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Kinetics and Mechanism of The Oxidation of 2-Methylindole by Alkaline Potassium Hexacyanoferrate(III)

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Abstract

The reaction of 2-methylindole with hexacyanoferrate(III) in alkaline media to produce the corresponding 2-methylindolin-3-one has been studied at constant temperature and ionic strength. The reaction followed first order kinetics with respect to [2-methylindole], [OH^-] and [$Fe(CN)_6^{3-}$]. The effects of added electrolytes, potassium hexacyanoferrate(II), relative permitivity and temperature have also been studied. On the basis of experimental observations, a probable reaction mechanism has been proposed.

Keywords: 2-methylindole; hexacyanoferrate(III); 2-methylindolin-3-one; kinetics and oxidation

1. Introduction

Kinetic studies on oxidation of a variety of organic nitrogen compounds by hexacyanoferrate(III) in alkaline medium have been undertaken by many workers [1-4]. However, very little work has been reported on the oxidation of heterocyclic compounds in general and indole and its derivatives in particular.

Oxidation of indole and its derivatives has received much attention because of the involvement of the indole derivatives in significant biological processes. They have antiinflammatory, tumor growth inhibitor, antiviral, antitubercular, antibacterial and psychotropic activities [5, 6]. Indole structures are present in a great number of compounds of biological importance, e.g., the plant growth hormone indoleacetic acid, the pineal gland hormone melatonin, serotonin and tryptophan [7].

Although the oxidation of certain substituted indoles by a wide variety of oxidizing agents has been reported in the literature [8], the lack of kinetic and mechanistic investigation on the oxidation of indoles by potassium hexacyanoferrate(III) instigated us to carry out this work. The usefulness of hexacyanoferrate(III) is due to its high stability, water solubility and its moderate reduction potential, leading to its reduction to hexacyanoferrate(II), a stable product [9,10].

Therefore, the present study reports our kinetic investigations of oxidation of 2-methylindole by potassium hexacyanoferrate(III) in alkaline medium containing (4%) ethanol.

2. Experimental

2.1. Reagents

Potassium hexacyanoferrate(III) (Alfa Aesar), 2-methylindole, potassium fluoride, potassium chloride, potassium bromide, potassium iodide, potassium nitrate, ammonium chloride and potassium hexacyanoferrate(II) (Aldrich), sodium chloride, sodium hydroxide and ethanol (Frutarom) were used in the purest form without further purification. Deionized distilled water was used for the preparation and dilution of all solutions. The desired hydroxide ion concentration was achieved using prestandardized NaOH solution. The required ionic strength was achieved by adding NaCl. The reaction was initiated by simultaneous addition of the required volume of $K_3Fe(CN)_6$ and 2-methylindole solutions to keep the total volume constant in all runs.

2.2. Kinetic Studies

The requisite amount of each reactant was first placed in a test tube and thermostated at 24°C to attain thermal equilibrium. The appropriate quantities of reactants were mixed in a 25-mL volumetric flask in a sequence of 2-methyindole, NaOH, and then the solvent, at a fixed ionic strength. The reaction was finally initiated by injecting $[Fe(CN)_6]^{3-}$ into the above mixture. The reaction mixture was properly

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shaken and quickly transferred to the spectrophotometer's cuvette, which had a path length of 10 mm. The extent of reaction was monitored by the decrease in absorbance at 420 nm corresponding to λ_{max} of $Fe(CN)_6^{3-}$ using Perkin Elmer UV/V spectrophotometer. The reaction was followed for at least two half-lives.

2.3. Stoichiometry

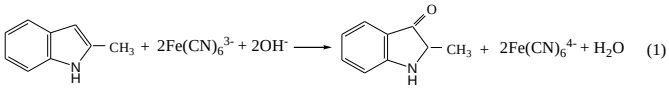
The stoichiometry for the oxidation of 2-methylindole was determined by allowing a large excess of hexacyanoferrate(III) to react with the 2-methylindole in the presence of 0.05 mol dm^{-3} NaOH, for 96 h, to insure a complete reaction as indicated by the constant absorbance of $Fe(CN)_6^{3-}$. The amount of oxidant left unreacted revealed that 2 moles of $Fe(CN)_6^{3-}$ were consumed per one mole of the 2-methylindole.

