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Experimental and Theoretical Investigation of the Reactions between Glucose and Cu$^+$ in the Gas Phase

Manuel Alcamí,*,† Alberto Luna,† Otilia Mó,† M. Yáñez,† Laurence Boutreau,‡ and Jeanine Tortajada‡,*

Departamento de Química, C-9, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain, and Laboratoire Analyze et Environnement, UMR CNRS 8587, Université d'Evry Val d'Essonne Institut des Sciences, Boulevard François Mitterrand, 91025 EVRY Cedex, France

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Tandem mass spectrometry was used in the analysis of Cu$^+$-D-glucose complexes. The MIKE spectrum of these complexes generated by FAB shows that the loss of a water molecule is the most important spontaneous fragmentation, followed by a second dehydration or the loss of H_2, whereas the metal ion Cu$^+$ is never eliminated. A theoretical survey of the potential energy surface, based on the use of density functional theory approaches, shows that the attachment of Cu$^+$ to the different basic centers of glucose induces nonnegligible bond activation phenomena within the sugar moiety. As a consequence, the cleavage of the C−O linkages of the six-membered ring leads to open complexes which are systematically much more stable than those in which the cyclic structure of the sugar is preserved. These significant stability differences reflect the preference of Cu$^+$ to yield bisligated complexes in which the metal forms almost linear arrangements with two oxygen atoms of the neutral through the participation of sd hybrids. The Cu$^+$ cation has a catalytic effect on these ring-opening mechanisms. Several pathways for the successive loss of two molecules of water can be envisaged with the origin in the cyclic and the open glucose−Cu$^+$ complexes. In general, the most stable product ions are those formed by a spontaneous fragmentation of the most stable open structures.

Introduction

It is well-known that carbohydrates play a crucial role in numerous biological processes, and metal ion-saccharide interactions are involved in key biological processes.[1−3] From an environmental point of view, one of their most important properties is their capacity to form very stable complexes with metal cations, because of the large number of basic sites present in these molecules. These particular properties attracted our attention, and we have carried out a series of experimental studies[4] aimed at gaining some understanding on the intrinsic complexation properties of several monosaccharides toward metal cations as well as on the unimolecular reactivity of the organometallic species resulting from such interactions. For this purpose, mass spectrometry techniques associated with fast atom bombardement (FAB) and electrospray ionization have been used. It is worth mentioning that the reactivity between carbohydrates and metal ions has been widely studied in solution.[1,2] In years past, several gas-phase mass spectrometry studies have deal with saccharides−metal complexes as a tool for stereochemical differentiation.[5−10] The existing theoretical studies[11,12] dealing with glucose−metal interactions have focused on the structures of the complexes, showing that in the case of Ca^{2+} [12] and Na$^+$ [11] the metal tries to interact with as many centers as possible, leading to structures in which the metal is tri- or even tetra-coordinated. Nevertheless there is an almost complete lack of theoretical information about the changes experienced by the bonds upon complex formation and about the possible fragmentations. The aim of this paper is to present the most significant experimental findings of the reactions between Cu$^+$ and glucose based on the use of mass spectrometry techniques and to offer a rationalization of the observed dominant fragmentations by exploring, using density functional theory approaches, the possible mechanisms involved.

Experimental Section

FAB mass spectra were recorded on a tandem ZAB−HSQ mass spectrometer (Fisons Instrument) of BEqQ configuration (B and E represent the magnetic and the electrostatic sectors, q, an r.f. only quadrupole collision cell, and Q, the mass selective quadrupole). The FAB ion source was used as follows: accelerating voltage of 8 kV, neutral xenon beam of 7 kV, and neutral current of ∼10 μA. Glucose was dissolved in a few drops of a mixture of glycerol and a saturated aqueous metallic copper salt solution ($CuCl_2$). A few microliters of the resulting mixture were then transferred onto the stainless steel FAB tip. Cu$^+$ ions are likely generated from Cu^{2+} by oxidation/reduction processes as has been previously postulated.[13] Mass calibration was achieved by using sodium iodide. Copper, presents several natural isotopes: 69% ^{63}Cu/31% ^{65}Cu. Unless otherwise noted, results presented hereafter refer to the study of complexes involving the most abundant isotope. Metallic salts and glucose are commercially available from Aldrich and Fluka and were used without any further purification

Unimolecular chemistry of the species of interest, which takes place in the second field-free region (2nd FFR) of the mass spectrometer, located just after the magnet, has been studied by mass analyzed ion kinetic energy (MIKE) spectroscopy. This technique consists of focusing the parent ion magnetically into the 2nd FFR, and detecting its spontaneous fragmentation

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* To whom correspondence should be addressed.
† Universidad Autónoma de Madrid.
‡ Université d'Evry Val d'Essonne Institut des Sciences.

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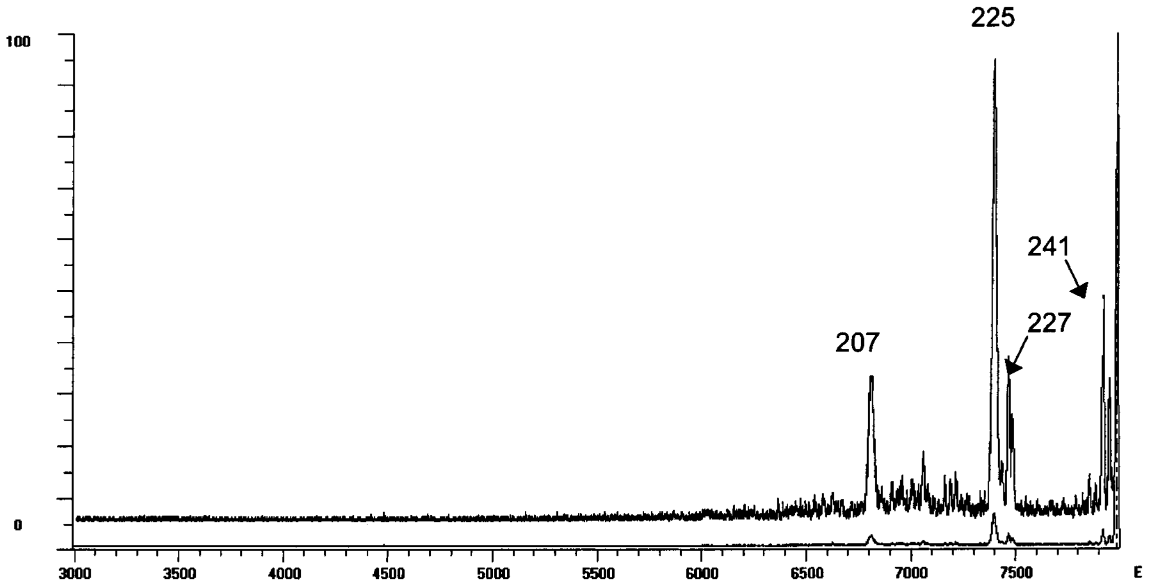


Figure 1. MIKE Spectrum of [glucose−Cu$^+$] complex.

products by scanning the electrostatic analyzer, E. The MIKE spectrum was recorded at a resolving power of ~1000. For collisionally activated decomposition (CAD) MS/MS spectrum, the pressure of argon in the collision cell was adjusted so that the main beam signal was reduced by approximately 30%.

