Mechanism of the Diels–Alder Reaction. Studies of the Addition of Maleic Anhydride to Furan and Methylfurans

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Abstract: Critical analysis of published work shows that there is no evidence that *any* Diels–Alder reaction takes place in a synchronous manner. On the contrary, reactions of unsymmetrical dienes or dienophiles have been shown to take place via very unsymmetrical transition states. There is no evidence that the same is not true for symmetrical reactants. Indeed, all the available evidence can be interpreted in terms of a very unsymmetrical transition state, close to a biradical or zwitterion. This conclusion has now been confirmed by detailed kinetic studies of the (reverse) Diels–Alder reactions of maleic anhydride with furan, 2-methylfuran, and 2,5-dimethylfuran.

The mechanism of the Diels–Alder (DA) reaction has been the subject of controversy during the half century since the reaction was first[2] discovered. While it is now generally agreed that most, if not all, such reactions are concerted[3] in view of the retention of stereochemistry during them, it is still not known whether all, or indeed any, are synchronous,[3] the two new CC bonds having been formed to equal extents in the transition state (TS).

Early discussions had revolved around a choice between a synchronous one-step mechanism, involving a cyclic aromatic TS[4,5] and a two-step or two-stage mechanism, involving an intermediate biradical or zwitterion (see Scheme I). It was assumed that, in the latter case, the first step must be rate determining, because it was taken for granted that such an intermediate would collapse to the product with little or no activation. Since several lines of evidence have shown[6] that *both* new CC bonds are formed to significant extents in the TS, only the first alternative seemed to remain. This conclusion was further strengthened by the work of Woodward and Hoffmann,[7] which has led to the general impression that "allowed" pericyclic reactions are always synchronous in the absence of major steric effects to the contrary. Many organic chemists indeed clearly believe that the synchronicity of DA reactions has been demonstrated unequivocally by experiment. This is by no means the case.

In an earlier communication[8] it was shown that the experimental evidence shows unambiguously that the DA reaction of an unsymmetrical diene or dienophile characteristically takes place via a very unsymmetrical TS. It was also shown that evidence for synchronicity in certain reactions of symmetrical reactants was inconclusive. Indeed, *all* the experimental evidence concerning

Scheme I
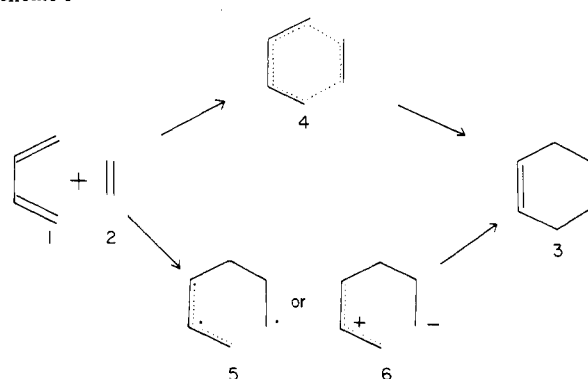
the relative rates and regioselectivity of DA reactions can be interpreted simply and comprehensively in terms of current qualitative MO theory if it is assumed that the TS of such a reaction is very unsymmetrical, one of the new CC bonds having been almost completely formed while the other is very weak. The TS can then be regarded as a weakly perturbed biradical (cf. **5**) or zwitterion (cf. **6**). The clearest evidence to this effect has come from recent studies of intramolecular DA reactions.[9]

Since most DA reactions are almost certainly nonsynchronous and since the course of all such reactions can be interpreted on the assumption of common nonsynchronicity, a basic principle of scientific methodology[10] requires *all* DA reactions to be regarded as nonsynchronous unless and until synchronicity has been demonstrated in at least one case. Since it can be assumed for all practical purposes that all DA reactions are nonsynchronous, the distinction might perhaps seem on the same level as determining how many angels can dance on the head of a pin. However, it does in fact raise several points of theoretical interest.

First, there is its bearing on the general validity of the Woodward–Hoffman rules.[7] If it can be shown that *no* DA reactions are synchronous, it would become evident that the "new principle" behind these rules is not as powerful as has often been assumed. It is indeed sufficiently surprising that minor substitution should lead to a demonstrably very unsymmetrical TS. For example, thermochemical analysis[11] shows that in the DA dimerization of butadiene (**1**) to 4-vinylcyclohexene (**7**), the TS differs in energy from the corresponding biradical (**8**) by ca. 1 kcal/mol, less than the possible errors in the thermochemical data. Indeed, the reaction may well proceed via **8** as a stable intermediate, being

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

(3) The terms concerted, synchronous, etc. are taken here to have the following meanings. A *concerted* reaction is one that takes place in a single kinetic step. A *synchronous* reaction is a concerted reaction in which the various changes in bonding have progressed to similar extents in the transition state. A *two-stage* reaction is one that is concerted but not synchronous, the changes in bonding occurring in two distinct stages, some mainly between the reactants and the transition state, the others mainly between the transition state and products. A *two-step* reaction takes place in two distinct kinetic steps, via a stable intermediate.

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

(5) Dewar, M. J. S. *Angew. Chem.* **1971**, *83*, 859; *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 761.

