

Kinetics of Oxidation of Nitrotoluenes by Acidic Hexacyanoferrate (III)

A. K. Bhattacharjee and M. K. Mahanti*

Department of Chemistry, North-Eastern Hill University, Shillong 793003, India (Received September, 1, 1982)

The reaction of hexacyanoferrate (III) with nitrotoluenes in aqueous acetic acid containing perchloric acid (1.0 M) at 50°C gave the corresponding aldehyde as the major product. The order with respect to each of the reactants—substrate, oxidant and acid—was found to be unity. The Hammett plot yielded a σ^+ value of -1.30 , and the kinetic isotope effect gave a k_H/k_D value of 6.2. The pathway for the conversion of the nitrotoluenes to the products has been mechanistically visualized as proceeding through the benzylic radical intermediate, formed in the rate determining step of the reaction.

Introduction

The oxidation of nitrotoluenes has been carried out using oxidants such as chromic acid¹⁻⁵, aqueous sodium dichromate at elevated temperatures⁶, chromyl chloride⁷⁻⁹, chromyl acetate¹⁰, permanganate ion¹¹, lead tetraacetate¹², ceric ions¹³⁻¹⁶, vanadium(V) in acid medium¹⁸, and by Co(III) in acetonitrile¹⁸.

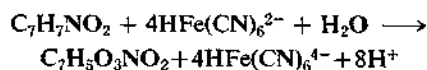
Potassium hexacyanoferrate(III) is an efficient one electron oxidant, and has been observed to be a substitution inert transition metal complex¹⁹. The mechanism of oxidation by hexacyanoferrate (III) would be through an outer sphere process, the transfer of an electron occurring from the substrate to the metal ion through the cyano ligand. In acid medium, potassium hexacyanoferrate(III) has not been used for the oxidation of organic substrates. The present paper reports the results of a kinetic investigation of the oxidation of nitrotoluenes by acidic hexacyanoferrate(III) under a nitrogen atmosphere at 50°C.

Experimental

Materials and Methods. Samples of *o*-nitrotoluene and *m*-nitrotoluene were obtained from Koch-Light Laboratories (UK), and were distilled before use; the bp's were 222°C and 229°C respectively. The *p*-nitrotoluene was a BDH sample, and was recrystallized before use (mp 54°C). $K_3Fe(CN)_6$ and $K_4Fe(CN)_6$ were BDH samples, and were used as such. Acetic acid was an E. Merck sample and was distilled before use (bp 116°C). Perchloric acid was a 'Baker analysed' sample. The deuterated compounds, $ArCD_3$, were obtained from Isotopes Inc., and the nmr spectrum of each of the samples in CCl_4 did not show any absorption for the methyl protons. The sample of $K_3Fe(CN)_6$ was prepared in the requisite quantities of acetic acid, perchloric acid and water. The solutions of the substrates were prepared in acetic acid and water. The two solutions (10 ml each) were separately thermostated at 50°C for 3h, under a nitrogen atmosphere, and were mixed in equal volumes. The progress of the reaction was followed by observing the disappearance of $Fe(CN)_6^{3-}$ at 420 nm, spectrophotometrically, as described in an earlier communication²⁰. IR spectra were recorded on an IR-297 (Perkin-Elmer) spectrophotometer; nmr spectra were recorded on an EM 390 (Varian) 90 MHz NMR spectrometer. All values of rate

constants were the average of two or more experiments, with agreement being $\pm 1.5\%$ or better. All reactions were followed up to 60% conversion, the relation between $\log k_{obs}$ and t being linear in this range.

Stoichiometry. Reaction mixtures containing the substrate and an excess of the oxidant were allowed to react to completion, and then analysed, spectrophotometrically, for the $Fe(CN)_6^{3-}$ which was left. The results gave a ratio of substrate to oxidant according to the equation:



Product analysis. Using approximately the same experimental conditions that were used for the kinetic determinations, the substrates in acetic acid: water (80:20, v/v) were mixed, separately, with $K_3Fe(CN)_6$ taken in acetic acid: water (80:20, v/v) and perchloric acid (1.0 M). The reaction mixture was kept at 50°C under a nitrogen atmosphere for 24h to enable the completion of the reaction. At the end of the reaction, the reaction mixture was neutralized with $NaHCO_3$, extracted with CH_2Cl_2 , washed with water, dried over anhydrous $MgSO_4$, and then concentrated. TLC showed two spots. Separation was effected on a silica gel column, using varying proportions of hexane and chloroform (100 : 0 to 70 : 30, v/v) for elution. The product obtained with lesser proportions of chloroform was tested for the aldehyde by TLC. One spot was obtained when the chromatogram was sprayed with 2,4-DNP. An aliquot (5 ml) was pipetted into 50 ml of 2N HCL saturated with 2,4-DNP at 0°C. The aldehyde was converted to the 2,4-dinitrophenylhydrazone, which was filtered, washed, dried and weighed. The yields were calculated from the amounts of 2,4-dinitrophenylhydrazones formed, and were found to vary between 80-90% for the three isomers. The melting points of the corresponding 2,4-dinitrophenylhydrazones were determined after one or more recrystallizations from ether (*para*- = 320°C; *meta*- = 292°C; *ortho*- = 265°C). Further proof of the formation of the corresponding aldehyde was obtained by isolating the aldehyde, using the standard method²¹. IR analysis gave a sharp band at 1700cm^{-1} , which was characteristic of the $C=O$ stretching for an aldehydic group attached to an aryl ring. Two weak bands at 2850cm^{-1} and 2750cm^{-1} were characteristic of the $C-H$ stretching.

TABLE 1: Rate Data for the Oxidation of Nitrotoluenes

[Substrate] ($M \times 10^2$)	[$K_3Fe(CN)_6$] ($M \times 10^4$)	Temp. ($\pm 0.1^\circ C$)	$10^5 \times k_{obs}, s^{-1}$			
			<i>m</i> -Nitrotoluene	<i>p</i> -Nitrotoluene	<i>o</i> -Nitrotoluene	Toluene
5.0	5.0	50.0	9.0	6.8	6.0	76.0
10.0	5.0	50.0	18.1	14.0	12.3	153.0
25.0	5.0	50.0	45.3	35.1	30.4	382.0
50.0	10.0	50.0	9.1	6.5	6.4	77.0
5.0	20.0	50.0	8.6	7.0	6.0	79.0
5.0	30.0	50.0	8.8	6.8	6.2	76.0
5.0	5.0	45.0	6.0	4.4	3.8	64.0
5.0	5.0	55.0	12.3	10.0	9.2	99.0
5.0	5.0	60.0	15.1	12.7	11.0	118.0

[HClO₄]=1.0M; HOAc=80 % (v/v).TABLE 2: Effect of Acid at 50.0 \pm 0.1 $^\circ C$

[HClO ₄] (M)	-log [H ⁺]	[HFe(CN) ₆ ²⁻]* ($M \times 10^3$)	$10^5 \times k_{obs}, S^{-1}$			
			<i>m</i> -Nitrotoluene	<i>p</i> -Nitrotoluene	<i>o</i> -Nitrotoluene	Toluene
0.25	0.61	1.23	2.2	1.6	1.4	18.9
0.50	0.29	2.56	4.5	3.4	3.0	38.1
1.0	0.00	5.00	9.0	6.8	6.0	76.0

[Substrates]= $5 \times 10^{-2} M$; [$K_3Fe(CN)_6$]= $5 \times 10^{-4} M$; HOAc=80 % (v/v). *calculated from the relation $[HFe(CN)_6^{2-}] = K[Fe(CN)_6^{3-}][H^+]$, where $K=10$ (ref. 22).

The second product, obtained in about 10 % yield, was a polymeric materials, and was not characterized.

Results and Discussion

Effect of Substrate, Oxidant and Acid. Being an electron withdrawing group, the nitro group should exert a deactivating influence on the rate of the reaction, as compared to toluene. This has been observed for all the isomers, where the rates are less than those for toluene. The rate of the reaction was found to be dependent on the first powers of the concentrations of the reactants—substrate, oxidant and acid (Tables 1–2).

