Reactivity–Selectivity Relationships. Part 11.[1] Effect of Leaving Group on Selectivity in S_N2 Reactions. A Frontier Orbital Analysis

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A perturbation molecular orbital treatment based on frontier orbitals is utilized to explain the selectivity order of a series of octyl, 1-methylheptyl, and benzyl derivatives toward *m*-chloroaniline and ethanol in a nucleophilic substitution reaction. The observed selectivity increases in the order $ROSO_2Ar < RCl < RBr < RI$. The model suggests that it is the differential HOMO–LUMO gap for a given substrate and the two reacting nucleophiles that governs substrate selectivity. Implications of this result to the reactivity–selectivity principle are discussed.

THE relationship between reactivity and selectivity in chemistry constitutes a subject of both theoretical and mechanistic interest.[2] The theoretical interest stems from the fundamental concepts on which the reactivity–selectivity principle (r.s.p.) is derived, primarily the Leffler–Hammond postulate.[3] The mechanistic interest stems from the utility of the r.s.p. as a tool in the study of reaction intermediates.[2,4] Selectivity studies are also useful in the determination of transition-state structure. Thus selectivity data are thought to provide a relative measure of bond formation or bond breaking in the transition state. However, in order to be able to utilize effectively the principle in the study of reaction intermediates or transition-state structure a clear understanding of both the scope and limitations of the principle are required.

In this work we have studied the selectivity of a number of model compounds, octyl, 1-methylheptyl, and benzyl derivatives during nucleophilic substitution towards the competing nucleophiles, *m*-chloroaniline and ethanol, in aqueous ethanol solution [equation (1)].

$$RX \xrightarrow[EtOH]{m\text{-}ClC_6H_4NH_2} ROEt + RNHC_6H_4Cl \quad (1)$$

The experimental results indicate that for these systems changes in the leaving group bring about drastic changes in selectivity. However these changes in no way correlate with leaving group reactivity. This paper presents an analysis based on frontier orbitals to explain both the selectivity pattern observed in this work as well as a range of selectivity data taken from the recent literature.

RESULTS AND DISCUSSION

Effect of Leaving Group.—The selectivity of a series of octyl derivatives toward the competing nucleophiles, *m*-chloroaniline and ethanol in aqueous ethanol solutions are listed in Table 1. Selectivity is defined as k_N/k_O where k_N is the bimolecular rate constant of the octyl derivatives with the amine, and k_O, the corresponding rate constant with the alcohol. Alcohol formation by water attack was not considered. The selectivity data are obtained using:

$$k_N/k_O = \frac{[\text{octyl amine}]}{[\text{octyl ether}]} \Big/ \frac{[m\text{-chloroaniline}]}{[\text{ethanol}]} \quad (2)$$

The amine to ether product ratio was established by response-calibrated g.l.c. All nucleophiles were present in pseudo-first-order concentration.

TABLE 1

Selectivity [a] of octyl derivatives toward competitive substitution by *m*-chloroaniline [b] and ethanol in aqueous ethanol at 75 °C

Octyl X X =	% Ethanol (v/v) 50	60	70	80	95
Cl	640	515	440	405	350
Br	695	570	455	*c*	*c*
I	1 670	1 520	1 300	1 200	1 130
p-$BrC_6H_4SO_3$	184	160	132	106	84
p-$NO_2C_6H_4SO_3$		154	133	115	87

[a] Selectivity defined as k_N/k_O and determined from equation (2) using response calibrated g.l.c. Estimated error in data <5%. [b] Amine concentration 0.2M. [c] Data unreliable due to decomposition products.

