Nucleophilic Substitution of Benzyl Benzenesulphonates with Anilines in Methanol–Acetonitrile Mixtures. Part 2.[1] Variation in Transition-state Structure

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Nucleophilic substitution reactions of benzyl benzenesulphonates ($YC_6H_4CH_2OSO_2C_6H_4Z$) with anilines ($XC_6H_4NH_2$) have been studied in a series of methanol–acetonitrile mixtures. A more electron-donating substituent in the nucleophile (X = *p*-MeO) and a more electron-withdrawing substituent in the leaving group (Z = *m*-NO_2) led to an increase in the rate and to a later transition state with a longer substrate–leaving group bond and a shorter nucleophile–substrate bond. An electron-withdrawing substituent in the substrate (Y = *p*-Cl) was also found to favour a later transition state. An increase in the methanol content of the solvent increased reactivity but decreased selectivity in accordance with the reactivity–selectivity principle; however, the results of variations in the nucleophile, the leaving group, and the substrate in general violated the reactivity–selectivity principle. An MO model based on energy decomposition analysis for predicting S_N2 transition-state structure has been shown to apply to the results of this work.

The nucleophilic substitution of benzyl benzenesulphonates with anilines [equation (i)] in methanol–acetonitrile mixtures

$$XC_6H_4NH_2 + YC_6H_4CH_2OSO_2C_6H_4Z \longrightarrow XC_6H_4\overset{+}{N}H_2CH_2C_6H_4Y + {}^{-}O_3SC_6H_4Z \quad \text{(i)}$$

serves as a convenient model reaction for study of comprehensive effects of substituents (X, Y, and Z) as well as of the effect of solvent. In our previous paper,[1] we reported that reaction (i) proceeds *via* a dissociative S_N2 mechanism with less than 50% bond formation and extensive bond breaking at the transition state (TS), bond formation being favoured by a more polar (higher MeCN content) solvent. We also pointed out that the resonance contribution of the substituent Y to TS stabilization was substantial. In this work, we extend our studies on reaction (i) to investigate variations in TS structure caused by simultaneous changes in X, Y, and Z in a series of MeOH–MeCN solvent mixtures, with special reference to the effects of substituents on the degrees of bond-making and -breaking in the TS. Predictions of TS variation based on an energy decomposition model[2] have been used in interpretation of the results.

Results and Discussion

Effect of Substituents.—Second-order rate constants for the reaction (i) (Y = H, *p*-Cl; Z = *p*-Me, H, *p*-Cl, or *m*-NO_2; X = *p*-MeO, *p*-Me, H, *p*-Cl, or *m*-NO_2) in MeOH–MeCN mixtures are summarized in Table 1. The rate is seen to increase with a more electron-donating substituent in the nucleophile (X = *p*-MeO) and with a more electron-withdrawing substituent in the leaving group (Z = *m*-NO_2). Table 1 also reveals that the effect of substituent on the rate is stronger in the leaving group than in the nucleophile, indicating that carbon-leaving group (C_α–L) bond-breaking is relatively more important than nucleophile-carbon (N–C_α) bond formation at the transition state (TS).

Variations of Hammett ρ_X values [obtained by changing substituents (X) in the nucleophile] with substituents in the substrate (Y) and in the leaving group (Z) are shown in Table 2 for various solvent mixtures. The ρ_X values range from −0.8 to −1.4, indicating that substantial charge transfer occurs from anilines to the reaction centre C_α at the TS. This Table shows that charge transfer and hence partial positive charge development at the nitrogen atom of aniline in the TS is greater for a more electron-withdrawing substituent in the substrate (Y = *p*-Cl) as well as in the leaving group (Z = *m*-NO_2). The magnitude of ρ_X can be used to give the degree of N–C_α bond formation in the TS;[3,4] the ρ_X values suggest that N–C_α bond-making increases with a more electron-withdrawing substituent both in the substrate and in the leaving group. The effect of increasing bond formation due to an electron-withdrawing substituent in the substrate is in accord with the results of Ballistreri *et al.*[5] for the reaction of substituted anilines with *para*-substituted benzyl derivatives. It is also in line with theoretical predictions given by energy decomposition analysis of interaction energies;[6–8] the bond formation of a substrate with an electron-withdrawing group (EWG) is shown to be favoured by all components of the interaction,[2] *i.e.* electrostatic (E_{es}), exchange repulsion (E_{ex}), polarization (E_{pl}), and charge-transfer (E_{ct}) terms, in S_N2 reactions. The MO theoretical model for predicting effects of substituents on TS variation in S_N2-type reactions provides a more general analysis than other quantum mechanical models,[9–11] by taking into account all (four) major components of interaction between reactant species.

