

## Kinetics and Mechanisms of Acid-Catalyzed Hydrolysis of Some *N*-(4-Substitutedaryl) Succinimide Compounds

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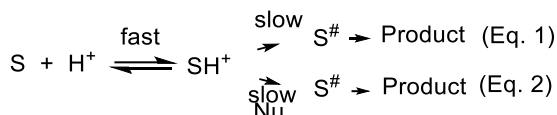
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**Summary:** In this study, the mechanism of acid catalyzed hydrolysis of *N*-(4-substitutedaryl) succinimides in different acids was investigated. These acids are hydrochloric acid, perchloric acid and sulfuric acid, which were studied at 50.0±0.1°C. Analyses of the results obtained with the entropy of activation, Excess Acidity treatment and substituent effect are consistent across the entire acid studied by an A-2 mechanism. The catalytic order of strong acids for the acid catalyzed hydrolysis of the compounds studied were as HCl > H<sub>2</sub>SO<sub>4</sub> > HClO<sub>4</sub> in the whole range of acidity. This order is characteristics for an A-2 mechanism.

**Keywords:** Arylsuccinimides; Excess acidity; Activation entropy; Substituent effect; Acid-catalyzed hydrolysis.

### Introduction

Acid-catalyzed reactions as general and specific acid catalysis occur in two different ways [1, 2]. In general acid catalysis, acidic kinds catalyse the reaction according to its own characteristics. The protonation of the substrate becomes the rate-determining step. In a quick step, the conjugate acid of the substrate then reacts to the products. The only source of protonation is H<sub>3</sub>O<sup>+</sup> in specific acid catalyzed, which can happen in two different processes. A unimolecular mechanism A-1, protonated substrate is formed in the rate-limiting step and afterward quickly transforms into products (Eq.1 in Scheme 1). In a bimolecular mechanism A-2, the protonated substrate is attacked by the nucleophile (Nu; e.g., always water) in the rate-limiting step (Eq.2 in Scheme 1). There are a number of criteria determined by kinetic data such as catalytic activity in low and high acidity mechanisms [3-6], shapes of profiles [7], excess acidity treatment [8], thermodynamic data [9], and affection of substituent [10].



**S:** Substrat

**SH<sup>+</sup>:** Protonated substrate

**Nu:** Nucleophile

(Eq.1) Unimolecular reaction A-1, (Eq.2) Bimolecular reaction A-2

Scheme-1: Specific acid-catalyzed reactions.

A bimolecular mechanism at low acidity is indicated by substituent effect, entropy effects and excess acidity method with analysis of the data by the Cox–Yates [11-13]. At higher acidities, an A-1 mechanism is observed. A unimolecular mechanism has ΔS<sup>‡</sup> of 0 to -41.7 JK<sup>-1</sup>mol<sup>-1</sup>, while the reaction with a bimolecular mechanism has ΔS<sup>‡</sup> of -62.9 to -125.6 JK<sup>-1</sup>mol<sup>-1</sup> in the acid catalyzed hydrolysis of compounds proceeding. Amidosulfites [14], *N*-(4-substitutedarylsulfonyl) phthalimides [15], (4-methoxybenzoyl)-4-tolueniminosulfonate [16], and substitutedarylthio phthalimides [17] kinetic studies have been reviewed in the literature.

Substituted succinimides are important compounds for drugs. In organic chemistry, the design and synthesis of molecules that are important in human health is one of the main objectives. Cyclic imides and derivatives are cross biological membranes in vivo [18]. Many studies have been conducted in terms of their biological activities and pharmaceutical uses. For example, succinimide forms the structure of many molecules with important activities such as analgesic [19], bacteriostatic [20], antifungal [21], hypotensive [22], muscle relaxant [23], antitumor [24], antimicrobial [25], CNS depressant [26], anorectic [27], anticonvulsant [28], anti-tubercular [29], nerve conduction blocking [30], antibacterial [31], antispasmodic [32] and cytostatic [33] activities.

There is no kinetic studies have been conducted on *N*-(4-substitutedaryl) succinimides. In this study, it was aimed to obtain more information about the hydrolysis of *N*-(4-substitutedaryl) succinimides **3a-c** in acid solutions of different concentrations at 50.0±0.1°C.

