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REGULAR ARTICLE

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Metal binding induced conformational interconversions in methyl ß -D-xylopyranoside

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Abstract A detailed conformational search for $^4C_1$, $^1C_4$, and ^2S_O ring structures of methyl ß-D-xylopyranoside is performed by density functional theory calculations. For low energy structures in addition a composite energy approach is used. Complexation by divalent metal cations (Mg^{2+}, Ca^{2+}, Zn^{2+}, Cd^{2+}) induces a conformational interconversion $^4C_1 \rightarrow {}^1C_4$. Relative Gibbs' free energy differences between these two forms of the complexes roughly follow the respective ionic radii. In addition, for each ring conformation different binding sites of the cation are considered. In $CHCl_3$ (PCM approximation for solvation), the shift toward the $^1C_4$ chair form is substantially reduced or, in the case of the Cd^{2+} complexes, even reversed.

Keywords Xylopyranosides metal complexes · Ring conformation · Density functional calculations · Solvent effect

1 Introduction

Complexation of metal cations by carbohydrates is of paramount importance in many areas of (bio)chemistry and technology [1–7], e.g., interaction between carbohydrates and the metal cations of metalloenzymes involved in carbohydrate metabolism [8], removal of metallic impurities from drinking or waste water by chelation [4], and in analytical chemistry. For instance, gas phase complex formation between oligosaccharides and metal cations has been used to determine linkage positions of isomeric oligosaccharides by tandem mass spectrometric methods [9–13]. Metal binding by sugars or, generally, oligo/polysaccharides is a complex process. Not only do different carbohydrate-cation binding sites exist, but also conformational as well as configurational changes can be induced thereby [14]. On the other hand, such metal-induced conformational changes ($^4C_1$–$^1C_4$ chair equilibria) have recently been exploited for sugar-based fluorescent metal sensors [15–17]. In view of the general importance of metal–carbohydrate interactions, several computational studies on this topic have appeared [11–13,18–20]. Here we present a detailed density functional theory study on conformational properties of methyl ß-D-xylopyranoside and its complexes with several divalent metal ions (Mg^{2+}, Ca^{2+}, Zn^{2+}, and Cd^{2+}). Special emphasis will be put on preferred binding sites of the metal cations as well as their influence on conformational equilibria, specifically $^4C_1$–$^1C_4$ chair equilibria, of the sugar molecule.

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2 Computational details

All computations have been performed with the Gaussian 03 suite of programs [21] with Becke's three-parameter hybrid Hartree–Fock density functional method [22] with the Lee–Yang–Parr correlation functional (B3LYP) [23] and the LANL2DZ basis set [24,25]. Initially, for both the $^4C_1$ and the $^1C_4$ chair conformation, all 81 possible rotamers resulting from staggered orientations [$\tau(C_{i+1} - C_i - O - H = \pm 60°$ and 180°), Fig. 1] of the hydroxyl (methoxy) groups were optimized (B3LYP/Lanl2DZ). All unique structures resulting thereby, including some non-chair conformations, e.g., skew (^2S_O) and boat ($^{2,5}B$) forms, were then re-optimized with polarization function (d for oxygen, $\alpha = 0.8$; p for hydrogen, $\alpha = 1.1$) and diffuse functions taken from the 6–311++G(d,p) standard basis set added to oxygen (sp) and hydroxyl-hydrogen (s) atoms [26–28], thereafter denoted as basis II. All structures were characterized by frequency calculations as true minima. Zero point energies (ZPE) and thermal corrections to Gibbs' free energies are obtained from the

