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Multibond Reactions Cannot Normally Be Synchronous

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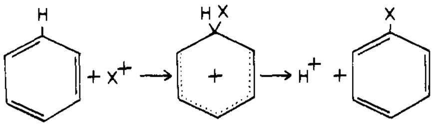
Abstract: Most organic reactions either are *one-bond* processes, involving the making and/or breaking of one bond, or take place in distinct steps, each of one-bond type. It is shown that synchronous multibond processes, involving the making and/or breaking of two or more bonds, are likely to have activation energies that are roughly double those of analogous one-bond ones, explaining the predominance of the latter. The only reactions that are currently thought to involve synchronous multibond mechanisms are multibond pericyclic reactions, the E2 reaction, and the S_N2' reaction. The evidence concerning the mechanisms of these is reviewed in detail and found to provide no clear support for synchronicity. On the contrary, it seems likely that the large majority of them are nonsynchronous, taking place in steps or stages, each of one-bond type. The few exceptions occur in clearly defined situations where the disadvantage of synchronicity is expected to be unusually small.

The two basic reactions of organic chemistry, substitution at a saturated carbon atom and addition to a multiple bond, resemble one another in that each involves the breaking of one bond and the formation of one; i.e.,

$$Y^- + R{-}X \rightarrow Y{-}R + X^- \qquad (1)$$

$$Y^- + X{=}Z \rightarrow Y{-}X + Z^- \qquad (2)$$

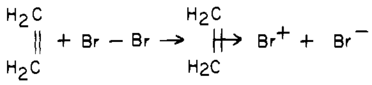
Such a process may be termed a *one-bond* reaction. The same is true in effect for the first step in aromatic substitution; e.g.,



(3)

Since formation of the intermediate involves loss of one carbon atom from a conjugated system, it corresponds in effect to breaking of half a π bond.

The first step in many electrophilic additions to olefins involves the formation of a π complex;[1] e.g.,



$$\begin{array}{c}H_2C\\ \| \\ H_2C\end{array} + Br-Br \rightarrow \begin{array}{c}H_2C\\ \| \!\rightarrow \\ H_2C\end{array} Br^+ + Br^- \qquad (4)$$

This again is a one-bond reaction since the bond between the olefin and the apical group in a π complex is in effect a dative π bond.[1]

A little consideration will show that the same is true of most of the other basic processes in organic chemistry whose mechanisms have been established unequivocally. The only apparent exceptions are multibond pericyclic reactions that are "allowed" by the Woodward–Hoffmann rules[2] or Evans' principle[3,4] and the E2 and S_N2' reactions. Reactions in which two or more bonds are formed or broken are otherwise known to take place in kinetically distinct steps, each of one-bond type.

This predominance of one-bond mechanisms in the basic processes of organic chemistry is rather surprising.[5] It suggests that there must be some factor, hitherto overlooked, that makes synchronous[6] multibond mechanisms unfavorable. If such a factor exists, why then should it not also operate in the cases noted above? It is easy to write mechanisms for them that involve only one-bond steps. Indeed, such a mechanism for the Diels–Alder reaction seemed at one time more likely than a synchronous one.[7] It is true that most organic chemists currently believe "allowed"[2-4] pericyclic reactions to be normally synchronous, all the bond-forming and bond-breaking processes taking place in unison, but this belief has been due more to the hypnotic effect of the Woodward–Hoffmann rules[2] than to concrete evidence.

Work in these laboratories, which will be referenced presently, has suggested very strongly that the current picture of pericyclic reactions is *not* correct, multibond processes of this type *not* being in general synchronous. Furthermore, it is easy to see, on the basis of current theory, a reason why synchronous multibond mechanisms might well be generally unfavorable. The purpose of this paper is to present these arguments in detail and to show that they lead to a new and apparently very powerful rule limiting the possible mechanisms of chemical reactions.

Why Should Two-Bond Reactions Be Difficult?

This question can be answered very simply by using the conventional Evans–Polanyi[8] approach. Here the changes taking place in a reaction are analyzed in terms of bond-breaking and bond-forming processes, represented as functions of a common reaction coordinate[9] (q), which represents the extent to which the reaction has taken place. First we plot (A in Figure 1) a *bond*-breaking curve showing how the total energy (E) changes as bonds that break during the reaction break. Next, starting with the products of bond breaking, we plot (B in Figure 1) a *bond-forming* curve that shows how E changes as bonds that form during the reaction form. B can equally be regarded as the bond-breaking curve and A as the bond-forming curve, for the reverse reaction. The crossing point (C) of A and B corresponds to the transition state (TS), the point where formation of the new bonds compensates for breaking of the old ones. This can be regarded as a resonance-type treatment where A represents the energies of reactant-like structures and B those of product-like structures, as a function

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(1) (a) Dewar, M. J. S. *Bull. Soc. Chim. Fr.* **1951**, *18*, C86. (b) Dewar, M. J. S.; Marchand, A. P. *Ann. Rev. Phys. Chem.* **1965**, *16*, 321. (c) Dewar, M. J. S.; Ford, G. P. *J. Am. Chem. Soc.* **1979**, *101*, 783.

(2) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.

(3) (a) Evans, M. G.; Warhurst, E. *Trans. Faraday Soc.* **1938**, *34*, 614. (b) Evans, M. G. *Ibid.* **1939**, *35*, 824.

(4) Dewar, M. J. S. *Angew. Chem., Int. Ed. Engl.* **1971**, 770, 761.

(5) It is certainly not due to failure to consider other possibilities because chemists have always felt free to postulate concerted multibond mechanisms.

(6) In our terminology a *synchronous* reaction is one where all the bond-making and bond-breaking processes take place in unison, having all proceeded to comparable extents in the transition state. A *concerted* reaction is one that takes place in a single kinetic step without necessarily being synchronous. A *two-stage* reaction is concerted but not synchronous, some of the changes in bonding taking place in the first part of the reaction, followed by the rest. A *two-step* reaction takes place in two kinetically distinct steps, via a stable intermediate.

(7) See, e.g.: Dewar, M. J. S. "The Electronic Theory of Organic Chemistry"; Clarendon Press: Oxford, 1949.

(8) Evans, M. G.; Polanyi, M. *Trans. Faraday Soc.* **1938**, *34*, 11.

(9) The term *reaction coordinate* is used here in its original sense, to imply a geometrical variable whose value changes during a reaction and whose magnitude can be taken as a measure of the extent to which the reaction has proceeded. The normal coordinate with negative curvature at a transition state is better described as the *transition coordinate*.

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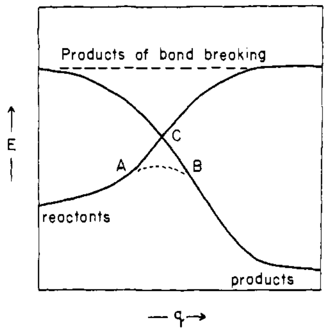

Figure 1. Evans–Polanyi plot for a reaction. The dotted line indicates the effect of resonance between reactant-like and product-like structures in the TS.

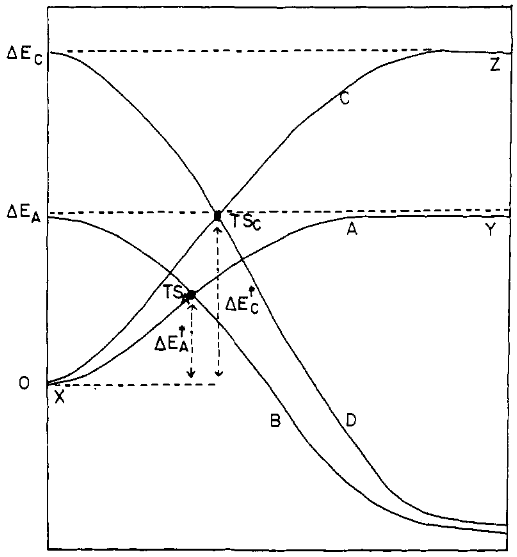

Figure 2. Evans–Polanyi plots for a one-bond reactiopn (A–TS$_A$–B) and an analogous two-bond reaction (C–TS$_C$–D).

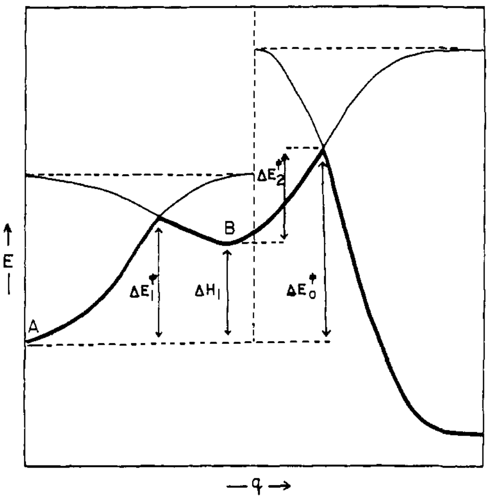

Figure 3. Evans–Polanyi plot for a two-step reaction involving a high-energy intermediate (B).

of geometry (q). Resonance between the two structures will lead to an avoided crossing, indicated by the broken line in Figure 1, so the energy of the TS will be correspondingly lower than the crossing point of A and B. However, the success[10] of the conventional approach, where such resonance effects are neglected, suggests that the difference is not normally significant.

In Figure 2, A and B represent such a plot for a one-bond reaction and C and D that for an analogous two-bond one, i.e., a reaction involving the synchronous breaking and/or formation of two bonds. Since twice as much energy is needed to break two bonds as to break one, the difference in energy (ΔE_C) between the reactants (X) and the upper terminus (Z) of C is about twice as great as that (ΔE_A) between X and the upper terminus (Y) of A. The difference in energy (ΔE_C) between X and the point (TS$_C$) where C and D cross is consequently also about twice as great as that (ΔE_A) between X and the crossing point (TS$_A$) of A and B. Thus the activation energy for a two-bond reaction should be roughly double that for an analogous one-bond one.

