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REACTIVITY-SELECTIVITY RELATIONSHIPS. PART 10.[1a]

ORBITAL CONTROL AND ITS EFFECT ON SELECTIVITY IN S_N2 REACTIONS.

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In recent papers[1-4] we have concerned ourselves with the application of the reactivity-selectivity principle to solvolytic reactions. For S_N1 type substrates, such as substituted benzyhydryl[2] an 1-arylethyl derivatives[5] the principle appears to operate since the more reactive ion pair intermediates exhibit lower selectivity than less reactive ones. In this communication we wish to report the breakdown in the reactivity-selectivity principle for the S_N2 reaction of 1-octyl derivatives toward the competing nucleophiles, m-chloroaniline and ethanol. The selectivities of 1-octyl halide and brosylate in a number of aqueous ethanol solutions are listed in Table 1.

It is apparent that the nature of the leaving group exerts a substantial influence on the substrate selectivity. Specifically, in all solvent compositions the selectivity order of RX for different leaving groups, X, increases in the order $\mathrm{ROBs} < \mathrm{RC}\ell < \mathrm{RBr} < \mathrm{RI}$, and is quite unrelated to the solvolytic reactivity of RX which increases in the order $\mathrm{RC}\ell < \mathrm{RBr} < \mathrm{RI} < \mathrm{ROBs}$.[6] Thus octyl iodide and brosylate, which are of similar reactivity, exhibit markedly different selectivities toward the competition of the two dissimilar nucleophiles. Our results are similar to data reported by Bram et al.[8] in which the selectivity of ethyl derivatives toward the enolate anion, an ambident nucleophile, also failed to correlate with reactivity. The above results however are in contrast to the behaviour of 1-octyl, 2-octyl and benzyl derivatives toward the competing nucleophiles, ethanol and water. Here no selectivity dependence on leaving group was observed.[3]

We believe the results may be understood in terms of orbital interactions between the nucleophile and electrophile. Frontier orbital theory treats the nucleophilic substitution reaction as being initiated by the interaction between the HOMO of the nucleophile with the LUMO of the electrophile.[9] The magnitude of the stabilizing energy, S.E., as these two orbitals interact is inversely proportional to the energy difference between the two orbitals, ΔE, (eq. 1).[9]

$$\text{S.E.} = c_{rj} c_{sk} \beta_{rs}^2 / \Delta E \qquad (1)$$

Table 1: Selectivity[a] of 1-octyl derivatives toward competitive substitution by m-chloroaniline[b] and ethanol in aqueous ethanol at 75°C.

1-Octyl X	% Ethanol (v/v)			
X=	50	60	70	80
Cℓ	639	514	442	404
Br	694	570	456	-
I	1674	1519	1296	1200
OBs	184	160	132	107

[a] Selectivity defined as the ratio of rate constants of amine and alcohol substitution and determined by response calibrated g.l.c. Error estimated as up to 5%.

[b] Amine concentration 0.2M.

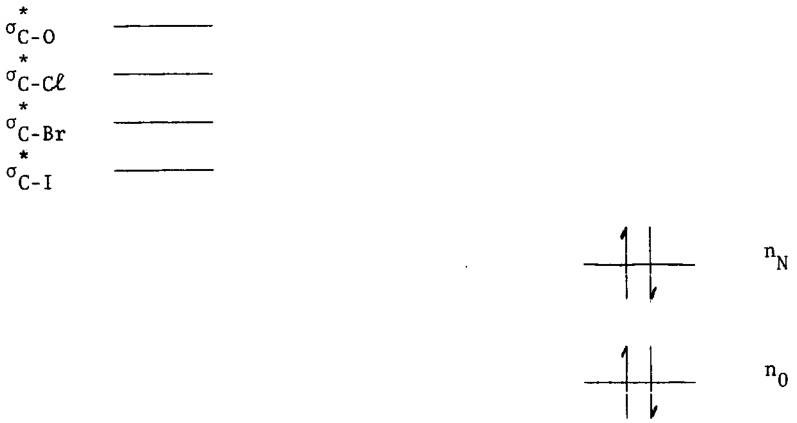

Figure 1: Schematic representation of the ordering of energy levels of the σ^*_{C-X} orbitals in RX (the LUMO'S) and the lone pair orbitals, n, in the amine and alcohol nucleophiles (the HOMO'S).[12]

Here the parameters c_{rj} and c_{sk} represent the coefficients of the atomic orbitals on interacting atoms r and s in the molecular orbitals j and k respectively, and β_{rs} represents the resonance integral associated with the corresponding atomic orbitals on atoms r and s.

