The Conservation of Orbital Symmetry

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MacMillan Group Meeting
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Woodward, R.B., Hoffmann, R. ACIEE, 1969, 8, 781
Dewar, M.J.S., ACIEE, 1971, 10, 761
Dougherty & Anslyn, Modern Physical Organic Chemistry, Chap. 15
**Orbital Symmetry and the Prediction of Organic Reactivity**

There are a number of central dogmas in organic chemistry that greatly aid in predicting and rationalizing chemical reactivity.

![Chemical structures](image)

**Lewis and Bronsted Acidity**

**Nucleophile / Electrophile Relationships**

**Hard / Soft Interactions**

Yet arguably, in terms of pure predictive power, the most successful of these central tenets is the conservation of orbital symmetry observed in pericyclic reactions.

![Pericyclic reaction](image)

Orbital symmetry considerations are able to account for thousands of complex reaction outcomes in a very straightforward way that requires no complex mathematical calculations.

**IUPAC Definition:** "Conservation of orbital symmetry requires the transformation of the molecular orbitals of reactants into those of products to proceed continuously by following a reaction path along which the symmetry of these orbitals remains unchanged."
A Quick Review of Pericyclic Reactions

Pericyclic processes are "reactions in which all first-order changes in bonding relationships take place in concert on a closed curve." Five classes of reactions meet this requirement:

- **Electrocyclic Reactions**

- **Chelotropic Reactions**

- **Group Transfer**

- **Sigmatropic Reactions**

- **Cycloadditions**

The allowedness of any of these pericyclic reaction, as well their stereochemical outcomes, can be rationalized using only orbital symmetry considerations.

Historically, these reactions represent one of the first successful unions of theory with experiment in organic chemistry, and were largely responsible for the widespread acceptance of molecular orbital theory in the organic community.
Nomenclature for Pericyclic Processes

- Pericyclic chemistry has a great deal of terminology associated with it. Below is a quick primer.

**Electroyclic Rotations**

- Conrotatory
- Disrotatory

If both termini rotate in the same direction, the motion is called conrotatory.

If both termini rotate in the opposite direction, the motion is called disrotatory.

**Sigmatropic, Chelotropic, and Cycloaddition Reactions**

- Suprafacial interactions occur on the same face of a \( \pi \) system

- Antarafacial interactions occur across opposite faces of a \( \pi \) system
Pericyclic Reactions Prior to 1965

By the early 1950's the Diels-Alder, Cope and Claisen reactions had become synthetically important reactions and were used routinely by organic chemists.

However, there were spirited and long-standing debates about the true nature of the reaction mechanisms. The commonly employed mechanistic probes (kinetics, thermodynamics, stereochemistry) were insufficient to definitively assign the precise mechanism by which bonds were made or broken.

"'No-Mechanism' is the designation given, half in jest, half in desperation, to "thermoreorganization" reactions like the Diels-Alder and the Claisen and Cope rearrangements in which modern, mechanistic scrutiny discloses insensitivity to catalysis, little response to change in medium and no involvement of common intermediates, such as carbanions, free radicals, carbonium ions and carbenes."

-Doering and Roth, *Tetrahedron*, 1962, 18, 67

It is important to remember that in the 1950's and early 1960's molecular orbital theory was still a relatively new and untested idea in organic chemistry. (In fact, MO theory itself was not fully rigorous and consistent until 1950.) As such, its application to problems of organic reactivity was left to the theoreticians, whose work was largely ignored.
**Vitamin B<sub>12</sub> and the Origins of Orbital Symmetry**

- Original impetus for Woodward's interest in pericyclic reactions came from a set of puzzling reactions observed in the synthesis of Vitamin B<sub>12</sub>

- In the synthesis of a fragment, Woodward planned to use an intramolecular Michael addition to close a six-membered ring and introduce two new stereogenic centers

**Proposed Reaction**

![Intramolecular Michael reaction](image)

- However, the reaction does not proceed under basic conditions. However, when attempting to take a melting point of the crystalline enol, the desired cyclization was found to take place!

![Thermal reaction](image)

- This thermal reaction produces the opposite diastereomer to the one postulated on steric grounds.

from Woodward's Lecture at Univ. of Sheffield, 8th July, 1966
A Pretty Set of Facts

- Further experimentation showed that the reaction could also be carried out in solution with heating.
- Careful examination of the reaction revealed that the olefin geometry of the starting material is isomerized under the reaction conditions, but that each olefin isomer stereospecifically gives rise to a distinct diastereomer of the product.

