

Kinetics and thermodynamic studies of the iodination of sultams using conductivity measurement

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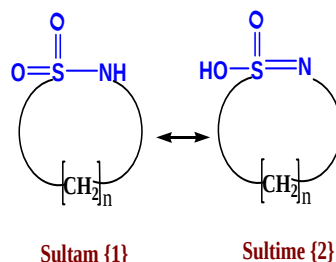
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Abstract: Kinetics and thermodynamic studies of iodination of (1,2-thiazine): N-(p-substituted phenyl) -3,5-dimethyl -1, 1-dioxo-1,2-thiazine ($C_4H_2(CH_3)_2SO_2 N C_6H_4-X$); {X = H, p-Cl, and p-OCH₃} by using iodine monochloride (ICl) in chloroform medium have been investigated by Isolation method the observed rate of iodination, pseudo first order for 1,2-thiazine and ICl and second order in overall reaction and using conductivity measurements. The reaction rate constant increases with increasing temperature from 273K to 318K. The kinetic and thermodynamic parameters k , E_a , $\Delta H^\ddagger$ and $\Delta S^\ddagger$ have been calculated. The corresponding halogenated 1,2-thiazine has been identified as a product of halogenation. A suitable reaction scheme is proposed and an appropriate rate law is deduced to account for the observed kinetic and thermodynamic data.

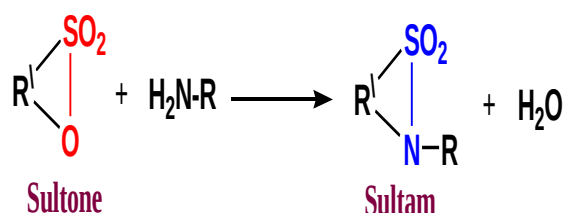
Keywords: 1,2-thiazine, Activation energy, iodine monochloride (ICl), Conductivity, rate constant, Sulfonamide.

I. Introduction

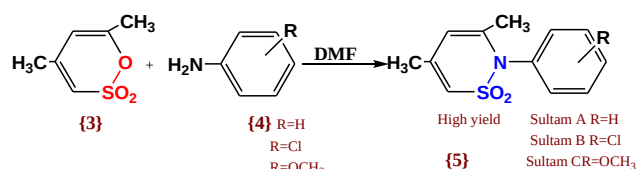
Sulfonamides have long been recognized for their wide range of biological activities^[1] and are among the most common causes of allergic reactions of drugs. Recently, much interest has been directed to their cyclic counterparts, the sultams, which also exhibit a vast variety of biological activities. A number of substituted sultams have proven to be useful heterocycles for medical applications^[2,3]. As a consequence, chemical syntheses towards sultams have continued to be an attractive topic for intense research^[4]. Sultams {1} are inner Sulfonamides in which the S-N bond is part of a ring, the tautomeric forms of sultams, having a sulfur-nitrogen double bond as part of a ring, are called Sultimes {2}. The chemical composition of which corresponds to the general formula^[5]:



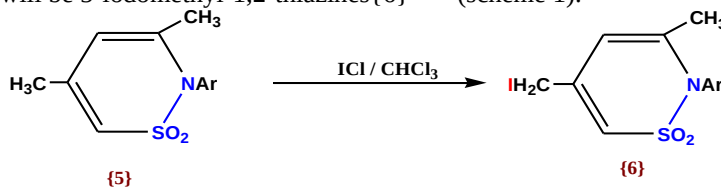
Unsaturated sultams prepared from the corresponding sultones, (Sultones are intramolecular cyclic esters of hydroxy sulfonic acids) it has surprisingly been found that unsaturated sultones may be condensed with ammonia or primary amines yielding unsaturated sultams. The reaction proceeds in accordance with the general reaction scheme^[6]:



The unsaturated sultams, in accordance with the invention are highly stable and permit further reactions in the sultam ring as well as in the substituents at the sultam nitrogen atom^[6]. 1,2-thiazine is a type of sultams, was prepared by mixing of 4,6-dimethyl-1,2-oxathiine-2,2-dioxide{3} with aniline {4} or p-substituted aniline and heated for 1.5 hr., giving N-(p-substitutedphenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine {5}^[7,8].



Reaction of 1,2-thiazine with iodine which dependence on the iodinating agent when reacted with iodine monochloride the product will be 5-iodomethyl-1,2-thiazines{6} ^[9,10] (scheme 1).



Scheme (1)

Because of our continuing interest in mild reagents for the introducing of halogens into organic molecules and because only limited kinetic and thermodynamic information is available on sultam reactions with iodine monochloride, we found it is important to determine kinetic and thermodynamic parameters of the halogenation reactions of 1,2-thiazine.

II. EXPERIMENTAL

A. Chemicals

All chemicals used were of an analytical grade reagent, and methanol (99.9% purity) was purchased from TEDIA Company, Inc. (USA). N,N-Dimethylformamide (DMF) 99.8% from BioSolve. Acetone 99.5%, Chloroform >99.4%, iodine monochloride (ICl) >97% hydrochloric acid (HCl) 97% by Fluka., Aniline 90% , Acetic anhydride 99%, Sulphuric acid and sultone 98% by Sigma Aldrich Co., 4-Chloroaniline, 4-methoxyaniline by Riedel-de Haën, Franc.

