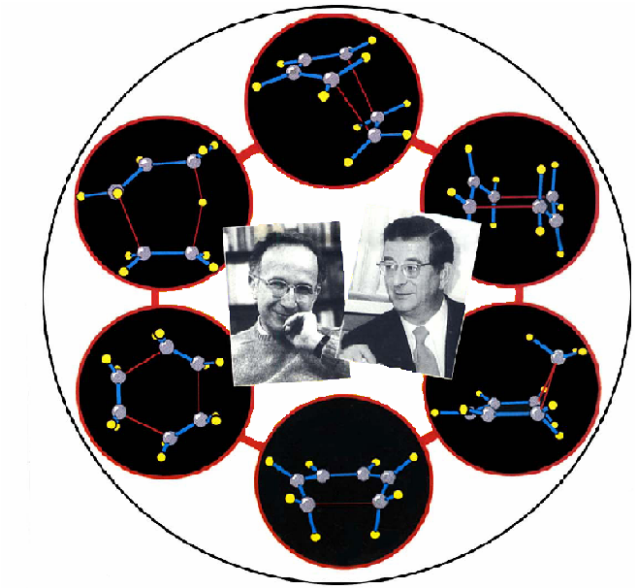
Work in Progress

25.01.08

Heuristic chemistry

An approach to a new perspective on organic reactions



Nicole Graulich

AG Schreiner

Contents

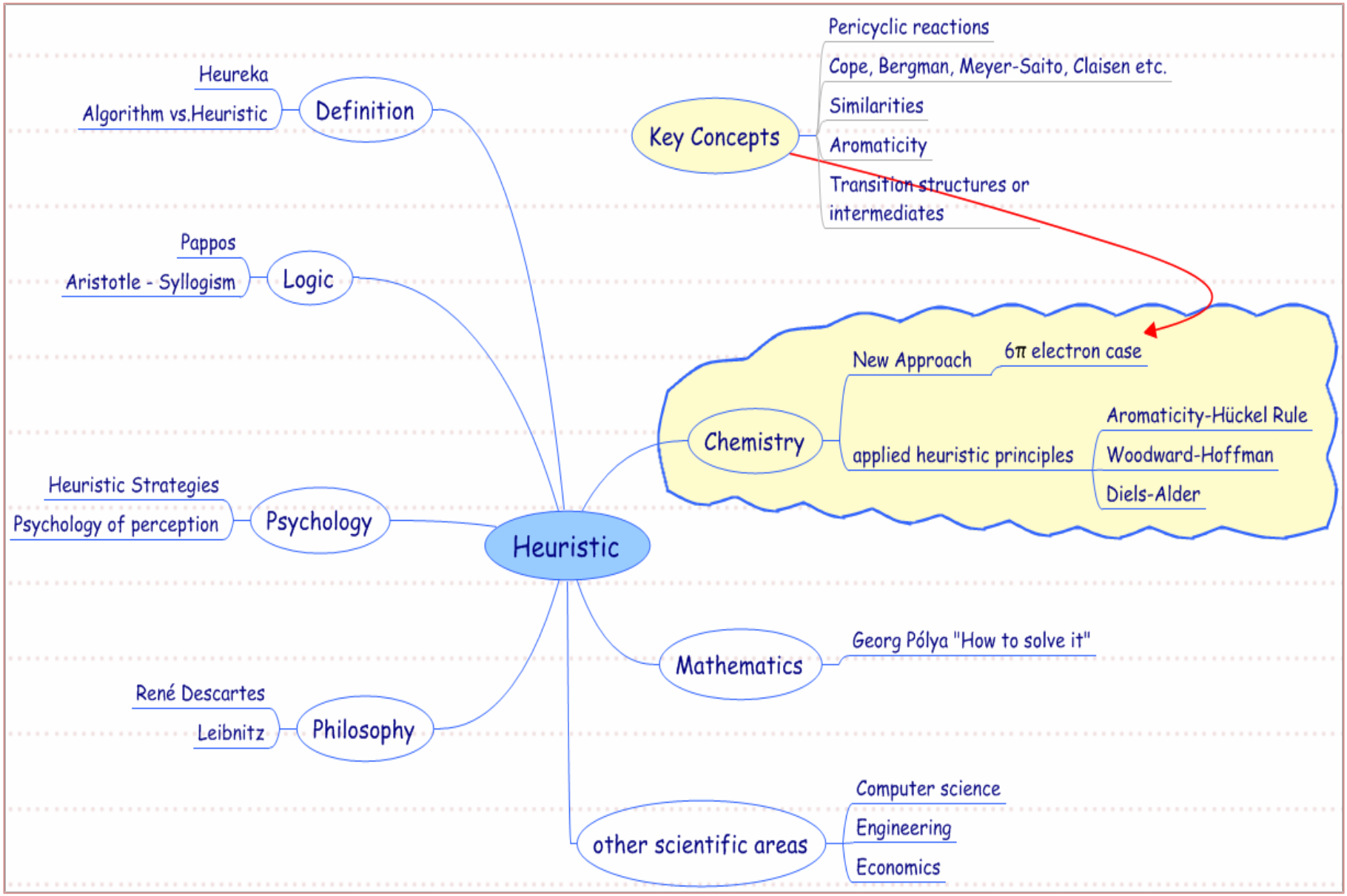
- Introduction about heuristic
- Heuristics in sciences
- The 6π electron case
- Summary and outlook

Titelbild: Cover Picture, *Angew. Chem. Int. Ed. Engl*. 1992, *6*.

