Indian Journal of Advances in Chemical Science

Article

On the Mechanism of Uric Acid Oxidation with Lead Dioxide and with Alkaline Hydrogen Peroxide

F. Sánchez-Viesca*, R. Gómez

Department of Organic Chemistry, Faculty of Chemistry, National Autonomous University of Mexico, Mexico City (CDMX), Mexico

ABSTRACT

The metabolic pathways of uric acid have been studied in biological chemistry (enzymatic reactions). However, the course of some reported chemical reactions is unknown. In this communication, we provide the route of two independent oxidations of uric acid, with different reagents and reaction media. The electron flow is given, step by step, until the final product: allantoin. The intermediate reactions are fully commented.

Key words: Allantoin, Epoxidation, Nitrene, Push-pull effects, Ring closure and opening.

1. INTRODUCTION

The importance of uric acid is shown by the many papers devoted to the metabolic routes related to the formation and degradation of this compound. In the early papers, there are chemical reactions on uric acid oxidation.

Although the end products are known, the reaction course is unknown. In this communication, we provide the reaction mechanism of uric acid oxidation with lead dioxide in slightly acidic medium and also the oxidation with alkaline hydrogen peroxide.

This study is a follow-up of our papers on reaction mechanisms [1-5].

2. ANTECEDENTS

The mechanism of oxidation reactions is many times unknown. Although lead dioxide has been used as oxidizer in several transformations [6], the mechanism has not been given.

Thus, the oxidation of uric acid by means of lead (IV) oxide has a double interest due to the biological importance of the substrate and to know the exact role of the lead compound.

The experimental part was described by Mulder [7]. Some data about lead dioxide are given. It appears as brown hexagonal crystals, insoluble in water, and has hydrogen bond count 2. Its chemical structure is linear [8].

Lead dioxide is not a peroxide but it will act as a powerful oxidizing agent [9].

The other uric acid oxidation studied is by means of slightly alkaline hydrogen peroxide [10]. This communication has been commented [11].

Further reaction leads to cyanuric acid, 1,3,5-triazinane-2,4,6-trione [12].

The formation of sodium hydroperoxide is well known and Michael addition to α,β-unsaturated ketones with epoxide formation has been reported [13].

Although there is no enone in uric acid, there is reaction with this reagent. This point will be discussed in the next section.

3. DISCUSSION

The linear O=Pb=O molecule is highly polarizable as it can be inferred from the corresponding electronegativities: Pb=1.5; O=3.5 [14]. The difference between them is a unit higher than in C=O, C=2.5; O=3.5. The IUPAC name for lead dioxide is dioxolead, which is in accordance with the above data.

The oxidation of uric acid by means of lead (IV) oxide is carried in water with a little acetic acid, at room temperature.

Thus, the initial interaction between uric acid and plumbic oxide is nucleophilic attack by the nitrogen atom of the reactive imido group to the protonated PbO_2, Figure 1, Flow Chart: a.

Hydrolysis of the organometallic intermediate involves a four atom concerted mechanism due to a push-pull effect coming from the carbon and the electron accepting properties of lead to form lead(II) derivatives, this enhanced by protonation of the remaining oxo group in lead, (b, c).

This way ring opening occurs and a singlet nitrene is formed, a powerful electrophile, (d).

Then there is electron shift from the double bond to the nitrene, with ring closure to a five member ring, (e). The concomitant dipolar ion formed is neutralized by water, (f, g). After decomposition of the reagent, the reaction medium is heated and there is carbon dioxide evolution, (h).

Isomerization to an imidol structure lefts a carbinolamine and there is a subsequent ring opening, (i). This way 5-ureido-2,4-dioxo-imidazolidine is formed. This is the product obtained experimentally and is known as allantoin.

