



## **Kinetics and Mechanism of Oxidation of Benzyl Ethers by N-Chloroisonicotinamide in Aqueous Acetic Acid Medium**

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**Abstract :** Kinetics of oxidation of five Benzyl ethers viz., Benzyl n-propyl ether, benzyl isobutyl ether, benzyl n-pentyl ether, benzyl t-butyl ether and dibenzyl ether by N-chloroisonicotinamide (NCIN) in aqueous acetic acid medium has been investigated. The observed rate of oxidation is first order in [oxidant] and [HCl], zero order in [substrate]. An increase in the dielectric constant of the medium decreases the rate. Variation in ionic strength of the medium has no significant effect on the rate and the addition of the reaction product, isonicotinamide has a slight retarding effect on the rate. The stoichiometry and product analysis have been carried out. From the effect of temperature on the reaction rate, the Arrhenius and thermodynamic activation parameters have been calculated. A suitable mechanism has been proposed and a rate law explaining the experimental results is obtained.

**Keywords:** Oxidation, Benzyl Ethers, N-Chloroisonicotinamide.

### **Introduction**

Kinetic study is an expanding field of research in chemistry. The role of N-halo compounds in this field is very wide. Halogens, N-haloamides and imides are the versatile agents used for the oxidation of a wide variety of organic compounds [1,2]. The electronegativities of chlorine, bromine and nitrogen are 2.83, 2.74 and 3.07 respectively, according to Pauling's electronegativity scale. Hence a halogen (except fluorine), when linked with nitrogen acquire a positive charge. The electronegativity of nitrogen is further enhanced by linking it with certain electron withdrawing groups such as acyl group. In the N-halo compounds, N-X bond is highly polar and they produce positive halogen ( $X^+$ ) in polar solvents due to protonation or hydrolysis. This positive halogen act as powerful electrophile [3]. Thus N-halo compounds are referred as positive halogen compounds.

N-chloroisonicotinamide (NCIN) is an important N-halo compound. N-chloroisonicotinamide, the derivative of isonicotinamide is a mild, stable, efficient and inexpensive oxidant for organic substrates[4]. The physical constants, stability in aqueous solution, the formal redox potential and elemental analysis confirms the presence of nitrogen-halogen bond. Hence the possibility of the compound serving as an effective source of positive halogen is established.

Benzyl ethers are commonly used as temporary protecting groups for alcohols, owing to the fact that they are stable to both acids and bases. Despite the numerous methods available for their cleavage, which include catalytic and chemical hydrogenolysis, transfer hydrogenation, bromination hydrolysis, acetolysis and the use of halosilane reagents or Lewis acid-thiol systems, problems associated with reagent incompatibility or slow debenzylatonrates often arise when multiple functionality is present. Kinetic study of oxidation of aromatic ethers by some N-halo compounds like, 1-chlorobenzotriazole [5] and N-bromonicotinamide [6] and N-chloronicotinamide [7] have been investigated.

A general review of the work done so far with NCIN as the oxidant, has shown that the kinetic study of oxidation of the chosen benzyl ethers has not been carried out and hence it has been proposed to carry out the title investigation.

## Experimental

Glacial acetic acid (Merck, unaffected by chromic acid GR) was used as a solvent for benzyl ethers, which were prepared by Williamson's synthesis. Benzyl ethers, after isolation were then characterized by boiling point. Final characterization of benzyl ethers was carried out using IR (Spectrum RX1, Perkin Elmer) and <sup>1</sup>H-NMR spectra (Bruker). The IR spectrum of benzyl ethers showed characteristic absorptions for C-O-C in the region 1020-1200 cm<sup>-1</sup>. The oxidant, N-chloroisonicotinamide was prepared by the chlorination of isonicotinamide. The melting point was 221<sup>o</sup>C-225<sup>o</sup>C. NCIN was characterized by <sup>1</sup>H-NMR spectra.