Computational Details. The theoretical treatment of the different species included in this work was carried out by using the B3LYP density functional theory approach as implemented in the Gaussian-98 series of programs.[14] This method combines Becke's three-parameter nonlocal hybrid exchange potential[15] with the nonlocal correlation functional of Lee, Yang, and Parr.[16] This formalism has been found to be very reliable as far as the description of ion−molecule complexes are concerned.[17,18] In general both, geometries and vibrational frequencies obtained at the B3LYP/6-31G* level are in fairly good agreement with experimental values.[19−22] On the other hand, this method is also well suited for the study of inter- and intramolecular hydrogen bonds.[23−25] It must be also emphasized that for the calculated frequencies the performance of this DFT method is superior to other correlated methods such as Moller−Plesset second-order perturbation theory (MP2). More importantly, the B3LYP approach is free of the pathologies which affect the description of Cu$^+$ complexes when high level ab initio formalisms, like the G2 theory[26] or even the CCSD(T) methods, are used.[27,28] Hence, the B3LYP/6-31G(d,p) is the level of theory adopted in this paper for the geometry optimizations. The same level was used to optimize the structures of the transition states (TS) associated with the hydrogen shifts leading to the breaking of the six-membered ring (vide infra). Although the description of TSs is less reliable than that of the minima at the B3LYP/6-31G* method, the values obtained for the activation barriers can be considered reasonably good in relative terms. For Cu the all electron basis (14s9p5d/9s5p3d) of Wachters−Hay,[29,30] supplemented with one set of an *f* polarization function was used. The same level of theory was employed to evaluate the harmonic vibrational frequencies which allow us to characterize the stationary points of the potential energy surface (PES) as local minima or transition states and to estimate the corresponding zero-point energy corrections. The final energies were obtained using an extended 6-311+G(2df,2p) basis set, which has been shown[27,31] to yield reliable results when dealing with Cu$^+$ complexes. Although for the sake of simplicity we keep the nomenclature 6-311+G(2df,2p) for all of the atoms, it must be kept in mind that for Cu$^+$ it corresponds to the (14s9p5d/9s5p3d) Wachters−Hay's basis supplemented with a set of (1s2p1d) diffuse components and with two sets of *f* (rather than *d*) and one set of *g* (rather than *f*) functions as polarization basis.

The atoms in molecules (AIM) theory of Bader[32] was used to investigate the possible bond activations undergone by the neutral upon Cu$^+$ attachment. For this purpose, we have evaluated the charge density as well as the energy density at the bond critical points (bcp). These values, together with the lengthening or shortening of the bond lengths and the shifting of the corresponding stretching frequencies, will provide a reliable description of these effects. We shall also show the usefulness of the energy density contour maps to characterize the nature of the bonding interactions between the metal cation and the basic centers of the sugar.

Results and Discussion

Reactivity of [Glucose−Cu]$^+$ Ions. The MIKE spectrum of the [glucose−Cu]$^+$ complex presented in Figure 1 shows that the *m*/*z* 243 ion undergoes fragmentation by distinct pathways. This complex gives rise to four spontaneous losses, the most important being that of H_2O at *m*/*z* 225 which is the base peak of the MIKE spectrum. The other ions correspond to elimination of H_2, 16 u, and a second dehydration leading to ions at *m*/*z* 241, 227 and 207, respectively. It is important to mention that a loss of 16 u was also observed[4] in the reactions between methyl glycosides and Cu$^+$.

Under collision conditions, one can note, in the resulting CAD spectrum displayed in Figure 2, that the relative intensity of the four peaks is unchanged. This spectrum also shows the presence of several minor ions at *m*/*z* 183 and 153. The weak intensity of these ions demonstrates that these two decomposing channels are high energy demanding processes. We also can notice that within the time scale of the experiment fragmentation of selected [glucose−Cu]$^+$ ion produces exclusively Cu$^+$-containing fragment ions; the metal ion Cu$^+$ is never eliminated.

We cannot measure the pressure in the FFR region, but taken into account that when the MIKE spectrum is obtained the pressure inside the cell is 10^{-7} Torr, we can reasonably assume that no significant collision dissociations should occur in the FFR region. On the other hand, under CAD conditions, we can discriminate between the product ions arising from unimolecular

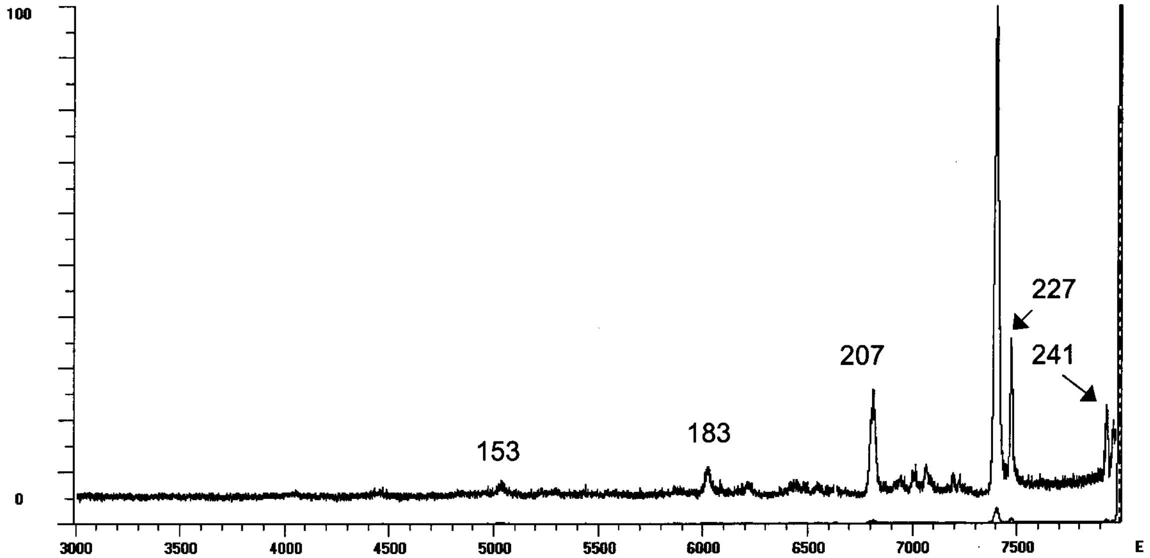


Figure 2. CAD Spectrum of [glucose$-$Cu$^+$] complex.

fragmentations and those produced in bimolecular processes, by applying an increasing voltage to the collision cell. Under these conditions only the peaks corresponding to ions produced by collisional dissociation will be shifted as a function of the voltage applied, whereas those arising from unimolecular decompositions will not. In this way, we have confirmed that the loss of water is essentially a unimolecular process. The fact that unimolecular processes dominate is mirrored in the similarity between the MIKE and the MIKE$-$CAD spectra.

To propose no purely speculative mechanisms associated with the loss of H_2 (2 u) and oxygen (16 u), it would be necessary to work with D and ^{18}O labeled componds. Unfortunately, only the D-glucose $^{18}O_1$ is commercially available, and the synthesis of other marked derivatives is not an easy task. Nevertheless, it is worth noting that the loss of 16 u is not observed[4] in reactions with other transition-metal monocations, such as Ag$^+$. In this respect, it is interesting to note that the ADN desoxynucleotides are synthesized[3] from ARN nucleotides by metal containing ribonucleotides reductases.

Structure, Bonding and Stability of Glucose$-$Cu$^+$ Complexes. To establish the possible mechanisms leading to the loss of water from glucose$-$Cu$^+$ complexes, we should consider all possible precursors. Hence, we shall first analyze the stability of the complexes which arise from a direct attachment of the metal cation to the different basic sites of the neutral. The second possibility which should be investigated is whether the Cu$^+$ association is followed by bond activations eventually leading to different bond cleavages of the glucose moiety.

It is well established that monosacharides represent challenging systems from the conformational analysis viewpoint.[33] It has to be taken into account that, for neutral glucose, three possible rotamers exist for each hydroxyl bond and for the C5$-$C6 bond (see Figure 3). Moreover, the ring structure can be found in different chair or boat arrangements, and glucose present two different anomeric forms (α or β) depending on the position of the hydroxyl group attached to C1 with respect to the ring (axial or equatorial, respectively). Actually, Cramer and Thrular[34] have estimated in nearly 3000 the number of potential conformers of glucopyranose. Among all of the possible rotamers, those in which the ring hydroxyl groups are organized in a cyclic internal array of hydrogen bonds generally present the highest stability. For the α- and β-glucose, we have taken as the most stable conformations those proposed by Jebber et al.[35] which are represented in Figure 3. Our calculations predict the most stable β and α anomers to be nearly degenerate (the former being 0.1 kJ/mol more stable) in agreement with the findings of refs 34 and 35.

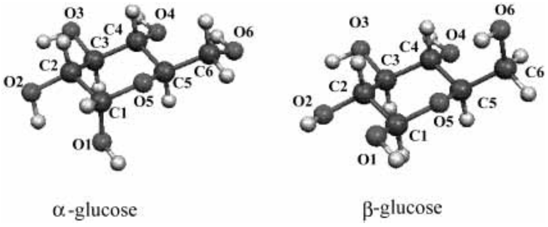


Figure 3. Conformation of neutral glucose, including atom numbers.

