The Cope Rearrangement – a Reaction with a Manifold Mechanism? [1]*

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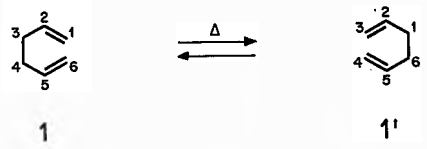
Summary

For the Cope rearrangement of hexa-1,5-dienes (cf. **1**) to isomeric forms (cf. **1'**), more mechanisms are at one's disposal than was hitherto accepted. Depending on the choise of the structure, the kind of substituents of the Cope system or on the reaction conditions, most of the thinkable mechanisms can be defined. Two-step Cope processes are characterized by dissociation and recombination or by the intervention of diradicals or zwitterions as intermediates. Concerted processes can occur via the "classical" pericyclic (aromatic) or via a diradicaloid transition state. Whereas the unsubstituted hexa-1,5-diene and its derivatives with conjugative substituents in positions 1,3,4 or 6 follow the pericyclic route, systems with radical stabilizing substituents in positions 2,5 prefer to react via the diradicaloid pathway. Thus, hexa-1,5-dienes represent, from a mechanistical standpoint, quite ductile systems.

I. The Mechanisms as Border-Line Cases

The Cope rearrangement of hexa-1,5-dienes (**1** ⇄ **1'**; scheme 1) and the Claisen rearrangement of 3-oxa-hexa-1,5-dienes (allyl vinyl ethers) to γ,δ-unsaturated carbonyl compounds, in general, are regarded as typical examples of orbital-symmetry controlled sigmatropic reactions [2]. In principle, however, the following mechanistic borderline cases can be discussed for transformations of type **1** ⇄ **1'**.

Scheme 1

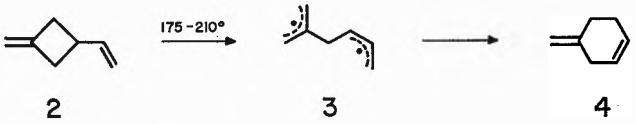


1. Two-Step Processes

These processes are characterized by the intervention of distinct, eventually short-living intermediates.

1.1. Homolytic or heterolytic cleavage of the central σ-bond of the Cope or Claisen system, followed by recombination of the radical-like or ionic fragments whereby (3,3), (1,3) or (1,1) products can result (cf. [3,4]). Unimolecular versions of the homolytic mechanism are well known from suitably bridged systems. The thermal isomerization of cyclobutane derivative **2** to the methylene-cyclohexene **4**, which occurs via the diallyl diradical **3** (scheme 2), may serve as an example (see [5] and literature cited therein).

Scheme 2



A pseudo-intramolecular mechanism, via radical geminates, is followed by the aromatic photo-Claisen rearrangement (cf. [6]).

1.2. Intramolecular [2 + 2]cycloaddition to give bicyclo[2.2.0]hexane derivatives **5** which undergo cycloreversion with inclusion of the original σ-bond of the Cope system (see scheme 3) [7].

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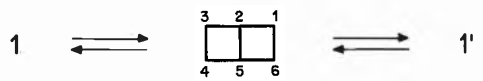
**** Prof. Dr. H.-J. Hansen, Institut de chimie organique de l'Université de Fribourg, Pérolles, CH-1700 Fribourg

Scheme 3



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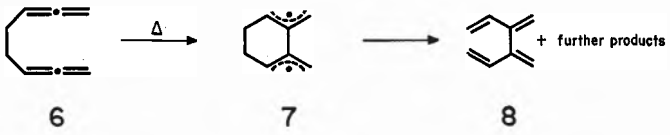
This mechanism will probably not operate in simple Cope systems. However, it may play a role in partially fluorinated (cf. [8]) and in some bicyclic Cope systems (cf. [8a]).

