

# Pericyclic Reaction Transition States: Passions and Punctilios, 1935–1995

KENDALL N. HOUK,\* JAVIER GONZÁLEZ,† AND YI LI‡

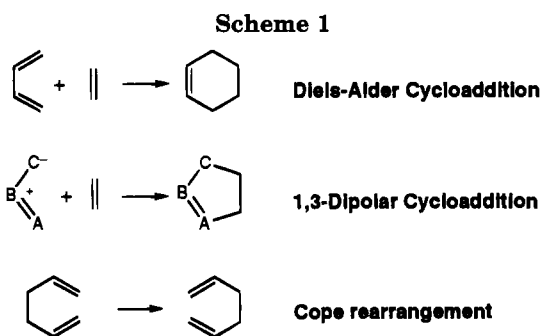
Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569

Received August 1, 1994

Pericyclic reactions may be the most important class of organic reactions. Certainly, the mechanisms of these reactions have been the subject of the most heated and interesting controversies. Woodward and Hoffmann defined the concept of a pericyclic reaction: a concerted reaction in which all bonds are made or broken around a circle. Although the Woodward–Hoffmann rules declare what may and may not happen, the rules served not to settle mechanistic questions but to raise the stakes on what were already lively controversies. This Account traces 60 years of discoveries made by dynamic and colorful chemists and the insights, arguments, and occasionally hilarious events which have shaped our 1995 vision of the nature of the transition states of pericyclic reactions.<sup>1</sup> Three of the pericyclic reactions which we have studied, which happen to be the most thoroughly investigated pericyclic reactions, are emphasized: the Diels–Alder reaction, 1,3-dipolar cycloaddition, and the Cope rearrangement (Scheme 1).

## Experimental Studies

**Diels–Alder Reaction: Concerted vs Stepwise Mechanisms.** The Diels–Alder reaction is the most widely used and best known pericyclic reaction. It was discovered in the 1920s by Otto Diels and Kurt Alder in Germany<sup>2</sup> and soon became a very useful tool in synthetic organic chemistry.<sup>3</sup> A Nobel prize was awarded in 1950 for its discovery.

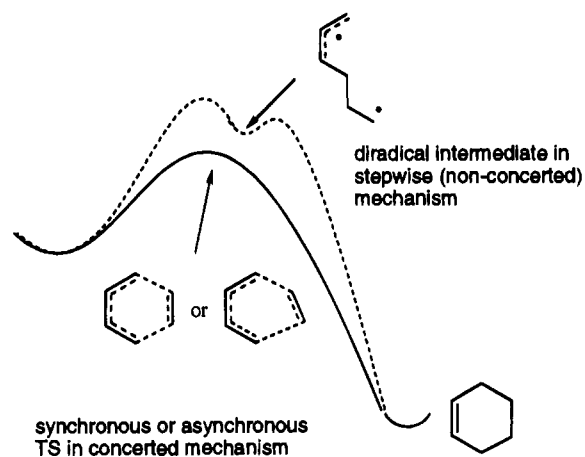


Two limiting mechanisms are possible in the Diels–Alder reaction (Figure 1). The reaction may take place

K. N. Houk is professor of chemistry at UCLA. His graduate research with R. B. Woodward at Harvard was at the time of the development of the Woodward–Hoffmann rules, and this immersed him forever in the subject of this Account. He has been on the faculty at Louisiana State University, Baton Rouge, and the University of Pittsburgh and has served as director of the Chemistry Division of the National Science Foundation. He recently completed a term as chair of the Department of Chemistry and Biochemistry at UCLA.

Javier González was born and educated in Oviedo in Spain, where he received his Ph.D. in experimental organic chemistry. He spent one year as a Fulbright Fellow with Professor Houk at UCLA and is now professor titular in Oviedo.

Yi Li received his B.S. degree in chemistry from Wuhan University in China. He came to the United States as part of the Chemistry Graduate Program. He studied at Pittsburgh and UCLA with Professor Houk, receiving his Ph.D. in 1988.



**Figure 1.** Energy versus reaction coordinate diagrams for concerted and stepwise mechanisms of the Diels–Alder reaction. The extended diradical is shown. Firestone invokes a “cyclo-diradical” as intermediate.

in a concerted fashion, with partial formation of the two new bonds in the single transition state. If both bonds are formed to exactly the same extent in the transition state, this is called a synchronous concerted reaction; otherwise, it is asynchronous. The other extreme is a stepwise process, involving first the formation of an intermediate with a single bond formed between diene and dienophile; subsequent formation of the second bond gives the cycloadduct. Either step may be rate determining, and such an intermediate may be either diradical or zwitterionic.

In 1935, the first transition state model for the Diels–Alder reaction was proposed by A. Wasserman,<sup>4</sup> who postulated a concerted transition state, with forming CC bond distances of 2.0 Å, a remarkably good guess in light of current knowledge.<sup>1</sup> Shortly thereafter, Littman proposed that what we now call diradicals were intermediates in the Diels–Alder reaction,

\* Francisco Javier González Fernández. Present address: Instituto Universitario de Química Organometálica, “Enrique Moles” Universidad de Oviedo, 33071-Oviedo, Spain.

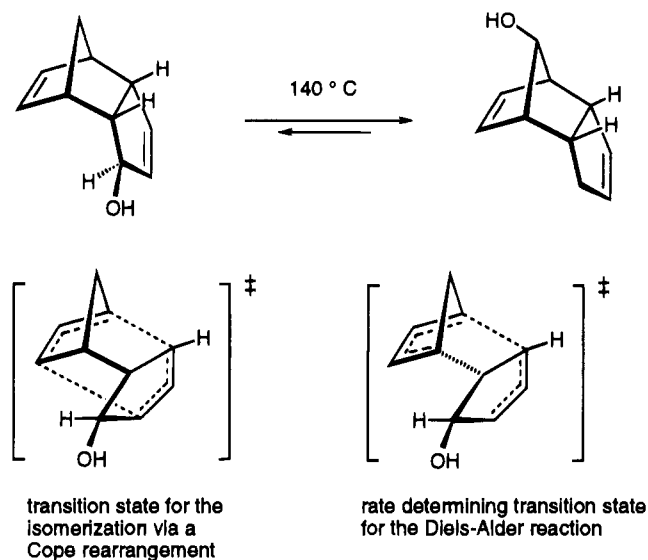
† Present address: Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT 06492.

(1) Houk, K. N.; Li, Y.; Evanseck, J. D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 682. We are delighted that Editor Peter Götzl adorned the cover with pictures of Woodward and Hoffmann and six of our calculated pericyclic transition structures.

(2) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98. An earlier paper reports a hetero-Diels–Alder reaction. A captivating review of the discovery of the Diels–Alder reaction including the fact that von Euler and Thiele earlier observed what we now know as a Diels–Alder reaction recently appeared: Berson, J. A. *Tetrahedron* (Perspective No. 1) **1992**, *48*, 3.

(3) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779. Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990. Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 315. Weinreb, S. M., op. cit., p 401; Boyes, D. L., op. cit., p 451; Roush, W. R., op. cit., p 513.

(4) Wasserman, A. *J. Chem. Soc.* **1935**, 828.



**Figure 2.** The Cope rearrangement studied by Woodward and Katz.<sup>8</sup>

and George Kistiakowsky (later a presidential science advisor) expressed a similar point of view.<sup>5</sup> Wasserman countered that the observed small Arrhenius A factors were best explained by a concerted mechanism in which two molecules have to come into contact simultaneously at two specific positions during a successful collision.<sup>6</sup> Ionic intermediates and transition states were also invoked in the early days to explain the regioselective formation of certain products.<sup>4,7</sup> Over 50 years ago, both stepwise and concerted mechanisms had eloquent champions!

R. B. Woodward (Nobel laureate for natural product synthesis) and graduate student Thomas Katz (now professor at Columbia) constructed an elegant mechanistic analysis based on a study of what we now consider a Cope rearrangement (Figure 2).<sup>8</sup> The interconversion was found to take place with complete retention of stereochemical integrity. Because both of these compounds could be formed by Diels–Alder reactions, Woodward and Katz considered the transition state that interconverts them to be related to the Diels–Alder transition state. The formation of a single bond between the diene and the dienophile was considered to be the rate-controlling step, while the other forming bond was barely beginning to form in the transition state.<sup>8</sup> This *two-stage* mechanism, in which the formation of two bonds takes place in separate, but overlapping, processes, would now be called an asynchronous concerted process.

