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Interaction of chitosan and chitin with Ni, Cu and Zn ions: A computational study

José R.B. Gomes^{a,*}, Miguel Jorge^b, Paula Gomes^c

^a CICECO, Departamento de Química, Universidade de Aveiro, Campus Universitário de Santiago, 3810-193 Aveiro, Portugal

^b Department of Chemical and Process Engineering, University of Strathclyde, 75 Montrose Street, Glasgow G1 1XJ, United Kingdom

^c Centro de Investigação em Química, Departamento de Química, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre, 687, P-4169-007 Porto, Portugal

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ABSTRACT

The interaction of chitosan and chitin with monovalent and divalent late transition metal ions was studied by means of density functional theory. The calculations were performed at the B3LYP/6-31+G** level of theory using glucosamine and *N*-acetylglucosamine monomers as models of chitosan and chitin, respectively, in the absence and in the presence of a few water molecules. The calculations suggest that *N*-acetylglucosamine is more acidic than glucosamine and that the most stable metal complexes with each of these two molecules have similar stabilities. In the case of the interaction of these two molecules with monovalent cations, the most stable complexes are those with Ni(I). In the case of the divalent cations, complexes with Cu(II) are more favourable, which is in good agreement with the available experimental data.

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1. Introduction

In recent years, there is a continuous interest in developing important non-toxic and biodegradable materials derived from cheap and renewable resources. Chitosan, a partially deacetylated derivative of chitin, is a biopolymer (polysaccharide) composed of randomly distributed β -(1-4)-linked *D*-glucosamine (deacetylated unit, [figure 1a](#)) and *N*-acetyl-*D*-glucosamine (acetylated unit, [figure 1b](#)) monomers. Chitosan is non-toxic and biodegradable, and possesses optimal sorption properties, easily establishing stable complexes with metal ions [1]. Chemical modifications of the parent polymer are usually performed for enhancing its selectivity, chelating properties, solubility and antioxidant properties [2–4]. Thus, several biological and environmental applications are known where chitosan-based materials are used for, e.g., controlled drug release *in vivo*, due to their remarkable biocompatibility, muco-adhesive and tissue regenerating properties, or water decontamination by removal of heavy metals from aqueous media [5]. The ability of chitosan to form stable complexes with heavy metals, e.g., lanthanides, has further been explored for potential applications in magnetic resonance-based bio-imaging (MRI) techniques [6].

The mechanism of metal complexation by chitosan has been studied in the literature by experimental and computational approaches. Such reports have essentially focused on the adsorption of divalent cations, especially copper. Ogawa and Oka [7] performed an X-ray diffraction study of chitosan complexes with Cd(II), Zn(II), and Cu(II), and proposed a coordination model where the metal cation is attached as a pendant to the amino groups of the chitosan chain. This so-called pendant model was supported by Domard *et al.* [8] based on the potentiometric properties of fully deacetylated chitosan-copper(II) complexes, investigated using pH and circular dichroism measurements. The latter suggested complexes of the type $[\text{CuNH}_2(\text{OH})_2\text{X}]$, $\text{X} = \text{ROH}$ or H_2O , *i.e.*, where the metal cation is coordinated by an amino group and two hydroxide anions, and where the fourth site could be occupied by an H_2O molecule or by chitosan's hydroxyl neighbouring the amino group. Based on electron spin resonance (ESR) spectra of copper at high dilution in chitin and chitosan at $T = 77\text{ K}$ and $T = 297\text{ K}$, Schlick *et al.* [9] suggested a different model, the so-called bridge model, where the metal ion is also tetra-coordinated, but only to nitrogen atoms from different chitosan chains, forming a square-planar structure. Rhazi *et al.* [10] proposed two different types of Cu(II)-chitosan complexes, depending on the pH of the solution. They suggested complexes of the type $[\text{CuNH}_2(\text{OH})_2\text{H}_2\text{O}]$ at pH between 5.3 and 5.8, and complexes of the type $[\text{Cu}(\text{NH}_2)_2(\text{OH})_2]$ at pH above 5.8. From these works, it seems clear that metal

* Corresponding author. Tel.: +351 234 401 423; fax: +351 234 401 470.
E-mail address: jrgomes@ua.pt (J.R.B. Gomes).

FIGURE 1. Views of the optimised structures of glucosamine (a) and *N*-acetylglucosamine (b). Internal hydrogen bond distances are shown in non-SI units Å, 1 Å = 0.1 nm. Colour code for spheres is: red is oxygen, blue is nitrogen, grey is carbon and white is hydrogen. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

cations are preferentially chelated by the amino groups of chitosan, eventually involving the neighbouring hydroxyl groups.

More recently, Hernández *et al.* [11] analysed by potentiometric and spectrophotometric titrations the distribution of species formed upon the aqueous HCl equilibrium of chitosan (Chit) and three transition metal cations, namely, Cu(II), Mn(II) and Zn(II) to understand the influence of pH in the complexation systems obtained. They found that chitosan coordinated with these cations at pH >4, >5, and >2, respectively, in ligand to metal ratio of 1:1. The same authors concluded that the order of complex stability was Cu(II) > Zn(II) > Mn(II) and that the coordination happened through amino and hydroxyl groups in bridge-like structure with the metallic centres, originating tetra-coordinated, penta-coordinated or hexa-coordinated compounds, where the metal ions are coordinating the amino and neighbouring OH groups, and Cl[−] and OH[−] or H₂O. The structures proposed are of the type M(Chit)Cl₂, M₂(Chit)₂Cl₄, M(Chit)Cl₂X, M₂(Chit)₂Cl₄X₂, M(Chit)₂X and M(Chit)₂, where M is the metal ion, Chit stands for a monomeric building unit coordinated to the ion by an amino and an OH group, Cl is the chloride anion, and X is OH[−] or water.

