CHEM 6352 Organic Reactions & Synthesis
Electrocyclic Reactions

Introduction[1-3]:

Molecular orbitals are constructed as combinations of atomic orbitals and are then populated by electrons. Two equivalent atomic orbitals, x_1 and x_2, can combine and yield a bonding combination and a corresponding antibonding orbital (**Figure 1**). In this case, bond formation and breaking can be interpreted as interactions of orbitals and electrons.

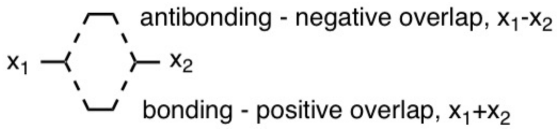


Figure 1 Combination of orbitals

Based on these fundamental orbital and bonding theories, we can define an electrocyclic reaction as the formation of a single bond between the termini of a linear system containing **m** π electrons as well as the converse process. (**Figure 2**)

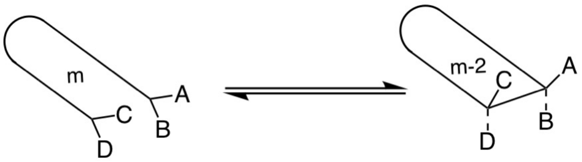


Figure 2 Electrocyclic reaction

If all four substituents at the termini of this polyene in **Figure 2** are different, we will have to take geometry into consideration when we turn the p orbitals in the π bonds of that polyene into a σ bond. As it says in the Nobel Prize winning book, The Conservation of Orbital Symmetry, "In such changes fixed geometrical isomerism imposed up the open-chain system is related to rigid tetrahedral isomerism in the cyclic array." (**Figure 3**)

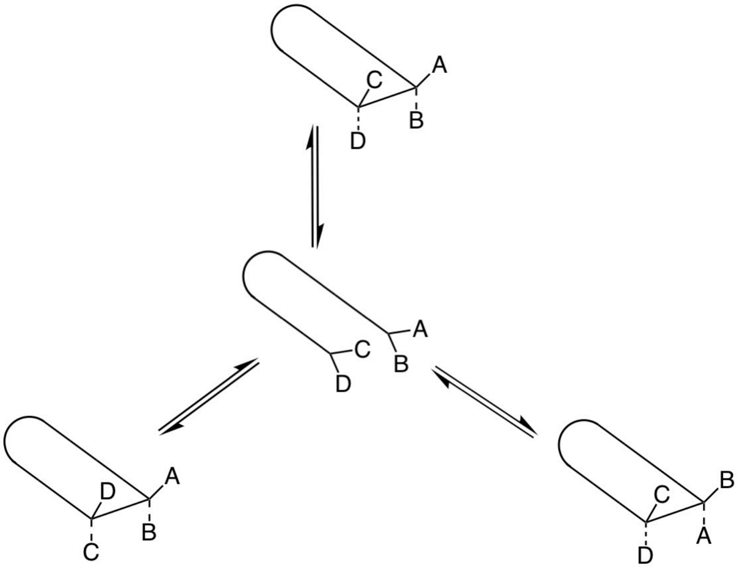


Figure 3 Potential isomerism in electrocyclic reaction

Will the p orbitals rotate in the same direction? How can we determine in which way this reaction is going to happen with a real molecule? Is there any rule we can follow? Before answering these questions, we shall introduce some new terminology to help us describe how p orbitals at the termini of a π system rotate.

