Can Multibond Reactions Be Synchronous?

A maverick theoretician touches off a debate on both synchronicity and the relative efficacies of molecular orbital calculations

Michael Dewar, an eminent theoretician at the University of Texas at Austin, has a reputation for taking extreme positions in lectures and in print, often, it would seem, as a way to provoke debate. Dewar's most recent provocation is a claim that chemical reactions involving more than one bond cannot normally be synchronous.*

Dewar seems to occupy a rather unusual position in the scientific community. One colleague calls him an "enfant terrible," another argues that he is "the bête noire of theoretical chemistry," and a third says simply that he is "a very contentious character." But virtually all agree that his ideas are normally well thought out and deserving of careful study. In this case, however, the dispute seems to center less on his contentions about synchronicity and more on the relative efficacies of alternative methods for calculating molecular orbitals.

Most organic reactions either are one-bond processes, involving the making and/or breaking of one bond, or take place in distinct steps, each of the one-bond type. A typical example is substitution at a saturated carbon atom:

$$\mathrm{Y^- + R{-}X \longrightarrow Y{-}R + X^-}$$

The main reactions that are thought to involve synchronous multibond mechanisms are multibond pericyclic reactions (in which bonds are exchanged cyclically around a ring), the E2 reaction, and the $\mathrm{S_N2'}$ reaction. Dewar argues that most of these are actually two-step reactions and that synchronous reactions can occur only under special conditions. (A *synchronous* reaction is one where all bond-making and bond-breaking processes take place in unison, having all proceeded to comparable extents in the transition state; the transition state is thus symmetrical. A *concerted* reaction is one that takes place in a single kinetic step without necessarily being synchronous; the transition state is unsymmetrical.)

Dewar argues first that a synchronous reaction involving more than one bond is energetically unfavorable. In a typical one-bond reaction, the activation energy for the reaction is about a third of the energy required to break the bond, since "you have to weaken the old bond before you form a new one." In a synchronous reaction involving two bonds, the activation energy should be roughly twice as large. It will thus "be easier to carry out the overall reaction by two successive inferior one-bond processes than by the optimum two-bond one."

The only important exceptions, Dewar contends, are when an aromatic transition state is formed or when a hydrogen shift is involved. In the former case, the stabilization derived from the transition state offsets the increased activation energy; a similar effect occurs in the latter case because hydrogen readily forms three-centered bonds. Dewar thus concludes: "Synchronous multibond mechanisms are normally prohibited."

The E2 reaction for elimination of H and X from adjacent carbon atoms is one of the exceptions:

In this case, there are two bond-making/bond-breaking processes, but one of them involves transfer of a hydrogen. Molecular orbital calculations show that the hydrogen transfer does not make a large contribution to the activation energy.

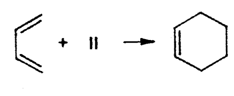
$\mathrm{S_N2'}$ reactions involve substitution and migration of a double bond:

This reaction is generally assumed to be synchronous, says Dewar, but "there is . . . no evidence that this is so." In fact, molecular orbital calculations for the reaction of chloride ion with allyl chloride show that formation of the new C-Cl bond takes place without activation to form an intermediate

$$\left[\mathrm{Cl{-}{-}{-}CH_2 \cdots CH \cdots CH_2{-}{-}{-}Cl}\right]^-$$

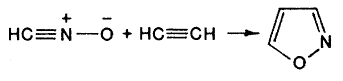
in which the old C-Cl bond is almost intact. "The calculations thus contradict the previously accepted conclusion that addition of nucleophile to the C-C bond cannot precede major weakening of the bond to the leaving group."

Another example is the Diels-Alder reaction, which involves cycloaddition of a 1,3-diene to an activated ethylene derivative to form a cyclohexene:

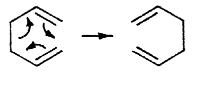


"Detailed analysis of the available data shows that there is *no* evidence that *any* Diels-Alder reaction takes place in a synchronous manner." There is, however, "very definite evidence," both experimental and calculational, that many Diels-Alder reactions involving unsymmetrical reactants are nonsynchronous. Since no reactions have been shown to be synchronous and some have been shown to be nonsynchronous, "scientific methodology requires *all* such reactions to be regarded as nonsynchronous unless and until synchronicity has been demonstrated in at least one case."

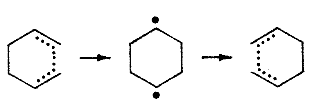
Two other examples are 1,3 dipolar additions, such as addition of fulminic acid to acetylene:



and the Cope rearrangement:



In the former case, Dewar asserts, molecular orbital calculations indicate that—as in the Diels-Alder reaction—one new bond is formed strongly in the transition state, while the second is very weak; the calculations show that formation of the second bond is then the rate-determining step. For the Cope rearrangement, "which I would have sworn was a synchronous process," the calculations indicate a two-step mechanism leading to an intermediate biradical:



These calculations, he says, are confirmed by experimentally observed substituent effects.

Does the question of synchronicity have any relevance for the practicing organic chemist? Dewar argues that it does. First, the knowledge can help predict steric effects. "In the Diels-Alder reaction, for example, if one of the nascent C-C bonds in the transition state is much longer and weaker than the other, adjacent substituents will interact correspondingly less with one another. Furthermore, if the reaction involves a biradical-like or zwitterionic intermediate, we can tell at once from general chemical theory which intermediate . . . is most

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

likely to be formed and which will be the weak bond in it."

Reactions to the paper have been mixed. Eminent physical organic chemist Paul Bartlett of Texas Christian University, for example, says "I don't disagree with Michael's conclusions; I think he is making a lot out of something . . . that has been very indistinct. . . . Since I read that article, I have been trying to find in the literature somewhere where somebody strongly expressed the opposite view, but I haven't been able to find it."