B. Synthesis of N-(p-substituted phenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine {5}A-C

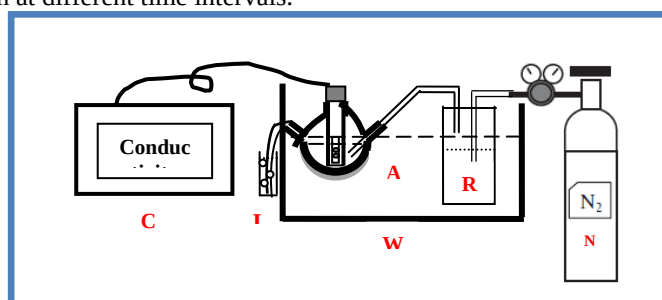
A mixture of 0.1mole (16gm) sultone {3} and 0.1 mole (9.1 ml) of aniline or p-substituted aniline were dissolved in 25ml N,N-dimethyl formamide (DMF), the contents refluxed for 1.5hr, then cooled to room temperature and 10ml of (0.1 N) HCl was added to remove the excess of aniline then the precipitate collected by filtration, washed with cold water dried and recrystallized in methanol^[11]. The physical properties are shown in table(1).

Table (1): some physical properties of the compounds (Sultam A, B, C)

Compounds		para-R (p-R)	Molecular formula	M.wt (g/mole)	Yield %
Sultam {5}	A	H	C ₁₂ H ₁₃ NO ₂ S	235.303	53
	B	Cl	C ₁₂ H ₁₂ NO ₂ SCl	269.749	42
	C	OCH ₃	C ₁₃ H ₁₅ NO ₂ S	265.329	49

C. Experimental techniques and apparatus

The conductivity of the dissolved hydrogen chloride was measured by Hanna conductivity meter that was readily adapted to automatic recording operation as in fig. (1) at temperatures (273, 283, 293, 298, 303, 318)K, for each temperature the conductivity was measured for a (200ml) water in a round bottom flask in which the hydrogen chloride (HCl) gas evolved as a side product of the reaction was dissolved by passing nitrogen gas flow through the reaction at different time intervals.



Figure(1): Illustrative schematic diagram of the electrical conductivity measurement.

a. Typical kinetic experiment of the molar ratio (1:15) (SultamA :ICl)

0.235g (0.001mol, 0.0928mol dm^{-3}) of 1,2-thiazine (Sultam A) was dissolved in 10ml of chloroform then added in a reaction vessel (R) which is clamped in a thermostat at constant 298K temperature (as illustrated in the fig. (1)) after thermal equilibrium has been reached, iodine monochloride (ICl) 0.7855ml (0.015mol, 1.39mol dm^{-3}) added which is also allowed in 298K thermostat to come to temperature equilibrium before use. A pure nitrogen gas with constant speed $10\text{ dm}^3/\text{hr.}$ by using gas flow meter was passed through a reaction mixture (R) that can transfer the hydrogen chloride (HCl) gas which is formed from the reaction, to the three necked flask (A) which contains (200ml) distilled water at 298K, and the conductivity cell was fitted with a rubber stopper and the conductivity readings from conductivity meter (C) were recorded (the conductivity of distilled water as a blank was excluded). The other neck of the flask (A) connected by a rubber tube to the flask (I) which contains 10ml distilled water and indicator, the color dose not changed indicating that all HCl gas are trapped and dissolved in the flask (A) insuring the accuracy of the conductivity measurement.

The experiment was repeated with the same weight and volumes of reactant at each (273, 283, 293, 303, 318)K, temperature, also for other sultams B and C.

b. Molar ratio (15:1) (SultamA :ICl)

Using concentrations by dissolving 3.5295g (0.015mol, 1.492mol dm^{-3}) of 1,2-thiazine (Sultam A) 10ml of chloroform at 298K and the iodinated agent, (ICl) 0.0513ml (0.001mol, 0.0994mol dm^{-3}) was added.

c. Molar ratio (1:1) (SultamA :ICl)

Using concentrations by dissolving 0.235g (0.001mol, 0.0994mol dm^{-3}) of 1,2-thiazine (Sultam A) 10ml of chloroform at 298K and the iodinated agent, (ICl) 0.0523ml (0.001mol, 0.0994mol dm^{-3}) was added.

III. RESULTS AND DISCUSSION

Conductivity of the hydrogen chloride (HCl) that is evolved as a side reaction was dissolved in water and the conductivity measured with time (for 1:15 molar ratio sultam :ICl)are shown in fig.(2), the conductivity increased with time for each temperature, as the temperature increased the reaction more quickly goes to the completion, indicating that no equilibrium occurred between the products and the reactants during the studied period of time.