The enhancement of bond-making for the leaving group with an EWG (Z = *m*-NO_2) is again in agreement with the results of experimental as well as theoretical studies. Westaway and Ali[4] concluded that increasing leaving-group ability by introducing an EWG leads to greater N–C_α bond formation and more extensive C_α–L bond-breaking. The MO model[2] shows that an EWG in the leaving group in S_N2 reactions should increase both bond-making and -breaking, since all four contributing interaction terms (E_{es}, E_{ex}, E_{pl}, and E_{ct}) are favourable. While the prediction of the leaving group effect on N–C_α bond formation by the quantum mechanical model of Pross and Shaik[9] was less clear-cut, there was no ambiguity in the energy decomposition model regarding the effect of substituents in the leaving group on the degrees of bond-making and -breaking.

Brønsted β_N values obtained from the plot of log k_2 *vs.* pK_a of the nucleophile are given in Table 3. The β_N values also increase with a more EWG in the substrate (Y = *p*-Cl) and in the leaving group (Z = *m*-NO_2). This is consistent with the trend exhibited by the ρ_X values, providing further evidence in support of increasing bond formation for a more EWG in the substrate and in the leaving group.

Hammett ρ_Z values obtained by changing substituents (Z) on the phenyl ring of the leaving group are summarized in Table 4. The positive sign of ρ_Z indicates that the negative charge on the sulphonate oxygen of the leaving group has increased in TS

Table 1. Second-order rate constants[a] ($10^3\ k_2$/dm^3 mol^{-1} s^{-1}) for the reactions of benzyl benzenesulphonates with anilines in methanol–acetonitrile mixtures at 35 °C

			X				
Solvent[b]	Y	Z	*p*-MeO	*p*-Me	H	*p*-Cl	*m*-NO$_2$
100% MeOH	H	*p*-Me[c]	22.8	16.3	11.5	8.71	3.28
		H	31.6	26.1	17.3	12.0	4.65
		p-Cl	69.8	56.3	40.2	26.8	9.55
		m-NO$_2$	293	235	164	101	37.2
	p-Cl	*p*-Me[c]	23.3	16.5	10.4	6.85	2.04
		H	35.6	24.3	15.4	9.51	2.88
		p-Cl	83.2	57.5	37.1	23.4	6.31
		m-NO$_2$	386	277	172	97.8	24.0
90% MeOH	H	*p*-Me[c]	19.9	14.0	9.71	6.76	2.38
		H	29.0	20.5	15.1	10.0	3.55
		p-Cl	64.1	50.2	34.6	22.3	7.59
		m-NO$_2$	272	212	149	89.1	29.5
	p-Cl	*p*-Me[c]	19.4	14.0	9.08	5.61	1.70
		H	30.0	19.5	13.8	8.14	2.14
		p-Cl	69.1	47.9	32.2	18.4	5.24
		m-NO$_2$	363	245	158	86.1	19.8
80% MeOH	H	*p*-Me[c]	16.6	11.9	7.75	5.49	1.84
		H	22.9	16.8	11.5	7.47	2.51
		p-Cl	58.1	42.9	30.2	18.1	5.75
		m-NO$_2$	250	201	132	75.9	22.9
	p-Cl	*p*-Me[c]	17.2	11.8	7.34	4.53	1.27
		H	24.0	16.2	10.5	5.70	1.59
		p-Cl	66.1	43.7	28.2	15.4	3.98
		m-NO$_2$	331	225	138	72.4	15.9
70% MeOH	H	*p*-Me[c]	15.1	10.0	6.66	4.45	1.38
		H	19.5	15.0	9.77	6.12	1.91
		p-Cl	51.8	37.0	26.3	16.4	4.79
		m-NO$_2$	238	188	124	70.8	21.4
	p-Cl	*p*-Me[c]	15.3	10.1	6.22	3.74	1.02
		H	19.2	12.6	7.94	4.47	1.18
		p-Cl	52.5	35.5	22.1	12.3	3.16
		m-NO$_2$	283	201	117	60.3	12.0
50% MeOH	H	*p*-Me[c]	10.9	7.04	4.45	2.78	0.920
		H	16.6	11.2	6.83	4.60	1.41
		p-Cl	41.1	27.0	18.6	10.8	2.88
		m-NO$_2$	220	146	90.7	51.3	13.8
	p-Cl	*p*-Me[c]	11.2	7.18	4.35	2.53	0.688
		H	14.2	8.54	5.63	2.95	0.708
		p-Cl	35.7	23.5	14.2	7.24	1.78
		m-NO$_2$	239	154	95.0	44.7	8.91

