Theoret. chim. Acta (Berl.) 8, 165—174 (1967)

Polyelectronic Perturbation Treatment of Chemical Reactivity

G. Klopman*, and R. F. Hudson**

Cyanamid European Research Institute, Geneva

Received January 20, 1967

The usual practice of relating reactivity to a particular MO index does not allow for changes in the relative reactivity of various positions in a conjugated electron donor with the nature of the electrophilic reagent. By regarding the formation of the transition state as a mutual perturbation of the Molecular Orbitals of both reagents, the relative reactivity of various reacting centers is shown to vary with the magnitude of the perturbation. This treatment determines the factors responsible for these changes in reactivity. It outlines the conditions under which the frontier orbitals may determine the course of a reaction and also draws attention to the importance of electrostatic interaction.

La pratique habituelle, qui consiste à corréler la réactivité et un indice particulier de la méthode des orbitales moléculaires, ne tient pas compte des variations relatives de réactivité des différentes positions d'un donneur d'électrons conjugué avec la nature du réactif électrophile. En considérant la formation de l'état de transition comme une perturbation mutuelle des orbitales moléculaires des deux réactifs, la réactivité relative des différents centres réactifs varie avec l'importance de la perturbation. Notre travail détermine les facteurs responsables de ces variations de réactivité. Il définit les conditions ou les orbitales frontières peuvent déterminer le cours d'une réaction, et attire l'attention sur l'importance de l'interaction électrostatique.

Im Rahmen der MO-Theorie wird die Reaktivität gewöhnlich nur zu gewissen Indizes in Verbindung gesetzt. Damit ist die Reaktivität an den verschiedenen Zentren eines konjugierten Donators aber unabhängig von der Art des elektrophilen Agens. Wenn man den Übergangszustand als eine wechselseitige Störung der Molekülorbitale beider Agentien auffaßt, ändert sich die relative Reaktivität verschiedener Zentren mit der Größe dieser Störung. Dieses Verfahren bestimmt verschiedene Faktoren, die für den Wechsel in der Reaktivität verantwortlich sind. Es erklärt, unter welchen Bedingungen die „Grenzorbitale" den Verlauf einer Reaktion bestimmen und verweist auf die Bedeutung von elektrostatischen Wechselwirkungen.

1. Introduction

Theoretical treatments of the reactivity of organic compounds have dealt almost exclusively with conjugated systems in view of the considerable success of MO theory in this area. We can immediately see the limitations of such an approach, as the reaction proceeds essentially through a σ-bonded structure. Three general approaches have been developed which we may term the static, the localisation and the *de*-localisation methods.

---

* Present address: Chemistry Department, Case Western Reserve University, Cleveland, Ohio.

** Present address: Chemistry Department, University of Kent at Canterbury, Canterbury, Kent.

According to the static approach, the reactivity of a particular position of a π-system is related to a reactivity index, a property which is determined from the ground state of the molecule. On the basis of a simple electrostatic treatment [*24*], the rate should be proportional to the electronic charge at position r. However, since it is equal to 1 for alternant hydrocarbons, the ground state structure cannot be used to give information on the reactivity differences. Satisfactory correlations are however found between charge density and reactivity of heterocyclic compounds [*3, 22, 25*], although DEWAR [*6*] considers the use of charge densities to be theoretically unsound. Other reactivity indices, e.g. free valency [*4*] and atom polarisability [*5*] have been used. These reactivity indices are appropriate for systems where the transition state resembles the initial state, e.g. for very reactive species.