This would indeed be expected on the basis of intuition. Exothermic reactions need activation because the new bond(s) formed during them cannot begin to form until the old one(s) have weakened to a considerable extent. Each breaking/forming bond contributes to the activation energy, so a reaction in which two bonds are formed, and two broken, in a single synchronous step, should have an activation energy twice as large as an analogous one-bond reaction.

This argument is based on the assumption that all the bond-forming and bond-breaking processes take place in parallel, the course of the reaction being represented in the Evans–Polanyi symbolism by a single bond-forming curve and a single bond-breaking one. The alternative is to split up the bond-forming processes, and the bond-breaking processes, in time, the overall reaction taking place in reality, or in effect, in separate steps, each of one-bond type. The extreme case, where the steps are kinetically distinct, is indicated in Figure 3. Here the overall activation energy ($\Delta E_o^{\ddagger}$) is given by

$$\Delta E_o^{\ddagger} = \Delta H_1 + \Delta E_2^{\ddagger} \tag{5}$$

where ΔH_1 is the heat of reaction for formation of the intermediate from the reactant and $\Delta E_2^{\ddagger}$ the activation energy for its conversion to the product. If the activation energy for the synchronous two-bond process is $\Delta E_S^{\ddagger}$, the two-step mechanism will be favored if

$$\Delta H_1 + \Delta E_2^{\ddagger} < \Delta E_S^{\ddagger} > \Delta E_1^{\ddagger} \tag{6}$$

where $\Delta E_1^{\ddagger}$ is the activation energy for formation of the intermediate from the reactants. Clearly both $\Delta E_1^{\ddagger}$ and $\Delta E_2^{\ddagger}$ can each be quite a lot bigger than half ΔE_S without violating this condition, provided that the intermediate does not have too high an energy. In other words, it will be easier to carry out the overall reaction by two successive inferior one-bond processes than by the optimum two-bond one. We may indeed expect this to happen whenever an overall two-bond reaction can be dissected into two reasonable one-bond steps. This is usually the case, as is indicated by the fact that two-step mechanisms have been seriously considered for nearly all two-bond reactions.

In Figure 3, it is implied that the intermediate in the reaction is not much higher in energy than the reactants. This, however, is not necessary. If the intermediate is a high-energy species, its conversion to the product is likely to require correspondingly little activation, as indicated in Figure 4a. The energy of the TS for the overall reaction will be equal to that of one of the individual one-bond steps. In the limiting case, where the intermediate is so unstable that it undergoes conversion either to the reactants or to the products, without activation (Figure 4b), the reaction will become concerted,[6] taking place in a single kinetic step. It will not, however, be synchronous because the two individual one-bond processes involved in it take place not in unison but at different stages in what may be termed[6] a *two-stage* reaction, the TS for which corresponds to that of one component stage.

There is also a third possibility, i.e., that the intermediate undergoes conversion without activation both to the products and to the reactants (Figure 4c). The intermediate then becomes the TS for the overall reaction, one component one-bond process taking place between the reactants and the TS, the other between the TS and the products.

A two-bond reaction should therefore take place in a synchronous manner only when there is no alternative two-step or

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(10) The existence of linear free-energy relationships between rate and equilibrium constants, for example the Brønsted and Hammett relations, can be explained only if the resonance interactions are small.[38]

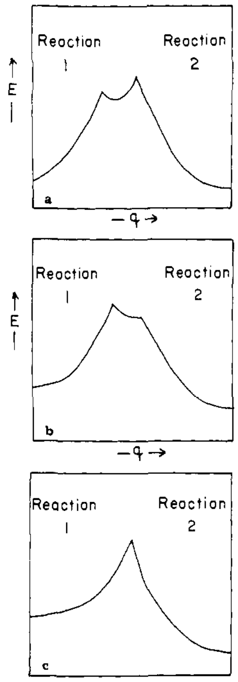

Figure 4. Evans-Polanyi plots for (a) a two-step reaction in which formation of the final product from the intermediate is rate determining, (b) a two-step/two-stage reaction in which conversion of the intermediate to the product requires no activation, and (c) a two-stage reaction in which the intermediate is the TS.

two-stage path involving an intermediate whose heat of formation is less than that of the transition state for the synchronous process. Similar considerations apply even more forcefully to reactions that involve the making/breaking of more than two bonds. Such processes should almost invariably take place in two or more kinetically distinct steps, each a one-bond reaction or a nonsynchronous two-bond one.

These arguments suggest that multibond reactions that are "allowed" by the Woodward-Hoffmann[2] rules or Evans' principle[3,4] may nevertheless take place in a nonsynchronous manner if they are of other than one-bond type. There is indeed no reason why this should not be the case. An "allowed" reaction is one where a synchronous TS is specifically stabilized by cyclic conjugation.[3,4] There is, however, no guarantee that this will compensate sufficiently for its inherently high energy if it is of multibond type. The original statement[2] of the Woodward–Hoffman rules seems unfortunate in this connection, the claim[11] that they are based on "a new principle of bonding", so powerful that "there are no exceptions", being both untrue and very misleading. The term "forbidden" is also unfortunate, implying as it does that a "forbidden" reaction is forbidden with the same finality as a symmetry-forbidden transition in spectroscopy. Even worse is the use of the term "orbital symmetry" for a phenomenon which in no way[4] depends on symmetry in the accepted sense of the word, particularly since there *are* phenomena which *are* controlled by the symmetries of the orbitals involved.[12] Since these terms are now entrenched in the literature, it would cause confusion to change them, but they should, as here, be placed in quotation marks to show that they are being used in a special sense. To avoid further confusion, the rule derived here will be stated in a more general way; i.e.,

synchronous multibond mechanisms are normally prohibited

They occur only in exceptional cases where special factors operate. The same is also true for mechanisms that are "forbidden" in the Woodward–Hoffman sense.

As implied earlier, this rule bars synchronous mechanisms for the majority of pericyclic reactions, even when they are "allowed". There is, however, a reason why reactions "allowed" by the Woodward–Hoffmann rules might represent at least partial exceptions to the new rule. This can be seen from Evans' original treatment[3] of the Diels–Alder reaction.

Evans was concerned with the possible role of resonance in the TS between reactant-like and product-like structures, in the approach[8] he and Polanyi had developed (cf. Figure 1). He was therefore looking for a reaction in which such resonance effects were likely to be unusually large. It occurred to him that this should be the case in the Diels–Alder reaction if it takes place in a synchronous manner, via a cyclic TS, because the cyclic interaction of p AOs of the six carbon atoms should then lead to a cyclic conjugated system, isoconjugate with the π system in benzene and therefore aromatic. The resonance interaction between the reactant-like and product-like structures in the Diels–Alder TS should therefore be large, like that between the analogous Kekulé structures in benzene, so this should be a case where the dashed line in Figure 1 lies unusually far below the crossing point of the lines representing bond breaking (A) and bond making (B). Evans pointed out that the resulting stabilization of the TS should facilitate the synchronous two-bond mechanism and so make it more competitive with two-step or two-stage alternatives. Similar considerations naturally apply to other "allowed" pericyclic reactions, so this is a place where exceptions to the new rule might well be found.

Pericyclic reactions also differ from acyclic processes in that it is much harder to dissect them into one-bond steps. Acyclic two-bond reactions can almost invariably be dissected into one-bond steps where the reactants and products contain the same number of electron-pair bonds. Indeed, the mechanisms of such reactions have often been, and sometimes still are, the subject of controversy, precisely because of the posssibility of writing equally reasonable synchronous and two-step mechanisms for them. Any such dissection of a pericyclic reaction, on the other hand, almost always involves an intermediate biradical or zwitterion in which there is one electron-pair bond less than in the reactants or products.[13] Any such two-step or two-stage mechanism consequently involves intermediates of relatively high energy.

A further factor that must be taken into account in reactions of this kind, where the reactants and products share, or can share common elements of symmetry, is a rule, formulated by McIver,[14] which limits the possible symmetry of the TS of a reaction in which the reactants and products share a common element of symmetry. This rule eliminates strictly synchronous mechanisms for many pericyclic reactions that are "allowed" by the Woodward–Hoffmann rules, in particular Diels–Alder reactions between symmetric dienes and symmetric dienophiles. McIver's argument, like others based on symmetry, cannot predict the extent to which symmetry must be broken or how much the reactants must deviate from symmetry for the rule to no longer operate.[15] It is therefore possible in principle that such reactions might take place via TSs that are so nearly symmetrical that the deviations from symmetry were chemically negligible. The same problem arises in any attempt to relate the rates and mechanisms of reactions to the symmetries of the electronic wave functions of the reactants and the TS, e.g., the treatment of pericyclic reactions by Longuet-Higgins and Abrahamson.[16] It should also be noted that the derivation[14] of McIver's rule is not completely rigorous in all cases. However, it then fails only if the force constants of the bonds in the symmetrical structure have very improbable values.

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(11) "Violations: There are none! Nor can violations be expected of so fundamental principle of maximum bonding" (ref 2, p 851).

(12) For two good examples of phenomena genuinely controlled by orbital symmetry, see: (a) Dewar, M. J. S., In "Steric Effects in Conjugated Systems"; Gray, G. W., Ed.; Butterworths: London, 1958, p 46. (b) Dewar, M. J. S.; Pakiari, A. H.; Pierini, A. B. *J. Am. Chem. Soc.* **1982**, *104*, 3242.

(13) The only exceptions are cycloaddition reactions involving ions, e.g., that of allyl cation to an olefin to generate a cyclopentyl cation.

(14) McIver, J. W. *Acc. Chem. Res.* **1974**, *7*, 72; *J. Am. Chem. Soc.* **1975**, *97*, 3632.

(15) The band at 208 nm in the spectrum of benzene would, for example, be rigorously forbidden if the molecule had static D_{6h} symmetry. Yet in practice it has an extinction coefficient of ca. 10^4 due to the minor perturbation caused by molecular vibrations.

