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Entropy controlled reaction of piperidine with isatin derivatives in 80% aqueous methanol

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Abstract

The reactions of 5- and 7-substituted isatin derivatives (H, Me, Cl, Br) with piperidine in 80% aqueous methanol gave the corresponding 1-(2'-amino-5'- or 3'- substituted phenyl)-2-(piperidin-1-yl) ethane-1,2-dione derivatives. The reaction is proceeded through nucleophilic attack on C-2 followed by ring opening process. The reaction showed a second order and the isokinetic temperature is 169 K indicating that the reaction is entropy controlled. The constant $\Delta G^{\#}$ value, the linear plot of $\Delta H^{\#}$ versus $\Delta S^{\#}$, plot of log k_N values at high temperature versus those at low temperatures indicated that a unified mechanism of the reactions for all substituents. The σ°-Taft's constants are linearly correlated with log k_N values and the ρ values are (2.01–1.86) pointing out that inductive effect of substituent is predominant and the rate-limiting is the breakdown of the tetrahedral intermediate T^{-} and the ring opening is catalyzed by water.

Keywords

Isatin, piperidine, kinetics, substituent effect, mechanism, methanol

Introduction

Isatin is an indole derivative (1H-indole-2,3-dione) and found in many plants and humans as it is a metabolic derivative of adrenaline.[1] It was reported that isatin participated a broad range of synthetic

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leading to its use as aprecursor molecule in medicinal chemistry.[2–5] Isatin has special properties due to the fact that it possess many reactive centers, so it undergoes electrophilic aromatic substitution (S_EAr) at carbon atoms on positions five and seven of the phenyl ring., It has been reported that isatin underwent condensation with primary amine and with active methylene compounds such as malononitrile $CH_2(CN)_2$ or ethyl cyanoacetate ($NCCH_2COOC_2H_5$) on C-3 carbonyl group.[6] Additionally, isatin showed ring opening via nucleophilic attack on C-2 amide group by secondary amine or negatively charge ions such as HO^- in which H_2O must be present,[7,8] or ring expansions as well as spiro-annulations. The rates of hydrolysis of isatins derivatives showed a complex dependence upon pH indicative of subtle changes in mechanisms and rate-limiting step.[9] Most reactions of hydroxide ions and secondary amines with isatins and *N*-alkyl isatin in aqueous cosolvents undergo nucleophilic substitution reactions at the amide linkage with ring opening process. The rate and mechanism of ring opening of isatin and *N*-substituted isatin derivatives showed great dependence on water molecules present in the reaction mixture.[10,11]

The aim of this work is to use the kinetic study as a tool to suggest the mechanisms for the reaction of some five- and seven- substituted isatin with piperidine in 80% aqueous methanol. Furthermore, the effect of a remote substituent on the sensitivity of the electronic character of the amide carbonyl group toward piperidine will be discussed.

Experimental

Melting points were measured by MEL-TEMP II melting point apparatus in open glass capillaries and are uncorrected. The UV spectra were carried out on a 160-A UV-VIS recording spectrophotometer Shimadzu. The IR spectra were recorded for potassium bromide (KBr) discs on a Perkin-Elemer FT-IR, System spectrum ratio recording infra-red spectrophotometer. The ^{1}H-NMR spectra were carried out at ambient temperature (~25 C) on a (JEOL) 500 MHz spectrophotometer using tetramethylsilane (TMS) as an internal standard, Faculty of Science, Central Laboratory Unit, Alexandria University.

Preparation of five and 7-substituted isatin

Step 1: Preparation of isonitrosoacetanilide derivatives 1a-f. 0.05 mol of chloral hydrate was taken into the round bottom flask and dissolved in 120 mL water to 0.09 mol of sodium sulphate, a solution of 0.05 mol of aniline derivatives in 30 mL of water containing 0.14 mol of concentrated hydrochloric acid (4.34 mL) to dissolve the amine and solution of 0.15 mol of hydroxylamine hydrochloride in 50 mL of water were added. Flask was then heated vigorously until the reaction was completed. Later, the solution containing beaker was cooled in running water followed by the filtration of reminder crystallized product with suction pump and air dried.

Step 2: synthesis of isatin derivatives 2a-f. Dry isonitrosoacetanilide derivatives 0.15 mol was added to 0.18 mol of concentrated sulphuric acid (10.0 mL) was warmed to 50°C in such a rate so as to keep the temperature between 60 and 70°C but not higher. External cooling was applied at this stage so that the reaction could be carried out more rapidly after the addition of isonitroso compound was finished. The solution was heated to 80°C and kept at this temperature for about 10 min to complete the reaction. Then the reaction mixture was cooled to room temperature and poured into 10 times its volume of cracked ice. After standing for 90 min, the final product was filtered with suction pump followed by washing with cold water to remove sulphuric acid and dried in air.[12,13]

