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Cope Reaction Families: To Be or Not to Be a Biradical

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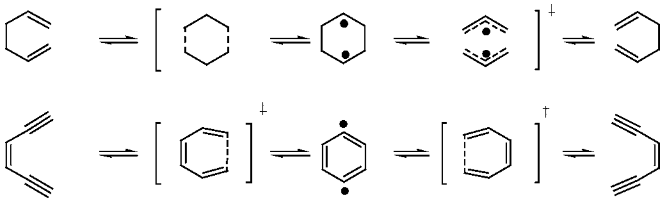
ABSTRACT



The cyclization reactions of polyunsaturated systems such as enediynes, enyne-allenes, as well as many others, can be structurally related to the Cope reaction and grouped into two branches: 6π (e.g., Cope, allenyl-Cope) and $[2\sigma + 4\pi]$ systems (e.g., Bergman, Myers–Saito). After extensive computional (BCCD(T)/cc-pVDZ//UBLYP/6-31G*) examination of a large set of Cope-related reactions, we derive the following simple rule: biradical intermediates are involved along the reaction path if they are stabilized by allylic resonance or aromaticity.

The archetypical $[3_s,3_s]$ sigmatropic shift reaction is undoubtedly the Cope rearrangement of 1,5-cyclohexadiene **1** (Figure 1). The simplest structural requirement is the presence of two π bonds in the 1,5-positions. From this point of view, well-known electrocyclizations of polyunsaturated systems such as the Bergman[1] or Myers−Saito[2] reactions can be brought under the umbrella of a "Cope" family.[3a] This similarity applies to structure and thermochemistry. For instance, Houk et al.[3b] pointed out that the concerted nature of the Cope rearrangement is the cause for kinetic monotony ($\Delta^{\ddagger}H = 31{-}35$ kcal/mol) in substrates with different degrees of unsaturation. This "monotony" can even be extended to the Bergman reaction with an experimentally determined $\Delta^{\ddagger}H = 28.2$ kcal/mol[4] (Figure 1).[5]

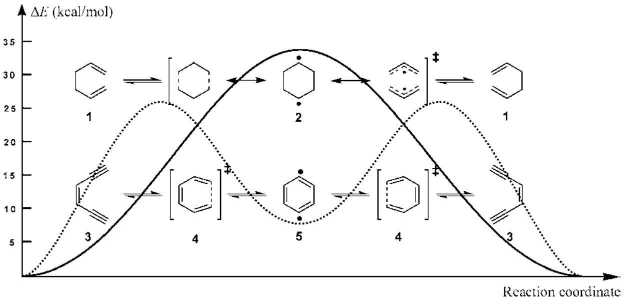


Figure 1. Cope vs Bergman cyclizations and their energy profiles.

However, subtle mechanistic differences complicate matters within this family (Figure 2). Even the mechanism of the Cope rearrangement of hexadiene **1** has been the object

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[1] (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660−661. (b) Darby, N.; Kim, C. U.; Salaun, J. A.; Shelton, K. W.; Takada, S.; Masamune, S. *Chem. Commun.* **1971**, 1516−1517. (c) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25−31.

[2] (a) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057−8059. (b) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 9130−9132. (c) Myers, A. G.; Dragovich, P. S.; Kuo, E. Y. *J. Am. Chem. Soc.* **1992**, *114*, 9369−9386.

[3] (a) Such heuristic approaches following an "Aufbauprinzip" have been proposed by others, see, for instance: Hopf, H. *Classics in Hydrocarbon Chemistry*; Wiley-VCH: Weinheim, Germany, 2000; pp 11−14. (b) Black, K. A.; Wilsey, S.; Houk, K. N. *J. Am. Chem. Soc.* **1998**, *120*, 5622−5627.

[4] Roth, W. R.; Hopf, H.; Horn, C. *Chem. Ber.* **1994**, *127*, 1765−1769.

[5] The Myers−Saito cyclization appreciably deviates from this trend ($\Delta^{\ddagger}H = 21.8 \pm 0.5$) due to its exothermicity ($\Delta H = -15 \pm 3$ kcal/mol). See ref 2c.

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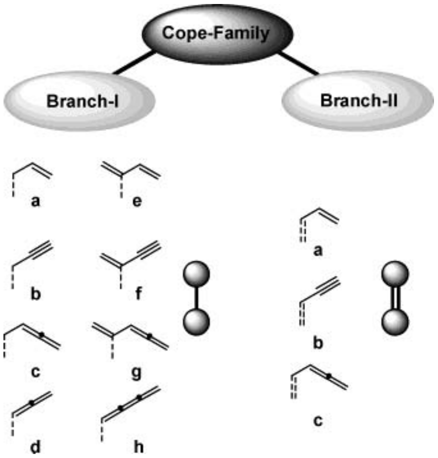

Figure 2. Cope reaction family.

and testing ground for theoretical studies[6,7] in attempts to ascertain the nature of the preferred reaction path. The main question was whether an "aromatic" transition state or a 1,4-diyl biradical lies along the reaction path. Undoubtedly, the latter is present in the Bergman reaction.

