NUCLEOPHILIC SUBSTITUTION REACTION OF BENZYL BENZENESULFONATES WITH ANILINES IN MeOH-MeCN MIXTURÉS-I.

EFFECTS OF SUBSTITUENT AND SOLVENT ON THE TRANSITION-STATE STRUCTURE.

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Abstract: Kinetic studies on nucleophilic substitution reaction of benzyl tosylates with anilines are reported. The reaction was found to proceed via a dissociative S_N^2 mechanism with less than 50 % bond formation and extensive bond breaking at the transition state. It was found that positive charge development at the benzylic carbon is substantial and para-substituent effect on the substrate is predominantly of resonance type. Bond formation is shown to be favored by a better nucleophile, by an electron withdrawing group on the substrate and by the more polar(higher MeCN content) solvent. The substrate, nucleophile and solvent were found to follow the RSP.

Nucleophilic substitution reaction of benzyl derivatives involving variations of substituent and solvent have been widely investigated. $^{1-10}$ Recent studies include investigations of substituent effect on kinetic isotope effect $^{3-5}$ and applications of linear free energy relationships. 4,7,10 These studies on benzyl derivatives were however mostly carried out using halides as the leaving group(LG), and there are relatively few which have examined nucleophilic substitution with benzenesulfonate leaving group. $^{11-13}$ Yoh 12 reported the result of his studies on substituent effect of reactants that the nucleophilic substitution of benzyl benzenesulfonates proceeds by an S_N^2 mechanism. Isotope effect studies of benzyl benzenesulfonates led Ando et al. 13 to conclude that the substitution on the benzyl moiety with an electron withdrawing group makes the transition state(TS) of the S_N^2 process more product-like.

Menschutkin reaction has long been of great importance in the systematic physical-organic investigation of the effect of solvent variation on reaction rates.

In this work, the variation of S_N2 transition state in the Menschutkin-type reaction of benzyl tosylates with anilines, (1), caused by substituents on the nucleophile and benzyl moiety as well as by the solvent is investigated.



The solvent mixtures we adopted, MeOH-MeCN, are known to have suitable properties for the investigation of solvent effect on the TS variation: dielectric constant of the mixtures are approximately constant(isodielectric), while an increase in the hydrogen bond donor acidity(α) is accompanied by a decrease in the polarity(π^*) in the spectrum of solvent composition change toward pure MeOH.¹⁴

RESULT and DISCUSSION

Substituent effect: Second-order rate constants for the reaction of para-substituted benzyl

MeOH(v/v %)	Y	х= _р -сн ₃ о	p-CH3	н	<i>p</i> -C1	<u></u> <i>m</i> −NO ₂
100	p-CH3	68.1	54.0	43.7	33.0	18.6
	н	22.8	16.3	11.5	8.71	3.28
	p-C1	23.3	16.5	10.4	6.85	2.04
	m-NO ₂	6.97	4.30	2.62	1.28	0.316
90	р-СН ₃	55.8	42.2	34.5	25.7	13.8
	н	19.9	14.0	9.71	6.76	2.38
	p-C1	19.4	14.0	9.08	5.61	1.70
	±-NO ₂	5.73	3.90	2.19	1.05	0.251
80	p-CH3	42.5	35.5	27.4	20.4	10.5
	н	16.6	11.9	7.75	5.49	1.84
	<i>p</i> C1	17.2	11.8	7.34	4.53	1.27
	m-NO2	5.00	3.16	1.82	0.871	0.199
70	p-CH3	36.9	29.2	22.9	16.2	7.94
	н	15.1	10.0	6.66	4.45	1.38
	p-C1	15.3	10.1	6.22	3.74	1.02
	m-NO2	4.62	2.75	1.42	0.742	0.155
50	p-CH3	31.8	24.2	17.8	12.0	5.25
	н	10.9	7.04	4.45	2.78	0.920
	<i>p</i> -C1	11.2	7.18	4.35	2.53	0.688
	m-NO ₂	3.53	2.06	1.14	0.567	0.112

Table 1. Rate constants($k_2 \times 10^3 \text{ M}^{-1}\text{s}^{-1}$) for reactions of Y-benzyl tosylate with X-anilines in methanol-acetonitrile mixtures at 35.0 °C.

tosylates with anilines in MeOH-MeCN mixtures are shown in Table 1. The table reveals that substitution of a more electron withdrawing group on the benzyl moiety as well as on aniline decreases the rate. The rate enhancement by an electron donating substituent on the substrate indicates that positive charge develops at the reaction center, C_{α} , which in turn means that bond rupture of the C_{α} -LG bond is more advanced than bond formation of the N- C_{α} bond at the transition-state.

