On the Mechanism of 1,3-Dipolar Cycloadditions. A Reply

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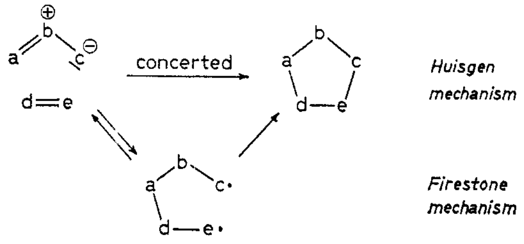
The arguments for a diradical intermediate proposed in the preceding paper are refuted. The available evidence speaks for a concerted addition. The "two-planes" orientation complex of 1,3 dipole and dipolarophile is experimentally well founded and with its $(4 + 2)\ \pi$ electrons allows a concerted thermal addition. Activation parameters, *cis* stereospecificity, and solvent dependence are in accord with this mechanism. Substituent effects and orientation phenomena are discussed.

Criticism and reply contribute to clarification. Dr. Firestone's valuable comments are welcomed because they present an opportunity to discuss some widespread significant misinterpretations. It will be up to the reader to decide whether the concept of a single-step concerted 1,3-dipolar cycloaddition[1] will be hardened in criticisms *fire* to *stone* or will crumble into dust.

Terminology.—Doering and Roth's[2] description of a "no-mechanism" reaction has wittily stressed the impossibility of obtaining *direct* mechanistic proof. In the meantime, the processes with cyclic electron shifts have grown into a rather large class of reactions, which are no less understood than many other single-step processes. Thus the pessimism which is implied in the term "no-mechanism" reaction seems no longer justified, especially since the principle of conservation of orbital symmetry[3] provides a fruitful theoretical basis for such processes.

cis **Stereospecificity.**—The greatest obstacle for the assumption of a diradical intermediate is the stereospecificity observed in the cycloadditions of the 1,3 dipole with *cis–trans* isomeric dipolarophiles. 1,3-Dipolar cycloaddition shares this characteristic as well as others with the Diels–Alder reaction. Firestone overcomes this obstacle by the ingenious, but improbable hypothesis that in the diradical **1** the energy barrier for rotation around single bonds is greater than the activation energy for ring closure or for reversion of **1** to the reactants. Thus, all diradicals **1** which are not formed in the correct conformation for ring closure will return to starting materials.



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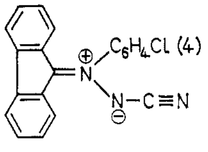
Reversion includes a change of hybridization at a and d and, concomitantly, a deep-seated alteration of molecular geometry. The bond ad of **1** must undergo considerable stretching before the retrograde process can profit from the incipient formation of the π bonds. A low activation barrier for reversion is contrary to our chemical intuition, but also is not reconcilable with known facts. Montgomery, Schueller, and Bartlett[4] observed a high degree of stereoequilibration in the cycloaddition of 1,1-dichloro-2,2-difluoroethylene to the geometrical isomers of 2,4-hexadiene. In the spin-paired diradical involved (it appears to be the 1,4 analog of **1**), the rotation competes well with the ring closure. Even open-chain 1,4 zwitterions, such as the one formed from 1,2-bis(trifluoromethyl)-1,2-dicyanoethylene and *cis*-propenyl propyl ether, do not fully retain configuration during ring closure[5] despite electrostatic attraction.

Firestone's hypothesis becomes the more artificial and the less tenable, since the strength of the bond ad in the intermediate **1** may vary. By linking the whole set of 1,3 dipoles with the dipolarophiles, the bond ad can be made up of nearly every combination of C, N, and O. A single example of a *cis*-stereospecific addition would not be a convincing mechanistic argument. However, stereospecificity is regarded a more weighty criterion for concertedness, if no exception is found in several dozen cases with a large variety of 1,3 dipoles. A scrupulous search for a mutual admixture of adducts has disclosed stereospecificity for cycloadditions of the following 1,3 dipoles: diphenylnitrilimine,[6,7] benzonitrile N-oxide,[8,9] diazomethane,[10,11] 4-nitrophenyl azide,[12] an azomethine ylide of the 1-pyrroline series,[13] the azomethine imines **2**[14] and **3**,[15,16] 3.4-dihydroisoquinoline N-oxide,[17] and the carbonyl ylide **4**.[18]



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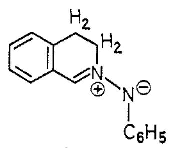

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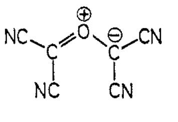

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In Scheme I, implied by Firestone's mechanism, the reversion of **1** to reactants must be at least 30 times

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(1) R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 633 (1963).

(2) W. v. E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).

(3) R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 395, 2046, 2511, 4388, 4389 (1965).

(4) L. K. Montgomery, K. Schueller, and P. D. Bartlett, *ibid.*, **86**, 622 (1964).

(5) S. Proskow, H. E. Simmons, and T. L. Cairns, *ibid.*, **88**, 5254 (1966).

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

(7) R. Huisgen, H. Knupfer, R. Sustmann, G. Wallbillich, and V. Weberndörfer, *Chem. Ber.*, **100**, 1580 (1967).

(8) A. Quilico, G. Stagno d'Alcontres, and P. Grünanger, *Gazz. Chim. Ital.*, **80**, 479 (1950).

(9) M. Christl, Diploma Thesis, University of München, 1966.

(10) K. v. Auwers and E. Cauer, *Ann.*, **470**, 284 (1929).