What is a heuristic?

- "heuristic" (greek) meaning "serving to find out or discover"
- "rules of thumb", not to be compared with algorithm
- Strategies readily available to solve problems and to create new theories
- Information to lead problem-solving in human reasoning
- With simple heuristics individuals are able to make useful decisions and solve problems in a shorter time, with less knowledge and efforts.

L. Müssler, W. Prinz, *Allgemeine Psychologie*, Spektrum akademischer Verlag, Heidelberg 2002.
J. Funke, *Problemlösendes Denken*, Kohlhammer, Stuttgart 2003.


Heuristic
Definition
Heureka
Algorithm vs.Heuristic
Logic
Pappos
Aristotle - Syllogism
Psychology
Heuristic Strategies
Psychology of perception
Philosophy
René Descartes
Leibnitz
Mathematics
Georg Pólya "How to solve it"
other scientific areas
Computer science
Engineering
Economics
Chemistry
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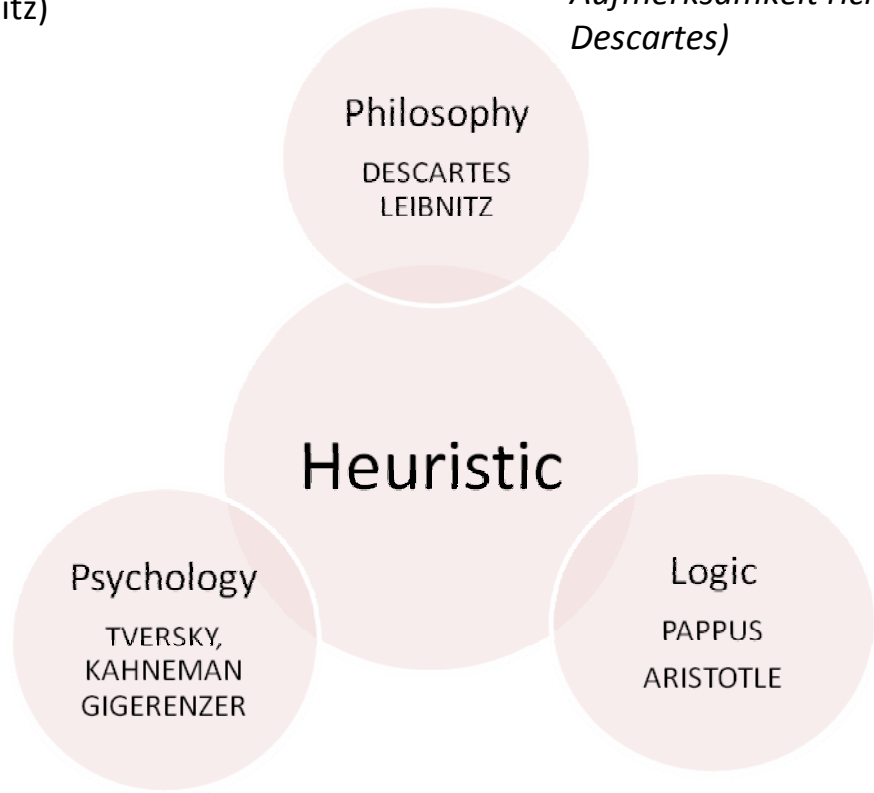
6π electron case
applied heuristic principles
Aromaticity-Hückel Rule
Woodward-Hoffman
Diels-Alder
Key Concepts
Pericyclic reactions
Cope, Bergman, Meyer-Saito, Claisen etc.
Similarities
Aromaticity
Transition structures or intermediates

„Nichts ist wichtiger als die Quellen des Erfindens zu sehen, die meiner Meinung nach interessanter sind, als die Erfindung selbst“ (Leibnitz)

Regel V: *„Die Methode besteht gänzlich in der angemessenen Anordnung und Disposition der Dinge, auf die wir unsere Aufmerksamkeit richten sollen.“(R. Descartes)*



„Heuristic as a cognitive process to judge probabilities of events.[…] But features given in the presentation of the probability and informations retrieved from the memory influence the response and induce bias.” (Kahneman, Tversky)

All men are mortal.
Socrates is a man.
Socrates is mortal.
(Syllogism)

D. Kahneman, A. Tversky, *Judgement under uncertainty – heuristics and biases*, Cambridge university press, Cambridge 1982.
G. Gigerenzer, P. M. Todd, *Simple heuristics that makes us smart*, Oxford University Press, Oxford 1999.
R. Descartes, *Regeln zur Ausrichtung der Erkenntniskraft*, übers. von Lüder Gäbe, Felix Meiner Verlag, Hamburg 1972.

Heuristic in mathematics

- Georg Pólya „How to solve it“ (hungarian mathematician)
- Pólya’s definition of heuristic methods: „reasoning not regarded as final and strict but as provisional and plausible only, whose purpose is to discover the solution of the present problem“

Rules for solving problems by G. Pólya

⇨If you are having difficulty understanding a problem, try drawing a picture.

⇨If you can't find a solution, try assuming that you have a solution and seeing what you can derive from that ("working backward").

⇨If the problem is abstract, try examining a concrete example.

⇨Try solving a more general problem first (the "inventor's paradox": the more ambitious plan may have more chances of success).

