Kinetic Studies on the Nucleophilic Substitution Reaction of 4-X-Substituted-2,6-dinitrochlorobenzene with Pyridines in MeOH-MeCN Mixtures

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Received May 21, 2009, Accepted May 26, 2009

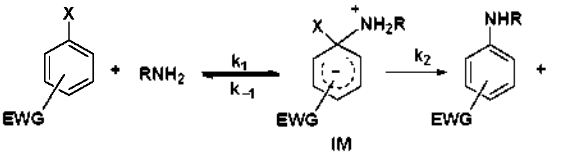
The reaction rates of 4-X-2,6-dinitrochlorobenzenes (X = NO_2, CN, CF_3) with Y-substituted pyridines (Y = 3-OCH_3, H, 3-CH_3, 4-CH_3) in methanol-acetonitrile mixtures were measured by conductometry at 25 °C. It was observed that the rate constant increased in the order of X = 4-NO_2 > 4-CN > 4-CF_3 and the rate constant also increased in the order of Y = 4-CH_3 > 3-CH_3 > H > 3-OCH_3. When the solvent composition was varied, the rate constant increased in order of MeCN > 50% MeOH > MeOH. The electrophilic catalysis by methanol may be ascribed to the formation of hydrogen bonds between alcoholic hydrogen and nitrogen of pyridines in ground state. Based on the transition parameters, ρ_S, ρ_N, β_Y, ρ_{XY} and solvent effects, the reaction seems to proceed *via* S_NAr-Ad.E mechanism. We also estimated the isokinetic solvent mixtures (ρ_{XY} = 0) based on cross-interaction constants, where the substituent effects of the substrate and nucleophile are compensated.

Key Words: Hydrogen bond, S_NAr-Ad.E mechanism, Cross-interaction constants, Isodielectric solvents, Isokinetic solvent mixtures

Introduction

Nucleophilic aromatic substitution reactions are known to undergo through three possible mechanisms: (i) bimolecular nucleophilic aromatic substitution, S_NAr-Ad.E, accompanying the formation of Meisenheimer σ-complex[1] as an intermediate (addition-elimination pathway).[2] (ii) elimination-addition process, S_NAr-E.Ad or S_N1Ar (similar to a S_N1 mechanism), which is more rare and is referred to as the unimolecular mechanism.[2,3] In this mechanism, the elimination of leaving group is already completed at the time of the nucleophilic attack. (iii) bimolecular concerted aromatic nucleophilic substitution, S_N2Ar (similar to a S_N2 mechanism).[2] In this mechanism, the elimination of the leaving group and the addition of the nucleophile occur more or less simultaneously without formation of an intermediate.[2]

However nucleophilic aromatic substitution reaction of aromatic compounds having strong electron withdrawing substituents with amines generally involves the S_NAr mechanism (eq 1).[4,5]

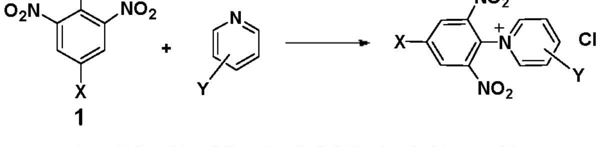


(1)

EWG = electron-withdrawing group

Many researchers have interested in the nature of specific solvent effects on the nucleophilic aromatic substitution in isodielectric solvents such as methanol-acetonitrile mixtures.[6,7] Rates of reactions between polar molecules are quite insensitive to the change from dipolar aprotic to protic solvent of the same dielectric constant when there exists only electrostatic interactions between reactants (or transition states) and solvents.[6,7] But when there exists specific solvation between them, the rate is remarkably changed in the same solvent transfer.[6,8]

Reaction mechanism, reactivity and solvents effects in these systems have been examined extensively[9-11] and we have recently studied the displacement reaction of strongly activated aromatic compounds by anilines of chloride in methanol-acetonitrile solvents.[12] This study showed that the N-C bond forming step made a great contribution to the overall second order rate constant. However, it was found that the electrophilic catalysis by methanol probably resulted from the hydrogen bonding between alcoholic hydrogen and leaving chloride in the transition state.[12] Therefore, mechanistic study on the nucleophilic substitution reaction between aromatic compounds having strong electron withdrawing substituents and amines is very important in examining the effects of protic solvent in the ground state or transition state. In this work, we determined the second-order rate constants for the reaction of 4-X-substituted-2,6-dinitrochloro benzenes (SDC, eq 2) with Y-substituted pyridines in methanol-acetonitrile mixtures at 25 °C.