5-Methyl isatin 2b: Yield: 75%; m. p (285–288) °C; lit: (288) °C, IR (KBr): 3287 (NH), 1744 (C = O), 1717 (C = O)cm^{-1}. **5-Chloro isatin 2c:** Yield: 70%; m. p (243) °C; lit: (247) °C, IR (KBr): 3049 (NH), 1748 (C = O),1706 (C = O)cm^{-1}**. 5-Bromo isatin 2d:** Yield: 75%; m. p (243–248)°C; lit: (247–252)°C, IR (KBr): 3093 (NH), 1746 (C = O), 1705 (C = O) cm^{-1}. **7-Methyl isatin 2e:** Yield: 40%; m. p (235-239) °C; lit: (238-242) °C, IR (KBr): 3199 (NH), 1733 (C = O),1600 (C = O) cm^{-1}**. 7-Chloro isatin 2f:** Yield: 75%; m. p (183-189) °C; lit: (187–191) °C, IR (KBr): 3181 (NH), 1739 (C = O),1614 (C = O)cm^{-1}**. 7-Bromoisatin 2g:** Yield: 70%; m. p (189–193) °C; lit: (191–198) °C, IR (KBr): 3175 (NH), 1740 (C = O),1611 (C = O) cm^{-1}.

Preparation of 1-(2'-amino substituted phenyl)-2-(piperidin-1-yl)ethane-1,2-dione. A solution (10 mL) of isatin derivatives **2a–g** (2 mmol) and piperidine (4 mmol) in 80% aqueous MeOH was refluxed for 3 hours. The reaction mixture was neutralized with 5% citric acid and the final product was filtered, dried, and crystallized from methylene chloride. The purity was checked by TLC (4:6 ethyl acetate: n-hexane).

1-(2'-aminophenyl)-2-(piperidin-1-yl)ethane-1,2-dione,3a. Yield: 45%; m. p: 184°C; (lit 185).[14]

1-(2'-amino-5'-methylphenyl)-2-(piperidin-1-yl)ethane-1,2-dione, 3b. Yield: 40%; m. p: 185°C; UV (MeOH: H_2O) (2:8): λ_{max} = 380 nm (ε = 4333), IR (KBr): 3429 (NH), 1630 (C = O), 1550 (C = O amide) cm^{-1}, 2950(C-H aliphatic) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.39 (m, 2H, *J* = 5.35, 5.35 Hz, H-4),1.54 (m, 2H, *J* = 8.4, 6.15 Hz, H-5), 1.58 (m, 2H, *J* = 6.9, 6.15 Hz, H-3), 2.11 (s, 3H, CH_3), 3.15 (t, 2H, *J* = 5.35, 6.20, H-6), 3.53 (t, 2H, *J* = 5.35 Hz, H-2), 6.73 (d, 1H, *J* = 8.4 Hz, H-3'), 6.99 (s, 1H, H-6'), 7.1 (d, 1H, *J* = 1.5, 8.5 Hz, H-4'), 7.20(sbr,2H, NH_2, D_2O exchangeable). $C_{14}H_{18}N_2O_2$: (Calc.) 4.87 C%; 0.41 H%; 5.65 N%. (Found): 5.17 C%; 0.51 H%; 5.84 N%.

1-(2'-amino-5'-chlorophenyl)-2-(piperidin-1-yl)ethane-1,2-dione, 3c. Yield: 53%; m. p: 190°C; UV (MeOH:H_2O) (2:8): λ_{max} = 380 nm (ε = 4333), IR (KBr): 3420 (NH), 1624 (C = O), 1543 (C = O amide) cm^{-1}.^{1}H NMR (DMSO-d_6): δ 1.40 (m, 2H, *J* = 3.05, 2.3 Hz, H-4), 1.51 (m, 2H, *J* = 6.90, 4.65 Hz, H-5), 1.59 (m, 2H, *J* = 6.1, 4.6 Hz, H-3), 3.17 (t, 2H, *J* = 5.35, 5.35, H-6), 3.55 (t, 2H, *J* = 6.1, 5.35 Hz, H-2), 6.81 (d, 1H, *J* = 8.4 Hz, H-3'),7.28 (d, 1H, *J* = 2.3 Hz, H-6'), 7.34-7.41 (dd, 1H, *J* = 2.3, 2.3, 6.1 Hz, H-4'), 7.52 (sbr, 2H, NH_2, D_2O exchangeable). $C_{13}H_{15}N_2O_2Cl$: (Calc.) 4.51 C %; 0.37 H%; 5.25 N%; 13.20 Cl %. (Found): 4.82 C%; 0.31 H%; 5.52 N%; 13.51 Cl%.

1-(2'-amino-5'-bromophenyl)-2-(piperidin-1-yl)ethane-1,2-dione, 3d. Yield: 38%; m. p: 200°C; UV (MeOH:H_2O) (2:8): λ_{max} = 380 nm (ε = 4000), IR (KBr): 3419 (NH), 1622 (C = O), 1541 (C = O amide) cm^{-1}.^{1}H NMR (DMSO-d_6): δ 1.39 (m, 2H, *J* = 6.1, 5.35 Hz, H-4), 1.53 (m, 2H, *J* = 6.1, 4.60 Hz, H-5), 1.58 (m, 2H, *J* = 4.55, 6.85 Hz, H-3), 3.17 (t,2H, *J* = 5.35, 5.35, H-6), 3.53 (t, 2H, J = 6.1, 4.60 Hz, H-2), 6.86 (d, 1H, *J* = 9.15 Hz, H-3'), 7.16 (d, 1H, *J* = 2.3 Hz, H-6'), 7.33 (dd, 1H, *J* = 3.05, 2.3, 6.16 Hz, H-4'), 7.51 (sbr, 2H, NH_2, D_2O exchangeable). $C_{13}H_{15}N_2O_2Br$: (Calc.) 3.86 C%; 0.32 H%; 4.50 N%; 25.7 Br%. (Found): 3.51 C%; 0.36 H%; 4.21 N%; 25.1 Br%.

