Ruthenium Catalyzed Oxidative Conversion of Isatins to Anthranilic Acids: Mechanistic Study

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*Oxidation of isatins (isatin, 5-methylisatin, 5-bromoisatin, and 5-nitroisatin) to their corresponding anthranilic acids was performed with sodium N-bromo-p-toluenesulfonamide or bromamine-T (BAT) as an oxidant and ruthenium trichloride (Ru(III)) as a catalyst in HCl medium at $30 \pm 0.1°C$. The four reactions follow identical kinetics with a first-order dependence each on $[BAT]_o$ and $[Ru(III)]$, zero-order on $[Isatin]_o$, and inverse fractional-order on $[H^+]$. Activation parameters have been deduced for the composite reaction. The rates satisfactorily correlate with the Hammett σ relationship and the reaction constant ρ is -0.36 signifies that the electron donating groups accelerate the reaction while the electron withdrawing groups retard the rate. An isokinetic relationship is observed with $\beta = 360$ K, indicating that enthalpy factors control the reaction rate. Oxidation products of isatins were identified as their corresponding anthranilic acids by GC-MS analysis and the yields were found to be >90%. Under similar experimental conditions, the kinetics of Ru(III)-catalyzed oxidation of isatins with BAT has been compared with that of uncatalyzed reactions, revealing that the catalyzed reactions are three to fourfold faster. The observed results have been explained by a plausible mechanism and the related rate law has been deduced. The method adopted for the oxidation of isatins to anthranilic acids in the present work offers several advantages and can be scaled up to industrial operation. © 2008 American Institute of Chemical Engineers AIChE J, 54: 756–765, 2008
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Introduction

Isatins (1H-indole-2, 3-diones) which occur in mammalian tissue and function as a modulator of biochemical processes have been the subject of interest.[1] Isatins, associated with amino heterocycles, have been used as pigments and dyes, since they are well-known color reagents for amino acids. In dyeing industry, isatin is used largely in the manufacture of vat dyes and also as analytical reagent for the estimation of a number of industrially important compounds. The synthetic versatility of isatin has been evolved from the interest in the biological and pharmaceutical properties of its derivatives. Oxidation of isatins to anthranilic acids is an important synthetic route in organic synthesis. The economic importance of anthranilates resides in their well established anti-inflammatory activity. Thus, many derivatives have bee synthesized with the objective of discovering new pharmacological agents such as immunosuppressant, fungicides, and agents for the prevention of nerve cell damage. Anthranilic acid has also been used in the syntheses of poly cyclic aromatic hydrocarbons.[1] Since anthranilic acids are synthetically versatile substrates, syntheses of anthranilic acid are an important subject.

There are several reports available in the literature about the syntheses of anthranilic acids including isatins.[1] Preliminary experiments revealed that bromamine-T (BAT) is an excellent oxidant which allows controlled conversion of isatins to anthranilic acids in presence of HCl and $RuCl_3$ catalyst. Consequently, optimum conditions for the formation of anthranilic acids were established. The method adopted for the oxidative conversion of isatins to anthranilic acid offers several advantages mainly high yield of products (>90%), short reaction times, ease of isolation of products, cost effective, and very simple and smooth process. Therefore, one can adopt the present method for the oxidative conversion of isatins to anthranilic acid and also can be scaled up to industrial operation.

Although, the kinetics of oxidation of isatins by chloramine-B in alkaline medium has been reported from our laboratory,[2] there seems to be no report on similar studies in acidic medium, and also no attention has been paid to the role of transition metal ions in the oxidation of these substrates. Hence, the need for the title reaction.

The diverse nature of the chemistry of aromatic sulfonyl haloamines is due to their ability to furnish cations, hypohalite species, and N-anions, which can act both as nucleophiles and electrophiles.[3–5] The prominent member of this group, chloramine-T (CAT) is a well-known analytical reagent and the mechanistic aspects of many of its reactions have been well documented.[6–8] The bromine analogue of CAT, sodium N-bromo-p-toluenesulfonamide or BAT, is a better oxidizing agent than CAT, and however meager information exists in the literature[7,8] on BAT.

The catalysis by transition metal ions in redox reactions is of immense interest[9] and it plays an important role in understanding the mechanism of redox reactions. Their oxidizing and catalytic properties are due to the existence of variable oxidation states, as a consequence of partly filled d or f orbitals. Their ability to form both σ and π bonds with other moieties or ligands is one of the chief factors for imparting catalytic properties to transition metals as well as their complexes. Most of the d-block elements show characteristic interligand migration reactions and such a process forms one of the most important types of reactions in homogeneous catalysis. Ruthenium(III) chloride (Ru(III)) has been widely used as a homogeneous catalyst in various redox reactions.[10] The mechanism of catalysis is quite complicated due to the formation of different intermediate complexes, free radicals, and different oxidizing states of Ru(III). Although many complexes of Ru(III) with various organic and inorganic substances have been reported,[10–14] a literature survey shows that there are no reports on the mechanistic investigations of isatins involving Ru(III) as a catalyst. In the background of the available information, it was intended to investigate the Ru(III) catalyzed oxidation-kinetics of isatin and substituted isatins (5-methylisatin, 5-bromoisatin, and 5-nitroisatin) by BAT in HCl medium in order to understand the mechanistic nature of Ru(III)-isatin-BAT reaction, relative rates, and structure reactivity correlations.

Experimental

Materials

BAT was obtained[15] by the partial debromination of dibromamine-T (DBT) by 4 mol dm^{-3} NaOH and its purity was checked iodometrically. An aqueous solution of the compound was prepared, standardized by iodometric procedure, and preserved in brown bottles to prevent its photochemical degradation.

