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Kinetics and Mechanism of Nucleophilic Substitution Reaction of 4-Substituted-2,6-dinitrochlorobenzene with Benzylamines in MeOH-MeCN Mixtures

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The reaction rates of 4-X-2,6-dinitrochlorobenzenes (X = NO_2, CN, CF_3) with Y-substituted benzylamines (Y = *p*-OCH_3, *p*-CH_3, H, *p*-Cl) in MeOH-MeCN mixtures were measured by conductometry at 25 °C. It was observed that the rate constant increased in the order of X = NO_2 > CN > CF_3 and in the order of Y = *p*-OCH_3 > *p*-CH_3 > H > *p*-Cl. When the solvent composition was varied, the rate constant increased in the order of 100% MeOH < 50% (v/v) MeOH-MeCN < 100% MeCN. These results may be ascribed to the formation of hydrogen bonds between the alcoholic hydrogen and nitrogen of benzylamines in groud state (GS). We conclude that the reaction takes place *via* S_NAr base on the transition state parameters ρ_X, ρ_Y, β_{nuc}, and solvent effects.

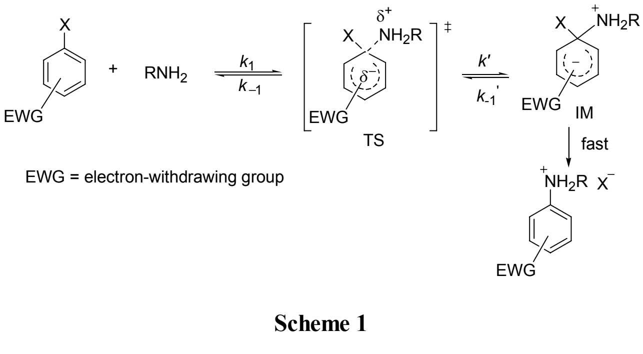
Key Words: Hydrogen bond, Isodielectric solvents, S_NAr-Ad.E mechanism

Introduction

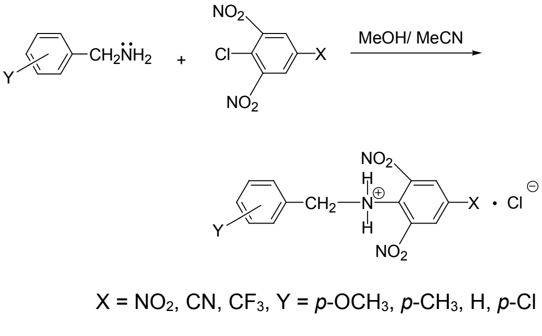
The nucleophilic aromatic substitution reaction of aromatic compounds that have strong electron withdrawing group (EWG) substituents with amines generally involves the S_NAr-Ad.E mechanism, as shown in Scheme 1.[1,2] Many researchers have become interested in the nature of specific solvent effects on the nucleophilic aromatic substitution in isodielectric solvents, such as MeOH-MeCN mixtures.[3,4] The rates of reactions between polar molecules are insensitive to the changes from dipolar aprotic to protic solvent of the same dielectric constant when only electrostatic interactions exist between reactants (or transition states; TS) and solvents.[3,4]

However, when a specific solvation exists between them, the rate remarkably changes in the same solvent effect.[3,5] The reaction mechanism, reactivity, and solvents effects on these systems have been examined extensively.[6-8] We also have recently reported on the displacement reaction of strongly activated aromatic compounds by anilines and pyridines of chloride in MeOH-MeCN solvents.[9,10] These studies showed that the N-C bond forming step gave a great contribution to the overall second order rate constant. In these kinds of reactions,[9,10] Kang and others reported that the electrophilic catalysis by methanol occurs, which probably resulted from the hydrogen bonding between the alcoholic hydrogen and leaving chloride in the TS.[9] Therefore, mechanistic studies on the nucleophilic substitution reaction between the aromatic compounds that have strong EWG substituents and amines are very important in examining the effects of protic solvent in the groud state (GS) or TS.

