Cobalt(III)-Binding of Gluconate and 2-Amino-2-Deoxy-Gluconate

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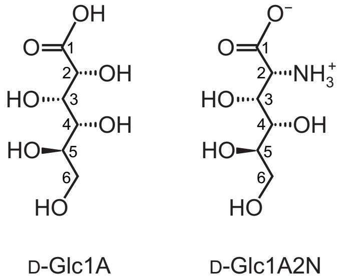
Dedicated to Professor Heinrich Nöth on the occasion of his 85th birthday

Two isomers of the [Co(tren)(D-Glc1A1,2H$_{-2}$-$\kappa^2 O^{1,2}$)]$^+$ (**1**) chelate are formed in equal parts in the reaction of [Co(tren)Cl$_2$]Cl and sodium gluconate. In contrast, the gluconate's 2-amino-2-deoxy derivative glucosaminate formed a single isomer of [Co(tren)(D-Glc1A2N1H$_{-1}$-$\kappa^2 N,O^2$)]$^{2+}$ (**2**). Crystals of the *OC*-6-34 isomer of **1**, [**1a**]PF$_6$·H$_2$O, showed the support of the metal-binding site by intramolecular hydrogen bonds. Due to the inertness of the cobalt(III) chelates, spectroscopy on redissolved crystals of [**1a**]PF$_6$·H$_2$O allowed the separation of the two ^{13}C NMR signal sets of the isomeric mixture. In a DFT approach, a small energy difference explained the formation of two isomers in the case of the gluconate. A larger difference was obtained for the glucosaminate, in line with the known rules for the stereospecific amino acid-Co(tren) chelation.

Key words: Gluconate, 2-Amino-2-deoxy-gluconate, Glucosaminate, Cobalt(III)

Introduction

D-Gluconate (Scheme 1) is a widely used chelator for di- and trivalent metal centres. Despite this fact, our knowledge of the structural principles of its chelates is sparse. In terms of X-ray analyses, only four crystal structures have been described as yet with the central metals being Pb^{II}, Mn^{II} and Cu^{II} [1 – 4]. To the best of our knowledge, no single-crystal X-ray data are available in the case of trivalent central metals. As a consequence, highly speculative formulae have been assigned to the medically used ferric gluconates, for example, which serve as iron-supplementing preparations in anemia therapy [5]. With this work we contribute to this issue by reporting the first crystal structure analysis of a gluconato chelate of a trivalent metal centre. Specifically, we describe gluconate chelation of the [Co^{III}(tren)]$^{2+}$ residue [tren = tris(2-aminoethyl)amine]. To highlight the peculiarities of gluconate coordination, the investigation was extended to a related ligand, the 2-amino-2-deoxy derivative of D-gluconate, D-glucosaminate (Scheme 1). Glucosaminic acid is a so-called ‘sugar amino acid’ which may be regarded as a higher homologue of serine.



Scheme 1. Stereochemical drawings and IUPAC-style abbreviations of D-gluconic acid (left) and the serine homologue 2-amino-2-deoxy-D-gluconic acid (D-glucosaminic acid), the latter in its zwitterionic form (right).

Results and Discussion

The reaction of equimolar amounts of gluconic acid and the CoN$_4$ (N = amine function) source [Co(tren)Cl$_2$]Cl resulted, in the presence of sodium hydroxide, in a solution whose ^{13}C NMR spectrum showed two sets of gluconate-chain signals arranged pairwise, together with twelve well-resolved signals for the tren carbon atoms (two sets of the three CH$_2$-NH$_2$ carbons at lower field and two sets of the three CH$_2$-NR$_2$ carbons at higher field). After the addition of hexafluoridophosphate, one component crystallised within six weeks. Fig. 1 shows the structure of the complex monocation in the crystals of [Co(tren)(D-Glc1A1,2H$_{-2}$-$\kappa^2 O^{1,2}$)]PF$_6$·H$_2$O ([**1a**]PF$_6$·H$_2$O). In **1a**, the free *cis*-coordination site of the Co(tren) moiety is occupied by the doubly deprotonated α-alkoxy-carboxylate function of gluconic acid, which forms a flat, almost unpuckered, five-membered chelate ring. The carboxylate oxygen atom is attached *trans* to the tertiary amine nitrogen atom. In terms of IUPAC's configuration index, **1a** thus resembles the notation *OC*-6-34 [6]. A second isomer of similar sta-

