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RESEARCH ARTICLE

The Mechanism of 2-Furaldehyde Formation from D-Xylose Dehydration in the Gas Phase. A Tandem Mass Spectrometric Study

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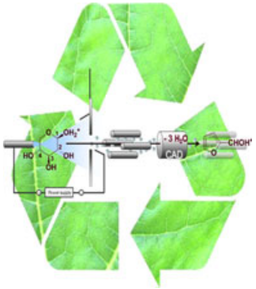

Abstract. The mechanism of reactions occurring in solution can be investigated also in the gas phase by suited mass spectrometric techniques, which allow to highlight fundamental mechanistic features independent of the influence of the medium and to clarifying controversial hypotheses proposed in solution studies. In this work, we report a gas-phase study performed by electrospray triple stage quadrupole mass spectrometry (ESI-TSQ/MS) on the dehydration of D-xylose, leading mainly to the formation of 2-furaldehyde (2-FA). It is generally known in carbohydrate chemistry that the thermal acid catalyzed dehydration of pentoses leads to the formation of 2-FA, but several aspects on the solution-phase mechanism are controversial. Here, gaseous reactant ions corresponding to protonated xylose molecules obtained from ESI of a solution containing D-xylose and ammonium acetate as protonating reagent were allowed to undergo collisionally activated decomposition (CAD) into the triple stage quadrupole analyzer. The product ion mass spectra of protonated xylose are characterized by the presence of ionic intermediates arising from xylose dehydration, which were structurally characterized by their fragmentation patterns. As expected, the xylose triple dehydration leads to the formation of the ion at *m/z* 97, corresponding to protonated 2-FA. On the basis of mass spectrometric evidences, we demonstrated that in the gas phase, the formation of 2-FA involves protonation at the OH group bound to the C1 atom of the sugar, the first ionic intermediate being characterized by a cyclic structure. Finally, energy resolved product ion mass spectra allowed to obtain information on the energetic features of the D-xylose→2-FA conversion.

Key words: Gas phase-reaction, D-xylose dehydration, 2-Furaldehyde, Tandem mass spectrometry, Biomass

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Introduction

Processes allowing the utilization of carbohydrate biomass [1] as a renewable resource have over the time received great attention, carbohydrates from lignocellulosic biomass representing the main fraction of terrestrial biomass feedstock [2].

It is generally known in carbohydrate chemistry that 5-hydroxymethyl furaldehyde (5-HMF) and 2-furaldehyde (2-FA) are the products of the thermal acid catalyzed dehydration of hexoses and pentoses (Scheme 1), respectively [3–5]. These processes represent an important chemical transformation for the production of sustainable energy and useful chemicals from biomass [2–4]. Already 50 y ago, in 1959, the world production of 2-FA ran to the order of 50 000 t per year, ranking it about 67th in annual volume among major organic chemicals [7]. Five years ago, the annual production was about 300 000 t/y [3]. This prompted strong scientific interest and focussed research efforts to investigate the mechanism of pentoses→2-FA conversion [6–17]. The first mechanistic hypothesis on this process dates back to 1932 [6]. Subsequently, Wolfrom et al. [8], on the basis of UV absorption spectra studies, proposed an alternative explanation extended to the pentose→2-FA conversion.

Dedicated to Professor Fulvio Cacace, whose teachings are for us still a source of inspiration and guidance 10 years after his death.

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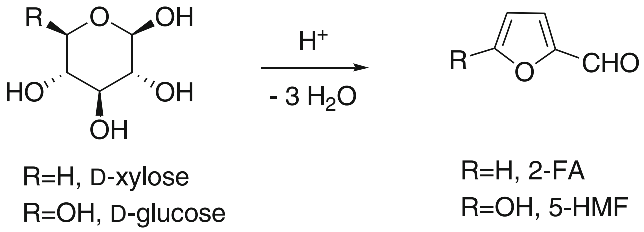


Scheme **1**

At the present, a debate exists in the literature on the mechanism of 2-FA formation from pentoses. Two main degradation pathways have been proposed for the formation of 2-FA from D-xylose: mechanism **I,** consisting of consecutive reactions involving the acyclic form of xylose [7–10] leading to formation of the 1,2-enediol, followed by three dehydration steps (Scheme 2), and the alternative mechanism **II** [11–17], represented by an acid-catalyzed reaction sequence proceeding from the pyranose form of xylose, which leads, after protonation and loss of the first water molecule, to a structure rearranging into the furanose ring (Scheme 3a, b).

