

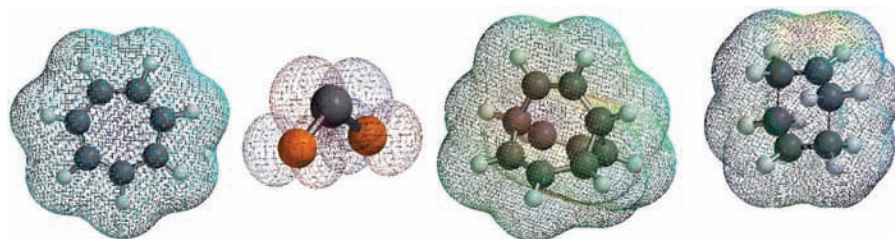
William von Eggers Doering's Many Research Achievements during the First 65 Years of his Career in Chemistry[†]

FRANK-GERRIT KLÄRNER,* MAITLAND JONES, JR., AND
RONALD M. MAGID

*Institut für Organische Chemie, Universität Duisburg-Essen, Essen, Germany,
Department of Chemistry, New York University, New York, New York, and
Department of Chemistry, The University of Tennessee, Knoxville, Tennessee*

RECEIVED ON APRIL 7, 2008

CON SPECTUS



This Account highlights William von Eggers Doering's important discoveries in many fields of chemistry. His synthetic and mechanistic studies have contributed to areas including non-benzenoid aromatics, carbenes, pericyclic reactions, and diradical intermediates. Doering's synthesis with L. H. Knox of the highly stable tropylium ion and their investigation of its reactivity were the starting point for the development of the field of non-benzenoid aromatics. Working with A. K. Hoffmann, Doering demonstrated the synthesis of dichloro- and dibromocarbene by base-induced α elimination of HCl or HBr from CHCl_3 or CHBr_3 under anhydrous conditions. These results allowed for the synthesis of a variety of cyclopropanes and derivatives including allenes. Using ^{14}C labeling experiments, Doering and Prinzbach showed that the mechanism of insertion of singlet methylene into a C–H bond was a concerted process.

In their work on the Cope rearrangement, Doering and Roth's outstanding stereochemical analysis showed that the rearrangement of acyclic 1,5-hexadienes proceeds concertedly, passing over a chairlike transition state. This work has had an enormous impact on the understanding of stereochemical control in synthetic organic chemistry, and many fruitful applications in synthesis have stemmed directly from this finding. Transition-state resonance structures analogous to those for ground-state aromatics can qualitatively explain the relatively large substituent effects on the rate of the Cope rearrangement. However, quantum chemical calculations have quantitatively described these effects. The rapid degenerate Cope rearrangements in the *cis*-divinylcyclopropane units of 3,4-homotropilidene, barbaralone, and bullvalene establish these molecules as having fluxional structures. The unique molecule bullvalene has more than 1.2 million possible structures interconnected by degenerate Cope rearrangements, which average all H and all C atoms. Doering has also examined stepwise thermal reorganizations that pass through intermediary 1,3- or 1,4-diradicals and do not show conformational equilibration as would be expected for classical intermediates. Doering calls these processes "not-obviously concerted". He discusses "continuous diradicals" as transition states and rationalizes the course of these reactions through the concept of a "caldera" (a flat surface with small energy wells as found on the top of volcanoes).

The understanding of fundamental chemical reactions remains the focus of Doering's research. In his terms, "understanding" means not only gaining deep insight but also the intellectual control that allows researchers to predict a reaction's course. Because the interplay between theory and experiment has led to great progress in this predictive ability, Doering's experimental work has provided an important input for computational chemistry and to the essential understanding of chemical reactions.

Introduction

In 1944, just at the beginning of his scientific career, W. von E. Doering and R. B. Woodward received much attention when they published the brilliant synthesis of quinoxaline, a precursor of quinine.¹ This work is remarkably fresh and has been recently reviewed in great detail by J. I. Seeman.² Most recent experimental work by Smith and Williams³ confirmed the conversion of *d*-quinotoxine into quinine reported by Rabe and Kindler in 1918. Throughout his career and continuing today, the elucidation of reaction mechanisms has been a central topic of Doering's research. His pioneering work has had great impact on the research of many other scientists and has been the starting point of many areas of chemistry. His most recent work has had an exceptionally strong influence on the dynamic picture of chemical reactions.

In this Account, we focus on the following topics: non-benzenoid aromatics, carbenes, Cope rearrangements, and reactions involving diradical intermediates. Figure 1 shows Doering with the structures of tropylium ion, dichlorocarbene, bullvalene, and the chairlike transition state of the Cope rearrangement of 1,5-hexadiene as symbols of these research topics. With this selection, we know that we omit many important contributions. Indeed we omit entire areas! Among these are the mechanism of the Baeyer–Villiger oxidation, asymmetric induction, the Doering–Zeiss mechanism for solvolysis, [2 + 2] and [4 + 2] cycloadditions, conjugative stabilization of closed-shell dienes, trienes, polyenes, and styrenes and open-shell radicals such as allyl, pentadienyl, and heptatrienyl radical.

Non-benzenoid Aromatics: Synthesis and Reactions of Tropylium Ion

Doering started his work in this area together with L. H. Knox in 1950. First they prepared tropolone by addition of methylene (photochemically generated from diazomethane) to benzene and subsequent oxidation of 1,3,5-cycloheptatriene with KMnO_4 .⁴ That tropolone behaves more like a carboxylic acid than like a hydroxy ketone can be explained by its dipolar resonance structure containing the tropylium ion as substructure (Scheme 1).⁵ The tropylium ion itself was synthesized 4 years later by Doering and Knox.^{6,7} Bromination of cycloheptatriene produced a complex mixture of isomeric dibromocycloheptadienes, which was not characterized. On heating, this mixture underwent a thermally induced HBr elimination leading to the desired tropylium bromide as a stable salt. In those days, the spectacular stability of the tropylium ion was surprising, and its isolation was also one of the first demonstrations that "carbonium ions" (as they were then called) were real and sometimes even isolable species. Prior to this, their existence was implied indirectly by kinetic, stereochemical, and other studies. This work certainly provided the most important experimental evidence for the validity of the Hückel rule concerning aromatic systems and opened the field of non-benzenoid aromatics that was extensively investigated in the following years by many scientists, including Ronald Breslow, Virgil Boekelheide, Franz Sondheimer, and Emanuel Vogel. A similar route starting with the methylene addition to anisole was used to synthesize tropone. Tropone is a stable unsaturated ketone with a highly polarized C=O bond owing to the importance of the dipolar resonance contributor "cycloheptatrienylium (tropylium) oxide".⁸

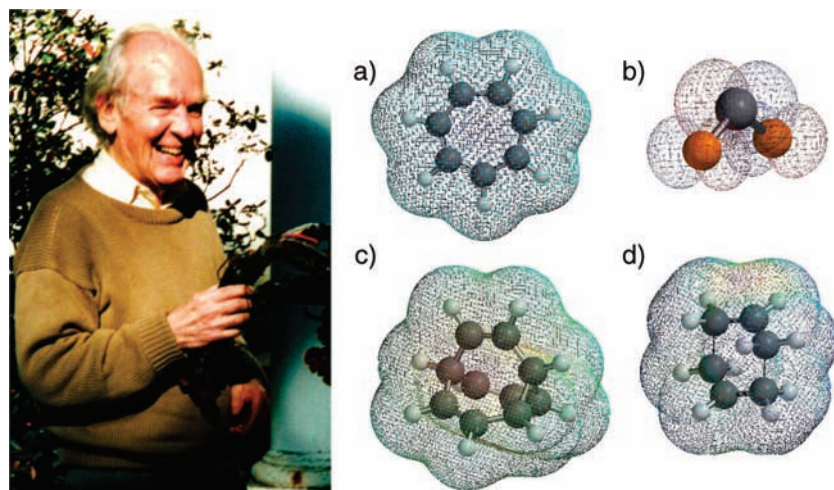
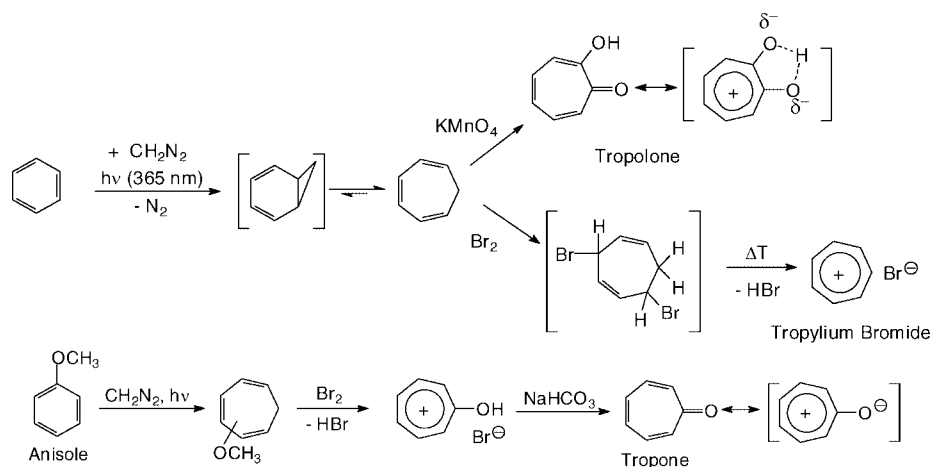