The number of conformational possibilities becomes larger when the interaction with Cu$^+$ is considered. To restrict our survey of the possible adducts to a reasonable number, we have considered only those structures in which the Cu$^+$ is attached to at least two different oxygens of glucose, assuming that the sugar moiety retains its cyclic structure. To identify the different isomers we have named each of them by numbering the oxygens (See Figure 3) to which the Cu$^+$ is attached. For instance, α**G1$-$5** designates the isomer in which Cu$^+$ is bonded to oxygens 1 and 5 of the α-glucose. For every possible position of the Cu$^+$ several arrangements of the hydrogen bonds between the hydroxyl groups have been investigated, and therefore, more than 40 different adducts between Cu$^+$ and glucose have been fully optimized at the B3LYP/6-31G* level. We have also included those structures in which Cu$^+$ appears tri- and tetracoordinated, namely, α**G-tri**, β**G-tri**, and β**G-tetra**. The relative stability of the most stable rotamer found for each relative position of Cu$^+$ with respect the hydroxyl groups is given in Table 1. The corresponding structures are shown in Figure 4.

Some general trends can be deduced from Table 1 and from the AIM analysis of the corresponding charge distributions, which are summarized in Table 2:

(a) Dicoordinated structures in which Cu$^+$ binds to the oxygen of the ring (O5) are the less stable ones, reflecting the lower basicity of this oxygen atom as compared with the basicity of the hydroxyl groups.[35]

(b) For the case of β-glucose, it is possible to obtain a conformation in which the Cu$^+$ is interacting with four different

TABLE 1: Relative Stabilities (Δ*E* in kJ/mol) for the Complexes between Cu$^+$ and Glucopyranose, and for the Open Forms of Glucose Considered[a]

Ring Structures

	α-glucose			β-glucose		
oxygen atoms	structure	Δ*E*		structure	Δ*E*	
1−5	**αG1−5**	106.9	80.5	βG1−5	112.4	69.0
1−2	**αG1−2**	61.9	19.1	βG1−2	66.7	24.0
2−3	**αG2−3**	36.8	0.1	βG2−3	54.6	10.6
3−4	**αG3−4**	44.9	1.7	βG3−4	45.0	0.0
4−6	**αG4−6**	24.8	21.5	βG4−6	23.6	16.7
6−5	**αG5−6**	75.4	22.2	βG5−6	evolves to β**G-tri**	
1−5−6	**αG-tri**	4.2	4.6	βG-tri	3.9	13.0
1−3−5−6				βG-tetra	0.0	22.7

Open Structures

	Δ*E*			Δ*E*			Δ*E*	
OG1a	−38.0	−6.5	**OG1b**	−12.3	−4.2			
OG2a	−152.8	−125.0	**OG2b**	−126.1	−101.8	**OG2c**	−91.0	−65.7
OG3a	−12.2	16.2	**OG3b**	4.1	46.9			

[a] The first column indicates the oxygen atoms to which Cu$^+$ binds upon complex formation. The first number corresponds to the B3LYP/6-31G(d,p) energies, and the second number corresponds to the B3LYP/6-311+G(2df,2p) ones. Both values include the ZPE corrections evaluated at the B3LYP/6-31G(d,p) level and refer to the most stable structure β**G-tetra** and β**G3−4**, respectively. For every position of Cu$^+$ some other structures have been calculated, and only the most stable one for each position is shown in the table.

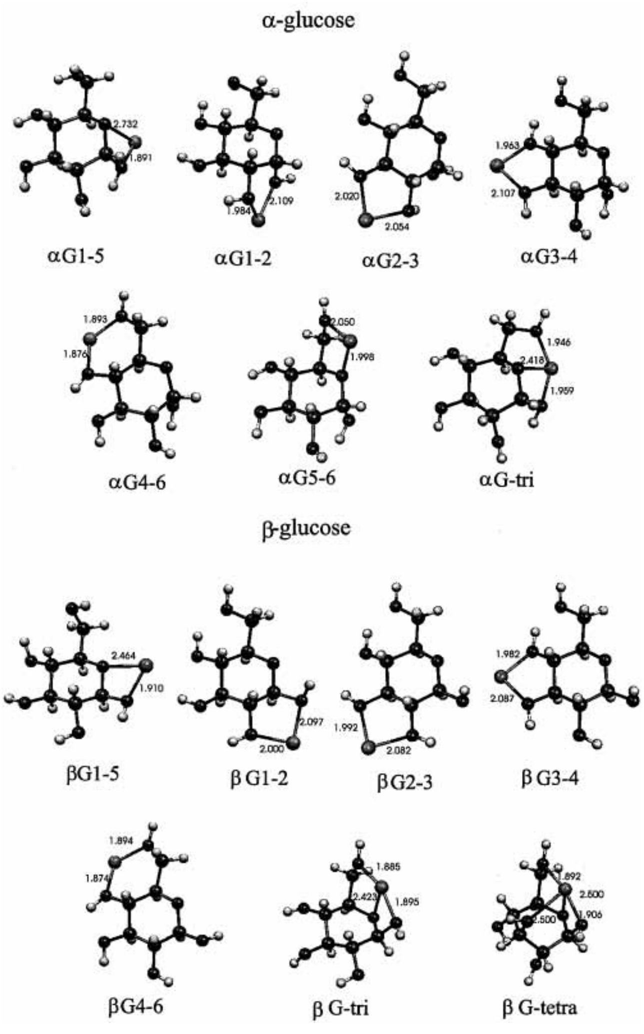


Figure 4. Glucose−Cu$^+$ complexes. Cyclic forms.

TABLE 2: Topological Analysis of the Charge Density for Neutral Glucose and the Most Representative Glucose−Cu$^+$ Complexes[a]

compound	bond	*R*	ρ	$\nabla^2\rho$	*H*(*r*)
α-glucose	C5−O5	1.441	0.272	−0.615	−0.390
	C1−O5	1.408	0.244	−0.462	−0.331
β-glucose	C5−O5	1.439	0.244	−0.441	−0.339
	C1−O5	1.421	0.263	−0.609	−0.369
βG3−4	C5−O5	1.419	0.259	−0.525	−0.366
	C1−O5	1.428	0.257	−0.583	−0.355
	Cu−O3	2.087	0.063	0.306	−0.009
	Cu−O4	1.982	0.079	0.451	−0.009
βG-tri	C5−O5	1.456	0.231	−0.415	−0.299
	C1−O5	1.395	0.272	−0.545	−0.405
	Cu−O6	1.885	0.097	0.646	−0.008
	Cu−O1	1.895	0.095	0.616	−0.007
	Cu−O5	2.423	0.032	0.132	−0.003
βG-tetra	C5−O5	1.460	0.229	−0.432	−0.289
	C1−O5	1.391	0.277	−0.543	−0.415
	Cu−O6	1.895	0.095	0.618	−0.007
	Cu−O1	1.928	0.091	0.557	−0.008
	Cu−O3	2.764	0.015	0.062	0.001
	Cu−O5	2.401	0.034	0.134	−0.004
OG1b	Cu−O2	1.880	0.098	0.651	−0.0054
	Cu−O6	1.892	0.096	0.633	−0.0072
	Cu−O3	2.463	0.030	0.108	−0.0035
OG2a	Cu−O5	1.867	0.103	0.679	−0.0078
	Cu−O6	1.879	0.098	0.661	−0.0066
	Cu−O3	2.427	0.032	0.116	−0.0037
OG3b	Cu−O1	1.850	0.108	0.721	−0.0090
	Cu−O6	1.861	0.103	0.698	−0.0097

[a] Interatomic distances (*R*) are given in Å. Charge densities (ρ), Laplacian of the charge density ($\nabla^2\rho$), and energy density (*H*(*r*)) (all values in a.u.) have been evaluated at the corresponding bond critical point.

hydroxyl groups. Similarly to what it has been described for alkali metal complexes, this is one of the most stable complexes among all of the adducts considered. Tricoordinated structures are also minima for both anomeric forms of glucose and correspond also to very stable conformers. These polycoordinated structures are particularly favored when dealing with β-glucose, explaining why the β**G5-6** isomer collapses to the β**G-tri** structure. The AIM analysis of complexes α**G-tri**, β**G-tri**, and β**G-tetra** (see Table 2) reveals that Cu is truly tri- or tetracoordinated, forming quite strong covalent bonds with the oxygens of the hydroxyl groups but, consistently with point a, a much weaker interaction with the O atom of the cycle. For the particular case of the β**G-tetra** complex, the contour maps of the energy density (see Figure 5) clearly show that the bonds between the metal and O1 and O6 can be considered as covalent

