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Stereoselective noncovalent interactions of monosaccharides with hydrazine

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In memory of Professor Chava Lifshiz in recognition of her outstanding contributions for many decades to gas-phase ion chemistry and physics.

Abstract

Proton-bound complexes between underivatized monosaccharides and hydrazine have been generated in an ion trap mass spectrometer by electrospray ionization (ESI) and their collision induced decomposition (CID) investigated. The CID spectra of the selected complexes are invariably characterized by losses of hydrazine and several water molecules in proportions and at collision energies which markedly depend upon the nature and the structural features of the specific monosaccharide. Structural analysis of the proton-bound monosaccharide/hydrazine complexes at the B3LYP/6-31G(d,p) level of theory allowed to interpret the mass spectrometric results in terms of the specific intracomplex interactions between the amine and the various functional groups of the monosaccharide.

Keywords: Glucosides; Hydrazine; Structural discrimination; Noncovalent complexes; Mass spectrometry

1. Introduction

Biomolecules mainly "communicate" with the surroundings through noncovalent interactions. Electrostatic forces, hydrogen bonds, hydrophobic and van der Waals interactions allow the formation of complexes like enzyme–substrate, protein–ligand, protein–protein, antigen–antibody, carbohydrate–protein adducts [1,2]. Albeit such interactions are much weaker (10–100 times) than covalent bonds, nevertheless they are of great importance. Large amplitude motion for noncovalent complex modes can play a crucial role in the dynamical processes connecting different minima on the free energy surface of a biological process. This means that a noncovalent aggregate should be thought as a dynamic system which cannot be described in terms of a well-defined fixed structure.

Carbohydrates are ubiquitous chiral compounds implicated in a host of biological functions. Either alone or as constituents of glycoproteins, proteoglycans and glycolipids, carbohydrates are mediators of a number of cellular events, such as intra- and extracellular recognition, differentiation, proliferation, signal transduction, and in numerous (patho)physiological processes [3–5]. As biological function and morphology are strongly correlated, the variety of structural and stereochemical features of carbohydrates are expected to mirror the complexity of noncovalent interactions they can establish in biological aggregates.

Such a complicate landscape represents a challenge for mass spectrometry (MS). Although MS is traditionally regarded as a "blind" tool for stereochemical determination, a body of evidence is nowadays available witnessing the potential of such a technique for structural analysis [6–8]. Soft ionization methods, such as electrospray (ESI) and matrix-assisted laser desorption (MALDI), in conjunction with tandem mass spectrometry (MS/MS) have been mainly used. Recently, Von Seggern and Cotter have studied noncovalent complexes of biologically interesting oligosaccharides by atmospheric pressure MALDI [9].

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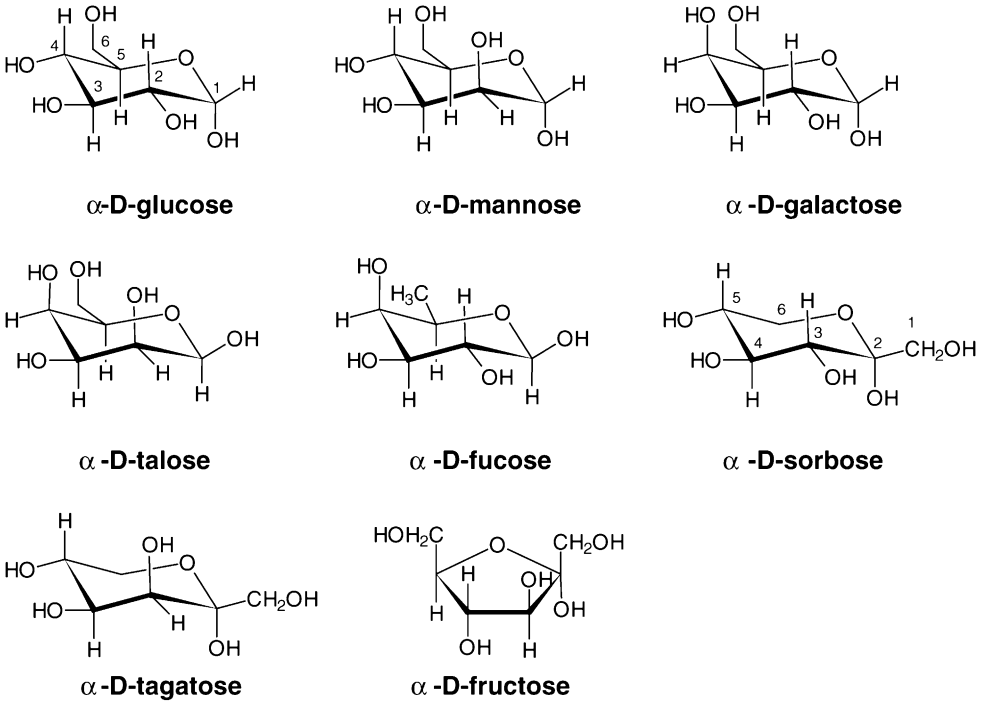

