ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2015, *60*(9), 881-889

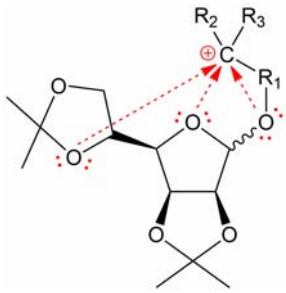
EXPLORING THE POSSIBILITY OF ANCHIMERIC ASSISTANCE IN ALKYL SUGAR CATIONS BY COMPUTATIONAL METHODS

Mihai-Cosmin PASCARIU,[a] Ioana-Ramona CIOPĂNOIU,[a] Carmen-Manuela MITAR,[a] Mircea MRACEC[b] and Eugen ȘIȘU[c,*]

[a] "Vasile Goldiş" Western University of Arad, Faculty of Medicine, Pharmacy and Dental Medicine, 86 Liviu Rebreanu Str., RO-310045 Arad, Roumania
[b] Institute of Chemistry of the Romanian Academy, 24 Mihai Viteazul Blvd., RO-300223 Timişoara, Roumania
[c] "Victor Babeş" University of Medicine and Pharmacy, Faculty of Medicine, 2 Eftimie Murgu Sq., RO-300041, Timişoara, Roumania

Received December 16, 2014

A series of alkyl mannofuranosides were analyzed using RM1 semi-empirical quantum chemical calculations. Cations resulted from loss of one methyl group from the alkyl chain were constructed and geometrically optimized. Their conformational analysis revealed strong interactions between mannose moiety oxygen atoms and alkyl positively charged centers, resulting in new cyclic enclosures which provide enhanced stability. Three- (oxirane), four- (oxetane), five- (1,3-dioxolane), six- (1,3-dioxane), seven- (1,3-dioxepane), eight- (1,3,6-trioxocane) and ten- (1,3,6-trioxecane) member structures were all obtained from primary or secondary carbenium ions, while the nine-member (1,3,6-trioxonane) ring remained elusive. Also, tertiary carbocations appear to avoid such stabilizations. Many cases of hydride and proton migrations, along with some chain rearrangements and decompositions were noted for branched alkyl glycoderivatives. Some energy differences could be directly calculated between stabilized (anchimerically assisted) and non-stabilized structures. These findings concern fields in which such cations are generated, like mass spectrometry analysis of side-chain glycoderivatives as well as of other oxygenated classes of compounds.



INTRODUCTION

In the last decades, gas-phase ion chemistry has been an important research field with implications in many scientific areas, mainly because of the great utility of mass spectrometry method of compounds analysis.[1,2] One example of such compounds are carbohydrates: oxygen-rich molecules, widely spread in nature and with critical importance for living systems.

These are probably the most densely functionalized naturally occurring organic molecules.[3] Among analytical methods which offer large amounts of reliable information regarding their structural details, mass spectrometry is immediately regarded as a top choice.

Sugars can be analyzed in both positive and negative modes.[4] With the introduction of modern mass spectrometry techniques (MS/MS or tandem MS) the isolation of fragments from the primary spectrum became possible. These fragments can be further subjected to collision fragmentation (CID-MS), giving the MS^2 spectrum.[5]

Nonetheless, when the sugar derivative allows for electron impact ionization mass spectrometric analysis, rich-in-information EI-MS spectra are obtained. The parent structure can then be determined from the analysis of 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

* Corresponding author: sisueugen@umft.ro, tel.: +40356420598

another.[1,3,6,7] When two or more fragmentation pathways are all deemed to be possible at first glance, one can invoke quantochemical calculations to provide additional data regarding which one has greater probability of occurring. If the calculation methods are calibrated on compounds heats of formation, it can be determined which ion is more thermodynamically stable and so more prone to be obtained during the fragmentation process.[8] By operating in positive ion mode using EI-MS, cations are obtained whose charged centers can be spontaneously stabilized by oxygen lone pair electrons resulting in ring enclosures of different sizes.

Computational chemistry is a convenient way to study exotic molecular species which are difficult to isolate, including fragmentation cations.[9-11] Although some positive charged species are stable,[12-14] their electron deficiency is generally responsible for an unusual reactivity,[15,16] strongly correlated with carbocations tendency to stabilize themselves by increasing coordination through bridging[11,17] or anchimeric assistance by heteroelements.[1,12,18-20] The latter effect plays an important role in the mechanism of fragmentation processes of gas-phase cations,[21] also providing explanations for the variations in ion abundance of stereoisomers.[19]

A series of papers from the last two decades have dealt with establishing the type of the glycosidic linkage using MS analysis and computational chemistry.[22-25] In a recent paper,[26] in which a pair of diisopropylidenemannofuranose anomers where analyzed using EI-MS, a qualitative correlation between $[M-15]^+$ peak intensity and the heat of formation for the cations producing that peak was revealed. These cations are known to be obtained by removing one methyl group from isopropylidene moieties connected at the sugar residue. This process also makes the molecular ion difficult to detect because of the very low intensity of the corresponding peak, as shown in many MS experiments regarding mono- and diisopropylidene derivatives.[7,27,28] The molecular mass of such compounds is therefore established using the $[M-15]^+$ peak.

However, breaking of one methyl radical from the side chain, as opposed to breaking of a methyl radical from one isopropylidene unit, is a process that was not previously considered in the literature concerning MS analysis of sugar isopropylidene derivatives. The carbocations thus obtained would generally be considered of low stability, appearing only as transient entities because of further decompositions or elimination reactions.[29] Nonetheless, if owing to stereoelectronic effects their stability was to be greatly enhanced, exceptions to the previously mentioned rule could be observed as well.

