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The Mechanism of Nitric Acid Degradation of the C-glycoside Aloin to Aloe-emodin

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Abstract Although the majority of natural glycosides are O-glycosides, there are many examples of C- glycosides. Since in these glycosides the aglycone and the sugar are linked by a C-C bond they cannot be cleaved by acid hydrolysis. So, various biochemical procedures using enzymes or bacteria have been described for this purpose. However, these methods are troublesome and time consuming. A chemical degradation using nitric acid has been informed in a U.S. Patent, but there is no theoretical approach to this procedure. In this communication we provide a sustained reaction mechanism for this hydrolytic and oxidative degradation. The electron flow for each step is given and also an explanation of why simple hydrolysis cannot work, pointing out at which step the reaction comes to a stop.

Keywords Aloe-emodin, Aloin, C-glycosides, Oxidative degradation, Reaction mechanisms, Reactive intermediates

1. Introduction

Most of the plant glycosides are O-glycosides, however there are many examples of C-glycosides. The structures of fifteen naturally occurring C-glycosides are displayed in a recent article [1].

Due to the firm C-C bond between sugar moieties and aglycones, C-glycosides cannot be deglycosylated by traditional hydrolysis.

An alternative for this purpose is the use of biological chemistry. For instance, a bacterial type capable of deglycosylating some C-glycosides has been just reported [2].

However, these methods are time consuming and imply a different scientific discipline.

A chemical degradation of a C-glycoside has been described in a U.S. Patent [3]. Of course it deals only with the experimental procedure. It employs nitric acid and ethyleneglycol as solvent.

In this communication we provide the reaction mechanism of this hydrolytic and oxidative cleavage, and explain also at what stage ordinary hydrolysis stops and why. This paper is a follow-up of our studies on chemical reaction mechanisms [4-7].

2. Antecedents

Some reactions related with the matter of this paper are commented next.

Nitric acid is a versatile acid. It can be part of the final product as in the reaction with polyalcohols to form organic-inorganic esters. These mixed esters are interesting due to their very different dual properties. For instance, glyceryltrinitrate (nitroglycerin) is the basic explosive of dynamite but this ester can be used for *angina pectoris* management [8,9].

Aromatic nitration, a well known reaction, is enhanced by phenols.

Other use of nitric acid is as oxidant in Carbohydrate Chemistry. The aldaric acids, α,ω-dicarboxylic acids, are obtained from open-chain sugars oxidized by nitric acid. Saccharic acid (glucaric acid) has been prepared this way [10]. The oxidation of selected alcohols and ketones by nitric acid has been informed [11]. More recently, the oxidation of aliphatic alcohols and diols to carboxylic acids by means of nitric acid has been carried out in Russia [12].

There is an interesting communication on modifications in the nitric acid oxidation of D-glucose to D-glucaric acid [13].

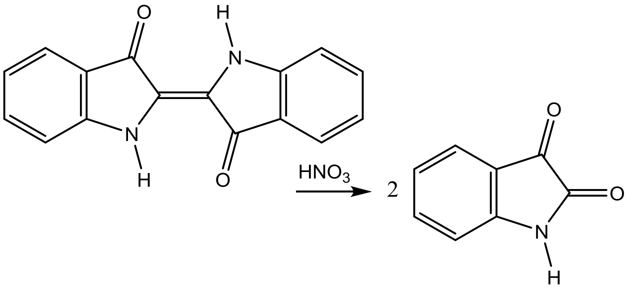

Figure 1. Cleavage of indigo blue by nitric acid

A third class of reactivity observed with nitric acid is

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oxidative degradation and this chemical deportment is important in the present study, as we will see.

An example of this is the oxidative degradation of indigo blue to isatin, Figure 1, [14]. In that communication we gave the mechanism of this reaction.

There is a U.S. Patent assigned to a Swiss Laboratory that deals on the transformation of aloin, a C-glycoside, to aloe-emodin, a trihydroxyanthraquinone, Figure 2.