Theoretical calculation performed in 2006 by Nimlos et al. identified the latter mechanism (Scheme 3) as the likely mechanism for furfural formation in the gas phase [11]. Antal et al. [13] reported that the cyclic mechanism is the most plausible because a kinetic model based on this hypothesis was found to be consistent with the experimental data.

Recently, the reaction has been the object of further theoretical studies, aimed at evaluating the role of solvation water molecules in the mechanism [14, 15]. Finally, a theoretical investigation reported that glucose dehydration to form HMF occurs via the direct cyclic form, rather than via the open chain one, involving formation of a five-membered ring intermediate and found strong dependence of the energetic profile from the solvent [16, 17]

Still, the formation mechanism of furfural remains an open question as well as that of reaction by-products, such as formaldehyde, formic acid, acetaldehyde, crotonaldehyde, lactic acid, dihydroxyacetone, glyceraldehyde, pyruvaldehyde, acetol, and glycoladehyde [13].

On the other hand, understanding sugar degradation pathways at the molecular level is necessary to increase selectivity, reducing degradation by-product yields, and to optimize catalytic strategies. To the best of our knowledge experimental studies on the D-xylose→2-FA conversion in the gas phase have never been reported.

The present gas-phase study was performed by using mass spectrometric techniques.

Gaseous reactants, namely protonated D-xylose molecules, generated in the ESI source of a triple stage quadrupole (TSQ) and of a quadrupole-time of flight (Q-TOF) mass spectrometers, were mass selected and allowed to undergo collisionally activated dissociation (CAD) to promote the thermodynamically/kinetically hampered dehydration reactions. The ionic intermediates and the final products were structurally characterized by comparison of their fragmentation patterns with those of suitable model ions.

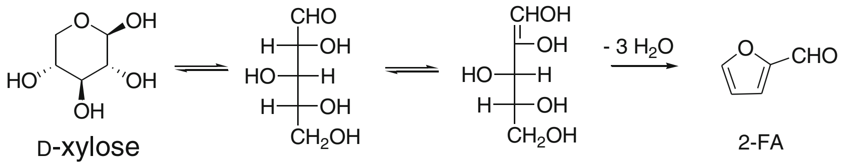
Experimental

Materials

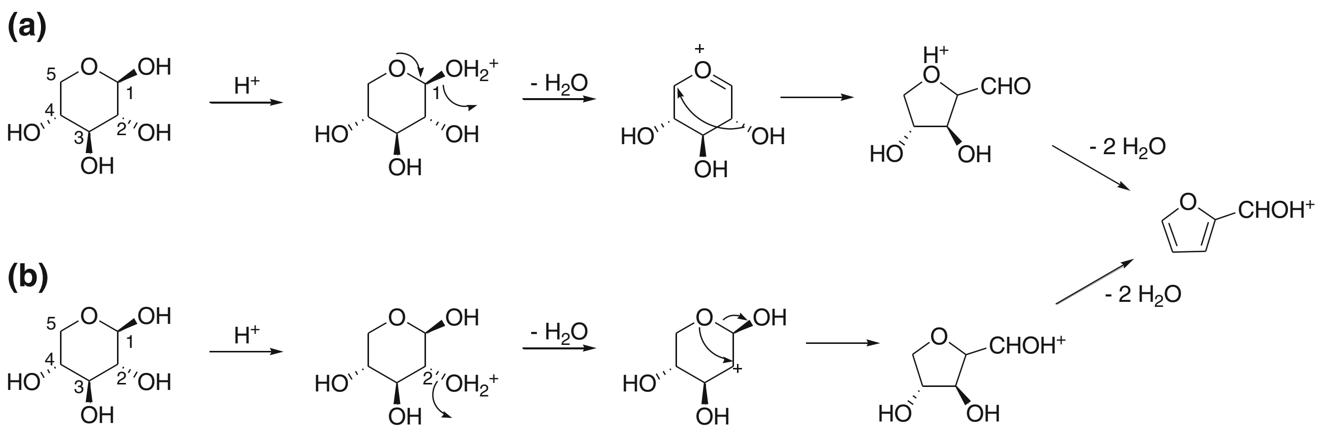
D-xylose, methanol (LC/MS grade), D_2O (99% grade), tetrahydro-2H-pyran-2-ol, tetrahydro-2H-pyran-3-ol, and all others chemicals were purchased from Sigma-Aldrich Ltd., Milano, Italy.