Nature of the Reacting Species. Since the rate of the reaction showed a first order dependence on the acidity of the medium, that is, on $[H^+]$, the first step of the reaction would be the protonation of $Fe(CN)_6^{3-}$ to give $HFe(CN)_6^{2-}$ as the reactive species. The formation of $HFe(CN)_6^{2-}$ was monitored when the absorption spectrum was investigated by varying the wave length setting and noting the absorbance about 3sec after the reaction had been initiated. In this way, an absorption maximum was located at 435nm. A spectral shift from 420 to 435nm would indicate the formation of $HFe(CN)_6^{2-}$. Moreover, if $HFe(CN)_6^{2-}$ is the reacting species at the rate determining step, then k_{obs} should depend linearly on $[HFe(CN)_6^{2-}]$. This has been observed (Table 2), and plots of $\log k_{obs}$ against $\log [HFe(CN)_6^{2-}]$ were linear, with slopes equal to unity.

Rate Law. The first step of the reaction would be the protonation of $Fe(CN)_6^{3-}$, that is,



where K is the first protonation constant of $Fe(CN)_6^{3-}$, whose value has been reported²² to be close to 10. Under the pre-

sent experimental conditions, the rate law could be expressed as:

$$\text{Rate} = -\frac{d[Fe(CN)_6^{3-}]}{dt} = k_{obs} [\text{substrate}] [HFe(CN)_6^{2-}] \quad (2)$$

where $[HFe(CN)_6^{2-}] = K[Fe(CN)_6^{3-}][H^+]$.

The pseudo first order rate constant, k_{obs} , was determined by keeping the concentrations of two out of the three reactants (substrate, oxidant and acid) constant, and was calculated from the equation²³:

$$k_{obs} = \frac{2.303}{t} \log \frac{D_0}{D_t} \quad (3)$$

where D_1 was the initial optical absorbance of the reaction mixture, and D_t that at time, t .

Effect of Solvent. The rate of the reaction was susceptible to changes in the polarity of the medium. In going from 75 % to 90 % acetic acid, the polarity decreases. This decrease in the polarity of the medium causes an increase in the rate of the reaction (Table 3). Plots of $\log k_{obs}$ against $1/D$ were linear, indicating that the reaction was of the ion–dipole type²⁴.

Effect of Temperature. The rate of the reaction was increased with an increase in temperature (Table 1), and the activation parameters have been evaluated (Table 4).

Hammett Plot. A plot of $\log k_{obs}$ against σ^+ (Figure 1), gave a ρ^+ value of -1.30 (correlation coefficient = 0.99), indicating that the rate determining step of the reaction was the abstraction of a hydrogen atom, forming the benzylic radical intermediate.

Isotope Effect. A kinetic isotope effect, $k_H/k_D=6.2$, was observed (Table 5), indicating that the rate determining step involved the cleavage of the carbon–hydrogen bond of the methyl group attached to the aryl ring. In the chromic acid

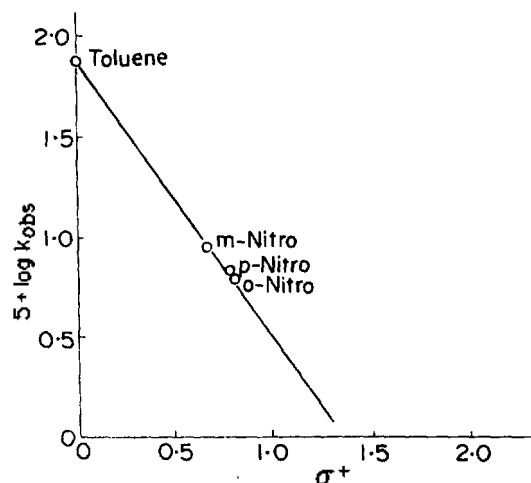
TABLE 3: Effect of Solvent at $50.0 \pm 0.1^\circ\text{C}$

HOAc-H ₂ O (%, v/v)	$10^5 \times k_{\text{obs}}, \text{s}^{-1}$			
	<i>m</i> -Nitro toluene	<i>p</i> -Nitro toluene	<i>o</i> -Nitro toluene	Toluene
75-25	6.6	4.6	4.0	52.4
80-20	9.0	6.8	6.0	76.0
85-15	19.0	15.7	14.4	155.0
90-10	50.5	40.2	35.2	406.0

[Substrates] = $5 \times 10^{-2} \text{M}$; $[\text{K}_3\text{Fe}(\text{CN})_6] = 5 \times 10^{-4} \text{M}$; $[\text{HClO}_4] = 1.0 \text{M}$.