(6) The most convincing evidence comes from studies of secondary deuterium isotope effects, considered later in this paper, and from negative volumes of activation that are too large to correspond to the formation of one bond only. See: Jenner, G. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 137.

(7) Woodward, R. B.; Hoffmann, R. *Angew. Chem.* **1969**, *81*, 797; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781.

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

(9) (a) Martin, S. F.; Tu, C.-y.; Kimura, M.; Simonsen, S. F. *J. Org. Chem.* **1982**, *47*, 3634. (b) References cited in (a).

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

(11) Doering, W. v. E.; Franck-Neumann, M.; Hasselmann, E.; Kaye, R. L. *J. Am. Chem. Soc.* **1972**, *94*, 3833.
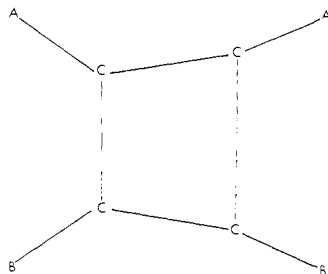
Figure 1.

not only not synchronous but not even concerted. The concomitant formation of 1,2-divinylcyclobutane (9) may well take place via the trans,trans isomer of 8.

Second, if the TS of a symmetrical DA reaction is symmetric, it must be phenomenally polarizable, because even a very minor perturbation of the symmetry is enough to lead to a transition state that is demonstrably unsymmetric. The possibility that transition states may be very polarizable has often been suggested in other connections, though never with any real evidence. The polarizable TS remains an awkward mechanistic skeleton in the cupboard, an ever present possibility which it is often very difficult to eliminate. The DA reaction offers an opportunity to do so in at least one important case.

Third, MINDO/3 calculations[8] for the simplest DA reaction, i.e., 1 + 2 → 3, have predicted it to follow a third mechanism, not previously considered, which seems to fit all the available data, i.e., a modification of the original two-step or two-stage mechanism of Scheme I in which the *second* step or stage is rate determining. The TS for this corresponds to a situation where one of the new CC bonds is almost completely formed while the other is beginning to form. Since the conversion of the intermediate to the product is very exothermic, the TS for this step should lie early in the reaction, corresponding to a situation where the second new CC bond is still very weak. Similar mechanisms have also been predicted for other DA reactions, by MINDO/3[12,13] and MNDO/[13]. Since there are very few cases on record where a new mechanism has been suggested for an old and well-studied reaction solely on the basis of theoretical calculations, it is a matter of some significance to find out whether or not the MINDO/3 mechanism for the DA reaction is correct.

Most of the experimental evidence in this connection has been reviewed in earlier papers.[8-13] As shown there, virtually all of it is consistent with the MINDO/3 mechanism. A new approach to the problem has, however, recently been claimed to demonstrate synchronicity in one particular case[14] and one of the earlier lines of evidence[15,16] also needs further consideration.

Our purpose here is first to show that neither of these investigations provides definite evidence for synchronicity in the reactions studied and second to present new experimental evidence which seems to make it unlikely that *any* DA reaction will ever prove to be synchronous.

Attempts To Demonstrate Synchronicity in DA Reactions

Most attempts to solve the problem outlined above have been based on a procedure first suggested by Dewar[17] and most easily explained by an example.

Consider the DA reactions of butadiene (1) with ethylene (2), a mono-X-substituted ethylene (10), and a corresponding 1,2-di-X-substituted ethylene (11 or 12). Let their rate constants
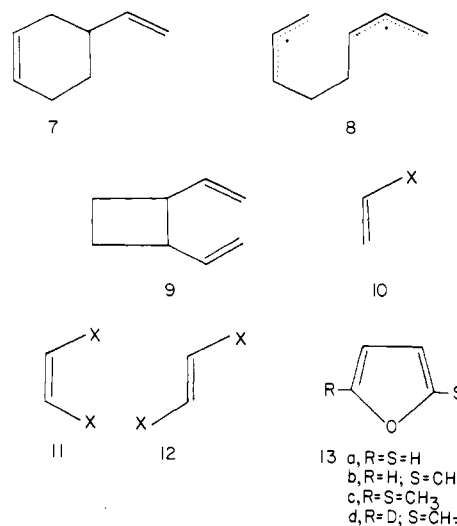
be k_1, k_2, and k_3, respectively. If the reactions are all synchronous, each taking place via a symmetrical TS (cf. 4) in which both new bonds have been formed to equal extents, the stabilizing effects of both groups (X) in the TS from 11 or 12 should be the same, being the same as that of the single substituent in the TS from 10. The ratios of rate constants, k_1/k_2 and k_2/k_3, should then be the same, so that

$$k_2 = (k_1 k_3)^{1/2} \qquad (1)$$

If on the other hand the reaction is of two-step[3] or two-stage[3] type, the rate–determining stage or step involving formation of an intermediate (e.g., 5 or 6) where only one new bond is formed, then one of the groups (X) in the TS from 11 or 12 will have no effect on the stability of the intermediate, because it will be attached to a saturated carbon atom. The rate of attack at the methylene group in 10 will then be the same as at either end of 11 or 12, the intermediate radical being stabilized by X in each case, while the rate of attack at CHX in 10 will be the same as at either end of 2, leading in each case to an unstabilized radical. The overall rate constant for the reaction of 10 (k_2) will then be the arithmetic mean of k_1 and k_3; i.e.,

$$k_2 = (k_1 + k_3)/2 \qquad (2)$$

Finally, if the reactions are concerted but not synchronous, so that both new bonds are present in the TS but one is stronger than the other, the value of k_2 should lie between those given by eq 1 (geometric mean) and 2 (arithmetic mean). The same kind of approach can naturally be used with other symmetric dienes (e.g., furan, 13a) or dienophiles (e.g., maleic anhydride, 14a), and the substituents can be introduced into either reactant.

