



Kinetics of oxidation of antidiabetic drug metformin hydrochloride by vanadium(V) in acidic and micellar medium

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Abstract

The kinetics of oxidation of antidiabetic drug metformin by vanadium(V) have been studied spectrophotometrically under pseudo-first order conditions in aqueous acidic and micellar medium. The observed rate of oxidation is first order with respect to both metformin and H^+ . The pseudo-first order rate constant is independent of ionic strength and varies inversely with dielectric constant of the medium. The effect of micelles (SDS and TX 100) on such reactions has been investigated. Sodiumdodecyl sulphate (SDS) and iso-octylphenoxy polyethoxyether (TX100) accelerate the rate of electron transfer reaction except for cationic CTAB due to the cloudiness of the reaction mixture. It is a one electron transfer process where vanadium(V) is reduced to vanadium(IV) supported by cyclic voltammetric study. The main oxidation product was identified as metformin N-oxide by FTIR and LCMS method. Activation parameters of such reaction have been calculated and reaction mechanism is suggested. Computational study based on Hartree–Fock method supports the reaction mechanism.

Keywords Metformin hydrochloride · Ammonium metavanadate · Oxidation · SDS and TX 100 · Kinetics · Computational study

1 Introduction

Metformin is an oral first line anti-hyperglycaemic agent which improves glucose tolerance in patients with type-2 diabetes mellitus, lowering both basal and post prandial glucose. Metformin decreases intestinal absorption of glucose and controls insulin sensitivity by increasing peripheral glucose uptake. It belongs to a class of compound known as biguanides which is identified as *N,N*-dimethyl imido diacarbonimide diamide [1, 2] having two imino ($\text{—C}=\text{NH}$) groups and one each of primary (—NH_2), secondary (—NH) and tertiary—N (CH_3)₂ group as donating centres (Fig. 1).

Vanadium has been recognised as an important trace element in biological system. It is non-carcinogenic and non-toxic [3] but concentration above 1×10^{-3} M shows toxic effect due to accumulation in tissue which causes irritation of lungs, throat, eyes and nasal cavities, damage the nervous system, liver and kidney [4]. Vanadium exists in many oxidation states from +2 to +5 but two of which are most common, Vanadium(IV) and Vanadium(V) as VO^{2+} (V^{4+}) and HVO_4^{2-} (V^{5+}) in biological system [5]. Vanadium is present as coenzyme in human body as vanadium nitrogenase and haloperoxidase [6]. Vanadium is distributed in body tissue and bones. Bones act as storage pool for Vanadate. Vanadium(V) is more easily taken up than Vanadium(IV) in gastro intestinal

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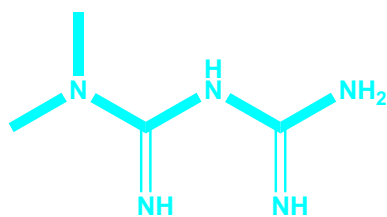


Fig. 1 Structure of metformin

tract [7]. However Vanadium(V) is particularly reduced in stomach and precipitate in the form of strongly soluble $VO(OH)_2^-$ due to slightly alkaline nature of intestine fluid [8, 9]. Aqueous chemistry of vanadium is very interesting. Both V(IV) and V(V) undergo very complex chemistry in aqueous solution forming a range of species. In aqueous solution at very low concentration it exists as vanadyl cation (VO^{2+}) [10]. At pH below 3, it exist in the form $[VO(H_2O)_5]^{2+}$ which is very stable cation known from the observed spectroscopy [11, 12]. However between pH3 to 10, the concentration of monomeric vanadium is very low. At a pH above 10, it becomes $[VO(OH)_3]^-$. Depending up on the pH, vanadium can be cationic or anionic species in aqueous solution. It becomes colourless at neutral and alkaline pH [13], but yellow in acid solution. Vanadium has a wide variety of pharmacological properties. Vanadium complexes have been tested as anti-parasitic, spermicidal, anti-viral, anti-tuberculosis and anti-tumour agents [10, 14, 15]. Besides pharmaceutical properties, it is also used in redox–flow battery (VRB) system which is an electrochemical energy storage by using redox system of VO^{2+}/VO_2^+ couple in acid medium [16]. A wide range of coordinate complexes with Vanadium(V) have been synthesized and known to exert insulin–enhancing effect such as pyridine-2, 6-dicarboxylate dioxo Vanadium(V) [17], Vanadium dipicolinate [13], bis (maltolato) oxovanadium(IV)[$VO-(malto)_2$] [18], Ammonium metavanadate [19]. Recently Trivino [20–22] and Crans [23–25] reported that metformin-decavanadate has shown pharmaceutical potential as hypoglycemic, lipid lowering, metabolic regulator. It reduces the dose and time of administration. It is not only insulin mimetic agent but also an insulin enhancing agent by observing its effect in vitro and in Vivo. Metformin decavanadate showed a protective effect on pancreatic beta cells of rats suggesting possible regeneration of these cells. Therefore it acts as insulin-enhancing effect.

Because of the above importance of vanadium, Vanadium(V) is selected as oxidant in our study. Although the importance of Vanadium is well known its necessity as a fundamental element in human body is still unclear. Thus much research in the clinical, biological, physiological fields has focused on Vanadium.

Various redox reactions of Vanadium(V) have been reported by biologically active agents like EDTA [26], paracetamol [27], ascorbic acid [28], L-tryptophan, glycolic acid [29], D-Fructose [30], 2-hydroxy cyclohexanone [31], tyrosine [32], D-glucose, D-Ribose [33].

D-arabinose, D-xylose [34], NADPH [35], glutathione [36], oxalic acid [37], hydroxyl urea [38]. Both inner and outer sphere electron transfer path ways have been reported. However literature of redox reaction of Vanadium by drug is very rare. Drug–metal interaction is an emerging research to understand the drug action at molecular level. Such type of study are useful for predicting the absorption of drugs, transport of drug across the biological membrane.

Several metal mediated oxidative reactions were investigated in aqueous and micellar medium. In most cases micelles play a crucial role to influence the kinetics of the oxidation pathways. The most prominent role of surfactant micelles is the improvement of a reaction velocity for a particular bimolecular reaction by concentrating both the reactants at their surfaces.

Surfactant is a special kind of amphiphilic compound composed of hydrophilic part (polar head group) and hydrophobic part (nonpolar tail group). Polar head group which forms outside as surface of micelles faces to water. The hydrophobic tail are inside away from water as they are non polar. Micelles are also at work in the human body. Micelles help the absorption of complicated lipids and lipid soluble vitamins (A, D, E and K) in small intestine. The product of fat digestion are dispersed into micelles by the action of bile salt which facilitates their absorption in small intestine [39].

