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ELECTRON TRANSFER MECHANISMS OF SOME BIOCHEMICALLY ACTIVE PURINES

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ABSTRACT

Free purines are found in some of the biological systems. Some types of purines as constituents of large molecules however are found in every living cell. Uric acid is a purine derivative which was discovered over one hundred years ago. It is found in blood, cerebral spinal fluid and milk. Bird excrement, guano contains a significant amount of uric acid. Uric acid as well as other oxypurines are the major products of purine metabolism in man.

Presence of adenine and guanine in nucleic acids is important in transfer of genetic information.

Oxidation and reduction of purine derivatives in human and animal metabolisms have been studied extensively. Electron transfer mechanisms of purines, are therefore important in studying their role in biological systems.

In the present study the electron transfer mechanisms of some biologically active purines are discussed.

INTRODUCTION

Purine was first named by Fischer (1884). Confusions on naming of purines were eliminated to a great extent by Robins (1967).

Purine derivatives have vital importance in all living cells. Some purines have been employed as drugs. Certain synthetic purines are being used in cancer chemoterapy. For the treatment of some types of leukemia, 6–mercapto purine is known to be among the most effective drugs (Karnofsky, 1967). Many other thiopurines are synthesized and used as antitumor drugs (Murray, 1970).

Excess of purines in the body, on the other hand can be the cause of some diseases. The disease gout, for example, is caused by the overproduction of uric acid. Uric acid is insoluble, and when it accumulates in joints it causes gout. Caffeine is known to be a stimulant for the central nervous system, heart and vascular system.

The important roles of purines in protein synthesis, storage and transfer of genetic information, in intermediary metabolism are well

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known. Purines are constituents of some coenzymes involved in electron transfer processes in living cells. Electrochemical behaviours of purines therefore have vital importance, in studying their roles in the body.

First electrochemical investigation of purines was reported by Pech (1934). A more detailed study was reported by Heath (1946). Heath reported that adenine could be reduced electrochemically on dropping mercury electrode (DME). It was suggested that the reduction was due to an electron transfer to N–1 C–6 double bond. Woodhouse et al (1953) later reported that daenine and hypoxanthine gave good polarographic waves where xanthine and guanine did not. Woodhouse also reported that when adenine was electrolytically reduced at constant potential, the product gave positive test for ammonia and formaldehyde. Smith and Elving (1962) studied reduction of purine and adenine. Dryhurst and Elving (1969) reported the electron transfer behaviour of purine by cyclic voltammetry.

Electro oxidation of purines were not examined as extensively as electro reduction measurements. Fichter and Kern (1926) reported oxidation of uric acid for the first time. Smith and Elving (1962) reported the destructive electrolysis of uric acid by oxidation. Coulometric studies on the oxidation of xanthine was reported by Dryhurst (1972).

Electrochemical oxidation of some purines on pyrolytic graphite yield identical products with those produced by peroxidase. Electron transfer mechanisms of enzyme catalysed and electrochemical reactions of purines have been studied extensively for that reason.

DISCUSSION

Adenine

Oxidation of adenine in animal tissues takes place in the presence of the enzyme xanthine oxidase. Enzyme catalysed oxidation yields 2,8–dioxyadenine. It is known that 8–oxy derivative is the main intermediate in the oxidation of adenine by xanthine oxidase (Robins 1967). Enzyme activation causes the first attack to occure on C–8 and then on C–2.

Electro oxidation of adenine in aqueous solution on pyrolytic graphite was reported by Dryhurst (1968). It was found that six electrons in total are transferred from adenine to anode. Various products can be obtained from constant potential electrolysis of adenine. Electrolytic oxidation products of adenine are parabanic acid, oxaluric acid, urea, ammonia and allantoin.

Electron transfer mechanism of electro oxidation of adenine can be summarized as in Figure 1.