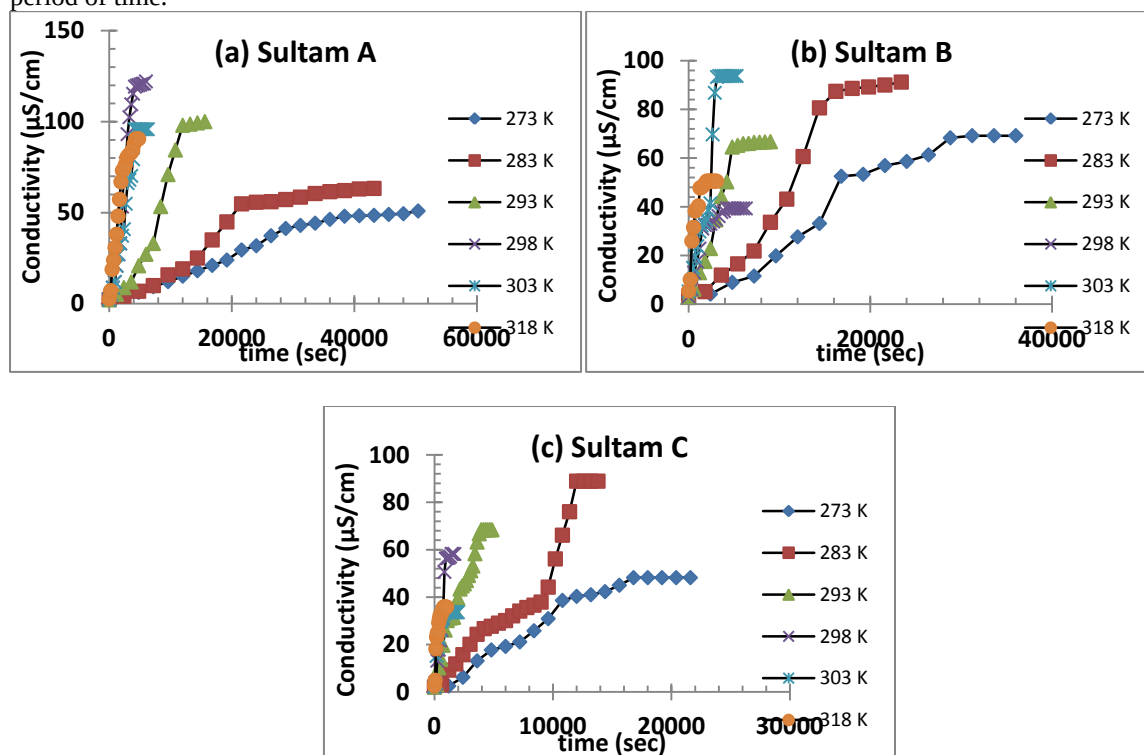


Figure (2): Variation of conductivity of the HCl with time for iodination of sultams (A, B, C) (molar ratio (1:15) sultam:ICl) at different temperature.

The results obtained from the kinetic data for the product of the iodination of sultams were found to follow pseudo first-order kinetics according to the equation (1).

The rate constant values (k_1) at different temperature were calculated for the product from the pseudo first order equation^[11,12]:

$$\ln(L_{\infty} - L_t) = \ln L_{\infty} - k_1 t \quad (1)$$

Where L_t : conductivity of the dissolved HCl gas at any time (t).

L_{∞} : conductivity of the dissolved HCl gas at infinite time (t_{∞}).

t: time in sec.

k_1 : first order rate constant of reaction in sec^{-1} .

$(L_{\infty} - L_t)$: concentration of product at any time.

The value of k_1 for each temperature was evaluated from the slope of the linear plots of $\ln(L_{\infty} - L_t)$ against (t), the data plots are shown in the fig. (3) and the summary of findings of k , $t_{1/2}$, and R^2 are given in the table(2), where $t_{1/2}$ is the half-life of the reaction R^2 is the correlation coefficient which is a measure of the goodness-of-fit of the regression and $0 \leq R^2 \leq 1$.

The k_1 -values that obtained from conductivity measurements in table (2) shows fair agreement with the absorbance measurements, as explained previously, the sultam (C) with (p-OCH₃) electron donating group are more faster reactions than the others.

Applying Arrhenius equation in fig.(4) and obtaining E_a , R^2 and A-factor are given in table(3) sultam (C) needs smaller energy ($E_a = 51.702 \text{ kJ.mol}^{-1}$) to reach transition state and sultam (B) needs higher energy($E_a=62.822 \text{ kJ.mol}^{-1}$) due to (p-Cl) electron withdrawing effect. $\Delta H^\ddagger$ have positive values which means endothermic reaction (table(4)), And $\Delta S^\ddagger$ values for sultam (C) has large negative values which means the formation of the more stable transition state.