The remarkable ability to influence the properties of surfaces and interfaces make the surfactant accessible for numerous applications from laboratory to industry [40]. A number of reviewers and scientific reports depict the widespread application of surfactant such as pharmaceutical, detergent, cosmetic, food science, nanotechnology and drug delivery [41]. They act as carrier of drug molecules to target site. They protect the drug molecules from degradation via hydrolysis or other physiological reactions which increases their shelf life and prolongs their stability during use. The particular nature of interaction between surfactant molecules and drug molecules is highly significant with the view point of stabilisation and solubilization of drug against degradation throughout its transportation in biological system. Since most biological processes occur at interface, structure, dynamic and reactivity of bio molecules differ at the interface than those observed in the bulk [42]. It influences the kinetics of various reactions when reactions takes place at the interface. A variety of electron transfer, proton transfer, ion transfer processes occur at the interface. Keeping this in view present study was carried out both in aqueous and micellar medium to understand the mode of action of the drug in biological domain.

Micellar effect has been studied by using sodium dodecylsulfate (SDS), CTAB (cetyltrimethylammonium bromide), Triton X-100 (iso-octylphenoxy polyethoxyether) as anionic, cationic and neutral surfactant respectively (Fig. 2).

Diabetes mellitus is ranked seventh among leading cause of death. Several drugs are presently available to reduce hyperglycaemia in diabetes mellitus. But these drugs have side effects, thus searching a new compound is essential to overcome this problem. There is continuous research for alternative drug. Management of diabetes without any side effect is still a challenge to medicinal chemist. This work is an attempt to synthesize and design a new anti-diabetic drug along with study of its mechanism of action through kinetic study.

2 Experimental

2.1 Materials and methods

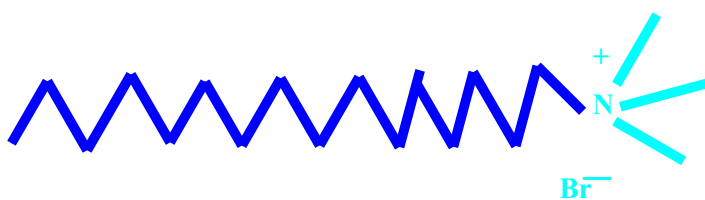
All chemicals used were of analar grade and double distilled water was used throughout the experiment. The

metformin hydrochloride sample was procured from Orissa Drugs and Chemicals Limited, Bhubaneswar, India. The purity of the sample was found to be 99% which was checked spectrophotometrically. Analytical grade ammonium metavanadate (NH_4VO_3) (99% pure) was procured from Merck. The surfactants such as SDS (sodium dodecylsulfate), CTAB (cetyltrimethylammonium bromide) and Triton X-100 were also procured from Merck. The concentration of Vanadium(V) was estimated by KIO_3 . The pH measurements were made using pre standardised digital pH meter (Systronics, India). The pH meter was standardised using NBS buffer of pH 4.01, 6.86 and 9.20. Ionic strength was maintained at $I = 0.5 \text{ mol dm}^{-3}$ by using freshly prepared standardised NaClO_4 solution. The strength of NaClO_4 was estimated by combined ion exchange alkali metric procedure using cation exchange resin Dowex 50 X 8(Na^+). The SDS (sodium dodecylsulfate), CTAB (cetyltrimethylammonium bromide), Triton X-100 were used as anionic, cationic and neutral surfactant respectively.

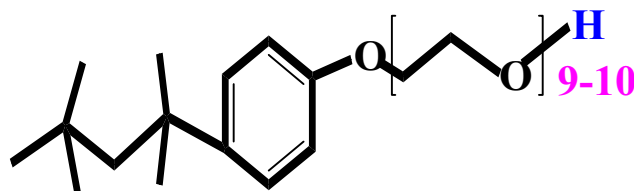
Fig. 2 Structure of surfactants
a SDS, b CTAB, c TX 100



(a) Structure of SDS



(b) Structure of CTAB



(c) Structure of TX-100

2.2 Kinetic measurements

The kinetics of the reaction between metformin and ammonium metavanadate in aqueous acidic medium was investigated spectrophotometrically under pseudo-first order conditions with excess of metformin at constant ionic strength, $I=0.5 \text{ mol dm}^{-3}$ using carry 100 (USA) UV-Vis spectrophotometer equipped with peltier system for temperature control. The progress of the reaction was followed spectrophotometrically by mixing the required amount of solution of metformin, ammonium metavanadate, NaClO_4 (for ionic strength variation), HCl (to maintain pH) in a thermo stated cell compartment. The reaction was followed spectrophotometrically at 262 nm by monitoring the decrease of absorbance at $\lambda_{max}=262 \text{ nm}$ as a function of time. The k_{obs} were calculated as the gradient of plot $\ln(A_t - A_\infty)$ versus t using following Eq. (1).

$$\ln(A_t - A_\infty) = \ln(A_0 - A_\infty) - k_{obs} \cdot t \quad (1)$$

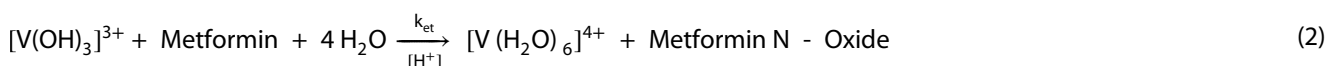
where A_0 , A_t , A_∞ denote optical density of reaction mixture at zero time, t time and infinite time respectively. A_∞ was measured after completion of the reaction ($5t_{1/2}$). The correlation coefficient (R^2) of the plot was found to be 0.99 in most of the cases. All calculations were made on PC using least square method. Again the kinetic measurements of the redox reaction was conducted in presence of micelle. The pseudo-first order rate constant (k_{obs}) data represents an average of duplicate run which are reproducible to within $\pm 5\%$.

3 Result and discussion

3.1 Stoichiometry and product analysis

The stoichiometry was determined for different reaction mixture containing various concentrations of ammonium metavanadate (V) and metformin in a molar ratio of 1:10 at $I=0.5 \text{ mol dm}^{-3}$ and $\text{pH}=2.0$. The reaction mixture was heated at 318 K for three hours till the reaction was completed. The unreacted Vanadium(V) concentration was estimated spectrophotometrically by measuring its absorbance at 262 nm.

The results indicated that 1 mol of metformin was consumed by 1 mol of vanadium to yield the oxidation product. The stoichiometry was found to be 1:1 as depicted in the Eq. (2).



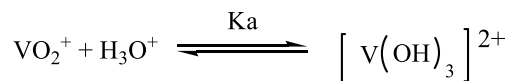
In order to get the product, 0.2 mol of ammonium metavanadate in 20 ml of water and 0.2 mol of metformin in 20 ml of water were mixed and $\text{pH}=2.0$ was maintained followed by heating the reaction till completion. From this solution metal ions were removed through cation exchange resin (Dowex 50 WX8). The solution was evaporated and concentrated slowly and was kept overnight, a brown crystalline product was formed. It was washed with ethanol several times and dried in a desiccator containing silica gel.