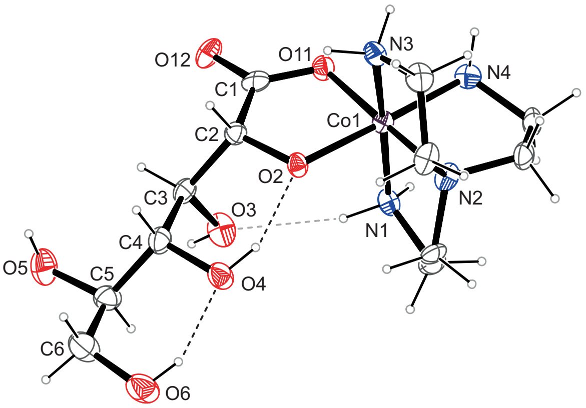


Fig. 1 (color online). The structure of the cation in crystals of [**1a**]$PF_6 \cdot H_2O$ (ORTEP representation with 50% probability ellipsoids). Distances (Å) from Co1 to: O2 1.896(2), O3 1.898(2), N1 1.960(3), N2 1.939(3), N3 1.956(3), N4 1.946(3); torsion angle O11–C1–C2–O2 −8.4°. The *intra*- and *inter*-molecular hydrogen bonds are specified in Table 2.

Table 1. ^{13}C NMR chemical shifts (δ) of **1** and **2** relative to $\delta(\text{MeOH}) = 49.5$, and coordination-induced shift (CIS) values defined by $\Delta\delta = \delta(\text{complex}) - \delta(\text{free ligand})$ in aqueous solution. CIS values for **1** and **2** refer to the gluconate anion and the glucosamine zwitterion as the free species, respectively.

	C1	C2	C3	C4	C5	C6
δ(**1a**)	191.3	80.8	76.6	72.0	70.3	63.7
$\Delta\delta$(**1a**)	12.1	6.1	3.2	0.2	−1.2	0.4
δ(**1b**)	190.0	82.4	74.7	71.7	69.9	63.5
$\Delta\delta$(**1b**)	10.9	7.7	1.5	−0.1	−1.6	0.2
δ(**2**)	184.2	62.4	68.7	72.7	71.2	62.9
$\Delta\delta$(**2**)	10.7	3.1	0.5	−1.1	−0.5	−0.8

Table 2. Hydrogen bonds in [**1a**]$PF_6 \cdot H_2O$. No standard deviation is given for values derived from calculated H atom positions; D: hydrogen bond donor, A: hydrogen bond acceptor. Symmetry codes: $^{\text{i}}$ $x+1/2, -y+3/2, -z$; $^{\text{ii}}$ $x+1, y+1, z$; $^{\text{iii}}$$x-1/2, -y+3/2, -z$; $^{\text{iv}}$ $x, y-1, z$; $^{\text{v}}$ $-x+1, y+1/2, -z+1/2$; $^{\text{vi}}$ $x-1/2, -y+3/2, -z$.

D	H	A	D–H (Å)	H–A (Å)	D···A (Å)	D–H···A (deg)
O3	H83	O7$^{\text{i}}$	0.84	1.95	2.749(4)	159
O4	H84	O2	0.84	1.85	2.592(3)	147
O5	H85	F6$^{\text{ii}}$	0.84	2.41	3.191(4)	154
O5	H85	F3$^{\text{ii}}$	0.84	2.62	3.295(5)	138
O6	H86	O4	0.84	1.95	2.633(3)	138
N1	H711	O3	0.92	2.28	3.164(4)	161
N1	H712	O12$^{\text{iii}}$	0.92	2.07	2.969(4)	164
N3	H731	O6$^{\text{iv}}$	0.92	1.93	2.829(4)	165
N3	H732	F5$^{\text{v}}$	0.92	2.41	3.185(4)	141
N3	H732	F4$^{\text{v}}$	0.92	2.53	3.403(4)	158
N4	H741	O12$^{\text{iii}}$	0.92	2.18	2.978(4)	144
N4	H742	O6$^{\text{iv}}$	0.92	2.33	3.115(4)	143
O7	H871	O4$^{\text{iv}}$	0.81(3)	2.16(3)	2.959(4)	165(4)
O7	H872	O5$^{\text{vi}}$	0.82(3)	2.17(3)	2.881(4)	146(4)