[a] Correlation coefficients $r > 0.999$. [b] Volume percent of methanol. [c] Data from ref. 1.

Table 2. Hammett ρ_X values[a]

		Z			
Y	Solvent[b]	*p*-Me[c]	H	*p*-Cl	*m*-NO$_2$
H	100%	−0.82	−0.84	−0.87	−0.97
	90%	−0.91	−0.90	−0.94	−0.98
	80%	−0.94	−0.96	−1.01	−1.06
	70%	−1.02	−1.02	−1.03	−1.07
	50%	−1.05	−1.05	−1.14	−1.20
p-Cl	100%	−1.05	−1.08	−1.11	−1.21
	90%	−1.06	−1.13	−1.12	−1.26
	80%	−1.12	−1.18	−1.22	−1.33
	70%	−1.16	−1.21	−1.22	−1.39
	50%	−1.20	−1.29	−1.31	−1.44

[a] Correlation coefficients r 0.997 ± 0.002. [b] Volume percent of methanol. [c] Data from ref. 1.

Table 3. Brønsted β_N values[a]

		Z			
Y	Solvent[b]	*p*-Me[c]	H	*p*-Cl	*m*-NO$_2$
H	100%	0.28	0.29	0.30	0.31
	90%	0.31	0.30	0.32	0.33
	80%	0.32	0.32	0.34	0.36
	70%	0.34	0.35	0.35	0.36
	50%	0.36	0.36	0.39	0.41
p-Cl	100%	0.36	0.37	0.38	0.41
	90%	0.36	0.38	0.38	0.43
	80%	0.38	0.40	0.41	0.45
	70%	0.39	0.41	0.42	0.47
	50%	0.41	0.44	0.44	0.49

[a] Correlation coefficients r 0.996 ± 0.003. [b] Volume percent of methanol. [c] Data from ref. 1.

formation. The magnitudes of the ρ_Z values are in general greater than those of $|\rho_X|$ in Table 2, implying that bond-breaking is relatively more extensive than bond formation at the TS. The degree of bond-breaking assessed by the magnitudes of the ρ_Z values is found to increase with a more electron-donating group (EDG) in the nucleophile; for a stronger nucleophile (X = *p*-MeO), greater C_α–L bond-breaking takes place than for a weaker nucleophile (X = *m*-NO$_2$), in agreement with

Table 4. Hammett ρ_Z values[a]