Furthermore, it was shown that when each product was irradiated it produced an olefin geometry of the starting material that was opposite to that from which it was created!!

from Woodward's Lecture at Univ. of Sheffield, 8th July, 1966
**Putting the Pieces Together**

- Woodward realized the B$_{12}$ reactions were very similar to earlier reports on the stereospecific opening of cyclobutenes but were different in the relative sense of rotation

\[
\text{Me} - \text{Me} \quad \xrightarrow{\Delta} \quad \text{Me} - \text{Me}
\]

conrotatory \(4\pi\)

\[
\text{Me} - \text{Me} \quad \xrightarrow{\Delta} \quad \text{Me} - \text{Me}
\]

conrotatory \(4\pi\)


- Furthermore, similar reports on the stereospecific ring closing of hexatrienes had been reported by Havinga in his studies on the chemistry of vitamin D (more on this to come)

\[
\text{HO Me Me R Me} \quad \xrightarrow{h\nu} \quad \text{HO Me Me R Me}
\]

6\(\pi\) conrotatory cyclization

\[
\text{HO Me Me R Me} \quad \xrightarrow{\Delta} \quad \text{HO Me Me R Me}
\]

6\(\pi\) disrotatory cyclization

**ergosterol**

**tachysterol**

**isopyrocalciferol**

- Clearly these processes were related in some fundamental way, but the exact nature of the relationship remained elusive.

Havinga, E. et al *Tetrahedron*, **1961**, *16*, 146
**One Rule to Rule Them All**

- The crucial insight came in relating the sense of rotation, the number of $\pi$ electrons involved, and the symmetries of the highest occupied molecular orbitals.

<table>
<thead>
<tr>
<th>HOMO of ethylene $2\pi$</th>
<th>HOMO of butadiene $4\pi$</th>
<th>HOMO of hexatriene $6\pi$</th>
<th>HOMO of octatetrene $8\pi$</th>
</tr>
</thead>
</table>

- The termini move so as to create new $\sigma$ bonding interactions in the transition state.
**Conservation of Orbital Symmetry**

- Woodward realized that the symmetry elements of the starting material HOMO were maintained in the product MO’s. The stroke of genius came in recognizing that the symmetry also had to be conserved in the transition state.

![Diagram](image1)

- Below is HOMO for the transition state structure in a $4\pi$ ring-opening reaction calculated at B3LYP / 3-21G

![Diagram](image2)

- This simple idea is incredibly powerful. It was able to rationalize a large body of experimental facts and make qualitative predictions about reactivity in a way that is still (given the 40 years past) completely unmatched.
The Woodward-Hoffmann Rules

- Beginning in late 1964 Woodward asked computational chemist Roald Hoffmann to make his ideas theoretically rigorous. The collaboration culminated in five papers detailing the consequences of conserving orbital symmetry in pericyclic reactions

- The first paper dealt specifically with the orbital symmetry considerations governing electrocyclization reactions

- A general form of the selection rules for electrocyclizations are given below:

  1. Thermal electrocyclic reactions involving 4n electrons proceed in a conrotatory fashion

  2. Thermal electrocyclic reactions involving 4n+2 electrons proceed in a disrotatory fashion

  3. Photochemical electrocyclic reactions involving 4n electrons proceed in a disrotatory fashion

  4. Photochemical electrocyclic reactions involving 4n+2 electrons proceed in a conrotatory fashion

- The binary nature of the selection rules makes them easy to apply. Change one variable and you get the opposite stereochemical outcome!

If You Have a Theory, You Should Make Predictions

- While the orbital symmetry arguments were compelling explanations for known cases, Woodward and Hoffmann boldly predicted that they would hold in reactions that were unexamined at the time.

  ![Disrotatory reaction](image)

- For both conrotatory and disrotatory reactions, the termini can rotate in one of two possible directions. Often the equilibrium lies towards the less sterically encumbered isomer, but kinetically stereoelectronic effects play a role.

  ![Conrotatory reaction](image)

- The rotating cyclopropane σ bond aids in the ionization event.

  ![Disrotatory reaction with rotating bond](image)

These three reactions were predicted to proceed in the manner described. In all cases, they were proven correct.