Considering this hypothesis and using semi-empirical calculations[30-34] we thus investigated in this paper a series of 144 sugar acetals, composed of a di-*O*-isopropylidene-D-mannofuranoside base structure connected at the anomeric position to different alkyl side chains. These include all the possible saturated C_2-C_6 isomers, linear or branched, and also considering the stereochemistry, but also linear C_7-C_{10}, C_{12}, C_{14}, C_{16}, C_{18}, C_{20} and C_{30} alkyl radicals. As already stated in literature, after removal of the isopropylidene protecting groups, such long chain glycoderivatives could function as biocompatible and biodegradable surfactants in a wide range of application from fields like medicine, pharmacy, biotechnologies and life-science research.[26] The current study consists of calculating the heat of formation of the cation obtained by removal of a methyl group from the side chain in all possible variants (Fig. 1).

Poking around in this direction to see if losing these methyl groups could have an impact on the intensity of the $[M-15]^+$ peak, we discovered that an anchimeric assistance from the sugar moiety oxygen atoms to the positive charged center on the side chain[18,35,36] could easily take place in some of the species analyzed.

METHODS

All structures were build using *HyperChem* molecular modeling software[50] and were optimized with RM1 semi-empirical method,[51] with and without molecular mechanics pre-optimization. RHF operators were used for "Spin Pairing" while the SCF "Convergence limit" was set at 10^{-5}, without using the "Accelerate convergence" procedure. Force fields used for cations pre-optimization include MM+, AMBER99, BIO+ (CHARMM27) and OPLS, with their default parameters as implemented in *HyperChem*. For geometry optimization and $\Delta_f H$ calculation, the "Polak-Ribière (conjugate gradient)" algorithm was selected with a RMS gradient of 0.01 kcal/(Å mol), the molecules being considered in vacuum (*in vacuo*). The initial molecules, from which all carbocations were constructed, were prior optimized with OPLS force field followed by RM1 semi-empirical method.

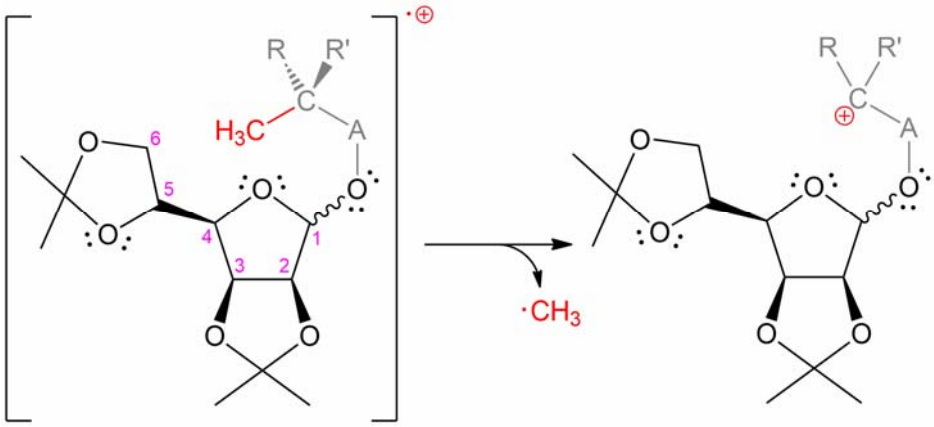


Fig. 1 – Breaking of one methyl radical from the side chain of an EI-MS molecular radical cation (A = linear or branched alkylene group, R and R' = H or short alkyl groups), with numbering of the mannose backbone.

RESULTS AND DISCUSSION

As the results have shown, an anchimeric-type stabilization, with the formation of new three- (oxirane), four- (oxetane), five- (1,3-dioxolane), six- (1,3-dioxane), seven- (1,3-dioxepane), eight- (1,3,6-trioxocane) or ten- (1,3,6-trioxecane) member cyclic structures,[37,38] can be taken into consideration for explaining the stability of some of the cations obtained (Fig. 2).

