

RELATION BETWEEN ELECTRONIC STRUCTURE AND CHEMICAL REACTIVITY OF ORGANIC MOLECULES

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ABSTRACT

This paper gives a brief history of the establishment of relations between electronic structure and chemical reactivity of molecules obtained by using quantum mechanical techniques. After a short introduction devoted to the qualitative period a more important part of the paper is concerned with the discussion of the methods which permit some estimations of the constant rates. Both static and dynamic indices are described. The effect of the solvent is taken into account. Various applications are given showing how it has become possible to predict theoretically new kinds of reactivity or even of reactions which have been really discovered later. The role of electronic computers is stressed. It is stated that quantum chemistry will become more and more important in the near future in the field of biochemistry, chemical industries and in particular pharmacology.

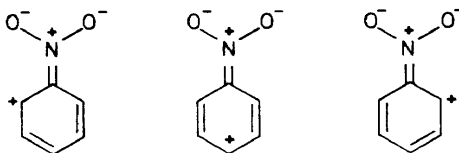
THE QUALITATIVE PERIOD

'THE study of the structure of molecules was originally carried on by chemists using methods of investigation which were essentially chemical in nature, relating to the chemical composition of substances', 'the nature of the chemical reactions in which a substance takes part'¹.

Following the discovery of the electron many attempts were made to build an electronic theory of the chemical bond and the famous paper of Lewis² remains the basis of modern theories relating structure and chemical reactivity. As is well known, another important concept, that of resonance, also had an important role in the development of the theory. Two different groups of organic chemists were responsible for the first important step in that direction. On the one hand, Arndt³ and collaborators developed the theory of intermediate stages. On the other hand, Robinson⁴ and Ingold⁵ built the theory of mesomerism.

'The significant feature which these theories had in common was that they considered it possible for the true state of a molecule not to be identical with that represented by any single classical valence bond structure, but to be intermediate between those represented by two or more different valence bond structures'⁶.

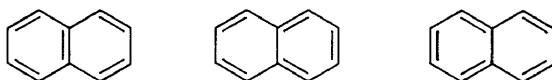
With such a theory nitrobenzene is represented by various structures like :



The resonance between these structures explains qualitatively the meta-directing power of the nitro-group for electrophilic reagents, as a positive charge only appears in the ortho and para positions.

Many chemical reactions⁶ have been interpreted by using the qualitative distribution of electronic atomic charges which results from this resonance phenomenon. In the case of conjugated hydrocarbons like butadiene and anthracene, as all the carbon atoms have the same electronegativity the concept of charge is of no interest in order to interpret the chemical reactivity of these molecules.

Another kind of concept was introduced by Pauling. If we consider the three Kekule structures of naphthalene for example :



it is obvious that the $\alpha\beta$ bonds are double in two of them and single in the third one. They are said to have a double bond character of two thirds. Similarly the double bond character of the central groups is one third. More precisely the double bond character of a bond was defined by Pauling⁷ as the ratio of the number of Kekule structures in which this bond appears as a double bond to the total number of Kekule structures.

The development of the valence bond treatment of conjugated molecules⁸ led to more precise concepts. As is well known, in this treatment the molecule is represented by Kekule and excited structures. An electronic function ϕ_i is associated with each of them. The wavefunction Ψ of the molecule is approximated with a linear combination of the ϕ s

$$\Psi = \sum_i c_i \phi_i$$

A simple wave-mechanical treatment permits calculation of the $|c_i|^2$ s which are considered to be the weights of the various structures. The refined double bond character which is calculated by following this procedure has been called bond order and it appeared that *in a given conjugated hydrocarbon it is the bonds possessing the highest bond order which add reagents like ozone, diazoacetic ester and osmium tetroxide.*

To understand the behaviour of substitution reactions in the same family

of compounds, following an idea of Svartholm⁹, Daudel and Pullman¹⁰ introduced the concept of free valence number. This concept is related to the idea of a residual affinity (Werner) or partial valence (Thiele). It is assumed that there is a maximum bonding power of which a given atom is capable. Then the difference between this and the actual degree of bonding in the molecule itself represents the maximum conceivable increase in bonding, and may legitimately be called the free valence.

It turned out that *in conjugated hydrocarbons substitution reactions take place on atoms possessing the highest free valence number.*

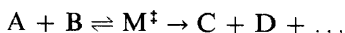
As recalled by Professor Mulliken, a rival theory of delocalized bonds based on the concept of molecular orbitals¹¹ began with the famous Hückel¹² approach. The notions of bond orders¹³ and of free valence numbers¹⁴ have been introduced by Coulson in the framework of molecular orbital theory. It became customary to represent a conjugated molecule by a *molecular diagram* showing the atomic charges, the free valence numbers and the bond orders; this permitted prediction of the chemical reactivity of the molecule.

