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THE DIRADICAL MECHANISM FOR 1,3-DIPOLAR CYCLOADDITIONS AND RELATED THERMAL PERICYCLIC REACTIONS

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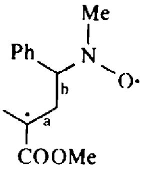
Abstract—A critical comparison is given of the diradical and concerted mechanisms for 1,3-dipolar cycloadditions, with references also to the Diels–Alder reaction and Cope rearrangement. The experimental facts for the field as a whole favor the diradical mechanism. Among the topics considered are stereospecificity, solvent effects, energetics, periselectivity, substituent effects, acetylenic dipolarophiles, U-shaped Hammett plots, orientation, steric effects, partial charges, conformation and scission of diradicals, hydrogen transfer in extended diradicals and cycloadditions of fluorinated olefins.

The question of concertedness in thermal pericyclic reactions has remained of intense interest for decades. The reason is that a definitive choice between the two chief contending mechanisms, stepwise-diradical and concerted, cannot be made despite the existence of a vast quantity of experimental and theoretical data. One characteristic of this class of reactions, which is here meant especially to include 1,3-dipolar cycloadditions, the Diels–Alder reaction and the Cope–Claisen rearrangements, is the small influence of solvent polarity on the rate, which makes other mechanisms involving ions or zwitterions unlikely. The appearance of the Woodward–Hoffmann rules[1] has further sharpened the issue, because these reactions are all symmetry-allowed to be concerted.

The question can be expressed for a typical 1,3-dipolar cycloaddition in Eqns (1) and (2), whose reaction coordinates (R.C.'s) are sketched beneath.

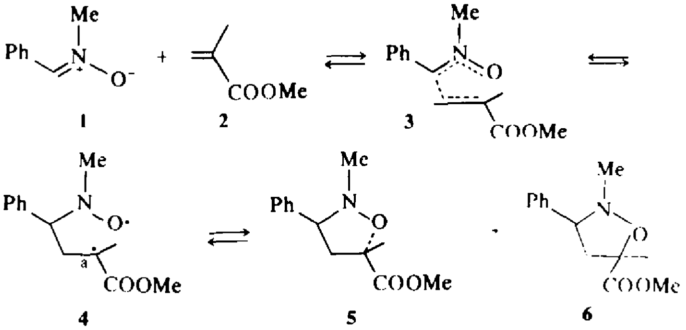
Diradical **4** is spin-paired, and so all species in Eqn (1) are singlet, with transition state (T.S.) **3** rate-determining in path A. Path B on R.C. (1) denotes the possibility that the diradical can arise not only in the cyclo form **4**, but also in an extended form such as **8**, whose energy is presumably the same as that of **4**, but which cannot cyclize easily to product **6**. Extended forms play an important role in diradical theory.



8

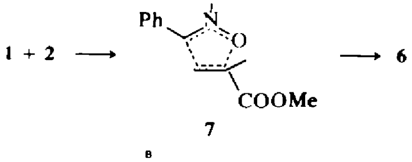
The concerted pathway, in contrast, traverses but one

Diradical:[2-4]



(1)

Concerted:[5-7]



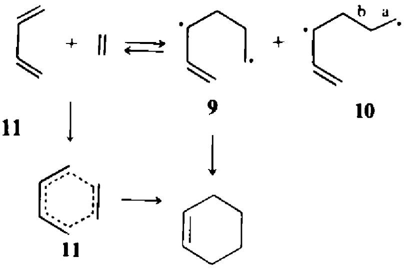
(2)

T.S., 7, in which both new bonds are forming simultaneously, though not necessarily to the same extent.

Similar considerations obtain for the Diels–Alder reaction, Eqn (3).

Diradical: via 9

Concerted: via 11



9 10 11

Diradical 9 is the cyclo form which can cyclize easily (path A), and 10 is an extended form which cannot (path B).

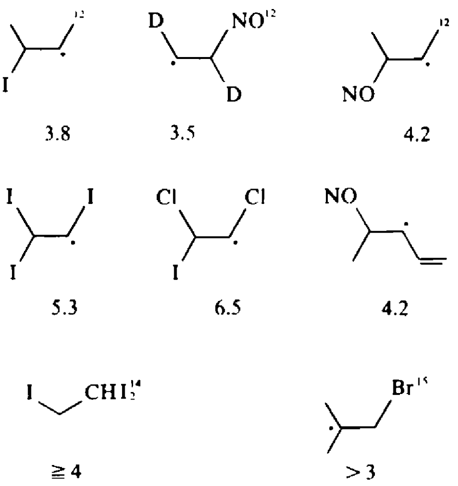
It is important to recognize that the T.S. comes early on the R.C. for the concerted reaction (2) since the overall reaction is exothermic, but late on the R.C. for Eqn (1), i.e. close to the diradical, whose formation is endothermic.[8]

Both 1,3-dipolar cycloadditions and Diels–Alder reactions are usually exothermic because the products possess two more σ-bonds than the reactants, at the cost of two π-bonds which are generally weaker. An important difference between transition states 3 and 7 is that, although in both of them two π-bonds are being sacrificed (raising the energy), 3 derives the benefit of forming only one new σ-bond (lowering the energy), while 7 has two new σ-bonds forming. The implication is that Eqn (2) should have a lower activation energy than Eqn (1).[9] To put it another way, 'a chemical reaction will proceed the more readily, the more *bonding* may be maintained throughout the transformation'.[1] It is principally for this reason that most authorities maintain that symmetry-allowed thermal pericyclic reactions are generally concerted. Nevertheless, it should be borne in mind that the orbital symmetry rules are *permissive* but not *obligatory*.

It is the purpose of this article to present the evidence favoring the diradical mechanism. This theory dates back to 1936[10] for the Diels–Alder reaction, and to 1968[2] for 1,3-dipolar cycloadditions. The latter will be the principal subject, with some allusions to the former, on the assumption that these two very similar reactions have fundamentally the same mechanism.

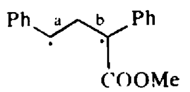
Stereospecificity. In all known examples of 1,3-dipolar cycloadditions to olefinic dipolarophiles bearing substituents at both ends, the *cis* or *trans* stereochemistry of the dipolarophile is maintained in the product within experimental error.[7] Thus for example, maleic acid derivatives always give cycloadducts in which the carboxy groups are *cis*, and fumaric acid derivatives give *trans* products. This fact obviously fits the concerted mechanism which indeed *requires* 100% stereospecificity. Can it also be reconciled with a diradical such as 4, in which rotation of the radical center derived from the dipolarophile (bond a) might bring about crossover between *cis* and *trans*?

If 4 is an intermediate, rotation of bond a must be slower than cyclization to 6 by about 2.4 kcal/mol in $\Delta G^{\neq}$, since few cycloadditions are done with a mass balance of >98%.[7a] Small radicals such as $RCH_2\cdot$ rotate with barriers much less than 2.4,[11] but steric and ponderal effects in encumbered diradicals such as 4 that are typical of 1,3-dipolar cycloadditions would be expected to give them barriers greater than 2.4. Thus the following rotation barriers for moderately encumbered free radicals have been reported (in kcal/mol):



It is unlikely that many of these radicals owe their high rotational barriers to bridging, especially in view of the fact that in the last example, the bromine and the odd-electron orbital are not eclipsed, but are at an angle of 75–80°.[16]

Another example of rotation at a radical center slowed by a ponderal effect is 12, in which rotation at bond a is 10× faster than at bond b.[17] Rotation of 1,4-diradicals is



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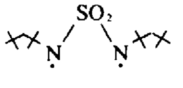


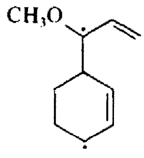
12a

slowed in large steps as progressively more massive rotors are added.[18a] Diradical **12a** forms reversibly at ≦80°[18b] but rotation occurs only at >110°.[18c]

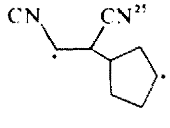
These data must be coupled with the fact that the competing process, cyclization of 4 to 6, is the strain-free intramolecular counterpart of free radical recombination, a process whose activation energy (Ea) typically is zero. Thus Ea = 0 for combination[19,20] of $CH_3\cdot$, Et·, i-Pr·, t-Bu·, $CF_3\cdot$, $CCl_3\cdot$, $Me_3Si\cdot$, allyl·, methallyl·,[21] crotyl·,[21] $Me_2N\cdot$[22] and $Et_2N\cdot$.[22] The list includes allylically stabilized, electronegative and moderately encumbered radicals. The intramolecular nature of radical combination in 4 means that it will go even faster than the many recombinations cited above.[23] Consequently there should be no problem maintaining stereospecificity during cyclization of 4 to 6.

It has been claimed that the diradical mechanism becomes concerted if the energy-R.C. profile contains no discrete dip for the diradical.[7] This argument is false, however; even with Ea = 0 for 4→6, which endows diradical 4 with an exceedingly short lifetime, the two mechanisms in Eqn (1) and (2) do not merge. This is because the two transition states 3 and 7 for the rate-determining steps remain quite different, and therefore predictions based on the two mechanisms, which for the most part rely on the properties of **3** and **7**, also remain different; cf. Ref. 2, footnote 11. The irreconcilability of **3** and **7** rests not only on the number of new bonds being formed, but also on the fact that **3**, unlike **7**, does not possess a continuous cyclic array of delocalized electrons, and therefore cannot be described as concerted in the Woodward–Hoffmann sense, no matter how little time elapses before the second bond begins to form.

Another test is to look at the cyclization/rotation ratios of diradicals prepared by other methods. A ratio of 50 or greater for strain-free cyclization is needed to sustain Eqn (1) in light of the observed stereospecificity of typical 1,3-dipolar cycloadditions. There are numerous examples in the literature of *bona fide* diradicals which meet this test. A few are given below, with the observed ratios of cyclization to rotation.



11.6



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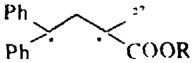
11



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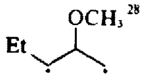
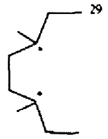


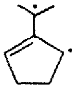
"stereospecific"



>50

All these diradicals cyclize to strained products, and it is reasonable to suppose that a portion of this strain is present in the transition states for cyclization. If this portion amounts to only 1.4 kcal/mol in each case—a conservative figure—then the cyclization/rotation ratios given above must be multiplied by ten to obtain the ratios for strain-free cyclization, pushing them well above the required ratio of 50.

Another way to look at rotation vs cyclization of diradicals is to examine cycloadditions to known singlet diradicals. Adducts **14** from **13** form with these stereospecificities: fumaric ester, >99.9%; maleic ester, >83%; fumaronitrile, >98%.[30] Naphthalene-1,8-diyl **15** accepts *cis* and *trans* dichlorobutene with almost 100% stereospecificity.[31]



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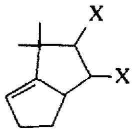

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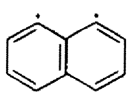

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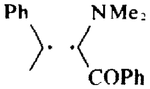
It is thus apparent that stereospecificity in cyclization of diradicals such as **4** is anticipated, and that this phenomenon therefore cannot be used to discredit the diradical mechanism.

Even free radical *pairs*, not connected by any bonds at all, often combine faster than they rotate. The following radicals combine within the solvent cage with 71–99% retention of optical activity:[32]

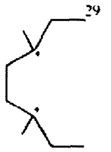


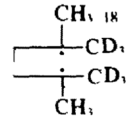
Both Stevens and Wittig rearrangements, for which the radical pair mechanism is well established, commonly exhibit 93–99% retention.[33]

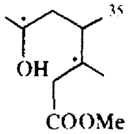
Another aspect of stereochemistry deals with extended diradicals such as **8** and **10**. Since they cannot cyclize easily, they might undergo bond rotation at bond b to cyclo diradicals. But if this happens, rotation at bond a could also happen, giving rise eventually to products with imperfect stereospecificity. It is therefore necessary to postulate that extended diradicals cleave back to reactants faster than single bonds within them can rotate. Thus cyclo and extended diradicals cannot equilibrate directly, but only via the reactants.

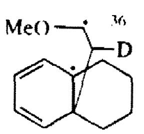
While it may seem difficult to believe that single bonds can break faster than they rotate, both theoretical and experimental studies show that it is possible, and indeed expected, for **8** and **10**. The following discussion deals only with 1,4-diradicals like **10** because examples are plentiful, but applies equally well to the electronically equivalent **8**.

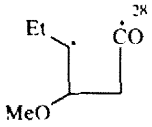
Calculations[34] indicate that 1,4-diradicals should cleave to olefins with near-zero activation energy. Below are examples from the literature of 1,4-diradicals, prepared in a variety of ways, whose cleavege/rotation ratios are very high, greater than required for compliance with the diradical mechanism for cycloadditions.



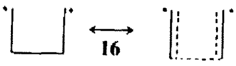








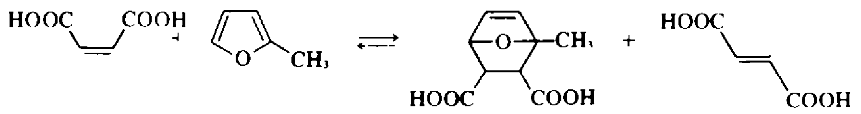
An interesting aspect of the stereospecificity issue is the possibility that through-bond coupling of cyclo and extended 1,4-diradicals might stiffen the 1,2- and 3,4-bonds as represented by the resonance hybrid **16**. Such resonance would of course improve the stereospecificity of diradical cycloadditions. Whether the two radical sites in spin-paired 1,4-diradicals actually interact in this way



16

is still an open question, but there is some theoretical support for the concept.[37]

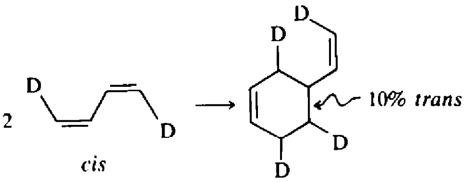
Finally, it is no longer necessary to reconcile the diradical mechanism with 100% stereospecificity, because this time-honored rule is now riddled with exceptions in the Diels–Alder reaction. There are several examples of loss of diene stereochemistry during Diels–Alder reactions under conditions where they would not isomerize by solely thermal means.[38] In the reversible cycloaddition of maleic acid to 2-methylfuran (Eqn (4)),



(4)

about one in every thousand encounters results in isomerization of maleic to fumaric acid.[39] Trivial mechanisms, such as intervention of ionic or free radical intermediates, were carefully excluded.[40] Although this could be viewed as a competition between a principally concerted and a minor diradical pathway,[40] it could also go entirely through diradicals, with rotation much slower than cyclization or cleavage.

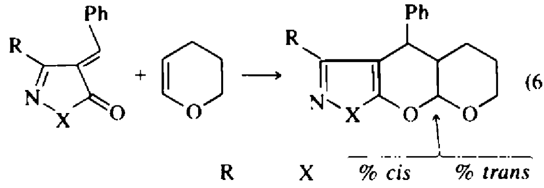
The dimerization of butadiene, a classic Diels–Alder, occurs with 10% loss of stereospecificity in the dienophile component (Eqn 5).[41]



(5)

Hexachlorocyclopentadiene, tetrachlorofuran and other highly substituted cyclopentadienes react under typical Diels–Alder conditions with trans-dichloroethylene, fumaronitrile, dimethyl fumarate and many other dienophiles with great loss of stereospecificity.[42] In the reactions between 2,4-hexadiene and butadiene with 1,1,2,2- and 1,2,1,2-dichlorodifluoroethylene, the (2 + 4) products were formed with imperfect stereospecificity in both the diene *and* dienophile components.[43] In this as well as earlier articles, it was concluded that the (2 + 4) cycloadducts must arise, at least in part, from diradical intermediates.[43]

The heterodiene cycloadditions of Eqn (6) occur with appreciable loss of *cis*-stereospecificity even though the dienophile is cyclic.[44]



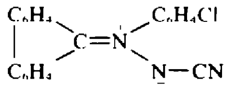
(6)

R	X	% *cis*	% *trans*
CH_3	NPh	65	2
Ph	O	54	6

These experimental facts prove that, for the Diels–Alder reaction at least, the rule of invariable 100% stereospecificity, which is required by the concerted mechanism, does not hold. Two principal mechanistic possibilities are allowed: either the diradical mechanism is the correct one, with rotation in the intermediate occasionally observable, or else both diradical and concerted mechanisms sometimes occur simultaneously in competition. This is a vital question to which we shall return.

Entropy of activation. Extended diradicals such as **8** and **10** make their existence known in a variety of ways. One of these is hydrogen transfer (*vide infra*), and another is in their effect on the entropy of activation. Typically, $\Delta S^{\ddagger}$ is about −30 e.u. for 1,3-dipolar cycloadditions,[5] and similar for Diels–Alder reactions.[45] Since the majority of collisions produce extended diradicals, which include all shapes that cannot close to product without significant bond rotation, and since extended diradicals can only revert to reactants under normal circumstances, low entropies of activation are naturally to be expected for the diradical mechanism. Of course, the concerted mechanism also predicts low $\Delta S^{\ddagger}$. Therefore this phenomenon fits both mechanisms and cannot be used to distinguish between them.

