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Studies on the early oxidation process of dopamine by electrochemical measurements and quantum chemical calculations

Iryane Ismail[a], Takeyoshi Okajima[a], Susumu Kawauchi[b], Takeo Ohsaka[a,*]

[a] Department of Electronic Chemistry, Interdisciplinary Graduate School of Science and Engineering, Tokyo Institute of Technology, 4259-G1-5 Nagatsuta, Midori-ku, Yokohama 226-8502, Japan

[b] Department of Organic and Polymeric Materials, Graduate School of Engineering, Tokyo Institute of Technology, 2-12-1-E4-6, Oo-okayama, Meguro-ku, Tokyo 152-8550, Japan

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ABSTRACT

The early oxidation process (EOP) of dopamine (DA) was investigated by cyclic voltammetric measurements under various experimental conditions (e.g., the rate, direction and number of potential scan, the solution pH and the concentration of DA were changed) and quantum chemical calculations. The oxidation of 5-methyldopamine (5-MDA) was also examined for comparison with the EOP of DA. The EOP of DA proceeds in an so-called ECC mechanism, i.e., a $2e^- - 2H^+$ process followed by an intracyclization of the oxidized form of DA (i.e., dopamine ◯-quinone) through an unprotonated amino group, which forms a leucodopaminechrome, and furthermore a homogeneous electron-exchange reaction between dopamine *o*-quinone and leucodopaminechrome, forming dopaminechrome. The redox reaction of the leucodopaminechrome/dopaminechrome couple was also observed. On the other hand, the electrooxidation of 5-MDA is simple, i.e., a $2e^- - 2H^+$ process without such follow-up chemical reactions because the 5-position of its benzene ring is occupied with methyl group and consequently such an intracyclization as in the case of DA does not occur. The cyclic voltammetric results obtained for DA and 5-MDA were reasonably supported by the quantum chemical calculations for DA, some products its oxidation produces and 5-MDA.

1. Introduction

Dopamine (DA) is one of the most important catecholamine neurotransmitters in the mammalian central nervous system (CNS) [1–5]. Its oxidation occurs easily and ubiquitously in the human body [3–9], e.g., as well-known as DA-related oxidative stress and neuromelanin synthesis in CNS and also being considered to be involved in the pathogenesis of neurodegenerative disorders such as Alzheimer and Parkinson diseases. An understanding of the electrochemical oxidation of DA is thus of great importance in elucidating its in vivo oxidation [10,11] and the resulting physiological phenomena [3–11] from a viewpoint of molecular chemistry as well as in developing its in vivo electroanalytical sensor [12–23] which is used to monitor its concentration, e.g., in the intact brain. Therefore, since the pioneering work on the electrochemical study of the oxidation pathways of catecholamines by Adams et al. [24], so much attention has been devoted to the electrochemistry of DA and other catecholamine neurotransmitters [25–36]. Most of previous studies are associated with the development of their electrochemical sensors and surprisingly the fundamental studies regarding the electrochemistry of DA are not so many [24–40] and the mechanism of the early oxidation process (EOP) seems to have been accepted ambiguously [24–30,33], e.g., as can be seen from the fact that both of the so-called ECC and ECE mechanisms are, in principle, possible for the EOP of DA (and other catecholamines) (Scheme 1) [41–46] and based on their theoretical calculations [41], Amatore and Saveant have demonstrated that the ECE mechanisms do not occur at conditions where they could be directly characterized by electrochemical kinetic techniques, but in fact both mechanisms are very often accepted ambiguously, resulting in considerable confusion in the understanding of the EOP of DA. The oxidation of DA is considered to finally lead to melanin-like polymers and thus the whole process is complicated [30,33,47,48].

In this study, in order to understand the EOP of DA comprehensively, the electrochemical oxidation of DA has been examined using cyclic voltammetry under various experimental

* Corresponding author.
E-mail address: ohsaka@echem.titech.ac.jp (T. Ohsaka).

