Oxidation of Diclofenac Sodium by Diperiodatoargantate(III) in Aqueous Alkaline Medium and Its Determination in Urine and Blood by Kinetic Methods

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Received 19 January 2009; revised 20 April 2009, 26 June 2009, 21 December 2009; accepted 4 January 2010

DOI 10.1002/kin.20486
Published online in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: The kinetics and oxidation of diclofenac sodium (DFS) by diperiodatoargentate(III) (DPA) in alkaline medium at 298 K and at a constant ionic strength of 0.60 mol dm^{-3} were studied spectrophotometrically. The oxidation products were [2-(2,6-dicloro-phynylamino)-phenyl]-methenol and Ag(I), identified by LC-ESI-MS and IR spectral studies. The reaction between DFS and DPA in alkaline medium exhibits 1:1 stoichiometry. The reaction is first order in [DPA] and has a less than unit order dependence each in [DFS] and [alkali]. Increasing concentrations of IO_4^- retard the reaction. The active species of DPA proposed to be monoperiodatoargentate(III), and a mechanism is suggested. The rate constants involved in the different steps of the mechanism were determined and are discussed. The activation parameters with respect to a rate-limiting step of the mechanism were determined. The thermodynamic quantities were also determined. Using the oxidation of DFS by DPA, DFS was analyzed by kinetic methods in urine and blood sample. The proposed method enables DFS analysis in the range from 5.0×10^{-5} to 5.0×10^{-3} mol dm^{-3}. © 2010 Wiley Periodicals, Inc. Int J Chem Kinet 42: 336–346, 2010

INTRODUCTION

Diclofenac sodium (DFS), i.e., [*o*-[(2,6-dichloro-phenyl)amino]phenyl] sodium acetate, belongs to the nonsteroidal anti-inflammatory drugs. There is a need to develop a simple and economical method for the assay of DFS in pharmaceutical preparations.

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Supporting Information containing figures and an appendix is available in the online issue at www.interscience.wiley.com.

Diperiodatoargentate(III) (DPA) is a powerful oxidizing agent in alkaline medium with the reduction potential [1] 1.74 V. It is widely used as a volumetric reagent for the determination of various organic and inorganic species [2]. Jayaprakash Rao et al. [3,4] have used DPA as an oxidizing agent for the kinetics of oxidation of various organic substrates by generalizing the DPA as $[Ag(HL)L]^{(x+1)-}$, where L is a periodate with an uncertain number of protons and HL is a protonated periodate of an uncertain number of protons. However, Kumar et al. [5–7] had made an effort to give evidence for the reactive form of DPA in the large scale of alkaline pH. In the present investigation, we have obtained the evidence for the reactive species for DPA in alkaline medium.

The present study deals with the title reaction to investigate the redox chemistry of DPA in such a medium, to identify the oxidation product of DFS, to arrive at a plausible mechanism. Of the existing techniques used for the determination of DFS, the potentiometric method [8] is less sensitive; spectrophotometry [9], fluorometry [10], chromatography methods [11], and recently, some electrochemical methods [12,13] and the reversed-phase high-performance liquid chromatography (HPLC) method based on UV detection [14] are laborious, expensive, and time consuming. This has prompted us to develop a sensitive, accurate, and economically viable technique for the determination of DFS in pharmaceutical preparations. The method is based on oxidation of the drug by DPA.

EXPERIMENTAL

Materials and Reagents

All chemicals used were of reagent grade, and double distilled water was used throughout the work. DFS (IP) was dissolved in water, and concentration was checked [8] potentiometrically. KNO_3 and KOH (BDH, Bangalore, India) were used to maintain ionic strength and alkalinity of the reaction, respectively. Aqueous solution of $AgNO_3$ was used to study the product effect, Ag(I). A stock standard solution of IO_4^- was prepared by dissolving a known weight of KIO_4 (Riedel-de Haen, Seelze, Germany) in hot water and was used after 24 h to attain equilibrium. Its concentration was ascertained iodometrically [15] at neutral pH maintained using phosphate buffer.

Preparation of DPA

DPA was prepared by oxidizing Ag(I) in the presence of KIO_4 as described elsewhere [16]. The complex was characterized by its UV spectrum, exhibited three peaks at 216, 255, and 362 nm. These spectral features were identical to those reported earlier for DPA [16]. The magnetic moment study revealed that the complex is diamagnetic. The prepared compound was analyzed [17] for silver and periodate by acidifying a solution of the material with HCl, recovering and weighing the AgCl for Ag, and titrating the iodine liberated when excess KI was added to the filtrate for IO_4^-. Thus the obtained DPA was dissolved in water and was used for the required [DPA] in the reaction mixture.

Kinetic Procedure

The kinetic measurements were performed with a Varian CARY 50 Bio UV–vis spectrophotometer. The reaction was followed under pseudo-first-order conditions where [DFS] $\gg$ [DPA] at 25 $\pm$ 0.1°C, unless otherwise specified. Reaction was initiated by mixing the DPA solution with diclofenac sodium solution, the latter also containing the required concentrations of KNO_3, KOH, and KIO_4 (see the Materials and Methods section). Reaction progress was followed spectrophotometrically at 360 nm by monitoring the decrease in absorbance of DPA, using the known molar absorbance index [18], $\varepsilon = 13,900 \pm 100$ dm^3 mol^{-1} cm^{-1}. It was verified that there is a negligible interference from other species present in the reaction mixture at this wavelength. The pseudo-first-order rate constants (k_{obs}) were determined from the slopes of plots log(absorbance) versus time (Supporting Information Fig. I). The equation used for the calculation of k_{obs} was $-2.303 \times$ slope. The plots were linear up to 85% completion of reaction. The rate constants were