Mass Spectrometry

Electrospray mass spectra were acquired using a Quattro Micro (Micromass, Manchester, UK) triple stage quadrupole instrument operating in the positive ion mode. Nitrogen was used as nebulization and desolvation gas at flow rates of 40 and 300 L/h, respectively. Source and desolvation temperatures were set at 120 and 300 °C. Applied potential on the electrospray capillary and on the cone ranged from 2.6 to 3.2 kV and from 15 to 50 V, respectively, and were optimized for each molecule. Product ion mass spectra were carried out by introducing argon as collision gas into the rf-only quadrupole. The Ar pressure was kept low (~3.0×10^{-3} mbar) to minimize multiple collisions. All displayed mass spectra represent the average of 50 scans of 1 s duration and were performed by direct infusion of 10^{-3} M solutions of purified compounds in methanol/water (0.1% CH_3COONH_4) (1:1, vol/vol) with a 10 μL/min flow rate. Full scan mass spectra were acquired from *m/z* 50 to 1500 in MS and from 20 to the *m/z* ratio of the precursor ion in MS/MS experiments, with a scan time and an interscan time of 0.2 and 0.1 s, respectively. TQ/MS^n spectra were performed by in-source CAD of precursor ions. H/D exchange experiments were performed by dissolving D-xylose in D_2O for about one hour and cleaning the ESI source with D_2O before recording mass spectra. Data acquisition and processing were carried out using the software MassLynx™ ver. 4.0 supplied with the instrument. Exact mass measurements were obtained with a



Scheme **2**



Scheme 3

Micromass ESI Q-TOF Ultima mass spectrometer by using the same experimental conditions described for the Quattro Micro. The energy resolved mass spectra were obtained by using a TSQ700 mass spectrometer from Finnigan Ltd. The energy-resolved product ion mass spectra were recorded using Ar as the target gas at pressures of about 0.1 mTorr and at collision energies ranging from 0 to 40 eV (laboratory frame). An upper limit of 2 eV for the kinetic energy of the reactant ion at nominal collision energy of 0 eV (laboratory frame) and an ion-beam energy spread of about 1 eV can be estimated by using cut-off potentials. Laboratory ion energies (lab) are converted to center-of-mass (CM) energies by using the formula $E_{CM} = E_{LAB}\, m/(m + M)$, where m is the mass of neutral reactant and M is the mass of the ionic reagent. Experimental cross sections, $sigma_{tot}$, were determined by the relation $I_R/It_{ot} = \exp^{(sigma \cdot n\ l)}$ where I_R is the intensity of the transmitted ion beam, I_{tot} is the total ion intensities, n is the number density of the neutral gas and l is the effective gas cell length. Individual product cross sections, $sigma_p$, (σ_p) were calculated by $\sigma_p = sigma_{tot}(I_p/I_{ptot})$ where I_p represents the intensity of the product ion and I_{ptot} the total product ion intensities.

Results and Discussion

The Gaseous Reactant Ions

In solution, the dehydration of pentose sugars is usually carried out in aqueous media with an added mineral acid. Typical conditions that offer high yields of 2-FA from D-xylose include temperatures ranging from 160 to 280 °C, sulphuric acid concentrations of 0.003 to 0.4 M, and reaction times of few min or less [3]. Other products were found to accompany 2-FA formation, such as glycolaldehyde (GA) (MW 60), formic acid (MW 45), acetaldehyde (ACTH) (MW 44), pyruvaldehyde (PYR) (MW 72), etc. [13].

In Figure 1 we report the mass scan of a 1.0×10^{-3} M D-xylose solution in H_2O (0.1% ammonium acetate)/CH_3OH (1:1, vol/vol). The addition of CH_3COONH_4 is usually employed to generate protonated adducts of the analyte of interest [18]. In agreement with previously reported evidence, very low intensities of the gaseous ionic reactants, protonated xylose $[M\cdots H]^+$ ions at *m/z* 151, were detected. In fact it was previously observed that in the positive ion mode, the mass spectra of pentose and hexose monosaccharides are dominated by Na^+-bound molecules, whereas protonated molecules are absent or detected at very low abundances [19, 20].

High intensities of the ions at *m/z* 173 and 168, corresponding to the D-xylose sodium and ammonium adducts, $[M\cdots Na]^+$ and $[M\cdots NH_4]^+$, respectively, are displayed in the ESI spectrum of Figure 2.

The ESI spectrum also shows the ion at *m/z* 133, 115, and 97 corresponding to the consecutive losses of three water molecules from protonated D-xylose.

The ion at *m/z* 150 and 132 were found to be present in the product ion mass spectrum of the ion at *m/z* 168 (the ammonium adduct of D-xylose). This evidence demonstrated that these ions are formed from the consecutive losses of a water molecule from the ion at *m/z* 168, and do not arise from the protonated xylose decomposition. This result was described in the text.