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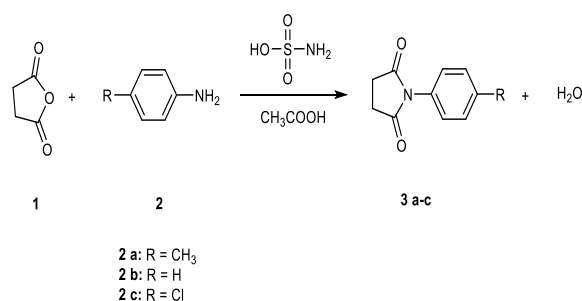
## Experimental

### Chemicals, Reagent and Apparatus

All chemical reagents were obtained from Merck and were used without further purification. The physical data of all synthesized products were characterized by comparing them with samples prepared by classical methods. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were determined in a Bruker Avance III 400 MHz NMR Spectrometer in  $\text{DMSO-d}_6$  using tetramethylsilane (TMS) as the internal standard. Perkin Elmer Spectrum Two FT-IR spectrophotometer equipped with an ATR module was used to carry out the IR spectra of the prepared compound in a region from  $4000\text{--}400\text{ cm}^{-1}$ . All kinetic measurements of the *N*-(4-substitutedaryl) succinimides were performed on Thermo Evolution 220 Ultraviolet-Visible Spectrophotometer. Melting points were determined on a Stuart SMP30 Electrothermal Digital Melting Point Apparatus.

### Synthesis

A mixture of succinic anhydride (5 mmol) and *p*-substitute aniline (5 mmol) was dissolved in acetic acid (25 mmol). Also, sulphamic acid (10 mol%) was added as a catalyst. The reaction mixture was refluxed at  $110^\circ\text{C}$  for 5 minutes as appropriate time. After that, the reactions mixture was poured into water. The solid was collected by filtration under vacuum, washed with cold water and recrystallized in ethyl acetate to give **3a-c** as white crystals [34] in Scheme-2.



Scheme-2: Synthesis of *N*-(4-substitutedaryl) succinimides (**3a-c**)

## Results and Discussion

### Spectral Evaluations

*N*-(4-Methylphenyl)succinimide (**3a**): White solid (0.80 g, 86%); m.p.  $154^\circ\text{C}$ ; Lit.<sup>[34]</sup> m.p.  $154^\circ\text{C}$ ; IR (ATR) ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3064, (Ar. CH), 2958 ( $-\text{CH}_3$ ), 1750–1715 ( $\text{C=O}$ ), 1600–1450 ( $\text{C=C}$ );  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ ) ( $\delta$ , ppm): 7.47, 7.45 (2H, d, Arom.), 7.09, 7.07 (2H, d, Arom.), 3.30 (4H, s, Succ.), 2.24 (3H, s, -

$\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ ) ( $\delta$ , ppm): 174.33, 170.26 ( $\text{C=O}$ ), 137.26, 132.21, 129.50, 119.36 (Arom. C), 31.40, 29.26 (Succ. C), 20.87 ( $-\text{CH}_3$ )

*N*-(Phenyl) succinimide (**3b**): White solid (0.80 g, 90%); m.p.  $154^\circ\text{C}$ ; Lit.<sup>[34]</sup> m.p.  $157^\circ\text{C}$ ; IR (ATR) ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3088, (Ar. CH), 1750–1715 ( $\text{C=O}$ ), 1600–1450 ( $\text{C=C}$ );  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ ) ( $\delta$ , ppm): 7.59, 7.57 (2H, d, Arom.), 7.30, 7.28, 7.27 (2H, t, Arom.), 7.04, 7.02, 7.00 (1H, t, Arom.), 3.40 (4H, s, Succ.);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ ) ( $\delta$ , ppm): 174.31, 170.54 ( $\text{C=O}$ ), 139.75, 129.14, 123.38, 119.34 (Arom. C) 31.46, 29.23 (Succ. C);

*N*-(4-Chlorophenyl) succinimide (**3c**): White solid (0.9, g, 92%); m.p.  $165^\circ\text{C}$  Lit.<sup>[34]</sup> m.p.  $165^\circ\text{C}$ ; IR (ATR) ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3043, (Ar. CH), 1750–1715 ( $\text{C=O}$ ), 1100–1035 ( $\text{C-Cl}$ );  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ ) ( $\delta$ , ppm): 7.62, 7.60 (2H, d, Arom.), 7.35–7.33 (2H, d, Arom.), 3.40 (4H, s, Succ.);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ ) ( $\delta$ , ppm): 174.26, 170.73 ( $\text{C=O}$ ), 138.68, 129.05, 126.88, 120.86 (Arom. C) 31.46, 29.23 (Succ. C)