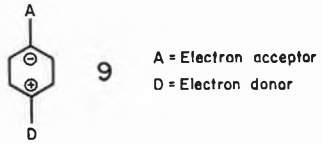
1.3. Formation of a detectable singlet cyclohexa-1,4-diyl diradical (cf. [9]) or zwitterion by linkage between the termini (1,6) of the Cope or Claisen system. The diradical mechanism seems to be attractive in such cases where the Cope system is rich in energy and bears substituents which exert a radical stabilizing effect (e.g. vinyl). The step to yield the diradical may then be exothermic. A typical example is given by the Cope rearrangement of octa-1,2,6,7-tetraene (**6**) which proceeds via 2,3-dimethylene-cyclohexa-1,4-diyl (**7**; scheme 4)

Scheme 4



6 7 8

[10]. 1,4-Zwitterions can intervene, when positions 2 and 5 of the Cope system **1** are occupied by substituents stabilizing carbenium ions and carbanions, respectively (see **9**). The ring closure is equivalent to an intramolecular Michael reaction.



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Cope rearrangements which occur by interceptable zwitterions of this type have recently been discovered [11].

2. One-Step or Pseudo-One-Step Processes

These processes are concerted per definitionem but they must not occur synchronously.

2.1. Synchronous Process

This process, formerly already suggested by Claisen [12] as well as by Cope [13] and generally accepted up till now, possesses a cyclic transition state which can be understood as formed by interaction of two allyl radicals [2]. Complete synchronism of bond breaking (3,4) and bond making (1,6) can only be expected in a degenerate system. The transition state is isoconjugate with benzene [14] and is therefore also called "aromatic".

2.2. Non-Synchronous Process

Such a process would lead by combination of the termini 1,6 of the Cope system **1** to a singlet cyclohexa-1,4-diyl (**10**; scheme 5) that—representing the transition

Scheme 5

10

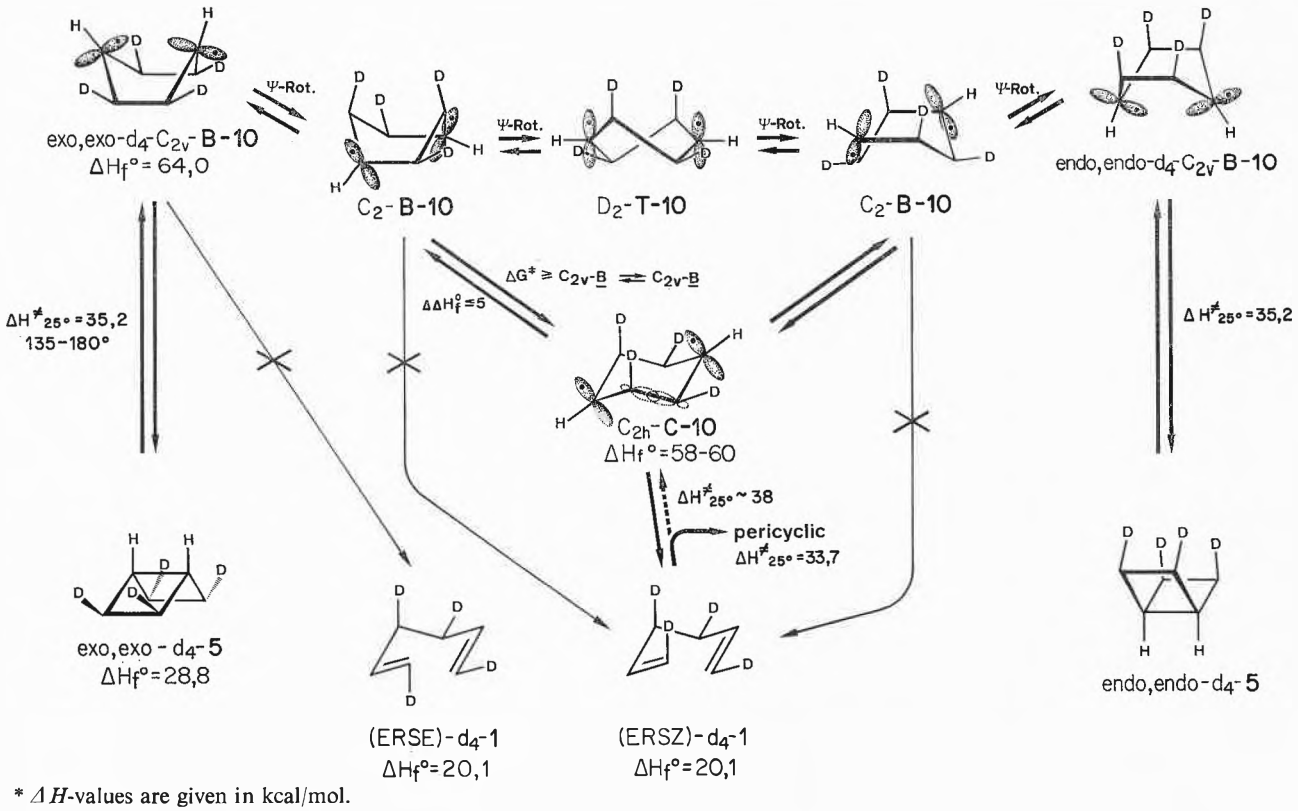
state [9,15]—will form the product **1'** by opening the former 3,4 bond. According to the stereochemical reactant-product relations, observed for Cope (and Claisen) rearrangements (cf. [16]), this diradicaloid transition state must possess a chair-like (**C**) conformation (cf. **C-10**; scheme 6).