G. Pólya, *How To Solve It: A New Aspect of Mathematical Method*, Princeton University Press, Princeton 1945.
J. Baron, *Thinking and Deciding*, Cambridge University Press, New York 2000.
http://www-gap.dcs.st-and.ac.uk/~history/PictDisplay/Polya.html

Heuristic principles in organic chemistry

- Aromaticity - Hückel rule (4n+2)

- Woodward-Hoffmann rules

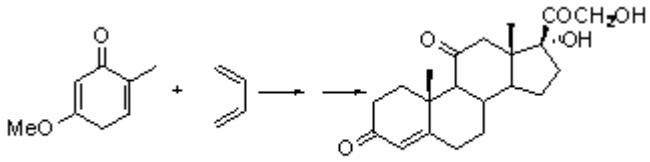
„Wenn eine neue Theorie nicht nur dieses entscheidende Experiment rational deutet, sondern aufgrund durchsichtiger Extrapolation andere, überraschende, der Intuition nicht zugängliche, aber leicht zu verifizierende experimentelle Ergebnisse vorhersagt, dann wird Wissenschaft zum ästhetischen Vergnügen und zur intellektuellen Genugtuung“ (Woodward/Hoffmann)

- Diels-Alder reaction

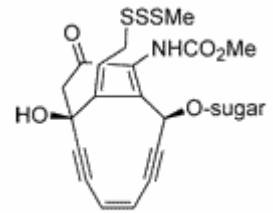
- ...

E. Hückel, *Z. Physik*, **1931**, *70*, 204.
R. Hoffmann , R. B. Woodward, *Chemie in unserer Zeit*, **1972**, *6*, 167-74.

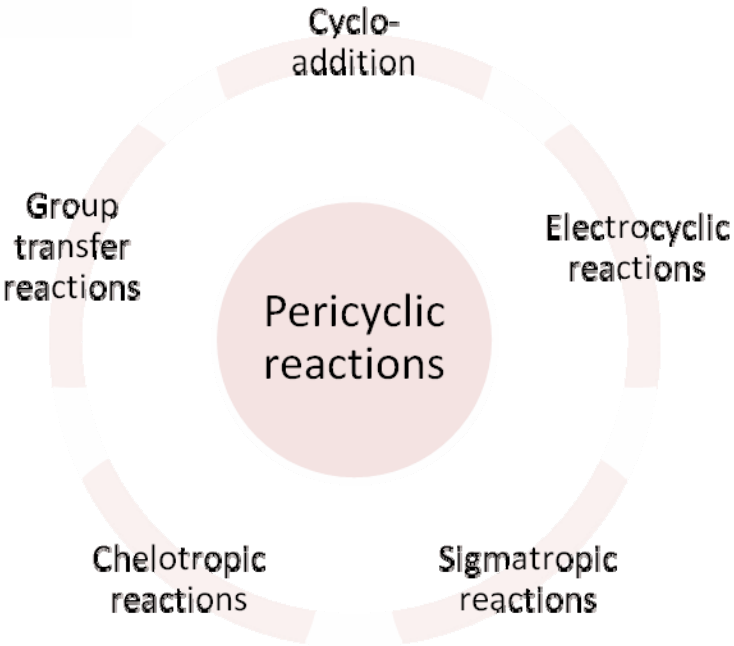
Pericyclic reactions – the 6π electron case

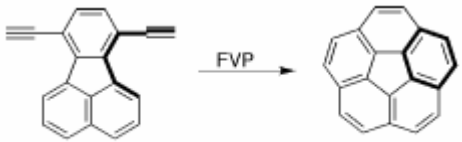


Cortison

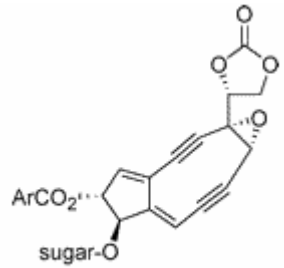


Calicheamicin





Corannulene

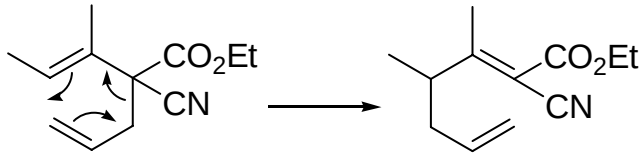


Neocarzinostatin

M. Prall, A. Krüger, P. R. Schreiner, H. Hopf, *Chem. Eur. J.* **2001**, *7*, 4386-4394.
R. B. Woodward et al., *J. Am. Chem. Soc.* **1952**, *74*, 4223-4251.

Cope rearrangement 1940

- "…structural changes similar to those occuring in the familiar Claisen rearrangement of allyl phenol, enol and vinyl ethers."



- With the development of the Hückel rule and the contributions of Evans, they considered an aromatic transition state for the Cope rearrangement.

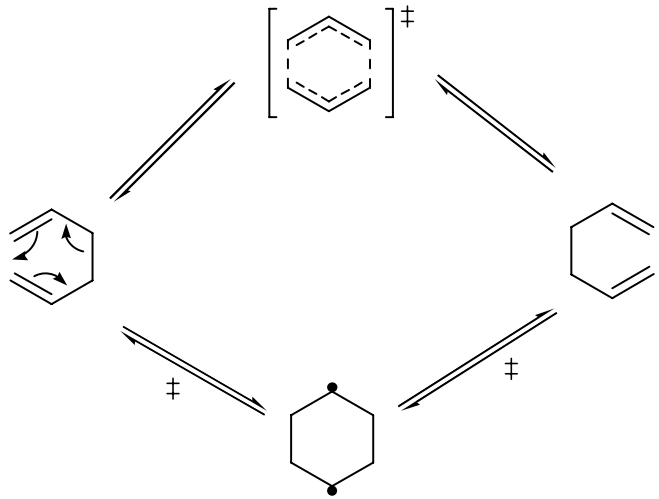
- "…consequently a cyclic mechanism is regarded as probable."