(11) P. Eberhard, Diploma Thesis, University of München, 1967.

(12) R. Huisgen and G. Szeimies, *Chem. Ber.*, **98**, 1153 (1965).

(13) R. Huisgen, H. Gotthardt, and H. O. Bayer, *Tetrahedron Lett.*, 481 (1964).

(14) A. Eckell, Ph.D. Thesis, University of München, 1962; see ref 1, p 636.

(15) R. Huisgen, R. Grashey, P. Laur, and H. Leitermann, *Angew. Chem.*, **72**, 416 (1960); see ref 16, p 583.

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

(17) R. Huisgen, H. Seidl, R. Grashey, and H. Hauck, *Chem. Ber.*, in press; see ref 1, p 637.

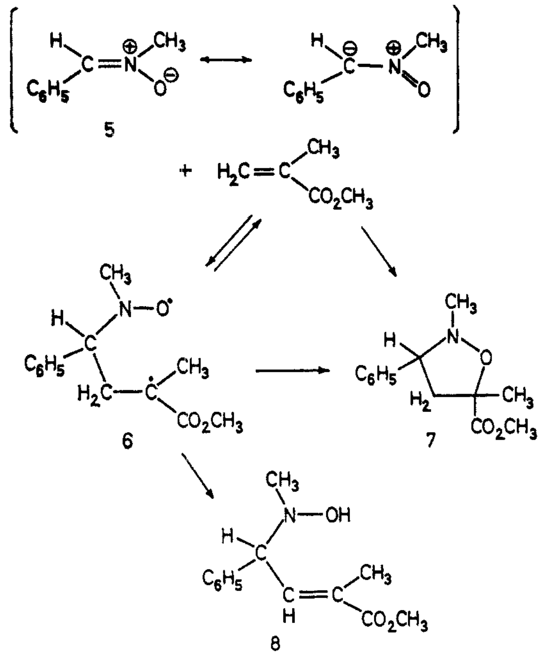
(18) W. J. Linn and R. E. Benson, *J. Amer. Chem. Soc.*, **87**, 3657 (1965).

SCHEME I

$$\begin{tikzcd}
\text{reactants} \arrow[r, shift left] & \text{diradical } \mathbf{1} \arrow[l, shift left] \arrow[r] \arrow[d, "\text{rotation around d-e}"] & \text{stereospecific product} \\
& \text{isomeric diradical} \arrow[r] & \text{nonstereospecific product}
\end{tikzcd}$$

faster than rotation around d-e to account for the observed stereospecificity ($\leqslant 3\%$ of isomeric adduct). Thus, $\Delta G^{\ddagger}$ of the retrograde process **1** → reactants is at least 2.1 kcal smaller than the rotation barrier which is probably not greater than 3.4 kcal. The activation energy of the reversion process must therefore be smaller than 1.3 kcal/mol!

Energetics of Firestone's Diradical Intermediate.—The spin-paired diradical intermediate **1** contains one σ bond more, but two π bonds less than the reactants. Furthermore, the resonance energy, which stems from the π delocalization of the 1,3 dipole, has to be sacrificed and the stabilization energy of the diradical is gained. On comparing the energy balance for the formation of **1** with experimental values of activation enthalpies, one becomes aware of a discrepancy which precludes the possible occurrence of **1**. Regrettably, some of the thermochemical data are unknown so that we must depend on "sound guesses."



The addition of N-methyl-C-phenylnitrone (**5**) to methyl methacrylate in toluene shows the following Eyring parameters: $\Delta H^{\ddagger} = 15.7$ kcal/mol, $\Delta S^{\ddagger} = -32$ eu.[19] For the formation of **6** we calculate a net loss of 54 kcal/mol in bond energy; the activation energy has to be larger (Table I).

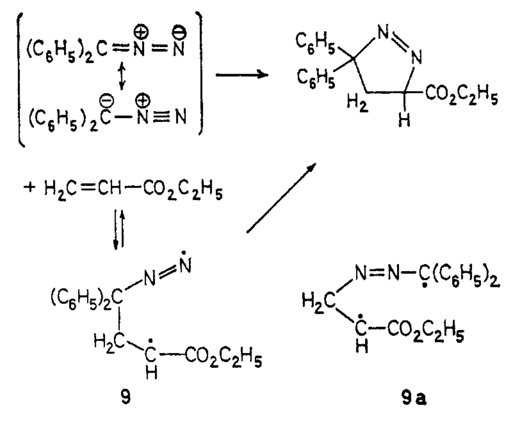
Furthermore, O radicals are notorious for their hydrogen affinity. The diradical **6** (were it formed) should produce the unsaturated hydroxylamine **8** *via* intramolecular disproportionation;[20] this conversion is expected to be exothermic by ≈ 55 kcal/mol. A side product of type **8** has never been isolated in cycloadditions of nitrones, nor has any other 1,3-dipole + dipolarophile system produced an analogous product. Also hydrogen transfer from the solvent to intermediate **1** has not been observed.

TABLE I

Loss	
$C{=}C \rightarrow C{-}C$	65 kcal/mol
$C{=}N \rightarrow C{-}N$[a]	68
$C_6H_5C{=}$ conjugation energy	4
Nitrone resonance[b]	20
$CH_3O_2C(CH_3)C{=}$ conjugation	4
	161 kcal/mol
Gain	
$C{-}C$	83
Resonance energy of the diradical **6**[c]	24
	107 kcal/mol

[a] A. F. Bedford, P. B. Edmondson, and C. T. Mortimer [*J. Chem. Soc.*, 2927 (1962)] found 74.7 kcal/mol for C—N and 142.6 for C=N. The more suitable data for $C{-}N^+$ and $C{=}N^+$ are not known. [b] From pK_a values, a resonance energy of the allyl anion of 9 kcal is derived: D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, p 19. The resonance energy of the carboxylate anion is 36 kcal: L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, 1960. The resonance energy of the nitrone should lie in between. [c] Partial use of data given by C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p 50.