Now the closer the energies of the interacting molecular orbitals, the greater the stabilizatio For the nucleophilic substitution reaction the orbitals in question are the lone pair on the nucleophile (the HOMO) and the σ^*_{C-X} orbital of the electrophile (the LUMO). The relevant orbitals and thei relative energy levels are illustrated schematically in Figure 1.[10]

It is clear that the lower the energy of the C-X antibonding orbital the greater the orbital interaction between the nucleophile HOMO and the electrophile LUMO. However since the stabilization energy, S.E., is inversely proportional to the energy difference between the two orbitals, ΔE, (eq. a reduction in the energy of the σ^*_{C-X} orbital (e.g., on going from C-Br to C-I), brings about a grea er increase in the interaction with the high lying N lone pair than with the lower lying O lone pair In other words, electrophiles posessing low lying σ^*_{C-X} orbitals will tend to differentiate more effectively between nucleophiles than those with high lying σ^*_{C-X} orbitals. *This means that the relative nucleophilicity of the amine and alcohol nucleophiles is not constant but is dependent on the electrophile.* This fact is well known when entirely different classes of electrophiles are considered, but our data suggest that even for a limited family of compounds, such as 1-octyl derivatives, changes in the leaving group bring about changes in the relative nucleophilicities of the two competing nucleophiles. As a result, based on this change, the intrinsic selectivity of RX i expected to increase in the order of energy levels of the σ^*_{C-X} orbital, i.e., ROBs<RCℓ<RBr<RI.[11] This is precisely the order observed experimentally and suggests that changes in relative nucleophilicity are more important in determining substrate selectivity than changes in transition state structure brought about by varying substrate reactivity. It is this latter effect operating alone which is responsible for the observation of a reactivity-selectivity correlation in certain systems.

The preceding analysis is based on the assumption of an orbital rather than a charge controlled reaction.[9c,d] We believe this is justified because the substitution reaction of alkyl halides are thought to exhibit orbital control even with charged nucleophiles.[9d] In our case, the use of neutral nucleophiles is clearly, even more likely to favour an orbital controlled reaction.

In conclusion, it appears that reactivity-selectivity correlations will only be observed within very restricted families of reactions. Thus even a structural variation, such as leaving group change which leaves the reaction mechanistically unaffected, is sufficiently powerful to dominate the underlying dependence between reactivity and selectivity, by changing the relative nucleophilicity of the competing nucleophiles.

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References and Notes

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10. Down a column of the periodic table the energy of the σ^*_{C-X} orbital decreases. Thus for the halogens, the energy level increases in the order $I<Br<C\ell<F$.[9b,d] Along a row, the energy of the σ^*_{C-X} bond also decreases. Thus the σ^*_{C-O} level lies higher in energy than the σ^*_{C-F} orbital[9b] (and hence also the $\sigma^*_{C-C\ell}$ orbital).
11. This argument assumes that the stabilization energy will be dominated by ΔE rather than $c_{rj}c_{sk}\beta^2_{rs}$. This is despite the fact that the coefficient on carbon in the σ^*_{C-X} orbital will tend to increase as the electronegativity of the C-X bond increases. This effect, therefore, will operate in the opposite direction to the energy trend. In the absence of quantitative data the relative importance of these two effects cannot be ascertained. However, if one accepts the present model, then the selectivity order suggests that the ΔE term is in fact dominant. For the case in which the resonance integral term were to be dominant, the reverse selectivity order would be expected.
12. Ab initio calculations (at the STO-3G level) confirm the relative HOMO levels of m-chloroaniline and ethanol.[13]
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