On the Mechanism of 1,3-Dipolar Cycloadditions

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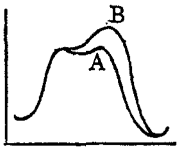
A mechanism for 1,3-dipolar cycloadditions is outlined in which, contrary to the four-center, "no-mechanism" theory, a spin-paired diradical intermediate is proposed.

The concept of 1,3-dipolar cycloadditions was first suggested in 1938 by Smith.[1] The generality of the reaction was recognized by Huisgen in a brilliant series of researches, during which many new reactions have been predicted and discovered.[2] The mechanism also has received much attention from Huisgen's group, and the picture which they have drawn in a convincing manner[3] is that of a single-step, four-center, "no-mechanism" cycloaddition, in which the two new bonds are both partially formed in the transition state, although not necessarily to the same extent. In accord with this mechanism are the kinetics, the large negative entropy of activation (*ca.* −30 eu), the general effects of structural variation in the dipoles and dipolarophiles, and, most particularly, the strictly *cis* nature of the additions. This mechanism has received wide acceptance, and has not been questioned, to our knowledge, anywhere.

The purpose of this paper is to present an alternative mechanism for 1,3-dipolar cycloadditions. It is true that the data concerning these additions are so manifold that no single mechanism can be written today that accommodates them all, but it is nevertheless hoped to cover the vast majority of these reactions, while yet recognizing that a duality of mechanism may exist in the field as a whole.

A. Mechanism.—In place of a one-step pathway with a single transition state, we propose a two-step reaction with a discrete intermediate, a spin-paired diradical, with the first step rate determining. The stereochemical facts impose upon this mechanism the further restriction that the activation energies for *both advance and retrograde* motion along the reaction coordinate from this intermediate be very small, smaller in fact than that for rotation around a single bond. The energy profile can be sketched as path A.



It is a corollary of this mechanism that, for every successful collision between the two partners, many others will occur in which the first bond can form but the orientation is poor for the second (path B). In these cases the intermediate reverts to starting materials, leaving no memory of itself except a reduced frequency factor. Low entropies of activation are thus to be expected.

It must be noted that the idea of diradical intermediates in thermal cycloaddition reactions is not a new one. It was proposed for the Diels–Alder reaction in 1937 by Kistiakowsky, *et al.*,[4] and revived more recently by Walling and Peisach[5] and it has been widely suggested for small-ring cycloadditions.[6]

B. Stereospecificity.—The *cis* nature of the reaction means that geometrical relationships among the substituents on both the reactants are preserved in the product. As mentioned previously, this is required by the one-step theory, but fits the two-step mechanism only if the activation energy for single-bond rotation in the intermediate is greater than that for either formation of the second bond or reversion to reactants. This is not unreasonable in view of the fact that, even in ethane, the least substituted carbon–carbon single bond, this figure is 2.9 kcal,[7] and a much larger value would be anticipated for the comparatively encumbered intermediates we propose. On the other hand, the activation energy for ring closure of a properly disposed spin-paired diradical is probably much less than 2.9 kcal/mol, possibly approaching zero.[8–11] As for reversion to reactants, we do not know how to estimate a likely number, but it could well be a very small one.

C. Dipolarophile Structure.—"The most striking phenomenon observed here is the promoting effect that conjugation exerts on the dipolarophilic activity of all multiple bonds." [12] This strongly supports the two-step theory, wherein the intermediate, be it dipolar[13] or diradical in nature, derives some stabilization through conjugation. The delocalization energy in a high-energy intermediate, and also in its transition state for formation,[14] might well be greater than that of the ground-state reactants. In a concerted cycloaddition, the situation is exactly reversed; whatever stabilization

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(1) L. I. Smith, *Chem. Rev.*, **23**, 193 (1938).

(2) R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 565 (1963).

(3) R. Huisgen, *ibid.*, **2**, 633 (1963).

(4) J. B. Harkness, G. B. Kistiakowsky, and W. H. Mears, *J. Chem. Phys.*, **5**, 682 (1937).

(5) C. Walling and J. Peisach, *J. Amer. Chem. Soc.*, **80**, 5819 (1958).

(6) (a) E. E. Lewis and M. A. Naylor, *ibid.*, **69**, 1968 (1947); (b) E. C. Coyner and W. S. Hillman, *ibid.*, **71**, 324 (1949); (c) J. D. Roberts and C. M. Sharts, *Org. Reactions*, **12**, 8 (1962); (d) P. D. Bartlett, L. K. Montgomery, and B. Seidel, *J. Amer. Chem. Soc.*, **86**, 616, 622, 628 (1964); (e) W. C. Solomon and L. A. Dee, *J. Org. Chem.*, **29**, 2790 (1964); (f) A. Cairncross and E. P. Blanchard, *J. Amer. Chem. Soc.*, **88**, 496 (1966); (g) P. S. Skell and R. C. Woodworth, *ibid.*, **78**, 4496 (1956); (h) P. Scheiner, *ibid.*, **88**, 4759 (1966).

