Journal of Saudi Chemical Society (2022) **26**, 101396

King Saud University

Journal of Saudi Chemical Society

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Auspicious water treatment approach. Oxidative degradation of fluconazole and voriconazole antibiotics by CrO_3 in different acidic environments: Kinetics, mechanistic and thermodynamic modelling

Ahmed Fawzy [a,b,*], **Nada Alqarni** [c], **Belal El-Gammal** [d], **Arafat Toghan** [e,f], **Nasser A. Hassan** [g,h], **Zaina Algarni** [i]

[a] *Chemistry Department, Faculty of Applied Sciences, Umm Al-Qura University, Makkah 21955, Saudi Arabia*
[b] *Chemistry Department, Faculty of Science, Assiut University, Assiut 71516, Egypt*
[c] *Department of Chemistry, College of Sciences and Arts in Balgarn, University of Bisha, Bisha 61922, Saudi Arabia*
[d] *Department of Chemistry, Faculty of Science, University of Bisha, Bisha 61922, Saudi Arabia*
[e] *Chemistry Department, Faculty of Science, South Valley University, Qena 83523, Egypt*
[f] *Chemistry Department, College of Science, Imam Mohammad Ibn Saud Islamic University, Riyadh 11623, Saudi Arabia*
[g] *Pharmaceutical Science Department, College of Pharmacy, Shaqra University, Shaqra 11961, Saudi Arabia*
[h] *Photochemistry Department, National Research Centre, Giza 12511, Egypt*
[i] *Department of Physics, College of Sciences and Arts in Balgarn, University of Bisha, Bisha 61922, Saudi Arabia*

Received 9 October 2021; revised 17 November 2021; accepted 21 November 2021
Available online 27 November 2021

KEYWORDS

Triazole antibiotics;
Chromium (VI) oxide;
Oxidative degradation;
Kinetics;
Mechanism

Abstract The kinetics of oxidative degradation of two significant triazole antibiotics (A), viz. fluconazole (Flz) and voriconazole (Vcz), was examined using chromium (VI) oxide (Cr^{VI}) in sulfuric and perchloric acid environments. The oxidation reactions were followed spectrophotometrically at fixed ionic strength and at different temperatures. In both acidic environments, the oxidative degradations of the two examined antibiotics were acid-catalyzed. The kinetics of the oxidative degradations in both acids were first order concerning to [Cr^{VI}] and fractional-first orders with regard to [A] and [H^+] during their alteration. The rates of oxidative reactions exhibited insignificant influences upon disparity of ionic strengths and dielectric constants of the reactions' media. No intervention of free radicals was detected during the degradation reactions. Some activation methods like heat and

* Corresponding author at: Chemistry Department, Faculty of Applied Sciences, Umm Al-Qura University, Makkah 21955, Saudi Arabia.
E-mail address: afsayed@uqu.edu.sa (A. Fawzy).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jscs.2021.101396

addition of certain metal cations (Mg^{2+} & Ca^{2+}) were also investigated. Under analogous experimental circumstances, the degradation rates in perchloric acid environment were slightly higher than those occurred in sulfuric acid one and the degradation rates of Flz were higher than those of Vcz. The believable oxidative degradation mechanism consistent with the kinetic outcomes was proposed. The derived rate-law expression was set to be in a good harmony with the acquired results. The activation and thermodynamic parameters were computed and discussed. This study announce a simple, safe and inexpensive promising procedure involving a double benefit for the environment and human health: degradation of Flz and Vcz drugs and transformation of the extremely toxic and carcinogenic Cr^{VI} oxide to a safe Cr^{III} compound.

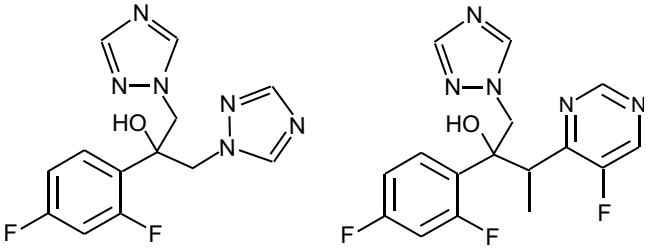
1. Introduction

Pharmaceutical drugs are chemical substances having properties for remedying or preventing diseases in human beings [1]. Antibiotics, natural and synthetic, are considered as the most important class of pharmaceutical drugs employed for treatment of diverse infection diseases caused by bacteria [2,3]. They have also a wide use in the prevention of diseases and promotion of growth purposes for animals and aquatic. Additionally, antibiotics are utilized extensively in agriculture and in a variety of food applications [4]. Therefore, more than 20 million tons of pharmaceutical drugs are manufactured every year all over the world [5]. However, antibiotics contain complex organic compounds in their structures and they are difficult biodegrade to simpler products that can persist and bioaccumulate in the aquatic environments for long times [6,7]. Also, about 10–20% only of the antibiotics which used orally are metabolized, while the rest is ejected from the body (in the urine) into the environment without metabolization as active substances [8]. Antibiotic-related problem is ascribed to the excretion of antibiotics or their metabolites into the environment (soil, ground and surface waters, etc.). Antibiotics enter the ecosystems across human and animal excreta after antibiotic metabolization, wastewater treatment plants, wastes coming from pharmaceutical industries, medical centers, households and hospitals [9,10]. This is particularly with high water soluble antibiotics, which makes their spread and toxicity in the ecosystem faster [11]. Hence, big quantities of antibiotics and their metabolites have been found in the environment [12] and these contaminations have been an issue of concern a long time ago resulted from their toxic impacts on the humans and natural life [13]. Furthermore, presence of these compounds in different water resources can result in growth of antibiotic-resistant bacteria, which destroy the natural aquatic microorganisms needed for treating biological wastewater. These contaminations are regarded as dangerous pollutants for the human health and ecosystem and responsible for uncompromising public health crisis in the globe [14].

Thus, a reasonable interest has been increased recently for find the most suitable techniques for removal or degradation of such pollutants to safeguard the environment and human health [15]. Though, the principal restrictions of these techniques are associated with their safety, cost, byproducts toxicity in the treated effluents, etc. [16,17]. Numerous traditional biological methods for treating antibiotic pollution still ineffective due to the complex nature of such antibiotics [18]. Lately, chemical oxidation for eliminating drug pollutants in water resources and wastewater, which cannot be removed proficiently by traditional biological methods, has been extensively well-known [19,20]. Oxidation of medicinal drugs may be a chief role in the interpretation of the metabolism of these drugs, in pharmacokinetics investigation [21–23]. Chemical oxidation has been considered as a high conceivable and professional treating strategy for medicinal drugs by using particular oxidants, like chlorine, ozone, fenton reagent, hydrogen peroxide, etc. [24]. Oxidizing agents were found to react favorably with electron-rich functional groups, which converts the toxic compounds to lower harmful ones that are safe to excrete into the environment [25–27].

Hexavalent chromium (Cr^{VI}) compounds are toxic materials because of their oxidizing power. They act a substantial function in the chemistry of biological molecules in the environment due to their mutagenic and carcinogenic reactivities [28]. Exposure to Cr^{VI} compounds can result in the risk of developing lung cancer or asthma. Thus, Cr^{VI} compounds are regarded as highly dangerous materials for biological systems, but Cr^{III} compound are comparatively non-toxic [29]. Also, chromium(VI) can be found in the public water systems and in drinking water [30]. On the other hand, Cr^{VI} is one of the supreme multipurpose obtainable oxidizers employed for oxidation of organic and inorganic compounds [31–38]. While a great number of literature is presented on the kinetics of chromic acid oxidation of different categories of compounds, a slight attentiveness was directed to the oxidation reactions using chromium trioxide oxidant [39–43] in spite of its lower price, higher water-solubility, availability and higher oxidation efficiency.

In biochemical reactions, kinetic understanding of medicinal drugs can be pointed to the optimization of the reaction conditions for clarifying a distinct mechanistic model for drug metabolism in the bio-systems. The rate constants of oxidation reactions of medicinal compounds with oxidizers may give information about the reactivity of such compounds towards the treating method and can be beneficial to demonstrate this method [21,22]. In this study, we are presenting the kinetic, mechanistic and thermodynamic aspects of oxidative degradation of two triazole drugs family, viz. fluconazole (Flz) and voriconazole (Vcz), their structures are shown in Fig. 1. These two drugs are the most commonly employed antifungals in clinical therapy and have a comprehensive spectrum of activity and reduced toxicity. The existing investigation was performed using Cr^{VI} oxide, a potent oxidizing agent for oxidation of numerous organic compounds [39–43], in both sulfuric and perchloric acidic



Fluconazole (Flz) **Voriconazole (Vcz)**

Fig. 1 Chemical structures of fluconazole and voriconazole antibiotics.

environments different temperatures. The chief goal of this investigation was to develop and validate a simple, convenient, low cost and safe method to be utilized for removal or degradation of Flz and Vcz in acidic environments. In this study, we planned to investigate the ability of the oxidant for the oxidative degradation of both antibiotics, to explore the influence of the nature of the acidic environment on the reactions' kinetics, the effect of various factors like reactants' concentrations, pH of the reactions' medium, etc. Furthermore, some activation methods like heat and addition of certain metal cation catalysts (Mg^{2+} & Ca^{2+}) to activate the oxidative degradation of the examined antibiotics was also investigated. We aimed to evaluate the activation and thermodynamic parameters, to suggest a reasonable oxidation mechanism and to derive a rate-law expression consistent with the gained investigational kinetic outcomes. This study announce a simple, safe and inexpensive promising procedure involving a double benefit for the environment and human health: degradation of fluconazole and voriconazole drugs and transformation of the extremely toxic and carcinogenic Cr^{VI} oxide to a safe Cr^{III} compound.

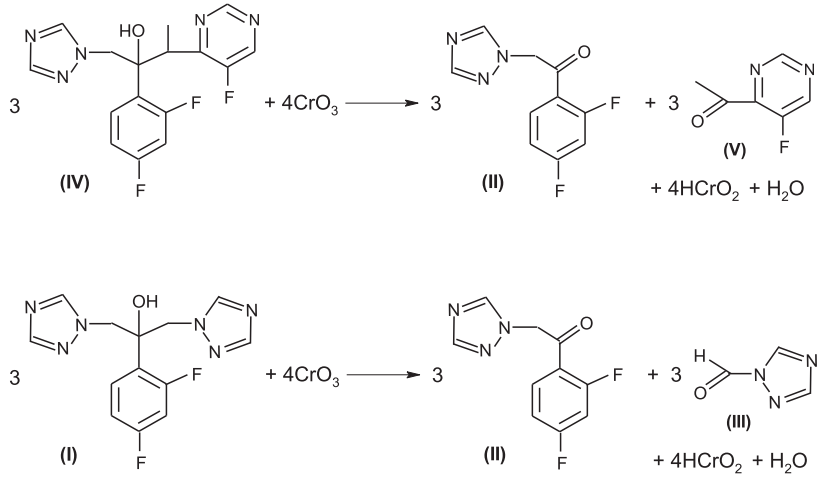
2. Experimental section

2.1. Chemicals and solutions

Most of the chemicals employed in this investigation were Sigma-Aldrich chemicals and their solutions were prepared using bidistilled water. Fluconazole and voriconazole antibiotics (purity > 98%) were Sigma-Aldrich and their solutions were prepared by dissolving their weights in DMSO and completing the required volumes with bidistilled water. A fresh solution of chromium (VI) oxide was prepared with bidistilled water and it was standardized by spectrophotometric technique. Stock solutions of sulfuric and perchloric acids (Merck) were prepared (4.0 mol dm^{-3}) by diluting a 99% H_2SO_4 and a 70% $HClO_4$, correspondingly, with bidistilled water, and the requisite concentrations were attained through dilution. Na_2SO_4 and $NaClO_4$ (BDH) were utilized to fix the ionic strengths (I) in sulfuric and perchloric acid solutions, correspondingly. Other utilized chemicals in this investigation were of reagent grade and their solutions were made by dissolving the requisite quantities of their samples in bidistilled water.