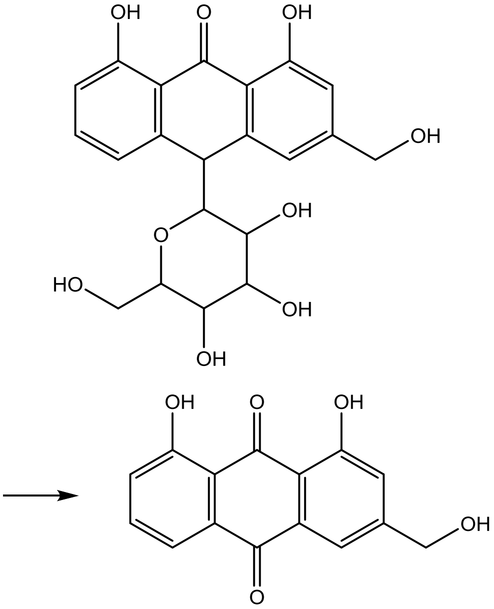

Figure 2. Obtention of aloe-emodin from aloin

Since the Patent is devoted entirely to the preparative procedure, we provide in this communication the reaction mechanism of this interesting degradation since it is well known that C-glycosides are not hydrolysed by common methods.

The main anthraquinone derivative of *Aloe's* latex is aloin. This is a mixture of two diastereomers, termed aloin A and aloin B, Figures 3 and 4.

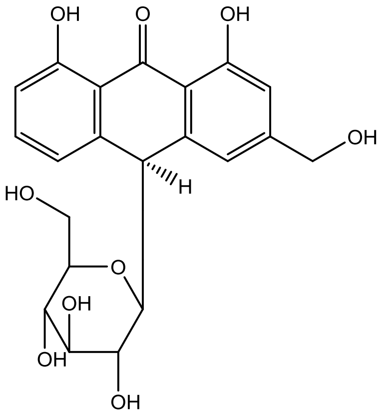

Figure 3. Aloin A structure

Aloin A, also called barbaloin, is the major anthrone C-glycoside in *Aloe's* latex, [15].

When oxidized by nitric acid, aloin yields an oxidized aglycone, aloe-emodin, 1,8-dihydroxy-3-hydroxymethyl-anthraquinone.

Besides the interest of a C-glycoside splitting, it must be noted that the primary alcohol was not oxidized nor nitric esters were obtained as final products. Neither aromatic nitration was observed. All this will be treated in the next section.

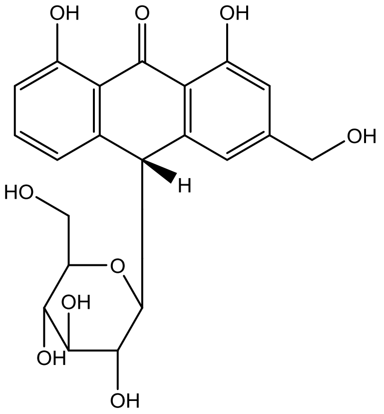

Figure 4. Aloin B structure

3. Discussion

With aloin, none of the possible reactions with nitric acid took place, excepting degradative oxidation. This is due to different or especial reaction conditions. For instance, nitric ester preparation requires both concentrated and fuming nitric acids.

In the case of aloin, a phenolic compound, aromatic nitration results interesting. Within the Patent reaction conditions there is not nuclear substitution, notwithstanding that it is known that the nitration of the phenols takes place readily [16]. This can be explained due to phenolic hydrogen bonding with the oxygen of anthraquinone. However, in a more drastic reaction aloetic acid is obtained, a tetranitro derivative [17-19], Figure 5.

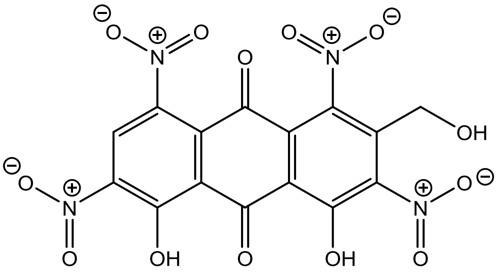

Figure 5.
4,5-Dihydroxy-2-hydroxymethyl-1,3,6,8-tetranitroanthraquinone
(Aloetic acid)

Neither the hydroxymethyl group in aloin is oxidized. It must be taken into account that the solvent used in the Patent is ethyleneglycol and this compound doesn't react either in the reaction conditions, moreover it is a competitor with the hydroxymethyl group in aloin.