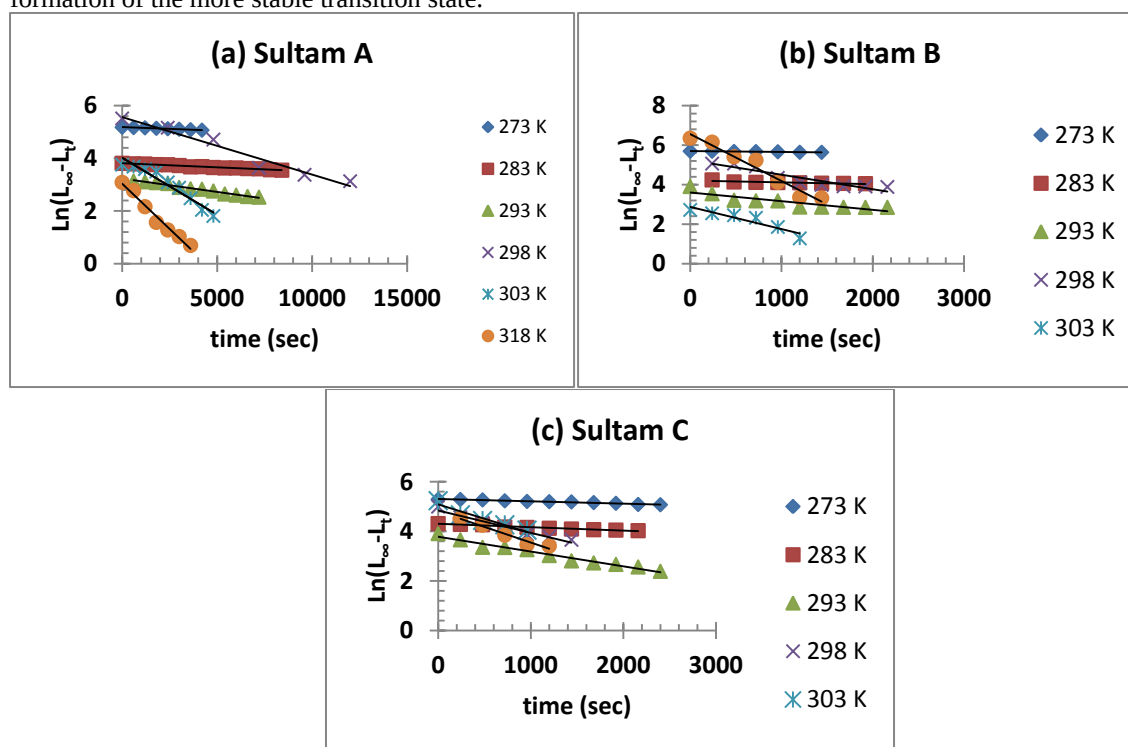


Figure (3): first order plot for the conductivity of the HCl of sultam (A, B, C) with iodine monochloride in chloroform using 1:15 molar ratio reactants.

Table (2): Observed rate constants, for the iodination of sultams by ICl with molar ratio (1:15).

(a) For sultam A

Temp. (K)	$k_1 \times 10^{-4} (\text{sec}^{-1})$	$t_{1/2} (\text{sec})$	R^2
273	0.3	23100.0	0.991
283	0.7	9900.0	0.983
293	1.5	4620.0	0.981
298	2.3	3013.0	0.964
303	3.3	2100.0	0.911
318	9	770.0	0.977

(b) For sultam B

Temp. (K)	$k_1 \times 10^{-4}(\text{sec}^{-1})$	$t_{1/2}(\text{sec})$	R^2
273	0.15	46200.0	0.949
283	0.34	20382.3	0.906
293	0.88	7875.0	0.992
298	1.3	5330.7	0.969
303	2.1	3300.0	0.981
318	7.4	936.4	0.957

(c) For sultam C

Temp. (K)	$k_1 \times 10^{-4}(\text{sec}^{-1})$	$t_{1/2}(\text{sec})$	R^2
273	0.89	7786.5	0.976
283	1.5	4620.0	0.967
293	4	1732.5	0.992
298	5.6	1237.5	0.957
303	8	866.2	0.931
318	20	346.5	0.975

The rate constants for the reaction at the six different temperatures were plotted against $1/T$ and the activation energy (E_a) was calculated from the slope of the Arrhenius plot (as shown in fig. (6)) which shows a good straight line with the slope of $(-E_a/R)$ as in the equation (2):

$$(2) \quad \ln k = \ln A - E_a / RT$$

From the obtained results of the activation energy E_a , the enthalpy of activation $\Delta H^\ddagger$, entropy $\Delta S^\ddagger$ and Gibbs free energy of activation $\Delta G^\ddagger$ can be obtained using equations^[13-15]:

$$\Delta H^\ddagger = E_a - RT \quad (3)$$

$$A = \frac{eKT}{h} e^{\frac{\Delta S^\ddagger}{R}} \quad (4)$$

$$A = \frac{eKT}{h} e^{\frac{\Delta S^\ddagger}{R}} \quad (5)$$

$$\Delta S^\ddagger = R(\ln A - \ln(e k_b T / h)) \quad (6)$$

$$\Delta S^\ddagger = R(\ln A - \ln(e k_b T / h))$$

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$

$$\text{where } k_b = 1.3806 \times 10^{-23} \text{ J K}^{-1}, h = 6.626 \times 10^{-34} \text{ J sec.}$$

