Semi-empirical Proof of Long Bond States as Intermediates in Mass Spectrometry Fragmentation of Aldohexofuranose Derivatives

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Abstract

Following the observation that the *m*/*z* 101 peak is usually the base peak in the electron ionization mass spectra of di-*O*-isopropylidenated aldohexofuranose derivatives, quantum chemical calculations were carried out in order to provide a judicious explanation for the preference of these derivatives towards the cleavage of the exocyclic dioxolane moiety. It was also established that geminal electron donor functional groups play an important part in the stabilization of the radical cation generated during the loss of one electron from these compounds (the ionization process). In this paper, by using the PM7 semi-empirical method we show that the radical character is preferentially located between the C4-C5 carbon atoms from the di-*O*-isopropylidenated derivatives, which is why the C4-C5 bond becomes elongated, thus justifying the cleavage that produces the high intensity peak at *m*/*z* 101.

Introduction

Carbohydrates are oxygen-rich compounds, widely spread in nature and, because of their involvement in the fundamental biological processes, with a large pharmaceutical and diagnostic potential. Examples of such compounds can be found in both drugs (e.g., aminoglycosides) and excipients (e.g. biocompatible surfactants, like long chain glycoderivatives) [1].

Among analytical methods, mass spectrometry offers rich and reliable information regarding the structural details of different compounds, including sugars. The parent structure can be reconstructed after analyzing the fragmentation ions. Their abundance is strictly correlated with their stability, and the diverse electronic or steric effects can give strong information for the predominance of a certain fragmentation path over another. When two fragmentation pathways seem to have equal probabilities of taking place, one can invoke molecular mechanics or quantum chemical calculations for deciding which has the highest probability of occurring.

Theoretically predicted structures of alkane radical cations are characterized by a unique valence, the elongated, one-electron bond (long bond). The optimum length calculated for the carbon/carbon bond of the ethane radical cation, for example, is 1.920 Å, and the dissociation energy (*D*) is 43 kcal mol^{-1}. More complex alkane radical cations appear to have one such long bond in which the SOMO (single occupied molecular orbital) and the "radical cation character" are rather highly localized. Recognition of such long bond structures has already proved fruitful in both vapor phase (e.g., mass spectrometry) and solution (e.g., cycloaddition) chemistry of radical cations. Theoretical research has further suggested that ground state long bond structures may be found for radical cations of such functionalized organic molecules as halocarbons, alcohols and ethers, so sugars could also represent promising candidates in this direction [2].

Ab initio theoretical studies suggest a unique stabilizing effect of vicinal electron donor substituents on long bond radical cation structures (Figure 1) for which the calculated structural minimum is instead a long bond structure. For example, the 1,2-ethanediamine radical cation long bond (2.030 Å) structure lies 11.2 kcal mol^{-1} below the best localized (aminium salt) type structure, with the long bond maintaining substantial bond strength (D = 22.6 kcal mol^{-1}), and a similar result is also produced for ethylene glycol (2.048 Å, D = 23.6 kcal mol^{-1}) [2].

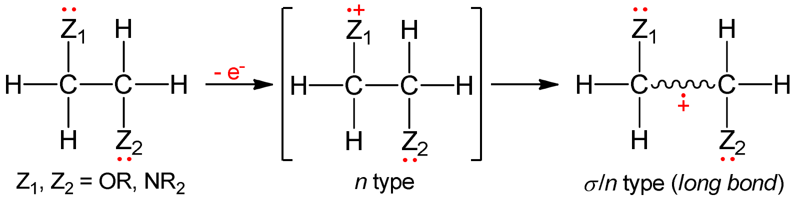

Figure 1. Stabilization of radical cations in vicinal groups containing compounds [2]

In this study we investigate the EI-MS (electron ionization mass spectrometry) fragmentation of di-*O*-isopropylidene derivatives of D-glucofuranose, D-galactofuranose and D-mannofuranose (Figure 2). The molecular radical cations were generated from the corresponding neutral molecules during EI-MS experiments conducted in positive ion mode, and were also theoretically analyzed using the PM7 (Parameterized Model 7) semi-empirical quantum chemical method. The findings confirm and explain the mode of cleavage which leads to the abundant m/z 101 ionic fragment in the EI-MS analysis of these sugar acetals (Figure 3). Such sugar derivatives are very useful in organic synthesis as building blocks for a multitude of more complex chiral compounds, including biocompatible and biodegradable surfactants [3].