Isatins (Lancaster, England) were of acceptable grades of purity (isatin 98.9%, 5-methylisatin 98%, 5-bromoisatin 98 %, and 5-nitroisatin 98 %) and were used without further purification. Aqueous solutions of isatins were prepared and employed. A stock solution of $RuCl_3$ (E-Merck) was prepared by dissolving the sample in 0.1 mol dm^{-3} HCl. Mercury was added to Ru(III) solution to reduce any Ru(IV) formed during the preparation of Ru(III) stock solution; the resulting solution was kept overnight. The Ru(III) concentration was assayed[16] by EDTA titration. Allowance was made for the amount of HCl present in catalyst solution, while preparing solution for kinetic runs. Heavy water (99.4% purity) employed for solvent isotope studies was obtained from Bhabha Atomic Research Centre, Mumbai, India. Solvent polarity or dielectric constant (D) of the medium was altered by the addition of methanol in varying proportions (v/v). All other chemicals used were of Analar grade and doubly distilled water was used throughout the work.

Kinetic measurements

Kinetic experiments were performed under pseudo first-order conditions of $[Isatin]_o >> [BAT]_o$ and the procedure followed is similar to the earlier reports.[8] The reaction was carried out in glass stoppered Pyrex boiling tubes whose outer surface was coated black to eliminate any photochemical effects. Solutions containing appropriate amounts of isatin, HCl, Ru(III), and water (to keep the total volume constant for all runs), were placed in the tube and thermostatted at (30 ± 0.1)°C. A measured amount of BAT solution, also thermostatted at the same temperature, was rapidly added to the mixture. The progress of the reaction was monitored by withdrawing
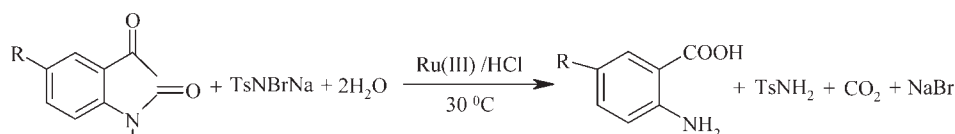
Isatin	Corresponding Anthranilic Acid (mg)	Weight of Zinc Anthranilate	% Yield of Zinc anthranilate
Isatin	Anthranilic acid	210 (231)	90.9%
5-Methylisatin	5-Methylanthranilic acid	245 (264)	92.8 %
5-Bromoisatin	5-Bromoanthranilic acid	192 (210)	91.4%
5-Nitroisatin	5-Nitroanthranilic acid	176 (192)	91.6%

Values in parentheses refer to expected weights

known aliquots (5 ml each) from the reaction mixtures at regular time intervals and determining the unreacted BAT iodometrically. The course of the reaction was followed up to two half-lives. Pseudo first-order rate constants, k', calculated from log [BAT] vs. time plots were reproducible within ± 3–5%. Regression coefficient (r) of the experimental data was performed with an f_x - 100 W scientific calculator.

Product analysis

The reactions were allowed to progress for 2–3 h with constant stirring at 303 K. After completion of the reaction, the reaction products were neutralized by alkali and extracted with ethyl acetate. The spot test and chromatographic analysis of the products shows the formation of corresponding anthranilic acids as the oxidation products of isatins and p-toluenesulfonamide as the reduction product of BAT. The reaction products were separated by column chromatography on silica gel (60–200 mesh) using dichloromethane as eluting agent. Further, the products were identified as follows:

Anthranilic acids: The oxidation products of isatins were found to be their corresponding anthranilic acids. The oxidation product of isatin was subjected to GC-MS analysis which showed a molecular ion peak of 137 amu confirming anthranilic acid. The GC-MS data was obtained on a 17A Shimadzu gas chromatograph with a QP-5050A Shimadzu mass spectrometer. Further, the procedure for the estimation of anthranilic acid was as follows: anthranilate was precipitated as its zinc salt.[16] To the reaction mixture calculated volume of 1 mol dm^{-3} HCl was added followed by 10 ml of buffer (pH 5) and 10 ml of 1% zinc sulfate. The precipitate formed was filtered, dried at 105–110°C, and weighed. Recovery of $(C_7H_6O_2N)_2$ Zn was above 90%. Estimation of anthranilic acid as zinc anthranilate in some typical experiments and their percent of yield are presented in Table 1. It was also noticed that there was no further oxidation of these

Stoichiometry

Reaction mixtures containing varying ratios of BAT to isatins in presence of 1.0×10^{-3} mol dm^{-3} HCl and 1.0×10^{-6} mol dm^{-3} Ru(III) were equilibrated at 303 K for 24 h. Iodometric determination of unreacted oxidant in the reaction mixture showed that one mole of isatin consumed one mole of BAT confirming the following stoichiometry.

$$(1)$$

here, Ts = p-CH$_3$C$_6$H$_4$SO$_2$ and R = H for isatin, CH$_3$ for 5-methylisatin, Br for 5-bromoisatin and NO$_2$ for 5-nitroisatin.

products under prevailing kinetic conditions. The liberated CO_2 was identified by lime water test.

p-toluenesulfonamide (PTS): The reduction product of BAT, p-toluenesulfonamide (TsNH$_2$), was detected[17] by paper chromatography using benzyl alcohol saturated with water as the solvent system and 0.5% vanillin in 1% HCl and EtOH as the spray reagent (R_f = 0.905). The molecular ion peak of 171 amu clearly confirms p-toluenesulfonamide.

Results and Discussion
Kinetic orders

The kinetics of oxidation of Isatin, 5-methylisatin, 5-bromoisatin, and 5-nitroisatin by BAT were investigated at several initial concentrations of the reactants in presence of HCl and Ru(III) chloride catalyst at 303 K. The same oxidation behavior was observed for all the four isatins studied in the present case.

Effect of varying reactant concentrations on the rate

The reaction performed in the presence of Ru(III) catalyst and HCl, under pseudo first-order conditions of [Isatin]$_o$ >> [BAT]$_o$, gave linear plots of log [BAT] vs. time (r > 0.9990). The linearity of these plots, together with the constancy of the slopes for various [BAT]$_o$, indicating a first-order dependence of the reaction rate on [BAT]$_o$. The pseudo first-order rate constants (k') obtained are listed in Table 2. Under the similar experimental conditions, values of k' did not alter with change in [Isatin]$_o$ (Table 2), confirming the zero-order dependence of rate on [Isatin]$_o$.