Alternatively, the transition state may be identified [*28*] with a σ-bonded "Wheland" intermediate the activation energy of which is given by the difference in π-electron energy of the intermediate and the ground state. This process can be treated [*7*] by conventional perturbation methods. In the case of even alternant hydrocarbons, the treatment is particularly simple [*7*] since the change in π-energy ΔE_π involves the N.B.O. of the remaining odd system only, and is given by the appropriate coefficients for the atoms joined to r, viz.

$$\Delta E_\pi = 2(a_{os} + a_{ot})\,\beta\,.$$

The experimental values [*8*] of β lie between 3 and 13 kcal/mole, i.e. considerably less than the usually accepted value of $\beta \sim 20$ kcal/mole. It follows that in general the Wheland intermediate is a poor model of the transition state, and the method can be used only for systems where the non-crossing rule of R. D. BROWN [*1*] holds. Other methods therefore have to be used in cases where the position of substitution changes with the nature of the reactant — one of the most interesting aspects of chemical reactivity.

The third general approach, the delocalisation method, has been very successful when introduced as an empirical concept, e.g. as in the frontier electron theory [*11*], but has been the subject of much theoretical criticism [*9, 23, 26*]. As introduced by FUKUI [*12*], and in a different form by R. D. BROWN [*2*], the transition state is supposed to be formed by the interaction of a pseudo-π orbital [*2*] of the electrophile with the π-system. This transition state resembles in fact the charge transfer complex described by NAGAKWA and TANAKA [*19*]. Perturbation theory applied to such a model [*2, 12*] predicts that usually the frontier orbitals (i.e. the highest occupied orbital of the donor and the lowest unoccupied orbital of the acceptor) determine the orientation. FUKUI [*11*] showed this to be the case for the electrophilic substitution of polycyclic aromatics, and subsequently R. D. BROWN [*2*] applied a similar perturbation treatment to substituted benzene derivatives.

As already mentioned, the use of a particular reactivity index precludes a change in orientation with the nature of the attacking reagent (nucleophile, electrophile or radical). Substitution in benzene derivatives frequently proceeds at different positions with different reagents, although the apparent anomalies are usually explained in terms of steric hindrance, chelation or some other specific effect. An electronic interpretation has however been advanced by NORMAN and RADDA [*20*], and we show in the following section that a simple perturbation treatment, in which electron-electron and Coulombic interactions are introduced, leads to the prediction of different orientations, depending on the nature of the reagent.

2. Theory

The theory is basically similar to classical perturbation theory [*7*], but allowance is made for ionic interaction (electron-electron interaction) and is not restricted to π-conjugated molecules.

Let two reagents R and S approach to a situation such that atom r of system R and s of System S interact.

Let ψ_m be the various molecular orbitals of molecule R and ψ_n those of S.

Suppose these orbitals can be represented by the LCAO approximation, then

$$\psi_m = \sum_{\varrho \neq r} c_\varrho^m \phi_\varrho + c_r^m \phi_r$$

and (1)

$$\psi_n = \sum_{\sigma \neq s} c_\sigma^n \phi_\sigma + c_s^n \phi_s$$

ϕ_r and ϕ_s being the atomic orbitals of the atoms r and s which are going to be bonded during the reaction.

The two sets of orbitals ψ_m and ψ_n combine on interaction of r and s to give new perturbed orbitals which themselves will be linear combinations of the unperturbed orbitals.

This interaction usually produces a change in energy, the magnitude of which depends on the systems R and S, the interacting atoms r and s and their distance. The nature of the solvent and the type of reaction (radical or ionic) will be important in the evaluation of the energy differences, but we shall be concerned in the first instance with electronic effects only. Other factors which control reaction rates and particularly solvent effects will be discussed at a later stage.

The new wave function can now be written as a Slater determinant including the various monoelectronic wave functions, and the Hamiltonian which operates on it can be written in a general way as follows,

$$H = H_0^R + H_0^S + H_1$$

where H_0^R and H_0^S are the Hamiltonian operators acting on the isolated systems, and applicable only to those systems, and H_1 the additional term produced by the union of R and S.

