

Oxidation of some Alicyclic Amines by Potassium Hexacyanoferrate (III) in Alkaline Medium: A Kinetic and Mechanistic Study

حركية وميكانيكية تأكسد بعض الأمينات الحلقية بواسطة $K_3Fe(CN)_6$ في وسط قاعدي

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Received: (14/2/2001), Accepted: (13/6/2001)

Abstract

Oxidation of some alicyclic amines (morpholine, piperazine and piperidine) by potassium hexacyanoferrate(III) in basic medium has been investigated at 35°C. Stoichiometric results showed that four moles of hexacyanoferrate(III) were consumed per mole of piperidine or morpholine whereas piperazine consumed eight moles of the oxidant to produce the corresponding lactams. Kinetic studies indicated that piperidine and morpholine also followed different kinetics from that of piperazine, being first order in the amine concentration and independent of the concentrations of hexacyanoferrate(III) and hydroxide ion, while in the case of piperazine, the reaction was first order in both oxidant and substrate concentrations and zero order with respect to the concentration of hydroxide ion. The changes in reaction rate due to changing ionic strength of the medium as well as other factors has also been investigated. The activation parameters of the oxidation process have been evaluated and a mechanism consistent with the observed kinetics has been proposed.

Keywords: Hexacyanoferrate(III), morpholine, piperazine, piperidine, oxidation, lactam.

ملخص

تناولت هذه الدراسة أكسدة بعض الأمينات الحلقية (Morpholine , Piperazine, Piperidine) بواسطة $K_3Fe(CN)_6$ في وسط قاعدي وعلى درجة حرارة ثابتة. تبين أن أكسدة مول واحد من مادة Morpholine أو مادة Piperidine تستهلك أربع مولات من $K_3Fe(CN)_6$ بينما احتاج المول الواحد من مادة Piperazine الى ثمان مولات من $K_3Fe(CN)_6$ ليتم تحويل الأمين الى اللاكتام (Lactam) المعني. كما تبين أن تأكسد Morpholine وكذلك Piperazine يتبع حركية تفاعل مختلفه عن تلك في حالة Piperazine كون

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التفاعل في الحالة الأولى لا يعتمد على تراكيز OH^- أو $\text{K}_3\text{Fe}(\text{CN})_6$ في حين يعتمد على تركيز Morpholine أو Piperadine للدرجة الأولى. أما في حالة Piporezine فقد كان التفاعل من الدرجة الأولى بالنسبة لتراكيز كل من الأمين والعامل المؤكسد ولكنه لا يعتمد على تركيز أيون OH^- . كذلك تم في هذا البحث دراسة تأثير كل من درجة الحرارة وعوامل أخرى على ميكانيكية التفاعل مما مكن من حساب بعض الثوابت المتعلقة بحركية التفاعل وبالتالي اقتراح ميكانيكية مناسبة لعملية أكسدة الأمينات تحت الدراسة.

Introduction

Tertiary amines, with at least one $\alpha\text{-C-H}$ bond, are susceptible to oxidation by a variety of reagents including chlorine dioxide, potassium hexacyanoferrate(III) as well as microsomal oxidation^[1-4].

The oxidation of tertiary amines by chlorine dioxide results in dealkylation of the amine to produce a secondary amine and the corresponding aldehyde^[5,6]. Oxidative demethylation of N-methyl tertiary amines by potassium hexacyanoferrate(III) occurs only when the methyl amino group is attached to a secondary or a tertiary carbon atom but not to a primary one^[7].

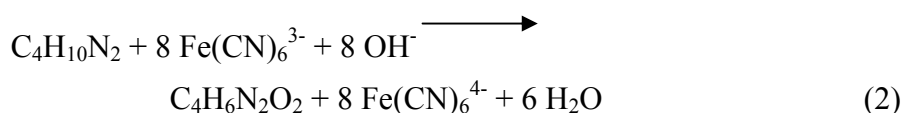
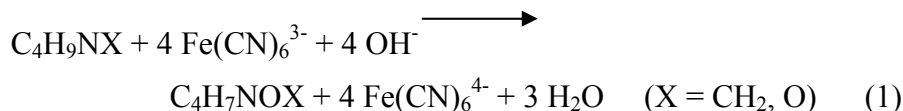
Nitrogen containing compounds are oxidized to lactams by a variety of oxidizing agents including chromium, osmium, platinum, ruthenium and manganese oxides, halogens and others^[8].

The present study aimed to investigate the kinetics of oxidation of the three amines: morpholine (tetrahydro-1,4-oxazine), piperidine (hexahydropyridine) and piperazine (hexahydropyrazine) using potassium hexacyanoferrate(III) in aqueous NaOH in order to postulate the appropriate mechanism(s). Besides being cyclic, the selected amines, differ in the type of atom occupying position 4 in the ring skeleton.