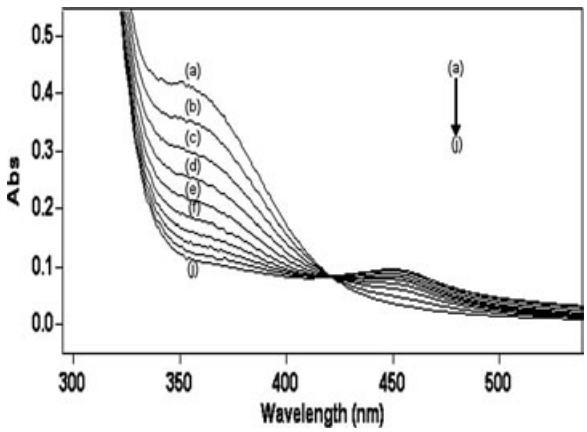


Figure 1 Spectroscopic changes occurring in the oxidation of diclofenac sodium by diperiodatoargantate(III) at 25°C, [DPA] = 5×10^{-5}, [DFS] = 5×10^{-4}, [OH$^-$] = 0.50, and I = 0.60 mol dm^{-3} with scanning time interval =1 min.

reproducible to within ±5%. The spectral changes during the reaction shown in Fig. 1 clearly show the decrease in the DPA absorbance at 360 nm. It is evident from Fig. 1 that the concentration of DPA is decreasing by observing the absorbance at 360 nm. Since periodate is also present in DPA, the possibility of oxidation of diclofenac sodium by periodate in alkaline medium at 25°C was checked. No significant reaction was found under the experimental conditions. The effect of dissolved oxygen on the rate of reaction was checked by preparing mixtures and carrying out the kinetic studies in an atmosphere of nitrogen. No significant difference between the results obtained under nitrogen and in the presence of air was observed. In view of the ubiquitous contamination by CO_3^{2-}, the effect of added carbonate on the reaction rate was studied and found to be negligible. Regression analysis of the experimental data to obtain regression coefficient r and the standard deviation S, of points from the regression line, was performed with the Microsoft office Excel 2003 program.

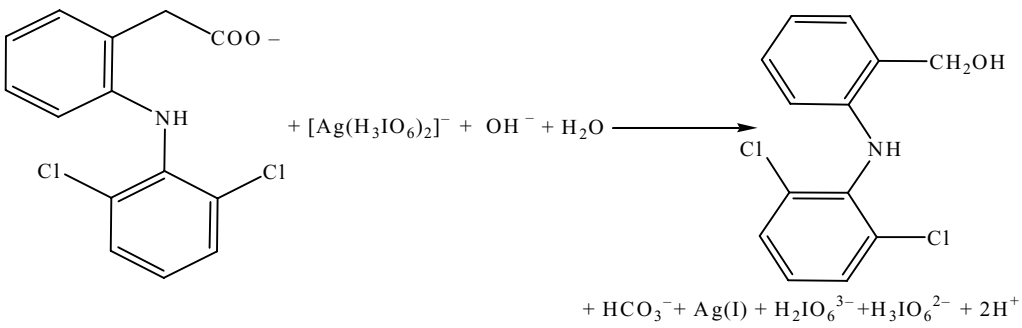
RESULTS

Stoichiometry and Product Characterization

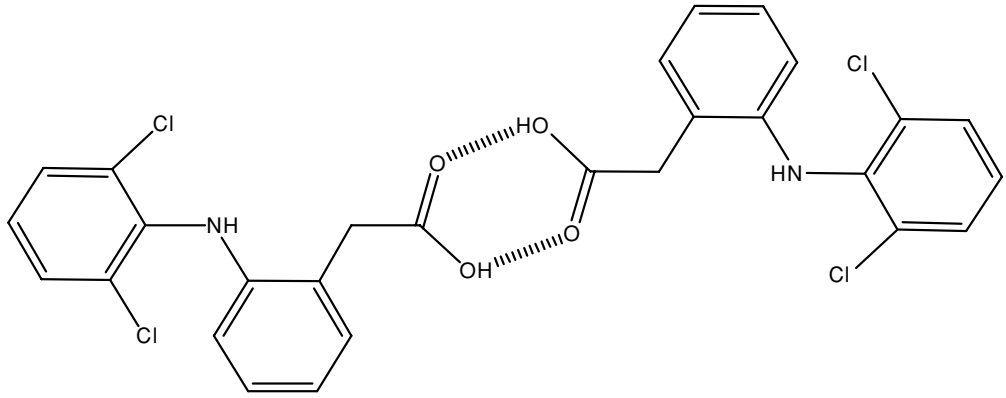
Different sets of reaction mixtures containing varying ratios of DPA to diclofenac sodium in the presence of a constant amount of OH^-, KNO_3 in reaction were kept for 3 h in a closed vessel under nitrogen atmosphere. The remaining concentration of DPA was estimated spectrophotometrically at 360 nm. Under the condition where [DFS] > [DPA], the unreacted diclofenac sodium was estimated [9] as mentioned above. The results indicate 1:1 stoichiometry for both the reactions as given in Eq. (1). The main reaction products were identified as [2-(2, 6-dicloro-phynylamino)-phenyl]-methenol and Ag(I).

The oxidation product of diclofenac sodium [2-(2,6-dicloro-phynylamino)-phenyl]-methenol was isolated with the help of preparative TLC and characterized by LC–ESI–MS, FTIR, and ^{1}H NMR spectral studies.