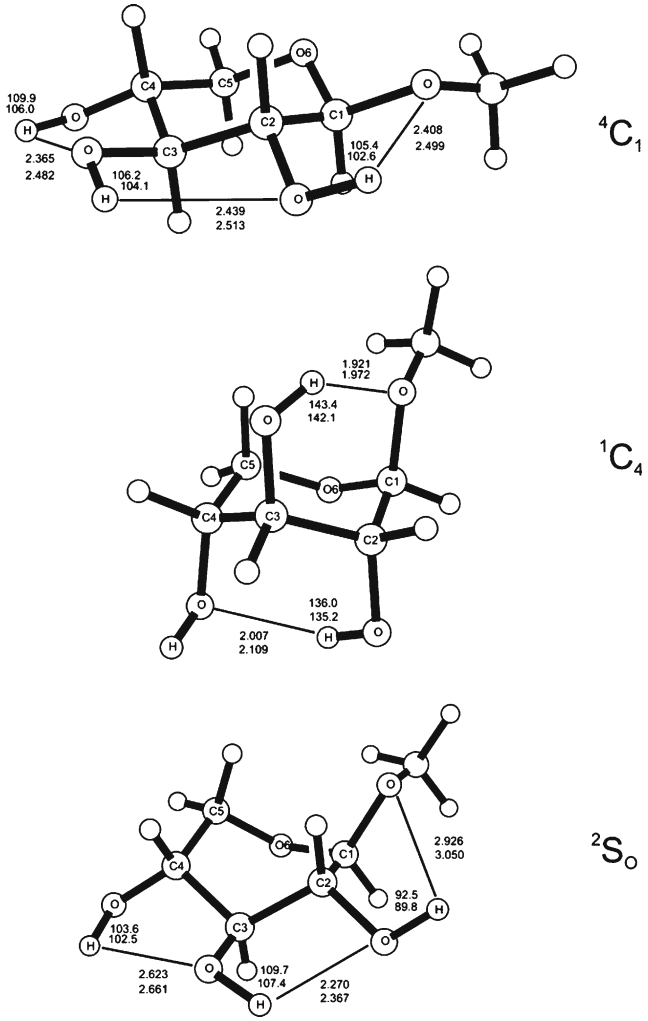

Fig. 1 Calculated lowest energy structures for the $^4C_1$, $^1C_4$, and ^2S_O ring conformations of methyl ß-D-xylopyranoside (*upper values*: MP2/cc-pVDZ; *lower values*: B3LYP/basis II; distances in Å, angles in degrees)

B3LYP/basis II calculations and are unscaled. In addition, for the lowest energy structures of each ring conformation (seven for $^4C_1$, six for $^1C_4$, and two for ^2S_O), a composite model [29] was used to assess correlation and basis size effects on conformational energies E(C):

$$\begin{aligned} E(\mathrm{C}) = {} & E(\mathrm{MP2/cc\text{-}pVTZ//MP2/cc\text{-}pVDZ}) \\ & + \{E(\mathrm{CCSD/6\text{-}31G(d)//MP2/6\text{-}31G(d)}) \\ & - E(\mathrm{MP2/6\text{-}31G(d)//MP2/6\text{-}31G(d)})\} \\ & + \{E(\mathrm{HF/cc\text{-}p^TVQZ//MP2/cc\text{-}pVDZ}) \\ & - E(\mathrm{HF/cc\text{-}pVTZ//MP2/cc\text{-}pVDZ})\} \end{aligned} \quad (1)$$

Here, cc-p^{T}VQZ means polarization functions taken from the cc-pVTZ basis. ZPE's and thermal corrections to Gibbs' free energies are unscaled and taken from the MP2/cc-pVDZ calculations. Since Dunning's correlation consistent basis sets [30] are not available for Mg, the composite energy E(C) for different conformations of Mg^{2+}-methyl ß-D-xylopyranoside complexes was obtained according to

$$\begin{aligned} E(\mathrm{C}) = {} & E(\mathrm{MP2/6\text{-}311{+}{+}G(2d,\,2p)//MP2/6\text{-}31{+}G(d,p)}) \\ & + \{E(\mathrm{CCSD/6\text{-}31G(d)//MP2/6\text{-}31G(d)}) \\ & - E(\mathrm{MP2/6\text{-}31G(d)//MP2/6\text{-}31G(d)})\} \end{aligned} \quad (2)$$

ZPE's and thermal corrections to Gibbs' free energies are unscaled and taken from the MP2/6-31+G(d,p) calculations. Solvent effects (chloroform, DMSO) were approximated by the IEF-PCM procedure (B3LYP/6-311++G(d,p)) [31]. For the complexes only the electrostatic contribution to solvation was taken into account since no cavity parameters for the metal cations are available in the G03 implementation of the PCM model.