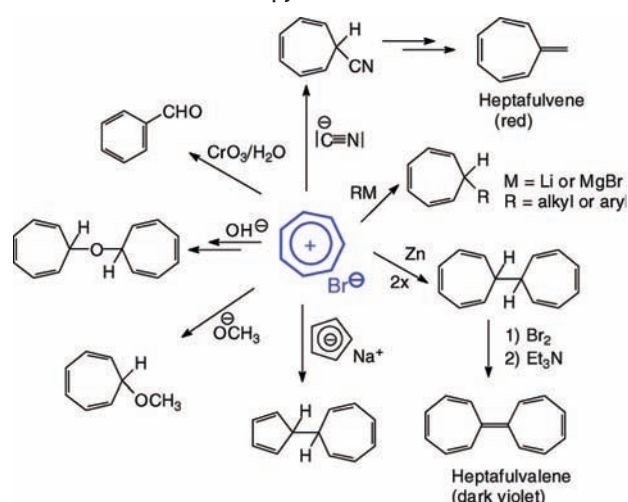
FIGURE 1. Bill Doering and the structures of (a) the tropylium ion, (b) dichlorocarbene, (c) bullvalene, and (d) the chairlike transition state of the Cope rearrangement of 1,5-hexadiene.

SCHEME 1. Synthesis of Tropolone,^{4,5} Tropylium Bromide,^{6,7} and Tropone⁸

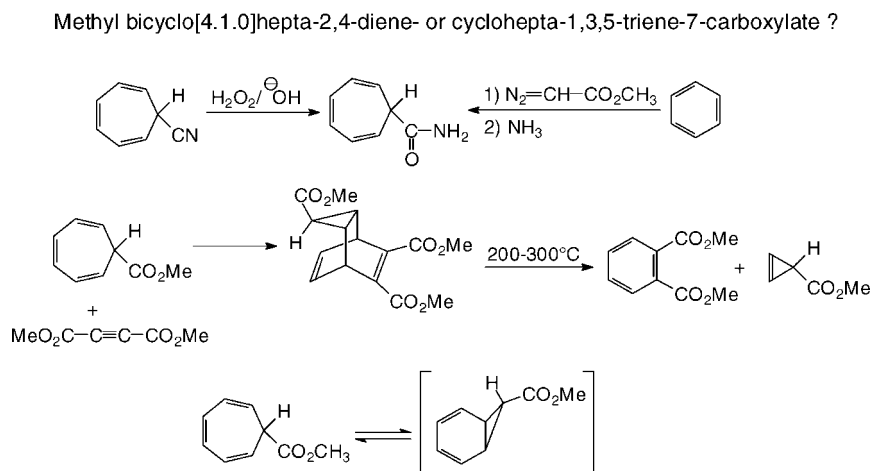
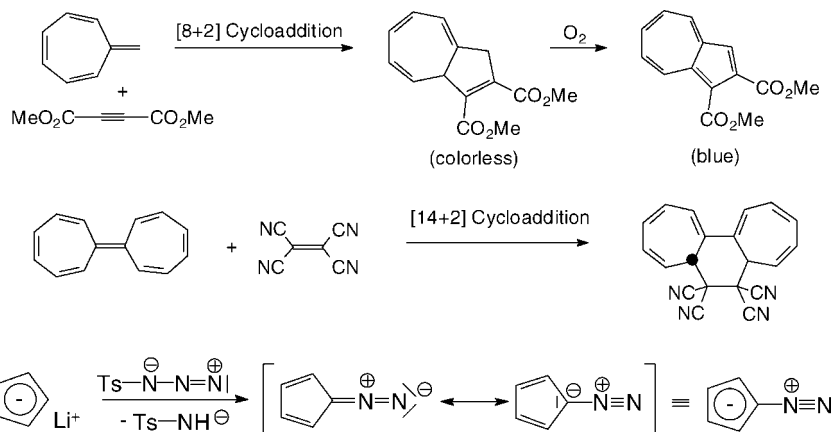
Tropylium bromide undergoes a variety of reactions (Scheme 2).⁹ It adds alkyl- or aryllithium reagents and alkyl- or arylmagnesium bromides, respectively, to give the correspondingly substituted cycloheptatriene derivatives. The addition of other nucleophiles like cyanide, methoxide, and cyclopentadienide occurs in a similar fashion. Oxidation with chromate leads to benzaldehyde, whereas reduction by Zn powder gives cycloheptatrienylcycloheptatriene, which can be converted in two steps into heptafulvalene, a dark violet unstable and air-sensitive conjugated polyolefin. Heptafulvene, another conjugated polyolefin, could be prepared in two steps starting from 7-cyano-1,3,5-cycloheptatriene.¹⁰

The finding that the amide from hydrolysis of 7-cyano-1,3,5-cycloheptatriene is identical to that obtained from aminolysis of the Buchner ester (produced by carbomethoxy-carbene addition to benzene) provided the first evidence that the Buchner ester does not exist in the norcaradiene form (methyl bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate) as proposed by Buchner but largely as the cycloheptatriene derivative (Scheme 3). However, Diels–Alder reaction of the Buchner ester with dimethyl acetylenedicarboxylate gave the adduct derived from the norcaradiene structure. Thermally induced retro-Diels–Alder reaction leading to dimethyl phthalate and methyl cyclopropene-3-carboxylate confirmed the structure assumed for the primary Diels–Alder adduct.¹¹ Later, the Buchner ester was confirmed by NMR analysis to be, indeed, a cycloheptatriene derivative.^{12,13} The equilibrium concentration of the valence tautomeric norcaradiene is just below the limit of NMR detection but is still the reactive diene in the Diels–Alder cycloaddition.

Heptafulvene reacts with dimethyl acetylene dicarboxylate in the fashion of an $[8 + 2]$ cycloaddition (Scheme 4).¹⁰ Although it could not be recognized at the time, this reac-

SCHEME 2. Reactions of Tropylium Bromide⁹

tion is a good example of a process described by the Woodward–Hoffmann rules as $[\pi^8s + \pi^2s]$ cycloaddition.¹⁶ The cycloadduct can be oxidized by air to give dimethyl azulene dicarboxylate, a non-benzenoid aromatic 10π system. Parent azulene was also prepared in two steps by methylene addition to indane followed by catalytic dehydrogenation of the methylene adduct.¹⁷ A further outstanding example of a higher type of cycloaddition is the reaction of heptafulvalene with tetracyanoethene (TCNE) leading to the adduct whose structure has been established by X-ray crystallographic methods.¹⁴ Later Woodward and Hoffmann¹⁶ emphasized that this adduct is the expected product of the symmetry-allowed ground-state $[\pi^{14}a + \pi^2s]$ process and noted that the twisted shape of the heptafulvalene molecule sets the stage ideally for the *antara* addition to the 14π electron system. Finally in this section on non-benzenoid aromatics, we want to mention diazocyclopentadiene prepared by the reaction of lithium cyclopentadienide with tosylazide.¹⁵ This diazo compound is

SCHEME 3. Elucidation of the Structure of the Buchner Ester¹¹**SCHEME 4.** Cycloadditions of Heptafulvene¹⁰ (Synthesis of Dimethyl Azulene Dicarboxylate) and Heptafulvalene¹⁴ and Preparation of Diazocyclopentadiene¹⁵

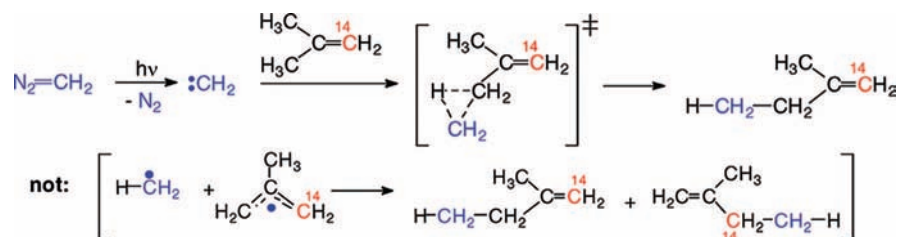
particularly stable because of its dipolar resonance structure containing an aromatic cyclopentadienide unit.