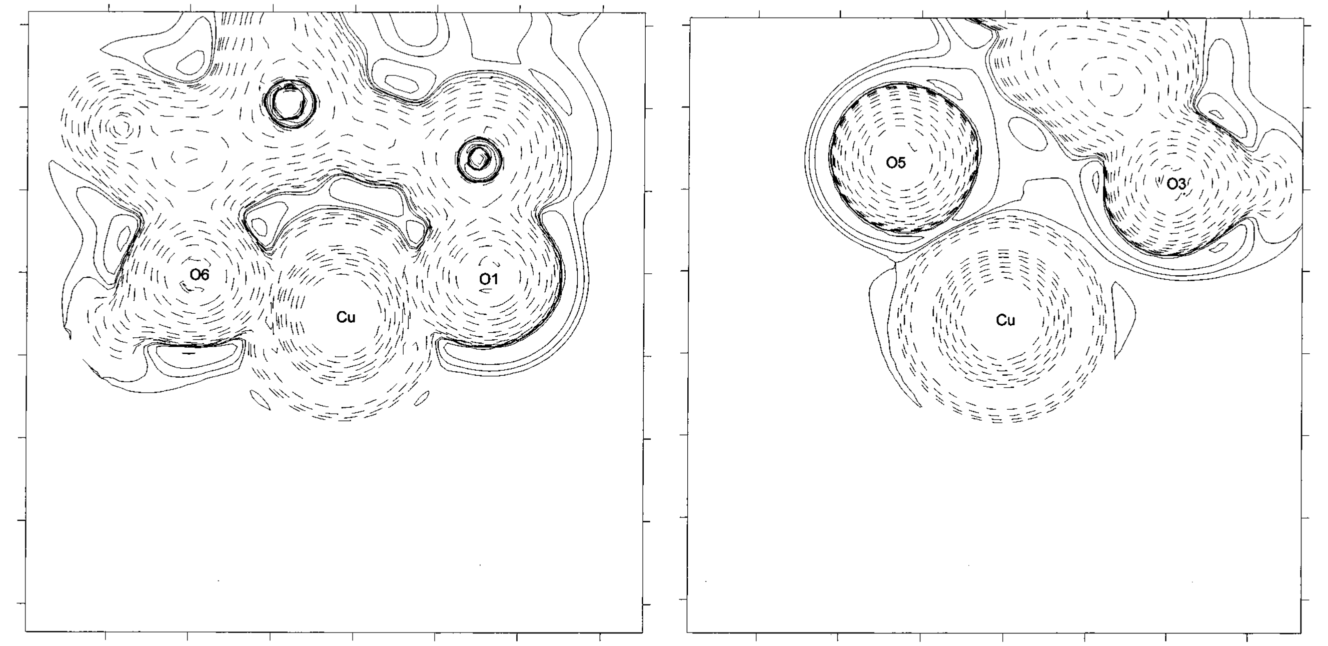


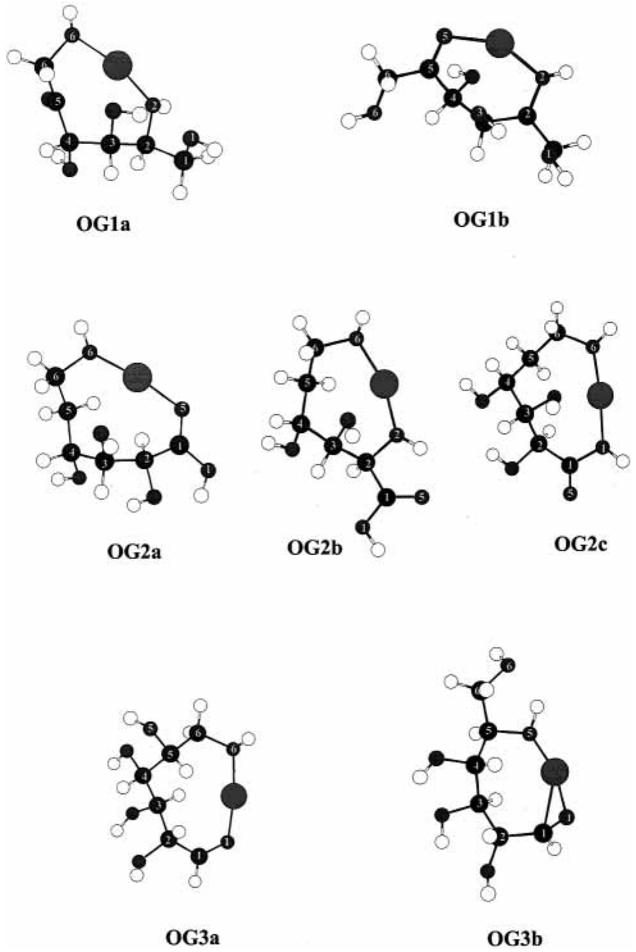
Figure 5. H(r) contour maps for β**G-tetra** complex.

linkages characterized by negative values of the energy density within the bonding region. In contrast, within the bonding regions between Cu and the other two oxygen atoms (O3 and O5), the energy density is positive, as it corresponds to essentially electrostatic interactions.

(c) The calculated relative stabilities are very sensitive to the quality of the basis set used. For instance, while at the B3LYP/6-31G* level, the global minimum is the tetracoordinated complex (β**G-tetra**) which lies 45.0 kJ mol^{-1} lower in energy than β**G3−4**; this stability order is reversed when the B3LYP/6-311+G(2df,2p) level is employed, and complex β**G3−4** is estimated to be 22.7 kJ mol^{-1} more stable than β**G-tetra**. In fact, Table 1 shows that relative energies can change as much as 50 kJ mol^{-1} depending on the level of the basis set used. Similar changes have been described previously in $Cu^+-PO_4H_3$ complexes.[36] No doubt the role of the intramolecular hydrogen bonds on the relative stability of these complexes is not negligible, as it has been discussed elsewhere.[37] Because the appropriate description of these hydrogen bonds requires flexible basis sets including, at least, diffuse functions, it is then not surprising to find a large dependency of the relative stability of glucose−Cu$^+$ complexes on the quality of the basis set used, specially when dealing with structures which differ in the number and type of their hydrogen bonds. This is one of the factors which explains the relative stability change when comparing structures β**G3−4** and β**G-tetra**. On the other hand, as mentioned above, in tri- and tetracoordinated structures one or two of the Cu−O interactions are essentially electrostatic, involving quite large bond distances, whose appropriate description requires also the use of diffuse components in the basis set

(d) Another important finding of this survey is that Cu$^+$ association produces large distortions of the conformation of the sugar ring. This is clearly illustrated when looking at the tricoordinated complexes (see Figure 4), where the interaction with Cu$^+$ changes the puckering of the six-membered ring and, therefore, we cannot talk any longer of boat or chair conformations.

(e) The differences in relative energies among different conformers are very small. As a consequence, we should expect to have a mixing of different conformers at room temperature. For this reason, it will be necessary to consider, in the next section, different initial conformations of the complex when discussing the possible fragmentation pathways. This is a clear difference with respect to similar structures found in the case of complexes with alkali metals, where the interactions are


OG1a **OG1b**

OG2a **OG2b** **OG2c**

OG3a **OG3b**

Figure 6. Glucose−Cu$^+$ complexes. Most stable open forms.

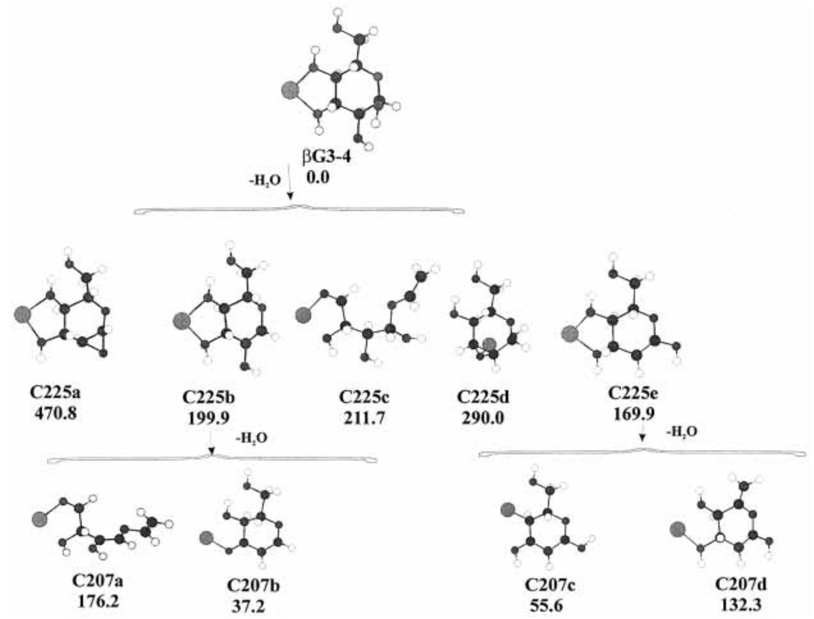


Figure 7. Water-loss mechanisms from cyclic structures β**G3−4.** The energies (kJ/mol) are referred to the most stable isomer in each case for the C225 and C207 cations. For the 243 au mass cations, the energies are referred to β**G3−4** complex.

essentially electrostatic and the isomers, in which the cation binds to several hydroxyl groups, are strongly favored.