Experimental studies for the interactions of chitosan or chitin with monovalent first row transition metal ions are not available in the literature because such ions are only stable in a nanoscale aqueous environment, and are only accessible by pulse radiolysis studies [12].

Only a few computational studies dealing with the binding of metal ions with chitosan are found in the literature [13–15]. Braier and Jishi [13] performed density functional theory (DFT) calculations, without specifying the exchange–correlation functional nor the basis sets used, on the interaction of disaccharides of chitosan with either Cu(II) or Ni(II) cations. Their calculations suggest that the coordination of copper to chitosan takes place in the vicinity of the interglycosidic linkage, and in the most stable configuration, the metal ion is bonded to the nitrogen atom from the amino group in one monomer (Cu–N distance is 0.187 nm) and to the oxygen atom from the hydroxymethyl group in the other monomer (Cu–O distance is also 0.197 nm), i.e., atoms corresponding to N(5) and O(2) atoms in figure 1a, and is interacting with the glycosidic oxygen (Cu–O distance is 0.224 nm). The metal and the three neighbouring atoms from the disaccharide are in the same plane. A less stable but similar structure was also found but the interaction occurs with N(5) from one monomer at 0.189 nm, with O(4) from the other monomer at 0.188 nm and also with the glycosidic oxygen at 0.251 nm. Nearly identical structures were obtained for the interaction with the Ni(II) cation which suggests a similar interaction scheme for these two cations with chitosan. DFT calculations at the BLYP/DND level of theory were performed by Lü *et al.* [14] to investigate the interactions between Cu(II) and chitosan (glucosamine) and the chitin (*N*-acetylglucosamine) residues. Only

hexa-coordinated configurations were considered by these authors who used two hydroxide anions to neutralise the charge of the complexes and, in some cases, two/three water molecules were also taken into account to obtain hexa-coordinated bridge/pendant complexes [14]. They concluded that the trend of coordination with Cu(II) is N(5)_{glucosamine} > (O3) > H₂O > N(5)_{*N*-acetylglucosamine} and that the bridge model is more favourable than the pendant model. In a similar DFT computational study but where only tetra-coordination to Cu(II) was considered, Terreux *et al.* [15] found that the most stable interactions involved an amino site or the heterocyclic oxygen atom and had pending-like structure, with [CuNH₂(OH)₂H₂O] or [CuO₂(OH)₂H₂O] local coordination, respectively. In agreement with the calculations of Lü *et al.* [14], the interaction with the amido group from *N*-acetylglucosamine was found to be less stable than with the amino group from glucosamine [15].

Despite the importance of the interaction between metal ions and chitosan, only a few computational works are available in the literature, mostly dealing with copper(II). Such studies were based on predetermined tetra- or hexa-coordinated models and the local origins of the metal-chitosan/chitin interactions were not studied in detail. The present study aims at providing enhanced knowledge about the interaction of metal ions with chitosan and chitin polymers.

2. Computational details

The DFT calculations were performed with the Gaussian 09 code [16]. The molecular structures were fully optimised at the B3LYP/6-31+G** level of theory [17,18] and vibrational frequencies were calculated, also with the B3LYP/6-31+G** approach, to obtain thermal corrections at *T* = 298.15 K and to confirm that the optimised configurations were true minima on the respective potential energy surfaces.

In the case of the glucosamine and *N*-acetylglucosamine monomers, the enthalpies of deprotonation (EoD, gas-phase acidities) and the O–H or N–H bond dissociation enthalpies (BDEs), both at *T* = 298.15 K, were calculated from the differences between the enthalpies of the charged species or of the radical species obtained from the parent molecules, respectively. The calculations involving transition metal ions were performed for the lowest spin state possible except for the calculations involving the Ni(II) species. In the latter, triplet state configurations were considered since they were found to be energetically more stable than the corresponding single state counterparts. The interaction enthalpies (*H*_{int}^{298.15 K}) for the complexes between the metal ions and the glucosamine or the *N*-acetylglucosamine compounds were obtained as:

$$H_{\text{int}}^{298.15 \text{ K}} = H_{\text{M}^{n+} \text{--compound}}^{298.15 \text{ K}} - H_{\text{M}^{n+}}^{298.15 \text{ K}} - H_{\text{compound}}^{298.15 \text{ K}}, \quad (1)$$

where $H_{M^{n+}-\text{compound}}^{298.15\text{ K}}$ is the enthalpy at $T = 298.15\text{ K}$ for the complex between a metal ion ($M = \text{Ni, Cu, or Zn}$, and $n = 1$ or 2) and glucosamine or *N*-acetylglucosamine, and $H_{M^{n+}}^{298.15\text{ K}}$ and $H_{\text{compound}}^{298.15\text{ K}}$ are the total enthalpies at $T = 298.15\text{ K}$ for the separated fragments. The energies of interaction, E_{int} , were obtained in a similar way but using the total energies for the complexes and for the isolated fragments, i.e., without using the thermal corrections for $T = 298.15\text{ K}$. In the cases of the metal cation-glucosamine-water complexes, the interaction enthalpies were calculated as:

$$H_{\text{int}}^{298.15\text{ K}} = H_{M^{2+}-\text{glucosamine}-(\text{H}_2\text{O})_m}^{298.15\text{ K}} - H_{M^{2+}}^{298.15\text{ K}} - H_{\text{glucosamine}}^{298.15\text{ K}} - mH_{\text{H}_2\text{O}}^{298.15\text{ K}}, \quad (2)$$

where $H_{M^{n+}-\text{compound}-(\text{H}_2\text{O})_m}^{298.15\text{ K}}$ stands for the enthalpy at $T = 298.15\text{ K}$ for the complex between a metal divalent cation ($M = \text{Ni, Cu, or Zn}$), glucosamine and m ($m = 1, 2$ or 3) water molecules, and $H_{M^{2+}}^{298.15\text{ K}}$, $H_{\text{glucosamine}}^{298.15\text{ K}}$ and $H_{\text{H}_2\text{O}}^{298.15\text{ K}}$ are the total enthalpies at $T = 298.15\text{ K}$ for the separated fragments.