Doering et al. [17] have brought into discussion such a mechanism since they observed that the measured enthalpy of activation for the pseudo-degenerated Cope rearrangement of 1,1-dideuterio-hexa-1,5-diene ($\Delta H^{\ddagger}_{25^\circ}$ = 33,7 kcal/mol) is in good accord with the difference of the enthalpy of formation ($\Delta\Delta H_f^\circ$ = 35–36 kcal/mol) of hexa-1,5-diene (ΔH_f° = + 20,1 kcal/mol [18]) and of the estimated for cyclohexa-1,4-diyl (ΔH_f° = 55–56 kcal/mol). The enthalpies of formation of such diradicals can be calculated with the aid of group increments derived and collected by Benson et al. [19, 20] (cf. however [21]).

II. Diradicaloids and Thermochemical Arguments

It is now generally accepted that the thermal ring opening of cyclopropane, cyclobutane and their derivatives occurs via the corresponding propa-1,3-diyls and buta-1,4-diyls respectively, in their singlet state. It is of importance to notice that the $\Delta\Delta H_f^\circ$-values for the enthalpy of activation of the ring opening reactions for these systems, estimated with the aid of group increments of Benson et al., are in all cases by a few kcal/mol lower than the $\Delta H^{\ddagger}_{25^\circ}$-values determined experimentally. This holds also if one takes into account that in some reactions diradicals are created in eclipsed conformations [22]. If one allows for the enthalpy of activation, estimated with group increments according to Benson et al., an empirical correction (derived from the measured values) of 3–4 kcal/mol, the $\Delta H^{\ddagger}_{25^\circ}$-value to be expected for the diradicaloid process **1** $\rightleftarrows$ **1'** would lie in the order of 38–40 kcal/mol. Thus, the enthalpy of formation for the chair-like cyclohexa-1,4-diyl (**C-10**) amounts to 58–60 kcal/mol (the experimentally determined enthalpy of formation for the transition state of the rearrangement of **1** is, as mentioned, (53,8 ± 1,0) kcal/mol). In other words the diradical hypothesis for the rearrangement of **1** seems not much attractive.

*Scheme 6**



* ΔH-values are given in kcal/mol.

It is of importance in this connection to discuss the thermal behaviour of exo,exo-2,3,5,6-tetradeuteriobicyclo [2.2.0]-hexane (exo,exo-d_4-**5**). According to Goldstein and Benzon [23] this substance shows 135–180° an inversion at and, within experimental error, stereospecific ring opening to yield endo,endo-d_4-**5** and (ERSZ)/(ESRZ)-d_4-**1**, respectively (see scheme 6). It can be assumed that the opening of the central bond occurs in accordance with the principle of least motion i.e. it leads to a boat-like cyclohexa-1,4-diyl (exo,exo-d_4-C_{2v}-**B-10**) [24]. The measured enthalpy of activation for this reaction is 35,2 kcal/mol. Thus, the enthalpy of formation of the diradical **10** can be calculated to be 64,0 kcal/mol since the enthalpy of formation of **5** can be quite reliably estimated by group increments to be 28,8 kcal/mol.

