

# Aromatic Nucleophilic Substitution Reactions : Kinetics of Substitution of 2-Chloropyrimidine and 2,4,6-Trichloro-1,3,5-triazine by various Nucleophiles

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Kinetics of substitution of 2-chloropyrimidine and 2,4,6-trichloro-1,3,5-triazine with a variety of nucleophiles are reported. The reactivity pattern shows that the halogens flanked by two heterocyclic nitrogens in a ring are displaced with facility. The reactions with pyridine of 2,4,6-trichloropyrimidine and 2,4,6-trichloro-1,3,5-triazine are routed through  $N^+$  cations formed in successive displacements which explain the overall displacement of halogens in these systems.

In continuation of our studies on aromatic nucleophilic substitution reactions<sup>1</sup>, we report in this communication, the kinetics of substitution of 2-chloropyrimidine with a few nucleophiles and of 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) with a variety of substituting agents. Recently we reported the kinetics of substitution of 2,4,6-trichloropyrimidine with various nucleophiles and established that 2-chloro position flanked by two heterocyclic nitrogens is more active than the other halogens in the ring<sup>2</sup>.

## Results and Discussion

**Kinetics of substitution of 2-chloropyrimidine :** The reactions are total second order, first order in substrate and first order in nucleophile. The reactions are quite facile in non-aqueous system than in partially aqueous systems. Hydroxide reactions in pure ethanol and aqueous ethanol make this point clear. ( $k_2 = 96.4 \times 10^{-4}$  at 50° in 100% EtOH;  $k_2 = 7.7 \times 10^{-4}$  at 40° in 30% aq. EtOH. It is clear from Table 1 that these reactions are second order and there is no perceptible acceleration observed with increase in amine concentration, thus showing that there is no base catalysis in these systems. The second order rate constants are given in Tables 2 and 3. The reactions are accelerated with nucleophiles of greater electron-releasing nature.

The data (Tables 2 and 3) indicate that the order of reactivity among the bases used is  $OH^- > \text{dimethylamine} > \text{piperidine} > \text{methylamine} > \text{diethylamine}$ .

TABLE 1

2-Chloropyrimidine = $4.5 \times 10^{-3} M$ , Solvent : Ethanol, Temp = 50°	
$10^2 [\text{Piperidine}]$ $\times 10^2 M$	$\times 10^4 k_2$ $dm^3 mol^{-1} s^{-1}$
3.84	19.00
6.2	23.62
9.94	21.14

TABLE 2

Substituting agent	$\times 10^4 k_2 (dm^3 mol^{-1} s^{-1})$		
	Ethanol	DMSO	DMSO : EtOH (1 : 1)
$OH^-$	96.4	—	—
Dimethylamine	58.87	91.31	60.7
Piperidine	21.14	41.23	23.66
Methylamine	2.13	7.66	3.7
Diethylamine	0.325	0.86	0.598

TABLE 3

Substitution agent	$10^4 k_2 (dm^3 mol^{-1} s^{-1})$		
	ACN = DMF (70 : 30)	ACN : EtOH (70 : 30)	ACN : DMSO (70 : 30)
Dimethylamine	21.7	28.9	65.3
Piperidine	14.12	19.00	37.4
Methylamine	1.118	1.158	2.25
Diethylamine	0.275	0.398	0.618

Due to insolubility and colour development acetonitrile and dimethylformamide could not be used as such but binary mixtures of these two dipolar aprotic solvents could be used in conjunction with ethanol and DMSO. The solvent effect observed in these binary mixtures is  $\text{ACN} : \text{DMSO} > \text{ACN} : \text{EtOH} > \text{ACN} : \text{DMF}$ . The reactions are quite susceptible to changes in dielectric constant of the medium. The dielectric constant of ACN-DMSO mixture is higher than that of ACN-DMF and ACN-EtOH mixtures. The intermediate complex that is formed in these reactions is stabilised by a medium of high dielectric constant. Hence, a faster rate is observed in ACN-DMSO mixtures. But from the observed trend it is quite clear that in ACN-DMF mixture a reverse trend is observed much against the principle of bulk dielectric constant being the controlling factor for the solvent effects observed. In ACN-DMF and ACN-EtOH mixtures this anomaly of reversal of observed rates being lower in ACN-DMF mixture, though the dielectric constant is higher, has to be traced to the presence of a protic solvent like alcohol in ACN-EtOH mixtures and the two organic components in ACN-DMF mixture being dipolar aprotic in nature.

The presence of protic solvent like acetic acid being a hydrogen bond acceptor and a donor alters the nature of ACN-EtOH mixture. In addition, the chemical potentials of the reactants also get altered due to the presence of protic solvent in the mixture. These factors are responsible for the higher rate observed in ACN-EtOH mixtures. Probably factors like cohesion, electrophilicity, nucleophilicity also are responsible for the higher rate in ACN-EtOH mixtures due to the presence of a protic component in this mixture.

