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*Perspective*

# Perspective on "A molecular orbital theory of reactivity in aromatic hydrocarbons"

## Fukui K, Yonezawa T, Shingu H (1952) J Chem Phys 20: 722

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**Abstract.** The development of theories for interpreting the course of chemical reactions is one of the most important achievements of theoretical chemistry in the twentieth century. I selected the paper by Fukui et al. from 1952, proposing the frontier electron density as the reactivity index for the orientation of electrophilic substitution reactions. This paper may be regarded as a bridge between an older reactivity theory, the electronic theory of organic chemistry, and new ones predicting the stereochemical courses of reactions such as frontier orbital theory and the Woodward–Hoffmann rule.

Rationalization of the chemical reactivity for organic compounds based on quantum mechanics is one of the goals of theoretical chemistry. In the early stages of the twentieth century, the electronic theory of organic chemistry had been established by Lapworth, Robinson and Ingold as a unified guiding principle for understanding complex organic reactions. [1] This assumed that the reactivity is determined by the electron density at a particular position in an organic molecule. Several concepts such as inductive, mesomeric and inductomeric effects were advanced for interpreting the electron distributions in organic reagents. Employing the Hückel molecular orbital (HMO) method, Coulson and Longuet-Higgins [2] developed the general theory for the electron distributions in conjugated molecules and proposed the $\pi$ electron density $q_r$ and self-polarizability $\pi_{rr}$ as the reactivity indices correlating the activation energies at different reactive positions in a conjugated molecule. Considering the energy changes which occur when a charged reagent approaches a particular position in a molecule, they deduced that electrophilic reagents react at the positions with high values of $q_r$, while nucleophilic reactions are favored by low values of $q_r$. They also related $\pi_{rr}$ to the reactivity for nonsubstituted aromatic hydrocarbons such as naphthalene in which $q_r$ are the same at all positions. Thus, the theory of Coulson and Longuet-Higgins is regared as the quantum mechanical generalization of the organic electronic theory which was derived empirically based on a large amount of experimental evidence in organic chemistry.

In 1952, Fukui, Yonezawa and Shingu [3] proposed an alternative reactivity index for aromatic hydrocarbons, referred to as the frontier electron density, $f_r$, which was different from the previous ones coming from the static [2] and localization [4] approaches, focusing on the electrons in the highest occupied (HO) $\pi$ MO. They carried out HMO calculations for the $\pi$ electronic structure of 15 aromatic hydrocarbons whose $\pi$ electron densities $q_r$ are the same at all sites. They assumed that the two electrons occupying the HOMO, distinct from the other $\pi$ electrons, are essential to the reactivity of the system and referred to them as the frontier electrons. It was found that the positions of the highest density of the frontier electrons, $f_r$, completely agreed with the experimental results of the structures of the reaction products of oxidation, halogenation, nitration and sulfonation for nine aromatic hydrocarbons including naphthalene, anthracene, phenanthrene, chrysene, naphthacene, perylene, pentacene and picene. The only discrepancy with experiment was for 3,4-benzophenanthrene, where the position of the largest frontier electron density is sterically hindered and the second largest position is correlated to the experimental results for the oxidation reactions.

Although the title paper from 1952 was only for electrophilic substitution reactions. Fukui et al. [5] further developed the frontier electron theory to be applicable to nucleophilic and radical reagents. In the case of reactions with a nucleophilic reagent, they postulated that the more susceptible position to attack has the higher density of the two electrons assumed to occupy the lowest unoccupied (LU) MO, while the position with the higher density of the two electrons, one occupying the HOMO and the other the LUMO, is more reactive with a radical reagent. With this extension of the theory, they reached the concept of frontier orbitals, i.e.

HOMO and LUMO, as particularly important MOs to predict the reactivities in many types of reaction. They also postulated that the electron delocalization or transfer between the reagent and reactant in the vicinity of the transition state is essential in determining the reactivity of organic compounds and the frontier orbitals play a most important role in such an electron delocalization.

Fukui [6] wrote a review paper in 1964 where the Diels–Alder reactivity was discussed by examining the stabilization energy due to the interconjugation between the diene and dienophile near the transition state using perturbation theory. He pointed out that the symmetry relation between the HOMO of diene and the LUMO of dienophile is crucial in determining the magnitude of the stabilization energy and showed that the symmetries of the HOMO and the LUMO are the same for all the diene–dienophile pairs (six dienes and nine dienophiles). This discovery of the importance of the symmetry relation between the HOMO and the LUMO was essentially the same as the symmetry rule proposed by Woodward and Hoffmann [7] for concerted cycloaddition reactions.

Although the frontier orbital theory had not received much attention from experimental organic chemists when proposed, the HOMO–LUMO interaction became widely recognized to be an important clue in interpreting the course of chemical reactions after the establishment of the Woodward–Hoffmann symmetry rule. In the 1960s and 1970s, theories of chemical reactivity were advanced remarkably by many theoretical chemists and the symmetry relation of the frontier orbitals, which is the essence of frontier orbital theory and the Woodward–Hoffmann rule, played the central role in these developments. Note that the MO theories of chemical reactivity are now standard methods for organic chemists and are included in many textbooks of organic chemistry. Fukui won the Nobel Prize with Hoffmann in 1981 for their theories, developed independently, concerning the course of chemical reactions.

As already described the theory of chemical reactivity has been developed in two stages in the twentieth century. The first is the electronic theory of organic chemistry, which was generalized by Coulson and Longuet-Higgins based on quantum mechnics. The second stage is the establishment of the symmetry rule for the MOs in predicting the course of a reaction, i.e. frontier orbital theory and the Woodward–Hoffmann rule. The title paper from 1952 may be regarded as a bridge connecting these two stages because it proposed the reactivity index, $f_r$, for interpreting the orientation effect in chemical reactions, the main subject of the electronic theory of organic chemistry, and was the starting point of the second stage after the concept of frontier orbitals was first introduced and it became the key ingredient in the further development of the theory.

At the present time, ab initio theoretical methods for calculating potential-energy surfaces have been greatly developed, providing quantitative information on the energies and structures of reactive species. Accurate calculations of the energy surfaces have become available for complex chemical reactions such as catalytic reactions including transition-metal compounds and reactions in solution. Considering that frontier orbital theory and the Woodward–Hoffmann rule were derived based on the HMO method, the third stage of chemical reaction theory will be developed based on highly accurate electronic structure theories, which can quantitatively predict reaction rates even for complex chemical reactions in solution.

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