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Kinetics of the Reaction of 2-Chloro-3,5-dinitrobenzotriflouride with Aniline in Toluene and Methanol-Toluene Mixed Solvents

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Kinetics of the reaction of 2-chloro-3,5-dinitrobenzotriflouride with aniline were studied in toluene, methanol-toluene binary solvents, benzene and chloroform. The reaction in toluene exhibits third-order kinetics consistent with aggregates of aniline. Thermodynamic parameters $\Delta H^{\#}$, $\Delta S^{\#}$ and $\Delta G^{\#}$ are calculated and discussed for the reaction of 2-chloro-3,5-dinitrobenzotriflouride with aniline in methanol-toluene. Molecular complexes between aniline and the substrate are rejected spectrophotometricaly. The mechanism is studied and compared with the reaction in presence of pyridine. It shows an amine dependence and formation of homo and/or hetero mixed aggregates between aniline and pyridine *i.e.* dimer mechanism.

Keywords kinetics, 2-chloro-3,5-dinitrobenzotriflouride, methanol-toluene

Introduction

2-Chloro-3,5-dinitrobenzotrifluoride, *in vitro* microtubule inhibitor of several Leishmania species, has been synthesized from 2-halo-5-(trifluoromethyl)-benzenesulfonyl chlorides.[1] The analogues exhibited moderate to excellent activity when tested against Leishmania donovani amastigotes.[1-3] Fluorine-containing aromatics have been incorporated into drugs (hypnotics, tranquilizers, anti-inflammatory agents and analgesics, antibacterial) and into crop-protection chemicals (herbicides, insecticides, fungicides).[4]

Aryl halides are common substrates to react with nucleophilic aromatic substitution. In recent years, the photo dissociation dynamics of aryl halides has been a subject of intensive studies, which is closely related to the atmospheric chemistry.[5]

Many aromatic nucleophilic substititution reactions, S_NAr, have been subject to general base catalysis.[6,7] The effect of basicity of nucleophile on this reaction has recently been shown by the dependence of the rate on structurally related nucleophiles.[8] Pervious kinetic studies on aromatic nucleophilic substitutions S_NAr of dinitro substituted benzene in aprotic solvent[9-11] have reported the existence of molecular complexes such as amine dimer, substrate-nucleophile or substrate-product complexes and the possible formation of mixed aggregates aniline-HBA additive (solvent as hydrogen-bond acceptor).[12-15]

Most studies of the solvent effects have been performed in pure solvents.[16,17] Nevertheless, different studies aimed at the characterization of mixed solvents and the determination of the kinetic data in binary mixtures.[17] In continuation to the previous work carried out in our laboratory in the field of aromatic nucleophilic substitutions,[19-27] the present work investigates the solvent effect on the reaction of 2-chloro-3,5-dinitrobenzotriflouride with aniline in pure toluene, benzene, chloroform and in mixed toluene-methanol. Further, the effect of external base such as pyridine is examined.

Experimental

Reagent and solvent

2-Chloro-3,5-dinitrobenzotriflouride was purest available material (Sigma-Aldrich D 89555 Steinheim), methanol (MeOH), toluene (Tol), benzene and pyridine were purified as reported previously.[28] Aniline and pyridine (BDH) were kept overnight over KOH and then distilled (b.p. 184 and 115 ℃, respectively). Caution: 2-chloro-3,5-dinitrobenzotriflouride: irritating to eyes, respiratory system and to skin. In case of contact with eyes, rinse immediately with plenty of water and seek medical. Also suitable gloves, eye face protection should be used

General procedures

A methanol solution of **1** (1.8 mmol, 5 mL methanol) was treated with the aniline (18 mmol, 5 mL methanol). The reaction was refluxed for approximately 1 h, and the solid precipitate was filtered and crystallized from benzene-petroleum ether to give *N*-(2,4-dinitro-6-trifluoromethylphenyl)aniline, which was reported previously.[19]