3 Results and discussion

3.1 Methyl ß-D-xylopyranoside

Optimization of the initial 81 possible conformations, described by the torsional angles $\tau_1 - \tau_4 (\tau_i = \tau(C_{i+1} - C_i - O-H) = +60°(g^+), 180°(t), -60°(g^-)$, see Fig. 1 for atom numbering) greatly reduces this number. For instance, of the three possible orientations of the methoxy group the *trans* ($\tau_1 \sim 180°$) form is preferred; for $^4C_1$ chairs no g^+ conformation of the MeO group is found at all and those obtained for $^1C_4$ are rather high in energy (> 9 kcal mol^{-1} above lowest energy structure). The absence of g^+ (MeO) rotamers in $^4C_1$ chairs may be attributed to stronger repulsive interactions between the MeO and equatorial C_2–OH group as opposed to an axial C_2–OH in $^1C_4$ conformers. Several of the initial $^1C_4$ chairs collapsed to ^2S_O skew or $^{2,5}B$ boat structures. Relative Gibbs' free energies ΔG (kcal mol^{-1}) for selected low energy conformations **1** – **13** of methyl ß-D-xylopyranoside are provided in Table 1 and pertinent structural parameters (torsional angles $\tau_1 - \tau_4$, ring puckering parameters q, θ, and ϕ [32,33]), characterizing these conformations are summarized in Table 2. The structures of the lowest energy $^4C_1$, $^1C_4$, and ^2S_O ring conformations are shown in Fig. 1. Total energies, zero point energies, and thermal corrections to enthalpy and Gibbs' free energy are provided in the supplementary material.

In the gas phase, both the composite energy [Eq. (1)] as well as B3LYP calculations using basis set II yield the stability order $^4C_1 > {}^1C_4 > {}^2S_O$. The Gibbs' free energy difference (Table 1) between the lowest $^4C_1$ and $^1C_4$ chair is 2.5 [E(C)] and 2.2 (B3LYP/basis II) kcal mol^{-1}, in close agreement with B3LYP/6-311++G(d,p) results for ß-D-xylopyranose itself [34]. For each ring conformation the respective structure with the maximum number of intramolecular hydrogen bonds (Fig. 1) has the lowest energy. Specifically, the $^1C_4$ chair is stabilized by an intramolecular H-bond between the C_3–OH and the methoxy group. Such stabilization by intramolecular hydrogen bonding has been inferred from the IR spectra of 2,4-diacylated derivatives of methyl ß-D-xylopyranoside [35]. In addition, previous calculations had also indicated the dominant role of hydrogen bonding interac-

Table 1 Calculated relative Gibbs' free energies (kcal mol^{-1}) for selected conformations of methyl ß-D-xylopyranoside in the gas phase and chloroform and DMSO solutions

No.[a]		Gas phase		$CHCl_3$[b]		DMSO[b]	
		ΔG^{c}_{rel}	ΔG^{d}_{rel}	ΔG^{c}_{rel}	ΔG^{d}_{rel}	ΔG^{c}_{rel}	ΔG^{d}_{rel}
1	$^4C_1$	0.00	0.00	0.00	0.00	0.00	0.18
2	$^1C_4$	2.49	2.21	2.00	2.47	2.03	2.94
3	$^1C_4$	2.54	2.19	1.86	2.54	1.78	3.12
4	$^4C_1$	2.66	2.77	2.57	2.79	2.73	3.00
5	$^1C_4$	3.08	2.89	2.44	2.87	2.41	3.29
6	$^4C_1$	3.31	3.71	0.81	1.24	−0.40	0.22
7	$^4C_1$	3.57	3.85	0.84	1.13	−0.47	0.00
8	$^1C_4$	3.58	3.42	2.35	3.03	2.02	3.22
9	^2S_O	4.05	3.02	2.49	1.37	1.81	1.03
10	$^4C_1$	4.22	4.67	1.78	2.26	0.30	0.98
11	$^4C_1$	4.33	4.69	1.74	2.06	0.23	0.72
12	$^4C_1$	4.40	4.69	1.87	2.19	0.51	1.02
13	^2S_O	5.33	4.33	3.19	2.57	2.14	1.91

[a] The individual structures 1–13 are characterized by the respective torsional angles τ_1–τ_4 and puckering parameters (q, θ, ϕ) according to the data given in Table 2

[b] IEF-PCM approximation for solvation; for the composite energy model, B3LYP/6-311++G(d,p) single points; for B3LYP/basis II solvation evaluated at this level

[c] Composite energy model [Eq. (1)]; ZPE's and thermal corrections to ΔG are unscaled and taken from the MP2/cc-pVDZ calculations

[d] B3LYP/basis II; ZPE's and thermal corrections to ΔG are unscaled and taken from the B3LYP/basis II calculations

Table 2 Methoxy and hydroxy torsional angles τ_1–τ_4 and ring puckering parameters q, θ and ϕ obtained by MP2/cc-pVDZ (upper lines) and B3LYP/basis II (lower lines) calculations

