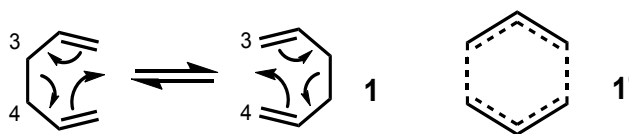


MOLECULES WITH FLUXIONAL STRUCTURE: AN INITIAL MOMENT IN THEIR CONCEPTION

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The structural theory of Kekulé (1), Couper (2) and Butlerow (3), marked the beginning of present day organic chemistry. It postulated that the individual atoms in a molecule are bonded with one another in a definite connectivity and that this connectivity defines the identity (i.e., structure) of a given compound composed of these molecules. This theory explained why different compounds with the same atomic composition exist (isomeric compounds) and how many different isomers are possible for a given composition. In order to convert one isomer of a given composition into another isomer, bonds between certain atoms have to be broken in the original isomer, and reconnected in a different fashion to reach the other isomer. This defines the bond changes that have to be accomplished in an isomerization reaction converting the structure of the initial compound into that of the product compound. Nothing is said at this stage about the number of steps and kinds of reagents necessary to effect this transformation. At least, it allows for a one-step intramolecular transformation without external reagents, simply triggered by supply of thermal or photochemical energy. Such processes are called *valence-isomerizations*, for which numerous examples are known (4). One could project a valence isomerization in which the structure of the initial and the final isomer are identical, a reaction with no net chemical transformation, i.e. a valence isomerization in which the breaking and forming bonds are related to one another by some symmetry element. In such a process the bonding situation between individual atoms is altered, while the overall bond pattern between

all atoms is maintained. A representative example of such a process would be the Cope rearrangement (5) of 1,5-hexadiene (**1**):



Provided this reaction is an intramolecular—not a dissociation-recombination—process, this constitutes a *degenerate* valence isomerization, in as much as the breaking and forming bonds are symmetry related in the transition state **1'**. The Cope rearrangement of 1,5-hexadiene was observed to occur at $>200^{\circ}\text{C}$; the fate of individual atoms was demonstrated by tagging the 3- and 4-positions with deuterium (6).

Yet, there was a further extension regarding degenerate valence isomerizations lying dormant: What if such a degenerate valence isomerization were to occur at or below room temperature? What would this imply for our concrete notion of “structure of a compound” as defined by a distinct connectivity of *individual* atoms in a molecule? Whenever a degenerate valence isomerization in a molecule is occurring with an appreciable rate, its structure would be fluxional, while its structural identity is conserved. This would constitute a case at the limits of structural theory, as holds for the classical valence bond description of benzene. Even more fascinating and important, such molecules with fluxional structures would be at the transition region between molecules with traditional

bonding and those with delocalized bonding! It is these insights that mark an important step in the conceptual development of organic chemistry and justify the question, when, where, and by whom was this intellectual process initiated? Was it a parallel discovery at several independent places, or did it occur in a flash of genius, a single *historic moment*, at a distinct site?

A Historic Moment

A “moment”—as used in this essay—is defined as an assembly of one or more persons, one or more objects in a defined location and time. That means a situation, reduced to the essentials like a stage setting in a play. Most moments are inconsequential, as driving through an intersection past a green light. Some moments are consequential, as driving through an intersection past a red light and hitting another car. Consequences that may originate from this moment are, e.g., damage to either car that will have to be repaired, injuries to the people involved that need extended medical treatment, a court case eventually leading to a prison sentence, loss of employment because of the latter, and so on. Some moments cause a major sequence of other moments, a chain of effects that may ramify, much like an avalanche. At some point later people may ask, where, when, and why did all this start? This looking back in time brings in the “historic” element. Identifying the moment at the root of a sequence of consequential moments then defines it as the (or one) historic moment of the development. It is only in hindsight that a specific consequential moment may acquire the attribute “historic,” and, the attribute



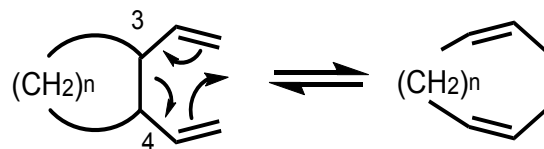
Figure 1. William von E. Doering (left) and Emanuel Vogel at Vogel's home, Cologne, ca. 2000. Photograph courtesy Mrs. E. Vogel.

“historic moment” should always be connected with a distinct sequence of events, a distinct development.