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Kinetic measurements

Kinetics of 2-chloro-3,5-dinitrobenzotriflouride, **1** (4×10^{-4} mol•L^{-1}) with different concentrations of aniline in toluene, benzene chloroform and methanol-toluene mixed solvent at 40 ℃ were measured spectrophotometrically using a Shimadzu 160 A spectrophotometer in conjunction with thermo-bath (TB-85) temperature control (±0.2 ℃). The reaction in presence of methanol-toluene was measured at different temperatures ranging from 25 to 45 ℃. The kinetic runs were performed by following the appearance of the product at $\lambda=370$ nm. In all cases the pseudo first order values, k_Ψ were calculated from the slope of the plot of $\ln(A_\infty - A_t)$ vs. time which exhibited straight line over nearly 80% of the reaction, where A_t and A_∞ are the optical density of the reaction mixture at time t and at the end of the reaction.

Results and Discussion

Effect of aniline concentrations

The rate of the reaction of **1** with aniline in toluene was measured using different aniline concentrations ranging from 0.5 to 3 mol•L^{-1}. The pseudo first order rate constant, k_Ψ values are given in Table 1. k_A values calculated from the k_Ψ/[Am] were found to increase rapidly with increasing aniline concentrations. Actually the k_A values are dependent of the aniline concentrations. Figure 1 indicated that the mechanism is suggested to proceed through either, (i) specific base [Scheme 1, pathway a or c] or (ii) a dimer process [Scheme 1, pathway b]. The proposed mechanism does not preclude attack by the monomer which straight forwardly would form intermediate S (Am), which undergoes specific base-general acid to the final product (SB-GA). It has been widely observed in catalysed S$_N$Ar, the deprotonation of the zwitterionic intermediate is the rate determine step.[22] The overall reaction comes from the conventional addition-elimination mechanism which is given by Eq. 1.[29,30]

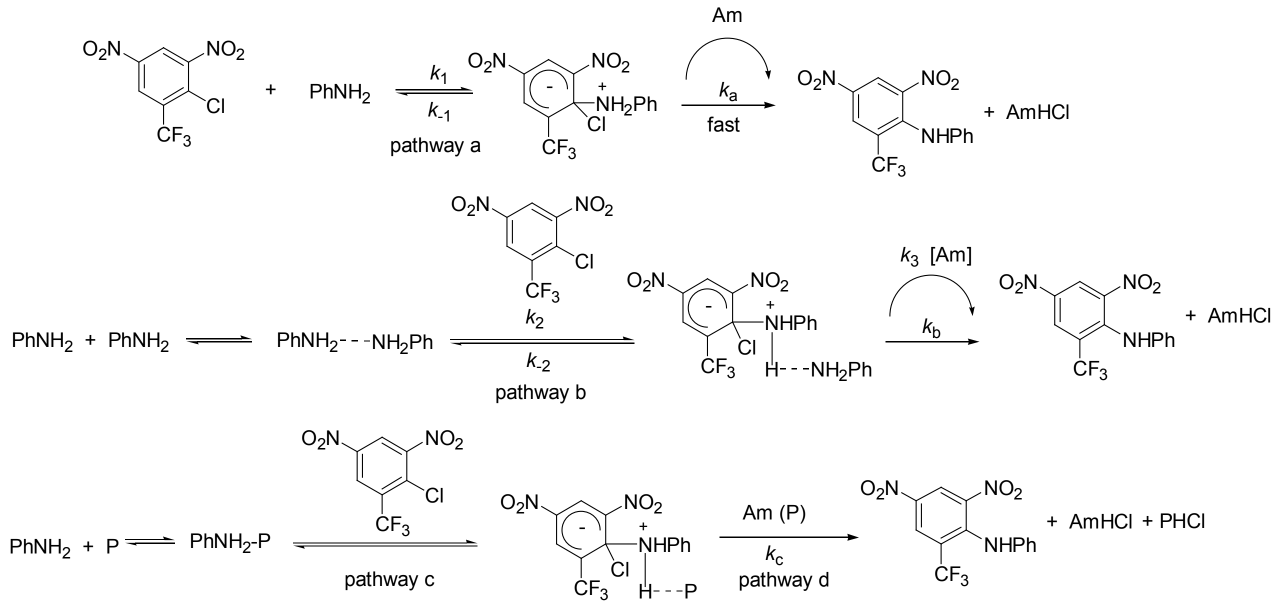
$$k_A = \frac{k_1k_2 + k_1k_3[\mathrm{Am}]}{k_{-1} + k_2 + k_3[\mathrm{Am}]} \qquad (1)$$