**Kinetics of substitution of 2,4,6-trichloro-1,3,5-triazine** : The reactions are very fast in solvent

systems containing dipolar aprotic solvents and partially aqueous systems. Hence, systems like benzene-ethanol (80 : 20) and carbon tetrachloride-ethanol (80 : 20) have been used with piperidine, benzylamine, diethylamine, aniline and *p*-chloroaniline. The reactions have been found to be total second order and the stoichiometry has been found to be 1 : 6 with primary and secondary bases. The reactions are three-step consecutive second order reactions. Plots of  $\log (a-2x)/(b-x)$  vs time yielded three straight lines giving the respective  $k_1$ ,  $k_2$  and  $k_3$ . Svirbley's method could not be used for the separation of rate constants as the ratio of  $k_1$ ,  $k_2$  and  $k_3$  is well beyond 3 : 2 : 1 which is one of the requirements for such analysis<sup>3</sup> Hence, evaluation has been done by individual plots for each run. The results are presented in Table 4. The reactivity of the nucleophiles follows the order piperidine > benzylamine > diethylamine > aniline > *p*-chloroaniline, once again establishing that electron-releasing substitution favour the substitution. The solvents effect is  $\text{CCl}_4\text{-EtOH} > \text{benzene-EtOH}$ . It appears that hydrogen bonding present between the EtOH molecule is the factor for the association in liquid state is relatively much more broken by carbon tetrachloride as compared to benzene leaving more free ethanol molecules to solvate the intermediate complex in  $\text{CCl}_4\text{-EtOH}$  mixture as compared to benzene-EtOH mixture. Hence, a higher rate is observed in  $\text{CCl}_4\text{-EtOH}$  mixtures.

**Comparison of reactions of 2-chloropyrimidine and 2,4,6-trichloro-1,3,5-triazine** : The reaction rates are quite fast for 2,4,6-trichloro-1,3,5-triazine which indicate that the triazine system as a whole accelerates the substitution reactions of halogen atoms with various nucleophiles. The rate constants are given in Table 5.

This clearly established the ease with which

TABLE 4

Temp = 60° Substituting agent	Benzene EtOH (80 20)			CCl <sub>4</sub> EtOH (80 20)		
	$k_1$	$k_2$ (dm <sup>3</sup> mol <sup>-1</sup> s <sup>-1</sup> )	$k_3$	$k_1$	$k_2$ (dm <sup>3</sup> mol <sup>-1</sup> s <sup>-1</sup> )	$k_3$
Piperidine	Fast	Fast	Fast	Fast	Fast	Fast
Benzylamine	15.0	5.03	0.3	36.4	16.38	5.3
Diethylamine	11.57	2.82	0.27	23.56	4.71	0.63
Aniline	9.43	1.0	0.25	10.14	1.52	0.481
<i>p</i> -Chloroaniline	1.08	0.469	0.067	3.8	1.02	0.18

TABLE 5

Solvent, CCl<sub>4</sub> - EtOH (80 : 20), Temp. = 40°

Substituting agent	Chloro-compd.	$k_1$	$k_2$ (dm <sup>3</sup> mol <sup>-1</sup> s <sup>-1</sup> )	$k_3$	Stoichiometry
Diethylamine	2,4,6-Trichloro-1,3,5-triazine	4.6	2.12	0.053	1 : 6
	2,4,6-Trichloropyrimidine	1.86	—	—	1 : 2
	2-Chloropyrimidine	0.00639	—	—	1 : 2
Pyridine	2,4,6-Trichloro-1,3,5-triazine	Instantaneous			1 : 3
	2,4,6-Trichloropyrimidine	0.1314	0.0697	0.036 <sup>a</sup>	1 : 3
	2-Chloropyrimidine	Sluggish			

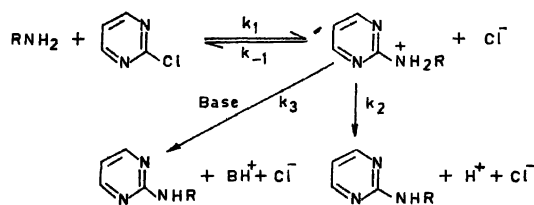
<sup>a</sup>Separation of rate constants done by Svirbley's method and the values are in conformity with those observed by log (a-x)/(b-x) vs time plots which yielded three distinct straight lines.

halogens flanked by two heterocyclic nitrogens are substituted. This also confirms that the 4,6-chloro substitution in pyrimidine which are inactive, get activated when the system is changed to triazine system. These facts lead to a generalisation that the halogens which are flanked by two nitrogens in a ring are substituted with ease by nucleophiles. Thus the order of reactivity is 2-chloropyrimidine < 2-chloro position in 2,4,6-trichloropyrimidine < 2,4,6-trichloro positions in 2,4,6-trichloro-1,3,5-triazine with primary and secondary bases.