## Kinetic Methods

### Preparation of Standard Solution

The standard stock solution of NCIN was prepared by dissolving the required quantity of it in water and standardized by titrating against standard sodium thiosulphate solution iodometrically. The benzyl ether solutions were prepared by dissolving required quantity of them in acetic acid and water mixture (V/V).

### Kinetic Measurements

In a typically experiment, the required quantities of the benzyl ether solution, hydrochloric acid, sodium perchlorate and acetic acid – water mixture were pipetted out in a clean dried reaction bottle, kept in thermostat, set at the desired temperature and the measurement was rate at 318 K. The reaction was started by pipetting out the required quantity of NCIN solution, which had also been thermostated for nearly half an hour. The total volume of the reaction mixture was always 25ml. 3ml of reaction mixture was pipette out into the conical flask and the progress of the reaction was followed iodometrically.

### Investigation of Stoichiometry

The stoichiometry of the reaction [NCIN]:[benzyl ethers] was determined by taking excess of NCIN over the substrate and the allowing the reaction for completion. Since the concentration of the benzyl ether taken was less compared to that of NCIN, all the benzyl ether would have been completely reacted leaving behind the unreacted NCIN, the concentration of which was estimated by iodometry. Estimation of unreacted NCIN showed that one of benzyl ether consumed one mole of NCIN.

### Product Study

For product study, the substrate was taken in excess compared to concentration of oxidant. The reaction mixture was kept aside for about 48 hours for the completion of the reaction. After that the residual mixture was poured into a separating funnel. Solvent ether was added and shaken well. Then it was washed with distilled water and the ether layer was separated, dried with anhydrous sodium sulphate. After washing several times with water, it was dried and the product was analysed. The major product was found to be benzaldehyde. It was confirmed by spot tests, IR and NMR spectrum.

## Result and Discussion

The oxidation of other benzyl ethers viz., benzyl isobutyl ether, benzyl n-pentyl ether, benzyl t-butyl ether and dibenzyl ether has been studied in the presence of HCl and NaClO<sub>4</sub>. The product of oxidation is benzaldehyde in all the cases.

The results obtained for all the benzyl ethers are similar to what obtained for benzyl n-propyl ether. It is seen that the pseudo first order rate constant remains the same with the increase in the initial concentration of the oxidant. There is no change in the first order rate constant with an increase in the [NCIN] (Table 1).

The zero order dependence of rate of benzyl ethers concentration is shown in (Table 2).

The kinetics of the effect of variation of [HCl] and [NaClO<sub>4</sub>] on the NCIN oxidation of benzyl ethers are studied. The reaction rate increases with the increases in [HCl] (Table 3). The plot of K<sub>obs</sub> Vs log [HCl] is found to be linear with positive slope of one. The reaction rate remains constant with the increasing strength of sodium perchlorate (Table 5).

The data in (Table 4) shows that the rate of oxidation increases with decrease of dielectric constant at the medium. Plot of log K<sub>obs</sub> Vs I/D is linear with positive slope.

The effect of added isonicotinamide shows small decrease in the rate constant for all the benzyl ethers (Table 6).

The temperature dependency of the rates of oxidation is determined by plotting log K<sub>obs</sub> Vs I/T for all the benzyl ethers. The rate constants at 313K, 318K, 323K and 328K for different benzyl ethers have been recorded in (Table 7).

**Table 1 Variation of k<sub>obs</sub> with [NCIN]**

[Benzyl ethers] = 2 x 10<sup>-2</sup>M  
 [NaClO<sub>4</sub>] = 0.1M  
 Solvent = 80% CH<sub>3</sub>COOH – 20% (H<sub>2</sub>O (v/v))

Temperature = 318 K  
 [HCl] = 0.1M

[NCIN] x 10 <sup>3</sup> M	k <sub>obs</sub> x 10 <sup>4</sup> S <sup>-1</sup>				
	Benzyl isobutyl ether	Benzyl n-pentyl ether	Benzyl t-butyl ether	Dibenzyl ether	Benzyl n-propyl ether
1.0	2.98	2.54	3.13	4.01	3.11
2.0	3.24	3.92	3.56	4.98	3.29
3.0	4.57	3.28	4.48	5.47	3.42
4.0	5.13	4.57	5.03	6.20	3.78
5.0	4.48	3.76	4.69	5.59	3.96