where, Am=PhNH$_2$, k_A represents the apparent second order rate constant obtained by dividing the pseudo-first order constant, k_ψ, by aniline concentration. Eq. 1 describes generally a dependence of k_A on [Aniline], which is linear at low concentration but changes to a plateau as the base concentration is increased. In fact at low [Am] value $k_{-1} >> (k_2 + k_3[\mathrm{Am}])$, then, $k_A = Kk_2 + Kk_3[\mathrm{Am}]$ where $K = k_1/k_{-1}$.[30-33] In contrast, when $(k_2 + k_3[\mathrm{Am}] >> k_{-1}$, Eq. 1 reduces to $k_A = k_1$ and the reaction is not base catalyzed.

Table 1 Reaction of **1** with aniline in toluene, pseudo-first (k_Ψ) and second k_A order rate constant at 40 ℃

[Aniline]/(mol•L^{-1})	10^4k_Ψ/s^{-1}	10^4k_A/(L•mol^{-1}•s^{-1})
0.5	0.24	0.48
1.0	0.72	0.72
1.4	1.32	0.94
1.8	2.00	1.11
2.0	2.46	1.23
2.5	3.93	1.57
2.8	501	1.79
3.0	6.06	2.02

Scheme 1



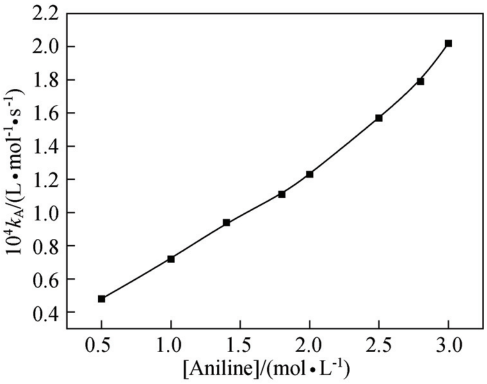


Figure 1 Second order rate constant, k_A for the reaction of **1** with aniline in toluene at 40 ℃ as a function of [Aniline].

It is of interest to examine the possibility of the formation of EDA complexes because aniline is known as better donor amines.[34] The absence of formation of the molecular complex between the substrate and aniline rejects this mechanism. This is because there is no absorbance of the adduct complex at $\lambda = 370$ nm (at zero time) for the reaction carried out at several aniline concentrations up to 3 mol•L^{-1}. Other alternative mechanism of the title reaction is presumably proceeding through a dimer process (Scheme 1). In pathway b, ($PhNH_2 \cdot PhNH_2$) attacks the substrate forming a zwitterionic intermediate involving the substrate and two amine molecules. The overall rate expression for the dimer mechanism is given by the application of the steady state approximation on all intermediates involved in Scheme 1, pathway b (Eq. 2).

$$k_A = \frac{k_1 k_2 K[\mathrm{Am}] + k_3 k_1 K[\mathrm{Am}]^2}{k_{-1} + k_2 + k_3[\mathrm{Am}]} \quad (2)$$

The dimer mechanism can be confirmed by many features such as: (a) the dimer amines are more reactive than amine monomer because of its higher basicity, (b) abnormal solvent effect such as effects of HBD (solvent as hydrogen bond donor) and HBA (solvent as hydrogen bond acceptor) additives. In this report the non-polar character of toluene ($\pi^* = 0.54$) possibly aggregates the aniline and thus a dimer mechanism is possible.[13]

Accordingly the mechanism for the reaction of **1** with aniline in toluene can proceed either by dimer mechanism pathway b or as in Scheme 1 (pathway b and c), in which k_A is linearly at low aniline concentration and shows a plateau at high aniline concentrations.

