PERKIN 2

Oxidation chemistry of indole-3-methanol

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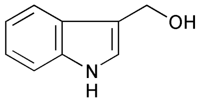
Received (in Cambridge, UK) 22nd August 2000, Accepted 19th January 2001

The electrochemically driven and persulfate-mediated oxidations of indole-3-methanol have been studied in phosphate buffers. The electrochemical oxidation was carried out at a pyrolytic graphite electrode and the electrode reaction is found to follow the ECE mechanism. The kinetics of the UV-absorbing intermediate were followed spectrophotometrically and decay occurred in a pseudo-first-order reaction. On the other hand, the oxidation of indole-3-methanol by persulfate followed pseudo-first-order kinetics having first-order with respect to substrate. This reaction takes place with a second-order rate constant of (0.13 ± 0.005) $dm^3 mol^{-1} s^{-1}$. A detailed interpretation of the redox mechanism for indole-3-methanol in both the oxidations has been suggested.

Introduction

Indole-3-methanol (**I**) is a phytochemical isolated from cruciferous vegetables and has been shown in pre-clinical experiments to be a promising nutrient. This fact may justify clinical evidence that eating cruciferous vegetables can stave off various forms of cancer in humans,[1] as these vegetables contain the most powerful anticancer compound, indole-3-methanol. The efficiency of indole-3-methanol in the prevention and treatment of breast tumors in rodents was reported by Loub *et al.*[2] Indole-3-methanol has also been found to prevent cervical-vaginal cancer in transgenic mice[3] as well as lung cancer in strain-A mice.[4] Additionally, indole-3-methanol shows potential in cardiovascular health since it lowered total cholesterol, LDL (low density lipoproteins) and VDL (very low density lipoproteins) levels in hypercholesterolemic rodents by inhibiting the cholesterol-converting enzyme acyl-CoA. Indole-3-methanol has also been found useful in preventing other kinds of cancers such as leukemia, colon and aflatoxin-induced liver cancer and prostate cancers.[5] Obese women experienced increased oestrogen 2-hydroxylation in response to the dietary agent indole-3-methanol, which may result in hormonal conditions that help reduce oestrogen-dependent cancer risk.[6] The importance of indole-3-methanol in decreasing the risk of breast cancer in women has been well documented in the literature.[7–12] Indole-3-methanol is a known inducer of oxidative P-450 metabolism in animals.[9] The literature survey revealed that oxidation of indole derivatives in biological systems has attracted considerable attention[13–15] whereas practically no information is available on the oxidation of indole-3-methanol.



I

In view of such importance of indole-3-methanol, an attempt has been made to study the electrochemical as well as the chemical oxidation of this compound. This paper presents results of electrochemical and persulfate† oxidation of indole-3-methanol (**I**). The electrochemical oxidation has been carried out at a pyrolytic graphite electrode and a comparison of electrochemical and chemical oxidation is presented. Persulfate reacts through the formation of $SO_4^{\bullet -}$, which is a one-electron oxidant and might induce oxidation similar to that observed electrochemically.

Experimental

Materials

Indole-3-methanol, obtained from Sigma, USA, was used as received. Persulfate (Merck) was purified by recrystallization to remove any traces of impurities formed due to its decomposition. The solutions of persulfate were prepared freshly before each experiment as it is known to undergo thermal and photochemical decomposition in solution.[16,17] Phosphate buffers of ionic strength 1.0 M were prepared according to the method of Christian and Purdy.[18] All potentials are quoted with respect to SCE (saturated calomel electrode) at an ambient temperature of 20 ± 2 °C. The equipment used for the linear and cyclic sweep voltammetry, controlled potential electrolysis and spectral studies was essentially similar to that described earlier.[19,20]

The pyrolytic graphite electrode (PGE) used as the working electrode for the electrochemical studies was manufactured in the laboratory by the reported method[21] and had a surface area of ~0.01 cm^2. After each voltammogram, the PGE surface was renewed by polishing it on a 600 grit metallographic disc. The surface was then washed with a jet of distilled water and dried by touching it on soft tissue paper. This procedure resulted in a significantly new surface for each run and showed a variation of ±10% in peak currents in repeated runs. Hence, for determining the peak current values an average of at least three runs was taken.

