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Mechanism of the Diels-Alder Reaction: Reactions of Butadiene with Ethylene and Cyanoethylenes

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Abstract: PMO theory suggests that the effects of substituents on the rate of the Diels-Alder reaction between ethylene and 1,3-butadiene cannot be explained on the basis of a synchronous mechanism. Calculations are reported, using the RHF, UHF, and CI versions of MNDO and AM1, for the Diels-Alder reactions of 1,3-butadiene with ethylene, acrylonitrile, maleonitrile, fumaronitrile, and 1,1-dicyanoethylene. The results confirm the PMO conclusions, indicating unambiguously that the reactions involving the cyanoethylenes cannot be synchronous. The evidence suggests that Diels-Alder reactions in general proceed via very unsymmetrical transition states, close to biradicals in structure and with energies differing little from those of the corresponding biradicals. The regioselectivities and rates of Diels-Alder reactions can be predicted on this basis, more simply and more reliably than they can in terms of frontier orbital theory. The mechanism of the simplest example, i.e., the reaction of ethylene with butadiene, remains uncertain.

The mechanism of the Diels-Alder (DA) reaction has been the subject of major interest and controversy, ever since it was discovered 60 years ago.[1] The chemical evidence seemed initially to favor a two-step[2] mechanism, involving a biradical or zwitterionic intermediate, since the regioselectivity of DA reactions can be interpreted very effectively on this basis (see below). It was, however, recognized that the observed stereochemistry is difficult to explain in such terms, DA reactions almost invariably involving exclusive cis addition to the dienophile.

In 1938 Evans and Warhurst[3] pointed out that the cyclic transition state (TS) involved in a synchronous[2] mechanism should be analogous to benzene and hence highly resonance stabilized. They suggested on this basis that DA reactions are in fact synchronous, unlike analogous dimerizations of olefins where the TS would be an analogue of cyclobutadiene. While this work was largely overlooked as a result of World War II and while good evidence for a nonconcerted[2] mechanism was later presented by Woodward and Katz,[4] the investigations of pericyclic reactions by Woodward and Hoffmann[5] revived the synchronous mechanism, and most organic chemists have assumed in recent years that DA reactions in general are not merely concerted[2] but also synchronous.

While the stereospecificity of DA reactions certainly suggests that they are concerted, this argument is not conclusive. The same would be true for a two-step mechanism if the intermediate biradicals or zwitterions collapse to the product faster than they isomerize by internal rotation. Several lines of evidence do, however, show that *both* of the new bonds are formed to significant extents in the TSs of certain specific DA reactions. These, and the properties involved (in parentheses), are as follows: (a) DA reaction of furan with maleic anhydride[6] (kinetic isotope effects); (b) reverse DA conversion of dibenzotricyclo[2.2.2]octadiene to anthracene and ethylene[7] (kinetic isotope effects); (c) DA reactions of diphenylisobenzofuran with methyl and menthyl furmarates[8] (induced optical activity); (d) DA reactions of anthracene and its benzo derivatives with maleic anhydride[9] (comparison of rates with localization and paralocalization energies).

However, contrary to claims in the original papers,[6-9] this evidence does *not* show that any of the reactions in question are synchronous. The arguments to this effect have been given in detail elsewhere[10] and so need not be repeated here. The only new evidence, an addition[11] to (c), is also inconclusive.[12] On the other hand, comparison of the rates of the DA reactions of 1,3-

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

(2) Problems have been caused in the past by loose terminology, the term "concerted" in particular having been used with a variety of meanings. The terminology used here, which now seems to be gaining general acceptance, is as follows. A *concerted* reaction is one which takes place in a single kinetic step. A *two*-step reaction is one which takes place in two distinct steps, via a stable intermediate. A *synchronous* reaction is a concerted reaction in which all the bond-breaking and bond-forming processes take place in parallel, all having proceeded to comparable extents in the TS. A *two-stage* reaction is concerted but not synchronous, some of the changes in bonding taking place mainly in the first half of the reaction, between the reactants and the TS, while the rest takes place in the second half, between the TS and the products. The new features are the precise definition of the term concerted and introduction of the term two-stage. The latter seems to have been first suggested by Goldstein and Thayer (Goldstein, M. J.; Thayer, J. L., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1925).

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

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

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

(6) Seltzer, S. *J. Am. Chem. Soc.* **1965**, *87*, 1534.

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

(8) Tolbert, L. M.; Ali, M. B. *J. Am. Chem. Soc.* **1981**, *103*, 2104; **1982**, *104*, 1742; **1984**, *106*, 3804.

(9) Dewar, M. J. S.; Pyron, R. S. *J. Am. Chem. Soc.* **1970**, *92*, 3098.

(10) Dewar, M. J. S.; Pierini, A. B. *J. Am. Chem. Soc.* **1984**, *106*, 203.

(11) Tolbert, L. M.; Ali, M. B. *J. Am. Chem. Soc.* **1984**, *106*, 3804.

(12) The earlier criticisms[10] apply equally to this work. The experimental results were explained in terms of compensation between two opposing steric effects. There is no reason to suppose that the cancellation may not be almost exact in any given case. The experiment by Tolbert and Ali was what may be termed a "one way" experiment, i.e., an experiment with two possible outcomes, one of which leads to a definite conclusion, whereas the other does not.

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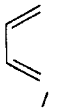
butadiene (**1**) with ethylene (**2**) and its cyano derivatives (**3**–**7**) shows[10] unambiguously that the reactions of the unsymmetrical dienophiles (**3**, **6**, and **7**) are not only not synchronous but probably also involve very unsymmetrical TSs.[10] Kinetic studies[13] of the DA dimerization of **1** have also indicated that the heat of formation of the corresponding TS is similar to that estimated for the biradical (**9**) that would be the intermediate in a two-step reaction. Thus, if the TS is in fact cyclic, the energy required to break one bond in it, forming **9**, must be very small. This suggests that the TS is again unsymmetrical, one of the forming CC bonds being already strong while the other is still very weak.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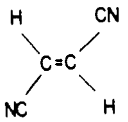
$H_2C=CH_2$

2

$H_2C=CH\text{-}CN$

3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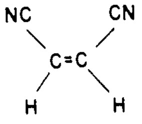
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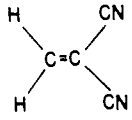
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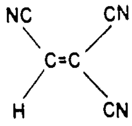
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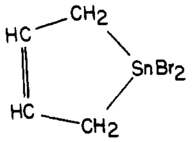
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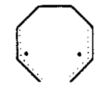
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This evidence refers only to unsymmetrical DA reactions. It leaves open the question concerning the synchronicity of DA reactions involving symmetrical reactants. Whether or not such reactions are synchronous is admittedly of little practical significance, having no direct bearing on their rates of stereochemistry. Important theoretical issues are, however, at stake.

It has been generally assumed that "allowed" pericyclic reactions are invariably synchronous in the absence of factors militating strongly against synchronicity. Any revision of these ideas would have a major impact on chemical theory. One possible revision of this kind was recently suggested[14] in the form of a general rule that multibond reactions tend not to be synchronous. Since the majority of pericyclic reactions are of multibond type, this rule, if substantiated, would have far reaching consequences. The DA reaction is a multibond process and, as indicated above, DA reactions involving unsymmetrical reactants are not only nonsynchronous but also seem to involve very unsymmetrical TSs. This evidence for the new rule would become even more cogent if "symmetrical" DA reactions also proved to be nonsynchronous.