1-(2'-amino-3'-methylphenyl)-2-(piperidin-1-yl)ethane-1,2-dione, 3e. Yield: 56%; m. p: 175°C; UV (MeOH:H_2O) (2:8): λ_{max} = 380 nm (ε = 4333), IR (KBr): 3428 (NH), 1617 (C = O), 1560 (C = O amide) cm^{-1}, 2941 (C-H aliphatic) cm^{-1}.^{1}H NMR (DMSO-d_6): δ 1.325 (m, 2H, H-4), 1.51 (m, 4H, H-3,5), 2.09 (s, 3H, CH_3), 3.102 (t, 2H, *J* = 5.35, 5.35 Hz, H-6), 3.476 (t, 2H, *J* = 5.35,5.35 Hz, H-2), 6.523 (t, 1H, *J* = 7.6, 7.65 Hz, H-5'), 7.117 (d, 1H, *J* = 8.4 Hz, H-4'),7.204 (sbr, 2H, NH_2, D_2O

exchangeable), 7.22 (d, 1H, J = 6.85 Hz, H-6'). $C_{14}H_{18}N_2O_2$: (Calc.) 4.87 C%; 0.41 H%; 5.65 N%. (Found):4.30 C%; 0.38 H%; 5.12 N%.

1-(2'-amino-3'-chlorophenyl)-2-(piperidin-1-yl) ethane-1,2-dione, 3f. Yield: 52%; m. p: 180°C; UV (MeOH:H_2O) (2:8): λ_{max} = 380 nm (ε = 4666), IR (KBr): 3419 (NH), 1638 (C = O), 1585 (C = O amide) cm^{-1}.^{1}H NMR (DMSO-d_6): δ 1.53 (m, 2H, H-4), 1.68 (m, 4H, H-3,5), 3.26 (t, 2H, J = 5.35, 5.35 Hz, H-6), 3.67 (t, 2H, J = 5.35,5.35 Hz, H-2), 6.5 (sbr, 2H, NH_2, D_2O exchangeable), 6.635 (t, 1H, J = 7.65, 7.6 Hz, H-5'),7.27 (d, 1H, J = 8.4 Hz, H-6'), 7.53 (d, 1H, J = 7.65 Hz, H-4'). $C_{13}H_{15}N_2O_2Cl$: (Calc.) 4.51 C%; 0.37 H%; 5.25 N%; 13.20 Cl %. (Found): 4.83 C%; 0.40 H%; 5.83 N%; 13.46 Cl%.

1-(2'-amino-3'-Bromophenyl)-2-(piperidin-1-yl) ethane-1,2-dione, 3g. Yield: 48%; m. p: 190°C; UV (MeOH:H_2O) (2:8): λ_{max} = 380 nm (ε = 5000), IR (KBr): 3415 (NH), 1637 (C = O), 1 (C = O amide) cm^{-1}.^{1}H NMR (DMSO-d_6): δ 1.53 (m, 2H, H-4), 1.532 (m, 4H, H-3,5), 3.122 (t, 2H, J = 5.35, 5.35 Hz, H-6), 3.4495 (t, 2H, J = 5.35,5.35 Hz, H-2), 6.602 (t, 1H, J = 7.65, 7.65 Hz, H-5'),7.34 (sbr, 2H, NH_2, D_2O exchangeable), 7.37 (d, 1H, J = 8.4 Hz, H-6'), 7.47 (d, 1H, J = 7.65 Hz, H-4'). $C_{13}H_{15}N_2O_2Br$: (Calc.) 3.86 C%; 0.32 H%; 4.50 N%; 25.7 Br%. (Found):3.46 C%; 0.36 H%; 4.28 N%; 25.34 Br%.

Kinetic measurements

The reactions of isatin derivatives with piperidine in 80% water-methanol mixed solvent were followed spectrophotometrically. The optical densities of the solutions measured after the completion of the reactions agreed with the authentic samples of the corresponding products having the same concentrations in the same mixed solvents. The resultant change of absorbance with time was recorded by kinetic mode or time scan mode on UV-VIS Shimadzu 160-A spectrophotometer.

