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The Concerted Nature of 1,3-Dipolar Cycloadditions and the Question of Diradical Intermediates[1]

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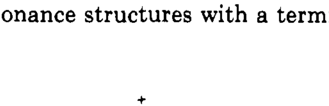
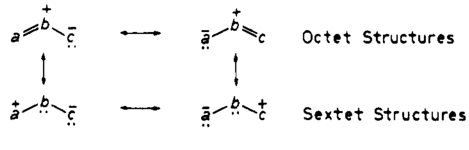
The concerted mechanism of 1,3-dipolar cycloadditions was challenged recently by Firestone, who proposed a diradical alternative on thermochemical and regiochemical grounds. His arguments are critically disproved here. The retention of configuration of 1,3-dipole and dipolarophile in the cycloaddition is incompatible with a diradical intermediate. 1,3-Dipoles are "heteroallyl anions" which lose the allylic resonance energy in forming a diradical intermediate; taking this into consideration, the energies of diradical formation exceed the experimental activation energies of cycloadditions. Following the symmetry-allowed scheme $[_{\pi}4_s + _{\pi}2_s]$, 1,3-dipoles undergo only cycloadditions of the ring size classification 3 + 2 → 5 while allyl cations are only amenable to 1,4 additions of the type 3 + 4 → 7. The activity sequences of dipolarophiles are 1,3-dipole specific; the diradical hypothesis fails to explain this phenomenon while recent MO perturbation treatments provide elegant interpretations for dipolarophile activities as well as for directions of addition. The frequently found "bidirectionality", i.e., different orientations of dipolarophiles with electron-releasing and electron-attracting substituents, is at variance with diradical intermediates. The regioselectivity is connected with the ambident nucleophilic and electrophilic properties of 1,3-dipoles. An independently synthesized 1,5-diradical does not show the reactivity postulated by Firestone.

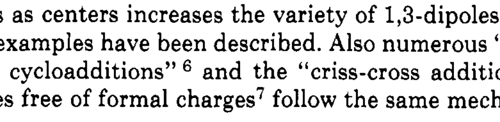
Definitions and Classification. A general principle for the synthesis of five-membered heterocycles, introduced in 1960 as "1,3-dipolar cycloaddition",[2] has turned out to be valuable, as the increasing number of applications testifies. The "1,3-dipole" is defined as a species which is represented by zwitterionic resonance structures and which undergoes 1,3 cycloadditions to a multiple bond system, the "dipolarophile".[3]



In 1963 it was deduced from experimental models that the allyl anion type orbital (four electrons in three parallel π orbitals) is responsible for the cycloaddition reaction.[4] While the terminal centers of the allyl anion are only nucleophilic, the termini of the "heteroallyl anion" systems of 1,3-dipoles are both *nucleophilic and electrophilic* (ambivalent) as the resonance structures with a terminal electron sextet suggest.



An element of variation of 1,3-dipoles is provided by the incorporation of an additional π bond in the plane perpendicular to the allyl anion MO. This additional π bond makes 1,3-dipoles of the propargyl–allenyl type[5] linear while those of the allyl type are bent.



If one restricts the atoms a, b, and c to carbon, nitrogen, and oxygen, the 1,3-dipoles shown in Table I result.[3] Representatives of all but two of these classes, many of them as short lived in situ intermediates, have been shown to undergo 1,3 cycloaddition. Inclusion of phosphorus and sulfur atoms as centers increases the variety of 1,3-dipoles manyfold; examples have been described. Also numerous "anionic 1,3 cycloadditions"[6] and the "criss-cross additions" to species free of formal charges[7] follow the same mechanistic pattern.

The formal analogy between ring-opened cyclopropanes and 1,3-dipoles was emphasized recently by ascribing a varying contribution of the diradical structure 1 to the

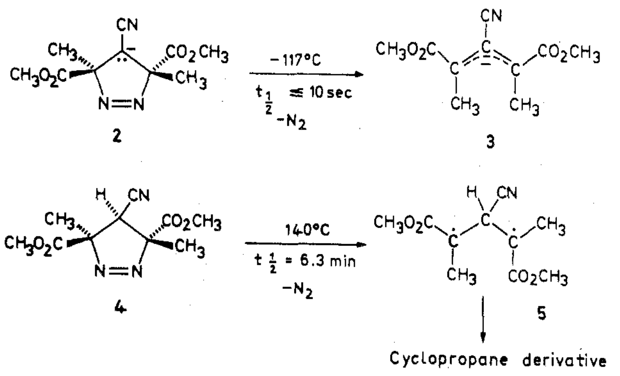

1

ground state of the 1,3-dipole.[8] As in trimethylene[9] one deals with a spin-paired diradical which still allows a weak bond of σ or π type to exist between the terminal centers.[10] The dramatic rate ratio of ⩾10^{29} between the reactions **2** → **3** (concerted cycloreversion **5** → **3** + **2**) and **4** → **5** (formation of a trimethylene) at −197° illustrates the energetic

Table I
Classification of 1,3-Dipoles Consisting of Carbon, Nitrogen, and Oxygen Centers

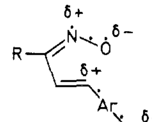
A. Propargyl-Allenyl Type			
$-C\equiv\overset{+}{N}-\overset{-}{C}<$	⟷	$-\overset{-}{C}=\overset{+}{N}=C<$	Nitrile Ylides
$-C\equiv\overset{+}{N}-\overset{-}{N}\diagup$	⟷	$-\overset{-}{C}=\overset{+}{N}=N\diagup$	Nitrile Imines
$-C\equiv\overset{+}{N}-\overset{-}{O}$	⟷	$-\overset{-}{C}=\overset{+}{N}=O$	Nitrile Oxides
$N\equiv\overset{+}{N}-\overset{-}{C}<$	⟷	$\overset{-}{N}=\overset{+}{N}=C<$	Diazoalkanes
$N\equiv\overset{+}{N}-\overset{-}{N}\diagup$	⟷	$\overset{-}{N}=\overset{+}{N}=N\diagup$	Azides
$N\equiv\overset{+}{N}-\overset{-}{O}$	⟷	$\overset{-}{N}=\overset{+}{N}=O$	Nitrous Oxide
B. Allyl Type			
$>C=\underset{\vert}{\overset{+}{N}}-\overset{-}{C}<$	⟷	$>\overset{-}{C}-\underset{\vert}{\overset{+}{N}}=C<$	Azomethine Ylides
$>C=\underset{\vert}{\overset{+}{N}}-\overset{-}{N}\diagdown$	⟷	$>\overset{-}{C}-\underset{\vert}{\overset{+}{N}}=N\diagdown$	Azomethine Imines
$>C=\underset{\vert}{\overset{+}{N}}-\overset{-}{O}$	⟷	$>\overset{-}{C}-\underset{\vert}{\overset{+}{N}}=O$	Nitrones
$\diagdown N=\underset{\vert}{\overset{+}{N}}-\overset{-}{N}\diagdown$	⟷	$\diagdown\overset{-}{N}-\underset{\vert}{\overset{+}{N}}=N\diagdown$	Azimines
$\diagdown N=\underset{\vert}{\overset{+}{N}}-\overset{-}{O}$	⟷	$\diagdown\overset{-}{N}-\underset{\vert}{\overset{+}{N}}=O$	Azoxy Compounds
$O=\underset{\vert}{\overset{+}{N}}-\overset{-}{O}$	⟷	$\overset{-}{O}-\underset{\vert}{\overset{+}{N}}=O$	Nitro Compounds
$>C=\overset{+}{O}-\overset{-}{C}<$	⟷	$>\overset{-}{C}-\overset{+}{O}=C<$	Carbonyl Ylides
$>C=\overset{+}{O}-\overset{-}{N}\diagdown$	⟷	$>\overset{-}{C}-\overset{+}{O}=N\diagdown$	Carbonyl Imines
$>C=\overset{+}{O}-\overset{-}{O}$	⟷	$>\overset{-}{C}-\overset{+}{O}=O$	Carbonyl Oxides
$\diagdown N=\overset{+}{O}-\overset{-}{N}\diagdown$	⟷	$\diagdown\overset{-}{N}-\overset{+}{O}=N\diagdown$	Nitrosimines
$\diagdown N=\overset{+}{O}-\overset{-}{O}$	⟷	$\diagdown\overset{-}{N}-\overset{+}{O}=O$	Nitrosoxides
$O=\overset{+}{O}-\overset{-}{O}$	⟷	$\overset{-}{O}-\overset{+}{O}=O$	Ozone

advantage of the allyl anion bond system over the long-bond trimethylene species.[11] However, with increasing electronegativity of the middle atom of a 1,3-dipole some ground state participation of the diradical structure 1 is conceivable.[12]



Mechanistic Proposals. The concerted mechanism of 1,3-dipolar cycloaddition, first discussed in 1960,[2] was supported by many experimental tests[4,13] and is generally accepted.[14,15] It is an orbital symmetry-allowed $[_{\pi}4_s + {}_{\pi}2_s]$ cycloaddition wherein the 1,3-dipole with its allyl anion type MO functions as $_{\pi}4$ reactant and the dipolarophile as $_{\pi}2$ reactant.[15] The MO symmetry correlation diagram of 1,3-dipolar cycloaddition[16] bears a more than superficial resemblance to that of the Diels-Alder reaction. Another description attributes the concertedness to a Hückel aromatic type MO of the transition state.[17-19]

As an alternative, Firestone[20] proposed a mechanism with a *diradical intermediate* in 1968. Although the original arguments were refuted,[13] the diradical hypothesis of 1,3-dipolar cycloaddition (and of the related Diels-Alder reaction) was recently refurbished on the basis of bond energy considerations[21] and orientation phenomena.[22]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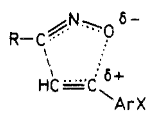
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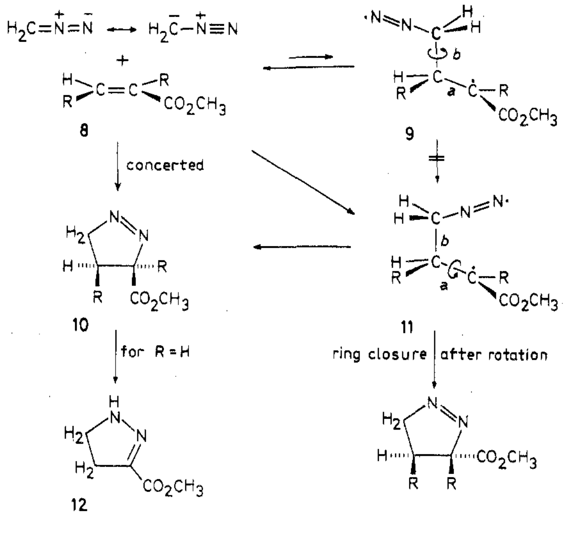
Firestone[22] recently equipped the formulae of the diradical intermediates with partial charges which are a consequence of Linnett notation[23] and which suggest electrostatic attraction. The diradical **6**, the assumed intermediate in the addition of a nitrile oxide to a substituted phenylacetylene,[22] is very similar to formula **7** which we have been using to illustrate the transition state of the concerted addition for 12 years.[4] The strength of the new CC σ bond in **7** is developed to a higher extent than that of the CO σ bond, thus creating partial charges. This depiction **7** of the transition state was recently modernized in a MO perturbational treatment which will be discussed below.

Though it is hard to discern a difference in the meaning of **6** and **7** except of notation, one has to pay a high price for designating **6** a diradical intermediate, as the following discussion will reveal. Duplication of earlier arguments[13] will be held to a minimum. Not all readers may be sufficiently familiar with the Linnett notation;[23] therefore, throughout this paper conventional structural formulae are used unless the Linnett notation is specifically required.

