Kenichi Fukui

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Kenichi Fukui, co-recipient of the 1981 Nobel Prize in Chemistry for "his frontier orbital theory of chemical reactivity," was born on 4 October 1918 in Nara, Japan, the eldest of three sons of Ryokichi Fukui, a foreign trade merchant and factory manager, and Chie Fukui (1, 2). After receiving a B.A. degree in Engineering from the Department of Industrial Chemistry of Kyoto Imperial University in 1941, Fukui took a position with the Japanese Army Fuel Laboratory, where he was involved in the development of synthetic fuels. In 1943 he returned to Kyoto University as a lecturer in the Engineering School's Department of Hydrocarbon Chemistry. Here he began work on a doctoral degree, while simultaneously advancing through the academic ranks, receiving his Ph.D. in Chemical Engineering in 1948 and the rank of full professor in 1951. Fukui remained at Kyoto University for the next 30 years, becoming Professor Emeritus in 1982 and President of the Kyoto Institute of Technology the same year.

In spite of the fact that he had been trained as an engineer and had begun his career as an experimentalist doing applied fuel research, Fukui had already developed an interest in quantum chemistry while still a student. Though he was, as a consequence, largely self-taught as a theoretician, he nevertheless began to actively cultivate this field after returning to the University and by the early 1950s had built up a small, but active, group of theoreticians within the largely experimentally-oriented Department of Hydrocarbon Chemistry. In the next three decades Fukui's group of experimentalists and theoreticians would produce more than 450 papers, dealing with such diverse topics as reaction engineering and catalysis, the statistical theory of gellation, the use of inorganic salts in organic synthesis and, most importantly from the standpoint of the Nobel Prize, the electronic theory of organic reactions.

Background to Fukui's Work

The central thread in Fukui's work on the theory of organic reactivity, like so much in the history of modern organic chemistry, can be traced back to the benzene molecule. Just as the elucidation of the structure of benzene became a central problem for the development of structural organic chemistry in the last half of the 19th century, so the understanding of its reactivity would become the central problem for the newly developing discipline of theoretical organic chemistry in the first half of this century. The basic problem was to explain why an attacking molecule or ion (usually called the reagent) chose to react more frequently at certain atoms of an organic molecule (usually called the substrate) than at others and why this frequency pattern changed when the substrate was modified or the attacking reagent was changed.

One of the first to approach this problem using the newly emerging electrical theory of matter, developed by physicists during the last decade of the 19th century and the early decades of the 20th century, was H. S. Fry of the University of Cincinnati (3). By using a polar bonding model derived from the atomic models of J. J. Thomson and assigning net positive and negative charges to alternate atoms in a manner similar to the modern assignment of formal oxidation numbers, Fry was able, as early as 1908, to qualitatively rationalize the reactivity of the various monosubstituted benzene species studied a decade earlier by the British team of A. Crum Brown and J. Gibson (4). The preferred site of attack in the monosubstituted benzene species was determined electrically, with positive reagents favoring the negative carbon sites (meta to a positive substituent and ortho-para to a negative

substituent) and negative reagents favoring the positive carbon sites (with the opposite distributions).

However, the ionic models of Fry and other early pioneers of the electronic theory of organic reactivity, such as K. G. Falk, J. M. Nelson, J. Stieglitz and A. A. Noyes, were not in keeping with the physical properties of organic molecules, and in the 1920s most of Fry's results were translated into the covalent or shared-electron pair bonding model of G. N. Lewis. Particularly prominent in this translation process were the American chemist H. J. Lucas, who showed that the evidence for the alternate polarity hypothesis central to the ionic model was faulty, and the English chemists A. Lapworth, T. Lowry, R. Robinson, and C. K. Ingold (5, 6). According to the new approach, differential reactivity was still a function of differential electrical charges on the various atoms of a molecule, though these were now "partial" charges, due either to an inherent inequality in the sharing of the bonding electrons (the static effect) or to their induction by the attacking reagent (the dynamic effect). By the early 1930s this had led to a qualitative electronic classification of reagents as radical (odd electron), electrophilic (electron-pair acceptor), and nucleophilic (electron-pair donor), which is still used today, and to a classification of substrate electronic-shift mechanisms as inductive, inductomeric, mesomeric and electromeric (7).

