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Influence of metal ion and coordination geometry on the gas phase dissociation and stereochemical differentiation of N-glycosides

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Abstract

A series of metal cationized N-glycoside complexes is studied by tandem mass spectrometry. The complexes are of the form $[M(dien)(hex)_n - H]^+$, $[M(dien)(hex)_nCl]^+$, or $[M(dien)(hex)_2]^{2+}$,where M = Co^{2+}, Cu^{2+}, Ni^{2+}, or Zn^{2+} and $n = 1$ or 2. The presence of a metal as the charge carrier promotes more extensive cleavage of the carbon backbone of the saccharide moiety compared to the protonated analogues, thus providing greater structural information. Results obtained for the four coordinate singly charged deprotonated complexes differentiate $[M(dien)(Glc) - H]^+$ versus $[M(dien)(Gal) - H]^+$ for a given metal. Such differentiation is not possible for the corresponding five coordinate complexes, indicating that the coordination number of the metal plays an important role. Tandem mass spectra for both of these four and five coordinate complexes indicate that the geometry around the metal dictates the observed dissociation patterns. Furthermore, the metals Zn and Cu promote unique modes of dissociation not observed for the Ni and Co complexes. Finally, the chlorinated and doubly charged complexes give rise to very few dissociation pathways by MS/MS. It is proposed that this lack of product ions is due to the absence of lone pair electrons on the metal alkoxide that drive the dissociation. (Int J Mass Spectrom 197 (2000) 139–148) © 2000 Elsevier Science B.V.

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1. Introduction

The advent of "soft" ionization techniques such as electrospray ionization (ESI) [1] has enabled many nonvolatile biologically relevant molecules to be ionized, thus allowing for analysis by mass spectrometry. This ionization process often involves proton or metal attachment to cationize the molecule of interest. Furthermore, the coupling of ESI to the ion trap mass spectrometer [2] has provided a convenient means of structural analysis of these molecules by sequential stages of mass spectrometry (MS^n) [3].

It has long been recognized that metals can form adducts with a variety of compounds and subsequently be transferred into the gas phase [4–16]. A fortuitous consequence of this metal attachment is that these adducts, unlike their protonated counterparts, often undergo significantly different types of dissociation when subjected to MS^n. For example, Brodbelt and co-workers [14] have compared MS^n spectra of a series of pharmaceutical compounds coordinated to

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copper, nickel, or cobalt along with a pyridyl or polyether auxiliary ligand. In many cases these complexes produced a greater number of product ions in the MS/MS spectra than the protonated substrates, thus leading to enhanced structural characterization. In fact, it has been shown that structural isomers can be differentiated when coordinated to certain metal ions: linkage positions of monosaccharide units within oligosaccharides have been determined by examining MS^n spectra of alkali, alkaline earth, or transition metal coordinated saccharides [17–31].

Recent work from our lab has also focused on differentiating *stereo*isomers, specifically isomeric monosaccharides [32–36] and isomeric disaccharides [26,31] by using mass spectrometry. To detect such subtle differences, cationization by a metal alone does not yield the desired information; an auxiliary ligand, covalently attached to the saccharide moiety through an N-glycoside bond, is required. In these cases the saccharides are allowed to react with various metal coordination compounds such as Ni(1,3-diaminopropane)$_3$Cl$_2$ [Ni(*dap*)$_3$Cl$_2$], Zn(diethylenetriamine)$_2$Cl$_2$ [Zn(*dien*)$_2$Cl$_2$], or Co(*dap*)$_2$Cl$_3$ using a microscaled version of a synthetic procedure reported previously [32–37]. The resulting metal-ligand-N-glycoside complexes produce MS^n spectra that are often dependent upon the glycosidic bond configuration or the axial/equatorial configuration of hydroxyl groups within the saccharide moiety. Thus, MS^n yields information about the stereochemistry of the saccharide moiety in these complexes.