The Diradical Hypothesis and the Stereochemical Criterion. The addition of diazomethane to methyl acrylate (**8**, R = H), which gives a quantitative yield of **12**[24] via the 1-pyrazoline **10**, R = H,[25] serves as a model. The activation parameters are $\Delta H^{\ddagger} = 7.5$ kcal/mol and $\Delta S^{\ddagger} = -33$ eu in DMF.[26] On replacing the acrylic ester by the cis-trans isomeric α,β-dimethylacrylic esters (**8**, R = CH_3, is angelic ester), diastereomeric 1-pyrazolines are formed; Van Auken



and Rinehart found the stereospecificity to be ≥98%.[27] A recent reinvestigation of the addition to methyl angelate by capillary GC demonstrated a stereospecificity greater than 99.8%.[28] Retention of 1,3-dipole[29,30] and dipolarophile[4,13] configurations is a characteristic of 1,3-dipolar cycloadditions; *no exceptions* have been observed.

While stereospecificity is an obvious requirement for the concerted process, it is an insurmountable obstacle to an advocate of the diradical mechanism, as illustrated by the following five points.

(1) If the diradical is formed in conformation **11** with all centers lined up for ring closure ("cyclo diradical"),[22] the cyclization to give **10** must be faster than rotation around *a*, the former double bond of the dipolarophile, otherwise the rule of stereospecificity would be violated. Allowing for <0.2% nonstereospecific reaction as the analytical limit, *the free energy of cyclization must be smaller than the barrier to rotation by >3.4 kcal/mol.*

(2) How large a rotational barrier is to be expected for bond *a* in diradical **11**? Alkanes possess barriers of 2.9–4.2 kcal/mol,[31] but these do not provide the best comparison. Carbon radicals like the one in **11** are known to be "π radicals" with sp^2-hybridized bond system.[32,33] The sixfold barriers to rotation between sp^3- and sp^2-hybridized carbon atoms are lower, e.g., V_6 = 0.014 and 0.006 kcal/mol for toluene and nitromethane, respectively. If such symmetrical substitution is lacking, the sp^3–sp^2 bond assumes again a threefold barrier but with lower heights than the sp^3–sp^3 bond; 0.78 and 2.1 kcal/mol were measured for V_3 of acetone and isobutene.[31]

Rotational barriers of alkyl radicals have recently been evaluated from ESR hfs line shape analysis. These barriers were found in the range of 0–1.2 kcal/mol[34] depending on the nature and the number of substituents.

$H_3C—\dot{C}H_2$ ~0

$CH_3CH_2—\dot{C}H_2$ 0.4

$(CH_3)_2CH—\dot{C}H_2$ 0.3

$CH_3CH_2—\dot{C}(CH_3)_2$ 0.6

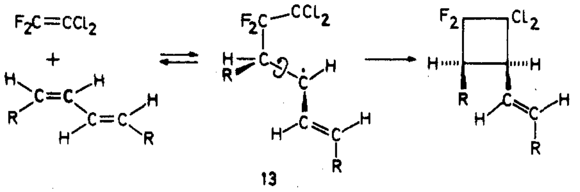
$(CH_3)_2CH—\dot{C}(CH_3)_2$ 1.2 kcal/mol

Should one expect a higher rotational barrier for bond *a* in the diradical **11**, R = CH_3, than 1.2 kcal/mol (tetramethylethyl radical)? Probably not. The barrier of the methylmalonic acid radical, CH_3-$\dot{C}(CO_2H)_2$, is immeasurably small.[35] For CH_3-CH_2CO_2H V_3 is 2.4 kcal/mol, i.e., an even smaller value than V_3 = 3.4 kcal/mol for CH_3-CH_2CH_3.[31] Thus, a carboxy group does not give rise to higher barriers than a methyl in sp^3–sp^3 bonds. Moreover, in cases of unsymmetrically substituted bonds *the energetically easier* of the two possible 180° rotations about the former double bond of the olefinic dipolarophile is sufficient to effect nonstereospecific addition.

Thus, it is safe to conclude: *the cyclization barrier of the diradical* **11** *should be nil if it has to be lower by 3.4 kcal/mol than that of rotation about bond a,* i.e., the cycloaddition must be concerted. The energy profile cannot contain the diradical as a discrete intermediate as postulated.[20,21]

(3) What happens to "extended diradicals" like **9**, i.e., those which are formed in other conformations than the "cyclo diradical" **11**? Conversion to **10** should be preceded by rotation about the axis *b* (sp^3–sp^3) in formula **9**. However, this rotation should require more energy than rotation about the former acrylic ester double bond a, which in turn would cause a drop in stereospecificity. To save the diradical hypothesis, one is forced to assume[20] that dissociation of the bond *b*, i.e., reversal of **9** to the reactants, takes place much faster than rotation around a. Taking into account the deep-seated structural changes accompanying the rehybridization during the dissociation of **9**, an activation barrier of ≪1.2 kcal/mol reveals the artificiality of the diradical concept.

(4) The behavior of relatives of the alleged 1,5-diradicals of type **9** and **11** is known. According to Bartlett's classic investigation, 1,4-diradicals occur as intermediates in the addition of 1,1-dichloro-2,2-difluoroethylene to the cis,-trans isomers of hexa-2,4-diene or 1,4-dichlorobutadiene; these [2 + 2] cycloadditions are forbidden as concerted processes. For the diradical **13**, R = CH_3, rotation around the marked bond takes place ten times faster than cyclization at 80°.[36] A temperature of 120° is needed for dissociation of **13**, R = CH_3, to become noticeable and to compete with ring closure.[37] For **13**, R = Cl, at 150° rotational equilibrium is nearly attained, and cyclization is still four times faster than cleavage to reactants.[38]



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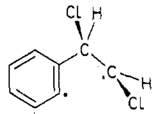
One might argue that cyclization of the diradical **11** is faster than that of **13** because **11** gives rise to a more favored ring size. It is noteworthy that **13** still undergoes cyclobutane ring closure much faster than dissociation.

In the nonstereospecific 2 + 2 → 4 addition of *cis*- and *trans*-1,2-dichloroethylene to benzyne the 1,4-diradical **14** is a putative intermediate. The ratio of ring closure to rotation was found to be 1.3 and 2.3 for *cis*- and *trans*-dichloroethylene.[39] The [2 + 2] additions of *cis*- and *trans*-propenyl alkyl ether to benzyne proceed likewise nonstereospecifically without reaching conformational equilibrium of the 1,4-diradical.[40] On the other hand, *meso*-**15** and *dl*-**15** produce at 145° the tetrasubstituted cyclobutanes with >98% retention of configuration, probably via the 1,4-diradical;[41] it is possible that the nitrogen elimination produces the substituted tetramethylene diradical in a state permitting some 1,4 bonding. Nearly half of the azo compound **15** is converted to 2-methyl-1-butene.[41]



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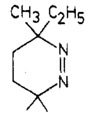

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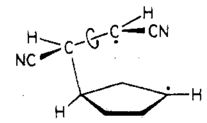

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Tetramethylene diradicals have been suggested as intermediates in the pyrolysis of cyclobutanes. The homolysis of one σ bond creates the tetramethylene in a conformation suitable for splitting into two molecules of olefin.[42] While the diradical from *cis*-1,2-dimethylcyclobutane undergoes dissociation to propylene four times faster (430°) than rotation and reclosure of the four-membered ring,[43] the corresponding ratio for the diradical from 1,1,2,2-tetramethylcyclobutane-d_6 is ≥22 at 401°.[44]

A 1,5-diradical is the intermediate **16** which Gassman et al. proposed for the cycloaddition of maleonitrile to bicyclo[2.1.0]pentane.[45] The analysis of the stereoisomeric 2,3-dicyanonorbornanes revealed that **16** undergoes cyclization ca. four times (ca. nine times in the case of fumaronitrile) faster than rotation. That the plethora of alleged 1,5-diradicals[20–22] from all tested combinations of 1,3-dipoles and dipolarophiles would suffer cyclization ≥50 times (>500 in the example of **11**, R = CH_3) faster than rotation (≥98% or

>99.8% stereospecificity, respectively), seems improbable.

An independently synthesized 1,5-diradical of the Firestone type whose reactivity differs from that postulated will be described in the last section.

(5) The assumption of the CC bond dissociation in the process **9** → **8** via a barrier of ≪1.2 kcal/mol, already highly artificial, becomes even more doubtful on scrutinizing the structure of the diazo diradical **9**. Diazo radicals $RN{=}N\cdot$ are hypothetical intermediates in the reaction of diazoalkanes with radicals.[46] It has also been suggested, though not generally accepted,[47] that the thermolysis and photolysis of certain azo compounds is initiated by rupture of *one* CN bond producing $RN{=}N\cdot$; the evidence rests on kinetics,[48] steric course,[49] and rearrangement.[50] The chemistry of the highly elusive diazo radicals is rather monotonous: except for some recombinations in caged radical pairs in the liquid phase, the radicals $RN{=}N\cdot$ only lose nitrogen. The species $C_6H_5N{=}N\cdot$ expels N_2 so fast that it cannot combine with triphenylmethyl in solution.[51] On the other hand, not a trace of N_2 is liberated during the cycloaddition of diazomethane to methyl acrylate. *The hypothesis that the conformation* **9** *exclusively suffers dissociation of the CC bond while the* $C{-}N_2\cdot$ *remains intact*[20,22] *is unreasonable.*

Potential Hypersurface of the Firestone Diradical. The cyclization of the postulated 1,3-diradical to the five-membered ring, e.g., **11** → **10**, would be a radical combination.

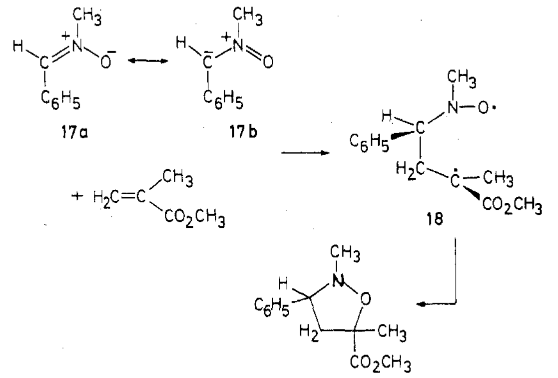
Although combination of methyl radicals is believed to take place without activation, the variation of the ESR measured termination (combination + disproportionation) rates of cumyl and related radicals[52] by a factor of 20 demonstrates that zero barriers cannot be the rule. Substantially lower termination rates for branched-chain alkyls have been reported recently.[53] The rate ratio of radical combination and disproportionation (k_c/k_d), originally regarded as purely entropy controlled, showed a temperature dependence which suggested finite barriers for both processes.[54] If $\Delta H_c^{\ddagger} - \Delta H_d^{\ddagger}$ equals 2.6 kcal/mol for the β,β-dimethyl-α-phenethyl radical,[55] the combination barrier must even be larger. *Barriers appear to occur if substantial structural changes accompany the rehybridization.* For the combination of triphenylmethyl radicals E_a = 7 kcal/mol,[56] and for the termination of di-*tert*-butylmethyl E_a = 19 kcal/mol[57] have been measured.

Intramolecular radical combination should be faster than structurally corresponding intermolecular processes. If one or both of the radical centers are well stabilized (see next section), a barrier to combination should be expected for the Firestone diradical.