### Kinetic studies

The hydrolysis rates of substrate **3a-c** were measured at wavelengths of 240 nm at  $50.0 \pm 0.1^\circ\text{C}$ . For all synthesized compounds, kinetic studies were performed by injecting  $20\text{ }\mu\text{L}$  of  $1.0 \times 10^{-2}\text{ M}$  stock solution of the substrate in acetonitrile into  $3.0\text{ mL}$  of the acid solution equilibrated at  $50.0 \pm 0.1^\circ\text{C}$  in a quartz cuvette. Clear isosbestic points were observed with good first order behaviour. Values of  $k_1$  were calculated from the standard equation using a least squares procedure (Eq.3.). Thus, a plot of  $\ln[A]$  against time is linear with slope  $-k_1$  and intercept  $\ln[A]_0$ . The solutions used in the kinetic studies were prepared with deionized water, HPLC grade acetonitrile, and analytical grade concentrated acids, making appropriate allowance for the water content of the acid.

$$\text{Rate} = -\frac{d[A]}{dt} = k_1[A] \text{ Therefore } \ln[A] - \ln[A]_0 = -k_1 \cdot t$$

Eq.3. Calculation of rate constant in first order reactions

$[A]_0$  : the initial concentration of A at time  $t=0$

First-order rate coefficients,  $k_1$ , in the hydrolysis of *N*-(phenyl) succinimide **3b**, one of the synthesized compounds, in the studied acid solutions are given in Fig 1. Increasing concentration of acids in the studied range raised the rates of hydrolysis continuously in all cases.

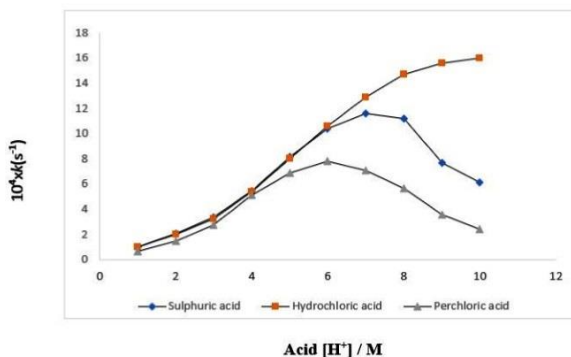


Fig. 1:  $k_1$  plots of different aqueous acid solutions for acid-catalyzed hydrolysis of **3b** at  $50.0 \pm 0.1^\circ\text{C}$ .

#### Product Analysis

After the kinetic experiment was completed, the UV spectrum of the hydrolysis products obtained was compared with the spectrum of the products thought to be formed under the same conditions. Therefore, it was observed that the UV spectrum of the hydrolysis of *N*-(4-chlorophenyl) succinimide was the same as that of a 1: 1 mixture of succinimide and 4-chloroaniline.

#### Electrolyte Effect

For the hydrolysis of **3b**, catalytic efficiency order of the acids was observed as  $\text{HCl} > \text{H}_2\text{SO}_4 > \text{HClO}_4$  or  $\text{H}_2\text{SO}_4 > \text{HCl} > \text{HClO}_4$  in the whole range of acidity. Bunton et al. put forward that the positive character transition states are characteristic for a bimolecular mechanism in such a case, as they are preferably stabilized by anions with high charge density. The opposite is generally true for a unimolecular mechanism [3, 4].