But nitric acid can form not only aloetic acid; chrysammic acid is obtained too, the tetranitro derivative in which the hydroxymethyl group is missing. This can be explained by oxidation to the acid and decarboxylation.

Now let's see the reaction reported in the Patent, the C-glycoside cleavage.

Being that the other possible reactions with nitric acid didn't take place then acid hydrolysis must be the starting point of the C-glycoside cleavage.

Since we are dealing with a glucofuranoside, the route of glucose to 5-hydroxymethylfurfural (HMF) was reminded [20,21].

In the case of aloin the C-glycoside has not anomeric carbon, that is, the hemiketal hydroxyl is missing. But in the transformation of glucose to HMF, reaction begins by protonation of O-2, notwithstanding the presence of the hydroxy group at C-1.

Thus reaction at O-2, with water elimination and generation of a carbocation, provokes a ring contraction by oxygen assistance. This step is also present in the reaction of D-xylopyranose to furfural [22], Figure 6.

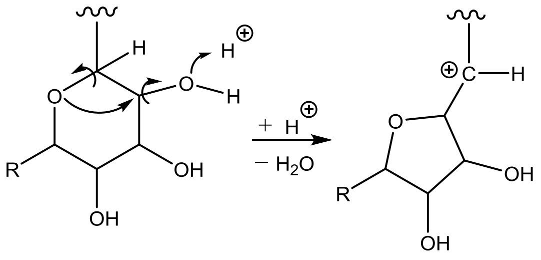

Figure 6. Dehydration of the glucopyranose

Of course in both cases the next step is different due to structural differences, [23].

At this stage two routes can follow: in the absence or in the presence of nitric acid.

Using non oxidative acids, such as hydrochloric or sulphuric acids, a substituted exomethlylene derivative must be formed. Thus, no splitting is possible by simple hydrolysis. Figures 7 and 8.

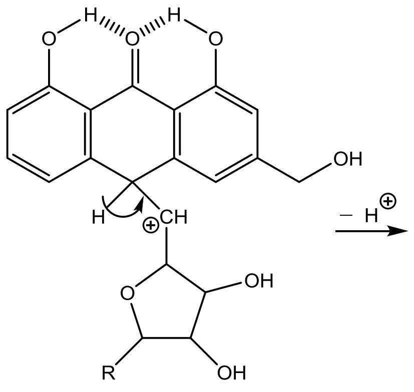

Figure 7. Neutralization of the carbonium ion in absence of nitric acid

On the other hand, if a nitrate ion combines with the carbocation, yielding an organic nitrate, oxidation and the desired C-C fission can occur as is shown in Figure 9.

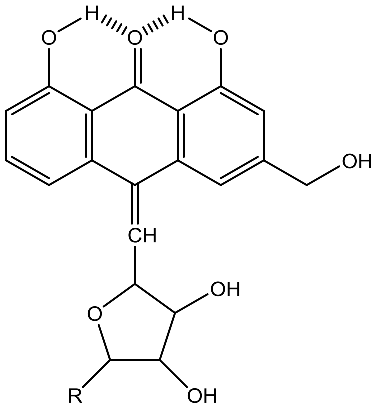

Figure 8. Product that impedes C-glycoside fragmentation

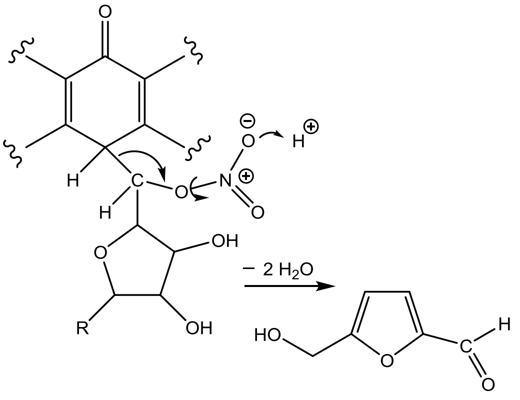

Figure 9. Oxido-degradation of the C-glycoside

Protonation at the negative oxygen in the nitro group produces a non compensated positive charge at nitrogen. Then, nitrous acid is eliminated leaving positive charged oxygen that provokes C-C fission. This rupture is possible since the intervening annular carbon atom is sp^3.

