

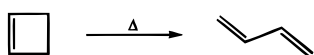
Electronic Control of Stereoselectivities of Electrocyclic Reactions of Cyclobutenes: A Triumph of Theory in the Prediction of Organic Reactions

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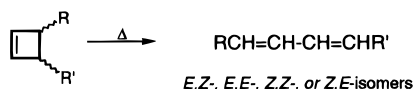
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The deceptively simple isomerization reaction shown below harbors the seeds of several major advances in the understanding of stereoselectivity by theoretical principles.



When a 3,4-disubstituted cyclobutene undergoes thermal ring-opening to butadiene, four different products are possible.

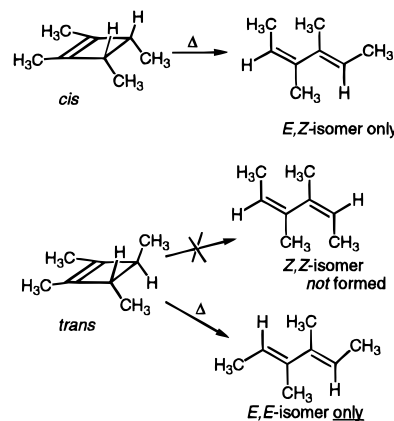


Before 1965, only a few examples of reactions of this type were known, and it was generally believed that steric effects determined the stereochemical course of such reactions. As anomalies were discovered, theories were developed to explain them. These theories led to predictions, which were tested by experiment and verified. Eventually, a comprehensive quantitative theory of stereoselectivity was developed, such that now the products of reactions of this type can be predicted with confidence.

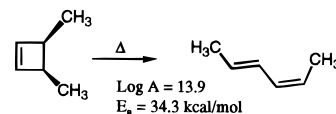
Cyclobutene was first prepared by Willstätter¹ in 1905. Although its ready thermal conversion to 1,3-butadiene was noted often in the early literature, it was not until the 1950s that mechanistic studies were undertaken. In 1958 Walters reported that the conversion of cyclobutene to butadiene was a well-

behaved unimolecular process occurring at 150 °C,² a relatively low temperature compared to the 350 °C required for thermal cleavage of the almost equally strained cyclobutane. Walters reported an activation energy of 32.5 kcal/mol for the reaction along with a log *A* of 13.1.

By that time initial reports of the stereochemistry of the ring-opening of 3-substituted and 3,4-disubstituted cyclobutenes had begun to appear, and by 1959 the substantial investigations of Vogel^{3,4} and particularly of Criegee and his co-workers^{5–7} had led to considerable mechanistic understanding of the reaction.



The reaction was depicted as being concerted, involving participation of the double bond in the breaking of the C₃–C₄ σ-bond, with substituents on C₃ and C₄ being required to move "in the same sense", either clockwise or counterclockwise with respect to the ring, as shown for *cis*-3,4-dimethylcyclobutene.⁸



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(1) Willstaetter, R.; von Schmaedel, W. *Ber. Deutsch. Chem. Ges.* **1905**, 38, 1992.

(2) Vogel, E. *Angew. Chem.* **1954**, 66, 640.

(3) Vogel, E. *Liebigs Ann. Chem.* **1958**, 615, 14.

(4) Criegee, R.; Noll, K. *Liebigs Ann. Chem.* **1959**, 1, 627.

(5) Criegee, R.; Seebach, D.; Winter, R. E.; Borretzen, B.; Burne, H.-A. *Chem. Ber.* **1965**, 98, 2339.

(6) Branton, G. R.; Frey, H. M.; Skinner, R. F. *Trans. Faraday Soc.* **1966**, 62, 1546.

(7) Cooper, W.; Walters, W. D. *J. Am. Chem. Soc.* **1958**, 80, 4220.

(8) Srinivasan, R. *J. Am. Chem. Soc.* **1969**, 91, 7557.

William R. Dolbier, Jr., was born in Elizabeth, NJ, on August 17, 1939, and he received his B.S. degree in chemistry from Stetson University in 1961. He obtained his Ph.D. in organic chemistry from Cornell University in 1965, working with Mel Goldstein, and after one and a half years of postdoc work with Bill Doering at Yale, joined the faculty at the University of Florida in 1966. He has been at UF ever since, serving as Chairman of the Department from 1983 to 1988. Bill's research interests are physical organic in nature, and he maintains long-term interests in thermal homolytic reactions, pericyclic reactions, and secondary deuterium isotope effects. In 1975, he began applying his physical organic methodologies to the study of molecules containing fluorine, and in recent years kinetic studies of fluorinated radicals have become the main focus of his research activity. When not immersed in such activity, Bill's main interests are his wife, Jing, new son, Stephen, and a little handball.

Henryk Koroniak was born in Jarocin, Poland. He obtained his Masters degree (1972) and Ph.D. (1976) from Adam Mickiewicz University, Poznań, Poland. He is now Professor of Chemistry and Chairman of the Department of Chemistry at Adam Mickiewicz University, Poznań, Poland. His main research interest focuses on various aspects of fluororganic chemistry, physical organic chemistry, studies of mechanisms, and reaction modeling.