Having obtained these results, interest arose in probing the roles of the auxiliary ligand and the metal in driving the dissociation of these complexes, i.e. how changing the ligand or the metal might promote different cleavage patterns. The former is the subject of another article [36], whereas the latter is discussed here. In particular, our experiments herein focus on substituting other metals for Zn in the Zn(*dien*)(hexose)Cl$_2$ complexes such as that shown in Fig. 1.

For such a study, each individual metal-*dien* complex would be required as a starting material, and therefore, would first need to be prepared. However, an alternative synthetic method was developed where diglycosyl-*dien* "templates" were prepared using glucose or galactose as the saccharide moiety [38]. In the study reported here, these templates are combined with one of the metal chlorides $CoCl_2$, $CuCl_2$, $NiCl_2$, or $ZnCl_2$ to easily form the metal-ligand-N-glycoside complex in solution (Fig. 2).

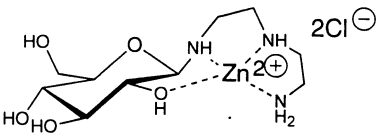


Fig. 1. Representative Zn(*dien*)(N-glycoside) complex where glucose is the chosen hexose.

2. Experimental

2.1. Materials

Diethylenetriamine and 1 M HCl in ether were purchased from Aldrich (Milwaukee, WI). Glucose, galactose, and spectro grade methanol were purchased from Sigma (St. Louis, MO). Ammonium hydroxide, zinc chloride, cobalt chloride, and nickel chloride were purchased from Fisher (Pittsburgh, PA). Copper chloride was purchased from Mallinckrodt (Phillipsburg, NJ). All reagents were used as received.

2.2. Sample preparation

Diglycosyl-diethylenetriamine "templates" were prepared as described elsewhere [38]. Briefly, one equivalent each of *dien* and 1 M HCl in ether were allowed to react in methanol to form a *dien*-HCl salt. Two equivalents of either glucose or galactose were added and the product, which precipitated from solution, was recrystallized from ethanol/water. This intermediate product is referred to as the "template" throughout the article.

Samples were prepared by first allowing 1–2 mg of template to partially hydrolyze in 10 μL H_2O for 1 h to form a mixture in solution of mono- and di-N-glycosides (see Fig. 2). A 200 μL portion of methanol was added along with approximately 2–4 equivalents of metal chloride and 1 μL concentrated NH_4OH

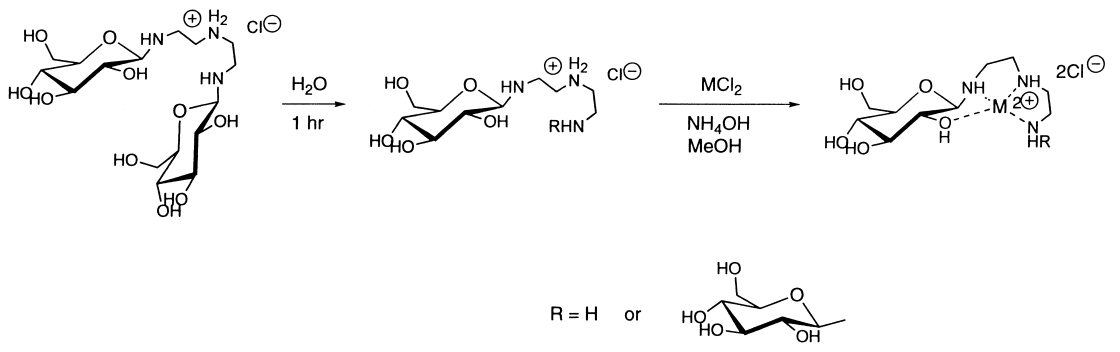


Fig. 2. After partial hydrolysis, the di-N-glycoside and mono-N-glycoside (R = H) formed in solution are coordinated to a transition metal (M = Co^{2+}, Ni^{2+}, Cu^{2+}, or Zn^{2+}) added as the chloride salt. Glucose (equatorial C4 hydroxyl) complexes are shown. The galactose moiety possesses an axial C4 hydroxyl.