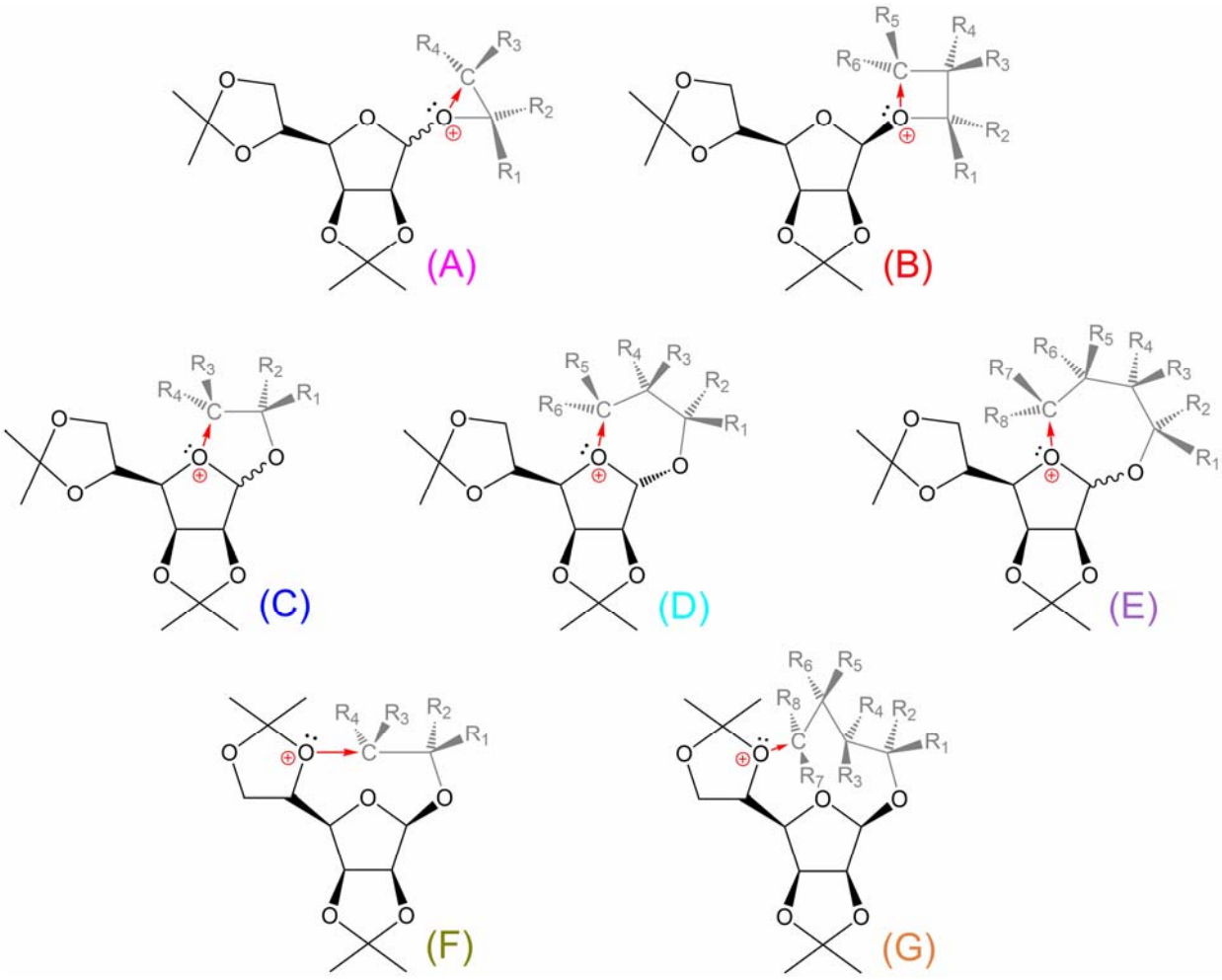


Fig. 2 – Anchimeric stabilization possibilities, as observed after RM1 optimization (R_1-R_8 = H or short alkyl chains).

The positively charged carbon atom approached one oxygen atom to a distance similar to a normal C-O single bond length (1.45 ÷ 1.49 Å) while at the same time changing from sp^2 to sp^3 hybridisation and thus acting as a prochiral center. These interactions can all be classified as *exo-tet*, according to Baldwin's rules, and at least for cycles with 3-7 atoms are known to be generally favored ring closures.[39-41]

All the isomers that gave one of the cyclic structures A-G (Fig. 2), along with dative bond lengths and corresponding heats of formation, are presented in Table 1a and Table 1b. As observed from heat of formation values, when compared with non-stabilized cations (from different initial conformations obtained with diverse force field methods), these enclosures imply increased stability (e.g., entries no. 8 and 12 in Table 1b).[42] The formation of anchimerically stabilized species generally depends on the stereochemical configuration of the structure considered (including the anomeric form and the *R*/*S* configuration of the side chain), because of the proper orbital overlap necessary in the transition state.[16,19] However, if the leaving methyl group was bounded to a chiral center, the initial configuration for that center can lose its influence on the outcome (*e.g.,* entries 22 and 23 in Table 1a and Table 1b).

As can be clearly seen in Table 2, the 1,3-dioxolane (C) is by far the most common structure formed,[16,42,43] comprising more than half of the total stabilized structures, followed by the three-membered (A), seven-membered (E) and eight-membered (F) rings. The first three species are also observed for both anomers, while structure F appears only for β anomers. The other entities appeared in only one case each in the considered set of compounds, with specific stereochemistry: α anomer for D and β anomers for B and G. Although some cations can lead to two distinct anchimeric structures (with different ring sizes), depending on the starting conformation obtained with force field pre-optimization, it is probable that, in practice, only the lowest energy conformation would be observed. The obtained results generally agree with the literature concerning the stability of organic cycles.[37,44]

The degree of stabilization owned to the anchimeric effect, or the dative bond energy, is shown in Table 3: at least 10.0 kcal/mol for a structure of type C, 25.0 kcal/mol for E and 21.4 kcal/mol for the G-type structure.

It can also be seen from Table 3 that, from a thermodynamic viewpoint, an A-type structure is less stable than a C-type structure (at least by 23.2 kcal/mol) or an F-type structure (by 20.6 kcal/mol), and also that structure E is more stable than structure G (by 6.7 kcal/mol).

