Mechanism of Oxidation of Ketorolac by Hexacyanoferrate(III) in Aqueous Alkali: A Thermodynamics and Kinetics Study

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Abstract The kinetics of the oxidation of ketorolac by hexacyanoferrate(III) (HCF) in aqueous alkaline medium at a constant ionic strength of 0.75 mol·dm⁻³ was studied spectrophotometrically at 300 K. A plausible mechanism was proposed and the rate law was derived. The mechanism of oxidation of ketorolac (KET) in alkaline medium has been shown to proceed via a KET-HCF complex, which decomposes in a slow step followed by other fast steps to give the products. The main oxidative product was identified as (2, 3-dihydro-1-hydroxy-1H-pyrrolizin-5-yl-)(phenyl)methanone and is characterized by its LC-ESI-MS spectrum. Thermodynamic parameters of various equilibria of the mechanism were calculated and activation parameters ΔH^{\neq} , ΔS^{\neq} , ΔG^{\neq} and $\log_{10} A$ were found to be 29.9 kJ·mol⁻¹, -220 J·K⁻¹·mol⁻¹, 96 kJ·mol⁻¹ and 2.70 respectively.

Keywords Hexacyanoferrate(III) \cdot Ketorolac \cdot Oxidation \cdot Kinetics \cdot Thermodynamics \cdot Mechanism

1 Introduction

Ketorolac (KET, systematic name: 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid) is a non-steroidal, anti-inflammatory drug (NSAID) with potent analgesic and anti-pyretic activity that exerts its actions through the inhibition of prostaglandin synthesis by acting as a non-selective competitive blocker of the cyclooxygenase pathway of arachid-onate metabolism [1, 2]. Prostaglandin is involved in multiple homeostatic processes; KET like other NSAIDS may induce adverse events involving the gastrointestinal, renal and blood clotting systems. It may exert its analgesic activity via its effects on the central nervous system. Both racemic forms of this compound are known, where the S antipode of

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Many transition and non-transition metal ions, in their complexed forms, act as good oxidants in acidic, basic or neutral media. However, their oxidation capacity depends on the redox potential, which is varied by changing the pH. Hexacyanoferrate(III) (HCF), one such oxidant in alkaline medium is well understood [6–12], particularly its oxidative capacity in oxidation of inorganic and organic compounds. The reduction potential of the $[Fe(CN)_6]^{3-}/[Fe(CN)_6]^4$ couple remains essentially constant at around +0.41 V in the pH range 4–13, with oxidized, reduced or protonated forms [13]. Therefore, $[Fe(CN)_6]^{3-}$ is considered as a mild oxidant. Only at higher acidities, due to the association with protons, the species $H[Fe(CN)_6]^{2-}$, $H_2[Fe(CN)_6]^{-}$ and even $H_3[Fe(CN)_6]$ can be formed [14] and the potential increases from +0.56 to +0.93 V in the concentration range 0.1–8.0 mol·dm⁻³ [H⁺]. This indicates that HCF is a moderate oxidant in aqueous alkali and strong at higher acidities. It is a single equivalent and stable oxidant, and oxidizes the organic compounds through an outer-sphere mechanism [15, 16]. Oxidation of organic compounds by such a stable oxidant adds less error to the experimental results and data can be analyzed meticulously to establish the reaction path.

It is also well known that HCF is an hydrogen abstracting agent [6] for most easily oxidizable substrates. Hence, it is used as an interceptor for free radicals and as an electron abstracting reagent [8, 10] both in alkali and neutral media [11]. HCF is employed to oxidize a verity of organic substrates including thiols, thiol acids and thioamides. The key step in the oxidation is an electron transfer, generally acknowledged to proceed by the formation of substrate-oxidant ion pair or outer sphere precursor complex in a pre equilibrium step. Formation of such species is expected to bring about changes into the vibrational movements [17].

Since the KET is non-sulfural compound, the present study is to understand whether its redox chemistry with HCF proceeds with the formation of an substrate–oxidant ion pair or outer sphere precursor complex, in a pre equilibrium step. Hence, the title reaction is undertaken to study the mechanism of oxidation of KET.