Solvent effects. The effect of polarity on the rates of 1,3-dipolar cycloadditions, the Diels–Alder reaction[45] and the Cope rearrangement is nil or almost nil.[5] Both mechanisms predict this result for the latter two reactions, but not for the first. Typical 1,3-dipoles have dipole moments ranging from 1.42 D for diphenyldiazomethane to 6.7 D for the azomethine imine **17**.[5] In a concerted T.S., the formal charges of the 1,3-dipole are disappearing, which means that rates should generally show an inverse dependence on solvent polarity, small with the less polar 1,3-dipoles, and large with those such as **17**. Yet most 1,3-dipolar cycloadditions show no solvent effect at all, and even the addition of **17** to dimethyl acetylene dicarboxylate diminishes in rate only sixfold as the solvent is changed from benzene to DMF.[5]



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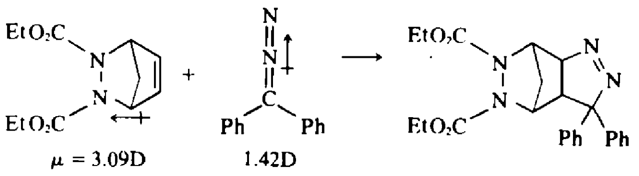
One answer to this problem has been to declare that the concerted T.S. is not far beyond just an orientation complex of the reactants, in which covalent bonding has hardly begun[5,6] (this belief is also required for the application of PMO to orientation; *vide infra*); an early T.S. is certainly expected for an exothermic reaction.[8] Another has been to apply the Kirkwood equation in the form (7),[5] which gives the dipole moment the T.S. must

$$\frac{\mu^2\ \text{1,3-dipole}}{\text{MV 1,3-dipole}} + \frac{\mu^2\ \text{dipolarophile}}{\text{MV dipolarophile}} = \frac{\mu^2\ \text{T.S.}}{\text{MV T.S.}} \qquad (7)$$

possess in order to account for zero solvent dependence (for approximation, the molecular weight is used instead of the molar volume MV). For Eqn (8) this turns out to be 4.6 D, and for (9), 2.16 D; both reactions show no solvent dependence. Estimates close to the required dipole moments were made for both cases, which amounted to approximately the sums of the two partners' dipole moments.[5]

Unfortunately, account was not taken of the relative positions in space necessarily assumed by the reaction partners for concerted cycloaddition. When this is done, even assuming no covalent interaction whatsoever in the T.S., the T.S. for (8) acquires a dipole moment of only *ca.* 3.4 D, and that for (9), 1.6 D.[2] These are far below those required for zero solvent dependence, and would be still lower if covalent interaction were allowed. Thus, in no way can the facts of low solvent dependence on rate be reconciled with the concerted mechanism. Furthermore, the assumption of the orientation-complex model for the T.S. leads into other difficulties with pre-



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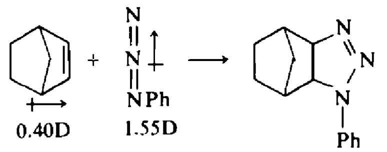
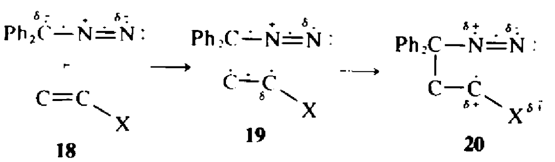


(9)

reaction electrostatic interactions, which will be discussed under Orientation.

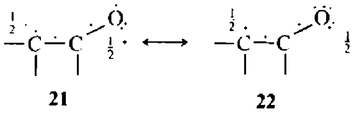
The diradical mechanism, in contrast, correctly predicts low solvent dependence.[2] Compare the three entities, **18**, **19** and **20**, which succeed each other as the reaction coordinate is traversed from reactants **18** to diradical **20**.

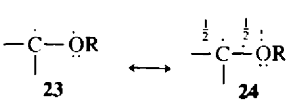


Since the T.S. for the endothermic formation of **20** comes presumably after the midpoint of the R.C. (**19**), it will resemble both **19** and **20**. All structures are drawn as Linnett forms[3,46,47] rather than the equivalent valence-bond resonance hybrids because they depict more simply the distribution of partial formal charges.

Clearly, in going from **18** to **19**, there will be no change in the demand for solvation, since the number and magnitude of partial formal charges does not change. In **20** there is an apparent diminution in charge separation, but when it is recognized that stabilization of the radical center by the substituent X also involves separation of charge,[47,48] it is seen that the solvation requirements of both **20** and the T.S. are approximately the same. This leads to the prediction of little or no solvent dependence for the diradical mechanism, in accord with observation.

Charge separation during radical stabilization comes about in this way. The principal canonical forms of a radical next to an electron-withdrawing group such as carbonyl are **21** ↔ **22**. Since oxygen is more electronegative than carbon, **22** will be the chief contributor to the resonanace hybrid. A radical next to an electron-releasing group looks like **23** ↔ **24**.





Electronegativity favors **23**, but **24** has more bonding electrons, so that both forms will contribute. Thus delocalization of a radical into carbonyl, cyano, nitro and the like imposes a partial positive charge on the radical center, and delocalization into amino, alkoxy, etc. imposes a partial negative charge.[4,48]

Energy of activation. The fact that only one new bond is forming in transition state **3** for the diradical mechanism, while two new bonds are forming in the concerted T.S. **7**, coupled with the requirement that both **3** and **7** sacrifice the same two π-bonds, leads to the prediction that the stepwise mechanism should have a significantly higher activation energy than the concerted one.[3,6,9] The difference ought to be an appreciable fraction of a single bond, whose energies are typically *ca.* 80 kcal/mol. Since a stepwise-diradical mechanism is always possible for any thermal pericyclic reaction, whether symmetry-allowed or forbidden,[1] the difference in energy between **3** and **7** is tantamount to the energy price for 'forbiddenness' that an otherwise symmetry-allowed reaction would have to pay. Although Woodward and Hoffmann refused to assign a number to forbiddenness, others have done so, and the majority of both experimental and theoretical estimates are in the range of 12–18 kcal/mole,[49] with some as high as 30.[50]

If, then, we could calculate what the Ea's should be for both Eqns (1) and (2), they should differ by 12–18 kcal/mol, and furthermore one of them should coincide, within the uncertainty of the calculation, with the experimental value. To calculate the Ea for Eqn (2) is very difficult, but it is possible to estimate the Ea for Eqn (1) by simply obtaining the difference between the energies of the bonds broken and those made.[6]

In order to avoid dealing with partial bonds, a simplifying assumption must be made, i.e. that the T.S. for Eqn (1) occurs late enough on the R.C. so that the total bond energy of the T.S. is about the same as that of the diradical **4**, which has no bonds of order less than unity. Another 1 kcal/mol is then added on in recognition of the fact that the T.S. is slightly higher in energy than the diradical. Thus the problem boils down to calculating the loss in bond energy incurred in forming the diradical **4** from the reactants **1** and **2**, making allowance for gains and losses of various sorts of stabilization energy (S.E.).

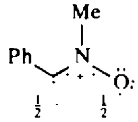
Such a calculation was first made by Huisgen[6] in an attempt to disprove the diradical mechanism. His analysis, given below in Table 1, reaches the conclusion that cycloaddition of **1** and **2** to form **6** requires a loss of 54 kcal/mol in bond energy, for an estimated Ea of 55; yet the experimental $\Delta H^{\neq}$ is only 15.7.[5] Thus the T.S. **3** stands 39 kcal/mol higher on the energy scale than the experimental T.S. In accord with the previous discussion, this was said to show that diradical intermediates would have unreasonably high energies be-

Table 1

Loss		Gain	
C=C → C–C	65	C–C	83
C=N → C–N	68	Dirad. res. E	24
PhC=C conjugation E	4		—
Nitrone resonance	20		107 kcal/mol
C=C–C=O conj. E	4		
	—		
	161 kcal/mol		

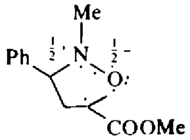
cause their formation requires the sacrifice of an excessive amount of π-bond energy. A more recent calculation found a deficit of 57 kcal/mol in bond energy.[7]

This calculation, however, is erroneous because it postulates the entire loss of the C=N π-bond, when actually only half of it is lost in the formation of **4**.[3] This becomes clear when **1** and **4** are rewritten as Linnett structures.



1

6 distant pairs



4

5 distant pairs

When the C=N loss of 68 is cut in half, the discrepancy of 39 kcal/mol is all but wiped out. The full Linnett analysis of this reaction is given in Table 2. Space limitations preclude giving here the methods of gauging energies of conjugation, electron correlation, L-strain and radical stabilization; consult Ref. 3 for complete details.

The loss in bond energy comes to 15 kcal/mol, and therefore the estimated Ea is 16, which equals the experimental value. Of course, the exact coincidence of calculated and experimental Ea's is fortuitous, since the method is too crude to give answers to within 1 kcal/mol; but it is clear that the diradical mechanism is energetically about right.

Application of this method to ten different cases gave the results in Table 3.[3] All but two are good to within 5 kcal/mol, and the average deviation is 4. Thus for a wide variety of 1,3-dipoles and dipolarophiles, the diradical mechanism predicts a reasonably correct activation energy. Objections to the Linnett analysis have been raised.[7] They are dealt with in the Appendix.

It is much easier to show that the companion reactions, Diels–Alder and Cope rearrangement, exhibit the right activation requirements for the diradical mechanism. The Diels–Alder calculation for the dimerization of butadiene is slightly updated from the 1970 one[3] (Table 4), and the Cope example, rearrangement of 1,5-hexadiene, is done similarly (Table 5).

The estimated Ea's are both very close to experiment, and if anything on the low side, showing that for these reactions as well as 1,3-dipolar cycloadditions, the observed energetics fit the diradical mechanism. More sophisticated computations for diradical intermediates in the Diels–Alder[54] and Cope reactions[53] come even closer to experiment than the above ones do. MINDO/3 calculations for the Diels–Alder also led to the conclusion that only by uncoupling the bond-forming steps via a two-stage T.S. with a 'biradicaloid' intermediate could the high activation requirements be accounted for;[55] of course, a diradical by any other name.....

Table 2

Loss		Gain	
C=C → C–C	63	C–C	83
$C\dot{-}N$ → C–N	34	$\dot{C}$–C=O S.E.	11
Conj. E	8	L-strain	5
Electron correl.	4		—
L-strain	5		99
	—		
	114		

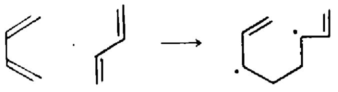
Table 3.

	Est. Ea	Exp. $\Delta H^{\neq}$
Eqn (1)	16	15.7
Ph_2CN_2 + ethyl acrylate	16	8.0
p + nitrophenyl azide + butyl vinyl ether	18†	16.0
ozone + benzene	15	13.2
phenyl azide + norbornene	15‡	14–15
C-methyl-N-phenylsydnone + MeOOCC≡CCOOMe	12	14.5
17 + ethyl acrylate	16	12.5
Eqn (8)	9	13.0
PhN_3 + MeOOCC≡CCOOMe	12	17.4
p-Cl-PhCNO + HC≡CPh	3	14.4

†Corrected for the inadvertent omission of OC=C conj. E, 5 kcal/mol,[51] from the loss column.

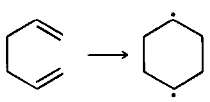
‡Corrected for the inadvertent omission of two Alk-C=C conj. E, 3.2 kcal/mol each,[51] from the loss column; only half is taken since half the radical S.E. was taken. If full conj. E and S.E. are taken, the calculated Ea comes 13 to kcal/mole.

Table 4.



Loss		Gain	
s-*trans* butadiene → s-*cis*	2	C–C	83
2 C=C → C–C	126	2R $\dot{w}$ S.E.	34
2 C=C–C=C S.E.	10[52]		—
	—		117
	138		
Bond energy loss	21		
Estimated Ea	22		
Experimental Ea	23.7		

Table 5.



Loss		Gain	
2 C=C→C–C	126	C–C	83
2 Alkyl–C=C S.E.	6[51]	2 $Me_2CH\cdot$ S.E.	19
	132		102
Bond energy loss	30		
Estimated Ea	31		
Exp. Ea	34.3[53]		

What, then, should the Ea be for the concerted mechanism? All are agreed (except Dewar[55]) that a large gap should exist between the two contenders,[3,7,9,49,50] and since diradicals already have the same ΔH_f as the transition states for the above thermal pericyclic reactions, there is no place for concerted T.S.'s on the energy scale but down, close to or below zero. This is not an unreasonable idea when one considers that negative activation energies—here meant in the sense not of a negative temperature coefficient of the rate, but rather of the T.S. being more stable than the reactants—are not uncommon. Examples are hydrogen-bonded species such as HF_2^-, trihalide ions (previously referred to as frozen transition states),[56] and most relevant to the present argument, benzene. The imaginary symmetrical Cope rearrangement of cyclohexatriene has benzene for its T.S.; i.e. when six π-electrons are somehow prevented from interacting, and then the restraint is removed, the energy of the system goes down by 36 kcal/mol.[57] This represents the aromaticity acquired by (imaginary) non-conjugated cyclohexatriene when six electrons are delocalized, with no change in the number of bonding electrons. Similarly, the T.S.'s of symmetry-allowed cyclic transformations are also aromatic[1,58] by virtue of delocalizing the proper number of electrons, and it matters little whether pi or sigma electrons are used.[59] Table 6 depicts four important reactions that have this in common: if concerted, their T.S.'s delocalize six electrons with no change in the number of bonding electrons. Since strain is insignificant in all cases, there is no reason why the question marks should not be negative numbers. In fact, the difference between −36 kcal/mol and the experimental numbers might well be named the 'credibility gap' for the concerted mechanism. These gaps are very large. For the diradical mechanism, in contrast, there are no gaps at all. The question of why a low-Ea pathway should be avoided in favor of one with higher Ea will be taken up at the end of the paper.

Periselectivity. This question is related to that of aromatic vs non-aromatic transition states. If a suprafacial reaction with a 6-electron T.S. is symmetry-allowed, then suprafacial reactions of the same sort having 4- or 8-electron T.S.'s are symmetry-forbidden, and with a forbidden-allowed energy difference of 12–18 kcal/mol, they ***should not be observable at all*** under conditions where the allowed ones occur. Thus we should not see 1,5- or 1,1-dipolar cycloadditions if 1,3-dipolar ones are possible, and we should not see (2+2) or (2+6) cycloadditions where normal (2+4) Diels–Alder reactions are possible.

By and large, periselectivity is observed. However, there are important exceptions. Compound **25** adds to dimethyl acetylenedicarboxylate (DMAD) as a 1,5-dipole[62]—a symmetry-forbidden cycloaddition—despite its ability to act as a 1,3-dipole as well. There is no reason to doubt that it adds suprafacially.

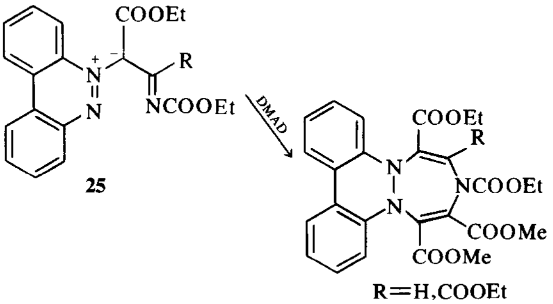
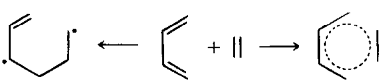
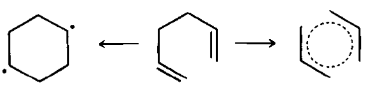
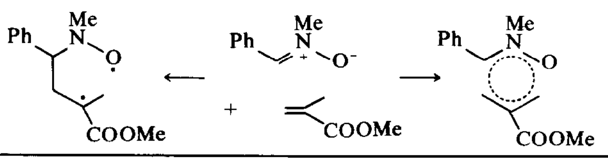
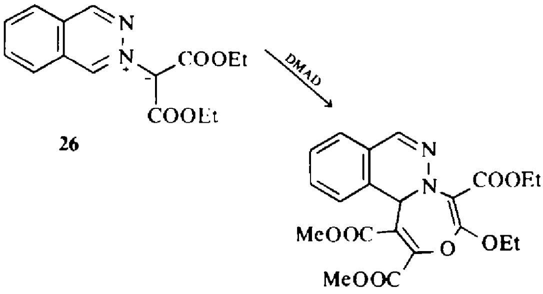


Table 6. Concerted vs diradical activation barriers for thermal pericyclic reactions

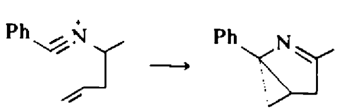
$\Delta H^{\neq}$ Calc.	$\Delta H^{\neq}$ Exp.		$\Delta H^{\neq}$ Calc.	$\Delta H^{\neq}$ Exp.
			−36	−36
+28[60]	+28[61]		?	+28
+34[53]	+34[53]		?	+34
+16[3]	+16[5]		?	+16

Another 1,5-dipolar cycloaddition is **26** with DMAD.[63]



26

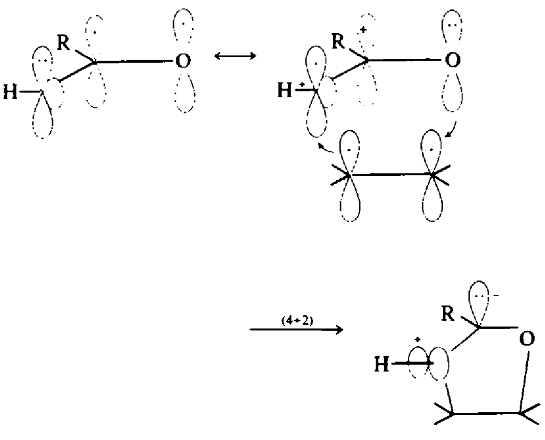
1,1-dipolar cycloadditions also occur, e.g. Eqn (10).[64]



(10)

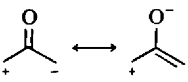
Many more examples are known.[65,66] This is not a concerted antarafacial cycloaddition.[65]

Ketocarbenes are sometimes classed as 1,3-dipoles,[67] and they undergo cycloadditions with dipolarophiles in the usual manner.[67,68] Yet these reactions are symmetry-forbidden because they are (2+2) cycloadditions. Concerted cycloaddition of ketocarbenes in a (4+2) manner is impossible because the products **27** would possess an orthogonal double bond in the 5-membered ring.