To summarize, I can say that this period, which I call the qualitative one, is characterized by the introduction of a set of indices associated with the initial state of a molecule which make it possible to predict the positions of its most reactive atoms or bonds with respect to various kinds of reagents.

These indices have been called *static indices*. At the limit we can introduce in this family of indices the symmetry properties of molecular orbitals recently put forward by Woodward and Hoffmann¹⁵ to predict the steric course of a thermal or photochemical cyclization and more precisely to indicate in which cases the mechanism must be conrotatory and in which cases it must be disrotatory.

ESTIMATING A RATE CONSTANT OF A CHEMICAL REACTION

We can consider that the transition state theory¹⁶ is the starting point of a more quantitative period for the analysis of relations existing between the structure of organic molecules and their chemical reactivity. It is well known that this theory is based on the hypothesis that a particular state of the intermediate complex which is formed during collision of the reacting molecules has a sufficiently long life to reach a thermodynamic equilibrium with those molecules. This state is called the transition state. Let M^\ddagger be this state for a bimolecular process. We can write:



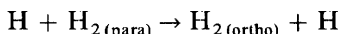
and the transition state theory leads to the following expression for the rate constant k_r of this reaction:

$$k_r = \frac{kT}{h} \eta(1 + t) \frac{f_{M^\ddagger}}{f_A f_B} \exp\left(-\frac{\Delta\epsilon^\ddagger}{kT}\right)$$

In the above expression k is Boltzmann's constant, η the transmission coefficient, t is related with the tunnel effect, the f s are the various partition functions and $\Delta\epsilon^\ddagger$ denotes the potential barrier (which must not be confused

with the experimental activation energy) that is to say the difference between the energy of M^\ddagger and the sum of the ground state energies of A and B.

This potential barrier can be estimated in principle from wave-mechanical calculations by computing the potential energy surface corresponding to the various possible conformations of the system consisting of the two molecules during the collision. *Figure 1* shows the very well known surface obtained for the reaction



by using a semi-empirical procedure due to Eyring and Polanyi¹⁷. It is normal to assume that the shallow basin at the top of the energy pass on that surface corresponds to the transition state.

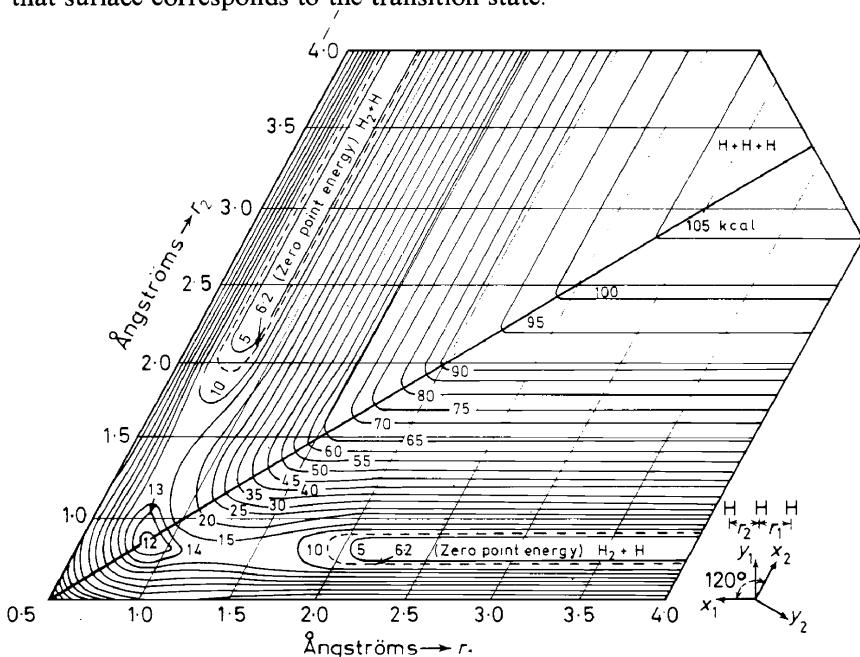


Figure 1

With such a hypothesis it has been possible to calculate the rate of reactions for various temperatures. *Table 1* recalls the results obtained by selecting only one empirical parameter and the fact that the transition state theory allows a good representation of the variation of the rate constant as a function of the temperature and a convenient explanation of the isotopic effect.

Many problems arise when the transition state theory is used to estimate the rate constant of an organic reaction. Even when the mechanism of the reaction is known the geometry of the transition state remains unknown and the calculation of the potential surface is practically impossible. Furthermore it is not easy to take account in a quantitative manner of the effect of the solvent which is often of prime importance. And finally the calculation of the various necessary partition functions is very difficult.