2 Experimental

2.1 Chemicals

All chemicals used were reagent grade and double distilled water was used throughout the study. The KET was obtained from Raptakos Brett and Co., Microlabs Ltd. KLAB, Mumbai, India as free sample with 98.8 % purity. Further, its purity was checked by its m.p. and TLC for single spot. A stock solution of KET was prepared by dissolving the required quantity of sample. The kinetics runs were checked with aqueous solutions of KET with different ageing of the solution to understand the stability of KET solutions. It was found that there was no difference between fresh and aged solutions. However, fresh solutions were used in all kinetic runs. Aqueous solutions of KOH and KCl were used to maintain required [OH⁻] and ionic strength, respectively. A solution of HCF was prepared by dissolving K₃[Fe(CN)₆] (BDH) in water and was standardized iodometrically in the presence of ZnSO₄ to avoid the reverse reaction of [Fe(CN)₆]⁴⁻ [18]. K₄ [Fe(CN)₆] was used to prepare [Fe(CN)₆]⁴⁻ to study the product effect. Earlier it was estimated quantitatively by oxidizing it into [Fe(CN)₆]³⁻.

2.2 Kinetic Measurements

The oxidation of KET by HCF was carried out under pseudo-first order conditions, where [KET] > [HCF] at 300 \pm 1 K unless otherwise specified. The reaction was initiated by mixing the required quantities of previously thermostated solutions of KET and HCF, which also contained the necessary quantities of KOH and KCl to maintain the required alkalinity and ionic strength. The course of the reaction was followed by measuring the decrease in absorbance of HCF in the reaction mixture in a 1 cm quartz cell in the thermostated compartment of a Specord-200 plus spectrophotometer, set up with a Peltier accessory to control temperature. The absorption measurements were performed at its absorbance maximum, 420 nm, as a function of time. Earlier, it was verified that there is negligible interference from other species present in the reaction mixture at this wavelength. The obedience of absorbance coefficient ' ε ' was found to be 1,050 (\pm 20) dm³·mol⁻¹·cm⁻¹. First order rate constants, k_{obs} , were calculated from plots, log₁₀[HCF] against time. Excellent first order plots were obtained up to 90 % completion. The results are reproducible within \pm 3 %.

2.3 Stoichiometry and Product Analysis

Eight different sets of concentrations of KET and HCF were kept at constant [OH⁻] and ionic strength in an inert atmosphere at 300 K for over 24 h in a closed vessel, under an inert atmosphere, for completion of the reaction. Unreacted HCF was estimated spectro-photometrically by measuring its absorbance at 420 nm. Further, the experiments were repeated at higher concentrations for titrimetric analysis. Under such conditions, and when HCF is in excess of KET, the unreacted HCF was estimated iodometrically.

The results indicated that two moles of HCF were consumed by one mole of KET as in Eq. 1.

The oxidative product of KET was identified as (2,3-dihydro-1-hydroxy-1H-pyrrolizin-5-yl-)(phenyl)methanone and was ascertained as follows. After completion of the reaction, the reaction mixture was subjected to TLC for separation of the constituents with reference to the KET. Iodine spray showed a single spot, indicating the presence of only one product. Further, the solution was subjected for LC–ESI–MS. The reaction mixture, after completing the reaction, was treated with 50 % methanol followed by acidification with HCl and 3 % acetonitrile and 1 % formic acid to make the solution suitable for a positive ion mode for the LC–ESI–MS analysis. The solution was subjected to LC–ESI–MS analysis at the rate of 5 μ L·min⁻¹, with retention time 0.51–0.98 s at the applied voltage of 30 kV, using a glass micro syringe. Nitrogen gas was used as nebulizer. The LC–ESI–MS analysis of reaction at positive ionic mode indicated the presence of a product with a molecular ion peak, $m \cdot z^{-1}$ at 225 ($m \cdot z^{-1}$ 224 ± 3) as was expected for (2,3-dihydro-1-hydroxy-1H-pyrrolizin-5-yl-)(phenyl)methanone (Fig. 1). Further, the retention of ketone and formation of new OH due to decarboxylation were confirmed by a spot test [19].

3 Results and Discussion

3.1 Reaction Order

The orders, with respect to [KET] and [alkali], were found from the graph of $\log_{10} k_{obs}$ against \log_{10} (concentration) plots by varying the concentration of reductant and alkali in turn while keeping the others constant.

3.2 Effect of [HCF]

The effect of [HCF] on the reaction rate was studied by varying the [HCF] from 8.0×10^{-5} to 10.0×10^{-4} mol·dm⁻³ at constant concentrations of KET, alkali and ionic strength at a constant temperature (Table 1). It was observed that slope of the plot of \log_{10} (conc.) against time remained constant for most of the [HCF] values. This was also confirmed from the linearity of plots of \log_{10} (absorbance) against time to about 80 % completion of the reaction. Hence, the order in [HCF] was considered as being unity.