(except in the case of $CoCl_2$ samples where no base was added). Solutions were briefly (~30 s) vortexed to ensure complete mixing and immediately diluted in 100% methanol for analysis. The final concentration of this solution was 50–100 pmol/μL.

2.3. Mass spectrometry

Mass spectral analyses were performed on a quadrupole ion trap mass analyzer (Finnigan LCQ, Finnigan MAT, San Jose, CA) fitted with the ESI source. Samples were infused into the instrument at a rate of 2 μL/min. The needle was held at a potential of 4.6–5.0 V. Ions were trapped by applying an rf-only potential to the ring electrode, and the automatic gain control was set to 5×10^7 counts and 3×10^7 counts for MS and MS^n, respectively, to regulate the number of ions present in the trap. The maximum ion injection time was set between 100 and 200 ms.

Ions were isolated for collision induced dissociation (CID) with the "isolation width" parameter set to 1.5. CID was performed at a q value of 0.25 by applying a supplementary rf voltage across the endcaps for 30 ms. The voltage was applied at the axial secular frequency of the precursor ion and with an amplitude of 0.55, 0.65, or 0.4 V for the $[M(dien)(hex) - H]^+$, $[M(dien)(hex)_2 - H]^+$, or $[M(dien)(hex)_2]^{2+}$ species, respectively. Spectra represent the average of 15–20 scans as defined by the scan function for the Finnigan LCQ instrument.

3. Results and discussion

3.1. Preparation of metal-ligand-N-glycoside complexes

The synthetic scheme used to generate the $M^{II}(dien)(hex)_n$ complexes (M = Zn, Co, Ni, or Cu; *dien* = diethylenetriamine; hex = glucose or galactose; n = 1 or 2) investigated in this study is outlined in Fig. 2. A typical mass spectrum for the metal chloride/template reaction mixtures is shown in Fig. 3. As shown in the spectrum, several types of complexes are generated including the deprotonated singly charged species, $[M(dien)(hex) - H]^+$ and $[M(dien)(hex)_2 - H]^+$, the chlorinated singly charged species, $[M(dien)(hex)Cl]^+$ and $[M(dien)(hex)_2Cl]^+$, and the doubly charged $[M(dien)(hex)_2]^{2+}$ species. Except for the doubly charged species, these complexes are similar to the ones observed when glucose or galactose was allowed to react with $Zn(dien)_2Cl_2$ in a previous study [33]. Furthermore, the MS/MS spectra for the $[Zn(dien)(hex) - H]^+$ ions at *m/z* 328 generated by either synthetic method are identical, indicating the similarity of these two methods.