Brønsted β values obtained from slopes of the plots of log k_2 vs pK_a of anilines are summarized in Table 2. The β value increases from ~ 0.20 for an electron donating substituent(Y=p-CH₃) to ~ 0.50 for an electron withdrawing one(Y=p-NO₂) on the substrate. Since the β value is the relative sensitivity of the TS to substitution on the aniline ring, degree of charging on N atom at the TS should be considered to vary from $\sim 20\%$ to $\sim 50\%$ of the (full) final charge as the substituent (Y) on the substrate is changed from p-CH₃ to p-NO₂. These values are comparable to those of Arnett and Reich¹⁵ (<30 %) and Matsui and Tokura¹⁶ (~ 0.48) for methylation of substituted pyridines and N,N-dimethyl anilines with methyl iodide respectively. Results of our extended Brønsted treatment thus indicate that the degree of the N-C_a bond formation at the TS is indeed variable and is less than 50 % complete as the substituent Y is varied, bond formation being

Table 2. Brønsted β values for reactions of Y-benzyl tosylate with X-anilines in methanol-acetonitrile mixtures at 35.0 °C.

MeOH(v/v %)	Y=p-СН3	н	p-C1	p-NO2
100	0.19	0.28	0.36	0.45
90	0.20	0.31	0.36	0.47
80	0.21	0.32	0.38	0.48
70	0.23	0.34	0.39	0,50
50	0.26	0.36	0.41	0.50

Correlation coefficients, r = 0.996 ± 0.003.

MeOH(v/v %)	Y=p-CH ₃	Н	p-C1	p-NO2
100	-0.56	-0.82	-1.05	-1.34
90	-0.59	-0.91	-1.06	-1.36
80	-0.61	-0.94	-1.12	-1.40
70	-0.67	-1.02	-1.16	-1.46
50	-0.78	-1.05	-1.20	-1.49

Table 3. Hammett ρ_X values for reactions of Y-benzyl tosylate with X-anilines in methanol-acetonitrile mixtures at 35.0 °C.

Correlation coefficients, $r = 0.997 \pm 0.002$.

favored by an electron withdrawing group on the substrate.

The Hammett ρ values (ρ_X) determined from linear plots of log k_2 vs σ_X (σ for a substituent on aniline) are shown in Table 3. The sign and size of ρ have been associated with the type and extent of charge development at the reaction center in passing from ground to transition state. Westaway et al.⁵ have made use of the Hammett ρ_X value for substituent variations on nucleophile as a measure of the degree of bond formation between nucleophile and substrate at the TS. Table 3 reveals that the ρ_X values are negative, implying that positive charge develops on the N atom as the TS is formed. The size $|\rho_X|$ is greater for a more electron withdrawing substituent Y on the benzyl moiety. This trend is in accord with the results of Ando et al.,¹³ and Yoh.¹² An electron withdrawing substituent on the substrate is thus conducive to charge development on the N atom and bond formation of the N-C_{α} bond. The greater magnitudes of both β and $|\rho_X|$ hence support an S_N² mechanism with increasing degree of bond formation at the TS as Y is varied to a more electron withdrawing one.

Hammett plots are shown in Fig. 1 for variation of substituent on the benzyl moiety. As it was found in the Hammett plots for the solvolysis of benzyl tosylate, ^{11,17} a better correlation was



Figure 1. Hammett plots for reaction of Y-benzyl tosylate with anilines in methanol-acetonitrile mixtures at 35.0 °C.

obtained with σ^{\dagger} rather than with σ indicating extensive positive charge development at the benzylic carbon C_c. Electron donating substituents have been found to show positive deviations in the Hammett plots of nucleophilic substitutions of benzyl derivatives. 1-3,5,18-20 This type of non-linear behavior is even more striking in the reaction involving anionic nucleophiles. The non-linear Hammmett plots are often imputed to (i) change in mechanism with substituent, 3,18 (ii) variation of TS structure with substituent in an otherwise single mechanism 19-20 and (iii) different relative contribution to TS stabilization by polar and resonance effect depending on an individual substituent.^{2,5} Large positive deviations exhibited by electron donating substituents in the Hammmett plots for solvolysis of para-substituted benzyl tosylates have been interpreted as due to strong resonance stabilization of the TS.¹¹ Westaway⁵ and Young² attributed the non-linear Rammett correlations of benzyl derivatives to a non-uniform relative contribution of the polar and resonance effects on the TS by the individual substituent. One should obtain a normal linear Hammett correlation in the absence of the resonance effect on the S_{N}^{2} transition state.^{21,22} Young and Jencks² determined the relative importance of polar and resonance substituent effects on the S_N^2 TS by using a modified Yukawa-Tsuno equation, (2).