Controlled potential electrolysis was carried out in a conventional H-type cell equipped with a three-electrode system having a platinum gauze as the counter electrode, saturated calomel as a reference electrode and a pyrolytic graphite plate (6×1 cm^2) as a working electrode.

Voltammetric studies were performed on a Micronics cyclic voltammeter coupled with an Omniscribe x,y-t series 2000 recorder. The pH of the buffer solutions were measured using a Century digital pH-meter model CP-901-P after due standardization. Coulometric studies were carried out using a BAS CV-50W potentiostat.

UV spectral studies during electro-oxidation were carried out in 1 cm quartz cells using a Shimadzu UV-2100/s spectrophotometer. Gas chromatographic analyses were carried out on

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† The IUPAC name for persulfate, $S_2O_8^{2-}$, is hexaoxo-μ-peroxodisulfate(VI).

DOI: 10.1039/b006855l

a Hewlett-Packard Model 5890 gas chromatograph equipped with integrator and F.I.D detector using HP-1/HR-1 column(s). GC-MS data were obtained on a Shimadzu QP-2000 instrument. The ^{1}H-NMR spectrum of the product was recorded in d$_6$-DMSO on a Varian XL 300 spectrophotometer and its mass spectrum was recorded using a JEOL, JMS D 300 instrument.

Procedures

For recording voltammograms, a stock solution (1 mM) of compound **I** was prepared in doubly distilled water. The solution (2.0 ml) was then mixed with 2 ml of a phosphate buffer of desired pH (1.0 M). The solutions were deaerated for 12–15 min by passing nitrogen gas through them and the voltammograms were then recorded.

The progress of electrolysis was monitored by recording spectral changes at different time intervals. For this purpose, electrolysis was carried out at a potential 100 mV more positive than the peak potential of the oxidation peak. For recording the UV–Vis spectrum, about 2–3 ml of the solution from the electrolysis cell was transferred each time to a 1 cm quartz cell and the spectrum was recorded in the range 200–350 nm.

The products of the electro-oxidation of indole-3-methanol were characterized at pH 6.9. For this purpose, about 15 mg of compound **I** were exhaustively electrolyzed in an H-cell at a potential 100 mV more positive than the peak potential of peak I$_a$. Nitrogen gas was slowly bubbled into the solution during electrolysis and the solution was stirred continuously using a Teflon-coated magnetic stirrer bar. The progress of electrolysis was monitored by recording cyclic voltammograms at different time intervals. When the oxidation peak I$_a$ completely disappeared, the electrolyzed solution was removed from the cell and lyophilized. The lyophilized material was treated with methanol (2 × 5 ml; AR grade) and the methanolic extract was analyzed by TLC using silica gel-G as adsorbent and benzene–methanol (8 : 2) as developer. A single product having R_f of 0.52 was found by TLC. To further confirm the formation of only one major product from the electrooxidation of **I**, the methanolic extract was also analyzed by GC. A single peak at R_t ~9.6 min confirmed the formation of only one product. The product was characterized by ^{1}H-NMR, IR, mp and mass spectra.

The kinetics of the persulfate reaction were studied spectrophotometrically by following the changes in absorbance at different wavelengths due to the consumption of indole-3-methanol and the formation of product. All kinetic experiments were performed under pseudo-kinetic conditions having an excess of persulfate at 27 ± 0.1 °C. Aliquots of 1 µl of chloroform extract of product obtained in the chemical reaction were subjected to GC analysis under non-isothermal conditions by varying the temperature from 100 to 275 °C at a heating rate of 10 °C min^{-1} and were analyzed by GC-MS.

Results and discussion

Electrochemical oxidation

In cyclic sweep voltammetry, indole-3-methanol, at a sweep rate of 100 mV s^{-1} exhibited a single oxidation peak I$_a$ in the pH range 2.4–10.7. At pH < 4.3, peak I$_a$ was ill-defined and usually noticed as a bump, whereas at pH ≥ 4.3, the peak was well-defined and clearly noticed. In the reverse sweep, only one reduction peak II$_c$ was observed at pH ≥ 3.6. Peak II$_c$ was well-defined in the pH range 3.6–6.9, and at pH > 6.9 it became broad in nature. Some typical cyclic voltammograms of a 0.5 mM solution of indole-3-methanol are presented in Fig. 1. The peak potential of oxidation peak I$_a$ was dependent on pH and shifted to less positive potentials with an increase in pH. This behaviour indicated the involvement of protons in the electrode process. The E_p *vs.* pH plot for the oxidation peak I$_a$ was linear (Fig. 2) and the dependence of E_p on pH using linear regression analysis can be expressed by relation (1) with a correlation coefficient ~0.99.