Other minor by-products, already known to be formed in solution [13], such as protonated pyruvaldehyde $(PYR\cdots H^+)$ at *m/z* 73 and protonated glycolaldehyde $(GA\cdots H^+)$ at *m/z* 61 were also detected. The mass attribution of all these ionic species was confirmed by exact mass measurements carried out with the ESI/Q-TOF mass spectrometer. To verify the hypothesis that the inability to detect protonated xylose (*m/z* 151) could depend on the protonation site of the sugar, the ESI mass spectra of two model compounds, tetrahydro-2H-pyran-2-ol and tetrahydro-2H-pyran-3-ol (Figure 2), were investigated. In fact, in accordance with the mechanism proposed by Nimlos et al. in their ab initio MD simulation study [11], protonation of the OH group at the C1 position is followed by the loss of a water molecule through a process assisted by the sugar hemiacetalic oxygen atom that is characterized by a very low energy barrier (4 kcal mol^{-1}). The ESI mass spectra of tetrahydro-2H-pyran-2-ol and tetrahydro-2H-pyran-3-ol are shown in Figure 2a and b.

It is evident that only in the ESI mass spectrum of tetrahydro-2H-pyran-3-ol the $[M\cdots H]^+$ ion, at *m/z* 103, is

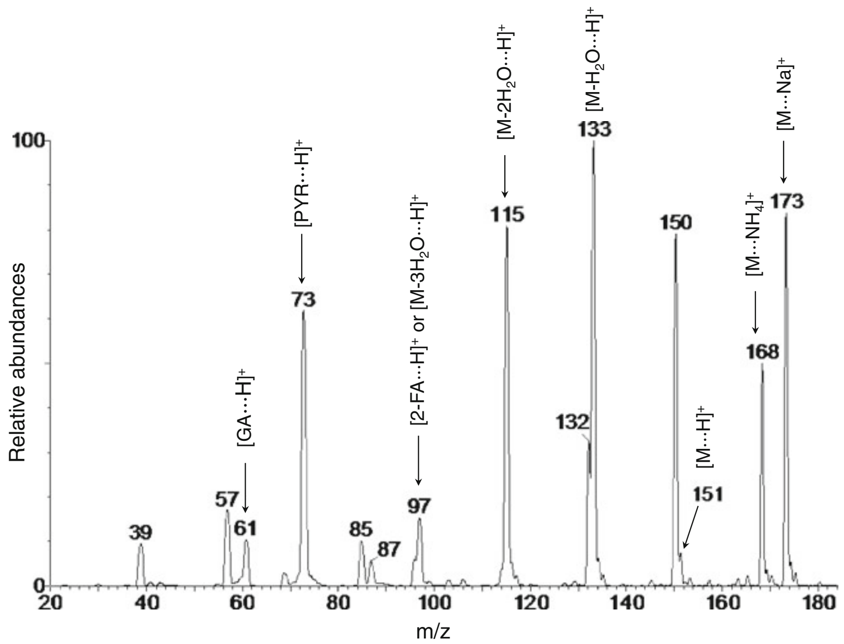


Figure 1. ESI mass scan of a $1 \cdot 10^{-3}$ M solution of D-xylose in H_2O (0.1% CH_3COONH_4)/MeOH (1:1, vol/vol)

present, likely surviving protonation at the most basic site of the molecule [11] (i.e., the alcoholic oxygen atom at the C3 position) . On the contrary, this ion is not present in the ESI mass spectrum of tetrahydro-2H-pyran-2-ol, thus confirming that the OH group at the C2 position, once protonated, undergoes the easy loss of a water molecule assisted by the hemiacetalic oxygen atom, as depicted in Scheme 3. It is likely that this could account for the low intensities of the ion at *m/z* 151 in the ESI mass spectrum of D-xylose.

The Gaseous Ionic Intermediates

In the CAD experiments [21, 22] following the collision between a translationally excited ion and a target atom, a fraction of the ion translation energy is converted into internal energy, exciting the reactant ion and allowing it to undergo unimolecular decomposition or/and endothermic and/or kinetically hampered reactions [22, 23]. The inability to detect high intensities of the ion at *m/z* 151 represents experimental evidence in favor of decomposition channels characterized by very low energy barriers. In Figure 3, we report the product ion mass spectrum of the ion at *m/z* 151 generated under very mild ionization conditions.