The FTIR spectrum of the substrate and the product was recorded by Nicolas iS 5 FTIR spectrophotometer (Thermo fisher) using KBr pellet of the sample and the spectra was presented in Fig. S1(a) and S1(b). Analysis of product [Fig. S1(b)] shows a sharp peak at 3425 cm^{-1} corresponds to N-H stretching in primary amine and C=NH stretching [43]. The peak at 2917 cm^{-1} corresponds to C-H stretching in CH_3 group, 1646 cm^{-1} corresponds to N-H stretching band and C=N stretching in amino linkage, 1556 cm^{-1} corresponds to secondary N-H stretching. A characteristic sharp peak at 1381 cm^{-1} is due to N-oxide stretching (aliphatic) which is not found in FTIR spectra of the substrate. The peak at 665 cm^{-1} is due to C-H out plane deformation (unsymmetrical) and peak at 804 cm^{-1} corresponds to N-H out plane bending. Comparison of Fig. S1(b) with Fig. S1(a) shows that metformin moiety remains unaffected during the oxidation reaction. Hence the oxidation product is metformin N-oxide. Similar product was reported by other authors for oxidation of metformin by Bromamine-T and Chloramines'-B [44].

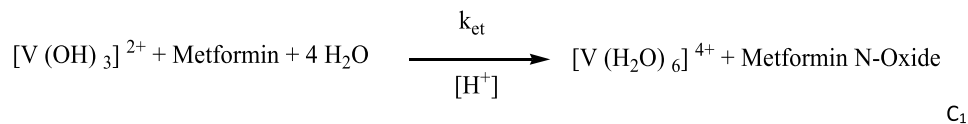
Product of the reaction was further confirmed by mass spectra. Fig. S2 (a) and S2 (b) representing the mass spectrum of metformin and product metformin N-oxide respectively.

It shows characteristic peaks at m/z 145, 129, 64, 60, 45, 30, 16 amu. Molecular ion peak of metformin N-oxide corresponds to 145 amu and metformin ion corresponds to 129 amu, 60 amu corresponds to $(\text{CH}_3)_2 \text{NO}^+$ and 30 amu corresponds to $\text{CH}_2=\text{NH}_2^+$, 45 amu corresponds to $\text{C}_2\text{H}_5\text{NH}_2^+$ whereas 16 amu corresponds to NH_2^+ . These peaks are in accordance with the proposed product metformin N-oxide.

Scheme 1 Mechanism of the redox reaction



$$K_a = \frac{[\text{V}(\text{OH})_3]^{2+}}{[\text{VO}_2^+]_e [\text{H}^+]_e}$$



3.2 Mechanism and rate law

Based on the above experimental results, the probable mechanism of the redox reaction may be delineated as in Scheme 1.

Vanadium(V) is amphoteric in nature and reduction of it in acidic medium involves cationic species [45]. In acidic medium Vanadium(V) exists as bright yellow pervanadyl ion VO_2^+ which coexist in equilibrium with the hydrated form $[\text{V}(\text{OH})_3]^{2+}$. It has been established that protonated form of oxidant is more reactive in acid medium [46]. It reacts with metformin forming intermediate complex prior to electron transfer. The intermediate complex decomposed to give the product as shown in Scheme 1. The transfer of reactant to form transition state proceeds rapidly under the experimental conditions which decomposed to give the product. From the above Eq. (2), the rate law can be derived as follows:

$$\text{Rate} = k_{\text{et}} [\text{C}_1]_e [\text{metformin}]_T \quad (3)$$

$$\text{since, } K_a = \frac{[\text{C}_1]_e}{[\text{VO}_2^+]_e [\text{H}^+]_e} \quad (4)$$

$$[\text{C}_1]_e = K_a [\text{VO}_2^+]_e [\text{H}^+]_e \quad (5)$$

Substituting the value of $[\text{C}_1]_e$ in Eq. (3)

$$\begin{aligned} \text{Rate} &= k_{\text{et}} K_a [\text{VO}_2^+]_e [\text{H}^+]_e [\text{VO}_2^+]_T \\ &= [\text{VO}_2^+]_e + [\text{C}_1]_e \\ &= [\text{VO}_2^+]_e + K_a [\text{VO}_2^+]_e [\text{H}^+]_e \end{aligned} \quad (6)$$

$$= [\text{VO}_2^+]_e + [1 + K_a [\text{H}^+]_e] \quad (7)$$

Or,

$$[\text{VO}_2^+] = \frac{[\text{VO}_2^+]_T}{[1 + K_a [\text{H}^+]_e]} \quad (8)$$

Substitute $[\text{VO}_2^+]_e$ in Eq. (6)

$$\text{Rate} = \frac{k_{\text{et}} K_a [\text{VO}_2^+]_T [\text{H}^+]_e [\text{metformin}]_T}{[1 + K_a [\text{H}^+]_e]} \quad (9)$$

$$\text{Rate} = k_{\text{obs}} [\text{VO}_2^+]_T \quad (10)$$

Comparing Eqs. (9) and (10)

$$k_{\text{obs}} = \frac{k_{\text{et}} K_a [\text{H}^+]_e [\text{metformin}]_T}{[1 + K_a [\text{H}^+]_e]} \quad (11)$$

Since $K_a [\text{H}^+]_e \leq 1.0$ Equation (11) is reduced to

$$k_{\text{obs}} = k_{\text{et}} K_a [\text{H}^+]_e [\text{metformin}]_T \quad (12)$$

Plot of k_{obs} versus $[\text{metformin}]_T$ keeping $[\text{H}^+]_e$ constant (Fig. 4) shows a straight line and k_{obs} versus $[\text{H}^+]_e$ keeping $[\text{metformin}]_T$ constant also shows a straight line (Fig. 5). This supports the rate law and the proposed mechanism.

From Eq. (12)

$$\frac{k_{\text{obs}}}{[\text{metformin}]_T} = k_{\text{et}} K_a [\text{H}^+]_e \quad (13)$$

Plot of $\frac{k_{\text{obs}}}{[\text{metformin}]_T}$ versus $[\text{H}^+]_e$ is a linear line with a slope which gives composite rate constant of the above electron transfer reaction (k).

Slope = $k_{\text{et}} K_a = k$ = composite rate constant

The k_{obs} data are collected in Table 1. The composite rate constant (k) are calculated at temperature range 293.15–308.15 K and tabulated in Table 2. The activation parameters of composite rate constant are calculated and tabulated in Table 2.

The mechanism of the reaction of C_1 with metformin to generate the product Metformin N-oxide is shown in Scheme 2.

This scheme of mechanism is similar to our earlier published paper [47].