2.2. Kinetic measurements

The oxidative degradation reactions were planned such that they were of pseudo-first order kinetics in which the examined antibiotics were inserted in a great excess regarding to the oxidant chromium (VI) oxide. These measurements were conveyed out on a thermostated Shimadzu UV–VIS-NIR-3600 double-beam spectrophotometer. The advancement of these reactions was followed by tracing the diminish in the absorbance of the CrO_3 oxidant at its maximum absorption wavelength (λ_{max} = 349 nm) where other reactants did not absorb substantially at such wavelength. First order plots, ln(Abs.) vs. time plots, were found to be straight lines and the observed pseudo-first order rate constant values (k_{obs}) were estimated as the gradients of these plots. The values of k_{obs} were the aver-



ages of at least two individualistic runs, which were reproducible to within about ±3%. The reaction orders with regard to the reactants in both acidic solutions were obtained from the gradients of the double-log plots (log k_{obs} vs. log conc. plots) for the examined antibiotics and acids, whereas other constituents were retained constant.

3. Results and discussion

3.1. Stoichiometry and product description

Various reactions' mixtures with unlike ratios of [CrO_3] / [A], where [A] points to the antibiotic concentration, at constant [H^+] of 1.0 mol dm^{-3} and ionic strength (I) of 2.0 mol dm^{-3} at 303 K were let to react in closed vessels for about 24 h till accomplishment of the reactions. The remaining (unreacted) [CrO_3] in both acidic environments were assessed spectrophotometrically which indicated depletion of 4 mol of CrO_3 per 3 mol of antibiotic (in the two cases) to form the acquired oxidation products as elucidated by the subsequent equations,

These stoichiometric equations (1) and (2) were in fully accordance with the product description. The compounds (I), (II) and (III), in equation (1), are fluconazole and its oxidation products: 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl) ethan-1-one and (1H-1,2,4-triazol-1-yl) formaldehyde, respectively. The compounds (IV) and (V), in equation (2), are voriconazole and its oxidation product (5-fluoropyrimidin-4-yl) acetaldehyde, respectively, in addition to the product 1-(2 ,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethan-1-one (II). The presence of carbonyl groups in the oxidation products were indicated by the orange-yellow precipitates produced via their reactions with 2,4-dinitrophenylhydrazine [44]. The products of each examined antibiotic were split by chromatography [45]. Then, the split products were identified by elemental examination using Schiff's, Tollens ($Ag(NH_3)_2OH$)) and sodium nitroprusside tests [46]. Moreover, the founding of Cr^{III} compounds was indicated by the reduction in the oxidation rates after adding $MnSO_4$ solution to the reaction mixtures [47].

3.2. Spectral changes

Fig. 2(a-d) shows the Cr^{VI} oxide absorption curves against wavelength with 2 min time intervals through its reactions with

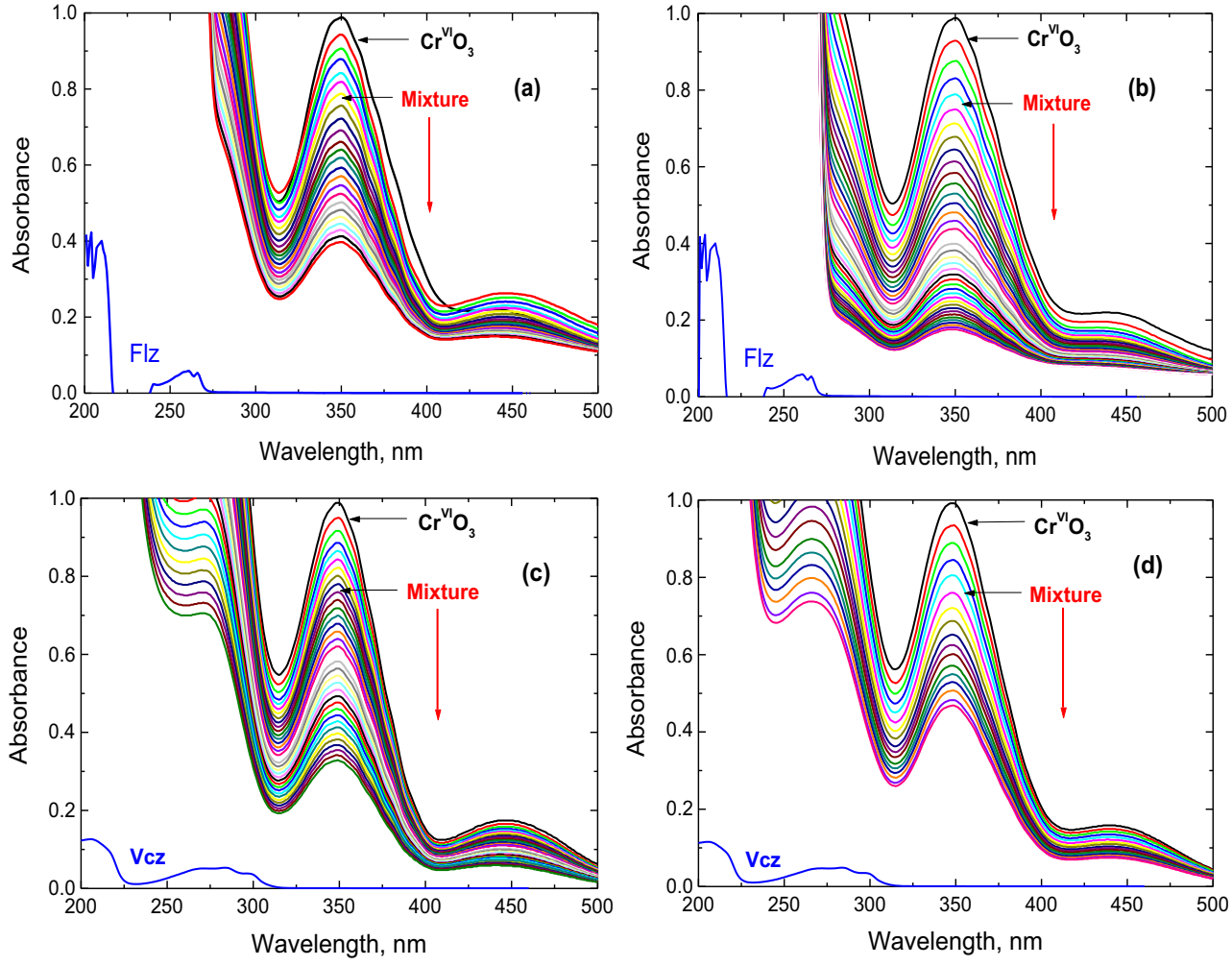


Fig. 2 Spectral variations for the oxidative degradation of fluconazole (Flz) and voriconazole (Vcz) by Cr^{VI} oxide in: (a) & (c) sulfuric acid, (b) & (d) perchloric acid solutions, respectively. [A] = 5.0×10^{-2}, [CrO_3] = 5.0×10^{-4}, [H^+] = 1.0, I = 2.0 mol dm^{-3} and T = 303 K. Scan time intervals = 2 min.

Table 1 Impact of [Cr^{VI}], [A], [H^+] and I on the values of k_{obs} in the oxidative degradation of fluconazole and voriconazole by Cr^{VI} oxide in sulfuric acid and perchloric acid solutions at 303 K.

10^4[CrO_3] mol dm^{-3}	10^2 [A]mol dm^{-3}	[H^+] mol dm^{-3}	I mol dm^{-3}	10^3 k_{obs} s^{-1}			
				Fluconazole		Voriconazole	
				Sulfuric acid	Perchloric acid	Sulfuric acid	Perchloric acid
1.0	5.0	1.0	2.0	20.3	28.1	14.9	23.7
3.0	5.0	1.0	2.0	21.1	29.2	16.1	25.3
5.0	**5.0**	**1.0**	**2.0**	**21.5**	**28.8**	**16.9**	**24.4**
7.0	5.0	1.0	2.0	20.9	28.3	17.4	23.5
10.0	5.0	1.0	2.0	22.0	27.9	16.7	22.9
5.0	**1.0**	1.0	2.0	8.3	10.8	6.3	8.5
5.0	**3.0**	1.0	2.0	16.3	21.7	12.2	19.2
5.0	**5.0**	**1.0**	**2.0**	**21.5**	**28.8**	**16.9**	**24.4**
5.0	**7.0**	1.0	2.0	27.1	40.3	19.7	34.9
5.0	**10.0**	1.0	2.0	37. 9	48.2	25.9	46.2
5.0	5.0	**0.2**	2.0	8.2	9.7	5.9	8.2
5.0	5.0	**0.6**	2.0	15.9	20.8	11.8	17.4
5.0	**5.0**	**1.0**	**2.0**	**21.5**	**28.8**	**16.9**	**24.4**
5.0	5.0	**1.4**	2.0	25.7	38.0	21.2	31.3
5.0	5.0	**1.8**	2.0	31.8	45.5	24.3	39.7
5.0	5.0	1.0	**2.0**	**21.5**	**28.8**	**16.9**	**24.4**
5.0	5.0	1.0	**2.5**	21.5	28.8	16.9	24.4
5.0	**5.0**	1.0	**3.0**	21.5	28.8	16.9	24.4
5.0	5.0	1.0	**3.5**	21.5	28.8	16.9	24.4
5.0	5.0	1.0	**4.0**	21.5	28.8	16.9	24.4

Experimental error ± 4%.

the examined antibiotics, fluconazole (Flz) and voriconazole (Vcz), in sulfuric and perchloric acid solutions at: [A] $= 5.0 \times 10^{-2}$, [Cr^{VI}] $= 5.0 \times 10^{-4}$, [H^+] = 1.0, I = 2.0 mol dm^{-3} and T = 303 K. These figures manifest gradual decrease in the maximum absorption wavelength of the Cr^{VI} band at 349 nm as the reactions progressed indicating reduction of Cr^{VI} to Cr^{III} ion by the examined antibiotics. Under analogous experimental circumstances, the degradation rates in perchloric acid environment were slightly higher than those occurred in sulfuric acid and the degradation rates of Flz were higher than those of Vcz. This variance in the oxidation rates of fluconazole and voriconazole may be ascribed to the structural difference between these two antibiotics as illustrated in Fig. 1.

3.3. Reliance of the oxidative degradation on Cr^{VI} oxide concentration

The impact of the concentration of Cr^{VI} oxide oxidant, [Cr^{VI}], was clarified in both acidic environments by varying [Cr^{VI}], i.e.

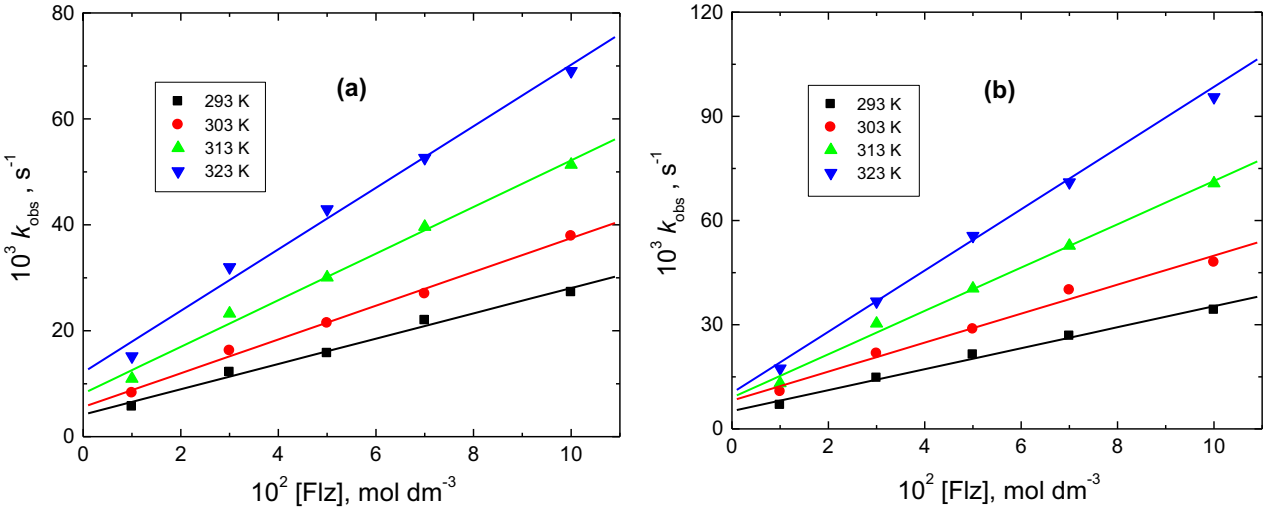


Fig. 3 Impact of [Flz] on the values of k_{obs} in the oxidative degradation of fluconazole by Cr^{VI} oxide in: (a) sulfuric acid, and (b) perchloric acid solutions. [CrO_3] $= 5.0 \times 10^{-4}$, [H^+] = 1.0 and I = 2.0 mol dm^{-3} at various temperatures.

