An MO Study of the Orientational Selectivity in Nucleophilic Substitution Reactions of Polyhalobenzenes

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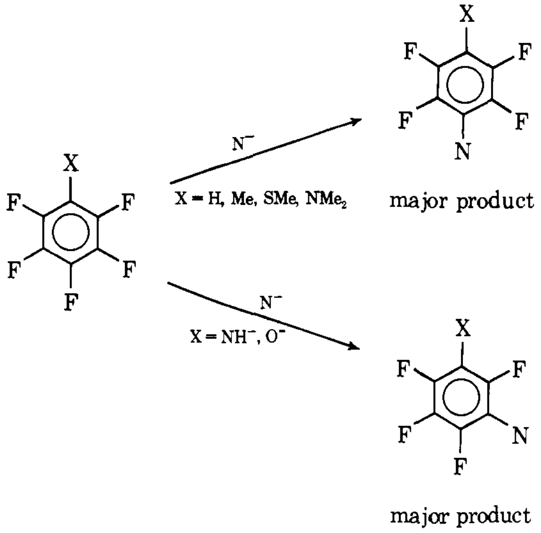
Abstract: A perturbation approach is employed to predict the nucleophilic substitution patterns of polyhalobenzenes of the type $C_6H_{6-n}X_n$. The method leads to the formulation of a qualitative index for predicting the orientation of nucleophilic substitution. The treatment is then extended to rationalize the substitution patterns encountered in molecules of the type C_6X_5Y, where X is a halogen and Y any substituent and, in all cases examined, the theoretical predictions compare favorably with the experimental results.

In recent years, the orientation of aromatic nucleophilic substitution of polysubstituted benzenes has received considerable attention. Some of the interesting trends observed in nucleophilic replacement reactions of C_6F_5X compounds are summarized by means of the equations below:[1]



It was originally suggested that the five fluorines direct substitution at the para positions and the substituent X can enhance or oppose the effect.[1] Burdon[2] pointed out that this argument is unsatisfactory in a number of cases. For example, C_6F_5Cl reacts with sodium methoxide much faster than pentafluorobenzene does[3] and this implies that chlorine activates the para attack more than hydrogen does. However, C_6Cl_5H reacts with nucleophiles at the position para to the hydrogen,[4] which seems to contradict the previous argument. Burdon further suggested that the orientation of nucleophilic replacement reactions of aromatic polyhalo compounds can be rationalized by considering the relative stabilities of the Wheland-type intermediates involved and making the assumption that the repulsion between the lone pair of a halogen and an adjacent π system varies in the order F > Cl > Br > I. This repulsive effect of the halogen atoms, labeled the I_π effect by one group of workers,[5] can be thought of as the combined effect of two-electron coulombic repulsion between the p_z lone pair of the halogen and the π electrons of the pentadienyl system as well as one-electron overlap repulsion arising from the interaction of the p_z halogen lone pair with the occupied MO's of the pentadienyl system.

In this work, we wish to point out that one-electron perturbation theory[6] with neglect of overlap and within the framework of the frontier orbital (FO) approximation[7] can be successfully utilized in order to predict orientation and reactivity patterns in aromatic nucleophilic substitution reactions of polyhalobenzenes and related molecules.

Our approach focuses attention on the transition state of the reaction, e.g., the complex between the aromatic molecule and the nucleophile, rather than the Wheland intermediate itself. The dominant orbital interactions stabilizing the transition state complex, within the context of the FO approximation, involve the HOMO of the nucleophile and the LUMO of the aromatic molecule. Benzene itself has a pair of degenerate HOMO's (ϕ_2, ϕ_3) and a pair of degenerate LUMO's (ϕ_4, ϕ_5). Polysubstitution of the benzene nucleus can lift the degeneracy. Hence, in the case of polyhalobenzene derivatives, our first task is to determine how a particular substitution pattern lifts the degeneracy of the benzenoid MO's ϕ_4 and ϕ_5, and, thus, identify the LUMO of the aromatic substrate. Once this is accomplished, nucleophilic attack is predicted to occur preferentially at the center of highest FO electron density, e.g., the carbon of highest LUMO electronic density. In this approach we assume that the benzenoid LUMO-nucleophile HOMO is the only interaction stabilizing the transition state. Of course, the next higher unfilled MO (originally, one of the benzenoid, unoccupied degenerate MO's) will also mix with the nucleophile HOMO and contribute to the stabilization of the transition state. However, this will only attenuate the dominant HOMO-LUMO interaction and will not change the qualitative results based on the neglect of this second interaction. Obviously, when the splitting of the degeneracy of the benzenoid MO's by substituents is very small, both interactions should be considered.