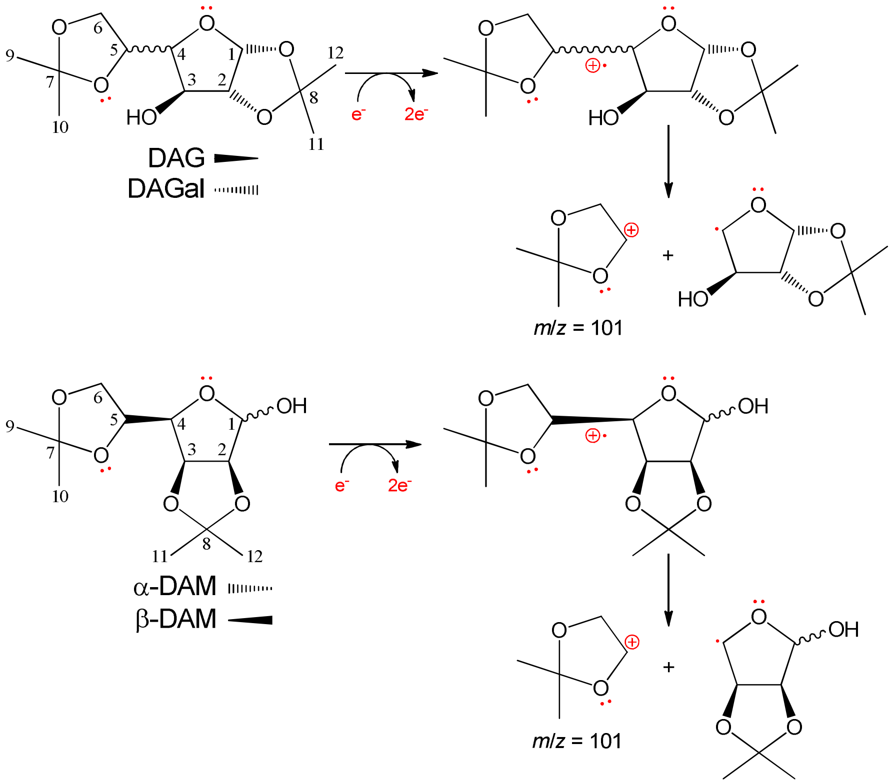

Figure 2. Genesis of the 2,2-dimethyl-1,3-dioxolan-4-ylium cation; the true orientation of the wavy bond is given for each family of compounds

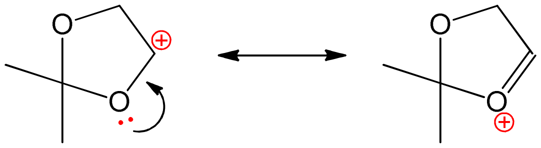

Figure 3. α-Oxy resonance stabilization in 2,2-dimethyl-1,3-dioxolan-4-ylium oxocarbenium ion (*m*/*z* = 101)

Experimental

The analyzed compounds can be obtained by bis-acetalation of D-glucose, D-mannose or D-galactose with acetone in acidic media. The synthesis of these glycoderivatives and the EI-MS analyses parameters were described in a previous work [3].

All structures were drawn using the *HyperChem* molecular modeling software. After the “Add H & Model Build” command, the starting neutral molecules were pre-optimized with the “MM+” force field (“Polak-Ribière” algorithm, RMS gradient of 0.01 kcal/(Å mol)).