3. Results

3.1. Glucosamine and *N*-acetylglucosamine

Views of the structures optimised for glucosamine and for *N*-acetylglucosamine are shown in figure 1. As can be seen, these two compounds are stabilized by a network of intramolecular hydrogen bonds of different type, namely, $\text{O}-\text{H} \cdots \text{O}-\text{H}$, $\text{O}-\text{H} \cdots \text{O}_{\text{ring}}$, and $\text{N}-\text{H} \cdots \text{O}-\text{H}$, seen in both compounds, and $\text{O}-\text{H} \cdots \text{N}-\text{H}$ in glucosamine and $\text{O}-\text{H} \cdots \text{O}=\text{C}$ in the acetylated compound. The hydrogen bonds have values of about (0.23 to 0.25) nm with the exception of the $\text{N}-\text{H} \cdots \text{O}-\text{H}$ bond in glucosamine, which is slightly longer (e.g., 0.275 nm) than other hydrogen bonds in the same molecule, and of the $\text{O}-\text{H} \cdots \text{O}=\text{C}$ bond in *N*-acetylglucosamine, which is significantly shorter than the other hydrogen bonds in the same molecule.

In table 1, we report the calculated bond dissociation enthalpies (BDEs) and enthalpies of deprotonation (EoD) for the $\text{O}-\text{H}$ and $\text{N}-\text{H}$ bonds in the two monomers. The former may be related with the antioxidant properties of the material while the latter can be related with the stability of the deprotonated species. The optimised structures and selected geometric parameters for the radicals and anions, obtained by homolytic or heterolytic $\text{X}-\text{H}$ ($\text{X} = \text{N, O}$) bond dissociation, are provided as Supporting Information. The analysis of the calculated BDEs suggests that the $\text{O}(1)-\text{H}$ bond in the two monomers is the easiest to cleave, i.e., the most stable radical is that obtained by removing an H atom from $\text{O}(1)$, while the hardest to break is the $\text{O}(4)-\text{H}$ bond. Despite not being perfect, there is some correlation between the BDEs and the lengths of the hydrogen bonds figure 1. The calculated BDEs are significantly larger than the $\text{O}-\text{H}$ BDE in phenol and the $\text{N}-\text{H}$ BDE in aniline, with experimental values in the intervals (362.8 to 371.1) and (368.2 to 386.2) $\text{kJ} \cdot \text{mol}^{-1}$, respectively [19]. This suggests that, as expected,

the aromatic rings of phenol and aniline stabilize the radicals more efficiently than the possible formation of internal hydrogen bonds in glucosamine and its *N*-acetylated derivative. Note that the $\text{O}-\text{H}$ BDE in cyclo-hexanol was estimated to be 438.5 kJ/mol [19], while the experimental BDEs reported for 2-propanol, 2-butanol and tert-butanol are (442.3 $\pm$ 2.8), (441.4 $\pm$ 4.2), and (444.9 $\pm$ 2.8) $\text{kJ} \cdot \text{mol}^{-1}$, respectively [19]; the latter values are similar to the calculated BDEs for the $\text{O}(3)-\text{H}$ bonds in glucosamine and in *N*-acetylglucosamine, which are those that have a chemical environment similar to that of the $\text{O}-\text{H}$ bond in cyclo-hexanol. Experimental data for the $\text{N}-\text{H}$ BDEs in benzylamine and in methylamine, respectively, 418.4 $\text{kJ} \cdot \text{mol}^{-1}$ and (425.1 $\pm$ 8.4) $\text{kJ} \cdot \text{mol}^{-1}$ [19], compare satisfactorily with the corresponding value in glucosamine, while the experimental result available for *N*-methylacetamide, 445.6 $\text{kJ} \cdot \text{mol}^{-1}$ [19], is not far from the calculated $\text{N}-\text{H}$ BDE for *N*-acetylglucosamine.