The significance of structure-reactivity relationships based on the parameters of mechanistic criteria such as Hammett ρ-value, Brönsted β coefficients, and cross-interaction constants ρ_{ij}, for nucleophilic substitution or addition reactions, as well as for proton transfer processes, has been discussed by Jenks,[11] Terrier,[12] and Lee.[12,13] The β_{nuc} values have been commonly accepted as measures of the degree of charge transfer in the TS for a priciple to acid partner.[11,14] However, as pointed out by Bordwell and others, such β_{nuc} values indicate the degree of bond formation in the rate-determining TS of S_NAr and S_N2 reactions.[15] The normal range of β_{nuc} values would be between 0 and 1.[12] Most of the S_N2 reactions are characterized by β_{nuc} values in the 0.2 - 0.5 range.[12] However, the β_{nuc} values close to or greater than 1.0 have been observed for other S_N2-type reactions of carbanions and nitranions with sulfonyl- and nitro-activated aromatic halides.[16] Bordwell *et al.*[16,17] noted that the 0.5 - 07 range of β_{nuc} values are S_NAr-Ad.E reactions with a relatively large electron transfer in the TS. In this work, we determined the second-order rate constants for the reaction of 4-X-substituted-2,6-dinitrochloro benzenes (SDCB, Eq. 1) with Y-substituted benzylamines in 100% MeOH, 50% (v/v) MeOH- MeCN and 100% MeCN at 25 °C.



Scheme 1



(1)

X = NO_2, CN, CF_3, Y = *p*-OCH_3, *p*-CH_3, H, *p*-Cl

In order to discuss the reaction mechanism and solvent effects, we determined the transition state parameters (ρ_X, ρ_Y, and β_{nuc}) by using Hammett equation and simple Brönsted relationships.

Results and Discussion

The present reactions obeyed the kinetic law given in Eq. 2. The plots of pseudo-first-order rate constants k_{obs} against [benzylamines] show good linear relationship as shown in Figure 1. The second-order rate constants k_2, were determined from the slopes of those plots. The second-order rate constants are summarized in Table 1. No third-order or higher-order terms were detected, and no complications were found in both the determination of k_{obs} and the linear plots of Eq. 2b. This suggests that there is no base-catalysis or noticeable side reactions, and the overall reaction follows the route given by Eq. 1.[18]

$$\text{Rate} = k_2[\text{benzylamines}][\text{substrates}] = k_{obs}[\text{substrates}] \tag{2a}$$

$$k_{obs} = k_2[\text{benzylamines}] \tag{2b}$$

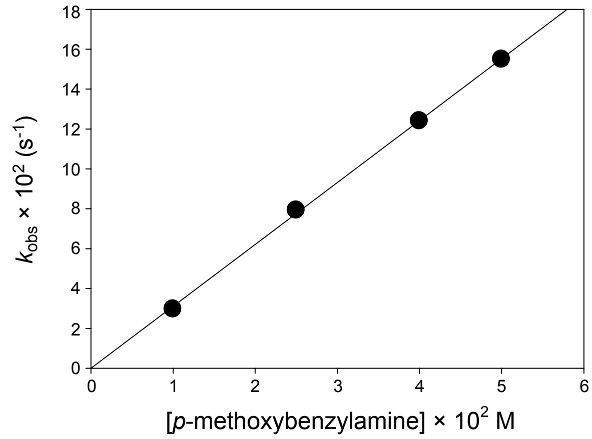


Figure 1. A plot of the observed first-order rate constants ($k_{obs} \times 10^2$, s^{-1}) against concentration of the *p*-methoxybenzylamine for the reaction of 2,4,6-trinitrochlorobenzene with *p*-methoxybenzylamine in MeOH solvent at 25 °C ($k_2 = 3.12$ $M^{-1}s^{-1}$, r = 0.995).

Table 1. The second-order rate constants (k_2, $M^{-1}s^{-1}$) for the reaction of 4-substituted-2,6-dintirochlorobenzenes with benzylamines in 50% (v/v) MeOH-MeCN mixtures and pure MeCN and MeOH at 25 °C

Solvents v/v %	X Substrates (pK_a)	Y-benzylamines (Nucleophiles)			
		p-OCH_3	p-CH_3	H	p-Cl
		(9.67)	(9.54)	(9.33)	(9.14)
MeCN	4-NO_2	37.0	31.0	19.7	11.3
	4-CN	8.93	7.96	5.03	2.87
	4-CF_3	1.06	0.882	0.622	0.350
50% (v/v) MeOH-MeCN	4-NO_2	5.19	4.34	2.75	1.75
	4-CN	1.68	1.23	0.858	0.506
	4-CF_3	0.240	0.196	0.147	0.406
MeOH	4-NO_2	3.12	2.47	2.34	1.66
	4-CN	0.748	0.563	0.498	0.356
	4-CF_3	0.100	0.0902	0.0744	0.0479