Table 2. Effect of Varying BAT and Isatin Concentrations on the Rate of Reaction

10^3 [BAT]$_o$ (mol dm^{-3})	10^2 [Isatin]$_o$ (mol dm^{-3})	10^4 k' (s^{-1})			
		5-Methyl-isatin	Isatin	5-Bromo-isatin	5-Nitro-isatin
0.5	2.0	9.98	8.25	6.11	4.43
1.0	2.0	10.1	8.30	6.13	4.41
2.0	2.0	10.0	8.20	6.10	4.40
4.0	2.0	10.2	8.10	6.00	4.35
8.0	2.0	9.89	8.18	5.99	4.38
2.0	0.5	10.0	8.16	6.20	4.44
2.0	1.0	9.95	8.00	6.21	4.46
2.0	2.0	10.0	8.20	6.10	4.40
2.0	4.0	9.98	8.36	6.21	4.50
2.0	8.0	10.0	8.31	6.19	4.49

[HCl] = 1.0×10^{-3} mol dm^{-3}; [Ru(III)] = 1.0×10^{-6} mol dm^{-3}; T = 303 K.

Effect of varying HCl and Ru(III) concentrations on the rate

The rate decreased with increase in [HCl] (Table 3) and plots of log k' vs. log [HCl] were linear (Figure 1: $r >$ 0.9906) with negative fractional slopes, showing an inverse fractional-order dependence of rate on [HCl]. The reaction rate increased with increase in [Ru(III)] (Table 3) and plots of log k' vs. log [Ru(III)] were linear (Figure 2: $r >$ 0.9968) with unit slopes, indicating a first-order dependence of rate on [Ru(III)].

Effect of varying H$^+$ and halide ions on the rate

At constant [H$^+$] = 0.001 mol dm^{-3} maintained with HCl, addition of NaCl (2.0×10^{-3}–8.0×10^{-3} mol dm^{-3}) did not affect the rate of the reaction. Hence, the dependence of rate on [HCl] confirms the effect of [H$^+$] only. Similarly, addition of Br$^-$ ions in the form of NaBr (1.0×10^{-3}–5.0×10^{-3} mol dm^{-3}) had no effect on the rate. These results indicate that the halide ions play no role in the reaction.

Effect of solvent isotope on the rate

Studies of the reaction rate in D$_2$O medium for isatin and 5-bromoisatin revealed that while k'(H$_2$O) = 8.20×10^{-4} s^{-1} and 6.10×10^{-4} s^{-1} and k'(D$_2$O) = 6.76×10^{-4} s^{-1} and 4.92×10^{-4} s^{-1}, respectively. The solvent isotope effect k'(H$_2$O)/k'(D$_2$O) = 1.21 and 1.24 for the two isatins.

Effect of varying p-toluenesulfonamide (PTS) on the rate

Addition of p-toluenesulfonamide, a reduction product of BAT, (1.0×10^{-3} – 4.0×10^{-3} mol dm^{-3}), to the reaction mixture did not affect the rate significantly. This indicates that PTS is not involved in any step prior to the rate-limiting step in the scheme proposed.

Effect of varying ionic strength of the medium on the rate

The effect of ionic strength of the medium was carried out in the range of 0.1–0.5 mol dm^{-3} NaClO$_4$, with all other conditions held constant. It was found that ionic strength had negligible effect on the reaction rate indicating that nonionic species are involved in the rate-limiting step. Subsequently, the ionic strength of the reaction mixture was not fixed constant for kinetic runs.

Effect of varying dielectric constant of the medium on the rate

The dielectric constant (D) of the medium was varied by adding methanol (0–30%, v/v) to the reaction mixture. The rate decreases with increase in methanol content (Table 4) and plots of log k' vs. 1/D were linear (Figure 3: $r >$ 0.9906) with negative slopes. Blank experiments with methanol indicated that the oxidation of methanol with BAT was

Table 3. Effect of Varying HCl and Ru(III) Concentrations on the Rate of Reaction

10^3 [HCl] (mol dm^{-3})	10^6 [Ru(III)] (mol dm^{-3})	10^4 k' (s^{-1})			
		5-Methyl-isatin	Isatin	5-Bromo-isatin	5-Nitro-isatin
0.2	1.0	14.2	12.4	10.0	6.80
0.5	1.0	11.2	9.56	8.20	5.20
1.0	1.0	10.0	8.20	6.10	4.40
2.0	1.0	8.01	6.62	5.12	3.21
4.0	1.0	6.62	5.21	4.16	2.30
1.0	0.2	2.30	1.80	1.20	0.91
1.0	0.5	4.90	4.10	3.00	2.30
1.0	1.0	10.0	8.20	6.10	4.40
1.0	2.0	20.1	16.5	12.0	9.00
1.0	4.0	39.2	32.4	24.1	18.1

[BAT]$_o$ = 2.0×10^{-3} mol dm^{-3}; [Isatin]$_o$ = 2.0×10^{-2} mol dm^{-3}; T = 303 K.
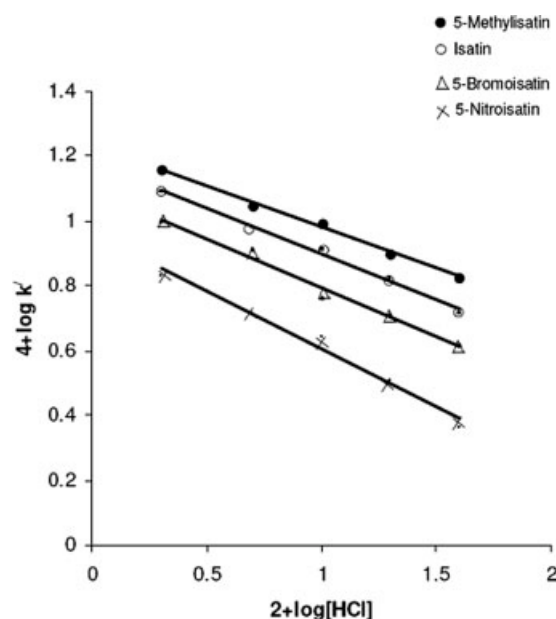
Figure 1. Plot of log k' vs. log[HCl].