Effect of pyridine additive

The reaction of **1** with aniline in toluene was studied in presence of pyridine as hydrogen bond acceptor catalyst (HBA) which is intrinsically involved in dimer mechanism.[35] The second order rate constants, k_A for the reaction in presence of fixed concentration of pyridine and different aniline concentrations (Table 2), showed linear behaviour for k_A, similar to that observed for k_A values for the reaction of **1** with different pyridine concentrations at fixed aniline concentration. Accordingly a dimer mechanism is suggested involving the formation of homo and hetero aggregate between aniline-aniline and aniline-pyridine, respectively (Scheme 1, pathway d).

Table 2 Second order rate constant [$10^4 k_A/(L \cdot mol^{-1} \cdot s^{-1})$] when **1** reacted with aniline in presence of pyridine in toluene at 40 ℃

[Pyridine]/(mol•L^{-1})	[Aniline]/(mol•L^{-1})		
	0.5	1.0	2.0
0	0.47	0.73	1.23
0.1	1.50	3.15	5.23
0.2	1.80	3.40	6.60
0.3	2.50	4.01	7.75
0.4	3.30	5.10	9.76
0.5	3.90	6.23	11.56

The overall reaction picture involves the monomer, the dimer and mixed aggregate thus the rate constant is represented by Eq. 3. Pathway a represents the uncatalyzed reaction, it is first order in amine and its attack is rate limiting. When the rate constants show a parabolic dependence on the amine concentration, it can be explained by a dimer mechanism[22] (pathway b). Pathway c represents the third order by assistance of external base.

$$k_A = a[\mathrm{Aniline}] + b[\mathrm{Aniline}]^2 + c[\mathrm{Aniline}][\mathrm{Pyridine}] + d[\mathrm{pyridine}] \quad (3)$$

The four constants a, b, c and d could be determined by linear regression which is expressed by Eq. 4.

$$k_A = (0.76 \pm 1.4)[\mathrm{Aniline}] + (0.144 \pm 0.5)[\mathrm{Aniline}]^2 + (8.23 \pm 1.1)[\mathrm{Aniline}][\mathrm{Pyridine}] + (2.02 \pm 1.5) \times [\mathrm{pyridine}] \ (n = 18,\ r = 0.988) \quad (4)$$

The coefficients of Eq. 4 show that the contribution of [Aniline][Pyridine] is the highest value indicating that the pathway involving hetero aggregates is predominant. This is presumably because aggregation by stronger pyridine ($pK_a = 5.2$) is more important than that by aniline ($pK_a = 4.6$) *i.e.* the mixed pyridine-aniline ($c = 8.23 \pm 1.1$) is more important than the self-associated aniline molecules ($b = 0.144 \pm 0.5$).

Solvent effect

The effect of solvent on the reaction of **1** with aniline was examined in benzene and chloroform (Table 3). It is of interest to note that the reaction in benzene and chloroform shows dependence of k_A on [Aniline]. This means that the overall order of the reaction in toluene is third order. Accordingly the following order was observed, $k_A(CHCl_3) > k_A(\text{toluene}) > k_A(\text{benzene})$. This order agrees with the polarity of the solvent [$\varepsilon(CHCl_3)=4.8$; $\varepsilon(\text{benzene})=2.3$; $\varepsilon(\text{toluene})=2.0$] and is in harmony with the E_T values [preferential solvation, $E_T(CHCl_3)=39.1$; $E_T(\text{benzene})=34.5$, $E_T(\text{toluene})=33.9$] and E_T^N values [$E_T^N(CHCl_3)=0.259$; $E_T^N(\text{benzene})=0.111$; $E_T^N(\text{toluene})=0.099$].[36] This points out that the mechanism in benzene and chloroform can proceed by a dimer mechanism in toluene.