Medium effects. The second-order rate constant (k_2) in the Table 1 increases in the order of 100% MeCN > 50% (v/v) MeOH-MeCN > 100% MeOH as shown in Table 1. In the present study, the rate constants (k_2) for the reaction of SDCB with benzylamines in MeCN increases with an increase in the basicity of benzylamines. Although changes in the overall reactivity of the variation of substituent Y in benzylamine show a similar tendency in three substrates, the rate enhancement due to the variation of substituent Y, $k_{4\text{-}OCH_3}/k_{4\text{-}Cl}$ in MeCN is larger than that in MeOH: the value of $k_{4\text{-}OCH_3}/k_{4\text{-}Cl}$ for the reaction of X = 4-NO_2 is 3.27 in MeCN, while the value is 1.88 in MeOH. This may be attributed to the reduced nucleophilicity of substituted benzylamines in the MeOH solvent because of the hydrogen bond between the nucleophiles (benzylamines) and methanol molecule. Table 1 also shows that the second-order rate constant (k_2) for the reaction of 2,4,6-trinitrochlorobenzene with benzylamines decreases with an increase in the methanol volume percent, i.e., decreases from 19.7 $M^{-1}s^{-1}$ in MeCN to 2.34 $M^{-1}s^{-1}$ in MeOH for X = 4-NO_2 and Y = H. These results are similar to the reaction of SDCB with pyridines in MeOH-MeCN solvents mixtures.[10] However, converse results were obtained for the reaction of SDCB with anilines in MeOH-MeCN solvents mixtures.[9] It is noted that the hydrogen bonded benzylamine by methanol molecule is less reactive than the free benzylamine in acetonitrile solvent: the attacking benzylamine is a weak nucleophile in MeOH, but becomes more reactive in MeCN. The reaction of SDCB with anilines in MeOH-MeCN solvents mixtures are important for the electrophilic catalysis, which probably consist of hydrogen bonding between the alcoholic hydrogen and leaving chloride in the TS.[19] However, in the present study, the decrease in the second-order rate constants (k_2) occurred by increasing the volume percent of methanol. Because the nitrogen atom of aniline (or pyridine) can conjugate with the aromatic ring, the hydrogen bond between the solvent (methanol) and the aniline (or pyridine) is weaker than that of benzylamine. This indicates that the ground state (GS) stabilization energy is larger than that of intermediate (IM) or TS, due to the hydrogen bonds between the alcoholic hydrogen and nitrogen atom of benzylamine at the GS.

Substituent effects. The various transition state parameters, Hammett coefficients ρ_X and ρ_Y values, and Brönsted β_Y values are summarized in Tables 2-4. Both the Hammett (for X and Y) and Brönsted plots show good linearity, as shown in Figures 2, 3 and 4. The β_Y (β_{nuc}) values were determined by plotting log k_2 (MeCN-MeOH) against pK_a (H_2O) of benzylamines.[19,20]

Table 2. Hammett ρ_y values for the reaction of benzylamines with 4-substituted-2,6-dinitrochlorobenzenes in 50% (v/v) MeOH-MeCN mixtures and pure MeCN and MeOH at 25 °C

Solvents (v/v %)	X-$C_6H_2(NO_2)Cl$					
	X = 4-NO_2		X = 4-CN		X = 4-CF_3	
	ρ_y	(r)	ρ_y	(r)	ρ_y	(r)
100% MeCN	−1.05	(0.997)	−1.02	(0.991)	−0.966	(0.996)
50% (v/v) MeOH-MeCN	−0.966	(0.995)	−1.021	(0.996)	−0.704	(0.995)
100% MeOH	−0.502	(0.941)	−0.598	(0.959)	−0.639	(0.978)

Table 3. Hammett ρ_x values for the reaction of 4-substituted-2,6-dinitrochlorobenzenes with benzylamines in 50% (v/v) MeOH-MeCN mixtures and pure MeCN and MeOH at 25 °C

Solvents (v/v %)	$Y-C_6H_4CH_2NH_2$							
	Y = p-OCH$_3$		Y = p-CH$_3$		Y = H		Y = p-Cl	
	ρ_x	(r)	ρ_x	(r)	ρ_x	(r)	ρ_x	(r)
100% MeCN	6.43	(0.987)	6.44	(0.982)	6.25	(0.986)	6.29	(0.985)
50% (v/v) MeOH-MeCN	5.56	(0.997)	5.61	(0.989)	5.30	(0.986)	5.07	(0.996)
100% MeOH	6.23	(0.990)	5.99	(0.996)	6.24	(0.997)	6.42	(0.994)