LC–ESI–MS analysis was carried out using reverse phase HPLC system with a phenomenes C-18 column, UV/–visible detector and series mass analyzer. 20 μL of acidified reaction mixture was injected. The mobile phase consisted of 10 mM ammonium acetate pH 3.0 (eluent A) and acetic acid (eluent B) at a flow rate of 1 mL/min. Gradient elution was run to separate substrate and reaction products. Gradient elution ratios are 0 min/50% A and 50% B, 5 min/50% A and 50% B, 15 min/30% A and 70%B, 17 min/30% A and 70%B, 20 min/50% A and 50% B, and 22 min/50% A and 50% B. LC–ESI–MS analysis indicated the presence of two main products with molecular ions of m/z at 273 (yield ca. 90%) and 598 (yield ca. 5%), respectively (Supporting Information Fig. II). The molecular ion of diclofenac sodium is m/z 299. The m/z at 598 corresponds to dimer product of DFS. The product [2-(2, 6-dicloro-phynylamino)-phenyl]-methenol was further confirmed by its characteristic IR and ^{1}H NMR spectrum. The disappearance of the sharp band (peak) at 1695 cm^{-1} due to acidic carbonyl in DFS confirms the product. A further secondary amine (–NH) group observed around 3387 cm^{-1} in DFS remains in the product (Supporting Information Fig. III). In ^{1}H NMR (DMSO) spectrum, the disappearance of the acidic OH band of DFS and the appearance of the alcoholic hydroxyl proton triplet band at 6.859 ppm confirm the product. Furthermore, the secondary amine (–NH) proton singlet band around 3.69 ppm and other aromatic proton bands in DFS remain in the product, which disappears on D_2O exchange, confirming the formation of product [2-(2, 6-dicloro-phynylamino)-phenyl]-methenol (Fig. 2). All these observations proved the formation of [2-(2,6-dicloro-phynylamino)-phenyl]-methenol as a major product. The dimer structure of DFS is as follows:



(1)



Reaction Orders

The reaction orders were determined from the slope of log k_{obs} versus log(concentration) plots (Supporting Information Fig. IV) by varying the concentrations of one reactant at a time while keeping all other concentrations and conditions constant except DPA concentration. The [DPA] was varied in the range from 1.0×10^{-5} to 1.0×10^{-4} mol dm^{-3}, and the constant k_{obs} values indicated that the order with respect to [DPA] was unity (Table I). This was also confirmed by linearity and parallelism of the plots of log (absorbance) versus time up to 85% completion of the reaction (Supporting Information Fig. I). The [DFS] was varied in the range 1.0×10^{-4} to 1.0×10^{-3} mol dm^{-3} at 25°C. The k_{obs} values increased with the increase in [DFS] (Table I)

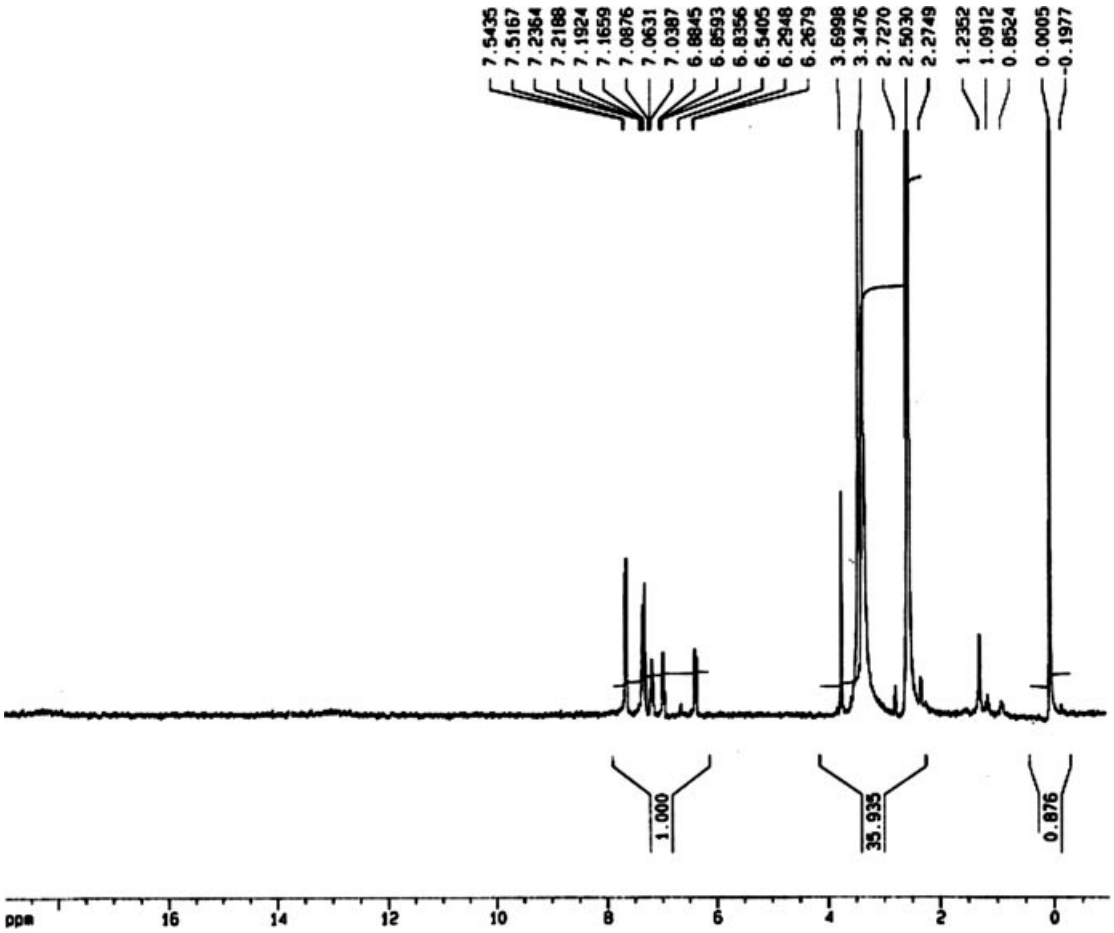


Figure 2 ^{1}H NMR spectra of the product of oxidation of diclofenac sodium by diperiodatoargantate(III).