If the substituents change the rate significantly and if eq 1 holds accurately, the implication will be that all three reactions are synchronous. If the rates follow eq 2, this will show that the reactions cannot all be synchronous, and it will indeed suggest that one at least is not even concerted. It is not necessary that they should all be nonsynchronous for eq 2 to hold. The unsymmetric monosubstituted species (e.g., 10) may alone react via an unsymmetrical TS. This, in principle, can happen if the (symmetrical) TS from 2 is easily polarized by the substituent in 10. If the rates follow a pattern intermediate between the extremes of eq 1 and 2, this will show that the two new bonds are formed to significant but unequal extents, at least in the TS from 10.

The conclusions reached by Dewar in his original paper[17] were vitiated by a numerical error.[8] When properly applied,[8] the available rate data for the reactions of 1 with substituted ethylenes, e.g., the cyanoethylenes 10, 11, and 12 (X = CN), show unambiguously that the TS for the unsymmetrically substituted species, at least, must be very unsymmetrical. Thus acrylonitrile (10, X = CN) reacts with 1 about 50 000 times faster than 2, whereas both maleonitrile (11, X = CN) and fumaronitrile (12, X = CN) react only about 10 times faster than 10. However, as indicated

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

(13) Dewar, M. J. S.; Pierini, A., *J. Am. Chem. Soc.*, submitted for publication.

(14) Tolbert, L. M.; Ali, M. B. *J. Am. Chem. Soc.* 1981, *103*, 2104.

(15) Taagepera, M.; Thornton, E. R. *J. Am. Chem. Soc.* 1972, *94*, 1168, and references cited there.

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

(17) Dewar, M. J. S. *Tetrahedron Lett.* 1959, *4*, 16.

(18) Dewar, M. J. S.; Olivella, S. *J. Am. Chem. Soc.* 1978, *100*, 5290.

(19) Personal communication from Dr. S. Olivella.

above, this result throws no light on the synchronicity of the reactions of the symmetric species, **2**, **11**, and **12**. It may be that the reactions of symmetrical dienes with symmetrical dienophiles are synchronous but involve highly polarizable transition states, even a single substituent being able to destroy its symmetry. This difficulty could be met by using a substituent whose effect on an adjacent system is so small that it could not realistically be expected to bring about massive changes in the structure of a TS. If such a substituent still led to results following eq 3, this would provide strong evidence that all DA transition states are unsymmetrical.

Two such lines have been tried.

One[14] of these was based on an ingenious use of induced optical activity. The DA adducts from 1,3-diphenylisobenzofuran (**15**)

R—CC—O—O—CO—S
14 a, R=S=H
b, R=H; S=D
c, R=S=D

15

COOmenthyl
ROOC
16 a, R=CH₃
b, R = menthyl

17
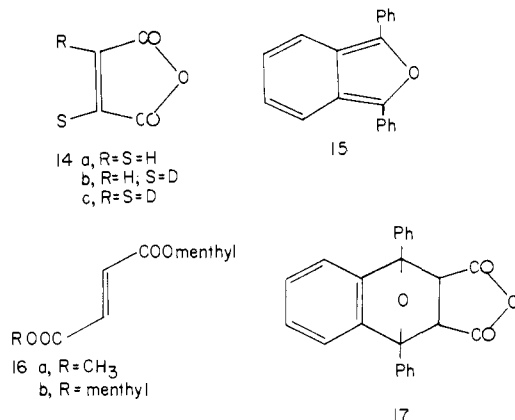
and dimenthyl or methyl menthyl fumarate (**16**) gave on hydrolysis optically active acids **17**, the optical activity arising from steric interactions between the phenyl and chiral (menthyloxy)carbonyl groups in the TS. The observed activities in the products were claimed[14] to show that the steric effects in the TS at both ends of the diene system are equal, which in turn was taken as evidence that the forming CC bonds in the TS are equal in length.

The last step in the argument is, however, invalidated by an oversight.

The steric interaction between groups attached to two adjacent carbon atoms depends not only on the length of the CC bond between them but also on the relevant bond angles, which depend on the states of hybridization of the carbon atoms. The situation is illustrated diagrammatically in Figure 1. The groups A and B are the same distance apart in both cases in spite of the fact that the CC bond lengths are very different. When the bond is long, the hybridization of the carbon atoms is near to sp² and their geometries are nearly planar, whereas when the bond is nearly formed, their hybridization is close to sp³ and their geometries nearly tetrahedral. During the DA reaction of **15** with **16**, the carbon atoms forming the new bonds change from planar to tetrahedral geometry. Consequently the steric interactions between groups attached to them may be equal in the TS even though the lengths of the forming bonds are different. Therefore even if Tolbert and Ali[14] were right in concluding that the steric effects in question are equal, this does not give any definite indication of the relative lengths of the CC bonds in the TS.