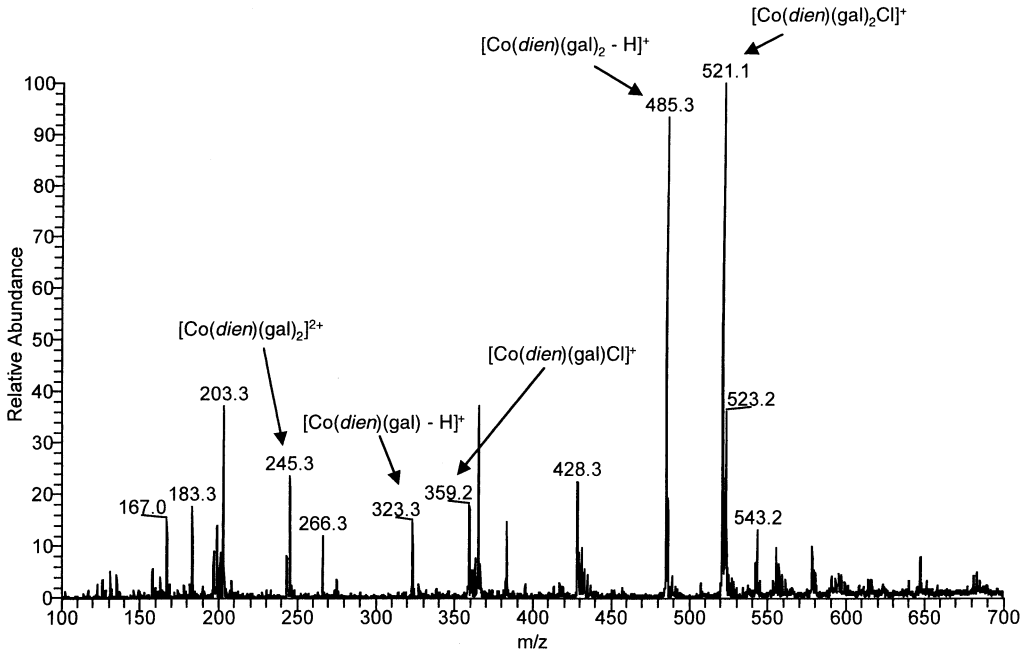


Fig. 3. The mass spectrum of a typical reaction mixture prepared using the scheme in Fig. 2 with $CoCl_2$ and the galactose template.

3.2. Dissociation in the absence of metal

As a control experiment, both the protonated mono- (*m/z* 266, R = H in Fig. 2) and di- (*m/z* 428) N-glycosyl templates for glucose and galactose were allowed to undergo CID. The results of these experiments are summarized in Table 1. As shown in the table, the primary dissociation pathways for all of these complexes are successive losses of H_2O from the precursor ion, a loss of $C_4H_8O_4$ (120 Da) or a combination of the two. Because the carbohydrate moiety is rich in hydroxyl groups, the copious loss of water is not surprising. The facile loss of the $C_4H_8O_4$ neutral can be rationalized through a mechanism such as the one provided in Scheme 1. Here the loss of hydroxy acetaldehyde and an ethylene diol is promoted by an electrocyclic reaction. Although labeling studies have not been performed on these protonated templates, studies of similar metal cationized complexes lead to the same type of electrocyclic mechanism [33].

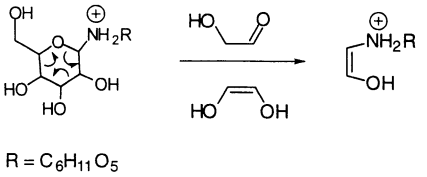
Stereochemical differentiation is not observed in the MS/MS spectra for either the mono- or di-glycosyl template as evidenced by the same MS/MS product ions for both the glucose and galactose analogues.

3.3. Singly charged five coordinate metal complexes

Replacing the proton with a transition metal has a profound effect on the way in which these complexes

Table 1
Neutral losses observed for protonated mono (*m/z* 266) and di (*m/z* 428) glycosylamine ligands of glucose and galactose

Precursor *m/z*	Neutral losses observed *m/z*										
	H_2O	$2H_2O$	$3H_2O$	$4H_2O$	$5H_2O$	$6H_2O$	$7H_2O$	$C_4H_8O_4$	$C_4H_8O_4/H_2O$	$C_4H_8O_4/2H_2O$	$C_4H_8O_4/3H_2O$
266	248	230	212					146	128		
428	410	392	374	356	338	320	302	308	290	272	254



Scheme 1.