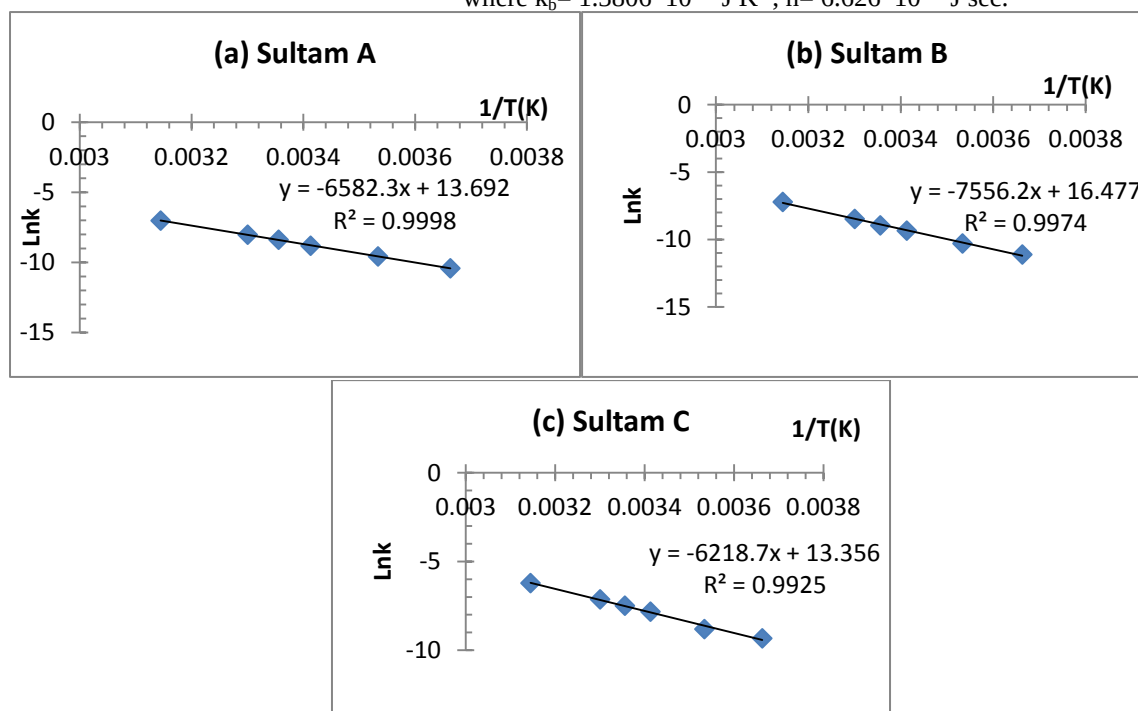


Figure (4): Arrhenius plots for iodination of sultams (A, B, C) at different temperatures using (1:15) molar ratio of sultam: ICl.

Table (3): Arrhenius parameters and entropies of activation for the iodination of sultams (A, B, C) using (1:15)

molar ratio of sultam: ICl.

Sultam	E_a (kJ.mol ⁻¹)	R^2	A-factor/ s ⁻¹	$\Delta S^\ddagger$ (J. K ⁻¹ .mol ⁻¹) at 298K
A	54.725	0.999	8.838×10^5	-139.384
B	62.822	0.997	1.431×10^7	-116.230
C	51.702	0.992	6.315×10^5	-142.178

Table (4): Thermodynamic parameters for the iodination reaction of sultams (A, B, C) using (1:15) molar ratio of sultam: ICl.

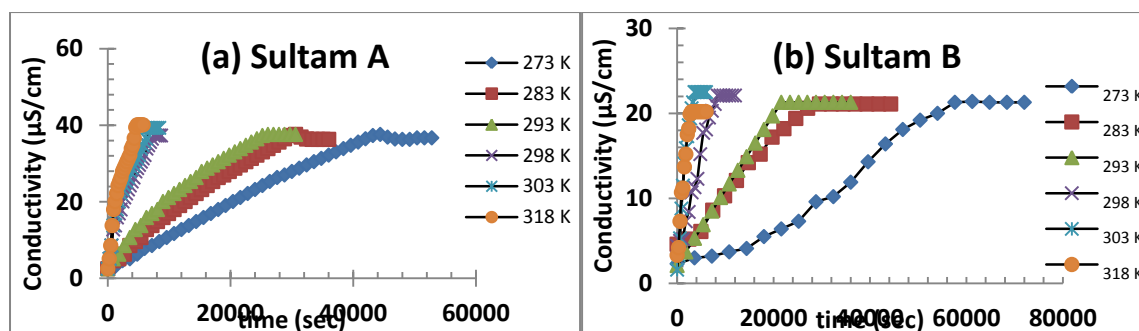
Sultam	Temp. (K)	$\Delta H^\ddagger$ (kJ.mol ⁻¹)	$\Delta S^\ddagger$ (J. K ⁻¹ .mol ⁻¹)
A	273	52.455	-138.656
	283	52.372	-138.955
	293	52.289	-139.243
	298	52.247	-139.384
	303	52.206	-139.522
	318	52.081	-139.924
B	273	60.552	-115.501
	283	60.469	-115.800
	293	60.386	-116.089
	298	60.344	-116.230
	303	60.303	-116.368
	318	60.178	-116.770
C	273	49.432	-141.449
	283	49.349	-141.748
	293	49.266	-142.037
	298	49.224	-142.178
	303	49.183	-142.316
	318	49.058	-142.718

A. The iodination using sultam :ICl(15:1) molar ratio

Sultam:ICl (15:1) the physical properties, H¹- and C¹³-nmr, IR and Uv-data are all very close to that of the unsubstituted (by iodine) sultams. Of course a reaction has been achieved between 1mmole of ICl and 15mmole sultam but the product disappeared between the large quantities of sultam, in addition to that the product is more soluble in solvents than sultam itself during recrystallization and this is one of the reason that the product is undetectable even by IR, H¹-nmr and C¹³-nmr and so it wasn't possible to do kinetic work for these reactions.