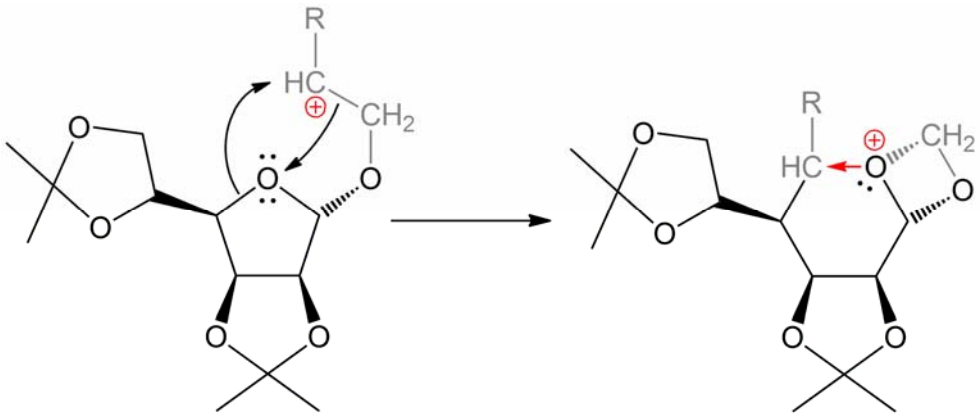


Fig. 3 – Complex rearrangement as seen for entries 7 and 10 in Table 1a, 1b (R = Me, Et).

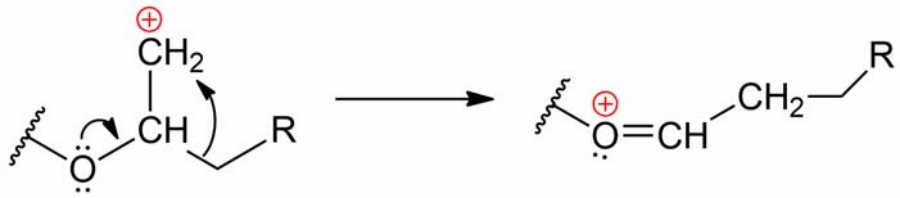


Fig. 4 – Rearrangement seen for entries 15 and 27 in Table 1a, 1b (R = Me, Et).

Table 1a

Dative bond lengths for cations after RM1 geometry optimization; the type of ring formed is indicated by the letter in parenthesis (see Fig. 2), the values obtained for non-stabilized structures (in black) being also included for reference; the final hybridisation (Hybr.) of the formally charged carbon atom is given (oxygen atoms are numbered as for mannose, while the lateral chain carbon atoms and the hydrogen atoms attached to them are referenced in the table footnotes as α, β, γ or δ, with increasing distance from O1)