Dewar objected to this formulation on the basis of the relative rates of reaction of isoprene with maleic anhydride (4300) and acrolein (61), and of butadiene

with ethylene (1).<sup>9</sup> Using these rate ratios, the differences in the rates of the reactions are similar for ethylene and acrolein (1:61), and acrolein and maleic anhydride (1:71). Dewar considered that this observation provided very strong evidence for the one-step mechanism for the Diels–Alder reaction, proceeding through a cyclic pseudoaromatic transition state. He vigorously advocated symmetric cyclic transition states for Diels–Alder reactions.<sup>9</sup> For the irony of this stance, see later in this Account!

Dewar's objections were colorfully rejected by Woodward and Katz,<sup>10a</sup> who humorously described Dewar's work as "a potentially useful punctilio...".<sup>10b</sup> Woodward and Katz noted the exceptional reactivity of maleic anhydride even in reactions such as radical additions involving initial attack upon only one terminus of its double bond. It is notable that this rapid exchange occurred in *Tetrahedron Letters* within three weeks in 1959 even before FAX machines!

Many other mechanistic studies followed, including many studies of stereoselectivity. The vast majority of these showed stereospecificity compatible with concertedness, although non-stereospecific reactions are also known.<sup>11a</sup> One of the most recent studies was our study of the reaction of 1,1,4,4-tetradeuteriobutadiene with *cis*- and *trans*-1,2-dideuterioethylene. The reactions proceed stereospecifically to within the analytical limits of the experiment.<sup>11b</sup> This proves unequivocally that no long-lived diradical intermediate can be formed in the simplest Diels–Alder reaction.

**1,3-Dipolar Cycloadditions: The Huisgen–Firestone Debates.** A 1,3-dipole, as defined by Huisgen,<sup>12</sup> is a molecule which can be represented by zwitterionic octet Lewis structures and combines in a 1,3-addition with a multiple bond. Cycloadditions of 1,3-dipoles may occur by concerted or stepwise mechanisms. Rolf Huisgen's institute in Munich carried out a most extraordinary series of investigations which led to a monumental collection of data for these reactions. Huisgen developed a detailed rationale for the concerted mechanism of this reaction. Raymond Firestone, a chemist then at Merck, now at Bristol-Myers Squibb, has had a long-standing interest in mechanisms. He presented a variety of challenges to the concerted mechanism, passionately favoring but also rationally defending stepwise reaction mechanisms involving diradical intermediates.

Huisgen's conclusion about mechanism was based on kinetic measurements, stereochemical results, and solvent and substituent effects.<sup>12,13</sup> Using molecular orbital theory, Huisgen<sup>12</sup> proposed a model for the transition state of the 1,3-dipolar reactions, in which the  $4\pi$  electron system present in all 1,3-dipoles interacts with the  $\pi$ -bond of the dipolarophile (Figure 3a).

Firestone, on the other hand,<sup>14</sup> considered these reactions to take place via singlet diradical intermediates (Figure 3b). This was based on a number of experimental facts, such as the observed small solvent

(5) (a) Littman, E. R. *J. Am. Chem. Soc.* **1936**, *58*, 1316. (b) Harkness, J. B.; Kistiakowsky, G. B.; Mears, W. H. *J. Chem. Phys.* **1937**, *5*, 682. (c) Kistiakowsky, G. B.; Ransom, W. W. *J. Chem. Phys.* **1939**, 725. These references are not always available ("Unfortunately, I do not have here this volume and the precedents; the library of the University was destroyed during the revolution and the civil war..."—J.G. letter from Spain during preparation of this manuscript).

(6) (a) Benford, G. A.; Wasserman, A. *J. Chem. Soc.* **1939**, 362. (b) Wasserman, A. *J. Chem. Soc.* **1942**, 612.

(7) (a) Woodward, R. B. *J. Am. Chem. Soc.* **1942**, *64*, 3058. (b) Woodward, R. B.; Baer, H. *J. Am. Chem. Soc.* **1944**, *66*, 645. (c) Hudson, B. J. F.; Robinson, R. *J. Chem. Soc.* **1941**, 715. (d) Bergmann, F.; Eschinazi, H. E. *J. Am. Chem. Soc.* **1943**, *65*, 1405.

(8) Woodward, R. B.; Katz, T. J. *Tetrahedron* **1959**, *5*, 70.

(9) Dewar, M. J. S. *Tetrahedron Lett.* **1959**, 16.

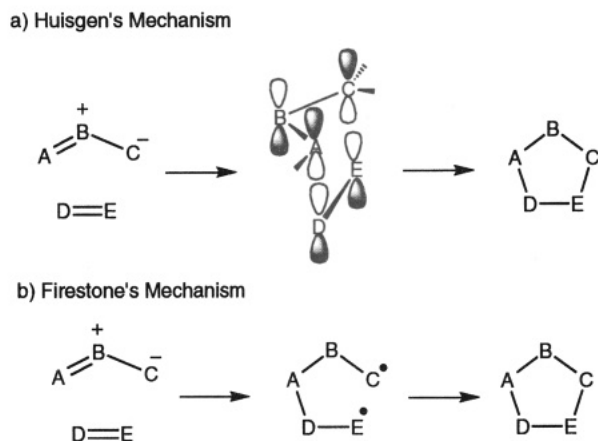
(10) (a) Woodward, R. B.; Katz, T. J. *Tetrahedron Lett.* **1959**, 19. (b) Punctilio = minute point.

(11) (a) Firestone, R. A. *Heterocycles* **1987**, *25*, 61. (b) Houk, K. N.; Lin, Y. T.; Brown, F. K. *J. Am. Chem. Soc.* **1986**, *108*, 554.

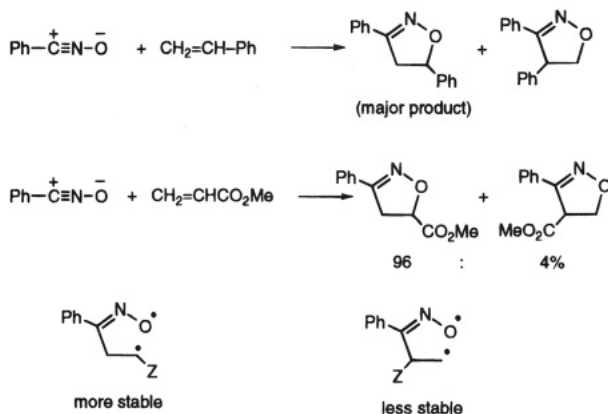
(12) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633; **1968**, *7*, 321. For a more recent review, see: Confalone, P. N.; Huie, E. M. *Org. React. (N.Y.)* **1988**, *36*, 1.

(13) (a) Huisgen, R. *J. Org. Chem.* **1968**, *33*, 2291; (b) **1976**, *41*, 403.

(14) (a) Firestone, R. A. *J. Org. Chem.* **1968**, *33*, 2285; **1972**, *37*, 2181. (b) Firestone, R. A. *Tetrahedron* **1977**, *33*, 3009. (c) Firestone, R. A. *J. Chem. Soc. A*, **1970**, 1570.



**Figure 3.** Postulated mechanisms for 1,3-dipolar cycloadditions.



**Figure 4.** Regioselectivities of two benzonitrile oxide cycloadditions and potential diradical intermediates.

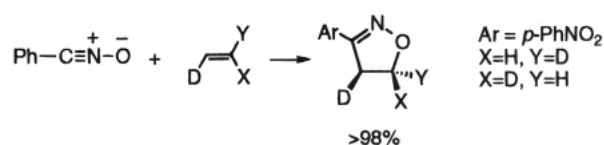
effects, byproducts obtained in a few cases, and considerations of factors controlling regioselectivity. For example, the cycloadditions of benzonitrile oxide with styrene and methyl acrylate both give predominantly the 5-substituted isoxazoline, a result not easily rationalized by polar arguments, but readily interpreted by a mechanism involving biradical intermediates (Figure 4). Other experimental observations, such as the stereospecificity of the reaction, were difficult to reconcile with a two-step process. Firestone proposed that the activation energy for single-bond rotation was greater than that for either formation of the second bond or reversion to reactants. Eventually, our group contributed to the partial resolution of this controversy, by showing how frontier molecular orbital theory could rationalize the reaction regioselectivity in the context of the concerted mechanism.<sup>15</sup> This led to an invitation to K.N.H. to visit Huisgen's institute in Munich, days of discussions of the theory of 1,3-dipolar transition states, and a breathtaking tour of expressionist art led by Professor Huisgen.<sup>16a</sup>

According to Firestone, the intent of his papers was to stimulate discussion. In this, he succeeded admirably!<sup>16b</sup> The classic back-to-back papers of Huisgen and Firestone in *The Journal of Organic Chemistry* were only the tip of the iceberg.<sup>13a,14a</sup> In a variety of

(15) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.