A comment about the reactions with pyridine is pertinent. In the case of pyridine the reactions are instantaneous with 2,4,6-trichloro-1,3,5-triazine whereas they are measurable with 2,4,6-trichloropyrimidine and there is almost no reaction with 2-chloropyrimidine. This indicates that the 2-chloro position in 2-chloropyrimidine is not susceptible to displacement due to the weak nucleophilic nature of pyridine, whereas the 2-chloro position in 2,4,6-trichloropyrimidine and 2,4,6-trichloro-1,3,5-triazine is displaced with facility due to the effect of 4,6-halogens in the former and 4,6-halogens and 5-nitrogen in the latter in spite of low nucleophilic power of pyridine. The other halogens 4 and 6 in 2,4,6-trichloropyrimidine are substituted with this tertiary base due to the successive N<sup>+</sup> cations that are formed after the displacement of each halogen. In the case of 2,4,6-trichloro-1,3,5-triazine, 4 and 6 halogens are displaced rapidly due to the cumulative effect of displacements. Hence, the three halogen

displacements occur with ease in 2,4,6-trichloro-1,3,5-triazine with all nucleophiles, whereas only 2-position is active and facile for substitution in 2,4,6-trichloropyrimidine with primary and secondary bases. The 4, 6 positions are substituted in 2,4,6-trichloropyrimidine only when the nucleophile is a tertiary base like pyridine due to the intermediacy of N<sup>+</sup> cation in subsequent steps of substitution reactions.

*Mechanism of the reaction* : The current acceptable theory seems to be a bimolecular mechanism taking place in two stages, one of which is rate-determining depending upon the attacking agent displaced group and the solvent system. The sequence of reactions for primary bases, for example, with 2-chloropyrimidine is presented in Scheme 1.



Scheme 1

Mechanism is similar for the other substrates also, i.e. 2,4,6-trichloro-1,3,5-triazine and 2,4,6-trichloropyrimidine.

The rate equation is represented as

$$k = \frac{k_1 k_2 + k_1 k_3 [B]}{k_{-1} + k_2 + k_3 [B]}$$

(a) if  $(k_2 k_3 [B])$  is  $\gg k_{-1}$ , then  $k = k_1$

(Rate-determining bond formation)

(b) if  $k_{-1}$  is  $\gg (k_2 + k_3 [B])$  then

$$k = \frac{k_1 k_2 [B]}{k_{-1}}$$

(Rate-determining product formation) The observed second order kinetics and the absence of base catalysis favour the mechanism of the formation of intermediate complex with rate-determining bond formation and the subsequent decomposition being rapid.

The other evidence for the intermediate complex mechanism with a rate-determining bond formation is the structural effect observed with the attacking bases. It has been pointed out earlier that the electron-donating groups in amines favour these substitution reactions which substantiates that the rate-determining bond formation is more important.

The solvent mixtures used are either dipolar aprotic solvent, or a mixture of dipolar aprotic solvents, or a mixture of dipolar aprotic and protic solvents or a protic solvent. Hence proton loss will be rapid in these systems and this shows that the rate-determining bond formation is more important. Based on all these observations it is postulated that these reactions are routed through the formation of intermediate complex with rate-determining bond formation. This mechanism finds support from the elaborate work done on these reactions<sup>4</sup> with special references to measurements from electrochemistry, cryoscopic, spectroscopic and deuterium exchange experiments.

## Experimental

2-Chloropyrimidine and 2,4,6-trichloro-1,3,5-triazine (Fluka; m.ps. 63–65°, 145–147°) were used. All other chemicals were of analytical reagent grade. The reaction kinetics were followed by estimating the liberated halide argentimetrically. Rates were followed at least upto 70% of the reaction and the results being reproducible with in  $\pm 3\%$  error. The stoichiometry of the reaction was found to be 1:2 for 2-chloropyrimidine and 1 : 6 for 2,4,6-trichloro-1,3,5-triazine with primary and secondary bases. With pyridine, the stoichiometry was found to be 1 : 3 for 2,4,6-trichloro-1,3,5-triazine. All the experiments were conducted with excess base (1 : 10 stoichiometry). Second order rate constants were computed by using the modified equation,

$$k_2 = \frac{2.303}{t(a-2b)} \log \frac{b(a-2x)}{a(b-x)}$$

for reactions with primary and secondary bases. The usual equation is used for reactions involving pyridine where the stoichiometry is 1 : 3.

## References

1. P. S. R. MURTI and J. SAHU, *Can. J. Chem.*, 1969, **47**, 4499, *Proc. Indian Acad. Sci., Sect A*, 1971, **73**, 192, *Indian J. Chem.*, 1971, **9**, 837; J. F. BUNNETT and R. J. MORATH, *J. Am. Chem. Soc.*, 1955, **77**, 5051, W. GREEZERSTEIN and J. A. BRIEUX, *J. Am. Chem. Soc.*, 1962, **84**, 1032; R. R. BISHOP, E. A. S. CAVELL and N. B. CHAPMAN, *J. Chem. Soc.*, 1952, 437.
2. A. RAMESH, B. S. SUNDAR and P. S. MURTI, *J. Indian Chem. Soc.*, 1995, **72**, 413.
3. W. J. SVIRBLEY, *J. Am. Chem. Soc.*, 1959, **81**, 255, W. J. SVIRBLEY and H. E. WEISBERG, *J. Am. Chem. Soc.*, 1959, **81**, 257.
4. S. ROSS, "Progress in Physical Organic Chemistry", Interscience, New York, 1963, Vol. 1.