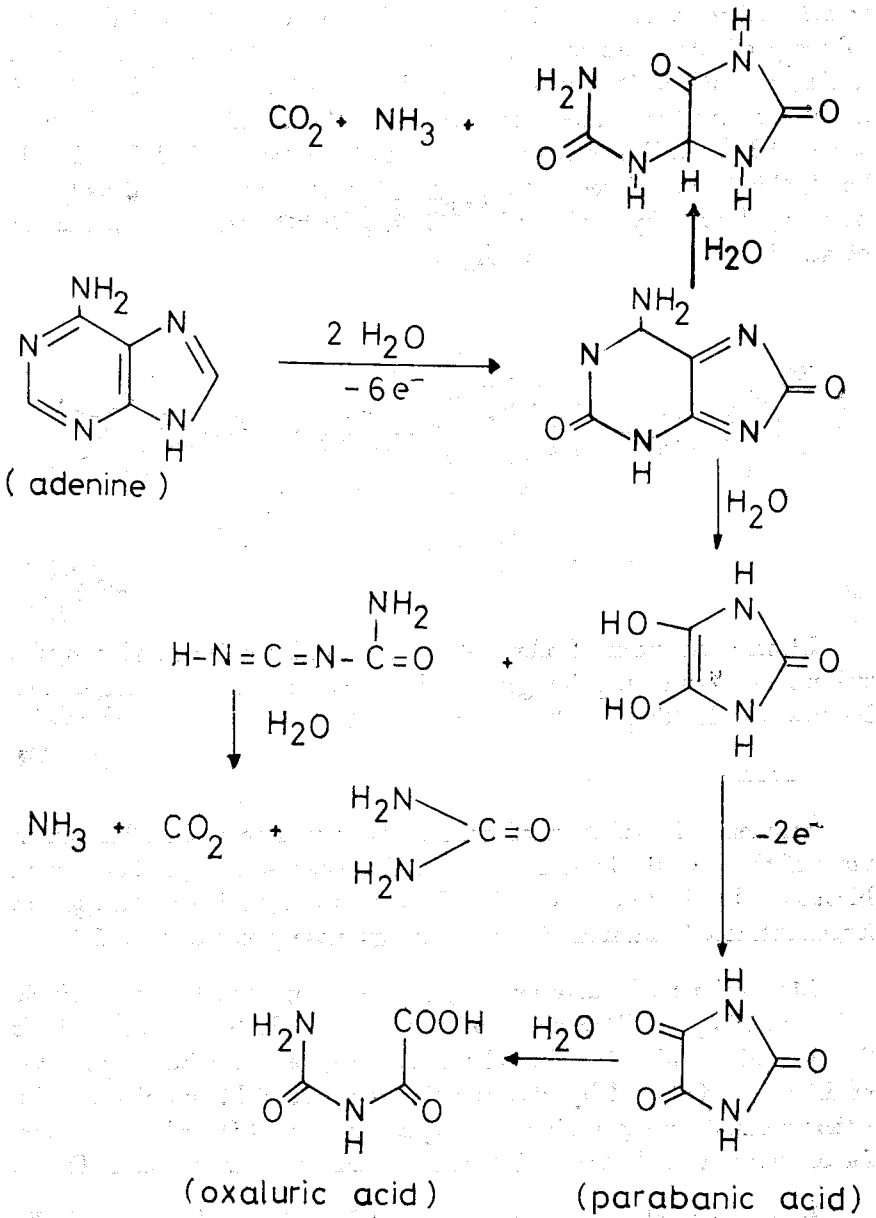
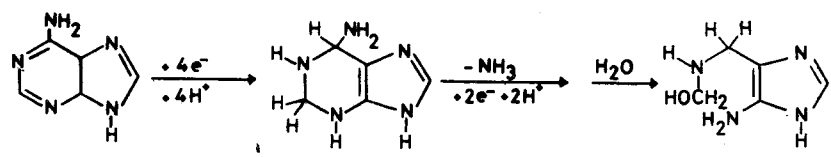


Figure 1

Electro reduction of adenine has been studied in detail by Smith (1962). The reduction potential of adenine is known to be pH-dependent. Complete reduction of adenine requires total of six electrons to be transferred from the cathode to the molecule. An analysis of the electrolysis products of adenine revealed the electron transfer mechanism during reduction. It was reported (Smith, 1962) that C–2 and C–6 double bonds were reduced first, and then the deamination of the 6 th carbon followed. Deamination causes the formation of N–1 C–6 dobule bond; this bond is later reduced by 2 electron transfer and finally 2,3 position cleaves by hydrolysis. Electron transfer steps of reduction of adenine is summarized in Fig. 2.



Figure

Electro reduction of adenine was studied by polarography, cyclic voltammetry and AC-polarography. The electron transfer was found to be irreversible (Smith 1962; Dryhurst, 1969).