Figure 2. Plot of log k' vs. log[Ru(III)].

negligible under the experimental conditions employed. Values of dielectric constant of methanol-water mixture reported in the literature[18] were employed.

Effect of varying temperature on the rate

The reaction was studied at different temperatures (293–313 K), keeping other experimental conditions constant. From the linear Arrhenius plots of log k' vs. $1/T$ ($r >$ 0.9985), values of activation parameters (E_a, $\Delta H^{\neq}$, $\Delta S^{\neq}$, and $\Delta G^{\neq}$) for the composite reaction were evaluated. These data are presented in Table 5.

Reaction mechanism

Bishop and Jennings,[3] Pryde and Soper,[19] Morris et al.,[20] and Higuchi et al.[21] have shown the existence of similar equilibria in acidic solutions of N-metallo-N-arylhalosulfonamides. Bromamine-T (TsNBrNa) like its chlorine analogue, BAT, acts as an oxidizing agent in both acidic and alkaline solutions. In general, BAT undergoes a two-electron reduction in its reactions. The oxidation potential of BAT/TsNH$_2$ is pH dependent and decreases with increase in the pH of the solution, having values of 1.14 V at pH 0.65 and 0.50 V at pH 12. Depending on the pH, BAT exhibits the following equilibria in aqueous solutions[19–21] and the possible oxidiz-
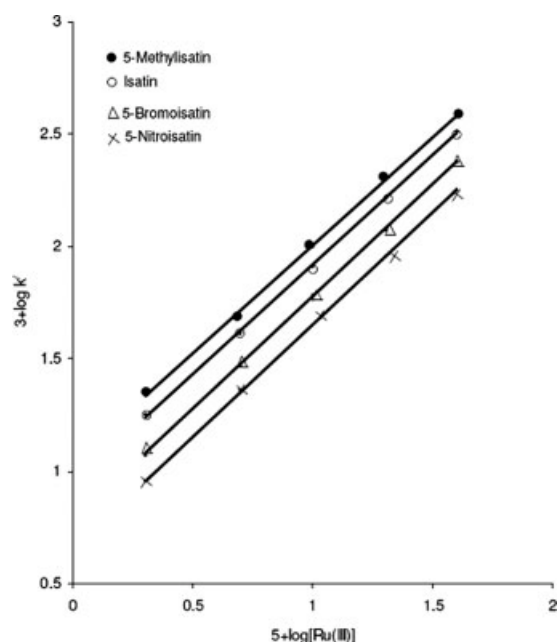
ing species in acidified BAT solution are TsNHBr, TsNBr$_2$, HOBr and possibly H$_2$OBr$^+$. Dibromamine-T (TsNBr$_2$) as the oxidizing species has been ruled out based on the fact that the rate is not retarded by the added TsNH$_2$ and also if it is the case the rate law should predict a second-order dependence of the rate on [BAT]$_o$. Both are contrary to experimental observations. If HOBr were to be involved as an active oxidant, a first-order retardation of rate by the added TsNH$_2$ would be expected. Since, no such effect was noticed, the species HOBr was also ruled out. On the basis of the knowledge of equilibrium, disproportionation and hydrolysis constants of reactions, Bishop and Jennings,[3] as a first approximation, have calculated the concentrations of different species in 0.05 mol dm^{-3} CAT solutions at different pH. The acid form of CAT, TsNHCl is found to be the predominant species under acidic conditions. In view of the similarity in properties of CAT and BAT, similar arguments can be employed for BAT solutions, and TsNHBr can be assumed as the oxidizing species under the present experimental conditions.

Further, Narayanan and Rao[22] and Subhashini et al.[23] have reported that monochloramine-T (CAT) can further be protonated as TsNH$_2$Cl$^+$ with a value of 1.0×10^2 dm^3 mol^{-1} at 25°C for the second protonation constant. Hence, it is reason-

Table 4. Effect of Varying Dielectric Constant (D) of the Medium on the Rate of Reaction

% [MeOH] (v/v)	D	$10^4 \; k' \; (s^{-1})$			
		5-Methyl-isatin	Isatin	5-Bromo-isatin	5-Nitro-isatin
0.0	76.73	10.0	8.20	6.10	4.40
10.0	72.37	7.06	6.60	4.00	3.00
20.0	67.48	5.66	4.40	2.90	2.00
30.0	62.71	4.01	3.20	1.70	0.90

[BAT]$_o$ = 2.0×10^{-3} mol dm^{-3}; [Isatin]$_o$ = 2.0×10^{-2} mol dm^{-3}; [HCl] = 1.0×10^{-3} mol dm^{-3}; [Ru(III)] = 1.0×10^{-6} mol dm^{-3}; T = 303 K.
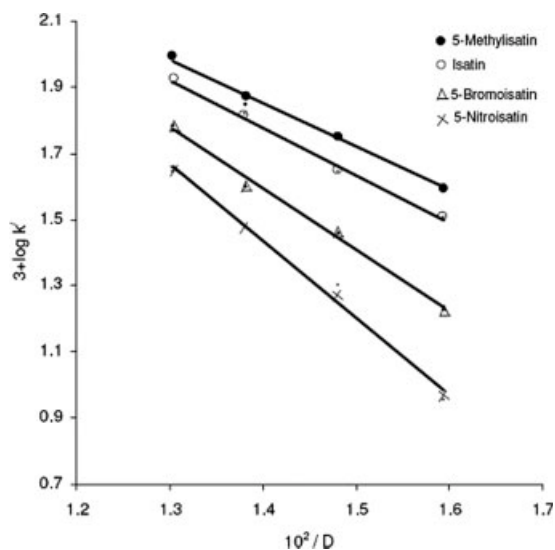
Figure 3. Plot of log k' vs. $1/D$.

able to expect the formation of a similar species of the type $TsNH_2Br^+$ for BAT. In the present work, an inverse dependence of rate on $[H^+]$ suggests that the deprotonation of $TsNH_2Br^+$ results in the formation of $TsNHBr$, which is the likely oxidizing species involved in the oxidation of isatins in acid medium.