Table 3 Second order rate constant $10^4k_A/(L\cdot mol^{-1}\cdot s^{-1})$ for the reaction of **1** with aniline in different solvents at 40 ℃

[Aniline]/($mol\cdot L^{-1}$)	Benzene	Chloroform
0.5	0.23	1.63
1.0	0.32	2.05
1.5	0.43	2.31
1.8	0.50	2.66
2.0	0.58	2.91
2.5	0.73	3.25
3.0	0.79	—

This concept directs the investigation of the reaction to study the effects of changing polarities of the medium, *e.g.* addition of methanol to toluene as well as the temperatures.

Effect of methanol addition

The effect of progressive addition of various amounts of methanol to toluene (0—100% ϕ_{methanol}) was studied at constant aniline concentrations (1.8 $mol\cdot L^{-1}$) at 40 ℃. Table 4 collects the values of k_A for the reaction of **1** with aniline in methanol-toluene binary solvents, and then the change in k_A should increase more than linear with increasing MeOH. Solvent effects on the reaction rate constants are generally correlated with one of the solvent parameters that represent polarity, hydrogen bonding and other properties. The only solvent polarity parameter derived from measurements of solvatochromic effects such as E_T (Table 4). To insure these explanations several correlations were made such as (i) plot of lg k_A versus mole fractions of methanol (not shown) to indicate what is the preferential solvent, (ii) a plot of lg k_A against E_T values[30] and $1/\varepsilon$ [ε, dielectric constant of the medium (not shown)] for various methanol-toluene mixed solvents to decide which effect controls the specific or non specific solvation. Table 4 shows an increase in rate upon going from methanol to toluene suggesting that adding methanol is probably associated with the hydrogen bond of the medium (specific solvation). It is found that non-linear relations exist between lg k_A values and E_T (preferential solvation) (Figure 2). Therefore, this non-linear correlation is due to specific solvation effect of the methanol-toluene mixed solvent. According to the discussion with respect to dimer mechanism the reactant-toluene are not reactive whereas the addition of small amount methanol affects the reaction than aniline-aniline aggregates.[37]

Table 4 Second order rate constant, $10^3k_A/(L\cdot mol^{-1}\cdot s^{-1})$ when **1** reacted with aniline (1.8 $mol\cdot L^{-1}$) in methanol-toluene binary solvents at 40 ℃

w(MeOH)	ϕ(MeOH)/%	E_T	10^4k_Ψ	10^3k_A
0	0	33.9	2.00	0.11
0.226	10	47.9	9.23	0.51
0.396	20	49.4	13.83	0.77
0.529	30	—	21.00	1.17
0.636	40	51.2	24.17	1.34
0.724	50	—	26.93	1.49
0.798	60	52.4	28.53	1.58
0.860	70	—	33.32	1.85
0.913	80	53.1	35.10	1.95
1.0	100	55.5	47.15	2.62

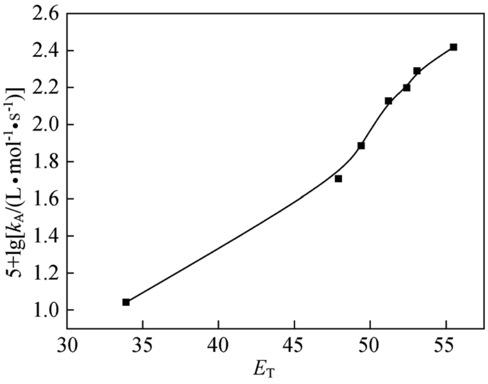


Figure 2 Second order rate constant for the reaction of **1** with 1.8 $mol\cdot L^{-1}$ aniline in toluene-methanol as a function of E_T values at 40 ℃.