3.3 Effect of [KET]

The effect of [KET] on rate of reaction was studied at different temperatures in the concentration range 1.0×10^{-3} to 1.0×10^{-2} mol·dm⁻³ at all other reaction



Fig. 1 LC-ESI-MS spectrum of the product, (2,3-dihydro-1-hydroxy-1H-pyrrolizin-5-yl-)(phenyl)methanone resulted due to the oxidation of ketorolac by hexacyanoferrate(III) in aqueous alkaline medium

$10^4 \times [\text{HCF}]$	$10^3 \times [\text{KET}]$	[OH ⁻]	$10^3 \times k_{\rm obs} \ ({\rm s}^{-1})$		
(mol·dm ⁻⁵)	(mol·dm ⁻⁵)	(mol·dm ⁻³)	Exptl. ^a	Calc. ^b	
0.8	4.0	0.50	3.00	_	
1.0	4.0	0.50	2.90	_	
2.0	4.0	0.50	3.09	-	
4.0	4.0	0.50	3.21	-	
6.0	4.0	0.50	3.20	-	
8.0	4.0	0.50	3.17	-	
10	4.0	0.50	3.13	-	
4.0	1.0	0.50	1.07	1.65	
4.0	2.0	0.50	2.53	3.07	
4.0	4.0	0.50	3.21	5.40	
4.0	6.0	0.50	4.70	7.23	
4.0	8.0	0.50	6.16	8.71	
4.0	10	0.50	7.67	9.93	
4.0	4.0	0.25	1.76	3.25	
4.0	4.0	0.30	2.11	3.75	
4.0	4.0	0.35	2.31	4.21	
4.0	4.0	0.40	2.58	4.63	
4.0	4.0	0.45	2.85	5.03	
4.0	4.0	0.50	3.21	5.40	
4.0	4.0	0.55	3.38	5.75	
4.0	4.0	0.60	3.69	6.07	
4.0	4.0	0.65	3.93	6.37	
4.0	4.0	0.70	4.20	6.66	
4.0	4.0	0.75	4.36	6.93	

Table 1 Effect of variations of [HCF], [KET] and [OH⁻] on oxidation of ketorolac by hexacyanoferrate(III) in aqueous alkaline medium at 300 K, $I = 0.75 \text{ mol·dm}^{-3}$

^a Experimental

^b Calculated: k_{obs} were calculated by using $k = 6.66 \times 10^{-2}$ s⁻¹, $K_1 = 1.02$ dm³·mol⁻¹ and $K_2 = 78.7$ dm³·mol⁻¹ at 300 K in Eq. 7

concentration constant (Table 2).The k_{obs} values increased with increase in [KET]. The order in [KET] from the plot of $\log_{10} k_{obs}$ against \log_{10} [KET] was found to be a positive fractional order but decreased marginally from 0.70 to 0.45 in the temperature range 300–320 K.

3.4 Effect of [OH⁻]

The influence of $[OH^-]$ on the rate of reaction was studied by varying [KOH] from 0.25 to 0.75 mol·dm⁻³ while keeping all other reaction concentration constant in the temperature range 300 to 320 K. It was observed that rates increased with increase in $[OH^-]$ (Table 3). The first order plots were linear for all the $[OH^-]$ in different temperatures, and the order from the plot of $\log_{10} k_{obs}$ against $\log_{10}[OH^-]$ was found to be positive fractional, but the order decreases from 0.82 to 0.56 as temperature increases, in the range 300–320 K, at a fixed ionic strength of 0.75 mol·dm⁻³.

Table 2 Effect of variation of [KET] on oxidation of ketorolac by hexacyanoferrate(III) in aqueous alkaline medium at different temperatures: $[HCF] = 4.0 \times 10^{-4} \text{ mol} \cdot \text{dm}^{-3}$, $[OH^-] = 0.50 \text{ mol} \cdot \text{dm}^{-3}$, and $I = 0.75 \text{ mol} \cdot \text{dm}^{-3}$

$10^3 \times [\text{KET}]$ (mol·dm ⁻³)	$10^3 \times k_{\rm obs} \ ({\rm s}^{-1})$								
	^a Exptl.	^b Calc.							
	300 K	305 K	310 K	315 K	320 K	for temp 300 K			
1.0	1.07	2.10	2.19	2.85	3.06	1.65			
2.0	2.53	3.18	3.67	4.53	5.14	3.07			
4.0	3.21	5.32	6.32	6.23	7.46	5.40			
6.0	4.70	6.95	8.27	9.10	10.7	7.23			
8.0	6.16	8.50	9.54	10.6	12.2	8.71			
10	7.67	9.47	10.6	13.4	13.5	9.93			
order	0.70	0.50	0.48	0.47	0.45	0.70			

^a Experimental

^b Calculated: k_{obs} were calculated by using $k = 6.66 \times 10^{-2} \text{ s}^{-1}$, $K_1 = 1.02 \text{ dm}^3 \cdot \text{mol}^{-1}$ and $K_2 = 78.7 \text{ dm}^3 \cdot \text{mol}^{-1}$ at 300 K in Eq. 7