No.	Initial lateral chain	AC*	RM1		MM+/RM1		AMBER/RM1		CHARMM/RM1		OPLS/RM1	
			C-O distance (Å)	Hybr.	C-O distance (Å)	Hybr.	C-O distance (Å)	Hybr.	C-O distance (Å)	Hybr.	C-O distance (Å)	Hybr.
Cations obtained from C_3 side-chains												
1	propyl	α	1.464 (C)	sp^3	1.464 (C)	sp^3	1.463 (C)	sp^3	1.464 (C)	sp^3	1.463 (C)	sp^3
2	propyl	β	1.456 (F)	sp^3	1.465 (C)	sp^3	1.465 (C)	sp^3	1.465 (C)	sp^3	1.466 (C)	sp^3
Cations obtained from C_4 side-chains												
3	(*R*)-1-methylpropyl	α	1.469 (A)	$\sim sp^3$	1.469 (A)	$\sim sp^3$	1.469 (A)	$\sim sp^3$	2.446 (A)[a]	sp^3	1.469 (A)	$\sim sp^3$
4	(*R*)-1-methylpropyl	β	1.463 (C)	sp^3	1.463 (C)	sp^3	4.089 (C)[a]	sp^3	1.463 (C)	sp^3	4.090 (C)[a]	sp^3
5	(*S*)-1-methylpropyl	α	1.462 (C)	sp^3	1.462 (C)	sp^3	Dec.	-	1.461 (C)	sp^3	2.820 (C)[a]	sp^3
6	(*S*)-1-methylpropyl	β	F.O.[b]	-	1.453 (F)	sp^3	1.453 (F)	sp^3	1.469 (A)	$\sim sp^3$	1.453 (F)	sp^3
7	2-methylpropyl	α	2.960 (C) 1.483 (C)	sp^2 sp^3	2.961 (C) 1.483 (C)	sp^2 sp^3	2.950 (C) 1.466 (C)[c]	sp^2 sp^3	1.483 (C) Dec.	sp^3 -	2.951 (C) 1.482 (C)	sp^2 sp^3
Cations obtained from C_5 side-chains												
8	pentyl	α	4.948 (E)	sp^2	1.470 (E)	sp^3	4.730 (E)	sp^2	4.951 (E)	sp^2	4.732 (E)	sp^2
9	pentyl	β	2.848 (E)[d]	sp^2	4.844 (E)	sp^2	4.983 (E)	sp^2	4.295 (E)[e]	sp^2	1.465 (E)	sp^3
10	(*R*)-2-methylbutyl	α	1.464 (C)[c]	sp^3	1.481 (C)	sp^3	1.482 (C)	sp^3	1.482 (C)	sp^3	1.481 (C)	sp^3
11	(*S*)-2-methylbutyl	α	1.481 (C)	sp^3	1.481 (C)	sp^3	1.481 (C)	sp^3	1.481 (C)	sp^3	2.066 (C)	sp^2
12	1,1-dimethylpropyl	α	3.918 (C)	sp^2	3.916 (C)	sp^2	3.918 (C)	sp^2	1.461 (C)	sp^3	3.918 (C)	sp^2
13	1,1-dimethylpropyl	β	1.455 (F)	sp^3	1.455 (F)	sp^3	1.455 (F)	sp^3	1.455 (F)	sp^3	1.455 (F)	sp^3
14	(*S*)-1,2-dimethylpropyl	α	1.481 (C) 1.481 (C)	sp^3 sp^3	1.484 (C) 1.480 (C)	sp^3 sp^3	2.909 (C) 1.481 (C)	sp^2 sp^3	1.484 (C) 1.481 (C)	sp^3 sp^3	2.902 (C) 1.480 (C)	sp^2 sp^3
15	1-ethylpropyl	α	1.463 (C) 1.471 (A)	sp^3 $\sim sp^3$	1.463 (C) 1.471 (A)	sp^3 $\sim sp^3$	1.464 (C) 1.471 (A)	sp^3 $\sim sp^3$	1.464 (C) 2.343 (A)[f]	sp^3 sp^3	1.463 (C) 1.471 (A)	sp^3 $\sim sp^3$
16	1-ethylpropyl	β	1.464 (C) 1.469 (A)	sp^3 $\sim sp^3$	1.464 (C) 2.447 (A)[a]	sp^3 sp^3	1.459 (F) 1.470 (A)	sp^3 $\sim sp^3$	1.464 (C) 1.471 (A)	sp^3 $\sim sp^3$	1.459 (F) 1.471 (A)	sp^3 $\sim sp^3$
Cations obtained from C_6 side-chains												
17	(*R*)-1-methylpentyl	β	1.462 (E)	sp^3	1.463 (G)	sp^3	1.458 (E)	sp^3	3.899 (G)	sp^2	1.464 (E)	sp^3
18	(*S*)-1-methylpentyl	α	2.798 (E)[d]	sp^2	1.462 (E)	sp^3	1.462 (E)	sp^3	1.462 (E)	sp^3	1.462 (E)	sp^3
19	(*R*)-2-methylpentyl	α	1.482 (C)	sp^3	1.483 (C)	sp^3	1.483 (C)	sp^3	1.482 (C)	sp^3	1.482 (C)	sp^3
20	(*S*)-2-methylpentyl	α	1.482 (C)	sp^3	1.483 (C)	sp^3	1.482 (C)	sp^3	1.483 (C)	sp^3	1.482 (C)	sp^3
21	(*S*)-2-methylpentyl	β	2.851 (E)[d]	sp^2	2.851 (E)[d]	sp^2	2.846 (E)[d]	sp^2	1.465 (E)	sp^3	2.855 (E)[d]	sp^2
22	(*S*,*R*)-1,2-dimethylbutyl	α	1.480 (C)	sp^3	1.480 (C)	sp^3	1.480 (C)	sp^3	1.480 (C)	sp^3	1.480 (C)	sp^3
23	(*S*,*S*)-1,2-dimethylbutyl	α	1.480 (C)	sp^3	1.480 (C)	sp^3	1.480 (C)	sp^3	1.480 (C)	sp^3	1.480 (C)	sp^3
24	(*R*)-2,3-dimethylbutyl	α	1.482 (C)	sp^3	1.480 (C)	sp^3	1.480 (C)	sp^3	2.061 (C)	sp^2	1.480 (C)	sp^3
25	(*S*)-2,3-dimethylbutyl	α	2.059 (C)	sp^2	1.480 (C)	sp^3	1.482 (C)	sp^3	2.620 (C)	sp^2	2.616 (C)	sp^2
26	(*R*)-1-ethylbutyl	α	1.462 (C)	sp^3	1.461 (C)	sp^3	1.461 (C)	sp^3	1.462 (C)	sp^3	1.461 (C)	sp^3
27	(*R*)-1-ethylbutyl	β	2.446 (A)[a]	sp^3	1.471 (A)	$\sim sp^3$	2.446 (A)[a]	sp^3	2.342 (A)[f]	sp^3	2.446 (A)[a]	sp^3
28	(*S*)-1-ethylbutyl	β	1.464 (C)	sp^3	1.464 (C)	sp^3	1.459 (F)	sp^3	1.464 (C)	sp^3	1.459 (F)	sp^3
29	2-ethylbutyl	α	3.312 (D)[g]	sp^2	3.319 (D)[g]	sp^2	2.946 (D)[h]	sp^3	2.939 (D)[h]	sp^3	1.473 (D)	sp^3
30	2-ethylbutyl	β	2.890 (B)[h]	sp^3	Dec.	-	1.492 (B)	sp^3	1.492 (B)	sp^3	1.492 (B)	sp^3
31	1-ethyl-1-methylpropyl	α	1.462 (C)	sp^3	1.463 (C)	sp^3	1.463 (C)	sp^3	1.463 (C)	sp^3	1.462 (C)	sp^3
32	1-ethyl-1-methylpropyl	β	1.463 (C)	sp^3	1.463 (C)	sp^3	1.463 (C)	sp^3	1.463 (C)	sp^3	1.463 (C)	sp^3
33	(*R*)-1-ethyl-2-methylpropyl	α	1.464 (C)	sp^3	1.463 (C)	sp^3	1.463 (C)	sp^3	1.464 (C)	sp^3	1.463 (C)	sp^3
34	(*S*)-1-ethyl-2-methylpropyl	α	2.992 (C) 1.483 (C)	sp^2 sp^3	2.997 (C) 1.483 (C)	sp^2 sp^3	1.482 (C) 1.483 (C)	sp^3 sp^3	2.995 (C) 1.483 (C)	sp^2 sp^3	2.982 (C) 1.483 (C)	sp^2 sp^3
35	(*S*)-1-ethyl-2-methylpropyl	β	1.465 (C)	sp^3	1.465 (C)	sp^3	1.465 (C)	sp^3	1.465 (C)	sp^3	1.465 (C)	sp^3