K. N. Houk has been a Professor at UCLA since 1986. After education at Harvard and a Ph.D. with R. B. Woodward, Houk was a faculty member at Louisiana State University and the University of Pittsburgh and was Director of the NSF Chemistry Division from 1988 to 1990. This is his fourth Account in this journal.

Chimin Sheu received his B.S. from the National Taiwan Normal University and his M.S. from National Taiwan University. He received his Ph.D. in 1993 with Professor Christopher Foote. He is presently a Postdoctoral Fellow with Professor Houk.

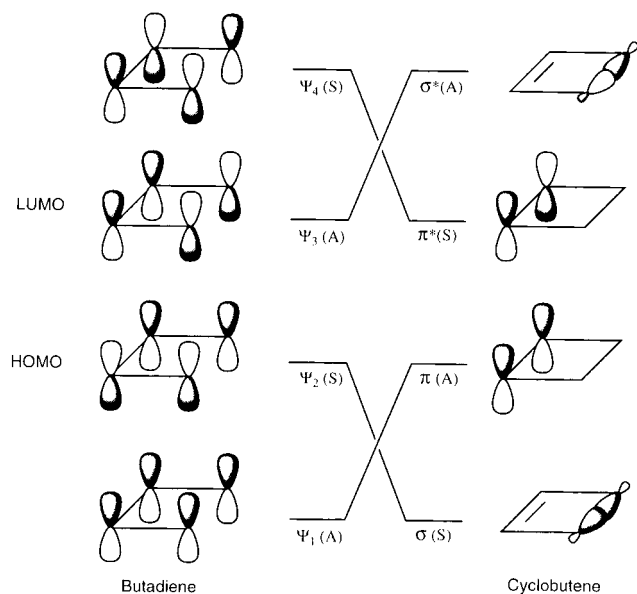
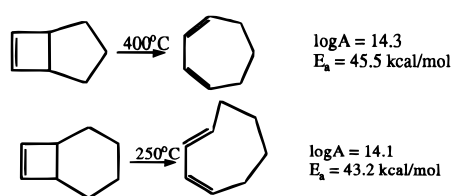


Figure 1. Woodward–Hoffmann correlation diagram for the conrotatory electrocyclic reaction.

Molecules which were structurally constrained so as to inhibit such preferred rotation, such as the bicyclic cyclobutenes shown below, underwent ring-openings with activation energies much higher than would otherwise have been predicted.^{6,9,10}



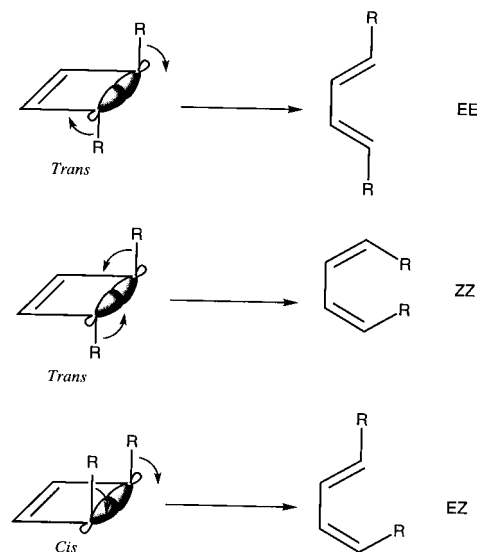
Thus, the fact that *conrotation* occurred was implicitly understood, but not yet defined. The idea that the symmetry characteristics of the HOMO of a polyene are in some way related to the stereochemistry of cyclization had been suggested in 1961 by Oosterhoff.¹¹ Nevertheless, the advent of the Woodward–Hoffmann theory of electrocyclic reactions in 1965 had a huge impact upon the mechanistic perception of electrocyclic reactions, particularly the cyclobutene–butadiene interconversion.^{12–14}

The conservation of molecular orbital symmetry, the basic concept of Woodward–Hoffmann theory, provides a clear explanation for the stereochemistry of the electrocyclic cyclobutene–butadiene isomerization. Since the reaction is carried out thermally, the HOMO (highest occupied molecular orbital) of the diene must correlate with an occupied orbital of the product. Figure 1 is a correlation diagram, first applied by

Longuet-Higgins to electrocyclic processes,¹⁵ and then avidly applied to all pericyclic reactions by Woodward and Hoffmann.^{12,13} The molecule has C_2 symmetry throughout the reaction. The symmetry of the HOMO of butadiene, ψ_2 , correlates with the σ -orbital of cyclobutene, and likewise, the HOMO π orbital of cyclobutene is antisymmetric (A) (regarding C_2 symmetry) and correlates with the ψ_1 orbital of butadiene.

Consequently, the thermal ring-opening of cyclobutene (or the cyclization of butadiene) will proceed in a *conrotatory* manner; that is, the orbital lobes involved in the bond-breaking or bond-forming processes will rotate in the same direction. The key idea here is that the conrotatory motion preserves bonding of all the occupied orbitals. The transition state is “aromatic” in the terminology of Dewar¹⁶ and Zimmerman,¹⁷ with a Möbius array of four electrons. By contrast, the disrotatory process has a Hückel array of four electrons and is antiaromatic. Consequently, the disrotatory process is much higher in energy than the conrotatory process.