B. The iodination using sultam :ICl(1:1) molar ratio

The variation of the conductivity of the HCl gas evolved in the reaction as a side product, dissolved in a particular volume of water with time at six different temperatures is shown in fig.(5) which is clearly indicates that the rate of the reaction improved with increasing temperature.



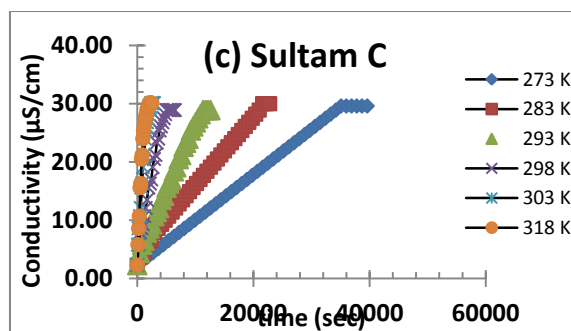


Figure (5): Variation of conductivity of HCl with time for iodination of sultams (A, B, C) at different temperatures using (1:1) molar ratio of sultam: ICl.

The rate law can be expressed by the equation:

$$\frac{d[\text{product}]}{dt} = k_2 [\text{Br}_2][\text{Sultam}] \quad (8)$$

These reactions were determined as second order equation; first-order with respect to each reactant and can be described by equation (9)^[11,12,16,17]:

$$(9) \quad \frac{L_t}{L_\infty(L_\infty - L_t)} = k_2 t$$

Which means that the straight line plot of $L_t/(L_\infty(L_\infty - L_t))$ with the time (t) has a slope (k_2) which is the second order rate constant, the plots show excellent fit to the second order equation as shown in fig. (6) and the data are tabulated in the table (5). This table shows that the rate constants are large for sultam (C) as comparing with sultam (B), as this was also noticed in the absorbance data, indicating that the conductivity and absorbance data are in the same trend.

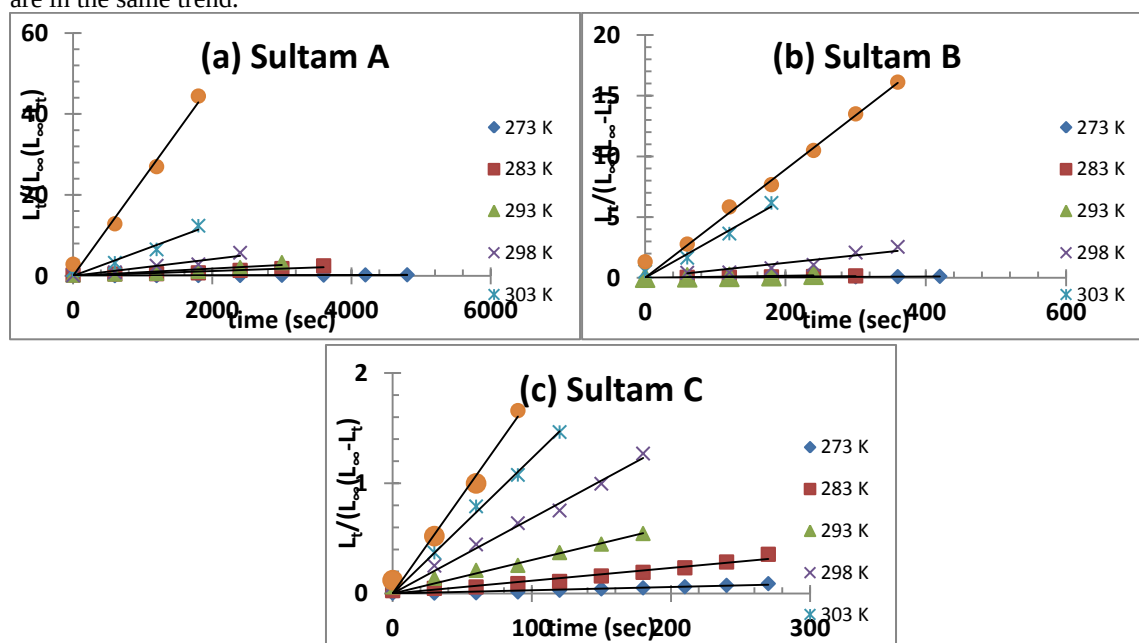


Figure (6): second order plot for the conductivity of HCl for iodination of sultams (A, B, C) at different temperatures using (1:1) molar ratio of sultam: ICl.

Table (5): Observed rate constants, for the iodination of sultams with ICl.