bility might have been expected with the gluconate ligand and turned 180° around the chelate ring's twist axis running through the cobalt atom. The IUPAC configuration index of this second isomer of the [Co(tren)(D-Glc1A1,2H_{-2}-$\kappa^2O^{1,2}$)] cation (**1b**) is *OC*-6-43. Since both isomers should have about the same energy, both should form in about the same molar amount [the N1···O3 hydrogen bond (Fig. 1) that provides another link between the gluconate and the Co(tren) moiety, in addition to the Co–O bonds, would be maintained *via* the N3 atom due to the Co(tren) residue's apparent C_s symmetry]. With a crystalline isomer in hand, a final assignment of the ^{13}C NMR spectrum was tangible since cobalt(III) complexes are normally inert towards ligand substitution. In fact, redissolved crystals of the salt of **1a** showed a single set of signals in its ^{13}C NMR spectrum and thus allowed the assignment of both species in the reaction mixture. The obtained δ and $\Delta\delta$ values (Table 1) underline the similarity of the species including the common $\kappa^2O^{1,2}$ bonding mode. It thus seems reasonable to consider **1b** the *OC*-6-43 isomer.

Further characteristics of the gluconato ligand are highlighted in Fig. 1. Most notably, two of the four hydrogen bond-donating hydroxy functions establish intramolecular bonds. Thus, a short cooperative sequence O6–H···O4–H···O2 stabilises the cobalt-binding alkoxy function. As with the N···O3 bonds, these interactions can be maintained in the second isomer. Table 2 shows a comprehensive list of the hydrogen bonds in the solid. The graph-set analysis showed the relevant patterns [7, 8]: *S*(6) (unitary graph set C4-O4-H84···O2-C2-C3), *S*(6) (unitary graph set C6-O6-H86···O4-C4-C5), *S*(7) (unitary graph set O2-Co-N1-H711···O3-C3-C2), *C*(10) (unitary graph set H731···O6-C6-C5-C4-C3-C2-O2-Co-N3), $C_2^2(7)$ (binary graph set H501···O4-C4-C3-O3···H83···O7), C_2^2 (13) (binary graph set H731···O6-C6-C4-C3-C2-C1-O12···H712-N1-Co-N3), R_2^2 (8) (binary graph set O3-H83···O7-H872···O5-C5-C4-C3), and $R_2^1(6)$ (binary graph set N3-H731···O6···H742-N4-Co).

Energetic equivalence of the isomers is not shared by the Co(tren) chelate of the gluconate derivative 2-amino-2-deoxy-gluconate (glucosaminate). Under similar conditions (one more mole of base added), according to ^{13}C NMR data, a single major κ^2O^1N-chelated product instead of two isomers was formed (Table 1). Being a 'sugar amino acid' and thus an amino acid, glucosaminic acid follows the rules of amino acid-Co(tren) chelation. Already in 1976, Mitsui *et al.* described the existence of two isomers of the $[Co(tren)(GlyH_{-1})]^{2+}$ ion (Gly = glycine) of different stability, a stable orange one and an unstable red one. The stable isomer has the amino acid NH_2 function *trans* to the tertiary nitrogen atom of the tren ligand (*OC*-6-43 in terms of the IUPAC configuration index), and the unstable isomer bears its carboxy function *trans* to N^{tert} (*OC*-6-34). The energy of the latter isomer was determined to be 2.8 kcal mol^{-1} (11.7 kJ mol^{-1}) higher by means of a force-field approach [9]. In agreement with the result for glucosaminate, other amino acids have been found to form the same stable isomer stereoselectively as the only product [10–12].

To explain the divergent result – two major isomers for the gluconate but a single major isomer in the case of the sugar amino acid – a comparative DFT approach was chosen. For the calculation, glucosaminate was truncated to glycinate, and gluconate to glycolate. The result is in agreement with the ^{13}C NMR-spectroscopic findings. Hence, at the BP/def2-TZVP level of theory, the glycinate isomers show an energy difference of 15.5 kJ mol^{-1}, close to the force-field value of ref. [9], with the *OC*-6-43 isomer as the stable species. In contrast, the glycolate isomers differed in energy by only 6.3 kJ mol^{-1}, which we interpret to be small enough to understand the presence of the two isomers in equal parts in the real-world experiment.

Conclusions

Different rules are valid for the chelation of the Co(tren) residue to gluconate and glucosaminate. Since the Co(tren) probe lacks C_2 symmetry, two isomers may be formed by the chelation of a specific metal-binding site by a 180° turn of the ligand. In line with energies calculated in a DFT approach, both isomers were detected with the gluconato ligand, whereas the glucosaminato ligand followed the known rules of amino acid-Co(tren) chelation and stereoselectively formed one isomer (**2**). Unfortunately, we did not succeed in isolating crystals of a salt of **2**. However, it seems reasonable to suppose that the observed species follows the rule and bears the amino acid nitrogen donor *trans* to the tren ligand's tertiary amine function.