dissociate in the gas phase. The dissociation pathways now open to the five coordinate complexes [M(*dien*)$(hex)_2 - H]^+$ where $M = Co^{2+}$, Ni^{2+}, Cu^{2+}, or Zn^{2+} are recorded in Table 2. These complexes dissociate solely through cross-ring cleavage of the carbon backbone by elimination of $C_nH_{2n}O_n$ where $n = 3$, 4, 6, 7, or 8. This is in contrast to the dissociation pathways open to the analogous protonated complex that involve predominantly water losses. Another interesting observation is that the dissociation patterns (both the identity of neutral losses and intensity of product ions) are virtually identical for Co^{2+} and Zn^{2+} complexes of a given monosaccharide. This phenomenon is also observed for the Cu^{2+} and Ni^{2+} complexes. Both Zn and Co promote neutral losses containing only three or four carbons, whereas Ni and Cu promote losses containing six and seven carbons. Because there are only six carbons on each monosaccharide ring, this implies that the latter metals facilitate cross ring cleavage of both monosaccharide rings simultaneously, whereas the former drive dissociation from one ring at a time. Equally important is the observation that none of these metal coordinated templates give rise to MS/MS spectra that could be used to differentiate glucose or galactose in these five coordinate complexes. This is somewhat contradictory to results obtained from five coordinate complexes in which *dap* was the chosen ligand [36]. This would suggest that not only metal ion and coordination geometry, but also the specific ligand, effect the dissociation process.

3.4. Singly charged four coordinate metal complexes

The corresponding four coordinate complexes of the form [M(*dien*)(hex) $- H]^+$ dissociate by cross ring cleavage, water loss, or a combination of the two. In contrast to the five coordinate complexes, these complexes do exhibit different MS/MS spectra for each of the glucose and galactose analogues as shown in Table 3. The galactose complexes containing either Zn or Co are distinguished from the corresponding glucose complexes by a loss of water from the precursor ion. The glucose complex containing Ni dissociates through a loss of formaldehyde not present in the corresponding galactose complex. The Cu containing galactose complex is differentiated from the glucose complex by a loss of 29 Da.

Comparing the MS/MS spectra for the Co and Zn complexes in Table 3 and Fig. 4, it can be seen that they are nearly identical. The exception is the unique neutral loss of $C_4H_6O_3$ at *m/z* 226 observed for the Zn complexes. The Cu and Ni complexes are also some-

Table 2
Summary of MS/MS spectra for [M(*dien*)$(hexose)_2 - H]^+$ complexes

		Neutral losses observed *m/z*				
Metal	Hexose	$C_3H_6O_3$	$C_4H_8O_4$	$C_6H_{12}O_6$	$C_7H_{14}O_7$	$C_8H_{16}O_8$
Zn	Glucose	(400)[a]	370			(250)
	Galactose	400	370			(250)
Co	Glucose	(395)	365			(245)
	Galactose	395	365			(245)
Ni	Glucose	394	364	304	274	
	Galactose	394	364	304	274	
Cu	Glucose	399	369	309	279	
	Galactose	399	369	309	279	

[a] Parentheses indicate an ion near the 3% relative abundance cutoff.

Table 3
Summary of MS/MS spectra for [M(*dien*)(hexose) − H]$^+$ complexes

		Neutral losses observed *m/z*								
Metal	Hexose	H_2O	CH_2O	CHO	$2H_2O$	CH_2O/H_2O	$C_2H_4O_2$	$C_3H_6O_3$	$C_4H_6O_3$	$C_4H_8O_4$
Zn	Glucose		298			280	268		266	208
	Galactose	310	298			280	268	238	266	208
Co	Glucose		293			275	263	233 (5%)		203
	Galactose	305	293			275	263	233 (30%)		203
Ni	Glucose		292				262	232		202
	Galactose						262	232		202
Cu	Glucose	309			291			237		207
	Galactose	309		298	291			237		207

what similar, although not identical, as was the case for the five coordinate complexes. Both of the four coordinate Cu and Ni complexes dissociate predominantly by loss of $C_3H_6O_3$ and $C_4H_8O_4$ from the precursor ion. The Cu complexes, however, also dissociate by loss of one and two water molecules from the precursor whereas the Ni complexes possess other dissociation pathways of the carbon backbone.