(16) (a) See: Huisgen, R. *The Adventure Playground of Mechanisms and Novel Reactions*; American Chemical Society: Washington, DC, 1994; pp 208–210. (b) As Huisgen said,<sup>13a</sup> "It will be up to the reader to decide whether the concept of a single-step concerted 1,3-dipolar cycloaddition will be hardened in criticisms *fire to stone* or will crumble into dust."

### Scheme 2



lectures and in voluminous correspondence between the two, the pros and cons of the two mechanisms were debated. Firestone lectured at many laboratories and conferences, and many organic chemists ranging from first-year graduate students to distinguished academicians did their best to deflate Firestone's arguments. These (often multihour) sessions created great interest in mechanisms and in ways to prove them experimentally. One of us (K.N.H.) debated Firestone on the stage at LSU's Mardi Gras Symposium in 1976; Firestone remained fully inflated in spite of the best shots from theory!

At least a partial meeting of the minds was achieved when we collaborated with Firestone on experiments which established that the reactions shown in Scheme 2 are concerted processes with no intermediates, on the basis of stereospecificity.<sup>17a</sup> For these cases, a diradical intermediate would have led to stereochemistry scrambling. We and Firestone agreed that the reaction was concerted!

Soon after this diplomatic coup, Huisgen turned the tables by reporting the first well-documented example of a stepwise 1,3-dipolar cycloaddition involving an intermediate!<sup>17b</sup> To him—and to us—this further supported the idea that most other 1,3-dipolar cycloadditions are concerted, since they lack the characteristic stereochemical scrambling expected, and now observed, in a stepwise reaction. Firestone decided that no degree of stereospecificity could rule out a diradical mechanism!<sup>11a</sup>

**Cope Rearrangement.** In 1940, Arthur Cope discovered a reaction which now bears his name.<sup>18</sup> The reaction is the prototype for the many 3,3-sigmatropic shifts, which have been used in synthesis and have attracted enormous mechanistic interest. Because of the apparent absence of intermediates, the inaccessibility of intermediates according to thermochemical criteria, and the stereospecificity of these reactions, Doering and Roth dubbed these as "no-mechanism reactions".<sup>19</sup>

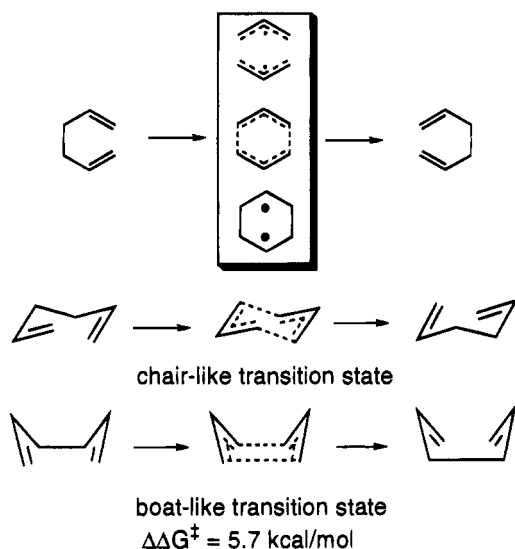
In work designed to reveal the geometry of the transition state, Doering and Roth studied the Cope rearrangement of the *meso*- and *rac*-3,4-dimethylhexa-1,5-diene.<sup>20</sup> This classic example of the use of stereochemistry to provide an indirect glimpse at the geometry of a transition state showed that the chair transition state is favored over the boat transition

(17) (a) Houk, K. N.; Firestone, R. A.; Munchausen, L. L.; Mueller, P. H.; Arison, B. H.; Garcia, L. A. *J. Am. Chem. Soc.* **1985**, *107*, 7227. (b) Huisgen, R.; Mloston, G.; Langhals, E. *J. Am. Chem. Soc.* **1986**, *108*, 6401; *J. Org. Chem.* **1986**, *51*, 4085. Mloston, G.; Langhals, E.; Huisgen, R. *Tetrahedron Lett.* **1989**, *30*, 5373. (c) Other stepwise 1,3-dipolar and Diels–Alder cycloadditions have been reported: Mayr, H.; Baran, J.; Heigl, U. W. *Gazz. Chim. Ital.* **1991**, *121*, 373 and references therein.

(18) Cope, A. C.; Hardy, E. M. *J. Am. Chem. Soc.* **1940**, *62*, 441. For a review on the Cope rearrangement, see: Rhoads, S. J.; Raulins, N. R. *Org. React. (N.Y.)* **1975**, *22*, 1.

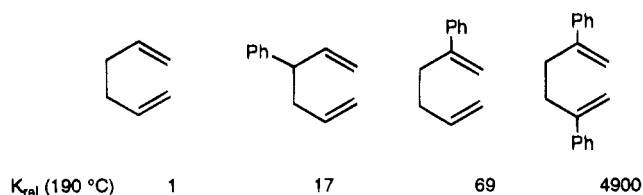
(19) According to Doering and Roth,<sup>20</sup> this designation was given "half in jest, half in desperation" because of the insensitivity of these reactions to reaction medium and catalysts and to the lack of evidence for intermediates.

(20) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67.



**Figure 5.** Possible intermediates in the Cope rearrangement. Chair and boat transition states are shown.

### Scheme 3



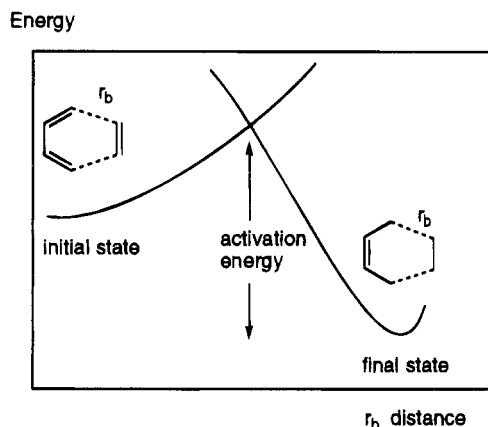
state by 5.7 kcal/mol.<sup>20,21</sup> Doering provided a detailed analysis of the possible mechanisms of the three limiting transition states or intermediates, shown in Figure 5. These are two allyl radicals, a concerted "aromatic" transition state, and cyclohexane-1,4-diylium. The degree of bonding between the two allyl groups is still very much a matter of discussion and debate. Dewar invoked the 1,4-diylium to rationalize some substituent effects measured experimentally, such as those shown in Scheme 3.<sup>22</sup>

Gajewski measured secondary deuterium isotope effects for a variety of substituted compounds and concluded that the position of the transition state varies, from nearly synchronous and "aromatic" for the parent to highly asynchronous in substituted cases such as 2,5-diphenyl, where much bond formation and little bond breaking occur in the transition state. This information was summarized elegantly in More-O'Ferrall-Jencks diagrams for such processes.<sup>23</sup>

## Theoretical Studies

### Evans's Model for the Diels–Alder Reaction.

The Diels–Alder cycloaddition was one of the first organic reactions treated quantitatively with the methods of the then newly developed quantum mechanics. In 1938, Evans and Warhurst reported their calculations of the activation energy of the Diels–Alder reaction,<sup>24</sup> making use of the diabatic method developed by Evans and Polanyi.<sup>25</sup> Two intersecting energy curves, corresponding to distortion of reactant