(a) For sultam A

Temp. (K)	$k_2 \times 10^{-4} (\text{sec}^{-1} \cdot \text{dm}^3 \cdot \text{mol}^{-1})$	$t_{1/2}(\text{sec})$	R^2
273	3	33534.5	0.937
283	8.3	12120.9	0.923
293	21	4790.6	0.976
298	44	2286.4	0.920
303	74	1359.5	0.985
318	202	498.0	0.923

(b) For sultam B

Temp. (K)	$k_2 \times 10^{-4} (\text{sec}^{-1} \cdot \text{dm}^3 \cdot \text{mol}^{-1})$	$t_{1/2}(\text{sec})$	R^2
273	2	50301.8	0.955
283	9	11178.1	0.958
293	13	7738.7	0.980
298	18	5589.0	0.967
303	68	1479.4	0.984
318	186	540.8	0.900

(c) For sultam C

Temp. (K)	$k_2 \times 10^{-4} (\text{sec}^{-1} \cdot \text{dm}^3 \cdot \text{mol}^{-1})$	$t_{1/2}(\text{sec})$	R^2
273	6	16767.2	0.945
283	15	6706.9	0.958
293	35	2874.3	0.960
298	50	2012.0	0.979
303	72	1397.2	0.972
318	171	588.3	0.959

From the Arrhenius plot the activation energies and A-factor were obtained. Sultam (B) has large E_a value ($72.104 \text{ kJ} \cdot \text{mol}^{-1}$) means that it needs large amount of energy for the reactants to reach the product, and this is due to the electron withdrawing group (p-Cl) that is present on the phenyl ring of the sultam (B) which decreases the electrophilicity of the sultam to attack the I^+ while sultam (C) has smaller E_a value ($54.143 \text{ kJ} \cdot \text{mol}^{-1}$) due to the effect of the (OCH_3) group at the para-position of phenyl ring of the sultam (C). The positive values of $\Delta H^\ddagger$ indicate the endothermic nature of the process. The A-values are low explained according to the transition state theory, which indicates the more rigid configuration with less degree of freedom for the activated complex. Moreover, the negative value of $\Delta S^\ddagger$ corresponds to a decrease in the degrees of freedom of the product.

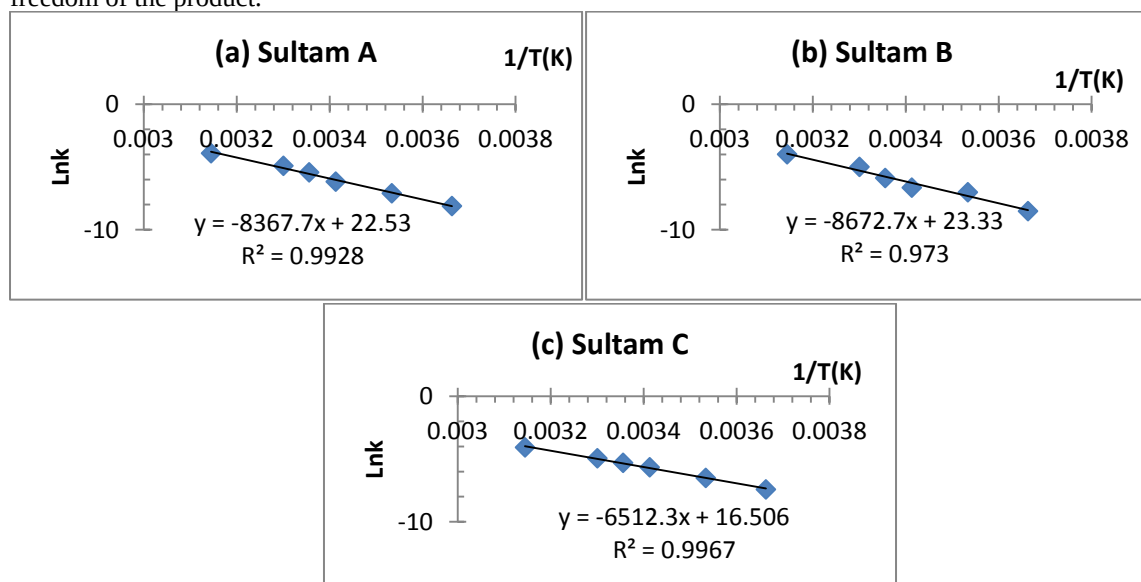


Figure (7) : Arrhenius plots for iodination of sultams (A, B, C) at different temperatures using (1:1) molar ratio of sultam: ICl.

Table (6): Arrhenius parameters and entropies of activation for the iodination of sultams (A, B, C) using (1:1) molar ratio of sultam: ICl.

Sultam	E_a ($\text{kJ} \cdot \text{mol}^{-1}$)	R^2	A-factor ($\text{s}^{-1} \cdot \text{dm}^3 \cdot \text{mol}^{-1}$)	$\Delta S^\ddagger$ ($\text{J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$) at 298K
A	69.569	0.992	6.090×10^9	-65.905

