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First synthesis and characterization of zinc(II) complexes containing *N*-glycosides derived from ethylenediamine and D-glucosamine

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Zinc(II) complexes containing *N*-glycosides derived from D-glucosamine (D-GlcN) and ethylenediamine (en), $[Zn(D\text{-GlcN-en})_2]X_2$ (**1a** X = Cl, **1b** $X_2 = SO_4^{2-}$), were prepared and characterized by elemental analysis and nuclear magnetic resonance spectroscopy involving X-ray crystallography, where D-GlcN-en = 1-{(2-aminoethyl)amino}-2-amino-1,2-dideoxy-D-glucose. The complex cation of **1a** has a nearly C_2 symmetry and the central zinc atom is octahedrally coordinated by two tridentate *N*-glycoside ligands from D-glucosamine and ethylenediamine. The *N*-glycoside ligand, D-GlcN-en, ligates to the zinc atom through the C^2 amino nitrogen atom of D-glucosamine and the two nitrogen atoms of the diamine in a meridional mode. The analysis of the solution conformation of the sugar ring in **1a** based on vicinal coupling constants confirmed the similar structure revealed by X-ray crystallography.

Introduction

Interactions of carbohydrates with metal ions have become an important subject in the bioinorganic field, since many sugar-processing enzymes have been revealed to function with redox non-active metal ions such as Mg^{2+}, Mn^{2+} and Zn^{2+} in the active sites.[1] Elucidation of the reactivity and behavior of sugars around redox active metal ions also involves their potential relevance to ribonucleotide reductases which utilize non-heme diiron or coenzyme B_{12} functional units.[2]

As a significant part of our program to clarify the nature of sugar–transition-metal interactions, we have synthesized and fully characterized metal complexes containing *N*-glycosides formed from polyamines and sugars[3] or amino sugars.[4] We have recently reported the mononuclear nickel(II) complexes ligated by a tridentate *N*-glycoside formed from ethylenediamine or trimethylenediamine (tn) and D-glucosamine, $[Ni(D\text{-GlcN-diamine})_2]Cl_2$, which showed effective antifungal activity against the pathogenic yeast *Candida albicans* which causes serious disease in HIV-seropositive patients.[5]

Zinc is commonly found to bind to proteins in nature, either as a part of a catalytic site in enzymes[6] or as a structural component, as in DNA binding "zinc fingers".[7] Complexes of Zn(II) with monosaccharides Fru[8] (fructose) and GlupA (D-glucopyranosiduronic acid)[9] have been described, as has electrostatic binding to oligogalacturonates.[10] The binding of Zn(II) to heparin and glycosylaminoglycans was also reported.[11–14] Therefore, the ability to clarify the nature of the coordination behavior of sugars around the Zn(II) center is highly desirable.

In this paper, we wish to report the first successful isolation and X-ray crystal structure determination of zinc(II) complexes containing *N*-glycosides derived from D-glucosamine (D-GlcN) and ethylenediamine including their structure analysis in solution by means of ^1H and ^{13}C NMR measurements.

Experimental

Materials

All reagents were of the best commercial grade and were used without further purification. $[Zn(en)_3]Cl_2\cdot H_2O$[15] was prepared by known methods. The following abbreviations are used; en = 1,2-diaminoethane; D-GlcN = 2-amino-2-deoxy-D-glucose; D-GlcN-en = 1-{(2-aminoethyl)amino}-2-amino-1,2-dideoxy-D-glucose.

Preparations of zinc(II) complexes containing *N*-glycosides of D-glucosamine

$[Zn(D\text{-GlcN-en})_2]Cl_2\cdot H_2O$ (1a·H_2O). D-GlcN·HCl (2.15 g, 0.01 mol) and $[Zn(en)_3]Cl_2\cdot 2H_2O$ (3.16 g, 0.01 mol) were dissolved in 200 mL of methanol, and the mixture was stirred for 2–3 days at room temperature. The solution was kept at room temperature to give white microcrystals, which were collected, washed with cold ethanol, and dried *in vacuo* (1.68 g, yield 22%). Calc. for $[Zn(D\text{-GlcN-en})_2]Cl_2\cdot H_2O$ (**1a**·H_2O): $C_{16}H_{40}N_6O_9Cl_2Zn$: C, 32.30; H, 6.71; N, 14.22. Found: C, 32.19; H, 6.76; N, 14.08%.