Thus, *trans*-3,4-disubstituted cyclobutenes will give rise to the formation of *E,E*- and/or *Z,Z*-disubstituted butadienes (formation of the *E,Z*-isomer is *forbidden*), and *cis*-3,4-disubstituted cyclobutenes will form butadiene derivatives having *E,Z* geometry (with formation of the *E,E*- and *Z,Z*-isomers being *forbidden* by orbital symmetry rules).



At the time of the announcement of the rules, there was considerable doubt about how large these effects were and whether they would be obliterated by unsymmetrical substituents. Experimental investigations were undertaken enthusiastically in order to determine the energetic impact of this concerted electrocyclic pathway and to quantify the stereospecificity of such reactions. In a reexamination of the *cis*-3,4-dimethyl system, Brauman and Archie demonstrated the stereoselectivity of its conversion to *cis,trans*-2,4-hexadiene to be 99.995%, which corresponds to a difference of 11 kcal/mol between the allowed-conrotatory and the forbidden-disrotatory tran-

(9) Goldstein, M. J.; Leight, R. S.; Lipton, M. S. *J. Am. Chem. Soc.* **1976**, *98*, 5717.

(10) Branton, G. R.; Frey, H. M.; Montague, D. C.; Stevens, I. D. R. *Trans. Faraday Soc.* **1966**, *16*, 146–152.

(11) Oosterhoff, L. J., as quoted in Havinga, E.; Schlatmann, J. L. M. A. *Tetrahedron* **1961**, *16*, 151.

(12) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970; *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781–932.

(13) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395–396.

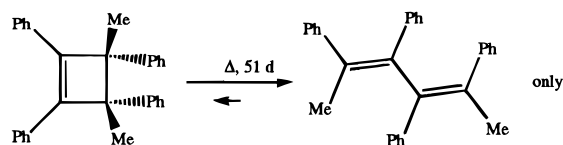
(14) For a generalized theoretical treatment see: Metiu, H.; Ross, J.; Whitesides, G. M. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 377.

(15) Longuet-Higgins, H. C.; Abrahamson, E. W. *J. Am. Chem. Soc.* **1965**, *87*, 2045.

(16) Dewar, M. J. S. *Tetrahedron, Suppl. B* **1966**, 76.

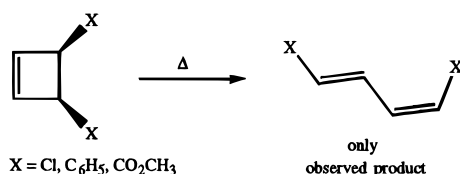
(17) Zimmerman, H. E. *J. Am. Chem. Soc.* **1966**, *88*, 1563, 1566.

sition state energies.¹⁸ Using a different approach, Doorakian and Freedman used the lack of detectability, after 51 days, of any disrotatory-derived products within the reversible equilibration of *cis*-3,4-dimethyltetraphenylcyclobutene with *cis,trans*-2,3,4,5-tetraphenyl-2,4-hexadiene to estimate such a difference to be 15.3 kcal/mol.¹⁹



Brauman and Golden also derived an estimate of 15 kcal/mol for the energetic benefit of conrotatory ring-opening from a kinetic study of the conversion of bicyclo[2.1.0]pentene to cyclopentadiene.²⁰ Thus, the importance of these effects was clearly established, even for highly-substituted components.

In addition to these studies, there are numerous additional examples which demonstrate the stereospecific, conrotatory nature of the cyclobutene electrocyclic ring-opening, including studies of the *cis*-3,4-dichloro-,⁵ -diphenyl-,^{21,22} and -dicarbomethoxycyclobutene systems.^{2,3}



Woodward and Hoffmann rationalized the stereochemistry not only of this 4- π -electron process but also of the whole broad class of concerted reactions which they defined as pericyclic reactions, on the basis of conservation of orbital symmetry.¹² This development led first to an explosion of experimental activity where the theory was thoroughly tested, and eventually to acceptance of virtually all of its ramifications. For at least the next 15 years, the Woodward-Hoffmann theory was considered the final and definitive word on the mechanism of the conversion of cyclobutene to 1,3-butadiene.

Somewhat obscured by the fervor directed at verification of orbital symmetry principles was the fact that there are *two* orbital-symmetry-allowed conrotatory processes available for each cyclobutene ring-opening. Generally such competitive processes were quite selective, if not stereospecific. It was found, for example, that the ring-opening of 3-methylcyclobutene gave only *trans*-1,3-pentadiene.²³ In practice, preferential outward rotation of substituents with concomitant formation of *trans*-products was the rule, and such observed stereospecificity was rationalized on the basis of a minimization of steric effects in the electrocyclic transition state.

(18) Brauman, J. I.; Archie, W. C., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 4262-4265.