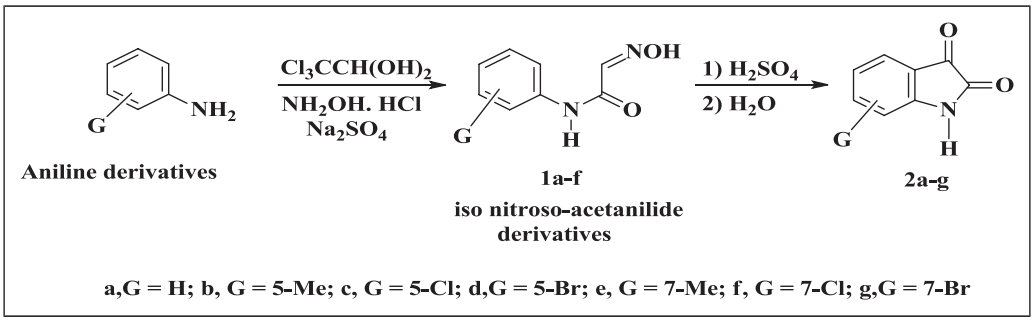
The reaction mixture was prepared by the transfer of 1 mL of the substrate solution (3×10^{-3} M) that gives a final concentration of 3×10^{-4} M to a 10 mL measuring flask and the volume is completed by a given volume of absolute methanol. The measuring flask and the stock solution of the piperidine are allowed to reach thermal equilibrium in a well stirred and thermostatic bath at the required temperature (±0.5°C). The reaction time started when the amine is mixed with the reaction mixture (final concentration of piperidine ranges from 0.3×10^{-2} to 12×10^{-2} M) and transfered quickly to a well thermostated chamber containing the UV cell. The absorbance A_t at the desired wavelength is recorded at several time intervals depending on the reaction rate. Measurements were usually carried out spectrophotometrically by following the increase in the reaction products absorbance with time at λ = 380 nm.

Results and discussion

Chemistry

The derivatives **2b-g** (G = 5- Me, 5-Cl, 5-Br, 7-Me, 7-Cl, 7-Br) were prepared by Sandmeyer methodology, while isatin is commercially available, Scheme 1.

The reaction of five- and 7-substituted isatin with piperidine in 80% aqueous MeOH at 25°C gave 1-(2'-amino-5'- or 3'- substituted phenyl)-2-(piperidin-1-yl) ethane-1,2-dione derivatives 3a–g, Scheme 2. Elemental analysis, IR and ^{1}H-NMR spectroscopy confirmed the formation of a ring opened 1-(2'-amino-5'- or 3'-substituted phenyl)-2-(piperidin-1-yl) ethane-1,2-dione derivatives



Scheme 1. Synthesis of isatin derivatives **2a–g**.

3a–g. The identification of these products led to suggestion that the reaction proceeded by nucleophilic attack at the carbonyl group at C-2 followed by ring opening process, Scheme 2.

Kinetic study

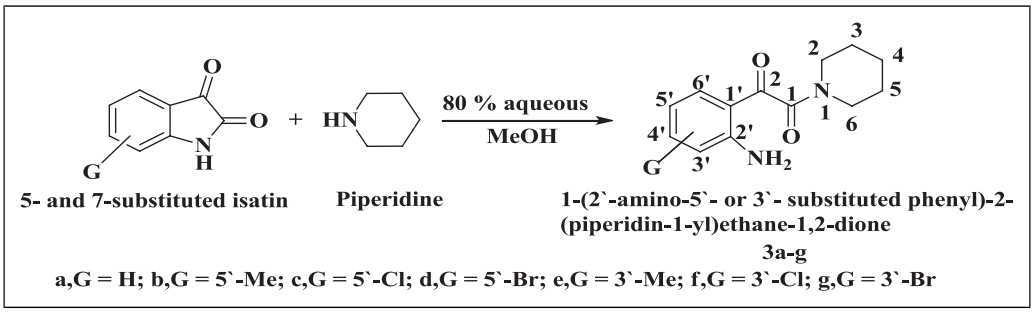
The rate of the piperidinolysis was followed spectrophotometrically by observing the increase in the optical density near λmax = 380 nm due to the formation of 1-(2'-amino-5'- or 3'- substitutedphenyl)-2-(piperidin-1-yl) ethane-1,2-dione derivatives **3a–g**. The kinetic measurement was carried out under pseudo–first-order conditions with the concentration of piperidine maintained in excess relative to the isatin concentration. The pseudo–first-order rate constants k_{obs} were obtained from the slope of the linear plot of ln $(A_\infty - A_t)$ versus time, equation (1)

$$\ln\,(A_\infty - A_t) = -k_{obs} + C \tag{1}$$

The pseudo first-order rate constants k_{obs} at 25°C, increased linearly with piperidine concentration, Figure 1(a) and (b) and Table 1. This result indicates that the reaction is not catalyzed by piperidine and it is first order in substituted isatin and first order in piperidine. i.e. an overall second order kinetics. The slope of the linear plots obtained from k_{obs} versus [Pip] gave the second-order rate constants (k_N) at 25°C. While, the values of k_N at different temperatures are obtained by dividing k_{obs} by the corresponding piperidine concentration, Table 2.

Mechanism of piperidinolysis of isatin derivatives

The reaction of isatin derivatives **2a–g** with piperidine in 80% aqueous MeOH is suggested to take place through the cleavage of amide bond and formation of a ring-opened products.[9] The mechanism is proposed which would account satisfactorily for the following facts: (i) The formation of a ring opened 1-(2'-amino-5'- or 3'- substituted phenyl)-2-(piperidin-1-yl) ethane-1,2-dione derivatives **3a–g**. (ii) It has been reported that the ring-opened form is predominated above pH 6[9] which is less than that used in the present study (pH ≈ 11) (iii) The catalysis by piperidine is rejected on the ground that the reaction is first order in piperidine (iv) The ring opening of isatin and N-substituted isatin must occur in the presence of water and the rate of reaction was found to be directly proportional to water concentration,[11] Scheme 3.



