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On the chemistry of the Archetti test for caffeine and uric acid

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Abstract

The Archetti colour test is based on the reduction of ferricyanide ions to ferrocyanide, giving Prussian blue. However, the oxidation sequence of reactions that take in the organic molecule has not been described. Some electroanalytical experiments on the oxidation of caffeine have been done but the results have not been adequately interpreted. Besides, they are incomplete since only the redox reactions can be detected, but not the isomerization and degradation path. In the present communication the complete oxidation route of caffeine is given, as well as the electron flow in each step. It involves hydration of the imino group and oxidation to 1,3,7-trimethyl-uric acid, formation of radical ion at C-9, interaction with the C—C double bond, aziridinone formation, carbon monoxide extrusion, carbonium ion neutralization, imine acidolysis, isomerization of carbinolamine and hydrolysis to the end products.

Keywords: Anodic voltammetry; Caffeine degradation; Caffeine oxidation; Electron flow; Reaction mechanism; Reactive intermediates

1 Introduction

Caffeine is a central nervous system stimulant, increasing alertness and attentional performance, and is the most widely consumed psychoactive drug. Caffeine appears as odourless white crystalline powder or white glistening needles. Solutions in water are neutral to litmus. Solubility, 21 mg/ml at 25°C, [1]. Caffeine may confer a modest protection effect against some diseases, [2].

This alkaloid is found in the seeds, nuts, or leaves of a number of plants native to South America and east Asia, with psychotropic and anti-inflammatory activities. Its chemical structure is 1,3,7-trimethylxanthine, Figure 1.

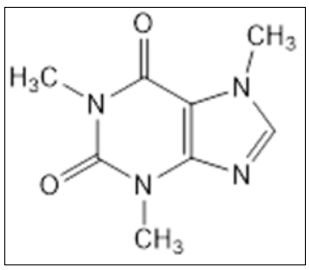

Figure 1 Caffeine, 1,3,7-trimethyl-2,6-dioxopurine

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Archetti used as reagent a solution of potassium ferricyanide with half its volume of nitric acid. If mixed with caffeine or its solution, and boiled, Prussian blue is obtained. See 'Antecedents'. The reaction route of this oxido-reduction process has not been described, although two inadequate intermediates have been proposed after electrochemical oxidation of caffeine. See 'Discussion'.

In this communication the electron flow is given in each step of the series of reactions that take place during this colour test. This paper is a follow up of our studies on reaction mechanism, [3-7].

2 Antecedents

The test under study is due to the Italian chemist Andrea Archetti. He published his assay in an analytical journal [8], and it was registered in Germany [9], and in the United States [10].

The Archetti test for caffeine and uric acid is based on the reduction of potassium ferricyanide to the ferrocyanide ion, giving Prussian blue. This test has been applied recently for the estimation of uric acid, [11].

The electrochemical oxidation of caffeine has been reported [12, 13]. However, the results have not been interpreted adequately. For instance, the hydration of the imino group is very slow in neutral medium, and the reaction must start at N-9, before hydration and oxidation of the hydroxyl group. The end product proposed by this method implies loss of an electron and reaction with water, but an internal reaction is faster. Thus, electron coupling with N-1 forms a five-member ring and an aziridinone. Then there is carbon monoxide release due to molecular strain. Until now a new inter-annular free radical is captured and the carbonium ion reacts with water.

Electrochemistry doesn't detect isomerizations nor eliminations, but only redox steps. So, the last steps of caffeine degradation are missing too.

In the liver, caffeine is broken down [14-16] into three compounds: paraxanthine, theobromine and theophylline, which are demethylated at N-3, N-l, and N-7, respectively. The percentages are 84, 12 and 4.

Most of the caffeine produced in the USA prior to 1945 was obtained by methylation of theobromine extracted from cocoa. The methylation agents used were dichloromethane

and dimethyl sulphate, [17].

An interesting Chinese patent [18] is based on methylation of theophylline (tea sodium) with methyl carbonate in N-methyl pyrrolidine and 18-crown ether-6, and heating with stirring at 160°C for 6 hr.

3 Discussion

The imino group in caffeine can be hydrated in acidic medium, Figure 2, a, b, and the hydroxyl group oxidized to carbonyl. The oxidation step involves radical cation formation at oxygen, proton elimination, c, d, electron capture to positive oxygen, e, and proton release for carbonyl formation, f. This way 1,3,7-trimethyl-uric acid results.