**Table 2 Variation of k<sub>obs</sub> with [benzyl ethers]**

[NCIN] = 3 x 10<sup>-3</sup>M  
 [NaClO<sub>4</sub>] = 0.1M  
 Solvent = 80% CH<sub>3</sub>COOH – 20% (H<sub>2</sub>O (v/v))

Temperature = 318 K  
 [HCl] = 0.1M

[S] x 10 <sup>2</sup> M	k <sub>obs</sub> x 10 <sup>4</sup> S <sup>-1</sup>				
	Benzyl isobutyl ether	Benzyl n-pentyl ether	Benzyl t-butyl ether	Dibenzyl ether	Benzyl n-propyl ether
1.0	4.78	3.45	5.32	5.95	4.34
2.0	4.57	3.28	4.48	5.47	3.42
3.0	4.58	2.87	4.98	4.75	3.03
4.0	4.26	2.64	4.11	5.09	2.53
5.0	4.12	3.50	4.51	5.65	2.12

**Table 3 Variation of  $k_{obs}$  with [HCl]**

[Benzyl ethers] =  $2 \times 10^{-2}$ M  
 [NaClO<sub>4</sub>] = 0.1M  
 Solvent = 80% CH<sub>3</sub>COOH – 20% (H<sub>2</sub>O (v/v))

Temperature = 318 K  
 [NCIN] =  $3 \times 10^{-3}$ M

[HCl] M	$k_{obs} \times 10^4 \text{ S}^{-1}$				
	Benzyl isobutyl ether	Benzyl n-pentyl ether	Benzyl t-butyl ether	Dibenzyl ether	Benzyl n-propyl ether
1.0	2.81	2.04	3.23	3.25	2.87
2.0	4.57	3.28	4.48	5.47	3.42
3.0	5.63	4.29	5.26	6.85	3.66
4.0	6.49	5.46	5.98	8.23	3.89
5.0	7.38	6.10	6.80	9.99	4.23

**Table 4 Variation of  $k_{obs}$  with [Dielectric constant]**

[Benzyl ethers] =  $2 \times 10^{-2}$ M  
 Temperature = 318 K  
 [NaClO<sub>4</sub>] = 0.1M

[NCIN] =  $3 \times 10^{-3}$ M  
 [HCl] = 0.1M

[NCIN] $\times 10^3 \text{ M}$	D*	$k_{obs} \times 10^4 \text{ S}^{-1}$				
		Benzyl isobutyl ether	Benzyl n-pentyl ether	Benzyl t-butyl ether	Dibenzyl ether	Benzyl n-propyl ether
70-30	27	2.99	2.53	3.29	3.17	2.53
75-25	23.5	3.63	2.89	3.73	3.81	2.98
80-20	20	4.47	3.28	4.48	5.47	3.42
85-15	16.4	5.53	4.26	5.61	7.99	5.51
90-10	13.5	6.61	5.64	7.88	13.32	7.24

**Table 5 Variation of  $k_{obs}$  with [NaClO<sub>4</sub>]**

[Benzyl ethers] =  $2 \times 10^{-2}$ M  
 Temperature = 318 K  
 Solvent = 80% CH<sub>3</sub>COOH – 20% (H<sub>2</sub>O (v/v))

[NCIN] =  $3 \times 10^{-3}$ M  
 [HCl] = 0.1M

[NaClO <sub>4</sub> ] M	$k_{obs} \times 10^4 \text{ S}^{-1}$				
	Benzyl isobutyl ether	Benzyl n-pentyl ether	Benzyl t-butyl ether	Dibenzyl ether	Benzyl n-propyl ether
0.025	2.54	2.38	2.95	3.78	3.03
0.050	2.97	2.91	3.24	4.05	3.12
0.075	3.32	3.24	3.56	4.31	3.38
0.100	4.57	3.28	4.48	5.47	3.42
0.125	5.56	4.65	5.72	6.48	3.61
0.150	6.98	5.98	6.19	7.85	3.98