It is apparent that the leaving group has a profound effect on the selectivity of the octyl derivatives. For octyl *p*-bromobenzenesulphonate in 80% ethanol a selectivity value of 106 is observed compared to 1 200 for octyl iodide. Furthermore, there is no relationship between reactivity and selectivity. The leaving group abilities of those leaving groups studied increase in the order $Cl < Br < I < p\text{-}BrC_6H_4SO_3 < p\text{-}NO_2C_6H_4SO_3$,† while the selectivities increase in the order $p\text{-}BrC_6H_4SO_3 = p\text{-}NO_2C_6H_4SO_3 < Cl < Br < I$. This behaviour resembles that observed by Bram *et al.*[6] with respect to the reaction of ethyl derivatives in dimethoxymethane toward the enolate anion, an ambident nucleophile. The selectivity order observed in this system was $ROSO_2F \sim ROSO_2CF_3 < ROSO_2Et < ROSO_2C_6H_4CH_3 < RBr < RI$. Similarly Koskikallio [7] noted that the selectivity of methyl derivatives toward a series of anionic nucleophiles in water increases in the order $MeONO_2 < MeCl < MeBr < MeI$. By contrast, however, methyl nitrate, perchlorate, and benzenesulphonate show similar selectivity toward the same series of nucleophiles.[7] Also, Kevill *et al.*[8] observed that the selectivity of methyl triflate and methyl iodide catalysed by silver ion, toward a series of substituted benzene-

† It should be noted that while leaving group ability is not a fixed property, numerical variations for S_N2 type reactions are limited, so that the order is generally the same under different reaction conditions.[5]

sulphonate anions was identical. These data and others obtained previously are summarized in Table 2.

A number of points emerge from the data. (1) If the attacking atom in each of the competing nucleophiles is different then there is usually a strong leaving-group influence on selectivity. However if the leaving groups are joined to the substrate by the same atom the effect of the leaving group is small.

(2) If the attacking atom in each of the competing nucleophiles is the same then the effect of the leaving group on selectivity is small, regardless of the nature of the leaving group.

(3) For those cases in which the attacking atom varies in the series of nucleophiles, and the atom which binds the different leaving groups to the substrates also varies, then the observed selectivity of the substrates decreases in the order RI > RBr > RCl > ROY (OY is any leaving group bound through O).

TABLE 2

Summary of data indicating the effect of leaving group on the selectivity of listed substrates toward various nucleophiles

System	Nucleophiles	Selectivity order as a function of leaving group	Ref.
Ethyl	$AcCHCO_2Et$ (C and O attack)	$I^- > Br^- > p\text{-}MeC_6H_4SO_3^- > EtSO_4^- > CF_3SO_3^- = FSO_3^-$	6
Methyl	$S_2O_3^{2-}$, I^-, Br^-, Cl^-, F^-, OH^-, CN^-, SCN^-, SO_3^{2-}, N_3^-, H_2O	$I^- > Br^- > Cl^- > PhSO_3^- = NO_3^- = ClO_4^-$	7
Methyl	$p\text{-}X\text{-}C_6H_4SO_3^-$, X = MeO, Me, H, F, Cl, Br, NO_2, $m\text{-}NO_2$	$CF_3SO_3^- = I\text{-}Ag$	8
Octyl	EtOH, H_2O	$Br^- = Cl^- = p\text{-}BrC_6H_4SO_3^- = p\text{-}CH_3C_6H_4SO_3^-$	10
Benzyl	EtOH, H_2O	$Br^- = Cl^-$	10
1-Methylheptyl	EtOH, H_2O	$Br^- = Cl^-$	10
Octyl	$m\text{-}ClC_6H_4NH_2$, EtOH	$I^- > Br^- > Cl^- > p\text{-}BrC_6H_4SO_3^- = p\text{-}NO_2C_6H_4SO_3^-$	

(4) Both charged and uncharged nucleophiles show a similar pattern suggesting the behaviour to be general in nature.

(5) In all cases there is no correlation between substrate reactivity and selectivity.

These points may be analysed as follows: since the selectivity order for different leaving groups is nucleophile dependent it is clear that the order is not merely based on the reactivity of the substrate. The fact that the order is quite unrelated to the leaving-group ability confirms this. Hence, the conclusion one reaches is that the variable selectivities are due to specific nucleophile–leaving group interactions. In other words, the relative nucleophilicity of two nucleophiles toward a series of S_N2 substrates is not constant, but is strongly dependent on the leaving group.

For a family of nucleophiles, attacking through the same atom, the specific nucleophile–leaving group interaction is apparently similar for the series and, as a result, the effect of leaving group on selectivity is small. Similarly, for a family of electrophiles, which are bound to the substrate by the same atom, the specific nucleophile–leaving group interaction is also essentially constant and, once again, almost invariant selectivity is observed. The question that arises therefore is what is the nature of the specific interaction which brings about such large changes in the selectivity of S_N2 substrates when the atoms at the two active sites are varied.