Carbenes: Generation, Addition, and C–H Insertion

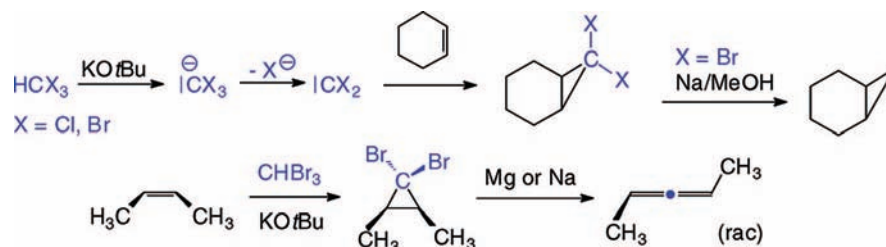
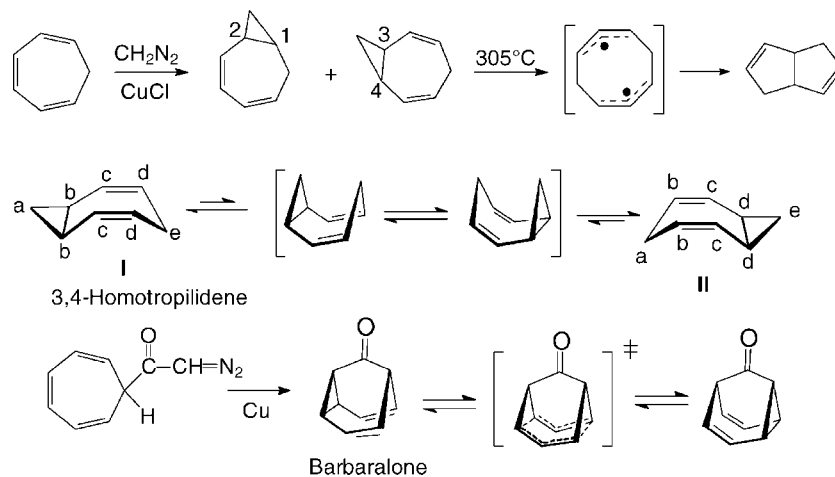
The addition of carbenes, methylene and carbomethoxycarbene generated by photochemically induced elimination of N_2 from the corresponding diazo compounds, to arenes and alkenes has been mentioned. These carbenes also add to alkynes producing the corresponding highly strained cyclopropene derivatives.¹⁸ The addition of carbenes generated in the electronic singlet state proceeds stereospecifically,^{19a,20} whereas stereochemical integrity is lost in the addition of triplet carbenes. Methylene is one of the most indiscriminate reagents known in organic chemistry. It undergoes a totally nonselective insertion into the different kinds of C–H bonds of pentane and 2,3-dimethylbutane.^{19b} Doering and Prinzbach²¹ investigated the mechanism of the C–H insertion of methylene by labeling the CH_2 group of isobutene with ^{14}C . The for-

mation of 1- ^{14}C -2-methyl-1-butene as the only product provides unambiguous evidence for a concerted C–H insertion of singlet methylene into an aliphatic C–H bond (Scheme 5). This finding excludes the alternative possible mechanism consisting of a hydrogen abstraction–radical pair recombination; had that been the case, scrambling of the ^{14}C label between C-1 and C-3 in the product would have been expected.

J. Hine²² explained the basic hydrolysis of chloroform in aqueous solution leading to sodium formate and carbon monoxide through the formation of dichlorocarbene as a reactive intermediate. A very useful preparative reaction studied by Doering and A. K. Hoffmann²³ is the α -elimination of HCl or HBr from chloroform or bromoform under anhydrous conditions using potassium *tert*-butylate as base. Under these conditions, dichlorocarbene or dibromocarbene adds to double bonds producing the corresponding dichloro- or dibromo-substituted cyclopropane derivatives (Scheme 6). The chloro or bromo substituents can be used for further transformations.

SCHEME 5. Elucidation of the Mechanism of C–H Insertion of Singlet Methylene by ^{14}C Labeling

SCHEME 6. Generation and Reactions of Dihalocarbenes

SCHEME 7. Synthesis and Degenerate Cope Rearrangement of Homotropilidene and Barbaralone^{25,26}

For example, the reduction of dibromocyclopropane derivatives with Mg or Na leads to allenes.²⁴ Nowadays the α -elimination of HCl or HBr from chloroform or bromoform can be carried out in a water/organic solvent two-phase system using NaOH or KOH as base and a phase-transfer catalyst, which transports the CCl_3^- or CBr_3^- anion from the aqueous to the organic phase, so that CCl_2 or CBr_2 is generated in the organic phase and adds to the π bond without hydrolysis.

Cope Rearrangement: Molecules with Fluxional Structures, Stereochemical Analysis, and Substituent Effects

The copper(I)-catalyzed decomposition of diazomethane in 1,3,5-cycloheptatriene leads to the two possible cyclopropane derivatives, 1,2- and 3,4-homotropilidene, which can be separated by GC. 1,2-Homotropilidene undergoes a degenerate butadienylcyclopropane rearrangement at 110 °C, whereas

3,4-homotropilidene isomerizes to tetrahydropentalene at high temperature (305 °C) via a formal vinylcyclopropane rearrangement presumably passing through a diradical intermediate. The temperature-dependent ^1H NMR spectrum of 3,4-homotropilidene shows that at room temperature it undergoes a rapid degenerate Cope rearrangement averaging the cyclopropane (a,b), vinyl (d), and methylene (e) atoms in structure I with the corresponding atoms in structure II (Scheme 7). In the case of barbaralone (prepared by an intramolecular carbenoid addition to the central cycloheptatriene double bond), the activation barrier determined by temperature-dependent ^1H NMR spectroscopy is even lower than that of 3,4-homotropilidene because in barbaralone the reacting *cis*-divinylcyclopropane system is fixed by the $\text{C}=\text{O}$ bridge in the *syn* conformation that is necessary for the Cope rearrangement. In the case of 3,4-homotropilidene, the sterically more hindered

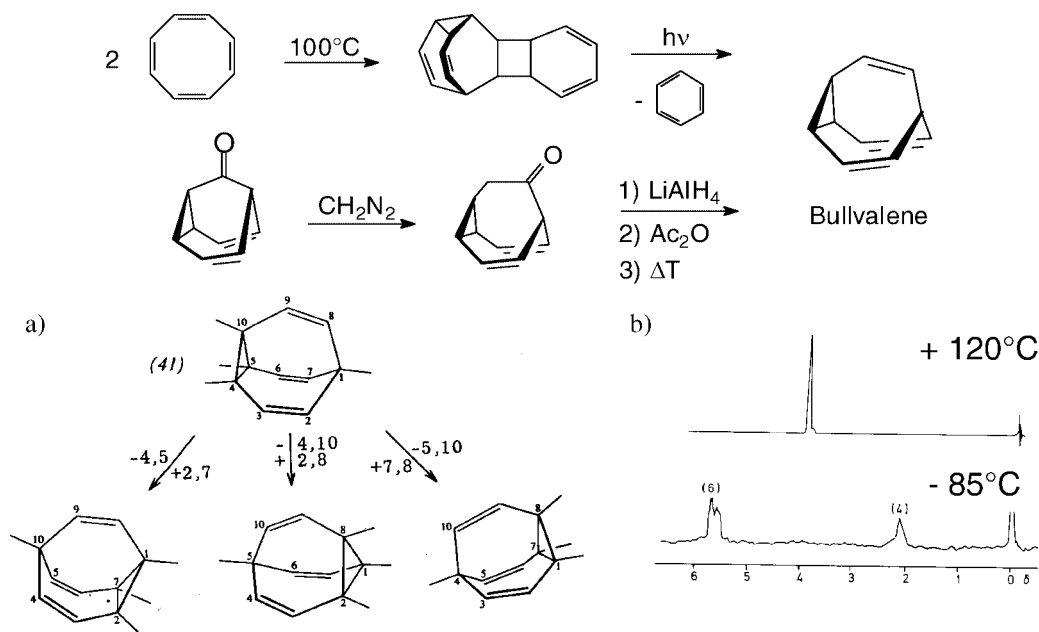


FIGURE 2. Synthesis of bullvalene and (a) degenerate cope rearrangements in bullvalene and (b) temperature-dependent ¹H NMR spectra of bullvalene.