Electronic spectral studies of Cady and Connick,[24] and Connick and Fine[25] reveal that species such as $[RuCl_5(H_2O)]^{2-}$, $[RuCl_4(H_2O)_2]^-$, $[RuCl_3(H_2O)_3]$, $[RuCl_2(H_2O)_4]^+$, and $[RuCl(H_2O)_5]^{2+}$ do not exist in an aqueous solution of $RuCl_3$. A study on the oxidation states of ruthenium has shown that Ru(III) exists[26–28] in the acid medium as

$$RuCl_3 \cdot xH_2O + 3HCl \longrightarrow [RuCl_6]^{3-} + xH_2O + 3H^+ \quad (2)$$

$$[RuCl_6]^{3-} + H_2O \rightleftharpoons [RuCl_5(H_2O)]^{2-} Cl^- \quad (3)$$

However, in the present study, addition of Cl^- ion in the form of NaCl at fixed $[H^+]$ had no effect on the rate, indicating that equilibrium (3) does not play a role in the reaction.

Hence, the complex ion $[RuCl_5(H_2O)]^{2-}$ is the most probable reactive catalyst species in the present case. The same complex ion species of Ru(III) catalyst has been postulated as the reactive species in earlier work.[29–32]

Evidence for the formation of complex between oxidant and catalyst

The existence of a complex between Ru(III) and oxidant was performed by UV–visible spectral studies. Absorption maxima in HCl medium appear at 222 nm for BAT, 352 nm for Ru(III), and 340 nm for a mixture of both (Figure 4). A hypsochromic shift of 12 nm i.e., 352–340 nm of Ru(III) suggests that complexation occurs between Ru(III) and BAT.

Further, for a general equilibrium (4)

$$M + n\,S \overset{K}{\rightleftharpoons} (MS_n) \quad (4)$$
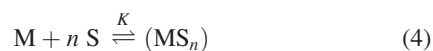
between two metal species, M and MS_n having different extinction coefficients, Ardon[33] has derived the following Eq. 5

$$1/\Delta A = 1/[S]^n \{1/\Delta E[M_{Total}]K\} + 1/\Delta E[M_{Total}] \quad (5)$$

where, K is the formation constant of the complex, $[S]$ is the concentration of BAT, ΔE is the difference in extinction coefficient between two metal species, $[M]_{Total}$ is the total concentration of metal species and ΔA is the absorbance difference of solution containing no S and one that contains a certain concentration of S represented by $[S]$. Equation 5 is valid provided that $[S]$ is so much greater than $[M]_{Total}$ that the amount of S tied up in the complex is negligible or it is subtracted from the initial concentration of S. According to Eq. 5, a plot of $1/\Delta A$ vs. $1/[S]$ or $1/[S]^2$ should be linear with an intercept in case of 1:1 or 1:2 type of complex formation between M and S. The ratio of intercept to slope of this linear plot gives the value of K.

Ruthenium(III) in HCl medium containing BAT showed an absorption peak at 340 nm (λ_{max} for the complex). The complex formation studies were made at this λ_{max} of 340 nm. In a set of experiments, the solutions were prepared by taking different amounts of BAT ($0.5 \times 10^{-3} - 8.0 \times 10^{-3}$ mol dm^{-3}) at constant amounts of $RuCl_3$ (1.0×10^{-6} mol dm^{-3}) and HCl (1.0×10^{-3} mol dm^{-3}) at 303 K. The ab-

Table 5. Temperature Dependence on the Rate of Reaction and Activation Parameters for Ru(III) Catalyzed and Uncatalyzed Oxidation of Isatins by BAT in HCl Medium

Temperature (K)	$10^4\,k'\,(s^{-1})$			
	5-Methyl-isatin	Isatin	5-Bromo-isatin	5-Nitro-isatin
293	5.01* (1.25)[†]	3.16* (0.83)[†]	2.10* (0.57)[†]	1.20* (0.31)[†]
298	7.01 (2.00)	5.61 (1.41)	6.10 (0.89)	4.40 (0.56)
303	10.0 (3.30)	8.20 (2.31)	6.10 (1.51)	4.40 (1.00)
308	14.6 (5.20)	11.6 (3.55)	7.90 (2.00)	6.30 (1.58)
313	19.9 (7.90)	16.3 (5.61)	12.5 (3.90)	10.0 (2.54)
E_a (kJ mol^{-1})	41.4 (72.4)	50.2 (79.5)	58.6 (87.9)	66.9 (96.2)
$\Delta H^{\neq}$ (kJ mol^{-1})	38.5 ± 0.45 (69.4 ± 0.20)	47.6 ± 0.62 (76.6 ± 0.29)	56.0 ± 0.15 (87.9 ± 0.34)	64.4 ± 0.64 (96.3 ± 0.37)
$\Delta G^{\neq}$ (kJ mol^{-1})	92.1 ± 0.38 (94.2 ± 0.84)	92.2 ± 0.92 (95.0 ± 0.55)	93.0 ± 0.62 (96.2 ± 0.98)	93.7 ± 0.44 (98.3 ± 0.58)
$\Delta S^{\neq}/$ (J K^{-1} mol^{-1})	−174 ± 0.10 (−81.2 ± 0.22)	−146 ± 0.35 (−60.1 ± 0.28)	−121 ± 0.75 (−36.6 ± 0.28)	−96.7 ± 0.18 (−16.2 ± 0.36)