Scheme 2. Reaction of 5- and 7-substituted isatins with piperidine.

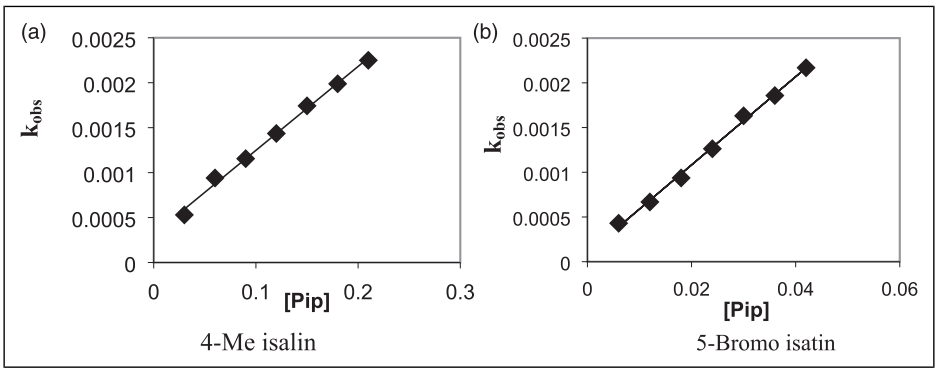


Figure 1. Plot of k_{obs} against [Pip] at 25°C. (a) 4-Me isalin (b) 5-Bromo isatin.

The mechanism is proceeded by an initial attack by piperidine (k_1) to generate reversibly the anionic tetrahedral intermediate T^- which spontaneously reverted to the reactants, k_{-1}, or be converted to products **3a**–**g** by water catalyzed expulsion of the amine, k_2. The reaction in part is suggested to proceed initially through solvated isatin derivatives,[11] Scheme 3.

The kinetic expression for the reaction is derived with reference to the mechanism in Scheme 3 and the application of the steady-state assumption and the great dependence of H_2O to complete the reaction as shown in equation (2)

$$Rate = \frac{k_2 k_1 [1][Nu][H_2O]^{n+1}}{k_1[s]^n + k_2[H_2O]} \tag{2}$$

where the term pip symbolizes piperidine.

If $k_{-1} \gg k_2$ and so k_2 $[H_2O]$ can be neglected in the denominator, then

$$\text{and} \quad Rate = K_1 k_2 [1][pip][H_2O]^{n+1} / [S]^n \tag{3}$$

$$k_N = K_1 k_2 [H_2O]^{n+1} / [S]^n \tag{4}$$

where $K_1 = k_1/k_{-1}$.

Table 1. Pseudo first order rate constants 10^5 k_{obs},s^{-1} and 10^2 k_N,$L{\cdot}mol^{-1}{\cdot}s^{-1}$ in different substituted isatin **2a–g** with Piperidine in 80% aqueous methanol at 25°C.

	H	5-Me	5-Br	5-Cl	7-Me	7-Br	7-Cl
[Pip]				10^5k_{obs}			
0.0030						22.07	24.10
0.0033						23.91	27.87
0.0036						26.48	30.13
0.0039						28.79	31.93
0.0042						30.32	33.85
0.0045						32.28	35.89
0.0048						34.97	39.92
0.0060			4.30	3.80			
0.0120			6.68	5.83			
0.0150	3.30						
0.0180			9.37	8.48			
0.0240			12.63	10.59			
0.0300	5.80	5.30	16.31	13.40	2.53		
0.0360			18.58	16.31			
0.0420			21.69	17.96			
0.0450	8.90						
0.0600	12.21	9.40			4.38		
0.0750	15.24						
0.0900	17.80	11.55			6.53		
0.1050	20.50						
0.1200		14.36			8.30		
0.1500		17.43			10.13		
0.1800		19.88			11.78		
0.2100		22.49			13.24		
10^2k_N	1.95	0.93	5.00	4.00	0.60	70.60	80.00

Thus, the rate varies directly proportional to $[H_2O]^{n+1}$ while it is inversely proportional to $[S]^n$. Consequently, the ring opening process is the rate determining step.

If $k_2 \gg k_{-1}$ and so $k_2[S]^n$ is neglected in the dominator, so equation (2) is reduced to equation (5)

$$k_N = k_1[H_2O]^n \tag{5}$$

This indicates that the formation of solvated tetrahedral intermediate is the rate determining step.