Guanine

Biochemical oxidation of guanine is known to yield allantoin in most of the animals. In some cases xanthine can also be produced upon biochemical oxidation of guanine. In rat liver, guanine is oxidized to hypoxanthine. Oxidation of guanine by guanase yields uric acid.

Electrochemical oxidation of guanine is reported to give a single voltammetric peak (Dryhurst, 1970). First two electron transfer yields 8–oxaguanine which is oxidized further to give a diimine. Hydrolysis of diimine is followed by electro oxidation and yields parabanic acid. Other products are guanidine, oxaylguanidine and CO_2. Electron transfer mechanism of electro oxidation of guanine is summarized in Fig. 3.

In aqueous solutions guanine can not be reduced electrochemically (Smith, 1962). Actually, absence of a polarographic wave may not mean

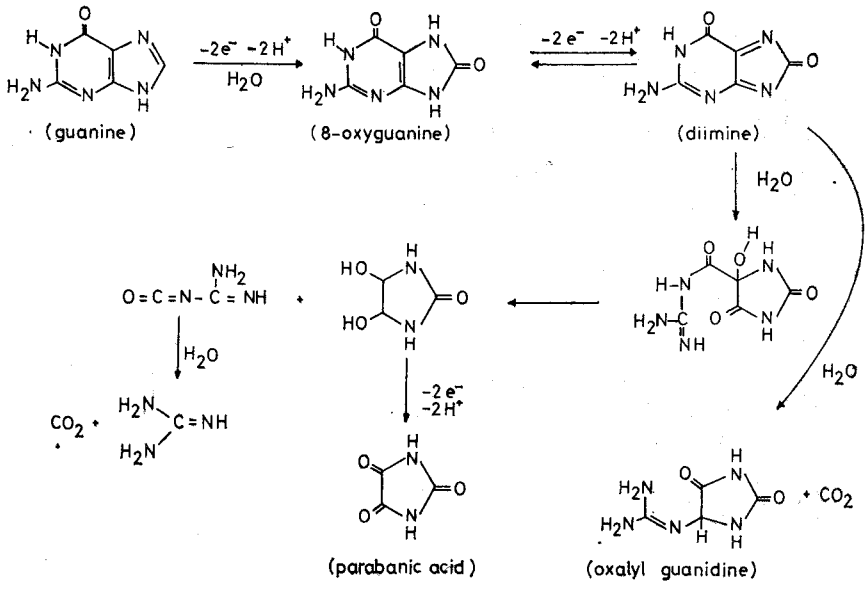


Figure 3

that guanine can not be reduced. There is a possibility of electrolytic reduction of guanine to occure at potentials where the solvent and electrolyte could also be reduced. Indeed, AC-current oscillopolarographic studies revealed that guanine reduces along with solvent (Jank, 1966).

Uric Acid

Uric acid is know to be one of the major products of purine metabolism in man. Biochemical oxidation of uric acid is catalyzed by uricase enzyme. Uricase acts as a catalyst to transfer two electrons from uric acid to oxygen Fig. 4 shows the electron transfer mechanism of biochemical oxidation of uric acid.

Allantoin is the major product of uricase oxidation of uric acid.

Electro oxidation of uric acid was studied in detail by Struck and Elving (1972). On graphite electrode and in acetic acid solution, a well defined voltammetric peak was obtained. Constant potential electrolysis indicated that allantoin, urea and alloxan are produced upon oxidation.