Correlation Diagram Case Studies: Cycloadditions

■ To extend the applicability of these orbital symmetry ideas to other pericyclic processes, Woodward and Hoffmann turned to correlation diagrams. Correlation diagrams track which orbitals of the starting materials become which orbitals of the products along the reaction coordinate.

■ Rules for the construction of a correlation diagram

1. Define a geometry for the proposed interaction

2. Draw MO’s of the reactants and the product in order of ascending energy

3. Define each MO as being either symmetric or antisymmetric with respect to the symmetry elements found in the structures of the starting material, products, and transitions states.

4. Populate the starting material orbitals with electrons, beginning with the ground state MO

5. Correlate reactant orbitals with product orbitals of like symmetry. If all the bonding MO’s of the reactant correlate with bonding MO’s of the product, the reaction is considered allowed. If a bonding MO in the reactant becomes an antibonding MO in the product, the reaction is forbidden.

■ Two Illustrative Cases: The [2 + 2] and [4+2] Cycloadditions

\[
[\pi^2_s + \pi^2_s] \quad \overset{\Delta}{\longrightarrow} \quad [\quad] \quad \overset{\#}{\longrightarrow} \quad \square
\]

\[
[\pi^4_s + \pi^2_s] \quad \overset{\Delta}{\longrightarrow} \quad [\quad] \quad \overset{\#}{\longrightarrow} \quad \text{Hexagon}
\]

To begin, choose an interaction geometry and build the MO's accordingly. In this case we will assume a simple face-to-face geometry in which all the $\pi$ orbitals lie in a single plane.
Correlation Diagram for the Thermal Dimerization of Ethylene

Next, assign whether each MO is symmetric or antisymmetric with respect to the symmetry elements present.

In this case, there are two mirror planes that are present in both the starting materials and the product. These will be called $\sigma_1$ and $\sigma_2$.
Correlation Diagram for the Thermal Dimerization of Ethylene

- Now fill in the electrons starting with the ground state MO. Correlate each orbital of the SM to an orbital of the product that has the same symmetry.

- Conserving orbital symmetry throughout the reaction forms a product in a doubly-excited electronic state.

The energy required to move two electrons from $\sigma_2$ and $\sigma_3^*$ is $\sim 115$ kcal/mol.

The extraordinarily high barrier to this thermal reaction is entirely symmetry-imposed.
Correlation Diagram: 4 + 2 Cycloaddition

- Conserving orbital symmetry throughout the reaction forms a product with all the electrons placed in bonding MO's.

This reaction has no symmetry-imposed barrier.
Correlation Diagram for the Photochemical Dimerization of Ethylene

- Placing a single electron into the first excited state gives a completely different orbital picture.

- The high-energy electron in an antibonding MO can correlate to a bonding MO in the product of like symmetry.

The reaction is now allowed, forming the product in a singly excited electronic state.
Exciting the diene in the Diels-Alder reaction makes this suprafacial reaction forbidden.
A Very General Principle

Using correlation diagrams, Woodward and Hoffmann were able to extend the ideas of symmetry conservation to the other classes of pericyclic reactions. These gave rise to new sets selection rules for each reaction type.

**Concerted Cycloaddition Selection Rules [ m + n ]**

<table>
<thead>
<tr>
<th>m+n</th>
<th>Allowed</th>
<th>Forbidden</th>
</tr>
</thead>
<tbody>
<tr>
<td>4q</td>
<td>s+a or a+s</td>
<td>s+s or a+a</td>
</tr>
<tr>
<td>4q+2</td>
<td>s+s or a+a</td>
<td>s+a or a+s</td>
</tr>
</tbody>
</table>

**Sigmatropic Rearrangement Selection Rules [ m , n ]**

<table>
<thead>
<tr>
<th>m+n</th>
<th>Allowed</th>
<th>Forbidden</th>
</tr>
</thead>
<tbody>
<tr>
<td>4q</td>
<td>s+a or a+s</td>
<td>s+s or a+a</td>
</tr>
<tr>
<td>4q+2</td>
<td>s+s or a+a</td>
<td>s+a or a+s</td>
</tr>
</tbody>
</table>

Thus we can predict that an [ 8 + 6 ] cycloadditions occur suprafacially on each component.

\[
\begin{align*}
8\pi & \quad + \quad 6\pi \\
\xrightarrow{[\pi8_s + \pi8_s]} & \\
& 14 \text{ electrons} \\
& 4(3) + 2 = 14 \\
& s+s \text{ allowed}
\end{align*}
\]

Similarly we can rationalize why [ 1,3 ] suprafacial allylic isomerizations are possible for carbons, but not for protons.