The enthalpy of activation of ring inversion of the cyclohexyl radical, determined experimentally, is 4,5 ± 0,5 kcal/mol [25]. It seems reasonable to take this value as a measure for the conformational energy of the boat form of cyclohexa-1,4-diyl (**B-10**). Thus, the enthalpy of formation of cyclohexa-1,4-diyl in the chair-like conformation can be calculated to be in the order of 59,5 kcal/mol. This value is in good agreement with the formerly estimated ΔH_f° of C_{2h}-**C-10**, based on the process **1** ⇄ **1**′.

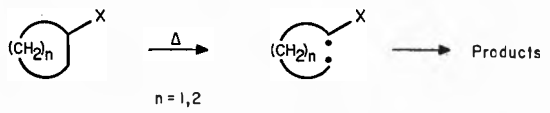
These considerations lead to the conclusion that the diradicaloid transition state of the Cope rearrangement of **1** lies only a few kcal/mol, at least so far as the enthalpy of activation is concerned, above the pericyclic one. Consequently, it should be possible to move the pericyclic, synchronous transition state in the direction of a diradicaloid one by introducing radical stabilizing substituents in position 2(5) of the hexa-1,5-diene (**1**). The rate of the pericyclic rearrangement should not be affected by substituents in position 2(5) since they are in conjugation with an ethylenic double bond in reactant and product as well as with a benzene analogue in the transition state (cf. [26]). However, before starting the discussion of results obtained with Cope system substituted by cyano and methoxycarbonyl groups in positions 2 and 5 a brief comment should be made on radical stabilization energies.

III. Radicals and Their Stabilization Energies

Radical stabilization energies *(RSE)* of substituents can be defined on the basis of bond dissociation energies according to (cf. [27]):

$RSE^\circ_{25^\circ}$(X-C˙) = $DH^\circ_{25^\circ}$(C-Y) − $DH^\circ_{25^\circ}$(X-C-Y), wherein X-C˙ stands for a carbon radical α-substituted by a stabilizing group X. $DH^\circ_{25^\circ}$ (X-C-Y) represents the enthalpy of dissociation of a C-Y bond in α-position to the group X and $DH^\circ_{25^\circ}$ (C-Y) is the enthalpy of dissociation of a system comparable to X-C-Y not having a stabilizing group in α-position to the C-Y bond [28]. Another possibility for the determination of *RSE* is to look at the lowering of the enthalpy of activation

($\Delta\Delta H_{25°}^{\ddagger}$) exerted by substituents X in ring opening reactions of small ring compounds compared with the parent systems:



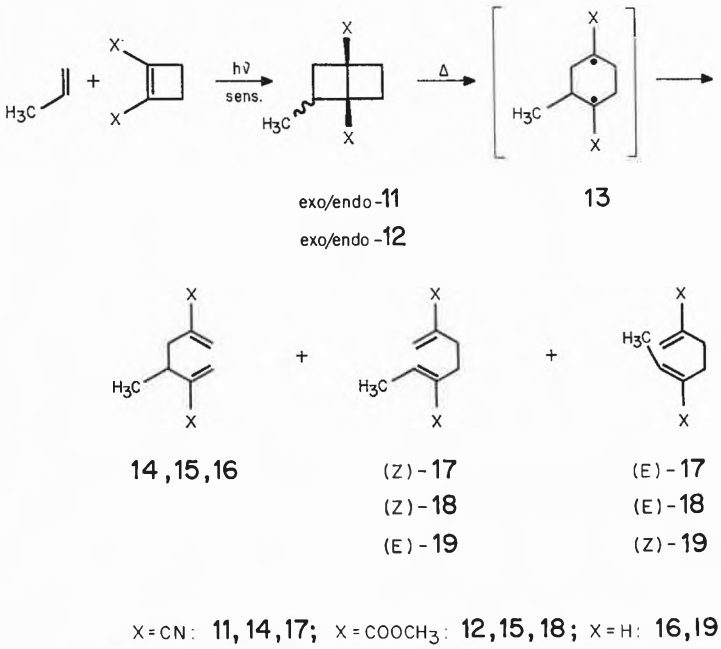
In this case we have $RSE_{25°}^{\circ} = \Delta\Delta H_{25°}^{\ddagger}$. Similarly, the enthalpies of activation of the thermal splitting of α,α'-disubstituted azo compounds [29] or that of ethanes [30] can be used to determine $RSE_{25°}^{\circ}$. The average *RSE* values obtained with the reactions discussed are e.g. the following: phenyl = 12,2 ± 2,0, cyano 6,4 ± 2,0 and alkoxycarbonyl = 5,5 ± 2,0 kcal/mol.

If we assume for the C-diradicaloid mechanism of the Cope rearrangement of **1** an enthalpy of activation of 38–40 kcal/mol (see section II), the introduction of phenyl substituents at C(2) and C(5) should lower this value by about 24,4 kcal/mol, i.e. $\Delta H_{25°}^{\ddagger}$ = 13,6 to 15,6 kcal/mol. For two cyano or two methoxycarbonyl groups one would expect $\Delta H_{25°}^{\ddagger}$ values of 25.2–27,2 kcal/ mol and 27,0–29,0 kcal/mol, respectively.

IV. Influence of Cyano and Methoxycarbonyl Groups at Positions 2 and 5 in the Cope Rearrangement

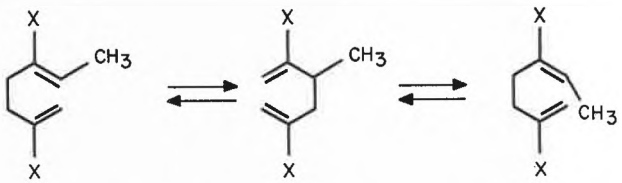
We have investigated the kinetics (decane, ampoule technique) of the Cope rearrangement of 2,5-dicyano-3-methyl-hexa-1,5-diene (**14**), 2,5-dicyano-hepta-1,5-diene ((E)- and (Z)-**17**) and of the corresponding methoxycarbonyl compounds **15**, (E)- and (Z)-**18**. These compounds were obtained by thermolysis of exo/endo mixtures of 1,4-dicyano-2-methyl-bicyclo [2.2.0] hexane (**11**) and of the corresponding dimethoxycarbonyl compound **12** at 50° and 100°, respectively. The resulting mixtures were separated by chromatography. The bicyclic compounds **11** and **12** can be synthesized in good yield by sensitized photo-cycloaddition (cf. [31]) of propene and 1,2-dicyano-cyclobutene [32] or dimethyl cyclobutene-1,2-dicarboxylate [32,33] at −70° (cf. scheme 7).

Scheme 7



The activation parameters of the Cope rearrangement of all cyano and methoxycarbonyl substituted systems were determined. The Cope rearrangement of 3-methyl-hexa-1,5-diene (**16**) and (E)- and (Z)-hepta-1,5-diene ((E)- and (Z)-**19**) which may serve as reference systems was already investigated by Frey and Solly [34] in the gas phase. Table 1 contains the activation parameters of these rearrangements which are calculated by using "apparent" rate constants obtained as the average of the four individual rate constants. It is obvious that the introduction of cyano and methoxycarbonyl substituents in positions 2 and 5 causes a dramatic acceleration of the Cope rearrangement; a factor of 10^5, for example, is found at 150°. The average energy of activation of the parent system **16, 19** is reduced by 5,4 kcal/mol by *one* cyano group and by 5,5 kcal/mol by *one* methoxycarbonyl group. These values match nearly the radical stabilization energies of these substituents (cf. section III). It is remarkable that the cyano and methoxycarbonyl groups influence also the entropies of activation, i.e. they are more negative in the substituted systems as is obvious from the lowered mean "apparent" log *A* values. A qualitative explanation for this fact may be found in a relative stiffening of the cyclohexa-1,4-diyls as a consequence of the conjugation of the substituents X with the radical-like centres (cf. [35,36]).