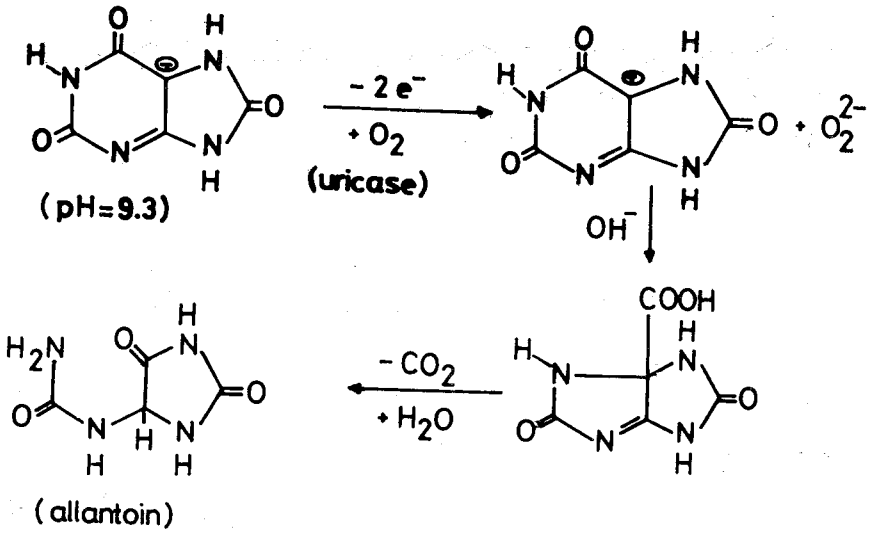


Figure 4

Electron transfer mechanism of electro oxidation of uric acid is given in Fig. 5.

In aqueous solution, no polarographic waves for electro reduction of uric acid have been obtained.

Xanthines

Xanthine oxidase enzyme is responsible for biochemical oxidation of various xanthines. This enzyme can not function without a coenzyme. Xanthine oxidase contains a flavin adenine dinucleatide prosthetic group which serves as coenzyme. Xanthine oxidase is not a very specific enzyme. Presence of molibdenum in the enzyme is reported to be important for its function (Bergman 1956). Methylated xanthines usually yield methyl uric acid upon oxidation with xanthine oxidize. Purine however, is converted to uric acid by xanthine oxidase.

Xanthine yields uric acid by electrochemical oxidation (Dryhurst, 1972) which is further oxidized to yield uric acid, as given in Fig. 4.

Methylated xanthines such as theobromine and caffeine can also be oxidized electrochemically. The products are methyl substituted

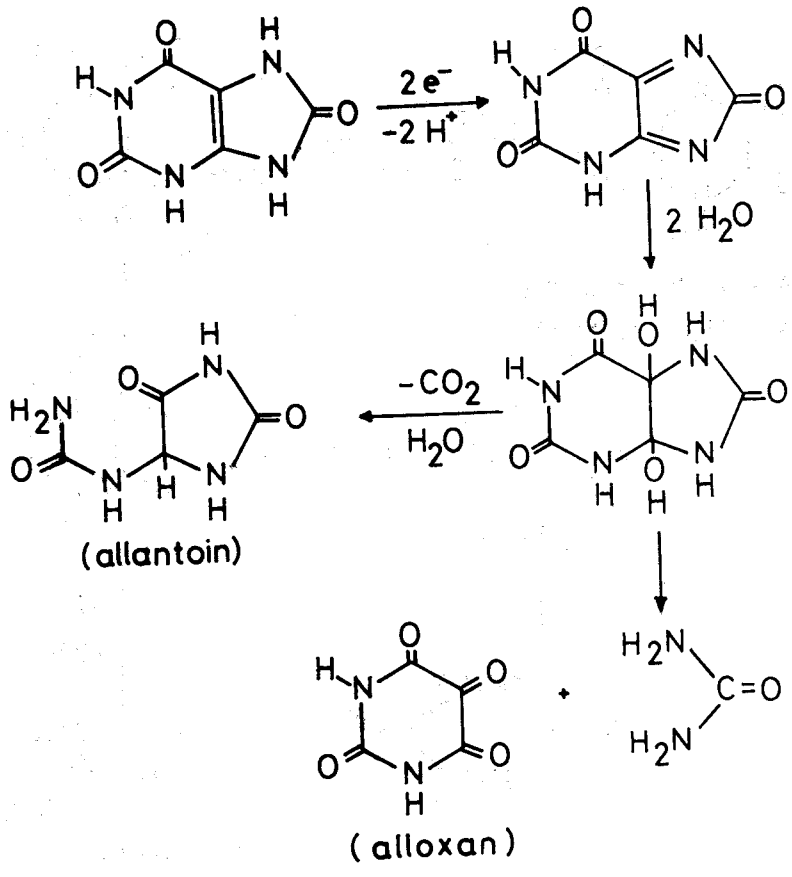


Figure 5

parabanic acids (Hansen, 1971), methyl urea and CO_2. Fig. 6 represents electro-oxidation of methylated xanthines.