In this work we examine a large set of Cope-like reactions in order to differentiate between paths that involve a single transition structure and stepwise mechanisms involving biradicals.

All structures were optimized at the DFT level of theory using the BLYP[8] functional and a 6-31G*[9] basis set. Stationary points and ZPVE corrections were characterized by second derivative computations. An unrestricted broken-spin symmetry methodology (UBS) was used for species with biradicaloid character.[10] Single-point energy computations were performed on DFT-optimized structures at the Brueckner doubles[11] coupled-cluster level of theory with a cc-pVDZ basis set[12] [BD(T)/cc-pVDZ].[13]

To assemble a common framework we designed the "Cope reaction family" of substrates **Sxx** from combination of eight different unsaturated moieties **a**−**h**, comprising alkene, allene, and alkyne groups. Attaching these moieties to a central single or double bond furnishes two branches, branch I having a central single bond and branch II with a double bond in the same position (Figure 2).

Nice agreement resulted from comparison of computed activation energies with selected experimental data,[3,14] which validates our methodology (Table 1).[15]

Table 1. Computed vs Experimental Activation Enthalpies

system	**Saa**	**Sab**	**S(II)bb** (**3**)	**S(II)bc**
BD(T)	36.7	33.4	27.1	20.6[c]
exptl	33.5[a]	32.7[a]	28.2[b]	17.8[c,d]

[a] Ref 3. [b] Ref 4. [c] From *s*-cis conformer. [d] Ref 5. Computed $\Delta H_{s-\mathrm{trans}\rightarrow s-\mathrm{cis}}$ subtracted.

Our results allow us to classify all possible reactions into three types (Figure 3):

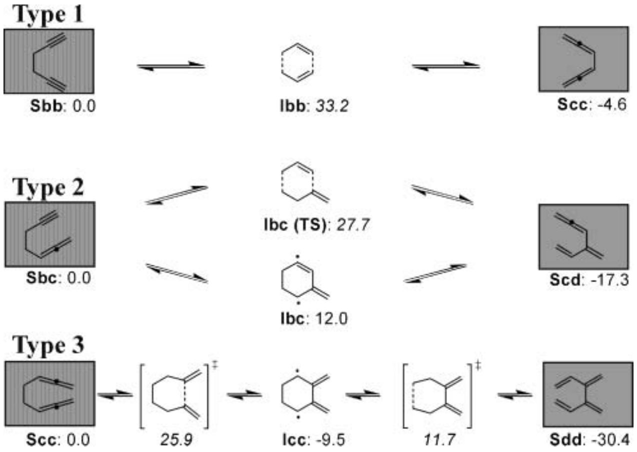

Figure 3. Cope family reaction types.

Type 1: concerted rearrangements that take place through a transition structure without involvement of biradical intermediates, like the rearrangement of hexa-1,6-diyne **Sbb**.

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(12) Davidson, E. R. *Chem. Phys. Lett*. **1996**, *260*, 514−518.

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(15) For some discussion on the application of pure vs hybrid functionals to the Cope potential surface, see: Staroverov, V. N.; Davidson, E. R. *J. Am. Chem. Soc*. **2000**, *122*, 7377−7385.

Type 2: rearrangements that may have two competing pathways either involving a transition structure or a biradical intermediate, e.g., the hexa-1,2-diene-5-yne **Sbc** rearrangement.

Type 3: nonconcerted rearrangements through a biradical intermediate, e.g., the octa-1,2,6,7-tetraene **Scc** rearrangement.

All reaction data can be conveniently summarized in the form of a "matrix".[3a] In this matrix, moieties to be combined in the reactants are presented in the upper row and left column, whereas the products are formed by combining the entries in the bottom row and in the right column. Matrixes with all possible combinations for branches I and II are shown in Figures 5 and 6. Data in the cells should be interpreted as follows: (a) The number in the lower right corner represents the reaction enthalpy. (b) If a double dagger (‡) is present and a transition structure is depicted (dashed lines) the reaction belongs to type 1; the left upper number represents the activation enthalpy. (c) If a dagger is present and a biradical is depicted, the reaction belongs to type 2; the left upper number represents the activation enthalpy, and the left lower number represents the enthalpy for biradical formation. (d) If no dagger is present and a biradical is depicted, the reaction belongs to type 3. Left and right upper numbers represent the activation enthalpies for the first and second transition states, and, as before, the left lower number represents the enthalpy for biradical formation.