Perturbation molecular orbital theory [9] may be utilised to rationalise the above behaviour. In its simplest form, the theory specifies that the ease with which a particular reaction proceeds, is based on the magnitude of the initial interaction between the two reacting species. The energy of interaction is composed of two main contributions—a charge component and an orbital component.[9a,c,d] The former is the simple coulombic contribution to the overall energy of interaction. The latter component consists of all the two-electron stabilising interactions between occupied and unoccupied orbitals in the reacting moieties. However due to the dominance of the HOMO–LUMO interactions in many systems, these are often the only ones that are explicitly considered.

In the case of a nucleophilic substitution reaction the relevant orbitals are the lone pair on the nucleophile (the HOMO) and the σ^*_{CX} orbital associated with the substrate (the LUMO). The magnitude of the stabilising interaction, SE, between an occupied and unoccupied orbital is given approximately by equation (3).[9b-e] β is the resonance integral associated with the two orbitals, and ΔE is the energy difference between the two orbitals.

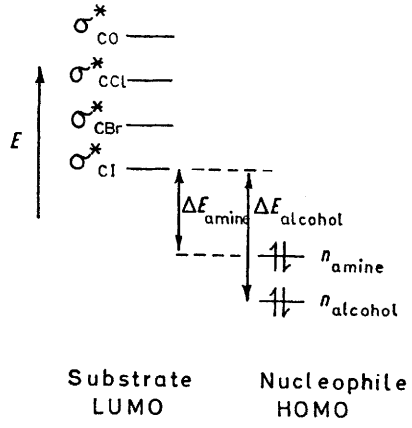

FIGURE 1 Schematic energy diagram for the interaction of the nucleophile HOMO for an amine and alcohol with the substrate LUMO for a series of alkyl derivatives

An energy diagram showing the relevant orbitals involved in the nucleophilic substitution of alkyl

$$SE = \frac{\beta^2}{\Delta E} \quad (3)$$

derivatives is shown in Figure 1. The energies of the σ^*_{CX} orbitals are considered to increase in the order $\sigma^*_{CI} < \sigma_{CBr} < \sigma^*_{CCl} < \sigma^*_{CO}$.[9b] This is because along a row of the periodic table the energy of both the σ and σ^* orbitals of a C–X bond decrease in energy. However, down a column of the periodic table, the σ bond increases in energy while the σ^* orbitals decrease in energy.

For the competitive reaction of the two nucleophiles with a given substrate, a differential stabilization will result as shown in equation (4). The greater this

$$SE_{amine} - SE_{alcohol} = \frac{\beta^2}{\Delta E_{amine}} - \frac{\beta^2}{\Delta E_{alcohol}} \quad (4)$$

differential stabilization, the greater the selectivity of the substrate toward the two nucleophiles. If the orbital interaction is dominated by the energy difference, ΔE, rather than the resonance integral, β, then it is clear that the difference between the interaction of the n_N and n_O orbitals, with the σ^*_{CI} orbital will be larger than with the σ^*_{CBr}, or even higher-lying orbitals. In the limit, for a very high-lying orbital, the stabilisation energy of interaction with n_N or n_O will approach one another. What this means is that regardless of any change in the position of the transition state along the reaction co-ordinate, the intrinsic selectivity of octyl iodide toward the two competing nucleophiles is expected to be larger than that of octyl bromide, chloride, or brosylate. If this effect were to be dominant then the substrate selectivity would be expected to increase in the order ROY < RCl < RBr < RI. This is the order we observe experimentally and it suggests that any change in the position of the transition state along the reaction co-ordinate brings about a minor change in selectivity in comparison to the relative nucleophilicity effect we have discussed.