For the addition of diphenyldiazomethane to ethyl acrylate in dimethylformamide, $\Delta H^{\ddagger} = 8.0$ kcal/mol and $\Delta S^{\ddagger} = -43$ eu were measured.[21] Diazomethane adds even faster by a factor of 10^2.[22] An analogous crude calculation reveals that the diradical **9** possesses ≈ 65 kcal/mol less bond energy than the reactants. The other addition direction (which was not observed) should furnish the better diradical **9a**.



Why does the diradical **9**, according to Firestone, revert to reactants instead of losing nitrogen? If the decarboxylation of the acetoxy radical is exothermic by 20 kcal/mol,[23] should not the tendency to cleave the C—N bond to form a diphenylmethyl radical + N_2 be still higher? In fact, the known reactions of diazoalkanes with triphenylmethyl,[24,25] trichloromethyl,[26,27]

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(19) Ph.D. Thesis, H. Seidl, University of München, 1964; see ref 1, p 637.

(20) For an example, see C. G. Overberger and J. G. Lombardino, *J. Amer. Chem. Soc.*, **80**, 2317 (1958).

(21) R. Huisgen, H. Stangl, H. J. Sturm, and H. Wagenhofer, *Angew. Chem.*, **73**, 170 (1961).

(22) Experiments of D. Jung, München, 1963.

(23) S. W. Benson, *J. Chem. Educ.*, **42**, 502 (1965).

(24) W. Schlenk and C. Bornhardt, *Ann.*, **394**, 183 (1912).

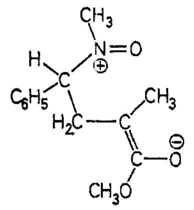
(25) D. B. Denney and N. F. Newman, *J. Amer. Chem. Soc.*, **89**, 4692 (1967).

(26) W. H. Urry and J. R. Eiszner, *ibid.*, **74**, 5822 (1952).

(27) W. H. Urry and J. W. Witt, *ibid.*, **76**, 2594 (1954).

or nitric oxide[28,29] are acompanied by immediate loss of nitrogen.

We see a better alternative to the concerted pathway of 1,3-dipolar cycloaddition in the formation of a zwitterionic intermediate; **10** and **11** would correspond with **6** and **9**. The zwitterions contain the same number of bonds as the reactants. We have discussed their possible intermediacy in detail elsewhere;[1] recently, such zwitterionic intermediates in the addition of organic azides were abandoned on the basis of hard experimental facts.[30]



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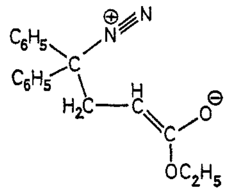

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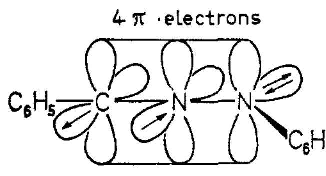
Electronic Structure of the 1,3 Dipole.—*A 1,3 dipole is a compound abc which undergoes 1,3 cycloadditions and is described by zwitterionic octet structures.*

The author does not understand the significance of Firestone's formula IIc for the 1,3 dipole. In the corresponding text a "blend of dipolar and radical qualities" and "diradical attributes of II" are mentioned. A diradical is by definition a structure with two electrons which do not form a bond. According to classical resonance theory,[31] diradical resonance contributions can be neglected, because they contain one bond less than the zwitterionic octet formulae **12** and **13** of the 1,3 dipole.

$$12 \qquad a\equiv\overset{\oplus}{b}-\overset{\ominus}{c} \longleftrightarrow \overset{\ominus}{a}=\overset{\oplus}{b}=c \qquad (b = N)$$

$$13 \qquad a=\overset{\oplus}{b}-\overset{\ominus}{c} \longleftrightarrow \overset{\ominus}{a}-\overset{\oplus}{b}=c \qquad (b = N-R, O)$$

The author is convinced that MO theory affords a superior description. All 1,3 dipoles contain four π electrons in three parallel p orbitals. As in the isoelectronic allyl anion, the four electrons occupy pairwise the two lowest molecular orbitals. Formulae **14** (diphenylnitrilimine) and **15** (N-methyl-C-phenylnitrone) illustrate this for one dipole of each class (with and without a double bond in the 1,3 sextet structure).[16] As pointed out below, this allyl anion structure is responsible for the ability of the 1,3 dipole to undergo cycloadditions.[32,33]



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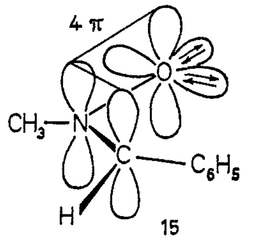

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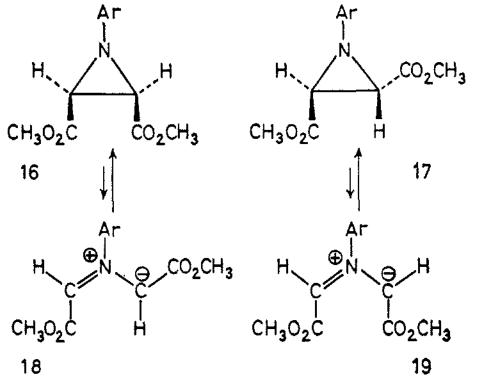
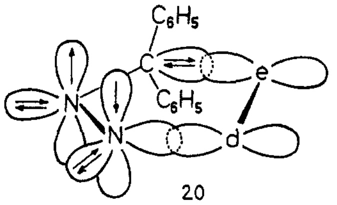
The molecular orbital description of the 1,3 dipole leaves no room for a "spin-paired diradical structure." Only by promoting one electron into the next higher molecular orbital—higher in energy by $2\sqrt{2\beta}$[34]—is a state reached where the two electrons do not form a bond. However, this excited singlet state has not much to do with the ground state which enters into cycloaddition reactions.