Bond Activation by Cu$^+$ Association. A second important question which needs to be addressed is whether Cu$^+$ interaction favors bond fissions within the glucose moiety leading to open intermediates. It is reasonable to expect that the two polar C−O bonds of the ring are the appropriate candidates to undergo cleavage. When the charge density at the corresponding bond critical points in the neutral molecule is compared (see Table 2) with that found for the most stable di- and tricoordinated [glucose−Cu]$^+$ complexes it is easy to realize that the activation of the C1−O5 bond is favored in dicoordinated complexes, whereas the activation of the C5−O5 bond is favored in tricoordinated ones.

The C1−O5 fission should be preceded by a 1,3-H shift from C5 to C1, so that **OG1(a,b)** open structures would be formed (See Figure 6). Alternatively, a 1,3-H shift from C1 toward C5 would lead to the C5−O5 bond fission, in such a way that the alternative **OG2** open structures are produced (see Figure 6). Finally, the C5−O5 bond fission can also be associated with a hydrogen shift from O1 to O5 giving structures **OG3**. Similarly to what happened in the cyclic forms, a large number of conformations are possible depending on the position of Cu$^+$. We have investigated the open conformations in which Cu$^+$ links between the terminal oxygens (6, 5, 1, or 2) which, in principle, should be the most stable ones. Their relative energies are given in Table 1. For **OG1** structure, two alternative conformations have been considered, namely, **OG1a** and **OG1b**. In the latter, the Cu$^+$ interacts with the carbonyl oxygen, whereas in the first one, 2.3 kJ mol^{-1} more stable, it interacts with two OH groups of the sugar moiety. Similarly, for species **OG2**, three different conformers have been investigated. In all of them, the Cu$^+$ appears dicoordinated between the hydroxyl group of the CH$_2$OH group of the sugar moiety and (a) the carbonyl group of the acidic function, (b) a hydroxyl group of the ring, or (c) the hydroxyl group of the acidic function. The most stable one corresponds to structure **OG2a**, where the second interaction involves the carbonyl group of the acidic function. In the case of species **OG3**, the interaction necessarily occurs between the keto group and one of the hydroxyl groups. Two different structures **OG3a** and **OG3b** have been considered depending on which hydroxyl group is involved (see Figure 6). Although both conformers are less stable than the rest of the open structures considered, they cannot be discarded in our survey because, in the experiment, they can be formed not only by the breaking of the C1−O5 bond after complex formation but also from the direct attachment of the Cu$^+$ to the open keto neutral form which is in equilibrium with the cyclic forms of glucose.

The activation barriers associated with these hydrogen shifts leading to the breaking of the six-membered ring are sizably high (being the highest 259 kJ mol^{-1} at the B3LYP/6-31G* level). It is important to note however that they are lower than the glucose−Cu$^+$ binding energy which is estimated to be 280 kJ mol^{-1} at the same level of theory. This implies that the complex formed by a direct attachment of Cu$^+$ to glucose has enough internal energy to overpass these activation barriers leading to the aforementioned open structures. Also importantly, these barriers are about 25 kJ mol^{-1} lower than those associated with similar processes in the isolated sugar molecule, which clearly indicates that the formation of open structures is catalyzed by the Cu$^+$ metal cations.

The second important quantitative result is that these open structures are also much more stable than the cyclic ones. For instance, the **OG2a** complex is estimated to be 125 kJ mol^{-1} more stable than the β**G3−4** structure which is the most stable cyclic complex. Consistently, the AIM analysis of the charge density of both complexes shows that in the former the corresponding Cu−O linkages are stronger, as reflected in a higher charge density (see Table 2). Also interestingly, this analysis indicates that in the **OG2a** complex Cu$^+$ is formally tricoordinated, because a bond critical point is also found between the metal and the hydroxyl group attached to C3.

The enhanced stability of the open structures is clearly associated with a more efficient bonding between Cu$^+$ and the oxygen atoms of the sugar moiety. As it is quite obvious by comparing the structures of Figures 5 and 6, in the open structures the O−Cu−O fragment exhibits a practically linear arrangement, whereas in cyclic structures, this possibility is hindered by the rigidity of the ring. In the first case, the bonding of Cu$^+$ implies the participation of σ-sd hybrids which, as has been already pointed out by Bauschlicher et al.,[38−41] contribute to further stabilize these kinds of complexes. In this respect, it

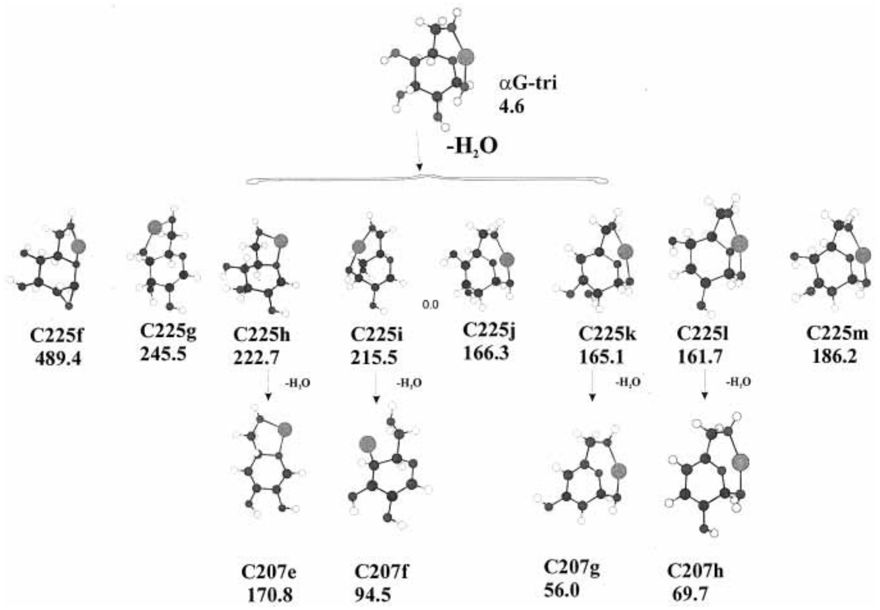


Figure 8. Water-loss mechanisms from cyclic structures α**G-tri**. Same conventions as in Figure 7.

is also important to emphasize that these linear arrangements were also found to be the most stable complexes formed in the gas-phase reactions between Cu$^+$ and a series of neutrals as formamide,[42] guanidine,[43] or urea.[44] It is also important to note that, in general, the open forms produced by C5−O5 bond fission (**OG2**) are systematically lower in energy than those formed by the cleavage of the C1−O5 bond (**OG1** or **OG3**). In fact, the **OG2a** structure is estimated to be 118.5 kJ mol^{-1} more stable than the **OG1a** form.

The enhanced stability of the **OG2a** species clearly reflects the high intrinsic basicity of the carbonyl group with regards to the intrinsic basicity of the hydroxyl groups. This is mirrored in a higher charge density at the corresponding Cu−O bond critical point as well as in a significant blue shifting (223 cm^{-1}) of the Cu−O stretching frequency. In general, the stability trends follow the corresponding intrinsic basicity trend: acidic carbonyl group > acidic hydroxyl group > sugar hydroxyl group > keto group.