We shall illustrate our approach by considering the simplest polyhalobenzene where orientational preference can arise, namely, 1,2,3-trifluorobenzene. We can consider the π MO's of this molecule to arise from the interaction of the benzenoid π MO's and the group π MO's of the three adjacent fluorines as shown in Figure 1. The splitting of the degeneracy of the benzenoid MO's ϕ_4 and ϕ_5 depends upon the magnitude of their interaction with the three-fluorine group MO's. According to perturbation theory, the energy increase of ϕ_4 and ϕ_5 upon interaction with ψ_1, ψ_2, and ψ_3 is proportional to the square of the matrix element and inversely proportional to the energy separation of the interacting MO's. By making the usual assumption that the resonance integral is proportional to the overlap integral (i.e., $H_{ij} = kS_{ij}$)[8] and expanding the MO's in terms of the appropriate AO's we find

$$\Delta E_{5,1} = \frac{[\langle \phi_5 | H | \psi_1 \rangle]^2}{\Delta\epsilon} = [(c_{15}b_{11} + c_{25}b_{21} + c_{35}b_{31})kS]^2/\Delta\epsilon_{5,1} \quad (1)$$

where $\Delta E_{5,1}$ is the energy increase of ϕ_5 due to its interaction with ψ_1, c_{ij} is the coefficient of the ith carbon atomic center in the jth benzenoid MO, b_{ij} is the coefficient of the ith fluorine atomic center in the jth F···F···F group MO, k is a constant, S is the overlap integral between adjacent carbon and fluorine[9] atoms, and $\Delta\epsilon_{5,1}$ is the energy difference between ϕ_5 and ψ_1. Likewise, we calculate

$$\Delta E_{5,3} = \frac{[\langle \phi_5 | H | \psi_3 \rangle]^2}{\Delta\epsilon} = [(c_{15}b_{13} + c_{25}b_{23} + c_{35}b_{33})kS]^2/\Delta\epsilon_{5,3} \quad (2)$$

$$\Delta E_{4,2} = \frac{[\langle \phi_4 | H | \psi_2 \rangle]^2}{\Delta\epsilon} = [(c_{14}b_{12} + c_{24}b_{22} + c_{34}b_{32})kS]^2/\Delta\epsilon_{4,2} \quad (3)$$

We can now make a further approximation to facilitate rapid evaluation of the energy increase of ϕ_4 relative to ϕ_5 upon interaction with the fluorines. Instead of mixing the benzenoid MO's with the group MO's of the fluorines, we will mix the benzenoid MO's individually with three degenerate fluorine AO's. The energy change of ϕ_5 is now given by

$$\Delta E_5 = \frac{\langle \phi_5 | H | \mathrm{F_1p_z} \rangle^2 + \langle \phi_5 | H | \mathrm{F_2p_z} \rangle^2 + \langle \phi_5 | H | \mathrm{F_3p_z} \rangle^2}{\Delta\epsilon} = [(c_{15}kS)^2 + (c_{25}kS)^2 + (c_{35}kS)^2]/\Delta\epsilon = [(c_{15}^2 + c_{25}^2 + c_{35}^2)k^2S^2]/\Delta\epsilon \quad (4)$$