The usual approximation is made, i.e. interactions between atoms r and s only are considered explicitly, i.e.

$$\int \phi_i H_1 \phi_j \, d\tau = \delta_{ir} \delta_{jr} \Gamma_{Sr} \; ; \qquad \int \phi_k H_1 \phi_l \, d\tau = \delta_{ks} \delta_{ls} \Gamma_{Rs} \tag{a}$$

where ϕ_i and ϕ_j belong to R and ϕ_k and ϕ_l belong to S. Γ_{Sr} and Γ_{Rs} are respectively the interactions between the core of atom s and the electrons in ϕ_r, and that between the core of atom r and the electrons in ϕ_s.

$$\int \phi_i H_1 \phi_k \, d\tau = \delta_{ir} \delta_{ks} \beta_{rs} \, . \tag{b}$$

(c) Similarly for the electron-electron interaction,

$$\int \phi_i(1) \phi_k(2) H_1 \phi_j(1) \phi_l(2) \, d\tau_1 \, d\tau_2 = \delta_{ir} \delta_{jr} \delta_{ls} \delta_{ks} \Gamma_{rs} \, .$$

This is partially justified by our approximation and partly also by the usual neglect of differential overlap.

(d) Finally, the core-core interactions will also be limited to that between atom r and s and equated to Γ_{RS}.

The problem can now be solved in principle by the usual computational methods [*15*]. However, an analysis of the various interaction terms might throw some light on the important factors responsible for the bonding in the transition state. This can be done by a perturbation treatment, by calculating separately the interactions of successive pairs of orbitals ψ_m and ψ_n, one on each reacting molecule, and then adding the various interactions due to all possible combinations. Several possibilities can arise depending on the occupancy number of the interacting orbitals. The various cases can however be deduced very easily from the consideration of one of them which will now be described in more detail.

Let us consider the case of the interaction of an orbital of R, ψ_m occupied by two electrons in the isolated system with an initially empty orbital ψ_n of S.

The partly perturbed molecular orbital ψ_p produced by the interaction of these two orbitals can be written as follows:

$$\psi_p = a\psi_m(1) + b\psi_n(1)$$

and the partly perturbed molecular wave function Ψ_q which would result if this perturbation was the only one produced by the combination of R and S would be

$$\Psi_q = \frac{1}{\sqrt{l\,!}} \sum_P (-1)^P\, P\psi_p(1)\overline{\psi}_p(2)\, \psi_{\nu \neq m}(3)\, \overline{\psi}_{\mu \neq n}(4) \ldots \psi_l(l)$$

where l is the total number of electrons in both R and S.

The resulting total energy, E_q, of the partly perturbed molecule is given by

$$E_q = \frac{\int \Psi_q H \Psi_q \, d\tau}{\int \Psi_q \Psi_q \, d\tau} = \frac{Z_R Z_S e^2}{R_{rs}} + \frac{\int \Psi_q H' \Psi_q \, d\tau}{\int \Psi_q \Psi_q \, d\tau}$$

where the first term in the right hand side of the equation is the core-core interaction and the second term is the electronic energy and $H' = H - e^2/R_{rs}$.

The electronic perturbation energy thus produced by this perturbation of orbital ψ_m by ψ_n alone is given by

$$\Delta E_{mn} = \frac{\int \Psi_q H' \Psi_q \, d\tau}{\int \Psi_q \Psi_q \, d\tau} - \frac{\int \Psi_R H_0^R \Psi_R \, d\tau}{\int \Psi_R \Psi_R \, d\tau} - \frac{\int \Psi_S H_0^S \Psi_S \, d\tau}{\int \Psi_S \Psi_S \, d\tau}$$

where Ψ_R and Ψ_S are the initial wave functions of molecule R and S respectively. It can be evaluated by a variational procedure involving the minimisation of the energy with respect to the two variational parameters a and b, and leads to a 2 by 2 secular equation whose matrix elements are:

$$\begin{aligned}
M(m,m) &= \int \psi_m(1)\, \psi_p(2)\, \psi_\nu(3) \ldots H' \psi_m(1)\, \psi_p(2)\, \psi(3) \ldots d\tau_1\, d\tau_2 \ldots \\
&\quad - \int \psi_m(1)\, \psi_m(2)\, \psi_\nu(3) \ldots (H_0^R + H_0^S)\, \psi_m(1)\, \psi_m(2)\, \psi_\nu(3) \ldots d\tau_1\, d\tau_2 \ldots \\
M(m,n) = M(n,m) &= \int \psi_m(1)\, \psi_p(2)\, \psi_\nu(3) \ldots H' \psi_n(1)\, \psi_p(2)\, \psi_\nu(3) \ldots d\tau_1\, d\tau_2 \ldots \\
M(n,n) &= \int \psi_n(1)\, \psi_p(2)\, \psi_\nu(3) \ldots H' \psi_n(1)\, \psi_p(2)\, \psi_\nu(3) \ldots d\tau_1\, d\tau_2 \ldots \\
&\quad - \int \psi_m(1)\, \psi_m(2)\, \psi_\nu(3) \ldots (H_0^R + H_0^S)\, \psi_m(1)\, \psi_m(2)\, \psi_\nu(3) \ldots d\tau_1\, d\tau_2 \ldots
\end{aligned}$$

In order to evaluate these matrix elements, use will be made of Eq. (1) and of the approximations (a—d) given above.

The nomenclature and approximations for the integrals used in a previous paper [*16*] will be used here. The central field approximation leads to a common value of the core-core, core-electron and electron-electron interaction between two particular centres, i.e.

$$-\Gamma_{RS} = +\Gamma_{rS} = +\Gamma_{Rs} = -\Gamma_{rs}\,.$$

Under these conditions the matrix elements can readily be evaluated. All terms which do not involve electrons 1 and 2 (initially belonging to orbital ψ_m) cancel, and the resulting matrix elements become

$$
\begin{aligned}
M(m,m) &= (c_r^m)^2\, q_s\, \Gamma_{rs} + b^2(A_m^- - (c_r^m)^2\, (c_r^n)^2\, \Gamma_{rs}) \\
M(m,n) &= M(n,m) = c_r^m\, c_s^n\, \beta_{rs} \\
M(n,n) &= B_n - B_m + (c_s^n)^2\, (q_r + 2(c_r^m)^2)\, \Gamma_{rs} + b^2(A_m^- - A_n^-) + \\
&\quad + a^2\, (A_m^- - (c_r^m\, c_s^m)^2\, \Gamma_{rs})
\end{aligned}
$$

where B_m and B_n are the respective one electron energies of the unperturbed ψ_m and ψ_n orbitals and A_m^- and A_n^- the electron electron interaction energies. c_r^m and c_s^n are the coefficients of the ϕ_r and ϕ_s orbitals in the ψ_m and ψ_n unperturbed orbitals respectively, q_r and q_s are the net initial charges of atom r and s respectively $= - \sum$ electronic charges $+$ core charge.

The problem still remains of the SCF type and successive iterations, starting with chosen initial values of a and b should normally be carried out to self consistency. Since we are, in fact, interested only in the first approximation of the perturbation, only one iteration will be made and the matrix elements will be calculated using the values of a and b for the isolated system, i.e. $a = 1$, $b = 0$ for the case under consideration.

The secular equation therefore becomes

$$
\begin{vmatrix}
(c_r^m)^2\, q_s\, \Gamma_{rs} - \tfrac{1}{2} \Delta E_{mn} & c_r^m\, c_s^n\, \beta_{rs} \\
c_r^m\, c_s^n\, \beta_{rs} & (\mathrm{IP}_n - EA_m + (c_s^n)^2\, (q_r + (c_r^m)^2)\, \Gamma_{rs} - \tfrac{1}{2} \Delta E_{mn}
\end{vmatrix} = 0
$$

where $IP_n = B_n$ is the energy gained by adding one electron on orbital ψ_n and $-EA_m = -B_m + A_m^-$ is the energy lost by removing one electron from orbital ψ_m. The stabilisation energy resulting from this part of the perturbation can immediately be calculated as