Several factors that might lead to violations of the new rule were noted in the original paper,[14] one of which relates directly to pericyclic processes. Since the TS of an "allowed" pericyclic reaction is aromatic,[3,15] it must have a correspondingly large (aromatic) stabilization energy, much or all of which will be lost if the TS is not symmetrical. Such a TS should therefore tend to be symmetrical for the same reason that the bonds in aromatic hydrocarbons tend to be equal in length. Is this factor enough to make DA reactions of symmetrical dienes with symmetrical dienophiles synchronous?

Problems of this kind, involving the timing of bond-forming/breaking processes, are notoriously difficult to solve by experiment. Indeed, as noted above, determined efforts to solve the present example by experiment have not led to a conclusive solution. Theoretical calculations can be of especial value in situations of this kind, and a number of calculations for DA reactions have indeed been reported. With the exception of some rather nontypical reactions of cyclobutadiene,[16] all have referred to the simplest case, i.e., the DA reaction of **1** with **2**.

To be meaningful in this kind of connection, calculations have to be carried out by using an adequate procedure and without making *any* assumptions concerning the form of the potential energy (PE) surface or the geometries of stationary points. The PE surface must also be searched in sufficient detail to ensure that all relevant stationary points have been located and properly characterized.

Earlier calculations failed to meet these criteria (for a discussion, see ref 18). The first to do so, a MINDO/3 study[17] of the reaction of **1** with **2**, predicted it to be nonsynchronous, involving a biradical-like intermediate. The TS corresponded to formation of the *second* CC bond. While the reaction was definitely predicted to be nonsynchronous, the calculations could not establish whether or not the biradical-like species corresponded to a minimum on the PE surface. If it does, the reaction takes place by a nonconcerted two-step mechanism; if not, then a concerted two-stage[2] mechanism is involved. The TS was in any case predicted to be very unsymmetrical, one of the forming CC bonds being still very long and weak.

It had previously been assumed[18] that if such a biradical-like species were an intermediate in the DA reaction, it would necessarily collapse to the product with little or no activation. The rate-determining step or stage in such a process would then necessarily be the first, corresponding to the formation of the intermediate, i.e., to formation of the first new CC bond. Since there are very strong reasons (see above) for believing that *both* new bonds are formed to significant extents in the TSs of typical DA reactions, it was assumed that such reactions must be synchronous.

This argument rests on the tacit assumption that the intermediate in such a reaction is in effect a genuine biradical, behaving in the same way as a pair of analogous but separate radicals. In fact, however, there is through-space interaction between the radical centers which, while weak, is sufficient to lead to the observed retention of stereochemistry. While species of this kind are not biradicals, they were often loosely referred to as such in the past for lack of an appropriate term. Much confusion has been caused by this ambiguity, the term "biradical mechanism" being taken to imply that a reaction involves genuine biradicals as intermediates. The term *biradicaloid* has been introduced recently to meet this need, a biradicaloid being a singlet closed-shell species derived from a biradical by a weak interaction between the radical centers. While a biradicaloid is expected to show biradical-like chemical behavior, it will be less reactive than a biradical because of the stabilization due to the interaction between the "radical centers". There is, therefore, no reason why combination of the latter should not require activation and this indeed is what MINDO/3 predicted for the biradicaloid derived from **1** and **2**. The MINDO/3 calculations provided the first challenge in recent times to the generally accepted belief that *all* DA reactions are synchronous.

There is little doubt that the large majority of DA reactions are concerted. The point at issue is whether or not the corresponding TSs are more or less symmetrical (or nearly symmetrical) and hence aromatic, or unsymmetrical biradicaloids, one of the new CC bonds being still very weak. While further theoretical studies of this problem have been reported,[19-21,23] none of them

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(13) See: Stephenson, L. M.; Gemmer, R. V.; Current, S. *J. Am. Chem. Soc.* **1975**, *97*, 5909 and references cited there.

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

(15) For a detailed discussion, see: Dewar, M. J. S. *Angew. Chem.* **1971**, *83*, 859; *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 761.

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

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

(18) For representative references to the very extensive literature, see ref 17.

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

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

(21) Houk, K. L.; Lin, Y.-T.; Brown, F. K. *J. Am. Chem. Soc.* **1986**, *108*, 554.

(22) See: Dewar, M. J. S.; Storch, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 3898.

(23) Bernardi, F.; Bottoni, A.; Robb, M. A.; Field, M. J.; Hillier, I. H.; Guest, M. F. *J. Chem. Soc., Chem. Commun.* **1985**, 1051.

has led to a definite solution because of their failure to meet the requirements indicated above.

Ortega et al.,[19] using the STO-3G model, found the TS to be symmetrical. However, as the authors themselves recognized, this result could well have been an artifact of the closed-shell (RHF) procedure they used. Since RHF procedures give energies for biradicals that are far too positive, they will also be strongly biased against mechanisms involving biradicaloid intermediates or TSs. Calculations including CI indeed suggested[19] that a more sophisticated treatment might well have predicted a nonsynchronous mechanism.

Brown and Houk[20] also used the STO-3G model, arriving not unnaturally at the same inconclusive result as Ortega et al. Very recently, in a paper published after ours had been submitted, Houk et al.[21] reported further calculations, using both RHF and UHF versions of the 3-21G model. While the former naturally led again to a symmetrical TS, the latter predicted it to be unsymmetrical, involving indeed a stable biradical intermediate. Houk et al. rejected this conclusion on the grounds that UHF treatments favor biradicals. However, while there are good reasons for expecting this to be the case, the resulting error in the case of the 3-21G model is not known. There is, therefore, no way to tell whether or not the UHF conclusion is correct, whereas the RHF calculation is definitely meaningless in this connection.

It should incidentally be noted that Houk et al.[21] misquoted the conclusions drawn by Dewar et al.[17] from their MINDO/3 calculations. While these did lead to the prediction of a minimum in the PE surface, corresponding to an intermediate, its estimated depth (6 kcal/mol) was not enough to make its existence certain. The only definite conclusion was that the TS must in any case be very unsymmetrical.

Apart from these criticisms, the STO-3G model is in any case known to give poor estimates of molecular energies. It, therefore, provides a poor guide to reaction mechanisms. While the 3-21G model is better, the molecular energies it gives are still generally inferior to those from MINDO/3.[22] Thus, in case of a conflict between either of these models and MINDO/3, the MINDO/3 conclusions are in general more likely to be right.

Bernardi et al.[23] used a better ab initio model (4-31G basis set, CAS (complete active space) SCF approximation) but assumed C_s symmetry. While the symmetrical TS found in this way was properly characterized as a saddle point, no attempt was made to locate a possible unsymmetrical alternative of lower energy. There is no theoretical reason why two such distinct reaction paths should not coexist, and we have indeed found two examples of such behavior. AM1 predicts this to be the case in the addition of ozone to ethylene[24a] and a similar situation has been found[24b] in MNDO studies of cycloadditions involving silicon. The following argument makes it seem likely that the same could be true here.

Consider first the symmetrical (synchronous) TS, where the forming CC bonds are equal in length. Because the distance between the carbon atoms in **1** is double that between the terminal atoms in **2**, the TS will be correspondingly strained. It is, however, stabilized by cyclic conjugation, being aromatic. A distortion which reduces its symmetry, by shortening one of the forming CC bonds with a corresponding increase in the length of the other, will reduce its aromatic energy. Its strain energy will, however, remain virtually unchanged, being invariant, to a first approximation, for such an antisymmetric distortion. The symmetrical structure is therefore likely to be a TS, corresponding to a saddle point rather than some other kind of stationary point on the PE surface, irrespective of whether or not there is another saddle point (TS) of lower energy.