The second line of evidence[15,16] was based on the use of secondary deuterium isotope effects, combined with a currently accepted interpretation of their relationship to the making or breaking of adjacent bonds. Since the arguments used here are of general applicability, the problem will be discussed in some detail.

When a CC bond is formed or broken, the carbon atoms normally change their hybridization. Since the vibration frequency of a CH bond depends on the hybridization of the carbon AO used to form it, increasing with the s character of that AO, the vibration frequencies of CH bonds adjacent to the carbon atoms at the end of a breaking or forming CC bond change as the bond is broken or formed. Since the vibration frequencies of CD bonds are less than those of CH bonds, their zero point energies are less and so

also the changes in them due to changes in hybridization of carbon. Replacement by deuterium of a hydrogen atom at the end of a breaking CC bond then leads to a change in rate. The magnitude of such a secondary deuterium isotope effect will depend on the change in hybridization of the relevant carbon atom on passing from the reactant to the TS. Deuteration of the dienophile, or of the diene at a terminal carbon atom, should then lead to a change of rate, the magnitude of which will depend on the degree to which the adjacent carbon atoms have changed their hybridization (initially sp²) in the TS. If the reaction is synchronous, the rates of reaction should then follow eq 1. Conversely, if the bonds are formed one at a time, if formation of the first bond is rate determining, and if the carbon atoms at the ends of the other forming CC bond retain sp² hybridization in the TS, the rates will follow eq 2. Since deuterium does not alter the internal energy of a molecule, it is inconceivable that it should alter the structure of the TS significantly.

Two careful studies[15,16] of this kind have been reported for DA reactions. Both, for convenience, referred to the reverse reactions, i.e., dissociation of the DA adduct into diene and dienophile. Taagepera and Thorton[15] measured the rates of the reverse DA conversions of the DA adducts **18** into anthracene (**19**) and

CR₂—CS₂

18, a, R=S=H
b, R=H; S=D
c, R=S=D

19

R₂C=CS₂

20 a, R=S=H
b, R=H; S=D
c, R=S=D

CH₃—CO—O—CO
O

21
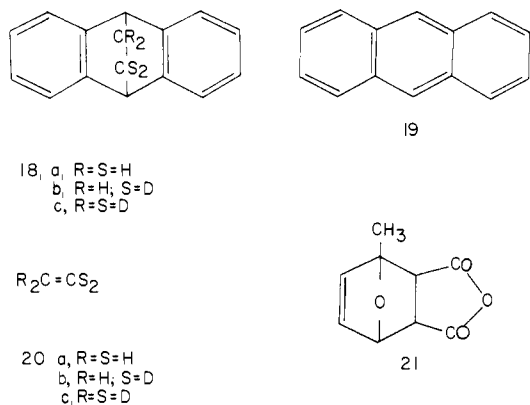
ethylene (**20a**), 1,1-dideuterioethylene (**20b**), or tetradeuterioethylene (**20c**). Seltzer[16] carried out similar measurements for the reverse DA reactions of the adducts (**21**) of maleic anhydride (**14a**) and of its mono- (**14b**) and dideuterio (**14c**) derivatives, with 2-methylfuran (**13b**) and 2-methyl-5-deuteriofuran (**13d**). The measured rates in both cases followed eq 1 more closely than eq 2, implying that the carbon atoms at the ends of the dienophile (**14 or 20a**) are comparably hybridized in the TS. In cases such as this, it has been commonly assumed that there is a one-to-one relationship between the change in hybridization of carbon and the extent to which the CC bond has formed or broken. Taagepera and Thorton[15] and Seltzer[16] claimed on this basis that the reactions they studied were synchronous processes, the lengths of both breaking CC bonds being the same in each TS.

There is, however, no theoretical justification for this last assumption. There is no reason why the hybridization of the carbon atom at the end of a breaking or forming CC bond should be directly related to the strength or length of that bond. There is indeed no reason why the hybridization of the carbon atoms at the two ends of a making or breaking CC bond should even change in unison.

Not only is there no theoretical reason for this assumption; there is clear experimental evidence to the contrary in at least one case,[8] i.e., the addition of methyl radical (**22**) to ethylene (**20a**) to form *n*-propyl radical (**23**). This reaction involves formation of a new

CH₃·

22

CH₃—CH₂—CH₂

23

CH₃—CH₂⁼CH₂

24
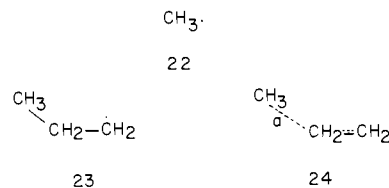
CC bond via a TS of the type indicated in **24**. Attempts have

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been made[9] to determine the structure of the TS by studying the effect of deuteration on its rate. However, while deuterattion of methyl led to a large increase in rate, implying, according to the current interpretation, that the methyl carbon has already adopted a tetrahedral geometry, deuteration of ethylene had little effect, implying that the ethylene moiety is still almost planar. In other words, according to the current interpretation, one piece of evidence indicates the TS to occur early in the reaction, the other late! Clearly there cannot be any fixed relationship between the extent to which a carbon atom has changed its hybridization in the TS of a reaction and the extent to which an adjacent CC bond has been formed or broken.