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

These arguments show that no qualitative theory can on its own lead to reliable conclusions concerning the mechanism of any multibond pericyclic reaction. The mechanisms of such reactions are also notoriously difficult to determine by experiment; indeed Doering[17] once suggested, for that reason and not altogether frivolously, that they be termed "no mechanism reactions".

Anti-BEP Character of Multibond Reactions

If a two-bond reaction takes place in steps via a biradical-like intermediate, the reactions leading to this intermediate from the reactants and from the products will usually be different. If so, there is no reason why the less endothermic step should have the lower activation energy. Such a reaction need not therefore follow the usual pattern predicted by application of the Evans–Polanyi approach (BEP principle).[18] In particular, it need not conform to Hammond's postulate.[19] Furthermore, the optimum nonsynchronous path may be of the kind indicated in Figure 4b, where the intermediate undergoes conversion to the products or to the reactants without activation. The reaction profile will then exhibit no secondary minimum, the overall reaction being a concerted process though not of course synchronous. The TS for the overall reaction will correspond to the step that requires specific[20] activation. Since conversion of the intermediate to the reactants and its conversion to the products are quite distinct processes, there is no reason why it should be the more exothermic of the two that requires activation. If it is not, the reaction will again violate Hammond's postulate, the TS being product like in the case of an endothermic reaction and reactant like in the case of an exothermic one. Nonsynchronous multibond reactions are therefore typical anti-BEP[18] processes.

Conditions Favoring Synchronous Multibond Reactions

As we have seen, there is nothing to prevent a two-bond reaction from taking place in a synchronous manner, if there is no better alternative. The same is equally true for a reaction that is "forbidden" by the Woodward–Hoffmann rules or Evans' principle. In each case the obstacle is quantitative, not qualitative, and it may consequently be overruled by other factors that make alternative routes even less favorable.

Exceptions to the new rule should be largely confined to two-bond reactions because the barrier to synchronicity should become progressively greater the greater the number of bonds that are being formed or broken. There are four factors that might favor synchronicity in such cases.

(a) The TS of a synchronous "allowed" pericyclic reaction is aromatic.[3] The corresponding aromatic stabilization is lost, or at least diminished, if the reaction takes place nonsynchronously, via an unsymmetrical TS. As we shall see presently, this in itself is not enough to enforce synchronicity. "Allowed" two-bond reactions usually take place by nonsynchronous mechanisms.

(b) If a reaction is assisted by a massive relief of steric strain, the relief of strain may be greater for a synchronous process, involving a symmetrical TS, than for an alternative nonsynchronous one, involving an unsymmetrical TS.[21]

(c) Synchronous mechanisms may be favored in the case of very exothermic processes where the activation energy of the synchronous reaction itself is very small (Figure 5). Since alternative two-step or two-stage mechanisms are likely to involve high-energy intermediates, they may well need more activation than the synchronous one.

(d) Two-bond reactions that involve the migration of a hydrogen atom tend to be synchronous, one of the bond breaking/making processes involving bonds to a common hydrogen atom. Ene and retro-ene reactions are typical examples, for instance the pericyclic decarboxylation of vinylacetic acid (**1**):

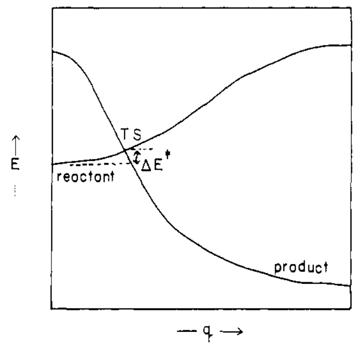
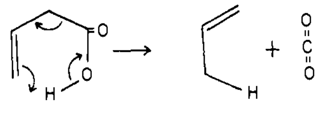


Figure 5. Evans–Polanyi plot for a very exothermic reaction.



1 2 3 (7)

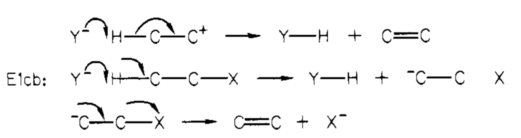
Here one of the breaking bonds and one of the forming bonds both involve the same hydrogen atom. Since there is one delocalized electron per bond in the TS of a typical pericyclic reaction, the hydrogen atom is attached to its neighbors in the TS by what amounts in effect to a two-electron three-center bond. Since hydrogen forms very strong bonds of this type, as indicated by the bonding in the boron hydrides and carboranes, the forming and breaking of the bonds to hydrogen should not contribute significantly to the activation energy of such a pericyclic reaction. It is therefore possible for a second bond-breaking/bond-forming process to occur at the same time as that involved in the migration of the hydrogen atom. Such a process, although of two-bond type, may then take place in a synchronous manner. This situation is peculiar to hydrogen because of its propensity to form three-center bonds. Furthermore, since migration of hydrogen to carbon involves an unfavorable change in hybridization of the carbon atom,[22] reactions of this kind should be easiest when they involve migration of hydrogen from one heteroatom to another, less facile when they involve migration of hydrogen from a heteroatom to carbon, or the reverse, and hardest when they involve migration of hydrogen from one carbon atom to another.

The role of three-center bonds will be discussed in more detail later.

Potential Two-Bond Reactions

The rest of this paper will be concerned with an analysis of reactions for which two-bond mechanisms have been postulated or are possible. As noted above, nearly all of these are of pericyclic type, the only exceptions being bimolecular nucleophilic substitution and the S_N2' reaction. We will begin with the latter.

(A) The E2 Reaction. There are several possible mechanisms for aliphatic elimination, i.e., the removal of H and X from two adjacent carbon atoms to form.a CC π bond; viz.,



$$\text{E2:}\quad Y^{-}\ \text{H—C—C—X} \longrightarrow \text{Y—H} + \text{C=C} + X^{-} \qquad (8a)$$

$$\text{E1:}\quad \text{H—C—C—X} \longrightarrow \text{H—C—C}^{+} + X^{-} \qquad (8b)$$

$$Y^{-}\ \text{H—C—C}^{+} \longrightarrow \text{Y—H} + \text{C=C}$$

$$\text{E1cb:}\quad Y^{-}\ \text{H—C—C—X} \longrightarrow \text{Y—H} + {}^{-}\text{C—C}\quad \text{X} \qquad (8c)$$

$${}^{-}\text{C—C—X} \longrightarrow \text{C=C} + X^{-}$$

The E1cB and E1 mechanisms are clearly of one-bond type. The classical E2 mechanism, however, involves the breaking of two

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[17] Doering, W. v. E.; Roth, W. R. *Tetrahedron*, **1962**, *18*, 67.

[18] Dewar, M. J. S.; Dougherty, R. C. "The PMO Theory of Organic Chemistry"; Plenum Press: New York, 1975; section 5.5.

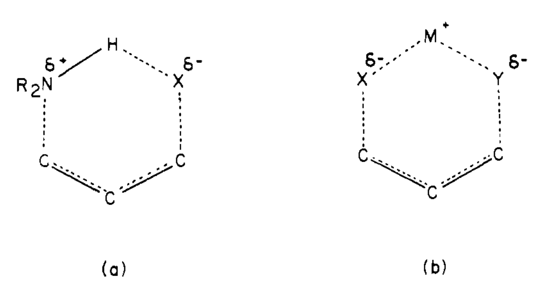
[19] Hammond *J. Am. Chem. Soc.* **1955**, *77*, 334.

[20] A reaction involves *specific activation* if both it and its reverse require activation. The *specific activation energy* is the lesser of these two quantities.

[21] Exceptions to the Woodward–Hoffmann rules can also be brought about by analogous steric effects, as in the electrocyclic conversion of bicyclo[2.1.0]pentene to cyclopentadiene, which is almost certainly synchronous though "forbidden". See: Dewar, M. J. S.; Kirschner, S. *J. Am. Chem. Soc.* **1975**, *97*, 461.

[22] Reference 18, section 5.11.

[23] Saunders, W. H., Jr.; Cockerill, A. F. "Mechanisms of Elimination Reactions"; Wiley: New York, 1973.



(a) (b)

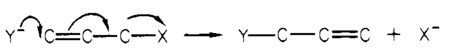
Figure 6. Illustrating the favoring of syn transition states for S_N2' reactions where (a) the nucleophile is an amine and (b) where the gegencation participates.

σ bonds and the formation of one σ bond and one π bond. If it were synchronous, it would apparently represent a clear violation of the new rule.

While many elimination reactions take place in steps by the E1 or E1cB mechanisms, some do seem to be concerted one-step processes. There is, however, no conclusive evidence that any of them is synchronous. They may well correspond to two-step reactions in which the individual steps have fused together into a two-stage process, concerted but not synchronous (Figure 4).

One of the bond-making/bond-breaking processes in an E2 reaction involves transfer of hydrogen. While the corresponding TS involves more delocalized electrons than does the TS for an analogous pericyclic reaction, it will be shown presently that the transfer of hydrogen in this way may still not make a large contribution to the overall activation energy. Therefore even if some elimination reactions prove to be synchronous E2 processes, they would exemplify exception d considered above.

(B) **The S_N2' Reaction.** The S_N2 reaction is vinylogue of the S_N2 reaction in which substitution is accompanied by migration of a double bond:



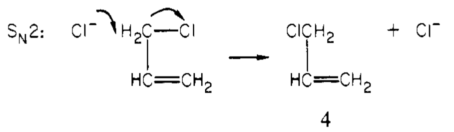
(9)

Since it involves the breaking of one σ bond and one π bond, and the formation of one σ bond and one π bond, it is a two-bond reaction and, if synchronous, should be forbidden by the new rule.