What consequences would the assumption of a zero barrier have for the cyclization of the hypothetical 1,5-diradical? There could no longer be an intermediate, i.e., a dip in the energy profile; the *two-step* process becomes at best a *two-stage* process. Rather flat potential hypersurfaces have been described for the trimethylene[9,58] and the tetramethylene diradicals.[42] However, *rotation still can take place on such flat surfaces,* the amount of rotation being dependent on substitution.[42,58] This suppression of rotation in favor of cyclization in Firestone's diradical would build discrete mountains into the energy surface with the effect that radical combination becomes the unequivocal minimum energy pathway. The one-step cycloaddition which must result is indistinguishable from the *concerted mechanism,* particularly since the transition state—only the diradical with the proper conformation will cyclize[20]—is inconceivable without partial bond between the radical centers. The signs of the orbitals allow a bonding overlap from the start.

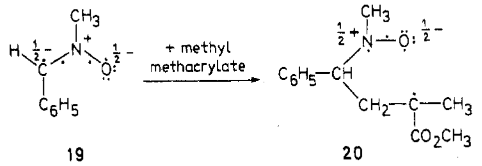
This conclusion is independent of the model used for the description of the diradical, e.g., valence bond structure, HMO, or Linnett formulae. On theoretical grounds, based on Linnett structures, Harcourt recently rejected 1,5-diradicals as *intermediates* in 1,3-dipolar cycloadditions.[10]

Energies of Formation of the Diradical Intermediates. In our earlier paper[13] we estimated the energy which should be required to convert a 1,3-dipole and a dipolarophile to the alleged 1,5-diradical. The lack of thermochemical data for bond energies in onium ions and for some radical stabilizations renders the estimates rather imprecise. Our approximation for the loss of bond energy in the formation of the diradical **18** from *N*-methyl-*C*-phenylnitrone (**17**) and methyl methacrylate, an arbitrarily chosen example, amounted to 54 kcal/mol while the measured activation enthalpy of the cycloaddition was only 15.7 kcal/mol.[59]



Huisgen's estimate[61]

Freezing of the allyl resonance by converting the nitrone to the fictitious resonance structure **17b**		34 kcal/mol
Conversion of N=O into N–O[62]		77
Loss of conjugation $C_6H_5{-}C^-$		6
Conversion C=C → C–C of dipolarophile		63
Loss of conjugation $C{=}C(CH_3)CO_2CH_3$		6
	Loss	186 kcal/mol
Formation of a new C–C		83 kcal/mol
Stabilization energy of $-\dot{C}(CH_3)CO_2CH_3$		11
Stabilization energy of $-N(CH_3){-}O^{\cdot}$		35
	Gain	129 kcal/mol



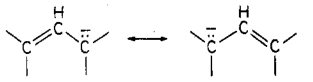
Firestone's estimate[21]

Conversion of the three-electron bond C–N into the two-electron bond C–N		34 kcal/mol
Electron correlation (see below)		4
Loss of substituent conjugation in both reactants		8
Conversion C=C → C–C of dipolarophile		63
L strain[21]		5
	Loss	114 kcal/mol
Formation of a new C–C		83 kcal/mol
Stabilization energy of $-\dot{C}(CH_3)CO_2CH_3$		11
L strain[21]		5
	Gain	99 kcal/mol

Corresponding data for the addition of diphenyldiazomethane to methyl acrylate were ≈65 kcal/mol calculated for diradical formation vs. $\Delta H^{\ddagger}$ = 8.0 kcal/mol found for the cycloaddition.[60] In contrast, Firestone's calculations of the formation enthalpies of the two 1,5-diradicals[21] were in astonishing agreement with the experimental activation enthalpies. How is this feasible? The two estimates may be contrasted.

The main differences between the formation enthalpies of the 1,5-diradical **18** (or **20**), 57 vs. 15 kcal/mol, rests in Firestone's overestimation of the nitroxide radical stabilization.

(1) How large is the *resonance energy of the allyl anion and of 1,3-dipoles?* Neither the pK_a value of propane nor that of propylene have been measured with sufficient precision nor are the pK_a's of protonated 1,3-dipoles and their saturated analogs known. An approximate figure of the allyl anion resonance is based on the rotational barrier.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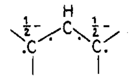
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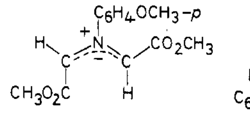
The bond system corresponding to one resonance structure of **21** is found in an allyl anion with 90° rotation about the formal single bond.[63] The rotational barrier of 1-phenylallylpotassium in THF amounts to >20 kcal/mol.[64] A recent ab initio calculation afforded 28 kcal/mol for the rotational barrier of the allyl anion.[65]

The allyl anion resonance energy of a 1,3-dipole should be influenced by the zwitterionic character—1,3-dipoles possess quadrupole moments—and by the exchange of carbon by heteroatoms. The rotational barrier of the substituted azomethine ylide **23** was measured to be 22 kcal/mol,[66] while an ab initio calculation provided 29 kcal/mol for the parent azomethine ylide.[65]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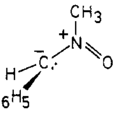
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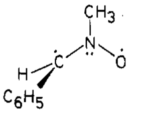
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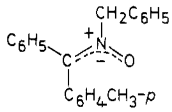
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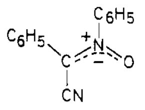
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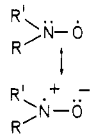
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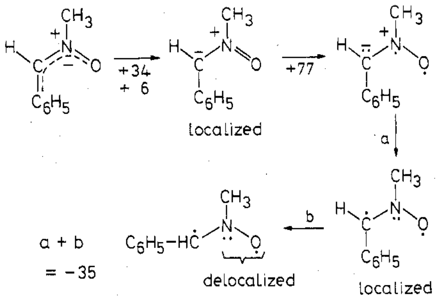
The two "frozen" resonance structures of methylphenylnitrone (**17**) are nonequivalent; the CN and NO bond energies calculated by additivity favor **17b** somewhat,[62] while the anionic charge is better accommodated by **17a**. Rotation about the nitrones CN bond converts the ground state to a 90° twist conformation **24** with the approximate bond energy of the fictitious resonance structure **17b**. Only a couple of rotational barriers for the cis,trans isomerization of nitrones have been measured; that of *N*-benzyl-*C*-phenyl-C-*p*-tolylnitrone (**26**) amounts to 33.6 kcal/mol.[67] The barrier to rotation should be higher for methylphenylnitrone (**17**),[68] because the aryl substituents on carbon—two in **26**, only one in **17**—contribute more to the stabilization of the carbanion in the twist form **24** than in the delocalized ground state. Thus, the energy loss in converting the ground state of **17** into **17b** is at least 34 kcal/mol.

It is a priori conceivable that the 90° twist conformation is the diradical **25**[69] instead of the zwitterion **24**. However, this is ruled out by a rotational barrier of 24.6 kcal/mol for *C*-cyano-*C*,*N*-diphenylnitrone (**27**).[70] The superior stabilization of the carbanion by the cyano group—acetonitrile is by 10–16 p*K* units more acidic than toluene[71]—lowers the energy of the 90° twist conformation and reduces the barrier height of **27** by 9 kcal/mol compared with **26**. One would expect no or even an opposite substituent influence on a diradical twist conformation of the type **25**. Phenyl stabilizes a carbon radical slightly better than cyano.[72]

(2) Nevertheless, it is the nitrone diradical like **25** (but planar) which combines in our thermochemical consideration with methyl methacrylate to give **18**. One electron has to be transferred from the nonbonding carbanion orbital of **17b** into an antibonding orbital of the nitroso group producing the nitroxide radical of **18**. The formal charges of **17b** are converted to those typical of the nitroxide resonance **28**. We account for the process on the debit side with the conversion of N=O to N–O and on the credit side with 35 kcal/mol for electron transfer and nitroxide resonance. The following scheme comprises the energetic changes (in kcal/mol).



(3) The Linnett structure **19** of methylphenylnitrone contains *two three-electron bonds* of which one is *retained* in the 1,4-diradical **20**.[21] Correspondingly, the 1,3-dipoles of the propargyl-allenyl type (nitrilium and diazonium betaines in Table I) are described by formulae with three- and five-electron bonds. The unknown *bond energies of three- and five-electron bonds* are assessed by Firestone in an ingenious way:[21] linear interpolation from experimental bond energies of single, double, and triple bonds! This standardization neglects major differences in the bond systems. While 1,3-dipoles like **17** accommodate the valence electrons in bonding orbitals (Ψ_2 weakly bonding), the diradicals of type **18** possess, like nitric oxide, in the MO description one electron in an *antibonding* MO.

For the allyl anion itself two three-electron bonds in **22** total 232 kcal/mol while the sum of C=C and C–C bond energies is 229 kcal/mol. Thus, the calculated[21] bond energy sum of the allyl anion comes very close to that of *one resonance contributor.* Though allylic stabilization was not mentioned,[21] it is taken care of[69] by "electron correlations", defined as stabilization energy for a distant pair of electrons relative to a close pair. The allyl anion possesses four such pairs corresponding to an increase of the bond energy by 4 × 4 = 16 kcal/mol, and the nitrone **19** contains six pairs amounting to 24 kcal/mol.[21]

(4) *What happens to the allylic stabilization of the 1,3-dipole in the 1,5-diradical formation?* In the resonance and MO description the allylic stabilization terminates with the destruction of the allylic system, and a new stabilization is introduced for the nitroxide radical. In the Linnett description, for the process **19** → **20** the nonbonding electron on the carbon of the nitrone group bonds to C-3 of methyl methacrylate, the three-electron CN bond changes to a two-electron CN bond with the third electron becoming a nonbonding electron on nitrogen, and the three-electron NO bond remains unchanged. For this overall process, Firestone also cancels one "distant pair" [21] electron correlation (4 kcal/mol). Thus, one finds the nitroxide group in **20** endowed with 119 kcal/mol for the three-electron bond.

Bond energy $N\dot{-}O$[21]	99 kcal/mol
Five-electron correlations in the nitroxide group	20
	119 kcal/mol

Such a high bond energy for the nitroxide system in **18/20** can be foreseen neither by the resonance description **28** nor by the MO model with an electron in an antibonding orbital.

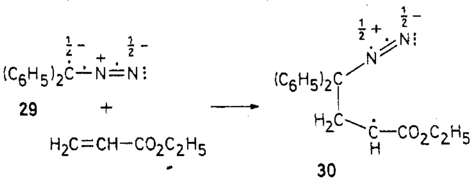
(5) While no thermochemical data are known about nitroxide radicals, one is better off with the related hydrazyl radicals, of which many representatives are known. The standard heats of formation (in kcal/mol)[73] listed below the formulae allow evaluation of the NN bond energy of $N_2H_3^+$ and the hydrazyl radical $N_2H_3\cdot$.

$$\begin{array}{ccccc} \overset{+}{H_2N}{=}NH & \longrightarrow & \overset{+}{NH_2} & + & NH \\ 237 & +146 & 304 & & 79 \end{array}$$

$$\begin{array}{ccccc} H_2\dot{N}{-}\dot{N}H & \longrightarrow & NH_2 & + & NH \\ 87 & +33 & 41 & & 79 \end{array}$$

Provided that the appearance potential measurements for the two N_2H_3 species[74] are correct, the electron in the antibonding orbital of $N_2H_3\cdot$ would reduce the NN bond strength by 113 kcal/mol to a value (33 kcal/mol) which is even somewhat below the N–N bond energy (39 kcal/mol). According to Firestone's interpolation, $N_2H_3\cdot$ should have a NN bond energy of 73 kcal/mol ($N\dot{-}N$ 66 kcal/mol + 3 electron correlations, minus L strain 5 kcal/mol).