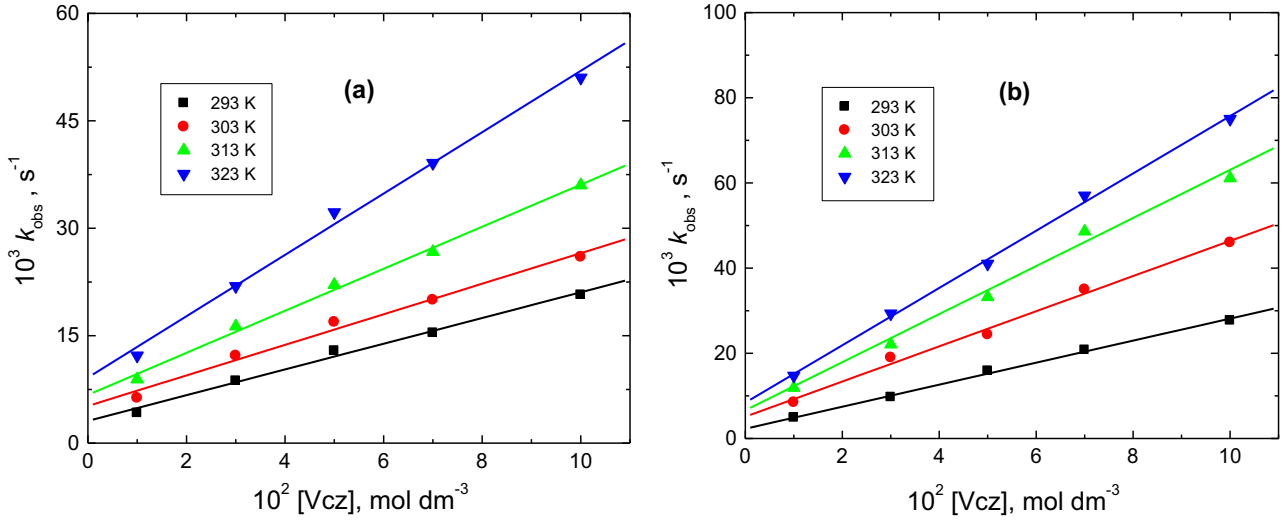


Fig. 4 Impact of [Vcz] on the values of k_{obs} in the oxidative degradation of voriconazole by Cr^{VI} oxide in: (a) sulfuric acid, and (b) perchloric acid solutions. $[CrO_3] = 5.0 \times 10^{-4}$, $[H^+] = 1.0$ and $I = 2.0$ mol dm^{-3} at various temperatures.

from 1.0×10^{-4} to 10.0×10^{-4} mol dm^{-3} at firm [A], $[H^+]$, I and at constant temperature of 303 K. The gained plots of ln Abs. vs. time provided straight lines (Figures not shown). Also, the values of k_{obs} were set to be unconstrained of the started concentration of Cr^{VI} as presented in Table 1. These results indicated that the oxidation rates are independent of $[Cr^{VI}]$ and the reactions order concerning to the oxidant is one.

3.4. Reliance of the oxidative degradation on antibiotics' concentrations

The rates of oxidative degradation reactions were measured at different concentrations of fluconazole and voriconazole (abbreviated [A]) in the range of $(1.0–10.0) \times 10^{-2}$ mol dm^{-3} keeping the concentrations of other ingredients stable. The acquired results at diverse temperatures (inserted in Table S1 in the supplementary information) designated that rising [A] enhanced the reactions' rates as also manifested from the values of k_{obs} presented in Table 1 (at 303 K). Plots of k_{obs} versus antibiotics' concentrations are illustrated in Figs. 3 (a,b) and 4 (a,b) for fluconazole and for voriconazole, respectively, in sulfuric and perchloric acid solutions at diverse temperatures are visibly linear with positive intercepts. These outcomes emphasize that the orders of the degradation reactions in both acidic media concerning to antibiotics' concentrations are lower than unity (0.64–0.72) (gained from the slopes of log k_{obs} vs. log [Flz] and log k_{obs} vs. log [Vcz] plots offered in the supplementary information as Fig. S1.

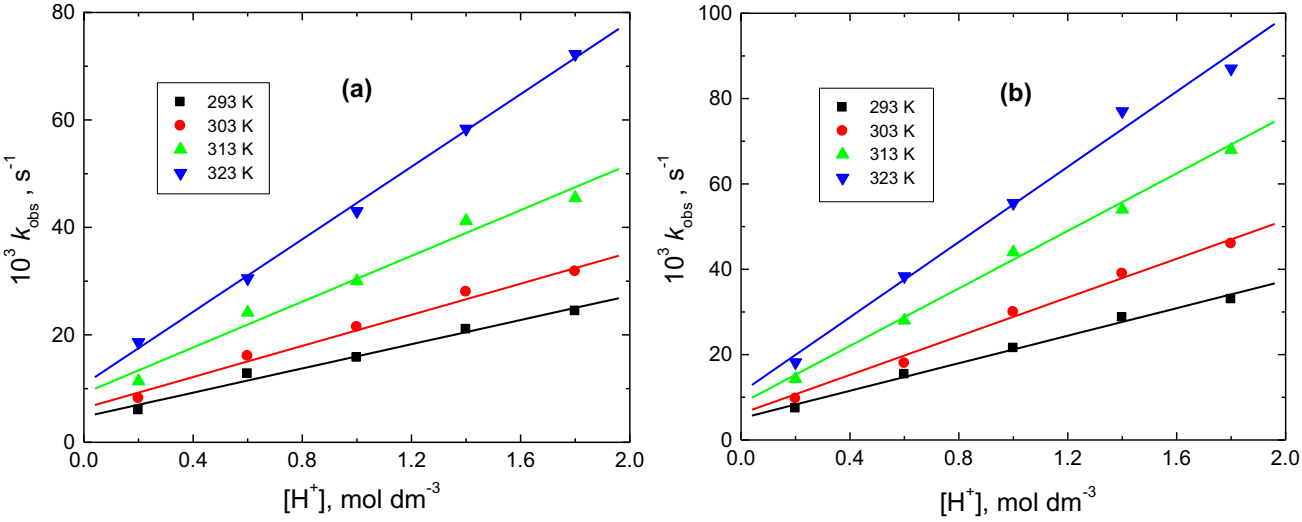


Fig. 5 Impact of $[H^+]$ on the values of k_{obs} in the oxidative degradation of fluconazole by Cr^{VI} oxide in: (a) sulfuric acid, and (b) perchloric acid solutions. $[CrO_3] = 5.0\text{x}10^{-4}$, [Flz] = $5.0\text{x}10^{-2}$ and $I = 2.0$ mol dm^{-3} at various temperatures.

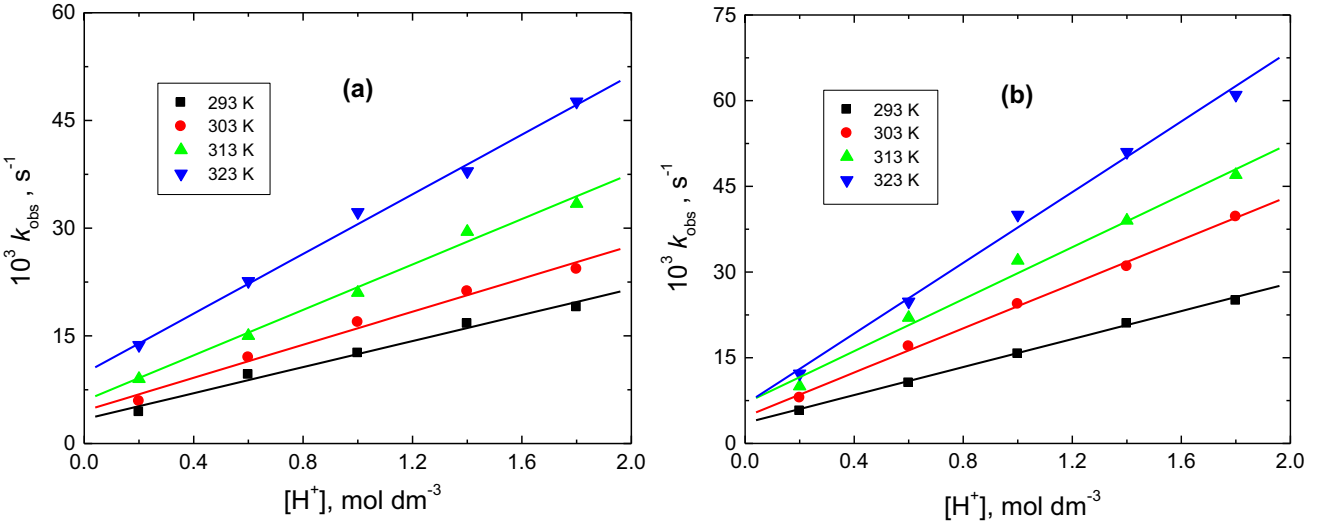


Fig. 6 Impact of $[H^+]$ on the values of k_{obs} in the oxidative degradation of voriconazole by Cr^{VI} oxide in: (a) sulfuric acid, and (b) perchloric acid solutions. $[CrO_3] = 5.0 \times 10^{-4}$, [Vcz] $= 5.0 \times 10^{-2}$ and $I = 2.0$ mol dm^{-3} at various temperatures.

3.5. Reliance of the oxidative degradation on pH

The impact of pH or $[H^+]$ of the reactions' media on the rates of the oxidative degradation was examined to clarify some features in the oxidation mechanism. In this respect, kinetic runs were performed at various $[H^+]$ (0.2 – 1.8 mol dm^{-3}) with sulfuric and perchloric acids conserving all other constituents stable. The obtained values of k_{obs} at different $[H^+]$ at 303 K only are listed in Table 1 and at different temperatures are listed in Table S1 in the supplementary information. Rising acids' concentrations increased the oxidation rates where the plots of k_{obs} versus $[H^+]$ gave straight lines with positive slopes as shown in Figs. 5 and 6 for Flz and Vcz, respectively, emphasizing fractional-first order credence with accord to $[H^+]$. Additionally, the plots of log k_{obs} versus log $[H^+]$ were also linear with slopes of 0.61 – 0.72, as presented in Fig. S2.

3.6. Reliance of the oxidative degradation on the ionic strengths and dielectric constants

In order to illuminate the signs of the reacting species in the rate-controlling step of the degradation reactions, the impact of the ionic strength (I) of the reactions' media on the degradation rates was examined. This can be attained by varying of I via supplement of definite concentrations of Na_2SO_4 and $NaClO_4$ (as inert electrolytes) in sulfuric acid and perchloric acid environments, correspondingly, at stable concentrations of other reactions constituents. The gained results signified that the degradation rates persist noticeably unaffected in both cases telling that either antibiotic or oxidant was uncharged.