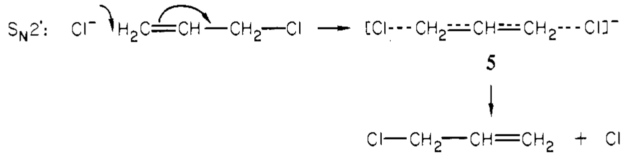
It has been generally assumed that the S_N2' reaction is synchronous, partly because of the apparent analogy between it and the S_N2 reaction and partly because there seemed to be no reasonable alternative. The experimental evidence[24] shows that formation of the bond to the nucleophile plays an essential role in the reaction; yet the usual nucleophiles do not add to C=C double bonds unless they carry strongly electron-attracting substituents. Breaking of the CX bond must therefore presumably act as a driving force for the addition and it cannot precede addition because the reaction would not then be of second order, as observed. Thus there seem to be good reasons for believing that reactions of this kind are synchronous.

There is, however, no evidence that this is so.[24] The stereochemistries of the S_N2 and S_N2' reactions indeed seem to suggest that their mechanisms are different. Thus while the S_N2 reaction always involves backside attack with inversion of configuration at the reaction center, the S_N2' reaction sometimes takes place by syn attack and sometimes anti. Exclusive syn attack is moreover observed only with nucleophiles (e.g., primary or secondary amines) that can hydrogen bond to the departing group if attack is syn or with anionic nucleophiles under ion-pairing conditions, where the entering and leaving groups are closer to the common gegencation in the transition state for syn attack (Figure 6).

This uncertainty now seems to have been resolved by a recent MNDO study[35] of the S_N2 and S_N2' reactions of chloride ion with allyl chloride (4):



(10a)

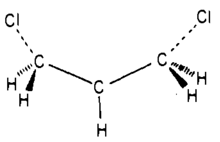


(10b)

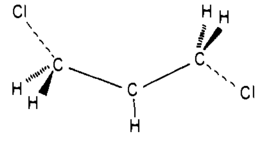
The S_N2 reaction was calculated to take place in a normal manner, being a typical one-bond process like the reactions of other alkyl chlorides. The S_N2' reaction, however, was found to take place in steps, formation of the new CCl bond taking place without activation to form an intermediate (**5**) in which the old CCl bond is almost intact. The calculations thus contradict the previously accepted conclusion, that addition of nucleophile to the CC bond cannot precede major weakening of the bond to the leaving group. The chlorine atom in **4** nevertheless plays a major role in the reaction because chloride ion is (correctly) predicted *not* to add to olefins and because the chlorine atoms in **4** are equivalent, the CCl bonds being a little longer than that in **4** itself.

The calculations refer of course to the gas phase. In solution, both the S_N2 and S_N2' reactions are retarded by the need to desolvate the chloride ion. Since the retardation is expected[26] to be much greater for S_N2' than S_N2, it is not surprising that the S_N2 reaction is usually the faster.

The intermediate **5** can exist in syn (**6**) and anti (**7**) forms, the



6



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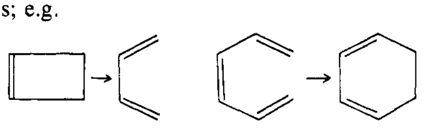
latter being a little lower in energy. However, since no activation is involved in forming either isomer from **4** and since there is a barrier to their interconversion, one would expect the S_N2' reaction to give both possible products if no other factors were involved. As noted above, this seems to be the case.

Since MNDO has also given a very satisfactory account of aliphatic substitution in general[25] and since its account of the S_N2' reaction is consistent with all the known facts, there seems no reason to doubt its conclusion, that the S_N2' reaction is *not* a synchronous process but takes place in stages.

(C) Electrocyclic Reactions. Simple electrocyclic reactions involve the cyclization of a conjugated system by formation of a σ bond between the terminal atoms in it or the reverse of this process; e.g.



8 9 10 11 (11)

According to the Woodward–Hoffmann rules[2] and Evans' principle[3,4] such reactions are "allowed" for conjugated systems that contain $4n$ π electrons if formation of the new σ bond involves disrotatory rotation of the terminal atoms and for $(4n + 2)$ π electrons if the rotation is conrotatory. Since the cyclization involves breaking of the terminal π bonds in a conjugated system and the formation of one σ bond, the argument given above in

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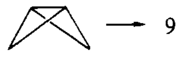
(24) (a) Shorter, J. *Org. React. Mech.* **1981**, 349. (b) Staroscik, J.; Rickborn, B. *J. Am. Chem. Soc.* **1971**, *93*, 3046. (c) Wieland, D. M.; Johnson, C. R. *Ibid.* **1971**, *93*, 3047. (d) Satoh, J. Y.; Takahashi, T. T. *Chem. Commun.* **1970**, 1714.

(25) Dewar, M. J. S.; Carrion, F. C., manuscript in preparation.

(26) At least one solvent molecule must be removed from the inner solvent shell around the anion in order that the allyl halide can approach. The replacement of a solvent molecule by allyl chloride is much less favorable if the ion is near the terminal methylene group, as required for the S_N2' reaction to occur, than if it is near the CCl bond, as in the S_N2 reaction, because the charge–dipole ($X^-\cdots C$–Cl) interaction is much greater in the latter case.

the case of aromatic sustitution indicates it to be effectively of one-bond type and so permitted. The available evidence, and theoretical calculations[27,28] indicate strongly that such reactions are indeed synchronous. It is interesting to note that "allowed" electrocyclic reactions of conjugated ions, e.g., cyclopentadienyl, take place much more readily than those of neutral polyenes. This would be expected on the basis of the present argument because the π bond orders of the terminal bonds in the ions are smaller.

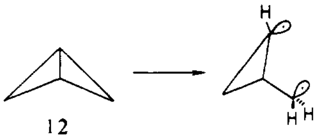
The conversion of bicyclobutane (**12**) to 1,3-butadiene (**9**) is a double electrocyclic process, involving the opening of two rings with the breaking of two π bonds and formation of two σ bonds:



(12)

12

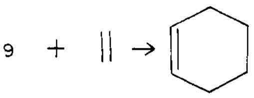
If synchronous, it must therefore be of two-bond type. Evans' principle,[3,4] which is easier[29] to apply in this case than the Woodward–Hoffmann rules, indicates that one ring should open disrotatorily, the other conrotatorily, a geometry observed by Closs and Pfeiffer[30] in the thermolytic ring opening of various derivatives of **12**. A detailed MINDO/3 study[31] of the reaction led, however, to the conclusion that it is not only not synchronous but not even concerted, taking place via an intermediate biradicaloid (**13**) as



12 13

a stable intermediate. The "radical centers" in **13** are pyramidal, not planar, due to through-space and through-bond[32] interactions between them. As a result, **13** retains a memory of the geometry of **12** and the opening of the second ring is consequently constrained to occur in accordance with Evans' principle. The biradical character of **13** is nevertheless sufficient to make isomerization of the methylene radical center facile. This leads to an isomeric biradicaloid in which the mode of opening of the second ring is reversed, giving a product "forbidden" by Evans' principle. The calculated difference in activation energy between the "allowed" and "forbidden" paths was only 2 kcal/mol, corresponding to a ratio of products at 200 °C (the temperature used by Closs and Pfeiffer[30]) of ca. 95:5. Closs and Pfeiffer found that the reactions were in fact stereoselective rather than stereospecific, 4–8% of the "forbidden" isomer being formed, as MINDO/3 predicts. Since the MINDO/3 calculation also gave an excellent estimate of the activation energy for the reaction of **12** itself (calcd. 40.3; obsd 40.6[33] kcal/mol), there seems little doubt that the reactions are not synchronous two-bond processes but take place in steps or stages via biradicaloid intermediates.

(D) Cycloaddition Reactions. (a) The Diels–Alder Reaction. The Diels–Alder reaction involves cycloaddition of a 1,3-diene to an ethylene derivative to form a cyclohexene; e.g.:



(13)

14 15

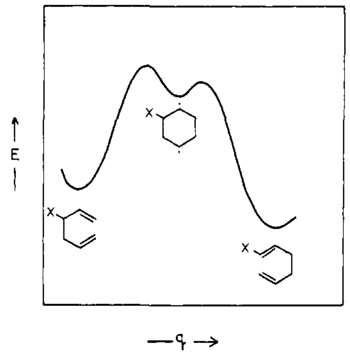


Figure 7. Minimum-energy reaction path (MERP) for the Cope rearrangement of a 3-monosubstituted hexa-1,5-diene.

Since it is "allowed" and since the geometry of the TS is very favorable for cyclic conjugation,[3] the current rules unambiguously predict it to be synchronous. Three π bonds are, however, broken during the reaction while two σ bonds and one π bond are formed. Even though two of the breaking π bonds are terminal bonds in a conjugated system, each of which counts as half a bond only, the reaction is clearly at least of two-bond type and a synchronous mechanism should therefore be prohibited.

Whether or not such reactions are synchronous is therefore a question of major concern in the present connection, as a direct test of the significance of the new rule. As noted earlier, most organic chemists believe Diels–Alder reacions to be synchronous processes, and many clearly believe that their synchronicity has been established unequivocally by experiment. This is certainly not the case. Detailed analysis[34,35] of the available data shows that there is *no* evidence that *any* DA reaction takes place in a synchronous manner. There is, on the other hand, very definite evidence that DA reactions involving unsymmetrical dienes, and/or unsymmetrical dienophiles, take place in a nonsynchronous manner, via very unsymmetrical TS.[34] Indeed, *all* the experimental evidence concerning the relative rates and regioselectivities of such reactions can be interpreted simply and comprehensively in terms of current qualitative MO theory if it is assumed that one of the new bonds in the TS is almost completely formed while the other is very weak, so that the TS can be regarded as a weakly perturbed biradical or zwitterion formed by combination of the diene and dienophile at one point only in each.[34]

Since many DA reactions undoubtedly take place via such very unsymmetrical TSs and since *none* is known to be synchronous, a basic principle of scientific methodology[37] requires *all* such reactions to be regarded as nonsynchronous unless and until synchronicity has been demonstrated in at least one case. It seems in fact unlikely such a case will be found, given that the TS for the reaction between maleic anhydride and 2-methylfuran is apparently very unsymmetrical.[35] It is difficult to believe that a single methyl substituent could exert so large a perturbation on an otherwise symmetrical TS.