		τ_1	τ_2	τ_3	τ_4	q	θ	ϕ
1	$^4C_1$	172.0	176.6	−176.6	169.3	0.59	3.1	11.9
	tttt	171.3	179.6	−177.8	174.1	0.58	3.9	11.9
2	$^1C_4$	173.5	53.9	−86.6	−179.7	0.56	178.7	260.0
	tg^+g^-t	171.4	53.7	−86.8	−174.7	0.55	177.6	270.6
3	$^1C_4$	173.1	44.3	−88.1	−49.5	0.56	178.7	105.1
	$tg^+g^-g^-$	171.1	43.8	−88.7	−46.4	0.55	178.8	83.8
4	$^4C_1$	−68.2	165.3	−177.8	168.5	0.59	1.8	43.0
	g^-ttt	−73.4	166.8	−179.5	173.1	0.58	2.8	30.7
5	$^1C_4$	174.1	−58.5	−84.4	63.5	0.56	176.5	99.5
	$tg^-g^-g^+$	172.6	−64.6	−84.3	64.3	0.55	177.7	100.0
6	$^4C_1$	170.8	−48.5	56.0	−76.8	0.58	4.1	335.6
	$tg^-g^+g^-$	168.5	−54.1	58.9	−80.6	0.58	5.6	321.7
7	$^4C_1$	170.1	174.8	53.2	−77.8	0.58	5.0	349.0
	ttg^+g^-	169.3	−179.6	58.9	−81.8	0.57	7.1	341.9
8	$^1C_4$	174.6	174.6	−82.7	75.3	0.56	178.2	118.3
	ttg^-g^+	173.4	175.5	−83.6	75.7	0.54	179.5	138.6
9	^2S_O	171.2	−167.6	−169.0	174.9	0.78	87.9	157.5
	tttt	170.6	−164.4	−173.2	177.4	0.76	88.0	159.5
10	$^4C_1$	171.0	−50.4	47.3	56.5	0.58	4.0	351.0
	$tg^-g^+g^+$	168.8	−56.1	49.3	53.4	0.57	4.9	333.7
11	$^4C_1$	170.4	175.1	44.3	60.5	0.57	5.2	359.1
	ttg^+g^+	169.6	−179.4	48.2	58.1	0.57	6.8	350.6
12	$^4C_1$	170.9	−41.5	−64.3	162.0	0.58	4.9	339.8
	tg^-g^-t	168.8	−46.3	−64.4	166.4	0.57	6.3	333.4
13	^2S_O	171.0	−169.6	−171.1	55.7	0.78	92.9	142.9
	$tttg^+$	170.1	−167.4	−176.7	53.2	0.75	94.0	140.6

Angles in degrees, puckering amplitude q in Å ; $\tau_1 = \tau$(Me–O–C1–C2); $\tau_2 = \tau$(H–O–C2–C3); $\tau_3 = \tau$(H–O–C3–C4); $\tau_4 = \tau$(H–O–C4–C5); for atom numbering, see Fig. 1

tions on gas phase relative stabilities of different aldopentose forms [34]. Completely in line with the present results for methyl ß-D-xylopyranoside, very recently also an all-trans chain of intramolecular hydrogen-bonding interactions (see $^4C_1$ structure shown in Fig. 1), has been found for phenyl ß-D-xylopyranoside in the gas phase by hole-burning conformer

