammartano, Coord. Chem. Rev. 252 (2008) 1093–1107.
[107] B. Kutus, Á. Buckó, G. Peintler, I. Pálinkó, P. Sipos, Dalton Trans. 45 (2016) 18281–18291.
[108] J.A. Rendleman, Adv. Carbohydr. Chem. 21 (1966) 209–271.
[109] B. Kutus, Complex Formation and Lactonization Reactions in Aqueous Solutions Containing Ca^{2+} or Nd^{3+} Ions and Sugar-Type Ligands Ph.D. Thesis, University of Szeged, Szeged, Hungary, 2018.
[110] T. Taga, T. Kaji, K. Osaki, Bull. Chem. Soc. Jpn. 58 (1985) 30–35.
[111] C.R. Groom, I.J. Bruno, M.P. Lightfoot, S.C. Ward, Acta Cryst. B 72 (2016) 171–179.
[112] M.W. Wieczorek, J. Blaszczyk, B.W. Król, Acta Cryst. C 52 (1996) 1193–1198.
[113] U. Berner, A Thermodynamic Description of the Evolution of Pore Water Chemistry and Uranium Speciation during the Degradation of Cement, PSI-Report No. 62, Paul Scherrer Institute, Villigen, Switzerland, 1990.
[114] V. Neck, M. Altmaier, Th. Rabung, J. Lützenkirchen, T. Fanghänel, Pure Appl. Chem. 9 (2009) 1555–1568.
[115] C. Bube, V. Metz, E. Bohnert, K. Garbev, D. Schild, B. Kienzler, Phys. Chem. Earth 64 (2013) 87–94.
[116] B.I. Whittington, Hydromet 43 (1996) 13–35.
[117] S.P. Rosenberg, D.J. Wilson, C.A. Heath, In Essential Readings in Light Metals. In: D. Donaldson, B. Raahauge (Eds.), Alumina and Bauxite, Vol. 1, John Wiley & Sons, New York, NY, U.S., 2013, pp. 210–216.
[118] A. Pallagi, Interaction of Calcium with Sugar Type Ligands in Solutions Related to the Bayer Process Ph.D. Thesis, University of Szeged, Szeged, Hungary, 2011.
[119] J. Clayden, N. Greeves, S. Warren, P. Wothers, Organic Chemistry, Oxford University Press, New York, NY, U.S., 2001, p. 196.
[120] Cs. Dudás, Complex Formation between Calcium and Hydroxy/Oxocarboxylates in Neutral and Highly Alkaline Aqueous Solutions, Ph.D. Thesis, University of Szeged, Szeged, Hungary, 2018.
[121] A. Gácsi, Structure and Equilibria of Some Ca-complexes Forming in Hyperalkaline Aqueous Solutions Ph.D. Thesis, University of Szeged, Szeged, Hungary, 2017.
[122] D.D. Perrin, B. Dempsey, E.P. Serjeant, pKa Prediction for Organic Acids and Bases, Chapman and Hall, New York, NY, U.S., 1981.
[123] K.H. Birjkumar, N.D. Bryan, N. Kaltsoyannis, Dalton Trans. 41 (2012) 5542–5552.
[124] M. van Duin, J.A. Peters, A.P.G. Kieboom, H. van Bekkum, Recl. Trav. Chim. Pays-Bas 108 (1989) 57–60.
[125] C.L. Mehltretter, B.H. Alexander, C.E. Rist, Ind. Eng. Chem. 45 (1953) 2782–2784.
[126] A. Pallagi, Á. Tasi, A. Gácsi, M. Csáti, I. Pálinkó, G. Peintler, P. Sipos, Cent. Eur. J. Chem. 10 (2012) 332–337.
[127] B. Kutus, A. Gácsi, A. Pallagi, I. Pálinkó, G. Peintler, P. Sipos, RSC Adv. 6 (2016) 45231–45240.
[128] Á. Buckó, B. Kutus, G. Peintler, I. Pálinkó, P. Sipos, Proceedings of the 35th International Conference on Solution Chemistry, Hungary, Szeged, 2018, p. 116.