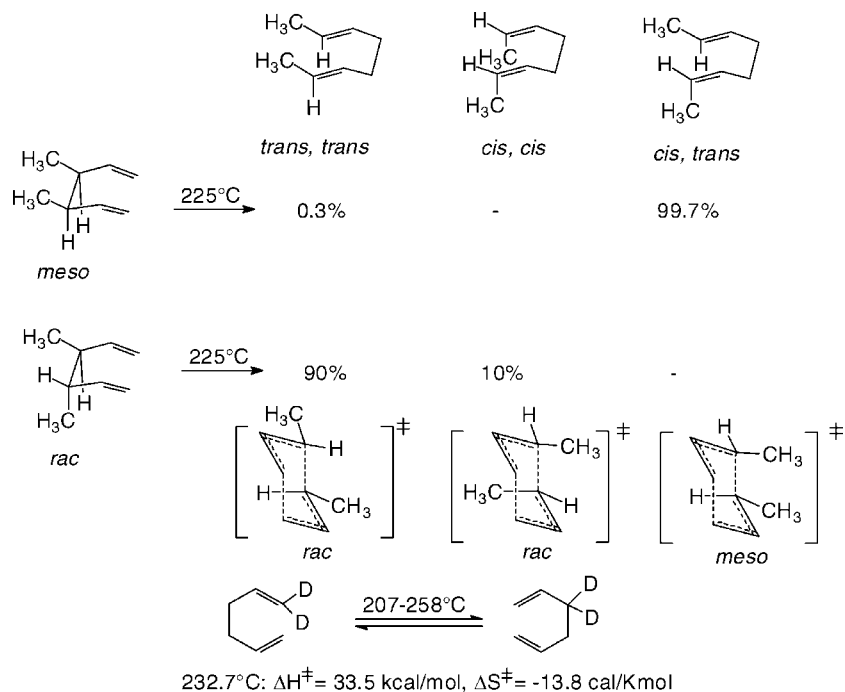
syn conformation has to be produced by ring inversion of the more stable *anti* conformation prior to the Cope rearrangement.^{25,26}

In 1963, Doering and Roth²⁵ predicted that bullvalene would be a fluxional molecule with over 1.2 million possible structures interconverted by degenerate Cope rearrangements averaging all H- and all C-atoms of the molecule. In 1964, Schröder (who had been a postdoctoral associate in Doering's laboratory few years earlier), Oth, and Merenyi^{27,28} observed that the photochemically induced [2 + 2] cycloversion of one of the cyclooctatetraene dimers produces bullvalene. This process is still the best synthesis of the molecule. Doering et al.²⁹ accomplished a rational synthesis of bullvalene in 1967 starting from barbaralone (Figure 2). The ¹H NMR spectrum of bullvalene at +120 °C shows only a sharp singlet for all protons as predicted for a Cope rearrangement proceeding rapidly on the NMR time scale. At -85 °C, at which temperature the Cope rearrangement is slow with respect to the NMR time scale, separate signals are observed, which can be assigned to the vinylic and aliphatic protons in the fixed structure.

Another highlight is the elucidation of the transition-state geometry of the Cope rearrangement of acyclic 1,5-hexadienes.^{26,30} The transition-state structures of the already discussed rearrangements of the *cis*-divinylcyclopropane units in homotropilidene, barbaralone, and bullvalene are restricted to a boat geometry. To determine the preferred transition state geometry for an acyclic diene, *meso*- and *rac*-3,4-dimethyl-1,5-hexadiene were shown to undergo nearly stereospecific

Cope rearrangement (Scheme 8). The *meso* starting material produced 99.7% of *cis,trans*-2,6-octadiene and only 0.3% of *trans,trans*-2,6-octadiene. The *racemic* reactant led only to *trans,trans*- and *cis,cis*-2,6-octadiene; no *cis,trans*-2,6-octadiene could be detected in this reaction. These findings exclude a boatlike transition state of the Cope rearrangement: if the boat were operative, rearrangement of the *meso* starting material would be expected to produce *cis,cis*- and *trans,trans*-2,6-octadiene, whereas the *racemic* would give *cis,trans*-2,6-octadiene, just opposite of the experimental results. These results, therefore, provide unambiguous evidence that the Cope rearrangement of acyclic 1,5-hexadienes proceeds through a chairlike transition state. If the trace of *trans,trans* diene from the *meso* reactant is an actual reaction product (and not the result of a small amount of *racemic* isomer in the starting material), then one can calculate that the reaction via the chairlike transition state is favored by $\Delta\Delta G^\ddagger = -5.8$ kcal/mol over that via the boatlike transition state; if it is an artifact, then the preference is even larger. In the case of *rac*-3,4-dimethyl-1,5-hexadiene, the absence of detectable *cis,trans*-diene suggests a preference for a chairlike transition state that is at least as great.

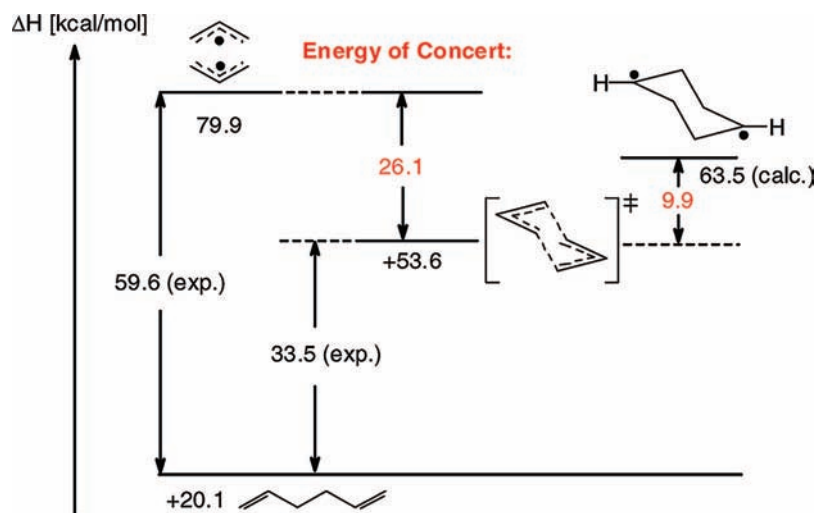
The enthalpy, ΔH^\ddagger , and entropy, ΔS^\ddagger , of activation have been determined for the Cope rearrangement of parent 1,5-hexadiene by means of specifically labeled 1,1-deuterio-1,5-hexadiene.³¹ The experimental ΔH^\ddagger value ($\Delta H^\ddagger_{\text{exp}} = 33.5$ kcal/mol) agrees very well with a value ($\Delta H^\ddagger_{\text{calc}} = 33.2$ kcal/mol) calculated by *ab initio* methods for the concerted reac-

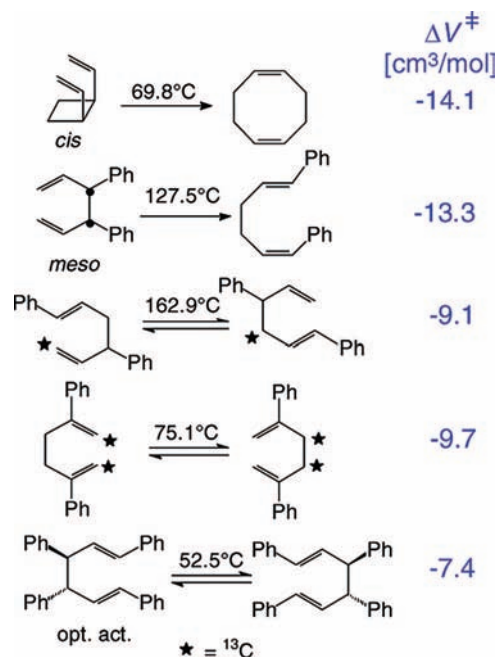
SCHEME 8. Stereochemical Course of the Cope Rearrangements of *meso*- and *rac*-3,4-Dimethyl-1,5-hexadiene^{26,30}

tion passing through the chairlike transition state.³² The energy of concert (which is defined analogously to the resonance energy of aromatic ground states) can be derived from the comparison of the experimental ΔH^{\ddagger} value with that determined or calculated for a suitable stepwise model reaction (Figure 3). The magnitude of the energy of concert depends on the choice of the model reaction. If the homolytic dissociation of 1,5-hexadiene into two allyl radicals and their recombination is used as potential stepwise reaction, then the energy of concert is calculated to be 26 kcal/mol, but if cyclo-

hexane-1,4-diyli is assumed to be an intermediate, then the energy of concerted is calculated to be only 10 kcal/mol.^{33,34}

High-pressure induced acceleration of rearrangements is a good criterion for the formation of cyclic transition states. Indeed, all of the Cope rearrangements shown in Scheme 9 are accelerated by high pressure, and the activation volumes determined from the pressure-dependence of the rate constants are negative. This finding is further good evidence that all these Cope rearrangements proceed through pericyclic