These observations could be due to the interaction of methanol with (i) the non-polar aprotic solvent, (ii) the substrate, (iii) intermediates through the reaction pathway or (iv) the amine.

Addition of methanol to non-polar aprotic solvent should increase the dielectric constant of the medium, thereby increasing the rate of S_NAr reactions due to the extra stabilization of the intermediate first formed from the reaction of the amine with substrate.

Complex formation between the substrate on addition of methanol could be a probable factor. Observations have shown, however, that a particular substrate in non-polar aprotic medium such as toluene could display rate acceleration in its reaction with one amine and a continuous rate diminish in its reaction with another amine both in progressive addition of methanol. For example, the reaction of **1** with aniline (present study) showed a rate increase similar to phenyl 2,4,6-trinitrophenyl ether with the same amine.[34] Also the reaction of 2,4-dinitrofluorobenzene with piperidine[35] in benzene displayed a rate increase with added methanol while the reaction of the same substrate produced the opposite effect in its reaction with *cis* and *trans* 1,2-dinitro cyclohexylamine.[38] It can therefore be reasonably assumed that a methanol-substrate interaction is not responsible for the observed increase in rate in present case.

Interaction of added methanol with zwitterionic intermediate first formed would assist the simultaneous abstraction of a proton and expulsion of the leaving group through hydrogen bonding in the transition state which in turn increase the rate of reaction.

The formation of aggregate via hydrogen-bonding between aniline and hydrogen-bond donor methanol has been widely studied.[39-41] The methanol molecule acts as a proton donor to amine resulting in the formation of an aggregate as shown in Eq. 5.[18]

$$ROH + RNH_2 \rightarrow ROH \cdots NH_2R \qquad (5)$$

The nitrogen atom, having thus used its lone pair of electrons partially for hydrogen-bond formation becomes less nucleophilic compared with the free amine. The amine-methanol aggregate of reduced nucleophilicity can either react with the substrate in the first step of the S_NAr reaction or the catalyzing entity in the decomposition of the zwitherionic intermediate complex in the second step. The second assumption is obviously more likely, since a catalysed reaction in the present study displayed rate increase on addition of methanol to toluene. It is therefore proposed that, the mechanism for the reaction of **1** with aniline on progressive addition of methanol to toluene medium is presumably becoming specific base or specific base-general acid mechanism[29] than dimer one suggested in the aprotic toluene.

Effect of temperature

The k_A values for the reaction of **1** with aniline in methanol-toluene binary mixtures (0—100%, ϕ) carried out at different temperatures ranging from 25 to 45 ℃ (interval temperature is 5 ℃) are listed in Table 5. Thermodynamic parameters were calculated by least square fit using the equation $\ln k_A = a + b(1/T)$, where, $a = \ln A$ and $b^* = -E/R$ and least square fit using the equation, $\ln k_A/T = aa + bb(1/T)$, where $aa = \ln(k_B/h) + \Delta S/R$ and $bb = -(\Delta H/R)$. The computed values of the thermodynamic parameters $\Delta H^\#$, $\Delta S^\#$ and $\Delta G^\#$ show that both $\Delta H^\#$ and $\Delta S^\#$ curves pass through a maximum or minimum at $x \approx 0.396$ and another at 0.860. While the $\Delta H^\#$ and $\Delta S^\#$ did not varied with mole fraction of solvent. Figure 3 is a criterion of specific solvation. This behaviour can be visualized in light of change of methanol structure in presence of toluene. Furthermore the highly negative values of $\Delta S^\#$ for the entire range of solvent composition support the formation of strongly ordered transition state. Moreover, the small change of $\Delta G^\#$ with the change of composition of MeOH is attributed to the compensation between $\Delta H^\#$ and $\Delta S^\#$. The plot of $\Delta H^\#$ versus $\Delta S^\#$ gives straight line ($r = 0.99$) where the slope β (isokinetic temperature) value was 214 K which is lower than experimental temperature, suggesting that the titled reactions are entropic control.