Problems involving the relative timing of the formation and breaking of bonds are notoriously difficult to solve by experiment. This is an area where quantitative quantum mechanical calculations could be correspondingly useful. Studies of reactions by ab initio methods have to be carried out at a very high level if they are to be at all significant[38] and such "state-of-the-art" procedures can be applied effectively[39] only to small systems. However, the parametric procedures developed in these labora-

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(27) Dewar, M. J. S.; Kirschner, S. *J. Am. Chem. Soc.* **1971**, *93*, 4290.

(28) See, e.g.: Merlet, P.; Peyerimhoff, S. D.; Buenker, R. J.; Shih, S, *J. Am. Chem. Soc.* **1974**, *96*, 959.

(29) The stereochemistry of this reaction cannot be predicted on the basis of the symmetries of the orbitals involved. It follows immediately from the fact that the TS is isoconjugate with bicyclobutadiene, which is aromatic only if it is of anti-Huckel type.[4]

(30) Closs, G. L.; Pfeffer, P. E. *J. Am. Chem. Soc.* **1968**, *90*, 2452.

(31) Dewar, M. J. S.; Kirschner, S. *J. Am. Chem. Soc.* **1975**, *97*, 2931.

(32) Hoffmann, R.; Imamura, A.; Hehre, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 1499.

(33) Frey, H. M.; Stevens, I. D. R. *Trans. Faraday Soc.* **1969**, *61*, 90.

(34) Dewar, M. J. S.; Olivella, S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 5650.

(35) Dewar, M. J. S.; Pierini, A. B., unpublished results.

(36) Dewar, M. J. S.; Griffin, A. C.; Kirschner, S. *J. Am. Chem. Soc.* **1974**, *96*, 6225.

(37) Occam's Razor: "Entia non sunt multiplicanda praeter necessitatem".

(38) This has been clearly demonstrated by recent calculations for a number of simple reactions. See, e.g.: Dykstra, C. E.; Schaefer, H. F., III *J. Am. Chem. Soc.* **1978**, *100*, 1378.

(39) To be useful in this connection, the calculation *must* be carried out without making any geometrical assumptions of any kind, and all stationary points *must* be characterized by calculating force constants.

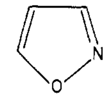
tories (MINDO/3,[40] MNDO[41]) have proved very succesful in this connection, calculations for a very wide variety of chemical reactions and other chemical problems having given very satisfactory results.[40-43] Reference has been made above to such calculations, e.g., for the S_N2' reaction, and other examples will be found throughout this paper. In the present connection MINDO/3[34-36] calculations for several Diels–Alder reactions suggest a mechanism completely consistent with the conclusions reached above, i.e., a two-stage process where an intermediate biradical-like or zwitterionic intermediate is formed without specific activation from the diene and dienophile and where the rate-determining step is its (activated) conversion to the adduct (cf. Figure 4b). This mechanism has never previously been considered in the half century since the Diels–Alder reaction was first discovered.[45] Everyone has assumed that such an intermediate, if formed, would collapse to the product without activation, in which case the rate-determining step of the overall reaction would have to be the formation of the intermediate rather than its conversion to the product. Several lines of evidence have refuted this possibility by showing that *both* the new CC bonds are formed to significant extents in the TS.[35]

(b) Dipolar Additions. The mechanisms of dipolar additions have been the subject of much recent discussion.[46,47] This has been based on the assumption that there are just two alternatives to be considered, i.e., a synchronous two-bond cycloaddition via an aromatic TS or a two-step one via an intermediate biradical or zwitterion whose formation is rate determining. However, as in the case of the Diels–Alder reaction, there is a third alternative, i.e., a two-step or two-stage mechanism in which the *second* step or stage, i.e., formation of the *second* bond, is rate determining. While the experimental evidence seems to indicate that these reactions are concerted, there is again no clear indication that any of them is synchronous.

Useful information has been provided by a recent "state-of-the-art" ab initio calculation by Schaefer's group[48] for the dipolar addition of fulminic acid (**16**) to acetylene to form isoxazole (**17**).

$HC\equiv\overset{+}{N}-\overset{-}{O}$

16



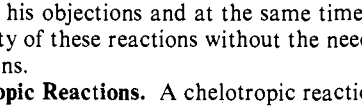
17

The structure calculated for the transition state seemed in itself to indicate a synchronous mechanism, the lengths of the two forming bonds being almost identical (CC, 2.20; CO, 2.24 Å). However, while the stretching force constant (3.0 mdyn/Å) for the CC bond indicated it to be strong, that (0.3 mdyn/Å) for the CO bond showed it to be extremely weak, corresponding to a bond strength of at most a few kcal/mol. The equality of the bond lengths is thus a misleading coincidence, due to the fact that CO bonds are shorter and stiffer than CC ones and so have almost vanished at a bond length of 2.24 Å. The transition state is in fact similar to those given by the MINDO/3 calculations for Diels–Alder reactions noted above, where one of the new bonds is already very strong while the other is still very weak.

A MNDO calculation[43] for this reaction predicted it to involve a biradical as a stable intermediate, paralleling the Diels–Alder calculations and in disagreement with the calculation by Schaefer et al. The error is due to the known tendency of MNDO to overestimate repulsions between atoms when they are separated by 1.5–2.5 times the length of a normal bond between them. As a result, a weak bond in a cyclic TS tends to come apart. This example suggests that most, if not all, of the analogous minima found in our calculations[34,36,44] for Diels–Alder reactions may also be spurious. It does not, however, throw doubt on the conclusion that the Diels–Alder reactions studied are all nonsynchronous.

The regioselectivity of dipolar additions can also be most simply interpreted on the basis that they are nonsynchronous processes, involving biradical-like species or zwitterions as intermediates. This was one of the points made by Firestone[47] in his claim that dipolar additions are not only not synchronous but not even concerted. The mechanism suggested here, i.e., a concerted but nonsynchronous one where the *second* stage is rate determining, seems to meet his objections and at the same time explains the stereospecificity of these reactions without the need to make ad hoc assumptions.

(c) Chelotropic Reactions. A chelotropic reaction is a cycloaddition in which two molecules, XAY and BC, combine to form a cyclic adduct by formation of new bonds to a single atom (B) in BC:



(14)

While the stereochemistry[2-4] of chelotropic reactions suggests that they are concerted, there is as yet no experimental evidence concerning their synchronicity, and no reliable theoretical studies of them have been reported. Detailed calculations have now been carried out in these laboratories for a number of such reactions[49,50]

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(40) Bingham, R. C.; Dewar, M. J. S.; Lo, D. H. *J. Am. Chem. Soc.* **1975**, *97*, 1285, 1294, 1302, 1307.

(41) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899, 4907; Dewar, M. J. S.; Rzepa, H. S. *Ibid.* **1978**, *100*, 58, 777.

(42) (a) Dewar, M. J. S.; Reynolds, C. H. *J. Am. Chem. Soc.* **1982**, *104*, 3244. (b) Dewar, M. J. S.; Pakiari, A. H.; Pierini, A. B. *Ibid.* **1982**, *104*, 3242. (c) Dewar, M. J. S. *Ibid.* **1982**, *104*, 1447. (d) Dewar, M. J. S.; Nelson, D. J. *J. Org. Chem.* **1982**, *47*, 2614. (e) Kollmar, F. C.; Carrion, F. A.; Dewar, M. J. S.; Bingham, R. C. *J. Am. Chem. Soc.* **1981**, *103*, 5292. (f) Dewar, M. J. S.; Nelson, D. J.; Shevlin, P. B.; McKee, M. L. *J. Mol. Struct.* **1981**, *103*, 105; (h) *Inorg. Chem.* **1980**, *19*, 2662; (i) *Pure Appl. Chem.* **1980**, *52*, 1431. (j) Dewar, M. J. S.; Fox, M. A., Nelson, D. J. *J. Organomet. Chem.* **1980**, *185*, 157. Dewar, M. J. S.; Yamaguchi, Y.; Suck, S. H. *Chem. Phys.* **1979**, *43*, 145. (l) Dewar, M. J. S.; Yamaguchi, Y.; Doraiswamy, S.; Sharma, S. D.; Suck, S. H. *Ibid.* **1979**, *41*, 21. (m) Dewar, M. J. S.; Olivella, S. *J. Am. Chem. Soc.* **1979**, *101*, 4958. (n) Dewar, M. J. S.; Rzepa, H. S. *Inorg. Chem.* **1979**, *18*, 602. (o) Dewar, M. J. S.; Ford, G. P. *J. Am. Chem. Soc.* **1979**, *101*, 783. (p) Dewar, M. J. S.; Ford, G. P.; Rzepa, H. S. *J. Mol. Struct.* **1979**, *51*, 275. (q) Yamaguchi, Y.; Suck, S. H.; Dewar, M. J. S. *Chem. Phys. Lett.* **1978**, *59*, 541. (r) Brown, S. B.; Dewar, M. J. S.; Ford, G. P., Nelson, D. J.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 7832. (s) Dewar, M. J. S.; McKee, M. L. *Ibid.* **1978**, *100*, 7499. (t) Dewar, M. J. S.; Olivella, S.; Rzepa, H. S. *Ibid.* **1978**, *100*, 5650. (u) Dewar, M. J. S.; Olivella, S. *Ibid.* **1978**, *100*, 5290. (v) Dewar, M. J. S.; Doubleday, C. *Ibid.* **1978**, *100*, 4935. (w) Dewar, M. J. S.; McKee, M. L. *Inorg. Chem.* **1978**, *17*, 1569; (x) *Inorg. Chem.* **1978**, *17*, 1075. (y) Dewar, M. J. S.; Ford, G. P.; Ritchie, J. P.; Rzepa, H. S. *J. Chem. Res.* **1978**, *26*, 0484. (z) Dewar, M. J. S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 784; (aa) *Ibid.* **1978**, *100*, 777. (bb) Dewar, M. J. S.; Ford, G. P.; McKee, M. L.; Rzepa, H. S.; Thiel, W.; Yamaguchi, Y. *J. Mol. Struct.* **1978**, *43*, 135. (cc) Dewar, M. J. S.; Ford, G. P.; Rzepa, H. S. *Chem. Commun.* **1977**, 728. (dd) Dewar, M. J. S.; Ford, G. P. *J. Am. Chem. Soc.* **1977**, *99*, 8343. (ee) Dewar, M. J. S.; Landman, D. *Ibid.* **1977**, *99*, 7439. (ff) Dewar, M. J. S.; Rzepa, H. S. *Ibid.* **1977**, *99*, 7432. (gg) Dewar, M. J. S.; Ford, G. P.; Rzepa, H. S. *Chem. Phys. Lett.* **1977**, *50*, 262. (hh) Dewar, M. J. S.; Landman, D. *Ibid.* **1977**, *99*, 6179. (ii) Dewar, M. J. S.; Yamaguchi, Y.; Suck, S. H. *Chem. Phys. Lett.* **1977**, *50*, 259; (jj) *Ibid.* **1977**, *50*, 175. (kk) Dewar, M. J. S.; Rzepa, H. S. *J. Mol. Struct.* **1977**, *40*, 145. (ll) Dewar, M. J. S.; *Symp. Faraday Soc.* **1977**, *62*, 197. (mm) Dewar, M. J. S.; McKee, M. L. *J. Am. Chem. Soc.* **1977**, *99*, 5231. (nn) Dewar, M. J. S.; Ford, G. P.; McKee, M. L.; Rzepa, H. S.; Wade, L. E. *Ibid.* **1977**, *99*, 5069. (oo) Dewar, M. J. S.; Landman, D. *Ibid.* **1977**, *99*, 4633; (pp) *Ibid.* **1977**, *99*, 2446; (qq) *Ibid.* **1977**, *99*, 372. (rr) Dewar, M. J. S.; Thiel, W. *Ibid.* **1977**, *99*, 2338. (ss) Dewar, M. J. S.; Ford, G. P. *Ibid.* **1977**, *99*, 1685. (tt) Dewar, M. J. S.; Haddon, R. C.; Komornicki, A.; Rzepa, H. S. *Ibid.* **1977**, *99*, 377. (uu) Bergman, J. G.; Suck, S. H.; Weiner, P. K. *Chem. Phys. Lett.* **1976**, *38*, 226, 228. (vv) Bodor, N.; Dewar, M. J. S.; Maksič, Z. B. *Croat. Chem. Acta* **1976**, *48*, **9**. (ww) Dewar, M. J. S. *Pure Appl. Chem.* **1975**, *44*, 767. (xx) Dewar, M. J. S.; Fonken, F. J.; Kirschner, S.; Minter, D. E. *J. Am. Chem. Soc.* **1975**, *97*, 6750. (yy) Dewar, M. J. S.; Kollmar, H. W.; Suck, S. H. *Ibid.* **1975**, *97*, 5590. (zz) Dewar, M. J. S.; Thiel, W. *Ibid.* **1975**, *77*, 3978. (aaa) Dewar, M. J. S.; Haddon, R. C.; Li, W.-K.; Thiel, W.; Weiner, P. K. *Ibid.* **1975**, *77*, 4540. (bbb) References to earlier papers cited above.