TABLE 4: Activation Parameters

Parameter	<i>m</i> -Nitro toluene	<i>p</i> -Nitro toluene	<i>o</i> -Nitro toluene	toluene
$E(\text{kJmol}^{-1})$	69.0 ± 1.1	70.2 ± 1.3	71.6 ± 1.2	38.3 ± 0.7
$A(\text{s}^{-1})$	1.3×10^7	1.5×10^7	2.2×10^7	1.2×10^7
$\Delta H^\ddagger(\text{kJmol}^{-1})$	66.3 ± 1.0	67.5 ± 1.2	86.9 ± 1.2	35.6 ± 0.6
$\Delta S^\ddagger(\text{JK}^{-1}\text{mol}^{-1})$	-118 ± 1.6	-116 ± 1.6	-113 ± 1.6	-106 ± 1.5

Figure 1. Plot of $\log k_{\text{obs}}$ Against σ^+ .TABLE 5: Kinetic Isotope Effect at $50.0 \pm 0.1^\circ\text{C}$

Ar-	$10^6 \times k_{\text{obs}}, \text{s}^{-1}$		
	$\text{ArCH}_3 (k_{\text{H}})$	$\text{ArCD}_3 (k_{\text{D}})$	$k_{\text{H}}/k_{\text{D}}$
<i>m</i> -NO ₂ -C ₆ H ₄ -	90.0	14.5	6.2
<i>p</i> -NO ₂ -C ₆ H ₄ -	68.0	11.0	6.2
<i>o</i> -NO ₂ -C ₆ H ₄ -	60.0	9.7	6.2

[Substrates] = $5 \times 10^{-2} \text{M}$; $[\text{K}_3\text{Fe}(\text{CN})_6] = 5 \times 10^{-4} \text{M}$; $[\text{HClO}_4] = 1.0 \text{M}$; HOAc = 80% (v/v).

TABLE 6: Rate Data for the Oxidation of Nitrobenzyl Alcohols

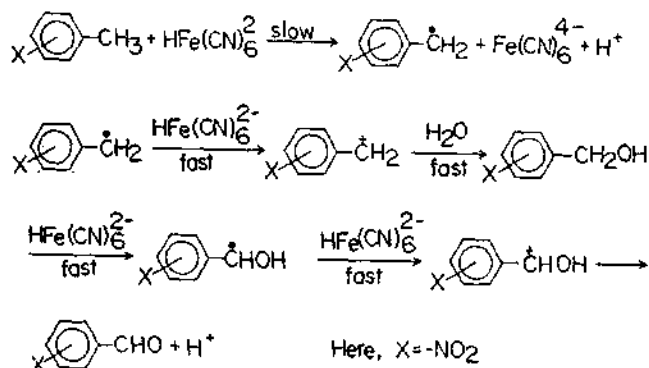
[Substrates]		$10^4 \times k_{\text{obs}}, \text{s}^{-1}$		
($\text{M} \times 10^2$)	Benzyl alcohol	<i>m</i> -Nitro- benzyl alcohol	<i>p</i> -Nitro- benzyl alcohol	<i>o</i> -Nitro- benzyl alcohol
5.0	60.0	7.0	5.5	5.0
10.0	122.0	14.5	11.5	10.5
50.0	605.0	72.0	56.0	53.0

$[\text{K}_3\text{Fe}(\text{CN})_6] = 5.0 \times 10^{-4} \text{M}$; $[\text{HClO}_4] = 1.0 \text{M}$; HOAc = 80% (v/v); temp. = $50.0 \pm 0.1^\circ\text{C}$.

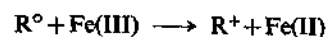
oxidation of diphenylmethane, a $k_{\text{H}}/k_{\text{D}}$ value of 6.4 was observed, which indicated that the rate determining step was

the cleavage of the methylene carbonhydrogen bond, yielding the benzhydryl radical²⁵.