In addition, the impact of dielectric constant of the degradation media was inspected by varying the acetic acid - water ratios in these media with all other conditions being stable. The rate constants were found to changed insignificantly with reducing the dielectric constants of the reactions' media.

3.7. Reliance of the oxidative degradation on [Mn^{II}] and [Cr^{III}]

For inspection of interfering of Cr^{IV} as an expected intermediate during the progress of the degradation reactions, different Mn^{II} concentrations (2–10 $\times 10^{-2}$ mol dm^{-3}) were added to the reactions' media in both acidic environments at constant concentrations of all reactions' constituents and at a temperature of 303 K. The experimental outcomes designated that the degradation rates reduced with increasing $[Mn^{II}]$ as manifested in Fig. 7 (for both antibiotics in only 1.0 mol dm^{-3} sulfuric acid solution as an illustrative example).

Moreover, the reliance of the degradation rates on the primarily added Cr^{III} ion, as a described reduction product of

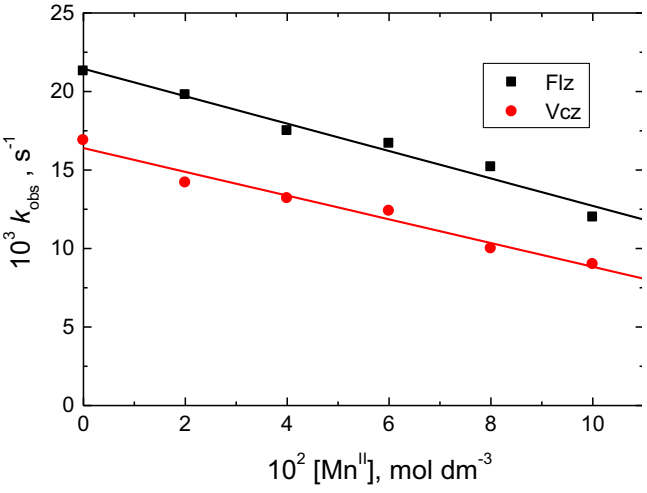


Fig. 7 Reliance of the values of k_{obs} on $[Mn^{II}]$ in the oxidative degradation of fluconazole (Flz) and voriconazole (Vcz) by Cr^{VI} oxide in sulfuric acid solution. $[CrO_3] = 5.0 \times 10^{-4}$, [A] $= 5.0 \times 10^{-2}$, $[H^+] = 1.0$ and $I = 2.0$ mol dm^{-3} at 303 K.

Cr^{VI} oxidant, was studied within the concentration range of Cr^{III} ion of (2.0×10^{-4}–10.0×10^{-4} mol dm^{-3}) at fixed other variables. The acquired results (not shown here) indicated that adding various concentrations of Cr^{III} ion did not alter appreciably the degradation rates in both acidic environments.

3.8. Reliance of the oxidative degradation on certain metal cation catalysts

The influence of certain environmentally safe metal cation catalysts, viz. Mg^{2+} and Ca^{2+} on the rates of oxidative degradation of the examined antibiotics, the degradation rates were recorded in the presence of different concentrations of Mg^{2+} and Ca^{2+} at constant other reactions' constituents. The gained experimental results (illustrated in Fig. 8) showed that the degradation rates were enhanced with rising the concentrations of the added metal cations.

3.9. Reliance of the oxidative degradation on temperature

The rates of the degradation reactions were carried out at several temperatures, 293, 303, 313 and 323 K at numerous concentrations of the examined antibiotics and the acids at stable [Cr^{VI}] and *I*. The investigational results (Figs. 3–6 and Tables 1 and S1) indicated that rising temperature enhanced the degradation rates.

3.10. Test for free radicals intervention

To examine the intervention of free radicals throughout the oxidative degradation reactions, known quantities of acrylonitrile were initially supplemented to the reaction mixtures in both acidic environments and were kept for about 2 h in an inert atmosphere. The results showed absence of white precipitates in the reactions' mixtures indicating that there was no free radicals intervention in the investigated reactions [48].

3.11. Mechanism of the oxidative degradation

It was stated [39–43] that Cr^{III} oxide (CrO_3), as one of the substantial Cr^{VI} compounds, is regarded as a powerful oxidizing agent for several organic substrates. In water, CrO_3 is hydrolyzed to produce chromic acid as indicated by the following equilibrium [49,50],

$$CrO_3 + H_2O \rightleftharpoons H_2CrO_4 \quad (3)$$

Also, it has been reported that oxidation reactions utilizing Cr^{VI} compounds proceeds by transfer of either one-electron with an interference of Cr^{V} intermediate [51] or two-electron with an interference of Cr^{IV} intermediate [32]. In the present work, the absence of free radicals intervention in the reactions (polymerization tests) omitted the idea of an interference of Cr^{IV} intermediate. Furthermore, decreasing the degradation rates on inserting Mn^{II} to the reactions mixtures supports this point because if Cr^{IV} species present in the reactions media, Mn^{II} will trapped Cr^{IV} species leading to a decrease in the degradation rates [52].

The existing oxidative degradation reactions between Cr^{VI} oxide and the investigated antibiotics (fluconazole and voriconazole) in both sulfuric and perchloric acid environments illuminated a stoichiometry of a 3: 4 (antibiotic: CrO_3) with a first order dependence in [Cr^{VI}] and lower-than unit orders regarding to both hydrogen ion and antibiotics' concentrations. The augmentation of the rates of the oxidative degradations by rising acids' concentrations with lower-than unit orders in [H^+] can be deliberated as a proof of protonation of antibiotics as signified by the following equilibrium,

$$\text{Antibiotic(A)} + H^+ \overset{k_1}{\rightleftharpoons} \text{Protonated Antibiotic}^{\cdot}\left(AH^+\right) \quad (4)$$

The protonated antibiotics may be considered as more reactive species, which act as the major role in the kinetics of the degradations reactions. The lower-than unit orders reliance on antibiotics' concentrations may be ascribed to complexes formation prior to the slow (rate-controlling) stage of the

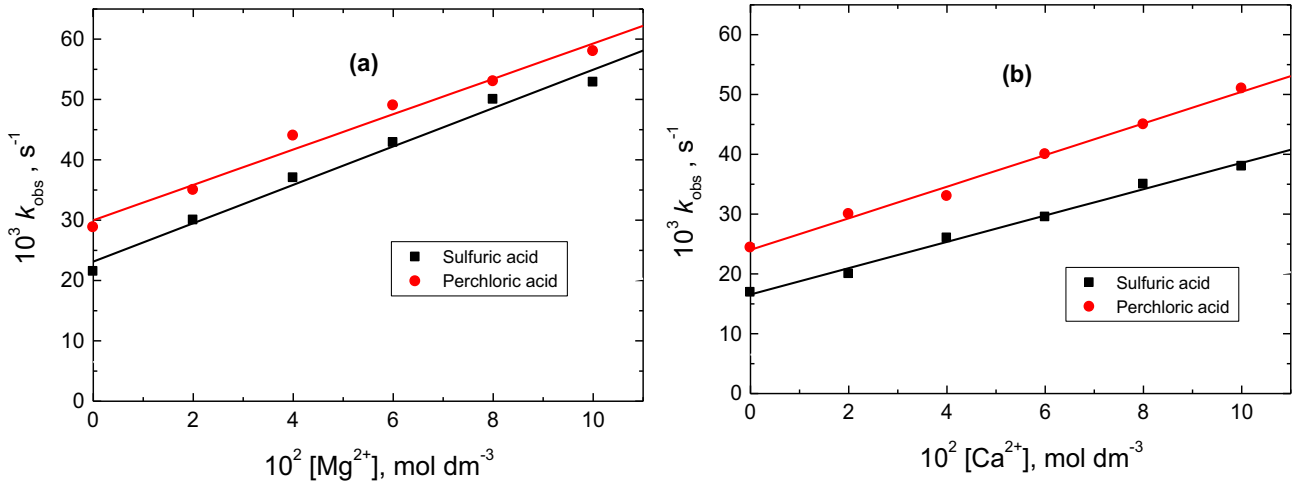


Fig. 8 Reliance of the values of k_{obs} on: (a) [Mg^{2+}] in the oxidative degradation of fluconazole; (b) [Ca^{2+}] in the oxidative degradation of voriconazole, by Cr^{VI} oxide in sulfuric acid and perchloric acid solutions. [CrO_3] = 5.0×10^{-4}, [A] = 5.0×10^{-2}, [H^+] = 1.0 and *I* = 2.0 mol dm^{-3} at 303 K.

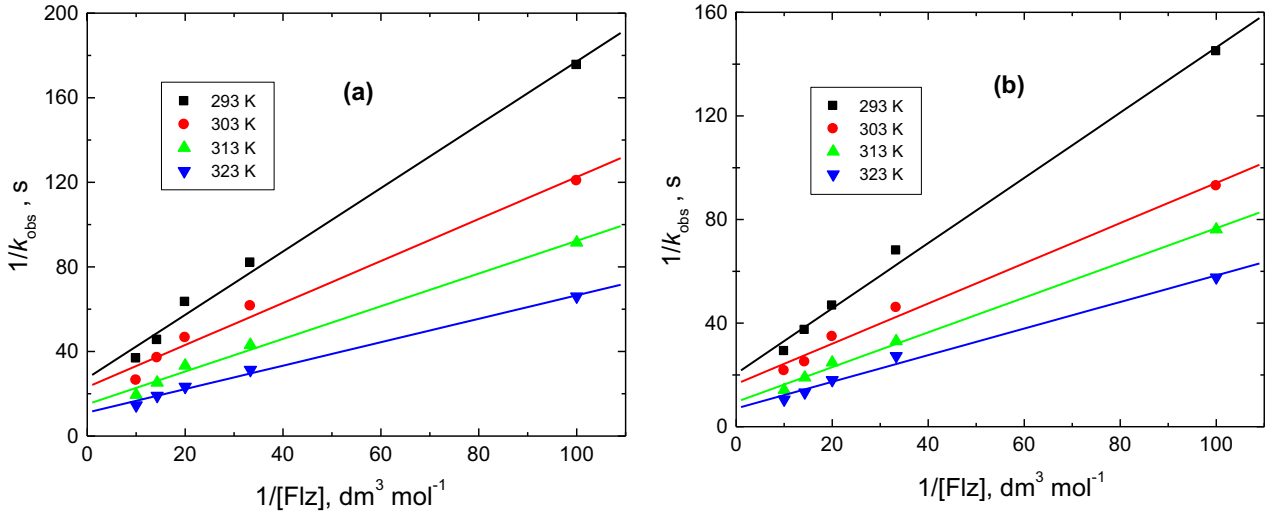


Fig. 9 Plots of $1/k_{obs}$ versus 1/[Flz] in the oxidative degradation of fluconazole (Flz) by Cr^{VI} oxide in: (a) sulfuric acid, and (b) perchloric acid solutions. $[CrO_3] = 5.0 \times 10^{-4}$, $[H^+] = 1.0$ and $I = 2.0$ mol dm^{-3} at various temperatures.

oxidative degradation mechanism. Complexes formation was also supported kinetically [53] by the gained non-zero intercepts of the plots of $1/k_{obs}$ vs. 1/[Flz] (Figs. 9 and 10) and $1/k_{obs}$ vs. 1/[Vcz] (Figs. 11 and 12). Furthermore, increasing the degradation rates as a result of addition of different concentration Mg^{2+} and Ca^{2+} can be discussed in the light of complexation between antibiotic and these metal cations in acidic environments as reported earlier [54–56].