(19) Doorakian, G. A.; Freedman, H. H. *J. Am. Chem. Soc.* **1968**, *90*, 5310-5311.

(20) Brauman, J. I.; Golden, D. M. *J. Am. Chem. Soc.* **1968**, *90*, 1920-1921.

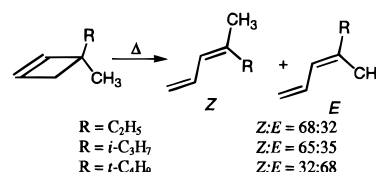
(21) Brauman, J. I.; Archie, W. C., Jr. *Tetrahedron Lett.* **1971**, *27*, 1275.

(22) Reinhoudt, D. N.; Leleveld, C. G. *Tetrahedron Lett.* **1972**, *27*, 3119.

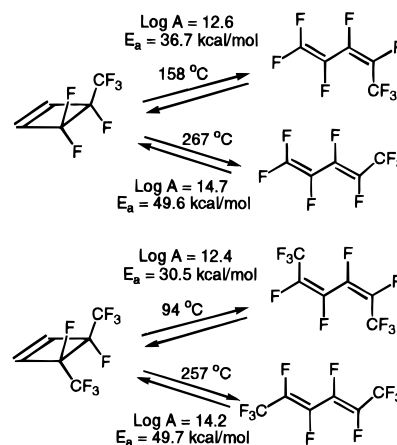
(23) Frey, H. M. *Trans. Faraday Soc.* **1962**, *58*, 957.

Until 1980, no one seemed particularly concerned with the fact that the exclusivity of *trans*-product formation from 3-methylcyclobutene was far out of line with what would have been expected on the basis of thermodynamics (<0.2% *cis*-isomer was detected although the ΔH^\ddagger for *cis-trans* equilibrium was only ~ 1 kcal/mol). Indeed, even Frey's observation in 1969 that the ring-opening of 3-ethyl-3-methylcyclobutene resulted in preferential rotation of the larger group, i.e., ethyl, inward was rationalized as an aberration and its significance ignored.²⁴

Curry and Stevens published a systematic study of the stereochemistry of ring-opening of 3,3-disubstituted cyclobutenes in 1980,²⁵ and in interpreting their surprising results, they made the first attempt to rationalize the stereochemistry of the ring-opening process in terms other than steric effects.



However, the full demise of the steric rationale did not occur until the papers of Dolbier, Burton, Koroniak, et al.²⁶ and Houk, Rondan, and Kirmse²⁷ appeared in 1984, wherein it became crystal clear that *electronic effects*, not steric effects, were dominant in determining both the kinetic and the stereochemical behavior of 3-substituted cyclobutenes. In studies of the reversible electrocyclic processes of the perfluoro-3-methyl- and -3,4-dimethylcyclobutene systems, Dolbier, Burton, Koroniak, and co-workers^{26,28,29} observed dramatic kinetic differences for the inward vs outward rotation of a fluorine substituent at the 3-position as exemplified below.



(24) Frey, H. M.; Solly, R. K. *Trans. Faraday Soc.* **1969**, *65*, 448.

(25) Curry, M. J.; Stevens, I. D. R. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1391.

(26) Dolbier, W. R., Jr.; Koroniak, H.; Burton, D. J.; Bailey, A. R.; Shaw, G. S.; Hansen, S. W. *J. Am. Chem. Soc.* **1984**, *106*, 1871.

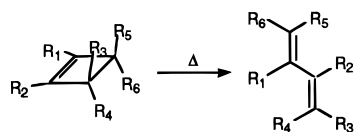
(27) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989.

(28) Dolbier, W. R., Jr.; Koroniak, H.; Burton, D. J.; Heinze, P. L.; Baily, A. R.; Shaw, G. S.; Hansen, S. W. *J. Am. Chem. Soc.* **1987**, *109*, 219.

(29) Dolbier, W. R., Jr.; Koroniak, H.; Burton, D. J.; Heinze, P. L. *Tetrahedron Lett.* **1986**, *27*, 4387.

(30) Dickens, D.; Frey, H. M.; Mercalf, J. *Trans. Faraday Soc.* **1971**, *67*, 2328.

(31) Sarner, S. F.; Gale, D. M.; Hall, H. K., Jr.; Richmond, A. B. *J. Phys. Chem.* **1972**, *76*, 2817.