(7) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 35.

(8) The dimerizations of both methyl[9] and *t*-butoxy[10] radicals have activation energies of approximately zero.

(9) R. Gomer and G. B. Kistiakowsky, *J. Chem. Phys.*, **19**, 85 (1951)

(10) D. J. Carlsson, J. A. Howard, and K. U. Ingold, *J. Amer. Chem. Soc.*, **88**, 4725 (1966).

(11) It is often alleged that an intermediate whose further transformation requires zero activation energy can be no more than an imaginary creature; under such circumstances, the two-step mechanism becomes identical with the one-step by this criterion. This notion is false, however, for even with such an intermediate the distinction made between the two mechanisms regarding the extent to which formation of the *second bond* has proceeded in the transition state is entirely preserved. Thus predictions based on the two theories remain divergent.

(12) See ref 3, p 638.

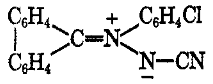
(13) W. I. Awad, S. M. A. R. Omran, and F. Nagieb, *Tetrahedron*, **19**, 1591 (1963).

(14) C. Walling in "Free Radicals in Solutions," John Wiley and Sons, Inc., New York, N. Y., 1957, p 124.

energy the dipolarophile possesses ought to diminish steadily along the reaction coordinate as the π bond is consumed.

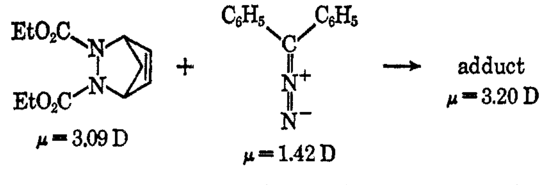
This question has been dealt with[12,15,16] by what can only be described as an important departure from the concerted cycloaddition theory: the formation of the two new bonds, though still simultaneous, is no longer held to be synchronous.

D. Solvent Effects.—Over a wide range of polarities, the rates of 1,3-dipolar cycloadditions show a remarkably small solvent dependence.[16-23] This fact is not consistent with a one-step mechanism, in which the dipolarity of the starting compound must be partially discharged in the transition state. Such a mechanism requires an inverse relation of rate to solvent polarity, the magnitude depending on the amount of charge dispersal; yet even for 1,3 dipoles of unusually high polarity the solvent effect is small. For the addition of I (μ = 6.7) to dimethylacetylenedicarboxylate,[17] for example, the rate diminishes by a factor of only 6 as the solvent is changed from benzene to dimethylformamide. For less polar 1,3 dipoles the factor is smaller, approximating 1 in many cases.



I

It is possible to reconcile with theory[24] the small solvent dependence of many examples, such as the one just cited, by postulating that the transition state is merely an orientation complex in which covalent bonding has hardly begun; a considerable part of the free energy of activation is accounted for by entropy changes. A proposal close to this postulate has been made for some[25] (but not all[16]) cases. There is a conflict, however, with a theory of orientational effects in which covalently bound resonance forms figure prominently.[15] Moreover, there are other examples whose transition states' dipole moments would be too low in any event. For instance, in the following reaction, the transition state must have a dipole moment of 4.6 D in order to have zero solvent dependence.[17] Its moment



was estimated at 4.4 D, in good agreement with the required value. However, the *vector* sum of the two dipoles in the orientation complex is only *ca.* 3.4 D, a good deal lower. Likewise, for the addition of phenyl azide (μ = 1.55[26]) to norbornene (μ = 0.40[27]), whose rate is also independent of solvent polarity,[18] theory requires a dipole moment of 2.16 D for the transition state of a concerted pathway, but the orientation complex would be only in the neighborhood of 1.6 D. Other cases could be cited also.[20]

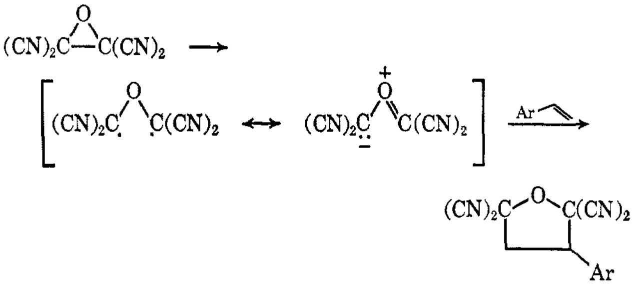
In a two-step mechanism, on the other hand, in which only one bond is partially formed in the transition state, this species might reasonably be expected to have approximately the same polarity as the orientation complex of the components. Consider the three principal canonical forms of a typical 1,3 dipole, II. These are all octet structures which have the same number of

$$-a\equiv\overset{+}{b}-\underset{|}{\overset{-}{c}}- \longleftrightarrow -\overset{-}{a}=\overset{+}{b}=\underset{|}{c}- \longleftrightarrow -\overset{\frac{1}{2}-\cdot}{a}=\overset{\cdot+\cdot}{b}-\underset{|}{\overset{\cdot\frac{1}{2}-}{c}}-$$