Mechanism. The oxidation process can be visualized as shown in the Scheme. The protonated species, $\text{HFe}(\text{CN})_6^{2-}$, would react with the substrate to yield the radical, in the rate determining step of the reaction. The presence of the radical was shown by the ability of the system to initiate the polymerization of acrylonitrile. The ρ^+ value of -1.30 , and the $k_{\text{H}}/k_{\text{D}}$ value of 6.2 would further support the formation of a radical intermediate in the rate determining step of the reaction. The observed increase in the rate of the reaction with a decrease in the polarity of the solvent medium (Table 3), would indicate that the transition state would be much less polar than the reactants. This would contribute to the facile formation of a radical intermediate, rather than an ionic species, in the rate determining step of the reaction.



Fe(III) is known to be an effective oxidizer of radical species²⁶, and it might be speculated that the Fe(III) could combine with the radical intermediate to yield a carbocation(R⁺), according to the equation:



This carbocation would presumably be formed in a fast step, and no evidence could be obtained for the formation of this carbocation. It would, therefore, be reasonable to postulate that the radical intermediate undergoes rapid conversion, in a series of steps, to give the product. No intermediate product(s) could be isolated from the reaction mixture. Efforts to isolate the intermediate, nitrobenzyl alcohol, were not successful. Independent kinetic experiments conducted in this laboratory showed that nitrobenzyl alcohol was rapidly oxidized. The rate data (Table 6) would indicate that the nitrobenzyl alcohol, when formed as an intermediate in the oxidation of nitrotoluenes by $\text{K}_3\text{Fe}(\text{CN})_6$, would undergo a rapid reaction to give the corresponding aldehyde.

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The Crystal Structure of Metoclopramide

Whanchul Shin[†], Tai Sik Chang and Chung Hoe Koo

Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151, Korea
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The crystal structure of metoclopramide, $C_{14}H_{22}ClN_3O_2$, has been determined by X-ray diffraction techniques using diffractometer data obtained by the ω - 2θ scan technique with Mo $K\alpha$ radiation from a crystal with space group symmetry $P\bar{1}$ and unit cell parameters $a = 7.500(1)$, $b = 8.707(2)$, $c = 13.292(2)$ Å; $\alpha = 101.70(2)$, $\beta = 81.20(2)$, and $\gamma = 114.90(1)^\circ$. The structure was solved by direct methods and refined by full-matrix least-squares to a final $R = 0.055$ for the 1524 observed reflections. The bent overall-conformation of the molecule seems to be determined mainly by the bifurcated intramolecular hydrogen bond from the amide nitrogen atom to the methoxy oxygen and the amine nitrogen atoms. The crystal packing consists of the hydrogen bonds, π - π interaction and hydrophobic interaction.

Introduction

Metoclopramide, N-(diethylaminoethyl)-2-methoxy-4-amino-5-chlorobenzamide, is a widely used antiemetic agent which stimulates orthograde peristalsis and thus suppresses the reflux of the bile.¹ The metoclopramide molecule has many rotatable single bonds especially in the trialkylamine portion of the molecule. The crystal structure analysis of the hydrochloride salt of metoclopramide has been recently published.² Comparison of the crystal structures in different protonation state and crystal environment will provide an opportunity to determine whether there is any salient feature in the stable overall conformation of this apparently flexible molecule and, if so, what are the major factors for assuming that conformation. The structural study is desirable to establish the structure-activity relationship and we report the results of the crystal structure analysis of the unprotonated metoclopramide.

Experimental

Metoclopramide was crystallized by slow evaporation from an aqueous methanol solution in the form of transparent rectangles at room temperature. The crystals were triclinic as determined from oscillation and Weissenberg photographs. The space group which was initially assumed to be $P\bar{1}$ was confirmed later in the crystal structure determination and refinement. The unit cell parameters were determined by a least-squares fit of the 2θ angles for 25 reflections measured with Mo $K\alpha$ radiation on a Rigaku AFC diffractometer.³ All of the pertinent crystal data are summarized in Table 1. The intensity data were collected with graphite-monochromated Mo $K\alpha$ radiation by the ω - 2θ scan technique over a scan range of $(1.2 + 0.5 \tan \theta)^\circ$ in ω at a scan rate of $4^\circ/\text{min}$ and a 10-s background count at each end of the scan range.

Three standard reflections were monitored after each 50 data reflections and showed no appreciable variations in