Table 3 Effect of variation of [OH⁻] on oxidation of ketorolac by hexacyanoferrate(III) in aqueous alkaline medium at different temperatures: [HCF] = 4.0×10^{-4} mol·dm⁻³, [KET] = 4.0×10^{-3} mol·dm⁻³, and I = 0.75 mol·dm⁻³

[OH ⁻] (mol·dm ⁻³)	$10^3 \times k_{\rm obs} ({\rm s}^{-1})$								
	^a Exptl.	^a Exptl.							
	300 K	305 K	310 K	315 K	320 K	temp 300 K			
0.25	1.76	2.70	2.92	3.54	4.33	3.25			
0.30	2.11	2.92	3.38	4.10	4.78	3.75			
0.35	2.31	3.26	3.85	4.01	4.68	4.21			
0.40	2.58	3.50	4.22	4.53	4.99	4.63			
0.45	2.85	3.81	4.56	4.47	6.58	5.03			
0.50	3.21	4.09	5.04	4.97	6.98	5.40			
0.55	3.38	4.24	5.16	5.34	6.91	5.75			
0.60	3.69	4.67	5.30	4.95	7.12	6.07			
0.65	3.93	3.97	5.52	5.51	7.30	6.37			
0.70	4.20	5.08	5.42	5.96	7.65	6.66			
0.75	4.36	5.40	5.97	6.08	8.35	6.93			
order	0.82	0.65	0.62	0.58	0.56	0.82			

^a Experimental

^b Calculated: k_{obs} were calculated by using $k = 6.66 \times 10^{-2} \cdot \text{s}^{-1}$, $K_1 = 1.02 \text{ dm}^3 \cdot \text{mol}^{-1}$ and $K_2 = 78.7 \text{ dm}^3 \cdot \text{mol}^{-1}$ at 300 K in Eq. 7

3.5 Effect of Initially Added Product

The effect of initially added $[Fe(CN)_6]^{4-}$ on the rate of reaction was studied by varying $K_4[Fe(CN)_6]^{4-}$ solution concentrations in the range of 8.0×10^{-5} to 8.0×10^{-4} mol·dm⁻³ at 300 K at constant $[Fe(CN)_6]^{3-}$, [KET], [OH⁻] and ionic strength. The added product did not alter the rate of reaction.

3.6 Effect of Ionic Strength and Dielectric Constant of the Medium

The ionic strength of the reaction medium was varied between 0.5 and 1.0 mol·dm⁻³ with potassium chloride at constant concentrations of alkali, oxidant and reductant at 300 K. It was found that as ionic strength increases, the rate of reaction increases. A plot of $\log_{10} k_{obs}$ against \sqrt{I} was linear with positive slope (0.7).

The relative permittivity (D) effect was studied by varying the *t*-butyl alcohol-water content in the reaction mixture with all other conditions being kept constant. The D values were computed [20] from the values of the pure liquids. In the reaction, as D increases the k_{obs} values increased. The graph of $\log_{10} k_{obs}$ against D^{-1} was found to be linear with a negative slope. Earlier the reaction between *t*-butyl alcohol and oxidant was studied. It was observed that there was no reaction between solvent and oxidant.

3.7 Effect of Temperature

The effect of temperature on the reaction rate was studied at various temperatures at constant concentrations of oxidant and reductant, with other reaction conditions being kept constant. The k_{obs} values were found increase with temperature (Table 4). The activation energy was calculated from the slope of Arrhenius plot and, by using this, the other activation parameters were calculated and tabulated in Table 5.

Since the reaction follows a multistep mechanism, the reaction constants: equilibrium constants and rate constant of the slow step are involved. In order to arrive at the values of these constants, the reaction was studied at 300, 305, 310, 315 and 320 K by varying [KET] and [OH⁻] in turn while other concentrations were kept constant (Tables 2 and 3).

The rate constants (k) of the slow step of Scheme 1 were obtained from the intercept of $(k_{obs})^{-1}$ against $[OH^{-}]^{-1}$ for the temperatures 300, 305, 310, 315 and 320 K. The values 'k' calculated for slow step decrease with increasing temperature. Hence, activation parameters for the slow step are not calculated. This may be due to the instability of the adduct at higher temperatures (discussed elsewhere).

The equilibrium constants K_1 and K_2 of the scheme were determined from the slopes and intercepts of the plots of $(k_{obs})^{-1}$ against $[\text{KET}]^{-1}$ and $[\text{OH}^-]^{-1}$ for different temperatures (Table 6). From the van't Hoff plot, the thermodynamic parameters ΔH^* , ΔS^* and ΔG^* (under the reaction conditions and temperature) for the formation of KET anion, and complex between HCF and KET anion, were determined (Table 7).