$$\log (k/k_{\rm r}) = \rho \sigma^{\rm n} + \rho^{\rm r} (\sigma^{\rm r} - \sigma^{\rm n})$$
⁽²⁾

where ρ and ρ^{r} are susceptibilities of a reaction to polar and resonance substituent effects respectively. The use of σ^{+} constant is required to correlate substituent effects in a reaction involving formation of an electron-deficient center in direct conjugation with a substituent, and σ^{n} and $(\sigma^{+} - \sigma^{n})$ represent polar and resonance substituent constants respectively. The resonance effect of an electron-releasing substituent, $(\sigma^{+} - \sigma^{n})$, is greater for p-CH₃ than for p-Cl, and is zero for the substituent (H or p-NO₂) which has no electron-releasing resonance effect. The $|\rho^{r}|$ value will be large in a reaction with large resonance substituent effect and it can be greater than $|\rho|$ in a reaction with dominant resonance effect. Since the resonance effect is absent for H and p-NO₂, eq. (2) simplies for the two compounds to,

$$\log (k/k_{\perp}) = \rho \sigma^{n} \tag{3}$$

The Hammett $p\sigma^n$ plots are shown in Fig. 2, where p-CH₃ and p-Cl are also included. The extent of



Figure 2. Hammett plots for reactions of Y-benzyl tosylate with X-anilines in methanol at 35.0 °C.

MeOH(v/v X) X=p-CH ₃ 0	<i>р</i> -СН ₃	н	<i>p</i> -C1	m-NO2
100	-0.69	-0.78	-0.84	-1.06	-1.25
90	-0.72	-0.74	-0.84	-1.04	-1.23
80	-0.71	-0.77	-0.83	-1.03	-1.21
70	-0.69	-0.75	-0.81	-1.02	-1.20
50	-0.66	-0.72	-0.79	-0.90	-1.16

Table 4. Hammett ρ_Y^+ values for reactions of Y-benzyl tosylate with X-anilines in methanol-acetonitrile mixtures at 35.0 °C.

Correlation coefficients, r = 0.994 ± 0.005.

positive deviation exhibited by $p-CH_3$ and p-Cl can be a measure of resonance contribution. $\Delta \log (k/k_{a}) = \rho^{r}(\sigma^{+} - \sigma^{n})$ (4)

The reaction constant ρ^{r} can then be determined using eq. (4). For the reaction series investigated all the ρ^{r} values were found to be greater by 5%10 times than ρ values. Although the ρ^{r} values were obtained with only two substituents, the results clearly demonstrate an overwhelming influence of the resonance effect in the TS formation.

Recently Afanas'ev²³ proposed another dual substituent parameter equation (5) with "universal" polar(σ^*) and resonance(σ^r) substituent constants.

$$\log (k/k_{\lambda}) = \rho^{T} \sigma^{T} + \rho^{T} \sigma^{T} + B$$
 (5)

where B is a constant. He maintained and has shown that the application of this equation leads us to a more accurate separation of polar and resonance substituent effects. The application of eq. (5) to the present data for four para-substituents, Y = H, p-CH₃, p-Cl and p-NO₂, shows again the predominant resonance contribution (R values²⁴ reaching to 74 \sim 95%) to the total substituent effect.

Hammett ρ_Y^+ values determined for the reaction with σ^+ constants of Y = H, p-C1 and $p-NO_2$ are summarized in Table 4. Here the sign of the ρ_Y^+ is an indicative of the relative importance of bond formation($\rho_{form} > 0$)²⁵ and bond breaking($\rho_{break} < 0$),^{1,6} since $\rho_Y^+ = \rho_{break} + \rho_{form}$. Table 4 reveals that ρ_Y^+ values are negative indicating that bond breaking is more advanced than bond formation at the TS, i. e., $|\rho_{break}| > |\rho_{form}|$; considering the partial cancellation of ρ_{break} by ρ_{form} which is positive, relatively large negative ρ_Y^+ values obtained should mean extensive bond breaking at the TS. The decrease in $|\rho_Y^+|$ for a more electron donating substituent on the nuclephile, e. g., $X = p-CH_3O$, is due to a greater degree of charge transfer for a better nucleophile resulting in an increase in $|\rho_{form}|$ and bond formation. According to Table 1, the rate is also greater with a better nucleophile.