Values in parentheses refer to oxidation of isatins in the absence of Ru(III) catalyst.
*$[BAT]_o = 2.0 \times 10^{-3}$ mol dm^{-3}; $[Isatin]_o = 2.0 \times 10^{-2}$ mol dm^{-3}; $[HCl] = 1.0 \times 10^{-3}$ mol dm^{-3}; $[Ru(III)] = 1.0 \times 10^{-6}$ mol dm^{-3}.
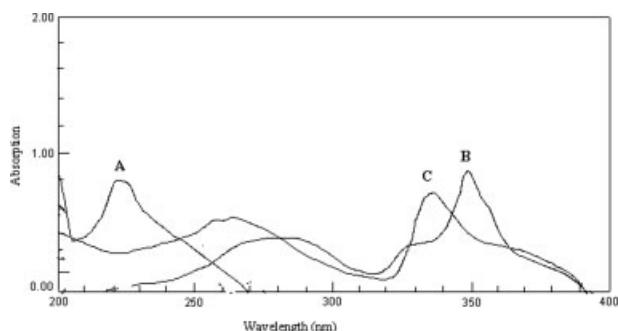[†]Experimental conditions are the same as '*' without Ru(III) catalyst.

Figure 4. UV–vis spectra of (A) BAT, (B) Ru(III), and (C) BAT + Ru(III) in HCl medium.

sorbance of these solutions was measured at 340 nm. The absorbance of the solution in the absence of BAT was also measured at the same wavelength. The difference of these absorbances (with and without BAT) gives the differential absorbance, ΔA. A plot of $1/\Delta A$ vs. $1/[BAT]$ was linear ($r = 0.9890$) with an intercept suggesting the formation of a 1:1 complex between BAT and Ru(III) catalyst. Further, the plot of log ($1/\Delta A$) vs. log ($1/[BAT]$) was also linear ($r = 0.9889$). From the slope and intercept of the plot $1/\Delta A$ vs. $1/[BAT]$, the value of the formation constant, K, of the complex was deduced and found to be 3.06×10^3.

Reaction scheme

On the basis of the preceding discussion, a detailed mechanistic interpretation (Scheme 1) for the Ru(III) catalyzed isatin-BAT reaction in hydrochloric acid medium is proposed to account for the observed kinetics:

In Scheme 1, X and X′ represent the complex intermediate species whose structure are shown in Scheme 2, where a detailed mechanistic interpretation of Ru(III) catalyzed Isatin-BAT reaction in acid medium is depicted. In the rate-limiting step, the oxidizing species, TsNHBr of BAT forms a complex intermediate (X) with the catalyst Ru(III). The reaction of the catalyst-oxidant complex with the isatin yields corresponding anthranilic acids as the final product.

Derivation of rate law

The total effective concentration BAT is $[BAT]_t$, then

$$[BAT]_t = [TsNH_2Br^+] + [TsNHBr] \qquad (6)$$
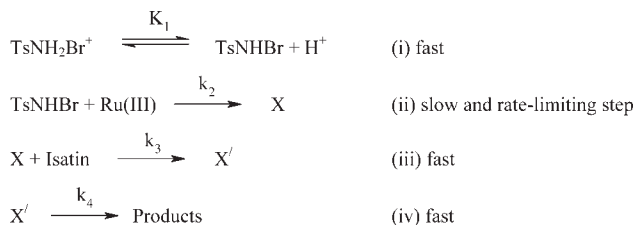
Scheme 1. A probable scheme for Ru(III) catalyzed oxidation of isatins by BAT in acid medium.

By substituting for $[TsNH_2Br^+]$ from equilibrium (i) of Scheme 1 in Eq. 6 and solving for $[TsNHBr]$, one obtains

$$[TsNHBr] = \frac{K_1[BAT]_t}{K_1 + [H^+]} \qquad (7)$$

From rate-limiting step (ii) of Scheme 1, the overall rate is given by

$$\text{Rate} = k_2[TsNHBr]\,[Ru(III)] \qquad (8)$$

Upon substituting for $[TsNHBr]$ from Eq. 7 into the rate Eq. 8, one can obtain the following rate law (9)

$$\text{Rate} = \frac{K_1 k_2 [BAT]_t [Ru(III)]}{K_1 + [H^+]} \qquad (9)$$

Rate law (9) and the mechanism (Scheme 1) are in good agreement with observed experimental results.

Since, rate $= k'\,[BAT]_t$ then the rate law (9) can be transformed into Eqs. 10 and 11

$$k' = \frac{K_1 k_2 [Ru(III)]}{K_1 + [H^+]} \qquad (10)$$

$$\frac{1}{k'} = \frac{[H^+]}{K_1 k_2 [Ru(III)]} + \frac{1}{k_2 [Ru(III)]} \qquad (11)$$

On the basis of Eq. 11, plots of $1/k'$ vs. $[H^+]$ at constant $[BAT]_o$, $[Isatin]_o$, $[Ru(III)]$, and temperature, were found to be linear ($r > 0.9822$). From the values of slope and intercept of such a plot, the formation constant (k_2) and deprotonation constant (K_1) were calculated for each isatin and are tabulated below:

	Isatin	5-Methylisatin	5-Bromoisatin	5-Nitroisatin
$10^4\,k_2$ $(dm^3\,mo^{-1}\,s^{-1})$	1.52	1.25	1.00	0.70
$10^3\,K_1$ $(mol\,dm^{-3})$	2.56	1.60	1.25	1.00

The proposed mechanism and the derived rate law are substantiated by the following experimental facts.