Now consider the alternative TS suggested here, i.e., an unstrained biradical-like structure where one of the forming bonds is still very long and correspondingly weak. Any increase in the length of the short, strong bond will lead to an increase in energy which will be much greater than the decrease due to a corresponding contraction of the long weak one. Any distortion tending to equalize the lengths of the forming bonds should therefore lead to an increase in the total energy. The corresponding unsymmetrical structure is therefore also likely to be a saddle point on the PE surface.

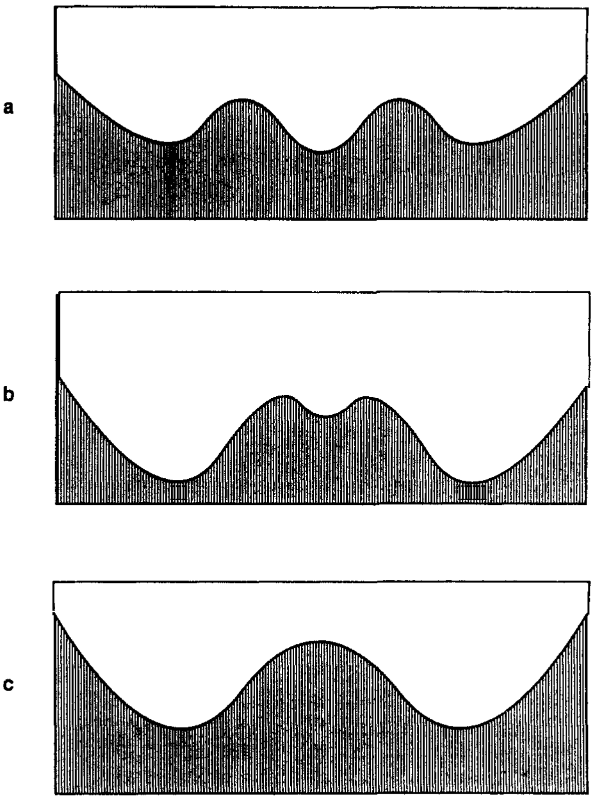

Figure 1. Schematic representation of the profile of the ridge separating the reactants from the products in a Diels–Alder reaction, seen from either side. (a) Reaction where the synchronous and two-stage mechanisms occur with equal ease; (b,c) reactions in which the two-stage mechanism becomes progressively more favorable.

The resulting situation is indicated schematically in Figure 1a. This represents the ridge in the PE surface that separates the reactants from the products, seen from either side. A TS corresponds to a minimum in the ridge. The middle TS corresponds, as indicated, to the synchronous mechanism, and the two side ones correspond to the two modes of reaction via biradicaloids. Figure 1a represents a case where both reactions occur with equal ease. This interpretation differs from the current one where it is assumed that the TSs of DA reactions can have a continuously graded range of structures, ranging from symmetrical to biradical-like. The argument given above makes this seem unlikely, the choice lying between the two extremes. If these differ greatly in energy, the TS of higher energy may well disappear; cf. Figure 1, parts a–c. If they do not differ significantly, the reaction will take place by two distinct paths, one synchronous and the other nonsynchronous, rather than by a single mechanism of intermediate character. Indeed, AM1 predicts this to be the case in the addition of ozone to ethylene,[24a] and a similar situation has been found[24b] in MNDO studies of cycloadditions involving silicon.

One point should be emphasized. The nonsynchronous mechanism under discussion here is *not* a biradical process. The weaker bond in the TS must still be quite strong because breaking it would lead to a genuine biradical with a large increase in entropy. The enthalpy of formation of the bond must be sufficient to compensate for this. Furthermore, if the bond is to have formed appreciably in the TS, it must start to form before the other new bond has formed completely. The TS must therefore still contain a delocalized cyclic system, and formation of the two new bonds in it must still synergize one another. Such a TS must, therefore, be aromatic and the corresponding reaction will still conform to the Woodward–Hoffman rules, although the aromatic energy of the TS will of course be less than that of an analogous symmetrical

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(24) (a) Dewar, M. J. S.; Kuhn, D. R., submitted for publication in *J. Am. Chem. Soc.* (b) Friedheim, J. E., unpublished work.

Table I. Properties Calculated by AM1 (MNDO)[a] for Stationary Points on the Potential Surfaces of Diels–Alder Reactions of Cyanoethylenes with Butadiene

	ΔH_f, kcal/mol			TS bond lengths, Å[b]		
dienophile	react.	TS	prod.	r_1	r_2	$\Delta H^{\ddagger}$, kcal/mol
2	46.4 (44.3)	70.2 (89.7)	-10.1 (-9.6)	2.119 (1.682)	2.119 (3.061)	23.8 (45.4)
3	74.9 (73.0)	99.2 (114.3)	22.7 (27.0)	2.053 (1.634)	2.210 (3.160)	24.3 (41.3)
4	106.5 (104.5)	132.0[c] (153.5)	59.2[c] (66.1)	2.134 (1.663)	2.134 (3.159)	25.5 (49.0)
5	105.9 (104.2)	131.6 (152.6)	59.8 (66.5)	2.146 (1.659)	2.131 (3.160)	25.7 (48.4)
6	109.5 (106.7)	133.7 (141.5)	63.2 (69.6)	1.995 (1.594)	2.335 (3.000)	24.2 (34.8)

[a] MNDO values in parentheses. [b] Lengths of the forming CC bonds in the TS. In the case of **3** and **6**, the shorter of the two bonds is that formed by the methylene group of the dienophile. [c] For exo addition.

one. Thus, both of the DA TSs are aromatic. One has a large aromatic energy tempered by a large strain energy, whereas the other is both less aromatic and less strained. In order to distinguish between them by computation, it would be necessary to use a procedure able to deal reliably with biradicaloids and to search the PE surface in sufficient detail to ensure that if both TSs exist, both have been located.

An adequate search of the (**1** + **2**) PE surface, using an adequate ab initio procedure, would admittedly be close to the limits of feasibility, using currently available computers. Even the calculations by Bernardi et al., which were greatly simplified by assuming symmetry, required the use of a Cray supercomputer. There is also the perennial problem that *no* current treatment is "chemically accurate" in an a priori sense. Even "state-of-the-art" ones can be trusted only insofar as they have been tested. Unfortunately tests of this kind for biradicaloids are restricted, as indicated above, by the lack of appropriate experimental data. Further studies of the reaction of **1** with **2**, therefore, seem unlikely to lead to definite conclusions concerning the mechanism of DA reactions in general, particularly since the simplest example of *any* reaction is often untypical.[25]

In the present state of quantum chemistry, there is only one approach to such problems that has any real hope of leading to a definite solution. This involves surveying a number of different examples of the reaction, with rates that have been studied experimentally and which vary over a wide range. Even if a given procedure cannot reproduce the absolute rate of any individual reaction well enough to distinguish between the alternative mechanisms, it should predict their relative rates, at least qualitatively. If the predicted trends from the different mechanisms differ, comparison with experiment should then allow a reasonably certain distinction between them.

We decided to apply this approach to the DA reactions of **1** with ethylene (**2**) and its mono- and dicyano derivatives **3**–**6**. Their relative rates can be estimated from experiment[17] and cover a wide range (>10⁹:1). For reasons indicated above, the method of choice for such a study is one of the semiempirical models developed here, i.e., MINDO/3,[26] MNDO,[27] or AM1.[28] While MINDO/3 performs very well for hydrocarbons, problems often arise in the case of molecules containing heteroatoms, due to the neglect of one-center overlap in the underlying INDO approximation. We therefore confined ourselves to MNDO and AM1.