The opposite view may not be expressed in the literature, but many chemists obviously think that it should be. Andrew Streitweiser of the University of California, Berkeley, says, "There is a strong element of truth in what Michael says, but he goes too far." Streitweiser cites experiments on the Diels-Alder reaction conducted two decades ago by Stan Seltzer of Brookhaven National Laboratory and Mel Goldstein of Cornell University. Seltzer studied deuterium isotope effects and "found that changes at both ends of the system occurred at the same time." Goldstein studied heavy atom isotope effects, which also indicated synchronicity.

But the investigators do not agree on the interpretation of their findings. Seltzer concurs with Streitweiser. Goldstein, however, says his results indicate that the transition state for the Diels-Alder reaction is highly unsymmetrical, suggesting a lack of synchronicity, and he argues that Seltzer's results are consistent with his. Dewar agrees with Goldstein and says that his own experimental measurements also favor a highly unsymmetrical transition state. Similar disagreements have arisen about other reactions, suggesting that labeling experiments are not as definitive as would be desirable. In many cases in which experiment and theory do not completely agree, adds Jerome Berson of Yale University, "the criteria of what should constitute proof are not agreed upon."

Most of the criticism directed against Dewar's hypothesis, however, involves the methods by which he calculates molecular orbitals. At one extreme, Streitweiser says simply that "Dewar would consider his results much more definitive than many other theoretical chemists." At the other extreme, Wes Borden of the University of Washington contends that "in some of the examples, such as the Cope rearrangement, I believe he is flat-out wrong."

The dispute involves ways to approach solutions to the Schroedinger equation, which describes the relation between the geometry of a molecule and its energy. "If we could solve the Schroedinger equation," says Dewar, "we would know all the answers. Unfortunately, we can't so we have to make some approximations."

The Schroedinger equation can be viewed as a set of integrals, each of which specifies the orbit of an electron with respect to the positions of other atoms. To make calculations manageable, it is necessary to neglect many integrals which correspond to very small interactions and to assign fixed values, obtained from experiments, to others.

The techniques Dewar uses to do this, called MINDO/3 and MNDO[†], are modified versions of approximations originally developed by John Pople of Carnegie-Mellon University. MNDO is used in most cases, but MINDO/3 is used for certain molecules, such as carbocations.

Using MNDO, Dewar says, it is possible to calculate the complete geometry of a molecule containing 20 atoms in about 15 minutes on a large computer such as a Digital Equipment Corporation VAX. On a Cray supercomputer, he adds, it is now possible to calculate the geometry of molecules as large as tetrapeptides. In contrast, with "ab initio" calculations—in which the only assumptions are an initial definition of each p and s orbital—the calculation for a molecule of 20 atoms would take 1000 times longer.

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The penalty for the increased speed of MNDO, however, is lowered reliability and versatility. Even the best MNDO calculations still "do not do some things well," Dewar adds. They don't, for example, predict hydrogen bonding.

In particular, says Ken Houk of the University of Pittsburgh, "MNDO has some inherent problems that bias it toward 2-step reactions." Adds Henry Schaefer of Berkeley, "The methods Michael uses always end up with unsymmetrical transition states. It is not entirely obvious that this is the way things go."

The principal problem with Dewar's calculations, says Borden, is that the values he uses for various integrals are derived from "nice, stable ground state molecules. Transition state bonds are going to have very different lengths than they will in normal molecules. It's not clear that his parameters will have the right dependence on distance to give good answers on transition states."

Borden, Houk, and Schaefer all use ab initio calculations. Until recently, it has been virtually impossible to perform such calculations on molecules containing more than a handful of atoms, but the capability has been increasing. Because of improvements in theory and in computers, says Schaefer, "Ab initio calculations have been improving by an order of magnitude every 3 years." In some of Dewar's examples, Schaefer says, ab initio calculations indicate that the reactions are synchronous.

Schaefer himself, for example, has performed ab initio calculations for the addition of fulminic acid to acetylene and found that the lengths of the two forming bonds are virtually identical, indicating that the reaction is synchronous. Dewar, however, argues that the two bonds have greatly different strengths and that the coincidence in lengths is just that, a coincidence, since C–O bonds are normally shorter than C–C bonds. In support of his own work, Schaefer cites work by Rolf Huisgen of the University of Munich in Germany. Huisgen argues that all 1,3-dipolar cycloadditions are synchronous, Schaefer says, and "most people would say that he has nailed the lid on the coffin."

Borden, along with colleagues at Washington and at the Institute for Molecular Science in Okazaki, Japan, has performed ab initio calculations for the Cope rearrangement and has found that the transition state is not a diradical, as Dewar argues. In a paper accepted by the *Journal of the American Chemical Society*, he argues "that the preferred pathway for the Cope rearrangement . . . is via a concerted pericyclic reaction." Dewar remains steadfast: "When you get the same results with MNDO and ab initio calculations, there is a strong presumption that the results are correct. If different results are obtained, it does not necessarily mean that MNDO is wrong." Most of the investigators would agree that it will probably be a few more years before this dispute is settled to everyone's satisfaction.

Schaefer offers what might be the best overall viewpoint: "Michael's paper is important because he has presented his case very well, but the whole story is a lot more complicated. It would have been better if there had been an accompanying paper in *JACS* by Houk presenting the opposite viewpoint."

—THOMAS H. MAUGH II

[†] MNDO, modified neglect of differential overlap. MINDO/3, modified intermediate neglect of differential overlaps.