(2)

X = NO_2, CN, CF_3, Y = 3-OCH_3, H, 3-CH_3, 4-CH_3

In order to discuss the reaction mechanism and solvent effects, we determined transition state parameters, ρ_X, ρ_Y, β_Y using Hammett and simple Brönsted relationships, and the cross-interaction constants,[13,14] ρ_{XY} in eq 3, where X and Y are substituents in the substrate and nucleophile, respectively.

$$\log(k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \quad (3a)$$

$$\rho_{XY} = \partial\rho_Y/\partial\sigma_X = \partial\rho_X/\partial\sigma_Y \quad (3b)$$

Results and Discussion

The present reactions obeyed the kinetic law given in eq 4. Plots of pseudo-first-order rate constants k_{obs} against [Pyridines] show good linear relationship as shown in Figure 1, and the second-order rate constants k_2, were determined from the slopes of these plots. The second-order rate constants are summarized in Table 1. No third-oder or higher-order terms were detected, and no complications were found in the determination of k_{obs} and also in the linear plots of eq 4b. This is suggest that there is no base-catalysis or noticeable side reactions, and the overall reaction follows the route given by eq 2.[11]

$$\text{Rate} = k_2[\text{Pyridines}][\text{Substrates}] = k_{obs}[\text{Substrates}] \quad (4a)$$

$$k_{obs} = k_2[\text{Pyridines}] \quad (4b)$$

Table 1. The second-order rate constants ($k_2 \times 10^3$) for the reaction of 4-X-2,6-dinitrochlorobenzenes with Y-pyridines in MeOH-MeCN mixtures at 25 °C

Solvents	X	Y-pyridines (pK_a)			
		3-OCH_3 (4.88)	H (5.25)	3-CH_3 (5.68)	4-CH_3 (6.02)
MeCN	4-NO_2	151	218	352	463
	4-CN	14.5	19.5	34.2	66.0
	4-CF_3	1.15	1.90	3.86	6.52
50% MeOH	4-NO_2	19.4	27.5	58.5	65.1
	4-CN	2.93	3.01	9.29	10.5
	4-CF_3	0.277	0.298	0.695	0.999
MeOH	4-NO_2	8.47	11.6	20.8	26.8
	4-CN	1.55	2.35	3.84	6.04
	4-CF_3	0.258	0.275	0.354	0.485

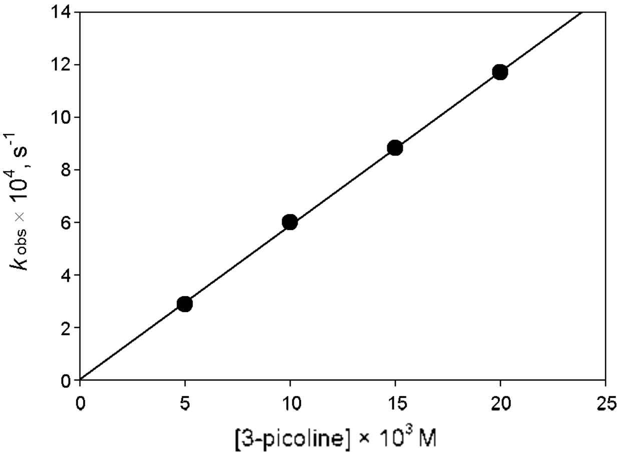


Figure 1. A plot of the observed first-order rate constants ($k_{obs} \times 10^4$ $M^{-1}s^{-1}$) against concentration of 3-picoline for the reaction of 2,4,6-trinitrochlorobenzene with 3-picoline in 50% MeOH - 50% MeCN mixtures at 25 °C ($k_2 = 3.52 \times 10^{-1}$).