Table 1 Pseudo-first order rate constants (k_{obs}) data at different [Metformin] and $[\text{H}^+]$ with temperature range 293.15–308.15 K (± 0.1)

[Metformin] mol dm ⁻³	[HCl] mol dm ⁻³	293 K 10 ³ k_{obs} (s ⁻¹)	298 K 10 ³ k_{obs} (s ⁻¹)	303 K 10 ³ k_{obs} (s ⁻¹)	308 K 10 ³ k_{obs} (s ⁻¹)
2×10^{-5}	0.05	1.97	3.17	5.25	7.25
	0.1	2.30	3.54	5.71	8.25
	0.15	3.33	4.27	7.23	9.15
	0.2	4.10	5.75	8.95	10.45
	0.25	4.50	6.34	10.25	11.25
3×10^{-5}	0.05	3.45	5.02	7.38	12.09
	0.1	5.21	6.57	11.32	13.54
	0.15	6.95	9.11	13.00	16.64
	0.2	8.74	11.24	14.29	20.05
	0.25	10.24	13.56	16.64	23.44
4×10^{-5}	0.05	6.55	8.69	11.84	13.56
	0.1	8.23	13.64	15.65	19.12
	0.15	11.21	17.21	23.93	31.01
	0.2	13.84	21.41	25.69	36.32
	0.25	17.56	23.36	27.74	41.23
5×10^{-5}	0.05	8.564	10.97	12.31	14.21
	0.1	11.86	12.25	16.45	19.56
	0.15	13.741	14.36	18.34	21.35
	0.2	16.56	17.59	23.87	23.45
	0.25	19.25	21.61	25.01	41.25
6×10^{-5}	0.05	10.84	12.15	16.78	19.45
	0.1	13.32	15.24	17.45	21.98
	0.15	15.49	18.35	21.73	24.66
	0.2	16.01	21.56	25.02	27.24
	0.25	20.33	23.45	29.36	44.64

Experimental error $\pm 5\%$ **Table 2** Composite rate constant(k) data for the rate controlling paths at different temperature range 293–308 K and activation parameters

Temperature (K)	10 ³ k (s ⁻¹)
293	99.58
298	127.94
303	141.85
308	145.04
Activation parameters	Value
E_a (kJ mol ⁻¹)	40.2
ΔH^\ddagger (kJ mol ⁻¹)	35.2
$\Delta S^\ddagger \pm$ (J K ⁻¹ mol ⁻¹)	-347.9
$\Delta G^\ddagger \pm$ (kJ mol ⁻¹)	68.5

3.3 Spectroscopic changes

UV–Vis time scan spectra (Fig. 3a) of the reaction mixture of metformin and Vanadium(V) in HCl medium shows continuous decrease in absorption spectra of V (V) by

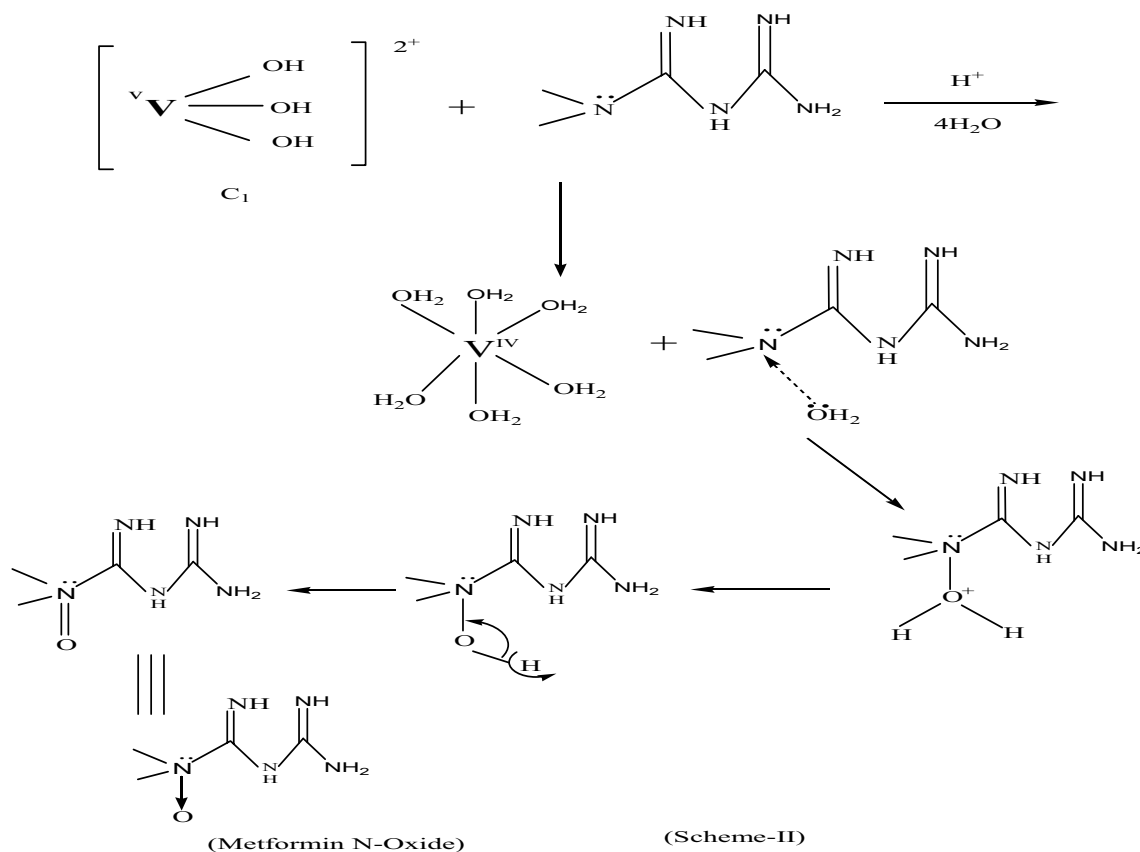
metformin in the whole range 250–400 nm indicating reduction of metal vanadium. The spectra after completion of the oxidation reaction (24 h) is shown in Fig. 3(b). Since there is no shifting of band in the time scan spectrum during reduction, outer sphere electron transfer mechanism is predicted.

3.4 Reaction order

The reaction order with respect to the reactants is determined from the plot of k_{obs} versus concentration of metformin and H^+ keeping other conditions constant. k_{obs} versus metformin and HCl is a straight line Figs. 4 and 5 with a positive slope suggesting order of the reaction is unit with respect to [Metformin] and $[\text{H}^+]$.

3.5 Effect of ionic strength

The effect of ionic strength on redox reaction was studied varying $I = 0.3$ – 0.8 mol dm⁻³ using of NaClO₄ as an inert electrolyte keeping the concentrations of all other



Scheme 2 Mechanism of formation of metformin N-oxide

reactants constant. The results are presented in Fig. S3 indicating that the redox reaction is independent of ionic strength.

3.6 Effect of dielectric constant

The effect of dielectric constant was studied at 293 K by varying 20% to 70% acetic acid keeping all other conditions constant. k_{obs} changes from $6.35 \times 10^{-3} \text{ s}^{-1}$ to $6.97 \times 10^{-3} \text{ s}^{-1}$ when dielectric constant varies from 81.5 to 38.5 (Table S2). Plot of $\log k_{\text{obs}}$ versus D^{-1} is linear (Fig. S4) with positive slope ($R^2 = 0.98$) indicating ion-dipolar interaction in rate determining step [48].

3.7 Test of free radicals

The involvement of free radicals in the reaction was examined by polymerization test. A known quantity of acrylonitrile scavenger was added to the reaction mixture of [metformin] = $5.0 \times 10^{-5} \text{ mol dm}^{-3}$, [V(V)] = $2.0 \times 10^{-4} \text{ mol dm}^{-3}$, $[\text{H}^+] = 0.01 \text{ mol dm}^{-3}$ in an inert atmosphere for two hours. Upon dilution with methanol no precipitate was formed

indicating absence of free radical in the reaction mixture. Hence there is no intervention of free radicals in the mechanism of the reaction.