Theoretical Procedure

The calculations were carried out by using the standard MNDO[27] and AM1[28] procedures, as implemented in the MOPAC and AMPAC programs.[29] For reasons indicated above, it was necessary to use procedures applicable to open-shell systems. The calculations were, therefore, carried out both with the normal (RHF) versions (MNDO, AM1) and with two open-shell ones, using either the "half-electron" approximation[30] with 3 × 3 CI[31] (MNDO-HE-CI, AM1-HE-CI) or the UHF formalism[32] (UMINDO, UAM1). Transition states were located by a recently developed procedure,[33] refined by minimizing the norm of the gradient,[34] and characterized by calculating force constants.[34] All geometries were found by minimizing the energy without making any assumptions. Options for all these procedures are included in MOPAC and AMPAC.

Results and Discussion

Table I summarizes the results from the RHF calculations. The quantities listed are the heats of formation (ΔH_f) for the reactant, TS, and product; the corresponding enthalpies of activation ($\Delta H^{\ddagger}$); and the lengths (r_1, r_2) of the forming CC bonds in each TS. In the case of **3** and **6**, the shorter of the two bonds is that formed by the methylene group of the dienophile. While AM1 predicts the TSs to be symmetrical, or nearly symmetrical, MNDO predicts them to be very unsymmetrical, r_1 and r_2 differing greatly.

AM1 thus agrees with the ab initio calculations[19-21,23] in predicting the reactions to be synchronous, in contrast to MINDO/3[17] and MNDO (Table I). It therefore seems clear that the reaction is predicted to be synchronous, at the RHF Hartree–Fock level. Houk et al.[35] had previously suggested that ZDO approximation may tend, in cases such as this, to predict spuriously unsymmetrical TSs, and they have recently restated[21] this suggestion. Their arguments to this effect are, however, scarcely convincing,[17] and both MINDO/3 and MNDO have indeed predicted symmetrical TSs in other analogous reactions. A striking example is the cheletropic addition of **1** to stannous bromide to form **8**, a DA-like reaction for which MNDO predicts[36] a symmetrical TS with a significant[37] (15 kcal/mol) activation energy. Our results throw new light on the problem, suggesting that MINDO/3 and MNDO do indeed disfavor a symmetrical TS in the case of the (**1** + **2**) reaction but not for the reason suggested by Houk.

The real explanation seems to lie in a well-known failing of MINDO/3 and MNDO, i.e., their tendency to overestimate repulsive interactions between atoms when the distance between them is 1.5–2 times the length of a corresponding covalent bond. As Table I shows, the lengths of the forming CC bonds in the TS predicted by AM1 lie in this region, and similar geometries were obtained in the ab initio calculations[19-21,23] referred to above. Both MINDO/3 and MNDO would be expected to give energies for such a species that are too positive. The corresponding errors could be reduced by making one of the CC bonds longer and the other shorter, removing both from the critical region. This is clearly the reason why both procedures predict the TS to be unsymmetrical. Problems of this kind arise only in exceptional cases with TSs containing unusually long bonds. The bonds in the symmetrical DA TS are long because of ring strain, as indicated above. This overestimation of interatomic repulsions has been corrected

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(25) For example, as Ingold pointed out some years ago, ethyl chloride is the *only* alkyl chloride (other than methyl chloride) that does not form an olefin with alcoholic potash, while methylamine is the *only* primary aliphatic amine that does not react with nitrous acid to form an alcohol.

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(36) Dewar, M. J. S.; Friedheim, J. E.; Grady, G. L. *Organometallics* **1985**, *4*, 1784.

(37) If the activation energy predicted for the synchronous route was very small, this would imply that the overestimation of repulsions was not in any case playing an effective role.

in AM1.[28] AM1 consequently predicts the DA TS to be symmetrical. This argument suggests that AM1 should be used in all future studies of pericyclic reactions in preference to MINDO/3 or MNDO, particularly since it seems to give generally better estimates of activation energies.[28]

The following discussion will therefore be based entirely on the AM1 calculations. The MNDO results are included for completeness and comparison.

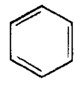
AM1 predicts TSs that are symmetrical, or almost symmetrical, for the reactions of **1** with the cyanoethylenes **3**–**6**, implying that they too are synchronous. This was to be expected for the reasons indicated earlier, AM1 being an RHF procedure, so the results do not eliminate the possibility of an easier alternative nonsynchronous mechanism. However, the AM1 results should in any case indicate what the effects of the cyano substituents should be if all the reactions are in fact synchronous.

As Table I shows, the activation energies for **3**–**6** are greater than that for **2** itself. Cyano substituents are thus predicted to retard the reaction. The relative rates at 300 K, estimated[17] from experimental data, are shown in eq 1. So, far from reaction retardation, cyano substituents accelerate it greatly.

$$\mathbf{2},\ 1;\quad \mathbf{3},\ 3.9 \times 10^4;\quad \mathbf{4},\ 3.4 \times 10^6;\quad \mathbf{5},\ 3.0 \times 10^6;\quad \mathbf{6},\ 1.5 \times 10^9 \qquad (1)$$

The reason for this discrepancy is simple. *Cyano substituents would be expected to retard the reaction if it involved a synchronous mechanism.* This surprising conclusion follows from the following argument, which, while obvious, seems to have been generally overlooked.

If the DA reaction of **1** with **2** were synchronous, the corresponding TS would be isoconjugate with benzene.[15] Such a species can be represented in terms of six localized[38] CC σ bonds linking the carbon atoms of **1** and **2** together with a delocalized system derived from the cyclic interaction of six carbon AOs. The latter is equivalent to the π system of benzene (**10**) because the behavior of a delocalized system depends only on the topology of overlap of the contributing AOs, not on the geometry of overlap. Any conjugative interaction between a substituent and the TS will therefore parallel the corresponding interaction between it and **10** in a corresponding derivative of **10**.



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Now PMO[39] theory shows[40] that the π interaction between any even substituent and any even alternant hydrocarbon is the same to a first approximation, being equal to $\beta/2$, where β is the π resonance integral of the CC bond linking the substituent to the hydrocarbon. This conclusion is strongly supported by the available thermochemical data, in particular for the cyano group. Thus, the observed[41] heats of formation of **2**, **3**, **10**, and benzonitrile (12.45, 19.81, 44.1, and 51.54 kcal/mol, respectively) show that the resonance interactions in **3** and benzonitrile are essentially identical.

$$H_2C{=}CH_2 + C_6H_5CN \leftrightarrow H_2C{=}CHCN + C_6H_6 \qquad (2)$$

$$\Delta H = -0.1 \text{ kcal/mol}$$

The same argument should apply to the TS for (**1** + **2**) because it is also in effect an AH. The only difference between the delocalized systems in it and in **10** lies in the values of the resonance integrals for the individual CC interactions. The PMO argument[40] does not depend on these values. A cyano substituent should therefore change the total energy of the TS by $\beta'/2$, where β' is the corresponding C–CN resonance integral. Now the value of this integral will be less than that (β) in a cyanoethylene because the hybridization of the carbon atom adjacent to CN is no longer sp^2 but intermediate between sp^2 and sp^3. The resulting decrease in the strength of the C–CN σ bond should then lead to an *increase* in the activation energy, as AM1 indeed predicts. The effect is less in the case of the unsymmetrical dienophiles **3** and **6** because the corresponding TSs are no longer completely symmetrical and the change in hybridization of the carbon atom adjacent to CN should be correspondingly less.

The fact that *all* the cyanoethylenes react much faster with butadiene than ethylene therefore implies that *none* of the reactions is synchronous, not even those of the symmetrical dienophiles **4** and **5**.

The validity of this analogy between benzene and a symmetric DA TS has been questioned on the grounds that the latter involves a three-dimensional structure where the distinction between σ and π MOs no longer holds. While our quantitative calculations completely confirm the results of the PMO analysis, a more direct vindication seems called for because the same kind of situation may arise again in other connections.