If the two p orbitals rotate in the same direction, which could be both clockwise or both counterclockwise, this process is termed **conrotatory**. If they rotate in opposite directions, one clockwise and one counterclockwise, the process is termed **disrotatory**. (**Figure 4**)

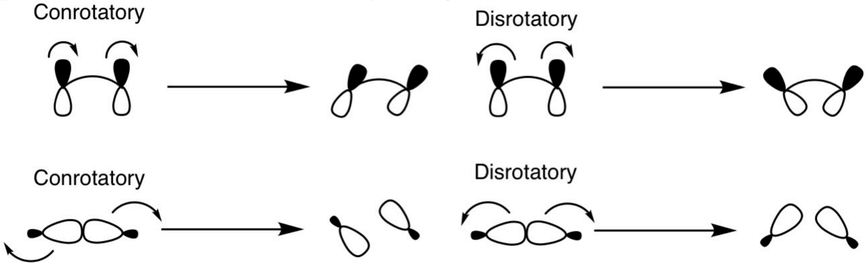
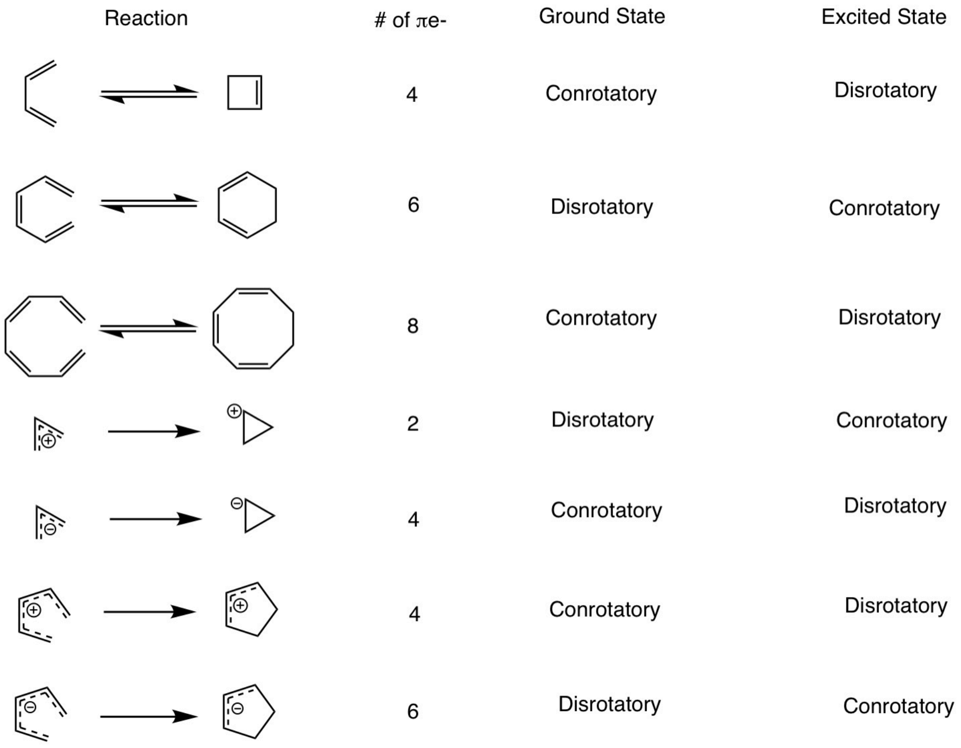


Figure 4 Conrotatory and disrotatory processes

The general rules for electrocyclic reactions are very easily derivable from the nodal properties of polyenes and polyenyl ions: the thermal electrocyclic reactions (from the ground state) of a **m** π electron system will be disrotatory for **m** = 4**n**+2, conrotatory for **m** = 4**n** (n = 0, 1, 2…); in the first excited state (photoactivation) these relationships will be disrotatory for **m** = 4**n**, conrotatory for **m** = 4**n**+2. Here are some examples to help you take a better look at the consequences of these rules. (**Figure 5**)



Reaction	# of πe-	Ground State	Excited State
	4	Conrotatory	Disrotatory
	6	Disrotatory	Conrotatory
	8	Conrotatory	Disrotatory
	2	Disrotatory	Conrotatory
	4	Conrotatory	Disrotatory
	4	Conrotatory	Disrotatory
	6	Disrotatory	Conrotatory