specific IR spectra (IR – HB), combined with B3LYP/6-31+G(d) calculations [36]. Notably, O–H . . . O hydrogen bonding distances are considerably shorter in the $^1C_4$ than either the $^4C_1$ or, especially, the ^2S_O ring conformations (see Fig. 1), indicating stronger hydrogen bonding in the former one. However, the presence of only two such hydrogen bonds in $^1C_4$ rather than three in $^4C_1$ makes this latter ring structure the most stable one. Adding to this stability is the all-equatorial arrangement of the substituents in the $^4C_1$ chair structure of methyl ß-xylopyranoside. Note also that the lowest energy $^4C_1$ chair structure contains a counter-clockwise arrangement of the hydrogen bonding network. In a clockwise orientation, as found, e.g., in D–glucuronic acid [28], here only two H-bonds with a concomitant diminished stability are possible. In chloroform (PCM approximation for solvation), the $^1C_4$–^2S_O ΔG difference is reduced by 1 kcal mol^{-1} (from 1.5 to 0.5, composite model) or even reversed (B3LYP/basisII, Table 1). Molecular mechanics calculations (MM3) with a dielectric constant $\epsilon = 3$ to mimic a condensed phase on ß-xylopyranose give ^2S_O and $^1C_4$ as the second- and third-lowest energy ring conformation [37]. For DMSO solutions, this shift from $^1C_4$ toward ^2S_O is even more pronounced (Table 1). The composite energy model leads to an almost equal Gibbs' free energy of these two ring conformations; with B3LYP/basis II the ^2S_O skew structures is predicted to be more stable than $^1C_4$ by ≈ 2 kcal mol^{-1} . ^{13}C NMR spectra, for methyl ß-D-xylopyranoside in DMSO, indicate that apparently only one single conformation is present. According to the present calculations, methyl ß-D-xylopyranoside should exist in DMSO almost exclusively (ca 97%, composite energy model; 92% with B3LYP/basis II) in the $^4C_1$ chair conformation, whereas in $CHCl_3$ this population should be slightly reduced to 92 and 89%. Previously, from coupling constants in chloroform/DMSO, a conformational equilibrium predominately consisting of the $^4C_1$ chair (88%) has been deduced [38,39]. It is interesting to note that in DMSO solution OH conformations with less than the maximum number of intramolecular hydrogen bonds (e.g., **6** or **7**, Table 1) become more stable than the $^4C_1$ structure **1**. Also, especially in DMSO, a few $^1C_4$ conformations are found to be somewhat lower in energy than those listed in Table 1. Specifically, B3LYP/basis II results in DMSO yield the tg^+g^+t structure of the $^1C_4$ chair with only one intramolecular hydrogen bond $C_2 - OH \ldots O - C_4$ as the most stable one. The orientations of both C_3–OH and C_4–OH indicate the presence of an intermolecular hydrogen bond with DMSO as an acceptor. Finally, it is worth mentioning that gas phase results, except for ^2S_O structures, obtained with the composite energy model [Eq. (1)] almost parallel those calculated by B3LYP/basis II.

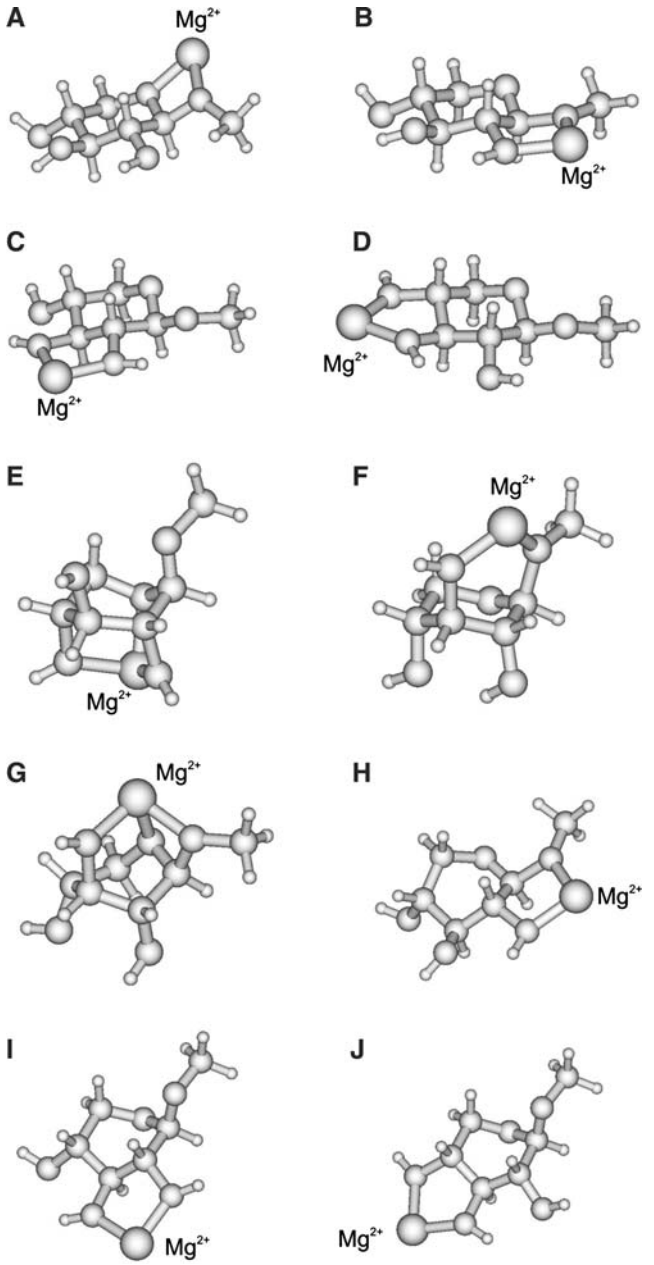

Fig. 2 Calculated lowest energy structures (B3LYP/basis II) for the different Mg^{2+} complexes of methyl ß-D-xylopyranoside