3.8 Polymerization Study

As HCF is a single equivalent oxidant, the oxidation of organic compounds by such an oxidant could lead to free radical generation. Hence, to test for the possible intervention of free radicals, the reaction mixture was mixed with acrylonitrile monomer and kept for 24 h. On dilution with methanol, a white precipitate of polymer formed, indicating that the reaction occurs with the intervention of free radicals. The experiment of either HCF or KET with acrylonitrile alone did not induce the polymerization under similar conditions as those induced with the reaction mixture. This was also evidenced by decrease in the k_{obs} values in the presence of initially added acrylonitrile.

When the HCF reaction order in the oxidation of organic substrates is unity or close to unity, both in oxidant and reductant species, the rate determining step is the transfer of one electron from substrate to oxidant to produce $[Fe(CN_6)]^{4-}$. When the product inhibits the overall reaction, this step becomes reversible [11, 21]. Both possibilities are unlikely to be

Table 4 Effect of temperature on the oxidation of ketorolac by hexacyanoferrate(III) in aqueous alkaline medium: [HCF] = 4.0×10^{-4} mol dm⁻³, [KET] = 4.0×10^{-3} mol dm⁻³, [OH⁻] = 0.50 mol dm⁻³, and I = 0.75 mol·dm⁻³

Temperature (K)	$10^3 \times k_{\rm obs} ({\rm s}^{-1}) ($	$10^2 \times k_{\rm obs} ({\rm s}^{-1})$	
	^a Exptl.	^b Calc.	Slow step
300	3.21	3.40	6.66
305	3.83	4.55	4.67
310	4.52	5.25	3.55
315	5.17	5.06	2.89
320	6.05	5.80	3.41

^a Experimental

^b Calculated: k_{obs} were calculated by using $k = 6.66 \times 10^{-2}$ s⁻¹, $K_1 = 1.02$ dm³·mol⁻¹ and $K_2 = 78.7$ dm³·mol⁻¹ at 300 K in Eq. 7

Table 5 Activation parameters for the oxidation of ketorolac by hexacyanoferrate(III) in aqueous alkaline medium at 300 K	Activation parameters	Values (overall reaction)		
	$\Delta H^{\neq} (\text{kJ} \cdot \text{mol}^{-1})$	29.9 ± 1		
	$\Delta S^{\neq} (\mathbf{J} \cdot \mathbf{K}^{-1} \cdot \mathrm{mol}^{-1})$	-220 ± 4		
	$\Delta G^{\neq} (\text{kJ·mol}^{-1})$	96 ± 2		
	$\log_{10} A$	2.70 ± 0.04		

operating in the present study as the reaction is first order in HCF and has fractional orders in [KET] and [OH⁻]. Thus, fractional orders each in [KET] and [OH⁻] can be accommodated as in the scheme in which KET forms an anion by reacting with OH⁻, and this anion forms a complex with the oxidant in a pre equilibrium step, before the rate determining step where the complex decomposes to give a free radical.

The formation of free radicals has been assayed by the initial polymerization test. The results show that test was negative in the absence of KET and positive in the presence of KET; the overall reaction became strikingly faster when KET was present concurrently with HCF, compared to KET alone in solution. The formation of a free radical from OH⁻ is excluded, which is a quite natural process in alkaline KMnO₄ oxidations [22]. Thus, these results denote that HCF is capable of generating free radicals from KET, either through its oxidation or, in a much slower way, through decarboxylation. The literature reveals that HCF(III) oxidations of free radicals usually are a diffusion controlled step [23– 25]. Hence, HCF being a single equivalent oxidant, and its product $[Fe(CN)_6]^{4-}$ did not show any retarding effect, the generation of free radicals might be from the oxidative decarboxylation of KET, as shown in Scheme 1.