Table I Effect of Variation of Diperiodatoargantate (III), Diclofenac Sodium, and Alkali Concentrations on the Oxidation of Diclofenac Sodium by Alkaline Diperiodatoargantate(III) at 25.0°C, I = 0.6 mol dm^{-3}

[DPA] × 10^5 (mol dm^{-3})	[DFS] × 10^4 (mol dm^{-3})	[OH^-] × 10^1 (mol dm^{-3})	[IO_4^-] × 10^5 (mol dm^{-3})	k_{obs} × 10^4 (s^{-1})	k_{cal} × 10^4 (s^{-1})
1.0	5.0	5.0	1.0	7.30	7.0
3.0	5.0	5.0	1.0	7.16	7.0
5.0	5.0	5.0	1.0	7.38	7.0
8.0	5.0	5.0	1.0	7.14	7.0
10	5.0	5.0	1.0	7.20	7.0
5.0	1.0	5.0	1.0	2.20	2.1
5.0	3.0	5.0	1.0	5.30	5.0
5.0	5.0	5.0	1.0	7.38	7.0
5.0	8.0	5.0	1.0	8.80	8.9
5.0	10	5.0	1.0	9.80	9.8
5.0	5.0	0.5	1.0	1.88	1.8
5.0	5.0	0.8	1.0	2.56	2.5
5.0	5.0	1.0	1.0	3.21	3.1
5.0	5.0	3.0	1.0	6.07	5.8
5.0	5.0	5.0	1.0	7.38	7.0
5.0	5.0	5.0	1.0	7.38	7.0
5.0	5.0	5.0	3.0	4.25	4.0
5.0	5.0	5.0	5.0	2.99	2.8
5.0	5.0	5.0	8.0	2.06	1.9
5.0	5.0	5.0	10.0	1.71	1.5

and found an apparent less than unit order dependence on [DFS]. The effect of alkali on the reaction rate was studied in the range of 0.05–0.50 mol dm^{-3}. The rate constants increased with increasing [OH^-] (Table I), and the order was found to be less than unity.

Effect of Periodate and Added Products

In the reaction, the periodate concentration was varied from 1.0 × 10^{-5} to 1.0 × 10^{-4} mol dm^{-3} at constant [DPA], [DFS], and ionic strength. It was observed that the rate constants decreased by increasing [IO_4^-] (Table I). Initially added products, Ag(I) and [2-(2, 6-dicloro-phynylamino)-phenyl]-methenol did not have any significant effect on the rate of reaction.

Effect of Ionic Strength (*I*) and Dielectric Constant of the Medium (*D*)

It was found that ionic strength and dielectric constant of the medium had no significant effect on the rate of reaction.

Polymerization Study

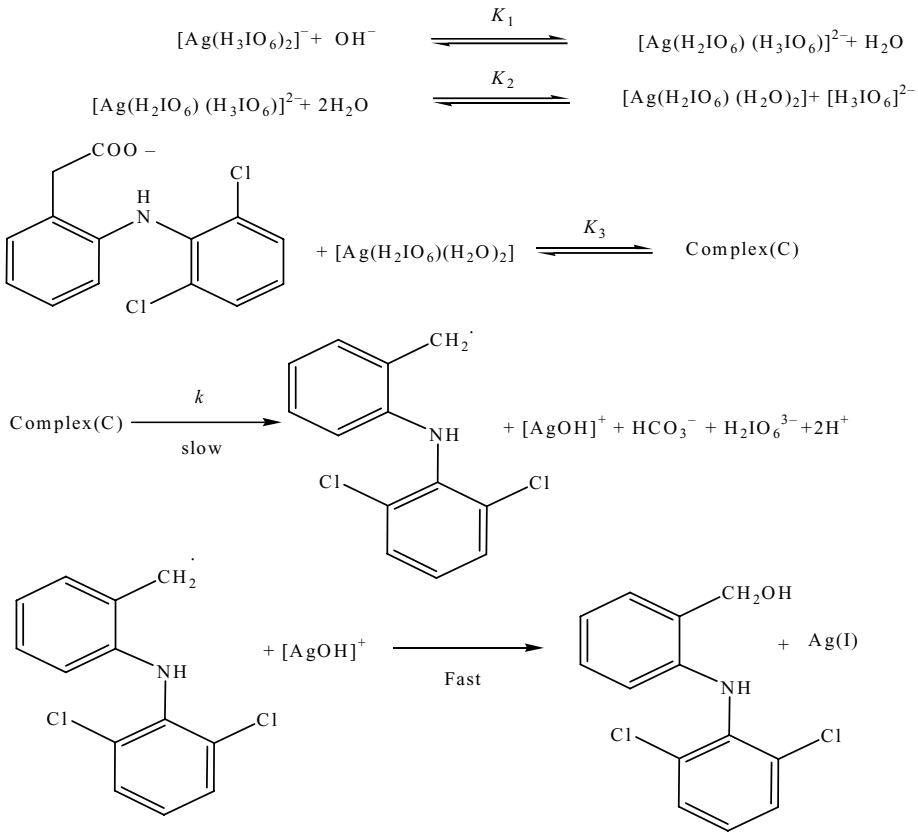
The participation of free radicals in the reaction was carried out according to the literature [18]. The reaction mixture to which a known quantity of acrylonitrile scavenger had been added initially, and the resulting polymer precipitate in methanol suggests a participation of free radicals in the reaction.

Effect of Temperature

The influence of temperature on the rate of reaction was studied at 20, 25, 30, and 40°C. The rate constants (k) of the slow step of Scheme 1 were obtained from the intercepts of the plots of $1/k_{obs}$ versus 1/[DFS] at 20, 25, 30, and 40°C and were calculated as 1.34 × 10^{-3}, 1.65 × 10^{-3}, 2.22 × 10^{-3}, and 4.60 × 10^{-3} s^{-1}. The energy of activation and the other activation parameters were evaluated from the Arrhenious plot of log k versus $1/T$, and the values of the energy of activation, enthalpy of activation $\Delta H^{\#}$, entropy of r activation $\Delta S^{\#}$, and free energy of activation $\Delta G^{\#}$ were calculated as 47.7 kJ mol^{-1}, 45.2 ± 2 kJ mol^{-1}, −146 ± 3 J K^{-1} mol^{-1}, and 88.8 k J mol^{-1}, respectively.