Table 4. Brönsted β values for the reaction of 4-substituted-2,6-dinitrochlorobenzenes with benzylamines in 50% (v/v) MeOH-MeCN mixtures and pure MeCN and MeOH at 25 °C

Solvents (v/v %)	$Y-C_6H_4CH_2NH_2$					
	X = 4-NO$_2$		X = 4-CN		X = 4-CF$_3$	
	β	(r)	β	(r)	β	(r)
100% MeCN	0.98	(0.982)	0.95	(0.969)	0.89	(0.970)
50% (v/v) MeOH-MeCN	0.90	(0.992)	0.95	(0.991)	0.66	(0.998)
100% MeOH	0.46	(0.916)	0.56	(0.951)	0.59	(0.935)

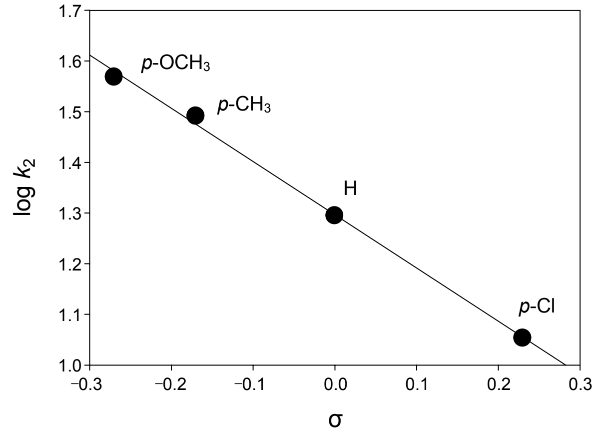


Figure 2. Typical Hammett plot for the reaction of Y-benzylamines with 4-nitro-2,6-dinitrochlorobenzene in MeCN solvent at 25 °C (ρ_y = −1.05, r = 0.997).

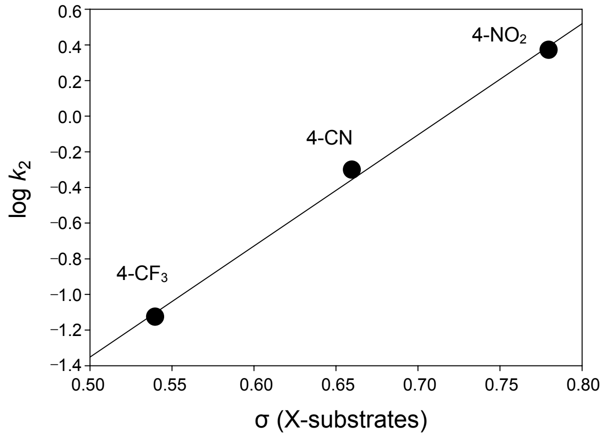


Figure 3. Typical Hammett plot for the reaction of 4-substitued-2,6-trinitrochlorobenzene with benzylamine in MeOH solvent at 25 °C (ρ_x = 6.24, r = 0.997).

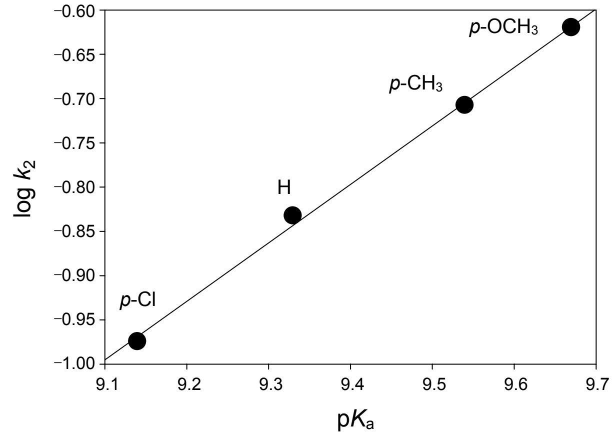
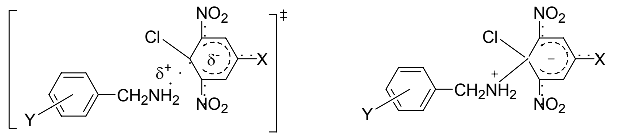


Figure 4. Typical Brönsted plot for the reaction of 4-substitued-2,6-trinitrochlorobenzene with benzylamines in 50% MeCN - 50% MeOH mixtures at 25 °C (β = 0.661, r = 0.998).

