Effect of anionic surfactant sodium dodecyl sulfate on the reaction of hexacyanoferrate(III) oxidation of levothyroxine in aqueous medium: a kinetic and mechanistic approach

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Abstract The effect of anionic surfactant sodium dodecyl sulfate (SDS) on the rate of oxidation of levothyroxine (LVT) by hexacyanoferrate(III) in alkaline medium has been investigated spectrophotometrically at different temperatures. The reaction follows a complex kinetics showing first order dependence of rate with respect to both alkali and LVT. The effect of SDS on the rate of reaction has been observed at the critical miceller concentration of the surfactant. indicating binding of the substrate with the surfactant micelle. The binding parameters have also been evaluated using the Menger and Portnoy model.

**Keywords** Levothyroxine · Kinetics · SDS · CMC

Introduction

Levothyroxine (LVT) (2S)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]propanoic acid (Fig. 1) is the sodium salt of levo isomer of the thyroid hormone thyroxine. Thyroid hormones affect growth, development of protein, lipid and carbohydrate metabolism [1, 2]. They stimulate the oxygen consumption of body cells, resulting in increased energy expenditure and heat production, and possess a cardiostimulatory effect that may be the result of a direct action on the heart. The production of LVT hormone is regulated by the hypothalamus–pituitary axis through a negative feedback system. When the hormone level becomes

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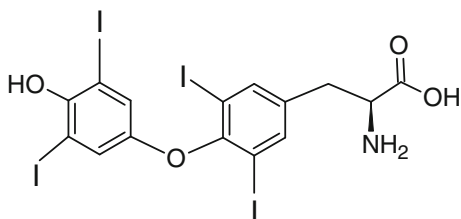
inadequate, the hypothalamus secretes thyroid stimulating hormone (TSH) which stimulates the thyroid gland to produce LVT. Synthetic LVT is used primarily in the treatment of hypothyroidism, and as a TSH suppressant in the treatment or prevention of various types of euthyroid goiters [3]. It is sensitive to light, temperature, and moisture, and the mechanism of oxidation depends on the nature of the substrate and pH of the system [4, 5]. Moreover, the kinetics of degradation of LVT in solution and in solid state has been reported [6]. Several methods have been reported for the analysis of LVT including enzyme immunoassays [7], fluorescence [8, 9], radioimmunoassay [10], capillary electrophoresis with laser-induced fluorescence [11], HPLC coupled to inductively coupled plasma mass spectrometry [12] chemiluminescence [13], flow-injection chemiluminescence [14] and cyclic-voltammetric [15].

Since there are no reports on the kinetics of oxidation of LVT by hexacyano-ferrate(III) (HCF), we are reporting the hydrophobic effect of sodium dodecyl sulfate (SDS) on the rate of decarboxylation and deamination of LVT by HCF(III) in aqueous medium. The activation parameters and thermodynamic quantities have been determined and are discussed.

Experimental procedure

The reaction was initiated by mixing previously thermostated solutions of Levofloxacin (Sigma Aldrich) with HCF(III) which also contained the required quantities of KOH and KNO_3 to maintain alkalinity and ionic strength, respectively. The anionic surfactant SDS was used as such; however, their purity was ascertained by determining their critical micelle concentration (CMC) from the curve of specific conductivity versus surfactant concentration, and the break point of two nearly straight lines was taken as an indication of micelle formation [16, 17] and the matching of them with the reported CMC, i.e. 8.4×10^{-3} mol dm^{-3}. The rate of reaction was measured by monitoring the absorbance by HCF(III) at its absorption maximum of 420 nm in Fig. 2. It has already been verified that there was no interference from other reagents in the range of absorption under consideration. Application of Beer's Law was verified, giving $\varepsilon = 1,060 \pm 50$ dm^3 mol^{-1} cm^{-1}. The pH of the reaction mixture at the beginning and at the end remained constant.