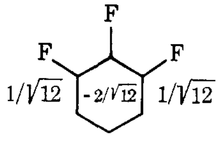
where $\Delta\epsilon$ is the energy difference between the degenerate benzenoid MO's and the degenerate F AO's. Likewise, the change of ϕ_4 is now given by

$$\Delta E_4 = [(c_{14}^2 + c_{24}^2 + c_{34}^2)k^2S^2]/\Delta\epsilon \quad (5)$$

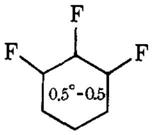
The ratio of ΔE_5 to ΔE_4 is then

$$\Delta E_5/\Delta E_4 = (c_{15}^2 + c_{25}^2 + c_{35}^2)/(c_{14}^2 + c_{24}^2 + c_{34}^2) \quad (6)$$

Therefore, to determine the LUMO in a polyhalobenzene all we need to do is compare the sum of the squares of the coefficients of the carbon atoms that are substituted with a halogen in the two originally degenerate benzenoid MO's, ϕ_4 and ϕ_5. This sum will be symbolized by Q_5 for the symmetric benzenoid MO and Q_4 for the antisymmetric MO. The calculations for 1,2,3-trifluorobenzene are illustrated below.



$$Q_5 = \sum_j c_{j5}^2 = (1/\sqrt{12})^2 + (-2/\sqrt{12})^2 + (1/\sqrt{12})^2 = 6/12 = 0.5$$



$$Q_4 = \sum_j c_{j4}^2 = (0.5)^2 + (-0.5)^2 = 0.5$$

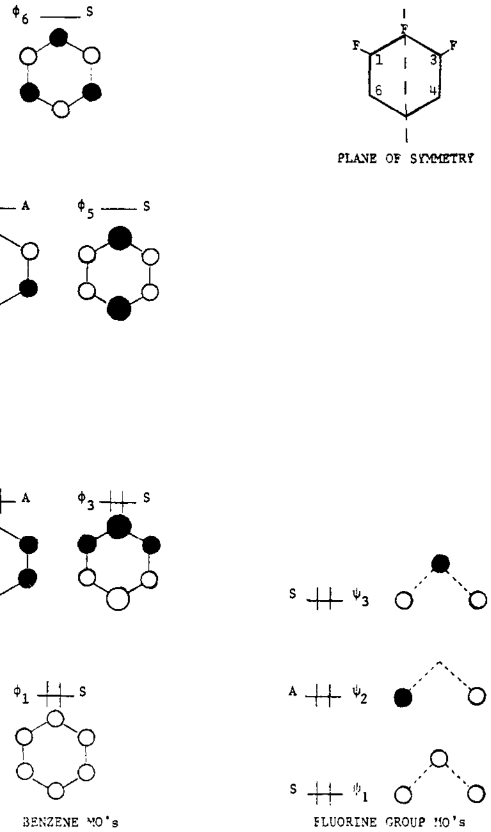
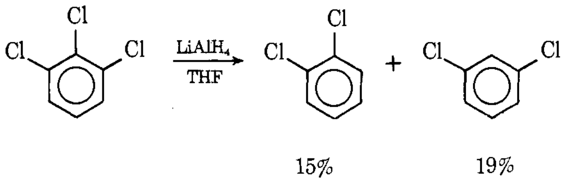


Figure 1. The MO's of benzene and the group orbitals of the three fluorines which can be used to construct the π MO's of 1,2,3-trifluorobenzene. Fluorine group orbitals are assumed to be degenerate.

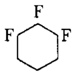
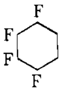
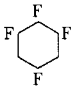
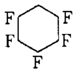
Thus, in trifluorobenzene ϕ_4 and ϕ_5 are still degenerate and nucleophilic attack is expected to occur equally at both the one and two position. Experimentally, when the statistical factor has been included it is found that both positions are attacked about equally.[10]



We have calculated the quantities Q_4 and Q_5 for several polyfluorobenzenes. These are shown in Table I. Also shown in Table I are the energies of ϕ_4 and ϕ_5 calculated using CNDO/2.[11] In all four cases our ordering of ϕ_4 and ϕ_5 agrees with the CNDO/2 results, thus confirming our previous assumption that individually mixing the $\mathrm{Fp_z}$ AO's with the benzene MO's gives qualitatively correct results. The predicted position of attack in these molecules is also shown in Table I. In all cases there is excellent agreement between the predicted and experimental positions of nucleophilic attack.