This conclusion has been confirmed by MINDO/3 calculations[8] which predicted the TS **24** to have a structure entirely consistent with the isotopic evidence. The methyl in it is already almost tetrahedral while the ethylene is still almost planar. The calculated activation energy agreed well with experiment (calcd 7.9, obsd 7.2, 7.9 kcal/mol), and the calculated[9] deuterium isotope effects also closely reproduced those observed. A particularly interesting feature of the calculated TS is the length (2.36 Å) in it of the partially formed CC bond. Clearly it is still very weak, corresponding to an "early" TS, as is also indicated by the near planarity of the adjacent methylene. Yet formation of this long weak bond is enough to make the methyl group adopt a geometry close to that in the final adduct.

It is easy to see why this is so.

A hybrid carbon AO forms much stronger bonds than does a pure 2p AO. Formation of the new CC bond in the reaction of **20a** with **22** should therefore act as a strong driving force for rehybridization of the carbon atoms at the ends of it in the TS. Rehybridization of a carbon atom in **20a** will, however, greatly weaken the adjacent π bond. The ethylenic carbon atom therefore resists changes in hybridization much more strongly than the methyl carbon. Formation of a weak bond between them is consequently sufficient to alter the hybridization and geometry of the methyl carbon greatly while leaving those of the ethylenic carbon little changed.

A similar situation is expected in the DA reaction if the TS is indeed very unsymmetrical (see **25**). The carbon atoms at the
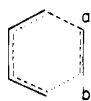
25

ends of the stronger forming bond (a in **25**) will in any case changed their hybridization nearly to sp^3. The structure of the TS will then be close to that of a biradical in which the π bond of the ethylene has almost vanished. One of the corresponding "radical centers" is like an alkyl radical, the other like an allyl radical. Formation of a weak bond between them should then make the former adopt a tetrahedral geometry, as it does for the methyl group in **24**. The allylic carbon atom will, however, resist pyramidalization because this will destroy the π bond between it and its neighbor in the allyl moiety. The effect should of course be less here than in **24** because the π bond in **25** is weaker, but it should still be very significant. One would therefore expect the changes in rate due to replacement of hydrogen atoms in **20** by deuterium to be almost additive, both carbon atoms in it being almost tetrahedral in the TS. The rates of reactions of deuterated ethylenes (**20**) should then follow eq **1** quite closley. One would also expect the isotope effects for substitution in the diene (e.g., **1**) to be very different from those for substitution in the dienophile (e.g., **2**). In the latter, the isotope effect should be relatively large (in the forward DA reaction) if deuterium is attached to the carbon atom at the end of the stronger of the two forming CC bonds (a in **25**) and smaller if it is at the end of the weaker one (b in **25**). Conversely, in the reverse DA reaction, deuterium at the end of bond b (see **25**) in the diene should lead to a larger decrease in the rate than if it is at the end of bond a. Deuteration at either end of the dienophile should lead to small but comparable decreases in the rate of the reverse DA reaction.

The results reported by Taagepera and Thornton[15] follow this pattern. They cannot therefore be taken as evidence for synchronicity. While they show that both the breaking CC bonds are still present to some extent in the TS, they give no indication of the extent to which they have been weakened. One of them could be much weaker than the other. The MINDO/3 calculations[8] for the analogous reverse DA reaction of cyclohexene (**3**) strongly support this possibility. According to MINDO/3, the corresponding forward reaction (**1** + **2** → **3**) is not even concerted, and the TS for the overall reaction is correspondingly unsymmetrical. Yet the isotope effects calculated for the conversion of **3** to **1** + **20** paralleled those observed by Taagepera and Thornton for the analogous reverse DA conversion of **18** to **19** + **20**. The MINDO/3 calculations are moreover supported by the good estimates they gave for both the entropy and the enthalpy of activation.

Similar remarks apply to Seltzer's[16] work on the reverse DA reaction of **21**. Here it was claimed that the effect of deuteration of **14a** followed eq 1 exactly, the ratio of two measured quantities, which we may term A and B, being unity when the results expected from eq 1 and 2 were 1.00 and 1.25, respectively. However, within the error limits quoted, A/B could have had any value between 0.9 and 1.1. Since the errors were moreover *average* deviations, the real value of A/B could have been even greater. Therefore while this work provides good evidence that both the new CC bonds have been formed to significant extents in the TS, it does not lead to any reliable estimate of their relative strengths.