**Figure 6.** Evans's model for Diels–Alder potential energy surface.

and distortion of product, are approximated (Figure 6). These two surfaces intersect at a point at which the configuration of atoms is assumed to be a close approximation to that of the transition state of the reaction. Using this method, an activation energy of 36 kcal/mol was approximated. Elements of the Evans–Polanyi treatment live on in more modern theories.<sup>26,27</sup> According to Evans,<sup>24</sup> the transition state of the Diels–Alder reaction has an electronic structure related to that of benzene. This was the first attempt at a quantitative description of the nature of the transition state of the Diels–Alder reaction, and it has been recalled by Dewar with considerable reverence.<sup>28</sup>

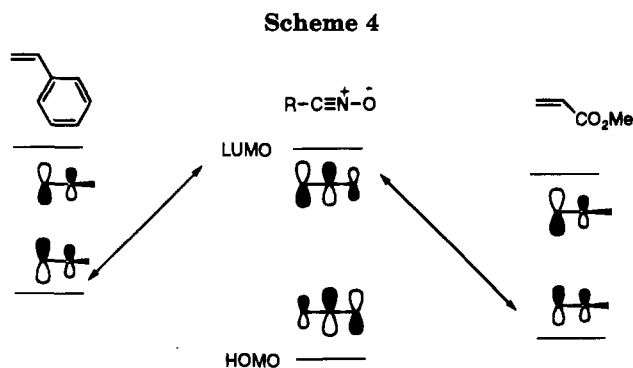
**Orbital Symmetry and the Woodward–Hoffmann Rules.** For the next 30 years, experimental studies on reaction mechanisms flowered. In the late 1960s, a development which thrust theory to the center stage in organic chemistry also changed forever the way we think about the transition states of organic reactions.

During the period from 1965 to 1969, R. B. Woodward and Roald Hoffmann<sup>29</sup> developed the concept of pericyclic reactions. They noted the similarities between a variety of reaction types: electrocyclic reactions, cycloadditions, sigmatropic shifts, cheletropic reactions, and group transfer and elimination reactions. They defined pericyclic reactions as "reactions in which all first-order changes in bonding relationships take place in concert on a closed curve."<sup>29</sup> They uncovered the principles of orbital symmetry conservation, according to which allowed reactions could be concerted and forbidden could not. They showed that allowed reactions could maintain bonding all along a concerted pathway, while forbidden reactions necessarily pass through a nonbonding electronic structure somewhere along the reaction path. Consequently, a stepwise reaction mechanism will be involved for forbidden reactions. Allowed reactions are not required to be concerted, but unless some factor destabilizes the concerted path, there is every reason to expect that the concerted pathway that maintains maximum bonding will be favored.

The importance of the symmetry of the frontier

(21) Goldstein, M. J.; Benzon, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 7147.  
 (22) Dewar, M. J. S.; Wade, L. E., Jr. *J. Am. Chem. Soc.* **1977**, *99*, 4417.  
 (23) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 6693.  
 (24) Evans, M. G.; Warhurst, E. *Trans. Faraday Soc.* **1938**, *34*, 614.  
 Evans, M. G. *Trans. Faraday Soc.* **1939**, *35*, 824.  
 (25) Evans, M. G.; Polanyi, J. *Trans. Faraday Soc.* **1938**, *34*, 11.

(26) (a) Shaik, S. S.; Pross, A. *J. Am. Chem. Soc.* **1982**, *104*, 2708. (b) Pross, A.; Shaik, S. S. *J. Am. Chem. Soc.* **1981**, *103*, 3702.  
 (27) Marcus, R. A. *Annu. Rev. Phys. Chem.* **1965**, *15*, 155. Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891; *J. Am. Chem. Soc.* **1969**, *91*, 7224.  
 (28) Dewar, M. J. S. *A Semiempirical Life*; American Chemical Society: Washington, DC, 1992; pp 141–144.  
 (29) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.



orbitals in pericyclic reactions was also discovered by K. Fukui.<sup>30</sup> He made the fundamental assumption that a majority of chemical reactions should take place at the position and in the direction of maximum overlapping of the HOMO and the LUMO of the reacting species.

Orbital symmetry and frontier molecular orbital theory (FMO)<sup>15,31</sup> together provided theoretical backing to the notion that pericyclic reactions occur by concerted mechanisms. For 1,3-dipolar cycloadditions, FMO theory offered a coherent mechanistic picture based on a concerted process. Reactivity could be understood by considering the dominant HOMO/LUMO interactions, as shown in a series of elegant papers by Sustmann.<sup>32a</sup> Regioselectivity, studied at the same time by our group, then in Baton Rouge, and by Bastide in France, could be understood with the use of the coefficients associated with the atomic orbitals of the FMOs.<sup>32b-e</sup>

In the frontier molecular orbital treatment of regioselectivity, the dominant orbital interaction between reactants is identified on the basis of the narrower HOMO–LUMO gap. An example is shown in Scheme 4. The overlap between the strongly interacting frontier orbitals (noted by the arrows) will be maximized by bringing together the termini with the larger coefficients. In the case of styrene and methyl acrylate, the HOMO coefficient is largest at the unsubstituted termini of these molecules. The interaction of the alkene HOMO with the nitrile oxide LUMO controls regioselectivity. Thus, the regioselectivity of both reactions can be rationalized even with a concerted transition state model.<sup>15</sup>

Alternative treatments of the selection rules for pericyclic reactions were developed by Dewar<sup>33</sup> and Zimmerman.<sup>34</sup> For the Diels–Alder reaction, Dewar termed the cyclic concerted transition state an *aromatic transition state*, following the ideas developed by Evans 30 years earlier.<sup>24</sup> On the basis of this concept, Dewar derived the rule which he named Evans's rule: *thermal pericyclic reactions take place via aromatic transition states*.<sup>33</sup> In Zimmerman's

model,<sup>34</sup> the “allowedness” of a reaction depends on the topological nature of the transition state: *if the number of electrons in a Möbius or Hückel system is (4N) or (4N+2), respectively, the reaction is allowed*.<sup>35</sup>

In the late 1960s and early 1970s, the prevailing opinion, fueled by the excitement over these new theoretical principles, was that pericyclic reactions occurred in one step involving an aromatic transition state. This accord was disturbed by the publication of a rule by McIver which seemed to forbid symmetrical transition states altogether!<sup>36</sup> McIver's symmetry arguments have had an important influence on the exploration of potential energy surfaces. However, the rule against symmetrical transition states was derived from estimates of magnitudes of force constants of transition states. MINDO/2 calculations incorrectly predicted that the Diels–Alder reaction and Cope rearrangement could not have symmetrical transition states,<sup>36</sup> but as shown below, that has been found to be an artifact, not a law of nature!

### Computational Studies

During the last two decades, the tools of computational chemistry have been applied to all of these reactions. Despite the amazing advances in the experimental studies of the transition states of simple chemical reactions,<sup>37</sup> the only way to obtain detailed information on the geometries of transition states of complex processes is the use of quantum mechanical calculations.<sup>38,39</sup> As methods and computers have been improved, better accuracy has been achieved; nevertheless, different methods give different answers. This has led to heated arguments among theoreticians and mistrust of all calculations by many experimentalists!

**Diels–Alder Reaction.** Kikuchi looked for the transition structure of the reaction of butadiene with ethylene, using the semiempirical CNDO/2 method.<sup>40</sup> He was unable to find any energy maximum corresponding to a transition state.

Using the MINDO/2 or MINDO/3 methods, Dewar and co-workers found a very asymmetric transition structure,<sup>41</sup> with one of the new CC  $\sigma$ -bonds fully formed (1.52 Å) and the other only starting to form (2.80 Å). The symmetrical concerted path ( $C_s$  transition structure) was found to be very much higher in energy. Calculations with configuration interaction involving only the doubly-excited configuration gave a biradical-like transition structure with an activation energy of 28.2 kcal/mol. On the basis of these calcula-

(30) (a) Fukui, K. *Tetrahedron Lett.* **1965**, 2009. (b) Fukui, K. *Acc. Chem. Res.* **1971**, 4, 57.

(31) Review: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*. J. Wiley & Sons, 1976.