* anomeric configuration;
F.O. = failed optimization;
Dec. = decomposition, cation fragmentation with two or more resulting fragments;
[a] $H_\alpha \rightarrow H_\beta$ hydride shift, C_α=O1 double bond formation (1.290 – 1.293 Å);
[b] structure did not attain convergence;
[c] complex rearrangement, see Fig. 3;
[d] H_γ proton shift to O4 (furanose oxygen), C_γ=C_δ double bond formation (1.343 – 1.346 Å);
[e] H_γ proton shift to O5 (lateral dioxolane oxygen), C_γ=C_δ double bond formation (1.327 Å);
[f] simple rearrangement, see Fig. 4 (C_α=O1 bond length: 1.283 – 1.287 Å);
[g] H_β proton shift to O4 (furanose oxygen), C_β=C_γ double bond formation (1.332 Å);
[h] $H_\beta \rightarrow H_\gamma$ hydride shift.

Table 1b

Heat of formation values and net atomic charges for cations after RM1 geometry optimization; the table entry numbers (first column) indicate the same initial lateral chain and anomeric configuration as those from Table 1a; the values obtained for non-stabilized structures (in black) are also given for reference

No.	RM1		MM+/RM1		AMBER/RM1		CHARMM27/RM1		OPLS/RM1	
	$\Delta_f H$ (kcal/mol)	Charge (C/O)	$\Delta_f H$ (kcal/mol)	Charge (C/O)	$\Delta_f H$ (kcal/mol)	Charge (C/O)	$\Delta_f H$ (kcal/mol)	Charge (C/O)	$\Delta_f H$ (kcal/mol)	Charge (C/O)
Cations obtained from C_3 side-chains										
1	-88.288	-0.029/-0.111	-88.288	-0.029/-0.111	-88.529	-0.031/-0.111	-88.288	-0.029/-0.111	-88.529	-0.031/-0.111
2	-83.471	-0.005/-0.155	-83.653	-0.014/-0.136	-83.653	-0.014/-0.136	-83.653	-0.014/-0.136	-82.469	-0.018/-0.137
Cations obtained from C_4 side-chains										
3	-68.433	-0.028/-0.160	-68.433	-0.028/-0.160	-68.433	-0.028/-0.160	-117.931[a]	-0.349/-0.186	-68.329	-0.028/-0.162
4	-92.258	-0.028/-0.140	-92.258	-0.028/-0.140	-119.281[a]	-0.299/-0.264	-92.258	-0.029/-0.140	-119.281[a]	-0.299/-0.264
5	-97.167	-0.046/-0.111	-97.167	-0.046/-0.111	Dec.	-	-97.391	-0.048/-0.110	-117.816[a]	-0.349/-0.276
6	F.O.[b]	-	-89.996	-0.023/-0.148	-89.996	-0.023/-0.148	-69.387	-0.024/-0.123	-89.996	-0.023/-0.148
7	-85.013 -98.146	0.400/-0.330 0.069/-0.128	-85.013 -98.146	0.400/-0.330 0.069/-0.128	-84.842 -69.330[c]	0.400/-0.332 0.118/-0.179	-98.146 Dec.	0.069/-0.128 -	-84.842 -98.374	0.400/-0.332 0.068/-0.127
Cations obtained from C_5 side-chains										
8	-73.082	0.403/-0.316	-103.318	0.045/-0.159	-70.507	0.430/-0.320	-73.082	0.403/-0.316	-70.507	0.430/-0.320
9	-93.852[d]	-0.163/-0.253	-70.017	0.424/-0.315	-71.919	0.403/-0.314	-98.780[e]	-0.174/-0.297	-96.920	0.030/-0.205
10	-75.438[c]	0.099/-0.175	-103.440	0.049/-0.128	-103.209	0.051/-0.128	-103.209	0.051/-0.128	-103.440	0.050/-0.128
11	-103.440	0.050/-0.128	-103.440	0.050/-0.128	-103.440	0.049/-0.128	-103.440	0.050/-0.128	-93.403	0.369/-0.317
12	-73.577	0.388/-0.298	-73.577	0.388/-0.298	-73.577	0.388/-0.298	-108.287	-0.049/-0.111	-73.577	0.388/-0.298
13	-99.113	-0.020/-0.149	-98.749	-0.021/-0.149	-99.113	-0.020/-0.149	-99.113	-0.020/-0.149	-99.113	-0.020/-0.149
14	-106.815 -106.815	0.052/-0.127 0.052/-0.127	-102.198 -107.028	0.083/-0.164 0.050/-0.126	-92.320 -106.815	0.406/-0.333 0.052/-0.127	-102.198 -106.815	0.083/-0.164 0.052/-0.127	-92.121 -107.028	0.406/-0.335 0.051/-0.126
15	-102.753 -73.651	-0.042/-0.112 -0.025/-0.159	-102.753 -73.650	-0.043/-0.112 -0.025/-0.159	-102.539 -73.651	-0.041/-0.112 -0.025/-0.159	-102.539 -112.541[f]	-0.041/-0.112 -0.240/-0.270	-102.753 -73.651	-0.043/-0.112 -0.024/-0.159