(6) Firestone estimated ΔH_a = 16 kcal/mol for the formation of the diradical **30** from **29** and ethyl acrylate;[21] this may serve as a second example. Diphenyldiazomethane possesses according to the Firestone thermochemistry a CN_2 bond energy of 257 kcal/mol ($C\dot{-}N$ 109, $N\dot{=}N$ 148 kcal/mol)[21] plus an electron correlation of 24 kcal/mol for six distant pairs, corresponding to the allylic resonance. On the debit side for diradical formation is included for the 1,3-dipole moiety: the conversion of $C\dot{-}N$ into C–N with 34 kcal/mol, one electron correlation of 4 kcal/mol for the loss of one distant pair, and 4 kcal/mol for the blocking of the phenyl conjugation. Thus, the bond energy of the diazo radical, $R{-}N_2\cdot$, in **30** would total 239 kcal/mol (281 − 42 kcal/mol). *The very fast decomposition of the notoriously labile diazo radical* (vide supra), $R{-}N_2\cdot \rightarrow R\cdot + N_2$ ($N{\equiv}N$ 226 kcal/mol), *would become endothermic* by 13 kcal/mol, diminished by whatever stabilization of R· is present. Thermochemical calculations based on improved ΔH_f values of azoalkanes have made accessible enthalpies for the *exothermic* decompositions of alkyl diazo radicals recently,[75] e.g.

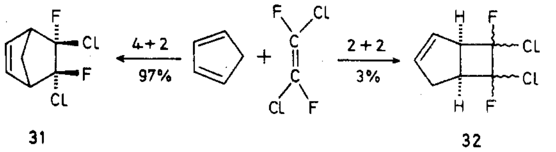


29
30

$$H_3C{-}N{=}N\cdot \rightarrow H_3C\cdot + N{\equiv}N \quad -16.1 \text{ kcal/mol}$$

The ΔH_f for higher alkyls is greater by the stabilization energy of the alkyl radical. Thus, the energy level of the diazo radicals is ~29 kcal/mol (13 + 16 kcal/mol) higher than assumed by Firestone.[21] On correcting his estimate for the formation enthalpy of **30** from the reactants by this amount, one reaches $\Delta H \approx +45$ kcal/mol, which is far above the experimental activation enthalpy of 8 kcal/mol[60] for the cycloaddition of **29** to ethyl acrylate. Firestone's erroneous assessment of diradical bond energies becomes obvious here.

The Criterion of Ring Size and Electronic Demand in Cycloadditions. Diels–Alder reactions and 1,3-dipolar cycloadditions owe their wide scope and synthetic potential to the very fact that they are concerted, i.e., that high-energy intermediates (diradicals, zwitterions) are avoided. In contrast to these $[_\pi4_s + _\pi2_s]$ processes, $[_\pi2_s + _\pi2_s]$ additions are not allowed to be concerted by orbital symmetry.[15] Unlike the cycloadditions 3 + 2 → 5 and 4 + 2 → 6,[76] the processes 2 + 2 → 4 are limited in application. Polyhaloethylene[36-38] and conjugated dienes[77] can enter into [2 + 2] cycloadditions owing to the stabilization of carbon radicals by adjacent halogen or vinyl groups, respectively. The combination of electron-rich and electron-deficient multiple bonds constitutes an alternative with 1,4-zwitterions as intermediates.[78-80]

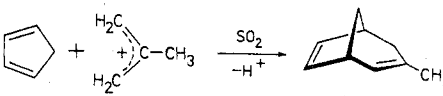


31
32

An experiment of Wheland and Bartlett[81] sheds light upon the relationship of rate, concertedness, and stereospecificity. *trans*-1,2-Dichloro-1,2-difluoroethylene reacts with cyclopentadiene to form the six-membered ring of **31** with retention of dienophile configuration, while the closure of the four-membered ring in a side reaction produces all the four conceivable diastereomers of **32.** If one would postulate diradical intermediates for the Diels–Alder reaction,[22] it should be *one and the same diradical intermediate which closes the six-membered ring stereospecifically and the four-membered ring nonstereospecifically.*

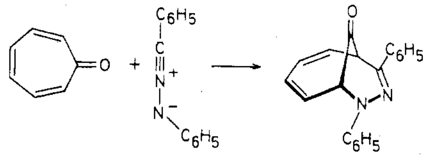
The cycloadditions of benzyne bring the diradical hypothesis into the same dilemma. The nonstereospecific four-membered ring formation with 1,2-dichloroethylene is contrasted by a stereospecific Diels–Alder reaction with *trans,trans*-2,4-hexadiene or *trans,trans*-muconic ester.[39]

1,3-Dipoles as zwitterionic heteroallyl anions add even to cis-fixed 1,3-dienes only in the 1,2 manner, furnishing five-membered rings; a 1,4 addition to produce a seven-membered ring would be the forbidden process $[_\pi4_s + _\pi4_s]$. Though allyl anions, the all-carbon system, do not share the propensity of 1,3-dipoles for the closure to five-membered rings, a few examples of [3 + 2] cycloadditions were described recently.[82]



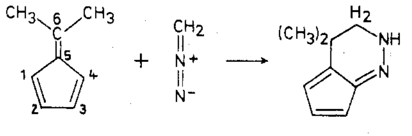
33

By way of contrast, allyl cations add to 1,4-dienes exclusively to produce seven-membered rings, as the formation of **33** from methallyl iodide and silver trichloroacetate in the presence of cyclopentadiene testifies.[83] This 4 + 3 → 7 addition is a new variant of the symmetry-allowed electronic type $[_\pi4_s + _\pi2_s]$. The formation of five-membered rings from allyl cations and alkenes, both as $_\pi2$ reactants, is not known.



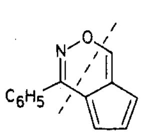
34

Spectacular cases of symmetry-allowed concerted cycloadditions in which larger numbers of π electrons cooperate were reported recently. Tropone combines as a triene with cyclopentadiene in a $[_\pi 6_s + _\pi 4_s]$ reaction giving a polycyclic adduct with ten-membered perimeter.[84] The synthesis of **34** from tropone and diphenylnitrilimine, along with [2 + 3] adduct,[85] illustrates the addition of a 1,3-dipole to the terminal positions of a triene system; electronically, this reaction is of the $[_\pi 6_s + _\pi 4_s]$ type, the ring size classification being 6 + 3 → 9.



35 36

Fulvenes also possess a triene system. Houk and Luskus[86] have observed that 6,6-dimethylfulvene (**35**) accepts diazomethane at the 1,6, rather than 1,2 or 1,4 positions to give **36**. While the addition of benzonitrile oxide to **35** takes place at the 1,2 positions, 6-dimethylaminofulvene combines 1,6 with the same 1,3-dipole producing **37** after subsequent elimination of dimethylamine.[87] Both the $[_\pi 6_s + _\pi 4_s]$ and $[_\pi 4_s + _\pi 2_s]$ cycloadditions are symmetry-allowed concerted processes, while the forbidden $[_\pi 4_s + _\pi 4_s]$ reaction, though easily acceptable from the standpoint of ring strain, has not been observed. The addition of dimethyl acetylenedicarboxylate to diazocyclopentadiene to yield **38**[88] follows another symmetry-allowed path, $[_\pi 8_s + _\pi 2_s]$.



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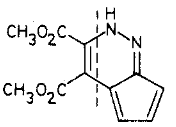

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This selectivity of cycloadditions with respect to the total number of π electrons involved overrides effects of ring size and must be more than a coincidence. Why does the dimerization of azepine-*N*-carboxylic ester choose a pathway[89] in which one molecule acts as a 1,3-diene and the second as a 1,3,5-triene system? No reason can be seen why in stepwise processes via diradicals or zwitterions such a discrimination should be obeyed. After the first σ bond has been established, the termini of the intermediate would no longer be conjugated and, therefore, would not influence one another; all conceivable encounters of the reactive centers should take place as long as not prevented by ring strain. The reason for the selectivity, however, has been found: the conservation of orbital symmetry[15] or the "aromatic" number of (4*q* + 2) π electrons in the transition state[17–19] of *concerted cycloadditions!*

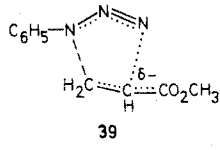
Reactivity Scale of Dipolarophiles. The dipolarophilic activities of the CC double or triple bond and heteromultiple bonds depends highly on substituents. The addition rate constants usually range over many powers of ten. A peculiar phenomenon frequently observed: common alkenes and alkynes add to the 1,3-dipoles rather slowly, whereas electron attraction as well as electron release by substituents increase the dipolarophilic activity of the multiple bond. U-Shaped curves result from plotting addition constants of dipolarophiles vs. the electron density of their multiple bond systems.[4,13] Such behavior has been found for the 1,3-dipolar cycloadditions of nitrile imines,[16] nitrile oxides,[90] azides,[91] azomethine imines,[92] azomethine oxides (nitrones),[59] and carbonyl ylides,[93] with curves specific for each class of 1,3-dipoles and, to a minor extent, even for each individual 1,3-dipole. The U-shapes can vary considerably and sometimes degenerate to the extent that only half of the U is preserved. The additions of nitrile ylides[94] and diazoalkanes[26,60,95] are accelerated only by electron-attracting substituents in the dipolarophile whereas ozone[96] and nitrous oxide[97] show a strong preference for electron-rich multiple bonds.

We ascribed earlier the large spread of dipolarophile activity to three effects.[4,16]

(a) The high activity of conjugated systems was attributed to increased polarizability.

(b) Unequal bond formation in the transition state creates partial charges which are stabilized by the moieties stemming from 1,3-dipole and dipolarophile.

(c) Steric hindrance increase with the degree of substitution of ethylene or acetylene; the large negative entropies of activation, observed for all concerted cycloadditions, emphasize steric requirements.



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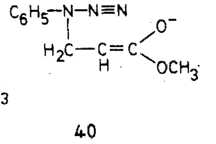

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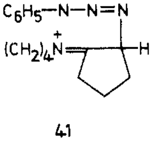

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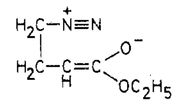
Two examples may illustrate the strengths and shortcomings of argument b. The addition of phenyl azide to ethyl acrylate yielding ethyl 1-phenyl-1,2,3-triazoline-4-carboxylate[98] is 40 times faster than the addition to 1-heptene.[91] This was interpreted by the stabilization of partial charges in the transition state **39** in which one of the two new σ bonds is developed to a greater extent than the other. The participation of **40** as a hyperconjugated contributor to the concerted transition state would be an alternative way of symbolizing the same idea. Analogously, the zwitterion **41** as a hyperconjugated structure contributes to the resonance hybrid of the transition state of the phenyl azide addition to 1-pyrrolidinocyclopentene, which is 480,000 times faster than the one to 1-heptene[91] and furnishes the 5-amino-substituted triazoline.[99,100] The structures **40** and **41** symbolize the capability of 1,3-dipoles to stabilize charges of either sign which is in accordance with the U-shaped activity sequence.

The hyperconjugated contributors **40** and **41** correspond to the adducts of an electrophilic and a nucleophilic reagent, respectively, with the azide system. The cycloaddition of phenyl azide to 1-pyrrolidinocyclopentene is only ten times faster in DMF than in cyclohexane;[91] thus the contribution of the zwitterionic structure **41** to the transition state cannot be very high. Why then is the rate constant for addition to enamines so large?