27

Cyclopropanones in their ring-opened form look like 1,3-dipoles but they too are actually 2π-electron species. Like allyl cation,[69] they may undergo symmetry-allowed

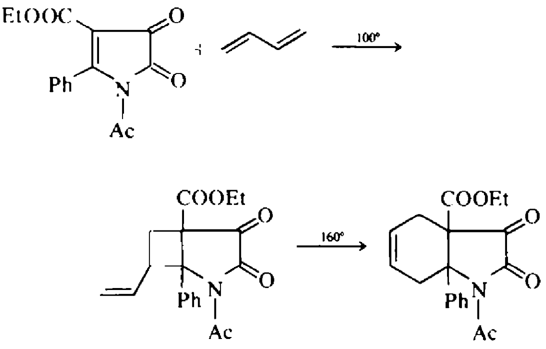


cycloaddition with dienes only in the 1,4 sense,[70] and they usually do cycloadd in this manner.[71] Yet, like ketocarbenes, they frequently add in the forbidden 1,2 sense also.[72]

The Diels–Alder field is rife with exceptions to periselectivity. Ethylene and butadiene give cyclohexene and vinylcyclobutane in 5000:1 ratio.[73] Acrylonitrile and butadiene give 0.5% of (2+2) product.[74] Butadiene dimer contains 2–8% divinylcyclobutane.[41,75] Butadiene with α-acetoxyacrylonitrile gives (2+2) and (2+4) products in 0.16 ratio, which varies but little with solvent or temperature, indicating a 2-step Diels–Alder with a common intermediate, since the Ea's for both the forbidden and allowed products are the same.[76] Likewise, chloroprene dimerizes to both (2+2) and (2+4) products with the same Ea for both.[75,77]

Many halogenated olefins give (2+2) and (2+4) cycloadducts with dienes,[78] often under circumstances where *at least a portion* of the (2+4) product must come from a diradical.[43,79] For example, butadiene and tetrafluoroethylene combine in both modes; of the normal Diels–Alder product at least 2/13 or >15% arises from a diradical.[79c] Very reactive dienophiles such as benzyne,[80] TCNE,[81] azodicarboxylic ester,[82] bis-trifluoromethyl ketene,[83] singlet oxygen,[84] diphenylketene,[85] ketene, N,N-dimethylketeneammonium ion and chlorosulfonyl isocyanate give mixtures of (2+2) and (2+4) cycloadducts, often with high stereospecificity.[86a]

A recent report describes a case in which the kinetic product **28a** is the forbidden one, and only after thermal equilibration is the symmetry-allowed product **28b** formed.[86b]



28a **28b**

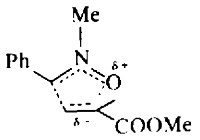
Symmetry-forbidden products larger than (2+4) are also common. Nitrosobenzene is normally a well-behaved dienophile but (2+2) and (2+6) cycloadditions are not unusual with it.[87] Benzyne and cycloheptatrienone form a (2+6) cycloadduct in low yield.[80b] N-substituted azepines form not only (2+6) but also (6+6) cycloadducts.[87d,88a,b] Even an (8+8) cycloaddition has been reported.[88c] In the dimerization of methyl butadienes, the similarity of activation parameters for 4-, 6- and 8-membered ring products led the authors to postulate diradical intermediates for all of them.[89]

In all the foregoing examples, symmetry-forbidden products are forming, presumably via diradicals, in the very same vessel as symmetry-allowed ones. Sometimes coincidence of activation energies and solvent effects for the two products have been demonstrated. In view of the 12–18 kcal/mole difference in Ea between the two pathways that is expected,[49] is it possible to believe that any concerted component can coexist with the diradical one?

Structure of the dipolarophile. An ethylenic dipolarophile loses its double bond during the course of a cycloaddition. If the double bond is conjugated with anything, the conjugation energy is lost also. If there is a diradical intermediate such as **4**, this loss is more than compensated by the gain in S.E. resulting from the interaction of the radical with the conjugating group, because substituents in general, whether electron-withdrawing or donating, interact with radicals more than they do with double bonds. Thus conjugating substituents on the dipolarophile ought to accelerate cycloadditions by the diradical mechanism.

The opposite is true for a simple concerted mechanism. To whatever extent the double bond is dissolved in the T.S., loss of ground-state conjugation energy ought to slow down the reaction: *cf.* 7.

The experimental fact is that conjugating substituents on dipolarophiles and dienophiles accelerate cycloadditions, and the stronger the conjugation, the greater the acceleration.[5] This fits the diradical mechanism, but not the simple concerted one. In order to make it fit, the principle 'concerted but not synchronous' has been adopted.[5] This means that in place of equally advanced formation of both new bonds as in 7, one of the new bonds is more advanced than the other, as in **29**.



29

The unequal progress of bond formation in the T.S. leads to partial charges, which can be stabilized by substituents. Another way of looking at T.S.'s like **29** is to say that interaction of atoms and groups with the aromatic delocalized sextet of electrons lowers the energy by distorting the sextet, just as conjugating substituents on benzene rings do, or hetero atoms in the ring itself, e.g. pyridine.

The concept of concerted but not synchronous has been accepted for years. However, recent ab initio MO calculations for concerted cycloaddition of fulminic acid to acetylene find *no requirement for non-synchrony.*[90] The ratio of lengths of the new C–C and C–O bonds in the T.S. is 1.104, and in the product 1.043, which is only 5% less. Since the theoretical barrier height, 30.4 kcal/mole, is probably close to twice the true one, the imposition of extra non-synchrony would only raise the barrier still higher. Thus in the absence of substituents there is no reason to postulate a distorted aromatic sextet in a concerted T.S.

More recently[7] Huisgen has espoused PMO theory to explain rates and orientation, in place of the older concerted-but-not-synchronous principle. In my opinion, this is a modernization but not a departure from the older principle.

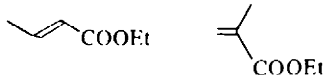
Disubstituted dipolarophiles. In a concerted T.S., substituents at both sites on the dipolarophile can interact with the pi-cloud. The addition of substituents to the synchronous concerted T.S. of Ref. 90 should have approximately the same effect at either end of the dipolarophile. Therefore, the sequence CH_2=CH_2, CH_2=CHX, XCH=CHX should react with any given 1,3-dipole at geometrically increasing rates, in the absence of large steric effects.[6,91] Since steric interactions in the T.S. are now regarded as generally small,[92] this prediction should be generally obeyed. Furthermore, 1,1-disubstituted olefins should in general react slower than 1,2-disubstituted ones because a steric inhibition on the approach of the 1,3-dipole is avoidable with the latter but not the former.

For the diradical mechanism, predictions are different. Symmetrically disubstituted olefins should react little faster or slower than monosubstituted ones because only one or the other substituent can play a part in stabilizing the diradical. The only effects of the second substituent should be a small steric one, and an electronic effect on the ground-state pi-bond energy of the olefin. Unsymmetrical disubstitution should be more efficacious than symmetrical, because now both groups can stabilize the diradical (assuming no steric interference with coplanarity), while sterically the crowding at one site will not interfere with the approach of the 1,3-dipole because the first bond is formed in the rate-determining step at the uncrowded site; the second bond can tolerate moderate interference since its formation is exothermic, and its intrinsic barrier low. More details on this point will be given under the topic 'Steric effects on orientation'.

The experimental data in this area uniformly favor the diradical mechanism. Toward phenyl azide, the relative reactivities of 1-heptene, ethyl acrylate, diethyl fumarate and diethyl maleate are 1.00, 41.0, 34.9, 1.42.[93] Even with the unlikely assumption that only the carbethoxy group, but not n-pentyl, stabilizes the concerted T.S., a geometric rate progression would be 1.00, 41.0, 1681, 1681.[94] Methacrylic ester (1,1-disubstituted) reacts 2.7× faster than crotonic ester (1,2-disubstituted).

Toward diphenyl nitrile imine, the relative reactivities of the same group are 1.00, 350, 2100, 58.4.[91] The geometric sequence would be 1.00, 350, 122500, 122500. Methacrylic ester reacts 17× faster than crotonic ester.

Toward C-phenyl N-methyl nitrone, the observed relative rates are 1.00, 151, 229, 85.6.[95] The geometric sequence would be 1.00, 151, 22801, 22801. Methacrylic ester reacts 4× faster than crotonic, and furthermore their activation parameters are interesting:



$\Delta H^{\neq}$	17.0	15.7
$\Delta S^{\neq}$	−23.4	−32.4

Methacrylic ester has the lower $\Delta H^{\neq}$, as befits better radical stabilization, and also the lower $\Delta S^{\neq}$, indicating some steric interference with the formation of the second bond and/or an increased proportion of extended diradicals. Were the reactions concerted, $\Delta H^{\neq}$ would be higher for methacrylic ester because bond formation at the crowded site would now perforce occur *during* and not *after* the rate-determining step.

Acetylenic dipolarophiles behave similarly. Toward C-methyl N-phenyl sydnone, relative rates for 1-tetradecyne, methyl propiolate and DMAD are 1.00, 137, 430.[6] Geometrically, they should be 1.00, 137, 18769.

Data such as these are commonplace, not only for 1,3-dipolar cycloadditions, but also for Diels–Alder reactions. Thus, in the addition of isoprene to ethylene, acrolein and maleic anhydride, whose relative rates are 1.00, 61000, 4.33×10^6 but geometrically would be 1.00, 61000, 3.72×10^9, the non-additivity of $\Delta G^{\neq}$ per substituent was taken as evidence for a diradical or very asymmetric-concerted mechanism.[96] Toward cyclopentadiene, relative rates for acrylonitrile, maleonitrile, fumaronitrile and 1,1-dicyanoethylene are 1.00, 87, 78, 43700,[45] showing that 1,1-disubstitution is better than 1,2-disubstitution; similar data exist for 9,10-dimethyl anthracene with the same group.[45] The latter diene also reacts 19× faster with methacrylonitrile than crotononitrile, and 30× faster with methacrylic ester than crotonic ester.[45] Free radicals also prefer 1,1- to 1,2-disubstituted olefins.[20]

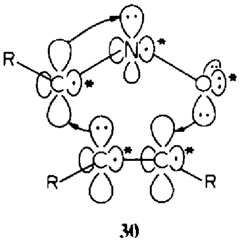
It is a general rule that *trans*-disubstituted olefins cycloadd faster than their *cis* isomers. This has been attributed to eclipsing forces in the concerted T.S.[5] However, it is noteworthy that free radicals consistently add faster to *trans* than *cis* olefins.[97]

Acetylenic dipolarophiles. The π-bond energy of a C=C bond is 63 kcal/mol, but the second π-bond of C≡C is worth only 54.[98] In a concerted cycloaddition, then, an acetylenic dipolarophile pays an energy price 9 kcal/mole less than an ethylenic one. Even a portion of this energy should significantly affect the rate, so that acetylenes should react consistently faster than olefins that have the same substituents.

This is not observed. In general, acetylenic and ethylenic dipolarophiles react at about the same rates, with sometimes one and sometimes the other having the edge. Toward benzonitrile oxide, for example, reactivity ratios are: ethylene/acetylene, 2.5; styrene/phenylacetylene, 10.0; dimethyl fumarate/DMAD, 2.0; methyl acrylate/propiolate, 6.7; 1-hexene/1-hexyne, 4.7; methyl cinnamate/methyl phenylpropiolate, 1.1.[92b] Similar data exist for phenyl azide,[93] diphenyl nitrile imine,[91] C-phenyl N-methyl nitrone,[95] diphenyldiazomethane[99] and munchnones,[100] and also for Diels–Alder reactions with cyclopentadiene and 9,10-dimethyl anthracene.[45] Sometimes the acetylene reacts a bit faster than the olefin, and sometimes slower, but the reactivity ratios are never far from unity.

Should not acetylenes form diradicals faster than olefins? In this case the full 9 kcal/mole difference in π-bond energies will be felt, which at room temperature is worth more than 10^6 in rate. However, acetylenes lead to vinyl radicals, which are destabilized by 10 kcal/mole relative to alkyl radicals.[101,102] Consequently, the diradical prediction is that acetylenes and olefins should react at about the same rates, as they do. In confirmation, it is known that free radicals add at comparable rates to acetylenes and the corresponding olefins.[97a]

Under certain circumstances, there is a second factor which should favor acetylenes.[2] With some 1,3-dipoles, cycloadditions of acetylenes, but not olefins, leads directly to an aromatic product. Among the most familiar 1,3-dipoles these are nitrile oxides, nitrile imines and azides, but *not* diazoalkanes or sydnones (*cf.* Ref. 6). For these 1,3-dipoles, the concerted T.S. for an acetylene would be planar, as in **30**.[2] (The electrons and arrows in **30** are depicted for counting purposes only, and are not meant to imply details of mechanism). The five orbitals marked with asterisks are almost parallel, do not take part in the bonding changes, and contain the six electrons that are to constitute the aromatic sextet in the product. Thus a portion of the aromaticity of the product should be present in the T.S., leading to consistently higher rates with acetylenes. Ab initio calculations for a typical case[90] find that p–π overlap across the long bonds in **30** is *ca.* 17% of that in the product, probably underestimated because $\Delta H^{\neq}$ is undoubtedly overestimated.

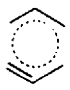


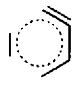
30

This prediction is contrary to fact, and indeed benzonitrile oxide,[92b] as seen above, and also diphenyl nitrile imine[91] consistently react *slower* with acetylenes than olefins; phenyl azide[93] is inconsistent in this respect. Thus the failure of acetylenes to react faster than olefins militates against the concerted mechanism for two reasons with some 1,3-dipoles, and one reason with all the others.

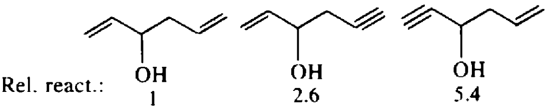
Let it be noted that the correctness of the planar T.S. **30** for a concerted cycloaddition, first postulated in 1968,[2] has been certified by four independent quantum-mechanical calculations,[90,103-105] and the 'two-planes' activated complex[5,6] for cycloadditions of nitrile oxides, diazoalkanes and similar 1,3-dipoles is no longer tenable.

There are other interesting aspects of the acetylene–olefin comparison in thermal pericyclic reactions. Substitution of a triple bond for a double bond in a Cope substrate, or of an ene-yne for a Diels–Alder diene, should lead to a great diminution of the rate because the T.S.'s become highly strained:

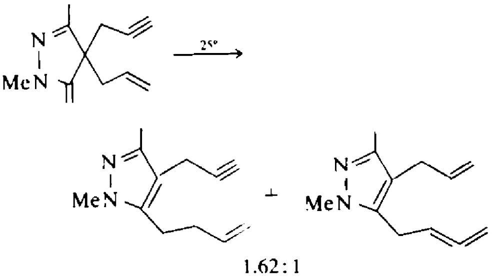




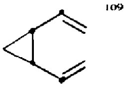
Yet the following data have been reported for Cope rearrangements:[106]



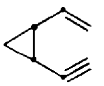
Rearrangement of 1,5-hexadiyne has an Ea of 34.4 kcal/mol,[107] the same as that of 1,5-hexadiene.[53] In the competitive Cope rearrangement of Eqn (11), the preference for olefinic over acetylenic participation is only 1.62.[108] Both **31** and **32** rearrange with the same $\Delta H^{\neq}$, 19.4 kcal/mol, and **33** rearranges at a similar rate.[109]



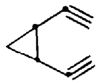
(11)



31 [109b]

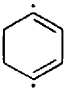


32 [109a]



33 [109c]

Such data are inexplicable on a concerted basis, but agree with a diradical intermediate such as **34**. Calculations for **34** similar to those given above for the Cope



34

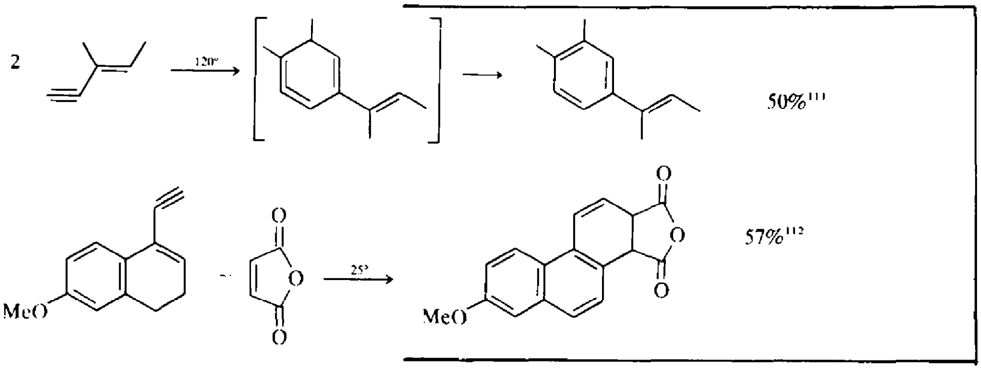
rearrangement lead to an estimated Ea of 26 + X, where X is the strain energy of two vinyl radicals bent to 120° from their preferred angle of *ca.* 150°.[110] This is reasonably close to 34.4 (*cf.* Table 7).