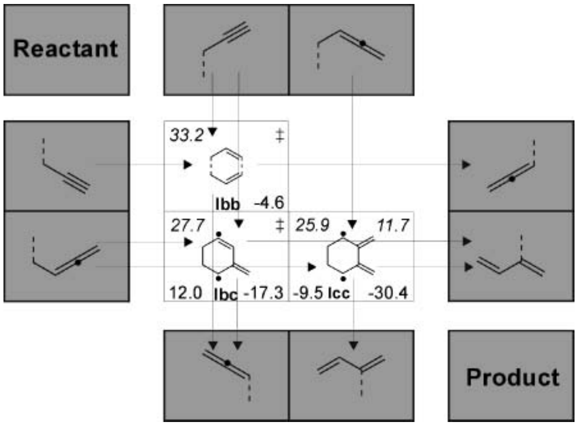


Figure 4. Cope family of reactions in matrix form (see text for an explanation).

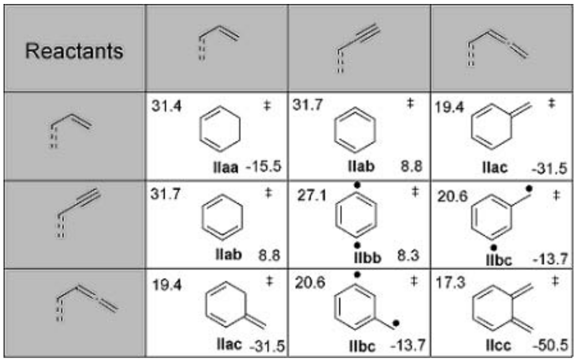
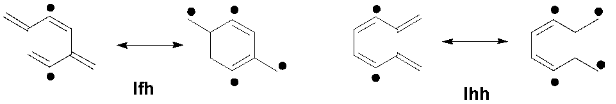


Figure 5. "Cope" branch II matrix.

From branch I (Figure 6) we conclude that in all cases in which a biradical intermediate can benefit from allyl stabilization there *is* an intermediate biradical (blue and red cells), whereas when this stabilization is not present, as in the prototypical Cope rearrangement, the reaction is concerted (green cells). Additionally, we find that biradical intermediates are also involved when *o*- and *p*-quinodimethane structures form, although they are apparently not stabilized (dark red cells). Our explanation for this finding is that these biradicals are partially stabilized due the contribution of aromatic resonance forms as depicted in Scheme 1.[16]

Scheme 1. Aromatic Resonance Stabilization of *p*- and *o*-Quinodimethane Biradicals



Branch II, which includes the Bergman and Myers−Saito reactions can be considered to be analogous to the Cope reaction where, instead of the σ-bond, the central π-bond is broken in the rearrangement. Obviously, aromaticity favors the biradical structures over alternative allene closed-shell forms.[17]

Note that when only one unsaturated group provides biradical stabilization, reactions belong to type II, whereas the cooperation of two or more substituents[18] moves the reaction to type III.[19]

Hence, by means of an elaborate, comprehensive study, we derive a simple rule that allows discernment of whether 1,4-diyl biradical intermediates or transition structures are to be expected along the reaction path of Cope-type rearrangements. This rule states that *a nonconcerted reaction takes place when biradical intermediates are stabilized either by allyl or aromatic resonance*.

This rule[20] follows the spirit of previous theoretical studies,[18,15] which stated that biradical intermediates are

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(16) It is possible that part of the stabilization could also be attributed to the 1,4 through-bond interaction of unpaired electrons via conjugation with the sp^2−sp^2 C−C σ orbitals as found for *p*-benzyne: (a) Galbraith, J. M.; Schreiner, P. R.; Harris, N.; Wei, W.; Wittkopp, A.; Shaik, S. *Chem. Eur. J.* **2000**, *6*, 1446−1454. (b) de Visser, S. P.; Filatov, M.; Schreiner, P. R.; Shaik, S. *Eur. J. Org. Chem.* **2003**, 4199−4204.

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(18) (a) Hrovat, D. A.; Beno, B. R.; Lange, H.; Yoo, H.-Y.; Houk, K. N.; Borden, W. T. *J. Am. Chem. Soc.* **1999**, *121*, 10529−10537. (b) Hrovat, D. A.; Chen, J.; Houk, K. N.; Borden, W. T. *J. Am. Chem. Soc.* **2000**, *122*, 7456−7450.

(19) The only exception is the **Sde** to **Sch** rearrangement, likely due to stabilization being lost in going from the transition state to biradical **Ide**.

(20) An exception can be found for highly strained hydrocarbons: Roth, W. R.; Gleiter, R.; Paschmann, V.; Hackler, U. E.; Fritzsche, G.; Lange, H. *Eur. J. Org. Chem.* **1998**, 961−967.