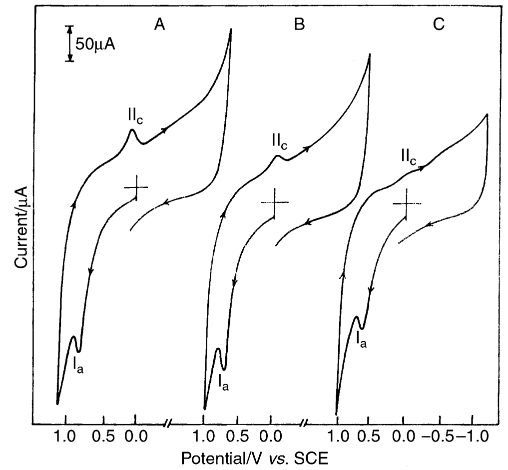


Fig. 1 Typical cyclic voltammograms of 0.5 mM indole-3-methanol at PGE in phosphate buffers of pH (A) 5.3; (B) 6.9 and (C) 9.6; sweep rate = 100 mV s^{-1}.

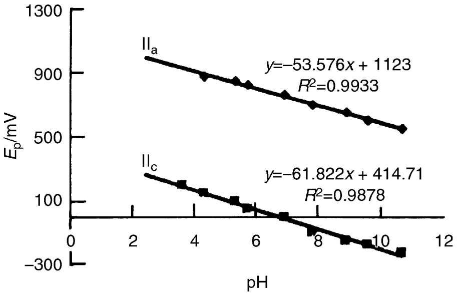


Fig. 2 Observed dependence of E_p on pH for the voltammetric peaks (I$_a$ and II$_c$) of 0.5 mM indole-3-methanol at PGE; sweep rate = 100 mV s^{-1}.

$$E_p\ (\mathrm{I_a})\ [\mathrm{pH}\ 2.4\text{–}10.7] = [1123 - 53.58\mathrm{pH}]\ \mathrm{mV}\ vs.\ \mathrm{SCE} \quad (1)$$

The peak potential of the reduction peak II$_c$ was also dependent on pH and shifted to more negative potentials with an increase in pH. The E_p *vs.* pH plot for peak II$_c$ was also found to be linear (Fig. 2). The dependence of cathodic peak II$_c$ on pH can be expressed by relation (2) with a correlation coefficient ~0.98.

$$E_p\ (\mathrm{II_c})\ [\mathrm{pH}\ 2.4\text{–}10.7] = [415 - 61.8\mathrm{pH}]\ \mathrm{mV}\ vs.\ \mathrm{SCE} \quad (2)$$

The peak current for peak I$_a$ increased linearly with an increase in concentration of indole-3-methanol in the range 0.01–0.5 mM. The i_p *vs.* concentration plot passed through the origin and indicated that this compound can be easily determined in this concentration range. The peak current of peak I$_a$ was also found to increase with an increase in the sweep rate over the range 10 to 900 mV s^{-1}. The plot of $i_p/\sqrt{v}$ *vs.* v is presented in Fig. 3 and the height corresponds to 3e at a low sweep rate to 1e at a high sweep rate, when one considers the rate of dimerization. Thus, the values of $i_p/\sqrt{v}$ were large at low sweep rates and decreased to constant values at higher sweep rates. This behaviour indicated that the nature of the electrode reaction is electrochemical–chemical–electrochemical (ECE) in which two charge-transfer steps are separated by the chemical step involved.[22]

The value of n, the number of electrons involved in the oxidation, was determined by bulk electrolysis in a 0.5 mM solution of indole-3-methanol. The electrolysis at pH 3.6 and 6.9 took approximately 1 h, after which the end current ratio

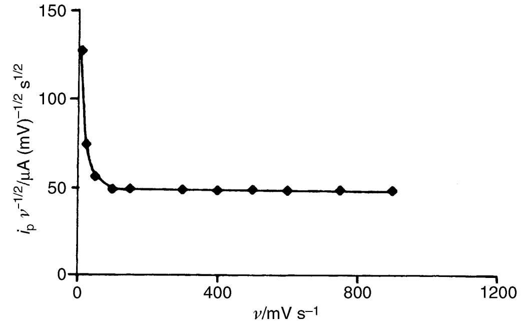


Fig. 3 Variation of the peak current function ($i_p/\sqrt{v}$) with sweep rate for 0.5 mM indole-3-methanol at pH 6.9.