According to the aforementioned attributes, the plausible oxidative degradation mechanism involves complexation amongst the protonated antibiotic (AH^+) and the hydrolyzed CrO_3 (chromic acid, H_2CrO_4) to produce an intermediate complex (C) as represented by the subsequent equilibrium,

$$AH^+ + H_2Cr^{VI}O_4 \overset{k_2}{\rightleftharpoons} \text{Intermediate Complex(C)} \quad (5)$$

This step was supported by the insignificant impacts of the changes of both ionic strengths and dielectric constants of the degradation media which were found to be in accordance with the reactions occurring between an ion with a neutral molecule [57,58], i.e. amongst AH^+ and H_2CrO_4. This intermediate decays in the rate-controlling step to produce antibiotic intermediate as a primary degradation product and Cr^{IV} intermediate,

$$\text{Intermediate Complex} \underset{slow}{\overset{k_1}{\rightarrow}} \text{Intermediate Oxidation Product} + HCr^{IV}O_3^- \quad (6)$$

The created intermediate product was rapidly reacted with another H_2CrO_4 molecule leading to production of the first-final degradation products of the antibiotic and also Cr^{IV} intermediate as clarified Eq. (7),

$$\text{Intermediate oxidation product} + H_2Cr^{VI}O_4 \underset{fast}{\rightarrow} \text{First - final oxidation products} + HCr^{IV}O_3^- \quad (7)$$

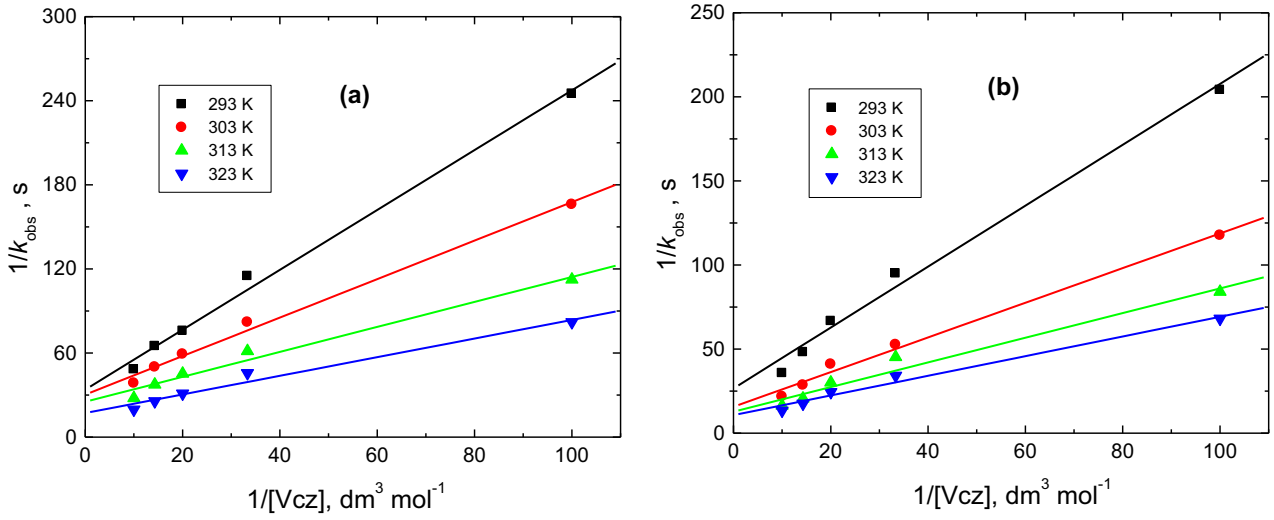


Fig. 10 Plots of $1/k_{obs}$ versus 1/[Vcz] in the oxidative degradation of voriconazole (Vcz) by Cr^{VI} oxide in: (a) sulfuric acid, and (b) perchloric acid solutions. $[CrO_3] = 5.0 \times 10^{-4}$, $[H^+] = 1.0$ and $I = 2.0$ mol dm^{-3} at various temperatures.

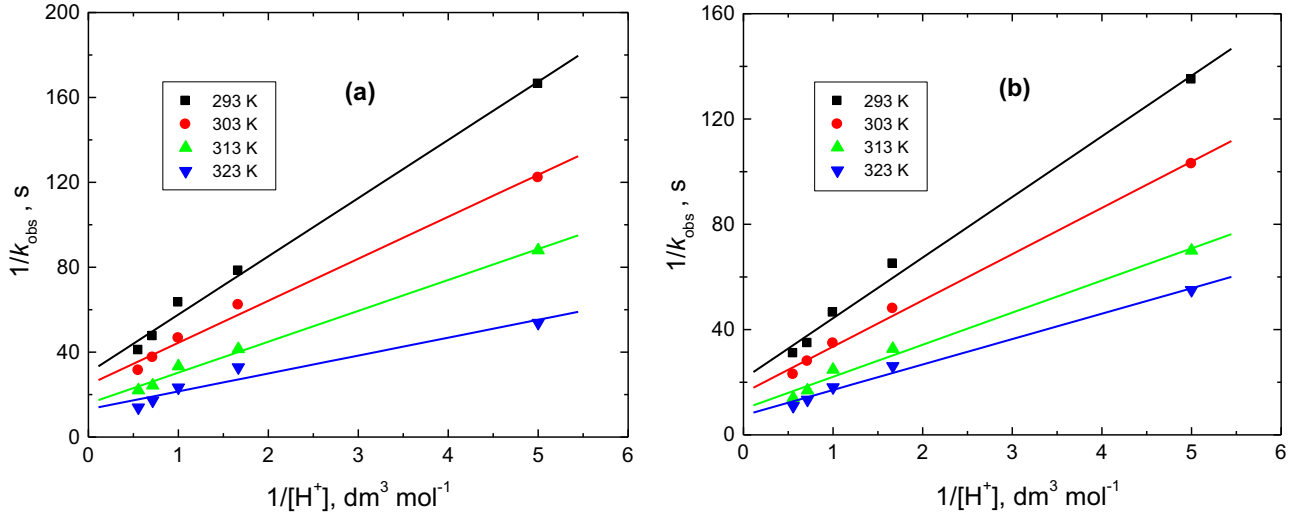


Fig. 11 Plots of $1/k_{obs}$ versus $1/[H^+]$ in the oxidative degradation of fluconazole (Flz) by Cr^{VI} oxide in: (a) sulfuric acid, and (b) perchloric acid solutions. $[CrO_3] = 5.0 \times 10^{-4}$, $[Flz] = 5.0 \times 10^{-2}$ and $I = 2.0$ mol dm^{-3} at various temperatures.

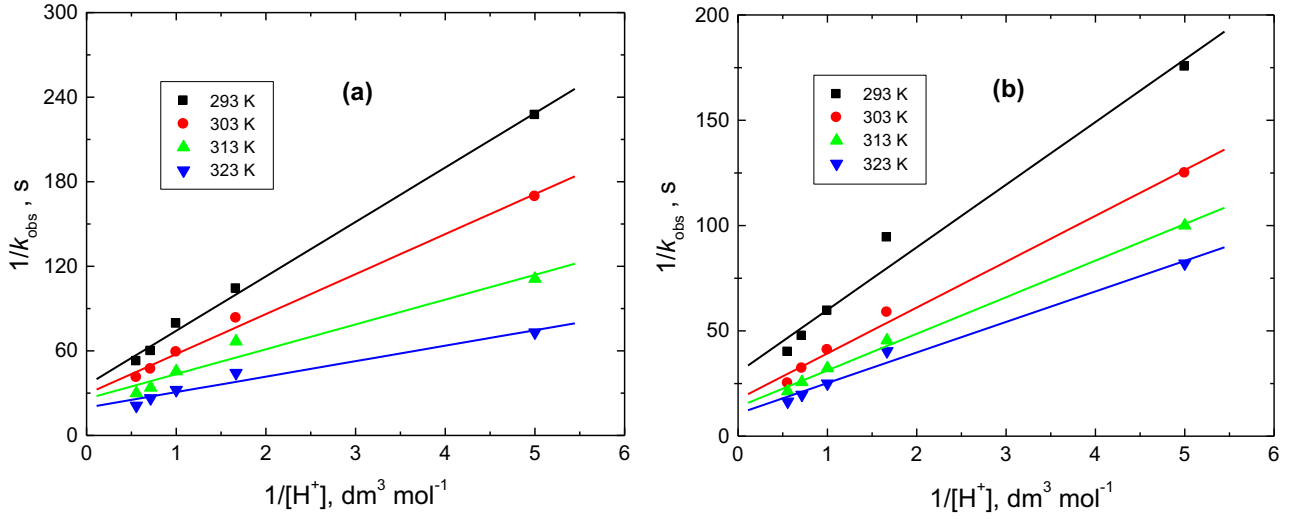


Fig. 12 Plots of $1/k_{obs}$ versus $1/[H^+]$ in the oxidative degradation of voriconazole (Vcz) by Cr^{VI} oxide in: (a) sulfuric acid, and (b) perchloric acid solutions. $[CrO_3] = 5.0 \times 10^{-4}$, $[Vcz] = 5.0 \times 10^{-2}$ and $I = 2.0$ mol dm^{-3} at various temperatures.

Subsequently, another molecule of antibiotic was further oxidized by additional two molecules of H_2CrO_4 to produce the second-final degradation products of antibiotic and two Cr^{IV} species. Finally, the produced four Cr^{IV} intermediate species are quickly attacked the third molecule of antibiotic to give rise to the last-final degradation products of the antibiotic as well as Cr^{III} species as the last reduction product of Cr^{VI} [48].

Table 2 Values of k_1 (x 10^2) at various temperatures in the oxidative degradation of fluconazole and voriconazole by Cr^{VI} oxide in sulfuric acid and perchloric acid solutions. $[CrO_3] = 5.0 \times 10^{-4}$ and $I = 2.0$ mol dm^{-3}.

Acidic medium	Fluconazole				Voriconazole			
	Temperature (K)				Temperature (K)			
	293	303	313	323	293	303	313	323
Sulfuric acid	3.41	4.54	6.37	9.52	2.98	3.70	4.65	5.88
Perchloric acid	4.45	6.25	9.09	14.28	4.34	5.56	7.14	9.35

Experimental Error ± 4%.

Table 3 Values of K_1 and K_2 at various temperatures in the oxidative degradation of fluconazole and voriconazole by Cr^{VI} oxide in sulfuric acid and perchloric acid solutions. $[CrO_3] = 5.0 \times 10^{-4}$ and $I = 2.0$ mol dm^{-3}.

Acidic medium	Equilibrium Constant (dm^3 mol^{-1})	Fluconazole				Voriconazole			
		Temperature (K)				Temperature (K)			
		293	303	313	323	293	303	313	323
Sulfuric acid	10^2 K_1	7.57	6.48	5.26	4.23	5.70	4.24	3.52	2.72
Perchloric acid		8.69	7.22	6.02	5.15	8.01	6.81	5.29	3.40
Sulfuric acid	10^{-2} K_2	2.94	3.14	4.49	5.25	3.04	4.50	6.14	8.07
Perchloric acid		2.25	2.46	2.71	2.83	1.92	2.40	3.21	4.28

Experimental error ± 4%.

3.12. Rate law expressions

The suggested oxidative degradation mechanism guides to the subsequent rate-law expressions (see Appendix A),

$$\text{Rate} = \frac{k_1 K_1 K_2 [Cr^{VI}][A][H^+]}{1 + K_1[H^+] + K_1 K_2 [A][H^+]} \quad (8)$$

In pseudo-first order statuses,

$$\text{Rate} = \frac{-d[Cr^{VI}]}{dt} = k_{obs}[Cr^{VI}] \quad (9)$$

Association of Eqs. (8) and (9) led to,

$$k_{obs} = \frac{k_1 K_1 K_2 [A][H^+]}{1 + K_1[H^+] + K_1 K_2 [A][H^+]} \quad (10)$$

Readjusting Eq. (10), the following two fundamental equations are developed,

$$\frac{1}{k_{obs}} = \left(\frac{1 + K_1[H^+]}{k_1 K_1 K_2 [H^+]}\right)\frac{1}{[A]} + \frac{1}{k_1} \quad (11)$$

$$\frac{1}{k_{obs}} = \left(\frac{1}{k_1 K_1 K_2 [A]}\right)\frac{1}{[H^+]} + \frac{1}{k_1 K_2 [A]} + \frac{1}{k_1} \quad (12)$$

Equations (11) and (12) required that the illustrations of $1/k_{obs}$ vs. $1/[A]$ at stable $[H^+]$ and $1/k_{obs}$ vs. $1/[H^+]$ at stable [A] offer linear graphs with positive intercepts, as were experimentally gained in both acidic environments (Fig. 9(a,b) & 10(a,b), and 11(a,b) & 12(a,b), correspondingly) approving the authority of the proposed degradation mechanism and the derived rate laws. The values of k_1, K_1 and K_2 at four different temperatures were evaluated from these graphs and were presented in Tables 2 and 3, correspondingly.