$$
\begin{aligned}
\Delta E_{mn} &= IP_n - EA_m + (c_r^m)^2\, q_s\, \Gamma_{rs} + c_s^2\, (q_r + (c_r^m)^2)\, \Gamma_{rs} + \\
&\quad + \{(EA_m - IP_n + [(c_r^m)^2\, q_s - (c_s^n)^2\, (q_r + (c_r^m)^2)]\, \Gamma_{rs})^2 + (2c_r^m\, c_s^n\, \beta_{rs})^2\}^{1/2} .
\end{aligned}
$$

This expression can be further simplified, leading to two cases depending on the degeneracy or lack of "degeneracy" between the two interacting orbitals.

a) For the following "degeneracy",

$$
\begin{aligned}
EA_m + (c_r^m)^2\, q_s\, \Gamma_{rs} &= IP_n + (c_s^n)^2\, (q_r + (c_r^m)^2)\, \Gamma_{rs} , \\
\Delta E_{mn} &= IP_n - EA_m + [(c_r^m)^2\, q_s + (c_s^n)^2\, (q_r + (c_r^m)^2)]\, \Gamma_{rs} + 2c_r^m\, c_s^n\, \beta_{rs} \\
&= 2(c_r^m)^2\, q_s\, \Gamma_{rs} + 2c_r^m\, c_s^n\, \beta_{rs} . \qquad (2)
\end{aligned}
$$

b) For "non-degeneracy", i.e.

$$
(2c_r^m\, c_s^n\, \beta_{rs})^2 < (EA_m - IP_n + [(c_r^m)^2\, q_s - (c_s^n)^2\, (q_r + (c_r^m)^2)]\, \Gamma_{rs})^2 ,
$$

the energy difference can be given approximately by

$$
\begin{aligned}
\Delta E_{mn} &= IP_n - EA_m + [(c_r^m)^2\, q_s + (c_s^n)^2\, (q_r + (c_r^m)^2)]\, \Gamma_{rs} + \\
&\quad + \{EA_m - IP_n + [(c_r^m)^2\, q_s - (c_s^n)^2\, (q_r + (c_r^m)^2)]\, \Gamma_{rs}\} \\
&\quad \left\{1 + \frac{2(c_r^m\, c_s^n\, \beta_{rs})^2}{\{EA_m - IP_n + [(c_r^m)^2 q_s - (c_s^n)^2 (q_r + (c_r^m)^2)]\, \Gamma_{rs}\}^2}\right\} \\
&= 2(c_r^m)^2\, q_s\, \Gamma_{rs} + \frac{2(c_r^m\, c_s^n\, \beta_{rs})^2}{E_m^* - E_n^*}
\end{aligned}
$$

where $E_m^* = EA_m + c_r^{m2}\, q_s\, \Gamma_{rs}$ is the energy of an electron in orbital ψ_m in the field of the S moiety, $E_n^* = IP_n + c_s^{n2}(q_r + c_r^{m2})\, \Gamma_{rs}$ is the energy that an electron of ψ_m would have if it were transferred to the orbital ψ_n in the field of the R moiety.

It is easy to extrapolate these results to all possible interacting orbitals, and the total perturbation then becomes

$$\Delta E = -\, q_s\, q_r\, \Gamma_{rs} + \sum_m \sum_n (\nu_m - \nu_n + \chi_{mn}) \left[\frac{2(c_r^m\, c_s^n\, \beta_{rs})^2 \varepsilon_{mn}}{E_m^* - E_n^*} + c_r^m\, c_s^n\, \beta_{rs}(1 - \varepsilon_{mn}) + \frac{\chi_{mn}(EA_m - IP_n)}{4} \right]$$

where ν_m and ν_n are the occupation numbers of orbital m and n respectively; $\varepsilon_{mn} = 0$ if the system is "degenerate", [i.e. obeys condition (2)] and 1 otherwise; $\chi_{mn} = 2$, if ν_m and ν_n are both equal to 1, and 0 otherwise. The core-core interaction and electron-electron interaction are included in this equation.