3.8 Effect of temperature

The rate of oxidation of metformin by V(V) was performed at five different temperatures in the range of 293–308 K at constant concentration of the reactants and ionic strength. The results indicate that pseudo-first order rate constant (k_{obs}) which shows an increasing trend with rise in temperature. With increase in temperature, the composite rate constant (k) also increases. Using Arrhenius and Eyring equation by plotting $\log(k/T)$ versus $1/T$, activation parameters such as activation enthalpy $\Delta H^\ddagger = 35.2 \text{ kJ mol}^{-1}$, activation entropy $\Delta S^\ddagger = -347.9 \text{ J K}^{-1} \text{ mol}^{-1}$ and activation free energy $\Delta G^\ddagger = 68.5 \text{ kJ mol}^{-1}$, activation energy $E_a = 40.2 \text{ kJ mol}^{-1}$ are tabulated in Table 2.

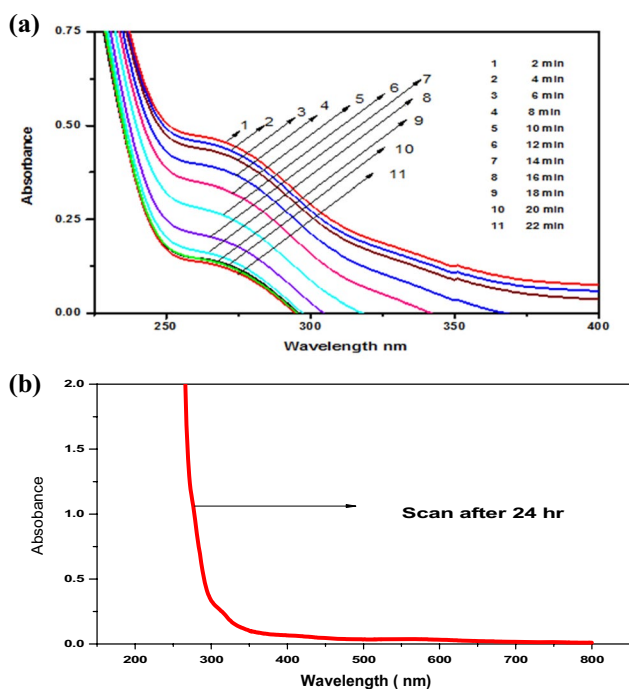


Fig. 3 **a** Time scan UV-Vis spectra of oxidation of metformin by V(V) in hydrochloric acid medium. [metformin]= 5.0×10^{-5} mol dm⁻³, [V(V)]= 2.0×10^{-4} mol dm⁻³, [H⁺]=0.01 mol dm⁻³, I=0.5 mol dm⁻³, 25 °C. Scan time intervals (Δt)=2 min (curve 1–11). **b** UV-Vis spectra of oxidation of metformin by V(V) in hydrochloric acid medium. [metformin]= 5.0×10^{-5} mol dm⁻³, [V(V)]= 2.0×10^{-4} mol dm⁻³, [H⁺]=0.01 mol dm⁻³, I=0.5 mol dm⁻³, 25 °C after 24 h

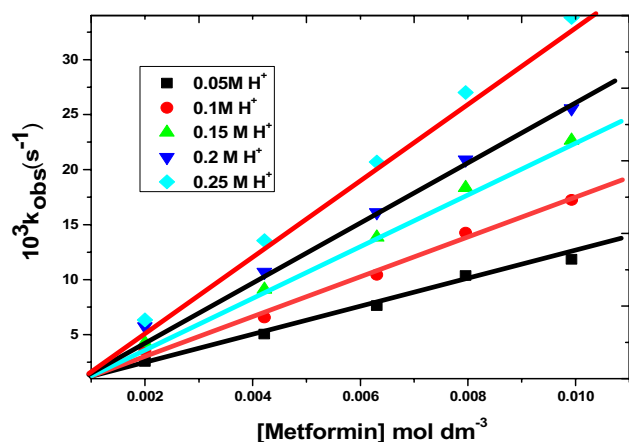


Fig. 4 Variation of k_{obs} versus [metformin]/mol dm⁻³ at different [H⁺] in the oxidation of metformin by Vanadium(V), [metformin]= 5.0×10^{-5} mol dm⁻³, V(V)= 2.0×10^{-4} mol dm⁻³, [H⁺]=0.01 mol dm⁻³, [NaClO₄]=0.5 mol dm⁻³, 25 °C

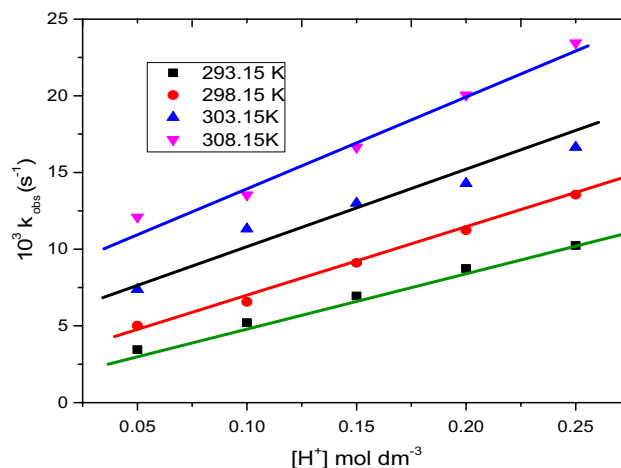


Fig. 5 Variation of $10^3 k_{obs}$ versus [H⁺]/mol dm⁻³ on the rate of oxidation of metformin by Vanadium(V) at different temperatures, [metformin]= 5.0×10^{-5} mol dm⁻³, V(V)= 2.0×10^{-4} mol dm⁻³, [H⁺]=0.01 mol dm⁻³, [NaClO₄]=0.5 mol dm⁻³

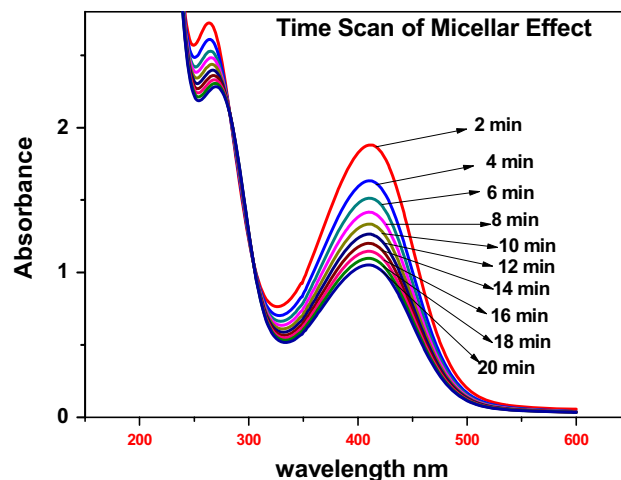


Fig. 6 UV-visible time scan of oxidation reaction of metformin by vanadium(V) in presence of SDS. [metformin]= 5.0×10^{-5} mol dm⁻³, V(V)= 2.0×10^{-4} mol dm⁻³, [H⁺]=0.01 mol dm⁻³, [NaClO₄]=0.5 mol dm⁻³, 25 °C