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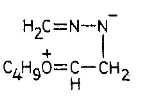

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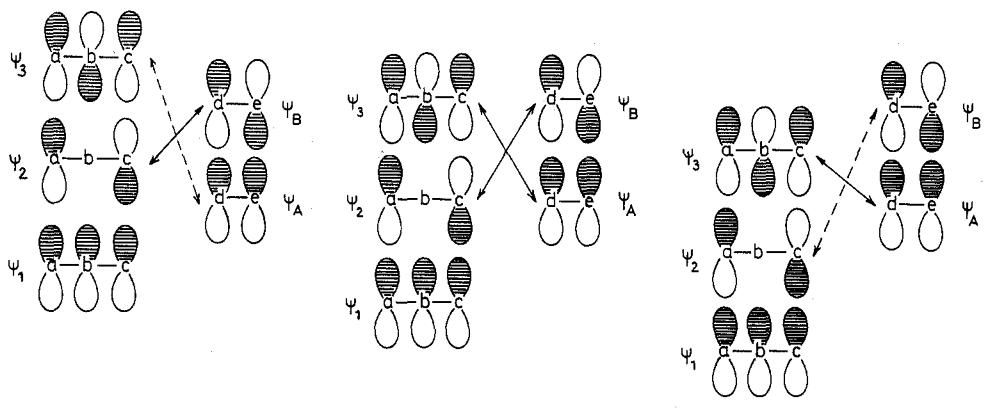
Correspondingly, **42** and **43** contribute to the transition state of the concerted additions of diazomethane to ethyl acrylate and to vinyl butyl ether. Formulae **42** and **43** do not disclose why diazomethane adds to ethyl acrylate 2700 times *faster* and to vinyl butyl ether 4500 times *slower* than to ethylene.[26] However, the basic and nucleophilic qualities of diazomethane are more pronounced than its electrophilicity. The correlation between the cycloaddition rates and the nucleophilicity of diazomethane finds its converse in the cycloadditions of ozone and of nitrous oxide, which act as electrophilic reagents. Thus, the various deviations from the U shape of dipolarophile activity scale can be rationalized.

The advantage of the concerted mechanism of cycloaddition lies in the partial compensation of the energy required for bond breaking by that of making two new σ bonds. Is it



Type I
Electron-donating substituents in 1,3-dipole or electron-attracting substituents in dipolarophile accelerate

Type II
Electron-donating and -attracting substituents in 1,3-dipole and dipolarophile accelerate

Type III
Electron-attracting substituents in 1,3-dipole or electron donating substituents in dipolarophile accelerate

Figure 1. The HOMO–LUMO interaction between 1,3-dipole and dipolarophile depends on the orbital energies of the 1,3-dipole: ——, strong; - - - -, weak interaction.

reasonable to ascribe the large rate accelerations of 1,3-dipolar cycloadditions by substituents to small contributions of zwitterionic structures in which *only one σ bond* connects the reactants?

One welcomes recent successful attempts of MO perturbation theory to cope with nucleophilicity scales[101] as well as with dienophile[102] and dipolarophile activity sequences. The reactions of nucleophilic with electrophilic reagents—cycloadditions provide specific examples—are controlled by the HOMO–LUMO interplay which depends on orbital energies and size of the eigenvector coefficients. *The rate of a cycloaddition is not simply a function of the nucleophilicity and electrophilicity of the reactants, but rather all these phenomena have common underlying reasons.*

As 1,3-dipole and dipolarophile approach each other, their frontier orbitals begin to interact and new MO's of C_s symmetry are formed in the transition state. According to perturbation theory, the interaction energy of the two HO–LU combinations is expressed by eq 1.[103] E_{I} and E_{II}

$$\Delta E = \frac{(c_a c'_d \beta_{ad} + c_c c'_e \beta_{ce})^2}{E_{\mathrm{I}}} + \frac{(c'_a c_d \beta_{ad} + c'_c c_e \beta_{ce})^2}{E_{\mathrm{II}}} \qquad (1)$$

$$E_{\mathrm{I}} = E_{\Psi_2} - E_{\Psi_B} = \text{HO(1,3-Dipole)} - \text{LU(Dipolarophile)}$$

$$E_{\mathrm{II}} = E_{\Psi_A} - E_{\Psi_3} = \text{HO(Dipolarophile)} - \text{LU(1,3-Dipole)}$$

are the orbital energy differences; c and c' the coefficients of the atomic orbitals of HO and LU, respectively. The subscripts are defined in Figure 1. The larger the number of heteroatoms (increased Coulomb integral) in a 1,3-dipole, the lower are its orbital energies compared with those of the parent allyl anion (Ψ_2 nonbonding in HMO). Ψ_2 is the HO, Ψ_3 the LU of 1,3-dipoles. The σ resonance integrals β in eq 1 depend not only on the distance of the atoms, but also on their nature ($\beta_{\mathrm{C-C}} > \beta_{\mathrm{C-N}} > \beta_{\mathrm{C-O}}$).

If the dipolarophile d=e is part of a conjugated system, then Ψ_A will be destabilized and Ψ_B stabilized. The decreased HO–LU distance leads via smaller values of E_{I} and E_{II} in eq 1 to a larger ΔE which effects rate acceleration.[104] Our earlier concept[4,16] of the increased polarizability of conjugated systems has thus achieved a more authoritative meaning.

Sustmann[104] deduced qualitatively the various U-shape dipolarophile activity scales from the three types of HO–LU interactions sketched in Figure 1. For 1,3-dipoles of type II the interactions Ψ_2–Ψ_B and Ψ_A–Ψ_3 are of comparable importance. Electron-attracting conjugated substituents like CO_2R, COR, and NO_2 will lower the orbital energies of ethylene. The increase of the first term in eq 1 due to a reduced E_{I} (energy difference $\Psi_2 - \Psi_B$) exceeds the loss in the second term caused by an increased E_{II}; rate acceleration will be the result. Electron-releasing substituents (OR, NR_2) raise the dipolarophile orbital energies. In this case the second term of eq 1 gains more than the first one loses; once more an increase of rate will result. Azides, nitrile imines, nitrile oxides, etc., belong to this type II.

For 1,3-dipoles of type I essentially the interaction Ψ_2–Ψ_B is important; owing to the larger energetic distance Ψ_A–Ψ_3, the second term in eq 1 becomes small. Electron-attracting substituents will lower, i.e., stabilize, Ψ_B and accelerate the reaction by reducing E_{I}; electron-donating substituents, however, deactivate the dipolarophile by raising Ψ_B. Nitrile ylides and diazoalkanes belong to type I. Correspondingly, for 1,3-dipoles of type III the dominating interaction $\Psi_A - \Psi_3$ (energy difference E_{II}) profits from lifting Ψ_A by electron-releasing substituents, but is weakened by electron-attracting groups. Cycloadditions of nitrous oxide and ozone follow this pattern.

$$\Delta E = A\beta^2 \left[\frac{1}{E_{\mathrm{I}} + X} + \frac{1}{E_{\mathrm{II}} - X} \right] \qquad (2)$$

A semiquantitative correlation can be achieved by drastic approximation. After setting equal the numerators of the two terms in eq 1 and assuming that the substituent changes the energy of Ψ_A and Ψ_B by the same amount, x, Sustmann and Trill[105] derived eq 2. On plotting log k_2 for cycloadditions of phenyl azide to 20 dipolarophiles[91] vs. the ionization potentials of the highest occupied π molecular orbitals of these dipolarophiles—the ionization potentials represent an experimental measure of Ψ_A energies—the data fit fairly well the paraboloid function (superposition of two hyperbolae) of eq 2. Similar curves were obtained for benzonitrile oxide and diphenylnitrilimine cycloadditions[90] (type II of Figure 1). In contrast, log k_2 values of diazomethane cycloadditions (type I) to ten monosubstituted

Table II
Substituent Influence Expected for the Formation of Firestone's Diradical from Dipolarophiles $H_2C{=}CHR$ and Relative Rate Constants of 1,3-Dipolar Cycloaddition

	R=H	Alkyl	CO_2R	OR	$CH{=}CH_2$	C_6H_5
A. Thermochemical Data (kcal/mol) for Diradical Formation from Monosubstituted Ethylenes						
Ground state conjugation free energy (ref 107)	$\equiv 0$	3.2	3.2	5.2[a]	4.9	4.9
Stabilization enthalpy of $H_2\dot{C}{-}R$ (ref 108)	0	6	8[b]	11	16	19
Stabilization free energy of $H_2\dot{C}{-}R$ (25°, ref 108)	0	7	9[b]	11	15	18
Gain of stabilization free energy[c]	0	4	6	6	10	13
B. Relative Rate Constants of 1,3-Dipolar Cycloadditions						
$C_6H_5C{=}\overset{+}{N}{-}\overset{-}{\bar{O}}$, 0° (ref 90)	3.2	$\equiv 1.0$	27	6.8		3.9
$C_6H_5C{\equiv}\overset{+}{N}{-}\overset{-}{N}{-}C_6H_5$, 80° (ref 16)		1.0	350	2.2	10.2	8.5
$H_2C{=}\overset{+}{N}{=}\overset{-}{N}$, 25° (ref 26)	103	1.0	280,000	0.02	49	101
$(C_6H_5)_2C{=}\overset{+}{N}{=}\overset{-}{N}$, 40° (ref 26, 60)		1.0	14,000		13	21
$C_6H_5N{=}\overset{+}{N}{=}\overset{-}{N}$, 25° (ref 91)		1.0	41	1.7	0.6	1.7
$C_6H_5CH{=}\overset{+}{N}(CH_3){-}\overset{-}{O}$, 80° (ref 59)		1.0	150	2.8		4.4

[a] Values for OCH_3. [b] 70% of the stabilization energy of $H_2\dot{C}COCH_3$; see H. E. O'Neal and S. W. Benson, *J. Phys. Chem.*, **72**, 1866, 1882 (1968). [c] Difference of third and first line.

ethylenes fit a good linear relation with $1/E_I$, i.e., the energy difference of HO(diazomethane) and LU(dipolarophile).[26]

Can the diradical hypothesis rationalize these specific dipolarophile activity sequences? No. Firestone deduces the regioselectivity from energy differences—sometimes quite small—of isomeric diradicals in which the dipolarophile has become attached to either terminus of the 1,3-dipole.[22] If the same kind of reasoning is applied to the variation of the dipolarophiles, these consequences follow.

(1) In combining with a 1,3-dipole to give a diradical, the dipolarophile loses its ground state conjugation energy, but contributes through its radical moiety to the stabilization energy of the diradical (Table IIA). Both these energies depend on the dipolarophile alone. The endothermicity of diradical formation (near zero activation energy of the reverse reaction) demands that the transition state is structurally very close to the diradical. Thus, *the dipolarophile activity scale should be uniform and independent of the nature of the 1,3-dipole.* The whole wondrous diversity of dipolarophile scales would be exterminated by assuming diradical intermediates.

(2) *The uniform sequence of dipolarophile activity* expected on the basis of rate-determining diradical formation *bears no resemblance to the experimental activity scales* observed for various 1,3-dipoles (Table IIB). The log k_2 of the cycloadditions should be proportional to the difference between the stabilization free energy of the dipolarophile moiety in the diradical and the conjugation free energy of the olefinic bond in the ground state.[106] While the latter is fairly well known,[107] the free energies of radical stabilization are less reliable and only available for monosubstituted methyls.[108] Therefore, the values for the gain of stabilization free energy, as given on the fourth line of Table IIA, provide an approximation.

Neither conjugation energies nor radical stabilization energies are strictly additive in polysubstituted structures. We had to be content with using the stabilization energies for $R{-}\dot{C}H_2$, because those of $R{-}\dot{C}H(CH_3)$, though a better model, are not available. The data of the fourth line of Table IIA may thus be somewhat too large, but their trend is expected to be correct.

Nevertheless, the discrepancy with the rate constants of Table IIB is obvious. In contrast to the expectation for radical stabilization, ethylene reacts faster than 1-alkenes. Styrene should exceed acrylic ester in dipolarophilic activity by $\sim 10^5$; the rate constants show acrylic ester to be faster than styrene by factors of 7–2800. The vinyl ether column of Table II is symptomatic. The diradicals from 1,3-dipoles and vinyl ethers should be formed $\sim 10^4$ times faster than the ones from ethylene. However, diazomethane (1,3-dipole of type I) reacts with vinyl butyl ether 4500 times slower than with ethylene. All the other 1,3-dipoles of Table II are of type II; they also respond to the ether function in the dipolarophile with a small rate increase.