Table 7.

Loss		Gain	
2 C≡C → C=C	108	C-C	83
2 C-C≡C conj. E	4	2 Alkyl-C=C conj E	6
2 C-Ċ=C	2†		—
Strain	X		89
	114 + X		

†C-Ċ=C is *de*stabilized relative to $CH_3\cdot$ by 1 kcal/mol because its C-H BDE is estimated to be 105 on this basis: Et-H, 98; vinyl-H, 108; i-Pr-H, 95;[102] i-propenyl-H, 105.

Diels-Alder reactions one ene-yne systems occur under moderate conditions:



The great strain in the first intermediates would be felt in a concerted T.S. and strongly inhibit or prevent reaction. A diradical intermediate, however, can be formed under normal conditions because the strain is not created until after the rate-determining step. Such reactions are common.[113]

U-shaped Hammett plots. In comparing the effect of substituents on reaction rates, reactions involving ionic intermediates usually give linear Hammett plots because if an electron-releasing substituent stabilizes an ionic center, an electron-withdrawing one will destabilize it, nd vice versa. Radical intermediates, in contrast, are stabilized by both types of substituents, and therefore reactions involving them generally exhibit U-shaped Hammett plots, with hydrogen as the slowest substituent and all others of both types faster.[114]

Curved Hammett plots are usually observed in 1,3-dipolar cycloadditions.[6,7] The data for Eqns (12) and (13) are typical.

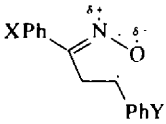
$$\text{p-X-PhCNO} + \text{p-Y-PhCH=CH}_2 \qquad (12)^{115}$$

$$\text{p-X-PhCNO} + \text{p-Y-PhC}\equiv\text{CH} \qquad (13)^{116}$$

	Substituent	NO_2	Cl	H	CH_3	OCH_3
Rel. Rate (X = H)	Y, Eqn (12)†	2.9	1.4	1	1.1	1.1
	Y, Eqn (13)	2.4	1.3	1	1.1	1.3
Rel. Rate (Y = H)	X, Eqn (12)	—	1.5	1	0.78	0.67
	X, Eqn (13)	—	1.5	1	0.84	0.73

†Mesitonitrile oxide in place of PhCNO.

These data are best explained in terms of diradicals **35** and **36**.



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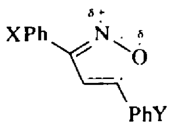
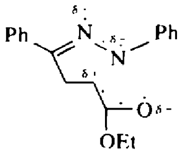


36

Of particular interest is the fact that substituents Y produce a curved Hammett plot, while substituents X produce a linear one. This comes about because Y is coupled to a radical center through a phenyl ring only, which attenuates but does not obliterate its effect; while X is screened from the radical in RCNO· not only by a phenyl ring, but also by two other powerful radical stabilizers, namely a C=N double bond and the unshared electron pair on N, which stabilize the radical as shown in **35** and **36**.[48] As a result, only a small ground-state effect is seen from X.

Other examples of curved substituent plots are numerous.[5,92b] Sometimes these curved plots are tipped, usually toward electron-releasing substituents.[91,92b,117] For instance, diphenyl nitrile imine adds to CH_2=CHX with these relative rates: X = COOEt, 48; n-pentyl, 0.137; OBu, 0.31.[91] It is in fact a general rule that 1,3-dipoles react faster with electron-poor olefins than with electron-rich ones.[118] Only with exceptionally electrophilic 1,3-dipoles such as ozone, carbonyl oxides or *p*-nitrophenyl azide are electron-rich olefins the more reactive kind. The reason for the general rule is apparent from the partial formal charges in diradicals **35** and **36**. Stabilization of the radical center in RCNO· by the unshared electrons on N involves a shift of negative charge onto 0, and this will be the case with all 1,3-dipoles because they all have a hetero central atom. However, the other radical center in the diradical, which arises from the dipolarophile, may have an induced negative *or* positive charge, as in **37** and **38**; *cf.* **22** and **24**.



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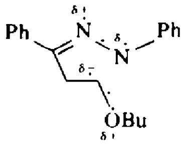
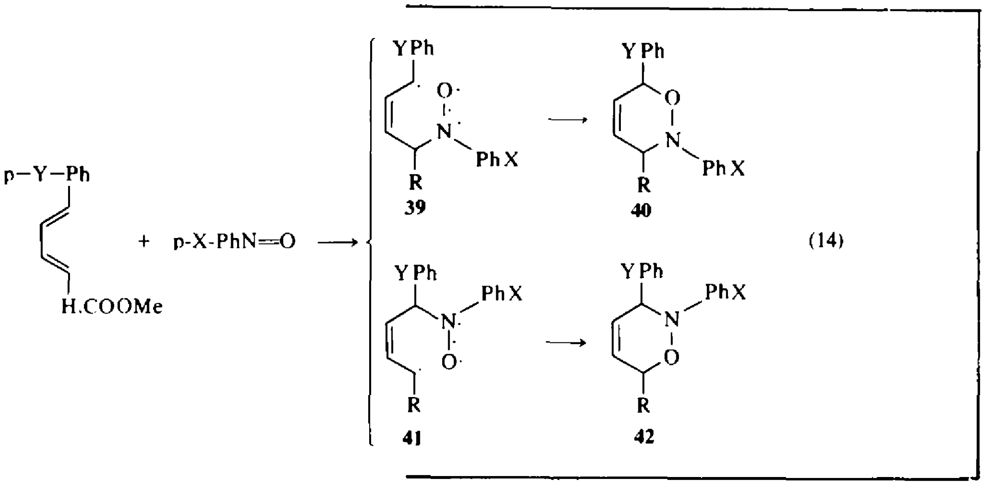


38

The atoms that are to unite in **37** bear unlike charges, and in **38**, like charges. Since the union of radical centers in both diradicals is highly exothermic, probably with Ea = 0, and cyclic to boot, it would be surprising if the difference in the array of charges affected the rates of cyclization of the cyclo forms. However, one would expect a larger proportion of extended diradicals for **38** than for **37**, and thus a slower rate for dipolarophiles bearing electron-releasing, rather than attracting, substituents with 1,3-dipoles in general (with the exceptions noted above).[119]

Diels–Alder reactions can also exhibit U-shaped Hammett plots.[120] In Eqn (14), as in (12) and (13), only substituents Y, not X, give rise to U-shaped plots, and furthermore only with products **40** and not **42**.

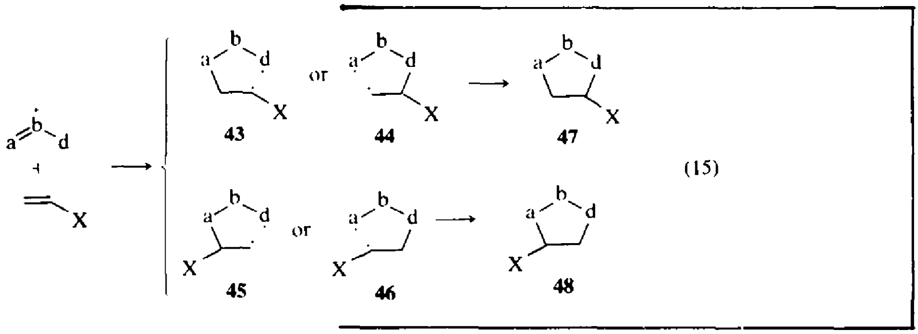


(14)

This rather subtle situation comes to pass in the same way as the results of Eqns (12) and (13). In diradical **39**, but not **41**, a radical center is attached to a Y-substituent phenyl; the other radical center is always insulated from X–Ph as a highly stabilized nitroxide radical.

Orientation. When an unsymmetrical 1,3-dipole reacts with an unsymmetrical dipolarophile, two different regioisomers may be formed. Sometimes only one of them is obtained, but usually both, with one predominating. Patterns of orientation can be discerned over the field as a whole which can be used as indicators of mechanism.

In Eqn (15), the two regioisomers **47** and **48** can be formed from four possible diradicals; **43** and **44** both produce **47**, while **45** and **46** both give **48**.



(15)

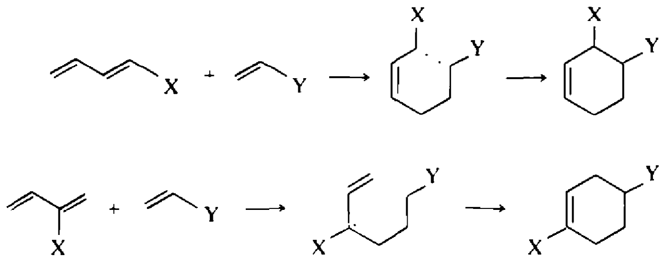
The predominant product will be that which arises from the best of the four diradicals. Clearly, **44** and **45** are inferior to **43** and **46** because the radical center arising from the dipolarophile will be better stabilized by any substituent X than by hydrogen; thus we need consider only **43** and **46**. In order that no ambiguity arise over which substituent in the dipolarophile better stabilizes a radical, the following discussion of orientation will be limited to monosubstituted dipolarophiles.

It is not yet apparent which terminus of the 1,3-dipole better supports a radical center, but for any given 1,3-dipole there should be a consistent preference, regardless of the nature of X. Thus for instance if R–a–b–d· is better than ·a–b–d–R, **47** should be formed rather than **48**, whether X is an electron-releasing or electron-withdrawing group. The preference need not be large, and in fact for most 1,3-dipoles it has been calculated to be small,[3] in accord with the fact that both regioisomers are usually formed. Nevertheless, the diradical mechanism predicts that each specific 1,3-dipole should orient in a unidirectional manner with both electron-rich and electron-poor dipolarophiles.

For the Diels–Alder reaction, unidirectionality is also predicted by the diradical mechanism for all four possible combinations of electron-rich and -poor dienes and dienophiles.[121] Thus in Eqn (16), 1-substituted dienes give ortho in preference to meta orientation, and 2-substituted dienes give para in preference to meta, regardless of the electronic nature of X and Y.

In contrast, it is my contention that the concerted mechanism should give rise to bidirectional orientation, i.e. opposite orientation with electron-rich and electron-poor olefins for each 1,3-dipole. There are two principal reasons, electronic and electrostatic.

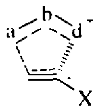
The 'concerted but not synchronous' mechanism[5] has transition states **49** or **50** which, like **29**, have opposite partial charges on the 1,3-dipole and dipolarophile. For

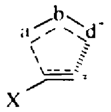


(16)

any given 1,3-dipole one cannot easily predict which sign is preferred in the T.S., but it should be consistent with

49





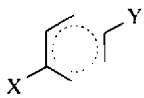
50

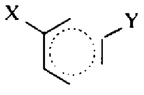
all partners, and the sign of the partial charge on the neighboring carbon atom in the T.S., which comes from the dipolarophile, will consistently tend to be the opposite. However, group X can stabilize either a positive or negative charge, but not both. Therefore, if X stabilizes the partial charge imposed on the dipolarophile by the 1,3-dipole, **49** will be preferred, and if it does not, **50** will be preferred.[121a] The prediction of bidirectionality for the concerted, and unidirectionality for the diradical mechanism, thus arises from the fact that substituents of opposite electronic type stabilize opposite charge types, but both types stabilize radicals.[2,4]

The same argument applies to the the Diels–Alder reaction. In the 'aromatic'[1,58] transition states **51** and **52**, X and Y will tend to stand *para* (or *ortho*) toward each other, giving **51** if they are of opposite types, because as in the benzene analog, they can favorably interact. But **52** will be preferred if both groups are the same because, as in the benzene analog,[122] their mutually inimical interaction is minimized in the *meta* isomer.

The electrostatic argument[4] is based on the dipole-dipole interaction of 1,3-dipole and dipolarophile as they approach the T.S., just before covalent interaction has begun, so that their electronic systems, in particular their dipole moments, are essentially in the ground state. For the concerted mechanism, the two reacting sites of each partner define approximately parallel lines about 2 Å apart in the T.S.[90,104] Therefore one may safely consider the electrostatic situation in as close as 3 Å.[104,123] By the time the reactants have approached this closely there can be no solvent molecules in between, so that the electrostatic energy of this array is given by Eqn (17),[124] in which E is in kcal/mol, μ is in Debye units, and a is the distance of separation in Å. Interaction is favorable when the dipoles line up

51





52

$$E = \pm\frac{14.4\mu_A\mu_B}{a^3} \qquad (17)$$

in antiparallel fashion, and unfavorable when they are parallel. Figure 1 depicts the situation graphically. The orientation of the 1,3-dipole toward electron-rich and -poor olefins must clearly be opposite as they approach the T.S. Here, then, is a second factor making for bidirectionality by the concerted mechanism.

PARALLEL APPROACH OF DIPOLES

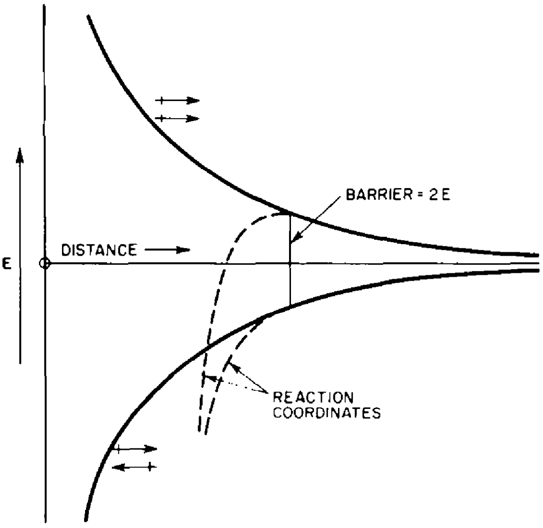
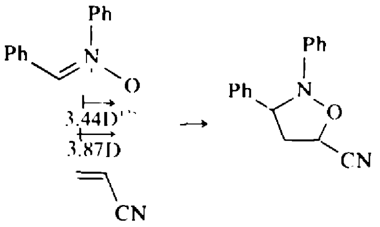


Fig. 1.

Is the electrostatic energy factor significant in magnitude? It is indeed; for Eqn (18) it is commensurate with the total activation energy.



(18)

The reactants in Eqn (18) are intermediate in dipole moments as 1,3-dipoles and dipolarophiles go; regiospecificity is high;[126] and the T.S. arises from the pre-reaction electrostatic complex of higher energy. Thus the reactants must approach along the lower energy path of Fig. 1, but before reacting they somehow climb to the higher energy path, acquiring 2E of Eqn (17), which at 3 Å amounts to *ca.* 14 kcal/mol.[4] Typical Ea's for nitrone cycloadditions are 16–18 kcal/mol.[95] It is true that Eqn (17) is not accurate at the closer distances, but for an order-of-magnitude computation it is satisfactory. Of course this argument does not prove that Eqn (18), and the numerous other examples to follow which have the 'wrong' array of dipoles, do not proceed concertedly, since it is possible that some factor in the T.S. favors the observed orientation by an amount even greater than the electrostatic one, which after all ceases to operate once covalent binding has begun. Indeed, HOMO-LUMO interactions have been proposed as being capable of overcoming the pre-reaction electrostatic factor.[123] What the above argument does is place a minimum value on the required energy difference between the more and less favorable HOMO-LUMO interactions. Since these interactions are based on the *ground states* of the 1,3-dipole and dipolarophile, 14 kcal/mol seems like a rather large figure to assign to their interactions at all, let alone the differences among them. In this connection, the earliness of the T.S. along the R.C. for a concerted cycloaddition should be remembered.[5,6,8,123]

Does not the electrostatic factor operate for diradicals too? It does not, for two reasons. The first is that, even in the T.S. such as **3** for a cyclo diradical, the two pre-radical sites do not have to be within bonding distance yet, as they do in the concerted T.S. **7**, and so they may not be required to relinquish solvation fully. The second and more compelling reason is that the rate-determining step is endothermic with consequently a late T.S. on the R.C.;[8] in fact, since reversion of the diradical to the reactants is, as we have seen, an almost unactivated process, microscopic reversibility requires us to place the T.S. almost all the down the R.C. to the diradical. Therefore, electrostatic interactions between the reactants will have virtually no effect on the structure of the T.S.