A. C. Cope, E. M. Hardy, *J. Am. Chem. Soc.*, **1940**, *62,* 441-444.
A. C. Cope, K. E. Hoyle, D. Heyl, *J. Am. Chem. Soc.*, **1940**, *63*, 1843-1852.

Mechanistic discussion I

- Grob, Schlink, Schies, and Doering, Roth suggested independently (20 years after Cope) a non-concerted way and a diradical intermediate as a mechanistic alternative to the concerted mechanism.

- Copes proposal of a synchronous transition state akin to an aromatic state has been accepted for a long time.

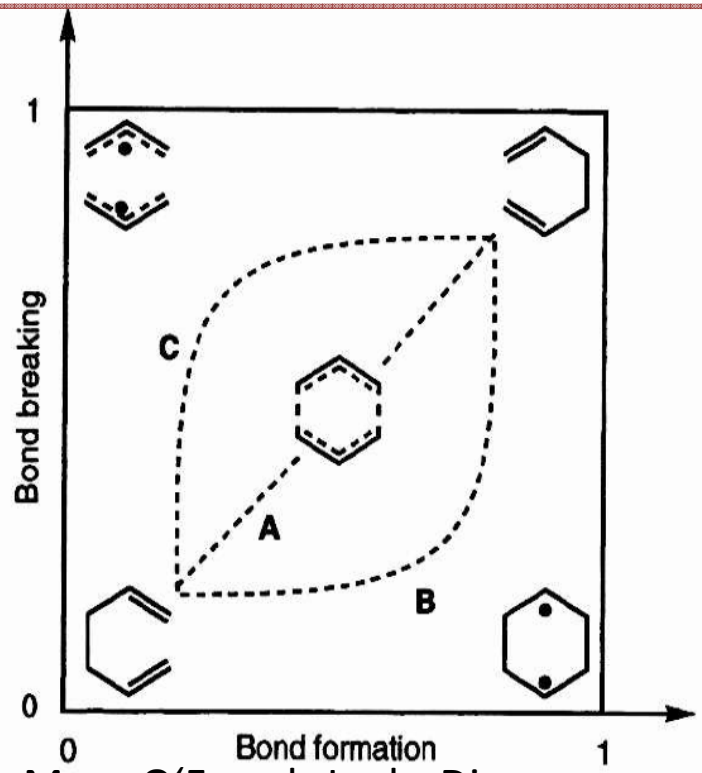


C. A. Grob, H. Link, P. W. Schiess, *Helv. Chem. Acta*, **1963**, *51*, 483-492.
W. von E. Doering, W. R. Roth, *Tetrahedron*, **1962**, *18*, 67-75.

Mechanistic discussion II

A: concerted mechanism
B: biradical mechanism (bond formation before bond breaking)
C: biradical mechanism (bond breaking before bond formation)

$\Delta H°_f \approx 55$ kcal/mole for the rate determing transition state diradical
$\Delta H°_f \approx 77$ kcal/mole for the allylic diradical



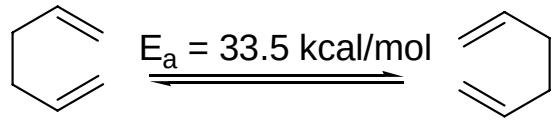
More O'Ferral- Jenks Diagramm

⇨ Studies on the dissociation of the 3,4-bond into a pair of allylic radicals failed, because no predicted cross-products of the recombination have been observed.

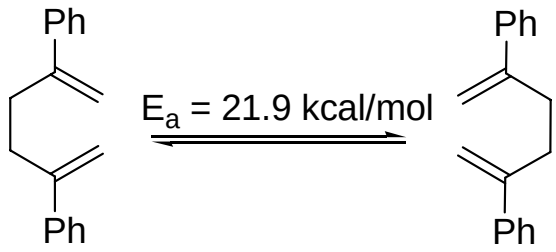
W. von E. Doering, W. R. Roth, *Angew. Chem.*, **1963**, *1*, 27-35.
W. von E. Doering, V. G. Toscano, G. H. Beasley, *Tetrahedron*, **1971**, *27*, 5299-5306.

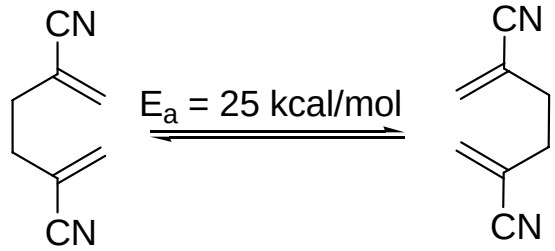
Concerted or non concerted Cope reaction?

- Wehrli et al. and Dewar, Wade explored the influence of radical-stabilizing substituents such as cyano or phenyl in the 2- and 5-position of the Cope rearrangement.



- The rearrangement appears to be responsive to radical stabilizing substituents.