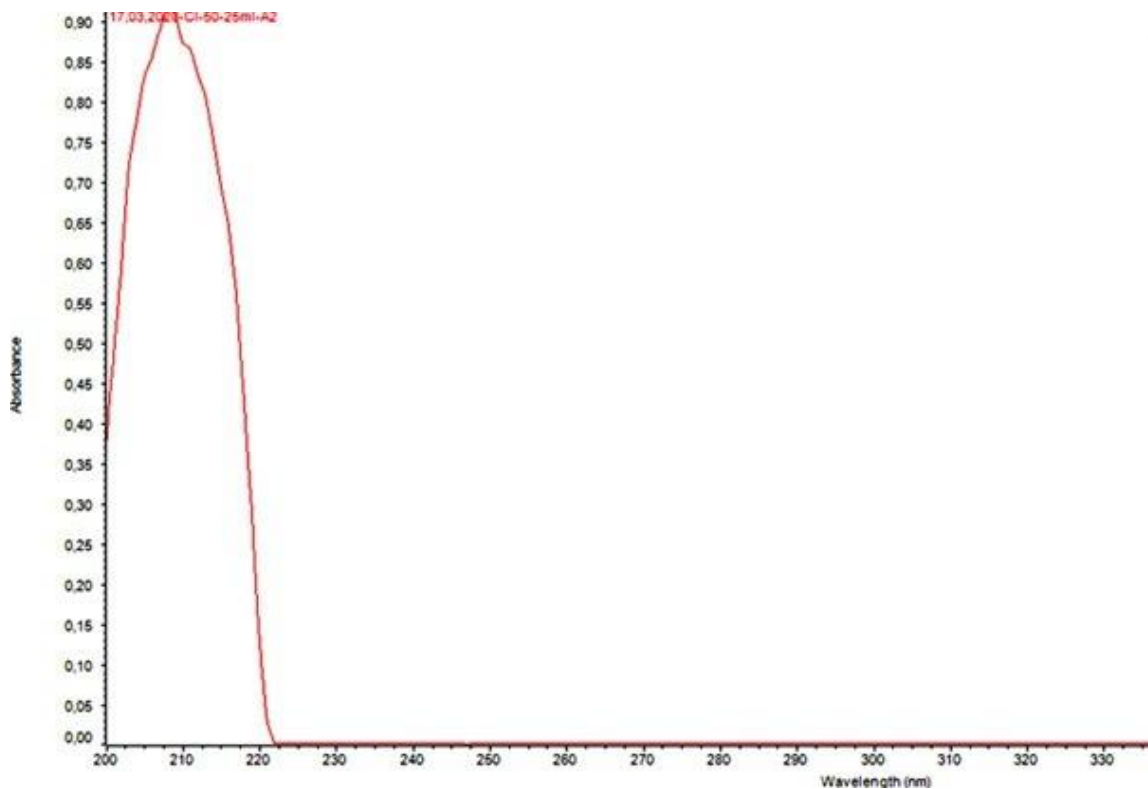


Fig. 2: Spectrum of *N*-(4-Chlorophenyl)succinimide in 6.00 M HCl acid solution.

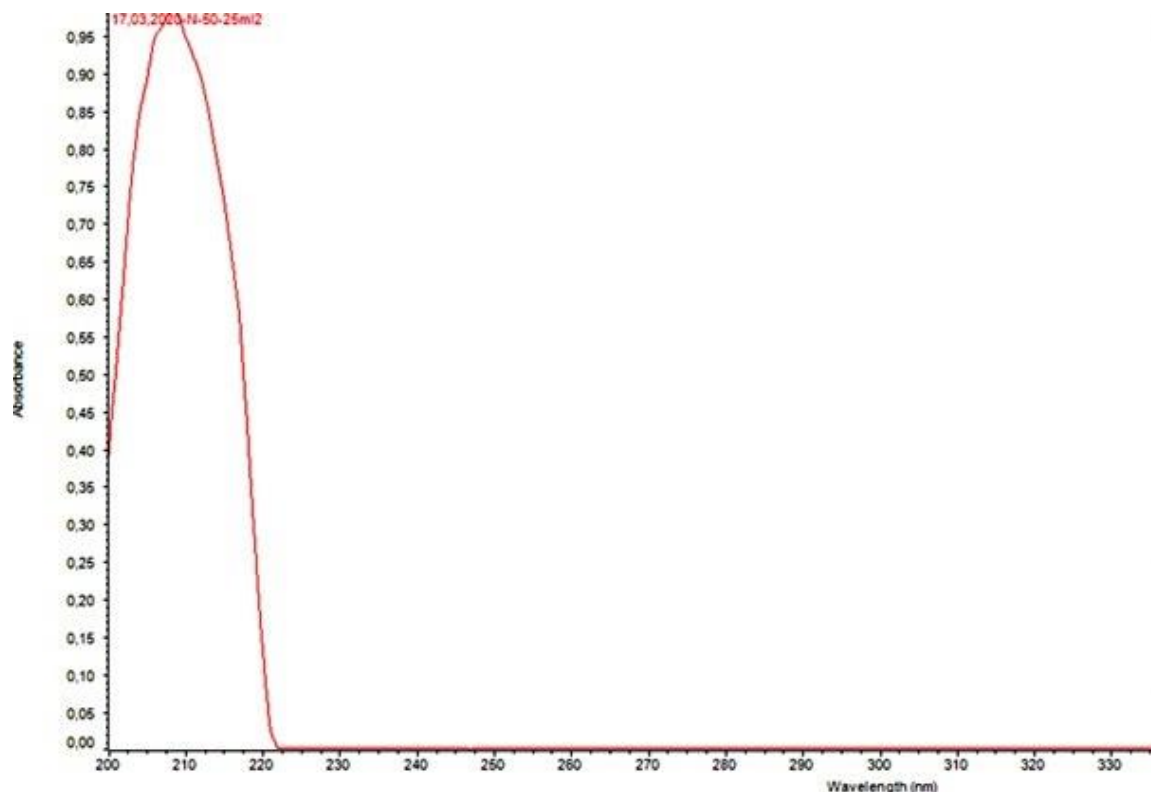


Fig. 3: Spectrum of succinic acid and 4-chloroaniline in 6.00 M HCl acid solution.