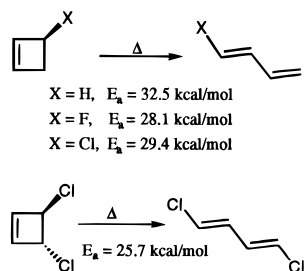
Table 1. Activation Parameters for Cyclobutene to Butadiene Thermal Conversion

| substituents | log A | E_a (kcal/mol) | stereochemistry of product | ref |
|---------------------------------------|-------|---------------------|-------------------------------|-----|
| none | 13.1 | 32.5 | | 9 |
| 1-Cl | 13.3 | 33.6 | | 26 |
| 1-Br | 13.5 | 33.8 | | 26 |
| 1-CN | 13.4 | 32.8 | | 27 |
| 3-Cl | 13.1 | 29.4 | <i>E</i> | 23 |
| <i>cis</i> -3,4-di-Cl | 13.9 | 35.6 | <i>E,Z</i> | 23 |
| <i>trans</i> -3,4-di-Cl | 13.0 | 25.7 | <i>E,E</i> | 23 |
| 3-OEt | 12.7 | 23.5 | <i>E</i> | 23 |
| 3-OAc | 12.6 | 27.8 | <i>E</i> | 23 |
| <i>cis</i> -3,4-di-OMe | 13.25 | 28.6 | <i>E,Z</i> | 23 |
| <i>cis</i> -3,4-di-OEt | 12.7 | 23.5 | <i>E,Z</i> | 23 |
| <i>cis</i> -3-Cl-4-Me | 12.7 | 31.6 | <i>E,Z</i> | 23 |
| <i>cis</i> -3-Cl-4-OMe | 12.9 | 29.1 | <i>E,E</i> | 23 |
| <i>cis</i> -3-OMe-4-Me | 11.7 | 25.2 | <i>E,Z</i> | 23 |
| 3,3-di-OMe | 13.7 | 32.8 | | 28 |
| 3-CH ₂ CH ₂ OAc | | 29.8 | <i>E</i> | 29 |
| 3-F | 12.5 | 28.1 | <i>E</i> | 30 |
| 3,3-di-F | 15.2 | 45.0 | | 30 |
| 3-CF ₃ | 14.3 | 36.3 | <i>E</i> (95%) | 30 |
| 3-CF ₃ | 13.2 | 37.4 | <i>Z</i> (5%) | 30 |
| 3-CHO | 14.2 | 27.2 | <i>Z</i> | 31 |

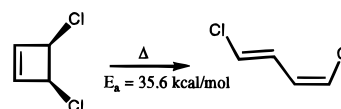
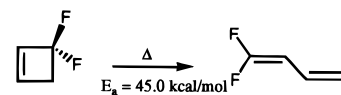
These two cyclobutene derivatives exhibit a remarkable selectivity in their conrotatory ring-openings, a selectivity which strongly favors rotation of the much larger CF₃ groups inward and the smaller fluorine substituents outward. For example, at 111.5 °C, the 19.2 kcal/mol difference in E_a values for the two competitive processes of perfluoro-*trans*-3,4-dimethylcyclobutene leads to a ratio of rates for ring-opening to the *Z,Z*- versus the *E,E*-diene of 1.9×10^9 , a value which is totally unreflective of the mere 1.2 kcal/mol difference in ΔH^\ddagger for the two processes.

Likewise, Kirmse, Rondan, and Houk shortly thereafter²⁷ a related study of substituent effects which clearly indicated that the energetic preference for substituents at C₃ and C₄ of cyclobutene to rotate outward increases as the π -donor nature of the substituent increases. The representative activation energies given in Table 1, which also includes some pertinent data for fluoro and trifluoromethyl substituents, certainly reflect such a proposition.

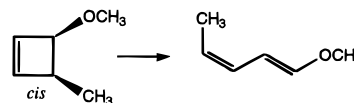
The beneficial trends in E_a observed for the 3-fluoro-, 3-chloro-, and *trans*-3,4-dichlorocyclobutene systems are particularly revealing,^{27,34}



as are the detrimental influences of the 3,3-difluoro and *cis*-3,4-dichloro systems, where one halogen is forced to rotate *inward*.^{27,34}

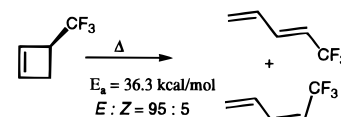


Also noteworthy was the observation that *cis*-3-methoxy-4-methylcyclobutene ring-opened stereospecifically,²⁷ with preferential outward rotation of the more potent electron-donor (but smaller) methoxy substituent.



Consistent with the relative π -donor abilities of the methyl, chloro, acetoxy, and alkoxy groups, the activation energies for ring-opening of each of these 3-substituted cyclobutenes were observed to be increasingly diminished.

The trifluoromethyl substituent exhibited unusual behavior in that (a) it proved to be the only substituent studied which gave rise to slower ring-opening than the parent and (b) ring-opening with inward rotation was observed to be competitive with outward rotation of CF₃.³⁴



The observations of the Dolbier and Kirmse groups prompted Nelson Rondan, then a graduate student in the Houk group at Pittsburgh, to undertake calculations on the transition states for the electrocyclic reactions of cyclobutene and dihydroxycyclobutene. The behavior of the orbitals in these calculations was startling, and produced an exciting revelation of the origin of the experimental results.

In 1985, Rondan, Kirmse, and Houk communicated their initial computational results,²⁷ which eventually became a comprehensive electronic theory which accounted for the stereoselectivity of these cyclobutene ring openings.³⁵ The observed stereoselective conrotation occurs because there is a preferential direction of twisting of the breaking σ -bonds in the transition states of these reactions. The term "torquoselectivity" was invented to describe this type of stereoselectivity which has now been found to have applicability which ranges far beyond the 4- π -electrocyclic system.