2.4. Product analysis

A stoichiometric mixture of the 2-methylindole and potassium hexacyanoferrate(III) was kept in NaOH until the completion of the reaction. The oxidation product was extracted from the mixture with several batches of chloroform. The chloroform was then evaporated from the extract using a water bath, thereafter the organic material was precipitated [1, 11]. The formation of 2-methylindolin-3-one as an end product was detected from the I.R and GC-MS spectra of the product.

3. Results and Discussion

The stoichiometric analysis showed that 1 mol of the 2-methylindole consumes 2 moles of $Fe(CN)_6^{3-}$. Furthermore, product analysis showed that the product of the reaction of $Fe(CN)_6^{3-}$ with 2-methylindole was 2-methylindolin-3-one. Accordingly, the overall balanced equation can be written as:



(1)

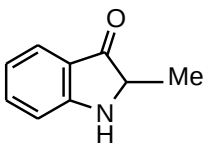
Valdecir et al [7], reported that the oxidation of 2-methylindole in the presence of H_2O_2 catalyzed by horseradish peroxidase gave 2-methyl-3-indolinone product (1) which then dimerizes to give 2,2′-dimethyl-2,2′-diindoxyl (2).

The rates of the reaction was observed to be directly dependent on the concentrations of the reacting species (2-methylindole, OH- and $Fe(CN)_6^{3}$). The order in [2-methylindole], $[OH^-]$ as well as in $[Fe(CN)_6^{3-}]$ is nearly 1 (Table 1).

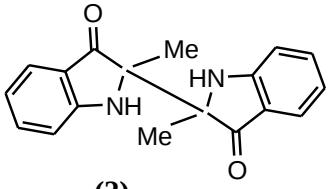
A plot of initial rate values versus concentration of $K_3Fe(CN)_6$ is a straight line. The line, if extrapolated, passes through the origin. This means that rate is proportional to concentration of $K_3Fe(CN)_6$; that is, rate = $k[K_3Fe(CN)_6]$. This must then be a first order reaction (Figure 1).

Table 1: Initial rate data for the oxidation of 2-methylindole at 24 ºC and μ = 0.15 mol dm^{-3}.

10^4[2-methylindole], mol dm^{-3}	10^3[$Fe(CN)_6^{3-}$], mol dm^{-3}	10^2[NaOH], mol dm^{-3}	10^3[initial rate], mol dm^{-3} s^{-1}
1.25	1.00	5.00	0.79
2.50	1.00	5.00	1.48
5.00	1.00	5.00	3.01
7.50	1.00	5.00	4.62
10.00	1.00	5.00	6.10
10.00	0.60	5.00	3.66
10.00	0.80	5.00	4.65
10.00	1.00	5.00	6.19
10.00	1.20	5.00	7.28
10.00	1.00	1.00	0.80
10.00	1.00	2.00	1.83
10.00	1.00	4.00	4.03
10.00	1.00	8.00	7.61
10.00	1.00	10.00	12.66



(1)



(2)

Added hexacyanoferrate(II) retards the rate (Table 2 and Figure 2), indicating that $[Fe(CN)_6]^{4-}$ is involved in a reversible step that could affect the rate determining step and suggesting that the reaction proceeds through a radical intermediate [1].

The rate was not affected by the variation in ionic strength of the reaction media using different added concentrations of sodium chloride (Table 2). This shows that the reaction occurs between a neutral species and a mononegative ion [12].

The rate of reaction decreased with increase in percentage of ethanol in the solvent medium (Table 2). This probably indicates that there is a charge development in the transition state involving a more polar activated complex than the reactants [12].

Insignificant effect on the rate was observed on varying the anion of the potassium salt added (Table 3). This indicates that the reaction occurs between a neutral species, namely 2-methylindole, and a negative ion [12, 13]. On the other hand, the rate of reaction increased according to the sequence ($K^+ \geq Na^+ >> NH_4^+$). This supports the enhancement in rate on increasing hexacyanoferrate(III), since the cation is assumed to act as a bridge for electron transfer.