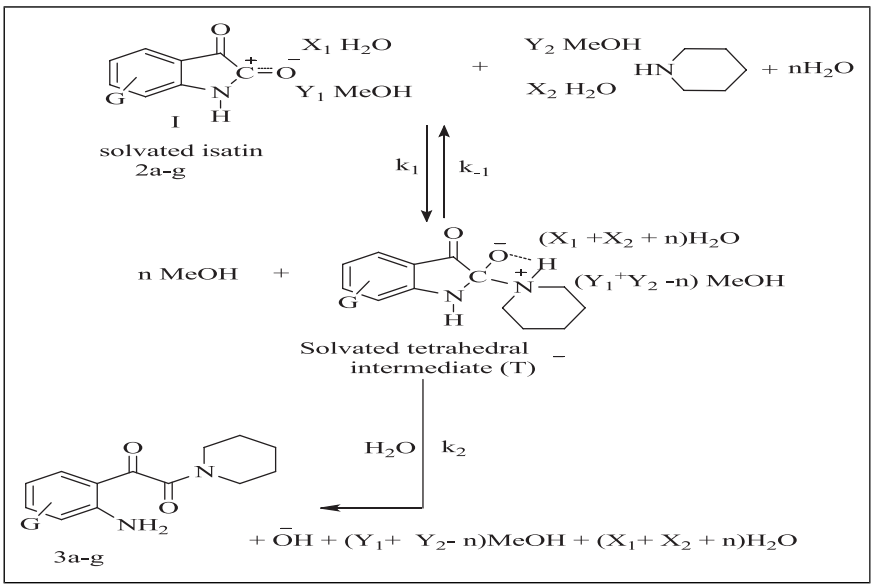
Therefore, the effect of temperature, nature and position of the substituent can be used to confirm what mechanism is suggested and determine the rate determining step if the reaction proceeded by stepwise mechanism as shown in Scheme 3 for the titled reaction.

Effect of temperature

The k_N values for the titled carried out at different temperatures ranging from 15°C to 40°C (interval temperature is 5°C) are listed in Table 2. Thermodynamic parameters were calculated by least square fit using the equation In k_N = a = b (1/T), where, a = ln A and $b = -\Delta E^{\#}/R$. The trend in

Table 2. Second order rate constants k_N l mol^{-1} s^{-1}, reaction constant *p* and activation parameter values for the piperidinolysis of isatin derivatives **2a–g** in 80% aqueous MeOH at different temperatures.

G	T°C	10^2 k_N l.mol^{-1}s^{-1}						$\Delta H^{\#}$ Kcal mol^{-1}	$-\Delta S^{\#}$ Cal mol^{-1} K^{-1}	$\Delta G^{\#}$ Kcal mol^{-1}
	σ	15	20	25	30	35	40			
H	0.00	–	0.75	0.90	1.20	1.50	1.90	8.72	69.22	29.70
5-CH_3	−0.15	–	5.50	7.00	8.50	11.50	14.00	8.00	65.40	27.84
5-Cl	0.27	–	4.30	5.50	7.00	9.00	11.50	8.14	65.85	28.10
5-Br	0.26	–	0.50	0.65	0.83	1.11	1.37	8.74	70.03	29.95
7-CH_3	−0.27	–	64.00	80.00	100.00	126.00	–	7.21	60.93	25.70
7-Cl	0.79	52.00	62.00	73.50	89.50	110.00	–	7.30	60.85	25.74
7-Br	0.78	41.00	1.700	2.200	2.90	3.70	4.55	8.42	67.54	28.88
ρ			2.011	1.995	1.97	1.953	1.860			



Scheme 3. Piperidinolysis of isatin derivatives **2a–g** in 80% aqueous MeOH.

variation of the activation parameters (enthalpy of activation $\Delta H^{\#}$, entropy of activation $\Delta S^{\#}$ and the free energy of activations $\Delta G^{\#}$) showed a regular variation with changing substituents in five- and 7-positins in isatin derivatives, Table 2. The electron-donating substituents increase and electron–withdrawing groups decrease $\Delta H^{\#}$. The $\Delta S^{\#}$ values indicate that the transition state is more solvated than the reactants. The relatively high $\Delta S^{\#}$ values are presumably due to occurrence of internal hydrogen bond in the tetrahedral zwitterion T^{-}, Scheme 2. The constancy of $\Delta G^{\#}$ value indicates that a unified reaction mechanism operates for all substituents in piperidinolysis process.

Isokinetic relationship. The isokinetic temperature, β for the reactions of isatin derivatives **2a**–**g** with piperidine is fitted in the Leffler's equation with equation $\Delta H^{\#} = \Delta H^{\circ} + \beta\Delta S^{\#}$ and the Leffler's modified equation with β value 169 K (r = 0.99. A value is less than the temperatures used in the kinetic runs (293–313 K)[14] and represents a temperature at which all reactions of the series should proceed at the same rate constant. Also, the β indicates that the reaction of isatin derivatives **2a–g** with piperidine is entropy controlled. The good linear of above relationships as well as Exner's correlations ($\log k_{(20)}$-$\log_{(35)}$) shown by all substituents indicated that the same mechanism prevails independent of the nature and position of substituent.[15]

Effect of substituent on reactivity

Effect of 5- and 7- substituent G on the reactivity of amide carbon atom in isatin derivatives and feasibility of the leaving group is used to probe the reaction mechanism, Figure 2.