The theory which explains this behavior can be understood with reference to the calculated correlation diagram shown in Figure 2, which shows the frontier orbitals for cyclobutene and for the conrotatory ring-opening transition state, calculated with the 6-31G* basis set. The σ -bonding orbital, the SHOMO of

(32) Kirmse, W., unpublished results cited in Moss, R. J.; White, R. O.; Rickborn, B. *J. Org. Chem.* **1985**, *50*, 5132.

(33) McDonald, R. N.; Lyznicky, E. P., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 5920.

(34) Dolbier, W. R., Jr.; Gray, T. A.; Keaffaber, J. J.; Celewicz, L.; Koroniak, J. *J. Am. Chem. Soc.* **1990**, *112*, 363.

(35) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099.

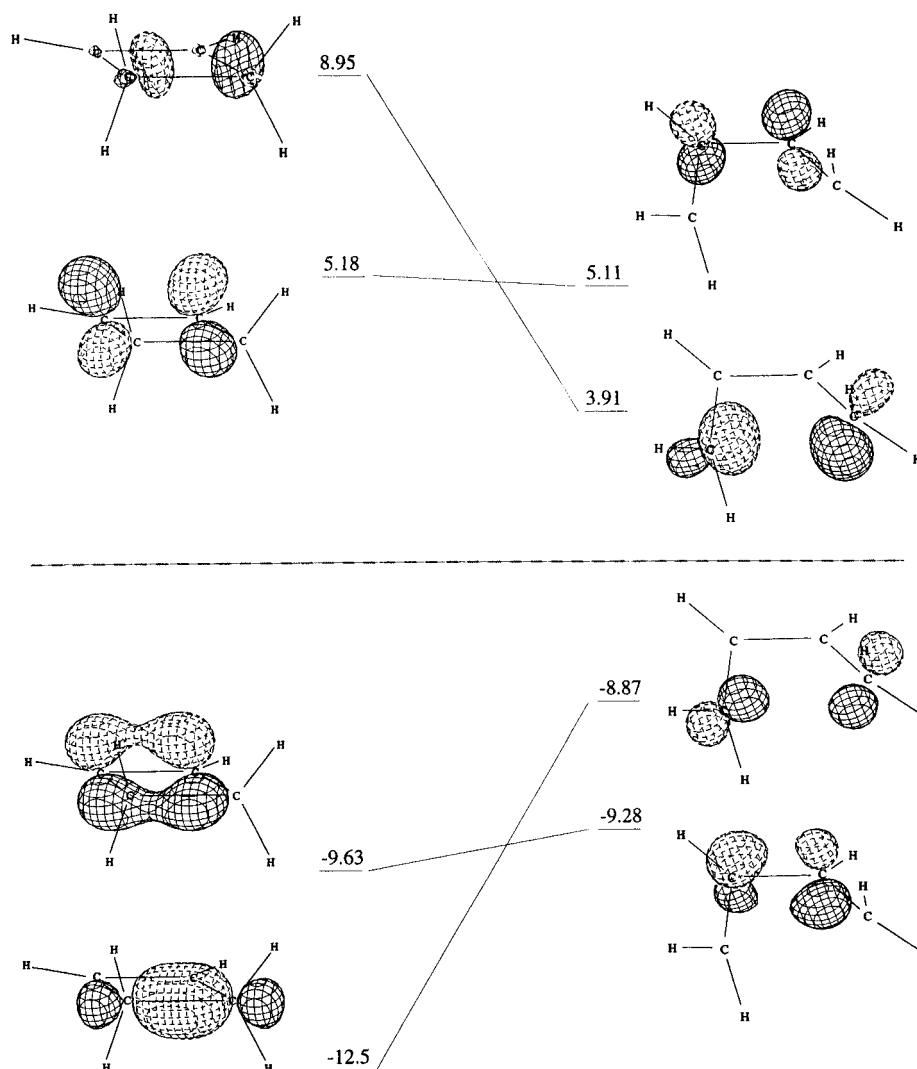


Figure 2. Orbital correlation between cyclobutene and the conrotatory transition structure (RHF/6-31G*, orbital energies in electronvolts).

cyclobutene, rises in energy from -12.5 eV in cyclobutene to -8.87 eV in the transition state as it twists and stretches. This makes the occupied σ -bond orbital a very good electron donor in the transition state. The decrease in energy of the σ^* -orbital from 8.95 to 3.91 eV causes the σ^* -orbital to become a much more efficient electron acceptor. This is a consequence of the decrease in antibonding with distortion. The π -bond is only elevated in energy by 0.35 eV, making it a slightly better donor in the transition state than in the reactant. The π^* -orbital comes down by only 0.07 eV and is virtually unchanged as an acceptor.