The kinetic runs were followed for more than 75 % completion of the reaction and first order kinetics was observed. The pseudo-first order rate constant, k_ψ, obtained from the slope of the plots of log(absorbance) versus time were linear. The
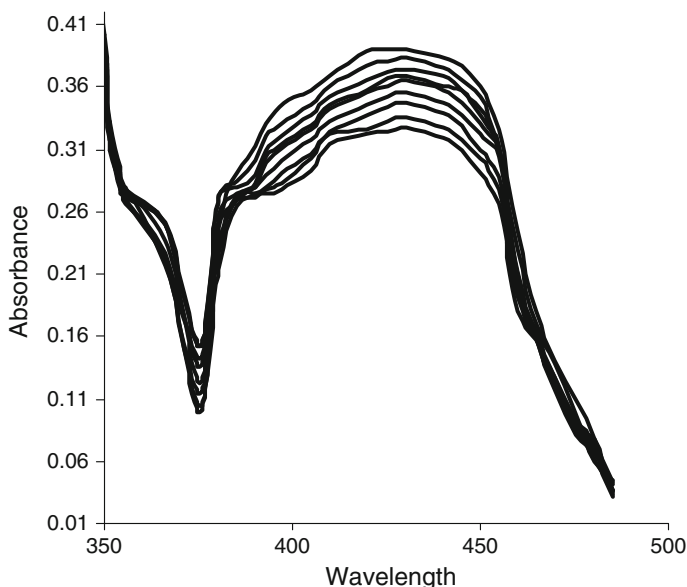
Fig. 2 Spectral changes during the formation of complex in the oxidation of LVT by alkaline HCF at 25 °C: [HCF] = 5×10^{-4}, LVT = 4×10^{-4}, [OH$^-$] = 0.2 and $I = 1.0$ mol dm^3 (scanning time intervals = 1 min)

k_ψ was reproducible within ±5 % and are the average of at least three independent kinetic runs (Table 1). All the reagents used were of analytical reagent (AR) grade and double-distilled water was used throughout.

Influence of varying concentration [Fe(CN)$_6$]$^{3-}$

The rate constant k_ψ was evaluated as a function of [Fe(CN)$_6$]$^{3-}$ by changing its concentration from 1×10^{-4} to 1×10^{-3} mol dm^{-3}, keeping all other parameters constant (Table 1). The plot of k_ψ versus [Fe(CN)$_6$]$^{3-}$ was linear with a variable order of dependence in [Fe(CN)$_6$]$^{3-}$. It is exhibited ranging from first order to higher concentration but certainly not tending towards zero in the absence of the surfactant, although in the presence of surfactant, the rate constant deviates from linearity at higher concentrations of the [Fe(CN)$_6$]$^{3-}$.

Influence of varying concentration of alkali

Keeping all other conditions constant, [OH$^-$] was varied (0.01–0.40 mol dm^{-3}). It was observed that the rate of reaction increases with increasing concentration of [OH$^-$] (Table 1) and the rate of oxidation in the absence and presence of the surfactant was identical. The plot of k_ψ versus [OH$^-$] was linear with a positive slope (0.9861), suggesting a first-order dependence of rate with respect to [OH$^-$].

Table 1 Effects of [LVT], [HCF], [OH$^-$] and SDS on the oxidation of levothyroxin by [HCF] at 25 °C and ionic strength $I = 1.0$ mol dm^{-3}

[HCF] $\times$ 10^4	[LVT] $\times$ 10^4	[OH$^-$] (mol dm^3)	SDS $\times$ 10^3	$k_\psi \times 10^4$ (s^{-1})
Variation [HCF] (mol dm^3)				
1.0	6.0	0.20	–	2.56
2.0	6.0	0.20	–	2.58
3.0	6.0	0.20	–	2.60
4.0	6.0	0.20	–	2.61
5.0	6.0	0.20	–	2.62
6.0	6.0	0.20	–	2.60
Variation [LVT] (mol dm^3)				
5.0	1.0	0.20	–	1.58
5.0	2.0	0.20	–	1.64
5.0	3.0	0.20	–	1.79
5.0	4.0	0.20	–	2.62
5.0	6.0	0.20	–	2.76
5.0	8.0	0.20	–	2.85
Variation [OH$^-$] (mol dm^3)				
5.0	4.0	0.05	–	2.34
5.0	4.0	0.10	–	2.56
5.0	4.0	0.20	–	2.62
5.0	4.0	0.30	–	2.76
5.0	4.0	0.40	–	2.83
5.0	4.0	0.50	–	2.85
Variation [SDS] (mol dm^3)				
5.0	4.0	0.20	3.00	22.2
5.0	4.0	0.20	4.50	13.5
5.0	4.0	0.20	8.40	11.0
5.0	4.0	0.20	10.0	4.00
5.0	4.0	0.20	12.5	1.60
5.0	4.0	0.20	15.0	1.10