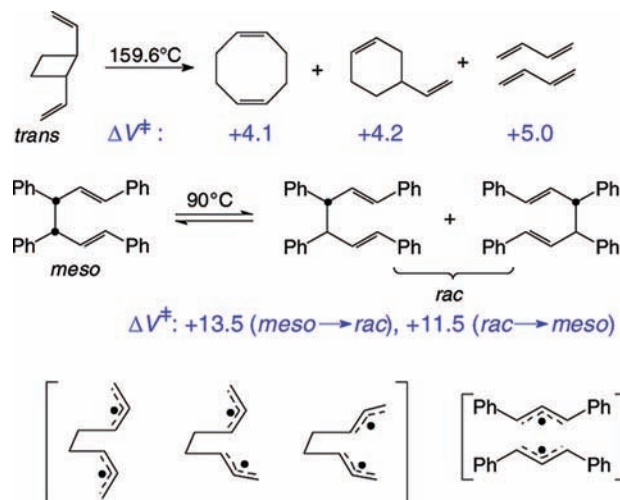
**FIGURE 3.** Activation parameters of the Cope rearrangement of 1,1-dideuterio-1,5-hexadiene and comparison of the enthalpy of activation with those calculated for stepwise dissociative and associative model reaction in order to determine the energy of concert.^{33,34}

SCHEME 9. Volumes of Activation (cm^3/mol) Determined from the Pressure Dependence of the Rate Constants of Various Cope Rearrangements^{35,36}

transition states in which the rotational degrees of freedom existing in the acyclic starting materials are restricted, leading to the decrease in the partial molar transition-state volumes observed by the negative ΔV^\ddagger values.^{35,36}

The rearrangements of *trans*-1,2-divinylcyclobutane and *meso,trans,trans*-1,3,4,6-tetraphenyl-1,5-hexadiene (Scheme 10) are retarded by high pressure. The activation volumes are positive indicating dissociation in the rate-determining step of these reactions. The comparison of these examples with those of the Cope rearrangements shows that high pressure is a good tool to distinguish between associative and dissociative rearrangements.

Substituents such as phenyl or cyano groups in the 2,5-positions or 1,3,4,6-positions of the 1,5-hexadiene molecule accelerate the Cope rearrangement substantially compared with the parent system (Scheme 11).^{34,37} This effect can be explained with the classical concept of resonance structures applied to transition states. The cyclohexane-1,4-diyl-like resonance structure explains the stabilizing effect of substituents in the 2,5-positions and the bisallyl-like structure rationalizes the stabilizing effect of substituents in the 1,3,4,6-positions. Accordingly, the transition state is like a chameleon favoring one or the other resonance structure depending on the substitution pattern. An interesting question, which cannot be answered by qualitative inspection of the transition-state resonance structures, is the following: What is the effect of substituents at C-1, -3, and -5 in a single hexadiene molecule?

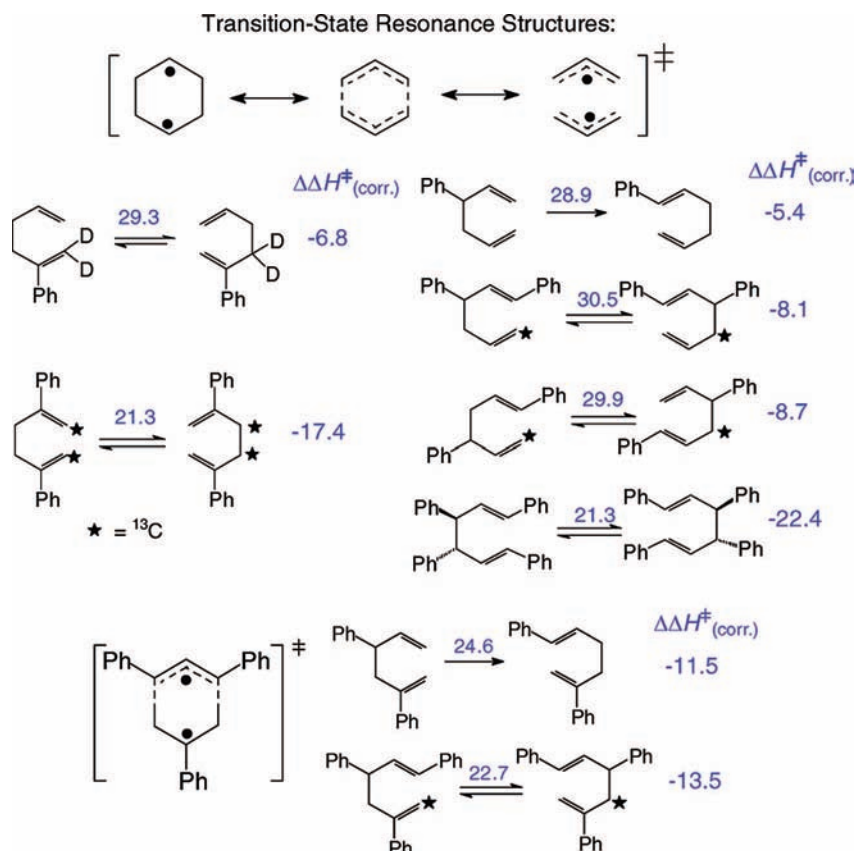
SCHEME 10. Volumes of Activation (cm^3/mol) Determined from the Pressure Dependence of the Rate Constants of Stepwise Rearrangements

The substituents at C-1 and -3 should favor the bisallyl-like and at C-5 the cyclohexane-1,4-diyl-like resonance structure. Does the transition state behave like a centaur; is it a hybrid beast? Indeed, the effect of substituents in these positions is larger than that of the separate 1,3- or 5-substituted system. However, the cooperative effects of phenyl groups in 2,5-diphenyl- and 1,3,4,6-tetraphenyl-1,5-hexadiene are larger than the competitive effect in the Cope rearrangement of 1,3,5-triphenyl-1,5-hexadiene. Ab initio calculations are in very good agreement with the experimental data. The calculated transition structures show very nicely the substitution-dependent shift of the geometry toward one or the other transition-state resonance structure.^{32,38}

Rearrangements Involving Diradical Intermediates: Continuous Diradicals and the Caldera

In the final topic, we will discuss a few rearrangements involving diradical intermediates. In 1961, Benson compared the activation enthalpies experimentally determined for the *cis*–*trans* isomerization of 1,2-dideuteriocyclopropane and the rearrangement of cyclopropane to propene with the enthalpy of formation calculated for 1,3-propanediyl by the use of bond increments. He concluded that ring closure and isomerization of the potential intermediate of these reactions, 1,3-propanediyl, should have substantial activation barriers (Table 1).^{39,40} Thus, a conformational equilibration of the diradical intermediate was expected to occur prior to the ring closure or isomerization.

In the 1960s and 1970s, the Doering group studied the kinetics and stereochemical course of several rearrangements

SCHEME 11. Substituent Effects on the Enthalpies of Activation (kcal/mol) Determined from the Temperature Dependence of the Rate Constants of Various Cope Rearrangements^{a,34,36}

^a $\Delta\Delta H^\ddagger = \Delta H^\ddagger(\text{subst}) - \Delta H^\ddagger(\text{parent})$ is corrected for the conjugative phenyl–vinyl interaction in the 1-, 2-, 5-, and 6-phenyl-substituted systems.