Water-Loss Mechanisms. For the sake of completeness we shall analyze the water-loss mechanisms with the origin in both the cyclic and the open structures, because even though the former are less stable than the latter, the evolution from cyclic to open intermediates requires overpassing sizable activation barriers. Therefore, it cannot be excluded a priori that some of the reaction paths leading to the loss of water have their origin in cyclic complexes. The relatives energies (at the B3LYP/6-31G(2df,2p)//B3LYP/6-31G*, including ZPE) of the different product ions investigated are summarized in Figures 7 to 11).

Water-Loss Processes from Cyclic Precursors. As indicated in preceding sections, the successive loss of two water molecules was experimentally observed in the unimolecular fragmentation of glucose−Cu$^+$ complexes, so that molecular cations of mass 225 and 207 are produced. In what follows, we shall identify them by indicating its mass (**C225** or **C207**) followed by a latin letter when the precursor is a cyclic glucose−Cu$^+$ complex and by a greek letter when the precursor is an open structure.

We shall start by exploring (see Figure 7) the water-loss mechanisms taking as suitable precursor the most stable cyclic complex, namely, β**G3−4**. One possible pathway would correspond to the proton transfer from the OH group attached to C2 toward the hydroxyl group attached to C1, so that an epoxy three-membered ring is formed upon loss of a molecule of water.

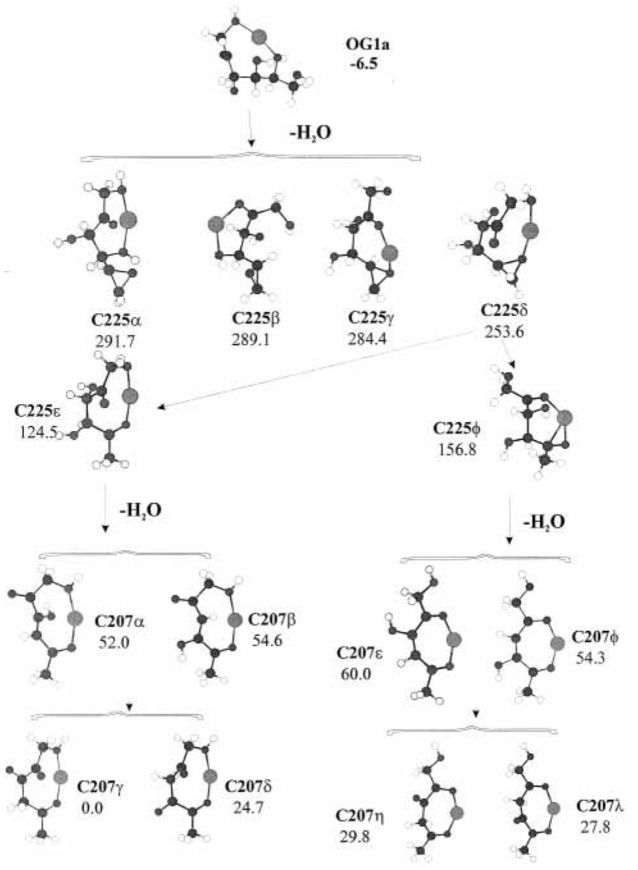


Figure 9. Water-loss mechanisms from structure **OG1a.** Same conventions as in Figure 7.

The structure of this complex of mass 225, namely, **C225a**, is given in Figure 7. An alternative process would involve the opposite proton transfer, i.e., from the OH group attached to C1 toward the OH group attached to C2. The resulting complex, **C225b**, would present a C═C double bond and is predicted to be 246 kJ mol^{-1} more stable than **C225a**, clearly reflecting the low stability of the three-membered ring subunit present in the latter. Other possible water-loss processes can be envisaged leading to structures **C225c**, which implies the opening of the ring, **C225d** which is very unstable because of the presence of

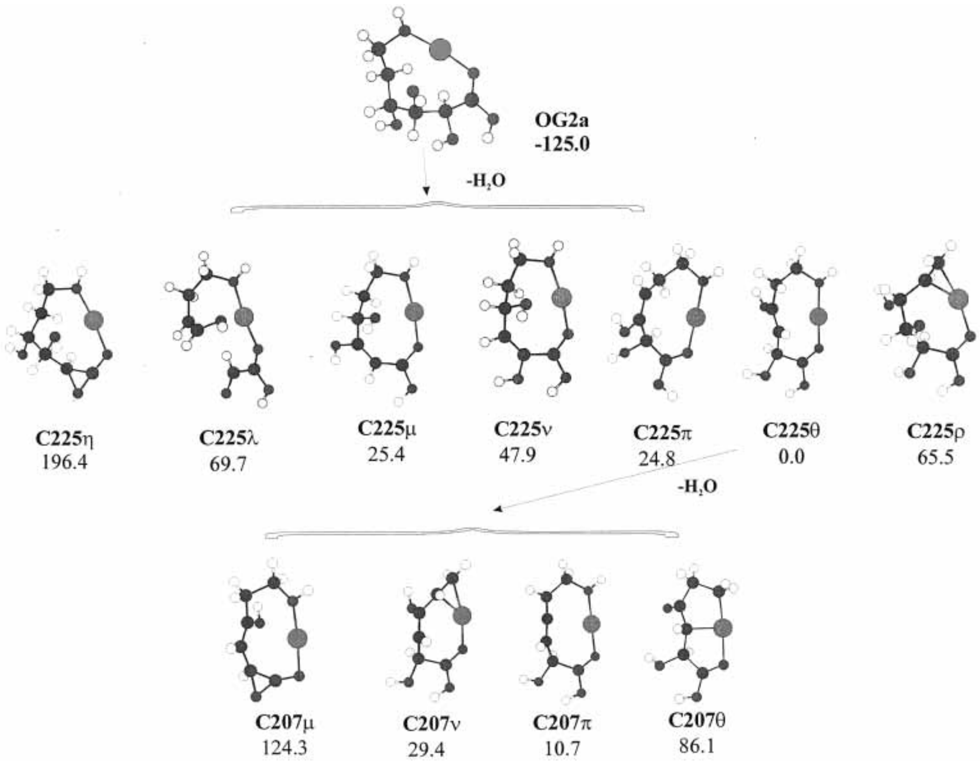


Figure 10. Water-loss mechanisms from structure **OG2a.** Same conventions as in Figure 7.

an epoxy group, and **C225e** which is found to be 30 kJ mol^{-1} more stable than structure **C225b** and present a similar C=C double bond.

Structure **C225b** is susceptible to undergoing a second water loss to yield complexes **C207a**−**b**, whose structures are also given in Figure 7. Similarly, a second water loss from structure **C225e** yields the **C207c**−**d** product ions, which are also less stable than those produced by the unimolecular dissociation of **C225b**.

For the sake of completeness, we have also considered the possible products that can be formed by loss of one molecule of water when the precursor is the α**G-tri** cyclic complex, which lies only 4.6 kJ mol^{-1} above the global minimum and where Cu$^+$ appears tricoordinated. As before, several mechanisms can be envisaged, yielding structures **C225f**−**m** (see Figure 8). Again the less stable one is **C225f** because of the strain of the three-membered ring formed. The most stable ones correspond systematically to those complexes, namely, **C225j**−**m**, where the metal cation is bridging between the hydroxyl group of the $-$CH$_2$OH substituent and the hydroxyl group attached to C1, again reflecting the preference of Cu$^+$ to yield linear bonding arrangements. These complexes differ in the relative positions of the other hydroxyl groups within the sugar ring, with the **C225l** being the most stable. The subsequent water loss from the **C225k** or **C225l** species would yield structures **C207g** and **C207h**, respectively, which are significantly more stable than complexes such as **C207e**−**f** with origin in less stable precursors (see Figure 8). The low stability of the **C207e** form reflects, once more, the low intrinsic basicity of the cyclic oxygen of the sugar moiety.

It is worth noting that the global minimum among the ions of mass 207 produced by the unimolecular fragmentation of cyclic [glucose-Cu]$^+$ complexes is **C207 g** structure, where Cu appears formally tricoordinated (see Figure 8). Consistently, very close in energy is complex **C207h**, where Cu is also tricoordinated.

Water-Loss Processes from Open Precursors. In this section, we will consider the possible water-loss mechanisms when the precursor is an open complex. As we have discussed above, there are three types of open complexes, and therefore, there will be three different sets of reaction paths depending on the nature of the precursor. In what follows, we will discuss exclusively the mechanisms associated with the most stable complex of each kind.