(32) (a) Sustmann, R. *Tetrahedron Lett.* **1971**, 2717; *Pure Appl. Chem.* **1974**, 40, 569. (b) Houk, K. N. *J. Am. Chem. Soc.* **1972**, 94, 8953. (c) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, 95, 7301. (d) Houk, K. N.; Sims, J.; Duke, R. E., Jr.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, 95, 7287. (e) Bastide, J.; Henri-Rousseau, O. *Bull. Soc. Chim. Fr.* **1973**, 2290.

(33) Dewar, M. J. S. *The Molecular Orbital Theory of Organic Chemistry*; McGraw-Hill Book Company: New York, 1969; pp 316–339.

(34) Zimmerman, H. *J. Am. Chem. Soc.* **1966**, 88, 1564. Zimmerman, H. *Acc. Chem. Res.* **1971**, 4, 272.

(35) Hückel systems have zero or an even number of sign inversions of the  $\pi$  orbitals in the cyclic array. Möbius systems have one or an odd number of sign inversions.

(36) McIver, J. W., Jr. *Acc. Chem. Res.* **1974**, 7, 72.

(37) Zewail, A.; Bernstein, R. In *The Chemical Bond. Structure and Dynamics*; Zewail, A., Ed.; Academic Press, Inc.: New York, 1992; pp 223–279. A recent relevant example: Pedersen, S.; Herek, J. L.; Zewail, A. H. *Science* **1994**, 266, 1359.

(38) For a review on semiempirical methods, see: Thiel, W. *Tetrahedron* **1988**, 44, 7393.

(39) (a) For a description of ab initio methods, including different basis sets, see: Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986. (b) Simons, J. *J. Phys. Chem.* **1991**, 95, 1017.

(40) Kikuchi, O. *Tetrahedron* **1971**, 27, 2791. W. L. Jorgensen also performed semiempirical calculations in 1971, referred to in footnote 51 of ref 42.

(41) (a) Dewar, M. J. S.; Griffin, A. C.; Kirschner, S. *J. Am. Chem. Soc.* **1974**, 96, 6225. (b) Dewar, M. J. S.; Olivella, S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, 100, 5650. (c) Dewar, M. J. S.; Pierini, A. *J. Am. Chem. Soc.* **1984**, 106, 203.

tions, Dewar *et al.* considered the reaction to be a *two-stage* process somewhat like the Woodward and Katz proposal.<sup>41</sup> The tables were turned! Dewar forcefully advocated the two-stage Woodward–Katz mechanism, while Woodward's orbital symmetry rules were on the side of a synchronous process!

The first *ab initio* calculations performed on the parent Diels–Alder reaction showed the reaction to proceed in a concerted manner via a symmetrical transition structure ( $C_s$  symmetry). In this pioneering *ab initio* study, Salem and co-workers used painfully slow computers—the best available at the time—and laborious manual variations of geometries to investigate both the concerted and the two-step mechanisms.<sup>42</sup> For the concerted pathway, using the 4-31G basis set,<sup>39</sup> they found a concerted transition structure with a forming bond length of 2.21 Å and an activation energy of 42.6 kcal/mol. The stepwise path through a diradical intermediate was 2 kcal/mol higher in energy. *Ab initio* calculations performed by Burke and Leroy around that time on the parent reaction came to the same conclusion.<sup>43</sup>

These early quantum mechanical calculations led to heated discussions and criticisms of *ab initio* and semiempirical calculations between champions of two sides. Semiempirical methods predicted a two-step mechanism, while *ab initio* calculations indicated that the synchronous concerted pathway was favored. This dichotomy between *ab initio* and semiempirical techniques was attributed by Caramella, Houk, and Domelsmith<sup>44</sup> to the fact that the neglect of differential overlap in semiempirical NDO calculations favors two-step mechanisms. Model calculations showed how overlap, and closed-shell repulsion which results from this overlap, favors synchronous transition states. After describing this at a talk at a New Orleans International Congress of Quantum Chemistry meeting, K.N.H. was approached by an excited Lionel Salem, who commented “superb, superb!” This comment from an excited chemist idol was a huge thrill!

Several other insights into this dichotomy were offered: Bertrán and co-workers showed that inclusion of correlation energy corrections preferentially stabilizes the diradical structures,<sup>45</sup> and the DuPont group showed that MINDO/2 bond energies dropped off too rapidly with bond stretching, which could cause the semiempirical calculations to be biased toward diradicals.<sup>46</sup> Unfazed, Dewar insisted that *ab initio* calculations were at fault both because of the neglect of electron correlation and because only partial geometry optimizations had been performed.<sup>41</sup>

At about this time, Dewar published an article entitled “Multibond Reactions Cannot Normally Be Synchronous”<sup>47</sup> in which he declared that reactions such as pericyclic reactions in which two or more bonds are made or broken could not be synchronous. He argued that when these reactions are concerted, they nevertheless have very different forming bond

lengths; that is, they are asynchronous. Some exceptions, such as reactions involving aromatic transition states, were permitted, thus allowing all pericyclic reactions to be exceptions! The “proof” was based upon the obvious, but irrelevant, argument that two independent, non-interacting bonds are harder to break than one. In pericyclic reactions, these two bonds are strongly interacting. Nevertheless, this received wide attention, including a news story in *Science*.<sup>48</sup>

Ten years ago, *ab initio* calculations were performed by Frank Brown in our group on the transition structures of the reaction of butadiene plus ethylene, using first the STO-3G<sup>49</sup> and then the 3-21G basis sets.<sup>10</sup> Gradient techniques with full optimization of the geometries were used; vibrational frequencies were calculated to determine the nature of the stationary points located. The synchronous concerted mechanism was found, and the saddle point was proven to be a transition structure with one negative force constant. This conclusion is now known to be true at the many *ab initio* levels studied.<sup>1,50</sup> Although the energetics are a sensitive function of level, the methods give virtually superimposable synchronous transition structures!

These results promoted further lively skirmishes at meetings and in the literature. In a review in *Annual Reports in Physical Chemistry*, we described the state of the art and noted that the Houk group T-shirt of this era featured the words of M. J. S. Dewar alongside those of British rock star Sting from the song “Synchronicity”:<sup>51</sup>

On the contrary, it seems likely	A connecting principle
the large majority are nonsynchronous	linked to the invisible almost imperceptible
...	Science unsusceptible
A new and apparently	something
very powerful rule	inexpressible,
...	logic so inflexible
Limits the possible mechanisms	causally connectible
of chemical reactions.	but nothing is invincible.
No clear support	...
Bell-Evans-Polanyi...	Effect without a cause
no clear support for synchronicity.	subatomic laws,
(M. J. S. Dewar,	Synchronicity...
Multibond Reactions Cannot Normally Be Synchronous)	(Sting, Synchronicity)

At a meeting at the University of Indiana, organized by Ernest Davidson to bring the opposing sides together (perhaps for his amusement à la Roman emperors), this T-shirt was revealed and was received with good humor by Professor Dewar! Chuckles aside, he remained unconvinced about the synchronicity of the butadiene–ethylene reaction until, in what surely must have been a cruel surprise, AM1 (Austin model

(42) Townshend, R. E.; Ramunni, G.; Segal, G.; Hehre, W. J.; Salem, L. *J. Am. Chem. Soc.* **1976**, *98*, 2190.

(43) (a) Burke, L. A.; Leroy, G.; Sana, M. *Theor. Chim. Acta* **1975**, *40*, 313. (b) Burke, L. A.; Leroy, G. *Theor. Chim. Acta* **1977**, *44*, 219.

(44) Caramella, P.; Houk, K. N.; Domelsmith, L. N. *J. Am. Chem. Soc.* **1977**, *99*, 4511.

(45) Ortega, M.; Oliva, A.; Lluch, J. M.; Bertrán, J. *Chem. Phys. Lett.* **1983**, *102*, 317.

(46) Gordon, M. D.; Fukunaga, T.; Simmons, H. E. *J. Am. Chem. Soc.* **1976**, *98*, 8401.