Table-1:  $10^4 k_1$  ( $s^{-1}$ ) Values for the hydrolysis of *N*-(4-substitutedaryl) succinimides at  $50.0 \pm 0.1^\circ C$

[H <sup>+</sup> ]/M	3a			3b			3c		
	H <sub>2</sub> SO <sub>4</sub>	HClO <sub>4</sub>	HCl	H <sub>2</sub> SO <sub>4</sub>	HClO <sub>4</sub>	HCl	H <sub>2</sub> SO <sub>4</sub>	HClO <sub>4</sub>	HCl
1.00	0.90	0.42	0.73	1.02	0.69	1.01	1.20	1.35	1.23
2.00	1.87	0.90	1.51	2.11	1.48	2.03	2.50	2.71	2.50
3.00	3.00	2.00	2.50	3.35	2.75	3.20	4.20	4.20	4.00
4.00	4.50	4.39	4.71	5.45	5.10	5.40	6.90	6.08	6.53
5.00	6.81	6.62	7.10	8.15	6.85	8.00	9.90	9.20	9.50
6.00	8.47	7.68	9.20	10.40	7.79	10.60	13.20	10.60	12.60
7.00	9.31	6.20	11.20	11.60	7.09	12.90	16.00	9.60	15.90
8.00	8.49	4.47	12.90	11.20	5.65	14.70	15.80	7.71	17.90
9.00	4.48	3.64	13.80	7.69	3.54	15.60	12.30	5.57	19.40
10.00	3.12	2.89	14.20	6.12	2.44	16.00	8.67	3.80	20.30

#### Excess Acidity Method

The kinetic data obtained using the Cox and Yates Excess Acidity method are shown in Table 1 [11, 12, 13]. Eq.4 is used in a simplified form of the equations for unprotonated substrates.

$$\log k_1 - \log C_{H^+} - [\log C_s / (C_s + C_{SH^+})] = m^* m^\ddagger X + r \log a_{Nu} + \log (k_0 / K_{SH^+}) \quad (\text{Eq.4})$$

In the equation (4),  $k_1$  is the pseudo first order rate constant in aqueous acid concentration  $C_{H^+}$  and of Excess Acidity  $X$  and  $m^* m^\ddagger$  are the slope parameters. In the same equation,  $m^\ddagger$  the nature of the type of reaction;  $r \log a_{Nu}$  for the bimolecular reaction indicates the activity of the nucleophile, where  $r$  is the

number of water molecules involved in the formation of the transition state [11-13].

Because of the low basicity of synthesized *N*-(4-substitutedaryl) succinimides, the term protonation correction  $[\log C_s / (C_s + C_{SH^+})]$  is negligible.  $X$  values were used for aqueous solution of the acid [11].

The graph of  $\log k_1 - \log C_{H^+}$  versus  $X$  for the hydrolysis of **3b** in HCl solution is shown in Fig 4. Similar plots were followed for **3a** and **3c** in HCl solution. Such plots for the arylphthalimides typically show the downward curvature of bimolecular reactions involving water in the low acidic region [7].

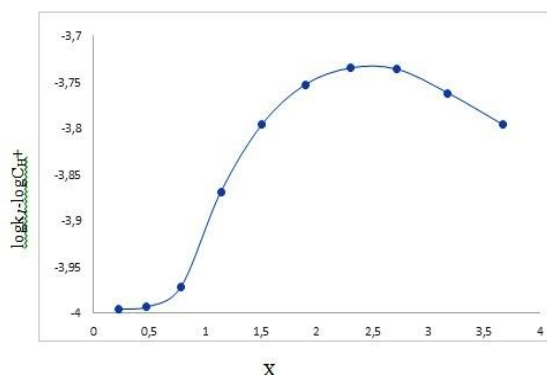


Fig. 4: Plots of excess acidity versus  $\log k_1 - \log C_{H^+}$  for the hydrochloric acid catalyzed hydrolysis of **3b** at  $50.0 \pm 0.1^\circ\text{C}$ .

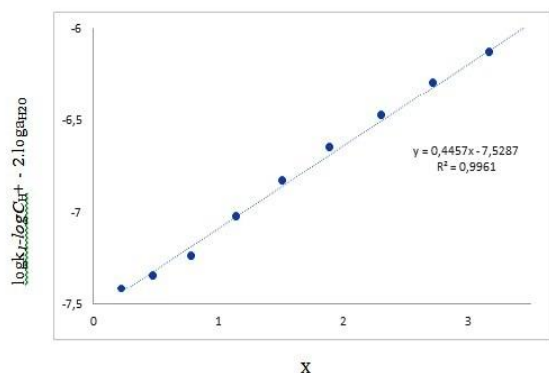


Fig. 5: Plots of excess acidity versus  $\log k_1 - \log C_{H^+} - 2 \log a_{H_2O}$  for the 1.00–10.00 M hydrochloric acid catalyzed hydrolysis of **3b** at  $50.0 \pm 0.1^\circ\text{C}$ .