Scheme 1.

They have shown that the structure of the saccharides influences the number and strength of intermolecular hydrogen bonds. A number of noncovalent complexes [10–12], including those between carbohydrates and proteins [13], have been characterized by ESI-MS/MS. Wang, Kitova and Klassen used ESI in conjunction with a Fourier-transform ion cyclotron resonance analyzer (ESI-FT-ICR), to measure the affinity of a carbohydrate toward a protein [14]. They showed that a good correlation exists between solution [15] and gas-phase affinity data. The geometrical isomers of aliphatic and cyclic diols have been differentiated by Tabet and coworkers through formation of $FeCl^+$-bound adducts with an enantiomerically pure saccharide [16]. The kinetic method developed by Cooks has been also applied in the quantitative analysis of chiral species [17–19]. Enantiodifferentiation of glucose, mannose, galactose and ribose was obtained by collision induced dissociation (CID) of their noncovalent complexes containing a reference modified amino acid and a bivalent transition metal ion [20].

The present study is aimed at providing more insights into the correlation between the structure and the stereochemistry of underivatized monosaccharides (S) and their interactions in proton-bound complexes with suitable acceptors. The α-D-fructose (**fru**) was selected, together with the following α-D-glucopyranoses: glucose (**glu**), mannose (**man**), galactose (**gal**), talose (**tal**), tagatose (**tag**), sorbose (**sor**), and fucose (**fuc**) (Scheme 1). After a long search of the most appropriate acceptor, the choice fell on N_2H_4 for two reasons: (i) its proton affinity (PA = 203.9 kcal mol^{-1}) [21] is comparable to those estimated for underivatized monosaccharides [22]; and (ii) it reveals suitable for their structural discrimination (vide infra). The approach used is based on the CID of the corresponding $[S{\bullet}H{\bullet}N_2H_4]^+$ adducts in conjunction with theoretical calculations.

2. Experimental

The electrospray experiments were performed using a commercial LCQ-Deca ThermoFinnigan ion trap mass spectrometer, equipped with an ESI source and a syringe pump. Operating conditions for the ESI source were as follows: spray voltage, 4.5 kV; capillary temperature in the 150–190 °C range; sheath gas (He) flow rate, ca. 0.75 L/min). The experiments were conducted in the positive ion mode. Reported spectra represent the average of about 150 scans, each requiring 0.1 s. The selected gas phase complexes were generated by electrospraying water/methanol solutions containing equimolar amounts of the hydrazine and the monosaccharide, 1.5 mM each. The sample was infused via a syringe pump at a flow rate of 5 μl/min. In the full scan MS/MS mode, the ion of interest was firstly isolated by broadband ejection of the accompanying ions and then subjected to collision induced dissociation (CID; colliding gas: He; collision energy: 0.5–1.0 eV (laboratory frame)).

The geometrical structures of the proton-bound monosaccharide/hydrazine clusters have been optimized with a density functional theory (DFT) approach using a medium size basis set by using the Gaussian 03 package [23]. The DFT Hamiltonian is Becke's three-parameter hybrid functional with the Lee, Yang, and Parr correlation functional [24]; the basis set is the 6–31 G(d,p). The final lowest-energy geometries were confirmed as a minimum on the molecular potential energy surface by normal-mode vibrational frequency calculations that produced all real frequences. Zero-point vibrational energies and statistical thermodynamic properties at 298.15 K and 1 atm were calculated at the B3LYP 6-31G(d,p) level of theory. All calculations were performed using a IBM SP5 supercomputer at Cineca (Bologna, Italy).