Tetrahedron Letters No.12, pp. 1103-1108, 1967. Pergamon Press Ltd. Printed in Great Britain.

A GENERAL PERTURBATION TREATMENT OF CHEMICAL REACTIVITY

R.F. Hudson and G. Klopman

Cyanamid European Research Institute,
1223 Cologny - Geneva, Switzerland.

(Received 18 November 1966)

The reactivity of a reagent towards a particular atom of a molecule can be estimated from the perturbation produced by their interaction. A simple perturbation treatment including electron-electron and Coulomb interaction terms leads to an equation for the interaction energy in which two main effects are predominant,

(1) An ionic effect due to the Coulomb interaction between charged species, with the form

$$\frac{q_r q_s e^2}{R_{rs}} \quad \ldots\ldots\ldots \quad (1)$$

where q_r and q_s are the respective charges of atoms r and s, e is the electronic charge and R_{rs} is the distance between r and s in the partially formed bond.

(2) A covalent interaction due to the formation of a bond between r and s. This is obtained as in the usual perturbation treatment[1],

$$\Delta E = \left(\sum_{\mathrm{occ}\ i}\ \sum_{\mathrm{unocc}\ j} + \sum_{\mathrm{unocc}\ i}\ \sum_{\mathrm{occ}\ j}\right) \delta E_{ij}$$

for non-degenerate levels, ($|E_i - E_j| = \Delta_{ij} \gg 0$) in the following general form,

$$-\delta E_{ij} = \frac{c_{ir}^2 c_{js}^2 \beta_{rs}^2}{E_i - E_j} \qquad \text{..........} \ (2)$$

where c_{ir} and c_{js} are the orbital coefficients of the atoms r and s, E_i and E_j are the energies of the orbitals i and j corresponding to the unperturbed orbitals of R and S, and β_{rs} is the resonance integral of the partially formed bond. For degenerate levels ($\Delta_{ij} \simeq 0$) an equation of the first order is obtained,

$$-\delta E_{ij} = c_{ir} c_{js} \beta_{rs} \qquad \text{..........} \ (3)$$

The relative importance of these terms depends, amongst other things, on the value of Δ_{ij}. When $\Delta_{ij} \gg 0$ for all pairs of interacting orbitals, then the covalent interaction tends to zero and the Coulomb term (eq. 1) determines the reaction which should therefore take place between the more polar centres*. This situation can be called a <u>charge controlling effect.</u> As Δ_{ij} decreases the covalent interaction term

---

* It should be noted that when the Δ_{ij} values are very large the covalent term is given by $-\Delta E = \Sigma c_{ir}^2 \Sigma c_{js}^2 \beta / \Delta_{ij}^{aver} \simeq \frac{q_r q_s}{\Delta_{ij}^{aver}}$ since the separations between the various levels of the same molecule are small relative to Δ_{ij}.

increases, and the contribution of each of the orbital interactions is determined mainly by the energy gap between them (c.f. superdelocalisability[2]). As Δ_{ij} approaches zero, the interaction of the highest occupied orbital of the donor (nucleophile) with the lowest unoccupied orbital of the acceptor (electrophile) becomes predominant. This interaction is given by the first order perturbation term (eq. 3), and may be called a frontier-controlling effect which augments or opposes the charge controlling effect.

It is therefore intrinsically incorrect to relate reactivity to a particular reactivity index, since this changes with the nature of the electrophilic reagent except in special cases (e.g. alternant hydrocarbons). According to our treatment, the reactivity of an atom in a molecule is determined either by (1) the total charge on the atom in the case of highly polar species, or when the perturbation producing the bond formation is small or by (2) the charge in the frontier orbital of the atom for large perturbations when the interacting orbitals are nearly degenerate, or when the Coulomb term is zero, as in the case of alternant hydrocarbons.

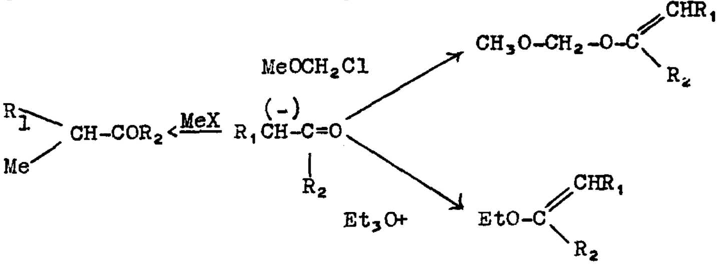
These rules may be applied to various kinds of system where comparative estimates of reactivity are required. From a general point of view we can draw an analogy between our treatment and the concept of hard and soft acids and bases[3].