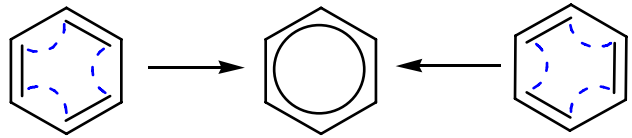




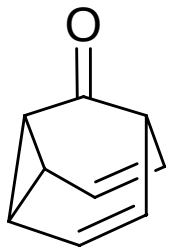
R. Wehrli, H. Schmid, D. Bellus, H.-J. Hansen, *Helv.* **1977**, *60*, 4, 1325-1356.
M. J. S. Dewar, L. E. Wade, *J. Am. Chem. Soc.* **1977**, 4417-4424.

Developments in the seventies

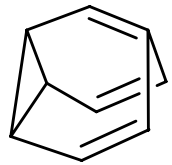
- "Symmetry-allowed reactions, though electronically favored, still proceed with sizable activations energies. Only the class of cyclopolyenes achieve a negative activation energy."
- "...benzene is the transition state for the symmetry-allowed $_{\pi}2_s + _{\pi}2_s + _{\pi}2_s$ cycloaddition in a cyclohexatriene"



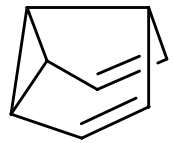
- "How can other structures be brought to such a stage of perfection???"
- Barbaralone, Semibullvalene (undergo degenerate Cope rearrangement)



Barbaralone
E_a = 9.3 kcal/mol



Bullvalene
E_a = 12.8 kcal/mol

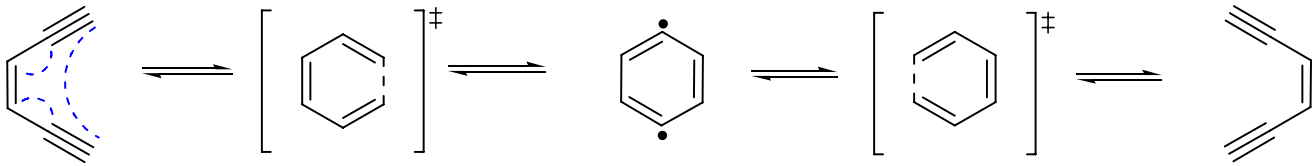


Semibullvalene
E_a = 6.4 kcal/mol

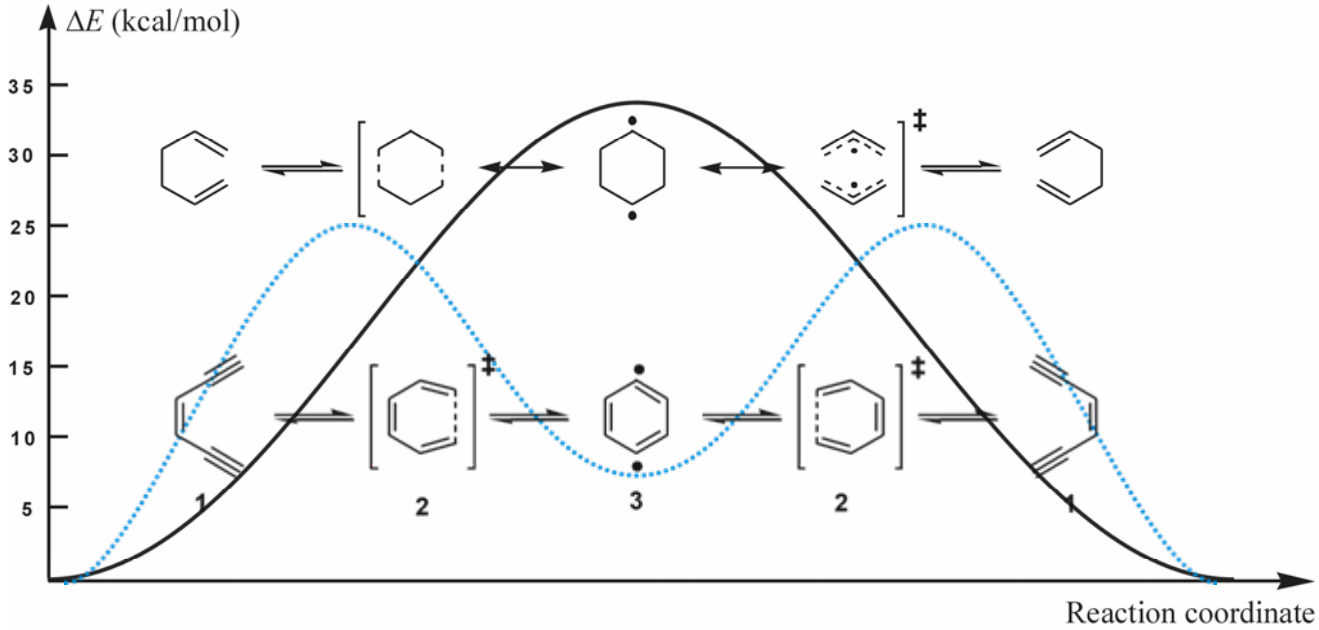
R. Hoffmann, W.-D. Stohrer, *J. Am. Chem. Soc.*, **1971**, 6941-6948.
F. A. L. Anet, G. E. Schenk, *Tetrahedron Letters*, **1970**, *48*, 4237-4240.