Similar arguments can be used in other cases, leading to an important general conclusion, i.e., that isotope effects cannot in themselves provide any quantitative information concerning the strengths of bonds in transition states. Their numerical values are useful only as a check on theoretical calculations. They cannot in themselves be used to distinguish between possible mechanisms for a reaction solely on the basis of their magnitudes. They are useful in this sense only in conjunction with calculations able to provide reliable estimates for the various alternatives.

A New Attempt To Study Synchronicity in a DA Reaction

The simplest way to find evidence for synchronicity in a DA reaction would be to use the procedure outlined above, with a weakly perturbing substituent that influences the rate by standard substituent effects. Since such effects, in particular ones involving conjugation, are more effective the closer the hybridization of the adjacent atom approaches sp^2, equality of the effects of each substituent in the TS from a symmetrical species (**11** or **12**) and of the single substituent in an analogously monosubstituted TS (**10**) would indicate that both the adjacent carbon atoms have similar hybridization and hence similar geometries, in the TS. This would constitute strong evidence that the TS in question is symmetrical and the reaction consequently synchronous.

We decided to use rigid reactants to avoid possible complications due to the TS adopting an unexpected conformation. Since we intended using the results in conjunction with MINDO/3 or MNDO calculations,[20] it was also desirable that the reacting molecules be small to minimize the cost. Therefore a good choice for the diene seemed to be furan (**13a**) and for the dienophile maleic anhydride (**14a**). Examination of models of the TS for a synchronous DA reaction shows that there are severe steric interactions between the diene (e.g., **13a**) and substituents in the dienophile (e.g., **14a**; see A in Figure 2) whereas a trans substituent in the diene interacts to a much lesser extent with the dienophile (cf. B in Figure 2). To avoid steric effects, which could complicate the interpretation, substituents are best placed in the latter position, and they should of course also be as small as possible. This, together with the requirement that the substituents should have only a small effect on the TS, made methyl an obvious choice. Methyl groups have little effect on the rates of nonionic reactions, except when they exert steric effects. The reactions we chose were accordingly those of **14a** with **13a**, 2-methylfuran (**13b**), and

(20) The calculations are reported in an accompanying paper: Dewar, M. J. S.; Pierini, A. B. *J. Am. Chem. Soc.*, to be published.
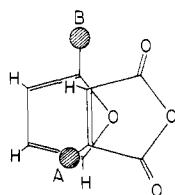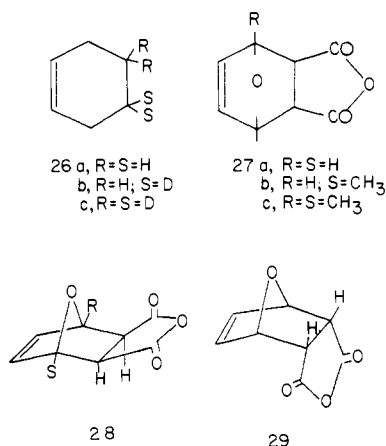
Figure 2.

2,5-dimethylfuran (**13c**), all of which are known to proceed readily to give DA adducts **27**.

26 a, R=S=H
　 b, R=H; S=D
　 c, R=S=D

27 a, R=S=H
　 b, R=H; S=CH₃
　 c, R=S=CH₃

2 8　　　　　　　29

A further advantage of these reactions is that each of them is easily reversed. In very dilute solutions (10^- M) virtually no adduct is present at equilibrium, so the reverse reaction, i.e., decomposition of the adduct into diene and dienophile, is in effect a simple irreversible first-order process. Processes of this kind can be followed accurately and simply by spectrophotometry. The rate constant for the forward reaction can then be found from the rate constant for the reverse reaction in conjunction with the corresponding equilibrium constant, which is also easily measured.

The reaction of **13a** and **14a** has been studied kinetically.[21] The product obtained under preparative conditions was, rather surprisingly, the exo adduct **28a**. It appeared,[11] however, that the initial (kinetically controlled) product is the expected endo isomer **29**, this rearranging to **28a** by fission to **13a** + **14a** and recombination. Since the amounts of endo adducts at equilibrium are small, we were able to avoid complications from this source by studying the reverse DA reactions of the pure exo isomers.

Experimental Section

The DA adducts **28** were prepared by procedures in the literature. The NMR spectra were measured in D₃CCN solution on a Varian EM 390 spectrometer.

7-Oxabicyclo[2.2.1]heptene-*exo*-2,3-dicarboxylic anhydride (27a): mp 124–125 °C (lit.[2] mp 125 °C); NMR 6.5 (m), 5.3 (m), 3.2 (s) ppm.

1-Methyl-7-oxabicyclo[2.2.1]heptene-*exo*-2,3-dicarboxylic anhydride (27b): mp 80–81 °C (lit.[22] mp 80, 84, 75 °C); NMR 1.74 (s), 2.97–3.27 (q), 5.26 (d), 6.26–6.58 (m) ppm.

1,4-Dimethyl-7-oxabicyclo[2.2.1]heptene-*exo*-2,3-dicarboxylic anhydride (27c): mp 75–76 °C (lit.[2] mp 78 °C); NMR 1.65 (s), 3.3 (s), 6.4 (s) ppm.