$[Zn(D\text{-GlcN-en})_2]SO_4\cdot 4H_2O$ (1b·$4H_2O$). A methanolic solution containing ethylenediamine (0.601 g, 0.01 mol) and D-GlcN·HCl (2.150 g, 0.01 mol) was heated at 60 °C for 80 min. The resultant pale yellow solution was cooled to room temperature, and a methanolic solution of $ZnSO_4\cdot 7H_2O$ (2.876 g, 0.01 mol) was added to the solution to yield a white powder, which was collected, washed with cold ethanol, and dried *in vacuo* (3.24 g, yield 48%). Calc. for $[Zn(D\text{-GlcN-en})_2]SO_4\cdot 4H_2O$ (**1b**·$4H_2O$): $C_{16}H_{46}N_6O_{16}SZn$: C, 28.43; H, 6.86; N, 12.43. Found: C, 28.42; H, 6.85; N, 12.43%.

Measurements

Infrared spectra were measured as KBr pellets or Nujol mulls on a JASCO FT/IR8900 recording spectrometer. All NMR spectra [^{1}H, ^{13}C, DEPT, ^{1}H–^{1}H, COSY, HMQC (heteronuclear multiple quantum correlation), HMBC (heteronuclear multiple bond correlation), NOESY and ROESY] were obtained on a Varian UNITY 500 MHz spectrometer in solutions of $(CD_3)_2SO$ and CD_3OD (2:1) at 40 °C. The residual solvent peak of CD_3OD was referenced to δ 3.3 in ^{1}H and δ 49.0 in ^{13}C NMR. One-dimensional ^{1}H NMR were recorded with a spectral width of 8000 Hz, 64 k data points. One-dimensional ^{13}C and DEPT NMR spectra were recorded with a spectral width of 28900 Hz, 65.5 k data points. Two-dimensional field gradient ^{1}H–^{1}H COSY were recorded with a spectral width of 2600 Hz with 1024 data points, 256 increments (zero filling to 2 k); four transients were recorded for each increment with a relaxation delay of 1 s.

Two-dimensional field gradient HMQC and HMBC (8 Hz, 4 Hz and 12 Hz) were recorded with a spectral width of 2600 Hz, 10254 points in the ^{1}H dimension and 13900 in the ^{13}C dimension, 256 increments (zero-filling to 8 k); 32 transients were recorded for each increment, with a relaxation delay of 1.8 s. ROESY spectra were obtained as follows. The standard pulse sequence *D*1-90°-*t*2-90°-SL-90°-FID acquisition was used to perform the ROESY experiment. The relaxation delay *D*1 was 1.5 s and the sweep width in both dimensions was 8000 Hz. Typical spectra were obtained from 8 scans and 256 increments and processed using a Gaussian weighting function. ROESY spectra with spin lock duration of 0.8 s were recorded. The 2 D ROESY experiments were recorded and displayed in the phase-sensitive mode. Mixing times of 1.5 s were used. The number of transients was set to 256 scans for each block: the other parameters were identical with those in ^{1}H–^{1}H COSY experiments. Zero filling was applied in the evolution time domain and the data were processed using a Gaussian weighting function in both dimensions.

Crystallography

Crystal data and intensity measurement for [Zn(D-GlcN-en)$_2$]Cl$_2$·2.75H$_2$O·0.5CH$_3$OH (1a·2.75H$_2$O·0.5CH$_3$OH). Microcrystals of **1a**·2.75H_2O·0.5CH_3OH were recrystallized from a minimum amount of water containing twice the amount of methanol to yield needle-like white crystals suitable for X-ray crystallography. The crystals were sensitive in air and became opaque after removal from the mother-liquor. A white crystal coated with epoxy cement on a glass fiber was mounted on the goniometer head on a Rigaku AFC5S four-circle automated diffractometer and was used to collect diffraction data at room temperature. The unit cell dimensions were determined by a least-squares method with 25 reflections in the range of $20 < 2\theta < 30°$. Three standard reflections were monitored every 150 reflections and showed only 1–4% random variation in intensity, for which no correction was made. The linear absorption coefficient for Cu-Kα (λ = 1.54178 Å) was 32.37 cm^{-1}. An empirical absorption correction by the ψ-scan method was applied. The data were corrected for Lorentz and polarization effects. The crystallographic and experimental data are summarized in Table 1.