As expected, the CAD of the ion at *m/z* 151 leads to the ionic product fragments arising from the loss of one and two water molecules, namely the ions at *m/z* 133 and 115, respectively.

The product ion mass spectrum shown in Figure 3 could be considered as the gas-phase analogue of the solution thermal dehydration of D-xylose in acidic conditions.

In addition, it should be noted that the presence of the ions at *m/z* 133 and 115 still appearing in the mass scan of D-xylose speaks in favor of very low dissociation energy barriers.

In order to consider the possibility of a dehydration process involving the D-xylose sodium adduct, the product ion mass spectrum of the ion at *m/z* 173 (the D-xylose sodium adduct) was performed but it did not show any fragmentation consisting of water losses. Because the

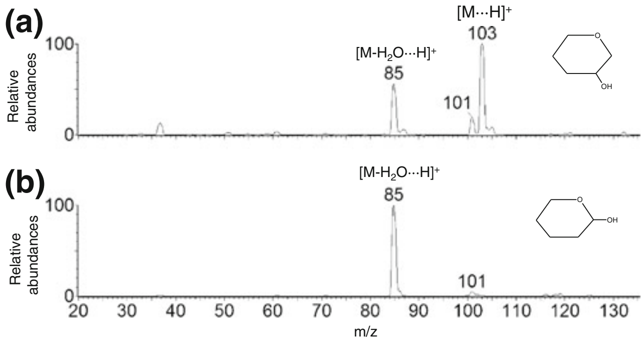


Figure 2. ESI mass scan of **(a)** tetrahydro-2H-pyran-3-ol and **(b)** tetrahydro-2H-pyran-2-ol

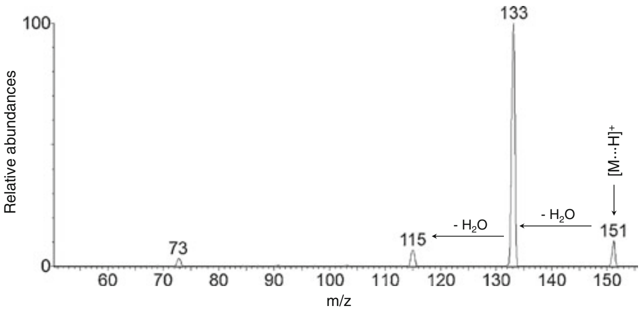


Figure 3. Product ion mass spectrum of protonated D-xylose at *m/z* 151

product ion mass spectrum is dominated by the presence of the Na^+ ion (at *m/z* 23) and no more informative fragments are detected, we do not show this spectrum figure in the paper.

For a deeper rationalization of the reaction mechanism, it is of fundamental importance to investigate the structure of the observed ionic intermediates.

The Ion at m/z 133

The structure of the ion at *m/z* 133 is of fundamental importance for the understanding of the gas-phase pentose dehydration mechanism. As shown in Scheme 4, at least in principle and according to the mechanisms previously reported, two possible structures can be hypothesized for the ion at *m/z* 133: an open chain (**I**) or a cyclic structure (**II**).

The product ion mass spectrum of the ion at *m/z* 133 (Figure 4) shows, besides the ion at *m/z* 115 and 97 arising from its consecutive dehydrations, an ion at *m/z* 73 representing the main fragmentation channel. This ion corresponds to the loss of 60 Da. Interestingly, such fragmentation, a typical cross ring cleavage of pentose sugars [19], speaks in favor of a cyclic structure for the ion at *m/z* 133 since, as depicted in Scheme 5, its formation would not be expected by an open chain intermediate.

A further support to such evidence of the cyclic nature of the ion at *m/z* 133 can be drawn from its fragmentation pattern after H/D isotopic exchange in solution. In accordance with the presence of three OH groups in the molecule, the m/z ratio of the precursor ion shifts from 133 to 136. As evident in Figure 5b, reporting the product ion mass spectrum of the ions at m/z 136, the *m/z* ratio of the fragment ion at *m/z* 73 shifts to 75 consistently with the presence of two deuterium atoms, thus supporting the fragmentation pattern shown in Scheme 5.

The Gaseous Ionic Product: Protonated 2-Furaldehyde

The loss of three water molecule from protonated D-xylose leads to the formation of the ion at *m/z* 97, which at least in principle should correspond to protonated 2-furaldehyde.

2-Furaldehyde, also known as furfural (Scheme 1), is a heterocyclic aldehyde formed from the thermal dehydration of pentose monosaccharides [3]. This molecule can be considered as an important sustainable intermediate for the preparation of a great variety of chemicals, pharmaceuticals, and furan-based polymers. The various production routes for lignocellulosic biofuels from 2-furaldehyde were recently reviewed [2]. A joint mass spectrometric and theoretical study on the gas-phase basicity of 2-FA was recently reported [24].