Neutralization of the carbocation in the ring can be achieved by reaction with water (65% HNO_3 was used) affording a trisubstituted oxanthrone, Figure 10.

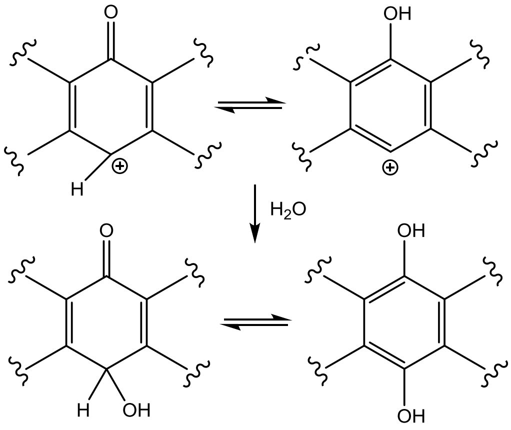

Figure 10. Formation of an oxanthrone derivative

However, since an anthraquinone derivative is obtained, a nitrate must neutralize again the positive charge and a second oxido-reduction step must occur, with formation of nitrous acid, Figure 11.

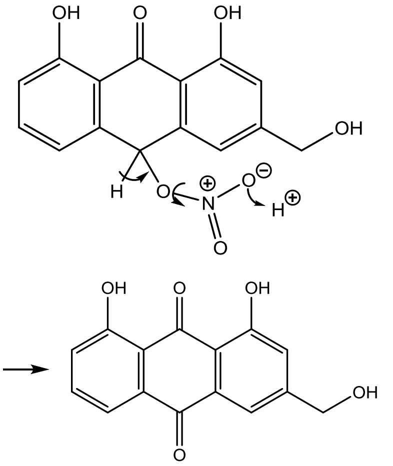

Figure 11. Obtention of aloe-emodin by a second redox reaction

This way aloe-emodin is formed from aloin by means of nitric acid degradative oxidation.

4. Conclusions

The O-glycosides can be hydrolysed but the C-glycosides are resistant to hydrolysis due to their C-C bond between aglycone and sugar.

Since there are many naturally occurring C-glycosides, the obtention of these aglycones is very important because it simplifies considerably the chemical work for structural elucidation. Besides, they are preferable for conservation during storage.

A U.S. Patent assigned to a Swiss Laboratory describes a method for the degradation of aloin, a C-glycoside, by means of nitric acid in ethlyleneglycol as solvent.

Since there is no reaction mechanism for this oxidative degradation, we provide in this communication the pertinent theoretical explanation.

The advanced mechanism is based on recent studies in Carbohydrate Chemistry. These results were applied to the pyranose structure in aloin, and the first part of the process was solved. This hydrolytic beginning yielded a key reactive intermediate.

Then, there are two oxido reduction steps due to the action of the nitric acid. It is in the first one that the C-C fission occurs, the degradative oxidation. In the second redox reaction the anthraquinone derivative is obtained (aloe-emodin).

Thus, the electron flow from aloin to aloe-emodin has been given step by step.

An explanation of why simple hydrolysis doesn't work has been supplied.

REFERENCES

[1] G. Grynkiewicz, “From plant metabolites to emergence of privileged C-glycosyl scaffolds comprising useful synthetic glycoconjugates”, Integrative Food, Nutrition and Metabolism (IFNM), 5, August 2018.

[2] Sh. Zheng, D. Geng, Sh. Liu, Q. Wang, S. Liu, and R. Wang, “A newly isolated human intestinal bacterium strain capable of deglycosylating flavone C-glycosides and its functional properties”, Microbiol. Cell Factories, 18, article no. 94, 2019.

[3] S. Carlino, and G. Di Napoli, “Process for preparing aloe-emodin”, U.S. Patent 7 453 004, Nov. 11, 2005.