3.9 Effect of surfactants

3.9.1 Effect of SDS

Time scan spectra of the oxidation reaction of metformin by vanadium in presence of anionic micelle SDS (Fig. 6) shows a remarkable change indicating the significant effect of SDS in the redox reaction. The kinetics of

oxidation of metformin by V (V) compound was studied by varying [SDS] from 0.002 to 0.014 mol dm⁻³ at 293 K and rate constants are tabulated in Table S1. The curve

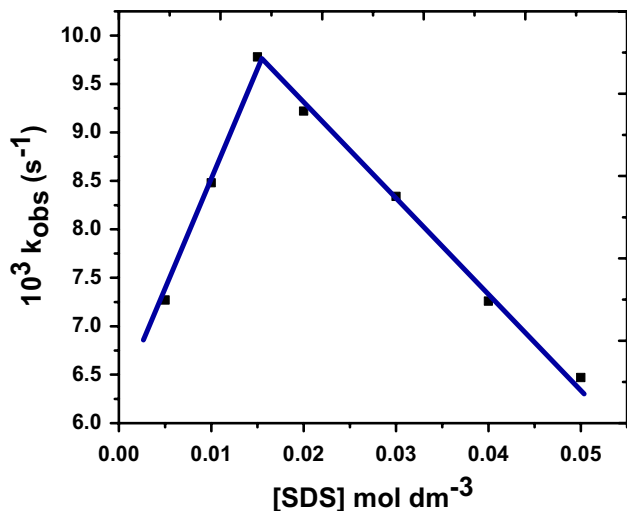


Fig. 7 Variation of pseudo-first order rate constant of $10^3 k_{\text{obs}}$ with [SDS] mol dm⁻³ in the oxidation of metformin by Vanadium(V), [metformin]= 5.0×10^{-5} mol dm⁻³, V (V)= 2.0×10^{-4} mol dm⁻³, [H⁺]=0.01 mol dm⁻³, [NaClO₄]=0.5 mol dm⁻³, 25 °C

(Fig. 7) shows increase of pseudo-first order rate constant with increase of [SDS] from 0.002 mol dm⁻³ and reaches maximum value at 0.006 mol dm⁻³ which is close to CMC of SDS=0.007 mol dm⁻³ [49]. On further increase beyond CMC of SDS, a decreasing trend of rate constant was observed.

The kinetic result has been explained by considering the preferential partitioning of reactants between the micellar and aqueous pseudo phase (Fig. 8) and local concentration effect. The rate enhancement can be explained in following manner.

The micellar surface of SDS is an anionic nature whereas the vanadium present inside the solution is cationic species. So electrostatic attraction taking place between two opposite charge species. Metformin also remains in cationic form therefore it preferably stay in micellar stern layer region (Fig. 8) so micelle assist the reactant molecules to come closer to each other hence increase the observed pseudo-first order rate of the reaction by decreasing the energy of activation of the reaction. There is also another reason for rate enhancement. The higher collision frequency among the reactant molecules in the small volume of the micelle like confined environment known as localization effect. This increase of the rate of reaction stops at [SDS]=0.006 mol dm⁻³ near the CMC of SDS which is

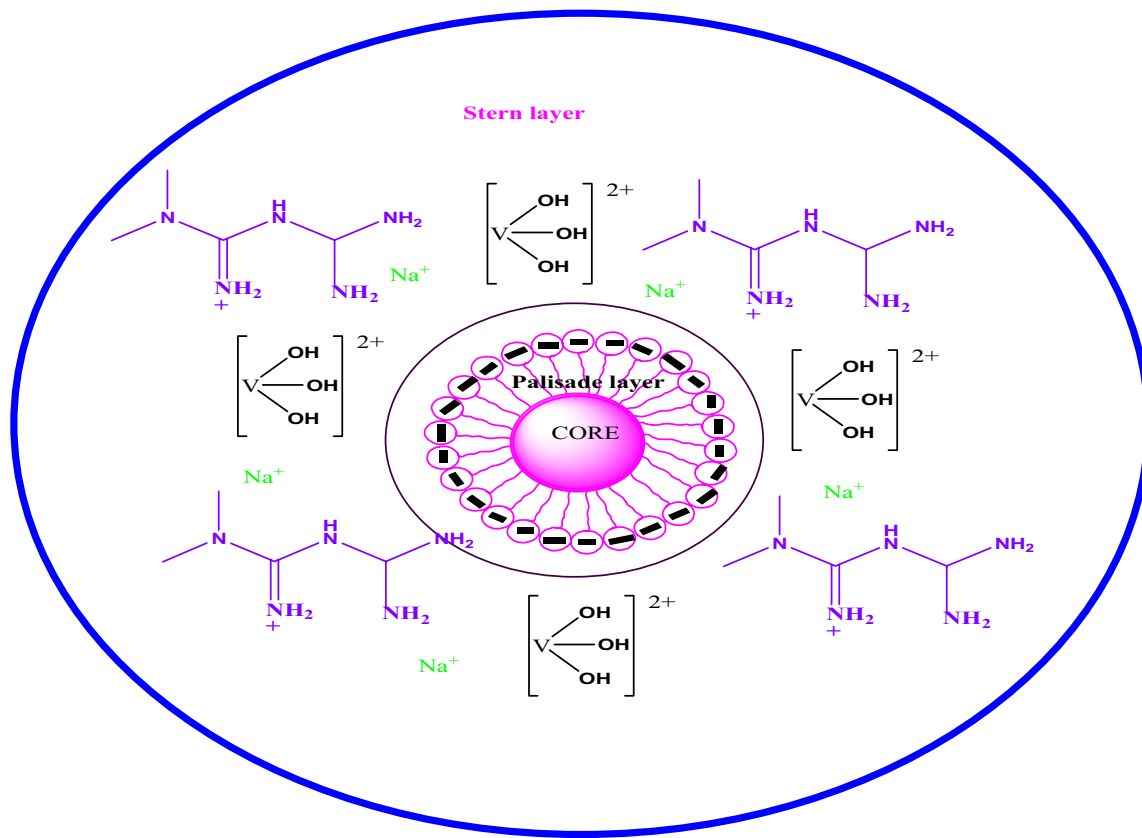


Fig. 8 Schematic representation of partitioning of V(V)⁺ species and metformin⁺ in aqueous medium anionic surfactant

0.007 mol dm⁻³ [50], after CMC there is retardation of rate constant due to micelle–micelle repulsion. This can also be explained mathematically by using Scheme 3 and its kinetic equation.

The variation of pseudo-first order rate constant can also be explained using the assumption that the surfactant is distributed between aqueous micellar pseudophase as shown in scheme 3 where subscript W and M represents aqueous and micellar pseudo phase respectively.