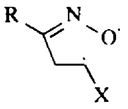
Patterns of orientation. Given below, in condensed form, is a summary of the observed orientations of the most well-studied 1,3-dipoles with carbon–carbon dipolarophiles substituted on only one side, so that there can be no doubt as to the best radical site from the dipolarophile. From this, the preferred radical sites of the 1,3-dipoles can be inferred, and subsequently they will be rationalized on the basis of bond energies and charge distribution. Only the major products are given, and the dashed lines show how they were formed. Frequently the other regioisomer was also found. Reactions in which pronounced steric effects operate are deferred to a later section of the paper.

There is a strong tendency toward unidirectionality of orientation with both electron-rich and -poor dipolarophiles for all the 1,3-dipoles listed except azides. This fact supports the diradical mechanism, and contradicts the concerted one. There are exceptions to the best-diradical pattern, but they are few.

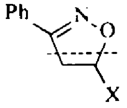
Nitrile oxides react via diradicals like **53**. Both types of olefins orient alike. A vast amount of data is summarized.[127]

Nitrile imines are similarly unidirectional, giving diradicals **54** analogous in structure to **53**.[127]

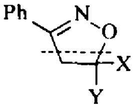
Diazoalkanes give diradicals of type **55** with both types



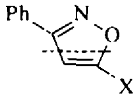
53



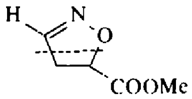
X = Ph, CN, COOEt, CH_3,
n-Alkyl, OAc, OR,
$CH{=}CH_2NMe_2$, PO_3Me_2,
$C{\equiv}CSiMe_3$

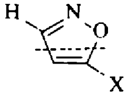


X = Y = CH_3, OEt

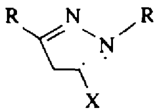


X = Ph, OMe, OEt,
COOMe





X = Ph, COOMe,
CH_2OH, CMe_2OH



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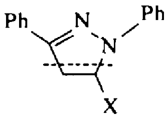
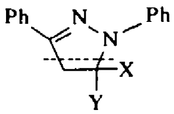
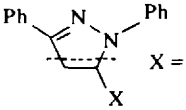


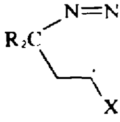
X = COOR, Ph, CN, Alkyl, NR_2,
OR, $C{\equiv}CSiMe_3$, PO_3Me_2, vinyl



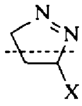
X = Y = CH_3, Ph, OEt
X = CH_3; Y = COOMe, OEt



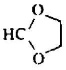
X = Ph, COOMe, $CH(OPr)_2$, *p*-PhY where Y = NMe_2, OMe, NO_2



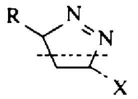
55



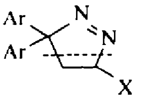
X = COOR, CHO, Ac, Ph, m-O_2NPh, p-MeOPh, vinyl,
$C{\equiv}CH$, $^+PPh_3Br^-$,



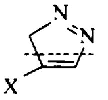
, OEt,[129] SPh,[130] SO_2R[131]



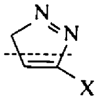
R = Ar, X = Ar
R = X = COOMe
R = CF$_3$, X = CF$_3$, CH$_3$



X = COOMe,
$^{+}$PPh$_3$Br



X = OEt,[133] O-i-Pr,[133]
SOAr,[132] SO$_2$Ar[132]



X = CH$_2$OH, SnEt$_3$,
CHO, CH=CHOMe,
SiMe$_3$, GeMe$_3$, PPh,
POPh$_2$, SnMe$_3$,
AsPh$_2$, PbPh$_3$,[132] SEt

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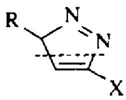
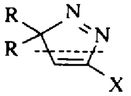
of dipolarophiles; alkoxyacetylenes are an exception, but not ethoxyethylene.[128]

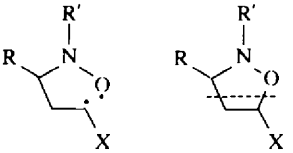
Nitrones are, for the most part, unidirectional via diradicals **56**.[127]



R = vinyl, X = Ac, COPh
R = CF$_3$, X = CF$_3$, Br
R = COOEt, X = CHO

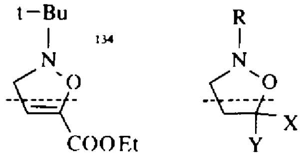


R = Ph, X = CHO, COOMe, CMe=CH$_2$
R = CH$_3$, X = CH=CHOMe



56

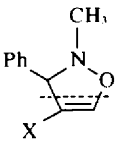
R,R' = Ph, Alkyl;
X = Ph, COOEt, CONH$_2$, CN,
2-Py, PO$_3$Me$_2$, C≡CSiMe$_3$,
CH$_2$OH, Alkyl, OEt, OBu, N-pyrrolidinyl



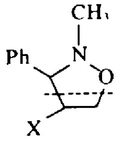
[134]

R = H, X = H, Y = CN, COOMe
R = H, X = CH$_3$, Y = COOMe
R = t-Bu, X = H, Y = NO$_2$,[134] SO$_2$Ph[134]

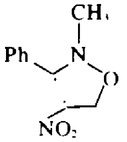
However, there are some exceptions to **56**. Reversal of orientation with acetylenic dipolarophiles is sometimes observed, as recorded here with nitrones and diazomethane, but does not constitute a contradiction to the diradical mechanism; *vide infra*. More difficult to explain are the orientations of C-phenyl N-methyl nitrone with phenyl vinyl sulfone and nitroethylene; these cases are noteworthy because they are predicted from PMO consideration.[134] When the C-phenyl, a radical-stabilizing group, is removed from the nitrone, however, all these exceptional dipolarophiles revert to normal orientation.[134] Thus it may be that, for some unknown reason, nitroethylene more than others induces a switchover to diradical **57**, whose energy is known to be very close that of **56**.



X = COOMe, CN[134]

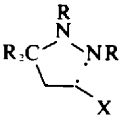


X = NO$_2$, SO$_2$Ph[134]

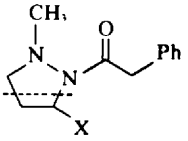


57

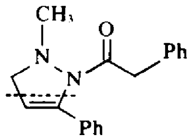
Azomethine imines with weakly substituted carbon orient without exception through diradical **58**.[128] With strongly substituted carbon, i.e. with radical-stabilizing substituents, and with acetylenic dipolarophiles, the same orientation is still found, but some reversals are now seen as they were with nitrones, which may be accounted for by diradical **59**.[128]



58



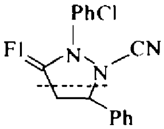
X = Ar, vinyl, COOEt, CN

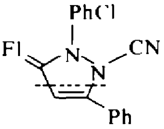


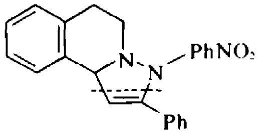
Sydnones are a special type of azomethine imine. They cycoadd via diradical **60**, analogous to **58**, with both types of olefins.[135]

The predominant unidirectionality of orientation of the 1,3-dipoles discussed to this point favors, in my opinion, the diradical mechanism. Were the cycloadditions concerted, for each 1,3-dipole the orientation would be incorrect for dipolarophiles of one or the other polarity. In azides, we now encounter for the first time a 1,3-dipole that orients oppositely with olefins of opposite polarity. Electron-poor dipolarophiles give diradical **61**, and electron-rich ones **62**.[135]

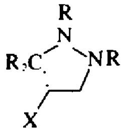
Nevertheless, despite their bidirectionality, azides' orientations do not support the concerted mechanism, at



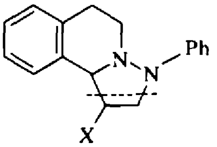




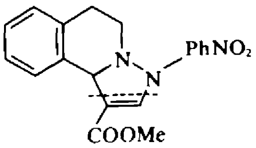
Fl≡9-Fluorenyl

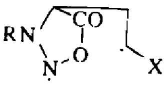


59

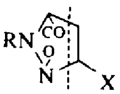


X = Ph, CN

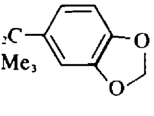




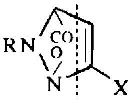
60



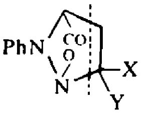
X = Ph, CN, CH_3, H_2C–



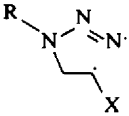
CH_2OAc, $C\equiv CSiMe_3$



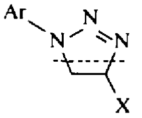
X = Ph, COOMe, CH_2OH



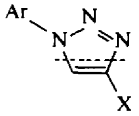
X = Y = CH_3, Ph
X = CH_3, Y = CN



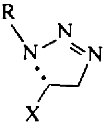
61



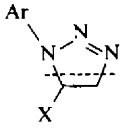
X = COOR, Ac, CN



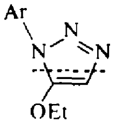
X = COOH, COOMe, CHO

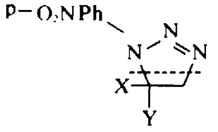


62



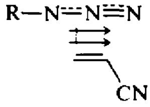
X = Ph, OR

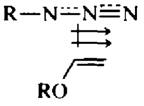




X = OMe, OEt, OBu
Y = H, CH_3, Ph

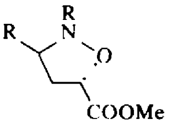
least by the electrostatic criterion. Whereas by this test half the dipolarophiles orient correctly with the other 1,3-dipoles, all of them orient incorrectly with azides, as shown below.



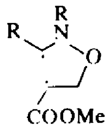


The Diels–Alder reaction, like the majority of 1,3-dipolar cycloadditions, exhibits unidirectionality of orientation. Regardless of whether the diene and dienophile are of the same or opposite charge type, 1- and 2-substituted butadienes give preferentially *ortho*- and *para*-substituted products respectively.[45] It has long been recognized that orientation in Diels–Alder reactions can be explained by diradicals, as in Eqn (16).[121]

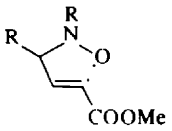
Reversal of orientation with acetylenes. As noted above, acetylenic dipolarophiles frequently give partial or complete reversal of orientation from their ethylenic counterparts. Examples were provided with diazoalkanes, nitrones and azomethine imines; less dramatic cases are known also. Such reversals are fully consonant with diradicals. Consider the four possible diradicals from a nitrone with acrylic vs propiolic ester. If attention is focussed on the olefinic systems of **65** and **66** rather than their radical sites, it will be seen that **66** is a vinyl ether, whose conjugation energy is greater by 2 kcal/mol



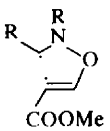
63



64



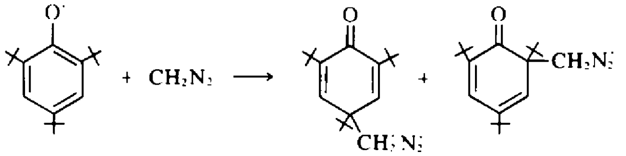
65



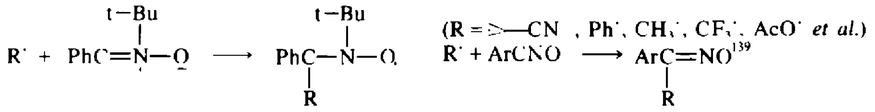
66

than that of the alkyl-substituted olefin in **65**.[51] Furthermore, the difference between **65** and **66** is probably increased by the electron-accepting carbomethoxy group. In contrast, **64** enjoys no comparable advantage over **63**. Thus in this group of diradicals, only **66**, which gives rise to reversed orientation from an acetylene, gains in stability over its regioisomer.

Orientation in the addition of free radicals. The nature of the best diradicals from the various 1,3-dipoles, inferred above from the structure of the cycloadducts, is supported by the addition of free radicals, which add to 1,3-dipoles at the same site that dipolarophiles do. In the examples below, to save space only the first intermediates are shown.



$Ph_3C^{\cdot} + CH_2N_2 \longrightarrow Ph_3CCH_2N_2^{\cdot}$[137]

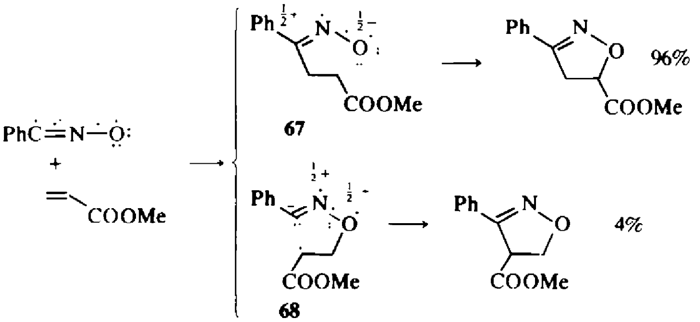


$R^{\cdot} + PhC{=}\overset{t-Bu}{N}{-}O \longrightarrow Ph\underset{R}{C}{-}\overset{t-Bu}{N}{-}O^{\cdot}$

(R = ⊳—CN, Ph·, CH₃·, CF₃·, AcO· *et al.*)

$R^{\cdot} + ArCNO \longrightarrow Ar\underset{R}{C}{=}NO^{\cdot}$[139]

Reversibility of orientation. In most 1,3-dipolar cycloadditions, the major regioisomer is accompanied by some of the opposite one. The activation energies for formation of both regioisomers must therefore be about the same, and this fact should be reflected in the bond energy calculations for the two regioisomeric diradicals. In Eqn (19) is shown such an example.



(19)

The ratio of major to minor isomers obtained was 24:1,[140] for a $\Delta\Delta G^{\neq}$ of about 2 kcal/mole, a difference too small to be reliably found by bond energy calculations for diradicals **67** and **68** such as those given earlier. The losses in bond energy attending the formation of these diradicals are 14 and 15 kcal/mole respectively,[3] which are the same within the error of the method. Most other examples gave a similar result.[3] Bond energy analysis thus accounts for the fact that regioselectivity rather than 100% regiospecificity is observed in most 1,3-dipolar cycloadditions.

Partial charges in diradicals. In view of the similarity in bond energy of most diradicals with their regioisomers, how can we account for the patterns of orientation in the field as a whole? For example, why are diradicals like **67** consistently, if only slightly, better than those like **68**?

In addition to bond energies, **67** and **68** possess partial formal charges, and they are decidedly unequal in this regard. Clearly, **67** has a better charge distribution than **68** because it has negative charge on oxygen, the most electronegative atom, while **68** has negative charge on the less electronegative carbon, and positive charge on oxygen. This factor will consistently favor **67** and **53** over their regioisomers.

To assist in accounting for the overall pattern of favored diradicals, a simplified form of bond energy analysis is presented,[4] which considers only those bond changes that are relevant to the question of orientation. Chart 1 gives the analysis for nitrile oxides, and the results of similar analyses for nitrile imines, nitrones, azomethine imines and diazoalkanes.

For each 1,3-dipole are depicted Linnett structures for the two regioisomeric diradicals, in which D represents the dipolarophile moiety. Only the bonds and charges within the 1,3-dipole are considered. For each diradical, bond energies, electron correlation and L-strain are added up in the usual manner.[3] The absolute values of the sums have no physical meaning, but the difference for each pair of isomers reflects their *relative* bond energies. These differences are the same as those derived in Ref. 3 except that conjugation with R is neglected here. In all cases, Linnett structures are chosen to maximize the bond energy.

For every 1,3-dipole in Chart 1, the favored isomer is the same as the best diradical deduced earlier, in the survey of orientational patterns. Not only do **53**, **54**, **56**,

Chart 1. Simplified orientation with 1,3-dipoles (kcal/mol)

Nitrile oxides

53

C=N	143	C=N	143
N–O	99	N–O	99
C–C	83	C–O	86
5 pairs	20	4 pairs	16
C=Ṅ–		C=Ṅ–	
L-strain	−3	L-strain	−3
	342		341

Advantage 1

Nitrile lamines

54

Advantage 4

Nitrones

56

Advantage 1

Azomethine imines

58 **59**

Advantage 7

Diazoalkanes

55

Advantage 17

58 and **55** have better charge distribution than their regioisomers, but in addition **55** has a significant advantage in bond energy as well. The bond energy advantage of **58** is borderline, and those of the others are not considered significant, although the trends are all in the right direction. Thus with the above 1,3-dipoles, it is chiefly the distribution of partial formal charges that is responsible for the observed patterns of orientation.[4]

Azides are the only important truly bidirectional 1,3-dipole. Nevertheless, their orientations are also controlled by charge distribution in the diradicals. In simplified orientation with azides below, both orientations have about the same bond energy, and since both terminal atoms are nitrogens, the electronegativity criterion cannot be used here as with the other 1,3-dipoles.

69 **70**

Advantage 1

Other things being equal, **69** should be favored over **70** owing to its having less separation of charge.[141,142] However, if we seek more clues by going backward along the reaction coordinate to the transition states (more accurately, the midpoints of the R.C.'s), we find that electron-rich and electron-poor olefins give rise to quite different charge distributions (Chart 2). It is assumed that the two types of olefins are nucleophilic and electrophilic, respectively, in the T.S.'s.