Influence of varying concentration of LVT

The effect of the LVT concentration on the rate of its oxidation in alkaline [HCF] at pH 7.5 and ionic strength (0.50 mol dm^{-3}) in the absence and presence of the surfactant was studied at 25 °C. All the parameters were kept constant while that of LVT was varied (1.0 $\times$ 10^{-4}–1.0 $\times$ 10^{-3} mol dm^{-3}). The plot of log k_ψ versus time has been drawn and found to be linear with an intercept in the absence of the surfactant, The results are presented in Table 1. In the presence of surfactant, the rate constant deviates from linearity at higher concentrations of the substrate, suggesting that, in the presence of surfactant, the order of reaction in thesubstrate decreases at higher [substrate].
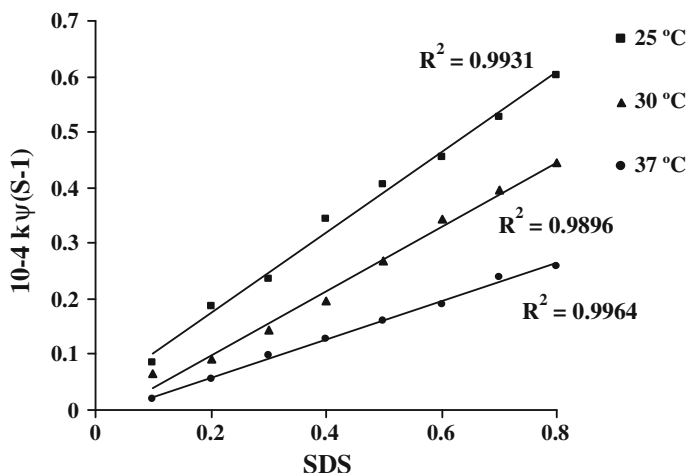
Fig. 3 Curves of k_ψ versus [SDS] at various temperatures. [HCF] $= 5.0 \times 10^{-4}$ mol dm^{-3}, [LVT] $= 4.0 \times 10^{-4}$ mol dm^{-3}, [OH$^-$] $= 0.2$ and $I = 1.0$ mol dm^{-3}

Influence of varying concentration of SDS

The effect of surfactant on the reaction rate has been studied over a wide concentration range of surfactant at different temperatures. It was observed that the rate constant decreases with increasing concentration of SDS (Fig. 3). The reported CMC of SDS is 8.4×10^{-3} mol dm^{-3} at room temperature. The inhibition effect by SDS may be due to increased concentration and affinity of unreactive counter ions for the stern layer. This may be due to competition between reactive and nonreactive ions for sites in the stern layer, when the rate of reaction decreases (Table 1).

Test of free radical

In order to test for the interference by the free radicals, the acrylonitrile was added to the reaction mixture and then left for 24 h under nitrogen atmosphere. Addition of methanol resulted in the precipitation of a polymer, suggesting the involvement of free radicals in the reaction. The blank experiment of reacting [HCF] and LVT alone with acrylonitrile did not induce polymerization under the same conditions. Initially, added acrylonitrile decreased the rate of reaction [18].