The formation of complex between KET anion and HCF is proven kinetically by the non zero intercept graph of $(k_{obs})^{-1}$ against $[KET]^{-1}$ (Michaelis-Menton plot). The involvement of the ketonic oxygen and/or the nitrogen from the pyrrole ring in the adduct formation with HCF can be ruled out, due to their steric hindrance. The participation of carboxylic oxygen may be considered in adduct formation. However, it is known that HCF is an inert complex and exchange of CN⁻ with the carboxylate anion of KET is quite unusual due to non labile nature of CN^{-} . Nevertheless, HCF is reported to be [26] involved in an outer sphere electron exchange with thio compounds through their intermediate complex as $[Fe(CN)_5-CNSO_3]^{5-}$, particularly with substrates SO_3^{2-} and $S_2O_3^{2-}$. Lancaster



Scheme 1 Mechanism of oxidation of ketorolac by hexacyanoferrate(III) in aqueous alkali

Table 6	Equilibrium	constants	involved in	the	mechanism	of	oxidation	of	ketorolac	by	hexacyanofer-
rate(III) i	in aqueous all	kaline med	lium at diffe	erent	temperatures	8				-	-

Equilibrium step (Scheme 1)	Equilibrium	Temperature (K)					
	constants	300	305	310	315	320	
i.	K_1 (dm ³ ·mol ⁻¹)	1.02 ± 0.02	1.21 ± 0.04	1.41 ± 0.04	1.60 ± 0.05	1.78 ± 0.05	
ii.	K_2 (dm ³ ·mol ⁻¹)	79 ± 2	115 ± 3	139 ± 3	162 ± 4	183 ± 4	

and Murray [15] have suggested that many oxidations by transition metal complexes of weak oxidants may proceed through intermediate complexes, as described in the case of $[Fe(CN)_5-CNSO_3]^{5-}$. In all such cases, the thio compounds are bonded with one CN^- ligand through $CN - SO_3^{2-}$. However, Leal et al. [27] proved that HCF decomposes to CN^- with dissolved oxygen. Moreover, six ligands around the central metal atom do not allow enough room for a seventh ligand in the octahedral complexes. Then, dissociative processes are the most frequent in substitution reaction of octahedral complexes. Thus, in

Equilibrium step	$\Delta H^* (\text{kJ} \cdot \text{mol}^{-1})$	$\Delta S^* (J \cdot K^{-1} \cdot mol^{-1})$	$\Delta G^* (\text{kJ} \cdot \text{mol}^{-1})$
i.	22.3 ± 1	74.5 ± 2	-0.057 ± 0.004
ii.	32.5 ± 0.1	145 ± 3	-10.9 ± 0.5

Table 7 Thermodynamic parameters of various steps of the mechanism of oxidation of ketorolac by hexacyanoferrate(III) in aqueous alkaline medium at 300 K

 ΔH^* , ΔS^* and ΔG^* refer to the concentration of the reactants maintained as in the reaction condition and for temperature, 300 K)

the present study, the HCF may form a complex by exchanging CN^- with the oxygen of carboxylate ion of KET, thereby the electron is transferred from KET to HCF giving a free radical followed by decarboxylation. If that is the case, then the mechanism of oxidation is of the inner sphere type. The small value of $\log_{10} A$ (2.70) clearly indicates that the reaction is an inner sphere reaction. However, the values, 'k' calculated for the slow step are found decrease with increasing temperature. This may be due to less easy formation of the KET anion compared to the adduct at higher temperature (Table 4).

The rate law for the scheme can be derived as:

rate =
$$-\frac{\mathrm{d}[\mathrm{HCF}]}{\mathrm{d}t} = k[\mathrm{complex}] = kK_1K_2\left[\mathrm{Fe}(\mathrm{CN})_6^{3-}\right]_{\mathrm{f}}[\mathrm{KET}]_{\mathrm{f}}[\mathrm{OH}^-]_{\mathrm{f}}$$
 (2)

However,

$$\begin{split} \left[\operatorname{Fe}(\operatorname{CN})_{6}^{3-} \right]_{\mathrm{T}} &= \left[\operatorname{Fe}(\operatorname{CN})_{6}^{3-} \right]_{\mathrm{f}} + [\operatorname{complex}] \\ &= \left[\operatorname{Fe}(\operatorname{CN})_{6}^{3-} \right]_{\mathrm{f}} + K_{1}K_{2} \left[\operatorname{Fe}(\operatorname{CN})_{6}^{3-} \right]_{\mathrm{f}} [\operatorname{KET}]_{\mathrm{f}} [\operatorname{OH}^{-}]_{\mathrm{f}} \\ &= \left[\operatorname{Fe}(\operatorname{CN})_{6}^{3-} \right]_{\mathrm{f}} \left(1 + K_{1}K_{2} [\operatorname{KET}]_{\mathrm{f}} [\operatorname{OH}^{-}]_{\mathrm{f}} \right) \\ \left[\operatorname{Fe}(\operatorname{CN})_{6}^{3-} \right]_{\mathrm{f}} &= \frac{\left[\operatorname{Fe}(\operatorname{CN})_{6}^{3-} \right]_{\mathrm{T}}}{1 + K_{1}K_{2} [\operatorname{KET}]_{\mathrm{f}} [\operatorname{OH}^{-}]_{\mathrm{f}}} \\ &= \left[\operatorname{OH}^{-}\right]_{\mathrm{f}} = \left[\operatorname{OH}^{-}\right]_{\mathrm{f}} + \left[\operatorname{KET}^{-}\right]_{\mathrm{f}} \\ &= \left[\operatorname{OH}^{-}\right]_{\mathrm{f}} + K_{1} [\operatorname{OH}^{-}]_{\mathrm{f}} [\operatorname{KET}]_{\mathrm{f}} \\ &= \left[\operatorname{OH}^{-}\right]_{\mathrm{f}} + K_{1} [\operatorname{OH}^{-}]_{\mathrm{f}} \\ &= \left[\operatorname{OH}^{-}\right]_{\mathrm{f}} \left(1 + K_{1} [\operatorname{KET}]_{\mathrm{f}} \right) \\ &\left[\operatorname{OH}^{-}\right]_{\mathrm{f}} = \frac{\left[\operatorname{OH}^{-}\right]_{\mathrm{f}}}{1 + K_{1} [\operatorname{KET}]_{\mathrm{f}}} \end{aligned} \tag{4}$$