Deuterium labelled carbon undergoes inversion

The hydrogen 1s orbital cannot be inverted
Fukui and the Rise of FMO

A very intuitive (and fully equivalent) understanding of pericyclic selection rules was developed in the mid-1960's by Prof. Kenichi Fukui, a theoretical chemist

Fukui made the observation that in a bimolecular reaction, the transition state can be thought of as a perturbation of the reactants. Two startling conclusions follow from this conceptual approach

1. Building on the work of Salem, Fukui realized the most significant term in the second-order perturbation treatment of a bimolecular reaction is the one corresponding to the interaction of filled orbitals on one component with empty orbitals of the other.

2. The magnitude of the interaction between the orbitals varies inversely as the difference in energy between them.

As a result of the second rule, it can clearly be seen why HOMO-LUMO interactions are so successful in describing the outcomes of bimolecular pericyclic reactions where the reaction partners are highly symmetric

Fukui, K. Nobel Lecture, Stockholm, 1981
Applications of FMO to Pericyclic Reactions

- FMO analysis can make quick work of results that are difficult to rationalize otherwise.

- For example, why are early transient metal alkylidenes able to undergo facile 2 + 2 cycloadditions with olefins, while for other olefins this is a disallowed process?

  ![Diagram of FMO analysis](image)

  FMO analysis is not limited to organic π orbitals. Any molecular system can be analyzed!

- Ketene - Olefin Cycloadditions: Violation of the Woodward-Hoffmann Rules?

  ![Diagram of ketene and olefin reaction](image)

- The HOMO of the olefin actually interacts with orthogonal lobes of the LUMO orbitals, a $\pi^2s + \pi^2s$ cycloaddition!
**Broken Symmetry**

- Correlation diagrams and FMO analysis are powerful and intuitive ideas but each relies heavily on symmetry.

- In cases where there is no symmetry, correlation diagrams are difficult to construct and interpret. Yet this does not mean that the forbidden reactions become allowed, or that stereospecific reactions become less so.

- The most obvious restriction of the FMO model is that one must know the shapes of the orbitals in question. While this is easy for small, symmetrical molecules it requires calculations for larger, less symmetric ones.

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**The Non-Crossing Rule**

In a state diagram, states of like symmetry cannot cross, rather they mix and then diverge to correlate with lower energy states.

This phenomenon is known as an avoided crossing and creates a high kinetic barrier for forbidden paths.

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Benzofuran

HOMO

LUMO
A Different Take on Things: Aromatic and Anti-Aromatic Transition States

In 1939, theoretician W.G. Evans put forth the idea that in the transition state for a Diels-Alder reaction, the electrons are completely delocalized to form a continuous circuit, much like the \( \pi \) electrons of benzene.

Therefore he argued that these transition state have "aromatic" character and should thus be stabilized in a way analogous to the resonance stabilization of ground state aromatic molecules.

![Diels-Alder reaction](image)

Evans calculated the resonance stabilization of the Diels-Alder TS to be \( \sim 18 \text{ kcal/mol} \) compared to \( \sim 36 \) for benzene.

Analogously, reactions which involve cyclic arrays of \( 4n \) electrons are antiaromatic and should be destabilized in a similar way to cyclobutadiene.

![Cyclobutadiene reaction](image)

To use this idea of aromatic TS's in a general way, we must first give ourselves a broader definition of aromaticity.

Dewar, M.J.S., *ACIEE*, 1971, 10, 761

Huckel and Mobius Transition State Topologies

Imagine that the electrons involved in a transition state form a continuous circuit. It is possible to connect every orbital on the ring without ever crossing the plane of the $\sigma$ framework. Flipping the sign of a single $p$ orbital introduces two phase inversions. Flipping two orbitals gives four phase inversions.

Even # of Phase Inversions: Huckel Topology

However, the circuit of electrons does not have to stay on the top side of the ring. It is also possible for an orbital lobe on top of the $\sigma$ framework to interact with a lobe below. This is equivalent to putting a twist into the loop.