Stoichiometry of the reaction

Four sets of reaction mixture containing LVT, OH$^-$ and [Fe(CN)$_6$]$^{3-}$ in the absence and presence of the surfactant were taken. The mixture was left to stand for 24 h at 25 °C and then absorbance was recorded. Figure 2 shows the $\lambda_{\max}$ (420 nm) determined. The stoichiometry of the reaction was studied adopting the limiting
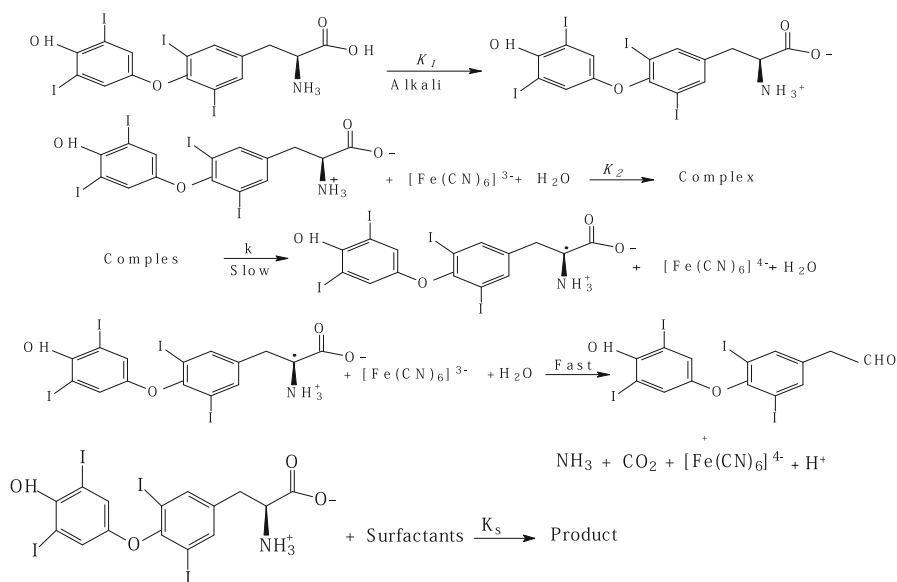
Scheme 1 Proposed reaction pathway of reaction mixture containing LVT, OH$^-$ and [Fe(CN)$_6$]$^{3-}$ in the absence and presence of the surfactant were taken

logarithmic method [19]. It was found that the ratio was 1:1. The proposed pathway is shown in Scheme 1. The main reaction products 2-[4-(4-hydroxy-3,5-diiodo-phenoxy)-3,5-diiodophenyl]acetaldehyde were identified and isolated with the help of TLC and characterized by FT-IR. The v(C=O) appears at 1,622 cm^{-1} which is the characteristic band of aldehyde. It does not undergo further oxidation. Ammonia was identified by Nessler's reagent [20]. The CO$_2$ liberated was qualitatively detected [21] by passing the gas into lime water.

$$+\ NH_3\ +\ CO_2\ +\ [Fe(CN)_6]^{4-}\ +\ H^+ \quad (1)$$

$$(1)$$
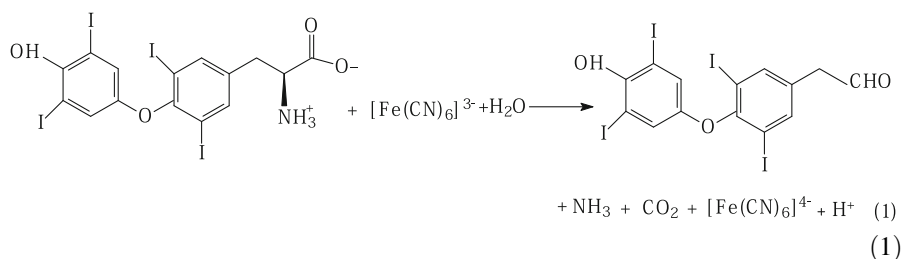
Influence of varying concentration of hexacyanoferrate(II) and sodium perchlorate

Effect of hexacyanoferrate(II) and sodium perchlorate in a reaction mixture had a negligible effect on the rate of oxidation in the presence of surfactants.

Activation parameters

The activation parameters (Ea, $\Delta H^{\#}$ and $\Delta S^{\#}$) in the presence as well as in the absence of the surfactant were evaluated using Arrhenius and Eyring equations and are reported in Table 2. The large values of Ea and $\Delta H^{\#}$ in the presence of the surfactant in comparison with aqueous medium are consistent with the accepted view that the slow reaction (in the presence of surfactant) would require a higher Ea and $\Delta H^{\#}$. A comparison of $\Delta S^{\#}$ values in aqueous medium and in the presence of surfactants shows that the entropy of activation is less negative in the presence of the surfactant. In the absence of the surfactant, a negative value of $\Delta S^{\#}$ indicates that two species, either two polar or an ionic species, combine in the rate-determining step to form a single intermediate complex that is more ordered [22, 23] than the reactants (Scheme 1). Almost the same value of the free energy change ($\Delta G^{\circ} \approx 45.8 \pm 1.0$ kJ mol) suggests the same mechanism of reaction in the absence and presence of surfactant.