(3) Only one of the two substituents in 1,2-disubstituted ethylenes or acetylenes can contribute to the stabilization of the Firestone diradical and assist in its formation. The second substituent loses its conjugation with the double bond and could even retard diradical formation. Nevertheless, for dimethyl fumarate–methyl acrylate the following addition rate ratios have been measured: *C*-methyl-*N*-phenylsydnone, 7; diphenylnitrilimine, 6; 3,4-dihydroisoquinoline *N*-phenylimine, 4; diphenyldiazomethane, 3.

The diradical hypothesis of the Diels–Alder reaction[22] encounters the same difficulties. 9,10-Dimethylanthracene reacts with tetracyanoethylene 10^5 times faster than with 1,1-dicyanoethylene;[109] diradical formation with tetracyanoethylene should be slower than with the 1,1-dicyano compound, because the conjugation energy of two cyano groups has to be sacrificed. However, the lower LU energy of tetracyanoethylene together with an early transition state of the concerted cycloaddition offers a satisfactory explanation.[102]

Regioselectivity. "The orientation phenomena in 1,3-dipolar as well as Diels–Alder addition offer perhaps the biggest *unsolved* problem in the field."[13] This was my opinion 7 years ago, and it was only recently that in this cloud of uncertainty a silver lining became visible. As the substituent effects offered by classic resonance theory are inadequate to interpret the regiochemistry of concerted cycloadditions, we were often tempted to overemphasize presumed steric effects.

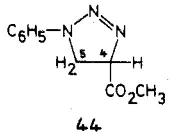
While the range of dipolarophile activity corresponds to differences in activation free energies of 10 kcal/mol and more, the competition of the two addition directions of a 1,3-dipole to a dipolarophile is energetically more subtle. A free energy difference of 3 kcal/mol suffices to make the minor isomer disappear below the 1% analytical limit. Regiochemistry is a phenomenon of kinetic competition and cannot be detached from the question of dipolarophile activity.

"The diradical mechanism predicts that the regiospecificity observed with both electron-poor and electron-rich olefins should be the same toward any given 1,3-dipole",[22] because relative to hydrogen all substituents stabilize a radical center. Thus, Firestone regards "unidirectionality" as normal, but admits that the "bidirectionality" of the additions of azides to monosubstituted ethylenes and acetylenes does not conform to this rule. The alleged superiority of the diradical concept was illustrated with 147 examples including six "exceptions".[22]

"The strong tendency for each 1,3-dipole to add in the same direction to both electron-rich and electron-poor olefins" [22] is basically erroneous. In fact, only the cycloadditions of nitrile imines and nitrile oxides are unidirectional and even these to a limited extent. Bidirectional are the cycloadditions to nitrile ylides,[94,110] diazoalkanes, azides, azomethine imines,[111] and nitrones. If the dipolarophiles are ordered by the electron density of their double or triple bonds, one finds that the point of switching from one orientation to the other is 1,3-dipole specific. As shown below, there is no sharp borderline between unidirectional and bidirectional behavior, but a mechanistically enlightening continuous transition. Even "unidirectionality" is not in conflict with the concerted mechanism as argued.[22]

The stabilization of partial charges in the transition state can make the concerted addition nonsynchronous. One would expect an orientational pattern in which the more nucleophilic end of the 1,3-dipole controls the addition to ethylenes and acetylenes with electron-withdrawing substituents, while the more electrophilic terminus would become attached to the β position of a dipolarophile bearing an electron-releasing substituent. The ambivalence of the termini of the 1,3-dipole (see above) occasionally complicates the assignment of the nucleophilic and electrophilic end. Nevertheless, it is tempting to see if there is an analogy between the directional behavior of 1,3-dipoles in their concerted cycloadditions and their nucleophilic and electrophilic properties in additions leading to acyclic products. By the way, an inherent polarity is not a requirement; ozone or azomethine ylides are not less reactive in concerted cycloadditions because their ends are identical.

A. Azides. Phenyl azide accepts acrylic ester and vinyl ethers (and enamines) in different addition directions as illustrated by the adduct structures **44**[98] and **45**[100] in accordance with the resonance contributors of the type **40** and **41** to the transition state. The allegation[22] that this regioselectivity both for electron-poor and for electron-rich olefins is incorrect for the concerted mechanism rests on the assumption that "azides are polarized with the outer nitrogen negative". This misunderstanding stems from the direction of the net dipole moment of phenyl azide; the azido group as a whole attracts electrons from the benzene ring. Firestone[22] invokes a dipole interaction between the two reactants as a potent orientational factor,[112] although the formation of his "cyclo diradical" requires virtually the same relative orientation of 1,3-dipole and dipolarophile in the activation process. This mentioned dipole interaction appears to be of minor importance for the orientation.[113,114]



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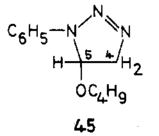

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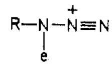
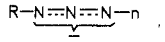
The acid-catalyzed decomposition of aryl azides is initiated by protonation at the inner nitrogen atom (**46**, e = H)[115] and the protonated hydrogen azide bears both hydrogens at the same nitrogen.[116] The azidium complexes of silyl, chloroantimonyl, and fluoroboryl azide[117] also correspond to type **46**. Thus, it is the inner nitrogen which is more basic and nucleophilic. The hyperconjugated contributor **40** to the transition state of the acrylic ester addition is likewise of the general type **46** and explains straightaway the formation of adduct **44**.



$R-\overset{+}{\underset{e}{N}}-N\equiv N$

46

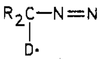


$R-\underbrace{N{\cdots}N{\cdots}N}_{-}-n$,

47

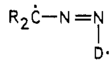
All additions of nucleophilic reagents n (cyanide, phosphines, carbanions, phosphorus and sulfur ylides, etc.) to organic azides take place via structures like **47** at the outer nitrogen atom,[118] thus marking the preferred electrophilic center. Likewise the β position of vinyl ethers and enamines in cycloadditions become bonded to the outer nitrogen; e.g., the resonance contributor **41** is of type **47**. Thus, the regioselective additions to electron-deficient and electron-rich olefins do not fit the unidirectionality expected for a diradical intermediate.

B. Diazoalkanes. Firestone[22] compared the formation energies of the two conceivable diradicals **48** and **49**, formed from a diazoalkane and a dipolarophile D, and estimated a preference for **48** as high as 17 kcal/mol. Therefore, all cycloadditions of diazoalkanes to monosubstituted ethylenes or acetylenes should take place unidirectionally via the diradical **48** to produce 3-substituted pyrazolines or pyrazoles.



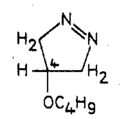
$R_2\underset{D\cdot}{C}-N=N\cdot$

48



$R_2\dot{C}-N=\underset{D\cdot}{N}$

49



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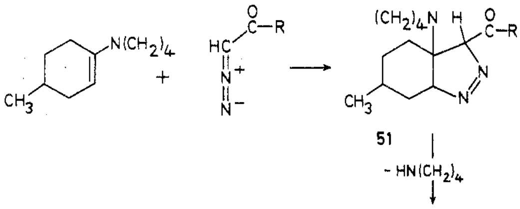
While the formation of **10** from diazomethane and methyl acrylate obeys this rule, the additions to electron-rich dipolarophiles are decidedly at variance. Butyl vinyl ether and diazomethane yield 4-butoxypyrazoline (**50**).[119] Diazoacetic ester and diazoketones combine with 1-pyrrolidine-4-methylcyclohexene to give the structurally secure tetrahydroindazoles **53**[120] via the primary adducts **51**. It is the nucleophilic enamine β position which becomes attached to the diazoalkane nitrogen. Finally, diazomethane and ethoxyacetylene produce solely 4-ethoxypyrazole (**52**) of established structure.[121]



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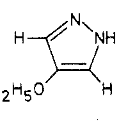

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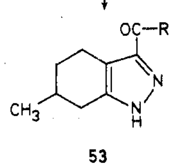

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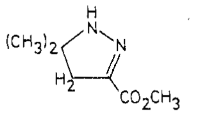
The regioselectivity toward electron-deficient and electron-rich dipolarophiles is thus symbolized by the zwitterionic contributors **42** and **43** to the transition state and these, again, would fit the anticipation for additions which are controlled by nucleophilicity and electrophilicity. Protonation on carbon induces the nitrogen loss from diazoalkanes; acylation, alkylation, and azo coupling (with aryldiazonium ions) of diazomethane also take place on carbon.[122] On the other hand, Grignard reagents add to the outer nitrogen of diazomethane[123] as does triphenylphosphine in the formation of triphenylphosphazine.[124] The more electron-depleted diazoalkane system in α-diazocarbonyl and

-dicarbonyl compounds easily reacts with thiolates, amines, and other nucleophiles, always at the terminal nitrogen atom.[122] Dicyanodiazomethane even undergoes azo coupling with dimethylaniline.[125] According to the diradical hypothesis, however, the opposite direction of cycloaddition to electron-rich multiple bonds should be favored by a rate factor of 10^{12} ($\Delta\Delta G^{\ddagger} = 17$ kcal/mol).[22]



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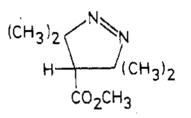

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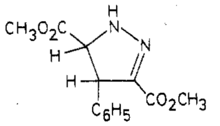

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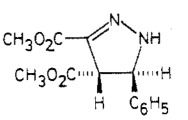

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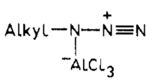
A revealing feature: the orientation rules of diazoalkane cycloadditions to electron-deficient multiple bonds (electron-attracting substituent ending up in pyrazoline 3 position) are not very strict. The normal addition direction to α,β-unsaturated nitro compounds and sulfones can be reversed by encumbering β substitution.[126,127] While dimethyldiazomethane combines with methyl acrylate to give the "normal" adduct **54** (analogous to **12**), β,β-dimethylacrylic ester adds dimethyldiazomethane in the opposite direction to give **55** and only a trace of the "normal" adduct.[128] Cinnamic ester accepts diazomethane with quantitative formation of the pyrazoline 3-carboxylate.[129] Diazoacetic ester, however, produces the "normal" adduct **56** and the "anomalous" adduct **57** in a 8:1 ratio.[130] The 2-pyrazolines **54**, **56**, and **57** are results of subsequent tautomerization of 1-pyrazolines.

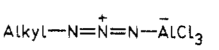
A similar reversal of the "normal" orientation has been observed in diazoalkane cycloadditions to the CC triple bond of tetrolic and arylpropiolic esters.[131] The anomalous adducts have been interpreted as the result of switching from electronic to steric control.[128] In our opinion the change in regioselectivity is strong evidence for the *ambident nucleophilicity* of diazoalkanes.