The 1930s and 1940s saw yet a further modification of these concepts under the impact of ideas imported from the newly developing field of quantum mechanics. Initially, the most important of these was the concept of resonance, developed by L. Pauling and extensively applied to problems of organic reactivity by G. W. Wheland of the University of Chicago (8). The "English School" of organic chemistry had already recognized that many organic molecules departed from the localized 2c-2e electron-pair models of Lewis by delocalizing or spreading out certain of their bonding electrons over more than two adjacent atoms - an effect related to the mesomeric and electromeric electron-shift mechanisms. Pauling pointed out that an analog to this process could be found in a quantum mechanical calculation procedure known as the valence bond (VB) method and that this analogy implied that so-called mesomeric delocalization or "resonance," as Pauling called it, should lead to an increase in the stability of the molecule. Pauling and Wheland proceeded to develop a series of rules for qualitatively estimating the relative stabilities of resonance-stabilized species based on the superposition of limiting-case localized electron-pair structures.

When applied to the problem of organic reactivity, resonance theory implied that one should compare the resonance stabilization of each of the various hypothetical transient "supermolecules" or "transition states" produced by weakly attaching the attacking reagent to each of the various kinds of carbon atoms in the substrate. The transition state displaying the greatest amount of resonance stabilization should correspond to the position showing the greatest frequency of attack. This procedure implied the use of a dynamic reactivity index, though in actual practice, it was usually applied to the isolated substrate itself and was quite successful in qualitatively rationalizing the static electrical partial charges used by the English school to explain the reactivity of the monosubstituted benzene derivatives originally studied by Fry.

Ultimately, however, the most significant impact of quantum mechanics lay in the introduction of methods for quantitatively calculating the relative reactivity of organic molecules. In this area a second computational method, known as molecular orbital (MO) theory, quickly supplanted the more difficult procedures of VB theory. This method was first extensively applied to benzene and other conjugated hydrocarbons by the German theoretician E. Hückel in 1931 (9). Though he had to use a large number of oversimplifications and estimations, Hückel was able to show that the method was capable of quantitatively mimicking the static partial charge distribution patterns in the monosubstituted benzene derivatives demanded by the older qualitative rationales, a result also confirmed by Pauling and Wheland a few years later (10).

Up to this point, virtually all of the work on organic reactivity had centered on substituted hydrocarbon substrates containing at least one atom other than carbon or hydrogen and especially on the monosubstituted derivatives of benzene. This "hetro" atom acted as a key or starting point relative to which the partial charges of the carbon atoms in the substrate could be determined. However, with the introduction of VB, MO, and resonance theory, procedures were developed for predicting the relative reactivity of neutral conjugated hydrocarbons containing carbon atoms which were nonequivalent by virtue of symmetry rather than bonding to a hetro atom of some kind. Since simple Huckel MO theory predicted that all of the carbon atoms in these species had the same total electron density, this required the development of relative reactivity indices based on something other than static partial charges. As early as 1938 Pauling had used qualitative resonance theory to predict both enhanced electrophilic and nucleophilic reactivity at the α-carbons in naphthalene, and in the late 1940s and early 1950s French theoreticians used the theory to develop a series of quantitative static reactivity indices for conjugated hydrocarbons based on the use of so-called π-bond orders and free valence numbers (11, 12). About the same time, the English theoretician C. A. Coulson showed that similar

static indices could be calculated on the basis of MO theory, as well as a new dynamic index called the self-atom polarizability.