Electro-reduction of hypoxanthine is very difficult, it occurs at a potential near background discharge potential. In acetate buffer a two-electron reduction wave has been reported (Smith, 1962). Possible reduction takes place at C–2 N–3 doule bond.

Thiopurines

Biochemical oxidation of thiopurines are cathalyzed by xanthine oxidase. 6–Thiopurine, which is very effective in treatment of leukemia,

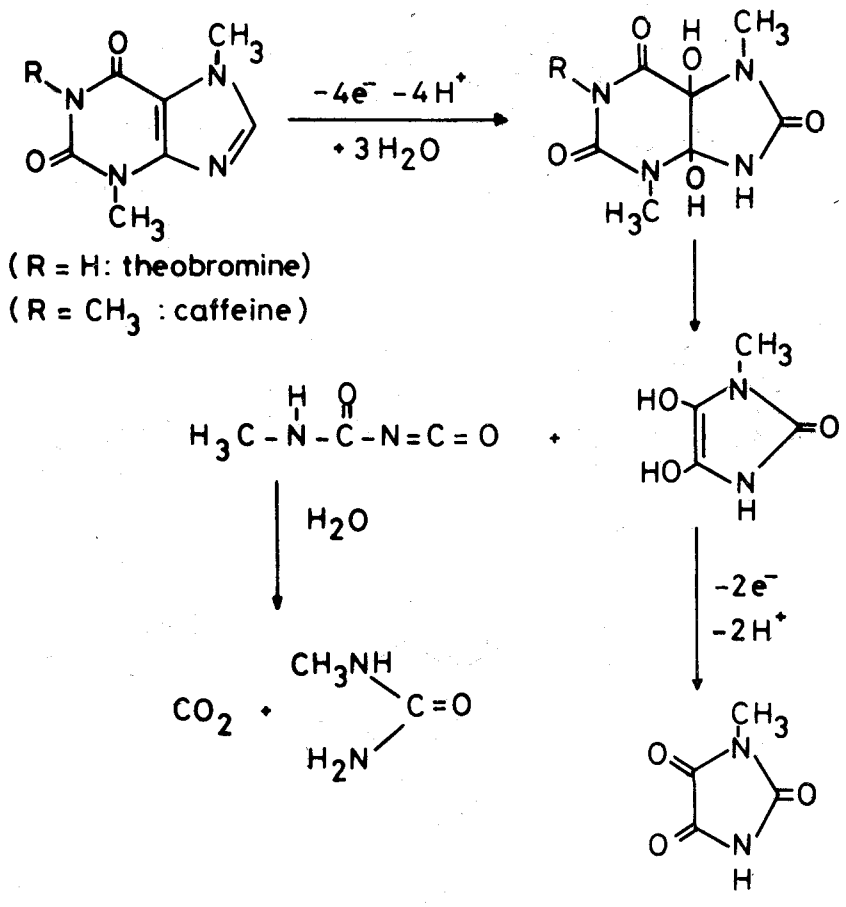


Figure 6

can be oxidized to thiouric acid by xanthine oxidase. 2,6–Dithiopurine can be oxidized by pseudomonas aeruginosa which has some xanthine oxidase activity. The product is 2,6–dithio–8–oxypurine.

6–Thiopurine is known to have three anodic peaks which are pH dependent. Constant potential electrolysis of 6–thiopurine yields purine–6–sulfonamide and purine–6–sulfinic acid. Electro oxidation or reduction of 6–thiopurine or 2,6–dithiopurine do not have similar electron transfer mechanisms with that of related enzymes.

Electron transfer mechanisms of purines, controlled either by enzymes or by electrolysis are similar in many cases. Electrochemical studies on purines (Juvanociv, 1986; Czochralska, 1985; Jelen, 1986; Palecek, 1986) are mostly aimed at to enlighten their roles in the body. Some electrochemical products are identical to those produced by enzymes and some are similar for various purines. However many of the enzyme catalyzed products still have not been produced electrohcemically. Therefore further electrochemical measurements under various conditions must be made in future. Effect of pH, temperature and various additives make it very difficult to give simple examplanations for electron transfer mechanisms of biological systems. In the present study, an attempt is made to examine electron transfer mechanisms of a small group of biologically active compoundc.

It is apparent that more extensive work is required on electrochemical behaviour of purines, to clearify their roles in the living systems.

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