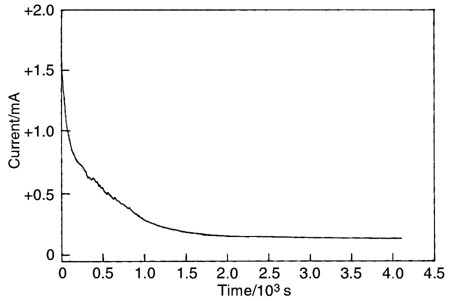


Fig. 4 Plot of current *versus* time observed for 0.5 mM indole-3-methanol in phosphate buffers of pH = 6.9.

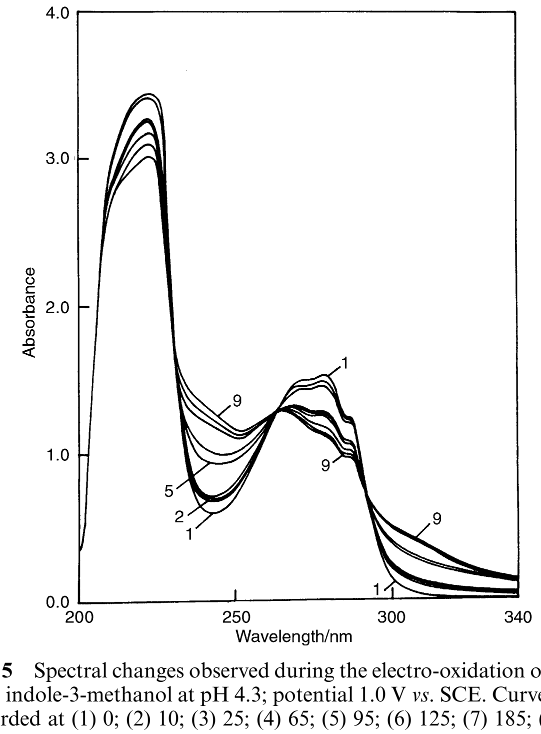


Fig. 5 Spectral changes observed during the electro-oxidation of 0.025 mM indole-3-methanol at pH 4.3; potential 1.0 V *vs.* SCE. Curves were recorded at (1) 0; (2) 10; (3) 25; (4) 65; (5) 95; (6) 125; (7) 185; (8) 245 and (9) 365 min of electrolysis.

became 1%. The plot of current *vs.* time was exponential in nature as shown in Fig. 4 and the value of n was found to be 3.0 ± 0.1 mol^{-1}.

Spectral changes

The spectral changes during electro-oxidation were monitored at pH 4.3, 6.9 and 8.9. The typical results of spectral changes at pH 4.3 are depicted in Fig. 5 in which indole-3-methanol exhibited two absorption maxima at 220 and 270 nm and a shoulder at around 285 nm. Upon application of the potential corresponding to peak I_a, the absorptions at λ_{max} 220 and 270 nm decreased. However, the absorptions in the regions 240–260 and 295–350 nm increased (curves 2–9; Fig. 5). A clear isosbestic point was noticed at around 290 nm, whereas the isosbestic point at 260 nm was not clear. Similar spectral changes were noticed at pH 6.9 and 8.9.

In the second set of experiments, the potentiostat was open-circuited after 20 min of electrolysis and the changes in the UV–Vis spectrum were monitored. A systematic decrease in the absorbance in the region 230–320 nm was observed. This behaviour indicated that a UV-absorbing intermediate is generated during electro-oxidation of the compound, which decays due to competitive chemical reactions. The kinetics of the decay of the UV-absorbing intermediate were monitored by plotting absorbance *versus* time at selected wavelengths (240, 275, 295 and 310 nm). It was found that the absorbance at these wavelengths decreased exponentially with time and that the plots of log $(A - A_\infty)$ *vs.* time were linear. This indicated that the decay of the UV-absorbing intermediate occurred as a pseudo-first-order reaction. The values of k for decay of the UV-absorbing intermediate were calculated from log $(A - A_\infty)$ *vs.* time curves and were found to be in the range $(0.60–0.66) \times 10^{-3}$ s^{-1}. The experiments carried out at pH 6.9 and 8.9 did not exhibit any changes in absorbance on open circuit relaxation. Thus, it appears reasonable to conclude that the k values become significantly higher at neutral and alkaline pH and hence the k value could not be determined.