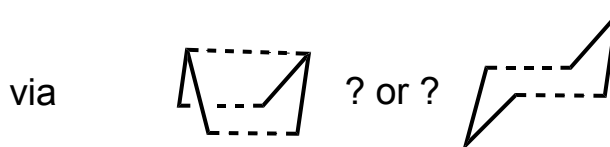
Molecules with Fluxional Structure

In hindsight, it appears probable that the phenomenon of molecules with fluxional structure would be discovered when studying variations of the Cope rearrangement. In the early 1960s there were two major players studying aspects of the Cope-rearrangement: Priv.Do. Dr. Emanuel Vogel in Karlsruhe, Germany, and Prof. W. von E. Doering at Yale University in New Haven, Connecticut, USA (Figure 1).

Vogel was studying the influence of ring-strain at the C3-C4-bond on the facility of the Cope rearrangement, with $n = 1-3$ (7).

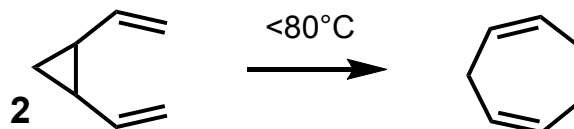


Doering was studying the transition state conformation of the Cope-rearrangement (8), probing, whether a six-center boat-like arrangement or a four-center chair-like arrangement is favored.



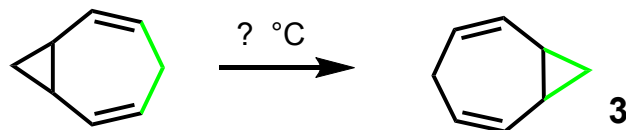
When Doering was scheduled to give a seminar speech on the “Mechanism of the Cope Rearrangement” in Heidelberg on April 25 (see (9, 10) and Figure 2), no results from these studies had been published beyond a three-sentence statement in a 1960 review by Vogel (11) on small carbon cycles.

Vogel came up from nearby Karlsruhe to attend. Doering's lecture focused on the studies on the transition state of the Cope-rearrangement. After the lecture had finished a handful of people (I was one of them) flocked together with Doering at the blackboard. After some other topics had been discussed, Vogel drew out at the blackboard his observations on the rearrangement of *cis*-divinyl-cyclopropane **2** to 1,4-cycloheptadiene,



demonstrating the major effect the release of ring-strain

had on the rate of the Cope rearrangement. The discussion went to the entropic penalty caused by confining the dangling vinyl groups of **2** in the transition state. Upon which Vogel suggested to incorporate them into an additional cycle and supplemented his scheme with colored chalk:



Before Vogel could finish to put all the lines on the blackboard, Doering remarked “Hey, that’s gonna be degenerate!” Most of the people present will have realized that when the rearrangement of **2** occurs well below 80°C—it later has been shown to occur at room temperature with a half-life of a few minutes (12)—molecules such as homotropilidene (**3**) would be fluxional at ambient temperature. The discussion ended shortly thereafter, and Doering, Vogel, and others adjourned for dinner. I do not know whether Vogel and Doering followed up on the discussion of a degenerate Cope rearrangement during the dinner. Any such discussion would however have been contingent upon the aftermath of Doering’s lecture on April 25 in Heidelberg, which thus marked the birth of the concept of degenerate rearrangements on the way to molecules with fluxional structures.



Homotropilidene



Barbaralane

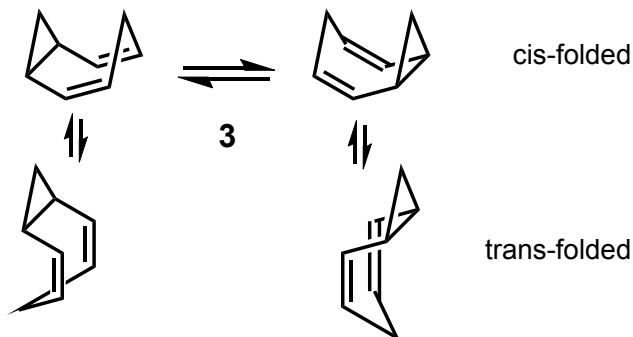


Bullvalene



Semibullvalene

The April 25 flash of genius led to a cascade of consequences, in which the conception and synthesis of compound **3** constituted only the first link. It was recognized that the resting state of compound **3** is a *trans*-folded conformation, which has to convert to the *cis*-folded conformation to allow the degenerate Cope rearrangement. Hence, bridging bow and stern of **3** would fix the *cis*-folded arrangement and should accelerate the Cope-rearrangement even further.



Accordingly, the bridged homotropilidene **4** dubbed barbaralane and derivatives thereof were envisaged and synthesized (13). Indeed compound **4** underwent an exceedingly fast degenerate rearrangement at 0°C (14)—a significant advance to generate molecules subject to rapidly degenerate rearrangement.