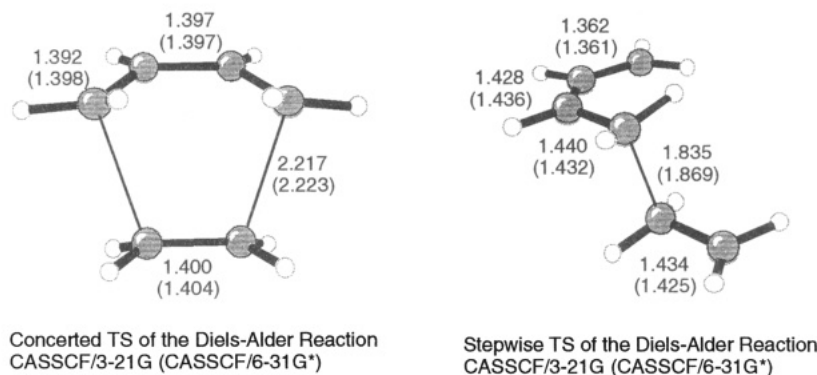
(47) Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 209.

(48) Maugh, T. H., II *Science* **1984**, *223*, 1162.

(49) Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1984**, *25*, 4609.

(50) Bach, R. D.; McDouall, J. J. W.; Schlegel, H. B. *J. Org. Chem.* **1989**, *54*, 2931.

(51) Borden, W. T.; Loncharich, R. J.; Houk, K. N. *Annu. Rev. Phys. Chem.* **1988**, *39*, 213.



**Figure 7.** Transition structures for the concerted and stepwise Diels–Alder reactions of butadiene and ethylene.

1), Dewar's new semiempirical method, predicted a concerted and synchronous transition structure for the parent reaction.<sup>52</sup>

By 1986, experimental and theoretical evidence converged on the synchronous concerted mechanism for the butadiene–ethylene Diels–Alder reaction. To determine how much higher the diradical mechanism is, MCSCF (multiconfiguration SCF) techniques must be used.<sup>53</sup> Bernardi *et al.* obtained 2 kcal/mol,<sup>54</sup> like Salem did before. Our CASSCF/6-31G\* calculations on the parent reaction with full geometry optimizations gave the transition structures for the concerted and stepwise reactions shown in Figure 7.<sup>55</sup> The synchronous concerted mechanism is predicted to be favored by 6 kcal/mol with inclusion of dynamic correlation energy at the QCISD(T)/6-31G\* level. This is in good agreement with experimental estimates of 2–7 kcal/mol.

**1,3-Dipolar Cycloadditions.** The evolution of computational studies on 1,3-dipolar cycloaddition reactions parallels that of the Diels–Alder reaction. Many calculations have been performed on the reaction of fulminic acid with acetylene, an example of a 1,3-dipolar cycloaddition involving a nitrile oxide. Pioneering *ab initio* calculations by Poppinger<sup>56</sup> gave a concerted transition state with  $C_s$  symmetry (Figure 8); the activation energy was calculated to be 30 kcal/mol (RHF/4-31G//STO-3G). While the *ab initio* calculations supported the one-step mechanism with an aromatic transition state, MNDO calculations predicted a two-step reaction involving a diradical intermediate.<sup>57</sup> *Ab initio* calculations carried out by Komornicki *et al.* confirmed the previous *ab initio* results; the transition structure is asynchronous, but the reaction is concerted.<sup>58</sup> This reaction provided further material for the debates about the relative merits of different calculations.<sup>44,47</sup>

These studies were followed by calculations by

(52) (a) Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1986**, *108*, 5771. (b) Interesting puntilio: Ray Firestone pointed out that the word *synchronicity* does not appear in dictionaries, but *synchronous* does.

(53) For a description of MCSCF formalism, see ref 39b and the following: Shepard, R. *Adv. Chem. Phys.* **1987**, *69*, 63.

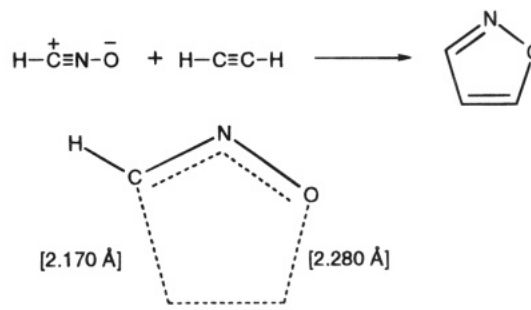
(54) Bernardi, F.; Bottoni, A.; Robb, M. A.; Field, M. J.; Hillier, I. H.; Guest, M. F. *J. Chem. Soc., Chem. Commun.* **1985**, 1051. Bernardi, F.; Bottoni, A.; Field, M. J.; Guest, M. F.; Hillier, I. H.; Robb, M. A.; Venturini, A. *J. Am. Chem. Soc.* **1988**, *110*, 3050.

(55) Houk, K. N.; Li, Y. *J. Am. Chem. Soc.* **1993**, *115*, 7478. For newer DFT calculations, see: Stanton, R. V.; Merz, K. M., Jr. *J. Chem. Phys.* **1994**, *100*, 434. Carpenter, J. E.; Sosa, C. *J. Mol. Struct.: THEOCHEM* **1994**, *117*, 325.

(56) Poppinger, D. *Aust. J. Chem.* **1976**, *29*, 465.

(57) Reported in footnote 18 of ref 41b.

(58) Komornicki, A.; Goddard, J. D.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1980**, *102*, 1763.



**Figure 8.** Fulminic acid–acetylene 1,3-dipolar cycloaddition and transition structures. Bond lengths are MCSCF/4-31G.<sup>58,60</sup>

Hiberty and co-workers.<sup>59</sup> Their multiconfigurational SCF plus CI calculations predicted that the stepwise biradical mechanism is favored. Here, *ab initio* calculations with electron correlation and semiempirical calculations appeared to agree with each other on a stepwise mechanism. However, MCSCF calculations by McDouall *et al.* showed that the concerted mechanism for the addition of fulminic acid to acetylene was favored by 5 kcal/mol (Figure 8).<sup>60</sup> This 1,3-dipolar cycloaddition, as in the case of the Diels–Alder reactions, is predicted to be concerted using high-level calculations.

**Cope Rearrangement.** The questions of concerted versus nonconcerted mechanisms and of reliability of theoretical methods have proved especially vexing for this reaction (Figure 5). Contrary to the nearly unanimous agreement on the concerted mechanism in the case of cycloadditions, theory continues to refine our picture of the transition state of the Cope rearrangement.

Calculations using MINDO/2 and MINDO/3 methods<sup>61</sup> predict that the Cope rearrangement of 1,5-hexadiene is a two-step process involving a stable cyclohexane-1,4-diyl intermediate, with the forming CC bond length of approximately 1.61 Å in both the chair and boat conformations. By contrast, *ab initio* calculations on the parent reaction at the SCF or MCSCF theory levels with small basis sets predicted

(59) Hiberty, P. C.; Ohanessian, G.; Schlegel, H. B. *J. Am. Chem. Soc.* **1983**, *105*, 719.

(60) McDouall, J. J. W.; Robb, M. A.; Niazi, U.; Bernardi, F.; Schlegel, H. B. *J. Am. Chem. Soc.* **1987**, *109*, 4642.

(61) Komornicki, A.; McIver, J. W. *J. Am. Chem. Soc.* **1976**, *98*, 4553. Dewar, M. J. S.; Ford, G. P.; McKee, M. L.; Rzepa, H. S.; Wade, L. E. *J. Am. Chem. Soc.* **1977**, *99*, 5069.

a concerted process with a synchronous aromatic transition structure.<sup>62</sup> By 1984, another clear dichotomy between semiempirical and *ab initio* results had been revealed.

The plot has thickened again in the last few years. Dewar and Jie<sup>63</sup> reported AM1 and even some *ab initio* calculations which predict that a concerted mechanism with an aromatic transition structure is only slightly higher in energy than a stepwise mechanism involving a cyclohexane-1,4-diyl intermediate. In response to Dewar's objections to their earlier *ab initio* studies, Morokuma, Borden, and Hrovat performed further CASSCF calculations with the 3-21G basis set and showed that both the chair and boat transition states involve synchronous aromatic transition structures, with bond-forming lengths of 2.09 and 2.32 Å, respectively.<sup>64</sup> Later, Dupuis, Murray, and Davidson reported MCSCF calculations with the 6-31G\* basis set and CI electron correlation corrections. They, like Dewar, predicted that both an aromatic transition state and an unsymmetrical transition state leading to the cyclohexanediyl diradical coexist on the same energy surface.<sup>65</sup> The calculated energies of these two transition states were nearly identical at various levels of theory.