This is a completely general equation, and reduces to the equation given by DEWAR [7] when the two interacting atoms of the two systems are neutral, i.e. $q_r = q_s = 0$ (the case of conjugated alternant hydrocarbons).

Our interpretation of reactivity is based on the limits of this equation which are governed mainly by the relative magnitude of

$$\text{(a) } 2(c_r^m\, c_s^n\, \beta_{rs})^2 \quad \text{and} \quad \text{(b) } E_m^* - E_r^* .$$

If the value of (b) is very large for all the orbitals m and n, the small variations due to the energy differences of the orbitals m may be neglected (see Fig. 1) and the change in energy, ΔE, is given by

$$\Delta E = -\, q_r\, q_s\, \Gamma_{rs} + \sum \sum (\nu_m - \nu_n)\, (c_r^m)^2\, (c_s^n)^2\, \gamma_{rs}$$

where

$$\gamma_{rs} = \left[\frac{\beta_{rs}^2}{E_m^* - E_n^*} \right]_{\text{average}}$$

It thus appears that, under these conditions, the perturbation is mainly due to the bond between the two atoms carrying the highest total charges.

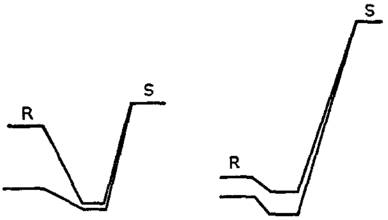
On the contrary, when one occupied orbital of m is degenerate or nearly degenerate under the conditions of the experiment with one empty orbital of n, or if they are both singly occupied, the perturbation produced by the interaction of these two frontier orbitals [12] becomes dominant and the covalent part of the perturbation energy will be due almost entirely to the following interaction,

$$\Delta E = -\, q_r\, q_s\, \Gamma_{rs} + 2 c_r^m\, c_s^n\, \beta_{rs} \,.$$

In this case a ionic contribution remains, but if the reaction centres are neutral (which is frequently the case where degeneracy of the kind under discussion is found, as in radical reactions or in aromatic substitution) the first term vanishes, and the reaction will take place between the two centres carrying the relatively highest frontier orbital charge density:

$$\Delta E = 2 c_r^m\, c_s^n\, \beta_{rs} \,.$$

These two cases represented in Fig. 1 are limiting cases, and for intermediate situations participation of all the orbitals m would have to be considered. One may however draw some conclusions from the general perturbation equation and determine the factors which will promote one or other type of interaction. For simplification of the discussion, when (a) > (b) we shall term the interaction *charge controlled effects*, when (b) > (a) *frontier controlled effects*, since in the first case the predominant reaction will occur at the atom carrying the highest total charge density, and in the second case at the atom whose frontier electron density is the highest. (Solvation energy, repulsion energy and β will modify this conclusion).



Small $E_m^*—E_n^*$ Large $E_m^*—E_n^*$

Large Perturbation Small Perturbation

Fig. 1

3. The rate determining factors

(a) *Charge controlled effects.* As indicated in the previous section, the reactivity will tend to follow the charge density when $E_m^* - E_n^* > \beta$, which may be promoted by the following conditions,

(i) When the reacting species are very polar, i.e. $q_s \simeq +1$ and $q_r \simeq -1$.

(ii) When the Coulomb interaction, Γ_{rs}, between these ionic species is large. The quantity Γ_{rs} has been defined previously as $\Gamma_{rs} = e^2/\sqrt{R_{rs}^2 + (\varrho_r + \varrho_s)^2}$ where R_{rs} is the bond distance in the transition state and ϱ_r and ϱ_s the radii of the orbitals ϕ_r and ϕ_s.