Effect of solvent isotope

The observed solvent isotope effect corroborates the proposed mechanism and the derived rate expression. For a reaction involving a fast equilibrium H^+ or OH^- ion transfer, the rate increases in D_2O, since D_3O^+ and OD^- are stronger acid and a stronger base ($\sim$two to three times greater) respectively, than H_3O^+ and OH^- ions.[34–36] The reverse holds for reactions involving retardation of rate by the H^+ ion. The decrease of reaction rate with D_2O in the present studies and the observed solvent isotope effect is $k'(H_2O)/k'(D_2O) > 1$ conform to the above theory and supports the proposed mechanism. The magnitude of $k'(H_2O)/k'(D_2O) = 1.21$ and 1.24 obtained in the present investiga-
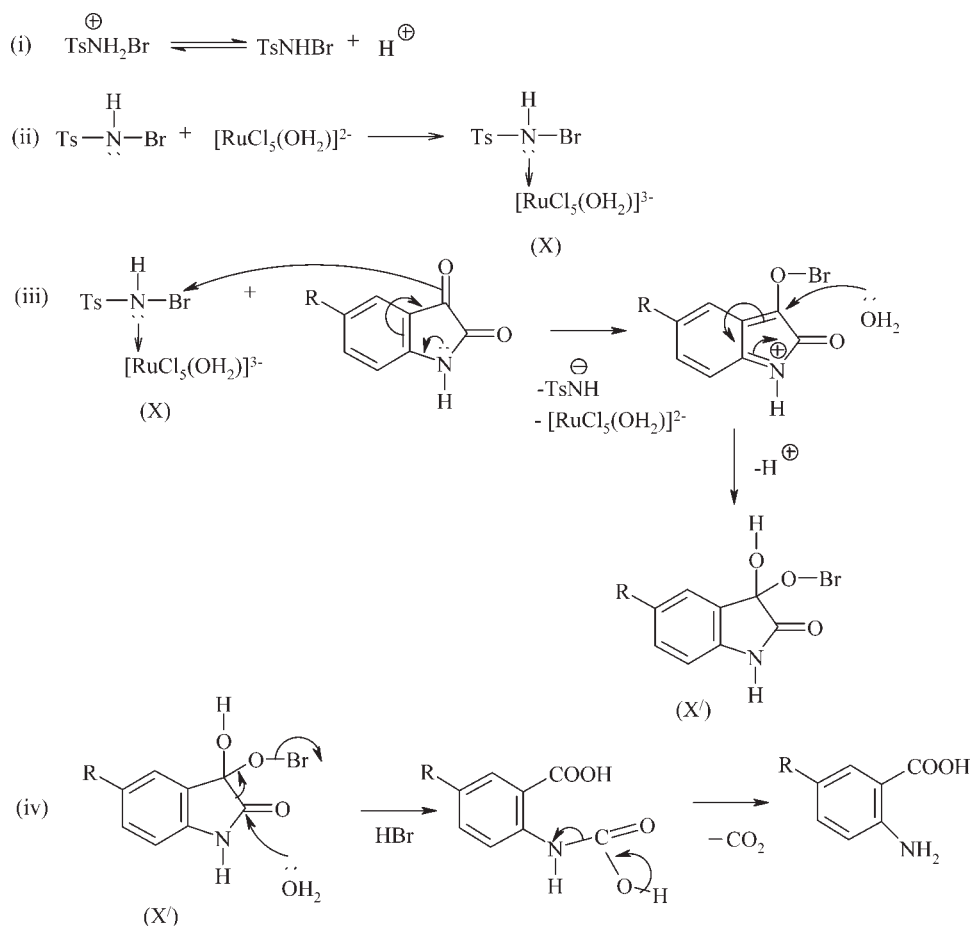
Scheme 2. Ru(III)-catalyzed oxidation of isatins by BAT in acid medium.

tions is the reflection of the inverse fractional-order dependence of rate on $[H^+]$.

Effect of dielectric permittivity

A decrease of reaction rate with a decrease in D of the medium supports the proposed mechanism. Amis and Jaffe[37] have shown that

$$\log k'_D = \log k' + Ze\mu/2.303 \, kTr^2D \qquad (12)$$

where k' is the rate constant in a medium of infinite dielectric constant and k'_D is the rate constant as function of dielectric constant D, Ze is the charge on the ion, μ is the dipole moment of the dipole, k is the Boltzmann constant, T is the absolute temperature and r is the distance of approach between the ion and dipole. Equation 12 predicts a linear relation between $\log k'$ vs. $1/D$. The slope of the line should be negative for a reaction between a negative ion and a dipole or between two dipoles, while a positive slope is obtained for positive ion-dipole reactions. In the present investigations, plots of $\log k'$ vs. $1/D$ were linear with negative slopes, supporting the participation of negative ion and dipole in the rate-limiting step (Scheme 2).

Effect of substituents

Substituent effect was used to probe the reaction mechanism. Structure reactivity relationships[38,39] are ascertained by

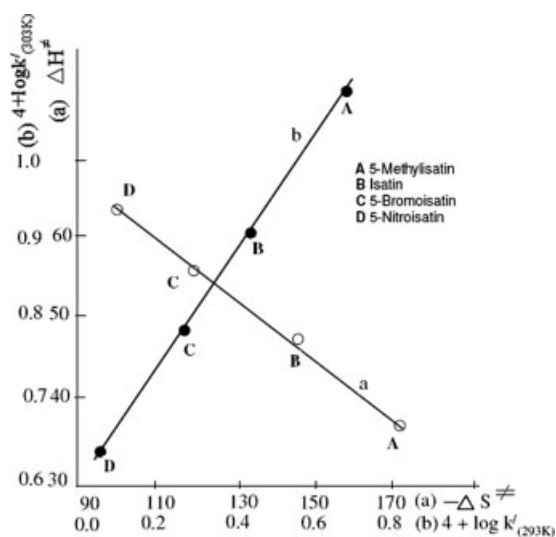**Figure 5. Plots of (a) $\Delta H^{\neq}$ vs. $\Delta S^{\neq}$ (b) $\log k'_{(303 \text{ K})}$ vs. $\log k'_{(293 \text{ K})}$.**