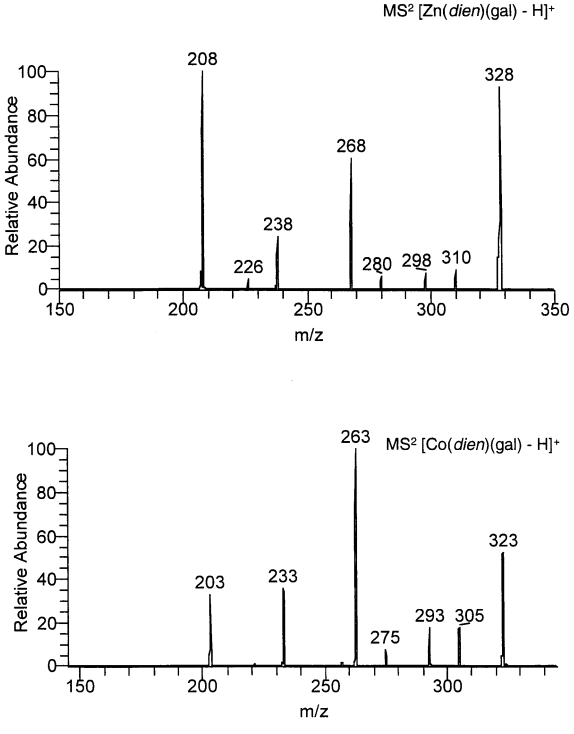


Fig. 4. MS/MS spectra for [Zn(*dien*)(gal) − H]$^+$ and [Co(*dien*)(gal) − H]$^+$ complexes.

Basic inorganic coordination chemistry [39] can be used to rationalize the observation that the Zn and Co ions appear to drive similar pathways of dissociation for the complexes studied here, as do the Ni and Cu. The geometry of the Zn(II) complexes, which possess a filled *d* orbital shell, is dictated only by sterics. These four coordinate complexes are, therefore, most likely tetrahedral. Likewise, the most common geometry for four coordinate Co(II), a d^7 metal, is tetrahedral because this leads to a *d* electron configuration of $e_g^4 t_{2g}^3$. This is in contrast to the Cu(II) and Ni(II) N-glycoside complexes that are likely to be square planar in this type of ligand environment. For example, studies on Ni(II) and Cu(II) interacting with tripeptides in solution (three nitrogens and one oxygen coordinated to the metal) have been shown to be square planar [40]. Therefore, it appears that metal geometry plays a role in dictating the dissociation of the complexes studied here. This effect was also observed in other studies in which metals and/or ligands were substituted in the three, four, and five coordinated complexes of monosaccharides [36].

Despite the similar dissociation patterns observed for metal complexes having the same ligand geometry, there are important and interesting differences apparently due to the metals themselves. Labeling studies conducted previously on the [Zn(*dien*)(glucose) − H]$^+$ complex did not indicate whether the

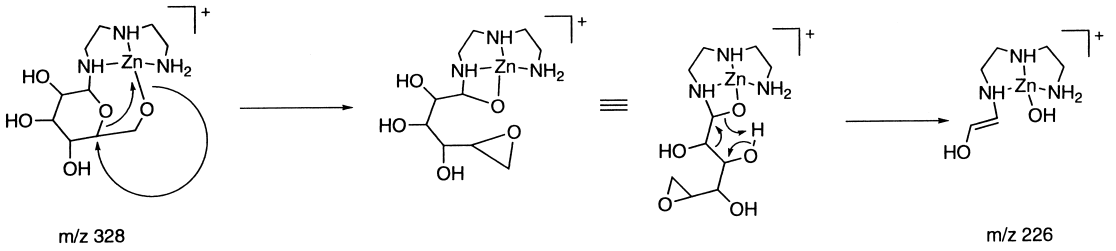


Fig. 5. Proposed mechanism for the formation of product ion at *m/z* 226 from [Zn(*dien*)(hexose) − H]$^+$ species.