Chart 2. Transition states for azides

electron-poor olefins

61p **62p**

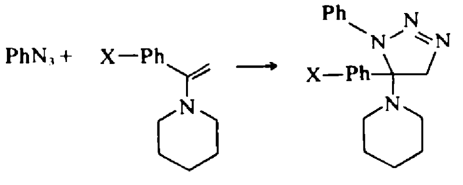
electron-rich olefins

61r **62r**

Transition states **61p** and **62p** have identical juxtapositions of localized dipoles, which leaves **69** slightly favored over **70**, as noted above. Consequently electron-poor olefins orient according to **61**. T.S.'s **61r** and **62r**, in contrast, have localized dipoles that face each other very differently. In **62r**, the electrostatic array is certainly lower in energy than in **61r**,[143] which accounts for the fact that electron-rich olefins orient according to diradical **62**.

The correctness of this rather unusual situation is shown in two ways; propensity for nitrogen loss (discussed later under the topic 'scission of diradicals'), and rate studies. From **69** vs **70**, the effect of varying group R on the rates with electron-poor olefins should be opposite to that with electron-rich ones; or in other words, azide reactivity should be most sensitive to olefin polarity when R accepts electrons, and least when it does not.

In Eqn (20) the Hammett ρ is -1.0, in keeping with T.S. **62r**, while in Eqn (21), ρ is $+2.1$, showing that the inner nitrogen bears negative charge as in **70** and **62r**. In contrast, ρ is of the opposite sign in Eqn (22) with an electron-poor olefin, with p-OMe faster than H, and p-NO_2 slower.



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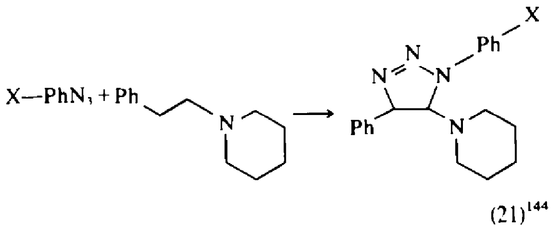

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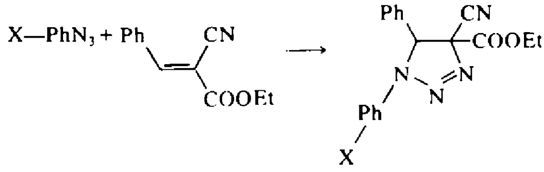


(22)[145]

In Table 8 are more confirming data. The enamine is much more sensitive to substituent in the azide and its ρ is +2.54, as expected for **70**, while maleic anhydride has low sensitivity and ρ of −1.1, in keeping with **69**. Sensitivity to olefin type is much greater with p-NO_2 than p-OMe.

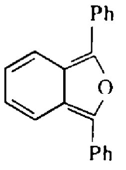
Table 8. Some reaction rates with azides†

	Maleic anhydride	1-pyrrolidino-cyclohexene	Rel. rate, enamine/anhydride
p-$MeOPhN_3$	20.8	3.15×10^3	151
p-O_2NPhN_3	1.28	1.42×10^6	1.1×10^6
Rel. rate, MeO/NO_2	16	1/450	
Hammett ρ	−1.1	+2.54	

†$10^7 k_2$, benzene, 25°, see Ref. 93.

Steric effects on orientation. In the original exposition of the concerted hypothesis for 1,3-dipolar cycloadditions,[5] steric effects were the cornerstone in the interpretation of orientation. However, it was subsequently pointed out in 1968[2] that orientation was basically an electronic, not a steric phenomenon, and finally the steric position was abandoned.[92]

Nevertheless, steric effects do operate in some cases, and when they do they uniformly favor the diradical over the concerted mechanism. The basic principle was first given by Newman, who observed that the dienes **71** and **72**, but not **73**, underwent Diels–Alder cycloadditions with vinylene carbonate, maleic anhydride and N-phenyl maleimide.[146] His interpretation was that a concerted reaction requires bonding at both termini of the diene simultaneously, so that not only **73**, but also **72** which has one highly hindered terminus, should be unreactive. But in a stepwise cycloaddition the first bond can form at the unhindered terminus of both **71** and **72**, with the second bond forming only afterwards in an exothermic step which is much less subject to steric hindrance. The conclusion was that the Diels–Alder reactions of **71** and **72** were stepwise and not concerted.



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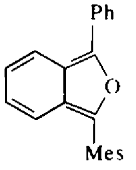

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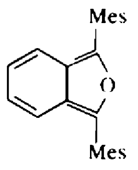
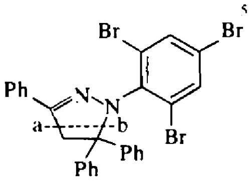


73

Products **74**, **75** and **76** are particularly crowded adducts whose orientation would certainly be the opposite if the reactions were concerted since regioselectivity, as noted previously, is so easily reversed. But applying Newman's principle, we see that they are the expected products for the diradical mechanism because the normal best diradicals result from the formation of the first bond, a, at an unhindered site. The hindered bond, b, is made only after the rate-determining step.



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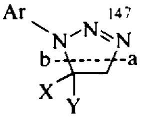
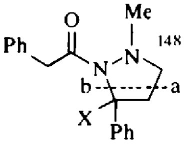
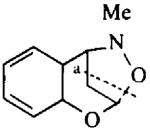


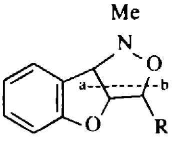
75 X = OR, NR_2
Y = Ph, CH_3



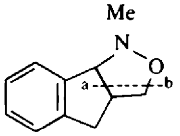
76 X = H, Ph, CH_3



77



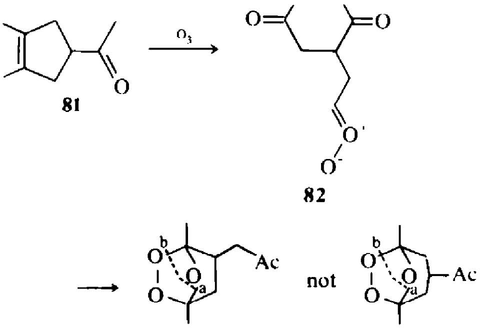
78: R = H
79: R = OR



80

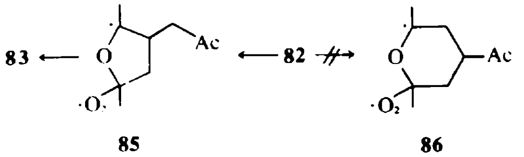
Adduct **77** is formed in preference to its less strained regioisomer **78**,[149] because formation of bond a gives a better-stabilized diradical in **77** than **78**; the extra strain is created only later. That **78** has indeed a better ring system than **77** in this general synthesis is shown by the facts that (1) **79** is obtained when the strong substituent alkoxy is added to the dipolarophile to compete with aryloxy;[149] (2) **80** is obtained when the aryloxy substituent is replaced by the weaker alkyl;[149] (3) free-radical cyclizations favor 5-membered over 6-membered rings kinetically.[150]

Another striking example of the same type is Eqn (23).



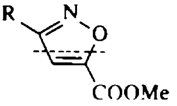
(23)

The authors found it surprising that in this and several other cases, the more strained ozonide was formed. However, it is actually a natural consequence of the fact that carbonyl oxide **82** forms diradical **85** faster than **86** because bond a in athe former creates a 5-membered ring, but in the latter a 6-membered ring.[150] A concerted cycloaddition would have led directly to the less strained ozonide **84**.

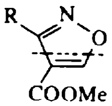


85 **86**

Although orientation with unhindered nitrile oxides, which give 5-substituted oxazolines and oxazoles predominantly, is no longer regarded as sterically caused,[92] one would hardly expect that increasing the size of R in RCNO would increase the proportion of the sterically disfavored 4-substituted product, if both new bonds formed simultaneously; yet this is exactly what is observed.[152a,b] The less room there is available in the 4-position, the greater the ratio **88**:**87**. The diradical explanation is simple: as R grows larger and larger, the increasing interference with bond formation at carbon, which gives the normally better diradical **89**, allows the first bond to form more frequently at oxygen, giving diradical **90**.

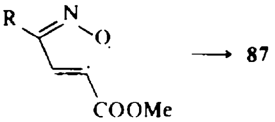


87



88

R	Ratio **87**:**88**
H	84:16
Ph	72:28
Mesityl	28:72



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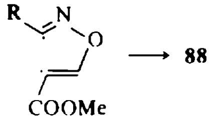
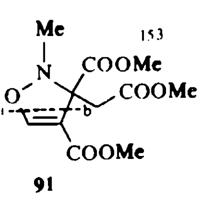


90

As shown earlier under 'Reversibility of orientation', **90** is never much poorer than **89** anyway, which makes the switchover quite natural with large R groups. The switchover is not caused by electronic factors (i.e. mesityl more electron-rich than phenyl) because it does not occur with *p*-OMe or even with 2,4,6-tri-OMe;[152c] OMe is effectively smaller than Me because it can rotate out of the way. For more examples of mesito- vs benzonitrile oxide, see Ref. 4, Table 3.

Adducts **91** and **92** illustrate steric reversal of regiochemistry, this time with nitrones. Again, highly crowded adducts are formed, via diradicals arising from initial formation of bond a at the least hindered sites.

Another type of steric effect may appropriately be discussed here, dealing with stereochemistry though not with orientation. Brown has pointed out that additions and cycloadditions to norbornenes syn to bulky 7-substituents are possible with stepwise but not concerted reactions, and has proposed this system as a test of mechanisn.[155] In the following two examples of 1,3-dipolar cycloadditions to 7-t-butoxy norbornene, the products *inter alia* contain both *syn* and *anti* exo adducts, with the advantage for *anti* so small that a concerted cycloaddition is scarcely conceivable.



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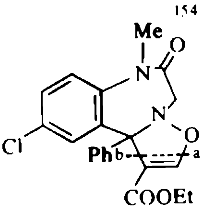
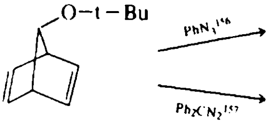
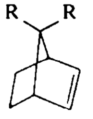


92



	Syn-exo	Anti-exo	ΔΔG‡
PhN_3[156]	15%	30%	0.4
Ph_2CN_2[157]	2.5%	36.5%	1.6

A closely related case is 7,7-dimethyl norbornene, which adds diphenyl nitrile imine and benzonitrile oxide principally from the exo side.[158] Relative to hydrogens, the methyl groups have no large effect on the exo/endo ratio.



	exo/endo	
	R = H	$R = CH_3$
PhCNNPh	>300	>110
PhCNO	>100	>70

The foregoing results with hindered norbornenes have been rationalized by saying that only 3- and 4-membered ring T.S.'s are governed by Brown's rule, since diimide, which is believed to add concertedly via a 6-ring T.S., adds to 7,7-dimethyl norbornene preferentially exo.[155,158] This rationalization is untenable in cycloadditions of linear 1,3-dipoles such as those mentioned here, which much approach to within about 2 Å with but slight bending in a *planar T.S.* if concerted.[90,104] Such a T.S. would be severely blocked by one of the 7-methyl groups.

In summary, all the foregoing steric examples have it in common that highly crowded products are formed which could hardly do so concertedly, but which are all possible and often predicted by the diradical mechanism. It allows the first bond to form freely, and the crowded situation does not arise until after the rate-determining step.

PMO interpretation of orientation. The modern theory of orientation according to the concerted mechanism rests entirely on PMO calculations.[7,159] The basic idea is to find the most favorable HOMO-LUMO or LUMO-HOMO interaction of the 1,3-dipole and dipolarophile in their ground states, and assume that this interaction will govern the formation of the main product. By this method it has been possible to rationalize most, though not all, of the patterns of orientation. Since numerous expositions of the strengths of PMO are already available, to save space only a brief summary of its weaknesses will be presented which, in my opinion, negate its support for concertedness.

(1) By basing its predictions on ground state interactions between the reactants, PMO ignores the fact that rate differences result from energy differences between transition states, which are further along the reaction coordinate. It is for this reason that concerted theorists emphasize the earliness of the T.S. along the R.C. However, although it is reasonable to say that the T.S. for a one-step exothermic reaction will be an early one, it seems unreasonable to say that a T.S. that stands 8–17 kcal/mole above the ground state (even higher for many Diels–Alders) has changed so little in electronic character from the reactants that calculations of ground-state orbitals are still meaningful for it. In other words, it is not safe to assume[160] that differences in the initial slope of energy along the R.C. will be maintained all the way up to the T.S. Thus the general hypothesis that 'the initial perturbation determines the course of a reaction' is 'an *alternative to the transition-state theory*'[161] (italics mine) and is valid only if a certain 'non-crossing rule'[162] holds. This non-crossing rule is unfortunately no more than a pious hope.

(2) The most favorable HOMO–LUMO interaction is a stabilizing one; that is, as the reactants approach in the proper way, the energy of the system goes *down*.[159] Further mixing of orbitals is yet more stabilizing, and so on until the product is reached.[163] Since the overall reaction is exothermic, there is no point on the R.C. at which the energy is higher than the ground state. Thus the existence of an energy barrier cannot be accounted for. This is simply another expression of the 'credibility gap' for the concerted mechanism mentioned earlier.

(3) Not all orientational facts are rationalized.[129,159] Further problems are the steric examples given above, and U-shaped Hammett plots. To account for data such as those in Eqns (12) and (13), it has been postulated that one leg of the U is dipole-HOMO controlled, and the other dipole-LUMO controlled.[159g] But this should sometimes result in reversal of regiochemistry, since the predictions for dipole HOMO and LUMO are often different. Regiochemistry is maintained, however.[115,116]

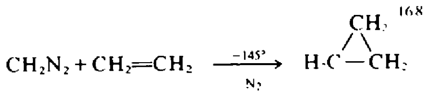
A related problem deals with the effect of HOMO–LUMO separation of the two reactants on rates; the narrower the gap, the faster the reaction should be. But the gap is the narrowest, or close to it, for electron-*rich* olefins with (*inter alia*) azides, diazomethane, nitrones, nitrole oxides and nitrile imines, despite the fact that all these 1,3-dipoles typically react faster—some of them much faster—with electron-*poor* olefins.[159a,b] Compare this situation with the discussion given earlier of diradicals **37** and **38** under 'U-shaped Hammett plots'.

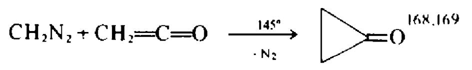
(4) PMO calculations for the Diels–Alder reaction predict, with one exception, that meta orientation will prevail when both diene and dienophile are both either electron-rich or -poor.[164,165] The exception finds ortho-para with both reactants electron-poor (with conjugating but not inductively electron-withdrawing groups) by assigning the larger HOMO coefficient to the β carbon of acrylonitrile and its kind.[166] This assignment, if correct, would make acrylonitrile more nucleophilic at the β than the α carbon. Calculations predicting which σ bond is formed first do correctly account for orientation.[167] However, this study, despite the label 'concerted', really vindicates the diradical mechanism because only one bond, not two, is forming in the postulated T.S.

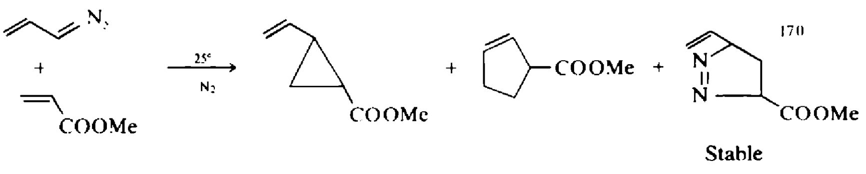
Scission of diradicals. Diradicals, lying in a shallow potential well, move so easily both forward and backward along the R.C. that they usually are detected only by their behavior in these two directions. But sometimes they betray their existence in other ways, and one such way is scission.

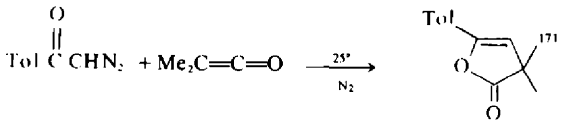
Sometimes diradicals, like free radicals, split off small stable molecules competitively with other processes. Loss of nitrogen from diazenyl diradicals arising from diazoalkanes is an uncommon but by no means rare event, as the following examples show. In each case there was no evidence for the existence of a pyrazoline, but even if one were transiently formed in equilibrium with the diradical that loses N_2, the instability of the hypothetical pyrazoline requires, by microscopic reversibility, that the diradical pathway be at least competitive with any other. Often the pyrazoline, if formed, would have been stable under the reaction conditions.

