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The mechanism of Fleury test for morphine

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Abstract

The test under study is due to M. Fleury. He used morphine dissolved, at room temperature, in 1/20 N sulphuric acid; added some lead superoxide (lead dioxide), stirred for 8 min., let stand 4 min; the water-clear liquid was separated, and a drop of ammonia was added. A brown colour occurs immediately. These experimental data indicate not a fast reaction, but a rather complex mechanism. In this communication a reaction mechanism is provided for the first time. Protonated lead dioxide is the reactive species which on interaction with the phenol group in morphine forms a mixed ortho-plumbate. Protonation of this ester does not favor further reaction. However, reaction with a second reactive species is favourable for a push-pull seven-member reaction mechanism. Enolization of the dienone formed restores aromaticity. Protonation of the Pb=O double bond in the obtained intermediate promotes a 7-atom concerted mechanism. 2,3-Dioxomorphine is formed along with an oxide hydrate that yields water and two molecules of plumbous oxide.

1. Introduction

Between 1805 and 1816 Friedrich Wilhelm Sertürner isolated the sleeping agent from crude opium as a yellowish-white crystalline compound and named it morphine in accordance to the Greek God Morpheus, [1].

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Morphine, previously known as Morphia in the early scientific literature, exists in opium as bi-meconate. Mohr isolated morphine making a strong infusion with water, added lime in the state of milk, boiled the mixture and filtered through linen. While still hot, ammonium chloride in fine powder is added, and morphine is deposited as the liquid cools. Good opium yields 10-13% of morphine. Crystallization from 30 parts of alcohol, yields brilliant prismatic crystals of adamantine luster. It exhibits alkaline reaction on test paper, [2]

In 1901, Fleury developed a test for morphine employing lead dioxide (lead superoxide) and diluted sulphuric acid. Since the reaction mechanism has not been described, it is provided in this communication because it is interesting know what is happening at molecular level in the test tube during the reaction.

This paper is a follow up of our studies on reaction mechanism, [3-7].

2. Antecedents

Fleury published his test for morphine in 1901, in Austria (Oesterreich), [8]. The test is as follows: to a small amount of the substance to be tested a drop of 1/20 N sulphuric acid is added and stirred until the alkaloid is dissolved. Some lead peroxide is added and stirred for 6-8 minutes. After standing for 3-4 minutes, the water-clear liquid is separated and a drop of ammonia is added to it. In the presence of morphine a brown colour appears immediately.

Lead (IV) oxide was used by Mulder [9] in the oxidation of uric acid. He only described the experimental part. Dilute acetic acid was used as catalyst and solvent, whereas Fleury employed dilute sulphuric acid.

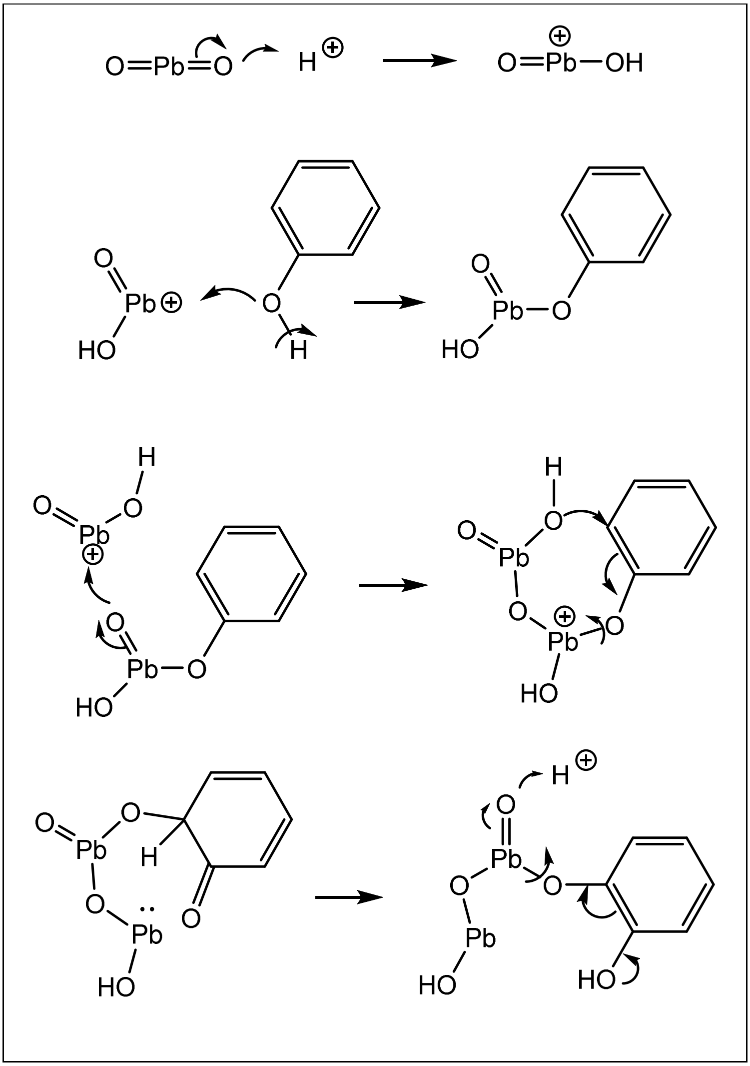
Some remarks on the reagent. Lead dioxide is not a peroxide since it does not have the -O-O- grouping, [10]. It appears as brown hexagonal crystals, insoluble in water. Its chemical structure is linear, [11].