3.13. Activation and thermodynamic parameters

The activation parameters associated to the rate constant k_1 (for the rate-controlling step in the proposed degradation reactions mechanism) were estimated by application of both Arrhenius and Eyring equations (Figs. 13 & 14 (a) and (b), correspondingly) and are presented in Table 4. Also, the thermodynamic parameters of the equilibrium constants (K_1 and K_2 appeared in the reactions' mechanism equations) were calculated from van't Hoff illustrations as shown in Figs. 15 & 16 (a) and (b), correspondingly and are inserted in Table 5.

The estimated activation parameters were set to obey the proposed degradation mechanism and the derived rate-laws. The obtained positive values of $\Delta G^{\neq}$ and $\Delta H^{\neq}$ indicated

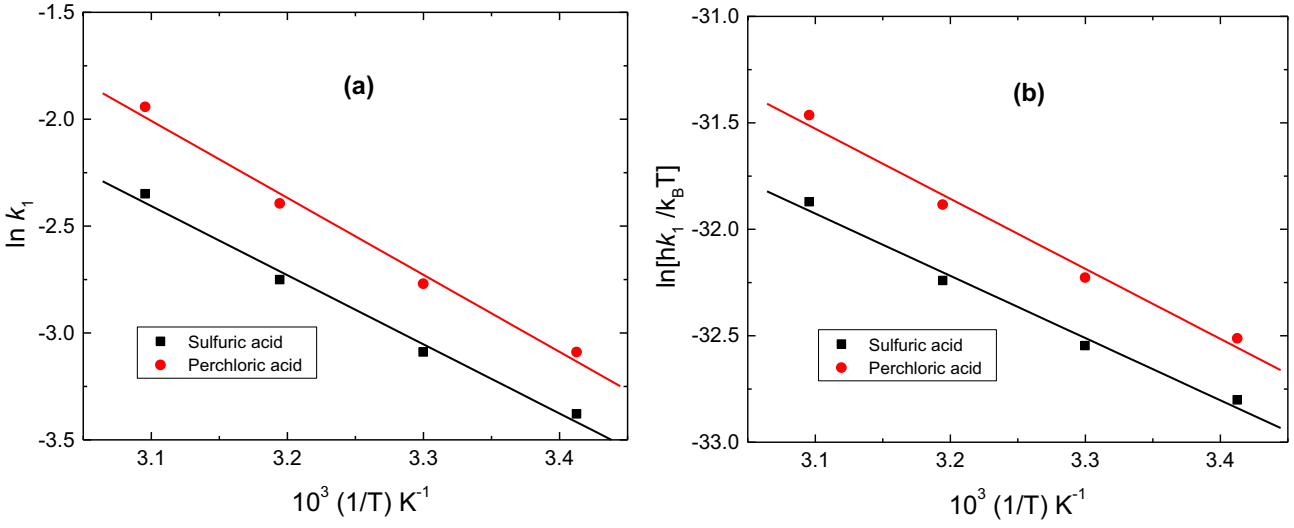


Fig. 13 (a) Arrhenius, and (b) Eyring plots of k_1 in the oxidative degradation of fluconazole (Flz) by Cr^{VI} oxide in: (a) sulfuric acid, and (b) perchloric acid solutions. $[CrO_3] = 5.0 \times 10^{-4}$, $[Flz] = 5.0 \times 10^{-2}$, $[H^+] = 1.0$ and $I = 2.0$ mol dm^{-3}.

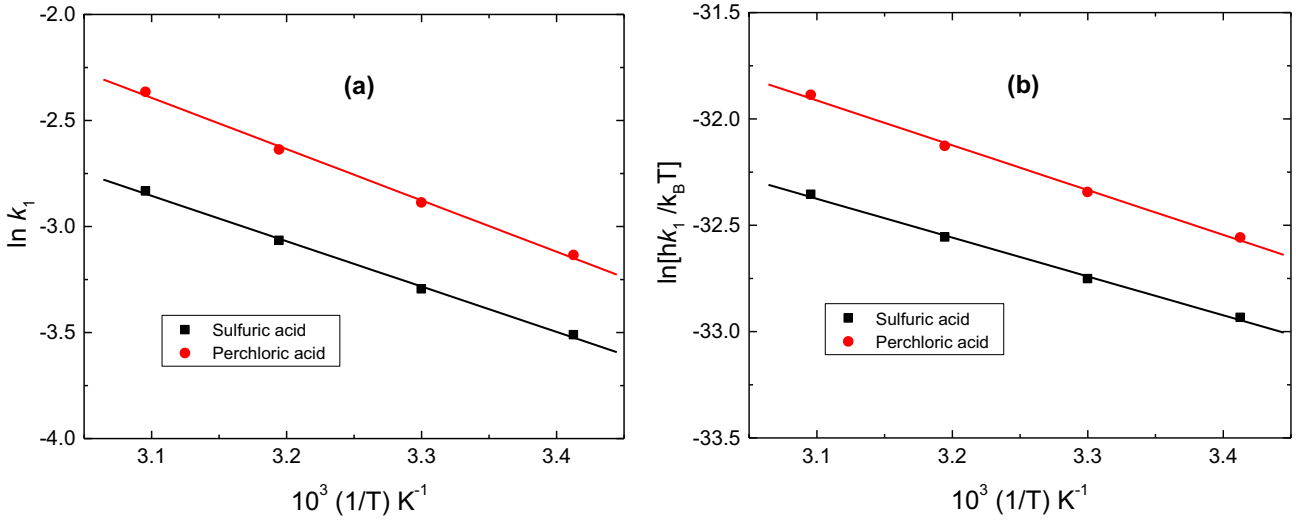


Fig. 14 (a) Arrhenius and (b) Eyring plots of k_1 in the oxidative degradation of voriconazole (Vcz) by Cr^{VI} oxide in: (a) sulfuric acid, and (b) perchloric acid solutions. $[CrO_3] = 5.0 \times 10^{-4}$, $[Vcz] = 5.0 \times 10^{-2}$, $[H^+] = 1.0$ and $I = 2.0$ mol dm^{-3}.

Table 4 Activation parameters of k_1 in the oxidative degradation of fluconazole and voriconazole by Cr^{VI} oxide in sulfuric acid and perchloric acid solutions. $[CrO_3] = 5.0 \times 10^{-4}$, $[A] = 5.0 \times 10^{-2}$, $[H^+] = 1.0$ and $I = 2.0$ mol dm^{-3}.

Acidic medium	Fluconazole				Voriconazole			
	$\Delta S^{\neq}$ (Jmol^{-1}K^{-1})	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta G^{\neq}_{303}$ (kJ mol^{-1})	$E_a^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (Jmol^{-1}K^{-1})	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta G^{\neq}_{303}$ (kJ mol^{-1})	$E_a^{\neq}$ (kJ mol^{-1})
Sulfuric acid	−182.90	24.28	79.69	26.89	−221.98	15.21	82.48	17.79
Perchloric acid	−174.59	27.35	80.25	29.93	−211.18	17.46	81.45	20.12

Experimental error ± 4%.

that the constructed intermediate complexes were solvated and their construction was non-spontaneous and endothermic, respectively. Additionally, the high negative values of $\Delta S^{\neq}$ indicated production of inflexible associative intermediate complexes and such activated complexes are assumed to be more ordered than the reactants themselves as a result of loss of degrees of freedom ($-\Delta S^{\neq}$) [59,60]. Moreover, the higher values of $E_a^{\neq}$ designated that the decomposition of constructed intermediate complexes into the degradation products is suggested to be slow step (rate-controlling step), where the higher the $E_a^{\neq}$, the slower the reaction will be.

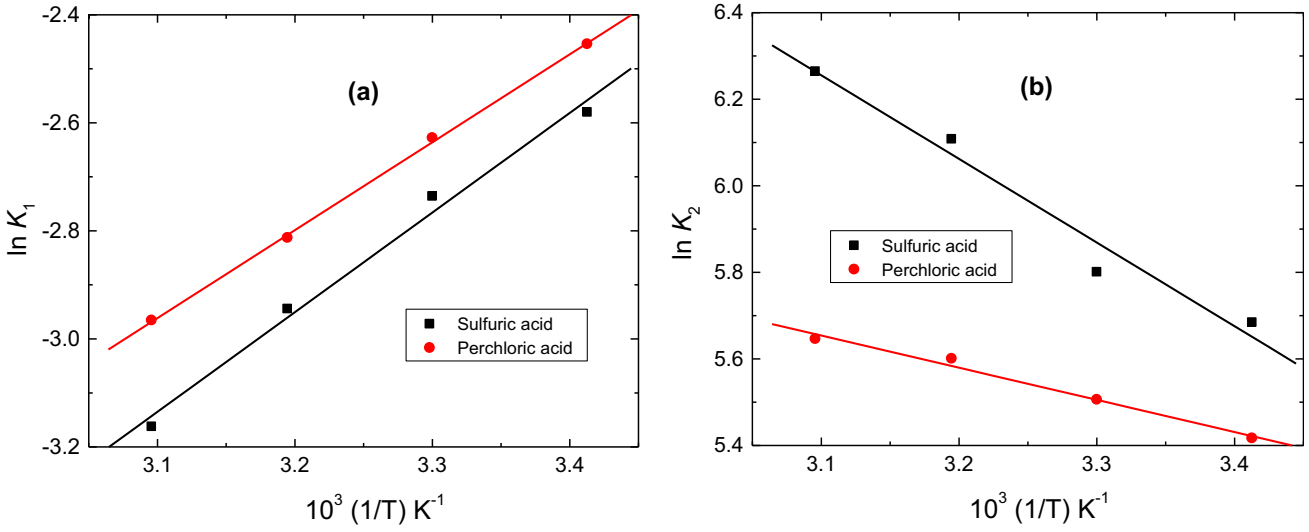


Fig. 15 Van't Hoff plots of the equilibrium constants: (a) K_1, and (b) K_2 in the oxidative degradation of fluconazole (Flz) by Cr^{VI} oxide in sulfuric acid and perchloric acid solutions. $[CrO_3] = 5.0 \times 10^{-4}$, $[Flz] = 5.0 \times 10^{-2}$, $[H^+] = 1.0$ and $I = 2.0$ mol dm^{-3}.