How can the transition state become a minimum?

- Via a Biradical… (**Bergman Cyclization** (1972-1973))



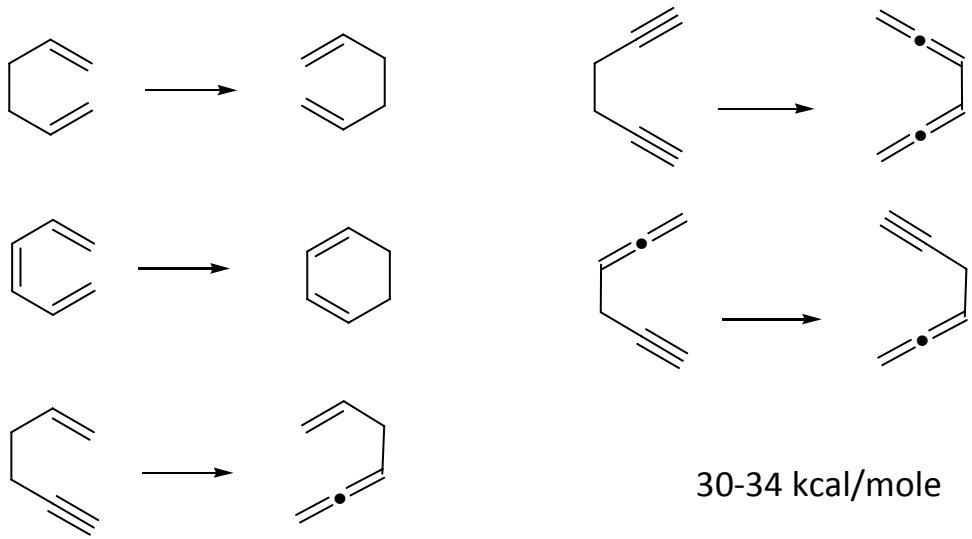
- Bergman reported the thermal rearrangement of 1,5-diacetylenes via a diradical structure - 1,4-dehydrobenzene



R. G. Bergman, *Acc. Chem. Res.*, **1973**, *6*, 25-31.
R. R. Jones, R. G. Bergman, *J. Am. Chem. Soc.*, **1971**, 660-661.
P. R. Schreiner, A. Navarro-Vazquez, and M. Prall *Acc. Chem. Res.* **2005**, *38*, 29–37.

How can they have monotonic kinetics?

- "In fact, the concerted nature of the transition states, and their aromatic character, leads to the activation energy monotony, even in the presence of structural diversity."
- The activation energy seems to be independent of the degree of unsaturation in each of the systems.

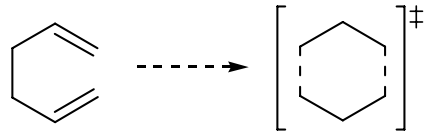


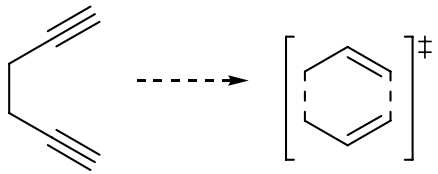
30-34 kcal/mole

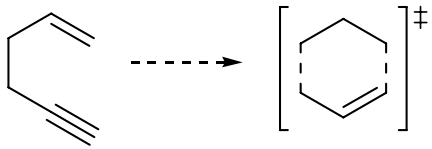
K. N. Houk, Yi Li, J. D. Evanseck, *Angew. Chem*. **1992**, *104*, 711-739.
K. A. Black, S. Wilsey, K. N. Houk, *J. Am. Chem. Soc.* **1998**, *120*, 5622-5627.

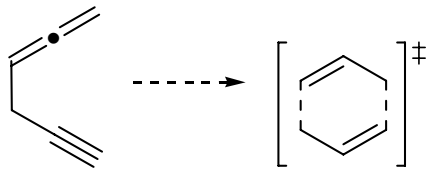
What is the common principle?

Cope family

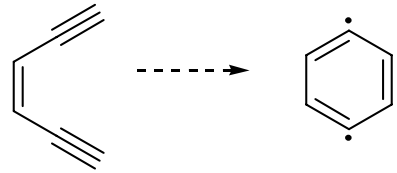




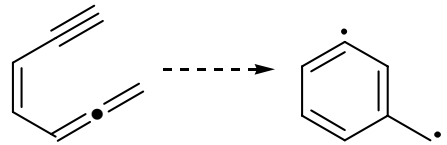




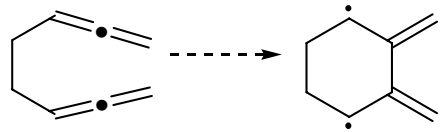
Bergman cyclization



Myers-Saito

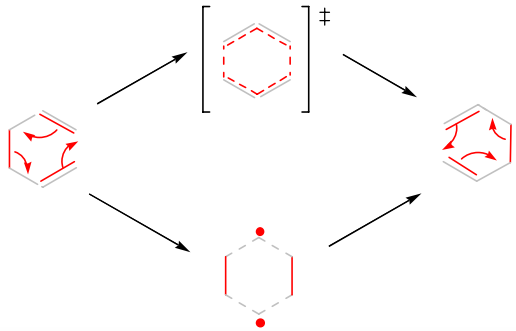


Cyclization of diallenes

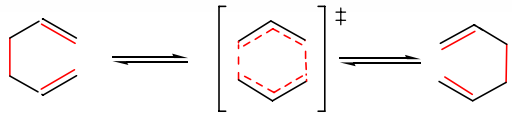


How to predict the TS or the intermediate?