Lead dioxide is prepared oxidizing lead acetate by calcium chloro-hypochlorite plus a water molecule. Besides the dioxide, acetic acid and calcium chloride are formed, [12]. Lead dioxide, reacting as an oxidizing agent, is soluble in concentrated hydrochloric acid, forming lead(II) chloride, water, and liberating chlorine, [13]. On heating it is transformed in minium, with evolution of oxygen, [14]. Pb_3O_4 is not an oxide but a salt, plumbous ortho-plumbate.

3. Discussion

The O=Pb=O molecule is highly polarizable as it can be inferred from the corresponding electronegativities: Pb=1.5; O=3.5 [15]. 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 first step in Fleury test is protonation of the PbO_2 molecule. This reactive species is neutralized by the electrodotic property [16] of the phenol group in morphine (nucleophilic reaction). Figure 1.



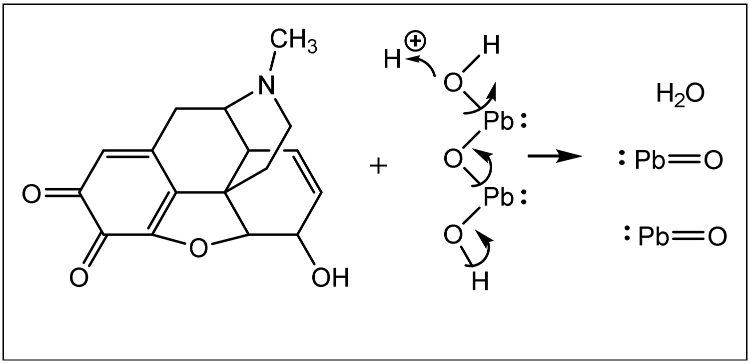


Figure 1. Reaction route of the interaction of morphine with lead dioxide in acidic medium involving a sui generis 7-member transient intermediate that promotes two electron-shifts.

The next step could be protonation of the mixed plumbic ester. The positively charged lead atom attracts electrons producing Umpolung at the vicinal position (C-2). However, there is no group or molecule present in order to react as nucleophile at C-2. Nevertheless, a protonated PbO_2 can act in similar form as a hydrion on the ester at C-3. This pseudo dimer with a 5-member chain can form a transient 7-member ring and react as nucleophile with the $\delta+$ at C-2. A plumbic ester is formed, along with a dienone, and the positive lead atom is neutralized and reduced to Pb (II) with concomitant ring opening (seven-atom synchronous mechanism). Enolization of the obtained dienone restores ring aromatization. Protonation of the lead-oxygen double bond in the chain causes a 7-member concerted mechanism. An ortho quinone is formed along with PbO hemihydrate whose protonation yields water and two molecules of Pb=O. For the oxide hydrate 3PbO▪H2O, see [17]. The observed brown colour after ammonia addition is due to halochromism, [18, 19].

In the above reaction mechanism, the double interaction of the same reactive species is remarkable, as well as the formation mode of Pb=O, the reduced compound.

4. Conclusion

The novelty of this communication is the use twice of a positively charged reactive species, instead of a proton, since a hydrion does not favour the continuation of the reaction. A transient 7-member ring results, a plumbic ester and a dienone are formed. After enolization of the latter and protonation of the chain at the P=O group, a seven member concerted mechanism takes place, producing an ortho-quinone and an oxide hydrate. Acidolysis of the latter gives water and two molecules of PbO.

5. Conflicts of Interest

There are no conflicts to declare.

6. Acknowledgement

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