The calculated EoDs for glucosamine also reported in table 1 show that the most stable anion is that resulting from the heterolytic $\text{O}(3)-\text{H}$ rupture, followed by $\text{O}(1)-\text{H}$ rupture. Convincingly, these are the two groups that condense to form the polymeric chains. The anions resulting from heterolytic $\text{O}(2)-\text{H}$ and $\text{N}(5)-\text{H}$ cleavage are the least stable. The enthalpic difference between the most and the least acidic bonds is 110 $\text{kJ} \cdot \text{mol}^{-1}$. Comparison of the EoDs calculated for glucosamine and *N*-acetylglucosamine shows that acidities in the latter are systematically smaller than those of the corresponding bonds in the former, especially in the case of the $\text{N}(5)-\text{H}$ bond, which is much more prone to cleavage in the *N*-acetylated monomer than in the deacetylated one by $\sim 140\text{ kJ} \cdot \text{mol}^{-1}$. The EoDs listed in table 1 can be compared with the calculated values for the heterolytic breakage of the $\text{O}-\text{H}$ bond in phenol (1462.2 $\text{kJ} \cdot \text{mol}^{-1}$) [20], or with available experimental data for the EoDs in several 6-member ring alicyclic alcohols, namely, 1-methylcyclohexanol, cis- and trans-2-methylcyclohexanol, cis- and trans-4-methylcyclohexanol with EoDs comprehended in the interval between (1551 $\pm$ 9.2) and (1563 $\pm$ 9.2) $\text{kJ} \cdot \text{mol}^{-1}$ [21]. Interestingly, calculated data for heterolytic $\text{O}(3)-\text{H}$, $\text{O}(1)-\text{H}$ and $\text{O}(4)-\text{H}$ rupture compare well with the value reported for phenol while the calculated EoD for heterolytic $\text{O}(2)-\text{H}$, cleavage is included in the interval of experimental results for several 6-member ring alicyclic alcohols. The calculated data for the heterolytic breakage of the $\text{N}-\text{H}$ bond in glucosamine and in *N*-acetylglucosamine can be compared with the result computed for aniline (1536.5 $\text{kJ} \cdot \text{mol}^{-1}$) [20] or with the experimental data available for *N*-methylformamide (1508 $\pm$ 9 $\text{kJ} \cdot \text{mol}^{-1}$) [21]. The latter results confirm that the small EoD for the $\text{N}(5)-\text{H}$ bond in *N*-acetylglucosamine is not common and that the resulting *N*-acetylglucosamine anion is very stable.

3.2. Interaction with monovalent cations

Many of the suggested applications for chitosan are based on its good ability to coordinate metal ions. Herewith, the interactions between the monomeric units of chitosan, i.e., glucosamine and *N*-acetylglucosamine, and Ni(I) , Cu(I) and Zn(I) ions were also studied by DFT. We have identified five different sites on glucosamine and on *N*-acetylglucosamine that can form stable complexes with metals, and these are illustrated in figure 2. Note that in the case of *N*-acetylglucosamine, there are two different possibilities for the metal coordination at c4 and c5 positions due to rotation of the acetyl group. Thus, the metals can bind $\text{O}(4)$ and $\text{N}(5)$ or $\text{O}(4)$ and $\text{O}(a)$ in the case of the c4 position, and can bind $\text{O}(1)$ and $\text{N}(5)$ or $\text{O}(1)$ and $\text{O}(a)$ in the case of the c5 site.

For each of the five different interaction sites studied on the two chitosan monomers, selected geometric parameters are reported in table 2, while the interaction energies and enthalpies at $T = 298.15\text{ K}$ are reported in table 3. Additionally, figure 3 shows

TABLE 1

Calculated gas-phase $\text{O}-\text{H}$ or $\text{N}-\text{H}$ bond dissociation enthalpies (BDE) and enthalpies of deprotonation (gas-phase acidity, EoD) for glucosamine and *N*-acetylglucosamine. Bond dissociation enthalpies (BDE) and enthalpies of deprotonation (EoD)/ $\text{kJ} \cdot \text{mol}^{-1}$.

X ($\text{X}-\text{H}$ bond) ^a	Glucosamine		<i>N</i> -acetylglucosamine	
	BDE	EoD	BDE	EoD
O1	406.6	1445.6	414.4	1408.3
O2	422.8	1555.2	424.5	1546.3
O3	432.8	1440.9	440.5	1420.8
O4	436.6	1462.3	517.3	1421.5
N5	412.2	1552.8	432.2	1425.5

^a For atomic labelling see figure 1.

FIGURE 2. Labelling scheme for different configurations studied for the complexes between Ni, Cu or Zn cations with glucosamine (a) or *N*-acetylglucosamine (b).

TABLE 2
Optimized lengths (nm) for complexes between Ni(I), Cu(I) or Zn(I) and glucosamine or *N*-acetylglucosamine. Views of the optimised structures appear in the Supporting Information.

Complex ^a	Metal	Glucosamine				<i>N</i> -acetylglucosamine			
		Atom ^a	Distance/nm	Atom ^a	Distance/nm	Atom ^a	Distance/nm	Atom ^a	Distance/nm
c1	Ni	r	0.1967	2	0.2024	r	0.1984	2	0.2005
	Cu	r	0.2032	2	0.2093	r	0.2049	2	0.2063
	Zn	r	0.2116	2	0.2201	r	0.2138	2	0.2150
c2	Ni	2	0.1973	3	0.1948	2	0.1987	3	0.1970
	Cu	2	0.1999	3	0.1964	2	0.2200	3	0.1924
	Zn	2	0.2126	3	0.2062	2	0.2162	3	0.2085
c3	Ni	3	0.2026	4	0.1980	3	0.2040	4	0.1943
	Cu	3	0.2100	4	0.2015	3	0.2144	4	0.1962
	Zn	3	0.2199	4	0.2106	3	0.2234	4	0.2018
c4	Ni	4	0.2015	5	0.1999	4	0.1966	a	0.1896
	Cu	4	0.2103	5	0.2015	4	0.1967	a	0.1921
	Zn	4	0.2175	5	0.2167	4	0.2176	a	0.1992
c5	Ni	1	0.2024	5	0.1995	1	0.1983	a	0.1894
	Cu	1	0.2130	5	0.2006	1	0.2000	a	0.1917
	Zn	1	0.2215	5	0.2155	1	0.2230	a	0.1992

^a For labelling see figure 2.

TABLE 3
Energies and enthalpies of interaction (kJ · mol^{−1}) for complexes between Ni(I), Cu(I) or Zn(I) and glucosamine or *N*-acetylglucosamine.