Table 1: Mean Activation Parameters of Cope Rearrangements in 2,5-Substituted Hexa-1,5-diene Systems



X	$\overline{\Delta H_{25°}^{\ddagger}}$ [kcal/mol]	$\overline{\log A}$	$\overline{k}_{150°} \cdot 10^5$ [s^{-1}]
H	34,1	10,4	0,003
CN	23,3	9,7	230
$COOCH_3$	23,1	10,1	730

The Cope rearrangement of **1** is according to Dewar and Wade [37] also accelerated by phenyl groups in positions 2 and 5. The enthalpy of activation of the rearrangement of 2-phenyl-hexa-1,5-diene is, compared to the basic system **1**, lowered by 3,1–4,1 kcal/mol, whereas that of the rearrangement of 2,5-diphenyl-

hexa-1,5-diene is reduced by 5,7–6,2 kcal/mol for *one* phenyl group. This means that on the basis of a diradicaloid mechanism for **1** ($\Delta H_{25°}^{\neq}$ = 38–40 kcal/mol), *RSE* (phenyl) amounts to 8–10 kcal/mol in the first case and 8–9 kcal/mol in the second case. Thus, whereas *RSE* (CN) and *RSE* ($COOCH_3$) come fully into play in the Cope rearrangement, that of a phenyl group (*RSE* = 12,2 ± 2 kcal/mol) is reduced to 65–82%. Models show that this may be due to steric effects: The coplanar arrangement of the phenyl groups with the sp^2-like radical centres in **C-10** (cf. scheme 6) is made more difficult by steric interactions between the ortho-H atoms at the phenyl ring and the methylene groups adjacent to the radical centres in **C-10** [38]. The problem of steric hindrance to coplanarity does not emerge in the cyano system and hardly in the methoxycarbonyl system.

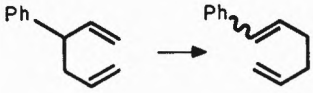
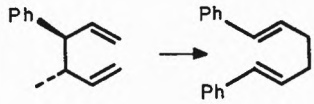
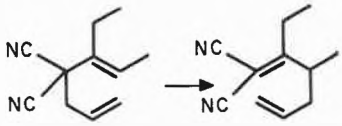
V. A General Concept for Cope Rearrangements

As for the simple hexa-1,5-diene system the diradicaloid model of the transition state of the Cope rearrangement is also not suitable to explain the very fast rearrangement of cis-1,2-divinylcyclopropane into cyclohepta-1,4-diene. $\Delta H_{25°}^{\neq}$ amounts only to 17,8 kcal/mol [39]. The degradation of ring strain (27,6 kcal/mol [19]) is developed to an extent of about 75% in the transition state of this rearrangement. The intervention of a bicyclo[4.1.0]hepta-2,5-diyl cannot explain the acceleration observed with respect to the rearrangement of hepta-1,5-diene [40]. Similar accelerations of Cope rearrangements which are only compatible with a pericyclic mechanism were also observed with other strained Cope systems (cf. [16]).

Regarding the strong rate enhancement of Cope rearrangements in systems carrying substituents with + or − mesomeric effects in position 3(4) (cf. table 2) it is again only the pericyclic model which can explain these observations: the substituents at position 3(4) come into conjugation with the benzene-isoconjugate transition state in the course of the rearrangement. Steric effects seem to play only a minor role.