IIa IIb IIc

bonding electrons. All other forms, such as sextet structures, have fewer bonding electrons and can be discounted. Form c is drawn according to Linnett's method[28] and is quantum-mechanically equivalent to a $\longleftrightarrow$ b. Since the dipole moments of most 1,3 dipoles are small compared with the theoretical values for full charge separation,[17] the expression c may usually be accepted as the principal representation of II. The diradical attributes of II are thus made apparent, and if the blend of polar and diradical qualities in the transition state leading to the diradical intermediate is about the same as that in II, solvent effects on the rate would be expected to be small.[29]

In the cycloaddition of tetracyanoethylene oxide to *para*-substituted styrenes, in which the TCNEO must first be activated to a 1,3 dipole, the small dependence of rate on either solvent or the nature of the *para* substituent led Linn[19] to propose a diradical structure for activated TCNEO.



E. Acetylenic Dipolarophiles.—A number of 1,3 dipoles react with acetylenes to produce aromatic systems directly, *e.g.*, nitrile imines, nitrile oxides, and azides. In a concerted reaction, a portion of this aromatic stabilization should exist in the transition state. With these dipoles, then, greatly enhanced reactivity is expected for acetylenic dipolarophiles over their ethylenic counterparts in a concerted cycloaddition; yet, in comparing the reaction rates of diphenyl(nitrile imine), benzonitrile oxide, and phenyl azide with the two pairs styrene–phenylacetylene and

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(15) A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, D. Grashey, and E. Spindler, *Chem. Ber.*, **100**, 2192 (1967).

(16) R. Huisgen, G. Szeimines, and L. Möbius, *ibid.*, **100**, 2494 (1967).

(17) See ref 3, p 635.

(18) P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Nowack, *J. Amer. Chem. Soc.*, **87**, 306 (1965).

(19) W. J. Linn, *ibid.*, **87**, 3665 (1965).

(20) R. Huisgen, L. Möbius, G. Müller, H. Stangl, G. Szeimies, and J. M. Vernon, *Chem. Ber.*, **98**, 3992 (1965).

(21) A. S. Bailey and J. E. White, *J. Chem. Soc., Sect. B*, 819 (1966).

(22) P. D. Kadaba, *Tetrahedron*, **22**, 2453 (1966).

(23) A. Ledwith and D. Parry, *J. Chem. Soc., Sect. C*, 1408 (1966).

(24) S. Glasstone, K. J. Laidler, and H. Eyring in "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p 419.

(25) See ref 3, p 645.

(26) L. G. Wesson, "Tables of Electric Dipole Moments," Technology Press, Cambridge, Mass., 1948.

(27) N. L. Allinger and J. Allinger, *J. Org. Chem.*, **24**, 1613 (1959).

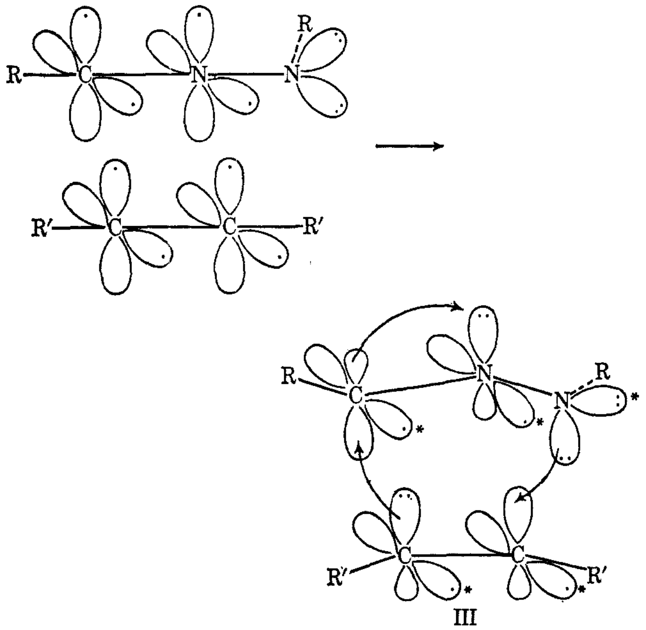
(28) J. W. Linnett, "The Electronic Structure of Molecules," Methuen and Co., London, 1964. See, for example, the structures for O_3, p 63, and N_2O, p 67.