Maleic anhydride was sublimed before use. Acetonitrile was of spectroscopic grade (Aldrich, Gold Label) and used without further purification. Furan, 2-methylfuran, and 2,5-dimethylfuran were redistilled before use.

Equilibrium constants were determined by NMR spectroscopy, the NMR spectra being measured on a Varian EM 390 spectrometer. Kinetic NMR studies were carried out in a Nicolet NT 200-MHz Fourier transform spectrometer with a thermostated probe, in D₃CCN with Me₄Si as internal standard.

Spectrophotometric measurements were made in acetonitrile solution, using a Beckman DU-2 spectrophotometer with a thermostated cell holder.

(21) Lee, M. W.; Herndon, W. C. *J. Org. Chem.* **1978**, *43*, 518.
(22) (a) Alder, K.; Backendorf, K. H. *Ann. Chem.* **1938**, *67535*, 101. (b) Rinkes, I. J. *Recl. Trav. Chim. Pays-Bays* **1931**, *50*, 1127. (c) Reference 17.

Table I. First-Order Rate Constants ($k_R{}^a$) for Reverse Diels–Alder Reactions

temp, °C	method[b]	28a $10^5 k_R$	28b $10^4 k_R$	28c $10 k_R$
33.2	S			2.49 ± 0.01
39.5	S	2.51 ± 0.02	2.44 ± 0.02	4.49 ± 0.01
49.5	S	8.81 ± 0.09	6.92 ± 0.10	16.4 ± 0.2
49.5	N	5.3	6.1	16.4
58.8	S	27.6 ± 0.5	18.2 ± 0.4	
$\Delta H^\ddagger$ (kcal/mol)		25.0	20.8	20.3
$\Delta S^\ddagger$ (eu)		0.17	−8.59	−2.17
$\Delta E^\ddagger$ (kcal/mol)		25.6	21.5	23.0

^{a} Rate constants in reciprocal seconds with standard deviations. ^{b} S = spectrophotometric; N = NMR. ^{c} Activation energy.

Table II. Equilibrium Constants (K) for Diels–Alder Reactions and Rate Constants for the Forward (k_F) and Reverse (k_R) Reactions[a]

reactants	K, L mol^{-1}	$10^4 k_R$, s^{-1}	$10^4 k_F$, L mol^{-1} s^{-1}
13a + 14a	1.237	0.881	1.09
13b + 14a	0.967	6.92	6.69
13c + 14a	0.683	16.4	11.2

^{a} In acetonitrile at 49.5 °C.

Kinetic Procedures. (a) Spectrophotometric. The absorption cell was filled with acetonitrile and brought to the operating temperature. An acetonitrile solution of known concentration (ca. 10^{-3} M) of the adduct **28** was prepared at −30 °C and allowed to warm to room temperature. Sufficient solution was then added to the absorption cell to give a final concentration in the range 3–5 × 10^{-5} M. The reactions were followed by the increase in absorbance at 211 nm where only the products absorbed significantly.

(b) NMR. A stock solution of the adduct in acetonitrile (ca. 10^{-2} M) was prepared at −30 °C, and aliquots were poured into NMR tubes, cooled in liquid nitrogen, and sealed. A batch of tubes was heated in a thermostated bath, tubes being removed at intervals for analysis. Initially the tubes were sealed under vacuum. Erratic results were then obtained, leading to rate constants that were too large. This error was tracked down to slow spin equilibration, a problem that often arises in quantitative studies by FT NMR. When the reactions were carried out in the presence of oxygen, reproducible results were obtained.

Results

Table I shows the first-order rate constants (s^{-1}), with standard deviations, for the reverse DA reactions of **27a–c**, each determined spectrophotometrically at three temperatures, together with the derived values for the heats (ΔH^*) and entropies (ΔS^*) of activation. Table I also shows the rate constants found by NMR at 49.5 °C. While the values measured by the two procedures for **27c** agree closely, those for **27b** and **27a** show increasing discrepancies, almost certainly due to errors in the NMR measurements. In order to avoid complications from the reverse (i.e., forward DA) reactions, the measurements were carried out using very dilute solutions where the integrations for single protons were not very accurate. In the case of **27a**, each signal corresponds to two equivalent protons, either a singlet or a multiplet. In **27b** or **27c**, however, the methyl signal appears as a single peak, corresponding to three protons in **27b** and six in **27c**. Similar comments apply to the spectra of the products, except that the proton signal for **14a** is a singlet corresponding to two protons.

Table II shows the equilibrium constants measured at 49.5 °C by NMR for more concentrated (0.1–0.2 M) solutions in acetonitrile-d_3. Equilibrium was approached from both sides with concordant results. Table II also shows second-order rate constants for the (forward) DA reactions, calculated from the equilibrium constants together with the (spectrometric) first-order rate constants for the reverse reactions. Equilibrium constants were not measured at other temperatures because, for the present purpose, comparative rates for the forward reactions were needed only at one temperature and because the results for the reverse reactions were sufficient to define the enthalpies and entropies of the transition states.