At low concentration of KET, $[OH^-]_f = [OH^-]_T$, so that:

$$[\text{KET}]_{\text{T}} = [\text{KET}]_{\text{f}} + [\text{KET}^{-}]_{\text{f}} + [\text{complex}]_{\text{f}}$$
$$= [\text{KET}]_{\text{f}} + K_{1}[\text{OH}^{-}]_{\text{f}}[\text{KET}^{-}]_{\text{f}} + K_{1}K_{2}\left[\text{Fe}(\text{CN})_{6}^{2-}\right]_{\text{f}}[\text{OH}^{-}]_{\text{f}}[\text{KET}]_{\text{f}}$$
$$= [\text{KET}]_{\text{f}} + \left(1 + K_{1}[\text{OH}^{-}]_{\text{f}} + K_{1}K_{2}\left[\text{Fe}(\text{CN})_{6}^{2-}\right]_{\text{f}}[\text{OH}^{-}]_{\text{f}}\right)$$
$$[\text{KET}]_{\text{f}} = \frac{[\text{KET}]_{\text{T}}}{\left(1 + K_{1}[\text{OH}^{-}]_{\text{f}} + K_{1}K_{2}\left[\text{Fe}(\text{CN})_{6}^{2-}\right]_{\text{f}}[\text{OH}^{-}]_{\text{f}}\right)}$$

In view of low concentration of $[Fe(CN)_6]^{3-}$ used in the experiments, the term $K_1K_2\left[Fe(CN)_6^{2-}\right]_f [OH^-]_f$ in the denominator of the right hand side can be neglected. Thus,

$$[\text{KET}]_f = \frac{[\text{KET}]_T}{\left(1 + \text{K}_1[\text{OH}^-]_f\right)}$$
(5)

On substituting Eqs. 3, 4, 5 into Eq. 2:

$$\operatorname{rate} = \frac{kK_{1}K_{2} \left[\operatorname{Fe}(\operatorname{CN})_{6}^{3-} \right]_{\mathrm{T}} \left[\operatorname{KET} \right]_{\mathrm{T}} \left[\operatorname{OH}^{-} \right]_{\mathrm{T}}}{\left(1 + K_{1}K_{2} \left[\operatorname{KET} \right]_{\mathrm{f}} \left[\operatorname{OH}^{-} \right]_{\mathrm{f}} \right) \left(1 + K_{1} \left[\operatorname{OH}^{-} \right]_{\mathrm{f}} \right)}$$

$$k_{\mathrm{obs}} = \frac{kK_{1}K_{2} \left[\operatorname{KET} \right]_{\mathrm{T}} \left[\operatorname{OH}^{-} \right]_{\mathrm{T}}}{1 + K_{1} \left[\operatorname{OH}^{-} \right]_{\mathrm{f}} + K_{1}K_{2} \left[\operatorname{KET} \right]_{\mathrm{f}} \left[\operatorname{OH}^{-} \right]_{\mathrm{f}} + K_{1}^{2}K_{2} \left[\operatorname{KET} \right]_{\mathrm{f}} \left[\operatorname{OH}^{-} \right]_{\mathrm{f}}^{2}}$$

$$(6)$$

The rate law (Eq. 6) explains the first order dependence on [HCF] and the fractional orders in [KET] and [OH⁻]