3.2 Metal complexes of methyl ß-D-xylopyranoside

In the following, the influence of complexation by metal cations on the dominant ring conformation as well as their preferred binding sites to the $^4C_1$,$^1C_4$, and ^2S_O structures will be described. Results obtained for the gas phase as well as in chloroform solution (PCM model for solvation) will be presented. Binding of metal cations (Mg^{2+}, Ca^{2+}, Zn^{2+}, and Cd^{2+}) to the xylopyranoside generally involves coordination to two oxygens of the sugar. Only in the $^1C_4$ chair conformation (structure **E**, Fig. 2) and in the complexes of type **G** derived from the ^2S_O ring form, interaction with three oxygen atoms, two hydroxyls, and the ring oxygen is possible. Chelation of the metal cations restricts the conformational freedom of hydroxy (methoxy) groups in the sugar. However, for each ring conformation, several different binding

Table 3 Relative Gibbs' free energies (kcal mol^{-1}) for metal cation complexes

	Gas phase Mg^{2+}	$CHCl_3$	Gas phase Ca^{2+}	$CHCl_3$	Gas phase Zn^{2+}	$CHCl_3$	Gas phase Cd^{2+}	$CHCl_3$
A	40.02 (38.13)	13.54	26.82	6.52	38.78	9.12	30.61	3.86
B	28.97 (28.24)	11.96	18.41	5.86	28.41	9.75	22.73	5.29
C	28.44 (27.50)	5.08	15.64	0.49	29.53	2.47	22.16	−3.07
D	32.69 (31.97)	5.78	19.87	0.57	32.87	2.06	25.46	−3.14
E	0.00 (0.00)	0.00	0.00	0.00	0.00	0.00	0.00	0.00
E-1	2.30 (2.28)	1.01	1.10	0.23	2.61	1.50	2.41	1.02
F	30.46 (29.63)	17.61	25.10	12.21	26.00	16.22	24.56	13.67
G	11.73 (11.37)	11.16	8.73	8.68	11.34	11.05	9.85	10.00
G-1	36.32 (–[a])	15.52	–[a]		33.84	12.16	26.42	6.19
H	31.65 (31.94)	15.75	22.59	10.43	29.36	14.18	24.52	9.42
I	32.91 (33.04)	6.81	20.56	2.37	34.12	4.71	27.07	−0.62
J	32.52 (33.10)	7.52	19.89	2.50	32.77	4.35	25.30	−1.29

B3LYP/basis II results. Composite Gibbs' free energies according to Eq. (2) for Mg^{2+} complexes are given in parentheses
[a] Collapses to structure **G**

sites are possible (Fig. 2). Structures **A**–**D** correspond to the four chelating sites of the $^4C_1$, **E**, and **F** to those of the $^1C_4$ chair, and **G**–**J** to different binding modes of the ^2S_O conformation. In the following discussion, only the respective lowest energy conformation for each one of these different types of complexes will be used. Relative Gibbs' free energies in the gas phase and $CHCl_3$ solution are summarized in Table 3. Total energies, zero point energies and thermal corrections to enthalpy, and Gibbs' free energy are provided in the supplementary material.