Complex ^a	Metal	Glucosamine		<i>N</i> -acetylglucosamine	
		$E_{int}/\text{kJ} \cdot \text{mol}^{-1}$	$H_{int}^{298.15\text{ K}}/\text{kJ} \cdot \text{mol}^{-1}$	$E_{int}/\text{kJ} \cdot \text{mol}^{-1}$	$H_{int}^{298.15\text{ K}}/\text{kJ} \cdot \text{mol}^{-1}$
c1	Ni	−340.9	−338.6	−329.9	−327.3
	Cu	−300.1	−298.4	−289.1	−287.1
	Zn	−216.3	−215.0	−252.0	−250.4
c2	Ni	−343.6	−340.7	−333.4	−331.0
	Cu	−309.3	−307.0	−295.7	−294.1
	Zn	−267.2	−265.0	−257.1	−255.7
c3	Ni	−312.8	−311.4	−348.2	−350.4
	Cu	−275.3	−274.6	−309.5	−312.1
	Zn	−239.4	−239.3	−282.0	−286.3
c4	Ni	−371.1	−366.4	−373.2	−371.3
	Cu	−331.1	−326.9	−329.4	−328.4
	Zn	−284.1	−280.6	−249.6	−249.5
c5	Ni	−359.7	−355.9	−366.3	−364.6
	Cu	−320.8	−317.7	−328.2	−327.3
	Zn	−272.8	−270.3	−280.1	−279.1

^a For labelling see figure 2. Bold is used to denote the most stable configurations.

the views of the most stable configurations optimised for each cation. Views of all the optimised configurations are supplied as Supporting Information.

As shown in table 2, the three different ions interact with the oxygen or nitrogen atoms of the cyclic monomers at distances of (0.20 ± 0.02) nm. Generally, the shorter distances are found for

FIGURE 3. Views of the most stable configurations optimised for the interaction of Ni(I), left, Cu(I), middle, and Zn(I), right, cations with glucosamine or with *N*-acetylglucosamine. Bond distances are shown in non-SI units Å, 1 Å = 0.1 nm.

TABLE 4

Optimized lengths (nm) for complexes between Ni(II), Cu(II) or Zn(II) and glucosamine or *N*-acetylglucosamine. Views of the optimised structures appear in the Supporting Information.

Complex ^a	Metal	Glucosamine		N-acetylglucosamine	
		Atom ^a	Distance/nm	Atom ^a	Distance/nm
c1	Ni	r	0.1979	1	0.2107
	Cu	r	0.2146 ^b	2	0.2049 ^b
	Zn	1	0.1976	2	0.1936
c2	Ni	2	0.2005 ^b	3	0.2030 ^b
	Cu	2	0.2038 ^b	3	0.2047 ^b
	Zn	2	0.1946	3	0.1906
c3	Ni	3	0.2028 ^b	4	0.2022 ^b
	Cu	3	0.2105 ^b	4	0.2095 ^b
	Zn	3	0.2015 ^c	4	0.1836 ^c
c4	Ni	4	0.1988	5	0.1999
	Cu	4	0.2161	5	0.2026
	Zn	4	0.1947	5	0.2010
c5	Ni	1	0.2008	5	0.2003
	Cu	1	0.2247	5	0.2030
	Zn	1	0.1948	5	0.1997

^a For labelling see figure 2.

^b Ring opens.

^c H atom jumps from O(4) to N(5).

^d H atom jumps from O(4) to O(a).

^e H atom jumps from O(3) to O(4).

the Ni(I) cation while the larger ones are found for Zn(I), *i.e.*, the distances are correlated with the atomic weight of the transition metals.

A similar correlation with metal atomic weight is found for the calculated energetic/enthalpic data displayed in table 3. In general, the stronger interactions are found for the nickel cation while the weakest ones are found for the zinc cation. In the case of the interaction with glucosamine, all three monovalent ions prefer to bind the cyclic molecule at position c4 (figure 3), with calculated enthalpies of interaction, at $T = 298.15$ K, of (−366.4, −326.9, and −280.6) kJ · mol^{−1} for Ni(I), Cu(I) and Zn(I) ions,

respectively. The least stable interaction site is c3 in the cases of Ni(I) and Cu(I), and c1 in the case of Zn(I), with calculated enthalpies of interaction of (−311.4, −274.6, and −215.0) kJ · mol^{−1}, respectively.

In the case of the interaction with *N*-acetylglucosamine, table 3 and figure 3, interactions with nickel and copper ions are also more favourable at position c4, while for Zn(I) two almost degenerate configurations were obtained, *i.e.*, for interactions at position c3 (the most stable) and c5. The calculated $H_{\text{int}}^{298.15 \text{ K}}$ for complexes with *N*-acetylglucosamine are more negative than those calculated for complexes with glucosamine, *i.e.*, interactions

TABLE 5
Energies and enthalpies of interaction ($\text{kJ} \cdot \text{mol}^{-1}$) for complexes between Ni(II), Cu(II) or Zn(II) and glucosamine or *N*-acetylglucosamine.