On the basis of the kinetic results, the mechanism of reaction in the absence and the presence of surfactant may be proposed (Scheme 1) for which all the observed orders for each constituent such as [oxidant], substrate and [OH$^-$] may be well accommodated. Oxidation of LVT by HCF(III) in alkaline medium is a non-complementary reaction with the oxidant undergoing four equivalent changes in the absence of SDS. The substrate with HCF(III) formed complex C in alkali medium which decomposes in slow steps to a free radical, and further reacts with 1 mol of HCF(III) in fast steps to give the products 2-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetaldehyde and HCF(II). Another 1 mol of free radical of LVT reacts with SDS to form the products 2-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetaldehyde and HCF(II). Another 1 mol of free radical of LVT with SDS steps to form the final products. The 3D structure of the product 2-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetaldehyde in shown in Fig. 4.

Table 2 Binding constants (K_s), rate constants in micellar media (km), partition coefficients (P), partial molar volume, free-energy transfer from water to micelle ($-\Delta\mu^{\circ}$) at different temperatures and activation parameters for the oxidation of LVT in absence and presence of SDS

Temperature (°C)	Sodium dodecyl sulfate (SDS)				
	km 10^4 (mol dm^{-3} s^{-1})	K_s 10^2	P	V	$-\Delta\mu^{\circ}$ (kJ mol^{-1})
25	3.8	143	645	22.12	97.3
30	2.9	122	431	28.10	95.4
35	1.6	120	398	30.08	92.0
Activation parameters	In the absence of SDS			In the presence of SDS	
Ea (kJ mol^{-1})	67.5 ± 0.02			84.5 ± 0.03	
$\Delta H^{\#}$ (kJ mol^{-1})	58.1 ± 0.03			76.0 ± 0.04	
$-\Delta S^{\#}$ (JK mol^{-1})	91.2 ± 0.02			65.5 ± 0.03	
$\Delta G^{\#}$ (kJ mol^{-1})	48.5 ± 0.05			48.0 ± 0.02	

Fig. 4 3D view of the product of LVT
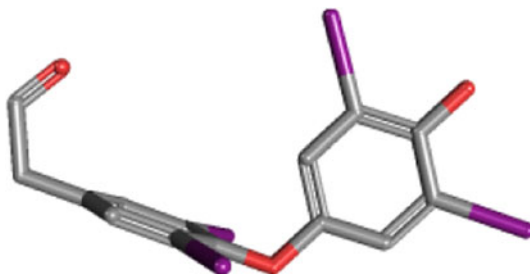
Table 3 Effect of [HCF] on the rate constant at 25 °C, [LVT] = 4.0×10^{-4} mol dm^{-3}, [SDS] = 8.4×10^{-3} mol dm^{-3} and [OH^{-}] = 0.2 and I = 1.0 mol dm^3

[HCF] 10^4 (mol dm^{-3})	[SDS]$k_\psi \times 10^4$ (mol dm^{-3} s^{-1})
6.0	11.2
8.0	11.0
10.0	11.2
12.0	11.4
14.0	11.2

The results can be accommodated by Scheme 1. The rate law is in agreement with the observed experimental results showing a first order with respect to alkali, oxidant and substrate concentration in the absence of the surfactant. The rate constants observed in the presence of the surfactant at different [HCF](III) were almost identical and are shown in Table 3.

Binding constant

To evaluate the binding constants between the substrate and surfactant (Scheme 2), the kinetic data have been analyzed in terms of Menger and Portnoy's [24] model reported for micellar catalysis/inhibition.

According to the Menger and Portnoy model, the substrate 'S' is distributed between the aqueous and micellar pseudo phases as given in Scheme 2.

According to Scheme 2, the observed rate constant may be given as

$$K_\psi = \frac{k_\omega + k_m K_s \{[D] - \text{CMC}\}}{1 + K_s \{[D] - \text{CMC}\}} \tag{2}$$

where k_ω, k_m, k_ψ are rate constants in aqueous phase and micellar media and the observed rate constant, respectively. K_s is the binding constant of substrate with surfactant. Dn, S, and SDn represent micellar surfactant, free substrate, and associated substrate, respectively.