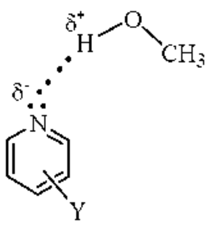
Medium Effects. The second-order rate constant (k_2) in the Table 1 increases in order of MeCN > 50% MeOH > MeOH. The second-order rate constant (k_2) for the reaction of 2,4,6-trinitrochlorobenzene with pyridines in acetonitrile decreases with decreasing the basicity of pyridines, i.e., decreases from 0.463 $M^{-1}s^{-1}$ to 0.218 and 0.151 $M^{-1}s^{-1}$ as the pK_a of pyridines decreases from 6.02 to 5.25 and 4.88, respectively. However, the rate constant (k_2) for the reaction of 4-CF_3-2,6-dinitrochlorobenzene in methanol decreases in a lesser degree with decreasing the basicity of pyridines, i.e., decreases from 0.485 × 10^{-3} $M^{-1}s^{-1}$ to 0.275 × 10^{-3} and 0.258 × 10^{-3} $M^{-1}s^{-1}$ as the pK_a of pyridines decreases from 6.02 to 5.25 and 4.88, respectively. Although changes in the overall reactivity with the variation of substituent Y in pyridine show similar tendency in three substrates, the rate enhancement due to the variation of substituent Y, $k_{4\text{-}CH_3}/k_{3\text{-}OCH_3}$ in methanol is smaller than in acetonitrile solvent: the value of $k_{4\text{-}CH_3}/k_{3\text{-}OCH_3}$ for the reaction of X = 4-CF_3 is 5.67 in MeCN, while the value is 1.88 in MeOH. This may be attributed to the reduced nucleophilicity of substituted pyridines in methanol solvent because of the hydrogen bond between nucleophiles (pyridines) and methanol molecule (Scheme 1).

Table 1 also shows that the second-order rate constant (k_2) for the reaction of 2,4,6-trinitrochlorobenzene with pyridines decreases with increasing the methanol volume percent, i.e., decreases from 463 × 10^{-3} $M^{-1}s^{-1}$ in acetonitrile to 26.8 × 10^{-3} $M^{-1}s^{-1}$ in methanol for X = 4-NO_2 and Y = 4-CH_3. It is noted that the hydrogen bonded pyridine by methanol molecule is less reactive than free pyridine in acetonitrile solvent: the attacking pyridine is a weak nucleophile in methanol, but becomes more reactive in acetonitrile.

The decrease in the second-order rate constant (k_2) by increasing the volume percent of methanol indicates that the ground state (GS) stabilization energy due to the hydrogen bond with methanol solvent is larger than that of transition state (TS) as depicted in Figure 2.

Substituent Effects. The various transition state parameters, Hammett coefficients ρ_X and ρ_Y values, cross-interaction constant ρ_{XY} (eq. 3), and Brönsted β_Y values are summarized in Tables 2 ~ 5. Both the Hammett (for X and Y) and Brönsted plots show good linearity as shown in Figures 3, 4 and 5. The β_X (β_{nuc}) values were determined by plotting log k_2 (MeCN-MeOH) against pK_a (H_2O) of pyridines. This procedure was found to be reliable since the pK_a (MeCN) varied in parallel with the pK_a (H_2O) with a reasonably constant difference of 7.5 (= pK_a (MeCN) - pK_a(H_2O)).[15,16]

Table 1 shows that the rate constant increases in the order of X = 4-NO_2 > 4-CN > 4-CF_3, and also increases in the order of



Scheme 1

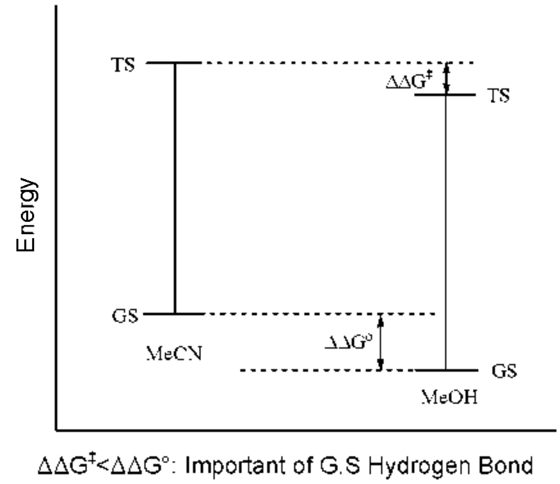


Figure 2. Stabilization energy of GS and TS by methanol.