The selected amines, or their compounds, have been used extensively as synthetic intermediates^[9] for a wide range of pharmaceuticals, insecticides, fungicides, herbicides, local anesthetic, antiseptics, polymers, dyes, corrosion inhibitors, rubber accelerators, surfactants, emulsifiers and antioxidants. The amines are also used as cheap solvents for resins, waxes and casein and as reagents for the determination of several compounds such as oxazolines.

Results and Discussion

Stoichiometric determination showed that four moles of ferricyanide were consumed per mole of morpholine or piperidine, and eight moles were consumed per mole of piperazine to produce 3-morpholinone, 2-piperidone and 2,5-piperazinedione respectively. Thus the stoichiometric equations for the reactions could be written as:



The rate of amine oxidation followed zero-order dependence in hexacyanoferrate(III) for both morpholine and piperidine and first-order dependence for piperazine, as found from $\log[\text{initial rate}]$ versus $\log[\text{Fe}(\text{CN})_6^{3-}]$ plots. However, and for the three amines, the reaction was first order in amine as indicated by the direct proportionality of initial rate with the concentration of amine. The initial rate of oxidation slightly increased upon increasing hydroxide ion concentration but no correlation could be generalized. Results are shown in Tables 1 & 2.

Based on these results, the experimental rate law could be written as: $-\text{d}[\text{Fe}(\text{CN})_6^{3-}]/\text{dt} = k_{\text{obs}} [\text{amine}]$ (amine = morpholine, piperidine) and $-\text{d}[\text{Fe}(\text{CN})_6^{3-}]/\text{dt} = k_{\text{obs}} [\text{piperazine}] [\text{Fe}(\text{CN})_6^{3-}]$

For morpholine and piperidine oxidation, electron abstraction is not the rate-determining step. This assumption is evident from the fact that no salt effect, on the rate, was observed upon changing ionic strength, the cation and anion type (Tables 3 & 4). The cation is assumed to act as a bridge for electron transfer^[10-16]. These results allow us to assume that the rate controlling step is most probably a step that precedes the electron abstraction.

Table 1: Initial rate data for the oxidation of morpholine and piperazine at 35°C, $\mu = 0.15$.

[amine]M	$10^3[\text{Fe}(\text{CN})_6^{3-}]$ M	10[NaOH]M	10^3 Init.rate M s ⁻¹	
			Morpholine	Piperidine
0.1	1.0	1.0	0.70	1.01
0.2	1.0	1.0	1.58	1.96
0.3	1.0	1.0	2.22	2.77
0.4	1.0	1.0	3.03	3.70
0.5	1.0	1.0	3.70	-
0.6	1.0	1.0	-	5.55
0.15	0.4	1.0	0.90	0.85
0.15	0.6	1.0	0.95	1.11
0.15	0.8	1.0	1.01	1.48
0.15	1.0	1.0	0.99	1.75
0.15	1.2	1.0	1.02	2.02
0.15	1.0	0.04	0.60	0.30
0.15	1.0	0.1	0.66	0.47
0.15	1.0	0.31	0.74	0.88
0.15	1.0	0.5	-	1.15
0.15	1.0	1.0	0.81	-

Table 2: Initial rate data for the oxidation of piperidine at 35°C, $\mu = 0.15$.

[piperidine] M	$10^3[\text{Fe}(\text{CN})_6^{3-}]$ M	10[NaOH] M	10^3 Init.rate (M s ⁻¹)
0.1	1.0	1.0	3.22
0.2	1.0	1.0	5.12
0.3	1.0	1.0	7.75
0.4	1.0	1.0	10.10
0.6	1.0	1.0	15.15
0.1	0.4	1.0	2.89
0.1	0.6	1.0	3.03
0.1	0.8	1.0	3.08
0.1	1.0	1.0	3.11
0.1	1.2	1.0	3.17
0.1	1.0	0.04	2.63
0.1	1.0	0.1	2.85
0.1	1.0	0.2	2.94
0.1	1.0	0.3	3.03
0.1	1.0	0.5	3.08

Table 3: Effect of added ferrocyanide, potassium chloride and ethanol on reaction rates.