3.2.1 Gas phase complexes

In contrast to free methyl ß-D-xylopyranoside, for each one of the four metal cations (Mg^{2+}, Ca^{2+}, Zn^{2+}, and Cd^{2+}), the calculations predict the greatest stability of the $^1C_4$ complex **E** in the gas phase. The complexation-induced $^4C_1$–$^1C_4$ interconversion (difference in Gibbs' free energies) follows the order $Mg^{2+} \approx Zn^{2+} > Cd^{2+} > Ca^{2+}$, which roughly corresponds to the ionic radii of these cations (86, 88, 109, and 114 pm, resp. [40]). Distances between the metal cations and the coordinating oxygen sites (Table S3 in the supplementary material) also follow this trend: 1.88–2.01 Å (Mg^{2+}), 1.88–2.05 Å (Zn^{2+}), 2.11–2.26 Å (Cd^{2+}), 2.30–2.43 Å (Ca^{2+}). The lowest energy structure **E** of the $^1C_4$ complexes resembles the *ax-ax-ax* metal cation binding motif of cyclic carbohydrates, which prefers cations with ionic radii in the range 60–100 pm [3,13]. To attain maximum chelation, the $^1C_4$ ring is distorted [$\theta = 161°$, $\phi = 180°$ (B3LYP/basis II) to be compared with $\theta = 178°$, $\phi = 271°$ for the uncomplexed glycoside, Table 2]. The second possible binding mode, **F**, of the $^1C_4$ chair is considerably less (25–30 kcal mol^{-1}, Table 3) favored. Among all the considered structures of the complexes, only **E** and **G** involve a triple coordination of the metal cation, which might explain the calculated stability. The structures obtained here for type **E** complexes with divalent metal cations (Mg^{2+}, Ca^{2+}, Zn^{2+}, Cd^{2+}) closely resemble those calculated [HF/6-31G(d)] for xylose-Na^+ complexes [11]. Surprisingly, in contrast to free methyl ß-D-xylopyranoside, the energy of the $^1C_4$ chair complex lacking the intramolecular C_3–OH . . . OMe hydrogen bond is comparable to or even lower than that with this H-bond (structure **E**–**1** in Table 3). Concerning the different binding sites of the $^4C_1$ chair, **A**–**D**, irrespective of the metal cation, binding to the ring oxygen and the glycosidic methoxy group (structure **A**, Fig. 2) is the least favorable one. This is in contrast to the calculated results for binding of various metal cations, e.g., Ca^{2+}, Cu^{2+}, Ni^{2+}, or Cd^{2+}, to ß-D-glucose, ß-D-glucosamine, or chitobiose [12, 13,20]. This contrasting behavior of xylopyranose or aldopentopyranosides in general can be attributed to the absence of the CH_2OH group at position 5 of the pyranose ring. In the hexopyranoses this group provides an additional coordination site leading to triply coordinated cations in type **A** complexes. Furthermore, this binding mode requires the unfavorable g^+ orientation of the methoxy group. Among the remaining three binding sites, Ca^{2+} should preferentially be complexed by the $C_2 - OH$ and C_3–OH hydroxyls (structure **C**). Completely in line with these calculated results, from the Ca^{2+} induced shifts of OH groups in a series of monosaccharides, it was concluded that glycosidic methoxy groups (structure **B**) do not coordinate with Ca^{2+} [41]. In contrast, for Mg^{2+}, Zn^{2+}, and Cd^{2+}, structures **B** and **C** have similar Gibbs' free energies (Table 3). Besides structure **A**, also irrespective of the metal cation, in the gas phase, chelation by C_3–OH and C_4–OH (structure **D**) is unfavorable. A possible explanation of the comparably high energy of type **D** complexes is their $tttg^-$ conformation, which is found to be unstable in the free methyl ß-D-xylopyranoside. It is also interesting to note that in contrast to the free sugar, the ^2S_O structures **G** of the complexes are considerably more stable than the lowest energy $^4C_1$ forms. The stability of the complex **G** can easily be understood from its structure: the ^2S_O ring conformation ($q = 0.78$, $\theta = 87°$, $\phi = 337°$) makes possible a triple coordination of the cation not only to the ring and methoxy oxygens but also to the C_3–OH group (Fig. 2). For Mg^{2+}, Zn^{2+}, and Cd^{2+}, but not for Ca^{2+}, besides the ^2S_O ring conformation **G**, a complex (**G-1**, Fig. 3) with a $^3S_1$ ring conformation ($q = 0.76$, $\theta = 94°$, $\phi = 42°$) was found.

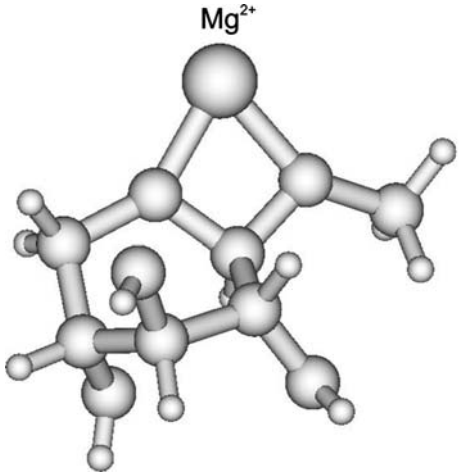

Fig. 3 Calculated structure (B3LYP/basis II) of the Mg^{2+} methyl ß-D-xylopyranoside corresponding to conformation **G-1**

Composite energy [Eq. (2)] results for Mg^{2+} complexes are in close agreement with B3LYP/basis II calculations. For structure **G-1**, the MP2/6-31+G(d,p) optimization leads to a collapse of the $^3S_1$ type ring conformation found by B3LYP/basis II to the ^2S_O structure with a triply coordinated Mg^{2+} cation.