dissociation mechanism that produced the $C_4H_6O_3$ loss involved the Zn metal ion [33]. The fact that this loss occurs only in the presence of Zn^{2+} and not Co^{2+}, despite the similar coordination geometry, implies that Zn^{2+} does play an important role in the dissociation process. Taking this information into account, the previously proposed mechanism may be modified slightly as shown in Fig. 5. In this proposed mechanism, the driving force for such a dissociation is the formation of the Zn–O bond. According to the Irving-Williams series [41] the bond between Zn and a given ligand will be stronger than the bond between Co and the same ligand. Therefore, the formation of Co–OH is not as favorable as Zn–OH and could explain the observation that Co does not promote such a dissociation. Important to understanding these fundamental issues is the fact that the loss of $C_4H_6O_3$ was essential in differentiating the Zn(*dien*)(N-glycoside) diastereomers by mass spectrometry [33].

For the system investigated in this study, Cu also appears to drive a unique dissociation pathway involving a loss of 29 Da. Only the galactose complex exhibits this feature and it is the distinguishing ion between the glucose and galactose analogues. An MS/MS spectrum recorded for the ^{65}Cu isotope of the galactose complex also contains this loss, and therefore, would suggest that isobaric interferences are unlikely. Extrapolating from results of labeling studies performed on Zn(*dien*) [33] and Ni(*dap*) [32,34] N-glycoside complexes, it is postulated that this neutral loss has the elemental composition CHO. This particular loss is unique to Cu^{2+} and is peculiar given that it is an odd mass loss. This would indicate a mechanism involving a radical loss. In fact, copper has been shown to promote radical mechanisms in other systems such as ternary copper coordination complexes of amino acids and diimine ligands investigated by Turecek and co-workers [42,43]. They observed certain elemental losses from the precursor ions that could only be formulated as radicals. At this time further studies are underway to identify the origins of this ion.

3.5. Chlorinated complexes

Both the mono- and diglycosylamine metal complexes have singly charged chlorinated analogues of the form [M(*dien*)(hex)Cl]$^+$ and [M(*dien*)(hex)$_2$Cl]$^+$, respectively. A subset of these [M(*dien*)(hex)$_n$Cl]$^+$ complexes was subjected to CID as recorded in Table 4. In all cases tested, the predominant, and usually

Table 4
Summary of MS/MS spectra for chlorinated complexes

Complex	*m/z*	Neutral losses observed
[Zn(*dien*)(glu)$_2$Cl]$^+$	526	36, 120, 156
[Zn(*dien*)(gal)$_2$Cl]$^+$	526	36
[Zn(*dien*)(glu)Cl]$^+$	364	36, 120, 156
[Zn(*dien*)(gal)Cl]$^+$	364	36, (120)[a], 156
[Co(*dien*)(glu)$_2$Cl]$^+$	521	36
[Co(*dien*)(glu)Cl]$^+$	359	36
[Co(*dien*)(gal)Cl]$^+$	359	36
[Ni(*dien*)(glu)$_2$Cl]$^+$	520	36
[Ni(*dien*)(gal)$_2$Cl]$^+$	520	36
[Ni(*dien*)(gal)Cl]$^+$	358	36
[Cu(*dien*)(glu)$_2$Cl]$^+$	525	36
[Cu(*dien*)(glu)Cl]$^+$	363	36
[Cu(*dien*)(gal)Cl]$^+$	363	36

[a] Parentheses indicate an ion near the 3% relative abundance cutoff.