On the other hand, Table 3 shows that the $|\rho_X|$ values are greater with an electron withdrawing substituent(Y = p-NO₂) on the substrate implying greater degree of charge transfer and bond formation compared with an electron donating one(Y = p-CH₃). However the rate is shown to be greater with an electron donating substituent(Y = p-CH₃) demonstrating that the bond breaking is dominant in determining the overall rate of the reaction.

<u>Solvent Effect</u>: The second-order rate constant in Table 1 is seen to increase with MeOH content of solvent mixtures. However the Brønsted β and $|\rho_{\chi}|$ values(Tables 2 and 3) increase with MeCN content of the solvent. Since we should expect bond breaking to increase with an increase in hydrogen bond donor acidity(α) of the solvent, the rate increase with MeOH content is consistent with the above conclusion that the dominant process is the bond breaking. This is supported by the fact that the increase in bond formation(increase in β and $|\rho_{\chi}|$) occurs with an increase in polarity(π^*) of the solvent accompanied by a decrease in MeOH content of the solvent mixtures. A decrease in $|\rho_{\chi}^+|$ values(table 4) with a decrease in MeOH content again reflects greater degree of bond formation in the more polar solvent causing greater charge transfer and bond formation at the TS(vide supra).

Reactivity-Selectivity Behavior: According to the reactivity-selectivity principle(RSP),²⁶

greater selectivity is exhibited by a less reactive reagent. Inspection of the results in Tables $1 \sim 4$ reveals that the RSP is adhered; for the less(more) reactive substrate $Y = p - NO_2$ $(Y = p - CH_{q})$, selectivity parameters β and $|\rho_{w}|$ are greater(smaller), and again for the less(more) reactive nucleophile $X = m - NO_2(X = p - CH_3O)$, $|\rho_{\chi}^+|$ is greater(smaller). Solvent variation also causes the change in selectivity parameters. The change is relatively small but nevertheless is significant for 8 and $|
ho_{\chi}|$ values, for which the RSP appears to hold; for the less(more) reactive solvent 50 % (100 %) MeOH, the β and $|\rho_{y}|$ values are greater(smaller).

CONCLUSIONS

Results of our studies involving substituent and solvent effects on the rates of nucleophilic substitution reactions of benzyl tosylates with anilines lead us to the conclusions: (i) The reaction proceeds via a dissociative S_N^2 mechanism; bond formation is $\sim 20-50$ % complete but bond breaking is extensive so that the rate of reaction is dominated by the bond breaking process. (ii). Applications of dual substituent parameter equations show that the effect of para-substituent on the substrate is predominantly of resonance type due to substantial positive charge development on the reaction center at the TS. (iii) Bond formation is favored by a better nucleophile, by an electron withdrawing substituent Y on the substrate and by the more polar solvent(higher MeCN content). (iv) Both substrates and nucleophiles follow the RSP. Although changes in selectivity parameters are small with the solvent change, the RSP appears to be adhered by the solvent also.

EXPERIMENTAL

Material: Merck GR grade methanol was used without further purification and acetonitrile was used after redistillation over phosphorus pentoxide. Aniline was distilled under reduced pressure (65 °C, 10 mm Hg) and substituted anilines were recrystallized from ethanol. para-Substituted benzyl para-toluenesulfonates(Y-benzyl tosylates) were prepared by reacting silver para-toluenesulfonate with para-substituted benzyl bromides.¹² The products were recrystallized more than twice from anhydrous ether. Melting points(uncorrected) were as follows $[Y, mp(^{\circ}C)]$: p-CH3, 57.5(1it. II 57.9 \diamond 58.5); H, 58.0(1it. II 58.5 \diamond 58.9); p-C1, 52.0(1it. ²⁷ 53.0 \diamond 53.5); p-NO₂, 103.0(1it.¹¹ 105 ~ 105.5).

<u>Rate Constants</u>: Rates were measured conductometrically using Beckmann Model RC-18A conductivity meter at 35.00 ± 0.03 °C. Large excess amounts(0.015 \sim 0.15 M) of anilines relative to substrate concentration were used in the reaction and pseudo-first-order rate constants, k_{obs} , were determined by the Guggenheim method.²⁸ The second-order rate constants, k_2 , were then obtained from the slope of the plots of (more than four) k_{obs} vs aniline concentration, (eq. 6). $k_{obs} = k_2$ [aniline] (6)

Good second-order kinetics (r > 0.999) were obtained in all cases.

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