To verify the rate law, the approximation that the free and total concentrations are substantially equal for Eq. 6 yields:

$$k_{\rm obs} = \frac{kK_1K_2[\text{KET}][\text{OH}^-]}{1 + K_1[\text{OH}^-] + K_1K_2[\text{KET}][\text{OH}^-] + K_1^2K_2[\text{KET}][\text{OH}^-]^2}$$
(7)

and inversion of Eq. 7 gives:

$$\frac{1}{k_{\rm obs}} = \frac{1}{kK_1K_2[{\rm KET}][{\rm OH}^-]} + \frac{1}{kK_2[{\rm KET}]} + \frac{1}{k} + \frac{K_1[{\rm OH}^-]}{k}$$
(8)

The mechanism in Scheme 1 and corresponding rate law, in the form of Eq. 8, are verified by plotting the graphs of $(k_{obs})^{-1}$ versus $[OH^-]^{-1}$ and $[KET]^{-1}$ at 300 K. They should be linear and are found to be so (Fig. 2). From the slopes and intercepts of the plots, the values of k, K_1 and K_2 are calculated as 6.66 (± 0.08) × 10⁻²·s⁻¹, 1.02 (± 0.02) dm³·mol⁻¹ and 78.7 (± 0.3) dm³·mol⁻¹, respectively, for 300 K.

Further, these values were used in the rate law (Eq. 7) under different experimental conditions to regenerate k_{obs} . The regenerated values are found to be in close agreement with the experimental values (Table 1). This supports the mechanism of oxidation shown in Scheme 1.

It was observed that rate of reaction increases with increasing the ionic strength. But, the slope (0.7) from the plot of $\log_{10} k_{obs}$ against \sqrt{I} is less than the expected value of -4.0, due to the interaction of triply charged HCF ([Fe(CN)₆]³⁻) and singly charged KET carboxylate anion. This clearly indicates that the reaction follows an inner sphere mechanism through a common bridging ligand (via the carboxylate anion). This is further supported by the relatively large value of 'k' of the slow step = $6.66 \times 10^{-2} \text{ s}^{-1}$.

The study of the variation of relative permittivity of the reaction medium (*D*), varied by varying the percentage compositions of t-butyl alcohol and water, on the rate of reaction reveals that as the relative permittivity of the medium increases, the rate of reaction increases. It can be concluded that the activated complex may be more solvated at higher dielectric constant as the adduct is ionic in nature. Further, this activated complex may be more rigid than the reactants, indicated by a large negative value of ΔS^{\neq} (-220 ± 4 J·K⁻¹·mol⁻¹) and a large positive value of ΔG^{\neq} (96 ± 2 kJ·mol⁻¹).



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Fig. 2 Verification of the rate law (Eq. 7) for the oxidation of ketorolac by hexacyanoferrate(III) in aqueous alkaline medium at 300 K

The thermodynamic quantities for the equilibrium steps (i) and (ii) of the reaction scheme can be evaluated as follows. The [KET] and [OH⁻] were varied at five different temperatures in turn while keeping others constant. According to rate law (Eq. 8), the plots of $(k_{obs})^{-1}$ against [OH⁻]⁻¹ and [KET]⁻¹ should be linear and were found to be so. From the slopes and intercepts of such plots, the values of K_1 were evaluated for all 5 temperatures (Table 6). A van't Hoff plot was made for the variation of K_1 with temperature $(\log_{10} K_1 \text{ against } T^{-1})$ and the enthalpy of reaction (ΔH^*) was evaluated from its slope. The ΔG^* value was obtained from the relation between ΔG^* and equilibrium constant, K_1 , for the temperature 300 K; using ΔH^* and ΔG^* , the value of ΔS^* was determined. Similarly, ΔH^* , ΔS^* and ΔG^* (under the reaction condition and temperature) were calculated for K_2 for the equilibrium (ii) (Table 7). The ΔH^* and ΔS^* values of equilibria (i) and (ii) indicate that formation of the KET carboxylate anion and formation of a complex between oxidant and reductant is endothermic in nature and they are formed by the loss of degrees of freedom. The small negative ΔG^* value of step (i) indicates that the formation of the KET carboxylate anion is kinetically governed and the large value of ΔG^* of step (ii) shows that formation of adduct is thermodynamically controlled, which is also evidenced by the small value of k_{obs} (3.21 × 10⁻³ s⁻¹ at 300 K).

4 Conclusion

Kinetics of oxidation of KET by HCF in alkali is routed through a formation of adduct, formed between its anionic form with oxidant in a prior equilibrium step. This adduct is decomposed by generating a free radical from KET. A small value of slope of $\log_{10} k_{obs}$

against \sqrt{I} plot indicates that the reaction mechanism is of the inner sphere type, which is against the nature of HCF oxidations wherein it is reported as oxidations are usually of the outer sphere type. The thermodynamic parameters indicate that the formation of the KET anion and adduct are endothermic in nature.

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