B	72.104	0.973	1.355×10^{10}	-59.254
C	54.143	0.997	1.473×10^7	-115.989

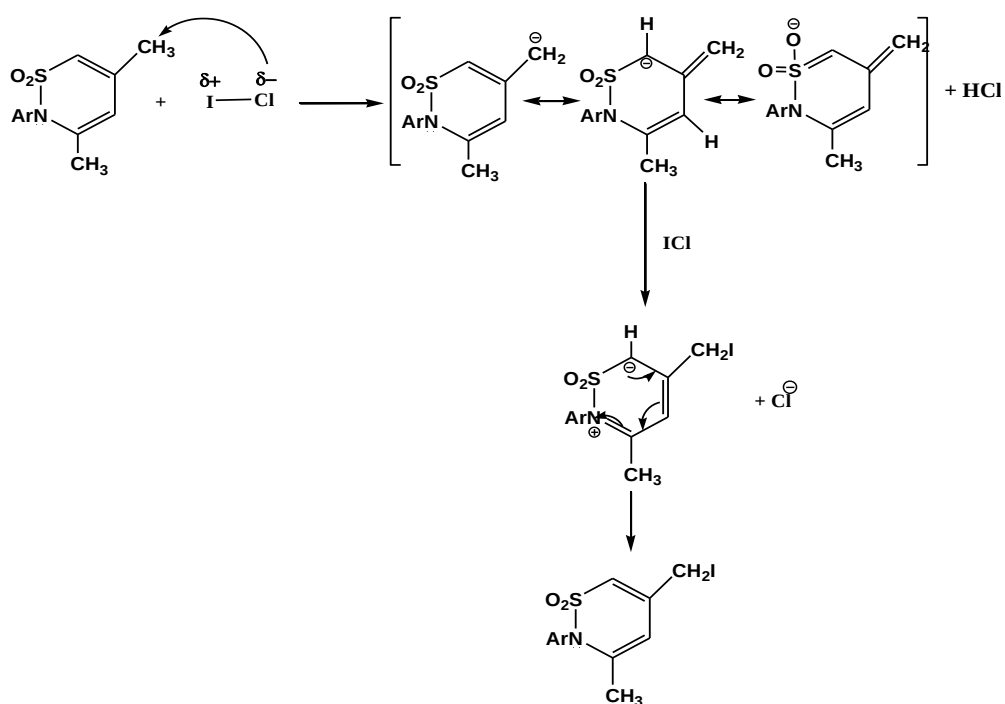
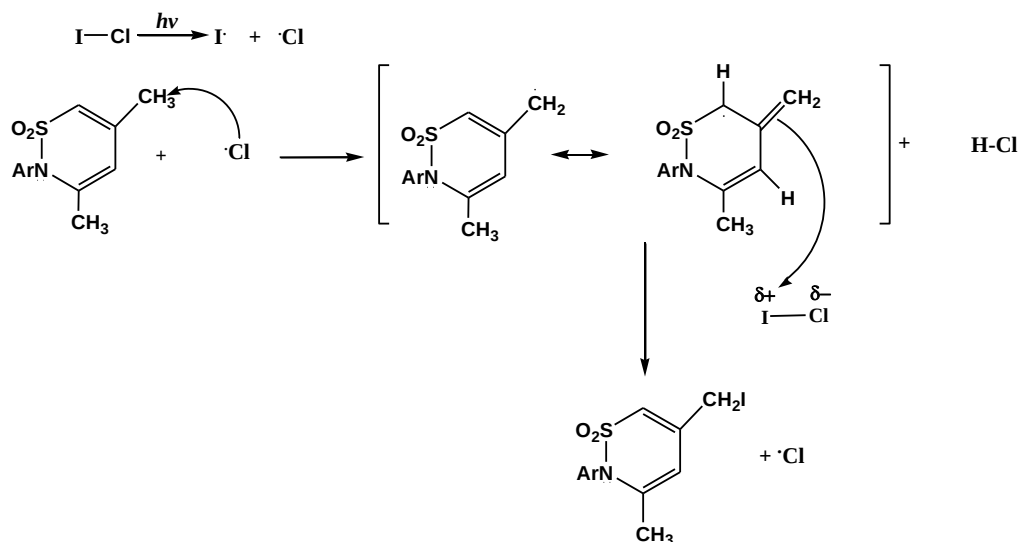
Table (7): Thermodynamic parameters for the iodination reaction of sultams (A, B, C) using (1:1) molar ratio of sultam: ICl.

Sultam	Temp. (K)	$\Delta H^\#$ (kJ.mol ⁻¹)	$\Delta S^\#$ (J. K ⁻¹ .mol ⁻¹)
A	273	67.299	-65.176
	283	67.216	-65.476
	293	67.133	-65.764
	298	67.091	-65.905
	303	67.049	-66.043
	318	66.925	-66.445
B	273	69.835	-58.525
	283	69.751	-58.824
	293	69.668	-59.113
	298	69.627	-59.254
	303	69.585	-59.392
	318	69.460	-59.794
C	273	51.873	-115.260
	283	51.790	-115.559
	293	51.707	-115.848
	298	51.665	-115.989
	303	51.624	-116.127
	318	51.499	-116.529

C. Reaction mechanism

It is seldom, if ever, possible to provide complete and entire information, structural, energetic, and stereochemical, about the pathway that is traversed by any chemical reaction: no reaction mechanism can ever be proved to be correct.

Based on the results obtained we propose a mechanistic explanation illustrated in scheme (2) and (3) to account for the products formed, but the most preferable and accepted mechanism is scheme(3) Due to the electronegativity difference between chlorine and iodine, ICl is highly polar and behaves as an iodinating reagent^[23].



IV. CONCLUSION

The proposed experimental techniques that have been used in kinetics and thermodynamic studies are quite simple and free from rigid experimental conditions and are characterized by wide linear dynamic ranges and high sensitivity. The importance of the present investigation is to demonstrate the possibility of using a modern conductometer to investigate these reaction kinetics.

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