C. 1,3-Dipoles as Ambident Nucleophiles and Electrophiles. The attack of numerous electrophilic reagents on the diazoalkane carbon is followed by fast subsequent reactions, usually loss of N_2.[122] The fast nitrogen evolution on treatment with acids prevents clarification of the possibility that protonation might take place on carbon *and* nitrogen competitively. N-Protonation is suggested by the formation of aminoisonitrile, $H_2N-N{=}C$, from diazomethyllithium with acid.[132] There is some evidence that alkyl azides are ambident nucleophiles. The intermediates **58** and **59** have been postulated as being responsible for the simultaneous loss of N_2 and azide ion in the reaction with aluminum chloride.[133]



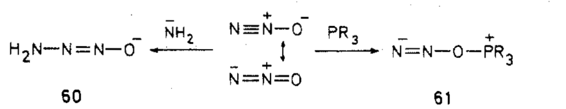
$\text{Alkyl}-\underset{^{-}AlCl_3}{\underset{|}{N}}-\overset{+}{N}\equiv N$

58



$\text{Alkyl}-N=\overset{+}{N}=N-\overset{-}{Al}Cl_3$

59



60 61

The sextet formulae suggest that 1,3-dipoles are ambident *electrophiles* as well. The conversion of nitrous oxide to alkali azide by alkali amide involves attack at the terminal nitrogen with **60** as intermediate.[134] On the other hand, the deoxygenation by triethylphosphine[135] probably takes place via **61**.

While nitrile oxides add nucleophiles HB on carbon to given hydroximoyl derivatives,[136] triphenylphosphine attacks on oxygen to effect reduction to nitriles.[137] Benzonitrile oxide reacts with benzyl mercaptan both at the carbon and oxygen atom forming the thiobenzhydroximic ester and benzonitrile, respectively.[138] Nitrones show a similar dual behavior toward nucleophilic reagents.[139]

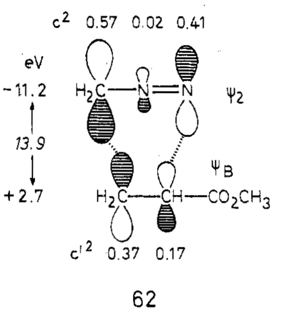
D. The Silver Lining. According to Fukui,[140] reactions take place in the direction of maximal HO–LU overlap. In concerted cycloadditions that orientation should be favored in which the centers with the largest atomic orbital coefficients interact. This principle allows the interpretation of most of the heretofore problematic orientation phenomena in Diels–Alder reactions.[141] Equation 1 contains in the numerator of the two terms the square of the sum of the products of orbital coefficients.

Bastide et al. used the perturbation approach, based on CNDO/2 calculations, to correlate the regioselectivity in cycloadditions of diazomethane[114] and substituted diazomethanes[142] to numerous olefinic and acetylenic dipolarophiles with the first interaction energy term of eq 1 for the two addition directions. These diazoalkanes belong to the 1,3-dipoles of Sustmann's type I[104] where only the interaction HO(diazoalkane) – LU(dipolarophile) is important. The treatment was refined by including all interactions between occupied and vacant orbitals of the reactants.[143,144] Also for fulminic acid, benzonitrile oxide, diphenylnitrilimine, and phenyl azide a satisfactory agreement between calculated and experimental orientations has been achieved; the addition directions of these 1,3-dipoles of type II are governed by both HO–LU interactions.

Independently, Houk calculated by CNDO/2 the orbital energies and atomic orbital coefficients of the three diazonium betaines and deduced the bidirectionality of the additions to dipolarophiles with donor and with acceptor substituents.[145] A similar procedure for all other classes of 1,3-dipoles led to rationalizations of addition directions.[146,147] The calculated orbital energies were adjusted with the help of known ionization potentials and $\pi \rightarrow \pi^*$ transitions.

Introduction of a conjugating substituent (C_6H_5, $CH{=}CH_2$) or an electron-attracting group (CO_2R, CN) into ethylene will influence the atomic orbital coefficients of the α and β carbon in the sense of $c_\alpha < c_\beta$ in both HO and LU, according to CNDO/2.[143,146] Electron-releasing substituents (OR, NR_2) also lead to $c_\alpha < c_\beta$ in HO, but to $c_\alpha > c_\beta$ in LU.

The HO of diazomethane possesses the largest atomic orbital coefficient on carbon; hence carbon has the greatest nucleophilicity. The size of the orbitals in the orientation complex formulae **62**–**65** reflect the squares of the atomic orbital coefficients.[114,148] The carbon orbital of diazomethane overlaps in the important Ψ_2–Ψ_B interaction preferably with that dipolarophilic carbon which possesses the



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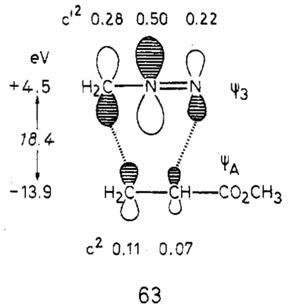

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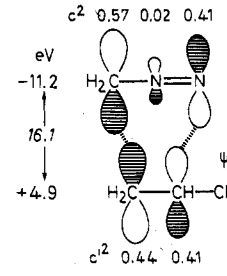

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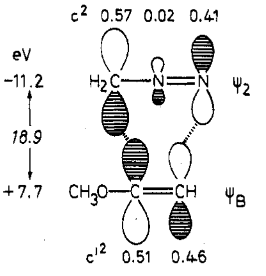

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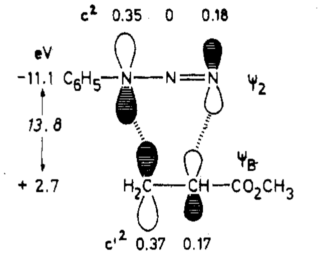
higher c'^2 values. The smaller energy distance Ψ_2–Ψ_B makes the contribution of **62** larger than **63** in the reaction with methyl acrylate though both result in the same orientation. The increasing Ψ_2–Ψ_B distance (nonadjusted CNDO/2 figures)[148] in **62**, **64**, and **65** indicates decreasing rate, and the squares of c' illustrate why diazomethane produces 3-substituted pyrazolines with acrylic ester and 1-alkenes, but the 4-alkoxypyrazole with ethoxyacetylene. Vinyl ethers and alkoxyacetylenes are borderline cases, because the two HO–LU interactions favor different orientations.

The "anomalous" orientation in the formation of **55** from dimethyldiazomethane and β,β-dimethylacrylic ester is also easily explained. The difference in the size of the terminal atomic orbital coefficients is diminished in both of the reactants[142] compared with diazomethane and acrylic ester. The less stringent electronic orientation is now overcome by steric control. The squares of c_α' and c_β' of phenylpropiolic ester are less different than in cinnamic ester;[142] therefore, only the triple-bonded ester accepts diazomethane in the two addition directions.[131]



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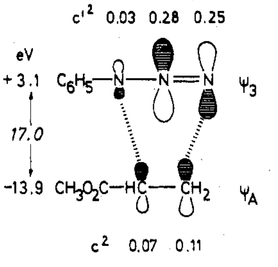

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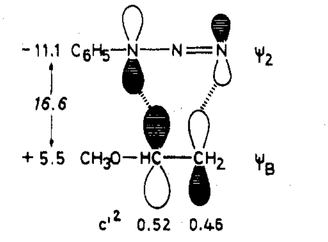

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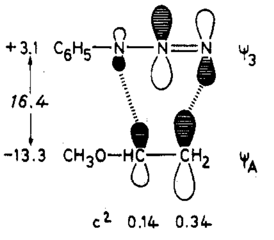
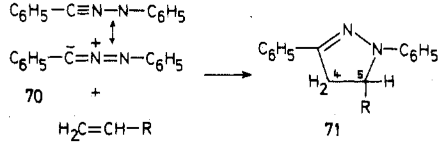


69

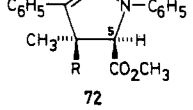
Replacement of the diazomethane carbon by nitrogen functions to give organic azides causes a lowering of Ψ_3. The dominant interaction of phenyl azide, a 1,3-dipole of type II,[104] in the reaction with acrylic ester is still Ψ_2–Ψ_B, i.e., **66** ≫ **67**. The contributions of Ψ_2–Ψ_B (**68**) and Ψ_A–Ψ_3 (**69**) to the transition state of the vinyl ether addition are nearly equal, while Ψ_A–Ψ_3 preponderates for enamines. Both the interactions **68** and **69** direct the donor substituent to the 5 position of the triazoline, while **66** and **67** influence the orientation in opposite directions

The opposite orientations obeyed in the cycloadditions of diazonium betaines to electron-deficient and electron-rich dipolarophiles, which can hardly be reconciled with the diradical hypothesis, are accounted for elegantly.

E. The Unidirectionality. Some 1,3-dipoles combine "unidirectionally" with both electron-rich and electron-poor monosubstituted ethylenes, i.e., the donor as well as the acceptor substituent ends up at the same position of the heterocyclic ring. This behavior is the heart of the diradical hypothesis.[20,22] On closer inspection one sees that the orientation rules are not strict; the argument loses its strength.



70 71



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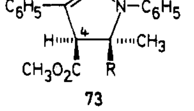
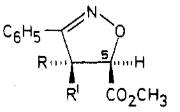


73

	72		73
R = H	64	:	36
R = CH₃	10	:	90

Diphenylnitrilimine (**70**) reacts with methyl acrylate,[149] styrene,[150] 1-hexene,[151] and vinyl butyl ether[150] to produce the 5-substituted pyrazolines **71** exclusively. While in all adducts of enol ethers and enamines the donor substituent is directed to the 5 position, the orientation in the cycloaddition to α,β-unsaturated esters can easily be reversed. Methyl crotonate and methyl β,β-dimethylacrylate produce **72** *and* **73** with increasing amounts of the 4 ester **73**.[149] The orientations with acetylenic dipolarophiles are even less strict: methyl propiolate, the monosubstituted acetylene, gives the methyl 1,3-diphenylpyrazole-5- and -4-carboxylates in a 78:22 ratio.[149]



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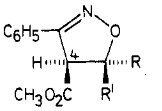
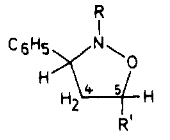


75

R	R'	74		75
H	H	96	:	4
CH₃	H	34	:	66
CH₃	CH₃	0	:	100
C₆H₅	H	30	:	70

Benzonitrile oxide cycloadditions show a related pattern of regioselectivity. Additions to 1-alkenes, styrene, vinyl ethers, and enamines give 2-isoxazolines bearing alkyl, phenyl, ether, or amino groups, respectively, in position 5.[152–154] The predominance of the 5-carboxylic ester in the addition to methyl acrylate (96% **74** and 4% **75**) is reversed in the adducts of β-substituted acrylic esters; β,β-dimethylacrylic ester affords the 4 ester **75** only.[155] Methyl propiolate, likewise, gives rise to isoxazole-5- and -4-carboxylic esters; ratios from 91:9 to 22:78 have been observed for 16 nitrile oxides.[156] In contrast, dipolarophiles with donor substituents produce 5-substituted products exclusively.

Nitrile imines, *nitrile oxides*, and *nitrones* belong to type II (Figure 1) where both frontier orbital interactions contribute. While the terminal nitrogen or oxygen possesses a larger atomic orbital coefficient than carbon in Ψ_2, it is the other way around in Ψ_3.[146,148] Both the interactions Ψ_2–Ψ_B and Ψ_A–Ψ_3 enforce one and the same addition direction for donor-substituted ethylenes or acetylenes. On the other hand, orientational forces on the acrylic ester type dipolarophile are *opposite* for the interactions Ψ_2–Ψ_B and Ψ_A–Ψ_3, as in the case of phenyl azide (**65** vs. **66**). In contrast to phenyl azide, the two HO–LU pairs are closer in energetic distance. The final outcome depends on a delicate balance, i.e., small structural changes can cause marked differences in the addition directions of unsaturated esters and nitriles. Occasionally the energetically greater interaction loses orientational control because the orbital coefficients of one reactant are not sufficiently different. PMO rationalizations of "unidirectional" behavior have been published recently.[143,144,147]



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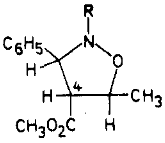

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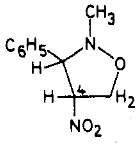
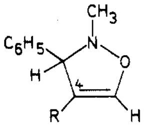


78

R= CH_3,C_6H_5



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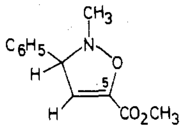


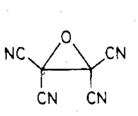
80

N-Methyl-*C*-phenylnitrone or *C*,*N*-diphenylnitrone combines with 1-alkenes,[157] styrene, vinyl ethers,[158] enamines,[159] acrylic ester, and acrylonitrile[160] to yield the 5-substituted isoxazolidines **76**. Both HO–LU interactions appear to direct alkyl, phenyl, and alkoxy to the 5 position. In the reaction with electron-deficient dipolarophiles the Ψ_2–Ψ_B interaction seems to dominate somewhat in energy,[147] but Ψ_A–Ψ_3 exerts stronger orientational control owing to a larger difference between $c_O\beta_{C-O}$ and $c_C\beta_{C-C}$. The reversal of the addition direction of methyl crotonate is noteworthy: the 4-carboxylic ester **77** is formed.[160] With c_α slightly larger than c_β in Ψ_A of methyl crotonate,[148] both HO–LU interactions now favor the 4-carboxylic ester.