Fleming [9a] has interpreted the data obtained by Bram *et al.*[6] in terms of charge considerations. His analysis could well apply to our results as well. Specifically, on changing the leaving group in octyl iodide to a more electronegative halogen one increases the polarity of the C–X bond. This, in turn, tends to increase the charge-control component of the reaction (since the C–I bond is the least polar of the carbon–halogen bonds) which, in turn, favours the ethanol nucleophile over *m*-chloroaniline. Thus for a charge-controlled reaction the selectivity order we anticipate is identical to that based on an orbital-controlled reaction. While both these factors are likely to influence the selectivity we believe the orbital effect is dominant. This is because for the reaction of neutral molecules, charge effects are likely to be small. Furthermore, examination of the enolate anion system,[6] where a charged nucleophile is used, shows that *C*-alkylation is greatly favoured over *O*-alkylation, for all leaving groups. In this case, therefore, an orbital-controlled reaction is indicated. For a charged-controlled reaction the reverse would be expected to be true (*e.g.* as in the protonation of the enolate ion) and dominant *O*-alkylation would result. We conclude, therefore, that since orbital interactions are of overriding importance, that changes in selectivity are likely to be dominated by changes in the magnitude of those orbital interactions. However, it is clear that any additional effect due to charge interactions will only reinforce the trend already present.

Viewed in this light it is now clear why selectivity is found to be invariant if either (*a*) competing nucleophiles possess the same attacking atom or (*b*) that the family of leaving groups are all bound to the substrate with the same atom. The appropriate energy diagrams are shown in Figure 2. For the case in which two unrelated nucleophiles, react with a series of substrate whose leaving groups are joined to carbon by the same atom (*e.g.* a series of sulphonate anions) then the LUMO

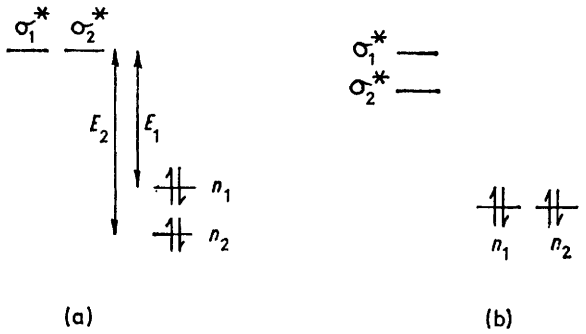

FIGURE 2 Energy diagram for the interaction of orbitals for (a) two dissimilar nucleophiles with two similar substrates and (b) two similar nucleophiles with two dissimilar substrates

energy levels will be close in energy (Figure 2a). As a result, the orbital contribution toward substrate selectivity (governed by $E_2 - E_1$) will be essentially constant for all the substrates. For the case in which two related nucleophiles (which possess the same attacking atom) are used, then the energy levels of the lone pairs will be of similar energy (Figure 2b). As a result the orbital contribution to selectivity will in this case be very small for all substrates, since the orbital interaction of each nucleophile with a particular substrate is similar in magnitude. On this basis, it is now apparent why essentially constant selectivity is observed in those cases where either the nucleophiles or the leaving groups belong to a limited family. Only when both unrelated nucleophiles *and* leaving groups are employed simultaneously does the anomalous selectivity order result.

One puzzling point arises from this analysis. If substrate selectivity is governed by the HOMO–LUMO gap why is the reactivity order unrelated to the selectivity order. It would appear that for a large HOMO–LUMO gap that not only low selectivity values but low reactivity values as well would occur, and that as the gap decreases both reactivity and selectivity would increase. This is clearly not the case. The fluorosulphonate leaving

group, for example, shows very high reactivity but low selectivity.[6]

We believe the different response of reactivity and selectivity to changes in the leaving group results from the fact that whereas selectivity is determined primarily by the magnitude of the HOMO–LUMO gap, reactivity is also influenced by the strength of the carbon-leaving group bond. The following analysis clarifies this point.

Let us assume that for a bimolecular substitution reaction, the free energy of activation, $\Delta G^{\ddagger}$, is determined essentially by two factors, (*a*) the orbital interaction term (*i.e.* mainly between the nucleophile HOMO and the electrophile LUMO) which is stabilizing and (*b*) the C–X bond-breaking term which is the primary contributor to the activation barrier, and destabilizing.* Therefore for the reaction of a nucleophile N_1 and a substrate RX_1 we may write:

$$\Delta G^{\ddagger}_{N_1,RX_1} = \Delta G^{\ddagger}(C{-}X_1) + \Delta G^{\ddagger}(N_1 \cdots CX_1) \quad (5)$$

where $\Delta G^{\ddagger}_{N_1,RX_1}$ is the free energy of activation for the reaction, $\Delta G^{\ddagger}(C{-}X_1)$ is the contribution of the breaking of the $C{-}X_1$ bond (a positive value) and $\Delta G^{\ddagger}(N_1 \cdots CX_1)$ is the contribution of the HOMO–LUMO interaction between the nucleophile, N_1, and the electrophile, RX_1 (a negative value).