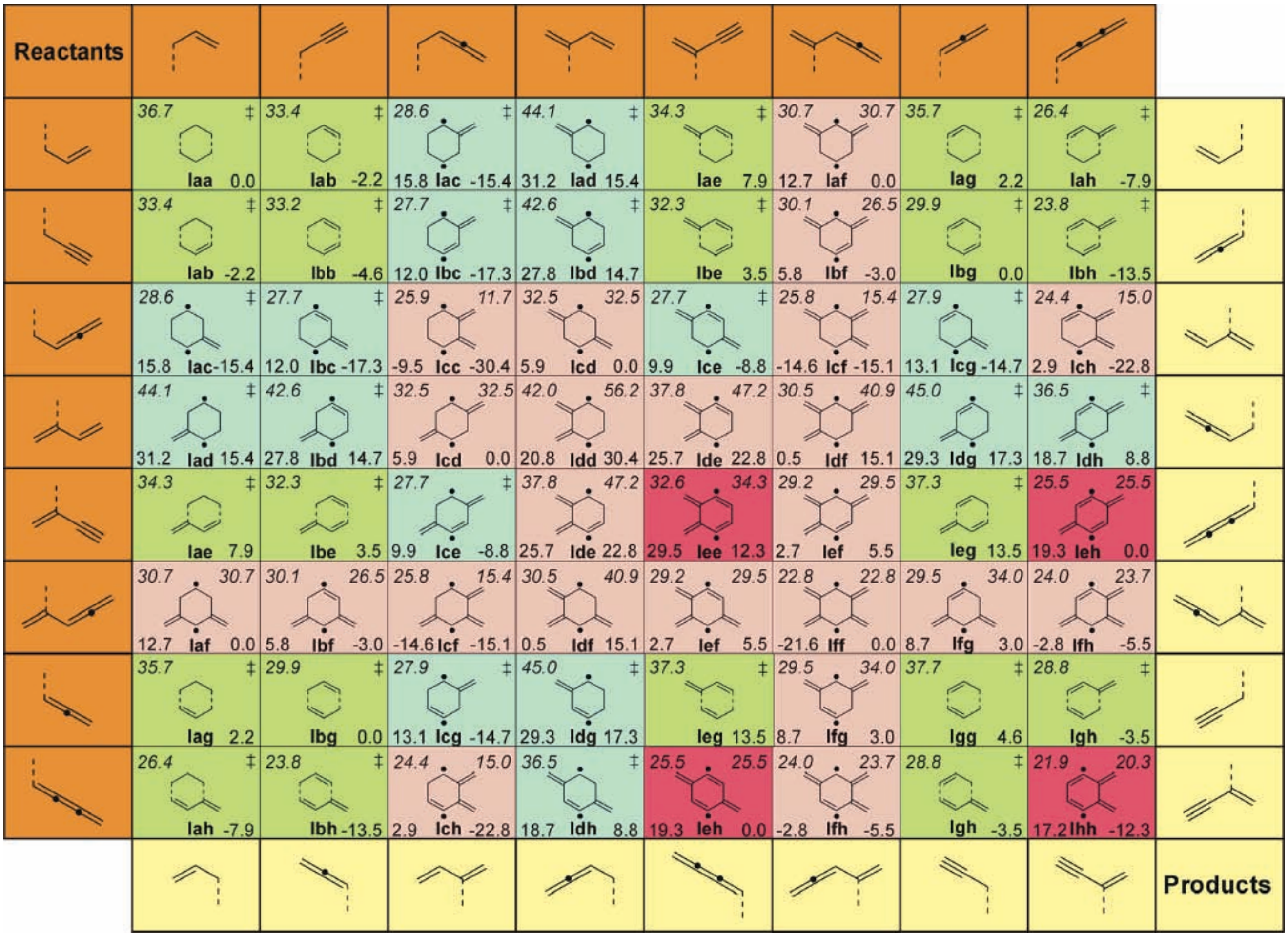

Figure 6. “Cope” branch I matrix. Green color, type I reactions; blue color, type II reactions; red color, type III reactions.

present when radical-stabilizing substituents (phenyl, vinyl, cyano) are connected to the 2- and/or 5-positions of the 1,5-hexadiene moiety, and also experimental[21] findings.

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Supporting Information Available: Tables with Cartesian coordinates for all optimized structures along with tables including absolute energies, ZPVE energies, and <S^2> values. This material is available free of charge via the Internet at http://pubs.acs.org.

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[21] Roth, W. R.; Wollweber, D.; Offerhaus, R.; Rekowski, V.; Lennartz, H.-W.; Sustmann, R.; Müller, W. *Chem. Ber*. **1993**, *126*, 2701−2715.