As can be seen in Fig 4, as the acid concentration increases up to 7.00 M the hydrolysis rate increases. After 7.00 M, the rate of reaction slows down with the increase in acid concentration. Water

activity decreases with increasing acid concentration and the reaction rate decreases due to the decrease in water activity. A curve is formed in the range of 1.00–10.00 M acid. The curve obtained shows that the reaction proceeds through to an A-2 mechanism in this range. Subtracting 2 moles of water activity according to Fig 5, a straight line was obtained. Accordingly, it is understood that there are 2 moles of water in the rate determination step of an A-2 mechanism.

#### Entropies of Activation

The relationship between temperature and rate constants was analyzed using the Eyring equation in the study (Eq.5.). Tables-2 and 3 show the values of Arrhenius parameters at different temperatures.

$$k = \left( \frac{k_B T}{h} \right) \exp \left( - \frac{\Delta G^\ddagger}{RT} \right) = \left( \frac{k_B T}{h} \right) \exp \left( - \frac{\Delta S^\ddagger}{R} \right) \exp \left( - \frac{\Delta H^\ddagger}{RT} \right)$$

Eq. 5. Eyring equation

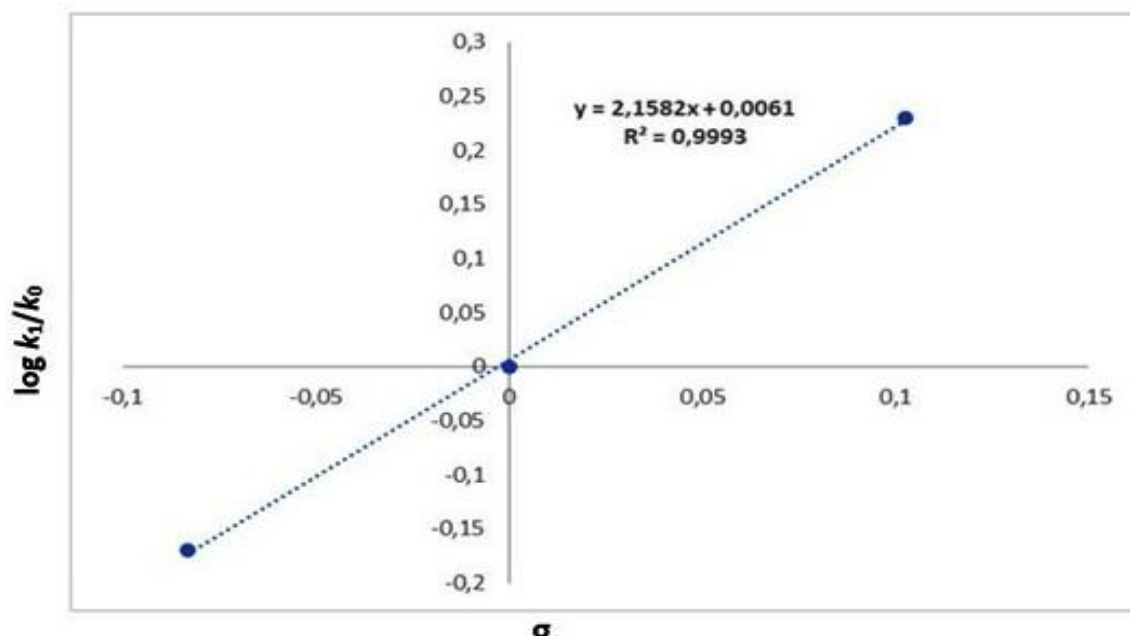
Acid catalyzed hydrolysis of esters and amides [9] proceeding by a unimolecular mechanism have  $\Delta S^\ddagger$  of about 0 to  $-41.8 \text{ Jmol}^{-1}\text{K}^{-1}$ , while those proceeding by a bimolecular mechanism have  $\Delta S^\ddagger$  of  $-62.9$  to  $-125.6 \text{ Jmol}^{-1}\text{K}^{-1}$ . For the hydrolysis of **3b** in 4.00 M and 8.00 M hydrochloric acid,  $\Delta S^\ddagger$  values are  $-70.20 \pm 0.84$ ,  $-67.24 \pm 0.27 \text{ Jmol}^{-1}\text{K}^{-1}$ , respectively. Moreover, the values obtained for the hydrolysis of **3a** and **3c** vary similarly as predicted. Also, hydrolysis of **3b** in 4.00 M and 8.00 M  $\text{H}_2\text{SO}_4$  and perchloric acid, the values of  $\Delta S^\ddagger$  are  $-78.11 \pm 0.72$ ,  $-67.05 \pm 0.36$ ,  $-66.69 \pm 0.79$  and  $-65.06 \pm 0.74 \text{ Jmol}^{-1}\text{K}^{-1}$ , respectively. In an A-2 mechanism, negative values of  $\Delta S^\ddagger$  indicate that the water molecule behaves like a nucleophile.