Experimental Section

$[Co(tren)Cl_2]Cl$ was prepared according to a protocol for $[Co(en)_2Cl_2]Cl$ [13].

*[Co(tren)Cl₂]Cl (**1**)*

(0.31 g, 1.0 mmol) was dissolved in water (8 mL). D-Gluconic-acid δ-lactone (0.18 g, 1.0 mmol), NaOH (0.080 g, 2.0 mmol) and charcoal (0.8 g) were added. The dark-red solution was heated for 1 h at 75 °C. The charcoal was filtered off. 0.1 M KPF_6 solution was allowed to diffuse into the filtrate at 4 °C. Red crystals of [**1a**]$PF_6\cdot H_2O$ formed within six weeks in 0.213 g yield (38 %). – Elemental analysis for $C_{12}H_{26}CoF_6N_4O_7P\cdot H_2O$: calcd. C 25.72, H 5.04, N 10.00; found: C 25.50, H 5.23, N 10.01; %.

*Crystallographic data for [**1a**]PF₆·H₂O*

$C_{12}H_{30}CoF_6N_4O_8P$, $M_r = 562.30$, orthorhombic, $P2_12_12_1$, $a = 8.7147(5)$, $b = 10.1638(5)$, $c = 23.5678(10)$ Å, $V = 2087.5(2)$ Å^3, $Z = 4$, $\rho = 1.79$ g cm^{-3}, $\mu = 1.0$ mm^{-1}, no absorption correction applied, crystal size: $0.31 \times 0.25 \times 0.12$ mm^3, $T = 200(2)$ K, Oxford Xcalibur KappaCCD, MoK_α, θ range: 3.99–26.37°, 10236 *hkl*, 3582 independent, $R_{int} = 0.0371$, $\sigma(I)/I = 0.0670$, 300 parameters, 3 restraints, $R(F_{obs}) = 0.0350$, $R_w(F^2) = 0.0662$, $S = 0.937$, shift/error$_{max}$ = 0.001, max. / min. residual electron density: 0.37 / −0.29 e Å^{-3}, Flack absolute-structure parameter x: 0.005(16). Programs used: SHELX, ORTEP [14, 15].

CCDC 927674 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

*[Co(tren)Cl₂]Cl (**2**)*

(0.39 g, 1.3 mmol) was dissolved in water (2.5 mL). D-Glucosaminic acid (0.24 g, 1.3 mmol), NaOH (0.10 g, 2.5 mmol) and charcoal (0.1 g) were added. The dark-red solution was heated for 1 h at 50 °C. The charcoal was filtered off. The ^{13}C NMR spectrum of the solution showed **2** as the single main product besides minute amounts of by-products.

NMR spectra were recorded at room temperature on a Jeol Eclipse 400 NMR (^{1}H: 400 MHz, $^{13}C\{^1H\}$: 101 MHz) or a Jeol Eclipse 270 spectrometer (^{1}H: 270 MHz; $^{13}C\{^1H\}$: 68 MHz). When D_2O was used as a solvent, one drop of methanol (referenced to 49.5 ppm) was added to the sample tube (5 mm) in order to obtain a reference signal in the $^{13}C\{^1H\}$ NMR spectra. The ^{1}H and $^{13}C\{^1H\}$ NMR signals were assigned by means of ^{1}H-^{1}H COSY, DEPT135, ^{1}H-^{13}C

HMQC and ^{1}H-^{13}C HMBC experiments. The values for the free ligands were determined in their neutral aqueous solutions, and were referenced to 49.5 ppm for the ^{13}C NMR signal of methanol. The results are listed in Table 1 for the glucose-derived ligands. – ^{13}C NMR data for the tren spectator ligand: **1a**: 63.0, 62.6, 60.9, 45.4, 45.0, 44.4; **1b**: 62.9, 62.1, 60.1, 45.2, 44.9, 44.2; **2**: 62.0, 61.6, 59.2, 45.3, 45.2, 44.4; free tren: 63.7, 63.3, 60.2, 45.8, 45.5, 44.1 ppm.

DFT calculations were performed with ORCA at the BP/def2-TZVP level of theory [16]. A solvent model was applied (COSMO with the dielectric constant of water) as well as Grimme's van der Waals correction [17].

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