DISCUSSION

Ag(III) species (two electron-oxidant) due to its strong versatile nature prompted studies on the kinetics of oxidation of various organic and inorganic substrates in late twentieth century. Among the various species of Ag(III), $Ag(OH)^{4-}$, diperiodatoargentate(III), and ethylenebis (biguanide) silver(III) (EBS) are of maximum attention to the researchers due to their relative



Scheme 1

stability. The stability of $Ag(OH)^{4-}$ is very sensitive toward traces of dissolved oxygen and other impurities in the reaction medium whereupon it had not drawn much attention. However, the other two forms of Ag(III) [3–7,19,20] are considerably stable; the DPA is used in highly alkaline medium, and EBS is used in highly acidic medium due to the considerable stability of DPA and EBS in the respective media.

The water-soluble silver(III) periodate complex is reported [16] to be $[Ag(IO_6)_2]^{7-}$. However, in an aqueous alkaline medium and at a high pH range as employed in the study, periodate is unlikely to exist as IO_6^{5-} (as present in the complex) as is evident from its involvement in the multiple equilibria (2)–(4). Such protolytic equilibria have been described for aqueous periodate chemistry [21,22]

$$H_5IO_6 \rightleftharpoons H_4IO_6^- + H^+ \quad K_a = 5.1 \times 10^{-4} \qquad (2)$$

$$H_4IO_6^- \rightleftharpoons H_3IO_6^{2-} + H^+ \quad K_\beta = 4.9 \times 10^{-9} \qquad (3)$$

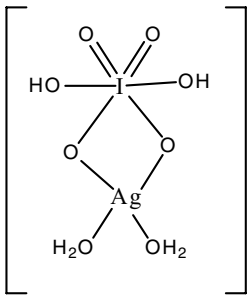
$$H_3IO_6^{2-} \rightleftharpoons H_2IO_6^{3-} + H^+ \quad K_Y = 2.5 \times 10^{-12} \qquad (4)$$

The protonated form of periodate, H_5IO_6, exists in acid medium and as $H_4IO_6^-$ at pH 7. Under the present alkaline conditions, the main species are expected to be $H_3IO_6^{2-}$ and $H_2IO_6^{3-}$. At higher concentrations, periodate tends to dimerize [1]. However, the formation of this species is negligible under conditions employed for kinetic studies. On the contrary, in their recent studies the authors [3,4] have proposed the DPA as $[Ag(HL)_2]^{x-}$ in which L is a periodate with uncertain number of protons and HL is a protonated periodate of uncertain number of protons. This can be ruled out by considering the alternative form [21] of IO_4^- at pH > 7, which is in the form of $H_3IO_6^{2-}$ and $H_2IO_6^{3-}$. Hence, DPA could exist as $[Ag(H_3IO_6)_2]^-$ or $[Ag(H_2IO_6)_2]^{3-}$ in alkaline medium. Under the present conditions, diperiodatoargentate(III) may be depicted as $[Ag(H_3IO_6)_2]^-$. The similar speciation of periodate in alkali was proposed [23] for diperiodatonickelate(IV).

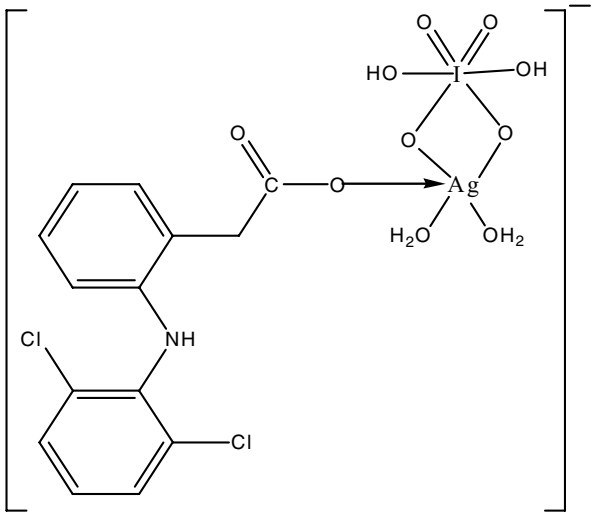
Since the rate of reaction was enhanced by $[OH^-]$, the added periodate retarded the rate, and the reaction had first-order dependence on [DPA] and fractional order dependence on [DFS]; a mechanism (Scheme 1) has been proposed that explains all other experimental observations.

In the prior equilibrium step 1, the $[OH^-]$ deprotonates the DPA to give a deprotonated diperiodatoargentate(III). In the second step, displacement of a ligand,

periodate, takes place to give free periodate, which is evidenced by the decrease in the rate with the increase in the concentration of periodate (Table I). It may be expected that a lower Ag(III) periodate species such as monoperiodatoargentate(III) (MPA) is more important in the reaction than the DPA. The inverse fractional order in $[H_3IO_6]^{2-}$ might also be due to this. In the prerate determining stage, this MPA combines with a molecule DFS to give a complex, which decomposes in a slow step to give an intermediate product Ag(II) and a free radical derived from DFS. This free radical of DFS combines with Ag (II) species in a fast step to give a [2-(2,6-dicloro-phynylamino)-phenyl]-methenol. When DFS was reacted with a pseudo-first-order excess of DFS, a single complex formation reaction was observed and expected. Under these conditions, a 1:1 DPA(III):DFS complex is formed by chelation of an DPA molecule at the carboxyl group of DFS. Spectrophotometric titrations showed the complex formation (Fig. 1). A decrease in the DPA absorption band at 360 nm is accompanied by the simultaneous increase in a unique absorption at 450 nm (5), which is ascribed to the 1:1 DPA:DFS complex. A unique isobestic point, observed at 426 nm, indicates the presence of a single complex [24]. The Michaelis–Menten plot proved the complex formation between oxidant and reductant, which explains the less than unit order in [DFS]. Spectroscopic evidence for the complex formation between oxidant and substrate was obtained from UV–vis spectra of DFS (5.0×10^{-4}), DPA (5.0×10^{-5}), $[OH^-]$ (0.50) mol dm^{-3}, and a mixture of both. A bathochromic shift of about 4 nm from 336 to 340 nm in the spectra of DPA was observed. The structure of MPA and complex (C) is given below.