ELECTRONIC STRUCTURE AND CHEMICAL REACTIVITY

Table 1. The rate of the para-ortho hydrogen conversion k , ($\text{cm}^3 \text{mole}^{-1} \text{sec}^{-1}$)

Reagents	300°K	1000°K
H + H ₂ , calc.	7.3×10^7	1.5×10^{12}
obs.	9×10^7	2×10^{12}
D + D ₂ , calc.	3×10^7	0.76×10^{12}
obs.		1.2×10^{12}
H + HD, calc.	2.2×10^7	0.52×10^{12}
obs.		0.68×10^{12}

This is why the only thing we can usually do is to calculate relative rates, that is to say the ratio of a rate constant to another one associated with a similar reaction. In such a case a careful discussion often leads to the conclusion that there are terms approximately equal in the expression of each rate. They disappear in the ratio. Then the calculation can be simplified, especially when the partition functions are among the vanishing terms.

The potential barrier which is then usually the most important factor can be written as:

$$\Delta\varepsilon^\ddagger = \Delta\varepsilon_v^\ddagger + \Delta\varepsilon_l^\ddagger + \Delta\varepsilon_d^\ddagger + \Delta\varepsilon_{nb}^\ddagger + \Delta\varepsilon_s^\ddagger(T)$$

where $\Delta\varepsilon_v^\ddagger$ represents the contribution of the vibrational energy, $\Delta\varepsilon_l^\ddagger$ that of the localized bonds, $\Delta\varepsilon_d^\ddagger$ that of the delocalized bonds, $\Delta\varepsilon_{nb}^\ddagger$ that of non-bonded atom interactions, and $\Delta\varepsilon_s^\ddagger(T)$ that of the solvent.

To calculate this potential barrier a hypothesis has to be made with respect to the structure of the intermediate state. For conjugated molecules two models of transition states have been proposed: the Wheland model and the delocalized model.

The Wheland model¹⁸ proposes a transition state in which there is a decrease in the extent of delocalization of the π electrons relative to the starting molecule. The energy lost, which is the energy needed to localize two electrons at the centre of reaction, is called the localization energy. It is the part $\Delta\varepsilon_d^\ddagger$ of the potential barrier. This model is illustrated in Figure 2 for an electrophilic substitution reaction on naphthalene.

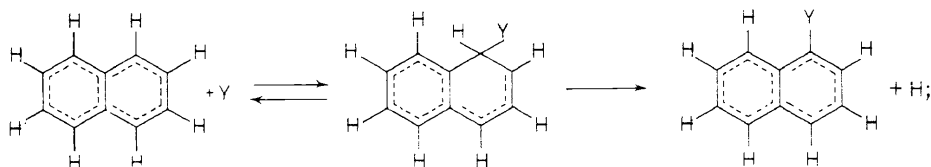


Figure 2

As an example of the use of the concept of localization energy we shall study the nitration of phenanthrene. Table 2 makes it possible to compare the $\Delta\varepsilon_d^\ddagger$ (calculated in an approximate way by Dewar and Warford¹⁹) associated with the various carbon atoms of phenanthrene and the percentage of corresponding mononitro compounds obtained by Schmidt and Heinle²⁰. As in simultaneous reactions the percentages of isomers obtained are directly

proportional to the rate constants of the reactions : the percentages should be a decreasing function of the Δe_a^\ddagger s if those localization energies were the only important terms in the potential barriers. As no such relation appears it could be thought that Δe_a^\ddagger is not the only important term. Dewar and Warford were led to another conclusion. They believed that the Schmidt and Heinle experiment was unreliable. For this reason they performed a new careful experiment. The results also appear in Table 2. It is now seen that, as expected, a good decreasing relationship exists between the localization energies and the percentages of mononitroisomers.

Table 2. The nitration of phenanthrene

Position of the carbon atom	Δe_a^\ddagger (in β units)	Percentage of isomer	
		Schmidt	Dewar and Warford
10	1.80	60	34
1	1.96	—	27
3	2.04	2	25
2	2.18	20	4

R. D. Brown²⁰ has extended the Wheland model in the case of addition reactions and has introduced the concept of ortho and para localization energies. The para localization energy is related to the reactivity of a hydrocarbon in the diene synthesis. The calculation of the ortho localization energies makes it possible to predict the position of the addition of a double bond reagent.