Electron elimination at the not hindered N-9 renders a radical ion that is neutralized by hydrion separation, g. The remaining free radical reacts with the C—C double bond. A new imine is formed, h, and the radical at the inter-annular position reacts with the electrodotic [19] N-1, yielding a very tensioned aziridinone, i, since besides the strain in the three-member ring, the constriction of the carbonyl bonds must be added. This situation is alleviated by extrusion of carbon monoxide and enhanced by boiling the reaction mixture, j, with concomitant hydration of the imine in the five-member ring.

N-1 has now its unshared electron pair, and the re-formed inter-annular free radical, k, is removed by reaction with the ferric salt, l. The carbonium ion is neutralized by reaction with water, and a symmetric dihydroxi intermediate is obtained, m.

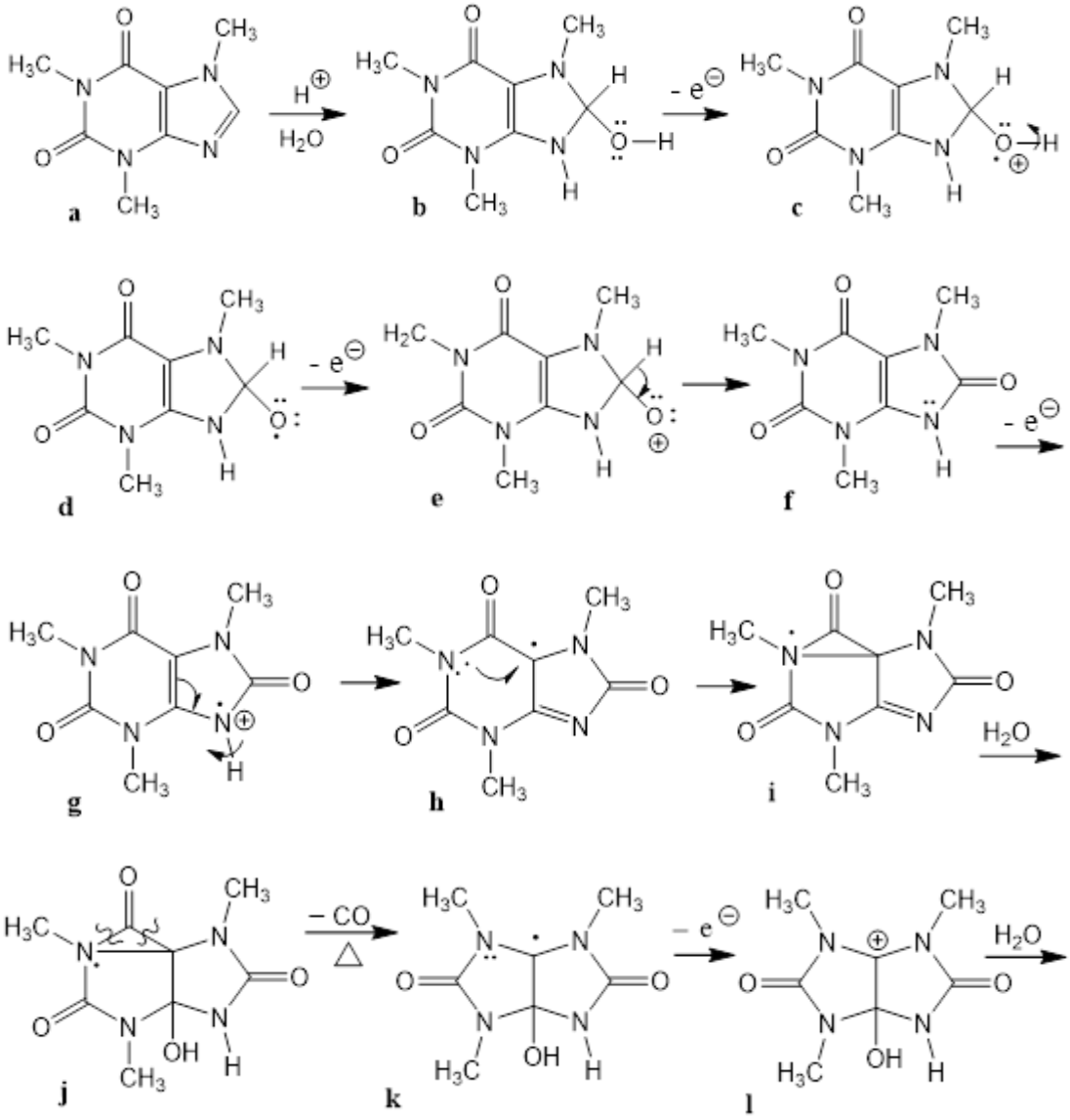

Figure 2 Redox reactions of caffeine oxidation by ferricyanide ions in acidic medium