Monoperiodatoargentate(III)



Complex (C)

The rate law for Scheme 1 could be derived as

$$\text{Rate} = -\frac{\mathrm{d[DPA]}}{\mathrm{d}t} = \frac{kK_1K_2K_3[\mathrm{DPA}][\mathrm{DFS}][\mathrm{OH^-}]}{\left[\mathrm{H_3IO_6^{2-}}\right] + K_1[\mathrm{OH^-}]\left[\mathrm{H_3IO_6^{2-}}\right] + K_1K_2[\mathrm{OH^-}] + K_1K_2K_3[\mathrm{OH^-}][\mathrm{DFS}]}$$

which explains all the observed kinetic orders of different species.

$$k_{\mathrm{obs}} = \frac{kK_1K_2K_3[\mathrm{DFS}][\mathrm{OH^-}]}{\left[\mathrm{H_3IO_6^{2-}}\right] + K_1[\mathrm{OH^-}]\left[\mathrm{H_3IO_6^{2-}}\right] + K_1K_2[\mathrm{OH^-}] + K_1K_2K_3[\mathrm{OH^-}][\mathrm{DFS}]} \tag{5}$$

The rate law (5) can be rearranged into the following form, which is suitable for verification:

$$\frac{1}{k_{\mathrm{obs}}} = \frac{\left[\mathrm{H_3IO_6^{2-}}\right]}{kK_1K_2K_3[\mathrm{OH^-}][\mathrm{DFS}]} + \frac{\left[\mathrm{H_3IO_6^{2-}}\right]}{kK_2K_3[\mathrm{DFS}]} + \frac{1}{kK_3[\mathrm{DFS}]} + \frac{1}{k} \tag{6}$$

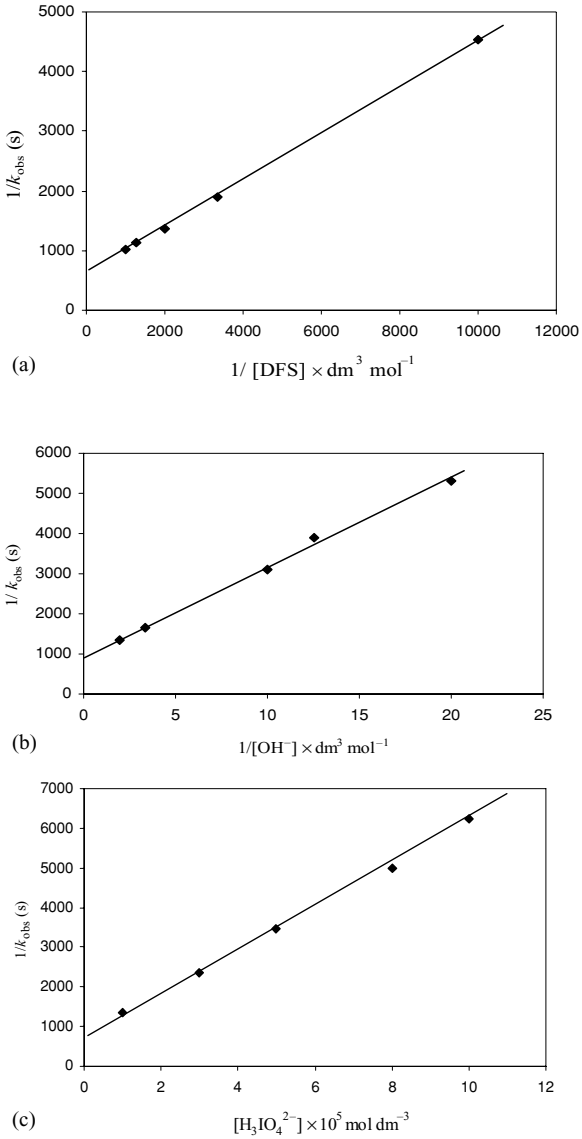


Figure 3 Verification of rate law (5) in the form of (6) for the oxidation of DFS by diperiodatoargentate(III). (a) $1/k_{obs}$ versus 1/[DFS], (b)$1/k_{obs}$ versus 1/[OH^-], and (c) $1/k_{obs}$ versus $[H_3IO_6]^{2-}$.

According to Eq. (6), other conditions being constant, the plots of $1/k_{obs}$ versus $[H_3IO_6^{2-}]$, 1/[OH^-], and 1/[DFS] were linear as shown in Fig. 3. From the intercepts and slopes of such plots, the reaction constants K_1, K_2, K_3, and k at room temperature were calculated as 0.465 dm^3 mol^{-1}, 2.65×10^{-5} mol dm^{-3}, 4.42×10^3 dm^3 mol^{-1}, and 1.65×10^{-3} s^{-1}, respectively. The values of K_1 and K_2 obtained are also in agreement with the values published in the earlier literature [25]. These constants were used to calculate the rate constants and compared with the experimental k_{obs} values and found to be in a reasonable agreement with each other, which fortifies Scheme 1. The equilibrium constant K_1 is far greater than K_2. This may be attributed to the greater tendency of DPA to undergo deprotonation compared to the formation of hydrolyzed species in alkaline medium.