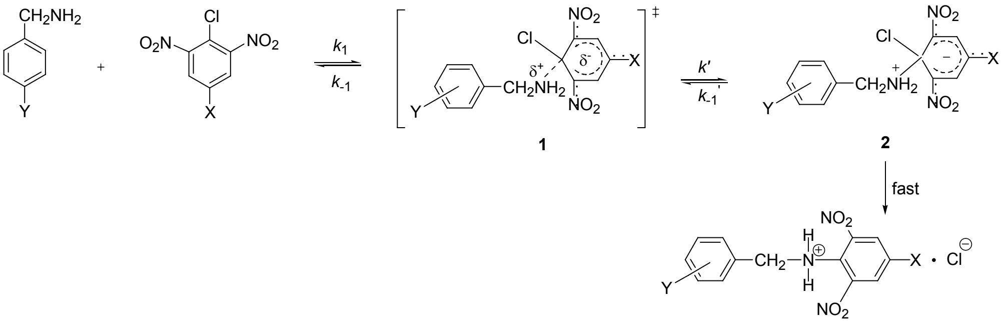


1   **2**

Scheme 2. Transition state structure (**1**) and Meisenheimer σ-complex (**2**)

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 Y = 4-OCH$_3$ > 4-CH$_3$ > H > 4-Cl. This result indicates that the rates are faster in a reaction between a stronger nucleophile ($\delta\sigma_Y < 0$) and substrate with a stronger electron-withdrawing group in the phenyl ring ($\delta\sigma_X > 0$). The large negative ρ_Y values obtained in the present work are clearly consistent with significant developments of positive charge at the nitrogen atom of benzylamine moiety in the TS. Also, the large positive ρ_X values indicate that the a significant negative charge is developed in the substrate phenyl ring at the TS **1**, which leads to a zwitterionic Meisenheimer σ-complex **2** is formed. The Meisenheimer σ-complex is stabilized through delocalizing negative charges of phenyl ring by resonance, as shown in Scheme 2.

The β_{nuc} values are in the range of 0.5 - 1.0 approxiately, as shown in Table 4. This range of β_{nuc} values indicates S$_N$Ar mechanism for reactions of nitrohalobenzenes with nucleophiles.[14] As mentioned by Bordwell and others, such β_{nuc} values are indicative of a rather advanced degree of bond formation in the



Scheme 3

rate determining TS of S_NAr reaction mechanisms. However, this is in contrast to the S_N2 process, for which much lower β_{nuc} values (0.2 - 0.5) are in the rule.[14] Based on the transition state parameters (ρ_X, ρ_Y, and β_{nuc}) and solvent effects, we conclude that the reaction proceeds *via* the S_NAr mechanism, as shown in Scheme 3.

Conclusion

When the solvent composition was varied, the rate constant increased in the order of 100% MeOH < 50% (v/v) MeOH-MeCN < 100% MeCN. These results may be ascribed to the formation of hydrogen bonds between the alcoholic hydrogen and nitrogen of benzylamines in groud state (GS). The present work can be ascribed to the formation of hydrogen bonds between the alcoholic hydrogen and nitrogen of benzylamines in GS. Based on the transition state parameters (ρ_S, ρ_N, and β_{nuc}) and solvent effects, we conclude that the reaction proceeds *via* the S_NAr 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 benzylamines (Aldrich-GR) were used commercial grade (> 98%). Merk GR-grade (< 0.1% water) methanol and acetonitrile were used without further purification.

Kinetics. Rates were measured conductimetrically at least in duplicate, which is similar to previous studies.[21-23]

Product analysis. Benzyl ammonium salts were liberated quantitatively and identified as one of the reaction products by comparing the UV-vis spectra with those of authentic samples under the same reaction conditions after the reactions were completed. For example, $\varepsilon = 13133\ M^{-1}cm^{-1}$ at 340 nm for benzylamonium salt ($X = CH_3$, $Y = NO_2$). Also, the products were identified by ^1H NMR spectrum (Bruker 300 MHz). ^1H NMR (300 MHz, $CDCl_3$, δ): 8.47 (d, NH_2^+), 7.34 (d, aromatic), 7.33 (s, aromatic), 7.05 (d, aromatic), 6.54 (d, CH_2), 3.98 (s, CH_3) for benzyl ammonium salt ($X = CH_3$, $Y = NO_2$).

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