(43) For summaries of earlier work, see: (a) Dewar, M. J. S. *Chem. Brit.* **1975**, *11*, **97**; (b) *J. Chem. Soc., Faraday Trans.* **1977**, *62*, 197; (c) "Further Perspectives in Organic Chemistry", Ciba Foundation Symposium 53 (new series), Elsevier: Amsterdam 1978; p 107.

(44) Dewar, M. J. S.; Griffin, A. C.; Kirschner, S. *J. Am. Chem. Soc.* **1974**, *96*, 6225.

(45) Diels, O.; Alder, K. *Chem. Ber.* **1929**, *62*, 554.

(46) Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403.

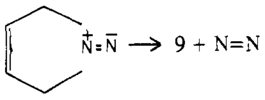
(47) Firestone, R. A. *J. Org. Chem.* **1972**, *37*, 218.

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

(49) Chantranupong, L.; Dewar, M. J. S. *J. Am. Chem. Soc.*, in press.

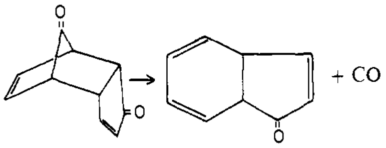
(50) Chantranupong, L.; Dewar, M. J. S. *J. Am. Chem. Soc.*, in press.

using both MINDO/3 and MNDO. Since 3d AOs are not included in these procedures, they cannot be used for compounds of sulfur in its higher valence states, in particular sulfur dioxide. We therefore studied a number of reverse chelotropic reactions involving loss of nitrogen or carbon monoxide from partially unsaturated rings, e.g.:



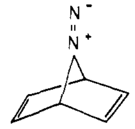
(15)

18



(16)

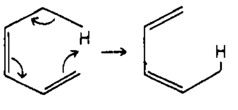
With one exception, these reactions were found to follow the same pattern as the other cycloadditions, each of them taking place via a very unsymmetrical transition state where one of the breaking bonds is still almost intact while the other is still very weak. The exception was the diazene **21**, which was predicted[50] by MNDO



21

to dissociate into N_2 and benzene via a symmetrical TS. While the MINDO/3 TS[50] was unsymmetrical, the lengths (1.596 and 1.867 Å) of the breaking bonds in it were much more nearly equal then they were in other similar reactions. Therefore even if the reaction is not exactly synchronous, it is much more nearly so than any of the others studied. However, it was also predicted to be extremely exothermic, again much more so than the reactions of any of the other diazenes, as indeed would be expected since it alone leads to an aromatic product. The calculated activation energies were correspondingly small (MINDO/3, 2.8; MNDO, 4.0 kcal/mol). It thus exemplifies one of the expected exceptions (d) to the new rule, particularly since the geometric constraints due to the fused rings probably also favor a symmetrical TS.

(d) Sigmatropic Rearrangements. Simple sigmatropic rearrangements involve the migration of an atom or univalent group from a position adjacent to a π system to a position in the original π system, with simultaneous reorganization of the π bonds, e.g.:



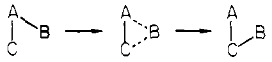
(17)

Such a reaction involves the breaking of one σ bond and one π bond and the formation of one σ bond and one π bond. It would therefore seem at first sight to be of two-bond type and consequently prohibited from being synchronous. There are, however, extenuating circumstances in this case.

First, it should be noted that the breaking and forming π bonds are adjacent to a common π system, so that they fuse together, in a synchronous TS, into a single (pentadienyl) π system. The arguments given earlier suggest that the forming/breaking π bonds should then count as only half a bond each in the present connection. This would make the reaction a one-and-a-half-bond process.

Second, as also already noted, synchronous mechanisms are favored in "allowed" pericyclic reactions because the TS in such a process is aromatic and because the corresponding aromatic stabilization is lost if the reaction takes place in a nonsynchronous manner. This is insufficient to ensure synchronicity in the Diels–Alder reaction, which is effectively of two-bond type (see above). It might, however, suffice in the case of a one-and-a-half-bond reaction.

Third, sigmatropic rearrangements differ from the reactions so far considered in that the forming and breaking σ bonds also share a common atom, i.e., the central atom of the migrating group:



(18)

In the TS for the reaction, A, B, and C are thus effectively linked by a three-center bond, formed by simultaneous interactions between an AO of B and AOs of A and C. This three-center σ bond is moreover analogous to the three-center π bond in an allyl radical or ion:

$$\text{(A---B---C) isoconjugate with } (H_2C \overset{..}{-} CH \overset{..}{-} CH_2)$$

Indeed, the two systems are isoconjugate. Now the three-center π bond in allyl is well recognized to be stronger than an isolated two-center π bond, e.g., in an olefin, the difference being attributed to resonance stabilization of allyl. Analogy suggests that, other things being equal, the three-center σ bond (A---B---C) in the TS for a sigmatropic reaction should be stronger than the two-center σ bonds in the reactant (A–B) or product (B–C). If so, the making and breaking of σ bonds should contribute little to the activation energy of the overall reaction, because formation of the new bond can start to take place before the old bond has even begun to break. The overall reaction would then be effectively of one-bond type. Analogous three-center four-electron bonds are now believed[53] to occur quite commonly in inorganic chemistry, e.g., in xenon difluoride, XeF_2, where xenon uses a p AO to bind two fluorine atoms.[54]

An obvious objection to this argument is that it seems to suggest that S_N2 reactions should require no activation, because the relationship between the reactants and the TS in a S_N2 reaction is similar to that in a sigmatropic reaction (cf. eq 18 and 19). Yet

$$A^- + B\text{-}C \rightarrow (A\text{---}B\text{---}C)^- \rightarrow A\text{-}B + C^- \qquad (19)$$

the symmetrical intermediates in S_N2 reactions definitely[25] correspond to saddlepoints on the potential surfaces, i.e., to TS, not stable species. This apparent anomaly has been resolved by a recent study[55] which showed that the high energy of the S_N2 TS is due to steric repulsions between the entering and leaving groups and the other groups attached to carbon, the small size of the carbon atom making it difficult for five groups to be attached to it simultaneously. Similar problems also arise in S_N2-type substitution reactions on other second-period elements because although there are less than five groups attached to the central atom in the TS, their place is taken by lone pairs of electrons, which also have significant steric requirements. Repulsions of this kind are also probably mainly responsible for the failure of second-period elements to form hypervalent compounds, e.g., NF_5.