We shall now examine the orientational preference exhibited in the nucleophilic replacement reactions of molecules of the type C_6F_5X. Once more, we have to determine how the six substituents split the degeneracy of the ϕ_4 and ϕ_5 benzenoid MO's. This can be conveniently done by considering how the substituent X modifies the energy separation of the two lowest unoccupied S and A benzenoid MO's of C_6F_5H. The lifting of the degeneracy of ϕ_4 and ϕ_5 has already been discussed. The diagram of Figure 2 shows the principal π-MO interactions between ϕ_4 and ϕ_5 and typical electron-donor and electron-acceptor substituents. Either electron-donor or -acceptor substituents can interact only with the S benzenoid MO since the A MO has a node

Table I. The Value of Q_5 and Q_4, Calculated Energies of ϕ_5 and ϕ_4, and the Predicted and Experimental Positions of Attack for Polyfluorobenzenes

	Q_5	Q_4	$E_5{}^d$	$E_4{}^d$	Predicted[e] position of attack	Exptl[e] position of attack	Ref
	0.5	0.5	0.1311	0.1306	1,2	1,2	*a*
	0.83	0.5	0.1229	0.1128	1	1	*b*
	0.83	0.5	0.1247	0.1149	1	1	*b*
	0.66	1.0	0.1014	0.1098	5	5	*c*

[a] Reference 10. [b] J. Burdon and W. B. Hollyhead, *J. Chem. Soc.*, 6328 (1965). [c] Reference 1. [d] CNDO/2 energies of the two lowest π unfilled MO's in atomic units. [e] See Figure 1 for numbering of benzenoid carbons.

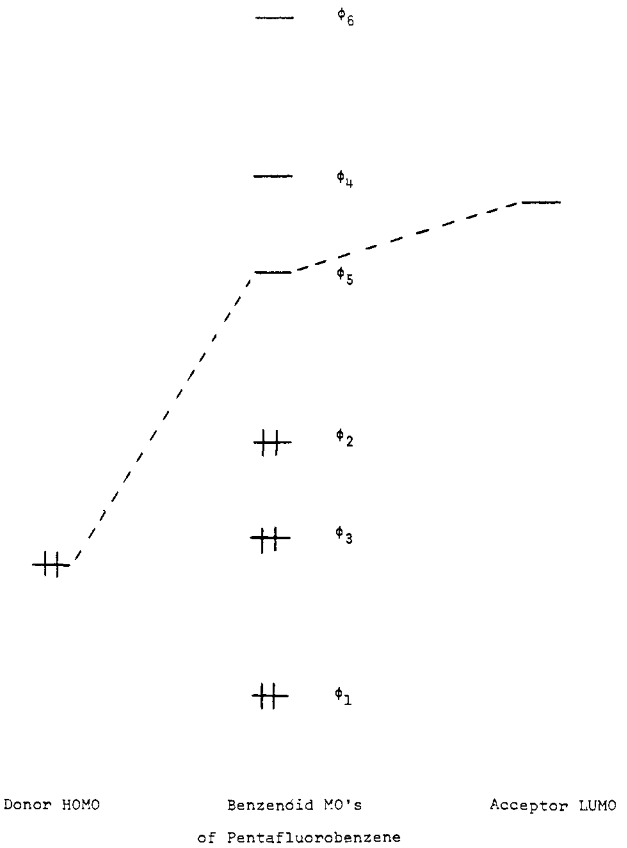


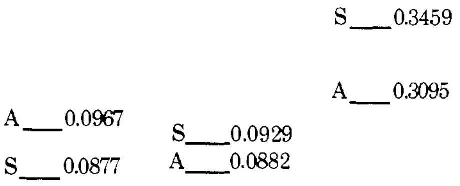
Figure 2. Dominant orbital interactions between the ϕ_4 and ϕ_5 unoccupied benzenoid π MO's of C_6F_5H and the HOMO of a donor or the LUMO of an acceptor substituent.