Odd # of Phase Inversions: Mobius Topology

Do not count phase inversions within an orbital!

Lowry, T.H., Richardson, K.S. Mechanism and Theory in Organic Chemistry, Chap. 10
Dewar-Zimmerman Analysis

Dewar and Zimmerman went on to generalize this principle for all classes of pericyclic reactions. The basic premise is that a process is allowed if it proceeds through an aromatic transition state and is forbidden if it does not.

Rules for Using Dewar-Zimmerman Approach

1. Choose a basis set of orbitals for all the atoms involved.
2. Arbitrarily assign phases to the orbitals. These phases do not need to correspond to any real MO.
3. Connect the orbitals that interact in the starting material prior the beginning of the reaction.
4. Predict a geometry for the reaction to follow (i.e. suprafacial, conrotatory, etc.) and connect the lobes that begin to interact in the transition state.
5. Count the number of phase inversions that occur as the reaction progressed. (Phase inversion within an orbital is not counted!)

Use the number of phase inversions to calculate the topology of the transition state

Even # of phase inversions: Huckel topology

Odd # of phase inversions: Mobius topology

Then apply the following selection rules

<table>
<thead>
<tr>
<th>Topology</th>
<th>Aromatic</th>
<th>Antiaromatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huckel</td>
<td>4n+2</td>
<td>4n</td>
</tr>
<tr>
<td>Mobius</td>
<td>4n</td>
<td>4n+2</td>
</tr>
</tbody>
</table>

Dewar, M.J.S., ACIEE, 1971, 10, 761
Evans Notes - Electrocyclic Reactions
Dewar-Zimmerman Analysis in Sigmatropic Rearrangements

- Examination of transition states for both suprafacial and antarafacial [1,3] migrations

**[1,3] suprafacial shift**

Prior to reaction

Transition State

2 Phase Inversions
Hückel Topology
4 Electrons
Thermally Forbidden

**[1,3] antarafacial shift**

Prior to reaction

Transition State

3 Phase Inversions
Mobius Topology
4 Electrons
Thermally Allowed

- While the [1,3] antarafacial shift is allowed, the transition state is so strained that it is rarely ever observed
Dewar-Zimmerman Analysis: More Difficult Cases

- [1,2] hydride suprafacial shift

  Cationic Case

  Transition State

  Anionic Case

  Transition State

  Stereochemical course of [1,7] hydride migration

  Suprafacial Migration

  Antarafacial Migration

  0 Phase Inversions
  Huckel Topology

  8 Electrons
  Thermally Forbidden

  1 Phase Inversions
  Mobius Topology

  8 Electrons
  Thermally Allowed

The hardest part about using this method is understanding why it works!
Modern Perspectives on Pericyclic Transition States

- More than 40 years after the annunciation of the Woodward-Hoffmann rules, the transition state structures for pericyclic reactions are still being investigated. So, with all our present advantages, what are the dominant views on pericyclic transition state structures?

- The hydrocarbon Diels-Alder Reaction

- In the activated case the bond forming steps are no longer synchronous, but the reaction is still considered to be a concerted process

- However, in Lewis acid catalyzed version of the above reaction, high-level calculations have found appreciable charge separation and only a single bond is thought to be formed in the transition state i.e. the reaction may occur stepwise

Transition State of the Claisen Rearrangement

The transition state structures for 3,3 sigmatropic rearrangements were debated for decades.

For the aliphatic Claisen rearrangement, three limiting possibilities exist.

Gajewski and Conrad devised a set of experiments to determine how isotopic substitution effects the rate of the Claisen

Key Assumptions

1. Substitution at C(4) will affect the rate of bond-breaking
2. Substitution at C(6) will affect the rate of bond-making
3. EIE's represent the largest possible 2° KIE

\[
\text{BBKIE} = \frac{\text{KIE (C4) - 1}}{\text{EIE (C4) - 1}} = \frac{1.092 - 1.0}{1.27 - 1.0} = 0.33
\]

\[
\text{BMKIE} = \frac{\text{KIE (C6) - 1}}{\text{EIE (C6) - 1}} = \frac{0.976 - 1.0}{0.84 - 1.0} = 0.15
\]

Bond breaking is more advanced at the TS than bond making

Gajewski, J, Conrad, N. JACS 1979, 101, 2747
**Remarkable Substituent Effects in the Oxy-Cope**

- Gajewski and coworkers also used this method to analyze a variety of Cope reactions.
- Cope rearrangements of substituted hexadienes show drastic variation in rate. It's postulated that the substituents are able to change the nature of the TS.