[4] F. Sánchez-Viesca, and R. Gómez, “On the mechanism of the Froehde reaction”, World J. Org. Chem., 7(1), 1-4, 2019.

[5] F. Sánchez-Viesca, and R. Gómez, “The chemistry of the Folin test for uric acid”, Am. J. Chem., 9(3), 91-94, 2019.

[6] F. Sánchez-Viesca, M. Berros, and R. Gómez, “A complete and sustained Clemmensen reduction mechanism”, Am. J. Chem., 8(1), 8-12, 2018.

[7] F. Sánchez-Viesca, and R. Gómez, “Reactivities involved in the regioselectivity of osazone formation”, World J. Org. Chem., 5(1), 11-6, 2017.

[8] F. Giral, and C. A. Rojahn, Productos Químicos y Farmacéuticos, Mexico City: Atlante, 1956, vol. 1, pp 327-329.

[9] Drugs and Supplements, Trinitrin. Online, Access with the title. Last login, Dec. 12, 2019.

[10] C. L. Mehltretter, and C. E. Rist, “Sugar oxidation, saccharic and oxalic acids by the nitric acid oxidation of dextrose”, J. Agric. Food Chem., 1(12), 779-783, 1953.

[11] K. Field, J.P. Shields, J. M. Standard, C. K. Ash, D. J. Moch, and K. E. Kolb, “The nitric acid oxidation of selected alcohols and ketones”, J.Chem. Ed., 62(7), 637-638, 1985.

[12] N.Svetlakov, V. Nikitin, and E. Nicolaeva, “Oxidation with nitric acid of aliphatic alcohols and diols to carboxylic acids”, Russ. J. Org. Chem., 43(5), 773-774, 2007.

[13] T. N. Smith, K. Hash, C. L. Davey, H. Mills, H. Williams, and D. E. Kiely, “Modifications in the nitric acid oxidation of D-glucose”, Carbohydr. Res., 350, 6-13, 2012.

[14] F. Sánchez-Viesca, and R. Gómez, “On the mechanism of indirubin formation in the Baeyer-Emmerling synthesis”, Am. J. Chem., 8(4), 85-89, 2018.

[15] M. Fouillaud, Y. Caro, M. Venkatachalam, I. Grondin, and L. Dufoseé, Anthraquinones, Online, access with the title. Last login, Dec. 12, 2019.

[16] W. J. Hickinbottom, Reactions of Organic Compounds, 3rd. ed., London, UK: Longman, 1962, p. 149.

[17] U. S. National Library of Medicine, National Center for Biotechnology Information, PubChem CID 5464178, Aloetic acid.

[18] R. Rajeswari, M Umadevi, C. Sh. Rahale, R. Pushpa, S. Selvavenkadesh, K. P. S. Kumar, and D. Bhowmik, “Aloe vera, the miracle plant its medicinal and traditional uses in India”, J. Pharmacog. & Phytochem., 1(4), 118-124, 2012.

[19] S. Sharma, “Chemical constitution, health benefits and side effects of Aloe Vera”, Indian J. Res., 4(6), 9-10, 2015.

[20] R. S. Assary, T. Kim, J. J. Low, J. Greeley, and L. A. Curtiss, “Glucose and fructose to platform chemicals: understanding the thermodynamic landscapes of acid catalyzed reactions using high-level ab initio methods”, Phys. Chem. Chem. Phys., 14, 16603-16611, 2012.

[21] X. Lin, Y. Qu, Y. Xi, D. L. Phillips, and Ch. Liu, “The first dehydration and the competing reaction pathways of glucose homogeneously and heterogeneously catalyzed by acids”, Phys. Chem. Chem. Phys., 15,2967-2982, 2013.

[22] J. B. Binder, J. J. Blank, A. V. Cefali, and R. T. Raines, ”Synthesis of furfural from xylose and xylan”, Chem. Sus. Chem., 3(11), 1268-1272, 2010.

[23] F. Sánchez-Viesca, and R. Gómez, “Reactivities involved in the Seliwanoff Reaction”, Modern Chemistry, 6(1), 1-5, 2018.