Structure solution and refinement. The structure was solved by direct methods (SAPI91) and cycles of Fourier and difference Fourier syntheses. The structure was refined by full-matrix least-squares techniques. All hydrogen atoms were determined by difference Fourier syntheses and refined with appropriate B_{iso}. The final refinement converged to $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.050$ and $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2} = 0.077$ [$w = 1/\sigma^2(F_o)$]. The atomic scattering factors and values of f' and f'' for Cl, Zn, O, N and C atoms were taken from refs. 16 and 17. The known absolute configurations of the asymmetric carbon atoms of D-glucosamine were used as internal references for asymmetric centers to determine the absolute configuration of the complex. Selected bond distances and angles are listed in Table 2. All calculations were performed on a Digital VAX station 3100 M38 computer with the TEXSAN-TEXRAY structure analysis package.[18] The perspective views were drawn by using the program ORTEP-II.[19]

CCDC reference number 186/1407.

See http://www.rsc.org/suppdata/dt/1999/1851/ for crystallographic files in .cif format.

Table 1 Crystallographic and experimental data for **1a**·2.75H_2O·0.5CH_3OH

Formula	$O_{11.25}N_6C_{16.5}H_{39.5}ZnCl_2$
Formula weight	638.31
Crystal system	Orthorhombic
Space group	$P2_12_12_1$ (No. 19)
a/Å	16.300(7)
b/Å	23.398(5)
c/Å	15.791(3)
V/Å^3	6022(2)
Z	8
D_c/g cm^{-3}	1.365
T/°C	23
No. obsd. unique reflections	3706 ($I > 3\sigma(I)$)

Table 2 Selected bond distances (Å) and angles (°) for complex **1a**·2.75H_2O·0.5CH_3OH[a]

Zn(1)–N(1)	2.172(7)	Zn(1)–N(2)	2.186(7)
Zn(1)–N(3)	2.297(7)	Zn(1)–N(4)	2.193(7)
Zn(1)–N(5)	2.195(6)	Zn(1)–N(6)	2.247(7)
Zn(2)–N(7)	2.178(7)	Zn(2)–N(8)	2.178(7)
Zn(2)–N(9)	2.268(7)	Zn(2)–N(10)	2.195(8)
Zn(2)–N(11)	2.149(7)	Zn(2)–N(12)	2.271(7)
N(2)–C(3)	1.44(1)	N(5)–C(11)	1.45(1)
N(8)–C(19)	1.42(1)	N(11)–C(27)	1.44(1)
N(1)–Zn(1)–N(2)	78.6(3)	N(9)–Zn(2)–N(12)	89.4(2)
N(1)–Zn(1)–N(3)	154.7(3)	N(10)–Zn(2)–N(11)	80.0(3)
N(1)–Zn(1)–N(4)	100.1(3)	N(10)–Zn(2)–N(12)	158.2(3)
N(1)–Zn(1)–N(5)	108.3(3)	N(11)–Zn(2)–N(12)	78.4(2)
N(1)–Zn(1)–N(6)	90.1(3)	N(2)–Zn(1)–N(3)	77.4(2)
N(2)–Zn(1)–N(4)	97.9(3)	N(2)–Zn(1)–N(5)	172.6(2)
N(2)–Zn(1)–N(6)	104.5(2)	N(3)–Zn(1)–N(4)	91.2(3)
N(3)–Zn(1)–N(5)	96.1(2)	N(3)–Zn(1)–N(6)	88.0(2)
N(4)–Zn(1)–N(5)	78.5(3)	N(4)–Zn(1)–N(6)	156.8(3)
N(5)–Zn(1)–N(6)	78.5(2)	N(7)–Zn(2)–N(8)	79.8(3)
N(7)–Zn(2)–N(9)	156.3(3)	N(7)–Zn(2)–N(12)	89.9(3)
N(8)–Zn(2)–N(9)	77.3(2)	N(8)–Zn(2)–N(10)	97.6(3)
N(8)–Zn(2)–N(11)	173.4(2)	N(8)–Zn(2)–N(12)	103.7(2)
N(9)–Zn(2)–N(10)	90.8(3)	N(9)–Zn(2)–N(11)	96.5(2)

[a] Estimated standard deviations are given in parentheses.