TABLE 1. Thermochemical Estimate of the Enthalpy of Activation of the Ring Closure and Isomerization of 1,3-Propanediyl to Cyclopropane and Propene, Respectively

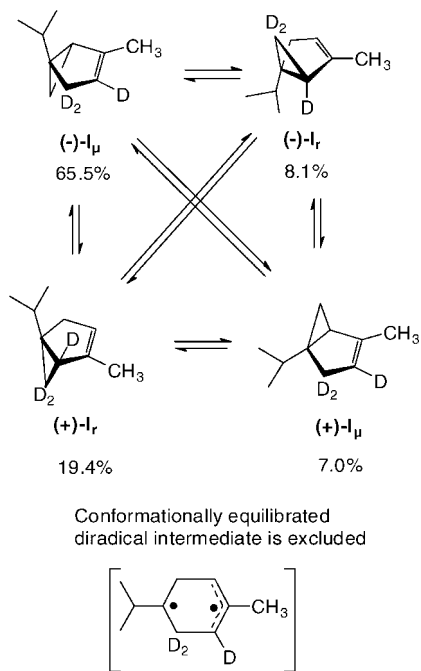
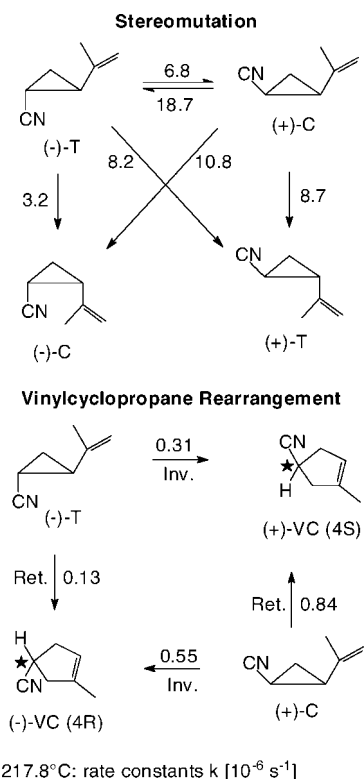
	Reaction	ΔH^\ddagger
		60.7
ΔH_f°		64.5
		+12.8
		+4.9
$\Delta H_f^\circ(\text{calc.})$		6.5
		+67.0 (Benson 1961) ^{39,40}
		+72.2 (Doering 1981) ⁴¹
<i>ab initio</i> calculation		2.0
		(Borden et al. 2004) ⁴²
		10.2
		(Benson 1961) ^{39,40}
		5.0
		(Doering 1981) ⁴¹

involving 1,3- and 1,4-diradicals in great detail. In most cases conformationally equilibrated diradical intermediates could be excluded. A very fine example is the vinylcyclopropane rearrangement and stereomutation of optically active specifically deuterium-labeled Δ^3 -thujene (Scheme 12).^{43–45} An intermediate conformationally equilibrated diradical is expected to give the three products a (1:1:1) ratio. The preferential forma-

tion of one product excludes a diradical intermediate in a well deep enough to experience conformational equilibration. Similar results were obtained by Cooke and Andrews⁴⁴ and Baldwin and Keliher⁴⁵ for the degenerate rearrangements of parent bicyclo[3.1.0]hex-2-ene only labeled by deuterium.

Similar results were obtained for the stereomutation and vinylcyclopropane rearrangement of optically active 1-cyano-2-isopropenylcyclopropane (Scheme 13).^{46,47} Here no preference of double over single rotation around the two substituted cyclopropane C atoms was observed as it was predicted by R. Hoffmann⁴⁸ for the parent cyclopropane. The single rotation around the cyano-substituted cyclopropane C atom was found to be faster than that around the isopropenyl-substituted C atom. In this system, the formal sigmatropic [1,3] carbon shift, the ring expansion of vinylcyclopropane to cyclopentene, proceeds slower than the stereomutation. The nonstereospecific course of the vinylcyclopropane rearrangement excludes an orbital-symmetry-controlled process. All these findings were explained with “continuous diradicals” as transition states.

In 1981, Doering⁴¹ used a newly available value of the enthalpy of formation of the ethyl radical (higher than the ear-

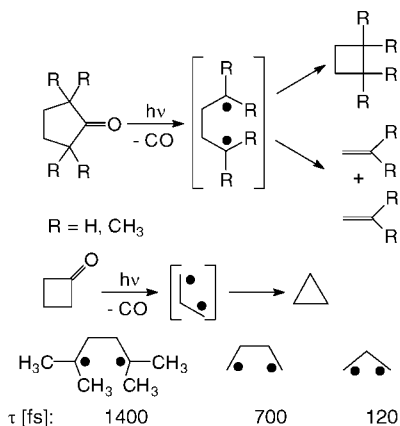
SCHEME 12. Stereomutation of Optically Active 3,4,4-Trideuterio- Δ^3 -thujene^{43–45}**SCHEME 13.** Stereomutation and Ring Expansion of Optically Active 1-Cyano-2-isopropenylcyclopropane^{46,47}

lier one used by Benson) to resolve the contradiction between the experimental results and the Benson estimate. This new value puts the 1,3-propanediyl only 1.3 kcal/mol below the TS enthalpy calculated from the enthalpy of formation of cyclo-

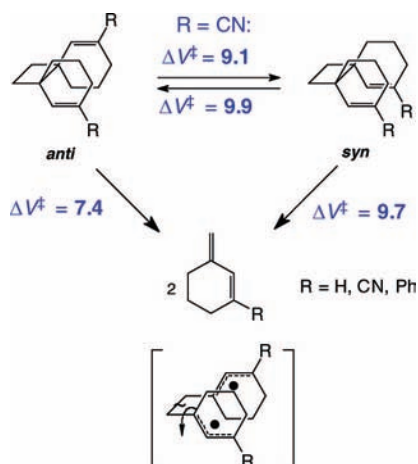
propane and the activation enthalpy of its stereomutation. This estimate is strongly supported by the most recent ab initio calculation.⁴² These calculations found no barrier to the ring closure of 1,3-propanediyl (the transition structure for conrotatory cyclopropane stereomutation) and put the calculated enthalpy of formation ca. 2 kcal/mol below the experimental barrier. Thus, ring closure and rotation around single bonds in the diradical are competitive processes, and the path of reaction depends on the conformation in which the diradical is initially formed and has to be described by an analysis of the dynamics. Dynamics calculations by Doubleday, Suhrada, and Houk⁴⁹ of the various pathways in the degenerate rearrangement of bicyclo[3.1.0]hex-2-ene derivatives are in very good agreement with the experimental data.^{43–45} Independent experimental evidence comes from studies with femtosecond spectroscopy. In the time-resolved flash photolysis of cyclopentanone and cyclobutanone, A. H. Zewail et al.⁵⁰ were able to observe 1,4- and 1,3-diradicals and found that the lifetimes of these diradicals are very short, in agreement with experimental and theoretical results described above.

The understanding of thermal reorganizations that pass through diradical intermediates (which Doering has called “not-obviously concerted” reactions) can be applied to the following question: Do diradicals continue on their way from educt through a “caldera” to products as “diradicals-in-transit” or do they pause in the “caldera” as “diradicals-as-intermediates” long enough to establish, or approach, equilibria among product-related conformations prior to exit. The divinylcyclobutane derivatives shown in Scheme 14 (in which the double bonds are fixed in transoid conformations by incorporating these bonds into six-membered rings) can only undergo stereomutation and formal [2 + 2] cycloreversion.^{51,52} Both processes are expected to pass through the bisallyl-stabilized diradical intermediate. The volumes of activation of the dicyano-substituted systems (as representative examples) were determined from the pressure dependence of the rates of reaction and the product ratio (Scheme 15). While the positive volumes of activation are consistent with the breaking of the weakest bond in the cyclobutanes leading to the intermediary diradical, the insensitivity of the product-determining exit channels to pressure argue against the obligatory second bond-breaking or bond-forming being significant factors for fragmentation and stereomutation, respectively. Evidently, pressure-independent bond rotations rather than bond cleavage or bond formation (which are expected both to be pressure-dependent in the diradical states positioned in the caldera) determine the product ratio. Today quantum chemical calculations combined with the calculation of reaction

SCHEME 14. The Lifetime of 1,3- and 1,4-Diradicals Generated by Time-Resolved Flash Photolysis of Cyclopentanone and Cyclobutanone by Means of Femtosecond Spectroscopy⁵⁰



SCHEME 15. Volumes of Activation (cm^3/mol) Determined from the Pressure Dependence of the Rate Constants of Stereomutation and Fragmentation of the Cyclodimers of 3-Methylenecyclohexene Derivatives^{51,52}



dynamics are performed with the aim to gain further insight into these reactions and to understand them. There remains much to do.

Concluding Remarks

The understanding of fundamental chemical reactions has been and still is the focus of Doering's research. In his terms, "understanding" means gaining not only deep insight but also the intellectual control that allows the prediction of the course of reaction. In order to explain what he means by intellectual control, Doering often uses the examples of concerted and "not obviously concerted" reactions, which have been investigated by his group in great detail. In the case of concerted reactions being controlled by orbital symmetry, the stereochemical course can be predicted by means of the Woodward–Hoffmann rules. But it is more difficult or even almost impossible to make a reliable prediction of the activa-

tion enthalpy. In the case of "not obviously concerted" reactions, the activation enthalpy can be mostly predicted by the use of the reliable thermochemical parameters available today. There is, however, no general way to make a reliable prediction for the stereochemical outcome of these reactions. Most recently, great progress in the understanding of chemical reactions has been achieved by the interplay between theory and experiment. Doering's experimental work provided an important input for computational chemistry and, hence, to the understanding of chemical reactions in his sense.