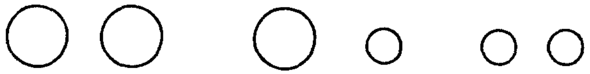
Consequently small interatomic distances, and also small orbitals, favour charge controlled effects in *very* polar reactions. A small radius also indicates a low polarisability of the corresponding atom.

(iii) $E_m^* \gg E_n^*$. This may be the case when the donor has a high electronegativity, i.e. a high tendency to accept electrons, and also by electrophiles with low ionisation potentials. This classification of "hard" acids and bases [*21*]* also applies to reactions in solution. Small ions tend to be very strongly solvated and consequently ionic solvents should emphasize this influence. In many cases however, the solvent itself can act as a strong charge controlled reagent. It then hinders further reaction and prevents the charge controlled reaction to occur.

---

* A more complete discussion of this application has been given at the Conference on Hard and Soft Acids and Bases in London and will be published elsewhere.

(iv) When β is small. This may be due to several factors, in particular (a) large interatomic distances in the transition state, since β probably decreases more rapidly than Γ with increasing distance, and (b) poor overlap of the interacting orbitals, due to the disposition of the nodes in the atomic orbitals, their symmetry properties, and also to differences in orbital size, as shown for example by the following comparison [17]:



	Li – Li	Li – H	H – H
r (Å)	2.67	2.04	0.74
S	0.58	0.38	0.75

It should be noted that substituents which alter the charge density will affect the orbital size which modifies the overlap.

(b) *Frontier controlled effects.* These will be promoted by the factors which reduce charge controlling effects,

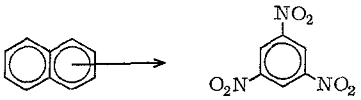
(i) Radicals, neutral or weakly polar species,

(ii) Small values of Γ, mainly due to large orbital radii and large polarisability. Large interatomic distances reduce Γ but reduce β to a greater extent, hence small distances promote frontier controlling effects,

(iii) Low electronegativity of the nucleophilic atom and high ionization potential of the electrophilic atom.

(iv) Good overlap leading to high β, i.e. strong covalent participation.

As an illustration of these different controlling effects in molecular interactions, the stability of a hydrogen bonded complex, e.g. $F^{-}\ldots H^{\delta+}-F^{\delta-}$, may be attributed to charge controlling effects. On the other hand the bonding in charge transfer complexes, e.g. between two neutral species of zero dipole moment, is due



mainly to the interaction of the highest occupied orbital of the donor (i.e. the frontier orbital) with the lowest unoccupied orbital of the acceptor. According to the theory of Mulliken [18], the bonding energy is determined mainly by the ionisation potential of the donor and the electron affinity of the acceptor (see also Ref. [19]).

These considerations lead to a generalisation similar to the classification of soft and hard acids and bases, which has been widely discussed recently [21]. Thus we may associate large orbitals with weakly ionic reagents (or radicals), leading to small Γ values, low electronegativities and "soft" character. The interaction between two such orbitals can potentially lead to high β values and short internuclear distances in the transition state. As described elsewhere [13] this leads to high reagent selectivity. The electrophilic atom would attack the centre of maximum electron density of the frontier orbital of a conjugated donor.

The reverse situation holds for interaction between two small orbitals, and the various possibilities are summarised in Tab. 1.

Table 1. *Important factors responsible for the bonding in the transition state*

	Factors		Conclusions			
	$E_m^* - E_n^*$	Orbital in r and s	β	Γ	Reaction center	Reactivity
1.	Large	both large	large	v. small	frontier controlled	low
2.	Large	one large one small	v. small	small	charge controlled	low
3.	Large	both small	small	large	charge controlled	high
4.	Small	both large	large	v. small	frontier controlled	high
5.	Small	one large one small	v. small	small	indef.	low
6.	Small	both small	small	large	indef.	low

This table includes several possible cases but it should be pointed out that cases 1 and 6 are very unrealistic as large values of $E_m^* - E_n^*$ are usually associated with small orbitals and vice versa. Although cases 2 and 5 are possible, the vast majority of reactions will conform to cases 3 and 4.