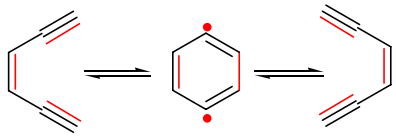
„Minimum requirement for the Cope reaction is the common structural element, the double bond in the 1,5-position of acyclic systems.“



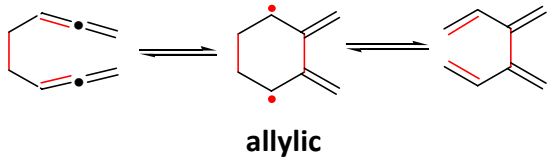
„...a non-concerted reaction takes place when biradical intermediates are stabilized either by allyl or aromatic resonance.“



aromatic TS



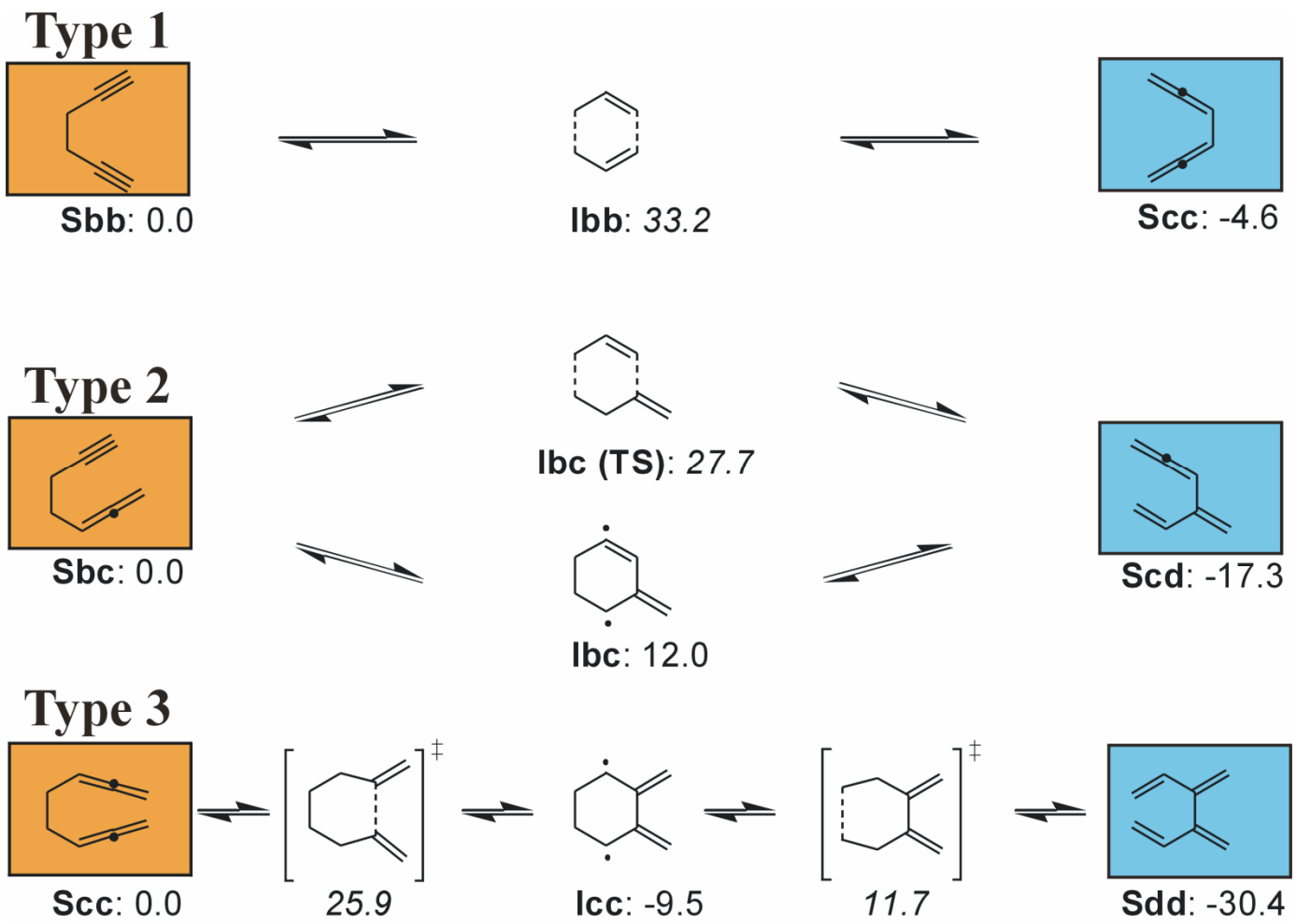
aromatic



allylic

P. R. Schreiner, A. Navarro-Vasquez, M. Prall, *Acc. Chem. Res.* **2005**, *38*, 29-37.
A. Navarro-Vasquez, M. Prall, P. R. Schreiner, *Org. Lett.* **2004**, *6*, 2981-2984.