through the carbon where the substituent X is attached. In the case of the electron-donor substituent, as the ionization potential of the π HOMO is lowered its interaction with the S level becomes stronger because the energy separation of the two orbitals decreases. As one goes from a weak to a powerful electron-donor substituent the relative ordering of the S and A levels of C_6F_5H will tend to be reversed. Thus, in the case of weak donors like CH_3, one expects nucleophilic substitution para to the substituent because the LUMO is the S benzenoid orbital. On the other hand, in the case of powerful donors, like O^-, NH^-, one may expect nucleophilic substitution ortho and meta to the substituent since the LUMO will be the A benzenoid orbital.[12] When X is an electron-donor group of intermediate strength, one expects the S and A levels to be nearly degenerate and an equal amount of para, meta, or ortho substitution. Consideration of conventional steric effects which are expected to be greater for the ortho position if X is larger in size than F leads us to the following final predictions regarding the orientation of nucleophilic attack on C_6F_5X:

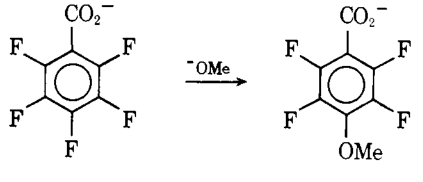
X	Preferred orientation
Weak donor	para ≫ meta > ortho
Strong donor	meta > ortho ≫ para

Once more, we have carried out CNDO/2 calculations to test these simple ideas. It was found that the relative energies of the S and A lowest unoccupied benzenoid orbitals of pentafluorobenzene vary as a function of the substituent X (Scheme I). It is clearly seen that as the ionization potential of the π HOMO of the donor substituent decreases, there is a progressive decrease in the energy separation between the S and A levels and eventually a reversal of their relative energy order. In accord with these predictions, it is found experimentally that as you go from X = CH_3, a weak π donor,[13] to X = O^-, a powerful donor, the orientation shifts from para to meta.[1] When X = OMe,[14] a donor of intermediate strength, both para and meta products are observed. An apparent anomaly occurs with the graded series of sub-

Scheme I



X	CH_3	OH	O^-
IP, eV	13.1[12]	12.5[12]	2.8[12]



major product

stituents Me_2N, which leads mostly to para, MeNH, which leads to both para and meta, and NH_2, which leads mostly to meta replacement. However, as has been demonstrated in related cases,[15] the methyl substituent on the nitrogen can lead to steric inhibition of conjugation, at least in the case of the Me_2N group. Furthermore, NH_2 in sodium methoxide probably exists in its basic form NH^-, a powerful donor expected to lead to meta orientation.

In the case of electron-acceptor groups, the dominant orbital interactions involve the π LUMO of the acceptor and the S benzenoid MO. This interaction always guarantees that the S level will be lower in energy than the A level. Hence, nucleophilic substitution is predicted to occur para to the substituent, as observed experimentally.[16,17]

In short, the model we have presented allows prediction of the orientation of nucleophilic substitution in polyhalobenzenes. By using the approximate indices we have suggested, one can deduce the preferred orientations with a minimum of work and no elaborate calculations.

References and Notes

(1) J. C. Tatlow, *Endeavour*, **22,** 89 (1963); J. G. Allen, J. Burdon, and J. C. Tatlow, *J. Chem. Soc.*, 1045 (1965).

(2) J. Burdon, *Tetrahedron*, **21,** 3373 (1965).

(3) J. Burdon, W. B. Hollyhead, C. R. Patrick, and K. V. Wilson, *J. Chem. Soc.*, 6323 (1965).

(4) A. F. Holleman, *Recl. Trav. Chim. Pays-Bas*, **39,** 736 (1920).

(5) D. T. Clark, J. N. Murrell, and J. M. Tedder, *J. Chem. Soc.*, 1250 (1963).

(6) M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry", McGraw-Hill, New York, N.Y., 1969.