***Corresponding author:**
E-mail: franviesca@yahoo.com

ISSN NO: 2320-0898 (p); 2320-0928 (e)
DOI: 10.22607/IJACS.2020.803001

Received: 04th May 2020;
Accepted: 26th May 2020;

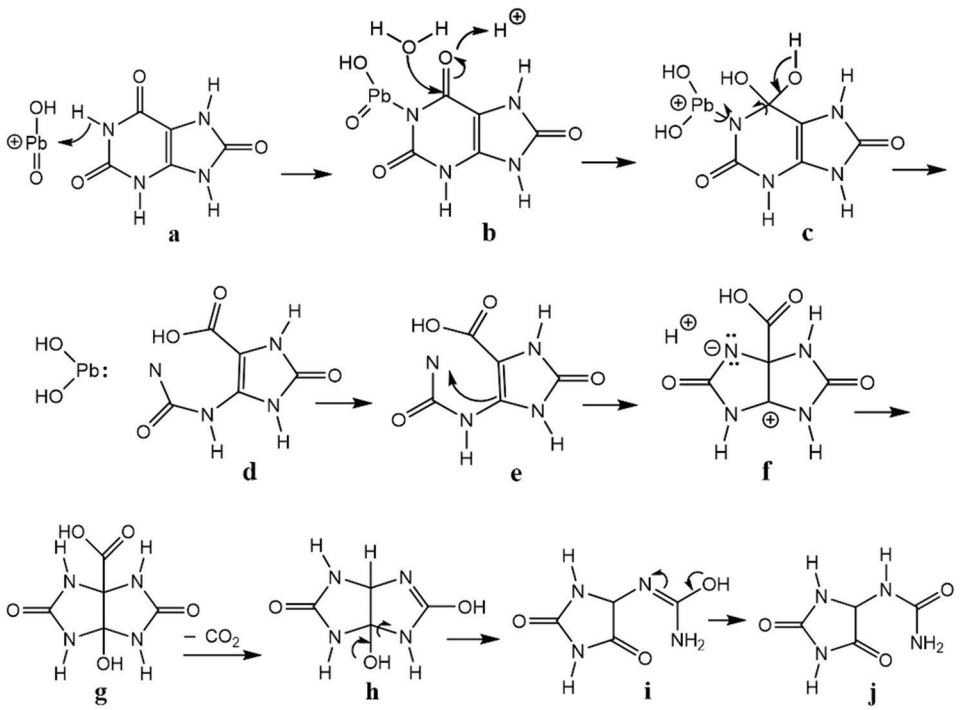

Figure 1: Route from uric acid to 5-ureido-2,4-dioxoimidazolidine by oxidation with lead (IV) oxide.