Such steric effects are absent in hydrogen. Hydrogen for this reason has an exceptional tendency to form strong three-center bonds. Nucleophilic displacements on hydrogen are correspondingly fast. Now the situation of the migrating group in a sigmatropic rearrangement is similar to that in an S_N2 reaction, the carbon in a migrating methyl, for example, being bonded to five other atoms. Steric crowding should therefore restrict the ease of such reactions. Since this problem does not arise for hydrogen, one would expect sigmatropic migrations of hydrogen to be easier than those of other group, as indeed seems to be the case. The only exceptions are allylic migrations which are "forbidden" unless the migrating group can use a p AO to form the three-center bond, as in the Berson rearrangement.[56]

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(51) MNDO calculations, using the published[52] parameters for sulfur, give energies for compounds of S^{IV} and S^{VI} that are too positive by >100 kcal/mol; see: Dewar, M. J. S.; McKee, M. L. *J. Comput. Chem.*, in press.

(52) Dewar, M. J. S.; Rzepa, H. S.; McKee, M. L. *J. Am. Chem. Soc.* **1978**, *100*, 3607.

(53) Musher, J. I. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 54.

(54) Rundle, R. E. *J. Am. Chem. Soc.* **1963**, *85*, 112.

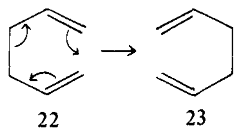
(55) Dewar, M. J. S.; Healy, E., unpublished results.

(56) Berson, J. A.; Nelson, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 5503; **1970**, *92*, 1096. Berson, J. A. *Acc. Chem. Res.* **1968**, *1*, 152.

Formation or breaking of a bond to a carbon atom involves a change in its hybridization and a corresponding contribution to the activation energy of the reaction in question.[22] Migration of hydrogen is therefore expected to be most facile when it takes place between two heteroatoms, less facile when it takes place from carbon to a heteroatom or conversely, and hardest when hydrogen is transferred from one carbon atom to another. This also seems to be the case.

The stereochemistry of these reactions suggest that they are concerted, but there is no good evidence concerning their synchronicity. Most authors have assumed them to be synchronous, and it is indeed difficult to see any very plausible alternative. Theoretical studies[57] support this conclusion.

In the sigmatropic reactions so far considered, the migrating group contributes one atom only to the pericyclic ring. A number of analogous processes are known where it contributes two or more atoms, the classical example being the Cope rearrangement:

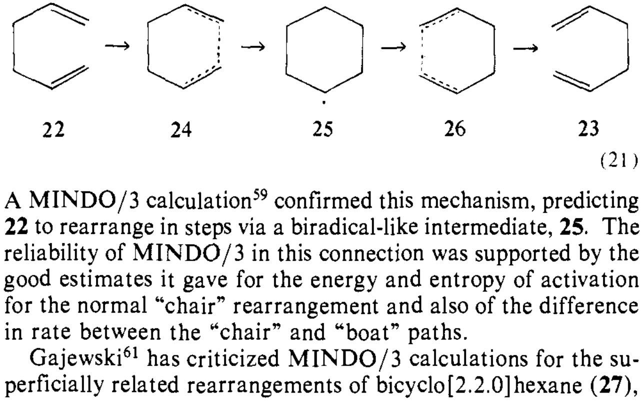


22 23

(20)

Such reactions involve the making of one σ bond and two π bonds and the breaking of one σ bond and two π bonds. Even if the π bonds each count as only half a bond, on the basis of the arguments given above, the reactions are still of two-bond type and should therefore be nonsynchronous.

The Cope rearrangement is not only "allowed" but it also has an ideal geometry to form a symmetrical aromatic TS. It was therefore confidently assumed until recently that it must be synchronous. Recent work[58,59] suggests very strongly that this is not in fact the case. The effect[8] of phenyl substituents on the rate of the reaction cannot be explained in terms of a synchronous mechanism. It is, however, consistent with the two-step mechanism suggested by Doering et al.[60] where the new CC bond is formed while the old one is still intact, leading to an intermediate biradical:

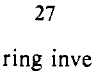


22 24 25 26 23

(21)

A MINDO/3 calculation[59] confirmed this mechanism, predicting **22** to rearrange in steps via a biradical-like intermediate, **25**. The reliability of MINDO/3 in this connection was supported by the good estimates it gave for the energy and entropy of activation for the normal "chair" rearrangement and also of the difference in rate between the "chair" and "boat" paths.

Gajewski[61] has criticized MINDO/3 calculations for the superficially related rearrangements of bicyclo[2.2.0]hexane (**27**),



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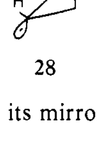

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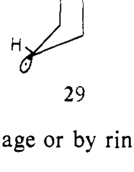

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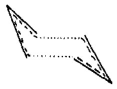
either by ring inversion to its mirror image or by ring opening to **22**. These reactions would seem to take place via the same biradical intermediate as that involved in the "boat" Cope rearrangement of **22**. These criticisms have no bearing on the calculations for the Cope rearrangement itself, which are consistent with the secondary deuterium isotope effects cited by Gajewski,[61] as the following discussion shows.

The MINDO/3 calculations[59] for the "boat" (**28**) and "chair" (**29**) intermediates in the Cope rearrangements indicate that they are not biradicals. The "radical centers" in them couple strongly via the intervening σ bonds. The bonds adjacent to the radical centers (C_1–C_2, C_2–C_3, C_4–C_5, C_5–C_6) are strengthened and shortened (1.44 Å) by this interaction while the other two CC bonds (C_3–C_4, C_1–C_6) are weakened and lengthened (1.61 Å). The intermediate consequently has a closed-shell structure. However, while inclusion of 3 × 3 CI had very little effect on the energies of the TS leading to it, it lowered the energy of the chair intermediate by 20 kcal/mol. This suggests that the intermediate has "biradical character" without being a true biradical, because inclusion of CI in MINDO/3 lowers the energies of typical biradicals by 40–60 kcal/mol.[62] Since MINDO/3-CI leads to energies that are too negative, the real heat of formation of the intermediate is probably close to the MINDO/3 value.[59]

The intermediate can be regarded[58] either as a mildly perturbed cyclohexylene (**25**) biradical or as the product of interaction between two allyl radicals (see **30**). As the interaction in the latter increases, its structure progressively changes in the direction of **25**. The MINDO/3 calculations indicate that the intermediate in the Cope rearrangement of **22** is much nearer to **25** than to **30** in structure, the carbon atoms at the ends of the forming/breaking bonds having geometries close to tetrahedral and hence hybridizations close to sp^3. Electromeric substituents at the 2- and 5-positions in the intermediate should stabilize the radical centers and so reduce the interaction between them, making the structure approximate even more closely to **25**. Conversely, similar substituents in the 1, 3, 4, or 5-positions should stabilize the adjacent allyl system in **30** and so make the intermediate tend in that direction. The forming/breaking CC bonds will correspondingly increase in length with a change in hybridization of the carbon atoms toward sp^2.



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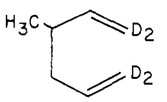
According to the calculations,[59] the intermediate corresponds to only a very shallow local minimum on the potential surface, the activation energies for its conversion to **22** or **23** being only 2.7 kcal/mol. The structure of each TS was correspondingly close to that of the intermediate. Substitution would therefore be expected to lead to similar changes in energy in the intermediate and the TS.

Since C_1, C_3, C_4, and C_6 are all close to sp^3 in the intermediate, replacement of hydrogen by deuterium in **22** should have a smaller effect on the rate if substitution is at C_3 or C_4 than if it is at C_1 or C_6. The same should hold for derivatives of **22** if the substituents exert only weak perturbing effects. The observed isotope effects conform to this expectation. Thus the deuterium atoms in **31** changed the rate of its conversion to **32** or **33** by factors (k_D/k_H) of 1.13 ± 0.02 or 1.16 ± 0.02 while the ratio for each of the reverse reactions was only 1.07 ± 0.02.



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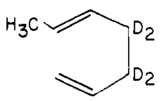

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Since electromeric substituents at C_2 or C_5 will make the hybridization of the other carbons still closer to sp^3, they should

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(57) (a) Bingham, R. C.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1972**, *94*, 9107. (b) Kwart, H.; Brechbiel, M. W.; Acheson, R. M.; Ward, D. C. *Ibid.* **1982**, *104*, 4671. (c) Papers cited in (a) and (b).

(58) Dewar, M. J. S.; Wade, L. E. *J. Am. Chem. Soc.* **1973**, *95*, 290.

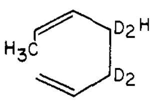
(59) Dewar, M. J. S.; Ford, G. P.; McKee, M. L.; Rzepa, H. S.; Wade, L. E. *J. Am. Chem. Soc.* **1977**, *99*, 5069.

(60) Doering, W. v. E.; Toscano, V. G.; Beasley, G. H. *Tetrahedron* **1971**, *27*, 299.

(61) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1978**, *100*, 6268, 6269.

(62) This was true, for example, in the case of the biradical TS in the dimerization of ethylene to cyclobutene: Dewar, M. J. S.; Kirschner, S. *J. Am. Chem. Soc.* **1974**, *96*, 5246.

reduce the effect of deuterium at C_3 or C_4 in **22** and increase its effect at C_1 or C_6. The latter effect is seen in the isotopic rate ratios for the conversion at **34** and **35** (1.18 ± 0.02) or to **36** (1.30 ± 0.00) and of **37** to **38** (1.57 ± 0.03). The experiments were not accurate enough to indicate whether or not there is a change in the rate ratios for the reverse reactions, given the rather large standard deviation (0.02) in the measured ratios.



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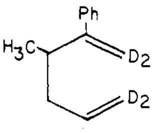

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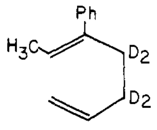

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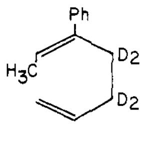

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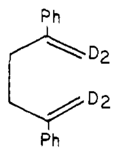

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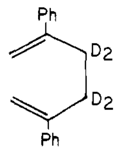

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Conversely, electromeric substituents at the other positions should increase the s character of C_1, C_3, C_4, and C_6 in the intermediate, thus reducing the effect of deuterium at C_1 or C_6 and increasing its effect at C_3 or C_4. Indeed, dideuteriation of **39** at C_4 had a *larger* effect than at C_6 (isotopic rate ratios, 1.19 and 1.06, respectively).