(29) Orientational phenomena and energetics can also be explained in terms of forms like IIc. This aspect of the mechanism will be reserved for a future publication.

acrylic–propiolic esters, no such differences in reactivity are found.[15,16,30]

This question has been treated in terms of hypothetical orbital changes during reaction.[15,25] The thesis is that orbital symmetry theory[31,32] requires an acetylenic dipolarophile to approach a 1,3 dipole, such as diphenyl (nitrile imine), from above or below. The transition state is puckered and cannot profit from the aromatic resonance of the product. The resemblance of the transition state to the orientation complex (whose new σ bonds are still quite long), rather than the product, has also been stressed.[25]

However, we believe that a cycloaddition leading to an aromatic product, if it were to occur concertedly, would not be required to eschew the arrangement III, in which the five reacting atoms are coplanar. The orbitals marked with asterisks constitute the developing aromatic π cloud; they are no less parallel in III than they are in the product. The implication is not intended that electrons are localized in the orbitals as shown, or that they must move according to the arrows. They are depicted for counting purposes only. Calculations show that III does not violate the Woodward–Hoffmann theory.[33] Therefore, rate accelerations are expected with a four-center mechanism.



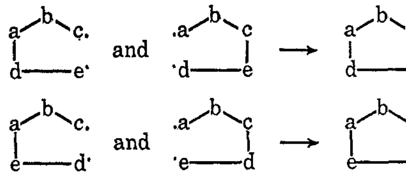
III

The normal reactivities of acetylenic dipolarophiles present no difficulty for a two-step mechanism because the appearance of the aromatic system is substantially delayed until after the rate-determining step.

F. Orientation.—Unsymmetrical dipolarophiles can add to unsymmetrical 1,3 dipoles in two directions, of which one only is usually found. An understanding of this problem requires consideration of both steric and electronic factors as well as the principle of maximum gain in σ-bond energy.[34] In addition, other forces not yet recognized may play a role.

Despite this complexity, many cases are known in which the variables seem well enough understood for predictions to be made. It is our contention that *the electronic factors, when the others are controlled, should direct the course of a concerted cycloaddition toward that orientation in which the more electrophilic end of the dipolarophile links with the negative end of the dipole.* For a two-step cycloaddition with a dipolar intermediate[13] the prediction is the same.

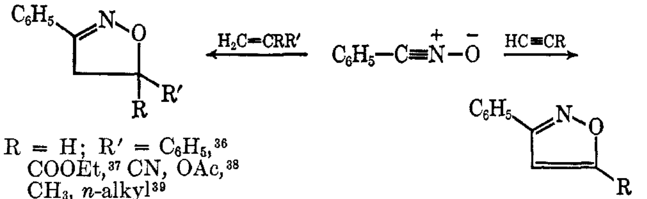
If the course of the cycloaddition passes through a diradical intermediate, however, the expected product sometimes has the opposite orientation from the one that would be formed through the other mechanisms. The method of prediction is to pick the best looking of the four possible diradical intermediates (taking into account steric, kinetic and σ-bond energy factors).



The chief difficulty is that the factors governing radical formation and stability are so poorly understood today that few secure predictions can be made. A further complication is created by the possibility that electrostatically bound prereaction complexes may sometimes influence orientation even of a fundamentally nonpolar reaction.

For these reasons, emphasis in the following section will be placed primarily on contradictions to concerted (and polar two-step) mechanisms. Diradical intermediates are drawn, not on the basis of predictions, but of orientational patterns whose principles of organization can be understood in terms of these intermediates.

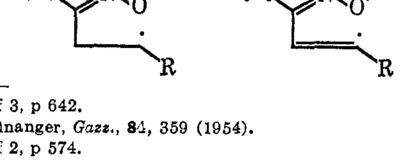
Benzonitrile N-oxide combines with all monosubstituted ethylenes or acetylenes predominantly in the same direction, whether the substituent be alkyl or aryl, electron attracting or electron donating.[35]



R = H; R′ = C_6H_5,[36] COOEt,[37] CN, OAc,[38] CH_3, *n*-alkyl[39]
R = R′ = CH_3,[39] OEt[40]

R = C_6H_5, OCH_3, OEt[40]

For one or the other group of substituents, this orientation must be wrong for a concerted cycloaddition. Both groups, however, would stabilize a diradical intermediate[41] if these structures were the preferred ones.



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[30] See ref 3, p 639.

[31] R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 2046 (1965).

[32] K. Fukui, *Bull. Chem. Soc. Jap.*, **39**, 498 (1966).