Calculation of the vicinal ^{1}H–^{1}H coupling constants of the sugar units and diamine groups of [Zn(D-GlcN-en)$_2$]$^{2+}$

Recently Altona *et al.* proposed an extended Karplus equation by considering empirical group electronegativities for vicinal NMR ^{1}H–^{1}H couplings along the C–C bond as shown in eqn. (1)[20] where λ_i are empirical group electronegativities (substituent parameters) and s_i stands for the 'sign factor' (formally denoted ξi) of the substituent attached to the H–C–C–H fragment in question, either +1 or −1.[21] The torsion angles were calculated for the H–C–C–H fragments on the sugar rings and diamine chelates from the atomic coordinates determined by the crystal structure of **1a**·2.75H_2O·0.5CH_3OH. The λ values defined in the literature[20] were used. In our study, the H^a–C^a–

$$^3J(H^a,H^b) = 14.63\cos^2(\varphi) - 0.78\cos(\varphi) + 0.60 + \sum_i \lambda_i\{0.34 - 2.31[s_i(\varphi) + 18.4|\lambda_i|]\} \quad (1)$$

C^b–H^b torsion angles (φ, $-180 < \varphi \leq 180°$) for sugar ring structures and diamine chelate conformations on [Zn(D-GlcN-en)$_2$]$^{2+}$ were converted into the vicinal proton–proton coupling constants [$^3J(H^a,H^b)$] on the basis of the empirical equations proposed by Altona *et al.* as shown in eqn. (1).

Results and discussion

When the insoluble D-GlcN·HCl was reacted with a methanol solution of [Zn(en)$_3$]Cl$_2$·2H$_2$O, complete solubilization was observed. Analytical data showed that the complexes **1a** and **1b** consisted of two diamines and two amino sugar residues per zinc atom together with some solvent water molecules. In the IR spectra, besides a broad band for hydroxyl groups, a moderate peak corresponding to δ(N–H) was observed around 1600 cm^{-1}, which shifted to higher energy compared with that of the starting complex [Zn(en)$_3$]$^{2+}$, suggesting glycosylamine formation just as observed in the reactions of [Ni(diamine)$_3$]$^{2+}$ (diamine = en or tn) with monosaccharides.[3]

From these analytical data, the zinc(II) complexes of D-glucosamine were assumed to have a pseudo-octahedral [ZnN$_6$] structure where two *N*-glycoside ligands from a diamine and an amino sugar coordinate to the zinc atom in a tridentate manner. Providing the proposed bis(tridentate)zinc(II) structure is correct, some isomers, including the Δ and Λ configurations around the metal center and the *mer* and *fac* geometrical modes, are possible, but they could not be determined by spectroscopic analyses alone. In order to clarify the detailed structure, an X-ray crystallographic study of [Zn(D-GlcN-en)$_2$]Cl$_2$·2.75H$_2$O·0.5CH$_3$OH was undertaken.