		X				
Y	Solvent[b]	*p*-MeO	*p*-Me[c]	H	*p*-Cl	*m*-NO$_2$
H	100%	1.29	1.33	1.33	1.24	1.22
	90%	1.31	1.37	1.37	1.29	1.26
	80%	1.38	1.43	1.43	1.33	1.28
	70%	1.41	1.48	1.48	1.41	1.39
	50%	1.51	1.52	1.52	1.45	1.35
p-Cl	100%	1.41	1.42	1.41	1.35	1.24
	90%	1.47	1.45	1.43	1.38	1.26
	80%	1.51	1.50	1.49	1.43	1.30
	70%	1.50	1.54	1.51	1.44	1.28
	50%	1.57	1.59	1.58	1.48	1.35

[a] Correlation coefficients r 0.994 ± 0.005. [b] Volume percent of methanol.

the results of Westaway and Ali[4] Thus not only is bond-breaking concerted with bond-making, but also the two processes are synchronous[1] in the TS formation for reaction (i).

More extensive bond-making and -breaking are also predicted by the MO model for the nucleophile with a more EDG, in agreement with the present experimental results. Table 4 reveals that the degree of bond breaking (ρ_Z) is in general greater for the substrate with an EWG (Y = *p*-Cl). The result is unexpected and somewhat surprising in view of the fact that both theoretical[2] and experimental results appear to support tightening of the TS by an EWG in the substrate, which should mean a decrease in C_α–L bond-breaking, in contrast to the present results. This is however in agreement with the results of Ando *et al.*[12] for kinetic isotope effects in the reaction of benzyl benzenesulphonates with *N,N*-dimethylanilines. They concluded, on the basis of their kinetic isotope effect studies, that an EWG in the substrate makes the TS more product-like, *i.e.* it has a longer C_α–L bond and a shorter N–C_α bond. According to the MO model,[2] the two components contributing to the extent of bond-breaking, E_{pl} and E_{ct}, predict opposing effects on the degree of C_α–L bond-breaking; the polarization term disfavours whereas the charge-transfer term favours C_α–L bond-loosening in the TS for a substrate with an EWG. Since both terms are second-order in perturbation (V^2),[2] but zero order for E_{pl} and second order for E_{ct} in overlap (S^0 and S^2, respectively),[2] the former appears to become dominant at a relatively early stage of the reaction (being a long-range effect) whereas the latter should become dominant at a relatively short distance between the reactants, especially when a good leaving group is involved. In a 'polarization-controlled' reaction, bond-breaking decreases, whereas in a 'charge-transfer-controlled' reaction, bond-breaking is predicted to increase in the TS. The charge-transfer term will become important as the energy gap between the highest occupied MO (HOMO) of the nucleophile and the lowest unoccupied MO (LUMO) of the substrate (C_α–L bond) decreases and as the overlap S between the two reaction site atoms (N $\cdots$ C_α) increases.[13]

These two conditions are indeed favoured by an EWG in the substrate: Y = EWG is known to depress the LUMO[2] so as to decrease the energy gap and to increase the AO coefficient in the LUMO of C_α,[2,13] causing greater overlap between the reaction site atoms. It appears therefore that the present work provides a rare example of a 'charge-transfer-controlled' reaction in determining the effect of substituents (Y) in the substrate on the degree of bond-breaking. Although the model of Pross and Shaik[9] also considers the mixing of the same two components, *i.e.* polarization and charge transfer, in the ground state configuration, a 'polarization-controlled' effect only was predicted.

The failure of various potential energy surface (PES) models[14–18] in predicting substituent effects on TS variation in the S_N2 reaction has been reviewed in great detail by Westaway and Ali,[4] using their results on the effect of changing leaving group on TS structure in the nucleophilic substitution reactions of *para*-substituted phenylbenzyldimethylammonium ions with benzenethiolate ions. Since the present results of the effects of substituents in the nucleophile (X) and the leaving group (Z) on TS structure are in complete agreement with those of Westaway and Ali,[4] the PES models[14–18] will also fail to rationalize our results. On the other hand the quantum mechanical model of Pross and Shaik[9] is able to predict correctly most of the effects of substituents, albeit in some cases the predictions are not clear-cut; the model however fails to predict our observation of an increase in the C_α–L bond-breaking for a substrate with a more EWG (Y = *p*-Cl).