*Water-Loss Processes from **OG1a** Complex.* Let us consider now the mechanisms with origin in the **OG1a** structure. One of the possible processes would be the proton transfer from the OH group attached to C2 toward the hydroxyl group attached to C1, so that an epoxy three-membered cycle is formed after the loss of a water molecule. The structure so formed, namely, **C225**α (see Figure 9), has different conformers **C225**β, **C225**γ, and **C225**δ depending on the groups directly bonded to the Cu$^+$ ion. According to our estimations, the **C225**δ complex is the most stable one. Once the **C225**δ structure is formed, there is the possibility of a subsequent hydrogen transfer which involves the opening of the three-membered ring and consequently a significant stabilization of the complex. The new structure formed **C225**ϵ has other possible conformations such as **C225**ϕ, but they are estimated to be less stable.

From **C225**ϵ, the loss of a second molecule of water can yield structures **C207**α or **C207**β. In the first case, the hydroxyl group lost is the one closer to the methyl group, whereas in the second case, it is the farther one. These two structures can evolve by a subsequent 1,3 H shift from the remaining OH group toward the near carbon atom to yield complexes **C207**γ and **C207**δ, respectively, with the former being the most stable. Again, in both structures, the metal cation is formally tricoordinated.

Similarly, the loss of a second water molecule from **C225**ϕ would yield complexes **C207**ϵ and **C207**ϕ, which would eventually evolve to yield **C207**η and **C207**λ through mechanisms similar to those invoked above when the precursor was the **C225**ϵ complex. It is worth noting that, although complexes

C207ϵ and **C207**ϕ have similar stabilities than their analogues **C207**α and **C207**β, the isomer **C207**γ is significantly more stable (29.8 kJ mol^{-1}) than its analogue **C207**η (see Figure 9).

Water-Loss Processes from ***OG2a*** *Complex.* In this section, we have considered all possible mechanisms leading to the loss of a water molecule from the global minimum of the glucose−Cu^+ PES which corresponds to the open structure **OG2a**. Seven different mechanisms can be envisaged which lead to complexes **C225**$\eta-\rho$ (see Figure 10). As expected, the less favorable process is the one leading to complex **C225**η, because of the ring strain of the three-membered ring formed. All of the other structures, with the exception of complex **C225**λ, where the cyclic structure is lost, lie within a gap of 43 kJ mol^{-1}, with the global minimum being the structure **C225**θ.

From **C225**θ structure, several water-loss processes can be also envisaged. The first one would imply the loss of the hydrogen atom of the hydroxyl group of the acidic function. The resulting species, namely, **C207**μ exhibits a low stability because of the presence of a three-membered ring. An alternative process would involve the terminal OH group directly attached to the Cu atom. In the new complex formed, **C207**ν, the metal cation interacts with the π system of the terminal $HC{=}CH_2$ group. Complex **C207**π is the result of a water loss involving the hydroxyl group contiguous to the CH_2 group of the ring. Finally, in complex **C207**θ, the metal cation is again tricoordinated, but because of the lower strength of the C−Cu linkages, it is predicted to be 75.4 and 56.7 kJ mol^{-1} less stable than complexes **C207**π and **C207**ν, respectively (see Table 3). It is worth noting that, although the open form **OG2a** yields the most stable **C225** cations, the corresponding **C207** complexes are less stable than those found by fragmentation of the open structure **OG1a** but much more stable than the products of the fragmentation of cyclic glucose−Cu^+ complexes.

Water-Loss Processes from ***OG3a*** *Complex.* Five different complexes, namely, **C225**$\sigma-\omega$, can be obtained by the loss of a molecule of water from species **OG3a** (see Figure 11). In all of them, the metal cation bridges between the carbonyl of the aldehyde function and the terminal hydroxyl group, structure **C225**ξ being the most stable. Although in general the less stable precursors lead also to less stable products ions, we have found that the **C225**ψ form with origin in the **OG3b** complex is more stable than any of the product ions with origin in **OG3a**. It can be seen that **C225**ι structure can be viewed as an alternative conformer of structure **C225**σ where the metal bridges between the carbonyl group and the hydroxyl group adjacent to the CH_2-OH one. In the same figure, we have schematized the structures of the ions produced by the loss of a second molecule of water from **C225**ψ.

As far as the water-loss mechanisms are concerned we can summarize the following observations:

(a) The most stable final product ions have their origin in open structures. In general, the relative stability of the conformers obtained upon water loss reflects the relative stability of the parent compounds. Therefore, among the ion products formed by loss of one molecule of water, **C225**, the most stable ones are those with an origin in the **OG2a** open structure because of the high intrinsic basicity of the acidic function. The next stable one (**C225**ϵ) comes from structure **OG1a**, and its relative stability (124.5 kJ/mol) is similar to that found for the parent compound (114.8 kJ/mol). Similar trends are obtained for the remaining structures, with the exception of those derived from β**G3−4** which are less stable than expected

(b) In contrast, the most stable product ions after the loss of a second molecule of water are those with origin in the **OG1a** open structure, where Cu is formally attached to one hydroxyl group and two carbonyl groups. In any case the less stable product ions are those with origin in the [glucose-Cu]$^+$ cyclic complexes.

TABLE 3: Total Energies (*E*, hartrees), Zero-Point Energies (ZPE, hartrees) and Relative Energies (ΔE, kJ mol^{-1}) for Cu^+ Complexes of Mass 225 and 207, which Result for the loss of One and Two Molecules of Water, Respectively, from Glucose−Cu^+ Complexes

	B3LYP/6-31G*		B3LYP/6-311+G(2df,2p)	
complex	*E*	ZPE	*E*	ΔE
C225a	−2250.81861	0.17070	−2251.13448	470.8
C225b	−2250.91224	0.17043	−2251.23741	199.9
C225c	−2250.90340	0.16667	−2251.22922	211.7
C225d	−2250.88721	0.17091	−2251.20355	290.0
C225e	−2250.92181	0.17066	−2251.24903	169.9
C225f	−2250.80956	0.16969	−2251.12642	489.4
C225 g	−2250.89036	0.16939	−2251.21900	245.5
C225h	−2250.91543	0.17056	−2251.22884	222.7
C225i	−2250.93070	0.17118	−2251.23217	215.5
C225j	−2250.94509	0.17100	−2251.25076	166.3
C225k	−2250.94534	0.17071	−2251.25092	165.1
C225l	−2250.95059	0.17206	−2251.25353	161.7
C225m	−2250.93833	0.17103	−2251.24319	186.2
C225α	−2250.91164	0.16936	−2251.20140	291.7
C225β	−2250.89621	0.16895	−2251.20197	289.1
C225γ	−2250.90585	0.16903	−2251.20385	284.4
C225δ	−2250.93096	0.16991	−2251.21643	253.6
C225ϵ	−2250.97334	0.16715	−2251.26289	124.5
C225ϕ	−2250.95243	0.16589	−2251.24938	156.8
C225η	−2250.94345	0.16961	−2251.23793	196.4
C225λ	−2250.98244	0.16668	−2251.28329	69.7
C225μ	−2251.00363	0.17077	−2251.30421	25.4
C225ν	−2250.99585	0.17046	−2251.29530	47.9
C225π	−2251.00274	0.17017	−2251.30382	24.8
C225θ	−2251.01091	0.17026	−2251.31336	0.0
C225ρ	−2250.99321	0.16888	−2251.28705	65.5
C225σ	−2250.94628	0.17045	−2251.24669	175.5
C225ι	−2250.96628	0.17066	−2251.26384	131.1
C225τ	−2250.94398	0.16892	−2251.24670	171.6
C225ξ	−2250.95501	0.16850	−2251.25862	139.2
C225ζ	−2250.95277	0.16838	−2251.25613	145.4
C225ω	−2250.94831	0.16871	−2251.24765	168.6
C207a	−2174.45282	0.13801	−2174.74078	176.2
C207b	−2174.51874	0.14364	−2174.79923	37.2
C207c	−2174.51555	0.14311	−2174.79172	55.6
C207d	−2174.46960	0.14138	−2174.76080	132.3
C207e	−2174.29274	0.14218	−2174.74692	170.8
C207f	−2174.49989	0.14171	−2174.77552	94.5
C207g	−2174.52166	0.14287	−2174.79133	56.0
C207h	−2174.51621	0.14249	−2174.78574	69.7
C207α	−2174.52803	0.13835	−2174.78841	52.0
C207β	−2174.52609	0.13844	−2174.78751	54.6
C207γ	−2174.56471	0.13947	−2174.80933	0.0
C207δ	−2174.55309	0.13918	−2174.79962	24.7
C207ϵ	−2174.52253	0.13884	−2174.78587	60.0
C207ϕ	−2174.52497	0.13909	−2174.78829	54.3
C207η	−2174.54231	0.13821	−2174.79676	29.8
C207λ	−2174.54297	0.13816	−2174.79745	27.8
C207μ	−2174.50507	0.13998	−2174.76249	124.3
C207ν	−2174.54013	0.14113	−2174.79976	29.4
C207π	−2174.53923	0.14090	−2174.80667	10.7
C207θ	−2174.53740	0.14100	−2174.77803	86.1
C207ρ	−2174.50467	0.14245	−2174.75907	139.6
C207σ	−2174.51694	0.14127	−2174.77905	84.1
C207τ	−2174.52671	0.14108	−2174.78750	61.5
C207ξ	−2174.49997	0.14089	−2174.76492	120.3
C207ζ	−2174.49185	0.14105	−2174.73289	204.8