**Table 6** Variation of  $K_{obs}$  with added [isonicotinamide]

[Benzyl ethers] =  $2 \times 10^{-2}M$  [NCIN] =  $3 \times 10^{-3}M$   
 Temperature = 318 K [HCl] = 0.1M  
 [NaClO<sub>4</sub>] = 0.1M  
 Solvent = 80% CH<sub>3</sub>COOH – 20% (H<sub>2</sub>O (v/v))

[isonicotinamide] $\times 10^3 M$	$k_{obs} \times 10^4 S^{-1}$				
	Benzyl isobutyl ether	Benzyl n-pentyl ether	Benzyl t-butyl ether	Dibenzyl ether	Benzyl- n-propyl ether
1.0	3.89	3.48	4.25	4.63	3.29
2.0	3.54	3.09	4.03	4.23	3.01
3.0	3.21	2.67	3.86	4.16	2.84
4.0	2.96	2.15	3.41	4.02	2.21

**Table 7** Variation of  $k_{obs}$  with added temperature

[Benzyl ethers] =  $2 \times 10^{-2}M$  [NCIN] =  $3 \times 10^{-3}M$   
 [HCl] = 0.1M [NaClO<sub>4</sub>] = 0.1M  
 Solvent = 80% CH<sub>3</sub>COOH – 20% (H<sub>2</sub>O (v/v))

Temperature K	$k_{obs} \times 10^4 S^{-1}$				
	Benzyl isobutyl ether	Benzyl n-pentyl ether	Benzyl t-butyl ether	Dibenzyl ether	Benzyl- n-propyl ether
313	3.68	2.44	3.25	3.71	2.25
318	4.57	3.28	4.48	5.47	3.42
323	5.96	4.50	6.24	8.39	5.13
328	7.84	5.79	8.05	12.60	7.98

**Table 8** Arrhenius Parameters at 318 K for the oxidation of benzyl ethers

Benzyl ethers	Ea KJmol <sup>-1</sup>	$\Delta H^\ddagger$ KJmol <sup>-1</sup>	$\Delta G^\ddagger$ KJmol <sup>-1</sup>	$\Delta S^\ddagger$ KJmol <sup>-1</sup>	Log A
Benzyl- n-propyl ether	64.717	62.073	78.176	-50.641	7.163
Benzyl isobutyl ether	53.038	50.394	71.236	-65.550	5.371
Benzyl n-pentyl ether	71.610	68.966	66.322	-41.370	8.277
Benzyl t-butyl ether	56.676	54.032	34.748	-60.642	5.959
Dibenzyl ether	47.867	45.223	22.332	-71.983	4.599

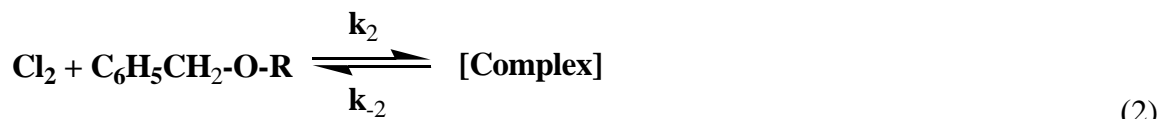
## Mechanism

The active oxidizing species has to be identified before any mechanistic interpretation should be advanced. Under the experimental conditions studied, Cl<sub>2</sub>, HOCl, H<sub>2</sub>OCl<sup>+</sup> and NCIN in aqueous solutions are important oxidizing species. The oxidation of amino acids by N-chlorobenzamide, have utilized chlorobenzotriazole as the oxidant for amino acids. Both the reactions have been reported to take place through the intermediate forms of protonated species of the oxidant or molecular chlorine. A similar formulation can activate oxidant, the reaction must show hydrogen and chloride ions are present in this case, we assume that molecular chlorine acts as the effective oxidant.