In a similar way we may write for all combinations of two nucleophiles with two substrates [in addition to equation (5)] equations (6)—(8). Now the selectivity

$$\Delta G^{\ddagger}_{N_2,RX_1} = \Delta G^{\ddagger}(C{-}X_1) + \Delta G^{\ddagger}(N_2 \cdots CX_1) \quad (6)$$

$$\Delta G^{\ddagger}_{N_1,RX_2} = \Delta G^{\ddagger}(C{-}X_2) + \Delta G^{\ddagger}(N_1 \cdots CX_2) \quad (7)$$

$$\Delta G^{\ddagger}_{N_2,RX_2} = \Delta G^{\ddagger}(C{-}X_2) + \Delta G^{\ddagger}(N_2 \cdots CX_2) \quad (8)$$

of RX_1 toward N_1 and N_2 is given by (9), obtained by subtracting (5) from (6) which is just the difference in the

$$\Delta\Delta G^{\ddagger}_{RX_1} = \Delta G^{\ddagger}(N_2 \cdots CX_1) - \Delta G^{\ddagger}(N_1 \cdots CX_1) \quad (9)$$

orbital interaction terms as implied by the model discussed earlier.

The relative reactivity of two substrates, however, is given by either (7) — (5) using N_1 as the standard nucleophile or (8) — (6) using N_2 as the standard nucleophile.

Using N_1 the relative reactivity of RX_1 and RX_2 is given by

$$\Delta G^{\ddagger}_{N_1,RX_2} - \Delta G^{\ddagger}_{N_1,RX_1} = \Delta G^{\ddagger}(C{-}X_2) + \Delta G^{\ddagger}(N_1 \cdots CX_2) - \Delta G^{\ddagger}(C{-}X_1) - \Delta G^{\ddagger}(N_1 \cdots CX_1) \quad (10)$$

Here no terms cancel out suggesting that relative reactivity is a complex blend of both orbital-interaction energy and bond-breaking energies.

It may now be understood why substituted sulphonates exhibit identical selectivities toward a pair of nucleophiles yet exhibit markedly different reactivities. Selectively, which is determined by (9), is essentially constant since for all sulphonate leaving groups a C–O linkage is involved whose σ^* energy levels appear to be similar. Relative reactivity, however, which is determined by (10), depends on the relative bond strengths since now the orbital terms cancel. Since the bond strengths are likely to be strongly influenced by the substituent a strong leaving-group dependence on reactivity is observed within the substituted sulphonate series.[6]

Effect of Substrate.—We have also examined the selectivity of two other systems, benzyl and 1-methylheptyl, toward the same two nucleophiles under identical conditions. The data are listed in Table 3.

TABLE 3

Selectivity [a] of benzyl and 1-methylheptyl chlorides and bromides toward *m*-chloroaniline and ethanol in aqueous ethanol at 75 °C

	% Ethanol (v/v)				
Substrate	50	60	70	80	95
1-Methylheptyl chloride [b]	82	78	63	61	57
1-Methylheptyl bromide [b]	146	113	98	90	82
Benzyl chloride [c]	1 440	1 250	1 130	1 080	835
Benzyl bromide [c]	3 780	2 470	2 300	2 025	1 475

[a] Selectivity defined as k_N/k_O and determined from equation (2) using response calibrated g.l.c. Estimated error in data $<5\%$. [b] Amine concentration 0.2M. [c] Amine concentration 0.1M.