A disadvantage of the Wheland model is that the attacking reagent is removed from the π system being used to calculate the localization energy and as a result the localization energy is invariant to the nature of the reagent in a series of isoelectronic reactions. An attempt to improve this model to include the nature of the reagent by allowing hyperconjugation between the tetrahedral centre and the remaining cationic π system was made by Müller, Pickett and Mulliken²¹. However, it has been shown²² that in a series of conjugated hydrocarbons inclusion of hyperconjugation does not significantly improve the correlations between chemical reactivity and localization energy.

The second type of transition state that has been used successfully to explain certain substitution and addition reactions in conjugated molecules

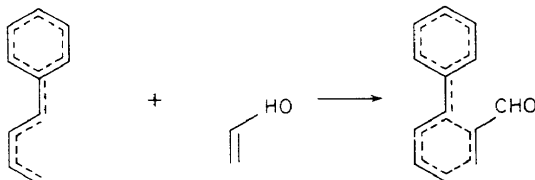


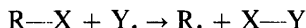
Figure 3

is the delocalized model, which corresponds to an extension of the delocalization of the ground state molecule to include the attacking reagent. This model was originally proposed by M. G. Evans²³ and is illustrated in *Figure 3* for the reaction of acrolein with 1-phenylbutadiene. This model has only been used infrequently. Streitwieser²⁴ proposed such a model for the transition state of the Diels–Alder reaction, as did Simonetta and Carra²⁵ for nucleophilic reactions on nitroderivatives.

An analogous development occurred, but more slowly, in the field of saturated hydrocarbons. A good discussion about the possible structure of the intermediate state in the Walden inversion for example has been given by Ingold²⁶.

For saturated hydrocarbons and related compounds two main procedures have been proposed for calculating the wavefunctions: the LCBO method (linear combination of bond orbitals) mainly due to Hall²⁷, and an adaptation of the Hückel approximation due to Sandorfy and Daudel²⁸ and called the LCVO (linear combination of valence orbitals).

Fukui and collaborators²⁹ and Yang³⁰ successfully used these methods in studying various reactions including radical reactions like



nucleophilic substitutions.

Yonezawa *et al.*³¹ and Fueno *et al.*³² have made interesting quantum mechanical calculations on polymerization reactions studying the rate of initiation and the rate of propagation of the chains. These calculations explain, for example, why styrene is better able to initiate a chain than vinyl acetate and why with vinyl acetate the rate of propagation of the chain is greater than that with styrene. Higasi's³³ book gives a good survey of this problem.

RELATIONSHIP BETWEEN STATIC AND DYNAMIC INDICES

We have recalled that atomic charges, bond orders and free valence numbers are called static indices. Similarly localization energies, and para and ortho localization energies are called dynamic indices because they take account of the reaction path as they depend on the structure of the intermediate state. We have seen that dynamic indices are directly and quantitatively related to rate constants. Initially static indices were only related to rates through chemical intuition.

But about 1950 relationships were found between static and dynamic indices, giving a better background for the use of the former.

Daudel *et al.*³⁴ using the valence bond method observed the existence of a good linear relationship between the free valence number of a carbon atom belonging to a conjugated hydrocarbon and its free valence number. That relation was also obtained by use of the molecular orbital method by Roux³⁵. This finding has been confirmed by Burkitt *et al.*³⁶. *Figure 4* shows the nature of that correlation.

In a similar way Chalvet *et al.*³⁷ and R. D. Brown³⁸ have shown that a nearly linear inverse relation exists between the para localization energies

and the sum of the free valences of the corresponding atoms in the same series of molecules. Brown³⁹ also found a linear relation between the ortho localization of a bond and its bond order for the same compound.

Therefore for conjugated hydrocarbons we can use either static or dynamic indices, and we shall obtain approximately the same results in predicting

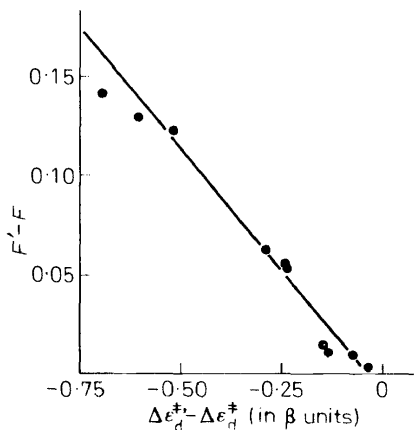


Figure 4

chemical reactivity. The relationships just described furnish therefore an excellent example of bridges between structure (represented by the static indices) and chemical reactivity (measured by the dynamic indices which are theoretically related to chemical reaction rates).