[33] We are indebted to Dr. P. I. Pollak of these laboratories for the calculations.

[34] See ref 3, p 641.

[35] See ref 3, p 642.

[36] P. Grünanger, *Gazz.*, **84**, 359 (1954).

[37] See ref 2, p 574.

[38] G. Stagno d'Alcontres and P. Grünanger, *Gazz. Chim. Ital.*, **80**, 741 (1950).

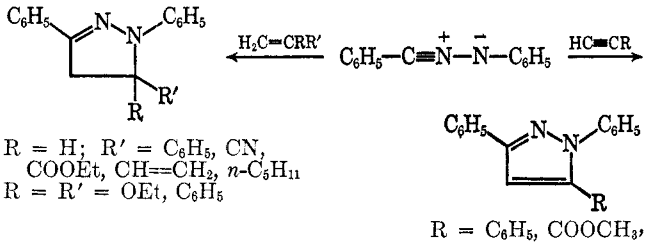
[39] G. Stagno d'Alcontres, *ibid.*, **82**, 627 (1952).

[40] P. Grünanger and M. R. Langella, *ibid.*, **89**, 1784 (1959).

[41] In accord with this idea is the report by A. Dondoni, *Tetrahedron Lett.*, 2397 (1967), that in the addition of C_6H_5CNO to p-X(C_6H_4)C≡CH, with X = NO_2, Cl, H, Me, and OMe, all substituents accelerate relative to H.

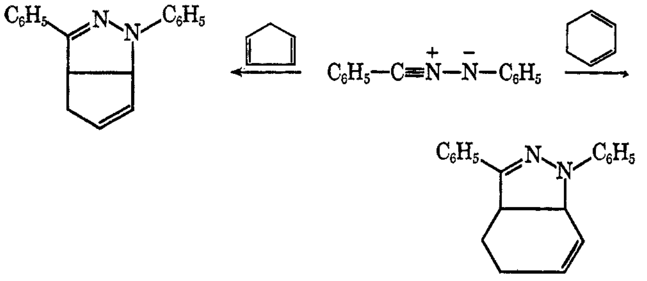
The explanation given[35] for this phenomenon was that steric factors outweighed electronic ones; yet even with $HCNO$, where steric factors are at a minimum for nitrile oxides, essentially no change in orientation is seen.[42-44]

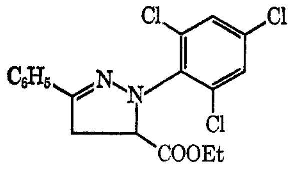
Furthermore, the same situation obtains with diphenyl(nitrile imine), a 1,3 dipole with analogous electronic structure but which now bears phenyl groups on both ends.[45,46] Even with cyclopentadiene and 1,3-cyclohexadiene, dipolarophiles which are sterically almost symmetrical, the rule is not relaxed.[45] The steric explanation is still defended,[15,47] however, based on the hypothesis that the phenyl group on the carbon atom in the 1,3 dipole, which is sp hybridized in the ground state, will suffer greater interference from the dipolarophile than will the phenyl group on the outer nitrogen atom, but the transition state for a concerted cycloaddition is sterically impossible unless the 1,3 dipole, linear in the ground state, undergoes considerable rehybridization so that it can bend. When this is done, according to our view (*vide supra*) the steric influence of the two phenyl groups is approximately equalized. Furthermore, it was impossible to reverse the direction of addition by placing bulky substituents on the N-phenyl group and the C_1 of the dipolarophile, as shown by the following adducts.[46-48] "The strictness with which the same orientation rule is followed is really remarkable and casts doubt on a purely steric interpretation."[47]

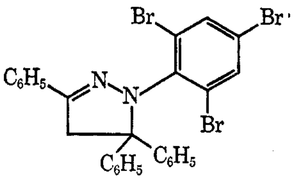


R = H; R′ = C_6H_5, CN, COOEt, $CH{=}CH_2$, $n\text{-}C_5H_{11}$
R = R′ = OEt, C_6H_5

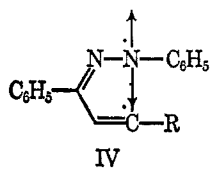
R = C_6H_5, $COOCH_3$, $CH(OPr)_2$





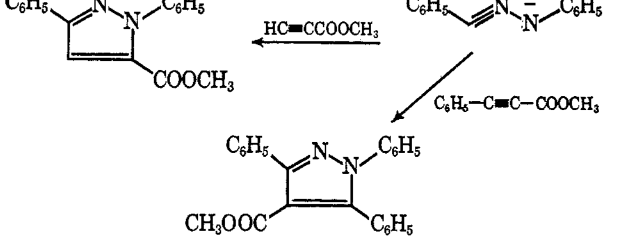


However, "the unidirectional addition to monosubstituted ethylenes and acetylenes can (admittedly) be understood in terms of the intermediate IV." We agree with this statement but Huisgen rejects it[47] on the following grounds.