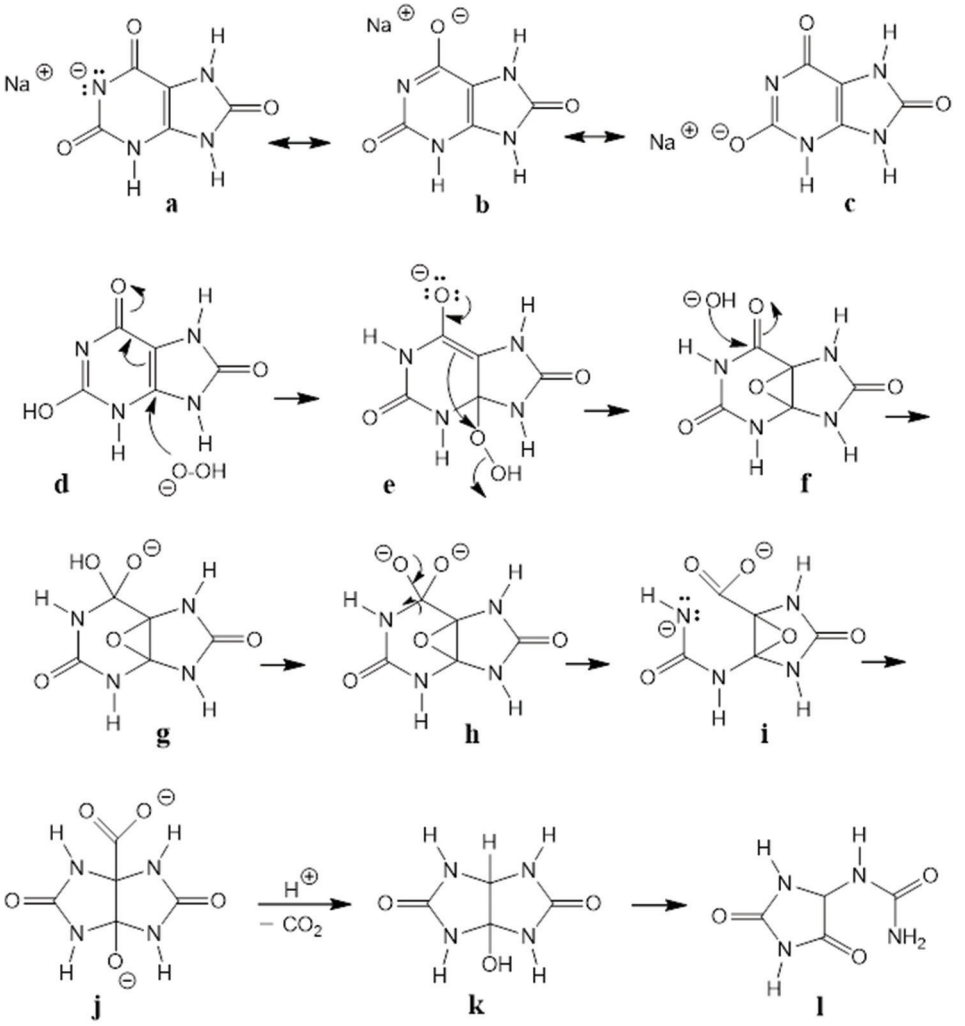

Figure 2: Sequence from uric acid to 5-ureidohydantoin (allantoin) by oxidation with alkaline hydrogen peroxide.

The other uric acid oxidation studied employs hydrogen peroxide in slightly alkaline solution. The reactive species is the hydroperoxide anion, and several 1,4-additions to α,β-unsaturated ketones have been reported [13]; electron return from the enolate gives rise to epoxides by reaction with the hydroperoxide group.

However, in uric acid there is an α,β-unsaturated imide, not an enone. Notwithstanding, there is reaction with hydrogen peroxide and this must be cleared up.

The acidic properties of the imido group are well known and the structure of sodium urate has been proposed with the negative charge at the nitrogen of this group [15], Figure 2: a.

This anion can be in resonance with two imidates from two imidol forms, b, c. The one with cross conjugation has been proposed as the structure of uric acid monosodium salt [16]. This structure has the particularity that has an enone, apt for reaction with hydrogen peroxide and epoxide formation, as indicated in the formulas, d, e, f.

Alkaline hydrolysis produces opening of the pyrimidine ring, g, h, i, and the resultant negative nitrogen forms a five member ring by reaction with the epoxide. A symmetric intermediate results after this ring contraction and reaction with water, j, k.

Decarboxylation and indiscriminate ring opening of one of the two rings gives rise to the final product, 5-ureido hydantoin (allantoin), l.

This ring fission occurs through a hemiketal, after imidol formation in the ureido group. See last steps of oxidation with lead dioxide.

4. CONCLUSION

The results of the study of uric acid oxidation with lead dioxide in very weak acidic conditions are shown in the ten formulas contained in Figure 1, Flow Chart 1. The route from the starting substrate to allantoin is given, step by step, with the corresponding electron flow. The especial reaction occurs after hydrolysis initiation, a four center push-pull mechanism leading to ring opening and nitrene formation. Then, there is ring closure to a five member ring.

Neutralization of the zwitterion affords a symmetric intermediate. The closing steps give the final product, 5-ureido-hydantoin, and allantoin.

The other reaction mechanism corresponds to the uric acid oxidation by means of hydrogen peroxide in slightly alkaline medium. The reaction route is given in Figure 2, Flow Chart 2. An especial reactivity is the reaction of hydroperoxide anion with an α,β-unsaturated imide, not with an enone. This chemical deportment was explained considering the importance of a cross conjugated structure resulting from imidol isomerism. In this isomer, there is an α,β-unsaturated ketone, capable of reaction and epoxide formation. Subsequent hydrolysis through the dianion gives a nucleofuge, a leaving group that carries away an electron pair.