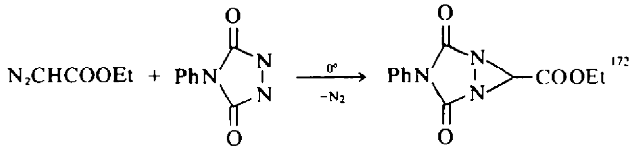
These are only a few of the many known cases. Since

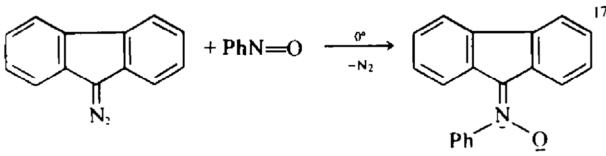


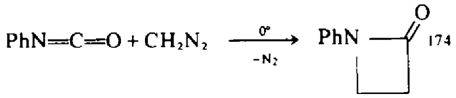






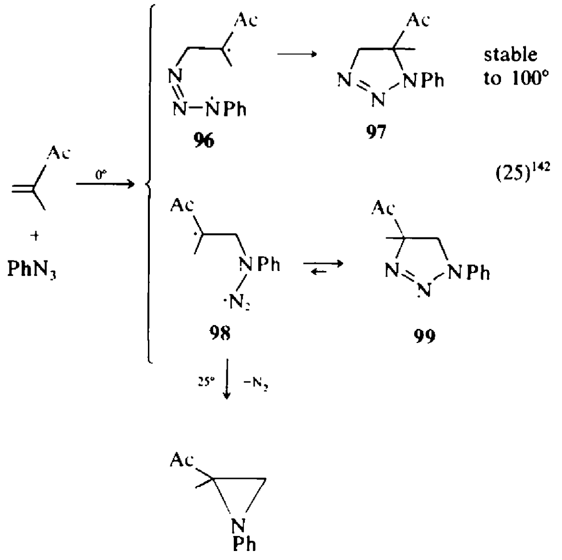






deamination of diazenyl radicals is exothermic,[175] why do diazenyl diradicals not *always* lose N_2?[7] Because the competing processes, cyclization or cleavage to reactants, are even more exothermic and almost unacitivated, so that deamination ought usually not to compete well against them.

Azides also are known to lose N_2, either during cycloaddition or from very unstable triazolines. From the earlier discussion about orientation, it can be seen that the tendency to lose N_2 should be greater with electron-poor olefins, which go through diradicals **61**, than with electron-rich ones, which go through **62**, because **61** has a terminal N_2 moiety and **62** an internal one. Thus the adduct of *p*-nitrophenyl azide with ethyl benzylidene cyanoacetate deaminates at 90°[145] while the adduct with 2-ethoxypropene does not lose N_2 even at 150°.[147] The adducts of phenyl azide with ethyl anisylidene cyanoacetate and norbornene decompose at 60°[145] and >150°[67] respectively. In Eqn (24) the triazoline **93** decomposed at 65° to the aziridine **94**, and yet **94** was formed *faster during cycloaddition* than from isolated **93**, indicating a common intermediate for both **93** and **94**. In contrast, **95** was stable at 70°.[176]



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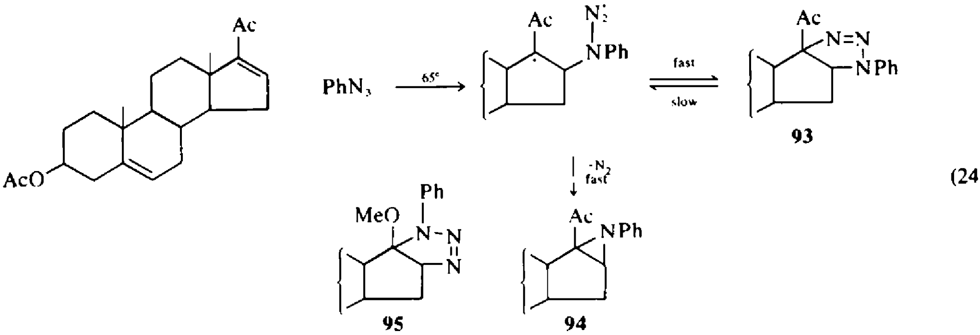
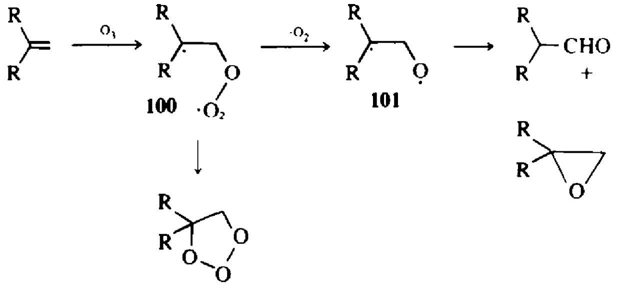


(24)[176]

Equation (25) is a particularly striking example.[142] Phenyl azide adds bidirectionally to 2-acetyl propene, giving **97** and **99** in 3:7 ratio. The preponderant adduct **99** is the normal one. It arises from diradical **98** with a terminal N_2 radical and deaminates at 25°. In contrast, **97** is stable to 100° because its diradical **96** has an internal azo group.

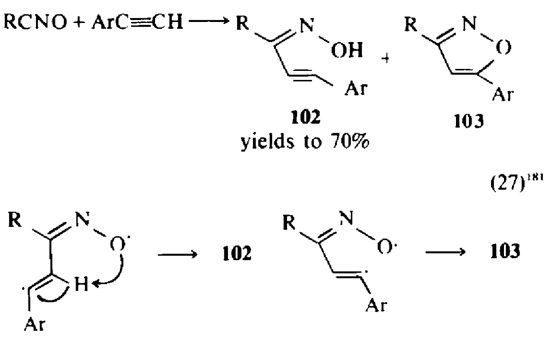
Nitrogen is not the only stable small molecule that can be lost from a diradical during 1,3-dipolar cycloadditions. The loss of oxygen during ozonolysis has long been known.[177] Important facts about oxygen transfer (Eqn 26), are: (1) It is most often seen with 1,1-disubstituted olefins,[178] implying easy bonding of O_3 to one end but some resistance at the other, and also preferential formation of extended diradicals. Thus the highly hindered olefin 1-t-butyl-1-tetramethylpropyl ethylene afforded 50% epoxide.[177b] Like other diradicals, **100** can revert to reactants, but unlike most others it can also suffer scission. (2) The solvent effect on oxygen transfer vs normal ozonolysis is small.[178a] (3) Both chemical evidence[179] and theoretical calculations[180] support the intermediacy of diradicals **100** and **101**.



100 **101** (26)

Hydrogen transfer in diradicals. In addition to scission, a second way not along the usual R.C. in which diradicals betray their existence is by transferring hydrogen. Normally, extended diradicals can do nothing except cleave back to reactants, leaving no trace of their existence other than a reduced frequency factor for cycloaddition. However, under favorable circumstances they undergo intramolecular hydrogen atom transfer, giving rise to new products.

The first observation was the formation of oximes **102** alongside the normal cycloadducts, isoxazoles **103**, from nitrile oxides and acetylenes (Eqn 27).[181] The group R may be aryl or alkyl. Evidence is now presented that **102** comes from extended diradical **104**.



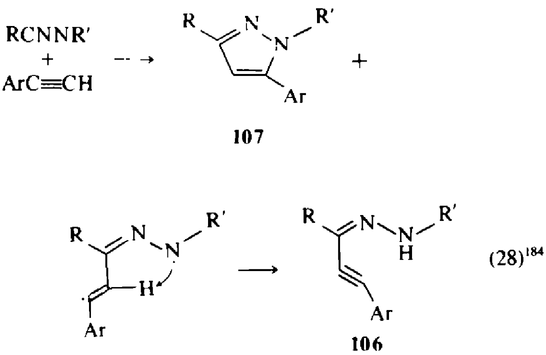
102 yields to 70% **103**

(27)[181]

104 ⟶ **102** **105** ⟶ **103**

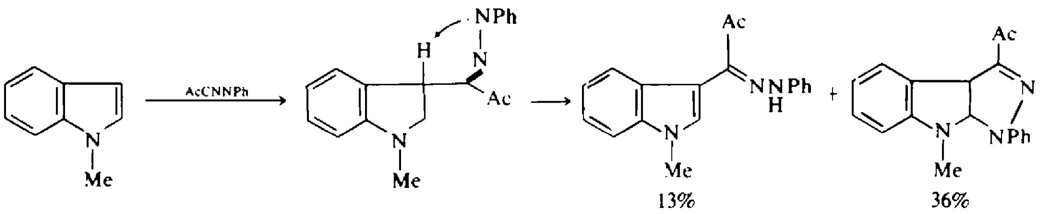
Diradicals **104** and **105** are, to a first approximation, equal in energy and polarity, and are not directly interconvertible (*vide supra*). This requires that they be formed independently by concurrent second-order processes,[116c,182] with the same Ea[116c,182b,183] and the same low solvent dependence.[116c,183] Since hydrogen is transferred after the rate-etermining step, there should be no hydrogen-deuterium isotope effect.[116c,183] Only the oxime syn to the acetylene, not anti, can arise from **104**.[116c] All these requirements have been amply met. The small solvent effect on the ratio **102**:**103**, and the ineffectiveness of added HCl,[181] rule out the suggested intermediacy[92a] of zwitterions. Concerted cycloaddition to the C-H bond, implausible in any case, is incompatible with $k_H/k_D = 1$. *These facts establish the correctness of the diradical mechanism for Eqn* (27) *beyond a reasonable doubt.*

Other examples of hydrogen transfer are accumulating. Nitrile imines react similarly with arylacetylenes, giving hydrazones **106** by hydrogen transfer alongside the normal cycloadducts **107** (Eqn 28).[184]

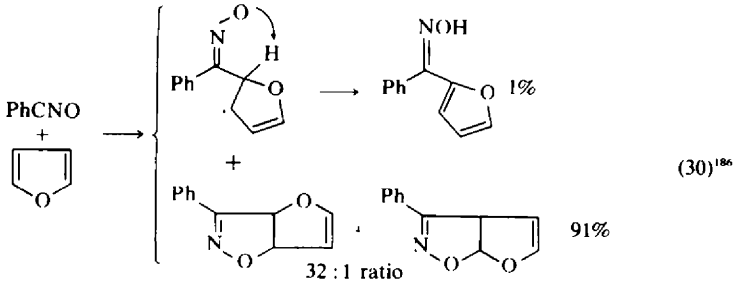


107 **106** (28)[184]

Hydrogen transfer is not limited to acetylenic dipolarophiles, as shown in Eqns (29) and (30); in (29), only one of several examples is shown.

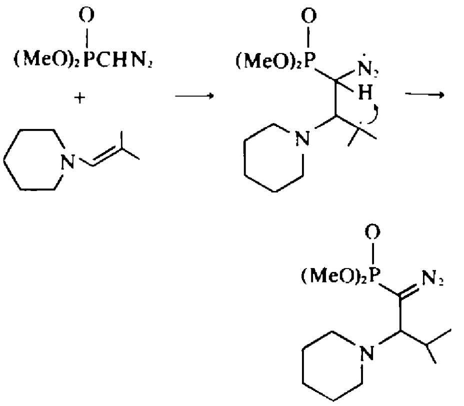


(29)[185]



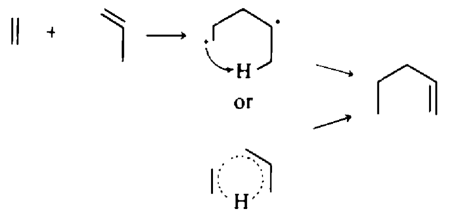
(30)[186]

It is also not limited to shift of hydrogen from the dipolarophile. In Eqn (31) the hydrogen atom comes from the 1,3-dipole.[187] Toluenesulfonyldiazomethane behaves similarly.[188]



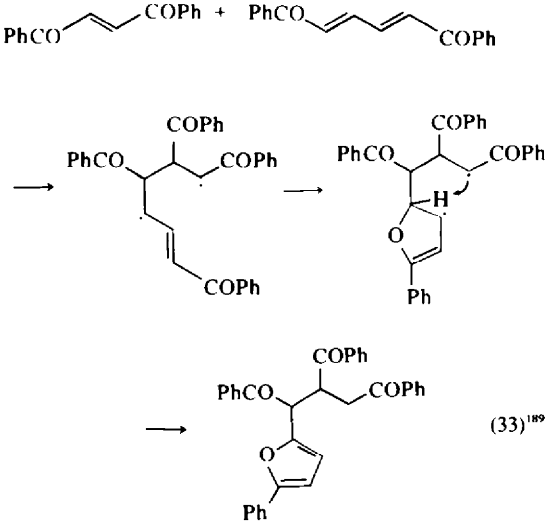
(31)[187]

Hydrogen transfer also occurs during Diels–Alder reactions. Most well-known is the ene reaction (Eqn 32), in which, unlike Eqns (27)–(31), a concerted mechanism is also conceivable. However, there are now examples



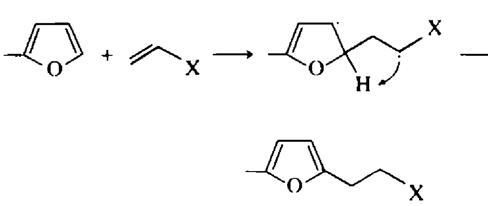
(32)

(Eqns 33 and 34), for which there is no reasonable concerted alternative. They are best regarded as H shifts within diradicals, just like Eqns (27)–(31).



(33)[189]

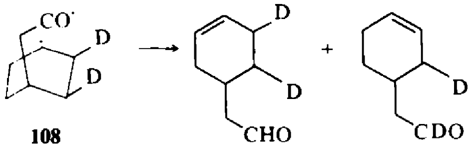
Equation (34) is reminiscent of the non-stereospecific reaction of 2-methyl furan with fumaric acid cited earlier.[39,40] In both cases, 2-methylfuran but not furan itself reveals the operation of the diradical mechanism because it sterically encourages the formation of extended diradicals. Actually, in Eqn (34) even furan gives a little H transfer with nitroethylene.



(34)[190]

X = NO$_2$, 70%
X = COCl, sole product

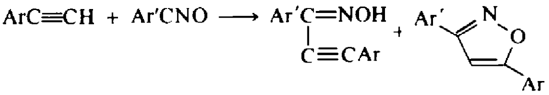
The abstraction of hydrogen atoms by radicals is marked by appreciable activation energies and isotope effects. Is it reasonable, then, for the H transfers of Eqns (27)–(34) to compete with such low-activation-energy processes as cleavage and cyclization of extended and cyclo diradicals, and to show no isotope effect (within about 15%)?[116c,183] Yes it is, because they are not simple H abstractions, but rather radical disproportionations, reactions which, like radical combinations, have vanishingly small Ea's.[20,191] In most systems, free radicals combine and disproportionate simultaneously with ratios that show little or no temperature dependence.[191] As for isotope effects, the average k_H/k_D for *inter*molecular disproportionations in a recent review was 1.60.[191] Even this number, when utilized in a proper kinetic analysis of a competition between cycloaddition and H transfer such as Eqn (27), gives a predicted experimental isotope effect of only about 1.05, which is well within the experimental error (see Appendix for details, Case 1). However, it has recently been found that *intra*molecular disproportionations are marked by much lower isotope effects. Thus diradical **108** exhibits k_H/k_D of only 1.07.[192] Application of 1.07—which is already within the experimental uncertainty for Eqn (27)—to the kinetic analysis in the Appendix results in a predicted k_H/k_D of 1.006.



108

Conformation of diradicals. The competition between cyclo and extended diradicals exemplified in Eqns (27) and (28) shows interesting substituent effects. Tables 9 and 10 display typical data for these reactions. Once again, the discussion is based upon partial formal charges in the diradicals.

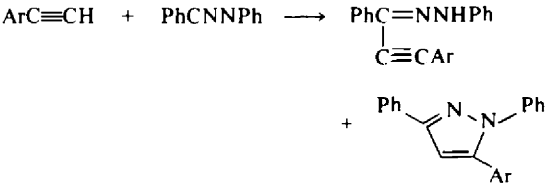
Table 9. Percentage of oxime from arylacetylenes and nitrile oxides†



Ar	Ar': *p*-MeOPh	Ph	*p*-ClPh	*p*-O$_2$NPh
p-O$_2$NPh	0	0	0	*ca.* 5
p-ClPh	7	7	9	11
Ph	10	12	15	18
p-MeOPh	24	28	32	24
p-Me$_2$NPh	52	53	65	74

†Oxime (oxime + isoxazole) × 100, see Ref. 193.

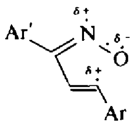
Table 10. Percentage of hydrazone from arylacetylenes and nitrile imines†



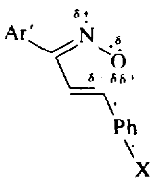
Ar	Hydrazone, %
p-O_2NPh	<17
Ph	23
p-MeOPh	32
p-Me_2NPh	50

†Hydrazone/(hydrazone + pyrazole) × 100, see Ref. 184.

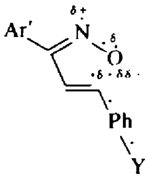
For **105** the charge distribution must be something like **109**, regardless of aryl substituents. The nitroxide radical will always have negative oxygen because its major source of stabilization involves a one-electron shift from the nitrogen's lone pair into the N–O bond, with Ar′ playing but a secondary role, while the vinyl radical will always have positive carbon because Ar is overall electron-withdrawing with all listed substituents. Superimposed on this general picture are the effects of substituents in Ar and Ar′, larger with the former than the latter because Ar is directly bonded to an otherwise unstabilized vinyl radical, while Ar′ is attached to an already highly stabilized nitroxide radical. Substituents in Ar impose secondary partial formal charges as depicted in **110** for electron-attracting, and **111** for electron-releasing ones.