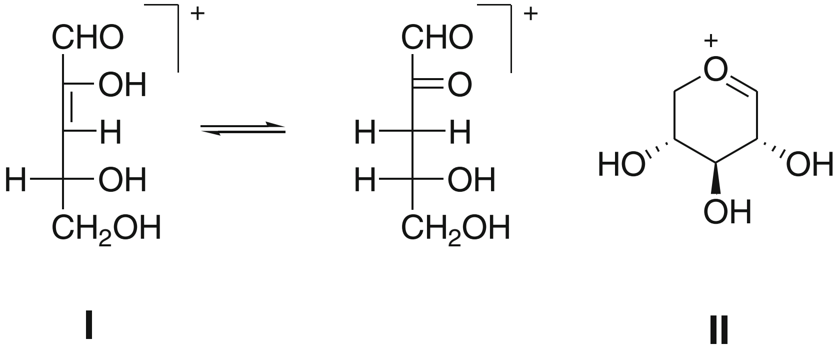
To structurally characterize the ions at *m/z* 97, the product ion mass spectrum of these ions, generated by in-source CAD, was compared with the product ion mass spectrum of a model ion at *m/z* 97, obtained from protonation of commercial 2-FA.The product ion mass spectra (data not shown) are nearly superimposable, thus demonstrating that in the gas phase, the dehydration of protonated xylose actually leads to the formation of protonated 2-furaldehyde.

H/D Solution Exchanges

Further evidences on the gas-phase mechanism of xylose dehydration, leading to the formation of 2-furaldehyde, were obtained from H/D isotope solution exchange experiments performed by dissolving the sugar in D_2O. The product ion mass spectrum of the precursor ion at *m/z* 156, corresponding to deuterated D-xylose(d_4) arising from H/D exchanges of all the acidic hydrogen atoms in the sugar, namely the OH groups, is reported in Figure 5a.

The product ion mass spectrum is dominated by the presence of the ion at *m/z* 136, suggesting the presence of three deuterium atoms in the ion at *m/z* 133 and demonstrating that the first dehydration step of deuteronated D-xylose(d_4) involves a loss of a D_2O molecule from the sugar.

Furthermore, in Figure 5b we reported the product ion mass spectrum of the ion at *m/z* 136 generated by in-source CAD after H/D solution exchange; the spectrum shows the ions at *m/z* 116 and 117 corresponding to the fragment ion at *m/z* 115 observed in the product ion mass spectrum of the ion at *m/z* 133 (Figure 4). The mass shift indicates the



Scheme 4

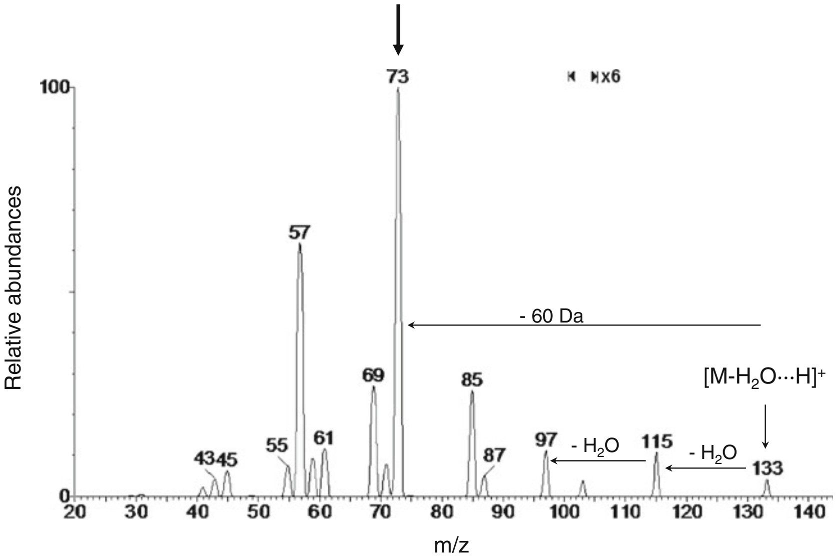
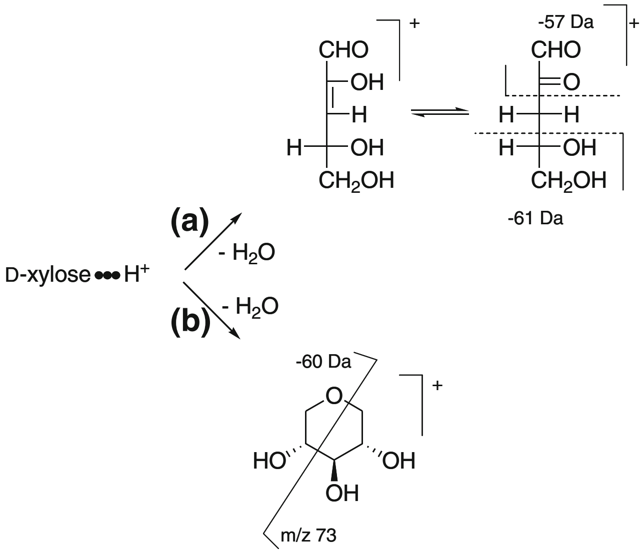