Chemical oxidation

Mixing of solutions of $S_2O_8^{2-}$ (1 mM) with indole-3-methanol (0.0075 mM) resulted in the formation of a pink-coloured product. The absorption due to indole-3-methanol decayed to yield a product that showed absorption in the visible region. These changes exhibited an isosbestic point at 290 nm. The kinetics of this reaction were monitored by following simultaneously the reactant (indole-3-methanol) and the product at 275 and 600 nm respectively. Persulfate did not interfere in these measurements as it does not possess any absorption beyond 240 nm.

In the kinetic experiments the concentration of indole-3-methanol was varied from 5 to 25 μM, keeping the concentration of persulfate at 1 mM. Both the decay of the absorption due to indole-3-methanol and the increase in absorption due to formation of the product followed pseudo-first-order kinetics and were found to take place at the same rate. Typical kinetic traces depicting these changes at 275 nm are shown as an insert in Fig. 6. A plot of the pseudo-first-order rate constant (k') varied linearly with [indole-3-methanol] from which the second-order rate constant of 0.13 ± 0.005 dm^3 mol^{-1} s^{-1} was computed for both the consumption of the reactant and the formation of product (Fig. 7).

Product characterization

Product of electrochemical oxidation. The colourless lyophilized product obtained from the methanolic extract of the exhaustively electrolyzed solution of indole-3-methanol showed a melting point of ~198 °C. The product showed a prominent band at 1670 cm^{-1} in its IR spectrum, indicating the presence of a carbonyl group. No further bands were noted in the region 1630–1660 cm^{-1}, corresponding to C=N, which ruled out the possibilty of dimerization at C5, because in such a case a quinonoid-type structure would be obtained having a C=N linkage. Other important bands observed in the IR spectrum were at 3973, 3887, 3720, 3666, 3200, 3104, 3035, 2062, 1404, 1300, 1157 and 1088 cm^{-1}. The mass spectrum of the product exhibited a clear molecular ion peak at m/z = 288 (4.1%), indicating the possibility of formation of a dimer. Careful interpretation suggested the product to be the N–N dimer (**V**) in which the –CH_2OH group of indole-3-methanol is oxidized to a CHO group. The other high molecular mass peaks observed in the fragmentation pattern were at 259 (20%, $M^+ - CHO$), 228

(14.1), 207 (18), 205 (50.5) and 193 (14.2). However, no detailed attempt was made to explain the fragmentation pattern. The oxidation of a methanol group to an aldehyde is a common reaction frequently noticed during the oxidation of variety of aliphatic[23] and aromatic[24,25] alcohols. To further confirm the presence of an aldehydic group in the product, a qualitative test with Schiff's reagent was also carried out and it was found that the colour of the solution turned to violet, which confirms the presence of an aldehydic group in the molecule.