The decrease in rate of oxidation in the presence of NH_4^+ might be explained by the consumption of hydroxide ions, which are necessary for rapid oxidation, by a neutralization reaction.

$$NH_4^+ + OH^- \rightleftharpoons NH_3 + H_2 \qquad (2)$$

The reaction was studied at different temperatures (25-45°C) at fixed concentration of [2-methylindole] = 1.00×10^{-3} mol dm^{-3}, $[Fe(CN)_6^{3-}] = 1.00\times10^{-3}$ mol dm^{-3}, $[OH^-] = 5.00\times10^{-2}$ mol dm^{-3}, $\mu = 0.15$ mol dm^{-3}. Rate constants were calculated (Table 4) using the found rate equation (Eq. (3)). The activation parameters Ea, ΔH^*, ΔS^*, ΔG^* were evaluated from the linear Arrhenius plot of log k_{obs} vs 1/T and Gibbs free energy [12] and found to be 9.82 kJ mol^{-1}, 7.26 kJ mol^{-1}, -31.37 J K^{-1} mol-1 and16.92 kJ mol^{-1} respectively.

Table 2: Effect of added ferrocyanide, sodium chloride and ethanol on initial rates.

$10^3[Fe(CN)_6^{4-}]$, mol dm^{-3}	$10^2[NaCl]$, mol dm^{-3}	%Ethanol (v/v)	10^3[initial rate], mol dm^{-3} s^{-1}
0.40			5.09
0.80			4.26
1.00			4.11
2.00			3.54
4.00			2.43
	0.50		3.81
	1.00		3.80
	2.00		3.99
	4.00		4.01
	8.00		4.35
		10.0	6.84
		20.0	1.27
		30.0	0.36
		40.0	0.18

10^3[2-methylindole] = 1.00, $10^3[Fe(CN)_6^{3-}] = 1.00$, $10^2[OH^-] = 5.00$ mol dm^{-3}, temperature = 24°C and $\mu = 0.15$ mol dm^{-3}.

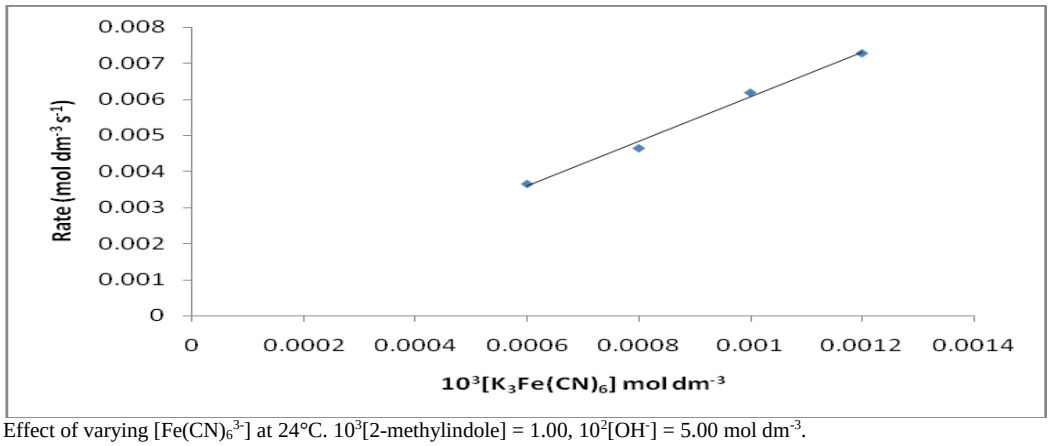


Fig. 1. Effect of varying $[Fe(CN)_6^{3-}]$ at 24°C. 10^3[2-methylindole] = 1.00, $10^2[OH^-] = 5.00$ mol dm^{-3}.