16	-97.763 -74.320	-0.024/-0.141 -0.020/-0.122	-97.763 -123.854[a]	-0.024/-0.141 -0.343/-0.158	-96.549 -73.638	-0.006/-0.157 -0.037/-0.126	-97.763 -74.591	-0.023/-0.141 -0.018/-0.122	-96.549 -74.591	-0.006/-0.157 -0.019/-0.122
Cations obtained from C_6 side-chains										
17	-105.313	0.036/-0.179	-98.747	0.030/-0.208	-105.122	0.022/-0.174	-77.307	0.417/-0.357	-105.447	0.037/-0.177
18	-105.069[d]	-0.177/-0.250	-108.421	0.030/-0.159	-108.421	0.030/-0.159	-108.059	0.031/-0.162	-108.421	0.030/-0.159
19	-108.556	0.050/-0.128	-108.332	0.052/-0.128	-108.332	0.052/-0.128	-108.556	0.050/-0.127	-108.556	0.050/-0.127
20	-108.555	0.050/-0.127	-108.332	0.052/-0.128	-108.555	0.050/-0.127	-108.332	0.052/-0.128	-108.555	0.050/-0.127
21	-101.385[d]	-0.159/-0.251	-101.385[d]	-0.158/-0.251	-101.385[d]	-0.162/-0.251	-103.759	0.029/-0.204	-101.386[d]	-0.156/-0.251
22	-111.785	0.035/-0.128	-112.002	0.033/-0.127	-112.002	0.033/-0.127	-111.785	0.035/-0.128	-112.002	0.034/-0.127
23	-111.786	0.035/-0.128	-112.002	0.034/-0.127	-112.002	0.033/-0.127	-111.785	0.035/-0.128	-112.002	0.033/-0.127
24	-108.717	0.042/-0.123	-108.871	0.040/-0.123	-108.871	0.040/-0.123	-97.685	0.369/-0.299	-108.661	0.040/-0.124
25	-97.684	0.368/-0.298	-108.871	0.040/-0.123	-108.717	0.042/-0.123	-97.378	0.402/-0.336	-97.378	0.402/-0.336
26	-107.498	-0.046/-0.110	-107.712	-0.048/-0.111	-107.712	-0.048/-0.110	-107.498	-0.046/-0.110	-107.712	-0.048/-0.110
27	-129.256[a]	-0.345/-0.158	-79.791	-0.020/-0.121	-129.254[a]	-0.345/-0.158	-120.269[f]	-0.237/-0.140	-129.256[a]	-0.345/-0.158
28	-102.833	-0.025/-0.141	-102.833	-0.025/-0.141	-101.425	-0.007/-0.157	-102.833	-0.025/-0.141	-101.425	-0.007/-0.157
29	-105.127[g]	-0.145/-0.172	-105.140[g]	-0.148/-0.170	-108.952[h]	-0.366/-0.331	-110.959[h]	-0.353/-0.345	-109.570	0.036/-0.153
30	-108.930[h]	-0.352/-0.234	Dec.	-	-97.184	0.044/-0.135	-97.184	0.044/-0.135	-97.184	0.044/-0.135
31	-112.938	-0.048/-0.111	-112.730	-0.046/-0.112	-112.730	-0.046/-0.111	-112.731	-0.046/-0.112	-112.938	-0.048/-0.111
32	-107.922	-0.027/-0.138	-107.922	-0.027/-0.138	-107.921	-0.028/-0.138	-107.921	-0.028/-0.138	-107.922	-0.028/-0.138
33	-109.168	-0.041/-0.113	-109.371	-0.042/-0.113	-109.371	-0.042/-0.112	-109.168	-0.041/-0.112	-109.371	-0.042/-0.112
34	-98.107 -111.150	0.408/-0.330 0.054/-0.127	-98.107 -111.150	0.408/-0.330 0.054/-0.127	-111.342 -111.150	0.053/-0.126 0.054/-0.127	-98.107 -111.150	0.408/-0.330 0.054/-0.127	-97.907 -111.150	0.408/-0.332 0.054/-0.127
35	-104.532	-0.024/-0.141	-104.532	-0.024/-0.141	-104.532	-0.024/-0.141	-104.532	-0.024/-0.141	-104.532	-0.024/-0.141

F.O. = failed optimization;
Dec. = decomposition, cation fragmentation with two or more resulting fragments;
[a-h] same as for Table 1a.

Using the minimal energy values, structure C seems somewhat more stable than structure F, but the energy differences are quite small (0.2-1.4 kcal/mol).[37] Some atom rearrangements (Fig. 3 and Fig. 4), including proton and hydride shifts,[17,45] have also been observed, and some of these processes appear more energetically favored when compared with simple anchimeric assistance (entries 3, 4, 5, 16, 27, 29, 30 in Table 1b). No anchimeric type interactions with the condensed dioxolane (O2, O3) or with O6 were noticed.