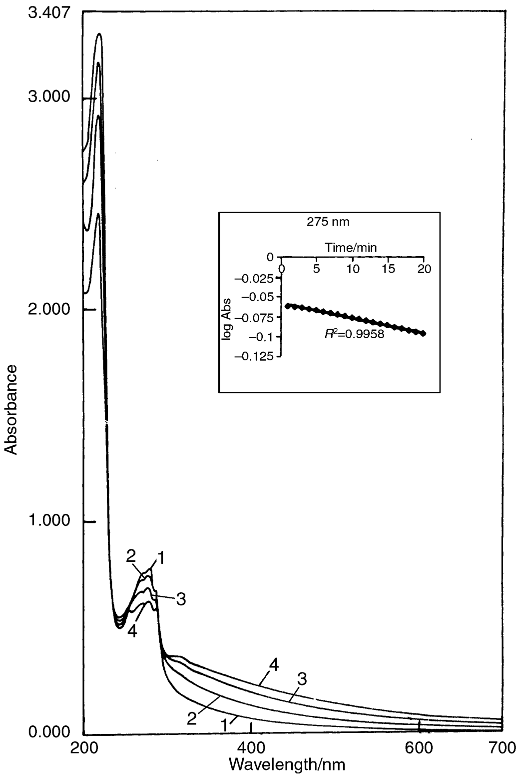


Fig. 6 Spectral changes observed upon mixing of $S_2O_8^{2-}$ (1 mM) and indole-3-methanol (0.0075 mM) at pH 4.3, recorded at different time intervals of oxidation of (1) 8; (2) 13; (3) 18 and (4) 28 min. Inset: kinetic trace recorded at 275 nm by mixing $S_2O_8^{2-}$ and indole-3-methanol at pH 4.3.

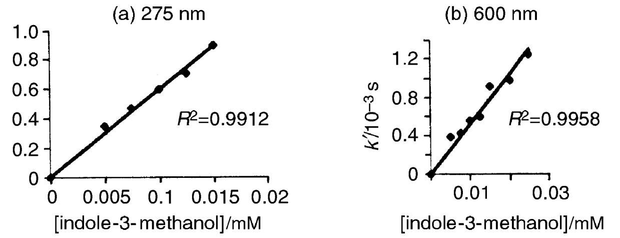


Fig. 7 Plot of k' *versus* [indole-3-methanol] at pH 4.3 at different wavelengths (a) 275 and (b) 600 nm.

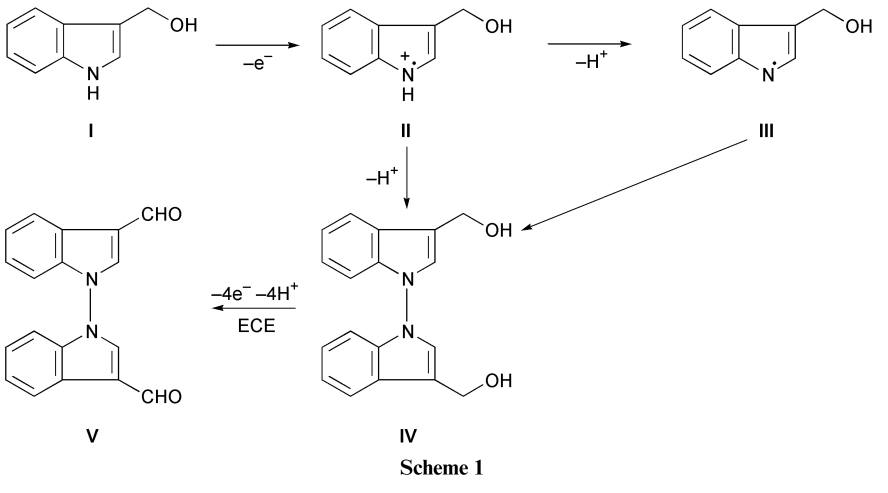
The ^{1}H-NMR spectrum of indole-3-methanol exhibited a clear signal at $\delta = 9.1$ (s, NH), whereas the NMR spectrum of its oxidation product did not show any signal corresponding to an NH proton, suggesting that the initial oxidation of indole-3-methanol occurs at the –NH linkage. Other signals observed in the NMR spectrum were at $\delta = 9.5$ (2H, 2 × –CHO) and a broad multiplet was noticed in the region $\delta = 6.8$–8.0 (10H, aromatic) corresponding to aromatic protons. Thus, it is concluded that the product of oxidation is an N–N linked dimer having a –CHO group in place of –CH_2OH.

Product of chemical oxidation. The gas chromatogram of the chloroform extract of the product showed the formation of nine components. Out of these, two components were dominant. Two of the main components having retention times 26.3 and 36 min were identified by GC-MS to be an N–N dimer of indole-3-methanol (**IV**) [m/z = 292 (10.8%), M^+] and a hydroxy dimer (**VIII**) [m/z = 308 (31.2%), M^+], respectively.