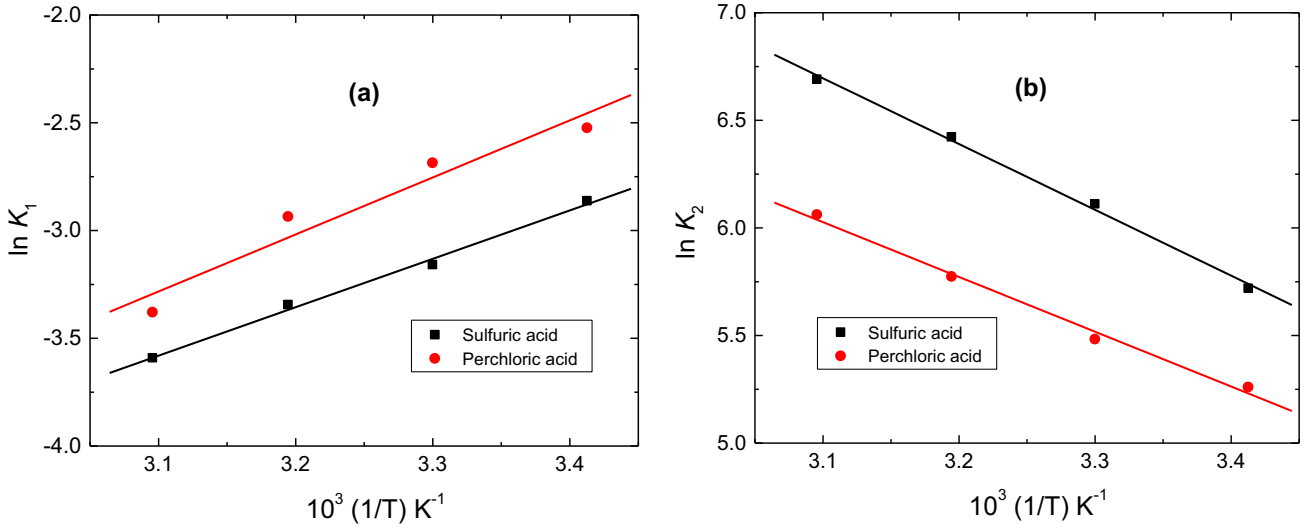


Fig. 16 Van't Hoff plots of: (a) K_1, and (b) K_2 in the oxidative degradation of voriconazole (Vcz) by Cr^{VI} oxide in sulfuric acid and perchloric acid solutions. $[CrO_3] = 5.0 \times 10^{-4}$, [Flz] = 5.0×10^{-2}, $[H^+] = 1.0$ and $I = 2.0$ mol dm^{-3}.

Table 5 Thermodynamic parameters of K_1 and K_2 in the oxidative degradation of fluconazole and voriconazole by Cr^{VI} oxide in sulfuric acid and perchloric acid solutions. $[CrO_3] = 5.0 \times 10^{-4}$, [A] = 5.0×10^{-2}, $[H^+] = 1.0$ and $I = 2.0$ mol dm^{-3}.

Acidic medium	Equilibrium Constant (dm^3 mol^{-1})	Fluconazole			Voriconazole		
		ΔH^o (kJ mol^{-1})	$\Delta G^o{}_{303}$ (kJ mol^{-1})	ΔS^o (Jmol^{-1}K^{-1})	ΔH^o (kJ mol^{-1})	$\Delta G^o{}_{303}$ (kJ mol^{-1})	ΔS^o (Jmol^{-1}K^{-1})
Sulfuric acid	K_1	−15.33	−2.86	−41.15	−18.71	−0.72	−59.37
Perchloric acid		−13.53	−3.49	−33.14	−22.03	−3.35	−61.65
Sulfuric acid	10^{-2} K_2	16.05	−24.60	134.16	25.44	−25.51	168.15
Perchloric acid		6.17	−23.98	99.50	21.20	−23.92	148.91

4. Conclusions

The kinetics of oxidative degradation of fluconazole and voriconazole was examined spectrophotometrically using chromium (VI) oxide in sulfuric and perchloric acid environments. In both acidic environments, the oxidative degradation of the two examined antibiotics were acid-catalyzed. Under analogous experimental circumstances, the oxidation rates in perchloric acid environment were slightly higher than those occurred in sulfuric acid and the oxidation rates of fluconazole were higher than those of voriconazole. The believable oxidative degradation mechanism consistent with the kinetic outcomes was proposed. The derived rate-law expression was set to be in a good harmony with the acquired results. The activation and thermodynamic parameters were computed and discussed. This study announce a simple, safe and inexpensive promising procedure involving a double benefit for the environment and human health: degradation of fluconazole and voriconazole drugs and transformation of the extremely toxic and carcinogenic Cr^{VI} oxide to a safe Cr^{III} compound.

5. Data availability statement

All data that support the findings of this study are included within the article.

CRediT authorship contribution statement

Ahmed Fawzy: Conceptualization, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Nada Alqarni:** Data curation, Funding acquisition, Project administration. **Belal El-Gammal:** Visualization, Supervision. **Arafat Toghan:** Formal analysis, Investigation. **Nasser A. Hassan:** Supervision. **Zaina Algarni:** Supervision, Validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors extend their appreciation to the Deanship of Scientific Research, University of Bisha, Saudi Arabia for funding their research work through Promising Initiative Project under Grant Number (UB-Promising - 7 -1442) for the financial support.

Appendix. A. Derivation of the rate-law expression:

The proposed oxidative degradation mechanism led to derivate the rate-law expression as indicated from the following equations,

According to Eq. (4) in the suggested mechanism,

$$K_1 = \frac{[AH^+]}{[A][H^+]}, \text{thus} : [AH^+] = K_1[A][H^+] \quad (A1)$$

where A and AH^+ point to antibiotic and its protonated species, respectively.

Also, concerning to Eq. (5),

$$K_2 = \frac{[C]}{[AH^+][Cr^{VI}]} \quad (A2)$$

The connection between Eqs. (A.1) and (A.2) leads to,

$$[C] = K_2[AH^+][Cr^{VI}] = K_1K_2[A][Cr^{VI}][H^+] \quad (A3)$$

Equation (6) directs to the following rate-law,

$$\text{Rate} = \frac{-d[Cr^{VI}]}{dt} = k_1[C] \quad (A4)$$

Replacing Eq. (A.3) in Eq. (A.4) imparts to,

$$\text{Rate} = k_1K_1K_2[A][Cr^{VI}][H^+] \quad (A5)$$

The total concentration of the antibiotic is donated by,

$$[A]_T = [A]_F + [AH^+] + [C] \quad (A6)$$

where 'T' and 'F' refers to the total and free.

Replacing Eq. (A.1) into Eq. (A.6) gives,

$$[A]_T = [A]_F + K_1[A][H^+] + K_1K_2[A][Cr^{VI}][H^+] \quad (A7)$$

$$[A]_T = [A]_F(1 + K_1[H^+] + K_1K_2[Cr^{VI}][H^+]) \quad (A8)$$

Accordingly,

$$[A]_F = \frac{[A]_T}{1 + K_1[H^+] + K_1K_2[Cr^{VI}][H^+]} \quad (A9)$$

Due to the very low concentration of Cr^{VI} used, the term $K_1K_2[Cr^{VI}][H^+]$ in the denominator can be ignored. So,

$$[A]_F = \frac{[A]_T}{1 + K_1[H^+]} \quad (A10)$$

$[Cr^{VI}]_T$ is donated by,

$$[Cr^{VI}]_T = [Cr^{VI}]_F + [C] = [Cr^{VI}]_F + K_1K_2[A][Cr^{VI}][H^+] \quad (A11)$$

$$[Cr^{VI}] = [Cr^{VI}]_F(1 + K_1K_2[A][H^+]) \quad (A12)$$

Then,

$$[Cr^{VI}]_F = \frac{[Cr^{VI}]_T}{1 + K_1K_2[A][H^+]} \quad (A13)$$

The high $[H^+]$ consumed in the current study directs to the following proposal,

$$[H^+]_F = [H^+]_T \quad (A14)$$

Replacing Eqs. (A10), (A13) and (A14) into Eq. (A6) (and forgetting 'T' and 'F' subscripts) gives,

$$\text{Rate} = \frac{k_1K_1K_2[Cr^{VI}][A][H^+]}{1 + K_1[H^+] + K_1K_2[A][H^+]} \quad (A15)$$

In pseudo-first order statuses,

$$\text{Rate} = \frac{-d[Cr^{VI}]}{dt} = k_{obs}[Cr^{VI}] \quad (A16)$$

Linking the two Eqs. (A.15) and (A.16), the following equation is gained,

$$k_{obs} = \frac{k_1K_1K_2[A][H^+]}{1 + K_1[H^+] + K_1K_2[A][H^+]} \quad (A17)$$

Readjusting Eq. (10), the following two fundamental equations are developed,

$$\frac{1}{k_{obs}} = \left(\frac{1 + K_1[H^+]}{k_1K_1K_2[H^+]}\right)\frac{1}{[A]} + \frac{1}{k_1} \quad (A18)$$

$$\frac{1}{k_{obs}} = \left(\frac{1}{k_1K_1K_2[A]}\right)\frac{1}{[H^+]} + \frac{1}{k_1K_2[A]} + \frac{1}{k_1} \quad (A19)$$

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jscs.2021.101396.

References

[1] "Drug definition US FDA Drug approval process". Pharmacists Pharma Journal. 11 November 2010.
[2] J.L. Martínez, Natural antibiotic resistance and contamination by antibiotic resistance determinants: the two ages in the evolution of resistance to antimicrobials, Front. Microbiol. 3 (2012) 1–3.
[3] M.R. Gillings, Evolutionary consequences of antibiotic use for the resistome, mobilome, and microbial pangenome, Front. Microbiol. 4 (2013) 1–10.
[4] D. Ann-Marie, Pharmaceuticals in industrial wastewater and their removal using photo-Fenton's oxidation, Ph.D. Research Thesis, School of Biotechnology Dublin City University Dublin 9 Ireland, 2011.
[5] D. Taylor, The pharmaceutical industry and the future of drug development, in *Pharmaceuticals in the Environment*, 2015, pp. 1-33 From Book Series: Issues in Environmental Science and Technology.
[6] K. Kümmerer, The presence of pharmaceuticals in the environment due to human use - present knowledge and future challenges, J. Environ. Manag. 90 (2009) 2354–2366.
[7] Y. Luo, W. Guo, H.H. Ngo, L.D. Nghiem, F.I. Hai, J. Zhang, S. Liang, X.C. Wang, A review on the occurrence of micropollutants in the aquatic environment and their fate and removal during wastewater treatment, Sci. Total Environ. 473-474 (2014) 619–641.
[8] M. Hernando, M. Mezcua, A. Fernandezalba, D. Barcelo, Environmental risk assessment of pharmaceutical residues in wastewater effluents, surface waters and sediments, Talanta 69 (2006) 334–342.