Table 2

Ring statistics

Ring type/ ring closure	A 3-exo-tet	B 4-exo-tet	C 5-exo-tet	D 6-exo-tet	E 7-exo-tet	F 8-exo-tet	G 10-exo-tet
Number of structures	5	1	24	1	5	5	1
Dative bond length (Å)	1.469÷1.471	1.492	1.461÷1.484	1.473	1.458÷1.470	1.453÷1.459	1.463
Dative carbon charge	-0.037÷-0.018	0.044	-0.049÷0.083	0.036	0.022÷0.045	-0.023÷-0.005	0.030
Dative oxygen charge	-0.162÷-0.121	-0.135	-0.164÷-0.110	-0.153	-0.205÷-0.159	-0.157÷-0.148	-0.208

Table 3

Heat of formation differences, in kcal/mol (Table 1 entries from which these were calculated are given in parenthesis)

open* - C	open* - E	open* - G	A - C	A - F	C - F	E - G
13.361 (7) 10.037 (11) 34.710 (12) 14.708 (14) 11.186 (24) 11.187 (25) 13.235 (34)	30.236 (8) 25.001 (9) 28.140 (17)	21.440 (17)	29.102 (15) 23.172 (16)	20.609 (6) 21.958 (16)	-0.182 (2) -1.214 (16) -1.408 (28)	-6.700 (17)

*structure in which, after geometry optimization, no anchimeric assistance was observed; the corresponding difference could therefore be interpreted as the dative bond energy.

Another confirmation for the formation of a dative bond lies in the electrical charges of atoms involved. Both carbon and oxygen atoms have decreased charges when compared with non-stabilized structures (*e.g.*, entries no. 8 and 12 in Table 1b).

No anchimeric assistance took place when the formal positive charge was located at the carbon atom adjacent to O1 (α-oxy carbenium ion). Instead, a decrease in the corresponding bond length (to about 1.26 ÷ 1.30 Å) suggested a delocalization of the positive charge over these two atoms, owing to the oxygen's ability to stabilize the carbenium ion center by resonance.[18,46,47]

Also, in contrast with primary and secondary carbenium ions, no tertiary carbocations were involved in any type of anchimeric configuration. There can be two obvious factors that can explain this difference: (1) the electron-donor inductive effect of the alkyl groups which substitute the positively charged carbon atom, stabilizing the charge,[15,18,48] and (2) the steric impedance of the same groups.[16,49] Although both effects can make the coordinative interaction less susceptible, it has been observed for some of the structures considered here that an approach between the positive center and one oxygen atom (an electrostatic interaction) still takes place even if the sp^2 charged carbon is completely substituted with alkyl groups, but without conversion into sp^3 configuration or with only a small degree of pyramidalization of the cationic center, and at a final distance greater than a conventional C-O bond length, which would suggest that the steric effect has a greater importance. This behavior has also been observed for some secondary carbenium ions from this study.

Glycoderivatives with longer linear alkyl chains (7-10, 12, 14, 16, 18, 20 and 30 carbon atoms) and compounds with general formula given in Fig. 5[26] did not give similar anchimeric stabilized structures, nor suffered any type of rearrangements.

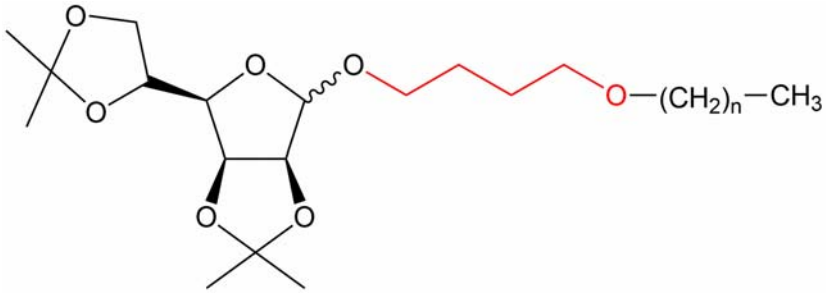


Fig. 5 – Other tested structures, which include a C_4 spacer (n = 1-9, 11, 13, 15, 17, 19, 29).

No nine-member (1,3,6-trioxonane) ring appeared in the analyses performed; structures of type B and D were obtained instead, in some cases, from possible candidates. This does not necessarily mean, however, that the formation of nine-membered ring is not possible at all. Migrations, rearrangements and decompositions[29,45] were recorded when dealing with branched alkyl positively charged chains (only a small part of them being reflected in Table 1a and Table 1b), which may have masked some of the possible anchimeric effects, including the formation of the nine-membered ring. Also, a single nine-member ring was obtained when branched C_7 alkyl chains were considered.[53]

CONCLUSIONS

It has been shown *in silico* that it is possible for the positively charged side chain to act as an electrophile for the nucleophilic centers of the mannose moiety, and that this anchimeric effect stabilizes the charge, producing at the same time an additional cycle in the molecule. Rings with three to eight members were all obtained, along with ten-member cycle, but a nine member ring remained elusive. Also, tertiary carbenium ions never took part in such arrangements, probably because of steric repulsions, but an intramolecular electrostatic interaction for these species was still observed. Although a methyl group was considered as departing moiety (Fig. 1) in connection with a previous study,[26] this could obviously be replaced with other leaving fragments. The results obtained in this work concern mainly mass spectrometry analysis of oxygen containing compounds like sugars derivatives, where such cations could be generated in molecular fragmentation processes, but could also find similarities in other classes of compounds which possess different heteroatoms with lone electron pairs. It should be kept in mind, however, that the statements in this article refer to isolated species, in conditions typical to the ones found in low pressure mass spectrometers. Therefore, it should not automatically be assumed that they may also be valid in solution chemistry (like S_N1 type reactions, and especially in strong nucleophilic solvents) or high pressure processes where intermolecular interactions, including ion solvation and ion-molecule pairing, become important and may interfere with the anchimeric assistance.[2,11,16,52]

Acknowledgements: The authors thank Prof. Dr. Eng. Nicolae Dincă for *HyperChem* software and for fruitful discussions. This work was supported by the Roumanian National Authority for Scientific Research (CNCS-UEFISCDI) through project PN-II-PCCA-2011-142.

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