The observed first order rate constant of the overall reaction in micellar medium is expressed by the Eq. (14)

$$\text{Rate} = k_{\text{obs}}[\text{substrate}]$$

$$k_{\text{obs}} = \frac{k_w[V]_w + k_2^M K_{\text{SB}}[[D_n][V]_M]}{1 + K_{\text{SB}} D_n} \quad (14)$$

$[V]_m$ → concentration of vanadium in micellar medium, k_w → second order rate constant in aqueous phase, k_2^M → second order rate constant in micellar medium, $[D_n] = [\text{SDS}] - \text{CMC}$, $[D_n]$ → micellized surfactant, K_{SB} → substrate binding constant

$$K_{\text{SB}} = \frac{[S_m]}{[S_w][D_n]} \quad (15)$$

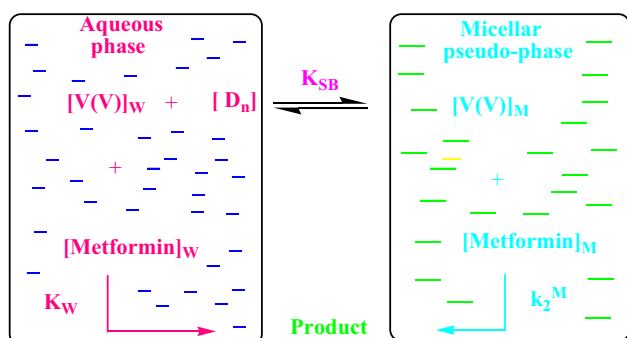
S_m and S_w denotes substrate in aqueous and micellar pseudophase respectively. As micellar pseudo phase occupies only a small fraction (2–3%) of total solution volume it may be assumed that

$$K_{\text{SB}}[D_n] \ll 1$$

The Eq. (14) becomes Eq. (16)

$$k_{\text{obs}} = k_w + k_2^M K_{\text{SB}}[D_n] \quad (16)$$

This shows linear increase of observe rate constant with an increase of [surfactant]. This explains the enhancement of pseudo first order (k_{obs}) rate constant as in Fig. 7. By



Scheme 3 Partitioning of reactant molecule in aqueous and micellar medium

assuming the rate in micellar pseudo-phase is zero that is $k_2^M = 0$ Eq. (14) is reduced to Eq. (17)

$$k_{\text{obs}} = \frac{k_w}{1 + K_{\text{SB}} [D_n]} \quad (17)$$

The above Eq. (17) explains the decrease of pseudo first order rate constant with increase in the substrate concentration beyond [surfactant] > 0.006 mol dm⁻³.

Similar micellar effect has been reported by different research groups Buntan [51], Richardson [52], for oxidation of organic sulfides with peroxy mono sulphate and bicarbonate-activated hydrogen peroxide respectively. Metal catalyzed Ce(IV) oxidation of formaldehyde to formic acid in aqueous medium [53]. Oxidation of propanol to propionaldehyde in vanadium(V) in aqueous medium [54], oxidation of methanol to formaldehyde in aqueous medium [55]. Oxidation of ascorbic acid by vanadium(V) in aqueous medium [56].

3.9.2 Effect of CTAB

The rate measurements in presence of cationic micelle CTAB could not be made even at very low concentration (0.001–0.005) mol dm⁻³ due to cloudiness of the reaction mixture.

3.9.3 Effect of Triton X-100

The rate constant measurements in presence of neutral micelle Triton X-100 was carried out at 303 K by varying [Triton X-100] = 0.002–0.014 mol dm⁻³ as displayed in Fig. S5 and reflected in Table S1. The rate enhancement effect was observed up to 0.012 mol dm⁻³ and then it reaches a limiting value at 0.014 mol dm⁻³. This may be due to hydrophobic effect which assists the micellar binding of the substrate. The micellar environment has an effect of rate magnification which is governed by both electrostatic and non-electrostatic effects. The substrate bound to the neutral micelle undergoes with a faster oxidation reaction ($k_m/k_w = 1.5$ –2.0) as compared to aqueous phase.

3.10 Cyclic voltammetry study

Voltammetry measurements were made on a CHI661 workstation with a normal three-electrode configuration, consisting of a glassy carbon electrode, an Ag/AgCl reference electrode and a Pt-wire auxiliary electrode. Prior to the measurement, the working electrode was polished with decreasing grades of alumina (1.0–0.1 μm) to achieve a mirror smooth surface, then it was ultrasonic washed in acetone and ultra-purified water in succession.

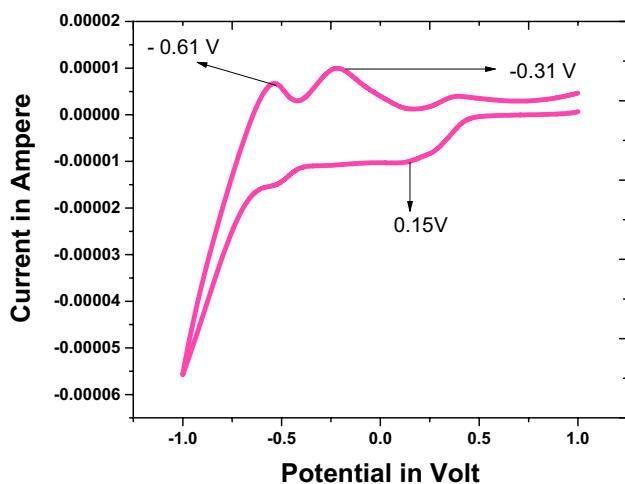


Fig. 9 Cyclic voltammogram of oxidation of metformin by V(V) at scan rate 100 mV/s, [metformin]= 5.0×10^{-5} mol dm $^{-3}$, V(V)= 2.0×10^{-4} mol dm $^{-3}$, [H $^{+}$]=0.01 mol dm $^{-3}$, [NaClO $_4$]=0.5 mol dm $^{-3}$, 25 °C

The cyclic voltammeter study of the redox reaction between Vanadium(V) and metformin containing 0.1 M KCl as supporting electrolyte was carried out using a glassy carbon as electrode and Ag/AgCl as reference electrode. CV results of the redox reaction are presented in Table S3. The representative cyclic voltammogram is shown in Fig. 9. A negative sweep initiated at 1.0 V in the potential range + 1.5 V to – 1.5 V with scan rate of 100 mV/s yields an irreversible couple corresponding V(V)/V(IV) redox process. The complex shows an irreversible reduction (peak) at $E_{pc} = 0.15$ V corresponding V(V)–V(IV) redox reaction. Oxidation wave at E_{pa1} at 0.61 V corresponding to V IV –V V oxidation reaction and E_{pa2} 0.3 V corresponds to V V . The peak current ratio $I_{pa1}/I_{pc} = 0.6$ which is less than unity showing one electron transfer process followed by chemical reduction.