Firestone mentioned, in this connection, that Linn[35] proposed a diradical structure for "activated" tetracyanoethylene oxide which undergoes cycloadditions; these, incidentally, obey all the criteria of 1,3-dipolar cycloadditions. Linn described the species as a zwitterion–biradical hybrid which is open to the same objections expressed above. Linn regarded a 1,3-dipolar ion as untenable, because the structure should be symmetrical; he overlooked the fact that resonance of the type **13**—two identical canonical structures—offers perfect symmetry.

Linn's intermediate is the carbonyl ylide **4**. This follows from the close analogy with the thermal opening of the aziridine ring in **16** and **17** which gives stereospecifically the *cis-trans* isomeric azomethine ylides **18** and **19**.[36,37] The conrotation established here is in accord with the Woodward-Hoffmann prediction[3] for the isoelectronic system cyclopropyl anion → allyl anion.



Electronic Pathway of 1,3-Dipolar Cycloaddition.—On the first glance at the general scheme, one is tempted to assume that all five centers of 1,3 dipole and dipolarophile form a planar transition state. This mistake is repeated by Firestone in section E.



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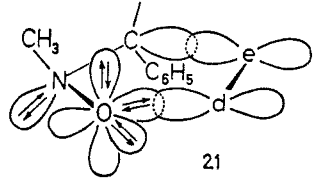

21

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(28) L. Horner, L. Hockenberger, and W. Kirmse, *Chem. Ber.*, **94**, 290 (1961).

(29) O. L. Chapman and D. C. Heckert, *Chem. Commun.*, 242 (1966).

(30) R. Huisgen, G. Szeimies, and L. Möbius, *Chem. Ber.*, **100**, 2494 (1967).

(31) G. W. Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p 15.

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

(33) See ref 1, p 644.

(34) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, p 40.

(35) W. J. Linn, *J. Amer. Chem. Soc.*, **87**, 3665 (1965).

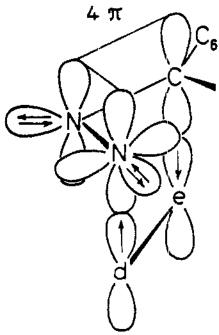
(36) R. Huisgen, W. Scheer, and H. Huber, *ibid.*, **89**, 1753 (1967).

(37) R. Huisgen, *Helv. Chim. Acta*, **50**, 2421 (1967).

A closer inspection reveals paradoxical consequences. The linear nitrilium and diazonium betaines must bend to make contact with the orbitals of the dipolarophile. The direction of bending in diphenyldiazomethane, shown in **20**, destroys the diazoalkane resonance. This kind of bending alone probably needs more energy than the $\Delta H^{\neq} = 8.0$ kcal/mol found for the whole activation process.

The nitrone **5** as an azomethine oxide is bent in the ground state. However, to reach the planar transition state **21**, twisting around the C—N bond must occur, so that the nitrone resonance is lost.

In contrast to Firestone's opinion, the Woodward–Hoffmann rules[3] cannot be applied to the transition states **20** and **21** for the cycloadditions.[38] The electrons involved on the side of the 1,3 dipole are not arranged in a proper molecular orbital. The four electrons are not even π bonded but occupy two lone-pair orbitals. Furthermore, in **21** the conjugation is damaged. A concerted cycloaddition through a low-energy transition state is inconceivable.



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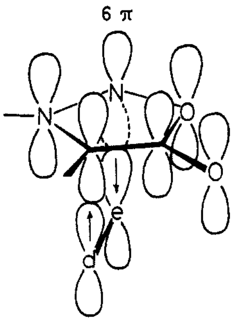
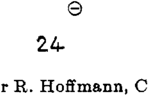


23

Formula **22** depicts the orientation complex preceding the transition state for the addition of diphenyldiazomethane to a dipolarophile de, according to our theory, first published in 1963.[33] Here, the bending of the linear 1,3 dipole *within* the horizontal plane preserves the allyl anion orbital which makes contact with the π bond of the dipolarophile. The gradual rehybridization from p to sp^3 and sp^2 orbitals, which occurs during the reaction, is accompanied by an uplifting of the middle diazoalkane nitrogen until it reaches the 1-pyrazoline plane in the product.

