Differentiation of Diastereomeric Nickel(II) *N*-Glycoside Complexes Using Tandem Mass Spectrometry and Kinetic Energy Release Measurements

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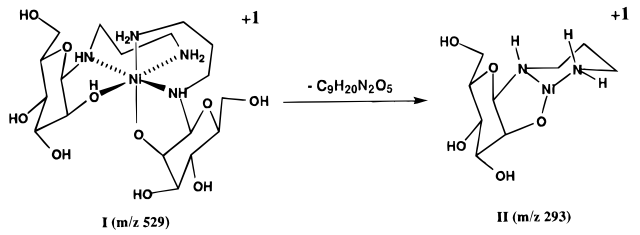
Traditionally, mass spectrometry has not been thought of as a technique which can be used to differentiate stereoisomers. This has long been the domain of NMR spectroscopy. In the work presented here however, we show that tandem mass spectrometry (MS/MS) in combination with kinetic energy release (KER) measurements of unimolecular dissociation product ions can be used to differentiate various stereochemical features of four different isomeric monosaccharides. Although others have published research describing stereochemical analysis using mass spectrometry,[1,2] this is the first time mass spectrometry, in combination with KER measurements, has been shown capable of distinguishing stereochemical features of metal-coordinated oligosaccharides.

Yano and co-workers[3] have prepared and characterized by X-ray crystallography many nickel(II) *N*-glycoside complexes of monosaccharides. Following their general procedure, we have reacted $Ni(NH_2(CH_2)_3NH_2)_3$ Cl_2 with four isomeric monosaccharides in refluxing methanol. Such reactions are expected to generate complexes of the type $Ni(NH_2(CH_2)_3NH$-(carbohydrate-H_2O))$_2$ Cl_2, where each *N*-glycoside unit functions as a tridentate ligand (**I**). Analysis of the crude reaction mixtures



by FAB[4] ionization shows ions at *m/z* 529 [Ni(*N*-glycoside)$_2$-H]$^+$ and *m/z* 293 [Ni(*N*-glycoside)-H]$^+$ for each of the mannose, glucose, galactose, and talose *N*-glycosides (**I** and **II** shown for mannose only). The importance in analyzing these four isomers lies in the fact that the C-2 and C-4 hydroxyl groups vary in their axial vs equatorial configuration. It is important to note here that although the structure of **I** is known from the literature, the structure of **II** is not known at this time. Furthermore, a proton has been arbitrarily removed from the C-2 hydroxyl group in the sugar in order to generate the +1 charge (nickel alkoxide complexes are known,[5] and precedence for three coordinate nickel complexes also exist[6]).

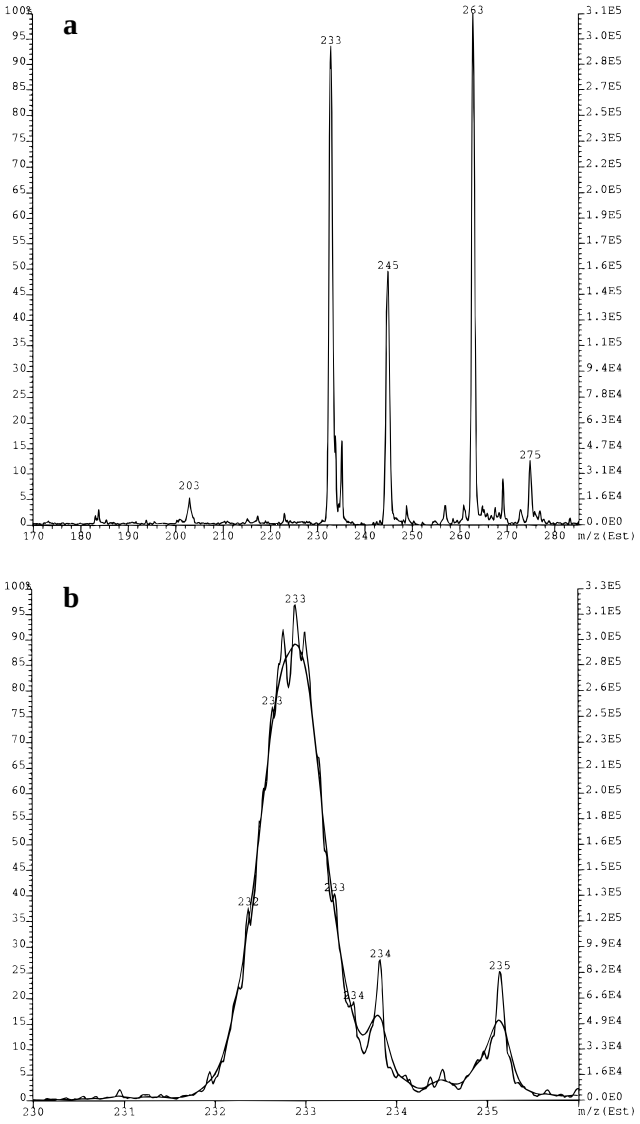


Figure 1. (A) MIKE spectrum of the metastable [Ni(glucose *N*-glycoside)-H]$^+$ (*m/z* 293) generated from a glycerol matrix. (B) Overlay of raw and processed partial MIKE spectra.