Figure 3 shows how p- or π -orbitals on a substituent at the 3- or 4-position interact with the breaking σ -bond. Upon inward rotation, a filled substituent donor orbital overlaps with the transition state HOMO of the cyclobutene transition state, which is primarily concentrated on the breaking C_3-C_4 σ -bond orbital. This overlap results in a destabilizing cyclic four-electron interaction, which substantially raises the activation energy for the inward rotation of a donor substituent. Outward rotation results in less repulsion, because these occupied orbitals overlap less upon outward rotation of a donor substituent, and the activation energy is lowered substantially, because the donor orbital of the substituent also overlaps with the LUMO of the transition state (the antibonding orbital

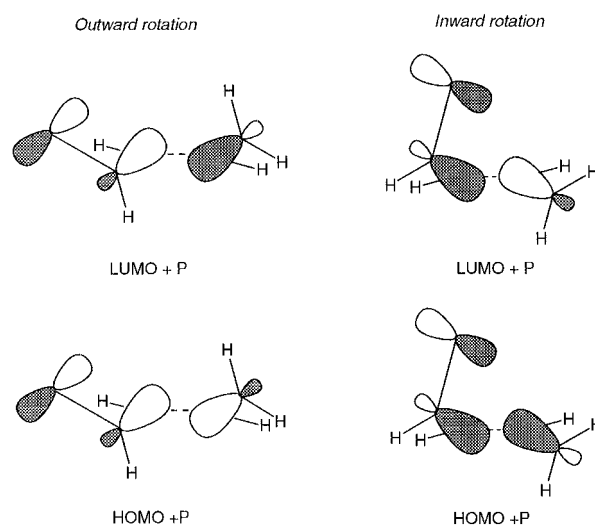


Figure 3. On the bottom line, the transition state HOMO (a stretched and twisted σ -orbital) is shown along with a substituent p-orbital during outward (left) or inward (right) rotation. On the top line, the transition state LUMO (a stretched and twisted σ^* -orbital) is shown along with a substituent p-orbital during outward or inward rotation.

of the breaking C_3-C_4 bond). Upon inward rotation, there is little stabilizing interaction, because the

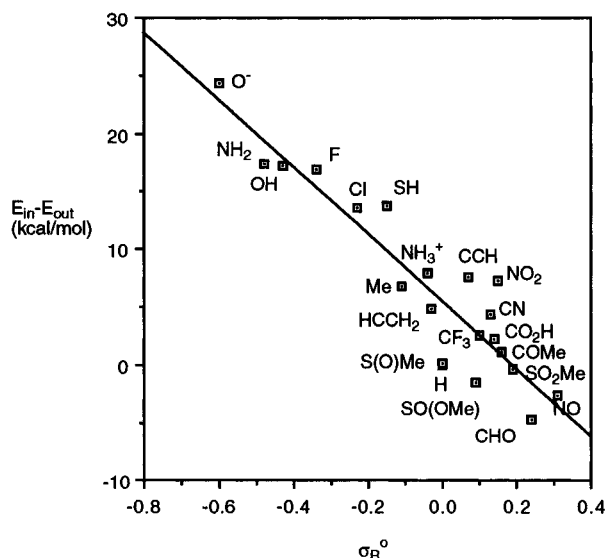


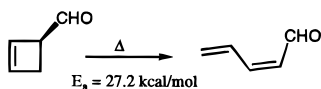
Figure 4. 6-31G**/3-21G activation energy differences plotted against Taft σ_R° Values.

overlap of the substituent orbital with the transition σ^* -orbital is minimal.

Acceptor substituents each possess a low-lying vacant orbital which, upon inward conrotation, overlaps with the HOMO of the transition state. This interaction is a two-electron interaction which stabilizes the transition state. The overlap on inward rotation is especially large and, consequently, lowers the energy of activation for this process a great deal. Outward conrotation of the acceptor substituent produces a smaller stabilizing effect, since overlap with the HOMO is smaller.

Since the original reports, calculations on a large number of substituents have been carried out. Figure 4 shows a plot of the calculated differences in activation energy for inward and outward rotation, versus a substituent constant, σ_R° , which measures the ability of the π -substituent to donate ($\sigma_R^\circ < 0$) or accept ($\sigma_R^\circ > 0$) electrons.³⁶

The validity of these dramatic predictions as to the relative kinetic influence of π -donor versus π -acceptor substituents at the 3(and/or 4) position of cyclobutene was unambiguously demonstrated by the observation that 3-formylcyclobutene ring-opens, with an enhanced rate, and exclusively with inward rotation, a result totally consistent with the theoretical calculations.³⁷ The *cis*-product formed is considerably less stable than the *trans*-isomer.

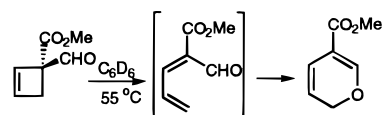


Since that time, the efficacy of the theory of torquoselectivity as it applies to 3-substituted cyclobutenes has been confirmed with each subsequent experimental finding. The preference for a CHO group to rotate inward in preference to an ester function was demonstrated:³⁸

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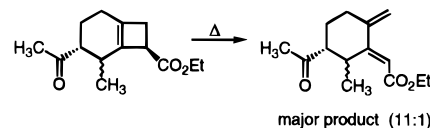
(37) Rudolf, K.; Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 3708.