Table III. Comparison of Rate Constants for DA Reactions
of 13b and 14a with Arithmetic and Geometric Means of Values
for Reactions of 13a or 13c with 14a

direction	$k(13)^a$	$^{1/2}[k(8) + k(14)]^a$	$[k(8)k(14)]^{1/2}$ ^{a}
forward	6.69	6.15	3.49
reverse	6.92	8.64	3.80

^{a} Rate constants ($\times 10^4$) from Table II.

No kinetic studies seem to have been reported for the DA reactions of 14a with 13b or 13c. Rate and equilibrium constants have been reported by Lee and Herndon[21] for the DA reaction between 13a and 14a in acetonitrile at 40.0 °C. Their value for the reverse reaction (4.4×10^{-6} s^{-1}) is much less than ours. The difference between their value for the equilibrium constant (0.265 L mol^{-1}) and ours at 49.5 °C is also clearly too large to be due to the difference in temperature. Lee and Herndon followed the reactions by NMR so the discrepancies may be due to the problems that can arise in NMR analysis (see Experimental Section). Our spectrophotometric measurements seem free from any possible ambiguity.

Discussion

It is immediately obvious from the rate constants for the forward (k_F) and reverse (k_R) reactions in Table II that introduction of the first methyl substituent into 13a, forming 13b, has a much larger effect on the rate than introduction of the second, to form 13c. This is shown quantitatively by the comparisons in Table III of k_F and k_R for 13b with the arithmetic and geometric means of the corresponding values for 13a and 13c. It is evident that the measured values are much closer to the arithmetic means than to the geometric means, implying (see eq 1 and 2) that the TS for the reaction of the unsymmetric diene 13b, at least, is unsymmetrical. Note that the relationship to the two means is somewhat different for the forward and reverse reactions. This can be attributed to small residual steric effects involving the methyl substituents. These will retard the reaction of 13c with 14a but not that of 13b with 14a, provided that the TS is unsymmetrical, with methyl attached to the longer of the two forming CC bonds. This difficulty does not, however, arise in the reverse reactions where the steric effects in the two steps are similar. The comparison (Table III) of the rates of the reverse reactions is therefore valid in any case, so the conclusion, that the TS for the reaction of 13b with 14a must be very unsymmetrical, still stands.

Introduction of the first methyl group into 13a to form 13b leads to an increase in rate of only a factor of 6.14 for the DA reaction with 14a. It is very difficult to believe that so small a perturbation could significantly alter the geometry of the TS. There are certainly no analogies for any such effect. Our results therefore seem to imply rather strongly that the transition states for the reactions of the symmetric dienes, 13a and 13c, are also very unsymmetric.

To put this in perspective, let us compare the asymmetry of rates for the DA reactions of 14a with 13a, 13b, and 13c with those of 1 with 2, acrylonitrile (10, X = CN), and maleonitrile (11, X = CN). In the former series, the accelerations brought about by the first and second substituents are by factors of 6.14 and 1.67, respectively. The corresponding changes in the free

energy of activation (ΔG) are 1.17 and 0.33 kcal/mol, the ratio between them being 3.5:1. The analogous ratio for the latter series, calculated from data in ref 8, is 4.7:1. If the transition states for the symmetrical reactions (13a or 13c with 14a; 2 or 11 (X = CN) with 1) are symmetrical, the perturbation of the symmetrical TS brought about by methyl in the former must then be about two-thirds that brought about by CN in the latter. However, while introduction of methyl increases the rate of the reaction between 13a and 14a only sixfold, the increase due to CN on passing from 2 to 10 (X = CN) is by a factor of 50 000. It seems very unlikely that substituents differing so much in activity could have such similar effects on the structures of the transition states of two such closely related reactions.

Conclusions

(1) The analysis given here, together with that in an earlier paper,[8] shows that there is at present no definite evidence that any DA reaction is synchronous. All the available data can be explained in terms of very unsymmetrical transition states where one of the forming CC bonds is short and strong, the other long and weak.

(2) The evidence shows unambiguously that the transition states for DA reactions of certain unsymmetrical dienophiles are very unsymmetrical. The work reported here shows the same to be true in a case where the disruption of symmetry is due only to the introduction of a single very weak substituent. This implies that DA reactions can be synchronous only if they involve reactants with almost complete twofold symmetry. Whether or not the TS for such a reaction is or is not symmetrical is of no chemical significance. For practical purposes it should therefore in any case be assumed that *all* DA reactions proceed via very unsymmetrical transition states. All the available evidence concerning the course of such reactions, in particular their regioselectivity, can be explained in this way.

(3) The general acceptance by organic chemists of synchronous mechanisms for DA reactions has undoubtedly been due to the Woodward–Hoffmann theory of pericyclic reactions[7] and to the arguments given earlier by Evans[4,5] concerning the possible aromaticity of synchronous pericyclic transition states. The use of the terms "allowed" and "forbidden" in this context has proved particularly unfortunate because it has led to a general belief that sterically feasible "allowed" pericyclic reactions are necessarily synchronous. Work in these laboratories, discussed in accompanying papers, suggests that this belief is unfounded. There is an additional factor controlling the mechanisms of reactions that makes synchronous two-bond[23] processes unfavorable.

(23) A two-bond reaction is one where two bonds are formed and/or two broken.