(7) K. Fukui, *Fortschr. Chem. Forsch.*, **15,** 1 (1970).

(8) For a discussion of this and other approximations of the off-diagonal matrix element, see S. P. McGlynn, L. G. Vanquickenborne, M. Kinoshita, and D. G. Carroll, "Introduction to Applied Quantum Chemistry", Holt, Rinehart and Winston, New York, N.Y., 1972, p 113.

(9) The overlap between nonadjacent carbon and fluorine p_z AO's is small and therefore neglected.

(10) P. Olani, I. Virtaner, and P. Jaakhola, *Tetrahedron Lett.*, 1223 (1969). This refers to substitution in 1,2,3-trichlorobenzene. However, our analysis of this molecule follows the same lines as the trifluoro case and is expected to have the same substitution patterns.

(11) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory", McGraw Hill, New York, N.Y., 1970.

(12) See G. Klopman, *J. Am. Chem. Soc.*, **90,** 223 (1968), for a tabulation of ionization potentials.

(13) Substituting a methyl group for the hydrogen in pentafluorobenzene results in a decrease in the energy difference between ϕ_4 and ϕ_5 since the methyl group has a vacant σ^* as well as an occupied σ MO that mixes with ϕ_5. It appears that the ϕ_5–σ^* interaction is somewhat greater than the ϕ_5–σ interaction.

(14) J. Burdon, W. B. Hollyhead, and J. C. Tatlow, *J. Chem. Soc.*, 5152 (1965).

(15) L. Hammett and M. Paul, *J. Am. Chem. Soc.*, **56,** 827 (1934).

(16) J. Burdon, W. B. Hollyhead, and J. C. Tatlow, *J. Chem. Soc.*, 6336 (1965).

(17) The carboxylate group CO_2^- is a four-electron allylic system with the π HOMO having a node through the central atom. Hence, the carboxylate group acts as an acceptor with respect to benzene; i.e., its principal interaction with the benzene system is with its π LUMO.

A Theoretical Analysis of the Factors Determining the Conformations and Stabilities of Oxy- and Thiocarbanions

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Abstract: A one-electron molecular-orbital model is proposed which rationalizes the enhanced stability of a carbanion adjacent to sulfur as compared to a carbanion adjacent to oxygen without requiring the postulate of $(p \rightarrow d)_\pi$ conjugation. It is found that the greater stability in the case of sulfur is the result of greater two-electron stabilization of the total carbanionic system, because of the enhanced electron accepting ability of SR compared to OR. The one electron factors responsible for the stabilization of an adjacent carbanionic center by XR are conformationally dependent. The model is supported by the results of detailed ab initio computations.

After some decades of fairly general acceptance,[2] the notion that expansion of the valence shell plays an important role in determining the chemical and stereochemical properties of atoms below the first row of the periodic table has begun to be questioned.[3] The questions arise because it has now become possible to evaluate in a reasonably rigorous way just what is the nature and magnitude of $(p \rightarrow d)_\pi$ conjugative effects. At the level of SCF-MO computations, such effects are negligibly small in a number of systems previously believed to constitute definitive demonstrations of valence shell expansion. For example, a recent[3a] comparative quantum chemical investigation of the static, dynamic, and chemical properties of the anions $^-CH_2OH$ (**1**) and $^-CH_2SH$ (**2**) found no evidence that d-orbital effects contribute significantly to any of the differences between the two systems, and in particular, to the enhanced acidity of protons adjacent to the second row heteroatom.

These results reveal a need for a rationalization of the different effects of oxygen and sulfur in organic molecules which does not invoke d-orbital conjugation. The purpose of the present paper is to present a model which rationalizes the behavior of the above carbanions, and to demonstrate the utility of this model via applications to some related problems of structure and reactivity. The treatment will focus particularly on the factors that influence the stabilization of a carbanionic center by adjacent SH and OH groups. The systems chosen for the discussion are the Y (**3**) and W (**4**) conformations of **1** and **2**; these conformations are energy minima on the rotation-inversion surfaces of both carbanions.[3a]