(c) Structures involving an epoxy group are systematically the less stable ones, whereas those in which a dienic species is form tend to be the most stable ones. Finally, internal hydrogen transfers can lead to species in which a CH_3 group is present

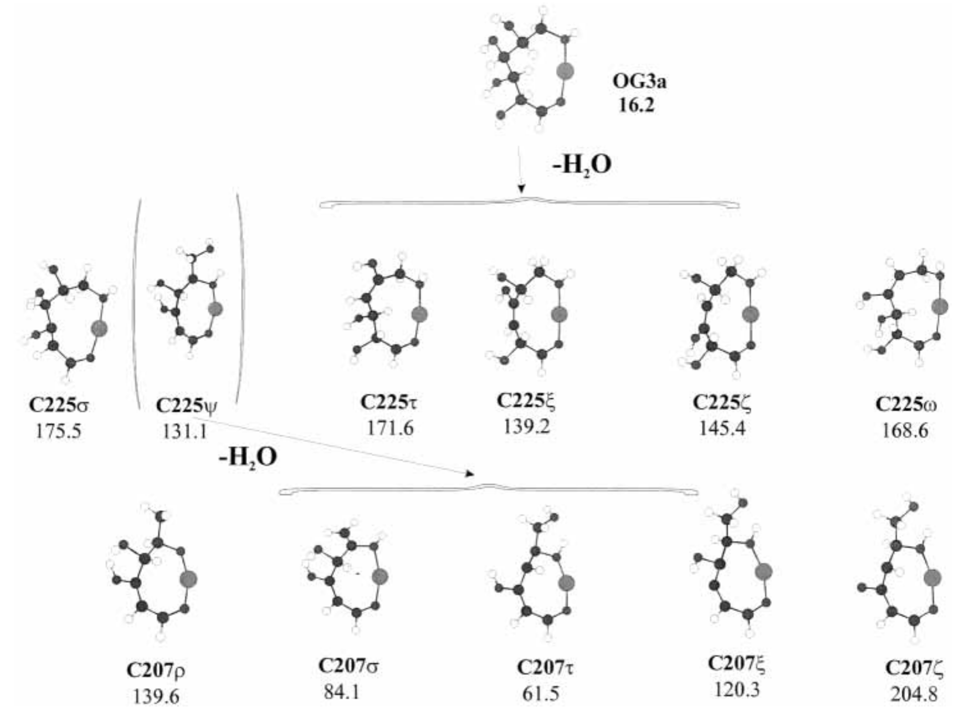


Figure 11. Water-loss mechanisms from structure **OG3b.** Same conventions as in Figure 7.

(such as in **C225**ϵ or **C225**ϕ), and these structures present also a large stability.

(d) Water loss from cyclic structures is always an endothermic process, whereas the same process with an origin in open structures can be exothermic. For instance, the one involving the most stable structures (**OG2a** to give **C225**θ) implies an energy change of −20.6 kJ/mol. Similarly, the processes from **OG1a** to **C225**ϵ or from **OG3a** to **C225**ψ are exothermic by −14.6 and −30.7 kJ/mol, respectively. The second loss of water was found to be, in many cases, also exothermic. For instance, the loss of water leading to the most stable C207 species (**C225**ϵ to **C207**γ) implies an energy change of −41.1 kJ/mol.

(e) The atoms from which the water is lost are very different depending on the initial complex considered. In general, open forms do not lose water from carbons 1 and 2 because the corresponding oxygens are involved in linkages with the Cu^+. A similar situation is found when starting from the tricoordinated complexes of cyclic glucose. These findings are in contrast with the experimental evidence[4] that predicts water loss to come from the anomeric hydroxyl (O1) and the C2 hydrogen. Nevertheless, it has to be considered that the experiments are based in methyl derivatives of glucopyranose, and the presence of the extra methyl group can modify the predicted stabilities of the open forms and should destabilize the tri- and tetracoordinated complexes of glucopyranose. Those experimental findings would be compatible with a loss of water from the most stable Cu^+−glucopyranose complex (β**G3**−**4**). On the other hand, a complete analysis of the site for the loss of water would imply a knowledge of the barriers for two competitive processes: (a) the opening of glucose cycle as a first step followed by a loss of water and (b) the loss of water from cyclic complexes as a first step and a subsequent opening of the remaining cyclic structure. Such study is beyond the objectives of the present work.

Conclusions

The MIKE spectrum of the $[\text{glucose}-\text{Cu}]^+$ complex shows that the loss of a water molecule is the most important spontaneous fragmentation, followed by a second dehydration or the loss of H_2. Under collision conditions, the relative intensity of the MIKE peaks is unchanged. We also can notice that within the time scale of the experiment, fragmentation of a selected $[\text{glucose}-\text{Cu}]^+$ ion produces exclusively Cu^+-containing fragment ions, where the metal ion Cu^+ is never eliminated. This is consistent with both the high binding energy estimated for the $[\text{glucose}-\text{Cu}]^+$ complexes and with the fact that the metal cation is bonded to several basic centers of the sugar moiety yielding bi-, tri-, or tetracoordinated structures.

From the theoretical survey of the glucose−Cu^+ PES we can conclude that the attachment of Cu^+ to the different basic centers of glucose induces nonnegligible bond activation phenomena within the sugar moiety. As a consequence, the cleavage of the C−O linkages of the six-membered ring leads to open complexes which are systematically much more stable than those in which the cyclic structure of the sugar is preserved. Among the open complexes, the most stable ones are those which present an acidic function.

Several pathways for the successive loss of two molecules of water can be envisaged with the origin in the cyclic and the open glucose−Cu^+ complexes. In general, the most stable product ions of mass 225 are those formed by a spontaneous fragmentation of the most stable open structure **OG2a**, although those formed by water loss from species **OG1a** are close in energy. The less stable complexes of mass 225 are those produced by the unimolecular dissociation of cyclic glucose−Cu^+ complexes. Something similar was found as far as the ions of mass 207 are concerned. The least stable ion products are those with the origin in the cyclic glucose−Cu^+ complexes. These significant stability differences reflect the preference of Cu^+ to yield bisligated complexes in which the metal forms almost linear arrangements with two oxygen atoms of the neutral through the participation of sd hybrids. These linear arrangements are particularly favored in the case of open structures but hindered in cases where the six-membered ring of the sugar moiety is preserved. It is important to emphasize that this ability of Cu^+ to yield linear arrangements was already found in previous studies of the gas-phase reactions of this metal cation with different neutrals as guanidine, formamide, and urea. The main difference is that in those cases Cu^+ appeared bisligated to two neutral stable molecules, as water, ammonia, or carbon monoxide, and in the present case, it is bonded to two different functional groups of a unique molecular system.

Although the activation barriers to go from the cyclic $[\text{glucose}-\text{Cu}]^+$ to open structures are relatively high, they are lower than the glucose$-Cu^+$ binding energy, so in principle, they can be overpassed during the reaction favoring the successive losses of water molecules from these open structures. On the other hand, the product ions of masses 225 and 207 so produced are significantly more stable that those obtained by unimolecular fragmentations of the cyclic $[\text{glucose}-\text{Cu}]^+$ complexes. Also importantly, the Cu^+ complexation has a catalytic effect because these activation barriers are sizably lower for $[\text{glucose}-\text{Cu}]^+$ complexes than for the corresponding neutral.

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