Complex ^a	Metal	Glucosamine		<i>N</i> -acetylglucosamine	
		$E_{\text{int}}/\text{kJ} \cdot \text{mol}^{-1}$	$H_{\text{int}}^{298.15 \text{ K}}/\text{kJ} \cdot \text{mol}^{-1}$	$E_{\text{int}}/\text{kJ} \cdot \text{mol}^{-1}$	$H_{\text{int}}^{298.15 \text{ K}}/\text{kJ} \cdot \text{mol}^{-1}$
c1	Ni	−1074.3	−1076.4	−1074.3	−1077.4
	Cu	−1179.5 ^b	−1180.8 ^b	−1174.4	−1172.8
	Zn	−979.2	−979.1	−992.8	−995.6
c2	Ni	−1077.3 ^b	−1077.1 ^b	−1049.8 ^b	−1051.4 ^b
	Cu	−1220.8 ^b	−1220.0 ^b	−1155.6	−1155.0
	Zn	−922.3	−924.6	−1079.9 ^{d,e}	−1078.5 ^d
c3	Ni	−1031.6 ^b	−1034.0 ^b	−1102.7 ^d	−1103.0 ^d
	Cu	−1167.4 ^b	−1168.6 ^b	−1160.1 ^d	−1162.9 ^d
	Zn	−996.6 ^c	−991.8 ^c	−1001.7 ^d	−1003.1 ^d
c4	Ni	−1050.7	−1049.8	−1081.9	−1084.2
	Cu	−1165.7	−1164.3	−1140.2	−1142.6
	Zn	−933.5	−932.4	−1005.3	−1007.4
c5	Ni	−1041.9	−1042.4	−1080.5	−1083.4
	Cu	−1160.2	−1160.1	−1174.5	−1178.4
	Zn	−920.1	−920.7	−999.8	−1002.0

^a For labelling see figure 2. Bold is used to denote the most stable configurations.

^b Ring opens.

^c H atom jumps from O(4) to N(5).

^d H atom jumps from O(4) to O(a).

^e H atom jumps from O(3) to O(4).

FIGURE 4. Views of the most stable configurations optimised for the interaction of Ni(II), left, Cu(II), middle, and Zn(II), right, cations with glucosamine or with *N*-acetylglucosamine. Bond distances are shown in non-SI units Å, 1 Å = 0.1 nm.

are more favourable in the acetylated units, but maintain the same ordering, with values (-371.3 , -328.4 , and -286.3) $\text{kJ} \cdot \text{mol}^{-1}$ for Ni(I), Cu(I) and Zn(I) species, respectively. Nevertheless, as it can be seen, the enthalpic differences between interactions with glucosamine or with *N*-acetylglucosamine are small. Note that positions c3 and c5 are not available in the polymeric chains due to polymerization by condensation of $-\text{O}(3)\text{H}$ and $-\text{O}(1)\text{H}$ hydroxyl groups (figure 2). Hence, Zn(I) will very probably interact with the amino groups of the polymeric chains, similarly to the other two metal ions considered in this work.

3.3. Interaction with divalent cations

Selected geometric parameters and energetic results calculated for the interaction of glucosamine or of *N*-acetylglucosamine with Ni(II), Cu(II) and Zn(II) cations are reported in tables 4 and 5, respectively. Views of the optimised configurations are depicted in figure 4 (only for the most favourable cases) and in the Supporting Information.

The analysis of the selected distances in table 4 shows that, as in the case of the monovalent cations, the divalent cations are also interacting with the oxygen or nitrogen atoms of the cyclic

molecules at distances of (0.20 ± 0.02) nm. However, distances calculated for the interactions with the copper cation are systematically larger than those optimised for the two other divalent ions; the lengths optimised for the complexes between the latter species and glucosamine or *N*-acetylglucosamine are quite similar. Note that the full geometry optimization of some of the complexes leads to structures where the ring opens (both for complexes with glucosamine or *N*-acetylglucosamine) or where the hydrogen atom of one of the hydroxyl groups eventually attaches to the nitrogen in *N*-acetylglucosamine. The following discussion will consider only the complexes that maintain the integrity of the cyclic glucosamine and *N*-acetylglucosamine monomers. The cation–molecule distances seem to be determinant for the stability of each of the configurations studied for each metal. In fact, as shown in table 5, the most stable sites for nickel and zinc are the same when these cations interact with glucosamine or with its *N*-acetylated derivative, and differ from the energetically more favourable configurations for Cu(II). In the former cases, c1 emerges as the most stable position for interaction with glucosamine while c4 is preferred in interactions with *N*-acetylglucosamine. Curiously, in the case of interactions with divalent copper cation, the c4 position is preferred in glucosamine whereas c1 site is more favourable in *N*-acetylglucosamine.

Comparison between results obtained for the monovalent and divalent cations shows that (i) the ordering of the interaction enthalpies is not the same, i.e., the complexes with Cu(II) are more stable than those with Ni(II), but the complexes with Zn(II) are still the least stable, (ii) the enthalpic difference for the interactions between divalent cations with glucosamine and with *N*-acetylglucosamine is significantly reduced, (iii) the interaction with the amino/amido group is not the most favourable in all the cases,

and (iv) the strong interaction between both monomers and the divalent cations leads to destabilisation of their structures, which in some cases suffer ring opening or intramolecular reorganisation.

Additionally, for the interaction of *N*-acetylglucosamine with either monovalent or divalent cations, c4 and c5 positions were found to be always preferred when the metal ion is coordinated to the oxygen atom of the amide group, than when it is coordinated to the nitrogen atom of the amide group. The latter configurations where the metal cations are interacting with the nitrogen atom were found to be less stable than in their counterparts where the ions are interacting with the amide's oxygen by (30 to 60) or (70 to 100) $\text{kJ} \cdot \text{mol}^{-1}$ in the case of c4 or c5 positions, respectively, (data not shown).