Figure 5 General rules exemplified

Now we can choose whether conrotatory or disrotatory rotation is preferred in a polyene/polyenyl ion system based on orbital symmetry. However, even when we can decide whether the reaction is “conrotatory” or “disrotatory”, the reaction can still proceed in two “directions”. In many systems, this gives two different products. In Woodward and Hoffmann’s time, scientists had already noticed this phenomenon in studying the opening of cis-dimethylcyclobutene. The two inverted modes of opening of a cis-dimethylcyclobutene are enantiomeric and lead to the same product, cis,trans-1,4-dimethylbutadiene. (**Figure 6**)

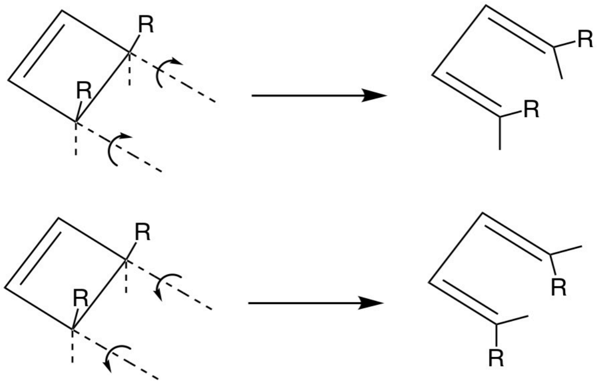


Figure 6 Conrotatory opening of cis-dimethylcyclobutene

The two conrotatory motions for a trans-dimethylcyclobutene lead to two different isomers: *cis*,*cis*- and *tran*,*trans*-1,4-dimethylbutadiene. (**Figure 7**) In fact, the *trans*,*trans*- product is found exclusively, so we can intuitively attribute this to the unfavorable steric interactions in the transition state leading to the *cis*,*cis*-product.

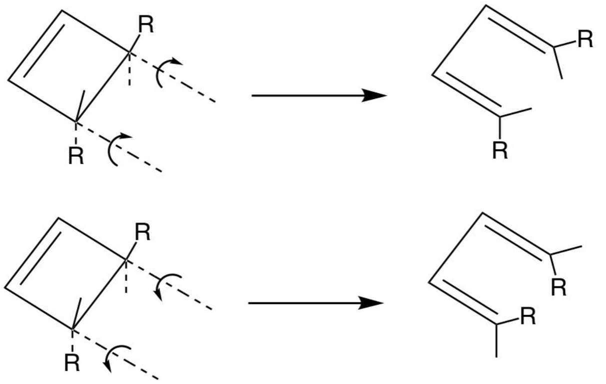


Figure 7 Conrotatory opening of trans-dimethylcyclobutene

Early observations were interpreted in terms of steric interactions, and results matched with this interpretation (**A** and **B** in **Figure 8**). However, further study revealed some intriguing non-steric effects (**C** and **D** in **Figure 8**).

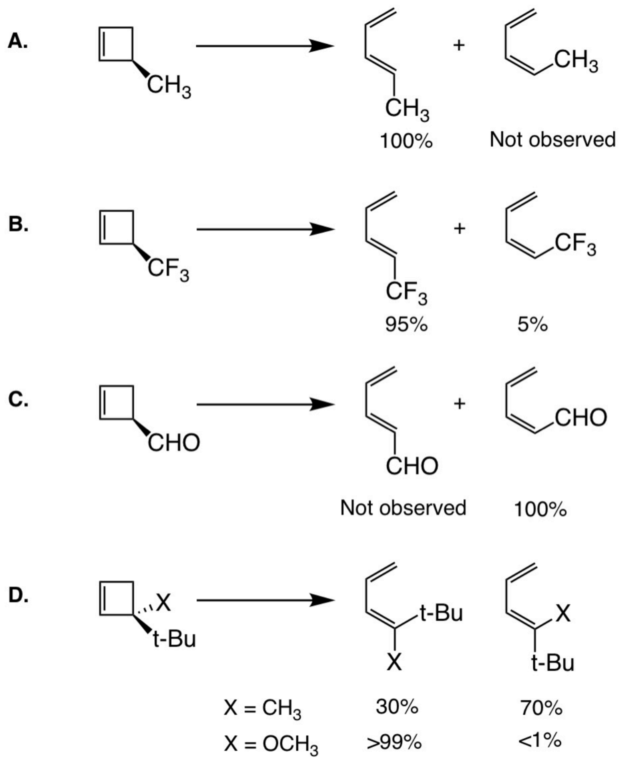


Figure 8 Selectivity in thermal electrocyclic openings

Dolbier, Houk, and co-workers developed a model for these systems that explains the reactivity trends and also rationalizes the stereochemical issue discussed. A new term, "**torquoselectivity**", was created to describe these rotational preferences as described briefly in **Figure 9**.