Now Eq. (2) yields the observed rate constants as expressed by Eq. (3)

Scheme 2 Binding constants between the substrate and surfactant

$$\frac{1}{k_{\bar{\omega}} - k_{\psi}} \frac{1}{k_{\bar{\omega}} - k_m} + \frac{1}{(k_{\omega} - k_m)K_s\{[D] - CMC\}} \tag{3}$$

Equation (2) is appropriate for the binding in different reactions. The applicability of Menger and Portnoy's [24] model is shown by the plot of $1/(k_{\omega} - k_{\psi})$ versus $1/\{[D] - CMC\}$. The k_m and K_s may also be evaluated with the help of intercept and slope of the graph. In this investigation, the binding of SDS has been observed at the lowest CMC concentration. Figure 5 shows that the validity of the equation has been verified by $1/(k_{\omega} - k_{\psi})$ against $1/\{[D] - CMC\}$ and the applicability of Mangar and Portnoy's model in the system. The k_m and K_s have also been evaluated for the slope and intercept of the plot. The K_s of the substrate with surfactant can also be correlated to the partition coefficient, P, i.e. [substrate]micelle/[substrate]water ratio [25–27], by the following relationship

$$K_s = P\bar{V}$$

where $\bar{V}$ is the partial molar volume of the surfactant monomer. The standard transfer free energy [28, 29] per mole $\Delta\mu°$ of a solute from water to micelle is also related to the binding constant by the following equation.

$$\Delta\mu+ = -RT \ln(45.8)K_s$$

The effect of organized structure on the rate of chemical reaction has been attributed to the hydrophobic and electrostatic interactions (Table 2). The electrostatic surface potential at the miceller surface can attract or repel the reaction species, and hydrophobic interactions can bring about incorporation into micelle even if the reagent bears the same charge. Thus, the rate and the mechanism of chemical reactions may be affected by electrostatic or hydrophobic interactions.

The observed kinetic data, retardation of the rate with an increase in surfactant concentration, and negative values of k_m in the presence of SDS indicate that the reaction between negatively charged LVT and HCF(III) is in the aqueous phase, not in the miceller phase. When the surfactant is present in the reaction mixture, it binds the substrate by hydrophobic interactions causing a decrease in the concentration of the substrate in aqueous phase, and thus a retarding effect of the surfactant on the rate of reaction was measured. In the presence of SDS, the electrostatic repulsion between negatively charged substrate and anionic surfactant opposes the binding between the surfactant and the substrate. Thus, the hydrophobic interaction favored the binding while electrostatic repulsions opposed it. The low values of K_s and P in the presence of SDS and their decrease with increasing temperature means that
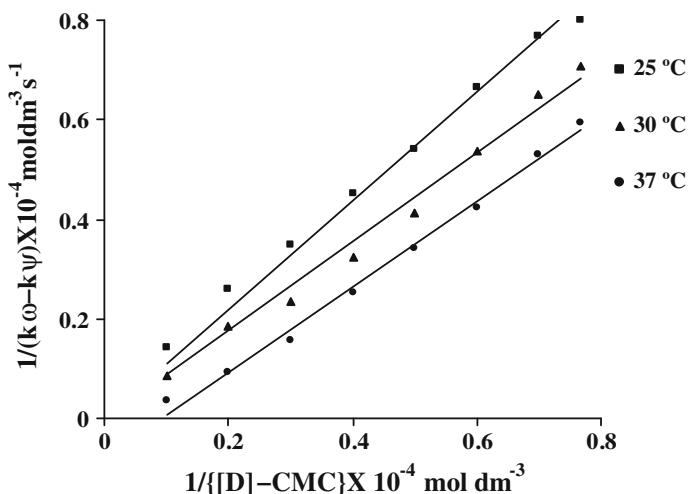
Fig. 5 Curves of $1/(k_\omega - k_\psi)$ versus $1/\{[D] - \mathrm{CMC}\}$ at different temperatures; $[\mathrm{HCF}] = 5.0 \times 10^{-4}$ mol dm^{-3}, $[\mathrm{LVT}] = 4.0 \times 10^{-4}$ mol dm^{-3}, $[\mathrm{OH}^-] = 0.2$ and $I = 1.0$ mol dm^{-3}

binding is an exothermic process. The transfer of free energy ($\Delta\mu^\circ$) is also favored in this results.

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