Unhappily no such good correlations remain between static and dynamic indices for heteromolecules. The analysis of the reactivity of quinoline will show what happens in that family of compounds. It has been observed that nucleophilic substitutions on 1-alkylquinolinium salts employing strong nucleophiles such as OH^- leads to substitution in the 2-position while attack by the weaker CN^- affords only the 4-substituted quinoline⁴⁰. It is not possible to interpret such results by using only a given static index (like the π electronic charge) or a given dynamic index (like the localization energy) which does not take account of the strength of the reagent. Brown and Harcourt⁴¹ observed that in 1-alkylquinolinium salts the greatest electronic charge is in position 2. On the other hand the lowest localization energy corresponds to position 4. Therefore they have suggested the use of different reactivity indices for weak and strong nucleophiles: namely electronic charges for strong reagents, localization energies for weak ones.

All that has been said until now refers to thermal reactions, that is to say to molecules reacting in their electronic ground state. A rather different picture appears if we are concerned with photochemical reactions.

Historically the first uses of static indices in photochemistry were mainly based on chemical intuition. Pullman and Daudel⁴² calculated the bond orders and the free valence numbers for the ground state and the first excited state of butadiene using the valence bond method. They found that in the ground state the two bonds 1—2 and 3—4 have the highest bond orders. The free

valence numbers in 1 and 4 are still important but they become very large in the first excited state in which the central bond 2—3 becomes similar to a double bond, the bond orders in 1—2 and 2—3 becoming on the contrary very small.

The same results can be described in another way.

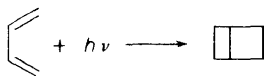
The wavefunction Ψ describing butadiene can be written as

$$\Psi = a\Psi_{\text{I}} + b\Psi_{\text{II}}$$

where Ψ_{I} represents the function associated with the Kekule formula (I) and Ψ_{II} the function associated with the Dewar formula (II).



In the ground state a is found to be large and b small. In the excited state the reverse is true. Therefore, the ground state is conveniently represented by the Kekule formula and the excited state by the Dewar formula. It might be anticipated that under the effect of light butadiene could be transformed into cyclobutene. In 1946, there was no experimental evidence for such a phenomenon, but recently Srinivasan⁴³ has found that when butadiene is irradiated in dilute ether solution, cyclobutene is formed.



In 1951 Fernandez-Alonso⁴⁴ calculated the distribution of the electronic charges for various electronic states of nitrobenzene. He found that for the ground state the ortho and para positions are the most positive ones, but that for one of the first excited states which could be reached under ordinary photochemical conditions the meta positions become the most positive ones. Therefore, the author claimed that light could reverse the orienting effect of the nitro group.

Later on, Havinga *et al.*⁴⁵ studied the photochemical hydrolysis of isomeric nitrophenyl dihydrogen phosphate and also the bisulphate esters. They found that the reaction is faster with the meta isomer than when other isomers are used. This fact may be understood if it is assumed that in one of the excited states of the meta derivative the nitro group withdraws an electron from the phenolic-phosphate oxygen atom as suggested by the quantum-mechanical calculations.

Zimmerman⁴⁶ studied the photochemical behaviour of the tritylestere of *m*-nitrophenol and *p*-nitrophenol in aqueous dioxane. He observed that in the dark at 25°, the meta compound is stable, the para slowly hydrolysed. Contrariwise under the effect of light the quantum yield is much greater for the meta compound than for the para derivative.

An interpretation can be given if we admit that in some excited states of these molecules the nitro-group withdraws electrons from the meta position. As nitrophenols and nitroanilines are π -isoelectronic they must have the

same qualitative behaviour. Zimmerman's results may be considered to be a support of Fernandez's predictions.

Many other studies of the photochemical reactivity of conjugated molecules have been made successfully using static indices. We must try to find the origin of this rather surprising success.

With molecules reacting in their ground state an explanation of the interest of static indices has been found in the relation existing between these indices and dynamic indices. Trsic *et al.*⁴⁷ tried to see if such a relation appears for conjugated hydrocarbons in their first electronic excited states. They found that *it is not so* when the Wheland model is used. Furthermore de Bie and Havinga⁴⁸ who studied experimentally the photodeuteration of nitrobenzene, anisol and nitro-anisols found that if the reactivity of the carbon atoms in these molecules follows the electronic charge it does not follow the localization energies. *Table 3* makes it possible to compare the experimental rates of photodeuteration with the various indices under consideration.

Table 3. Photo-deuteration of nitrobenzene

<i>Position</i>	<i>Rate % in 4h</i>	<i>Electronic charge</i>	<i>Localization energy (in β unit)</i>
ortho	1.0	0.91	0.180
meta	0.5	0.89	0.161
para	8.6	0.99	0.213

Therefore the situations for photodeuteration and for fast substitution reactions on heteromolecules look similar: the rates run parallel to the charges but there is no relationship between these rates and the localization energies. As the two cases considered are concerned with fast reactions, that is to say with small potential barriers, it is normal to think that the origin of this situation lies in the fact that the transition state looks similar to the initial state and that as a consequence the structure corresponding to the Wheland model is not reached.