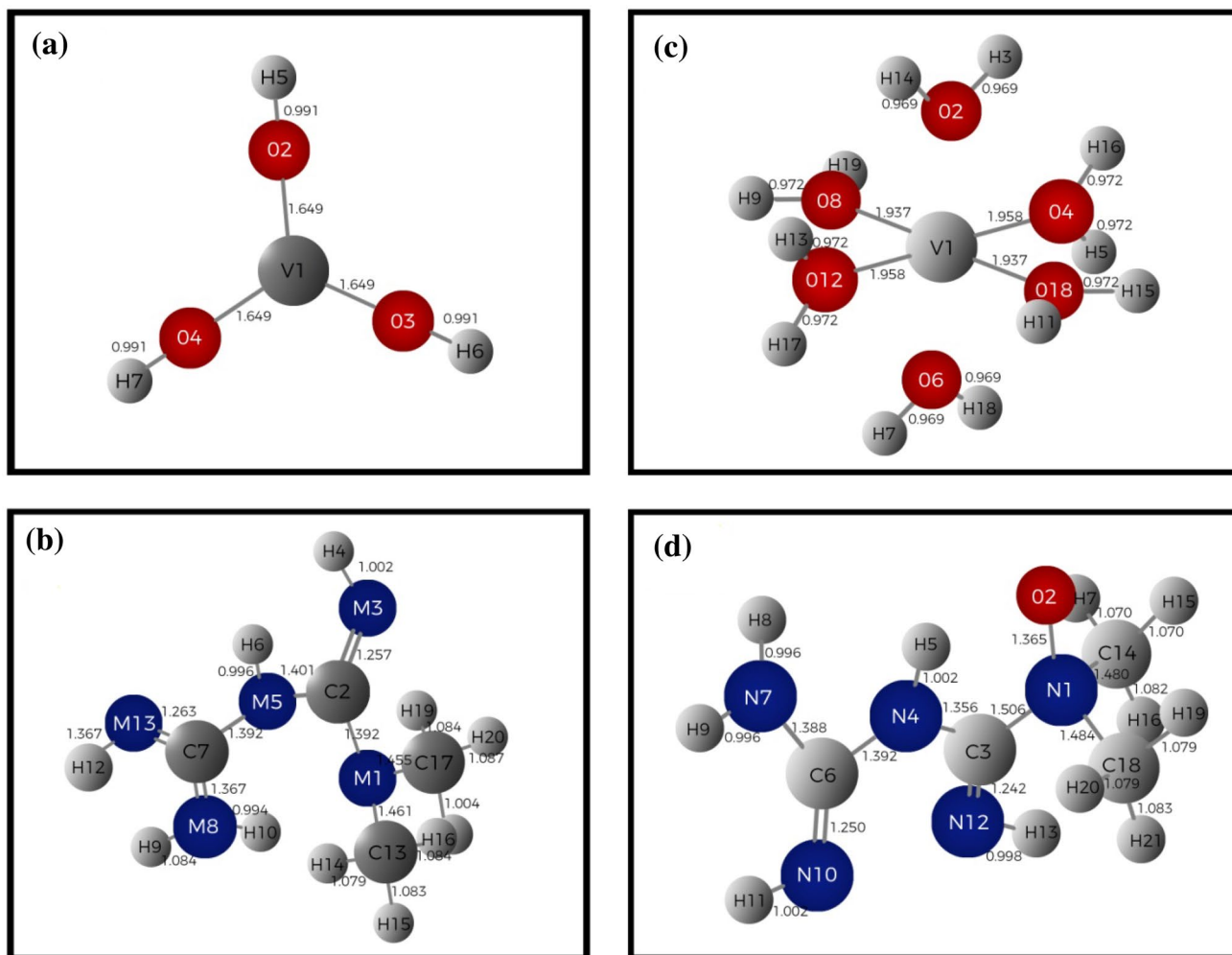


Fig. 10 Optimized structure of reactants and products by Hartree–Fock method

3.11 Computational study

Quantum mechanical calculation of thermodynamic parameters such as free energy, entropy, enthalpy change and change in molecular parameters such as bond angle, bond length, point group of the reaction between $[V(OH)_3]^{2+}$ and metformin is based on Hartree–Fock theory with no imaginary frequency. The calculations are based on several basis sets for the reactants and products. They are 6-31G (d,p) (for a), LAN2DZ (for b), 6-31 + G (df,p) (for c) and 6-31G (d,p) (for d) where, d, f, p stands for polarization function, + indicates diffused function and G represents Gaussian type orbital's (GTO). The geometry of the reactants(a, b) and the products(c, d) are fully optimized which is shown in Fig. 10. The respective points group of a, b, c, d are C_1 , C_1 , D_{2h} and C_1 . All calculations are implemented using Gaussian-16 software package and the parameters are represented in Tables S4, S5 and S6.

From the data in the above table it is observed that the bond angle N(1)–C(2)–N(5) and N(5)–C(7)–N(8) is almost constant in reactants and products. The structural moiety of metformin N-oxide almost remains same as metformin. There is a slight increase of bond length (N₁–C₂ = 1.506 Å) in metformin N-oxide as compared to metformin (1.395 Å) due to co-ordination of N with more electronegative oxygen but all other bond lengths remains constant. Dipole moment of metformin is found to be 3.091D where as in metformin N-oxide it is 1.383D. Hartree–Fock calculation of the above reaction shows $\Delta H = -7.9 \times 10^5 \text{ kJ mol}^{-1}$, $\Delta S = 14.75 \times 10^{-2} \text{ JK}^{-1} \text{ mol}^{-1}$, $\Delta G = -7.92 \times 10^5 = \text{kJ mol}^{-1}$. Low value of ΔH and ΔS favours the electron transfer process. Negative value of ΔG indicates the feasibility of the reaction of metformin as in Eq. (1) and negative value of ΔH indicates exothermic reaction. All these data from Hartree–Fock calculation supports the predicted reaction mechanism as indicated in Scheme 1.

4 Conclusion

The kinetics of oxidation of metformin by Vanadium(V) was studied in aqueous acidic and micellar medium. Followings are the conclusions from the above study.

1. The stoichiometry of metformin and Vanadium(V) reaction is found to be 1:1.
2. The reaction is found to be first order with respect to metformin and H^+ .
3. The reaction is independent of ionic strength and varies inversely with dielectric constant of the medium.

4. SDS and Triton X100 anionic and neutral surfactants accelerate the rate of electron transfer reaction.
5. The main product of the oxidation reaction is identified as metformin N-oxide through outer sphere electron transfer pathway which is supported by mechanism of the reaction.
6. Positive value of activation free energy and activation enthalpy indicates that the transition state is highly solvated and negative entropy of activation suggests the formation of compact activated complexes.
7. The lower activation enthalpy 35.2 kJ mol^{-1} obtained in this study and CV study suggest that it is a one electron transfer process.
8. The geometry optimization and calculated thermochemical parameters of reactants and products by Hartree–Fock method using Gaussian-16 software also supports the reaction mechanism.
9. This kinetic study is helpful in determining the drug potency and mode of action of drug towards the biological targets.
10. Thermodynamic and kinetic signature, in combination with structural biology helps to elucidate the driving mechanism of target-drug binding.
11. Metal bound drug also increases the serum half life of the drug than the free drug.

It is a model reaction between the drug metformin and the trace element, insulin mimic vanadium in biological system. More research is to be carried out for interaction of drug with other metal ions present in biological system.

The present study would definitely forecast new dimensions in understanding the interaction of drug with metal ions in biological system. We hope the present study will not only help in academic sphere but also in biological and pharmaceutical premises.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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