![Diagram showing chemical structures and reaction paths]

Different substitution can alter the nature of the TS structure

Gajewski, J, Conrad, N. *JACS* 1979, 101, 6693
Remarkable Substituent Effects in the Oxy-Cope

■ In 1975 Evans and coworkers found that the anionically charged version of the oxy-cope reaction was dramatically faster than the parent reaction.

\[
\begin{align*}
\text{parent reaction} & \quad \text{anionically charged reaction} \\
\text{BDE} = 90.7 & \quad \text{BDE} = 74.2 \\
\end{align*}
\]

\[
\text{K}_{\text{rel}} = 1 \times 10^{17} \quad \Delta \Delta G^{\ddagger} = 15 \text{ kcal/mol}
\]

Evans, D.A., Golob, A.M. JACS, 1975, 97, 4765

■ The root of this phenomenon lies in the ability of the anion to captodatively stabilize radical character on the adjacent carbon. This suggests some radical character in the transition state.

Anionic charge causes a dramatic weakening of the adjacent bond

■ This bond weakening is a general phenomenon and can be applied to accelerate other pericyclic processes

The Woodward-Corey-Hoffmann Rules?

■ In his Priestly Medal address in 2004 E.J. Corey made public a claim that he had made privately for years. He contends that in May of 1964 he proposed the idea that the symmetry of the HOMO controls the stereochemical outcome of electrocyclic reactions to Woodward, and that Woodward essentially claimed the idea as his own.

■ However, by this time this story became a public matter, Woodward had been deceased for nearly 25 years. There was no way hear his side of the events, to either verify or dismiss the allegations.

■ Hoffmann has written an open letter rejecting Corey's claim. He describes in detail a personal correspondence he has carried on with Corey about the subject for nearly 25 years. He purports that he had no knowledge of Corey ever making such a suggestion to Woodward and never that Woodward himself never gave any indication of such an event occurring.

■ Perhaps only history will tell what the true sequence of events was and who first realized what became a Nobel-prize winning set of ideas.

Corey, E.J. JOC, 2004, 69, 2917
Hoffmann, R. ACIEE, 2005, 43, 6586
The Oosterhoff-Havinga Rules?

Prof. Havinga (Univ. of Leiden) was the preeminent reseacher in the Vitamin D field, publishing many papers on the photoisomerization and interconversion of the vitamin D precursors in the early 1960’s.

In 1961 he correctly realized that the stereochemical course of \(6\pi\) cyclizations was opposite in the case of the thermal and photochemical reactions

![Diagram showing the stereochemical course of 6\(\pi\) cyclizations.]

Ergosterol and tachysterol undergo 6\(\pi\) conrotatory cyclization, while isopyrocalciferol undergoes 6\(\pi\) disrotatory cyclization.

To explain the stereochemical outcome of these reactions, Prof. Havinga refers to a suggestion by a colleague, L.J. Oosterhoff, a noted physical organic chemist.

"As Prof. Oosterhoff pointed out, another factor that possibly contributes to the stereochemical difference between the thermal and photo induced ring closure may be found in the symmetry characteristics of the highest occupied \(\pi\) orbital of the conjugated hexatriene system. In the photo excited state this highest occupied orbital is antisymmetric with regard to the plane that is perpendicular to the bond, making syn approach less favourable."

Oosterhoff and Havinga had found the correct answer to the problem of electrocyclic reactivity four full years before Woodward and Hoffmann, but they never went on to generalize their results and the notion received very little currency.

Havinga, E. et al *Tetrahedron*, 1961, 16, 146
Orbital Symmetry and the Prediction of Organic Reactivity

- Orbital symmetry arguments provide simple but powerful avenue for the analysis of concerted processes.

- The success of a variety of different formulations of the same idea hint that truly fundamental forces are at work.

- These developments are extremely important historically, as they really opened up organic chemists to thinking about chemistry in terms of MO's. Computational chemistry is now indispensable to the field, and grows more so all the time.

The lack of numbers in our discussion is not a weakness - it is its greatest strength

- R.B. Woodward