IV

Diphenyl(nitrile imine) adds to propiolic and phenylpropiolic esters in the opposite direction (diphenyldiazomethane behaves similarly). This is said to reflect steric control, with phenyl bulkier than carbethoxy, and to disprove control through diradical stability because carbethoxy is more activating than phenyl. The statement is supported by the relative rate constants for addition of a variety of 1,3 dipoles onto styrene *vs.* acrylic ester; the latter is more reactive in all cases by factors ranging from 7 to 500.[12]



This argument is not convincing, however, because it assumes that the two activating groups, conjugated with each other through the same multiple bond, behave exactly as they do in separate molecules, and do not interact with each other; yet the phenyl group, normally electron attracting, undoubtedly is electron releasing toward carbethoxy in cinnamic[49] and phenylpropiolic esters. Furthermore, reversal of orientation of exactly this type is a known characteristic of radical addition; *i.e.*, carbethoxy, which normally determines the direction of radical addition in acrylic and crotonic esters, yields control to phenyl in cinnamic esters;[50,51] yet cinnamic ester is strongly deactivated relative to styrene,[52] while acrylic ester is not.[53,54]

The whole question of relative dipolarophile reactivities is shrouded with uncertainty, as shown not only by the wide range of factors previously mentioned, but also the even wider range in other comparisons, for which no rational interpretation yet exists. For example, the list of relative reactivities of ethyl acrylate *vs.* norbornene toward four varied 1,3 dipoles[30] ranges from 0.052 to 244!

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[42] A. Quilico and G. Stagno d'Alcontres, *Gazz. Chim. Ital.*, **79**, 654, 703 (1949).

[43] G. Stagno d'Alcontres and G. Fenech, *ibid.*, **82**, 175 (1952).

[44] R. Huisgen and M. Christl, *Angew. Chem. Intern. Ed. Engl.*, **6**, 456 (1967).

[45] R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, **17**, 3 (1962).

[46] J. S. Clovis, A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, and V. Weberndorfer, *Chem. Ber.*, **100**, 1593 (1967).

[47] See ref 3, p 643.

[48] R. Huisgen, R. Sustmann, and G. Wallbillich, *Chem. Ber.*, **100**, 1786 (1967).

[49] F. G. Bordwell and K. Rohde, *J. Amer. Chem. Soc.*, **70**, 1191 (1948).

[50] C. F. Koelsch and V. Boekelheide, *ibid.*, **66**, 412 (1944).

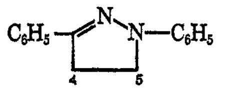
[51] M. S. Kharasch and M. Sage, *J. Org. Chem.*, **14**, 537 (1949).

[52] Toward addition of $\cdot CCl_3$, the rate ratio of ethyl cinnamate to styrene is 0.008.[51]

[53] Toward addition of a variety of radicals, the rate ratio of methyl acrylate to styrene varies from 0.18 to 1.9.[54]

[54] See ref 14, p 123.

A recent attempt has been made to put the concerted mechanism on a more quantitative basis.[15] In the addition of a large variety of dipolarophiles to diphenyl(nitrile imine), the tendency of each of the substituents methyl, isopropyl, carbalkoxy, and phenyl to occupy either the 4 or 5 position in the product was divided into a steric and an electronic component. These factors were different for each substituent but constant throughout the series for mono- and disubstituted ethylenes. In keeping with the concerted mechanism, it was found that the electronic factor for each substituent was about the same in both positions, but not the steric factor, which was generally *ca.* 0.01 for the 4 position and unity (*i.e.*, no effect at all) in the 5 position.

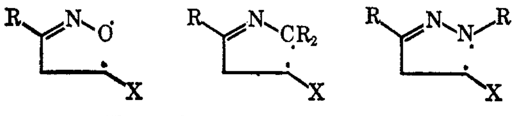


In addition to what has been said earlier about the steric phenomena, it may be pointed out that the consistency of this method rests upon the assumption, which we deem unlikely, that alkyl groups exert no electronic effect in the transition state, but a steric one only. Moreover, it is difficult to see why, in a concerted cycloaddition, the 4 but not the 5 position should be so hindered (*cf.* III), although there is no problem with a two-step mechanism (*vide infra*). As for the electronic aspect, not all substituents have a constant factor for both positions, and not all disubstituted ethylenes fit the additivity rule. The explanations have stressed the nonsynchronous nature of the reaction, but this (in addition to the point raised in section D) does not account for the constancy of the electronic factor for -COOMe in both acrylic and fumaric esters, or for the abnormally low rate for methyl 3-dimethylaminoacrylate. Space limitations preclude further discussion of this very interesting paper, whose study is recommended.