High-resolution mass measurements using a VG ZAB-2EQ reverse geometry instrument confirmed the elemental compositions of the glucose *N*-glycoside precursor ion complexes thus eliminating the question of isobaric interferences.[7]

The ions at *m/z* 293 produced by FAB were then transmitted into the mass ion kinetic energy (MIKE) cell and allowed to undergo unimolecular dissociation. The resulting product ions were measured for their KER value according to previously published procedures.[2e,8] Figure 1A,B show the MIKE spectra

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(4) Low-resolution FAB data were obtained using a VG ZAB-2EQ mass spectrometer (VG Organic, Manchester, UK). Two different matrices used were glycerol or NBA, either of which were mixed 1:1 with sample solution of methanol. Data collected at 1:1000 resolution at 8 kV accelerating voltage. In all MIKE data care was taken not to saturate the precursor ion. Collision cell was at ground potential. Resolution for the precursor ion was 1:1000 (main beam width at half height = 2.5 eV) as measured after the ESA.

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(7) Accurate mass measurements for the glucose complex were collected at 1:10000 resolution by peak matching *m/z* 529 and 293 against PEG ions 547.3329 and 283.1757, respectively. Measured masses were 529.2010 (Δ 0.6 mmu) and 293.0641 (Δ 1.0 mmu), respectively.

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Table 1. MIKE Study of [Ni(*N*-glycoside)-H]$^+$

monosaccharide	C-2-OH config	C-4-OH config	KER (meV)[a]
D-glucose	equatorial	equatorial	30 ± 2
D-galactose	equatorial	axial	30 ± 3
D-mannose	axial	equatorial	9 ± 2
D-talose	axial	axial	9 ± 1

[a] KER values are mean values for five experiments. Error values are standard deviation of the mean. The reported values are KER values of the *m/z* 293 product ion.

of the glucose *N*-glycoside and an expansion of the mass region around *m/z* 233, respectively. Figure 1B shows the raw data collected with the superimposed smoothed data to show that the gaussian peak shape has not been altered due to over smoothing. Table 1 lists the KER values measured along with statistics generated for five independent experiments for all the diastereomeric complexes for the *m/z* 233 ion which represents a $C_2H_4O_2$ loss from *m/z* 293. The most striking feature of this data is the large KER difference between those diastereomers whose C-2 hydroxyl of the monosaccharide is in the axial vs the equatorial position. There is a 3-fold difference between the KER measured for the mannose vs that of the glucose complex and similarly so between the galactose and talose complexes. The dependence of the KER upon the configuration of the C-2 substituent is not surprising considering that the C-2 hydroxyl is observed to be directly coordinated to the central Ni(II) atom.[3] The MIKE spectra for these complexes were also quite dissimilar in terms of the relative abundances for the *m/z* 233 ion (intensities of *m/z* 233 vs base peak at *m/z* 263 were 95% for glucose and <20% for mannose, 95% for galactose and <20% for talose complexes), again reflecting the importance of the configuration of the C-2 substituent. Although differences in kinetic energy may reflect differences in internal energy,[9] it is also well known that the kinetic energy released in metastable transitions is less sensitive to internal energy and more sensitive to ion structure.[8] On the basis of this data and the fact that some of these complexes have been characterized by crystallography,[3] it would appear that the differences observed in our study are due to different precursor ion structures rather than a difference in precursor ion internal energy. These data confirm that the gas phase structures of the diastereomeric complexes are different, as previously shown for the solid Ni (*N*-glycoside)$_2$ complexes by X-ray diffraction,[3] and that it may be possible to distinguish stereochemical differences using mass spectrometry.

Future studies include site specific deuterium-labeling experiments to determine from where the losses are occurring and synthesis and analysis of additional Ni *N*-glycosides of other mono- and disaccharides to establish trends for methodology development. Also of critical importance will be investigations into generation of these complexes by electrospray and further KER analysis of the electrospray-generated ions.

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