The thermodynamic quantities for the different equilibrium steps, shown in Scheme 1, can be evaluated as follows: The DFS, $H_3IO_6^{2-}$, and hydroxide ion concentrations as given in Table I were varied at 293, 298, 303, and 313 K. The plots of $1/k_{obs}$ versus 1/[DFS], $1/k_{obs}$ versus $[H_3IO_6]^{2-}$, and $1/k_{obs}$ versus 1/[OH^-] should be linear as shown in Fig. 3. From the slopes and intercepts, the values of K_1 (dm^3 mol^{-1}) were calculated as 0.54, 0.47, 0.34, and 0.17, respectively. In the same manner, $K_2 \times 10^4$ (mol dm^{-3}) values were calculated as 0.15, 0.26, 0.71, and 2.90, and $K_3 \times 10^{-3}$ (dm^3 mol^{-1}) values were calculated as 6.28, 2.21×10^{-3} dm^3 mol^{-1}, and 0.71, respectively, at different temperatures. A van't Hoff's plot was drawn for the variation of K_1 with temperature (i.e., log K_1 vs. $1/T$), and the values of the enthalpy of reaction ΔH, entropy of reaction ΔS, and free energy of reaction ΔG were calculated as -45.0 kJ mol^{-1}, -158 J K^{-1} mol^{-1}, and 1.90 kJ mol^{-1}, respectively. In the same manner, thermodynamic quantities for K_2 were calculated as 116 kJ mol^{-1}, 302 J K^{-1} mol^{-1}, and 26.1 kJ mol^{-1} and thermodynamic quantities for K_3 were calculated as -85.5 kJ mol^{-1}, -218 J K^{-1} mol^{-1}, and -20.8 kJ mol^{-1}, respectively. A comparison of the thermodynamic quantity obtained from K_2 values with those obtained for the slow step of the reaction shows that these values mainly refer to the rate-limiting step, supporting the fact that the reaction before the rate-determining step is fairly slow and involves high activation energy [26]. The values of $\Delta S^{\neq}$ and $\Delta H^{\neq}$ were both favorable for electron transfer processes. The favorable enthalpy was due to release of energy on solution changes in the transition state. The high negative value of $\Delta S^{\neq}$ (-146.1 J K^{-1} mol^{-1}) suggests that the intermediate complex is more ordered than the reactants [27]. The observed modest enthalpy of activation and a higher rate constant for the slow step indicate that the oxidation presumably occurs via an inner-sphere mechanism. This conclusion is supported by earlier observations [28,29]. The negligible effect of ionic strength and dielectric constant on the rate explains qualitatively the reaction between negatively charged ion and a neutral molecule [30], as shown in Scheme 1.

DETERMINATION OF DICLOFENAC SODIUM BY KINETIC METHODS

The initial rate, rate constant, constant concentration, and constant time method were used for determining

Table II Determination of Diclofenac Sodium by Different Kinetic Methods at 25°C, $I = 0.6$ mol dm^{-3}

[DFS] $\times 10^4$ (mol dm^{-3})	Fixed-Time Method ($t = 120$ s) Absorbance	Fixed Concentration Method (Absorbance = 0.54) $1/t$ (s)	Rate-Constant Method $k_{obs} \times 10^4$ (s^{-1})
0.50	0.668	0.048	1.30
0.80	0.660	0.054	1.60
1.00	0.658	0.063	2.10
3.00	0.625	0.201	4.64
5.00	0.602	0.313	6.97
8.00	0.568	0.417	9.66
10.0	0.552	0.516	11.6
15.0	0.499	0.714	16.5
20.0	0.452	0.833	21.0
30.0	0.448	1.012	28.7
40.0	0.428	1.080	31.6
50.0	0.415	1.120	33.5

diclofenac sodium, and the best method was chosen based on applicability, the slope of the calibration graph, the intercept, and the correlation coefficient (r).

Initial Rate Method

In this method, graphs of the rate (at the beginning of the reaction) versus the diclofenac sodium concentration were not easy to obtain because the reaction was fast. Thus, the tangents to the curves at zero were not easy to draw. This method was therefore abandoned.

Fixed Concentration Method

A preselected value of the absorbance was fixed, and the time was measured for different diclofenac sodium concentrations (Table II). The reciprocal of time ($1/t$) versus the initial concentration of diclofenac sodium was plotted, which could be used as a calibration graph and the following equation was obtained:

$$1/t = 0.0371 + 464.48\,[\text{DFS}](r = 0.9907)$$

The range of the diclofenac sodium concentration giving the most acceptable calibration graph with the above-mentioned equation was very limited, 5.0×10^{-5} to 1.5×10^{-3} mol dm^{-3} (i.e., 14.80–444.22 μg/cm^3), which could be a disadvantage.

Fixed-Time Method

A preselected time was fixed (120 s), and the absorbance was measured for different concentrations of diclofenac sodium (Table II). A plot of the absorbance versus the initial concentration of diclofenac sodium was drawn, which is linear and can be used as a calibration graph and the flowing equation is obtained:

$$\text{Absorbance} = 0.664 - 109.51[\text{DFS}](r = 0.9914)$$

The range of the diclofenac sodium concentrations giving the acceptable calibration graph with the above-mentioned equation was limited, 5.0×10^{-5} to 2.0×10^{-3} mol dm^{-3} (i.e., 14.80–590 μg/cm^3), which could be a disadvantage.

Rate Constant Method

Pseudo-first-order rate constants were calculated for diclofenac sodium concentrations in the range from 5.0×10^{-5} to 5.0×10^{-3} mol dm^{-3} and are presented in Table II. A plot of K_{obs} versus [DFS] was drawn, which is used as a calibration graph as shown in Fig. 4, and the following equation was obtained:

$$k_{obs} = 0.0002 + 0.9323\,[\text{DFS}](r = 0.9937)$$

The range of diclofenac sodium concentrations giving the most acceptable calibration graph with the above-mentioned equation was 5.0×10^{-5} to 3.0×10^{-3} mol dm^{-3} (i.e., 14.80–888.44 μg/cm^3).