The electronic effect of the substituents in the leaving group moiety can be quantified by the use of a Hammett equation (6),[16] σ is the substituent constant and ρ is the reaction constant.

$$\log k_N = \rho\sigma + \log k_o \tag{6}$$

The value of ρ is a measure of the sensitivity of the rate constant for a given mechanism of a given reaction type to the influence of substituents.[17–20] Table 2 reveals that electron withdrawing substituent enhances the reactivity while electron releasing substituent inhibit the rate[9,21] [.and showed that the effect of substituents follows the order: 7-chloro > 7-bromo > 5-Chloro > 5-bromo > H > 7-CH_3 > 5-CH_3. The relative values of k_N showed little dependence on the 5-substitutent and great dependence of 7-substituent.

This points out that the electronic effect of the five- and 7-substitutent is inductive rather than resonance. While the greater effect of 7-substituent than 5-substitutent is presumably due to proximity effect. The steric effect of the substituent can be ruled out because the G-substituents are placed too far away from the carbonyl carbon to provide a significant shielding effect.

The correlations of k_N values with σ-Hammett-σ*-Taft's (in one plot), σ-Hammett constants (for para-like substituent), σ*-Taft's substituent constants (for ortho-like substituents) at various temperatures (20°–40°C) gave different ρ values as shown in Table 2. It shows that using these σ values is not suitable for the titled reaction due to (i) correlations between combined σ-Hammett and σ*-Taft's and k_N values for the reactions of isatin derivatives **2a–g** with piperidine showed poor correlation coefficient values. (ii) The correlations of σ-Hammett constants with k_N values for the reactions of 5-substitued isatins **2a–d**

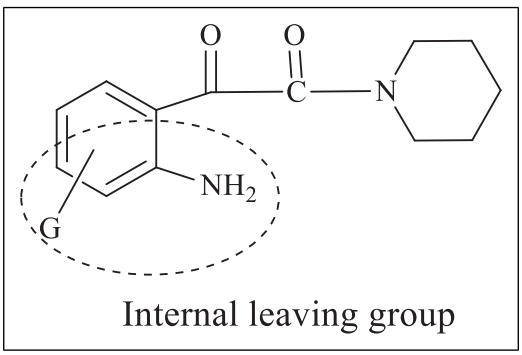
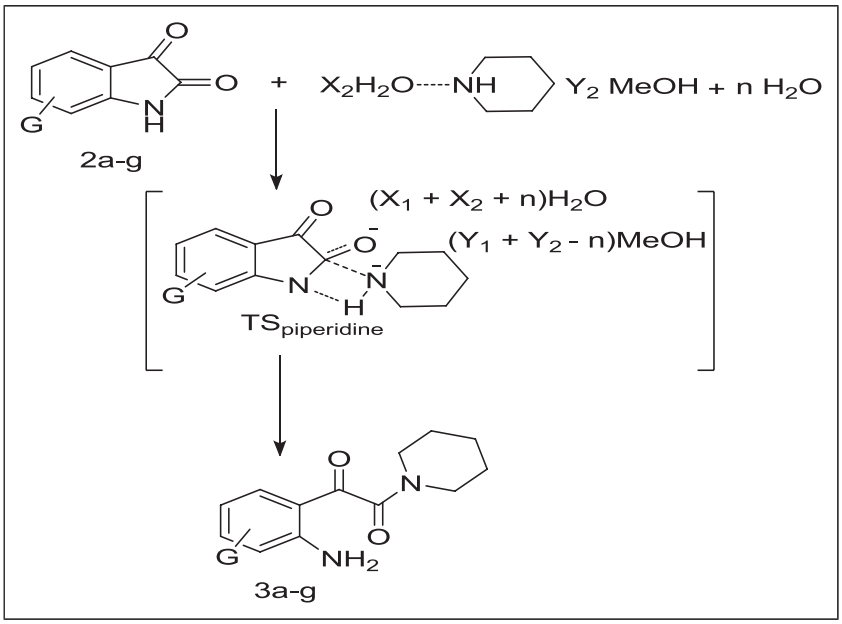


Figure 2. Internal leaving group in isatin.

with piperidine gave good straight lines but with negligible difference in the obtained ρ values with increasing temperature. Also, the correlations between σ*-Taft's constants and k_N values for the reactions of 7-substituted isatin **2a, 2e–g** with piperidine gave good straight lines with good correlations. Table 2 reveals that the ρ values from σ-Hammett plots ($\rho_{piperidine}$ = 2.02–2.05) are different from those of σ*-Taft's plots ($\rho^*_{piperidine}$ = 0.72–0.69). The correlations of k_N values with σ-Hammett-σ*-Taft's (not shown), σ-Hammett constants (for para-like substituent), σ*-Taft's substituent constants (for ortho-like substituents) at various temperatures (20°–40°C) are not suitable for the titled reaction. Thus, σ°-Taft's constant values for substituted phenyl ring[22] are more suitable with our system in which the substituent is far from the reaction centre and attached to benzene ring. The σ°-Taft's values represent inductive constants for substituted phenyl groups (-Ar) relative to the unsubstituted one C_6H_5-. σ°-Taft's for 5-Me, 5-Cl and 5-Br phenyl were reported while the same substituents at positions seven- are not. Following the same procedure recommended by Taft and Lewis[23] for the reactions of 5-substituted isatin **2a–d**, a regression line is fitted to the log k_N against σ° data for 5-(para-) substituted aryl groups containing substituents H, Br, Cl, Me: $slope_{(piperidine)}$ = 1.99, correlation coefficient r = 0.99 at 25°C. The σ° values for 7-Cl, 7-Br and 7-Me (ortho substituent) aryl group are then evaluated from the relationship $\sigma_{Calc.} = (\log k_N - \log k_H)/\rho$, Table 2. It is found that a regression line is fitted to the of log k_N against σ° and σ°_{calc} for five- and 7-substituted isatins respectively. The plot showed a linear straight line with positive slope with ρ values ranged between 1.86 and 2.01 depending on the temperature, Table 2.