The objection rests on a misunderstanding of the localized bond model.[38,39b,39c] This is effective *not* because the electrons involved in bonding are localized but because the interactions between the "localized" bonds in any "classical" molecule make constant contributions to its collective properties (energy, geometry, etc.), a classical molecule being one for which only a single classical structure can be written. These contributions can be allowed for by appropriate choice of the corresponding bond properties (bond lengths, bond energies, etc.[38,39b,39c]). Classical molecules, therefore, behave as if the bonds in them were localized, their collective properties being expressible as additive sums of bond properties. The PMO arguments[38,40] on which this conclusion is based apply equally to all types of interactions, conjugative, hyperconjugative, or sigmaconjugative, and also equally to compounds containing heteroatoms. It can moreover be shown[40] that the same is true for essential single and double bonds in a molecule, even if other parts of it are delocalized. Since the bonds linking the CN groups to the TSs of the DA reactions considered here are essential single bonds, they are therefore localized in the sense indicated above and their bond energies will consequently depend only on the hybridization of the carbon atom adjacent to the substituent.

As noted in the introduction, the experimental evidence suggests strongly that the TSs of DA reactions of unsymmetrical dienophiles are very unsymmetrical, one of the forming CC bonds still being very weak. Such a species will be a biradicaloid, derived from the corresponding biradical by a weak through-space interaction. Since the interaction is small, such a species should interact with a substituent at one of the "radical" centers in a manner similar to the corresponding biradical. Substituents which stabilize the biradical should therefore have a similar, if smaller, stabilizing effect on the biradicaloid. This will be true for a substituent in the dienophile only if it is attached to the carbon atom at the end of the weak bond in the TS. A substituent attached to the other dienophilic carbon atom should have a much smaller effect.

Since the cyano group stabilizes radicals very effectively, the DA reactions of cyanoethylenes with **1** should be faster than that of ethylene if the TSs are in fact very unsymmetrical. The cyano group must of course be attached to one of the radical centers in the TS, i.e., to one or other end of the weaker of the two forming bonds. A cyano group attached to one end of the stronger forming bond will have no such effect. The reactions of **3**, **4**, and **5** with **1** should be comparably faster than that of **2**, while the rate of that of **6** should be as great again. This is the pattern observed;[17] see eq 1. The observed rates are therefore consistent with the conclusion reached above that the DA reactions of all the cyanoethylenes with butadiene take place via unsymmetrical biradicaloid TSs. We next set out to test this conclusion by carrying out appropriate calculations.

The reason why AM1 incorrectly predicts synchronous mechanisms for these reactions was given earlier. It is an RHF pro-

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(38) See: Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 669.

(39) Dewar, M. J. S. *J. Am. Chem. Soc.* **1952**, *74*, 3341, 3345, 3350, 3353, 3357. (b) Dewar, M. J. S. *The Molecular Orbital Theory of Organic Chemistry*; McGraw-Hill: New York, 1969; Chapter 6. (c) Dewar, M. J. S.; Dougherty, R. C. *The PMO Theory of Organic Chemistry*; Plenum: New York, 1975.

(40) (a) Reference 39b, Section 6.7. (b) Reference 39c, Section 3.18.

(41) Cox, J. D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*; Academic: New York, 1970.

cedure and consequently predicts energies for biradical-like species that are much too positive. To study nonsynchronous DA mechanisms, it is therefore necessary to use an appropriate open-shell treatment. The versions of MNDO and AM1 commonly used in such connections are those based on the UHF formalism[32] (UMNDO, UAM1) or the "half-electron" approximation,[30] preferably with 3 × 3 CI[31] (MNDO-HE-CI, AM1-HE-CI). Experience has shown that the HE-CI approach is the better, but it requires far more computing time. Since both methods lead to similar geometries, the most cost-effective procedure is first to carry out a UHF calculation and then to use the resulting geometries as initial geometries in a HE-CI calculation. This technique was applied to the DA reactions of **1** with **2–6** with the results summarized in Tables II–VII. While the UHF values (Table III) are less reliable, they are included for completeness. The following discussion will be based entirely on the HE-CI results.

Use of almost any procedure for including electron correlation leads to complete compensation for the extreme correlation between the unpaired electrons in a biradical. As a result, all current procedures are expected to overestimate the stability of a biradical relative to that of an isomeric closed-shell species. In the case of ab initio procedures, the error arises from the underestimation of correlation energies in normal molecules. While the pair correlation energies are all underestimated in a normal molecule, one of them is calculated correctly in the case of a biradical. In our semiempirical procedures, where allowance for "normal" electron correlation is included implicitly via the parametrization, the correlation energy of the unpaired electrons is allowed for twice over in the CI or UHF versions, once by the CI or UHF procedure and once via the parameters. Our error for biradicals thus amounts to the average electron pair correlation energy, i.e., 20–25 kcal/mol. The error should presumably be less for species which are biradical-like but not true biradicals. Lack of thermochemical data for such species has unfortunately made it impossible to quantify the relationship.

The results in Tables III–VII, taken at face value, predict the first step in each reaction, i.e., formation of the first new CC bond, to be rate determining. The experimental evidence, however, indicates strongly that DA reactions are normally concerted, even if they are not synchronous, both new bonds being formed to significant extents in the TS. This discrepancy can be attributed to the error discussed above. While we have not been able to quantify it as a function of biradical character, the CI coefficients listed in Tables III–VII show that the biradical character of the first TS is small in each case, implying that no correction is needed to its calculated heat of formation. Equally, the coefficients for the intermediates and second TSs show them to be close to biradicals in character, so their calculated energies are likely to be too negative by ca. 20 kcal/mol. With this correction, the first saddle point (TS) disappears, the second becoming the TS for the overall reaction. A similar analysis led to similar conclusions in the earlier MINDO/3 study[17] of the reaction of **1** with **2**. This conclusion is also supported, as before,[17] by the entropies of activation calculated for the reverse DA reaction of cyclohexene, leading to **1** and **2**. If the first TS (corresponding to the second TS of the forward reaction) is the overall TS, the calculated (AM1) entropy of activation at 600 K is 7.1 eu, while if it is the second it is 18.0 eu. The observed[17] value is 6.74 eu.

Table VIII compares the relative AM1 activation energies for the DA reactions of **1** with **2–6**, calculated on the same basis (i.e., assuming the second TS to correspond to the overall TS) with the relative free energies of activation estimated from eq 2. The effect of the second CN group in **6** is underestimated, while the activation energies calculated for **4** and **5** are too large.