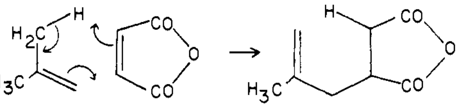
The isotopic data are therefore consistent with the mechanism suggested by the MINDO/3 calculations[59] and also with the changes in the electronic structure of the intermediate expected[8] to be brought about by substituents. They certainly do not show the reaction to be synchronous. Evidence of this kind could not in any case throw light on its synchronicity. *Any* mechanism must involve a symmetric species (**25**), either as the TS or as a stable intermediate. If it is a stable intermediate, its energy must parallel that of the TS. The properties of the TS cannot therefore show whether or not it itself is the symmetric species.

The MINDO/3 calculations for ring inversion in **27** and for its conversion to **22** are subject to much greater uncertainties, MINDO/3 is known[40] to give heats of formation that are too negative for compounds containing four-membered rings and this is the case for **27**, as Gajewski[61] points out. The experimental value was not yet available at the time our paper[59] was submitted, two years before it was published. Furthermore, as was clearly stated in our paper energies calculated for biradical-like species by MINDO/3-CI are too negative, usually by ca. 15 kcal/mol. The TS for the inversion of **27** is a biradical, inclusion of CI lowering its energy by 48 kcal/mol.[59] As we also clearly pointed out, our description of this part of the potential surface was correspondingly uncertain. The "discrepancies" claimed by Gajewski do not therefore exist.

The reason why biradicals are involved in the reactions of **27** is related to the reason why the intermediate in the Cope rearrangement is a biradicaloid, not a biradical. In the "boat" biradical (**28**) the radical centers can couple either through bonds or through space. The two couplings, however, act in opposition to one another.[58,63] In the "boat" Cope intermediate, the through-bond interaction dominates, while in the species from **27**, the through-space one wins. Consequently the two radicals are lumomers,[63] and their interconversion, being "forbidden", requires activation.

Studies of the Claisen rearrangement, currently in progress,[64] show that it takes place, as expected, by a nonsynchronous mechanism analogous to that of the Cope rearrangement. Here again no reliable information concerning its synchronicity could be provided by studies of isotope effects.

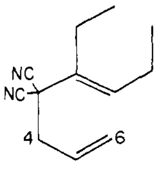
(e) Ene Reactions. Ene reactions are analogues of cycloadditions involving migration of hydrogen in place of ring formation, e.g.:



(22)

Since they involve the breaking of one π bond and two σ bonds and the formation of two π bonds and one σ bond, it might seem at first sight that a synchronous mechanism is prohibited. However, the arguments given above suggest that the forming/breaking of bonds to the migrating hydrogen atom should not contribute significantly to the activation energy. Furthermore, one of the breaking π bonds and the forming π bond share a common atom. The arguments in section d suggest that the corresponding contribution to the activation energy may also be small. The reaction could then be regarded as effectively of one-and-a-half bond type. Such a reaction might well be synchronous, due to the aromatic stabilization of the corresponding symmetrical TS.

For reasons indicated earlier (see "Conditions Favouring Synchronous Multibond Reactions"), the contribution of the bonds to hydrogen should be least when the hydrogen atom is migrating from one heteroatom to another, greater when migration is from a saturated carbon atom to a heteroatom or conversely, and greatest when the migration is from one carbon atom to another. The tendency to synchronous mechanisms should decrease in the same order. MINDO/3 calculations[65,66] suggest that this is indeed the case. Thus the transition state (**40**) for the decarboxylation of vinylacetic acid (**1**; see eq 7) is predicted[65] to have a symmetrical structure in which the CC bonds in the allyl moiety are equal in length (1.42 Å), and similar results were obtained in studies[66] of other ene reactions in which the hydrogen atom migrates to or from oxygen. On the other hand, several reactions involving migration of hydrogen from carbon to carbon were found[66] to take place via very unsymmetrical TS.



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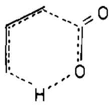

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Steps or Stages?

The new rule prohibits multibond reactions from taking place in a synchronous manner. It does not, however, distinguish between concerted and nonconcerted alternatives. Can we make any predictions in this regard? And is there any real operational difference, so far as the practicing organic chemist is concerned, between a synchronous mechanism and one which, while nonsynchronous, is still concerted?

The latter question is easily answered. There are two very real differences. First, there are steric effects to be taken into account. These will depend on the detailed geometry of the TS. If we are to assess them, as an aid to developing, e.g., stereoselective or regioselective reactions, we need to know just what that geometry is. In the Diels–Alder reaction, for example, if one of the nascent CC bonds in the TS 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 of this kind is most likely to be formed and which will be the weak bond in it. As noted above, the course of Diels–Alder reactions can be interpreted very effectively on this basis, and recent studies[67] of intramolecular

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(63) (a) Dewar, M. J. S.; Kirschner, S.; Kollmar, H. W. *J. Am. Chem. Soc.* **1974**, *96*, 5240. (b) Dewar, M. J. S.; Kirschner, S.; Kollmar, H. W.; Wade, L. E. *Ibid.* **1974**, *96*, 5242.

(64) Healy, E. J., unpublished results.

(65) Dewar, M. J. S.; Ford, G. P. *J. Am. Chem. Soc.* **1977**, *99*, 8343.

(66) Brown, S. B., unpublished results.

(67) Martin, S. F.; Tu, C.-y.; Kimura, M.; Simonsen, S. H. *J. Org. Chem.* **1982**, *47*, 3634 and papers cited therein.

Diels–Alder reactions have shown the value of this approach.

An unsymmetrical cyclic TS for a pericyclic process in analogous to a cyclic conjugated hydrocarbon in which the CC bonds vary in length. Such a variation reduces[68] the aromatic or antiaromatic energy but it does not destroy it. There will therefore still be a tendency for two-bond pericyclic reactions to take place in a concerted manner, this tendency being stronger the less the resonance energies of the relevant bonds alternate in the cyclic TS. Reactions where the geometry of the cyclic TS disfavors the necessary overlap of orbitals will tend to take place in distinct one-bond steps and the tendency to retain stereochemistry will be correspondingly small; cf. the double electrocyclic ring opening of bicyclobutane (section C). These arguments emphasize the futility of attempts to discover synchronous pericyclic reactions in cases where the corresponding TS would be impossibly strained, on the grounds that they "ought" to occur because they are "allowed" by the Woodward–Hoffmann rules. The apparent power of the rule presented here also makes it seem extremely unlikely that *any* three-bond reaction can take place in a synchronous manner, for example, the trimerization of an olefin to a benzene derivative, unless four of the switching bonds are involved in migrations of hydrogen. The reduction of olefins by diimide would be an example of this and recent calculations by Olivella[69] indicate that it is indeed synchronous.

Summary and Conclusions

(1) The basic reactions of organic chemistry are mostly of one-bond type. Reasons are given for this, indicating that the activation energy of a synchronous two-bond reaction should be roughly double that of an analogous one-bond one. This conclusion is summarized in a new rule regulating the course of reactions; i.e., *synchronous multibond reactions are normally prohibited.* They occur only in specific cases where special circumstances make them unusually favorable.

(2) The only expected exceptions occur (a) when making/breaking bonds involve migration of a hydrogen atom from one atom to another, (X–H Y) → (X H–Y), particularly when one, or better still both, of the atoms X and Y are heteroatoms and (b) in cases where the activation energy of the synchronous reaction is very small, particularly when steric factors favor the synchronous mechanism in comparison with alternative two-stage or two-step ones.

(3) The only apparent exceptions to the new rule are the E2 reaction, the S_N2' reaction, and certain multibond pericyclic reactions that are "allowed" by the Woodward–Hoffmann rules.

(a) The E2 reaction has not been proved to be synchronous; however, it in any case exemplifies exception a above.

(b) Theoretical calculations indicate the S_N2' reaction to be a two-step process, formation of the new bond preceding rupture of the old one.

(c) Detailed analysis of the available data indicates that multibond pericyclic reactions, even if "allowed" by the Woodward–Hoffmann rules, nevertheless take place in a nonsynchronous manner if they violate the new rule and to not come under the heading of one of the expected exceptions to it.

(4) Many of the mechanisms suggested by the new rule have been supported by MINDO/3 and/or MNDO calculations, leading, in at least one case, to a mechanism that had not previously been considered and that yet is in agreement with all the available facts. In view of the success of these procedures in studies of a very large number of very varied reactions,[42,43] this both provides strong support for the new rule and also confirms the usefulness of MINDO/3 and MNDO as a guide to reaction mechanisms.

(5) Indications are given of possible applications of the new rule both in mechanistic studies and as an aid in organic synthesis.

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Cytochrome c_3 Modified Artificial Liposome. Structure, Electron Transport, and pH Gradient Generation

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Abstract: Detailed studies on the structure, electron transport rates, and proton transport rates coupled to electron transport were carried out for artificial lecithin liposomes functionalized with cyt c_3 or cyt c. Artificial liposomes modified with cyt c_3 were found to be single-walled, normal liposomes of ca. 250-Å diameter based on electron micrographs. The electron transport rate across the membrane was very much accelerated in the presence of cyt c_3, and the electron influx was coupled with rapid proton transport from the outside to the inside of the artificial liposome, generating a large pH gradient across the membrane. The maximum pH gradient is determined by the accelerated proton influx and slower passive proton efflux. The permeability coefficients of passive proton flow, P_{H^+}, and of accelerated coupled proton flow, P_{H^+}, were estimated. The observed permeability for the coupled transport is by a factor of 10^1–10^2 larger than the usual passive proton permeability.

In biological systems, the electrochemical potential gradient across the cell membrane is maintained by the inside–outside unequal distribution of lipids or proteins bound to the cell membrane. This potential difference induces the generation of a pH gradient or an ion concentration gradient across the membrane via coupling to a downhill chemical reaction. The pH gradient drives many important and complicated biological functions such as active transport,[1-4] stimulus-response,[5] and ATP synthesis.[6]

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