Molecular structure of [Zn(D-GlcN-en)$_2$]Cl$_2$·2.75H$_2$O·0.5CH$_3$OH

There are two complexes in the asymmetrical unit. Since the structures of both the complex cations are nearly identical, the following description of the molecular structure applies equally to both the complex ions. A perspective drawing of the complex cation is given in Fig. 1, and some selected bond distances and angles are listed in Table 2. The compound consists of one complex cation, two chloride anions and methanol and water molecules of crystallization. The zinc atom is octahedrally coordinated by two *N*-glycoside ligands, D-GlcN-en, 1-{(2-aminoethyl)amino}-2-amino-1,2-dideoxy-D-glucose, through six nitrogen atoms. The complex cation has a nearly C_2 symmetry and is fairly distorted from ideal O_h symmetry with the average *trans* angle of 170.0° for the tridentate *N*-glycoside ligands. The two *N*-glycoside ligands coordinate to the zinc atom in a meridional mode with Δ configuration around the metal center defined by the two sugar chelate rings. The configuration around the metal center in **1a** is same as that in [Ni(D-GlcN-en)$_2$]$^{2+}$ **2**.[4] Each ligand coordinates to the metal at three points, through the C^2 amino nitrogen atom of the glucosamine moiety and through the two nitrogen atoms of the 1,2-diaminoethane residue. The pyranoid ring of the sugar unit in D-GlcN-en adopts the usual β-$^4C_1$ chair conformation. In our series of nickel(II)-sugar complexes, also including the present complex, the anomeric form of the *N*-glycosides is exclusively β and no complex with the α-*N*-glycoside conformation was isolated thus far except for [Ni(D-Ara-tn)$_2$]$^{2+}$.[3g] The five-membered chelate rings involving the sugar moiety, {[Zn(1)N(2)C(3)C(4)N(3)], [Zn(1)N(5)C(11)C(12)N(6)], [Zn(2)N(8)C(19)C(20)N(9)], [Zn(2)N(11)C(27)C(28)N(12)]} take a λ-*gauche* conformation and the five-membered chelate rings of the diamine part, {[Zn(1)N(1)C(1)C(2)N(2)], {[Zn(1)N(4)C(9)C(10)N(5)], {[Zn(2)N(7)C(17)C(18)N(8)], {[Zn(2)N(10)C(25)C(26)N(11)]}, adopt a δ gauche form. The absolute configuration around the glycosidic nitrogen atoms is *S* in the notation of Cahn, Ingold and Prelog.[22] These configurational aspects, just the same as those found in **2**, closely relate to the configuration around the C^2 carbon atom of the sugar moiety (*R*). The pyranoid ring is arranged to be planar with respect to the sugar chelate ring, which is interestingly contrasted to that found in [Ni(L-Rha-tn)$_2$]$^{2+}$,[3e] the pyranoid ring being considerably tilted with respect to the sugar chelate ring. The average bite angle of the five-membered chelate rings including the diamine part {N(1)–Zn(1)–N(2), N(4)–Zn(1)–N(5), N(7)–Zn(2)–N(8), N(11)–Zn(2)–N(12)}, is 78.6°, and that of the five-membered one comprising the sugar moiety {N(2)–Zn(1)–N(3), N(5)–Zn(1)–N(6), N(8)–Zn(2)–N(9), N(11)–Zn(2)–N(12)} is 77.9° which are normal values for the five-membered diamine rings. The average *trans* angle between the terminally coordinating atoms of the *N*-glycoside ligand to the zinc {N(1)–Zn(1)–N(3), N(2)–Zn(1)–N(5), N(4)–Zn(1)–N(6), N(7)–Zn(2)–N(9), N(8)–Zn(2)–N(11), N(10)–Zn(2)–N(12)} is 162.0° which is similar to those in **2**. The unit cell consists of the 8 complex cations, 16 Cl counter anions and 22 waters and 4 methanols of crystallization, in which disorder for some of the H$_2$O has been observed.

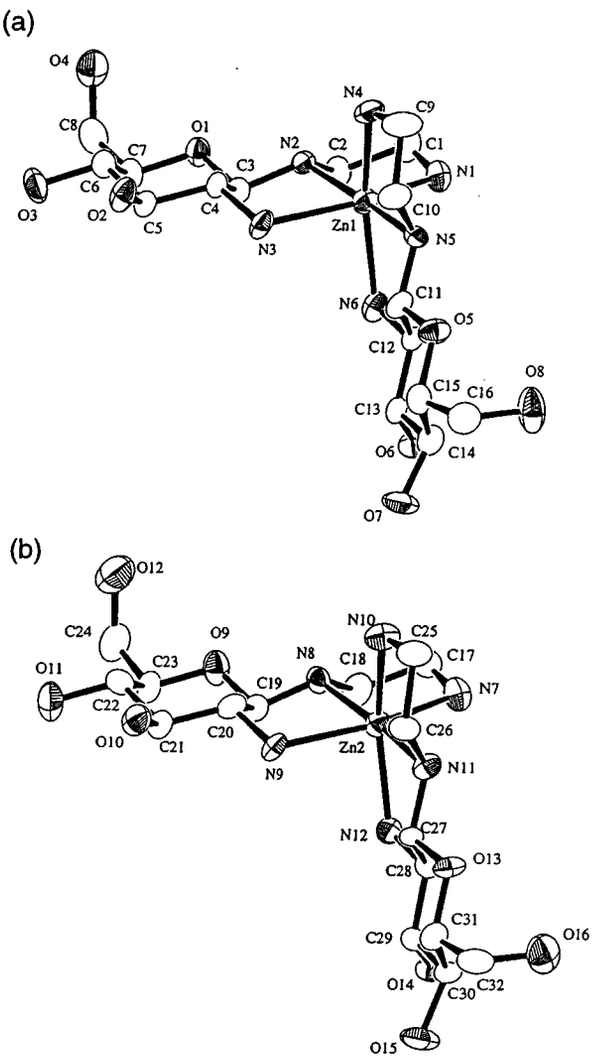

Fig. 1 Perspective drawing of [Zn(D-GlcN-en)$_2$]$^{2+}$ with the atomic numbering scheme in an asymmetric unit.