Even earlier, in 1942, Wheland had introduced a picture of the transition state for aromatic substitution reactions known as the localization model, in which the resonance energy of the isolated substrate was compared to that of various alternative transition states in which the reacting carbon atom, as well as two π-electrons (in the case of electrophilic attack), were deleted from the conjugated system (13). In the case of nucleophilic attack, two additional electrons were added to the shortened conjugated system instead. The localized transition state showing the least resonance destabilization corresponded to the site with the greatest reactivity. By the early 1950s, various modifications of this procedure had added a number of dynamic localization indices for predicting reactivity to the array of already competing static indices.

Fukui's Contribution

This was the state of affairs when Fukui published his first paper on organic reactivity in 1952 (14). Here he introduced yet another static reactivity index for predicting the favored site of electrophilic attack on aromatic hydrocarbons. This was based on an examination of the substrate molecular orbital containing the electrons with the greatest energy (later called the highest occupied molecular orbital or HOMO). Fukui referred to these as the species' "frontier electrons" and postulated that electrophilic attack would occur at the carbon atom having the greatest frontier electron density, rather than at the atom with the greatest total electron density (which, as we have seen, was the same at all carbon atoms). Though this index worked as well, if not better, than the other competing indices, Fukui could not provide a good theoretical rationale for its use and, as a result, the index was criticized by a number of theoreticians.

Luckily, R. S. Mulliken, one of the founders of MO theory, began to publish a series of papers about this time dealing with the quantum mechanical treatment of charge-transfer complexes or weakly-bonded Lewis acid-base adducts (15). Lewis acids and bases are essentially the inorganic chemist's equivalent of electrophilic and nucleophilic reagents, and Mulliken was able to show that the structures of the resulting complexes (which could be viewed as weak electrophilic-nucleophilic addition reactions) were the result of maximizing the overlap between the highest occupied MO of the base (the donor orbital) and the lowest unoccupied MO of the acid (the acceptor orbital). This result became known as the "overlap - orientation principle" and inspired Fukui to continue his

exploration of the frontier electron index.

In 1954 he and his coworkers produced two more important papers (16, 17). In the first of these, Fukui extended his method to include nucleophilic and free radical attack on conjugated hydrocarbons, showing that they could be correlated, respectively, with the substrate position having the greatest virtual electron density for lowest unoccupied MO (or LUMO as it was later called) and the position having the greatest combined HOMO-LUMO densities. He also extended his substrates and reaction types to include substitution reactions for heteroaromatics and addition reactions for conjugated alkenes and began to speak of frontier orbitals as well as frontier electrons.

In the second paper, Fukui used perturbation theory to provide the missing theoretical rationale for his approach. Perturbation theory indicated that, when two species began to react with or perturb each other, stabilizing interactions could result only when the occupied MOs of one species interacted with the unoccupied MOs of the other species and that the extent of this stabilization depended directly on the overlap between the orbitals and inversely on their energy separation. Since, of all the orbitals on the substrate and reagent, the HOMO and LUMO had the smallest energy separation, this explained their importance in determining reactivity, while the criterion of maximum overlap explained why the favored position of attack corresponded to the maximum in the frontier orbital density.

Throughout the late 1950s and early 1960s, Fukui and his coworkers continued to refine and extend the frontier orbital method. They used various combinations of frontier electron densities to generate new reactivity indices (known as the "delocalizability" and "superdelocalizability" indices), explored new theoretical derivations and, most importantly, continued to apply the method to new classes of reactions and substrates, including polycentric cycloaddition reactions, substitution reactions for saturated alkanes, three-species interactions, catalysis, and photochemical reactions. This work was eventually summarized in a monograph written in 1975, but before its publication two important events happened which would bring Fukui's work to the attention of a much broader range of practicing organic and inorganic chemists (18).