Addition of nicotinamide decreases the rate of oxidation. This retarding effect suggest that the pre-equilibrium step involves a process in which nicotinamide (NA) is one of the products.



Taking into consideration the set of kinetic data presented and the evidence for the formation of reactive molecular chlorine in the course of the reaction, the following mechanism may be proposed.



Slow

The mechanism leads to the rate law (4)

$$\frac{-d[\text{NCIN}]}{dt} = k_3[\text{complex}] \quad \dots\dots\dots (4)$$

Applying steady-state approximation to the complex and the chlorine intermediate, the rate law assumes the form,

$$\text{Rate} = \frac{k_1 k_2 [\text{C}_6\text{H}_5\text{CH}_2 - \text{O} - \text{R}] [\text{NCIN}] [\text{H}^+] [\text{Cl}^-]}{k_{-2} k_3 \{k_{-1} [\text{NA}] + k_2 [\text{C}_6\text{H}_5\text{CH}_2 - \text{O} - \text{R}]\}} \quad \dots\dots\dots (5)$$

$$K_{-1} [\text{NA}] \ll k_2 [\text{C}_6\text{H}_5\text{CH}_2\text{-O-R}]$$

Assumption in the oxidation of histidine by N-chlorobenzamide in aqueous methanol, where  $k_{-1} [\text{NA}] \ll K_2$  [substrate].

$$\text{Rate} = \frac{k_1 [\text{NCIN}] [\text{H}^+] [\text{Cl}^-]}{k_{-2} + k_3} \quad \dots\dots\dots (6)$$

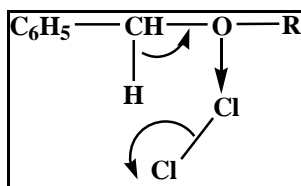
$$\text{Rate} = k_{\text{obs}} [\text{NCIN}] [\text{H}^+] [\text{Cl}^-] \quad \dots\dots\dots (7)$$

Where

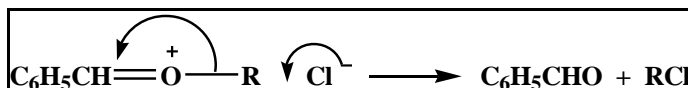
$$k_{\text{obs}} = \frac{k_1}{k_{-2} + k_3}$$

Equation (7) accounts for the first order dependence of rate on [NCN] and [HCl] zero order dependence on [substrate].

The complex formed in the course of the reaction and the formation of the product from it may be represented in the following way:

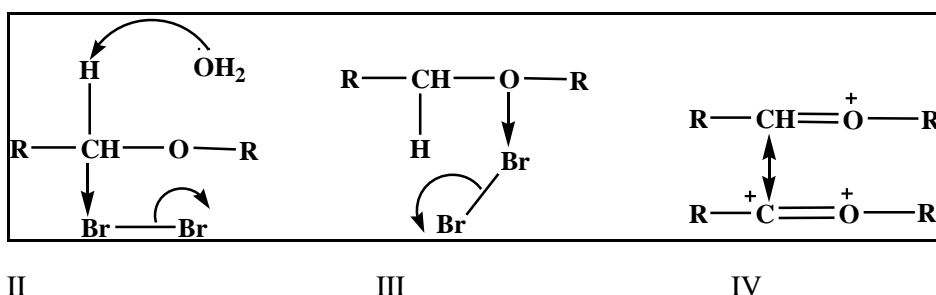


I



R = n-propyl, isobutyl, n-pentyl, t-butyl and dibenzyl.

Mechanism for bromine oxidation of aromatic ethers which involves simultaneous loss of  $H^+$  from  $\alpha$ -carbon and an electron pair from the ether oxygen. This mechanism is isoelectronic with the Westheimer mechanism for the oxidation of alcohols by chromic acid.