[9] A. Fawzy, Removal of toxic tellurium (IV) compounds via bioreduction using flucloxacillin in aqueous acidic medium: a kinetic and mechanistic approach, J. Mol. Liq. 292 (2019) 111436.
[10] K. Kümmerer, A. Al-Ahmad, V. Mersch-Sundermann, Biodegradability of some antibiotics, elimination of the genotoxicity and affection of wastewater bacteria in a simple test, Chemosphere 40 (2000) 701–710.
[11] L. Du, W. Liu, Occurrence, fate and ecotoxicity of antibiotics in agro-ecosystems. A review, Agron. Sustain. Dev. 32 (2002) 309–327.
[12] M.S. Fram, K. Belitz, Occurrence and concentrations of pharmaceutical compounds in groundwater used for public drinking-water supply in California, Sci. Total Environ. 409 (2011) 3409–3417.
[13] N.A. Doerr-MacEwen, M.E. Haight, Expert stakeholders' views on the management of human pharmaceuticals in the environment, Environ. Manage. 38 (2006) 853–866.
[14] C. Xi, Y. Zhang, C.F. Marrs, W. Ye, C. Simon, B. Foxman, J. Nriagu, Prevalence of antibiotic resistance in drinking water treatment and distribution systems, Appl. Environ. Microbiol. 75 (2009) 5714–5718.
[15] E. Gurtekin, N. Şekerdag, An advanced oxidation process: Fenton process, J. Eng. Sci. 14 (2008) 229–239.
[16] A. Fawzy, I.A. Zaafarany, F.A. Tirkistani, B.H. Asghar, Oxidative degradation of atropine drug by permanganate ion in perchloric and sulfuric acid solutions: a comparative kinetic study, Adv. Biochem. 4 (2016) 58–65.
[17] S.O. Ganiyu, E.D. van Hullebusch, M. Cretin, G. Esposito, M. A. Oturan, Coupling of membrane filtration and advanced oxidation processes for removal of pharmaceutical residues: a critical review, Sep. Purif. Technol. 156 (2015) 891–914.
[18] A.G. Trovó, R.F.P. Nogueira, A. Agüera, A.R. Fernandez-Alba, C. Sirtori, S. Malato, Degradation of sulfamethoxazole in water by solar photo-Fenton. Chemical and toxicological evaluation, Water Res. 43 (2009) 3922–3931.
[19] M.O. Buffle, J. Schumacher, E. Salhi, M. Jekel, U. von Gunten, Measurement of the initial phase of ozone decomposition in water and wastewater by means of a continuous quench-flow system: Application to disinfection and pharmaceutical oxidation, Water Res. 40 (2006) 1884–1894.
[20] F.J. Benitez, J.L. Acero, F.J. Real, G. Roldan, Ozonation of pharmaceutical compounds: Rate constants and elimination in various water matrices, Chemosphere 77 (2009) 53–59.
[21] A.K. Singh, R. Negi, B. Jain, Y. Katre, S.P. Singh, V.K. Sharma, Kinetics and mechanism of Ru(III)-catalyzed oxidation of paracetamol by chloramine-T in aqueous acidic medium, Catal. Lett. 132 (2009) 285–291.
[22] R.V. Hosahalli, K.S. Byadagi, S.T. Nandibewoor, S.A. Chimatadar, Kinetics and mechanism of ruthenium(III) catalyzed oxidation of chloramphenicol - an antibiotic drug by diperiodatocuprate(III) in aqueous alkaline medium, Kinet. Catal. 53 (2012) 65–74.
[23] N.P. Shetti, R.N. Hegde, S.T. Nandibewoor, Structure reactivity and thermodynamic analysis on the oxidation of ampicillin drug by copper(III) complex in aqueous alkaline medium (stopped-flow technique), J. Mol. Str. 930 (2009) 180–186.
[24] M.M. Huber, A. Göbel, A. Joss, N. Hermann, D. Löffler, C.S. McArdell, A. Ried, H. Siegrist, T.A. Ternes, U. von Gunten, Oxidation of pharmaceuticals during ozonation of municipal wastewater effluents: a pilot study, Environ. Sci. Technol. 39 (2005) 4290–4299.
[25] Y. Lee, U. von Gunten, Oxidative transformation of micropollutants during municipal wastewater treatment: comparison of kinetic aspects of selective (chlorine, chlorine dioxide, ferrate(VI), and ozone) and non-selective oxidants (hydroxyl radical), Water Res. 44 (2010) 555–566.
[26] A. Fawzy, I.A. Zaafarany, K.S. Khairou, L.S. Almazroai, B.A. Al-Jahdali, T.M. Bawazeer, Oxidation of caffeine by permanganate ion in perchloric and sulfuric acid solutions: a comparative kinetic study, Sci. J. Chem. 4 (2016) 19-28; A. Fawzy, I.A. Zaafarany, I.I. Althagafi, H.M. Altass, Silver-catalyzed oxidation of atropine drug by cerium(IV) in aqueous perchlorate solutions: a kinetics and mechanistic approach, J. Drug Design Med. Chem. 2 (2016) 51-59.
[27] A. Fawzy, M. Abdallah, N. Alqarni, Oxidative degradation of neomycin and streptomycin by cerium(IV) in sulphuric and perchloric acid solutions, J. Mol. Liq. 312 (2020) 113439; degradation of ampicillin and flucloxacillin antibiotics via oxidation by alkaline hexacyanoferrate(III): Kinetics and mechanistic aspects, Ind. Eng. Chem. Res. 59 (2020) 16217−16224; Oxidative degradation of some antibiotics by permanganate ion in alkaline medium: A kinetic and mechanistic approach, Trop. J. Pharm. Res. 19 (2020) 1999-2007; mechanistic and thermodynamic aspects of oxidative removal of flucloxacillin by different oxidants in an acidic medium, J. Mol. Liq. 325 (2021) 115160.
[28] M. Costa, Toxicity and carcinogenicity of Cr^{VI} in animal models and humans, CRC Crit. Rev. Toxicol. 27 (1997) 431–442.
[29] P.T. Kostecki, Chromium in soil: perspectives in chemistry, health, and environmental regulation, J. Soil. Contamin. 6 (1998) 561–568.
[30] Y. Xie, S. Holmgren, D.M.K. Andrews, M.S. Wolfe, Evaluating the impact of the U.S. national toxicology program: A case study on hexavalent chromium, Environ. Health Perspect. 125 (2017) 181–188.
[31] A. Fawzy, I.A. Zaafarany, K.S. Khairou, I. Althagafi, J. Alfahemi, Kinetics and mechanism of oxidation of vanillin by chromium(VI) in sulfuric acid solutions, Modern Chem. Appl. 4 (2016) 179-188; A. Fawzy, I. A. Zaafarany, R.S. Jassas, R.J. Obaid, S.A. Ahmed, Kinetics and mechanistic approach to the chromic acid oxidative degradation of atropine drug in perchlorate solutions and the effect of ruthenium(III) catalyst, Modern Chem. Appl. 4 (2016) 196-204.
[32] R.M. Hassan, S.M. Ahmed, A. Fawzy, D.A. Abdel-Kader, Y. Ikeda, H.D. Takagi, Acid-catalyzed oxidation of carboxymethyl cellulose polysaccharide by chromic acid in aqueous perchlorate solutions. A kinetics study, Cat. Commun. 11 (2010) 611–615.
[33] A. Fawzy, I. Althagafi, K. Khairou, R. Hassan, N. Yarkandi, L. Almazroai, T. Bawazeer, Kinetics and mechanistic aspects of oxidation of iota- and lambda-carrageenans by chromium(VI) in aqueous perchlorate solutions, Chem. Sci. Rev. Lett. 4 (2016) 1293–1304.
[34] A. Fawzy, H.M. Altass, Ruthenium(III)-catalyzed oxidation of alginate and pectate biopolymers by chromic acid in aqueous perchlorate solutions: a comparative kinetic study, Trans. Met. Chem. 41 (2016) 115–124.
[35] A. Fawzy, S.S. Ashour, M.A. Musleh, R.M. Hassan, B.H. Asghar, Kinetics and mechanistic approach to the chromic acid oxidation of L-tryptophan with a spectral detection of chromium(III) product, J. Saudi Chem. Soc. 20 (2016) 450–458.
[36] A. Fawzy, I. Althagafi, F. Tirkistani, M. Shaaban, M. Morad, Chromic acid oxidation of methylaminopyrazole formamidine in sulfuric acid medium: a kinetic and mechanistic approach, Am. J. Phys. Chem. 5 (2016) 1–9.
[37] A. Fawzy, N. Elguesmi, I.I. Althagafi, B.H. Asghar, A study of the kinetics and mechanism of chromic acid oxidation of isosorbide, a chiral biomass-derived substrate, in aqueous perchlorate solution, Transition Met. Chem. 42 (2017) 229–236.
[38] A. Fawzy, R.S. Jassas, S.A. Ahmed, H.M. Ali, M. Abdallah, M. A.S. Abourehab, N.S. Abbas, Fluorenones formation via effective chromium(VI) oxidation in perchlorate solutions: kinetic and mechanistic features, J. Mater. Env. Sci. 8 (2017) 4032–4039.

[39] E. Piers, P.M. Worster, Oxidation with chromium(VI) oxide - pyridine complex. A study of reaction parameters using cholesterol as substrate, Can. J. Chem. 55 (1977) 733–736.
[40] U.Z. Faruq, A.A. Zuru, E.O. Odebunmi, S.M. Dangoggo, Mechanism for partial oxidation of cyclohexene by chromium (VI) oxide in acetic acid, Global J. Pure Appl. Sci. 17 (2011) 1–9.
[41] A. Fawzy, O. Solo, M. Morad, Oxidation of barbituric and thiobarbituric acids by chromium trioxide in different acidic media: a kinetic and mechanistic aspects, J. Mol. Str. 1224 (2021) 129495.
[42] F. Ciminale, M. Camporeale, R. Mello, L. Troisiand, R. Curci, Oxidation of tertiary amines by chromium(VI) oxide diperoxide, J. Chem. Soc., Perkin Trans. 2 (1989) 417–423.
[43] A. Fawzy, A. Toghan, Unprecedented treatment strategy of aquatic environments. Oxidative degradation of penicillin G by chromium trioxide in acidic media and the impact of metal ion catalysts: Kinetics and mechanistic insights, ACS Omega 5 (2020) 32781–32791.
[44] F. Feigl, Spot Tests in Organic Analysis, Elsevier, New York, 1975, p. 195.
[45] A.R. Rendina, W.W. Cleland, Separation of aldehydes and ketones by chromatography on dowex-50 in the ethylenediamine form, Anal. Biochem. 117 (1981) 213–218.
[46] B.S. Furniss, A.J. Hannaford, W.J. Smith, A.R. Tatchell, Vogel's Textbook of Practical Organic Chemistry, 5th edn., Pearson Education Ltd, London, 2004.
[47] J.H. Espenson, Oxidation of transition metal complexes by chromium(VI), Acc. Chem. Rev. 3 (1970) 347–351; J.H. Espenson, R.T. Wang, The oxidation of uranium(IV) by chromium(VI) and the induced oxidation of iodide ions, Inorg. Chem. 11 (1972) 955–959.
[48] R.M. Kulkarni, V.S. Bhamare, B. Santhakumari, Oxidative transformation of antiretroviral drug zidovudine during water treatment with permanganate: reaction kinetics and pathways, Desalin. Water Treat. 57 (2016) 24999–25010.
[49] J.T. Baker, "Chromium Trioxide (MSDS)". Retrieved 2007-09-13.
[50] H.O. House, Oxidation with chromium and manganese compounds in; modern synthetic reaction. In: Benjamin WA, editor. London (1972).
[51] K.K. Sen Gupta, J.K. Chakladar, A.K. Chatterjee, Kinetics of the oxidation of hypophosphorous and phosphorous acids by chromium(VI), J. Inorg. Nucl. Chem. 35 (1973) 901–908.
[52] G. Milazzo, S. Caroli, V.K. Sharma, Tables of standard electrode metal potentials, Wiley, New York, 1978.
[53] L. Michaelis, M.L. Menten, The kinetics of invertase action, Biochem. Z. 49 (1913) 333–369.
[54] V.F. Chemie, PhD Thesis, Duisburg University, Germany, 2005.
[55] L.E. Karpukhin, M.A. Feofanova, L.S. Nikolaeva, M.N. Mamontov, N.A. Dobrynina, Complexation of magnesium and calcium ions with heparin, Russ. J. Inorg. Chem. 51 (2006) 908–914.
[56] C. Leggett, L. Rao, Complexation of calcium and magnesium with glutarimidedioxime: implications for the extraction of uranium from seawater, Polyhedron 95 (2015) 54–59.
[57] A.A. Frost, R.G. Person, Kinetics and Mechanism, Wiley Eastern, New Delhi (1970); C. H. Rochester, Progress in Reaction Kinetics, Pergamon Press, Oxford, Laidler, K.: Chemical Kinetics, McGraw-Hill, New York, 1965.
[58] E.S. Amis, Solvent Effects on Reaction Rates and Mechanism, Academic Press, New York, 1966.
[59] F. Freeman, C.O. Fuselier, C.R. Armstead, C.E. Dalton, P.A. Davidson, E.M. Karchesfski, D.E. Krochman, M.N. Johnson, N.K. Jones, Permanganate ion oxidations. 13. Soluble manganese(IV) species in the oxidation of 2,4(1H,3H)-pyrimidinediones (uracils), J. Am. Chem. Soc. 103 (1981) 1154–1159.
[60] K.W. Hicks, D.L. Toppen, R.G. Linck, Inner-sphere electron-transfer reactions of vanadium(II) with azidoamine complexes of cobalt(III), Inorg. Chem. 11 (1972) 310–315.