Effect of Solvent.—The rate constants in Table 1 increase with MeOH content of the solvent mixtures. This is in accord with the general observation that the rates of reaction between alkyl halides and primary amines are faster in a protic than in an aprotic solvent,[19] the reverse is true for a similar reaction with tertiary amines.[20] Since an increase of MeOH content is expected to enhance the proton-donor ability (α) of the solvent,[21] the rate increase with MeOH content indicates electrophilic assistance of bond-breaking by hydrogen-bonding of MeOH to the leaving group.

Tables 2—4 show that all the selectivity parameters, $|\rho_X|$, $|\rho_Z|$, and β_N, increase as the polarity (π^*) of the solvent[21] increases (with MeCN content). This indicates that the stabilizing effect of the more polar solvent (MeCN) increases as the TS becomes more polar, because charge formation is expected to advance further as the bond formation ($|\rho_X|$ and β_N) progresses; a parallel increase of $|\rho_Z|$ with $|\rho_X|$ and β_N in a more polar solvent (higher MeCN content) is further evidence supporting the synchronous nature of the mechanism, *i.e.* an increase in the bond formation ($|\rho_X|$ and β_N) is accompanied by a simultaneous increase in bond breaking ($|\rho_Z|$) at the TS.

Reactivity–Selectivity Principle (*RSP*).—The rates (Table 1) increase as the substituent (X) in the nucleophile is changed from an EWG (X = *m*-NO$_2$) to an EDG (X = *p*-MeO). However, corresponding substituent changes in the nucleophile are also accompanied by an increase in selectivity (ρ_Z value in Table 4), in violation of the RSP.[22–25] Similar violation of the RSP is also found for substituent changes in the leaving group; a more reactive (greater rate in Table 1) leaving group (Z = *m*-NO$_2$) is also a more selective one (greater $|\rho_X|$ and β_N values in Tables 2 and 3).

These RSP failures for substituent variations in the nucleophile and the leaving group are in contrast to the correct RSP behaviour of substituent changes in the substrate found previously.[1] The RSP behaviour of substrate variation in the present work is complex; the rate and hence the reactivity increases for a nucleophile with an EDG (X = *p*-MeO) whereas it decreases for a nucleophile with an EWG (X = *m*-NO$_2$) as the substituent in the substrate is changed to an EWG (Y = *p*-Cl). However, the selectivity ($|\rho_X|$ and β_N) increases for a substrate with an EWG (Y = *p*-Cl), irrespective of whether the substituent in the nucleophile is an EDG or an EWG. Thus the substrate changes violate the RSP if X = EDG while the RSP is adhered to if X = EWG. The RSP is found to hold for solvent variation in agreement with our previous results;[1] for a less reactive solvent (50% MeOH) the selectivity ($|\rho_X|$, β_N, and ρ_Z) is greater.

Experimental

Materials.—Purifications of solvent and anilines were carried out as described previously.[1] Benzyl benzenesulphonates ($YC_6H_4CH_2OSO_2C_6H_4Z$) were prepared by literature methods[26,27] or by appropriate modifications, and were recrystallized more than twice from anhydrous ether (except *p*-chlorobenzyl benzenesulphonate); melting points were as follows [Y,Z, m.p. (°C)]: H,H, 57—58 (lit.,[26] 57—58); *p*-Cl,H, oil; H,*p*-Cl, 55—57 (lit.,[26] 56—57); *p*-Cl,*p*-Cl, 78; H,*m*-NO_2, 66 (lit.,[26] 68); *p*-Cl,*m*-NO_2, 65.

Rate Constants.—Rates were measured conductimetrically at 35.00 ± 0.03 °C and second-order rate constants, k_2, were determined as reported previously.[1] Good second-order kinetics ($r > 0.999$) were obtained in all cases.

Acknowledgements

We thank the Korea Science and Engineering Foundation for support of this work.

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Received 9*th January* 1986; *Paper* 6/073