Isomerization of the carbinolamine to carbonyl and ring opening is facilitated by the dipolar structure proper of amide, which helps an easy C—N fission, Figure 3 n. Isomerization, o, and repeated reaction in ring p, takes place, yielding methylurea and 1,3-dimethyl-2,4.5-trioxo-imidazolidine, q, which is hydrolysed to oxalic acid and N,N'-dimethylurea, r.

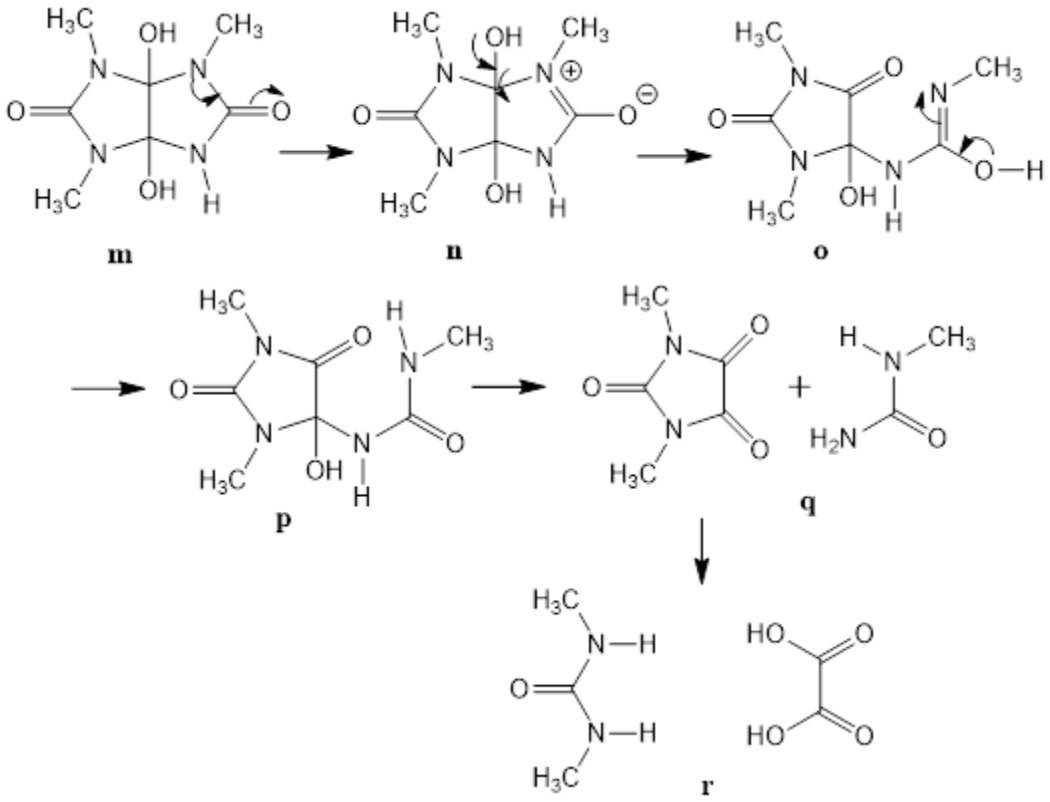

Figure 3 Degradation of caffeine by isomerization and hydrolysis after initial oxidation

The degradation route after the redox-reactions is in accordance with the end products obtained in the cognate Neubauer reaction which employs ferric chloride, [20].

4 Conclusion

The Archetti test involves two parts: the oxidation of caffeine by means of ferricyanide ions, which occurs via radical ion whose stabilization produces a series of steps. The second part comprises isomerization and hydrolysis reactions. The complete process is given, as well as the electron flow in each step.

This is in contrast with electroanalytical experiments which are incomplete by nature since they only register redox steps, but not isomerization and degradation steps. Besides, the results obtained can be interpreted otherwise as mentioned before.

The proposed reaction route is in accordance with the end products obtained in the cognate test due to Neubauer employing ferric chloride. Both tests are carried out in strong acidic medium.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

There are no conflicts of interest to declare.

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