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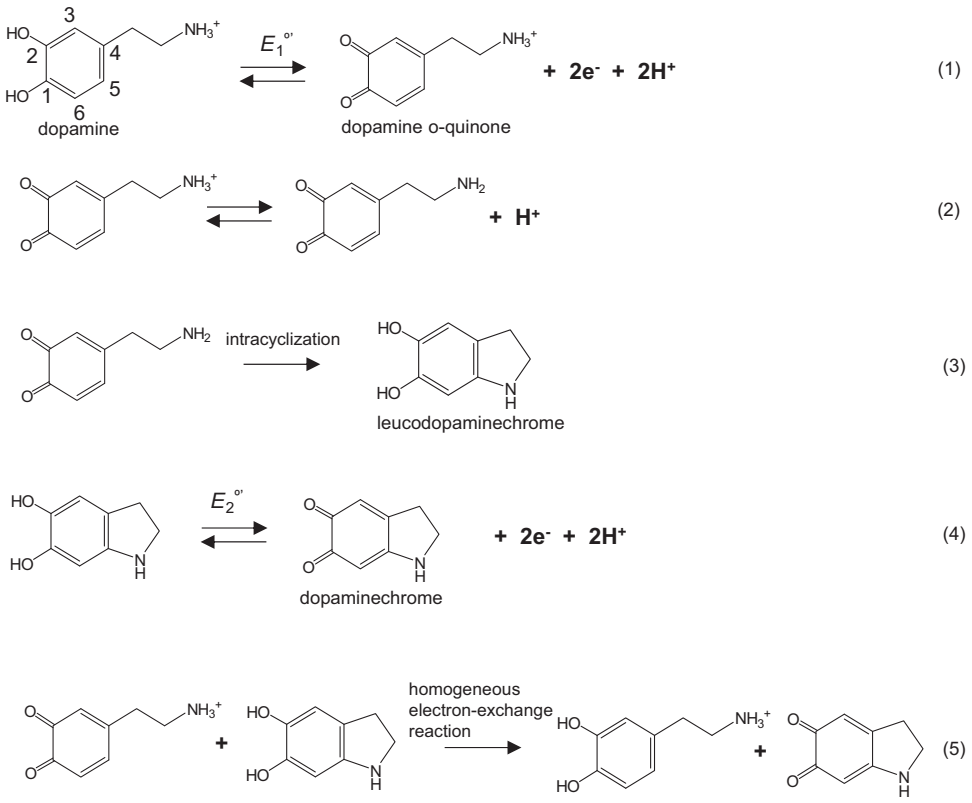

Scheme 1. Possible oxidative pathways of dopamine (e.g., at pH 7.5). $E1^{o\prime}$ (formal potential of electrode reaction (1)) > $E2^{o\prime}$ (formal potential of electrode reaction (4)) ECE mechanism : (1) → (2) → (3) → (4) ECC mechanism: (1) → (2) → (3) → (5).

conditions of pH, potential scan rate, the concentration of DA, the number of potential scan and the direction of potential scan as well as using quantum chemical calculations for optimized molecular structures of the most stable conformers regarding DA and the compounds which could be formed chemically or electrochemically after its electrochemical oxidation. In addition, the electrooxidation of 5-methyldopamine (5-MDA) has been also carried out with a view to comparing its process with the EOP of DA, because the 5-position of the benzene ring of 5-MDA is occupied with methyl group and thus it can be expected that the so-called intracyclization of its oxidized form may not occur unlike DA and consequently only one couple of the redox peaks corresponding to the oxidation of 5-MDA and the reduction of its oxidized form is observed.

2. Material and methods

2.1. Reagents

Dopamine hydrochloride (DA, 4-(2-aminoethyl)benzene-1,2-diol, hydrochloride salt), citric acid monohydrate, and trisodium phosphate dodecahydrate ($Na_3PO_4{\cdot}12H_2O$) were purchased from Kanto Chem. Co., Inc., Japan. Boric acid and sodium chloride were commercially available from Wako Pure Chem. Ind., Ltd., Japan. 5-Methyldopamine hydrochloride (5-MDA, 4-(2-aminoethyl)-5-methylbenzene-1,2-diol, hydrochloride salt) was commercially supplied from Otava Ltd., Canada. All the reagents were of analytical grade and used without any further purification.

Universal buffer solutions (pH range from 3.25 to 10.41) containing 0.1 M (1 M = 1 mol dm^{-3}) NaCl were composed of 0.005 or 0.050 M H_3BO_3 – citric acid – Na_3PO_4 three-component solutions. The solution of pH 1.69 was composed of 0.02 M HCl and 0.1 M NaCl. All the aqueous solutions were prepared using water purified by a Millipore Milli-Q system (MILLIPORE, Japan).

2.2. Electrochemical measurements

Electrochemical analyzer ALS/Chi Model 750Cz (Bioanalytical System Inc. (BAS), Japan) was used to perform controlled-potential electrolysis and cyclic voltammetric measurements. Cyclic voltammetry was performed under various experimental conditions, i.e., in the pH range of 1 to 11, at potential scan rates of 10 to 500 mV s^{-1}, at various concentrations (i.e., 0.1, 1 and 5 mM of DA and 5-MDA) and by changing the number (i.e., 1 to 100 cycles) and the direction (i.e., positive and negative directions of potential) of potential scan. All the electrochemical experiments were conducted with a three-electrode system at room temperature ($25 \pm 1\,^{\circ}C$) under Argon (Ar) gas atmosphere. A glassy carbon (GC) disk electrode (disk diameter: 3.0 mm, BAS, Japan) was used as working electrode, and a platinum spiral wire and potassium chloride-saturated silver | silver chloride electrode (Ag | AgCl | KCl (sat.), TDA-DKK, Japan) were used as auxiliary and reference electrodes, respectively. Before use for measuring each CV, GC electrode surfaces were polished on a polishing pad with water-wetted 1 and 0.06 μm alumina powders (used in this order), and then sonicated to remove the abrasive particles in Milli-Q water for 10 min.

2.3. Quantum chemical calculations

All quantum chemical calculations for optimized molecular structures of the most stable conformers regarding dopamine and its derivatives were carried out using the Gaussian 09 (revision D. 01) program package [49]. The structures of reactants and products