3.4. Effect of water on the interaction with divalent cations

The calculations performed in the gaseous phase, discussed above, suggest that interactions with the amino groups are generally more favourable, which is in agreement with the chelation models based on available experimental information, especially for the Cu(II) cation, that suggests that the amino group is directly involved in the complexation mechanism [7]. Nevertheless, in some cases, the gas-phase calculations indicate the c1 configuration as preferred. Note that upon polymerization, the hydroxyl groups with oxygen atoms 1 and 3 are condensed, but sites c1 and c4 remain available in polymeric chains. Since some of the chelation models suggest that water molecules are involved in the complexation mechanism, the DFT calculations were also extended to analyse the effect of water on the interaction of divalent cations with glucosamine. To this end, we have re-optimised the structures obtained for interactions between the divalent cations and glucosamine at the c1 and c4 positions in the presence of one, two and three water molecules. Views of the optimised configurations for the most favourable cases with three water molecules are shown in figure 5, whereas those for the other optimised configurations in the presence of water are provided as Supporting Information. The enthalpies of interaction calculated using Equation (2) for the different systems studied are reported in table 6.

In glucosamine–Ni(II) complexes in the presence of water, c4 configurations are more stable than the corresponding c1 structures by (4 to 12) $\text{kJ} \cdot \text{mol}^{-1}$, the largest difference being found for complexes involving three water molecules; this contrasts with enthalpic data for the complexes in the gaseous-phase, where the c1 conformation was significantly more stable than the c4 one ($\Delta H_{\text{int}}^{298.15 \text{ K}} = 27 \text{ kJ} \cdot \text{mol}^{-1}$ for $m_{\text{water}} = 0$). The optimised configurations for the complexes with the Ni(II) cation show that the third water molecule is not interacting directly with the metal ion but bridging the remaining water molecules (figure 5), which suggests that square planar complexes are preferred. In fact, from the enthalpic variations (Δ) given in table 6, it is seen that the introduction of a second water molecule has a larger contribution to the stabilization of the resulting complex than the introduction of the first or the third molecule.

In the case of Cu(II), the introduction of a single water molecule to the c1 and c4 complexes has a more dramatic effect in the former than in the latter, and the stability order is reversed when compared with complexes where water molecules are absent. The linear water–Cu(II)–glucosamine complex for the c1 configuration is more stable than the triangular complex found when the cation is at the c4 site. The c4 configuration becomes the most stable upon introduction of a second and of a third water molecule. As found for Ni(II), the c4 configurations with two or three water molecules are more stable, by a few $\text{kJ} \cdot \text{mol}^{-1}$, than the c1 configurations. Note that the third molecule is also bridging the other two water molecules that bind directly to the metal cation, as found

FIGURE 5. Views of the optimised structures for the c4 configurations of the [TM(II)–glucosamine–(H_2O)₃] complexes (TM = Ni, Cu, or Zn). Bond distances are shown in non-SI units Å, 1 Å = 0.1 nm.

TABLE 6

Enthalpies of interaction ($\text{kJ} \cdot \text{mol}^{-1}$) for complexes between Ni(II), Cu(II) or Zn(II), glucosamine and m water molecules.

Complex ^a	m_{water}	Ni(II)		Cu(II)		Zn(II)	
		$H_{\text{int}}^{298.15 \text{ K}} / \text{kJ} \cdot \text{mol}^{-1}$	$\Delta \text{kJ} \cdot \text{mol}^{-1}$	$H_{\text{int}}^{298.15 \text{ K}} / \text{kJ} \cdot \text{mol}^{-1}$	$\Delta \text{kJ} \cdot \text{mol}^{-1}$	$H_{\text{int}}^{298.15 \text{ K}} / \text{kJ} \cdot \text{mol}^{-1}$	$\Delta \text{kJ} \cdot \text{mol}^{-1}$
c1	0	−1076.4	0.0	−1180.8	0.0	−979.1	0.0
	1	−1176.4	−100.0	−1358.6	−177.8	−1189.1	−210.0
	2	−1348.0	−171.6	−1435.8	−77.1	−1325.6	−136.5
	3	−1449.1	−101.1	−1533.2	−97.5	−1430.5	−104.9
c4	0	−1049.8	0.0	−1164.3	0.0	−932.4	0.0
	1	−1180.3	−130.5	−1335.5	−171.2	−1172.2	−239.8
	2	−1352.4	−172.1	−1438.2	−102.7	−1323.4	−151.1
	3	−1460.9	−108.5	−1539.6	−101.4	−1431.7	−108.3

^a For labelling see figure 2.

for Ni(II), which is in agreement with the chelating models suggested for Cu(II) where the cation is tetra-coordinated. Note that hexa-coordinated structures were also suggested for the interactions with Cu(II) and may be more stable when more ligands are available. In the case of copper, the first water molecule has a larger contribution than the second or the third ones to the calculated enthalpies of interaction.

The analysis of the data compiled in table 6 for the Zn(II) cation shows that addition of water molecules reduces the difference between the stabilities of the c1 and c4 configurations, the former being 47 kJ/mol more stable than the latter in the absence of water, whereas in the presence of three water molecules the latter (c4) becomes more stable. Note that the local structure of the Zn(II) in configurations with two and three water molecules is tetrahedral, not square-planar as for the complexes with Ni(II) and Cu(II). As in the case of Cu(II), the largest contribution to the computed enthalpy of interaction of the complexes with Zn(II) occurs upon the addition of the first water molecule. Interestingly, in $[\text{Zn(II)}\text{-glucosamine-(H}_2\text{O)}_3]$, configuration c1, shown in the Supporting Information, the third molecule binds directly to the cation, which suggests a different coordination environment for Zn(II). The introduction of a fourth molecule (results not shown) yields hexa-coordinated Zn(II) complexes, with the cation interacting with two atoms from glucosamine and two water molecules in one plane, and with two other water molecules, above and below that plane (octahedral geometry). Thus, the present calculations suggest that the coordination for Zn(II) may be different from those reported in the literature for Ni(II) and Cu(II) cations [8–10], and these findings are supported by the more recent experimental results of Hernández *et al.* [11]. These authors suggested that tetra-, penta-, and hexa-coordinated structures can be also formed in solution [11], which is very encouraging.