Figure 4. Product ion mass spectrum of the ion at *m/z* 133 generated in the ESI source from a D-xylose solution in CH_3OH/H_2O (ammonium acetate 0.1%)

presence of one/two deuterium atoms. This evidence clearly indicates that the second step of D-xylose dehydration involves the loss of a D_2O or an HDO molecule. In the latter case, the dehydration step should involve the shift of a non-acidic hydrogen atom, likely a proton bound to a carbon atom of the pentose ring, to an OH group.

Finally, as shown in the product ion mass spectrum of the ion at *m/z* 116 (Figure 5c), this species decomposes, giving the fragment ions at *m/z* 97 and 98, suggesting that the third dehydration step of the gas-phase D-xylose dehydration mechanism involves the loss of both a H_2O and a HDO moiety and, indeed, it could occur through a mechanism analogous to that observed for the previous HDO loss.



Scheme **5**

In summary, in Scheme 6 we reassume the main results of H/D isotopic solution experiments.

Energy Resolved Mass Spectra (ERMS)

Information on the energetic features of the mechanism of the D-xylose→2-FA conversion can be obtained from the Energy Resolved Mass Spectra. In fact, triple stage quadrupole energy-resolved product ion mass spectra of the ions at *m/z* 133 and 115, recorded at collision energies ranging from 0 to 4 eV (center-of-mass), allowed the relative water loss dissociation energies to be investigated. Unfortunately, the low intensities of the precursor ion at *m/z* 151 and its very low stability (the parent ion disappears at very low dissociation energy) precludes the acquisition of useful energy resolved mass spectra and indeed of the relative energy information on the first dehydration step.

In Figure 6a, the profile of the collision cross section relative to the loss of the second water molecule from

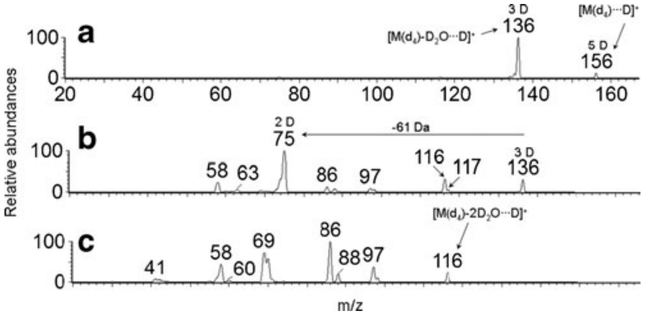
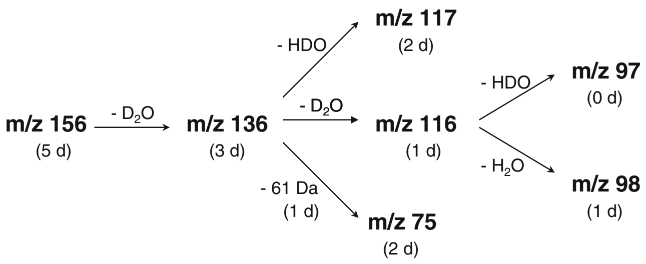


Figure 5. Product ion mass spectrum of the ion at *m/z* **(a)** 156, **(b)** 136, **(c)** 116 generated in the ESI source from D-xylose after H/D solution isotopic exchange



Scheme 6

the ion at *m/z* 133 is reported as a function of the increasing collision energy, whereas in Figure 6b the same plot is reported for the third water loss from the ions at *m/z* 115.