$10^3[\text{Fe}(\text{CN})_6^{4-}] \text{M}$	$10^2[\text{KCl}] \text{M}$	%Ethanol	10^3 Initial rate (M.S^{-1})		
			Morpholine	Piperidine	Piperazine
0.4			0.86	0.87	0.66
0.7			-	0.78	0.39
1.0			0.85	0.75	0.30
2.0			0.83	0.66	0.16
3.0			0.83	0.57	0.11
	0.5		0.66	1.33	1.30
	1.0		-	1.36	1.33
	1.5		0.67	1.36	1.36
	2.0		-	1.37	1.38
	2.5		0.67	1.38	1.38
		0.0	0.82	1.28	1.12
		10	0.92	1.26	0.99
		20	1.05	1.25	0.86
		30	1.23	1.23	0.70
		40	1.66	1.22	0.68
		50	2.03	1.21	0.66

[Amine] = 0.15 M, $[\text{Fe}(\text{CN})_6^{3-}] = 10^{-3}$ M, $[\text{OH}^-] = 0.1 \text{M}$, $t = 35^\circ\text{C}$, $\mu = 0.15$

Table 4: Effect of added salts on rates of oxidation.

Salt (3.5×10^{-2} M)	10^3 Initial Rate .		
	Morpholine	Piperidine	Piperazine
KF	0.81	1.38	-
KCl	0.88	1.38	1.33
KBr	0.83	1.36	1.34
KI	0.79	1.33	1.34
KNO ₃	0.82	1.44	1.41
NaCl	0.87	1.36	1.11
NH ₄ Cl	0.85	1.25	0.76

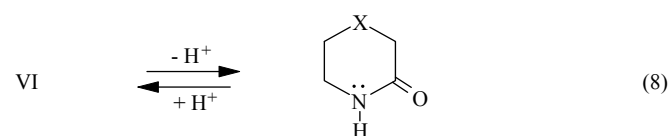
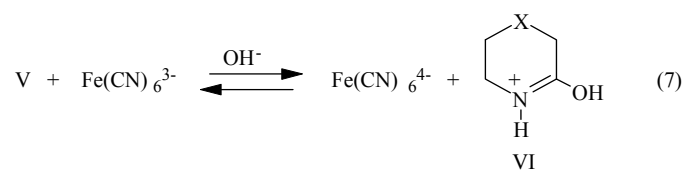
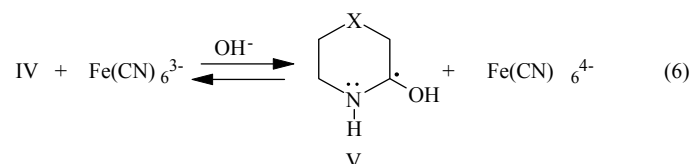
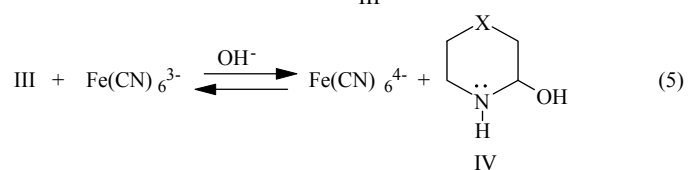
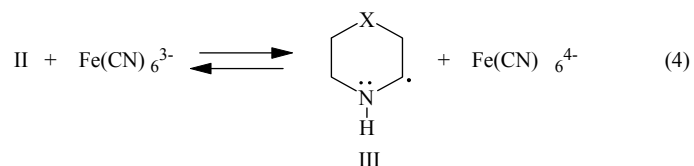
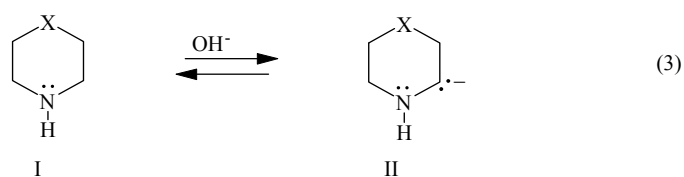
[Amine] = 0.15M, $[\text{Fe}(\text{CN})_6^{3-}] = 10^{-3}$ M, $[\text{OH}^-] = 0.1 \text{M}$, $t = 35^\circ\text{C}$, $\mu = 0.15$

On the other hand, the oxidation of piperazine was dependent on hexacyanoferrate(3) concentration (Table 2) and changed noticeably upon changing the cation type (Table 4). Accordingly, the rate-determining step is assumed to involve electron transfer to ferricyanide. Variations of the ionic strength of the media using potassium chloride (Table 3), and other potassium salts (Table 4) had also no effect on the rate of piperazine oxidation as expected in the presence of a strong base such as the hydroxide ion. However, a remarkable rate retardation was observed upon addition of potassium ferrocyanide to the reaction medium (Table 3), which indicates the reversibility of the rate limiting step^[17-19].

To account for the kinetic results, the following mechanism has been proposed (scheme 1).