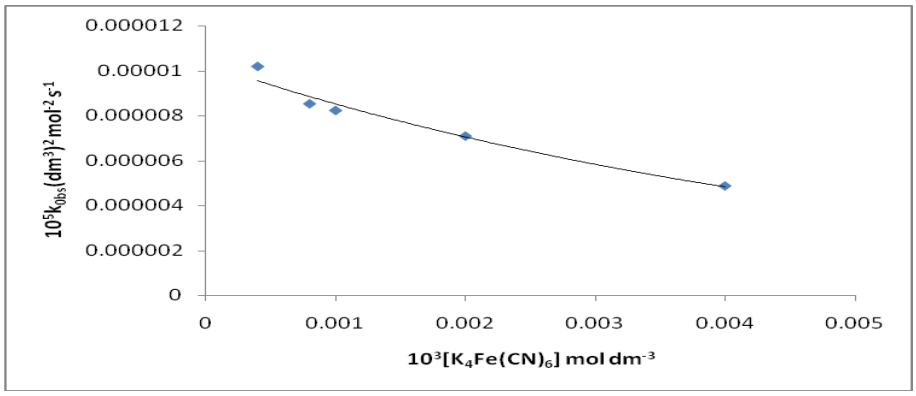


Fig. 2. Effect of varying $[Fe(CN)_6^{4-}]$ at 24°C. 10^3[2-methylindole] = 1.00, $10^3[Fe(CN)_6^{3-}]$ = 1.00, $10^2[OH^-]$ = 5.00 mol dm^{-3}.

Table 3: Effect of added salts on rate of oxidation**.**

Salt	10^3[initial rate], mol dm^{-3} s^{-1}
KF	4.87
KCl	5.17
KBr	5.55
KI	5.31
KNO_3	5.39
NaCl	5.05
NH_4Cl	0.31

10^2[salt] = 4.00, 10^3[2-methylindole] = 1.00, $10^3[Fe(CN)_6^{3-}]$ = 1.00, $10^2[OH^-]$ = 5.00 mol dm^{-3}, temperature = 24ºC and μ = 0.15 mol dm^{-3}.

The negative value of ΔS^* in the present oxidation indicates that the transition state is more ordered than the reactants due to loss of degree of freedom [2].

Moderately large negative values of the entropy of activation suggest that the rate determining step involves two negatively charged ions to give a bigger complex ion [14, 15], resulting in the loss of freedom of motion.

The results suggest an experimental rate law for the initial rate that could be written as:

$$-d[Fe(CN)_6^{3-}]/dt = k\,[2\text{-methylindole}]\,[OH^-]\,[Fe(CN)_6^{3-}] \quad (3)$$

Based on the experimental results, the following reaction sequence presented in equations (4)-(8) has been proposed.

The first step (Eq. 4) is reversible and involves the formation of a radical intermediate. In the second step (Eq. 5), deprotonation of C-3 takes place by hydroxide ion to give another intermediate which then oxidized by another hexacyanoferrate(III) ion followed by adding OH- ion to C-3 to give the oxidation product.

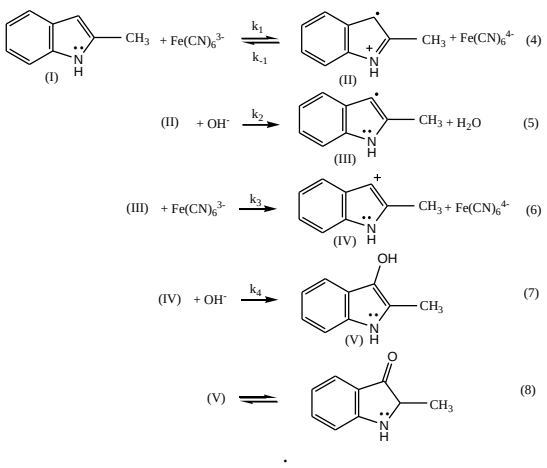
The removal of an acidic proton by hydroxide ion (Eq. 5) has been proposed because only substrates with acidic protons undergo the reaction and also the reaction does not take place at low hydroxide ion concentration. The removal of an acidic proton has been shown in a variety of hexacyanoferrate(III) oxidations [16-18, 19]. Recently, the abstraction of the acidic proton from the 3-position of 2-methylindole by hydroxide ion in the hexacyanoferrate(III) oxidation has been suggested. The first order dependence on $[OH^-]$ suggests the involvement of hydroxide ion presumably in the formation of an intermediate.

Since the overall process is two electron-oxidation on the grounds of single electron transfer, two molecules of hexacyanoferrate(III) must be consumed in the reaction.

Table 4: Thermodynamic parameters of activation.

T (ºC)	25	35	45
10^{-5} k_{obs}, $(dm^3)^2$ mol^{-2} sec^{-1}	1.17	1.52	2.20

10^3[2-methylindole] = 1.00, $10^3[Fe(CN)_6^{3-}]$ = 1.00, $10^2[OH^-]$ = 5.00 mol dm^{-3}, and μ = 0.15 mol dm^{-3}



The reversible nature of the first step (Eq. 4) stems from the rate retardation by added hexacyanoferrate(II). At low concentrations of hexacyanoferrate(II) the backward reaction of this step is slow compared to the forward reaction.