Table 6. Values of Catalytic Constant (K_C) at Different Temperatures and Activation Parameters Calculated Using K_C Values

Temperature (K)	$10^2\, K_C$			
	5-Methyl- isatin	Isatin	5-Bromo- isatin	5-Nitro- isatin
293	3.76	2.33	1.53	0.90
298	5.01	4.20	2.72	1.95
303	6.70	5.90	4.59	3.40
308	9.40	8.05	6.00	4.72
313	12.0	10.7	8.60	7.10
E_a (kJ mol^{-1})	54.4	60.7	70.0.	71.1
$\Delta H^{\neq}$ (kJ mol^{-1})	51.4 ± 0.84	57.7 ± 0.62	64.4 ± 0.38	68.2 ± 0.42
$\Delta G^{\neq}$ (kJ mol^{-1})	61.5 ± 0.20	62.7 ± 0.40	63.6 ± 0.52	64.0 ± 0.82
$\Delta S^{\neq}$ (J K^{-1} mol^{-1})	−32.6 ± 0.56	−16.7 ± 0.18	−5.02 ± 0.25	−1.88 ± 0.90

[BAT]$_o$ = 2.0 × 10^{-3} mol dm^{-3}; [Isatin]$_o$ = 2.0 ×10^{-2} mol dm^{-3}; [HCl] = 1.0 × 10^{-3} mol dm^{-3}.

employing three ortho-substituted isatins and the kinetic observations reveal that electron donating group enhances the reactivity while electron withdrawing groups inhibit the rate. The rate data are correlated with the Hammett plot of log k' vs. σ which is fairly linear (r = 0.9852). From the above plot, the value of the reaction constant ρ is found to be −0.36 which signifies that the electron donating group (CH$_3$) in the benzene ring accelerates the reaction while the electron withdrawing groups (Br and NO$_2$) retard the rate. From an inspection of the rate data, the rate of oxidation of isatins follows the order: 5-methylisatin > isatin > 5-bromoisatin > 5-nitroisatin. The trend may be attributed to the inductive effect of both, the electron donating and electron withdrawing groups in the present study.

Activation parameters in presence of Ru(III)

The date given in Table 5 indicates that the activation energy is highest for the slowest reaction and vice-versa, confirming that the reaction is enthalpy controlled. Further, the values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ can be correlated linearly (Figure 5: r = 0.9961), resulting in an isokinetic relation, which indicates the operation of similar mechanism for the oxidation of all the four isatins by BAT. From the slope, the value of isokinetic temperature (β) is 360 K, which is much higher than the experimental value, 303 K. The genuinity nature of the isokinetic relationship was verified by the Exner criterion[40] by plotting log $k'_{(303\ K)}$ vs. log $k'_{(293\ K)}$ (Figure 5; r = 0.9896). The value of β was calculated from the equation $\beta = T_1\ (1 − q)/(T_1/T_2) − q$ where q is the slope of Exner plot and $T_1 > T_2$. The value of β is 362 K, which is higher than the experimental temperature indicating a common enthalpy-controlled pathway for the reactions. The high negative $\Delta S^{\neq}$ values point towards the formation of a rigid associated transition state with a reduction in the degrees of freedom of molecules for each isatin. Further, the near constancy of $\Delta G^{\#}$ shows the operation of similar mechanisms for the oxidation of these isatins by BAT in acid medium.

Activation parameters in absence of Ru(III)

It was felt reasonable to compare the oxidation of these four isatins towards BAT in the absence of Ru(III) catalyst under identical experimental conditions, in order to evaluate the catalytic efficiency of Ru(III). The reactions were studied at different temperatures (293–313 K) and activation parameters for the uncatalyzed reactions were determined (Table 5).

The rate of oxidation of isatins in the absence of Ru(III) catalyst was also found to be in the order: 5-methylisatin > isatin > 5-bromoisatin > 5-nitroisatin. However, the Ru(III) catalyzed reactions were found to be three to fourfold faster than the uncatalyzed reactions.

Catalytic activity

The general equation relating for uncatalyzed and catalyzed reactions has been derived by Moelwyn and Hughes[41] as

$$k_1 = k_o + K_C[\text{catalyst}]^x \qquad (13)$$

Here k_1 is the observed pseudo first-order rate constant in presence of Ru(III) catalyst, k_o is that for uncatalyzed reaction (in the absence of Ru(III) catalyst), K_C is the catalytic constant, and x is the order of the reaction with respect to Ru(III). In the present investigations, for the standard run the values of x was found to be unity for all the isatins. Then the value of K_C is calculated using the equation:

$$K_C = (k_1 − k_o)/[\text{Ru(III)}]^x \qquad (14)$$

The values of K_C were evaluated for each isatin at various temperatures and found to depend on temperature. Further, plots of log K_C vs. $1/T$ were found to be linear ($r > 0.9916$) and the values of activation parameters with respect to catalyst for each isatin were computed (Table 6).

Conclusions

Ru(III) catalyzed oxidation of isatins to their corresponding anthranilic acids was performed efficiently with BAT in acid medium at 303 K. All the four reactions followed identical kinetics with a first-order dependence on [CAB]$_o$, zero-order on [Isatin]$_o$, and a negative fractional-order dependence on [H$^+$]. Activation parameters and isokinetic temperature were deduced. Relative reactivity of these isatins follows the order: 5-methylisatin > isatin > 5-bromoisatin > 5-nitroisatin and the Hammett relationship is observed for the reaction with ρ = −0.36, showing that the electron donating groups enhances the rate and the electron withdrawing groups retard the rate. Ru(III)-catalyzed reactions showed that the rates are three to fourfold faster than the uncatalyzed reactions. The observed results have been explained by a plausible mechanism and the related rate law has been deduced. The method adopted for the oxidation of isatins to anthranilic acids in the

present work offers several advantages and can be scaled up to industrial operation.

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