Relative complex stabilities, using the respective lowest energy structure **E**, are obtained from the reaction

$$\mathbf{E} - Mg^{2+} + Me^{2+} \rightarrow \mathbf{E} - Me^{2+} + Mg^{2+} \quad (3)$$

where $Me^{2+} = Ca^{2+}, Zn^{2+}, Cd^{2+}$

B3LYP/basis II results for Gibbs' free energy differences are 66 (Ca^{2+}), −30(Zn^{2+}), and 11 (Cd^{2+}) kcal mol^{-1} ; with B3LYP/6-311++G(d,p) one finds 57 (Ca^{2+}) and −36(Zn^{2+}) kcal mol^{-1} [for Cd the 6-311++G(d,p) basis is not available]. Thus, among the four metal cations, Zn^{2+} should form the strongest, and Ca^{2+} the weakest complexes, at least in the gas phase.

3.2.2 Complexes in chloroform solution

The interaction of sugars in neutral or acidic aqueous solution with metal cations is generally very weak, since the OH groups can barely compete with H_2O for coordinating with the cation [13]. Even DMSO as a solvent can prevent complex formation [15]. Thus, in the following the discussion will be restricted to chloroform as the solvent. The most significant effect of this solvent is a substantial reduction of the $^1C_4$(**E**)–$^4C_1$ energy differences (Table 3): whereas binding of Mg^{2+} and Zn^{2+} should lead to a $^4C_1$– $^1C_4$ interconversion also in chloroform solution, no such conformational change should be observable in the case of Cd^{2+}; for this latter cation, $^4C_1$ complexes with binding of Cd^{2+} to C_2–OH and C_3–OH (**C**) or C_3–OH and C_4–OH (**D**) should be more stable than the $^1C_4$(**E**) structure. In the case of Ca^{2+},$^4C_1$ and $^1C_4$ forms are nearly isoenergetic. For all four metal cations, solvation substantially stabilizes complexes of type **D**. This can be attributed to their extended structure with the largest separation between positive and negative centers. Relative complex stabilities obtained from B3LYP/6-311++G(d,p) calculations according to Eq. (3) are 14 (Ca^{2+}) and −1 (Zn^{2+}) kcal mol^{-1}, significantly lower than that found for the gas phase. Also noteworthy is the strong stabilization of ^2S_O-type complexes, especially structures **I** and **J**. For Cd^{2+}, this leads even to a greater stability of these structures compared to the $^1C_4$ complex **E** (Table 3). In contrast, solvent effects on complexes of type **G,** i.e., like **E** those with triply coordinated cations, are quite small.

4 Conclusions and outlook

A detailed conformational analysis of $^4C_1$,$^1C_4$, and ^2S_O ring structures of methyl ß-D-xylopyranoside has been done by density functional (B3LYP/Lanl2DZ + diffuse and polarization functions on oxygen and hydroxyl hydrogen) methods. Selected structures have been reevaluated with a composite energy method [Eq. (1), [29]]. In line with all experimental evidence [38,39], the uncomplexed sugar preferentially adopts the $^4C_1$ chair conformation (≈ 90%). The $^1C_4$ chair and the skew conformation ^2S_O are calculated to have comparable energies. The lowest energy $^1C_4$ structure contains a stabilizing intramolecular hydrogen bond C_3–OH . . . OMe, as also inferred from IR spectra of acylated derivatives [35]. Upon metal (Mg^{2+}, Ca^{2+}, Zn^{2+}, Cd^{2+}) complexation, a $^4C_1$–$^1C_4$ conformational interconversion is induced. The stabilization of the $^1C_4$ compared to the $^4C_1$ chair depends on the ionic radii of the metal cations. In solution, a much smaller conformational shift is obtained by the calculations. The preferred binding site of the $^4C_1$ chair depends on the respective cation. In all cases, binding of the cation between the glycosidic methoxy group and the ring oxygen atom is the least favorable motif. Characteristic for the lowest energy $^1C_4$ complex structures are triply coordinated metal ions. As in the present investigation, most previous calculations have considered the interaction of a sugar or oligosaccharide with isolated metal ions [12,13]. Only recently, the effect of coordination of the cation to different numbers of water molecules has been considered [20]. Although in the present study $CHCl_3$ is used as a solvent for the complexes, interaction of the cation with counterions and/or formation of 2:1 sugar:metal stoichiometry [16] is expected to influence the $^4C_1$–$^1C_4$ chair–chair equilibrium. Saturation of the coordination number of the metal cations and modeling of such 2:1 complexes is in progress and the results will be reported in due course.

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