II

III

IV

The transition state in the oxidation of ether by bromine would be structure II or III and the initial product structure IV. Structure II is preferred over III because  $H_2O$  is more basic than  $Br^-$ . These authors have reported a reaction constant ( $\rho$ ) value of -1.75 for the bromine oxidation of substituted aromatic ethers.

These reactions have been shown to take place through the formation of a similar complex(I) on analogy with these accepted mechanisms, we have ventured to suggest the formation of the complex with the structure (1). The rate-determining step proposed in the above mechanism predicts negligible salt effect which has been experimentally observed. The formation of the complex involves the charge separation, which points to negative solvent effects. This has been confirmed by the increase in rate with decreasing dielectric constant of the medium. The positive values of the free energy of activation and the enthalpy of activation indicate that the transition state is highly solvated and the negative entropy of activation indicates the same.

## References

1. R.Filler. (1963). Chem. Rev., 63: 21.
2. M. Fieser and L.F. Fieser, L.F. "Reagents for Organic Synthesis" John Wiley and Sons, New York., (1967), 21.
3. J.Anil Kumar and S.Sondu. (2007). Indian J Chem.,(2007), 46A:1792.
4. K.Vivekanandan and K.Nambi. Indian J. Chem.,(1996), 35B:1117.
5. L.Pushpalatha. Int. let. chem. phys. Astron., (2015), 52:120.
6. K.Vivekanandan and K.Nambi.J. Indian Chem. Soc.,(1999), 76:198.
7. V.Ramasamy and K.Nambi. Asian J. Chem., (2006). 18(4):2605.
8. N.Mathiyalagan,C.Vijayaraj, and R.Sridharan. (2005), Orient. J. Chem., 21(1):125.
9. K.Sathiyarayanan,R.Suseela, and J.Lee Chang Woo. Ind. Eng.Chem., (2006),12:(2).
10. F.A Patrocino. J. Organomet. Chem., (2000), 603:220.
11. A.K Singh; VK Sharma. Transition. Met. Chem., (2009), 4:521.
12. D.V Praphu. J. Indian Chem. Soc., (2007), 84, 1135.
13. R.V Jagadeesh; J Puttaswamy. Phy. Org. Chem., (2008), 21:844.

14. A.L Baumstark; C Pedro. *Hetero. Commun.*,(2002), 8:9.
15. P.S Ramakrishnan. *Asian J. Chem.*,(2000), 12:1096.
16. N. Mathiyalagan, R. Sridharan, and V. Priya, *J. Indian Chem. Soc.*, (2005), 82:795.
17. V. Priya and N. Mathiyalagan, *Asian J. Chem.*, (2010), 22:5218.
18. N. Mathiyalagan, V. Priya and J.J. Bosco, *J. Indian Chem. Soc.*, (2009), 86:453.
19. V.Priya and N. Mathiyalagan, *Asian J. Chem.*, (2011), 23(4):1871.
20. K. Ashok Sharma, K.PunitMudgal and K.S Gupta *J. Indian Chem. Soc.*, (2008), 85: 920.
21. N. Mathiyalagan, V. Priya, J. John Bosco, *J. Indian Chem. Soc.*, (2006), 86:453.
22. N. Mathiyalagan, M. Balasubramanian, *Orient J. Chem.*, (2010), 26:1541.
23. M Balasubramanian, V Priya, N Mathiyalagan. *IntJ.Chem Tech Rech.*, 2011, 3(3):1096.
24. L Pusphalatha; K Vivekanandan. *J. Indian Chem. Soc.*, (2009),86:875.
25. C. Karunakaran, V. Chidambaranathan, *Croat. Chem. Acta.* (2001), 74:51.
26. N.A. MahamedFarook. *J. Iran. Chem. Soc.*, (2006), 3(4):378.
27. R.V. Jagadeesh and J. Puttaswamy. *Phy. Org. Chem.*, (2008), 21:844.

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