At least part of the latter discrepancy may well be due to overestimation of steric repulsions in the TS, the TSs from **4** and **5** alone having a CN group attached to the end of the shorter of the two forming bonds. While AM1 does not overestimate nonbonded repulsions as badly as MNDO, it may still do so to some extent.[28] However, the major factor is probably the acceleration of polar DA reactions by solvent, the calculations re-

Table II. Properties Calculated by UAM1 (UMNDO)[a] for Stationary Points[b] on the Potential Surface of Diels–Alder Reactions of Cyanoethylenes (CE) with Butadiene

	TS1[c]				INT[d]			TS2[e]			
CE	ΔH_f	$\langle S^2\rangle$	r_1	r_2	ΔH_f	$\langle S^2\rangle$	r_1	ΔH_f	$\langle S^2\rangle$	r_1	r_2
2	63.7 (67.5)	1.11 (1.25)	1.987 (2.088)	4.927 (5.081)	40.1 (35.8)	1.19 (1.26)	1.518 (1.543)	44.1 (49.4)	1.08 (1.09)	1.530 (1.548)	2.409 (2.307)
3	90.1 (95.1)	1.11 (1.26)	2.004 (2.099)	5.027 (5.140)	65.7 (63.0)	1.22 (1.28)	1.519 (1.544)	70.8 (79.5)	1.04 (1.05)	1.529 (1.548)	2.341 (2.281)
4	125.2 (130.3)	1.17 (1.33)	2.005 (2.097)	5.076 (5.246)	102.7 (101.9)	1.23 (1.28)	1.530 (1.566)	107.3 (118.9)	1.04 (1.04)	1.543 (1.564)	2.344 (2.282)
5	122.9 (129.9)	1.16 (1.33)	2.008 (2.101)	5.000 (5.107)	102.7 (101.9)	1.23 (1.28)	1.530 (1.566)	106.7 (118.2)	1.05 (1.04)	1.542 (1.564)	2.363 (2.281)
6	122.7 (127.6)	1.09 (1.24)	2.012 (2.108)	5.003 (5.107)	98.6 (96.1)	1.24 (1.29)	1.519 (1.544)	105.2 (117.4)	1.01 (0.88)	1.529 (1.541)	2.363 (2.326)

[a] MNDO values in parentheses. For units, see Table I. [b] Values for reactants and product identical with RHF value (Table I). [c] TS for conversion of (**1** + **2**) to the intermediate. [d] Stable intermediate. [e] TS for conversion of the intermediate to the product.

Table III. Properties Calculated by AM1-CI (MNDO-CI) for Stationary Points on the Potential Surface of Diels–Alder (DA) Reaction of Ethylene (**2**) with Butadiene (**1**)[a]

	reactants	first TS	intermediate	second TS	product
ΔH_f[b]	35.5 (32.5)	69.8 (76.7)	51.2 (48.2)	52.1 (53.2)	−15.7 (−16.9)
a^1b^1[c]		0.055 (−0.026)	0.872 (0.966)	−0.241 (−0.018)	0.000 (0.000)
a^2		−0.933 (−0.952)	0.359 (−0.188)	−0.794 (−0.818)	0.828 (0.976)
b^2		0.356 (0.306)	−0.332 (0.178)	0.558 (0.574)	−0.561 (−0.216)
r_1, Å[d]	∞	1.933 (2.087)	1.519 (1.541)	1.532 (1.540)	1.517 (1.542)
r_2, Å	∞	4.989 (5.080)	5.192 (5.350)	2.903 (2.700)	1.517 (1.542)
$\Delta H^{\ddagger}$[b]		34.3 (44.2)		16.6 (20.7)	

[a] MNDO values in parentheses. [b] In kcal/mol. [c] This and the two following entries list the coefficients of the three configurations (a^1b^1, a^2, b^2) involved in the CI wave function, where a and b represent the HOMO and LUMO, respectively. [d] See footnote *b* in Table I.

Table IV. AM1-CI (MNDO-CI)[a] Results (See Table III) for DA Reaction of **3** with **1**

	reactants	first TS	intermediate	second TS	product
$\Delta H_f^{\,b}$	67.5 (69.4)	97.3 (105.1)	78.5 (76.9)	80.1 (83.9)	17.2 (19.8)
a^1b^{1c}		0.112 (0.054)	0.990 (0.909)	0.590 (0.528)	0.004 (−0.006)
a^2		−0.932 (−0.954)	0.111 (−0.337)	−0.685 (−0.735)	−0.982 (−0.976)
b^2		0.344 (0.295)	−0.086 (0.246)	0.428 (0.425)	0.190 (0.216)
r_1, Å^d	∞	1.946 (2.046)	1.518 (1.549)	1.535 (1.541)	1.517 (1.542)
r_2, Å	∞	4.817 (5.082)	5.236 (4.986)	2.850 (2.618)	1.528 (1.555)
$\Delta H^{\ddagger b}$		29.8 (40.7)		12.6 (19.5)	

[a–d] See Table III.

Table V. AM1-CI (MNDO-CI)[a] Results (See Table III) for DA Reaction of **4** with **1**

	reactants	first TS	intermediate	second TS	product
$\Delta H_f^{\,b}$	101.5 (97.7)	133.1 (140.8)	116.1 (116.6)	116.7 (122.8)	53.6 (58.8)
a^1b^{1c}		−0.119 (−0.001)	0.993 (0.933)	0.657 (0.606)	0.004 (−0.002)
a^2		−0.922 (−0.946)	−0.095 (−0.297)	−0.640 (−0.697)	−0.982 (−0.977)
b^2		0.368 (0.325)	0.064 (0.201)	0.399 (0.385)	0.189 (0.215)
r_1, Å^d	∞	1.941 (2.045)	1.531 (1.566)	1.548 (1.556)	1.528 (1.557)
r_2, Å	∞	5.072 (5.268)	5.229 (5.120)	2.853 (2.620)	1.530 (1.559)
$\Delta H^{\ddagger B}$		31.6 (43.1)		15.2 (25.1)	

[a–d] See Table III.

Table VI. AM1-CI (MNDO-CI)[a] Results (See Table III) for DA Reaction of **5** with **1**

	reactants	first TS	intermediate	second TS	product
$\Delta H_f^{\,b}$	101.0 (97.8)	130.8 (140.7)	116.1 (116.6)	116.4 (122.8)	54.2 (59.2)
a^1b^{1c}		0.076 (0.020)	0.993 (0.933)	−0.692 (0.614)	0.001 (0.001)
a^2		−0.926 (−0.947)	−0.095 (−0.297)	−0.626 (−0.692)	−0.982 (−0.977)
b^2		0.368 (0.320)	0.064 (0.201)	0.358 (0.379)	0.189 (0.215)
r_1, Å^d	∞	1.946 (2.053)	1.531 (1.566)	1.549 (1.557)	1.533 (1.558)
r_2, Å	∞	4.808 (5.092)	5.229 (5.120)	2.842 (2.621)	1.528 (1.555)
$\Delta H^{\ddagger b}$		29.8 (42.9)		15.4 (25.0)	

[a–d] See Table III.

Table VII. AM1-CI (MNDO-CI)[a] Results (See Table III) for DA Reaction of **6** with **1**

	reactants	first TS	intermediate	second TS	product
$\Delta H_f^{\,b}$	102.9 (99.0)	129.7 (137.4)	112.6 (110.6)	114.4 (119.4)	57.6 (62.4)
a^1b^{1c}		0.227 (−0.117)	0.989 (0.973)	0.739 (0.633)	0.011 (0.013)
a^2		−0.922 (−0.954)	0.132 (0.202)	−0.621 (−0.710)	−0.982 (−0.976)
b^2		0.313 (0.276)	−0.070 (−0.111)	0.261 (0.308)	0.189 (0.215)
r_1, Å^d	∞	1.953 (2.108)	1.520 (1.550)	1.538 (1.540)	1.515 (1.542)
r_2, Å	∞	4.802 (5.062)	5.363 (5.509)	2.750 (2.540)	1.543 (1.574)
$\Delta H^{\ddagger b}$		26.8 (38.4)		11.5 (20.4)	

[a–d] See Table III.