109



110



111

The differences in attractive force between the two radical sites of **110** vs **111** result in differences in the proportion of cyclo vs extended diradicals: *cf.* the earlier discussion under 'U-shaped Hammett plots'. Clearly, **110** will have a greater proportion of cyclo diradicals than **111**, and *vice versa.* Thus electron-attracting substituents in Ar should give more cycloadduct, and electron-releasing ones more oxime. A parallel situation exists for Eqn (28). Tables 9 and 10 show that this is precisely what is observed, and the effect is large, with per cent oxime varying from 0 to 74, and per cent hydrazone from <17 to 50. Many more data, not given here to save space, show exactly the same trend.[116c,184,193]

Substituents in Ar′ affect the terminal negative charge in the nitroxide radical, but in a smaller way. Reading across Table 9, one sees a just discernible increase in per cent oxime as Ar′ becomes progressively more electron-poor. This is because reducing the negative charge on the oxygen atom reduces the attraction between the two radical sites, resulting in more of the extended form. Thus even the fine details of the hydrogen transfer phenomenon are reproduced by the diradical model.

The hydrogen transfer phenomenon proves the existence of extended diradicals. Cyclo diradicals must then also exist because they cannot differ significantly in energy from extended ones. Therefore *at least a portion* of the 1,3-dipolar cycloadducts must arise via diradicals, since is inconceivable that cyclo diradicals would not cyclize.

Conclusions. Although many facts can be explained by either the diradical or concerted mechanisms, the weight of evidence favors the diradical mechanism, and some of the facts can be explained in no other reasonable way. This is not to say that the concerted mechanism is thereby ruled out, but rather that its operation can be imagined only alongside diradicals, *simultaneously and in the same reaction vessel and with the same activation parameters.* Whether peaceful coexistence is possible for two such different mechanisms is a matter that each person must decide for himself.

Is it possible to reconcile the two extreme viewpoints, by saying that the concerted transition states are so non-synchronous that they are almost, but not quite, clear-cut diradicals? Of course it is, provided one is willing to accept a picture in which the weaker of the two new bonds is so weak that it is powerless to prevent the formation of extended diradicals. In cyclo diradicals, the two radical sites could conceivably interact through space, but not in extended diradicals, which nevertheless are formed, sometimes preponderantly. Thus the weaker bond is limited to an interaction so small that such a T.S. probably could not be said to possess a continuous cyclic array of delocalized electrons in the Woodward–Hoffmann sense.

Furthermore, it is no longer possible to postulate a high degree of asynchronism to concerted 1,3-dipolar cycloadditions. Two recent ab initio MO studies, the most advanced yet published, find that T.S.'s that are concerted would also be largely synchronous. Thus in the cycloaddition of diazomethane to ethylene, formation of the new C–N bond in the T.S. was calculated to be 87% as advanced as that of the new C–C bond.[104] Likewise, for the cycloaddition of fulminic acid to acetylene, the ratios of lengths of the two new bonds in the T.S. and in the product were almost identical; in the author's words, 'the computed reaction path must clearly be labeled as synchronous'.[90]

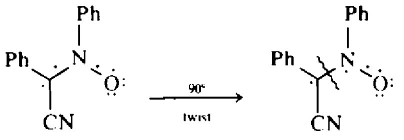
The question is often asked, 'why should reactions eschew a symmetry-allowed, i.e. low-Ea pathway in favor of one that requires a higher Ea?' Asked in this way, the question seems unanswerable. The flaw, however, lies not in the answer but in the question, for it contains within itself a hidden assumption which may be false. The assumption is that now that the first selection rules for thermal pericyclic reactions, the Woodward–Hoffmann rules,[1] have been discovered, *there are no more selection rules that have not yet been discovered.* The patent absurdity of the italicized statement now allows us to answer the question. Reactions eschew a low-Ea pathway in favor of a high-Ea one, despite the Woodward–Hoffmann rules, because some other rule not yet discovered[194] compels them to do so. Thus, answering one question about chemical transformations only leads to a new and bigger question.

APPENDIX

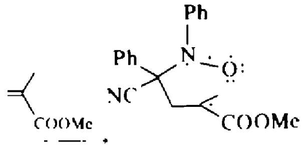
Recently a long attack on the diradical mechanism was published.[7] Little space has been devoted in the body of the present article to defence against these criticisms, but there are certain points raised by Huisgen that need a reply owing to their subtlety. These points are covered here.

Energy of activation. In the Linnett analysis given in Table 2, the energies of bonds of intermediate multiplicity, i.e. 3- and 5-electron bonds, were taken from smooth plots of 2-, 4- and 6-electron bond energies, correcting afterwards for changes in electron correlation. This procedure is perfectly proper, but it was nevertheless criticized by Huisgen, who felt that the loss of pi-bond energy of the 1,3-dipole would better be approximated by using the experimental bond energy required for twisting the 1,3-dipole through 90°. This energy is presumably the same as that lost in the addition of the dipolarophile to form the diradical. Using this method, once again a very high figure, was obtained for the diradical mechanism's activation energy.

A detailed analysis of the errors in this calculation is not necessary here. It will suffice to show that substitution of twisting barriers into the previous calculation gives the same answer anyway. In place of **1**, C-phenyl C-cyano N-phenyl nitrone **112** will be used, since this is a nitrone for which the twisting barrier was supplied.[195]



112 **113**



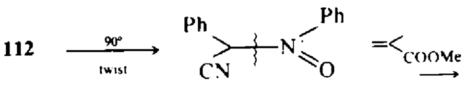
114 (35)

Loss		Gain	
Twist	25^{195}	C-C	83
C=C→C-C	63	·C-C=O S.E.	11
Conj. E	4		—
·C-CN S.E.	18^{196}		94
	—		
	119		

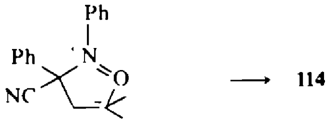
No figures for odd-electron bonds are used in this calculation. The loss in bond energy comes to 16 kcal/mol, and the estimated Ea is 17. The experimental Ea is not available for Eqn (35), but presumably it is not very different from Eqn (1), so that once again the diradical mechanism comes off well.

When bonds are broken in the absence of an external reagent, as in twisting or stretching them, homolysis as always favored over heterolysis because the energy required to change a radical pair into an ion pair is large. Nevertheless, it has been held[7] that the proper species to obtain by twisting **112** is not **113**, but rather **115**. Yet another calculation, quite arbitrary in nature this time, again yields a very high Ea for the diradical mechanism. Although **115** is an improper model for twisted **112**, it is possible to carry out a computation of the bond energy loss based on it. It is now necessary to introduce a correction for electron transfer to reach the diradical. In order to reduce arbitrariness, this is left as an unknown, and then approached afterward as a separate problem.

Loss		Gain	
Twist	25	C-C	83
C=C→C-C	63	·C-C=O S.E.	11
-C-C(Ph)CN S.E.	38^{197}	Electron correlation	20
N=O→N∸O	46	Electron transfer	x
	—		—
	172		114 + x



115



116

The bond energy lost in the formation of **114** is 58 − x. How can we find x? The best way is to use the difference between homolytic and heterolytic bond dissociation energies for the C–N bond, which is > 142 kcal/mol,[102] corrected for the electrostatic energy of the C^-N^+ pair at their distance d in **116** (>3 Å) which is given in kcal/mol by the expression 331.5/dD. Even with the dielectric constant = 1, x > (142–110) = 32, so that the bond energy lost must be a great deal less than 26 kcal/mol. Thus even this calculation upholds the diradical mechanism.

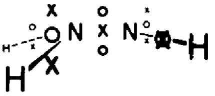
Hydrazyl radical. In a further attempt to disprove the validity of the concept of intermediate multiplicity of odd-electron bonds, the long history[46,47,198] and strong experimental support[47,48] for this concept were ignored in favor of a calculation on the hydrazyl radical **117**, that concluded

$$H_2\ddot{N}{-}\underset{\cdot\cdot}{\dot{N}}H \leftrightarrow H_2\dot{N}\dot{-}\underset{\cdot\cdot}{\dot{N}}H$$

117

that the 3-electron bond in **117** is actually 6 kcal/mol *weaker* than a normal 2-electron N–N bond![7]

The incorrectness of this calculation is shown by experimental data. Hydrazyl radicals are long known to be highly stabilized,[47,199] They are non-planar,[200] as befits Linnett structure **118**.



The hydrazyl radical itself has been studied.[201] Its shape is that of **118** and the N–N bond distance is 1.38 Å, right in between those for hydrazine (1.47 Å) and azomethane (1.24 Å),[47] showing that the 3-electron bond has indeed the multiplicity 1.5.

A step higher in oxidation state is the radical HNN·, for which the Linnett structure **119** has a 5-electron bond. An ab initio MO study of

$$H{-}\dot{N}\dot{=}\dot{N}{:}\quad \mathbf{119}$$

this species came out with a N–N bond length of 1.18 Å; *cf.* N=N above, and N_2 (1.10 Å).[202] This closely fits the multiplicity 2.5 as in **119**.

There is indeed ample evidence to show that not only hydrazyl and diazenyl radicals, but all radicals containing a 7-valence-electron atom bonded to an atom bearing unshared electrons (i.e. a hetero atom or a carbanion) are stabilized by donation of one of the unshared electrons into the bond.[48]

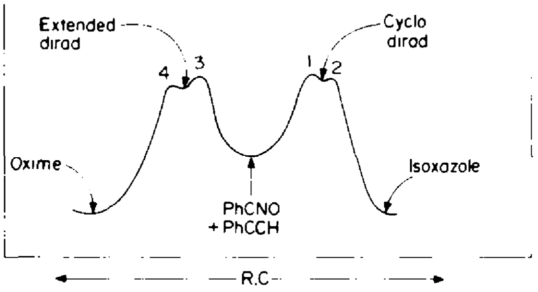
Substituent influence on cycloaddition rates. In Ref. 7, Table 2, the calculated gains in stabilization free energy for the formation of many diradicals are compared with the rates for the corresponding 1,3-dipolar cycloadditions, and found not to correlate. The model used for the diradical was $H_2\dot{C}$–R, in which R is the substituent in the dipolarophile. Only the radical site from the dipolarophile was examined in the calculation because, in reacting any group of olefins with a given 1,3-dipole, the radical site from the dipole is constant.

Unfortunately, it is impossible for any 1,3-dipole and dipolarophile $CH_2{=}CHR$ tor produce a diradical that looks like $H_2\dot{C}{-}R$, a primary radical. With 1,3-dipole D, *at the very least* the diradical must look like $D{-}\dot{C}H_2{-}\dot{C}H{-}R$, which is a secondary radical. The S.E.'s for secondary radicals are by no means parallel to those of primary ones. When the proper model is substituted, the upper part of Table 2, Ref. 7, looks like this:

	R=H	Alkyl	COOMe	OR	vinyl	Ph
Ground state conj. E[51]	0	3.2	3.2	5.2	4.9	4.9
BDE of $DCH_2CHR{-}H$	98[102]	95[102]	93[3,7]	92[102,203]	85[204]	84[205]
S.E. of $D\ \dot{\curlyvee}\ R$	≡0[206]	3	5	6	13	14
Gain of S.E.	0(0)	0(4)	2(6)	1(6)	8(10)	9(13)

In parentheses are the old figures. The correlation between the gain in stabilization energy and reaction rate, although still not perfect, is now much improved, and within the claimed error limits for calculation of Ea's in Ref. 3, especially in view of the fact that rates are here being compared with energies, i.e. differences in $\Delta S^{\neq}$ are not taken into account.

Isotope effect for hydrogen transfer. The full kinetic analysis is given here, using $k_H/k_D = 1.07$.[192]



$$\text{Oxime} \xleftarrow{k_4} \begin{matrix}\text{extended}\\ \text{dirad.}\end{matrix} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \begin{matrix}\text{PhCNO}\\ \text{+ PhCCH}\end{matrix} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \begin{matrix}\text{cyclo}\\ \text{dirad.}\end{matrix} \xrightarrow{k_2} \text{isoxazole}$$

Let [PhCNO][PhCCH] ≡ A
[extended dirad.] ≡ R
[oxime] ≡ Ox

$$\frac{dR}{dt} = k_3A - k_{-3}R - k_4R = 0 \text{ (steady-state assumption)}$$

$$R = \frac{k_3A}{k_{-3} - k_4}$$

Case 1. Assume $k_4 = 10k_{-3}$, i.e. $\Delta\Delta G^{\neq} = 1.4$ kcal/mol

$$\text{For H transfer, } \frac{dOx}{dt} = k_4R = \frac{10k_3A}{11}$$

$$\text{For D transfer, } \frac{d^DOx}{dt} = \frac{k_4R}{1.07} \text{ where } R = \frac{k_3A}{k_{-3} + \frac{k_4}{1.07}}$$

$$\frac{d^DOx}{dt} = \frac{10k_3A}{11.07}$$

$$\frac{k_H}{k_D} = \frac{dOx}{dt} - \frac{d^DOx}{dt} = \frac{11.07}{11} = 1.006.$$

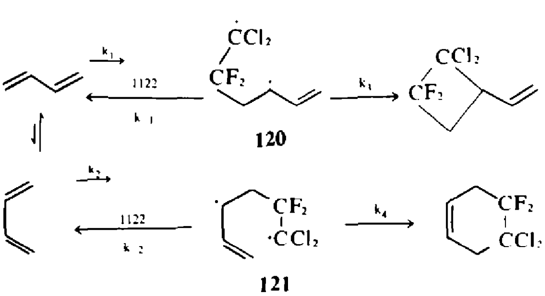
Case 2. Assume $k_4 = 2k_{-3}$, i.e. $\Delta\Delta G^{\neq} = 0.4$ kcal/mol

$$\frac{k_H}{k_D} = \frac{3.07}{3} = 1.02.$$

The reaction coordinate goes in both directions, starting from the reactants in the center, reflecting the requirement stated earlier that extended and cyclo diradicals can equilibrate only via the reactants. It is reasonable to postulate that $k_4 = 10k_{-3}$ because not only is k_4 a radical disproportionation whose Ea is the same as radical combination such as k_2,[191] but also it is an intramolecular disproportionation with a strain-free 5-membered ring T.S. It is well established that such reactions proceed immensely faster than their intermolecular counterparts.[23] Thus the predicted isotope effect is 1.006. Even if k_4 were only $2k_{-3}$, the predicted isotope effect rises to only 1.02, undetectably small.

Cycloadditions of fluorinated olefins. The extensive experimental work of Bartlett *et al.* on cycloadditions of fluorinated olefins to dienes is often cited in support of the concerted mechanism for the Diels–Alder reaction.[7] Such olefins, particularly 1,1-difluoro-2,2-dichloro ethylene (1122) have a pronounced tendency to undergo (2+2) rather than (2+4) cycloadditions with dienes.[78] Reactivity of various dienes toward 1122 in the (2+4) but not the (2+2) sense parallels their reactivity toward maleic anhydride in the Diels–Alder reaction.[78b] The (2+4) products, but not the (2+2), are formed stereospecifically. These and other observations have been interpreted as meaning that (1) and (2+2) products are formed by a diradical mechanism; (2) the Diels–Alder reaction is concerted, although at least a *portion* of the (2+4) cycloadducts come from diradicals[43,79] (*vide infra*); and (3) there is something special about fluorinated olefins that causes them to react by the diradical mechanism.

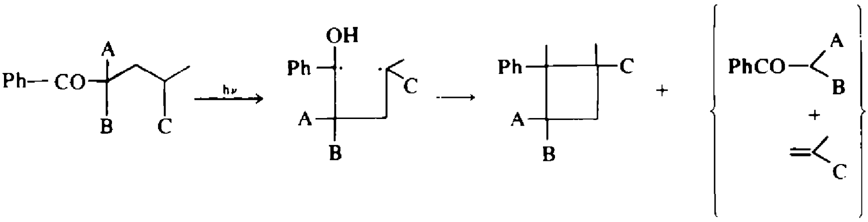
This whole body of work can be interpreted in terms of diradicals alone (Scheme 1). Diradicals **120** normally predominate over **121** because most dienes prefer the s-trans conformation. However, with normal dienophiles only 6-ring products are formed because both k_{-1} and $k_4 \gg k_3$, owing to the strain present in step 3[54a,207] but absent in step 4. Since, as discussed earlier, $k_{-1} \gg k_{\text{rotation}}$, loss of stereospecificity is usually prevented.



Scheme 1.

What, then, is special about 1122? *It is that* k_{-1} *is slightly retarded relative to the other steps*, compared with normal dienophiles. This has the following effects: cyclization to the 4-ring product can compete more effectively; and rotation can now compete with k_3 and k_{-1}.

The inhibition of k_{-1} by the fluorine substituents, first proposed in 1970 as a hypothesis,[208] has recently been experimentally verified. The data given with Eqn (36) show that 1,4-diradicals like **120** have a greatly enhanced cyclization/cleavage ratio when fluorines are substituted on the bond to be broken, but not elsewhere on the 4-ring being formed. This means that fluorinated dienophiles such as 1122 will exhibit enhanced k_3/k_{-1} ratios in Scheme 1, and that this enhancement arises from reducing



A	B	C	cycliz./cleavage
H	H	H	0.226
F	H	H	1.03
F	F	H	60
H	H	F	0.195

(36)[209]

k_{-1}, not increasing k_3. Thus there is no longer a need to postulate any concerted component in Diels–Alder reactions of fluorinated dienophiles.

Acknowledgement—I wish to thank Prof. Huisgen for an extended and interesting correspondence.

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