The oxidations with hexacyanoferrate(III) proceed by outer-sphere mechanisms and takes place between the metallic centers, thus the redox couple $[Fe(CN)_6^{3-}]/[Fe(CN)_6^{4-}]$ is a monoelectronic system. The key step in any of its redox processes is an electron transfer. For this to take place, an ion pair, oxidant-substrate intermediate should be formed in a rapid pre-equilibrium [20].

The second step in the mechanism (Eq. 5) is considered to be the slow one, so the proposed mechanism enables us to derive the following rate law:

$$-d[Fe(CN)_6^{3-}]/dt = \frac{k_1 k_2 [I][OH^-][Fe(CN)_6^{3-}]}{k_{-1}[Fe(CN)_6^{4-}] + k_2[OH^-]} \qquad (9)$$

Since step 2 in the mechanism is the slow one, we can simplify the equation by assuming $k_2[OH^-] << k_{-1}[Fe(CN)_6^{4-}]$

$$-d[Fe(CN)_6^{3-}]/dt = \frac{k_1 k_2 [I][OH^-][Fe(CN)_6^{3-}]}{k_{-1}[Fe(CN)_6^{4-}]} \qquad (10)$$

It is obvious from the rate equation that, the reaction is first order in each 2-methylindole, hydroxide ion and hexacyanoferrate(III). Thus the derived rate law is in complete agreement with the obtained experimental results.

The derived rate expression enables us to explain the observed effect of added $[Fe(CN)_6^{4-}]$ on the experimentally determined rate constant when added $[Fe(CN)_6^{4-}]$ is varied from one experiment to the other. Since $[Fe(CN)_6^{3-}]/[Fe(CN)_6^{4-}]$ is incorporated in the rate expression, so changing $[Fe(CN)_6^{3-}]/[Fe(CN)_6^{4-}]$ will change the reaction rate.

Thus the proposed mechanism and the derived rate law satisfactorily explain all the experimental observations.

4. Conclusions:

The rate of the studied reaction followed first-order kinetics with respect to 2-methylindole, hydroxide ion and hexacyanoferrate(III). The rate decreased with increasing the concentration of $K_4Fe(CN)_6$ and increased with varying the cation of the added salt. However, the rate was not affected by varying the anion of the added salt.

5. Conflicts of interest:

There are no conflicts to declare.

6. Acknowledgment:

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كينيتية وميكانيكية أكسدة مركب 2-ميثيل اندول بواسطة بوتاسيوم هكساسيانو الحديديك في وسط قلوي

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تتناول هذه الدراسة أكسدة مركب 2-ميثيل اندول (2-methylindole) باستعمال حديدي سيانات البوتاسيوم $[K_3Fe(CN)_6]$ كعامل مؤكسد في وسط قاعدي ذي درجة حموضة pH (12.7) تقريبا ودرجة حرارة ثابتة.

وجد في هذه الدراسة أن مول واحد من مركب 2-ميثيل اندول يتأكسد بمولين من مادة $[K_3Fe(CN)_6]$ ليعطي مركب (2-methylindolin-3-one). وقد تم بحث تأثير تركيز كل من مواد التفاعل مثل تركيز 2-ميثيل اندول، تركيز حديدي سيانات البوتاسيوم وتركيز ايون الهيدروكسيد وتبين أن سرعة التفاعل تعتمد على تركيز كل من 2-ميثيل اندول، حديدي سيانات البوتاسيوم وأيون الهيدروكسيد للدرجة الأولى.

لوحظ ان معدل سرعة التفاعل يقل باضافة مادة حديدو سيانات البوتاسيوم $[K_4Fe(CN)_6]$ وهذا يثبت ان خطوة التفاعل التي يتم فيها نزع الالكترون بواسطة العامل المؤكسد عكسية.

كذلك تم في هذا البحث دراسة تاثير كل من درجة الحرارة وعوامل اخرى على ميكانيكية التفاعل مما مكن من حساب بعض الثوابت المتعلقة بحركية التفاعل وبالتالي اقتراح ميكانيكية مناسبة لعملية اكسدة المركب تحت الدراسة.