The ion at *m/z* 133 derived from D-xylose dehydration loses a water molecule in a process that is characterized by a very low activation barrier, since no threshold energy can be derived from its energy resolved mass spectrum (Figure 6a). Conversely, the loss of the water molecule from the ions at *m/z* 115 to give the ion at *m/z* 97 is characterized by a threshold energy of about 1–1.2 eV. Indeed, the energy resolved product ion mass spectra demonstrate that increasing energy barriers characterize the D-xylose→2-FA conversion. In particular, the loss of the first and second water molecules seem to involve very low activation energies.

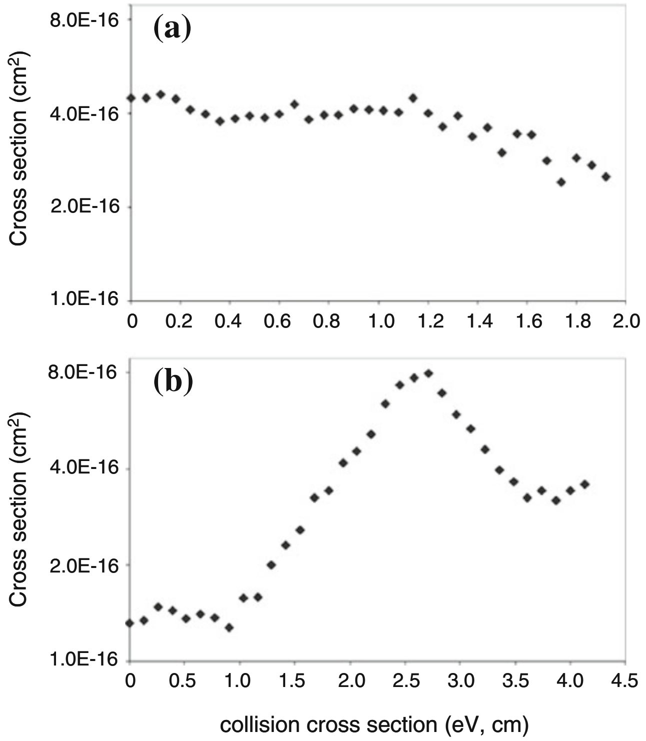


Figure 6. Triple stage quadrupole energy resolved product ion mass spectra of the ions **(a)** at *m/z* 133 and **(b)** at *m/z* 115, (only the fragmentation corresponding to the loss of a water molecule is shown)

Conclusions

The gas phase dehydration reactions of D-xylose leading to protonated 2-furaldehyde was investigated by mass spectrometric techniques. The experimental results allow drawing some conclusion about the gas phase acid D-xylose→2-FA conversion:

1. The formation mechanism of 2-FA involves protonation on the OH group bound to the C1 position of the sugar.
2. The ionic intermediate arising from the loss of the first water molecule is characterized by a cyclic structure.
3. The energy resolved product ion mass spectra allow obtaining information on the energetic behavior of the D-xylose→2-FA conversion.

In conclusions, our experimental results do not find a complete rationalization in the theoretical mechanistic investigation previously reported [11].

In fact, the experimental findings support a mechanism where the gas-phase D-xylose→2-FA conversion proceeds through the protonation at the OH group bound to the C1 position of the sugar ring. The resulting ionic intermediate keeps the cyclic structure and loses the second water molecule in a low barrier process.

From ERMS evidences no high energy barriers for any isomerization process are observed before the second water loss, in disagreement with the energy barrier found by Nimlos et al. [11] for the formation of a furanosic ring from C1-OH protonation.

Finally, the mechanistic information from H/D solution exchange experiments suggests that elimination of the second water molecule (D_2O or HDO) should predominantly occur at the expense of an OH group pre-existing in the sugar ring and of a hydrogen atom bound either to the adjacent OH group, or to a carbon atom.

On the basis of the gas-phase reaction features previously described, we hope that our mass spectrometric results may stimulate a new theoretical investigation on the mechanism of D- xylose dehydration in the gas phase, linking the 3a and 3b routes postulated by Nimlos et al. [11], thus bridging the species formed from the first dehydration step arising from the C1-OH protonation to the furanose ring intermediate of 3b route through a low barrier process.

The results presented in this study offer the first experimental picture on the energetics and the mechanism of xylose dehydration in the gas phase, and could provide a benchmark for enhanced understanding of the mechanisms and factors controlling these processes in solution. Nevertheless, theoretical calculations demonstrated that barrier for sugar reactions are largely solvent-dependent. Indeed, the direct extension of our results to the solution phase should consider this influence.

Acknowledgments

ESI-MS spectra were obtained using a LC-TQ MS instrument of the CRdC 'Analisi e monitoraggio del rischio ambientale', AMRA (P.O.R. 2000–2006, misura 3.16).

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