Just when MCSCF/CI calculations and AM1 appeared to converge on the dual competing mechanisms, two events shattered this fragile truce. First, in his most recent discussion of the Cope rearrangement, Dewar retracted the claim of two transition states, noting a computational error in the reported AM1 studies; AM1 actually predicts only one path, the stepwise mechanism involving a diradical intermediate.<sup>66</sup> The second event comes from the Seattle–Atlanta–Bloomington *ab initio* camps. Borden, Morokuma, and Hrovat have used Roos's CASSCF/MP2 technique with large basis sets to explore the region of the potential surface from biradical to aromatic transition state. They find that there is only one transition state for the Cope rearrangement.<sup>67</sup> It is of the aromatic type, and no cyclohexanediyl intermediate is found. Davidson has developed a similar method and also now predicts a single concerted transition state.<sup>67b</sup> Studies by our group with density functional theory using non-local gradient corrections (Becke3-LYP) and large basis sets also predict a single concerted aromatic transition state.<sup>67c</sup> The best available calculations now suggest that the Cope rearrangement has a concerted mechanism and an "aromatic" transition state.<sup>1,67</sup> To obtain accurate activation energies, both nondynamic and dynamic correlation energy corrections are necessary.

**Other Theoretical Studies.** There have been computational studies of a variety of Diels–Alder reactions and Cope rearrangements of substituted

cases.<sup>1,55,68</sup> As expected, the transition state geometries are altered by substituents, and when two different mechanisms compete, the relative energy barriers of two mechanisms are influenced by substituents. Readers interested in these examples are referred to the original literature. In general, concerted mechanisms are found, but substituents cause substantial deviations from the synchronous transition state. Another major advance has involved the calculation of solvent effects on the rates of pericyclic reactions using a variety of new methods.<sup>68e–g</sup>

#### A Bridge between Theory and Experiment: Kinetic Isotope Effects on Pericyclic Reactions.

The measurement of the influence of isotopic substitution on the rates of chemical reactions is an important mechanistic tool.<sup>69</sup> Many experimental studies of secondary kinetic isotope effects (KIEs) on pericyclic reactions have been reported. KIEs provide an experimental measure of the change in vibrational frequencies in the rate-determining transition state as compared to reactants. Since vibrational frequencies are determined by force constants, KIEs tell a great deal about transition states. Using the Bigeleisen–Meyer theory<sup>70</sup> and high-quality *ab initio* calculations, a comparison between the experimental KIEs and those calculated for different reaction mechanisms can be used to determine the nature of the actual transition state.

The important studies carried out by Thornton and Taagepera in the 1960s and 1970s provided good evidence in favor of a concerted mechanism for forward Diels–Alder and retro-Diels–Alder reactions.<sup>71</sup> Certain assumptions had to be made about magnitudes of force constants for different mechanisms, but the authors made a very thorough and convincing analysis. Dewar disputed this conclusion on the basis of calculated isotope effects for the stepwise mechanism, even though the predictions were in poor agreement with experiment.<sup>41</sup>

More recently, Gajewski and co-workers measured a series of isotope effects for simple Diels–Alder reactions and interpreted the results in terms of concerted mechanisms.<sup>72</sup> We have reported computed isotope effects for various possible mechanisms for several Diels–Alder reactions and Cope rearrangements. Comparisons with experiment provide further evidence for the concerted mechanism. Figure 9 shows isotope effects calculated for various positions

(62) Osamura, Y.; Kato, S.; Morokuma, K.; Feller, D.; Davidson, E. R.; Borden, W. T. *J. Am. Chem. Soc.* **1984**, *106*, 3362.

(63) (a) Dewar, M. J. S.; Jie, C. *J. Chem. Soc., Chem. Commun.* **1987**, 1451. (b) Dewar, M. J. S.; Jie, C. *J. Am. Chem. Soc.* **1987**, *109*, 5893.

(64) Morokuma, K.; Borden, W. T.; Hrovat, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 4474.

(65) Dupuis, M.; Murray, C.; Davidson, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 9756.

(66) Dewar, M. J. S.; Jie, C. *Acc. Chem. Res.* **1992**, *25*, 537.

(67) (a) Hrovat, D. A.; Morokuma, K.; Borden, W. T. *J. Am. Chem. Soc.* **1994**, *116*, 1072. (b) Kozłowski, P. M.; Dupuis, M.; Davidson, E. R. Unpublished results. (c) Wiest, O.; Black, K. A.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 10336.

(68) (a) Loncharich, R. J.; Brown, F. K.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 1134. Birney, D. M.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4127. (b) Houk, K. N.; Loncharich, R. J.; Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 9172. (c) Hrovat, D. A.; Borden, W. T.; Vance, R. L.; Rondan, N. G.; Houk, K. N.; Morokuma, K. *J. Am. Chem. Soc.* **1990**, *112*, 2018. (d) Jorgensen, W. L.; Lim, D.; Blake, J. F. *J. Am. Chem. Soc.* **1993**, *115*, 2936. (e) Jorgensen, W. L.; Lim, D.; Blake, J. F.; Severance, D. L. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 1727. (f) Storer, J. W.; Giesen, D. G.; Hawkins, G. D.; Lynch, G. C.; Cramer, C. J.; Truhlar, D. G.; Liotard, D. A. In *Structure and Reactivity in Aqueous Solution*; ACS Symposium Series 568; Cramer, C. J., Truhlar, D. G., Eds.; American Chemical Society: Washington, DC, 1994; p 24. (g) Davidson, M. M.; Hillier, I. H.; Hall, R. J.; Burton, N. A. *J. Am. Chem. Soc.* **1994**, *116*, 9294.

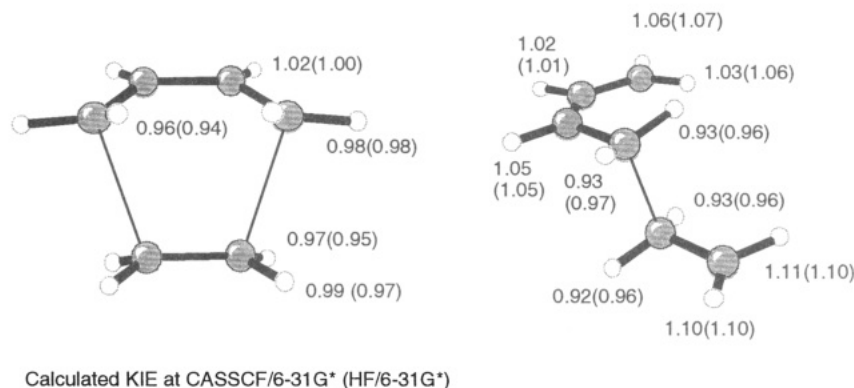
(69) Carpenter, B. K. *Determination of Organic Reaction Mechanisms*; J. Wiley & Sons: New York, 1984; pp 83–111.

(70) Bigeleisen, J.; Mayer, M. G. *J. Chem. Phys.* **1947**, *15*, 261. Bigeleisen, J. *J. Chem. Phys.* **1949**, *17*, 675. Bigeleisen, J.; Wolfsberg, M. *Adv. Chem. Phys.* **1958**, *1*, 15. Wolfsberg, M.; Stern, M. *J. Pure Appl. Chem.* **1964**, *8*, 225.

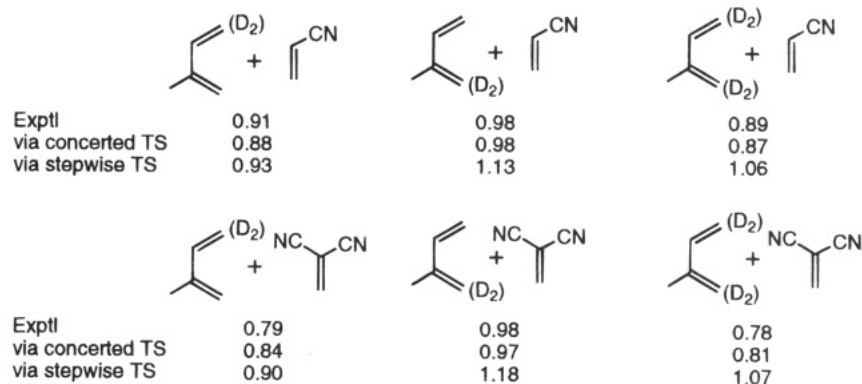
(71) Thornton, E. R.; Taagepera, M. *J. Am. Chem. Soc.* **1972**, *94*, 1168.