The 1,3 dipoles discussed above are two of the three members of a class of dipoles which can be imagined as having been built upon the nitrile group (see below).

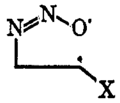
$R{-}C{\equiv}\overset{+}{N}{-}\overset{-}{O}$	nitrile oxides
$R{-}C{\equiv}\overset{+}{N}{-}\overset{-}{N}{-}R'$	nitrile imines
$R{-}C{\equiv}\overset{+}{N}{-}\overset{-}{C}R'_2$	nitrile ylides

This group as a whole shows a strong unidirectional pattern of orientations which, in our opinion, is not polar in origin, and yet is clearly electronic in nature rather than steric. When consideration is limited to dipolarophiles whose sites of favored radical addition can be "safely" predicted, such as acrylic esters, styrene, 1,3-butadiene, etc., the predicted best diradical intermediates look very much alike. Within this framework, of course, steric effects are still to be anticipated; *cf.* diphenyl(nitrile imine).

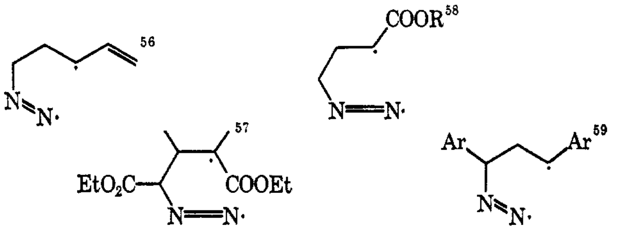


X = $-COOR, -C_6H_5, -CH{=}CH_2$

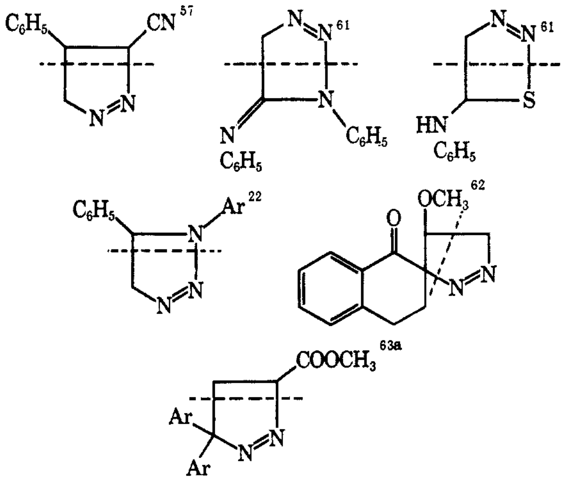
The group of 1,3 dipoles built similarly upon the nitrogen molecule consists of nitrous oxide, diazoalkanes, and alkyl and aryl azides. The first dipole fits the best diradical rule, although data are sparse.[55]



Diazoalkanes, however, add in the opposite sense, although it remains true that the predicted best diradical is always of the same type (that shown below).



It should be noted that in some of these cases, as well as in the adducts shown below, the orientation is contrary to that predicted by our interpretation of the one-step mechanism because diazoalkanes are polarized with the outer nitrogen negative.[60]



The addition of azides, however, cannot be fitted to a best diradical rule. With dipolarophiles containing electron-releasing substituents they add predominantly in one direction, which is reversed when the substituents are electron attracting.

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(55) See ref 2, p 580.

(56) E. Müller and O. Roser, *J. Prakt. Chem.*, **133**, 291 (1932).

(57) K. v. Auwers and O. Ungemach, *Ber.*, **66**, 1198, 1205 (1933).

(58) See ref 2, p 576.

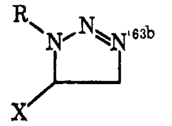
(59) C. G. Overberger, N. Weinshenker, and J-P. Anselme, *J. Amer. Chem. Soc.*, **87**, 4119 (1965).

(60) See ref 2, p 575.

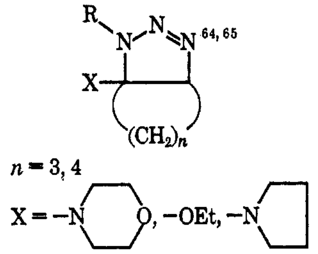
(61) See ref 2, p 577.

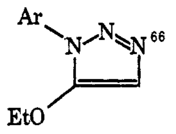
(62) D. Nasipuri and K. K. Biswas, *Tetrahedron Lett.*, 2963 (1966).