Table 5
Summary of MS/MS spectra for $[M(dien)(hexose)_2]^{2+}$

		Neutral losses observed (*m/z*)				
Metal	Hexose	H_2O	$2H_2O$	$C_4H_8O_4$	$C_4H_9O_4^+$	$C_8H_{16}O_4^+$
Zn	Glucose	236.6		185.5	370.0	250.0
m/z 245.5	Galactose	236.6		185.5		
Co	Glucose	(234.0)[a]		183.0		(245.0)
m/z 243.0	Galactose	234.0		183.0		
Ni	Glucose			182.5	364.0	
m/z 242.5	Galactose	233.5		182.5	364.0	
Cu	Glucose	236.0		185.0		
m/z 245.0	Galactose	236.0	227.0	185.0		

[a] Parentheses indicate an ion near the 3% relative abundance cutoff.

only, dissociation was the loss of HCl. The resulting product ion is simply the deprotonated metal complex. This product ion does not undergo further dissociation at this stage of MS because it is no longer in resonance with the supplementary rf voltage being applied to the endcap electrodes. Thus, it is no longer undergoing energetic collisions with the helium buffer gas. Because the loss of HCl is so facile and precludes other pathways of dissociation, these chlorinated complexes do not provide any stereochemical information when using MS/MS with an ion trap. The only complexes possessing another dissociation pathway that was competitive with the loss of HCl were those containing Zn. Here, the loss of $C_4H_8O_4$ was sufficiently favorable that this neutral loss was also observed from these chlorinated N-glycoside complexes.

3.6. Doubly charged complexes

Unlike the mass spectra resulting from the previous syntheses of these coordination complexes [33], the mass spectra resulting from insertion of metals into the N-glycoside "templates" had an abundance of doubly charged species of the form $[M(dien)(hex)_2]^{2+}$. These complexes are analogous to the five coordinate complexes studied earlier except that they are not deprotonated and therefore do not have a lone pair of electrons to initiate dissociation. Consequently, it is not surprising that when these complexes are subjected to CID, the product ions observed are quite limited (Table 5). In all cases the predominant neutral loss is that of $C_4H_8O_4$. In addition, for a given metal, a water loss is observed for the galactose analogues that is present in greater abundance than for the glucose complexes. The importance of this data may lie in the realization that pursuing the doubly charged species of larger molecular weight N-glycosides may not be possible for stereochemical differentiation. One of the reasons for undertaking the "template" synthesis method was the anticipation that oligomers of varying size and heterogeneity could be investigated with a wide variety of metal ions. If at some point these syntheses give rise to only doubly charged complexes, then the differentiation process may not be viable. These data also support many previous studies in which it has been postulated that the presence of a metal alkoxide dictates a specific dissociation process that is not available to the protonated or nonmetal containing deprotonated species [7,19,29,32–36].

4. Conclusions

Dissociation patterns for several transition metal coordinated N-glycoside complexes were examined. These metallated species were found to dissociate primarily through carbon–carbon bond cleavages. The MS/MS spectra of four coordinate $[M(dien)(hex) - H]^+$ ($M = Co^{2+}$, Ni^{2+}, Cu^{2+}, Zn^{2+}; hex = glucose or galactose) complexes of a given metal

were sufficient to differentiate the glucose from the galactose moiety. Metal coordination of the N-glycoside was necessary to obtain stereochemical information: protonated analogues dissociated primarily through successive losses of water, and MS/MS spectra were identical.

Coordination number of the metal plays a role in the dissociation process, however, as seen by the fact that the five coordinate $[M(\textit{dien})(hex)_2 - H]^+$ complexes have virtually identical MS/MS spectra for a given metal. For both the four and five coordinate complexes, similar dissociation products were seen for the Zn and Co complexes. Likewise, both Ni and Cu promoted similar dissociation pathways, thus indicating that the coordination geometry also plays an important role in dictating dissociation behavior.

Chloride adducts $[M(\textit{dien})(hex)_nCl]^+$ ($n = 1$ or 2) were examined but were not useful for obtaining stereochemical information. The elimination of HCl, a facile process, precluded the formation of other product ions. Doubly charged complexes $[M(\textit{dien})(hex)_2]^{2+}$ may also prove inadequate for obtaining stereochemical information because these complexes lack an alkoxide that appears to be a driving force in several important dissociation channels.

Acknowledgement

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