MOPAC 2012 software was used for PM7 semi-empirical method. The neutral molecules were optimized first, while the radical cations were subsequently obtained from them. Some additional work, like setting the C4-C5 bond length to 2 Å, had to be done. The line of parameters included “GNORM=0.01”, “BONDS”, “AUX”, “GRAPHF” and “PDBOUT”, and also the keyword “OPT” whenever possible. The keyword “SINGLET” was used for neutral molecules, while “CHARGE=+1”, “UHF” and “DOUBLET” were set for radical cations. The data set was obtained by using the “BFGS” algorithm (the “EF” algorithm giving similar results). The resulting structures were analyzed with *Jmol* software.

Results and discussion

The EI-MS spectra for 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (DAG), 1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose (DAGal), 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (α-DAM) and 2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranose (β-DAM), taken at 20 eV ionization energy, are given in Figure 4, while the peak intensity values for the *m*/*z* = 101 peak are shown in Table 1. As can be seen, this peak, which appears due to the 2,2-dimethyl-1,3-dioxolan-4-ylium cation (Figure 3), has strong intensity, being the base peak in three out of four spectra.

In the case of the radical cations analyzed with the PM7 semi-empirical method, long bonds were observed in the ground state (geometry and heat of formation data given in Table 1), being located for all considered structures between C4 and C5 (where the side 2,2-dimethyl-1,3-dioxolan is connected). It has a length between 2.027 and 2.079 Å (as opposed to 1.528-1.538 Å for the neutral molecule). The O4-C4-C5 and O5-C5-C4 angle values for the radical cations suggest a tendency toward sp^2 geometry with the long bong being almost (but not quite) perpendicular on the plane made by the other three bonds.

Table 1. Experimental / calculated parameters (BP = base peak, TIC = total ion current, N = neutral molecule, RC = molecular radical cation)

Compound	**Peak intensity (%)**		**C4-C5 (Å)**		**O4-C4-C5 (°)**		**O5-C5-C4 (°)**		**O4-C4-C5-O5 (°)**		**$\Delta_f H$ (kcal mol^{-1})**	
	To BP	**To TIC**	**N**	**RC**	**N**	**RC**	**N**	**RC**	**N**	**RC**	**N**	**RC**
DAG	100.0	18.8	1.538	2.079	104.6	98.7	108.1	99.7	-173.1	165.0	-280.8	-79.7
DAGal	100.0	20.7	1.528	2.027	109.8	102.9	111.0	101.4	66.7	25.3	-278.9	-76.3
α-DAM	86.4	16.7	1.535	2.052	106.8	98.6	106.9	99.9	153.7	171.3	-281.6	-79.2
β-DAM	100.0	31.3	1.535	2.051	108.0	99.1	106.7	100.0	139.0	169.3	-278.3	-80.0

The relatively weak long bond, together with the mentioned α-oxy resonance stabilization (Figure 3), explain very well the high intensity *m/z* 101 peak.

Conclusion

The theoretically confirmed long bonds are a strong argument regarding the genesis of the high intensity *m/z* 101 peak observed in the EI-MS analysis of di-*O*-isopropylidene furanose (glucose, mannose or galactose) derivatives. The results presented in this paper support the utility of such quantum chemical calculations that constitute a strong theoretical background for explaining the experimental data.