BIOGRAPHICAL INFORMATION

William von Eggers Doering (b. 1917) was educated as an undergraduate and graduate student at Harvard, receiving the Ph.D. in 1943 for work in the laboratory of Sir Reginald Patrick Linstead. His academic career began at Columbia in 1943 and continued there until 1952, at which time he moved to Yale where he stayed until 1967, becoming Whitehead Professor in 1956. In 1968, he returned to Harvard, as Mallinckrodt Professor. He formally retired in 1986 but has kept up a thriving research group to this day. He has received many prestigious awards beginning with the John Scott Medal of the City of Philadelphia (synthesis of quinine) in 1945 and culminating in the Kosolapoff Award of the Auburn Section of the American Chemical Society (1995). In between, he received the ACS Award in Pure Chemistry (1953), the ACS Award for Creative Work in Synthetic Organic Chemistry (1966), the A. W. Hofmann Medal of the Gesellschaft Deutscher Chemiker (1962), the William C. DeVane Medal from Yale (1967), and the James Flack Norris Award for Physical Organic Chemistry of the Northeastern Section of the American Chemical Society (1989). There have been honorary degrees from Texas Christian University and University of Karlsruhe, and an honorary Professorship from Fudan University in Shanghai. He is member of American Academy of Arts and Sciences (since 1962) and the National Academy of Science (since 1965).

Frank-Gerrit Klärner (b. 1941) studied chemistry at the University of Köln (Cologne, Germany) and received his Ph.D. there for work in the laboratory of Professor Emanuel Vogel in 1968. In 1974, he finished his "Habilitation" at the Ruhr-University of Bochum, was associate professor in Bochum from 1980 to 1992 and visiting professor at University of Wisconsin, Madison, in 1983. Since 1992, he has been full professor at the University of Duisburg-Essen, chaired the DFG center of supramolecular research at the Universities in Essen and Bochum ("Sonderforschungsbereich, SFB 452") from 1998–2005, and retired in 2006. His research interests are in the field of supramolecular chemistry (molecular tweezers and clips, molecular recognition, development of synthetic receptors for bioactive chemical compounds) and high-pressure chemistry (up to 14 kbar).

Maitland Jones, Jr. (b. 1937) earned his B.A. and Ph.D. degrees from Yale University in 1959 and 1963. For 43 years, he taught at Princeton University, from which he retired as David B. Jones

Professor of Chemistry to take up a position at New York University. He has been a visiting professor many places, including Columbia, Harvard, The Vrije Universiteit in Amsterdam, The Kiev Polytechnic in Ukraine, Fudan University in Shanghai, and the University of Basel in Switzerland. His research interests are in the area of reactive intermediates. With his students, he published over 200 research papers, and he has authored or edited ten books, among them a textbook on organic chemistry. These days, he is mainly interested in developing new methods of teaching organic chemistry, chief among them getting rid of the traditional lecture.

Ronald Magid (b. 1938) did his undergraduate and graduate work at Yale, earning his Ph.D. in 1963 under the guidance of William von E. Doering. After a postdoctoral year at Stanford, he joined the chemistry faculty at Rice University where he remained for six years. In 1970, he moved to The University of Tennessee from which he retired in 2006. His research interests were in the areas of carbene chemistry, pericyclic reactions, and allylic reactivity and stereochemistry. He now resides in Gig Harbor, WA, where he does his best to stay out of the rain.

FOOTNOTES

[†]Dedicated to Professor Bill Doering on the occasion of his 90th Birthday.

REFERENCES

- Woodward, R. B.; Doering, W. v. E. The total synthesis of quinine. *J. Am. Chem. Soc.* **1944**, *66*, 849. Woodward, R. B.; Doering, W. v. E. The total synthesis of quinine. *J. Am. Chem. Soc.* **1945**, *67*, 860–874.
- Seeman, J. I. The Woodward-Doering/Rabe-Kindler total synthesis of quinine: Setting the record straight. *Angew. Chem., Int. Ed.* **2007**, *46*, 1378–1413.
- Smith, A. C.; Williams, R. M. Rabe rest in peace: Confirmation of the Rabe-Kindler conversion of d-quinotoxine into quinine: Experimental affirmation of the Woodward-Doering formal synthesis of quinine. *Angew. Chem., Int. Ed.* **2008**, *47*, 1736–1740.
- Doering, W. v. E.; Knox, L. H. Synthesis of tropolone. *J. Am. Chem. Soc.* **1950**, *72*, 2305–2306.
- Doering, W. v. E.; Knox, L. H. Tropolone. *J. Am. Chem. Soc.* **1951**, *73*, 828–838.
- Doering, W. v. E.; Knox, L. H. The cycloheptatrienylium (tropylium) ion. *J. Am. Chem. Soc.* **1954**, *76*, 3203–3206.
- Doering, W. v. E.; Krauch, H. Das tropylium ion. *Angew. Chem.* **1956**, *68*, 661–667.
- Doering, W. v. E.; Detert, F. L. Cycloheptatrienylium oxide. *J. Am. Chem. Soc.* **1951**, *73*, 876–877.
- Doering, W. v. E.; Knox, L. H. Reactions of the cycloheptatrienylium (tropylium) ion. *J. Am. Chem. Soc.* **1957**, *79*, 352–356.
- Doering, W. v. E.; Wiley, D. W., Jr. Heptafulvene (methylenecycloheptatriene). *Tetrahedron* **1960**, *11*, 183–198.
- Doering, W. v. E.; Laber, G.; Vonderwahl, R.; Chamberlin, N. F.; Williams, R. B. The structure of the Buchner acids. *J. Am. Chem. Soc.* **1956**, *78*, 5448.
- Wehner, R.; Günther, H. Direct observation of Buchner's acid using carbon-13 and proton nuclear magnetic resonance spectroscopy. *J. Am. Chem. Soc.* **1975**, *97*, 923–924.
- Balci, M.; Fischer, H.; Günther, H. The dynamic behavior of 2,4,6-cycloheptatriene-1-carbaldehyde. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 301–302.
- Doering, W. v. E. personal communication cited by Woodward and Hoffmann. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781–932.
- Doering, W. v. E.; DePuy, C. H. Diazocyclopentadiene. *J. Am. Chem. Soc.* **1953**, *75*, 5955–5957.
- Woodward, R. B.; Hoffmann, R. The conservation of orbital symmetry. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781–932.
- Doering, W. v. E.; Mayer, J. R.; DePuy, C. H. Two-step synthesis of azulene. *J. Am. Chem. Soc.* **1953**, *75*, 2386.
- Doering, W. v. E.; Mole, T. Cyclopropenes from carbenes and acetylenes. stereo-selectivity in the reaction of carbomethoxycarbene with *cis*-butene. *Tetrahedron* **1960**, *10*, 65–70.
- (a) Doering, W. v. E.; LaFlamme, P. M. The *cis* addition of dibromocarbene and methylene to *cis*- and *trans*-butene. *J. Am. Chem. Soc.* **1956**, *78*, 5447–5448. (b) Doering, W. v. E.; Buttery, R. G.; Laughlin, R. G.; Chauduri, N. Indiscriminate reaction of methylene with the carbon-hydrogen bond. *J. Am. Chem. Soc.* **1956**, *78*, 3224.
- Skell, P. S.; Garner, A. Y. The stereochemistry of carbene-olefin reactions. reactions of dibromocarbene with the *cis*- and *trans*-2-butenes. *J. Am. Chem. Soc.* **1956**, *78*, 3409–3411. For a full discussion of the stereochemistry of singlet and triplet additions see: Jones, M., Jr.; Moss, R. A. Singlet Carbenes. In *Reactive Intermediate Chemistry*; Moss, R. A.; Platz, M. S.; Jones, M., Jr., Eds; Wiley: Hoboken, NJ, 2004. Tomioka, H. Triplet Carbenes. In *Reactive Intermediate Chemistry*; Moss, R. A.; Platz, M. S.; Jones, M., Jr., Eds; Wiley: Hoboken, NJ, 2004.
- Doering, W. v. E.; Prinzbach, H. Mechanism of reaction of methylene with carbon-hydrogen bond. Evidence for direct insertion. *Tetrahedron* **1959**, *6*, 24–30.
- Hine, J. Carbon dichloride as an intermediate in the basic hydrolysis of chloroform. A mechanism for substitution reactions at a saturated carbon atom. *J. Am. Chem. Soc.* **1950**, *72*, 2438–2445.
- Doering, W. v. E.; Hoffmann, A. K. The addition of dichlorocarbene to olefins. *J. Am. Chem. Soc.* **1954**, *76*, 6162–6165.
- Doering, W. v. E.; LaFlamme, P. M. A two-step synthesis of allenes from olefins. *Tetrahedron* **1958**, *2*, 75–79.
- Doering, W. v. E.; Roth, W. R. A rapidly reversible degenerate cope rearrangement. Bicyclo[5.1.0]octa-2,5-diene. *Tetrahedron* **1963**, *19*, 715–737. Doering, W. v. E.; Roth, W. R. Thermal rearrangements. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 115–122.
- Grimme, W.; Doering, W. v. E. A degenerate butadienylcyclopropane rearrangement in bicyclo[5.1.0]octa-2,4-diene. *Chem. Ber.* **1973**, *106*, 1765–1780.
- Merényi, R.; Oth, J. F. M.; Schröder, G. Die temperaturabhängigen NMR-spektren von tricyclo[3.3.2.0^{4,6}]deca-2,7,9-trien, einigen seiner derivate und von tricyclo[3.3.2.0^{4,6}]decatrien-(2,7,9) (Bullvalen). *Chem. Ber.* **1964**, *97*, 3150–3161.
- Schröder, G.; Oth, J. F. M.; Merényi, R. Molecules undergoing fast, reversible valence-bond isomerization (molecules with fluctuating bonds). *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 752–761.
- Doering, W. v. E.; Ferrier, B. M.; Fossel, E. T.; Hartenstein, J. H.; Jones, M., Jr.; Klumpp, G.; Rubin, R. M.; Saunders, M. A rational synthesis of bullvalene, barbalone and derivatives; bullvalone. *Tetrahedron* **1967**, *23*, 3943–3963.
- Doering, W. v. E.; Roth, W. R. Overlap of two allyl radicals or a four-centered transition state in cope rearrangement. *Tetrahedron* **1962**, *18*, 67–74.
- Doering, W. v. E.; Toscano, v. G.; Beasley, G. H. Kinetics of Cope rearrangement of 1,1-dideuteriohexa-1,5-diene. *Tetrahedron* **1971**, *27*, 5299–5306.
- Hrovat, D. A.; Chen, J. G.; Houk, K. N.; Borden, W. T. Cooperative and competitive substituent effects on the Cope rearrangements of phenyl-substituted 1,5-hexadienes elucidated by Becke3LYP/6-31G* calculations. *J. Am. Chem. Soc.* **2000**, *122*, 7456–7460.
- Roth, W. R.; Lennartz, H. W.; Doering, W. v. E.; Birladeanu, L.; Guyton, C. A.; Kitagawa, T. A frustrated Cope rearrangement - Thermal interconversion of 2,6-diphenylhepta-1,6-diene and 1,5-diphenylbicyclo[3.2.0]heptane. *J. Am. Chem. Soc.* **1990**, *112*, 1722–1732.
- Doering, W. v. E.; Wang, Y. H. Perturbation of Cope's rearrangement: 1,3,5-Triphenylhexa-1,5-diene. Chameleonic or centaauric transition region. *J. Am. Chem. Soc.* **1999**, *121*, 10112–10118.
- Doering, W. v. E.; Birladeanu, L.; Sarma, K.; Teles, J. H.; Klärner, F.-G.; Gehrke, J. S. Perturbation of the degenerate, concerted Cope rearrangement by 2 phenyl groups in active positions of (*E*)-1,4-diphenylhexa-1,5-diene - Acceleration by high-pressure as criterion of cyclic transition states. *J. Am. Chem. Soc.* **1994**, *116*, 4289–4297.
- Doering, W. v. E.; Birladeanu, L.; Sarma, K.; Blaschke, G.; Scheidemantel, U.; Boese, R.; Benet-Bucholz, J.; Klärner, F.-G.; Gehrke, J. S.; Zimny, B. U.; Sustmann, R.; Korth, H. G. A non-Cope among the Cope rearrangements of 1,3,4,6-tetraphenylhexa-1,5-dienes. *J. Am. Chem. Soc.* **2000**, *122*, 193–203.
- Doering, W. v. E.; Wang, Y. H. CryptoCope rearrangement of 1,3-dicyano-5-phenyl-4,4-d(2)-hexa-2,5-diene. Chameleonic or centaauric. *J. Am. Chem. Soc.* **1999**, *121*, 10967–10975.
- Hrovat, D. A.; Beno, B. R.; Lange, H.; Yoo, H. Y.; Houk, K. N.; Borden, W. T. A Becke3LYP/6-31G* study of the Cope rearrangements of substituted 1,5-hexadienes provides computational evidence for a chameleonic transition state. *J. Am. Chem. Soc.* **1999**, *121*, 10529–10537.
- Benson, S. W. Reaction of cyclopropane with iodine and some observations on the isomerization of cyclopropane. *J. Chem. Phys.* **1961**, *34*, 521–526.
- Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley: New York, 1976; pp 117–120.
- Doering, W. v. E. Impact of upwardly revised $\Delta_i H^\ddagger$ of primary, secondary, and tertiary radicals on mechanistic constructs in thermal reorganizations. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 5279–5283.
- Isborn, C.; Hrovat, D. A.; Borden, W. T. Does formation of singlet propane-1,3-diyli