It was tempting to see what happens when another model is used to describe the intermediate state. This is why the delocalized model has been introduced in the theory of photodeuteration⁴⁹ and in that of photo-oxidation⁵⁰. The results were extremely good.

In particular, the delocalized model is the only known procedure which gives a possible explanation of the effect of substituents upon the position of addition of excited oxygen to anthracene.

This observation has been the starting point for an attempt to develop a unified treatment of the transition state in the reactions of unsaturated molecules⁵¹. By careful choice of parameters the delocalized transition state model is able to encompass the results obtained from the use of the Wheland model. Furthermore, the orientation of substitution reactions on quinoline can be explained by means of the delocalized model. In particular, the calculations emphasize the importance of the nature of the reagent and correctly predict the changes in orientation with different reagents possessing the same qualitative character.

ELECTRONIC STRUCTURE AND CHEMICAL REACTIVITY

Figure 5 represents (in the case of nucleophilic reagents) the π energy $\epsilon_{\pi}(r)$ associated with the transition state resulting from a substitution on the carbon atom r as a function of the electronegativity of the reagent when the delocalized model is used*. $\epsilon_{\pi}(4)$ is taken as the energy origin. There is a marked 'crossing' in the energies for the 2 and 4 positions. Hence for a nucleophile possessing a small electronegativity the 4 position is preferentially substituted whereas for a nucleophile having a large electronegativity

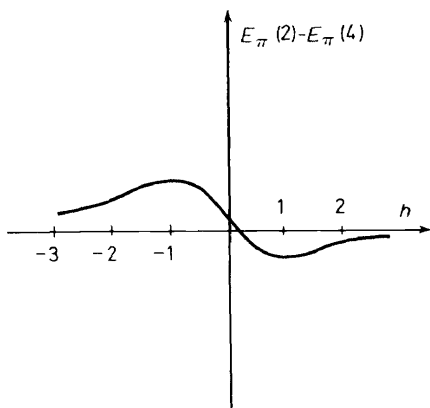


Figure 5

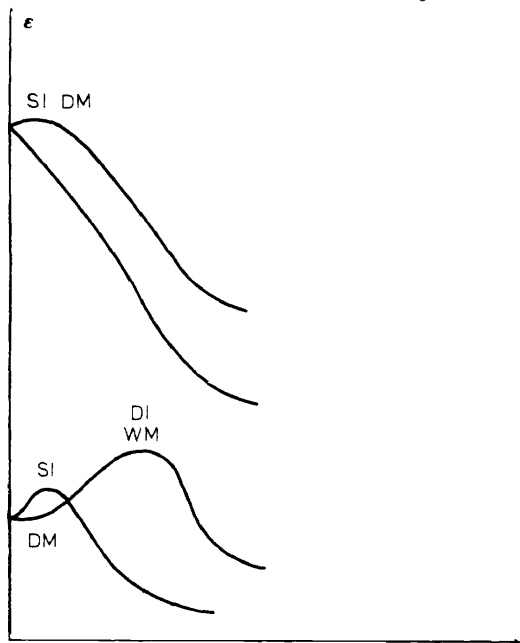


Figure 6

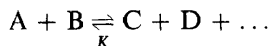
* This electronegativity is related to the coulomb integral $\alpha = \alpha_c + h\beta_{cc}$ which is introduced in the calculation, α_c and β_{cc} being the parameters associated with a carbon atom.

the 2 position becomes more favoured. Such a prediction is in complete agreement with the experimental facts as 1-alkyl quinolinium salts undergo 4-substitutions with the weak CN^- nucleophile but yield only a 2-substituted product with OH^- which contains a more electronegative atom. As the delocalized model is also convenient for photochemical reactions it becomes clear that this model can be successfully used in every case.

Figure 6 shows various possible reaction paths and indicates the indices which give good results. (SI stands for static indices, DM for delocalized model, DI for dynamic indices and WM for Wheland model.)

ESTIMATING EQUILIBRIUM CONSTANTS

The behaviour of an equilibrated reaction like



is described by the equilibrium constant K . For small concentrations the equilibrium constant K satisfies the following equation

$$K = \frac{f_A f_B}{f_C f_D} \exp\left(-\frac{\Delta\varepsilon}{kT}\right)$$

where the f s denote partition functions and

$$\Delta\varepsilon = \varepsilon_{0C} + \varepsilon_{0D} + \dots - \varepsilon_{0A} - \varepsilon_{0B}$$

Here the ε_0 s represent the ground state energies of the various molecular species.