The first step in the suggested mechanism (Eq. 3) involves a proton abstraction from the α - carbon atom of the amine (I) resulting in the formation of the α -carbanion (II). This step is assumed to be rate-controlling step in the oxidation of morpholine and piperidine. In the next step (Eq. 4), an electron is abstracted by the oxidant from the carbanion in a reversible step to produce the radical intermediate (III), and this step is assumed to be slow step in the oxidation of piperazine. The rate of oxidation of piperazine decreased by increasing the percentage of ethanol, this might be explained by the lowered dielectric constant of the reaction medium.

The initial rate values followed the sequence: piperidine > piperazine > morpholine which agrees with the electronegativity reverse order of the atom occupying position 4 in the cyclic amine. It also agrees with the basicity of amines as indicated by their K_b values (1.6×10^{-3} , 6.4×10^{-5} & 2.5×10^{-6} for piperidine, piperazine and morpholine respectively).



X = CH₂, NH, O

Scheme 1

The values of the thermodynamic parameters, E_a , ΔH^* , ΔS^* , and ΔG^* , for the oxidation of the amines under consideration, were calculated and are found to agree well with the basicity of the amines and the proposed mechanism (Table V).

Table 5: Thermodynamic parameters of activation.

	t (°C)	26	31	36	41
Morpholine	$10^3 k_{\text{obs}} (\text{s}^{-1})$	5.05	5.53	6.20	6.94
	$E_a (\text{kJ/mol})$	17.8			
	$\Delta S^* (\text{J/mol.deg})$	-239.2			
	$\Delta H^* (\text{kJ/mol})$	12.2			
	$\Delta G^* (\text{kJ/mol})$	86.1			
Piperidine	$10^3 k_{\text{obs}} (\text{s}^{-1})$	10.0	12.9	15.8	20.2
	$E_a (\text{kJ/mol})$	34.9			
	$\Delta S^* (\text{J/mol.deg})$	-166.5			
	$\Delta H^* (\text{kJ/mol})$	32.3			
	$\Delta G^* (\text{kJ/mol})$	83.7			
Piperazine	$k_{\text{obs}} (\text{M.s}^{-1})$	6.53	7.26	8.2	9.6
	$E_a (\text{kJ/mol})$	23.3			
	$\Delta S^* (\text{J/mol.deg})$	-151.9			
	$\Delta H^* (\text{kJ/mol})$	20.7			
	$\Delta G^* (\text{kJ/mol})$	67.1			

The fact that eight moles of ferricyanide were consumed per mole of piperazine is explained by assuming that two consecutive oxidations have occurred on positions 2 and 5 of the ring (both α positions to nitrogen atoms), a fact further supported by the formation of 2,5- piperazinedione as a final product.

Conclusion

The alicyclic amines studied, though secondary amines, are oxidized by alkaline hexacyanoferrate(III) as tertiary amines do. The kinetics and mechanism of oxidation are different from the case of tertiary amines as

the secondary produce lactams rather than the lower amine and aldehyde. The atom occupying position 4 in the six membered rings and thus the basicity of amine have significant effects on rate of oxidation and could lead to different mechanistic pathway.

Experimental Section

Chemicals

Potassium ferricyanide, potassium ferrocyanide, piperidine, morpholine and piperazine were A.C.S. reagents (Aldrich) and used as received without further purification. Doubly distilled water was used for the preparation and dilution of all solutions.

Kinetic measurement

The kinetics of oxidation of the amines under study were followed spectrophotometrically by monitoring the absorbance of potassium hexacyanoferrate(III) with the progress of time at 414 nm. Sodium chloride was added to adjust the ionic strength of the reaction mixture to the required value. The required amounts of the amine and potassium hexacyanoferrate (III) were dissolved, separately, in portions of sodium hydroxide solution in two volumetric flasks. The contents of the two flasks were mixed, keeping the total volume constant by controlling the amount of distilled water, and a stopwatch was started at the same time. A portion of the reaction mixture was transferred to the cell of the spectrophotometer. The absorbance was recorded at appropriate intervals right after mixing. The same procedure was followed to study the effects of added potassium ferrocyanide and other salts on the rate of reaction.

Stoichiometry and Product Analysis

To determine the number of moles of ferricyanide consumed per mole of the amine, a known excess of ferricyanide over the amine was allowed to react at room temperature in the presence of 0.1M sodium hydroxide until the reaction was completed. Unreacted ferricyanide was determined spectrophotometrically and iodometrically.

Infrared and mass spectra of the products showed that oxidation of morpholine, piperidine and piperazine by potassium hexacyanoferrate (III) leads to the formation of 3- morpholinone , 2-piperidone and 2,5-piperazinedione respectively.

The reproducibility of initial rate values was *ca.* $\pm 7\%$.

Acknowledgement

The authors are grateful to An-Najah N. University for financial support of the present work.

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