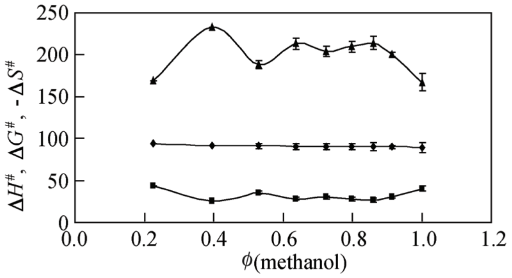


Figure 3 Variation of activation parameters with mole fraction of methanol at 25 ℃. ◆ $\Delta G^\#$ in kJ•mol^{-1}, ● $\Delta H^\#$ in kJ•mol^{-1}, and ▲ $-\Delta S^\#$ in J•mol^{-1}•K^{-1}.

The base catalysis has previously been reported for a few reactions of dinitrochlorobenzene in non polar aprotic solvents.[42-46] This explanation agrees with Scheme 1, pathway a and b, where the proposed reaction route is a reversible nucleophilic attack by the amine dimer followed by the base-catalyzed transformation of intermediate to product.

Table 5 Second order rate constant 10^4k_A/(L•mol^{-1}•s^{-1}) of the reaction of **1** with aniline (1.8 mol•L^{-1}) in binary methanol-toluene mixtures at different temperatures, and activation parameters at 25 ℃

w(MeOH)	ϕ(MeOH)/%	Temperature/℃				$\Delta G^\#$/(kJ•mol^{-1})	$\Delta H^\#$/(kJ•mol^{-1})	$-\Delta S^\#$/(J•mol^{-1}•K^{-1})
		25	35	40	45			
0.226	10	2.10	3.83	5.10	6.73	93.5±2.1	41.0±1.1	176.3±3.5
0.396	20	4.43	6.41	7.64	9.05	92.2±0.1	25.6±0.1	233.1±0.1
0.529	30	5.40	8.84	11.67	13.85	91.6±3.1	35.4±1.6	188.4±5.1
0.636	40	7.23	10.33	13.43	15.42	90.9±3.8	28.1±1.9	213.2±6.3
0.724	50	8.10	11.61	14.96	18.31	90.7±3.7	29.8±1.9	204.3±6.1
0.798	60	9.00	12.52	15.85	19.41	90.4±4.0	27.8±2.1	210.1±6.6
0.860	70	10.00	14.68	18.51	20.09	90.1±4.8	26.1±2.4	214.1±8.0
0.913	80	10.56	16.31	19.50	24.44	90.0±1.6	30.2±0.8	200.4±2.6
1.0	100	11.60	18.29	26.19	33.76	89.8±6.1	40.0±3.1	167.1±10.1

Conclusions

In this work kinetics of 2-chloro-3,5-dinitrobenzotriflourid, **1** with aniline of different concentrations were investigated spectrophotometrically in toluene. The reaction in aprotic solvents exhibits a third-order kinetics. The effect of pyridine was studied. The reaction is explained by a dimer mechanism which involves the formation of homo and hetero aggregate between aniline-aniline and aniline-pyridine respectively (Scheme 1). The effect of solvent on the reaction of **1** with aniline in toluene, benzene and chloroform follows the order of $k_A(CHCl_3) > k_A(Toluene) > k_A(Benzene)$. The effect of adding amounts of methanol to toluene till 100% methanol is studied at constant aniline concentrations. Thermodynamic parameters were calculated in case of methanol-toluene binary solvent at different temperatures showing the non linear variation of $\Delta H^{\#}$ and $\Delta S^{\#}$ with mole fraction of solvent. This behaviour can be visualized in light of change of methanol structure in presence of toluene.

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