The sign and magnitude of reaction constant ρ was used as mechanistic criteria to gain insight into the concerted or stepwise nature of the process.[17,19,20] The sign of reaction constant ρ is invariably positive for stepwise reaction.[24–26] When the ρ values are larger than 2, the reaction proceeds by a stepwise mechanism, Scheme 3 in which the rate-limiting is the expulsion of leaving group anion from T^- (ρ ≈ 6.24 – 4.78).[27] i.e. rate-limiting breakdown of a tetrahedral intermediate T^-. When ρ is positive and smaller than 2 (ρ < 2) and more than 1, the reaction proceeds by a



Scheme 4. Concerted mechanism of piperidinolysis of isatin derivatives **2a–g** in 80% aqueous methanol.

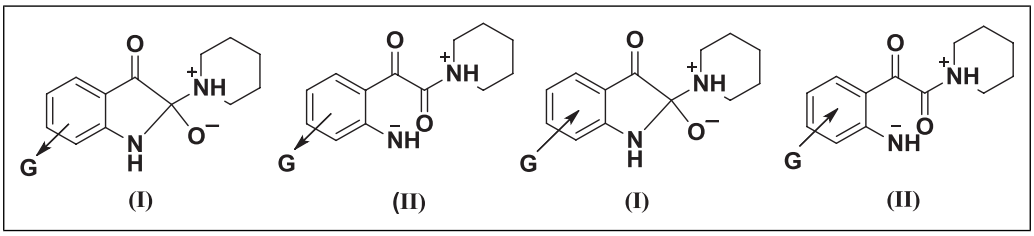


Figure 3. Effect of electron withdrawing and donating groups on the intermediates (I) and (II).

stepwise mechanism in which the rate-limiting step is the formation of the tetrahedral intermediate.[28] While for small ρ values (ρ < 1) indicated a concerted mechanism.[29] Scheme 4. For examples, ρ = 0.54 for the piperidinolysis of four- nitrophenyl X-substituted-benzoates[30] and ρ = −0.63 for aminolysis of aryl N-phenythio-carbamates.[31] It involved simultaneous bond breakage and bond formation in $T^{\pm}$concerted, Scheme 4.[27]

The ρ values of 2.01–1.86 for the titled reactions are compatible for a reaction mechanism shown in Scheme 3 with rate-limiting breakdown of the tetrahedral intermediate T^{-}. The relatively low ρ values can be explained by the responding to changes in the substituent on the leaving group. Such substituent can alter the partial positive charge on the carbonyl carbon and hence perturb the rate of bond formation between C-2 and nucleophile. He suggested mechanism is consistent with the explanation that an electron attracting substituents, for example, Cl, Br, would accelerate the rate of reaction and electron releasing group such as CH_3 group inhibit the rate, while the rate determining step is the breakdown of tetrahedral intermediate, so the substituents will effect on the stability of the intermediate (I, and II). Thus, the inductive effect of Cl, and Br group increase the stability of the negative charge developed on the nitrogen atom of the intermediate (I) when it compared with the stability tetrahedral intermediate T^{-}. While electron donating substituent at the same positions such as CH_3 group inductively decreases the stability of the intermediate (II) relative to the stability of tetrahedral intermediate T^{-}, (Figure 3). The effect of substituents is more significant on 7-positon than substituent on 5-position, that confirm that the main effect of the substituent is the inductive effect.

Conclusion

The five- and 7-substituted isatin derivatives (5- Me, 5-Cl, 5-Br, 7-Me, 7-Cl, 7-Br) were prepared by Sandmeyer methodology while isatin is commercially available. The reaction of 2a–g with piperidine in 80% aqueous MeOH at 25°C gave 1-(2'-amino-5'- or 3'- substituted phenyl)-2-(piperidin-1-yl)ethane-1,2-dione derivatives and their structures were confirmed by elemental analysis, IR and ^{1}H-NMR spectroscopy. Thus, the reaction proceeds by nucleophilic attack at the carbonyl group at C-2 followed by ring opening process. The linear increase of pseudo first-order rate constants k_{obs} at 25°C with negligible intercept against various excess of piperidine concentrations indicated that the reaction is not catalyzed by piperidine and second-order overall. Many facts are used to select the suitable mechanism for the titled reaction namely: (i) The need of water to complete the reaction of isatin derivatives with nucleophiles. (ii) The amine catalysis was rejected on the grounds that the reaction is second-order (iii) the kinetic dependence on nature of G-substituent are explicable in terms of the normal tetrahedral intermediates, Scheme 3. The previous facts, the activation parameter values and ρ values led to suggestion that the reaction of piperidine

with of isatin derivatives proceeded by two step mechanism and the ring opening is catalyzed by water in the fast step.

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