Table VIII. Relative Activation Energies[a]

dienophile	$\delta H_{cal}{}^b$	$\delta H_{cor}{}^c$	$\delta G_{obsd}{}^d$
2	(0)	(0)	(0)
3	−4.0	−7.0	−6.3
4	−1.4	−7.4	−8.9
5	−1.2	−7.2	−8.9
6	−5.1	−11.1	−12.6

[a] In kcal/mol. [b] Relative (AM1-CI) heats of activation. [c] Corrected AM1 values. [d] Observed relative free energies of activation at 300 K.

ferring to reactions in the gas phase while the measurements were carried out in solution. This interpretation is strongly supported by the fact that the observed ratios of rate constants, $k(\mathbf{3})/k(\mathbf{2})$ and $k(\mathbf{6})/k(\mathbf{3})$, are similar. Duplication of a substituent at a given carbon atom normally leads to a large "saturation" effect. Thus, while the pK of acetylmethane (acetone) is less than that of methane by ca. 50 pK units, the further decrease brought about by a second acetyl group, in acetylacetone, is only 11 pK units. Therefore, $k(\mathbf{6})/k(\mathbf{3})$ should be much smaller than $k(\mathbf{3})/k(\mathbf{2})$, as our calculations indeed predict. While the rates of DA reactions of hydrocarbons in solution are the same as in the gas phase, reactions involving polar reactants exhibit large solvent effects.[42] As Table VIII shows, the calculated values can in fact be brought into satisfactory agreement with experiment if it is assumed that solvation lowers the activation energy in solution by 3 kcal/mol per CN group.

Our calculations thus confirm the conclusion reached above that the DA reactions of **3**–**6** are nonsynchronous, proceeding via biradical-like intermediates. This is true even for the reactions of the symmetrical dienophiles **3** and **6**. Our calculations are also consistent with the conclusion from the earlier MINDO/3 study[17] that the TSs correspond to the cyclization of the biradicaloid intermediates, not to their formation. As before, our calculations cannot distinguish between two-step and two-stage mechanisms. The results do, however, suggest that the difference between them may not be large. As noted earlier, while the experimental evidence suggests that DA reactions are usually concerted, it suggests that a relatively minor perturbation is sufficient to make the biradical-like species a stable intermediate.

Whether or not the prototypical DA reaction, i.e., that of **1** with **2**, is synchronous remains an open question. The available evidence suggests that the difference between the energies of the corresponding synchronous and nonsynchronous TSs is in any case small. since any conjugative substituent stabilizes a radical more effectively than it does an even AH,[43] any such substituent in **1** or **2** should tend to tip the balance in favor of the nonsynchronous route. It therefore, seems likely that DA reactions of dienes and dienophiles containing such substituents are invariably non-

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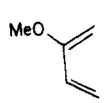
[42] See e.g.: Dewar, M. J. S.; Pyron, R. S. *J. Am. Chem. Soc.* **1970**, *92*, 3098.

[43] Thus, any conjugative substituent accelerates addition of radicals to ethylene, an even AH, because the resulting adduct, an odd AH, is stabilized more effectively by the substituent.

synchronous. If so, and if the reaction of **1** with **2** is indeed synchronous, it represents another illustration of the axiom that the simplest example of any reaction often differs from all the others.

Substituent Effects and Regioselectivity. If DA reactions in general do indeed take place by the nonsynchronous biradicaloid mechanism, the energies of their TSs should differ little from those of the corresponding biradicals. It should then be possible to predict their regioselectivities and rates, in a qualitative sense, by simply assuming that the TS corresponds in each case to the biradical. Since any conjugative substituent stabilizes radicals and since the stabilization is available in the DA biradical TS only if the substituent is at the radical end of the dienophile or at an allylic position in the radical derived from the diene, the preferred mode of addition can usually be predicted immediately.

Consider for example the reaction of 2-methoxybutadiene (**11**) with acrolein (**12**). The possible biradicals are **13**–**16**. Of these **13** alone has both radical centers stabilized. The reaction should therefore lead to **17** rather than **18** as indeed it does. Likewise in the reaction of a sorbic ester (**19**) with acrylic acid (**20**), the best intermediate biradical is **21**. Therefore, **22** should be the main product, as indeed it is.[43] Indeed, if the diene and dienophile each contain just one conjugative substituent, the favored product is invariably the "ortho" or "para" isomer, as our argument predicts.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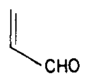
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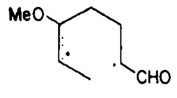
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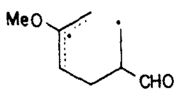
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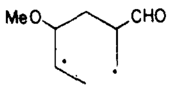
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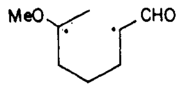
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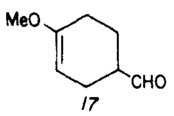
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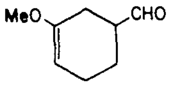
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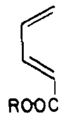
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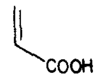
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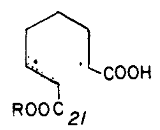
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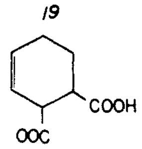
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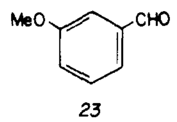
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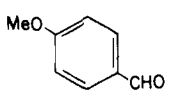
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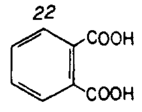
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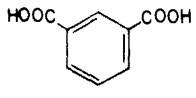
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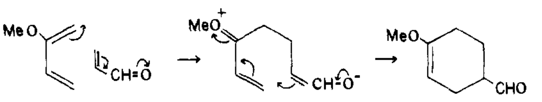
There is, however, a further factor to be considered. Biradicals are very polarizable[44] species, a situation that can be represented in resonance terminology by a large contribution from a corresponding zwitterionic structure. For example, in the case of the biradical derived from **1** and **2**,

$$(H_2\dot{C}{-}CH{=}CH{-}CH_2{-}CH_2{-}\dot{C}H_2) \leftrightarrow (H_2\dot{C}{-}CH{=}CH{-}CH_2{-}CH_2{-}{}^{+}CH_2)$$

or

$$(H_2\dot{C}{-}CH{=}CH{-}CH_2{-}CH_2{-}\dot{C}H_2) \leftrightarrow (H_2C^{+}{-}CH{=}CH{-}CH_2{-}{}^{-}CH_2) \quad (3)$$

Electron releasing (−E) or attracting (+E) conjugative substituents should, therefore, polarize the TS and so further stabilize it. If two substituents are present, one in each component, and if one is of the +E type and the other of the −E type, their effects may reinforce one another.[45] Since this will occur only in the TS leading to the ortho or para adduct, the effect will be to reinforce the tendency to form such an adduct. Since the biradicaloid TS is unusually polarizable, such stabilization by mutual conjugation[45] should moreover be unusually large.[45] The fact that DA reactions usually involve reactants where one is a "donor" (i.e., has a −E substituent) while the other is an acceptor (i.e., has a +E substituent) can thus be explained immediately in terms of biradical-like TSs. Indeed, since the majority of DA reactions are of this type, DA regioselectivities can usually be predicted in terms of mutual conjugation alone, a fact well-known to organic chemists before the synchronicity of DA reactions became established dogma. The reaction of **11** with **12** would, for example, have been represented as in eq 4. This "classical" approach naturally fails if both substituents are of the same type, as in the reaction of **19** with **20**.



(4)

Consider now what the situation would be in these two cases if the reactions were in fact synchronous. Since the TS of a synchronous DA reaction is isoconjugate with benzene, the stabilizing or destabilizing effects of substituents should be the same in both. The relative energies of the pairs of TSs should therefore parallel those of the corresponding derivatives of benzene. Thus, the TSs for meta or para addition of **11** to **12** should parallel *m*-(**23**) and *p*- anisaldehyde, (**24**) respectively, while those for ortho or meta addition of **19** to **20** parallel the corresponding monoesters of, respectively, phthalic (**25**) and isophthalic (**26**) acids. Since **24** is more stable than **23**, being stabilized by mutual conjugation, the analogous DA reaction is correctly predicted to give mainly the para adduct **17**. Likewise since **26** is more stable than **25**, the DA reaction of **19** with **20** is expected to give the meta adduct rather than **22**. Here, however, the prediction is wrong. The error is not indeed surprising because the success in the case of **11** and **12** depended on mutual conjugation between them. Attempts to interpret DA reactions in terms of synchronous (aromatic) TSs are expected to fail whenever the classical approach (cf. eq 4) fails.