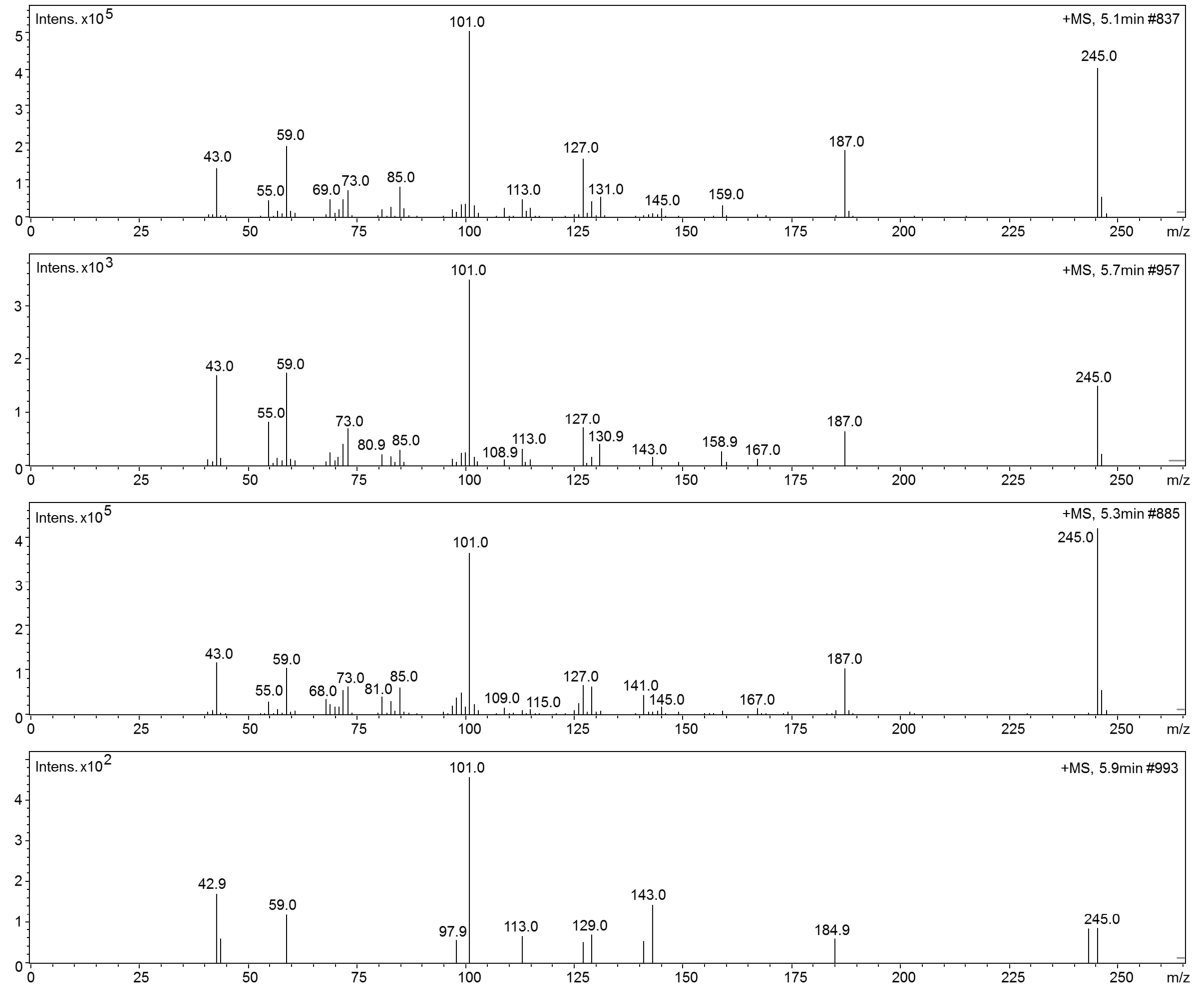

Figure 4. EI-MS spectra for (from top to bottom) DAG, DAGal, α-DAM, β-DAM

Acknowledgements

This work was supported by the Romanian National Authority for Scientific Research (CNCS-UEFISCDI) through project PN-II-PCCA-2011-142. The research was done in the Center of Genomic Medicine from the "Victor Babeș" University of Medicine and Pharmacy of Timișoara, POSCCE Project ID: 1854, cod SMIS: 48749, contract 677/09.04.2015.

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