(72) (a) Gajewski, J. J.; Peterson, K. B.; Kagel, J. R.; Huang, Y. C. *J. Am. Chem. Soc.* **1989**, *111*, 9078. (b) Gajewski, J. J.; Peterson, K. B.; Kagel, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 5545.





**Figure 9.** Calculated secondary kinetic isotope effects,  $k_H/k_D$ , for concerted and stepwise Diels–Alder reactions.



**Figure 10.** Experimental secondary kinetic isotope effects,  $k_H/k_{D_2}$  or  $k_H/k_{D_1}$ , and calculated isotope effects for concerted and stepwise reactions of models (butadiene + ethylene for top line, and butadiene + acrolein for second line of reactions).

for the synchronous concerted and stepwise diradical Diels–Alder reaction of butadiene with ethylene.<sup>73</sup> Calculations show that there is a large normal isotope effect at the centers which become radical centers in the diradical intermediate, because the out-of-plane CCH bending frequencies decrease upon conversion of an alkene to a radical, whereas they increase upon alkene to alkane conversion. This makes the interpretation of the isotope effect much simpler than anticipated earlier. Figure 10 compares some experimental<sup>72</sup> and calculated<sup>73</sup> isotope effects for both mechanisms. Experimental isotope effects are in very good agreement with the concerted mechanism, but they are in very poor agreement with the stepwise mechanism.

For the Cope rearrangement, Gajewski and co-workers measured the kinetic and equilibrium isotope effects for a variety of substituted cases. Gajewski has presented More–O’Ferrall–Jencks diagrams which show qualitatively the extent of bond making and bond breaking occurring in the transition state of the reaction and how this changes with substitution.<sup>23</sup> A definitive interpretation of these isotope effects has come from comparison between calculated values for different mechanisms, and those measured experimentally.<sup>74</sup>

For the parent Cope rearrangement, the theoretical isotope effects for the concerted aromatic transition state were found to be in best agreement with the experimental values (Figure 11).<sup>74</sup> The experimen-

tally measured kinetic isotope effects for the Cope rearrangement of 1,1,6,6-tetradeuterio-3-methyl-1,5-hexadiene and 3,3,4,4-tetradeuterio-1,5-heptadiene are  $1.07 \pm 0.025$  and  $0.89 \pm 0.018$ , respectively. The corresponding values calculated for the concerted aromatic mechanism are 1.05 and 0.89 at the RHF/6-31G\* level. DFT calculations (Becke3LYP/6-311+G\*) are essentially perfect with calculated KIEs of 1.07 and 0.88.<sup>67c</sup> In contrast, semiempirical calculations using the AM1 method on either the concerted pathway or biradical intermediates could not reproduce the experimental values within the range of error, in spite of being cited as in good agreement with experiment.<sup>75</sup>

**The Present.** Passionate pronouncements about pericyclic reactions continue. Soon after our *Angewandte Chemie* article of the transition structures of pericyclic reactions, and during the preparation of this Account, Dewar and Jie reported in this journal the current view of the “anti-ab-initioists” about pericyclic transition structures.<sup>66</sup> Aside from an amusing footnote error, which prompted a retraction,<sup>76</sup> the Account clings to the obsolete view of pericyclic reactions as stepwise processes. The statement that all pericyclic reactions involve asynchronous mechanisms (by AM1, PM3, or SAM1)<sup>77</sup> contradicts our conclusions as well as published calculations by Dewar and others. But old controversies take long to fade, and only prestidigitation will prove what passions and punctilios remain to be pronounced about pericyclic processes!

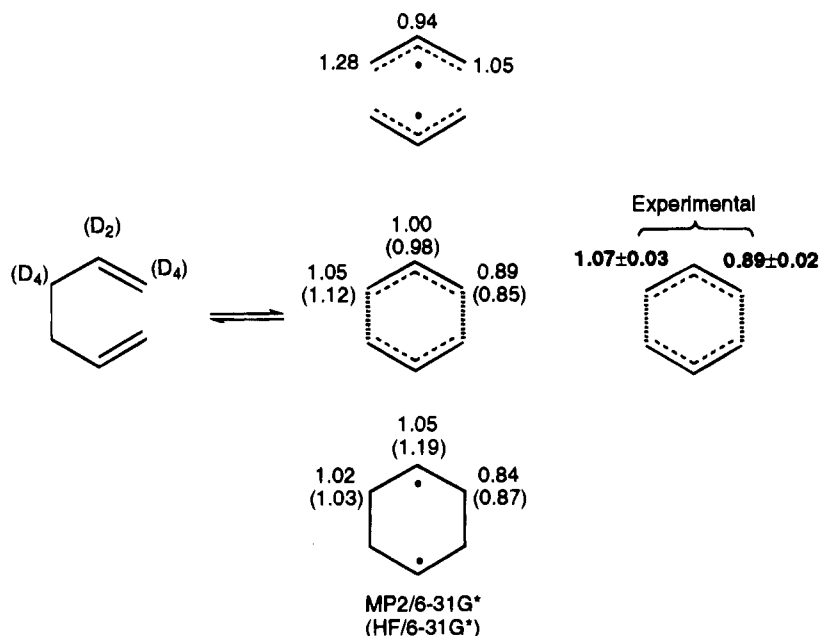
(73) Storer, J. W.; Raimondi, L.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 9675.

(74) Houk, K. N.; Gustafson, S. M.; Black, K. A. *J. Am. Chem. Soc.* **1992**, *114*, 8565.

(75) Dewar, M. J. S.; Jie, C. *J. Chem. Soc., Chem. Commun.* **1989**, 98.

(76) Dewar, M. J. S.; Jie, C. *Acc. Chem. Res.* **1993**, *26*, 226.

(77) Dewar, M. J. S.; Jie, C.; Yu, J. *Tetrahedron* **1993**, *49*, 5003.



**Figure 11.** Experimental secondary kinetic isotope effects,  $k_{\text{H}}/k_{\text{D}_2}$  or  $k_{\text{H}}/k_{\text{D}_1}$ , and calculated isotope effects for various types of Cope rearrangement transition states.

## Conclusion

In this Account, we have documented the evolution of organic chemists' views of the transition states of pericyclic reactions. These reactions, originally considered to be "no mechanism" processes, are now understood in terms of aromatic transition structures, a proposal consistent with experimental and computational evidence.<sup>1</sup> Quantum mechanics, developed in the 1920s,<sup>78</sup> at essentially the same time as Diels and Alder discovered the famous cycloaddition,<sup>2</sup> has played an instrumental role in the evolution and development of the mechanistic concepts in organic chemistry. The modern computational implementation of the techniques of quantum chemistry opens a door to the investigation of transition states of chemical reactions, which at the present time are not accessible to experimental methods.

The scientific debate has caused our thinking to evolve to a consistent view of pericyclic reactions,<sup>1</sup> useful for understanding and prediction of transition

state geometries and energies for an enormous body of reactions. It has done so in spite of the fact that, at times, the scientists in the argument have been

...mobile  
Qual piuma al vento  
Muta d'accento  
E di pensiero.

(G. Verdi, "Rigoletto")<sup>79</sup>

*We are grateful to the National Science Foundation and National Institutes of Health for financial support of our research. The members of "Houk's Horde" named in the references provided insights into pericyclic reactions by their brilliant efforts for 20 years in Baton Rouge, Pittsburgh, and Los Angeles. K.N.H. expresses warm thanks for the thoughtful comments about our manuscript and the wonderful friendship of Rolf Huisgen, Ray Firestone, Bill Jorgensen, Wes Borden, and our friend and frequent scientific antagonist, Michael Dewar.*

AR9400507

(78) The announcement of the Schrödinger equation: Schrödinger, E. *Ann. Phys.* **1926**, 79, 361.

(79) A loose translation: "...wayward as a feather in the breeze, capricious in word and in thought."