- from propane deviate from bond enthalpy additivity? Results of ab initio calculations that bear on the existence of the benson barrier to diradical ring closure. *J. Phys. Chem. A* **2004**, *108*, 3024–3029.
- 43 Doering, W. v. E.; Lambert, J. B. Thermal reorganization of α - and β -thujene. A degenerate rearrangement of the vinylcyclopropane type. *Tetrahedron* **1963**, *19*, 1989–1994. Doering, W. v. E.; Schmidt, E. K. G. Conformational control of stereochemistry in non-concerted, degenerate rearrangement of a vinylcyclopropane. (–)- Δ^3 -Thujene. *Tetrahedron* **1971**, *27*, 2005–2030. Doering, W. v. E.; Zhang, T. H.; Schmidt, E. K. G. Kinetics of thermal rearrangements in the Δ^2 -thujene system: A full quadrisection of a perturbed bicyclo[3.1.0]hex-2-ene. *J. Org. Chem.* **2006**, *71*, 5688–5693.
- 44 Cooke, R. S.; Andrews, U. H. Thermal rearrangements of bicyclo[3.1.0]hex-2-ene. Studies of degenerate rearrangements. *J. Am. Chem. Soc.* **1974**, *96*, 2974–2980.
- 45 Baldwin, J. E.; Kelliher, E. J. Activation parameters for three reactions interconverting isomeric 4- and 6-deuteriobicyclo[3.1.0]hex-2-enes. *J. Am. Chem. Soc.* **2002**, *124*, 380–381.
- 46 Doering, W. v. E.; Sachdev, K. Continuous diradical as transition state. Internal rotational preference in thermal enantiomerization and diastereoisomerization of *cis*- and *trans*-1-cyano-2-isopropenylcyclopropane. *J. Am. Chem. Soc.* **1974**, *96*, 1168–1187.
- 47 Doering, W. v. E.; Sachdev, K. Continuous diradical as transition state. II. Internal rotational preference in cyclopentene rearrangement of the vinylcyclopropanes, (1*S*,2*R*)-(+)-*cis*- and (1*R*,2*R*)-(–)-*trans*-1-cyano-2-isopropenylcyclopropane. *J. Am. Chem. Soc.* **1975**, *97*, 5512–5520.
- 48 Hoffmann, R. Trimethylene and the addition of methylene to ethylene. *J. Am. Chem. Soc.* **1968**, *90*, 1475–1485.
- 49 Doubleday, C.; Suhrada, C. P.; Houk, K. N. Dynamics of the degenerate rearrangement of bicyclo[3.1.0]hex-2-ene. *J. Am. Chem. Soc.* **2006**, *128*, 90–94.
- 50 Pedersen, S.; Herek, J. L.; Zewail, A. H. The validity of the “diradical” hypothesis: Direct femtosecond studies of the transition-state structures. *Science* **1994**, *266*, 1359–1364. Zewail, A. H. Femtochemistry: Atomic-scale dynamics of the chemical bond using ultrafast lasers (Nobel Lecture). *Angew. Chem., Int. Ed.* **2000**, *39*, 2586–2631.
- 51 Doering, W. v. E.; Ekmanis, J. L.; Belfield, K. D.; Klärner, F.-G.; Krawczyk, B. Thermal reactions of *anti*- and *syn*-dispiro[5.0.5.2]tetradeca-1,8-dienes: Stereomutation and fragmentation to 3-methylenecyclohexenes. Entropy-dictated product ratios from diradical intermediates. *J. Am. Chem. Soc.* **2001**, *123*, 5532–5541.
- 52 Klärner, F.-G.; Wurche, F.; Doering, W. v. E.; Yang, J. D. Pressure independence of stereomutation and fragmentation in the bis-spirocyclobutanes, *anti*- and *syn*-2,9-dicyanodispiro[5.0.5.2]tetradeca-1,8-dienes. *J. Am. Chem. Soc.* **2005**, *127*, 18107–18113.