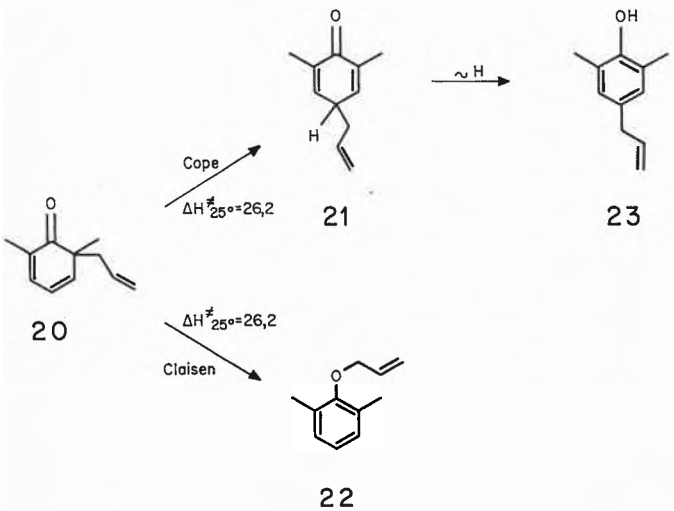
A further example, explicable only by taking the pericyclic mechanism as a basis, are the Cope and Claisen rearrangements of the cyclohexa-2,4-dienone **20** which occur already at 75° as competetive reactions [45] (scheme 8). The rate enhancement is understandable if the transition state is pericyclic and realized as an interaction complex of an allyl radical and an especially good stabilized phenoxyl radical. The pericyclic mechanism works also in the usual Claisen rearrangement: the transformation of allyl vinyl ether into 4-pentenal is characterized by $\Delta H_{25°}^{\neq}$ = 30,0 kcal/mol [46] whereas $\Delta\Delta H_f^{\circ}$ of tetrahydropyran-2,5-diyl can be estimated to be about 37 kcal/mol (increments from [19]).

Table 2: Relative Rates of Cope Rearrangements in 3(4)-Substituted Hexa-1,5-diene Systems

System	Phase[1]	k_{rel} (150°)	$\Delta H_{25°}^{\neq}$ [kcal/mol]	Ref.
	G	1,0	33,7	[17]
	G	4,0	34,0	[42]
	G	6,8	35,5	[17]
	G ODCB	21 134	31,9 28,5	[37] [37]
	S	$5 \cdot 10^5$[2]	–	[43]
	S	$1 \cdot 10^5$	25,2	[44]

[1] G = gas phase; ODCB = o-dichlorobenzene; S = neat.
[2] Estimated value from $t_{½}$ (80°) [43] and the temperature dependence of k (3-phenyl-hexa-1,5-diene) [37].

Scheme 8 *



* ΔH-values are given in kcal/mol.

The most likely mechanisms for the rearrangement of hexa-1,5-diene systems are summarized in fig. 1. The basic system (—) follows the pericyclic pathway (with