Preliminary applications of this treatment have already been made for a few cases and the results published elsewhere [*14*].

This discussion illustrates some of the main factors determining reactivity in heterolytic processes in a general way, and in particular provides a theoretical basis for four-parameter free energy equations of the kind advanced by Edwards [*10*] to interpret nucleophilic reactivity and the stability constants of inorganic complexes.

References

1. Brown, R. D.: Quart. Rev. **6**, 63 (1952).
2. — J. Chem. Soc. (London) **1959**, 2232.
3. Coulson, C. A., and H. C. Longuet-Higgins: J. Chem. Soc. (London) **1949**, 971.
4. — J. Chim. physique **45**, 243 (1948); Discussions Faraday Soc. **2**, 9 (1947).
5. —, and H. C. Longuet-Higgins: Proc. Roy. Soc. (London) **A 191**, 39 (1947); **A 195**, 188 (1948).
6. Dewar, M. J. S.: Advances chem. Physics 8, 105 (1965).
7. — J. Amer. Chem. Soc. **74**, 3341, 3345, 3350, 3353, 3355, 3357 (1952).
8. —, T. Mole, and E. W. T. Warford: J. Chem. Soc. (London) **1956**, 3581.
— — J. Chem. Soc. (London) **1957**, 342.
9. — Advances chem. Physics 8, 110 (1965).
10. Edwards, J. O.: J. Amer. chem. Soc. **76**, 1540 (1954).
11. Fukui, K., T. Yonezawa, and H. Shingu: J. chem. Physics **20**, 722 (1952).
12. — —, and C. Nagata: J. chem. Physics **27**, 1247 (1957); **31**, 550 (1959). — Bull. chem. Soc. Japan **27**, 423 (1954).
13. Hudson, R. F.: Chimia **16**, 173 (1962).
14. —, and G. Klopman: Tetrah. Letters **12**, 1103 (1967).

15. KLOPMAN, G.: J. Amer. chem. Soc. **86**, 4550 (1964); **87**, 3300 (1965).
16. — J. Amer. chem. Soc. **86**, 4550 (1964).
17. Overlap integrals are those given by:
MULLIKEN, R. S., C. A. RIECKE, D. ORLOFF, and H. ORLOFF: J. chem. Physics **17**, 1248 (1949).
18. MULLIKEN, R. S.: J. Amer. chem. Soc. **74**, 811 (1952). — J. physic. Chem. **56**, 801 (1952).
19. NAGAKURA, S., and J. TANAKA: Bull. chem. Soc. Japan **32**, 734 (1959).
20. NORMAN, R. O. C., and G. K. RADDA: J. Chem. Soc. (London) **1961**, 3610.
21. PEARSON, R. G.: J. Amer. chem. Soc. **85**, 3533 (1963).
22. PULLMAN, B., and A. PULLMAN: Les théories électroniques de la chimie organique, p. 615. Masson: Paris 1952.
23. — J. chem. Physics **31**, 551 (1959).
24. e.g. RI, T., and H. EYRING: J. chem. Physics **8**, 433 (1940).
25. SANDORFY, C., and P. YVAN: Bull. Soc. chim. France **17**, 131 (1950).
26. —, C. VROELANT, P. YVAN, O. CHALVET, and R. DAUDEL: Bull. Soc. chim. France **17**, 304 (1950).
27. SUNG, S. S., O. CHALVET, and R. DAUDEL: J. chem. Physics **31**, 553 (1959).
28. WHELAND, G. W., and L. PAULING: J. Amer. chem. Soc. **57**, 2086 (1935).
29. — J. Amer. chem. Soc. **64**, 900 (1942).

Dr. G. KLOPMAN
Cyonamid European Research Institute
91, Route de la Capite
Cologny, Geneva, Switzerland