This result naturally provides further strong support for our contention that the TSs of DA reactions are not symmetrical aromatic species, being in general very unsymmetrical and close to biradicals in structure. The regioselectivity of all DA reactions can indeed be predicted reliably on this basis, without any recourse to theoretical calculations or special pleading, subject of course to the limitations inevitable in a qualitative theory[46] and to intervention by possible steric effects. Since this fact seems not to be generally recognized[47] and since it is of obvious practical importance in organic synthesis, providing a simple and reliable way to predict products from DA reactions, some further examples may be given.

The first two involve addition of 1-vinylcyclohexene (**27**) to 3-(carbomethoxy)- (**28**) or 4-(carbomethoxy)-*o*-benzoquinone (**29**).

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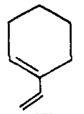
[44] See: Dewar, M. J. S.; Healy, E. F. *J. Am. Chem. Soc.* **1984**, *106*, 7127.

[45] Dewar, M. J. S. *J. Am. Chem. Soc.* **1952**, *74*, 3350, Theorems 47–53. The greater effect in the DA TS follows at once from a consideration of the relevant NBMO coefficients.

[46] In cases where there is a close choice between two alternatives, no qualitative theory can be expected to distinguish between them. Problems also clearly arise in the case of steric effects. The essential point is that the treatment of DA reactions in terms of the biradicaloid mechanism encounters problems only, if at all, when there are such ambiguities, whereas the alternatives, in particular FO theory, not infrequently fail in cases where there are no redeeming circumstances.

[47] Nearly all the standard textbooks of organic chemistry diligently avoid mention of unsymmetrical DA reactions, presumably because of the difficulty of explaining them in terms of the synchronous mechanism naturally adopted for all DA reactions. The only exception we have found is the textbook by Streitwieser and Heathcock (Streitwieser, A., Jr.; Heathcock, C. H. *Introduction to Organic Chemistry*, 2nd ed.; MacMillan: New York, 1981) where the biradical interpretation of DA reactions is introduced as a pedagogical convenience, with, however, a warning that its success does not imply that biradicals are intermediates. To our knowledge, no interpretation of the regioselectivity of a DA reaction in terms of the biradical mechanism has appeared in any recent paper reporting experimental studies of such a process.

The diene is expected to react first at the exocyclic methylene, both for steric reasons and because the resulting allyl radical is stabilized by more alkyl substituents than would be the one derived by attack in the ring. Since the other component contains, in each case, two distinct dienophilic C=C bonds, there are four possible intermediate biradicals to consider, i.e., **30**–**33**. Of these the first (**30**) is expected to be the most stable because it alone has *two* +E groups attached to the radical center derived from the dienophile. The preferred product is thus predicted to be **34**, as indeed is the case.[48] Applying the same arguments to **29**, the preferred radical is seen to be **35**, so the main product from the reaction is predicted to be **36**. This is again correct.[48]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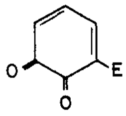
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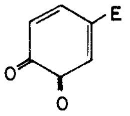
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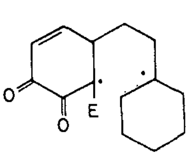
E = COOEt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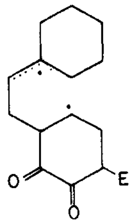
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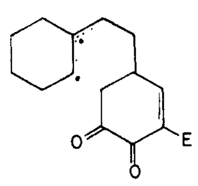
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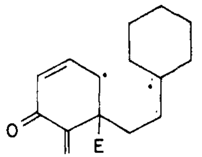
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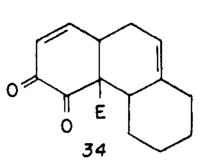
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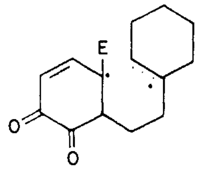
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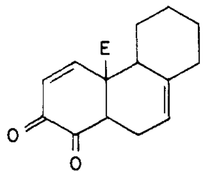
The third example involves the reactions of the dienes (**37**) with acrolein (**12**). Since the initial attack on the latter will naturally take place at methylene, two biradicals (**38** and **39**) need to be considered in each case. In one of these the allyl moiety is stabilized by urethane, in the other by PhS, PhSO, or $PhSO_2$. Since the stabilizing effects of these groups on radicals are comparable, none of them being very effective, each pair of biradicals would be similar in energy if they were indeed simple biradicals. However, since they are biradicaloids, there is a possibility of mutual conjugation between the substituents, if one is of the +E and the other of the –E type. Since PhSO and $PhSO_2$ are +E groups and since the –E activity of PhS is much less than that of EtOOCNH, mutual conjugation should in each case favor **38** over **39**. The preferred products are, therefore, predicted to be the isomers (**40**) with the urethane and ester groups adjacent to one another, which is indeed the case.[49]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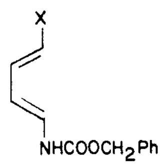
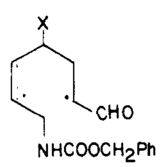

a, X = PhS
37 b, X = PhSO
c, X = $PhSO_2$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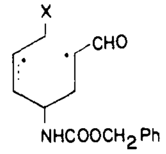
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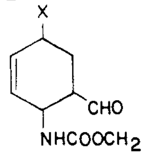
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Practical Interpretation of DA Reactions. In recent years it seems to have become generally accepted that DA reactions can be explained satisfactorily only in terms of the frontier orbital theory.[50] Difficulties certainly arise if attempts are made to interpret them on the assumption that they must be synchronous in view of the Woodward–Hoffman rules.[5] The evidence and arguments presented here suggest that this assumption is in fact incorrect, the TSs of DA reactions being in general unsymmetrical biradicaloids. If so, their energies should run parallel to those of the corresponding biradicals, and it should be possible to interpret their relative rates and regioselectivities on this basis. Such is in fact the case. Use of FO theory in this connection is, therefore, unnecessary, and it also requires a knowledge of orbital coefficients that can be obtained only by using a computer. Furthermore, while the present treatment almost invariably leads to unambiguous and correct predictions of regioselectivity, FO theory not infrequently fails. Indeed, it has been stated to do so in all the DA reactions discussed above, except the first, i.e., that of **11** with **12**; see the cited references. Since the approach suggested here is both simpler and apparently more reliable, it should commend itself to organic chemists concerned with practical applications of DA reactions in organic synthesis.

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Registry No. 1, 106-99-0; **2**, 74-85-1; **3**, 107-13-1; **4**, 928-53-0; **5**, 764-42-1; **6**, 922-64-5.

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[48] See: Pitea, D.; Gastaldi, M.; Orsini, F.; Pelizzoni, F.; Mugnoli, A.; Abbondanti, E. *J. Org. Chem.* **1984**, *50*, 1853.

[49] Overman, L. E.; Petty, C. B.; Ban, T.; Huang, G. T. *J. Am. Chem. Soc.* **1983**, *105*, 6335.

[50] (a) Fukui, K.; Yonezawa, T.; Shingu, H. *J. Chem. Phys.* **1952**, *20*, 722. (b) Fleming, I. *Frontier Orbitals and Organic Reactions*; Wiley: New York, 1976.