The "two-planes" orientation complex **22** indicates that (4 + 2) π electrons are involved in the cycloaddition process exactly as in the Diels–Alder reaction. The symmetry considerations[39] with the correlation diagrams reveal that the concerted thermal cycloaddition is allowed.[32]

We proposed the orientation complex **22** before Woodward and Hoffmann[3] published the rules for conservation of orbital symmetry. This proposal was supported by our experimental finding that sydnones **24** and mesoionic oxazolones **25** react as 1,3 dipoles with alkenes and alkynes.[40,41] These cycloadditions showed all the typical features of the 1,3-dipolar type: moderate activation enthalpies, high negative activation entropies, small solvent dependence, the usual activity scale of dipolarophiles.[42]



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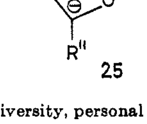

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Sydnone **24** and ψ-oxazolones **25** are planar aromatic structures. Since they exhibit azomethine imine or azomethine ylide reactivity, respectively, only an orientation complex like **23** is possible.[43] To avoid a highly improbable dichotomy of mechanistic pathways, we postulated that *all* 1,3-dipolar cycloadditions follow the pattern shown in **22** and **23**. It is quite satisfying that the "two-planes" model strengthens the close relation to Diels–Alder addition in the application of the Woodward–Hoffmann rules.

If this model for the steric course is accepted, Firestone's arguments concerning relative rates of addition to acetylenic and olefinic dipolarophiles become irrelevant. The reader is referred to our earlier discussion.[44]

Solvent Effects on Rates.—Our kinetic studies disclose that 1,3-dipolar cycloadditions are only moderately influenced by solvent polarity;[1] spreads of rate constants by a factor of no less than $^1/_6$ and no more than 10 with increasing polarity of the solvent were found.[14,30] Firestone's intuitive criticism stems from the false expectation that the disappearance of the 1,3 dipole should bring about a strong inverse dependence on solvent polarity.

However, the term 1,3 dipole should not be misunderstood to imply a high dipole moment. The charge compensation by resonance of type **12** or **13** is often quite extensive as shown by μ = 1.42 D for diphenyldiazomethane or 1.56 D for phenyl azide. Furthermore, if one sums the resonance structures of **12** and **13**, the anionic charge is distributed on either side of the positive center, giving a "tripole."[45] Such "tripoles" seem to be poorly solvated. On the other hand, the dipole moments of cycloadducts often approach the ones of the corresponding 1,3 dipoles or even exceed them.

We regard the magnitude of solvent effects as entirely adequate for the concerted pathway of 1,3-dipolar cycloaddition. With the supposition of zero solvent dependence on rate, one can calculate the dipole moment of the transition state from those of the two reactants on the basis of Kirkwood's theory.[46] We have compared such values with dipole moments of the adducts. Successful estimates of solvent influences on rates were based on the model of a continuous transition from reactants to adduct (one-step process).[1,47]

Even additions of those 1,3 dipoles whose dipole moment exceeds 5 D are slowed down only moderately with increasing solvent polarity. How far has bond

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(38) Professor R. Hoffmann, Cornell University, personal communication.

(39) H. C. Longuet-Higgins and E. W. Abrahamson, *J. Amer. Chem. Soc.*, **87**, 2045 (1965).

(40) R. Huisgen, R. Grashey, H. Gotthardt, and R. Schmidt, *Angew. Chem. Intern. Ed. Engl.*, **1**, 48 (1962).

(41) R. Huisgen, H. Gotthardt, and R. Grashey, *ibid.*, **1**, 49 (1962).

(42) R. Huisgen, The Chemical Society, Special Publication No. 21, The Chemical Society, London, 1967, p 51.

(43) For the sake of clarity, lone pair orbitals of the N and O atoms of the sydnone ring in formula **23** have been omitted.

(44) See ref 1, pp 639 and 645.

(45) In a correcter terminology it would be a quadrupole.

(46) J. G. Kirkwood, *J. Chem. Phys.*, **2**, 351 (1934). This theory has been developed into a correlation between rate constants of bimolecular reactions and dielectric constants of solvents by S. Glasstone, K. L. Laidler, and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p 419.

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

formation progressed in the transition state? If the orientation complex (like **22** and **23**) is formed, the major part of the "entropy price" is paid. Our guess, that the formation of the two new σ bonds has reached some 20 or 30%, should not be taken too literally. Nevertheless, 1,3 dipoles with large moments should still possess much of their polarity in the transition state.

In our opinion, the low solvent dependence is much less compatible with the formation of Firestone's diradical intermediate in the rate-determining step. According to recognized principles, the transition state should be close to the structure of a high-energy intermediate. In cases of more polar 1,3 dipoles, one should anticipate a sharper drop of rate constant with increasing solvent polarity.

Conjugation and the Activity of the Dipolarophile.—Conjugation with *electron-attracting* or *electron-releasing* substituents increases the dipolarophilic activity of a multiple bond. If one plots the electron density of an olefinic double bond *vs.* cycloaddition rates, U-shaped curves are obtained which are different for various 1,3 dipoles.

We have explained this phenomenon by two effects which might well be interrelated:[1,32] (1) conjugation increases the polarizability of the π bond of the dipolarophile; (2) concerted formation of the two new σ bonds is not necessarily synchronous, *i.e.*, a precise "marching-in-step." Unequal progress of bond formation in the transition state leads to partial charges, which can be stabilized by substituents.

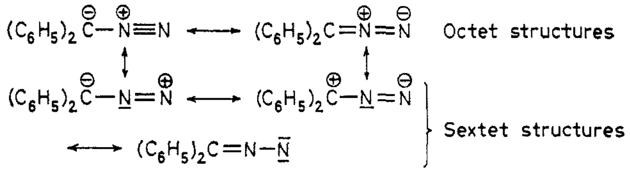
Firestone regards effect 2 as "an important departure from the concerted cycloaddition theory." We cannot agree. The idea of unequal bond formation and breaking has become a fruitful rationale in the interpretation of many mechanisms. Is it necessary to remind the reader of the spectrum of solvolysis reactions which varies in the amount of bonding by the nucleophile in the transition state? Has not the same principle been very successful in classifying E2 reactions?[48,49] There is no theoretical reason to renounce this principle in the treatment of cycloadditions.