The Impact of Frontier Orbital Theory

The first of these resulted from the publication of a series of short communications by R. B. Woodward and R. Hoffmann in 1965 (19-21). In these notes Woodward and Hoffmann showed how an increasing number of previously unclassified reactions could be organized into three

major groups, which they called electrocyclic, cycloaddition, and sigmatropic. Common to all three classes was the existence of a cyclic transition state and a set of simple rules for predicting the stereochemistry and photo-thermal "allowedness" of the reactions as a function of the π-electron counts. Even more importantly, Woodward and Hoffmann showed how these rules could be rationalized using the criterion of positive overlap between various lobes of the species' frontier orbitals. The impact on the organic chemistry community of the resulting "principle of the conservation of orbital symmetry," as it became known, was immediate and a literal deluge of extensions and alternative theoretical derivations began to appear in the literature (22). Most prominent among these were the orbital correlation diagram approach of H. C. Longuet-Higgins and E. W. Abrahamson (also extensively used by Woodward and Hoffmann), the concept of aromatic and antiaromatic transition states developed by M. J. S. Dewar, the concept of Hückel and Mobius transition states developed by H. E. Zimmerman, and the work of R. F. W. Bader and its elaboration by L. Salem and R. G. Pearson (23-26). However, it eventually became clear that, in terms of both simplicity and breadth of application (though not necessarily rigor), the frontier orbital method was by far the most attractive.

The second event of importance was the publication of a paper in 1968 by G. Klopman of Case Western-Reserve University in which he showed that a more extended perturbational treatment of chemical reactions actually resulted in a two-term reactivity index (27). The first term, which Klopman called the orbital-control term, corresponded to Fukui's approach, and pointed to the importance of maximizing the overlap between the frontier orbitals of the reactants. The second term, which Klopman called the charge-control term, pointed to the importance of net partial charges in determining reactivity. The two indices frequently predicted two different points of attack, though a simple consideration of the relative energies of the frontier orbitals of the reagent and substrate allowed one to determine which index was the most important for the reaction in question, with a small energy separation resulting in orbital control and a large separation in charge control. This result could be linked to the observation that two alternative competing reactivity sites were frequently present in organic substrates, corresponding to thermodynamic-controlled versus kinetic-controlled reactivity, and that preference for them varied with the nature of the attacking reagent. Even more importantly, Klopman was able to link his result to the concept of hard and soft Lewis acids and bases (the HSAB Principle), which had been developed in the 1960s by R. G. Pearson, and so direct the attention of most inorganic

chemists to the concept of frontier orbitals and their implications for chemical reactivity (28, 29).

A final and more subtle result also came out of the Woodward-Hoffmann-Klopman results. Though the computational superiority of MO theory had been apparent to theoreticians since the early 1950s, most of the early results discussed above, including Fukui's, had little impact outside of a small circle of practicing theoretical organic chemists. Textbooks and most papers by synthetic organic chemists continued to use qualitative resonance theory to explain reactivity. This was because it was not only qualitative and easy to use, but also because it had a simple and effective symbolism involving the use of curved arrows (to indicate electron shifts) and conventional Lewis structures. The delocalized orbitals of MO theory, on the other hand, appeared to be too difficult to draw and the computational results of Fukui and others too laborious for a nonspecialist to calculate.

The development of orbital symmetry, however, focused attention on a qualitative consideration of the orbital nodal signs and sizes in order to evaluate the relative extent of positive orbital overlap. This, coupled with the introduction of the convention of representing MOs in terms of combinations of their constituent atomic orbitals, by superimposing p-type atomic orbital lobes on the conventional line formula for the underlying sigma bonding framework, seemed to provide the missing qualitative symbolism for MO theory. The further simple identification of the conventional donor electron pair with the HOMO frontier orbital and the conventional acceptor site with the LUMO frontier orbital appears to have completed this translation process and, since the 1960s, MO theory has increasingly become a part of every chemist's conceptual repertoire. This, in turn, has greatly facilitated the acceptance of Fukui's frontier orbital theory of reactivity, which is rapidly attaining a similar status, if one is to judge from both the number of specialist monographs and introductory textbook treatments appearing in recent years (30-33).

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