The negatively charged nitrogen opens the constrained oxirane ring and a five member ring results. Neutralization and decarboxylation gives a symmetric intermediate equal to the obtained in the previous oxidation with plumbic oxide. The last steps are the same.

5. ACKNOWLEDGMENTS

The authors would like to thank co-worker Martha Berros for useful dialogue.

6. REFERENCES

1. F. Sánchez-Viesca, R. Gómez, (2020) The mechanism of nitric acid degradation of C-glycoside aloin to aloe-emodin, ***American Journal of Chemistry***, **10**: 1-5.
2. F. Sánchez-Viesca, R. Gómez, (2019) On the mechanism of the Treumann test for theobromine, ***International Journal of Chemical Science***, **3**: 46-49.
3. F. Sánchez-Viesca, R. Gómez, (2019) On the mechanism of the Neumann-Wender glucose test, ***American Journal of Chemistry***, **9**: 123-126.
4. F. Sánchez-Viesca, R. Gómez, (2020) Formation mechanism of the coloured compounds derived from eserine (physostigmine), ***World Journal of Organic Chemistry***, **8**: 1-4.
5. F. Sánchez-Viesca, M. Berros, R. Gómez, (2018) A complete and sustained Clemmensen reduction mechanism, ***American Journal of Chemistry***, **8**: 8-12.
6. L. F. Fieser, M. Fieser, (1967) ***Reagents for Organic Synthesis, Hoboken***, New Jersey: John Wiley, p533-536.
7. E. Mulder, (1871) Sur l'allantoïne et ses dérivés, ***Bulletin de la Societé Chimique de Paris***, **16**: 267-270.
8. Lead Dioxide, (2020) ***U.S. National Library of Medicine. Online, Access with the Title***. Last Log in, April 30, 2020.
9. J. H. White, (1962) **Inorganic Chemistry**, London, United Kingdom: University of London Press, p305.
10. C. S. Venable, (1918) The action of hydrogen peroxide upon uric acid, ***Journal of the American Chemical Society***, **40**: 1099-1120.
11. E. S. Gatewood, (1919) ***The Action of Hydrogen Peroxide and Alkali on Some Uric Acid Derivatives***, Columbia: B.S. Barnard College, Columbia University.
12. A. R. Katritzky, Ed., (1963) **Advances in Heterocyclic Chemistry**, Vol. 1, Cambridge, Massachusetts: Academic Press, p193-194.
13. H. O. House, (1972) **Modern Synthetic Reactions**, 2nd ed., New York: W.A. Benjamin, p307-310.
14. D. A. Brown, (1967) **Comparative Inorganic Chemistry**, New York: McGraw-Hill, p71.
15. National Institutes of Health, (2020) ***Sodium Urate Structure***. National Institutes of Health, USA, Inxight: Drugs. Online, Access with the Title. Last Log in, April 30.
16. National Institutes of Health, (2020) ***Sodiumurate/C5H3N4O3/ Chem Spider Online***, Access with the Title. Last Log in, April 30.

***Bibliographical Sketch**

I am in Research Gate, at Berlin. In the last weekly report, April 25, my papers had 325 more reads. My article on the Seliwanoff Reaction reached 9,681 reads. My work is read all over the world. I have worked and published in all the fields of Organic Chemistry: Natural Products, Organic Synthesis, Heterocyclic Chemistry, Infrared and NMR spectroscopy, Mass Spectrometry, and Computational Chemistry. This research has been published in the following Journals: Tetrahedron, Phytochemistry, Organic Preparations and Procedures International (Boston, U.S.A.), Heterocyclic Communications, Heterocycles (Japan), Sadtler Collection of Standard Spectra (Philadelphia, U.S.A.), Journal of the American Chemical Society, Rapid Communications in Mass Spectrometry (Canada-U.K.), American Journal of Chemistry, World Journal of Organic Chemistry, International Journal of Chemical Science, and others. During synthetic work I have found mechanistic deviations in the Bischler indole synthesis and also in the Houben-Hoesch reaction. My last papers deal on the mechanism of several organic preparations and colour reactions. They have had ample reading in Research Gate.