Rate increase by conjugation is one of many characteristics which strengthens the close mechanistic relationship between 1,3-dipolar cycloaddition and the Diels–Alder reaction. A careful weighing of all mechanistic criteria recently led Sauer[50] to favor strongly the concerted mechanism for the latter reaction.[51]

Orientation Phenomena.—The largest section of Firestone's paper deals with orientation. These phenomena constituted the starting point and the central argument of the diradical hypothesis. We join Firestone in the opinion that the addition reactions of azomethine imines do not fit the diradical theory, and the orientations followed by organic azides do not conform to a best diradical rule. In our eyes, diazoalkanes also preferably show orientations which are not in harmony with the best diradical. By supplementing the examples above with unpublished data or reactions not considered by Firestone, one approaches a statistical 50:50 of orientations consonant and dissonant with the diradical hypothesis; only two orientations are possible.

Some 1,3-dipolar cycloadditions are reversible. The suspicion raised by Firestone that separation of kinetic and thermodynamic control has not always been achieved is undeserved. We investigated this point carefully. The orientation phenomena which we published in our some 70 papers in the field are *kinetically* determined.

Instead of expanding grossly the list of discrepancies between observed orientations and the ones predicted for the diradical intermediate, we wish to emphasize a major point. Firestone's assumption that many orientations are in conflict with the concerted mechanism is the result of a misconception. The widespread contention that the electrophilic end of the dipolarophile should link with the negative end of the 1,3 dipole is built on sand. The formal negative charge of the 1,3 dipole is distributed on either side of the onium center as illustrated by diphenyldiazomethane. In the sextet structures, the formal charges are interchangeable. (Normally we avoid the use of sextet structures in formulation, because they are often misinterpreted as "reaction formulae.") What is the nucleophilic end of diphenyldiazomethane? The direction of the small dipole moment indicates that the outer nitrogen bears a larger part of the negative charge. However, a carbanion is more nucleophilic than an anionic nitrogen.[52]



As we have pointed out repeatedly,[1,53] *it is not meaningful to assign an electrophilic and a nucleophilic end to a 1,3 dipole.* Otherwise, it would be possible to define a direction of the cyclic electron shift in the addition process—clockwise or counterclockwise. Does the fact that the two ends of ozone are identical decrease its 1,3-dipolar activity? A consideration of the MO description of concerted additions reveals that it is only meaningful to attribute a certain electron density to the incipient σ bonds in the transition state.

The orientation phenomena in 1,3-dipolar as well as Diels–Alder addition offer perhaps the biggest *unsolved* problem in the field. We have discussed the possible interplay of steric and electronic factors, but we never pretended to have a full understanding. Rate and orientation phenomena in aromatic and aliphatic substitutions have been studied for decades; one knows a lot, but consistency is still lacking. Systematic exploration of substituent effects in concerted cycloaddition is still in its infancy. Thus, the detailed discussion may be limited to a few examples which prove the concertedness of the cycloaddition in question.

1. Many additions which were described earlier as unidirectional turned out to give mixtures. Firestone

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(48) C. K. Ingold, *Proc. Chem. Soc.*, 265 (1962).

(49) J. F. Bunnett, *Angew. Chem.*, **74**, 731 (1962).

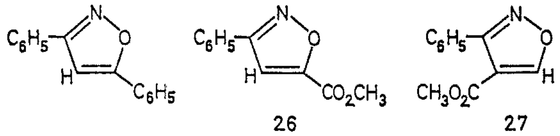
(50) J. Sauer, *Angew. Chem. Intern. Ed. Engl.*, **6**, 16 (1967).

(51) Compare R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, Inc., London, 1964, p 739.

(52) In the discussion of diazoalkane and azide additions, Firestone does not distinguish properly between nucleophilicity and the amount of negative charge.

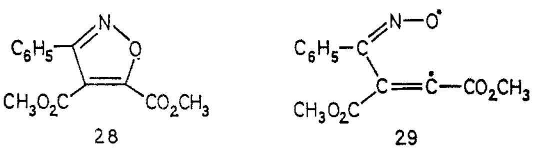
(53) R. Huisgen, *Bull. Soc. Chim. Fr.*, 3431 (1965).

uses benzonitrile N-oxide additions as witness no. 1 for the diradical concept. This nitrile oxide combines with methyl propiolate to give a 72:28 mixture of the isoxazoles **26** and **27**,[54] hardly compatible with a diradical intermediate. Why should the relative addition constant, measured by competition experiments,[55] be larger for dimethyl acetylenedicarboxylate (formation of **28**) than for methyl propiolate? The second methoxycarbonyl group cannot contribute much to the stability of **29**. The acceleration by conjugating substituents at *either* side of the acetylenic bond leaves no doubt that *both centers* participate in the rate-determining step.