Recommended Method

The above-mentioned kinetic procedure was applied for a series of standard solutions of DFS (Table II). The best correlation coefficient and high concentration range of determination were obtained for the rate constant method compared with the other kinetic methods.

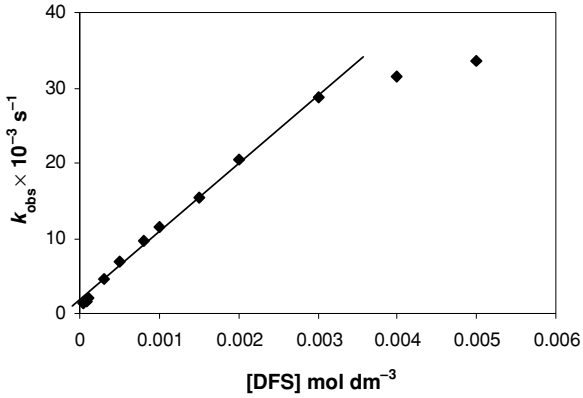


Figure 4 Plot of k_{obs} versus [DFS] for diclofenac sodium analysis by a kinetic method (the rate constant method); conditions as mentioned in Table III.

Hence, the rate-constant method was found to be more applicable.

Application of the Method

The applicability of the rate constant method was examined as an assay of DFS in blood and urine samples. The results of urine and blood samples are given in Table III and are compared with those of the official method. This kinetic method has shown better recovery than the reported method [8]. The performance of the proposed method was judged by calculating the recovery percentage from five replicate measurements (Table III). The recovery percentage from five replicate measurements was found to be more than 98%. Analytical application of the proposed kinetic method is for the determination of diclofenac sodium in urine and blood samples. This aspect of the kinetic method of determination is of major interest in analytical pharmacy, since it offers a distinct possibility for the assay of a particular component in blood and urine.

Assay Procedure for Drug in Urine. A known amount of DFS was added to 5 mL of urine sample. To this was added 0.5 g of lead nitrate to precipitate the chlorides present. The solution was filtered, and excess lead present in the filtrate was removed by adding potassium sulfate. The solution was again filtered. A suitable amount of an aliquot was analyzed for the quantification of DFS, as described for the pure drug.

Assay Procedure for Drug in Blood. One milliliter of blood was spiked with a known amount of DFS before the addition of sodium citrate. The citrated blood was deprotonated with trichloroacetic acid and filtered. The filtrate was diluted with distilled water to 100 mL in a calibrated flask. An appropriate amount of an aliquot was taken, neutralized with dilute sodium hydroxide solution, and analyzed as described for the pure drug.

CONCLUSION

Among the various species of Ag(III) in alkaline medium, monoperiodatoargantate(III) was considered to be the active species for the title reaction. Thermodynamic quantities involved in the mechanism were evaluated, and activation parameters with respect to slow step of the reaction were computed. From an analytical point of view, it is concluded that the described procedure allows for the determination of diclofenac sodium in pure and pharmaceutical dosage forms. Unlike the spectrofluorometer, as well as gas chromatographic and HPLC procedures, the instrument is simple and inexpensive. Its importance lies

Table III Analysis of Diclofenac Sodium in Blood and Urine Sample

		Proposed Method		Potentiometric Method [8]	
Sample	DFS Spiked (μg/mL)	DFS Found[a] (μg/mL)	Recovery ± RSD%	DFS Found[a] (μg/mL)	Recovery ± RSD%
Blood 1	5.0	4.95	99.01 ± 0.24	4.88	97.6 ± 0.25
Blood 2	10.0	9.82	98.16 ± 1.23	9.61	96.1 ± 1.26
Blood 3	15.0	14.74	98.25 ± 0.82	14.7	97.6 ± 0.82
Blood 4	20.0	19.68	98.43 ± 1.52	19.5	97.6 ± 1.61
Urine 1	5.0	4.98	99.66 ± 1.69	4.80	96.0 ± 1.754
Urine 2	10.0	9.81	98.07 ± 0.57	9.85	97.5 ± 0.74
Urine 3	15.0	14.8	98.73 ± 2.65	14.4	96.0 ± 2.72
Urine 4	20.0	19.7	98.67 ± 0.28	19.7	98.5 ± 0.36

Rate constant method conditions as given in Table II.

[a] Average of five determinations.

in the chemical reaction upon which the procedure is based, rather than sophistication of the instrument. This aspect of the kinetic method of determination is of major interest in analytical pharmacy.

NOMENCLATURE AND ABBREVIATIONS

D	Dielectric constant of the medium
I	Ionic strength of the medium
K_1 and K_2	Equilibrium constants
k	Rate constant with respect to slow step of the mechanism
k_{obs}	Observed rate constant
ε	Molar absorption coefficient
ΔG	Change in free energy of reaction
ΔH	Change in enthalpy of reaction
ΔS	Change in entropy of reaction
$\Delta G^{\#}$	Free energy of activation
$\Delta H^{\#}$	Enthalpy of activation
$\Delta S^{\#}$	Entropy of activation
DPA	Diperiodatoargentate(III)
DFS	Diclofenac sodium
FT-IR	Fourier transform infrared spectra
^{1}H NMR	Proton nuclear magnetic resonance
LC–ESI–MS	Liquid chromatography electrospray ionization tandem mass spectrometry
TLC	Thin-layer chromatography
UV	Ultraviolet spectra

One of the authors (P. N. Naik) thanks UGC, New Delhi, for the award of a Research Fellowship in Science for Meritorious Students.

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