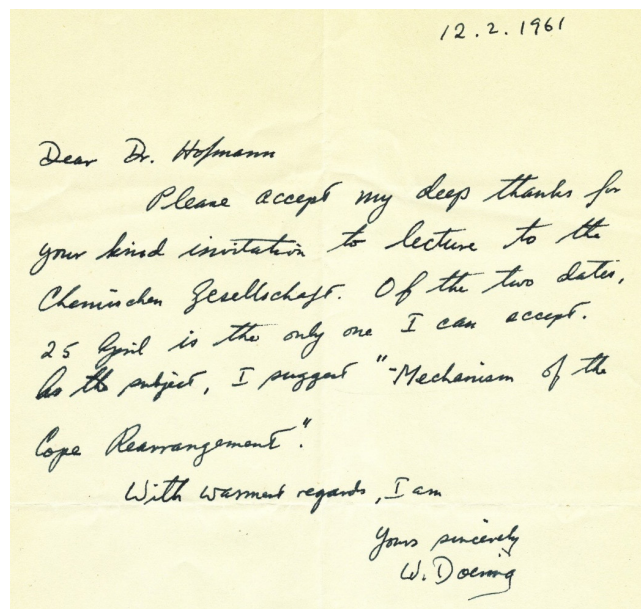


Figure 2. Letter by W. v. E. Doering to Prof. U. Hofmann, the then Chairman of the Chemische Gesellschaft zu Heidelberg. Courtesy of Prof. G. Helmchen, Heidelberg 26.10.2021.

Another extension was initiated (first conceptually by Doering and Roth (9)) by bridging the bow and stern positions in **3** by a 1,2-ethenylidene bridge to result in compound **5**. The famous “bullvalene” **5** should be fully fluxional exchanging the positions of every C-H unit in its structure by degenerate Cope rearrangement. In due course, bullvalene was synthesized, first by G. Schröder (15), and subsequently by several differing routes later (14, 16). As anticipated, the $^1\text{H-NMR}$ spectrum of **5** is temperature dependent, showing only a single sharp C-H signal at 100°C (15).

Comparing the bridged homotropilidenes **4** and **5**, compound **4** with a one-carbon bridge rearranged substantially faster than compound **5** and related structures with a two-carbon bridge (14). This led one to expect, that compound **6**, semibullvalene might rearrange even faster.

When semibullvalene **6** was obtained by H. E. Zimmerman and G. L. Grunewald in 1965 (17), its degenerate rearrangement could not be frozen out even at -110°C . This led Zimmerman to speculate, that **6** might have or



come close to having a fully delocalized homoaromatic ground state **6'**.

A decade later, the free energy of activation for the isomerization of **6** could be determined to $\Delta^\ddagger G^\circ = 5.5$ kcal/mol (18), validating Zimmerman's conclusion, that compound **6** is fluxional, but not delocalized (**6'**). Yet as R. V. Williams puts it (19), “It is generally recognized that semibullvalene (**6**) is the species most closely approaching the holy grail of neutral homoaromaticity” (20). Cf. **6'** with a delocalized six-electron system.

Thus semibullvalene (**6**) turned into a starting point of still ongoing worldwide research activities (19) to reach a delocalized derivative of **6'** by adding substituents or annelating rings to semibullvalene.

Conclusions

The aftermath of Doering's lecture at April 25, 1961, in the lecture hall of the old chemistry building of the University of Heidelberg in Akademiestrasse 5 in Heidelberg was not just any moment in chemistry. The consequences and sequence of consequences of this moment led to research activities that continue even today, 60 years later. This moment in Heidelberg can now be

assigned to likely (21) be the key “historic moment for the development of molecules with fluxional structure.”

The story of molecules with fluxional structure has been told before (22). Yet, every time a story is told, different details are revealed and highlighted, as holds for the present essay.

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 20. While aromaticity refers to cyclic systems in which each ring atom contributes one p-orbital to the cyclic conjugation, **homoaromaticity** likewise refers to cyclic systems in which each ring atom *except one* contributes one p-orbital to the cyclic conjugation. Thus, cyclic conjugation has to bridge a one-atom gap. Bis-homoaromatic would refer to rings with two such bridging situations.
 21. One may be tempted to consider an alternate scenario, that Doering had conceived homotropilidene (**3**) and had started working towards it *prior to* April 25, 1961. In this case, however, Doering’s reaction to the disclosure of Vogel at the blackboard would probably have been a different one.
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Bite-sized Pieces of History

Every issue of the *Bulletin* contains short items, mainly announcements, in spaces like this, at the end of articles. It has been suggested to me that such spaces could also be used for short items of historical interest. I would welcome such short pieces to be collected and run as space permits. Please send such items of approximately 200-300 words to the Editor at giunta@lemoyne.edu under the subject heading “bite-sized history.” Pieces will be subject to editing. Authors will be credited and notified.

—the Editor