26 27

k_2(rel.) ≡ 1.0 7.0 2.7

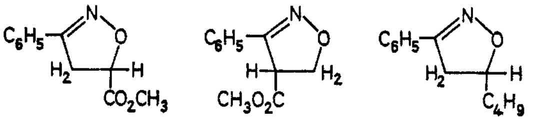


28 29

k_2(rel.) 27

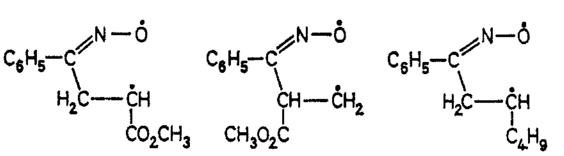
The same effect appears in the cycloadditions of the azomethine imine **2** (chlorobenzene, 80°)[56] or N-methyl-C-phenylnitrone **5** (toluene, 85°),[19] where dimethyl acetylenedicarboxylate adds 11 times or 29 times faster, respectively, than methyl propiolate. Using C-methyl-N-phenylsydnone (**24**) the following values for 10^5k_2 were found: 1-tetradecyne, 6.0; methyl propiolate, 823; dimethyl acetylenedicarboxylate, 2580 (*p*-cymene, 140°).[57]

2. Benzonitrile N-oxide adds to methyl acrylate to give the methyl 5-carboxylate **30** and the 4-carboxylate **31** in 96 and 4% yield.[9] That corresponds to $\Delta\Delta G^\ddagger$ = 1.9 kcal/mol for the two directions; the energy difference between the corresponding diradicals **33** and **34** should amount to well above 12 kcal/mol. The better stabilization of **35** compared with that of **34** does not show up in the rate factors.



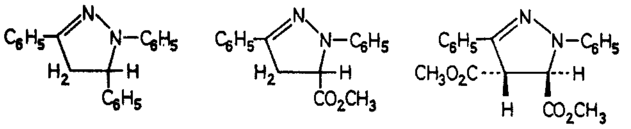
30 31 32

k_2(rel.) 27 1.1 ≡ 1.0



33 34 35

3. The *quantitative* evaluation of substituent effects is more advanced for cycloadditions of diphenylnitrilimine. The following sequence discloses the increasing dipolarophilic activity in the series 1-alkene, methyl acrylate, dimethyl fumarate.[32] Substituents at either end of the ethylene system contribute additively to the activation energy of the cycloaddition as demonstrated for many dipolarophiles.[32] Our numerical separation of substituent effects into steric and electronic factors contains some arbitrariness, as Firestone mentions. However, the net effects satisfy the additivity principle within certain limits.

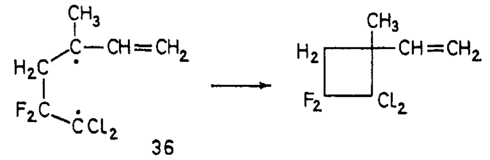


k_2(rel.) ≡ 1 343 2 050

One anticipates that the rate constant of a concerted addition to a substituted ethylene will be the product of k_2 (ethylene) and all substituent factors, but how should the Firestone diradical from diphenylnitrilimine and dimethyl fumarate profit from the second methoxycarbonyl, located at a saturated center?

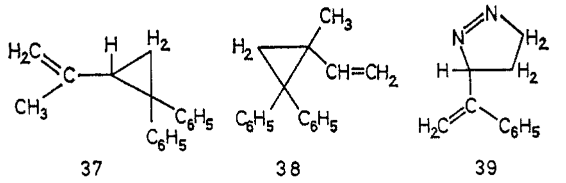
4. Also the dienophilic activity of ethylene in Diels–Alder reactions is increased by substitution at either carbon atom. Rate constants for cyclopentadiene additions to cyanoethylenes[58] at 20° spread over an impressive range ($10^5k_2 \cdot \text{mol}^{-1}\ \text{sec}^{-1}$): $H_2C{=}CHCN$ (1.0); $NCCH{=}CHCN$ (81); $H_2C{=}C(CN)_2$ (45,500); $NCCH{=}C(CN)_2$ (~500,000); $(NC)_2C{=}C(CN)_2$ (~43,000,000).

5. The methylated double bond of isoprene adds 1,1-dichloro-2,2-difluoroethylene 5.5 times faster than the 3,4 double bond.[59] The diradical **36** is stabilized by the methyl group as well as the vinyl residue.



36

In contrast, isoprene combines with diphenyldiazomethane at 20° preferentially at the *unmethylated* double bond. The pyrazolines suffer nitrogen loss and the cyclopropanes **37** and **38** were obtained in an 88:12 ratio.[60]



37 38 39

The phenyl group in 2-phenylbutadiene should stabilize an intermediate radical even better. However, diphenyldiazomethane and diazomethane add solely to the *unsubstituted* double bond; in the latter case, the 1-pyrazoline **39** was isolated.[60]

The transition state of polycentric additions is very sensitive to *steric* effects. The least substituted dipolarophilic multiple bond is normally preferred. Thus,

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(54) R. Sustmann, Ph.D. Thesis, University of München, 1965.

(55) M. Christl, W. Mack, and K. Bast, München, unpublished experiments.

(56) Measurements by M. V. George and A. S. Kende, München, 1962.

(57) R. Huisgen and H. Gotthardt, *Chem. Ber.*, **101**, 1059 (1968).

(58) J. Sauer, H. Wiest, and A. Mielert, *ibid.*, **97**, 3183 (1964).

(59) P. D. Bartlett and L. K. Montgomery, *J. Amer. Chem. Soc.*, **86**, 628 (1964).

(60) Unpublished experiments by A. Ohta, München, 1966.

2-substituted butadienes offer a sensitive probe to distinguish between a diradical intermediate and a concerted pathway. Encumbrance of the dipolarophilic center and diradical stabilization lead to opposite predictions for the activity of substituted *vs.* unsubstituted double bonds.