It is apparent that the strong selectivity dependence on leaving group is present in these systems as well. In both cases the selectivity of the bromide exceeds that of the corresponding chloride as was noted for the octyl system. However the data indicate that the observed selectivity is also largely influenced by the nature of the substrate. It is again tempting to treat the selectivity data as relative measures of transition state structure; that is, large selectivity values as being indicative of a highly developed nucleophile–substrate bond and *vice versa*. Once again, it appears the conclusions derived in this way are incorrect. While it is true that the degree of carbon–nucleophile bond formation in the transition state is more advanced for octyl than for 1-methylheptyl derivatives (consistent with the selectivity criterion) for a concerted S_N2 process, benzyl derivatives are thought to have looser transition states than octyl derivatives. As a result *lower* selectivity is anticipated for the benzyl system than the octyl system. The data provide the opposite result. Benzyl derivatives are *more* selective than octyl derivatives, again suggesting that for two structurally distinct nucleophiles, such as *m*-chloroaniline and ethanol, that selectivity reflects specific substrate–nucleophile interactions rather than an accurate measure of bond formation in the transition state.

It is intriguing to note that the selectivity of the three model substrates, which increases in the order 1-methylheptyl < octyl < benzyl is the same as that observed for these substrates toward ethanol and water.[10] This suggests that earlier conclusions reached by some of us,

* While other factors, particularly solvation, are certainly involved, for simplicity we assume only two terms contribute to the activation barrier.

regarding the significance of this order,[10] are uncertain. The breakdown of the r.s.p. with respect to S_N2 reactions as indicated in this work suggests that application of the principle to a range of solvolytic substrates, even for two similar nucleophiles such as ethanol and water, may not be valid, and the implications of the low selectivity exhibited by octyl derivatives toward ethanol and water unclear.

Solvent Effect.—Perusal of the selectivity data in Tables 1 and 3 shows that there is a clear influence of solvent composition on selectivity. For all substrates studied higher selectivity is observed in the more aqueous solvents. This behaviour has previously been noted for a wide range of substrates for competing ethanol and water nucleophiles.[4,10] For those substrates it was concluded that a linear increase in log S as a function of solvent ionizing power could be attributed to changes in the relative nucleophilicities of ethanol and water.[4b] We believe the present results may also be explained in this way. That is, in more aqueous solutions *m*-chloroaniline, relatively speaking, is a more powerful nucleophile than ethanol, in comparison to less aqueous mixtures. We can only speculate as to the reason for this behaviour, but it is conceivable that the increase in ethanol solvation in more aqueous mixtures is greater than that for the less-polar amine molecule.

The preceding discussion makes the point therefore that changes in the relative nucleophilicities of two nucleophiles are liable to occur for even a limited family of S_N2 substrates such as octyl derivatives. The immediate consequence is that selectivity values derived from two unrelated nucleophiles cannot be utilized as a measure of transition-state structure in these systems and as a direct corollary, that the r.s.p. will be invalid. One question remains to be answered. How appropriate a measure of transition state structure for S_N2 reactions are selectivity values, in which a series of related nucleophiles and leaving groups (which possess a common active atom) are utilized. This, of course, touches upon the problem of the scope of the r.s.p. Conflicting data which both support [11,12] and question [13] the possibility of using selectivity values as measures of transition-state structures have recently appeared. Further work to resolve this dilemma is required.

EXPERIMENTAL

Materials.—Alkyl halides were commercially available and were distilled prior to use. Octyl brosylate and *p*-nitrobenzenesulphonate were prepared from octanol and the corresponding sulphonyl chloride and found to be pure by n.m.r. spectroscopy. *m*-Chloroaniline was distilled prior to use. Analytical grade absolute ethanol was stored over molecular sieves and used directly.

Product Determination.—Reactions were performed in pressure tubes containing substrate (0.01M), *m*-chloroaniline (0.2M), and aqueous ethanol (5 ml). Reactions were conducted in thermostatted oil-baths (±0.05 °C) for 10 half-lives. Products were established as stable under the reaction conditions. Only for octyl bromide were significant decomposition products detected. These comprised up to 25% of the products in the 95% aqueous ethanol solution. The possibility of reaction in the g.l.c. injection port was eliminated by injecting reaction mixtures at zero time. No products were detected. The possibility of the formation of the alkylammonium salt so as to render product ratios insignificant was eliminated through the addition of an excess of lutidine to the reacted mixtures. No difference in product ratios was detected. Product ratios were established using response calibrated g.l.c. on a 1/4 in × 1.5 m column packed with 5% GE XE-60 on Chromasorb WAW DMCS 80—100 mesh. Results are the average of at least 3 determinations on at least duplicate runs. An error of up to 5% is estimated in product ratios.

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