The data calculated for the hydrated M(II)-glucosamine ($M = \text{Ni, Cu, or Zn}$) complexes suggest that the c4 configurations where the ions are bound to the amino and to a neighbouring hydroxyl group are more favourable. Additionally, copper complexes are visibly more stable than those optimised for the other two cations. These findings are in good agreement with available experimental data in aqueous media, which indicates that chitosan complexes with Cu(II) are more stable than those with other transition metal divalent cations [11,22], and that hydroxyl groups are also involved in the metal complexation mechanism [22]. The complexes studied in this work for Ni(II) are more stable than those optimised for Zn(II), while experimental work suggests the contrary [22]. This is probably due to the fact that Zn(II) is under-coordinated in the complexes studied in this work. A comparison of the interaction enthalpies for Ni(II) and Zn(II) complexes with glucosamine and more than three water molecules is needed to answer that question, but such studies would require the deployment of larger computational power.

4. Conclusions

Density functional theory calculations performed at the B3LYP/6-31+G** level of theory were used to calculate the enthalpies of O–H or N–H bond dissociation and of deprotonation in glucosamine and *N*-acetylglucosamine compounds. It was found that the most stable radicals are those obtained by removing an H atom from O(1) in both compounds, and that the most stable anions are that obtained by removing a proton from O(3) in glucosamine and from O(1) in *N*-acetylglucosamine. The same level of theory was also used to calculate the interactions of monovalent and divalent nickel, copper and zinc cations with glucosamine and *N*-acetylglucosamine. In the case of the monovalent cations, interactions are preferentially in c4 configuration, and the most stable complexes are those with Ni(I). The calculations with the divalent cations show that c1 configurations compete with c4 configurations and the relative preference is highly dependent on the degree of hydration. Finally, the complexes with Cu(II) are more favourable than those with Ni(II) and Zn(II) cations, which is in very good agreement with available experimental data.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jct.2013.11.016>.

References

- [1] B. Sarmiento, J. das Neves, in: *Chitosan-Based Systems for Biopharmaceuticals: Delivery, Targeting and Polymer Therapeutics*, John Wiley & Sons Ltd, Chichester, United Kingdom, 2012.
- [2] A.J. Varma, S.V. Deshpande, J.F. Kennedy, *Carbohydr. Polym.* 55 (2004) 88.
- [3] P. Gomes, C.A.R. Gomes, M.K.S. Batista, L.F. Pinto, P.A.P. Silva, *Carbohydr. Polym.* 71 (2008) 54.
- [4] Y.A. Skorik, N.V. Podberezskaya, G.V. Romanenko, E.V. Osintseva, L.K. Neudachina, A.A. Vshivkov, *Russ. J. Inorg. Chem.* 48 (2003) 199.
- [5] Z. Aiping, L. Jianhong, Y. Wenhui, *Carbohydr. Polym.* 63 (2006) 89.
- [6] P. Agrawal, G.J. Strijkers, K. Nicolay, *Adv. Drug Delivery Rev.* 62 (2010) 42.
- [7] K. Ogawa, K. Oka, *Chem. Mater.* 5 (1993) 726.
- [8] A. Domard, *Int. J. Biol. Macromol.* 9 (1986) 98.
- [9] S. Schlick, *Macromolecules* 19 (1985) 192.
- [10] M. Rhazi, J. Desbrières, A. Tolaimate, M. Rinaudo, P. Vottero, A. Alagui, *Polymer* 43 (2002) 1267.
- [11] R.B. Hernández, O.R. Yola, A.L.R. Mercê, J. Braz. Chem. Soc. 18 (2007) 1388.

- [12] C. van der Linde, S. Hemmann, R.F. Höckendorf, O.P. Balaj, M.K. Beyer, J. Phys. Chem. A 117 (2013) 1011.
- [13] N.C. Braier, R.A. Jishi, J. Mol. Struct. THEOCHEM 499 (2000) 51.
- [14] R. Lü, Z. Gao, G. Shen, J. Mol. Struct. THEOCHEM 860 (2008) 80.
- [15] R. Terreux, M. Domard, C. Viton, A. Domard, Biomacromolecules 7 (2006) 31.
- [16] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery Jr., J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R. L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, Ö. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian 09 Rev. B.01, Gaussian Inc, Wallingford CT, 2009.
- [17] A.D. Becke, J. Chem. Phys. 98 (1993) 5648–5652.
- [18] C.T. Lee, W.T. Yang, R.G. Parr, Phys. Rev. B 37 (1988) 785–789.
- [19] Y.R. Luo, Comprehensive Handbook of Chemical Bond Energies, CRC Press, Taylor & Francis Group, Boca Raton, 2007.
- [20] J.R.B. Gomes, J. Phys. Chem. A 113 (2009) 1628–1634.
- [21] J.E. Bartmess, Negative ion energetics data in NIST Chemistry WebBook, NIST Standard Reference Database Number 69, in: P.J. Linstrom, W.G. Mallard (Eds.), National Institute of Standards and Technology, Gaithersburg MD, 20899, <http://webbook.nist.gov>, (retrieved November 6, 2013).
- [22] M. Rinaudo, Progr. Polym. Sci. 31 (2006) 603.

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