Thus when the interacting species form ionic transition states or when $E_i \gg E_j$ (i.e. when the donor has a high ionisation potential and the acceptor a low electron affinity), the interaction is determined by the large charge controlling effect.

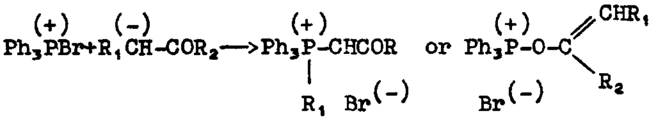
This is equivalent to a hard-acid-hard base interaction. On the other hand a large perturbation, produced by reagents of high polarisability leading to extensive covalent interaction, is controlled by the frontier orbital. This is typical of a soft base-soft acid interaction.

Now frequently the charge distribution in the frontier orbital is quite different from the total charge distribution, so that a change in the relative reactivity and position of attack in a polyfunctional reagent is produced by a change in $E_i - E_j$, i.e. by a change in the nature of the electrophile (or by a change in the nature of the reaction media, since a more polar solvent enhances ionic transition states). The treatment is therefore of particular interest in the interpretation of ambident reactivity[4].

For small perturbations, i.e. weak bond formation in the transition state as for example in a reaction with a large S_N1 component, the relative reactivity is determined by total charge densities. As the bond becomes stronger in the transition state, the importance of the frontier orbital increases, and the position of reaction changes, e.g. from oxygen to carbon as in the following reactions[4,5].



We have interpreted the product ratio of the following reaction,



by the relative charge densities on carbon and oxygen in the frontier orbital[6]. In this case the electron affinity of the phosphonium intermediate (3d ionisation potential of phosphorus) and the ionisation potential of an enolate ion are similar.

Electrophilic aromatic substitution may also be treated in a similar way[7]. In the case of alternant hydrocarbons (where $q_r = 0$), the frontier controlling effect determines the rate of reaction and position of attack[8], the selectivity gradually decreasing to zero as the electronic affinity of the attacking electrophilic centre decreases. Similarly for electrocyclic reactions, the coefficients c_{ir} and c_{js} and the symmetry of the frontier orbitals of both reagents determine the stereochemistry, as stated in the Hoffmann-Woodward rule[9]. For the same reason, in radical recombinations one may expect the frontier controlling effects to control the reaction, owing to the near degeneracy of the singly occupied orbitals. On the other hand, substitution in heterocyclic aromatics is given more closely by the total charge densities[10]. This again follows from our treatment since the Coulomb term (equation 1) is important, and for relatively small perturbations controls the orientation.

The change in the o/p ratio in the electrophilic reactions of substituted benzenes[11] (e.g. toluene, anisole) may be explained in a similar way. For large perturbations, represented by strong bond formation in the transition state and high reagent selectivity, the frontier orbital strongly directs the reaction to the p-position. As the value of Δ_{ij} increases, i.e. as the interaction decreases, the charge controlling effect may direct the substitution to the o-position. With the exception of the electrostatic treatment of Norman and Radda,[11] this is to our knowledge the only electronic interpretation of such changes in orientation with the electrophile.

The details of the perturbation treatment together with further examples will appear in a forthcoming paper.

1. M.J.S. Dewar, *J.Amer.Chem.Soc.*, *74*, 3341 (1952).
2. K. Fukui, T. Yonezawa and H. Shingu, *J.Chem.Phys.*, *20*, 722 (1952).
3. R.G. Pearson, *J.Amer.Chem.Soc.*, *85*, 3533 (1963).
4. N. Kornblum, R.A. Smiley, R.K. Blackwood and D.C. Iffland, *J.Amer.Chem.Soc.*, *77*, 6269 (1955).
5. G.J. Heiszwolf and H. Kloosterziel, *Chem.Comm.*, (1966) 51.
6. P.A. Chopard, R.F. Hudson and G. Klopman, *J.Chem.Soc.*, (1965), 1379.
7. R.D. Brown, *J.Chem.Soc.*, (1959), 2232.
8. K. Fukui, T. Yonezawa and C. Nagata, *J.Chem.Phys.*, *27*, 1247 (1957).
9. R.B. Woodward and R. Hoffmann, *J.Amer.Chem.Soc.*, *87*, 395; 4388 (1965).
10. M.J.S. Dewar, *Advances in Chemical Physics*, *8*, 106 (1965).
11. R.O.C. Norman and G.K. Radda, *J.Chem.Soc.*, (1961), 3610.