The energy $\Delta\varepsilon$ can be divided, as was $\Delta\varepsilon^\ddagger$, into various parts:

$$\Delta\varepsilon = \Delta\varepsilon_v + \Delta\varepsilon_l + \Delta\varepsilon_d + \Delta\varepsilon_{nb} + \Delta\varepsilon_s(T)$$

the notation being analogous to that used in the corresponding expression for $\Delta\varepsilon^\ddagger$. Therefore the calculation of *relative* equilibrium constants presents many similarities to the computation of relative rate constants. In fact the former problem is simple because no transition state is involved.

If for example we are concerned with the acid-base equilibrium



it is often sufficient to compute the protonation energy to understand the behaviour of pK in a family of molecules.

Figure 7 shows for example the results obtained⁵² when the pK of a set of amino derivatives of pyridine, isoquinoline, quinoline and acridine is plotted as a function of $\Delta\varepsilon_d$ calculated following the Pariser and Parr approxi-

ELECTRONIC STRUCTURE AND CHEMICAL REACTIVITY

mation⁵³. It is seen that the points corresponding to the set of compounds derived from a given skeleton lie along a given straight line. If now the same pKs are plotted⁵³ as a function of $\Delta\epsilon_d + \Delta\epsilon_s(T)$, the solvation energy change being evaluated from a formula derived from the Born approximation⁵⁴ by Hoijtink *et al.*⁵⁵, the various points lie near the same straight lines*. This result shows that the segregation of the various families of molecules which appears on Figure 7 is due to a solvent effect. As in the case of rate constants static indices have been used.

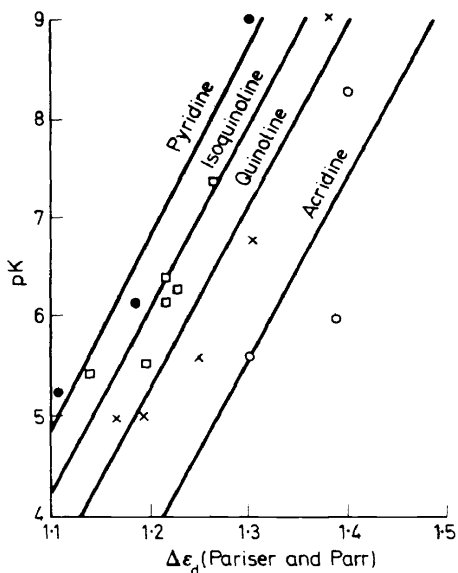


Figure 7

Coulson and Jacobs⁵⁶ studied theoretically charge migration in aniline under the effect of irradiation. They observed that the electronic charge of nitrogen is smaller in the first singlet excited state than in the ground state, that is to say, it should be less basic. Förster⁵⁷ has effectively observed that if a base, such as 3-aminopyrene (which must have similar behaviour) is irradiated by normal light, the excited molecules have acidic properties.

Jaffe *et al.*⁵⁸ observed that the pK of some excited states of azobenzene follows the charge of nitrogen atoms and that in the case of azoxybenzene there is a satisfactory relation between the charge of the oxygen atom and the pK.

Recently Bertran *et al.*⁵⁹ have shown that a group which is slightly donor in the ground state becomes more donor in the first excited singlet state and that a group slightly acceptor in the ground state becomes more acceptor in the first excited singlet state. These rules make it possible to predict the

* Except those corresponding to molecules in which the amino group is in an ortho or peri position with respect to the nitrogen heteroatom.

qualitative behaviour of the pK of many conjugated molecules under the effect of the light.

THE ROLE OF ELECTRONIC COMPUTERS

Most of the main results reported so far have been obtained by using the simplest methods of calculating the wavefunction, namely, the LCAO procedure with Hückel approximations for conjugated molecules, and the LCVO and the LCBO methods for saturated ones.

The possibility of using electronic computers permits the calculation of wavefunctions by following much more elaborate methods. As an introduction to the last symposium on heteromolecules organized in Jerusalem A. Pullman ask the following question: 'Is the use of elaborate methods an evolution or a revolution?' and her answer was

'simply an evolution'

This statement needs explanation.

If we are only concerned with π -orbitals we must emphasize that really the Hückel approximation is a very powerful procedure. The main behaviour of thermal and photochemical reactivity of a conjugated molecule is explained by using this simple method.

The more elaborate procedure introduced by Pariser and Parr⁶⁰ and by Pople⁶¹ leads to improvements⁶² when quantitative rate constants are needed but that method is only really necessary when we try to understand the differences of behaviour between singlet and triplet states. In such a case the use of a quasi-complete configuration interaction is suggested⁶³.