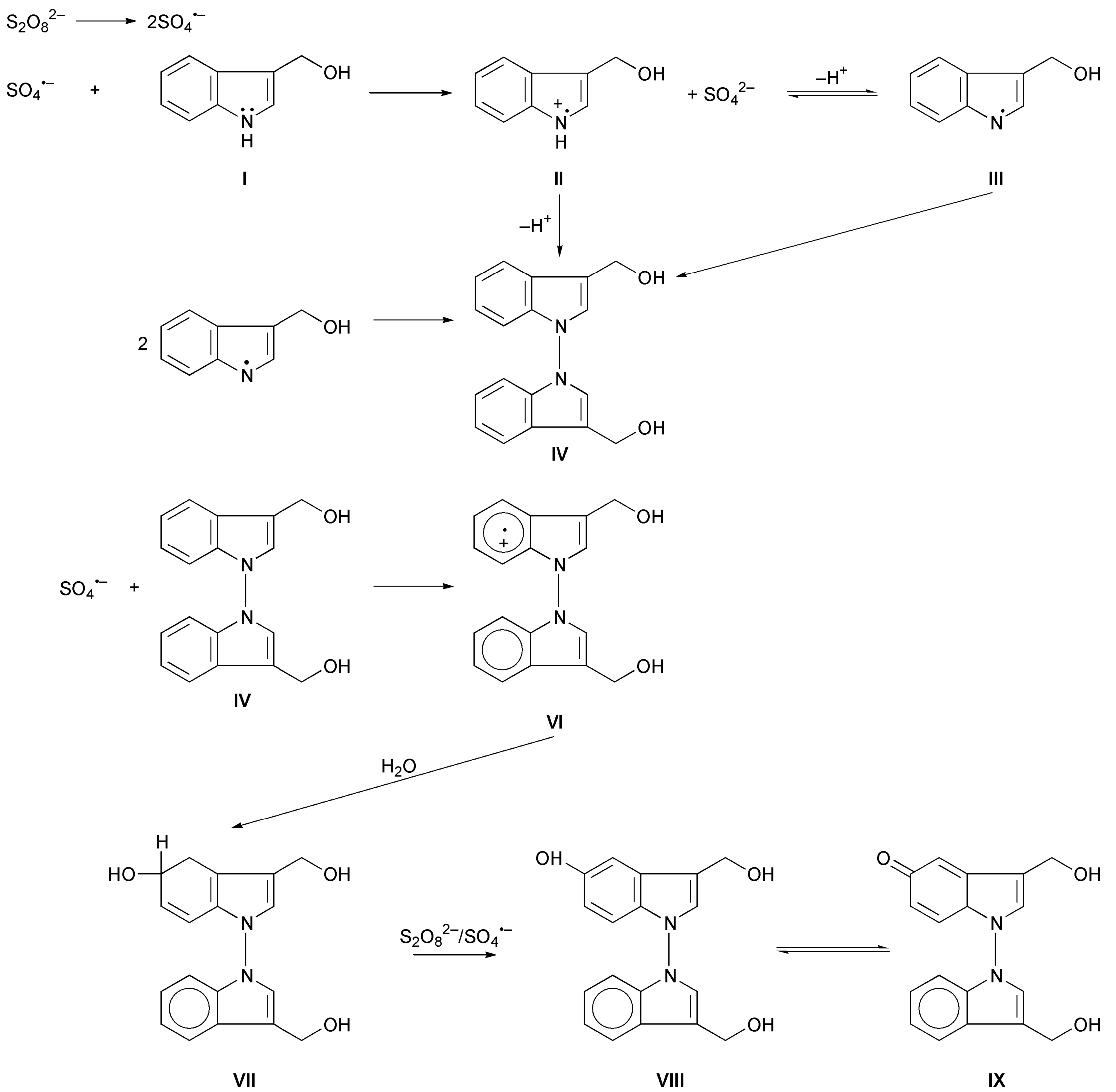
Oxidation mechanism

Electrochemical. On the basis of voltammetric behaviour, spectral behaviour, coulometry and product characterization, the following mechanism can be suggested for the oxidation of indole-3-methanol at PGE. In the first step, indole-3-methanol is oxidized in a 1e step to give a radical cation moiety (**II**) as shown in Scheme 1. The initial removal of an electron occurs from the –NH of the pyrrole ring of indole as has already been reported during oxidation of indole.[26] The cation radical formed can either undergo loss of a proton to give neutral free radical **III** or it can dimerize with loss of two protons to give dimer **IV**. The free radical **III** can also dimerize to give **IV**. The possibility of free radical formation appears to be less on the basis of the slopes of dEp/dlog v and dEp/dlog c, which were much higher than expected for radical–radical coupling reactions.[27] However, the participation of the free indolyl radical in this step was not completely ruled out in view of the pK_a of the indolyl radical cation which is ~5.0 as reported in the literature.[28] Thus, the radical cation rapidly dimerizes to give the N–N linked dimer **IV**. The oxidation of the methanol group then occurs in a 2e, $2H^+$ process *via* the ECE mechanism to give the aldehydic dimer **V**, which has been characterized by its mass and NMR spectra. Peak II_c observed by cyclic voltammetry appears to be due to the reduction of dimer **V** to the corresponding methanol.