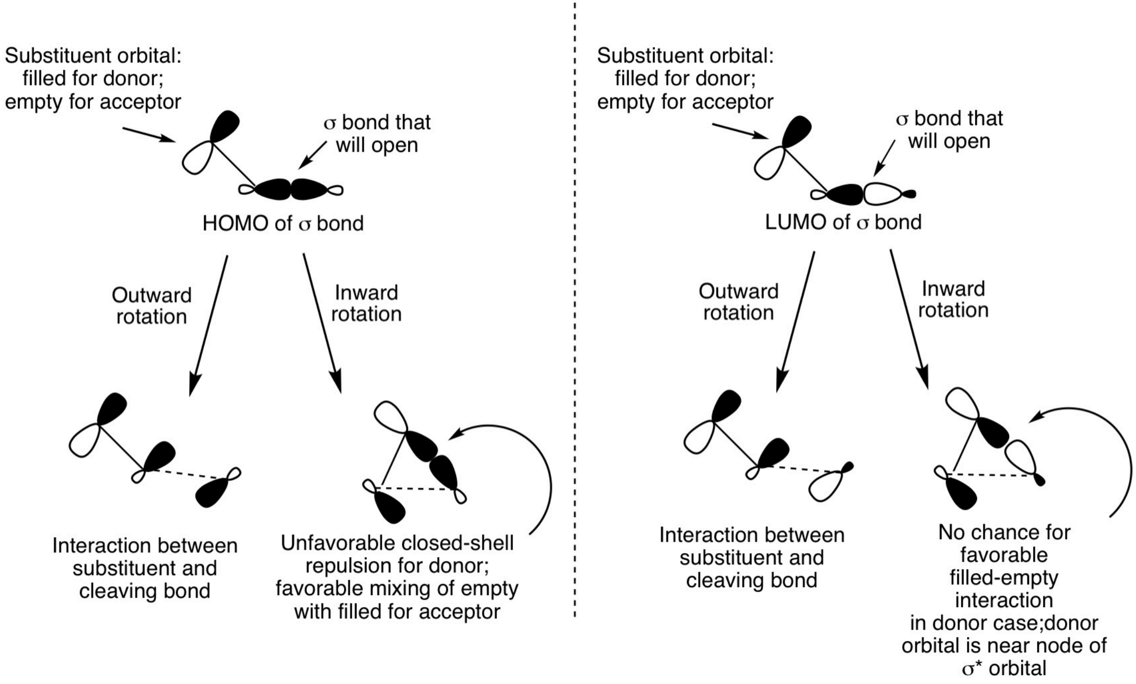


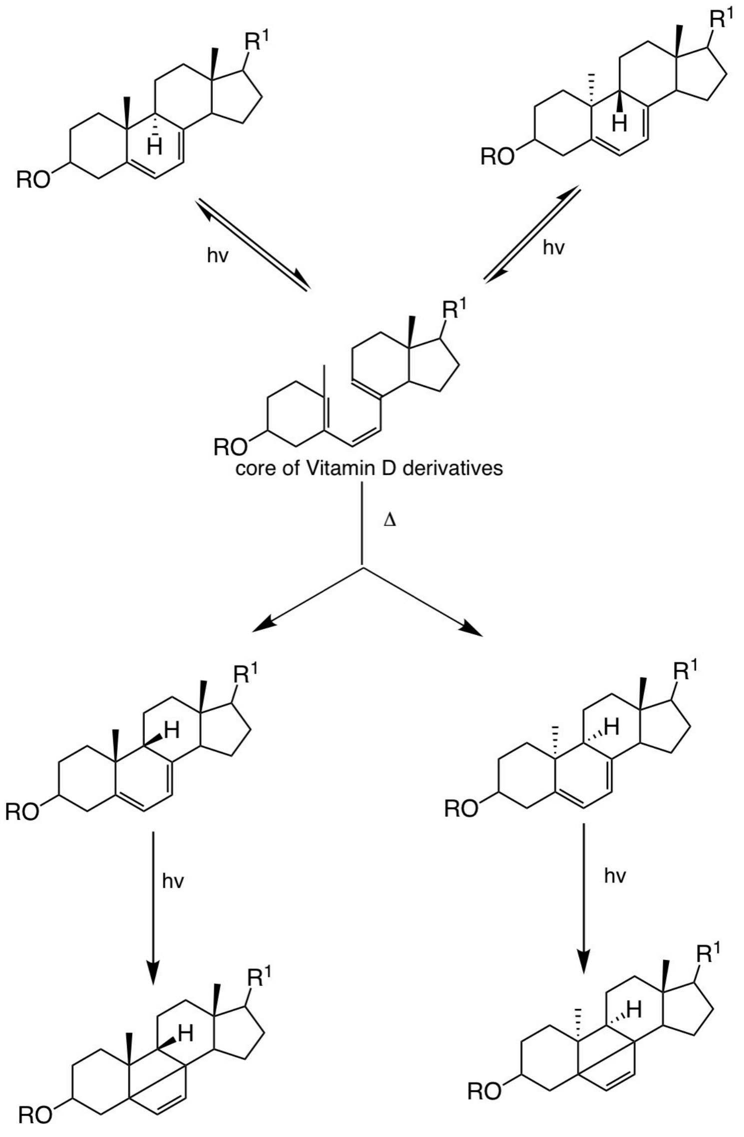
Figure 9 Orbital interactions explaining inward or outward rotation

In summary, orbital symmetry provides us with the basic rules to predict the product of electrocyclic reactions. We also need to consider a substituent's effect on electrocyclic ring-opening. Inward rotation is favored with donors; outward rotation is favored with strong acceptors. For substituents that are somewhat in between π donor and acceptor ability, or when two donors compete, mixed results are observed.

Synthetic Applications of Electrocyclic Reactions[1,4,5]:

A. Vitamin D and its derivatives.

The symmetry-allowed photochemical conrotatory cyclizations of cis-hexatrienes, and the reverse reactions, were first recognized in studies related to vitamin D.



B. Nazarov cyclization (name reaction):

The protic or Lewis acid catalyzed ring-closure of divinyl ketones (and their acid-labile precursors) via pentadienylic cations is known as the *Nazarov cyclization*.