Other 1,3 dipoles show analogous phenomena. Diphenylnitrilimine adds to the less encumbered double bond of isoprene 4.0 times faster than to the one bearing the methyl group.[61]

Historical Note.—The cycloadditions of aliphatic diazo compounds were discovered[62] in 1888, and those of organic azides[63] in 1893. In a very valuable paper, published in 1938, Smith[64] collected the available data on 1,3 additions without differentiating between additions of bases H–B and cycloadditions. The special driving force for the cyclic reaction path stemming from a fundamentally dissimilar mechanism was not recognized. In 1938 (as in 1900) only cycloadditions of diazoalkanes and azides were known.

That Staudinger's nitrenes[65] and nitrones were considered in this paper[64] as formally derived from ketenes and allenes did not contribute to a clear classification of dipolar reagents. Perhaps for this reason, Smith's review did not attract much attention as shown by the small number of papers on the subject published between 1938 and 1958.

We have reported elsewhere the train of thought which led to the general concept of 1,3-dipolar cycloaddition in 1958;[66] the original mechanistic consideration concerned the addition of diazoalkanes to angle-strained double bonds.

Another generalization recently revealed a synthetic principle which makes accessible a large number of six-membered heterocycles.[67] The term *1,4-dipolar cycloaddition* should not be misinterpreted; there is good experimental evidence and theoretical reason to characterize this scheme as a two-step process passing through a zwitterionic intermediate.[68] The *1,4 dipole* combines only with those dipolarophiles which display pronounced electrophilic or nucleophilic reactivity. This limits severely the range of applicable dipolarophiles.[69]

Just the opposite is observed for *1,3-dipolar cycloaddition.* Here nearly every multiple-bond system including heteroatoms can act as a dipolarophile. The result is an amazingly wide scope of this synthetic principle[16] which is far from being exhausted. It is a fascinating idea that 1,3-dipolar addition owes this wide scope to the concerted mechanism which avoids the necessity of charge separation along the reaction pathway.

The position that 1,3-dipolar cycloadditions, at least those studied so far, do *not* conform to one general mechanism is unfounded.

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[61] Experiments by W. Fliege, München, 1967.

[62] E. Buchner, *Ber. Deut. Chem. Ges.*, **21**, 2637 (1888).

[63] A. Michael, *J. Prakt. Chem.*, [2] **48**, 94 (1893).

[64] L. I. Smith, *Chem. Rev.*, **23**, 193 (1938).

[65] Staudinger's nitrenes had another structure. Cycloadditions of azomethine ylids *alias* nitrenes were first described by R. Huisgen, R. Grashey, and E. Steingruber, *Tetrahedron Lett.*, 1441 (1963).

[66] R. Huisgen, *Proc. Chem. Soc.*, 357 (1961).

[67] R. Huisgen and K. Herbig, *Ann.*, **688**, 98 (1965).

[68] R. Huisgen, M. Morikawa, K. Herbig, and E. Brunn, *Chem. Ber.*, **100**, 1094 (1967).

[69] A brief review on 1,4-dipolar cycloaddition will be published in the Proceedings of the First International Congress of Heterocyclic Chemistry, Interscience Publishers, Inc., New York, N. Y., 1968.

Photochemistry of Cyclic Mercaptoles[1]

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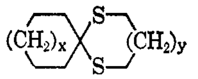
The photochemistry of the mercaptoles **1–4** has been investigated. The major pathway for reaction of the ethylene mercaptoles **1** and **2** involved elimination of the elements of ethylene sulfide to form the corresponding cyclic thione which was isolated as the dimer in the case of **1**. The thione or its dimer underwent secondary photochemical reactions to form the corresponding disulfide, sulfide, and mercaptan. The major pathway for reaction of the propylene mercaptoles, **3** and **4**, involved over-all isomerization of one of the geminal sulfur atoms to an adjacent carbon atom; the ratio of *cis/trans* product in each case was approximately 8:1.

The ultraviolet spectra of mercaptals and mercaptoles show an absorption band in the region of 235–250 mμ (ϵ ~250–850) which has been attributed to an excited state involving sulfur–sulfur interaction.[4,5] In view of this excited-state interaction, the photochemistry of mercaptoles has been investigated to determine the nature of products from excitation at this long-wavelength absorption band. The compounds selected for study were the ethylene and propylene mercaptoles **1–4**. Mercaptole **1** was studied under a variety of conditions to determine those which gave optimum yield of the major products; these conditions were then applied to mercaptoles **2–4**.



1, $x = 1$; $y = 0$ **3**, $x = 1$; $y = 1$
2, $x = 0$; $y = 0$ **4**, $x = 0$; $y = 1$

The photolysis of 1,4-dithiaspiro[4.5]decane (**1**) under various conditions yielded the product mixtures listed in Table I. Runs 5–7 were analyzed only for the major product (**7**). A thin film of brown polymer coated the walls of the reaction vessel when the Hanovia high-pressure Hg lamp was used; no such polymer formation was observed with the low-pressure Hg lamps. Cyclohexane, *n*-hexane, and Freon-113 were satisfactory solvents. The formation of a similar product mixture in these three solvents indicates that no significant amount of products arises from reaction with solvent. No reaction was observed in anhydrous methanol.

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[1] Supported by National Science Foundation Grant No. GP-5761.

[2] National Institutes of Health Predoctoral Fellow.

[3] Alfred P. Sloan Fellow, 1963–1967.

[4] E. A. Fehnel and M. Carmack, *J. Amer. Chem. Soc.*, **71**, 84 (1949).

[5] S. Oae, W. Tagaki, and A. Ohno, *Tetrahedron*, **20**, 437 (1964).