Table 2. Hammett ρ_Y values for the reaction of pyridines with 4-X-substituted-2,6-dinitrochlorobenzenes in MeOH-MeCN mixtures at 25 °C

Solvents	**$X\text{-}C_6H_5(NO_2)_2Cl$**					
	X = CF_3		**X** = 4-CN		**X** = 4-NO_2	
	ρ_Y	$(r)^a$	ρ_Y	$(r)^a$	ρ_Y	$(r)^a$
MeCN	-2.69	(0.987)	-2.32	(0.972)	-1.75	(0.986)
50% MeOH	-2.09	(0.925)	-2.18	(0.980)	-1.98	(0.947)
MeOH	-0.97	(0.945)	-2.09	(0.992)	-1.83	(0.974)

[a] Correlation coefficient

Table 3. Hammett ρ_X values for the reaction of 4-X-substituted-2,6-dinitrochlorobenzenes with pyridines in MeOH-MeCN mixtures at 25 °C

Solvents	**$Y\text{-}C_6H_5N$**							
	Y = 3-OCH_3		**Y** = H		**Y** = 3-CH_3		**Y** = 4-CH_3	
	ρ_X	$(r)^a$	ρ_X	$(r)^a$	ρ_X	$(r)^a$	ρ_X	$(r)^a$
MeCN	8.83	(0.999)	8.58	(0.999)	8.17	(0.999)	7.71	(0.999)
50% MeOH	7.69	(0.998)	8.19	(0.999)	8.02	(0.995)	7.56	(0.997)
MeOH	6.32	(0.999)	6.77	(0.996)	7.37	(0.995)	7.26	(0.989)

[a] Correlation coefficient

Table 4. Cross-interaction constants, ρ_{XY}, for the reactions of 4-X-2,6-dinitrochlorobenzenes with Y-substituted pyridines in MeOH-MeCN mixtures at 25 °C

Solvents	ρ_{XY}
MeCN	3.95
50% MeOH	0.46
MeOH	-3.44

Y = 4-CH_3 > 3-CH_3 > H > 3-OCH_3. This result indicates that the rates are faster for a stronger nucleophile ($\delta\sigma_Y < 0$) and the substrate (SDC) with a stronger electron-withdrawing group in phenyl ring ($\delta\sigma_X > 0$). The large positive ρ_X and β_Y values and the large negative ρ_Y values indicate that the negative charge is developed in the substrate phenyl ring at the TS, and the anion intermediate (Meisenheimer complex) is stabilized through the delocalization of negative charge by resonance as shown in Scheme 2.

Table 5. Brönsted β values for the reaction of 4-X-2,6-dinitrochlorobenzenes with pyridines in MeOH-MeCN mixtures at 25 °C

Solvents	**$X\text{-}C_6H_5(NO_2)_2Cl$**					
	X = CF_3		**X** = 4-CN		**X** = 4-NO_2	
	β_Y	$(r)^a$	β_Y	$(r)^a$	β_Y	$(r)^a$
MeCN	0.67	(0.999)	0.57	(0.985)	0.43	(0.998)
50% MeOH	0.53	(0.964)	0.57	(0.933)	0.50	(0.976)
MeOH	0.24	(0.963)	0.52	(0.999)	0.46	(0.994)

[a] Correlation coefficient

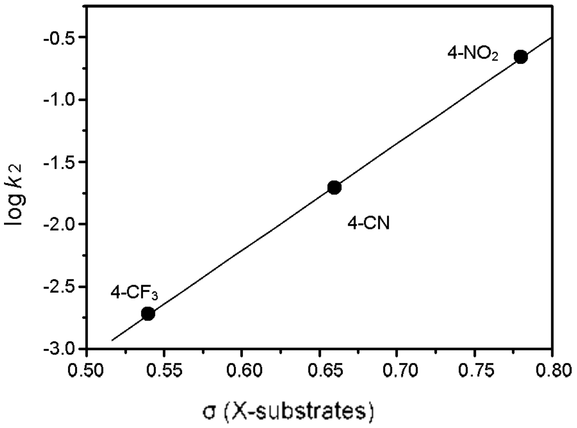


Figure 3. Typical Hammett plot for the reaction of 4-substituted-2,6-dinitrochlorobenzenes with pyridine in MeCN solvent at 25 °C (ρ_X = 8.58).

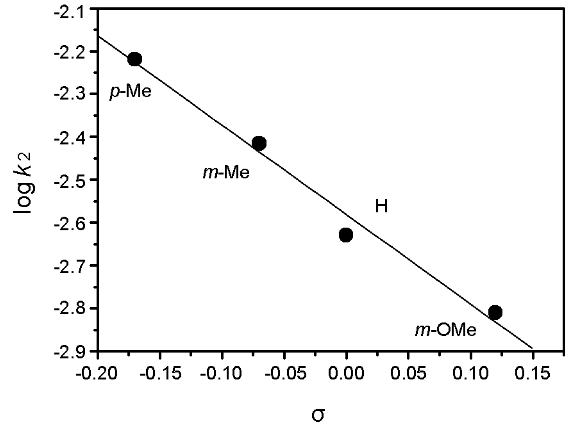


Figure 4. Typical Hammett plot for the reaction of Y-pyridines with 4-cyano-2,6-dinitrochlorobenzenes in MeOH solvent at 25 °C (ρ_Y = -2.09).