Table-2:  $10^4 k_1 (\text{s}^{-1})$  values for the hydrolysis of the **3a-c** at varied temperatures ( $^\circ\text{C}$ )

Compounds	Acid	$[H^+]/M$	40.0	45.0	50.0	55.0
3a	HCl	4.00	1.90	3.00	4.71	7.40
		8.00	5.30	8.01	12.90	20.00
	$\text{H}_2\text{SO}_4$	4.00	1.80	3.00	4.50	7.30
		8.00	3.80	5.81	8.49	1.48
	$\text{HClO}_4$	4.00	1.80	2.80	4.39	7.10
		8.00	1.80	2.86	4.47	6.91
3b	HCl	4.00	2.12	3.35	5.40	8.11
		8.00	6.00	9.00	14.70	22.10
	$\text{H}_2\text{SO}_4$	4.00	2.40	3.84	5.45	9.08
		8.00	4.99	7.15	11.20	18.90
	$\text{HClO}_4$	4.00	2.25	3.59	5.10	9.17
		8.00	2.40	3.95	5.65	9.81
3c	HCl	4.00	2.55	4.20	6.53	9.89
		8.00	7.51	12.80	17.90	29.10
	$\text{H}_2\text{SO}_4$	4.00	2.90	4.50	6.90	11.40
		8.00	7.34	11.00	15.80	27.20
	$\text{HClO}_4$	4.00	2.30	3.45	6.08	8.51
		8.00	3.40	5.30	7.71	13.00

Table-3: Values of  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  for the hydrolysis of *N*-(4-substituedaryl) succinimides.

Compounds	Acid	[H <sup>+</sup> ] / M	$\Delta H^\ddagger$ (kJ/mol)	$\Delta S^\ddagger$ (J/molK)	Temperature Range (°C) <sup>a</sup>	R <sup>2</sup>
3a	HCl	4.00	77.40±0.31	-69.74±0.94	40-55	1.0000
		8.00	76.08±0.04	-65.49±0.13	40-55	0.9993
	H <sub>2</sub> SO <sub>4</sub>	4.00	78.46±0.68	-66.63±2.03	40-55	0.9982
		8.00	76.11±0.18	-68.26±0.54	40-55	0.9932
	HClO <sub>4</sub>	4.00	78.00±0.33	-68.35±1.00	40-55	0.9996
3b		8.00	76.59±0.33	-72.72±0.99	40-55	0.9998
	HCl	4.00	76.95±0.28	-70.20±0.84	40-55	0.9990
		8.00	75.21±0.09	-67.24±0.27	40-55	0.9985
	H <sub>2</sub> SO <sub>4</sub>	4.00	74.16±0.24	-78.11±0.72	40-55	0.9947
		8.00	75.84±0.12	-67.05±0.36	40-55	0.9933
3c	HClO <sub>4</sub>	4.00	77.95±0.26	-66.69±0.79	40-55	0.9907
		8.00	78.25±0.25	-65.06±0.74	40-55	0.9940
	HCl	4.00	77.05±0.23	-68.21±0.70	40-55	0.9982
		8.00	75.18±0.08	-65.17±0.23	40-55	0.9932
	H <sub>2</sub> SO <sub>4</sub>	4.00	77.43±0.20	-66.22±0.62	40-55	0.9987
		8.00	73.25±0.08	-71.95±0.24	40-55	0.9921
	HClO <sub>4</sub>	4.00	76.77±0.26	-70.18±0.78	40-55	0.9913
		8.00	74.95±0.11	-72.78±0.40	40-55	0.9960

<sup>a</sup> The measurements were made at 5°C intervals.Fig. 6: The plot of Hammett  $\sigma$  versus  $\log k$  values for acid catalyzed hydrolysis (4.00 M H<sub>2</sub>SO<sub>4</sub>) of *N*-(4-substituedaryl) succinimides at 50.0 ± 0.1°C.