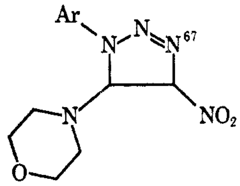
(63) (a) W. M. Jones, P. O. Sanderfer, and D. G. Baarda, *J. Org. Chem.*, **32**, 1367 (1967); (b) see ref 2, p 579.

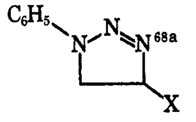


X = –C_6H_5, –OR, –NR_2

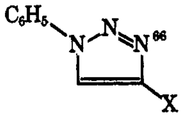








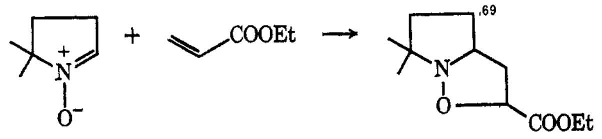
X = –$COOCH_3$, –Ac, –CN

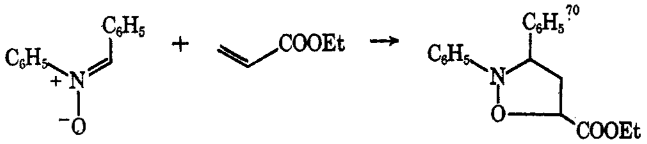


X = –COOH, –$COOCH_3$

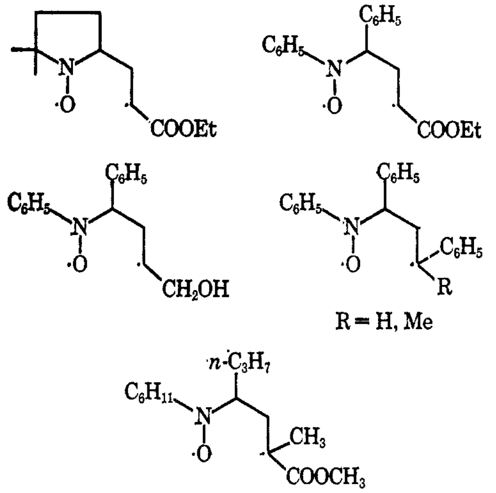
In all these cases, the orientations are not those predicted for concerted cycloadditions because azides are polarized with the outer nitrogen negative.[68b]

Nitrones are another class of 1,3 dipoles whose direction of addition is frequently incorrect for polar and one-step pathways.





Moreover, a strong pattern of "favored diradical" intermediates is again discernible.[70,71]



It is true that a steric explanation could also account for orientation with nitrones, but in most of these examples the expected steric effect seems to us rather small.

In the preceding discussion, stress has been placed on the unidirectional nature of addition of many classes of 1,3 dipoles to olefins whose activating groups can all stabilize radicals but not always the proper type of charge. Attention must therefore now be drawn to azomethine imines, a class that does not add unidirectionally. The orientation among their adducts cannot easily be rationalized by the diradical mechanism,[72] and we must admit the likelihood of a concerted or two-step polar pathway. Another peculiarity of azomethine imines, however, is that their cycloadditions are frequently reversible, and perhaps the products that have been isolated are not always the first ones formed; this difficulty has cropped up in the nitrone series.[69]

G. Conclusion.—The extensive and rapid development of the field of 1,3-dipolar cycloadditions, for which Professor Huisgen's group is almost entirely responsible, has been accompanied, in our opinion, by insufficient debate on the part of other chemists as to the details of mechanism; yet even tiny differences among possible reaction pathways can be of great importance because they affect our picture of the nature of chemical binding, a matter of vital interest to chemists. The intent of this paper, therefore, is not to settle controversy but to arouse discussion.

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(64) R. Fusco, S. Rossi, and S. Maiorana, *Tetrahedron Lett.*, 1965 (1965).

(65) R. Huisgen, L. Möbius, and G. Szeimies, *Chem. Ber.*, **98**, 1138 (1965).

(66) R. Huisgen, R. Knorr, L. Möbius, and G. Szeimies, *ibid.*, **98**, 4014 (1965).

(67) S. Maiorana, D. Pocar, and P. Dalla Croce, *Tetrahedron Lett.*, 6043 (1966).

(68) (a) R. Huisgen, G. Szeimies, and L. Möbius, *Chem. Ber.*, **99**, 475 (1966); (b) see ref 2, p 578.

(69) G. R. Delpierre and M. Lamchen, *J. Chem. Soc.*, 4963 (1963).

(70) See ref 2, p 588.

(71) M. Iwamura and N. Inamoto [*Bull. Chem. Soc. Jap.*, **40**, 702, 703 (1967)] report that nitrones undergo 1,3 addition of two free radicals, with the first most probably adding to carbon.

(72) See ref 2, p 583.