Chemical. On the basis of the above observations, the mechanism shown in Scheme 2 has been suggested for this reaction. Persulfate is known to decompose thermally to produce



Scheme 1



Scheme 2

$SO_4^{\bullet-}$.[26,29] The possibility of the involvement of $^{\bullet}OH$ in the first step of Scheme 2, which might be formed by the reaction: $SO_4^{\bullet-} + H_2O \rightarrow {}^{\bullet}OH + H^+ + SO_4^{2-}$, has been discounted[30] at pH 4.3, as used in the present study. This pathway becomes important only in basic media at pH ≥ 9. The sulfate radical is shown to oxidize indole-3-methanol to yield the corresponding indolyl radical cation **II**, which remains in acid–base equilibrium with its neutral form **III**. In view of the known pK_a (5.0 ± 0.1) of the related radical cation in literature,[28] it is estimated that at pH 4.3, the ratio of **II** to **III** will be 80 : 20. The sulfate radical is also known to attack the aromatic ring rapidly but its initial path of attack is to abstract an electron from the lone pair of the nitrogen present in the pyrrole ring as oxidation at this site is more facile and has earlier been observed with similar substrates employing other inorganic oxidants such as $Br_2^{\bullet-}$ and $(SCN)_2^{\bullet-}$,[31] *etc.* Thus, at pH 4.3 both the cation **II** and indolyl radical **III** formed would participate in coupling to yield the N–N linked dimer **IV**. In the secondary reaction, $SO_4^{\bullet-}$ attacks the benzene ring by oxidizing it to the corresponding radical cation **VI**, which reacts with water to yield cyclohexadienyl radical **VII** to finally form **VIII**. The lack of an aldehydic product like **V** in electrochemical oxidation was verified by its negative test with Schiff's reagent. The formation of a cyclohexadienyl radical has earlier been observed by attack of $SO_4^{\bullet-}$ on the benzene ring of other aromatics by both pulse radiolysis[32,33] and EPR[34–36] experiments. With benzene, $SO_4^{\bullet-}$ reacts with a rate constant of 3×10^9 $dm^3\ mol^{-1}\ s^{-1}$[31] and this pathway was verified by Walling and Camaioni[37] by isolating the products of oxidation of aromatics by $S_2O_8^{2-}$.

It is interesting to note that the electronic spectral changes observed in the initial course of oxidation, both electrochemically as well as chemically, are very similar. These changes exhibited an isosbestic point at 290 nm and increased absorption in the visible region. The identification of the products suggests their formation to involve initially the abstraction of an electron from the lone pair of the N of the pyrrole ring to yield a radical cation, which, upon deprotonation, produces the indolyl-type radical **II**. These radicals then recombine to result in the formation of the N–N coupling product. However, the secondary products in electrochemical and chemical oxidations are different. Electrochemical reaction leads to oxidation of the alcoholic group to form the aldehydic product **V**, whereas chemical reaction produces 5-hydroxydimer **VIII**.

In summary, both electrochemical and persulfate oxidation of indole-3-methanol occur through stepwise electron transfer. The electrode reactions followed the ECE mechanism. A comparison of electrochemical and chemical oxidation clearly indicates that the final products of oxidation of the two mechanisms are different, in spite of the similar initial 1e, $1H^+$ step that gave the N–N dimer **V**.

Acknowledgements

One of the authors (P. G.) is thankful to University Grants Commission for awarding a Senior Research Fellowship. Thanks are also due to the Director, O.N.G.C., Dehradun for permitting GC-Mass studies on the samples. Financial assistance for this work was provided by the Department of Science and Technology, New Delhi through grant no. SP/S1/06/97.

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