This complex decomposed gradually in water. However, ^{1}H and ^{13}C NMR spectra of **1a** were obtained in (CD$_3$)$_2$SO–CD$_3$OD and unambiguously assigned by ^{1}H–^{1}H and ^{13}C–^{1}H COSY two-dimensional NMR spectroscopy. Proton and ^{13}C NMR spectra of the complex are summarized in Table 3. All hydrogen atoms of OH, NH and NH$_2$ groups were replaced by deuterium. The structure of the D-GlcN-en unit is shown in Fig. 2. In the ^{13}C NMR spectrum of **1a** only eight signals were observed although the complex cation contains 16

Table 3 Carbon and proton chemical shifts (ppm) of **1a**

^{13}C resonances							
Sugar units						(en) units	
C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8
88.97	56.92	76.81	71.42	78.84	61.73	45.27	38.76
^{1}H resonances							
Sugar units							
H^1	H^2	H^3	H^4	H^5	H^6, H^7		
3.73	2.22	3.40	3.11	3.15	3.52, 3.72		

Table 4 Average torsion angles of the H–C–C–H fragments of the sugar rings (φ/°)

Fragment	φ
H^1–C^1–C^2–H^2	177.3
H^2–C^2–C^3–H^3	−176.9
H^3–C^3–C^4–H^4	173.2
H^4–C^4–C^5–H^5	−174.0

Table 5 Vicinal ^{1}H–^{1}H spin–spin coupling constants (Hz) for sugar units

	Observed	Calculated
$^3J_{1,2}$	9.0	8.9
$^3J_{2,3}$	9.8	10.1
$^3J_{3,4}$	9.0	9.6
$^3J_{4,5}$	8.3	9.7

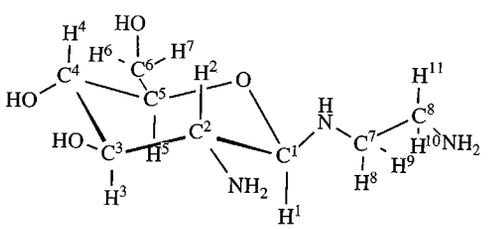

Fig. 2 Drawing of D-GlcN-en unit with the atomic numbering scheme.

carbon atoms. Thus the ^{13}C spectral data strongly suggest that the two *N*-glycoside ligands are equivalent, consistent with the C_2 symmetrical structure as confirmed by X-ray analysis.

Conformational analysis of sugar units and diamine chelates on $[Zn(D\text{-}GlcN\text{-}en)_2]^{2+}$

The successful use of proton NMR spectroscopy for the elucidation of structural details in conformational analysis depends largely on the availability of a reliable functional relationship between vicinal proton–proton coupling constants and associated φ (H–C–C–H) torsional angles, usually referred to as a Karplus-type equation. In our previous paper,[23] we analyzed the structures of the sugar units of cobalt(III) complexes containing an *N*-glycoside derived from ethylenediamine and an aldose by means of the semiempirical AM1 calculations coupled with the conversion of the vicinal ^{1}H–^{1}H spin–spin coupling constants in the ^{1}H NMR spectra into torsion angles of the corresponding H–C–C–H fragments, where we used the empirical Karplus-type equation proposed by Haasnoot *et al*.[21] Recently Altona *et al*. proposed an extended Karplus equation by considering empirical group electronegativities as described in eqn. (1).[20] This generalized Karplus–Altona equation was effectively used in the recent reports on the anomeric effect in purine nucleotides[24] and vicinal coupling constants to H–C–C–F torsion angles.[25] The $^4C_1$ conformation of the pyranose rings in **1a** was confirmed by ^{1}H NMR spectroscopy and by using eqn. (1). The torsional angles of the H–C–C–H fragments and the observed and calculated vicinal coupling constants are listed in Tables 4 and 5, respectively. The corresponding couplings resemble each other. Therefore, it can be concluded that the hydrogens at C^1, C^2, C^3, C^4 and C^5 are in the *trans* axial orientation corresponding to a β-$^4C_1$ conformation as revealed by X-ray crystallography.

The results observed in this work are promising for the development of new and effective zinc-containing compounds in medicine. The screening of these complexes for bioactivity is now in progress.

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