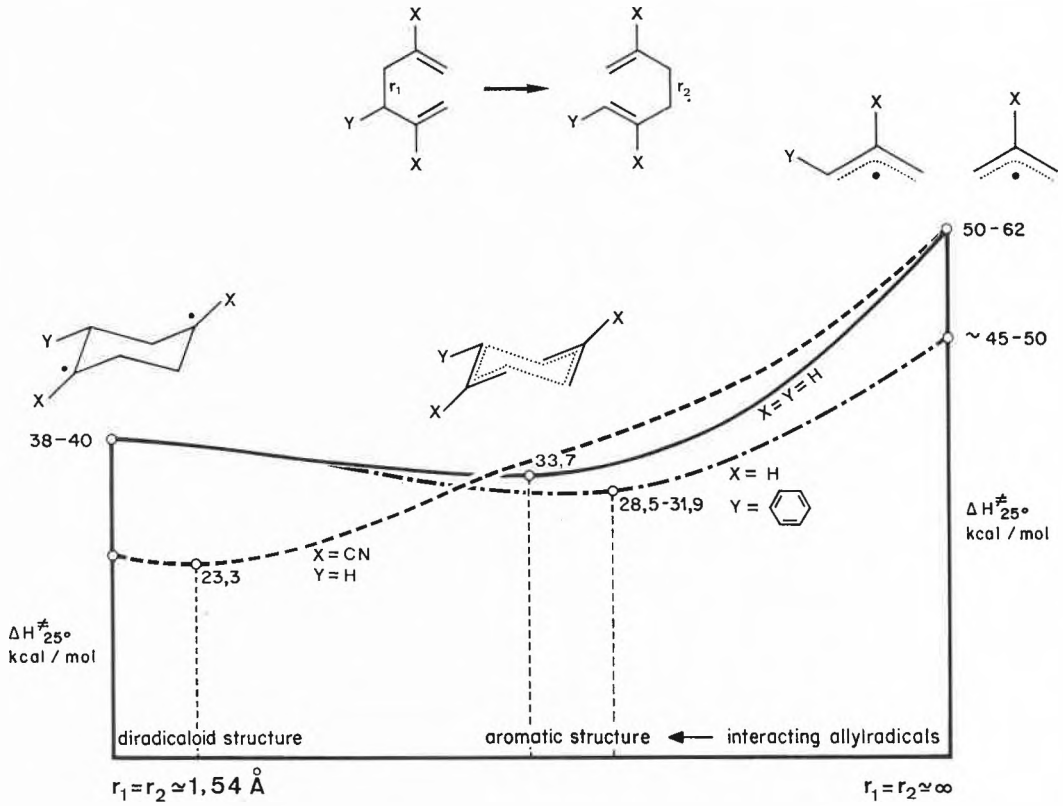


Fig. 1: Cross-Section through a Part of the Hypersurface of the Cope Rearrangement

$\Delta H^{\neq}_{25°} = 33{,}7$ kcal/mol) which is shifted towards the diradicaloid side (left in fig. 1) by radical stabilizing substituents in positions 2 and 5 [47] (– – –). Substituents with + or − mesomeric effect in position 3(4) augment, as mentioned, the rate of the pericyclic process (– · – · –). On the other hand, these substituents facilitate the homolysis of the σ-bond to be shifted since they possess radical stabilizing abilities. Normally, the enthalpy of activation for homolysis is appreciably higher than for the pericyclic process, so that the former, in general, is not observed (right in fig. 1).

In the pericyclic as well as in the diradicaloid [49] mechanisms, as a rule, the chair-like **C**-transition states are prefered on steric grounds ($\Delta\Delta G^{\neq}_{25°} \sim 6$ kcal/mol [16]). By change of steric interaction, however, the boat-like **B**-transition state may be favoured [16]. The **B**-state can also be reached by the elevation of temperature, provided that the rearrangement via **C** is reversible. In the case of the "high-temperature Cope rearrangement" of tetradeuterio-hexa-1,5-dienes [50] the **B**-form of the pericyclic or diradicaloid transition state must be passed. The pericyclic variant is perhaps energetically more favourable (cf. scheme 6).

In conclusion we return to scheme 6 and look at the conversion exo,exo-d_4-**5**→endo,endo-d_4-**5** which can occur via the sequence exo,exo-d_4-C_{2v}-**B-10** ⇄ C_2-**B-10** ⇄ D_2-**T-10** ⇄ C_2-**B-10** ⇄ endo,endo-d_4-C_{2v}-**B-10** [51]. These pseudorotations of the diradical **10** must possess very small energy barriers [52]. They must be smaller than the energy barrier which separates them from the C_{2h}-**C**-cyclohexa-1,4-diyl (d_4-C_{2h}-**C-10**). It is therefore understandable that the ring inversion of exo,exo-d_4-**5** into endo,endo-d_4-**5** is more rapid than the ring opening reaction to give d_4-**1**. For stereoelectronic reasons the ring opening can only take place in the C_{2h}-**C**-form, eventually also in the C_{2v}-**B**-form [54]. Obviously, only the path via the **C**-form is followed because **B**-cyclohexa-1,4-diyls seem to recyclize more rapidly then they undergo the ring opening reaction [55].

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References and Remarks

1 The following article is a draft of a full paper which will appear in Helv. Chim. Acta.

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