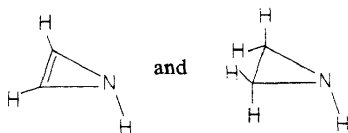
When the introduction of σ orbitals is necessary the use of the Del Ré⁶⁴ procedure which may be considered as a simplification of the LCVO method leads to satisfactory results⁶⁵. In many cases the extended Hückel method agrees⁶⁶ with a superposition of π orbitals calculated following standard Hückel procedure and of σ orbitals resulting from Del Ré procedure.

The CNDO approach corresponds to the introduction of Pariser, Parr, Pople improvements in the extended Hückel method. It has been used with success⁶⁷ to compare the energies of various conformations. In Pople's opinion⁶⁸ use of the actual CNDO method must be avoided for calculating the change in the energy of a molecule with the variation of the length of a strong bond. Therefore we must consider with caution the potential energy surface built by using that procedure. The CNDO method used recently⁶⁹ for studying the pK of various electronic states of conjugated molecules has led to results analogous to that resulting from the use of the Pariser, Parr and Pople π -approximation. From the theoretical viewpoint application of the CNDO method to the unified theory of the transition state⁵¹ would be interesting.

Clementi⁷⁰ has done many all-electron SCF-LCAO-MO computations for conjugated molecules. Some results of these calculations did not agree with the results of the standard Hückel treatment. Pople⁶⁸ has shown that when the various exponents which are introduced in the atomic orbitals are optimized with respect to energy the main discrepancy disappears.

Therefore the *ab initio* method does not mean a revolution. It is mainly needed to build potential energy surfaces. Clementi⁷¹ has built such a surface for the $\text{NH}_3 + \text{HCl} \rightarrow \text{NH}_4\text{Cl}$ reaction. He found that no potential barrier occurs for it.

Another interesting use of the *ab initio* method was made recently by Clark⁷². He calculated the protonation energy of the two following molecules :



As a consequence of the antiaromatic character of the former molecule he found about the same protonation energy for the two compounds in agreement with experimental evidence which shows the same pK value for both.

PROSPECTIVE

The field of true quantum chemistry, i.e. the application of wave-mechanics to chemical reactivity, is now open to many important investigations.

Conjugated molecules have been discussed first because delocalized bonds are specially convenient for wave-mechanical calculations. But now we are also able to study saturated molecules. Therefore the whole realm of organic chemistry can be explored.

Inorganic chemistry will remain a more difficult field because many kinds of atoms are concerned and parametrization is not easy. But in this field *ab initio* calculations will be a great help. The main problem will be, as it now is, to find convenient reaction mechanisms and appropriate geometry for the transition state.

Molecular beam experiments will certainly bring important information particularly for the theory of gas phase reactions. In this area collision theory could be of great interest. But in organic chemistry, reactions are mainly produced in liquid solution and we can anticipate that this is the actual spectacular development of molecular liquid physics which will become the more important source of progress for the theory of chemical reactivity. Also solid state physics must be taken into consideration particularly to improve the rather rough theory of heterogeneous catalysed reactions.

Therefore, during the next few years it is obvious that quantum chemistry will become important for chemical industries.

Quantum chemistry is already of great interest in biochemistry⁷³. We organized for example last year in collaboration with Professor B. Pullman a NATO summer institute devoted to biochemical applications of the quantum theory of chemical reactivity of excited organic molecules including some discussions on the photochemistry of nucleic acids and particularly the theory of mutagenesis, and also some studies of prebiological systems and a discussion on the origin of life on Earth.

A. and B. Pullman⁷⁴, who are the main pioneers in quantum biochemistry, said: 'The essential fluidity of life agrees with the fluidity of the electronic

cloud in conjugated molecules. Such a system may thus be considered as both the cradle and the main backbone of life'. This is why quantum chemistry will become more and more important in biochemistry and therefore in related fields.

Many papers have already been published on the application of quantum chemistry to pharmacology and the following topics are quoted by B. Pullman⁷⁵:

On the mechanism of action of chlorpromazine—Electronic structure and activity of organophosphorus inhibitors and esterases—Electronic features of some psychopharmacological compounds.

The action of anaesthetics on excitable membranes—A quantum chemical analysis.

A relationship between the hallucinogenic activity of drugs and their electronic configuration.

The application of quantum mechanics to pharmacology: some substances active in the nervous system,

But a new and very exciting field seems to be open to scientific research: the interaction between spirit and matter. A book has already been devoted to the molecular basis of memory⁷⁶ and a section of the next international biophysics congress is devoted to that topic. I expect that quantum chemistry will play a role in that fascinating area.

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ELECTRONIC STRUCTURE AND CHEMICAL REACTIVITY

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