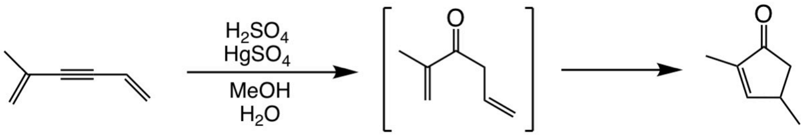


Figure 10 The original reaction studied by Nazarov

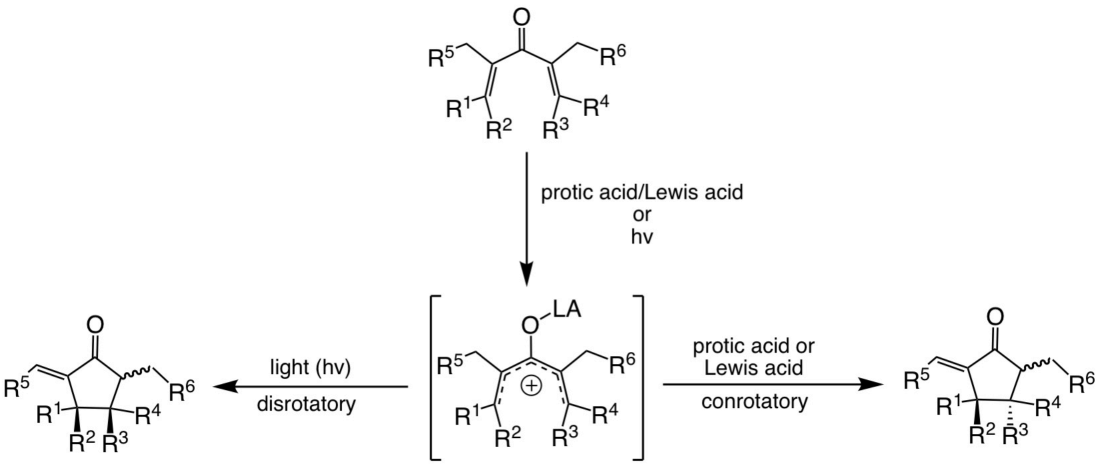


Figure 11 General scheme for thermal and photochemical Nazarov cyclization

C. Endiandric Acids A-D:

This work was done by K. C. Nicolaou in 1982. Endiandric acids D-G have similar structures, and endiandric acids E-G are also precursors of endiandric acids A-C. This strategy makes the full use of electrocyclization and cycloaddition reactions.

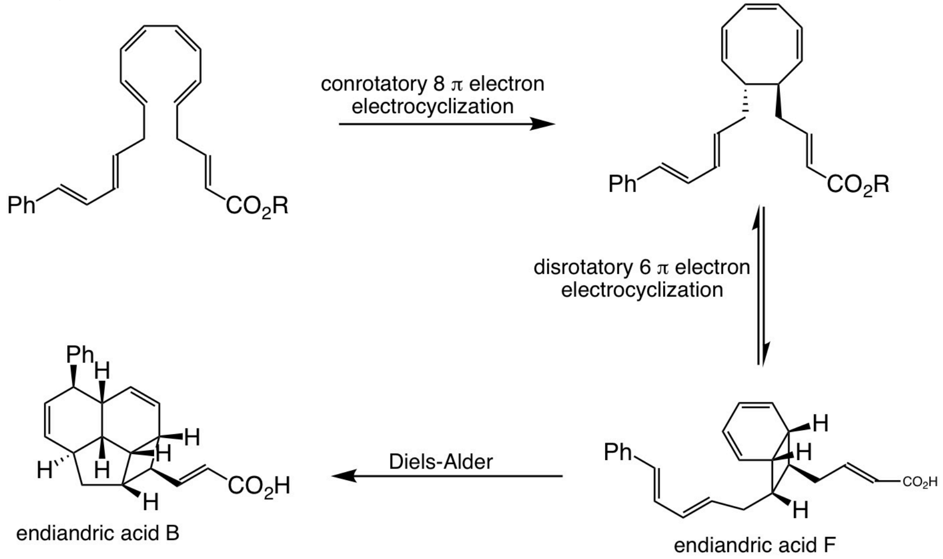


Figure 12 The endiandric acid cascade (use only B and F as example)

It is worth noting that the principles of Orbital Symmetry discussed are also applicable to other pericyclic reactions such as sigmatropic rearrangements and cycloadditions.

References:

[1] The Conservation of Orbital Symmetry; R. B. Woodward, R. Hoffmann, Verlag Chemie Academic Press, 1970, Chapter 1-5

[2] Modern Physical Organic Chemistry; Eric V. Anslyn, Dennis A. Dougherty, University Science Books, 2006, pp903-910

[3] The Art of Writing Reasonable Organic Reaction Mechanisms; Robert B. Grossman, Springer New York, 2003, Chapter 4

[4] Strategic Applications of Named Reactions in Organic Synthesis; Laszlo Kurti, Barbara Czako, Elsevier Inc., 2005, pp304-305

[5] Classics in Total Synthesis I, K. C. Nicolaou, E. J. Sorensen, VCH Publisers, Inc., 1996, Chapter 17

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