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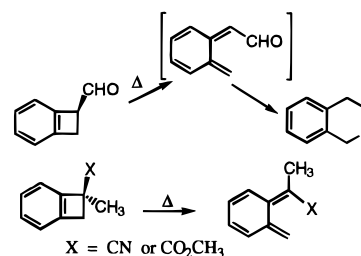


The greater reactivity of *cis*-3,4- versus 3,3-disubstituted cyclobutenes, which cannot be due to torquoselectivity, was determined to derive from a destabilizing steric interaction which elevates the energy of the ground state of the *cis*-3,4-system, whereas the preferred inward rotation of some larger groups, such as ethyl, in the ring-opening reactions of the 3-alkyl-3-methylcyclobutene systems studied by Curry and Stevens can be explained as deriving from more favorable gauche interactions upon inward rotation of the larger ethyl group.³⁹

Ester groups were found by Piers to exhibit a moderate preference for outward rotation in his study of *fused bicyclic* cyclobutene systems,⁴⁰ a result consistent with Houk's study of rotational preferences on such systems.⁴¹ Further computational studies of this system by a combination of quantum mechanics and molecular mechanics provided additional information about the role of steric effects on modulating the electronic effects of 3-substituents.⁴²



Likewise, torquoselectivity theory was found to be applicable to studies of the ring-openings of benzocyclobutenes to *o*-xylylenes. An interesting result is that 3-methyl-3-cyano- or -carbomethoxycyclobutene systems undergo ring-opening with a strong preference for outward rotation of methyl, which overrides the small outward preference of nitrile or ester groups and obliges them to rotate inward.^{43,44}



An experiment which spectacularly demonstrates the dominance of electronic control over steric influences involves 3-methoxy-3-*tert*-butylcyclobutene. This cyclobutene opens with exclusive inward rotation of the bulkier *tert*-butyl substituent.⁴⁵ The potent electronic effect of the methoxy substituent is thus forcing the large *tert*-butyl group to rotate inward.

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(40) Piers, E.; Lu, Y.-F. *J. Org. Chem.* **1989**, *54*, 2267.

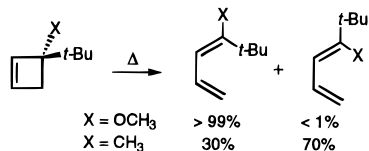
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Over the last 40 years, an abundance of experimental data on the kinetics and stereochemistry of cyclobutene ring-opening processes have been accumulated, the sum of which provides very strong confidence in the combined Woodward–Hoffmann and torquoselectivity theories as being sufficient to explain virtually every known kinetic and stereochemical facet of this electrocyclic reaction.⁴⁶

Figure 5 represents an example of a disubstituted cyclobutene which can hypothetically undergo four different electrocyclic ring openings, where D and A represent donor and acceptor substituents. Which is favored? Theory now gives an unequivocal answer: orbital symmetry rules out the two disrotatory processes on the left; the stereoselective principle of torquoselectivity favors rotation of acceptor in and donor out. Therefore, the process at the upper right of the figure will occur much faster than the others and will be virtually the only observable process.

This powerful predictive principle for cyclobutene stereoselectivities has been extended to other electrocyclic reactions. Torquoselectivity has been predicted for the pentadienyl cation cyclization,⁴⁷ the hexatriene–cyclohexadiene interconversion,⁴⁸ the octatetraene–cyclooctatriene interconversion,⁴⁹ the electrocyclic ring openings of azetines, oxetenes, and thietenes,⁵⁰ the ring-opening of cyclopropenes,⁵¹ and the electrocyclic

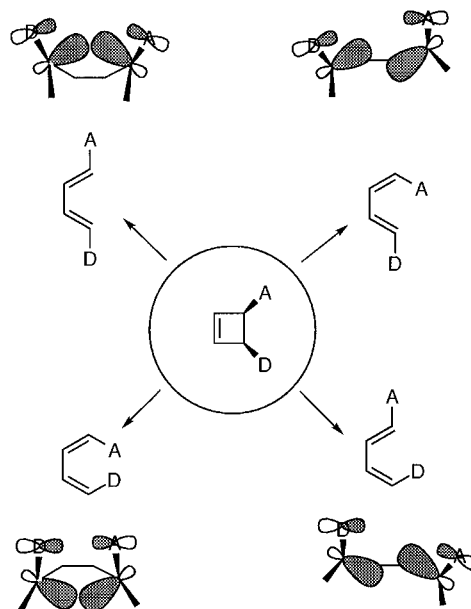


Figure 5. Four possible products from electrocyclic ring-opening of a *cis*-3-donor-4-acceptor-cyclobutene. Theory makes an unequivocal prediction of the preferred product.

openings of aziridines and oxiranes,⁵² as well as the more obvious extension to cyclobutenones.⁵³ Indeed, it is likely that similar effects will operate whenever a σ -bond-breaking or formation is accompanied by a twist away from colinear interaction of the orbitals forming the σ -bond.

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