#### Substituent Effect

It was observed that electron-withdrawing substituents caused a high rate of hydrolysis in the studied acidity range, (**3c**>**3a**), and the Hammett  $\rho\sigma$  plot consistent with the substituent effects [at 4.00 M H<sub>2</sub>SO<sub>4</sub>,  $\rho = 2.158$  (corr. 0.999)] is given in Fig 6. Obviously at these acidity values studied, electron withdrawing groups both stabilize the nitrogen cation and facilitate protonation of the substrate in a bimolecular mechanism. However, [e.g., 8.00 M HCl,  $\rho = 2.802$  (corr. 0.999)] as shown in Fig 7, **3c** was hydrolyzed faster than **3a**. It is predominantly consistent with the bimolecular mechanism, with protonation and slow step substitution effects. Similar behaviours have been observed for

arylsulfonyl phthalimides [15] and substitutedarylthio phthalimides [17] and *N,N*-diarylsulfamides [35] an A-2 mechanism at lower acidities. 2.00 M perchloric acid,  $\rho = 0.848$  (corr. 0.999) for *N*-(4-bromophenylsulfonyl) phthalimides hydrolyzes more rapidly than *N*-(4-methylphenylsulfonyl) phthalimides, predominantly compatible with an A-2 mechanism [15]. Likewise, 1.00 M HClO<sub>4</sub>,  $\rho = 0.803$  (corr. 0.996) for *N*-(4-chlorophenylthio) phthalimides hydrolyzes more rapidly than *N*-(4-methylphenylthio) phthalimides [17]. No study has been conducted of the protonation site of *N*-(4-substituedaryl) succinimides; however, *N*-(4-substituedarylsulfonyl) phthalimides [15] and *N*-(4-substituedarylthio) phthalimides [17] occur preferably at the nitrogen atom

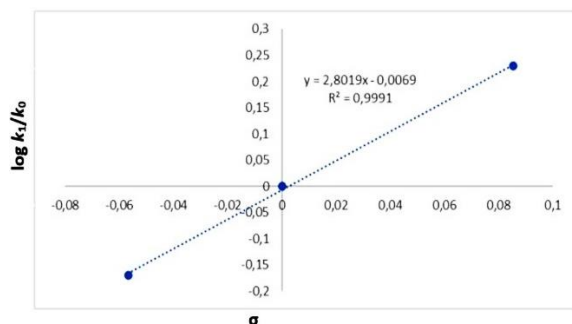
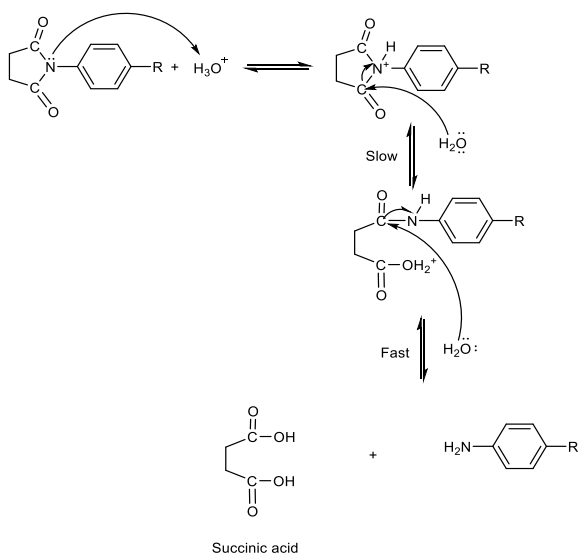


Fig. 7: The plot of Hammett  $\sigma$  versus  $\log k$  values for acid catalyzed hydrolysis (8.00 M HCl) of *N*-(4-substituedaryl) succinimides at  $50.0 \pm 0.1^\circ\text{C}$ .

Based on all these data, we suggested the acid-catalyzed hydrolysis mechanism of the compounds proceeds with an A-2 mechanism in the whole range of acidity as given in Scheme 3. Here, the first step involves rapid pre-equilibrium protonation of the aryl succinimides. It is suggested that two water molecules attack the carbon atom of carbonyl group as the nucleophile in the rate-determining step and the protonation occurs on the nitrogen atom. Then, the products of acid-catalyzed hydrolysis were observed to form succinic acid and 4-substitued aniline.



Scheme-3: A plausible acid-catalyzed hydrolysis mechanism of the *N*-(4-substituedaryl) succinimides.

## Conclusions

The acid-catalyzed hydrolysis of *N*-(4-substituedaryl) succinimide compounds was studied for

the first time. The reaction mechanism was determined by kinetic studies and brought to the literature.

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