Types of reactions in the Cope family

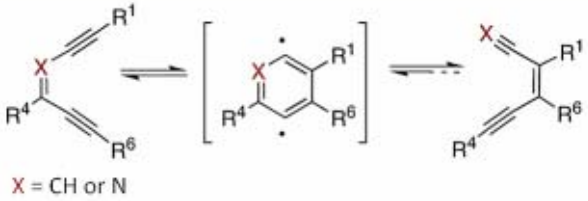


P. R. Schreiner, A. Navarro-Vasquez, M. Prall, *Acc. Chem. Res.* **2005**, *38*, 29-37.
A. Navarro-Vasquez, M. Prall, P. R. Schreiner, *Org. Lett.* **2004**, *6*, 2981-2984.

Reactants								
	36.7 ‡ **laa** 0.0	33.4 ‡ **lab** -2.2	28.6 ‡ 15.8 **lac** -15.4	44.1 ‡ 31.2 **lad** 15.4	34.3 ‡ **lae** 7.9	30.7 30.7 12.7 **laf** 0.0	35.7 ‡ **lag** 2.2	26.4 ‡ **lah** -7.9
	33.4 ‡ **lab** -2.2	33.2 ‡ **lbb** -4.6	27.7 ‡ 12.0 **lbc** -17.3	42.6 ‡ 27.8 **lbd** 14.7	32.3 ‡ **lbe** 3.5	30.1 26.5 5.8 **lbf** -3.0	29.9 ‡ **lbg** 0.0	23.8 ‡ **lbh** -13.5
	28.6 ‡ 15.8 **lac** -15.4	27.7 ‡ 12.0 **lbc** -17.3	25.9 11.7 -9.5 **lcc** -30.4	32.5 32.5 5.9 **lcd** 0.0	27.7 ‡ 9.9 **lce** -8.8	25.8 15.4 -14.6 **lcf** -15.1	27.9 ‡ 13.1 **lcg** -14.7	24.4 15.0 2.9 **lch** -22.8
	44.1 ‡ 31.2 **lad** 15.4	42.6 ‡ 27.8 **lbd** 14.7	32.5 32.5 5.9 **lcd** 0.0	42.0 56.2 20.8 **ldd** 30.4	37.8 47.2 25.7 **lde** 22.8	30.5 40.9 0.5 **ldf** 15.1	45.0 ‡ 29.3 **ldg** 17.3	36.5 ‡ 18.7 **ldh** 8.8
	34.3 ‡ **lae** 7.9	32.3 ‡ **lbe** 3.5	27.7 ‡ 9.9 **lce** -8.8	37.8 47.2 25.7 **lde** 22.8	32.6 34.3 29.5 **lee** 12.3	29.2 29.5 2.7 **lef** 5.5	37.3 ‡ **leg** 13.5	25.5 25.5 19.3 **leh** 0.0
	30.7 30.7 12.7 **laf** 0.0	30.1 26.5 5.8 **lbf** -3.0	25.8 15.4 -14.6 **lcf** -15.1	30.5 40.9 0.5 **ldf** 15.1	29.2 29.5 2.7 **lef** 5.5	22.8 22.8 -21.6 **lff** 0.0	29.5 34.0 8.7 **lfg** 3.0	24.0 23.7 -2.8 **lfh** -5.5
	35.7 ‡ **lag** 2.2	29.9 ‡ **lbg** 0.0	27.9 ‡ 13.1 **lcg** -14.7	45.0 ‡ 29.3 **ldg** 17.3	37.3 ‡ **leg** 13.5	29.5 34.0 8.7 **lfg** 3.0	37.7 ‡ **lgg** 4.6	28.8 ‡ **lgh** -3.5
	26.4 ‡ **lah** -7.9	23.8 ‡ **lbh** -13.5	24.4 15.0 2.9 **lch** -22.8	36.5 ‡ 18.7 **ldh** 8.8	25.5 25.5 19.3 **leh** 0.0	24.0 23.7 -2.8 **lfh** -5.5	28.8 ‡ **lgh** -3.5	21.9 20.3 17.2 **lhh** -12.3
								Products

Summary….

- Heuristic as a strategy to guide thinking and problem solving
- Heuristic chemistry search for common principles and generalities to find “reaction families”.
- Heuristic principles concerning the structural element and the stability of intermediates for the 6π electron case
- The purpose is now to find new unknown reactions with the help of the heuristic rule



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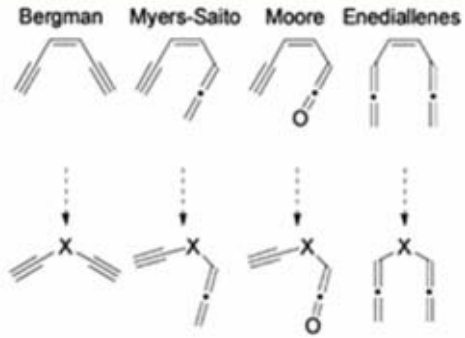

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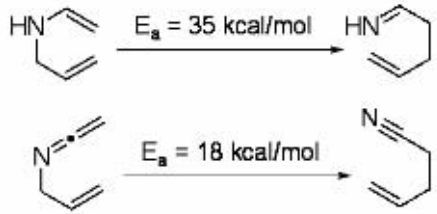

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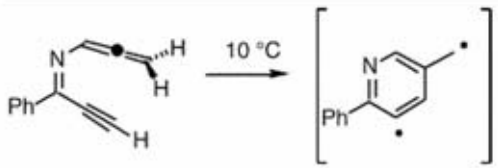

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New rearrangements and structures?????

Thank you for your attention!

Questions????