The sign of ρ_{XY} shown in Table 4 is changed, and the value of ρ_{XY} is reduced as the volume percent of methanol increase. This is very unexceptional result because it is conflicted with the known mechanistic criteria. The positive ρ_{XY} value in MeCN solvent system indicates that the rate limiting step is bond formation process, and is in good agreement with an

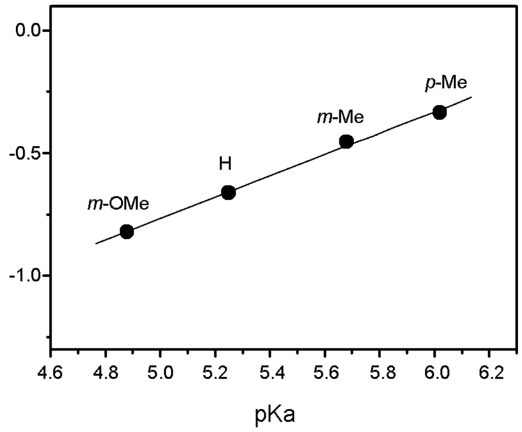
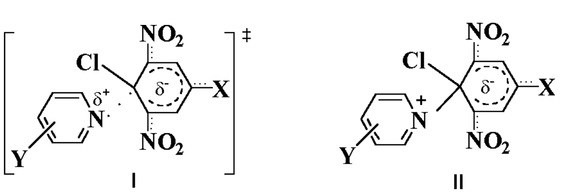


Figure 5. Typical Bronsted plot for the reaction of 4-nitro-2,6-dinitrochlorobenzene with pyridines in MeCN solvent at 25 °C ($\beta = 0.43$).



Scheme 2. Transition state structure (I) and Meisenheimer complex (II).

addition transition state and Meisenheimer complex (Scheme 2) in this study such as nucleophilic substitution and addition reactions.[17] However, negative ρ_{XY} value in MeOH solvent system reveals that the hydrogen bonded pyridine by MeOH is less reactive than free pyridine in MeCN. From the reversal of the sign in ρ_{XY} on going from MeCN to MeOH solvent, we can estimate zero (0) value of ρ_{XY} at near 50 ~ 60% MeOH (or 40 ~ 50% MeCN) solvent mixture which is an isokinetic solvent mixture. The isokinetic solvent mixture observed in the present work is the result of compensation for the substituents effects in the substrate and nucleophilic.[18]

Conclusion

The electrophilic catalysis by methanol may be ascribed to the formation of hydrogen bonds between alcoholic hydrogen and nitrogen of pyridines in ground state. We found that the isokinetic solvent mixtures corresponding to $\rho_{XY} = 0$, where the substituent effects of the substrate and nucleophile are compensated each other. Based on the transition state parameters (ρ_S, ρ_N, β, and ρ_{XY}) and solvent effects, we conclude that the reaction proceeds *via* S_NAr-Ad.E mechanism.

Experimental Section

Materials. 2,4,6-Trinitrochlorobenzene (TCI-GR), 4-cyano-2,6-dinitrochlorobenzene (Alfa Aesar-GR), 4-trifluoromethyl-2,6-dinitrochlorobenzene (Alfa-Aesar-GR), and pyridines (Aldrich-GR) were used commercial grade (> 98%). Merk GR-grade (< 0.1% water) methanol and acetonitrile were used without further purification. Distilled water was redistilled with Buchi Fontavapor 210 and treated using ELGA UHQ PS to obtain specific conductivity of less than 1.0×10^{-6} mhos/cm.

Kinetics. Rates were measured conductimetrically at least in duplicate as in previous work.[19]

Product Analysis. Pyridinium salts were liberated quantitatively and identified as one of the reaction products by comparison of the UV-Vis spectra after the completion of the reactions with those of the authentic samples under same reaction conditions. For example, $\varepsilon = 6092\ M^{-1}cm^{-1}$ at 376 nm for pyridinium salt (X = 4-NO_2, Y = H).

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