The reversal can also be effected by another trick: lowering of the orbital energies in going from acrylic ester to nitroethylene results in an accretion of the Ψ_2–Ψ_B interaction which directs the ethylenic substituent into position 4. According to Sims and Houk,[161] *N*-methyl-*C*-phenylnitrone and nitroethylene produce the 4-nitroisoxazolidine **78**. Methyl propiolate, a borderline case, no longer accepts the nitrone unidirectionally, but gives the isoxazole-4-carboxylate **79**, R = CO_2CH_3, and the 5 isomer **80** in a 58:42 ratio;[162] cyanoacetylene affords only **79**, R = CN,[161] as an outcome of further lowering of orbital energies.

These satisfying results of PMO foster the hope that the vexing orientation problem in 1,3-dipolar cycloadditions will be completely solved in the near future. Urgently needed are additional data on HO energies from ionization potentials, on LU energies from electron affinities and more reliable quantum-chemical values for eigenvectors and orbital energies. CNDO/2 exaggerates the energy distance of HO and LU.

Kinetic Isotope Effects. Dolbier et al.[163] studied the 1,3-dipolar cycloaddition of the carbonyl ylide **82**, which is in thermal equilibrium with tetracyanoethylene oxide (**81**),[164] to 1,1-dideuterioallene (**83**). The result, k_H/k_D = 0.93, agrees with the secondary kinetic isotope effect found in the Diels–Alder reaction of **83** with hexachlorocyclopentadiene. The cycloadditions of acrylonitrile and tetrafluoroethylene to **83** as well as the dimerization of **83** show k_H/k_D = 1.14–1.21; these reactions probably include diradical intermediates.



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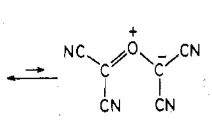
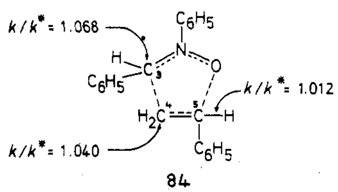


82

$D_2C{=}C{=}CH_2$

83

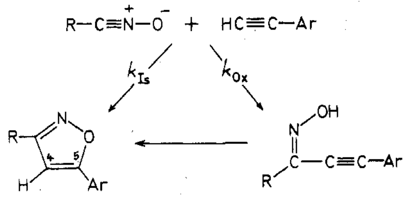
Bayne and Snyder[165] investigated the cycloaddition of **82** to the three isomeric monodeuterated styrenes specifically labeled at the olefinic positions. The identical secondary isotope effects observed, k_H/k_D = 0.96–0.97, render it highly probable that both olefinic centers are equally involved in bond reorganization in the transition state of the concerted process.



84

Benjamin and Collins[166] recently labeled the α-carbon atom of *C*,*N*-diphenylnitrone and the α- or β-carbon atom of styrene with ^{14}C and found the primary kinetic isotope effects (see **84**) in the formation of 2,3,5-triphenylisoxazolidine to be compatible only with the concerted mechanism. The diradical hypothesis would suggest that one of the isotope effects should be *secondary*. However, the observed k/k^* values in **84** are larger than known secondary $^{14}C/^{12}C$ isotope effects, which, moreover, are generally <1.

Crucial Tests. A. Oxime Formation from Nitrile Oxides and Arylacetylenes. Alkyl radicals not only recombine, but also disproportionate to give alkane + alkene. The alleged diradical intermediates of 1,3-dipolar cycloadditions might be expected to undergo at least some hydrogen transfer reaction to form open-chain compounds along with cyclization and dissociation.

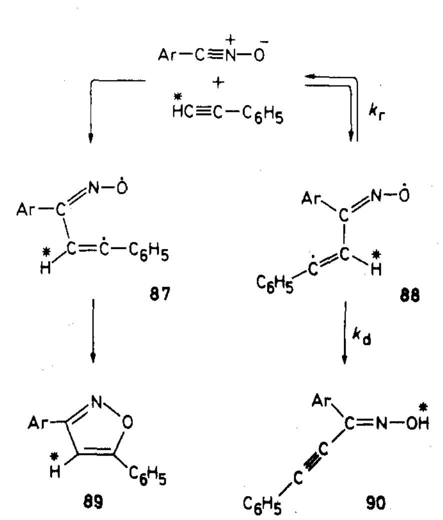


85 **86**

Grünanger et al.[167] noticed that the synthesis of isoxazoles **85** from nitrile oxides and arylacetylenes is accompanied by the formation of acetylenic oximes **86** which cyclize to **85** on heating or under base catalysis. When the reaction was run in THF–D_2O, the cyclization **86** → **85**, but not the cycloaddition (k_{Is}), is accompanied by deuterium incorporation into the 4 position of **85**.[168] Therefore, the Italian authors proposed the scheme above with simultaneous reactions leading to **85** and **86**.[167–169] Analogously, diarylnitrilimines and arylacetylenes produce pyrazoles and acetylenic hydrazones in concurrent reactions.[170]

Investigating the reaction of 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide with phenylacetylene, Beltrame et al.[171] found that a deuterium label in the starred position neither affected the overall rate constant *nor the ratio* **89**:**90**, 0.18. A careful reinvestigation by Dondoni et al.,[172] who used *p*-chloro- and *p*-methylbenzonitrile oxide, confirmed the absence of an isotope effect.

Beltrame et al.[171] considered a common (diradical or zwitterionic) intermediate, but later dismissed that idea.[173] Firestone[22] ascribes the oxime formation to the "extended diradical" **88** which is postulated to be in a highly mobile



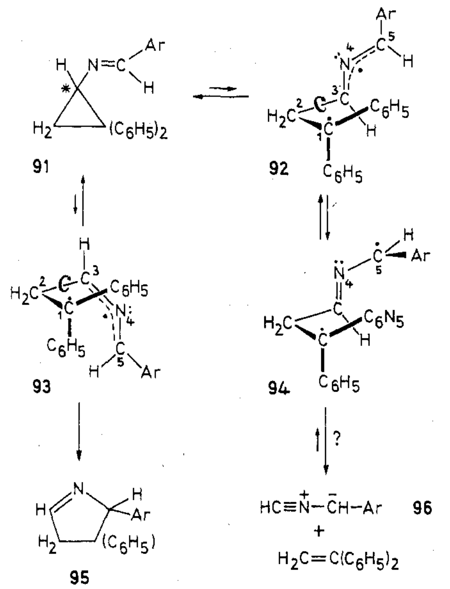
equilibrium with the reactants, while **89** is conjectured to be produced via the "cyclo diradical" **87**.

Only the hydrogen transfer in **88** → **90**, but not the conversion **87** → **89**, should be subject to a primary kinetic isotope effect. The process **88** → **90** would be comparable to a radical disproportionation which has an early transition state. Therefore, one should perhaps not expect the sizable isotope effects known for hydrogen abstractions by oxygen radicals,[174] but a smaller magnitude; e.g., $k_H/k_D = 1.87$ has been measured for the disproportionation of the α-phenethyl radical.[55] The replacement of H* by D should result in an increase of the isoxazole yield at the expense of oxime formation. The nonoccurrence of this effect makes it improbable that the C–H* bond-breaking step is connected by mobile reversible reactions with the product-determining step leading to **89**. The diradical scheme above would be compatible with the facts only under the stringent condition that the step *88 → 90 (k_d) is much faster than the* dissociation of **88** to reactants (k_r) for which we deduced a very small barrier above ($E_a \ll 1.2$ kcal for **9**). For example, if $k_H/k_D = 1.6$, a ratio $k_d/k_r = 1, 5$, or 10 would increase the product ratio **89**:**90** by 30, 10, or 5%, respectively.

I agree with the Italian authors[167–173] that the concomitant formation of isoxazoles and acetylenic oximes does not "establish the correctness of the diradical mechanism beyond a reasonable doubt." [22] No objections can be raised against an *irreversibly* formed diradical **87** or a zwitterion[171] as precursor of the acetylenic oxime. The recently proposed 1,1-cycloadduct as intermediate[172] constitutes an interesting alternative.

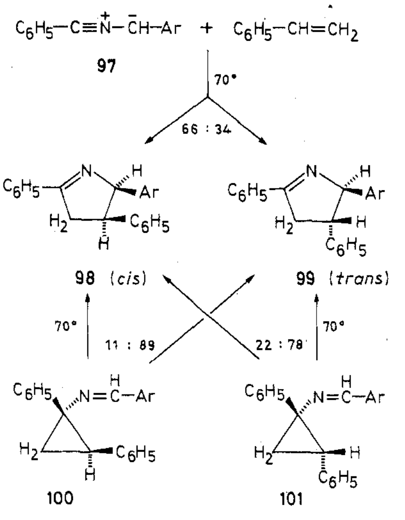
B. Independent Synthesis of 1,5-Diradicals. Close relatives of Firestone-type diradicals have recently become accessible; they do not show the asserted behavior.

The rate constants of racemization of the optically active *N*-cyclopropylazomethines **91** and the *k* values of their ring expansion to the pyrrolines **95** display a linear relation on the log scale for 12 different Ar's. The log *k* values also correlate linearly with the logarithms of the partial rate factors of radical aromatic phenylation and methylation as well as with atom localization energies.[175] This corroborates the widespread assumption that the vinylcyclopropane rearrangement proceeds via diradical intermediates[176] as does the racemization (or cis–trans isomerization) of substituted cyclopropanes.[9] The racemization of **91** may take place by ring opening to **92** or **93**, rotation about the 2,3 bond, and reclosure of the three-membered ring; **92** contains an exo,exo and **93** an endo,exo disubstituted azaallyl radical. Only **93** can undergo 1,5 combination to give the pyrroline **95**.



According to the diradical hypothesis,[22] the allyl anion type orbital of the (unknown) nitrile ylide **96** should interact with diphenylethylene to produce reversibly the "extended diradical" **94** and a related "cyclo diradical" which closes the ring to **95**. The diradical **94** differs from **92** only by a 90° rotation about the 4,5 bond and this also differentiates the "cyclo diradical" from **93**. It is hard to predict whether the allylic resonance in **92** or the three-electron bond in **94** will provide greater stabilization. Is it conceivable that diradical manifolds of the types **92** and **94** are separated by substantial energy barriers?[69] A smooth conversion *to the more stable conformation* is expected because the rotational barrier between **92** and **94** should be wiped out owing to the $\cos^2 \alpha$ relation for the interaction energy of twisted π systems.

According to Firestone,[22] the "extended diradical" **94** should dissociate very rapidly to 1,3-dipole and dipolarophile. However, even at 165° the conversion **91** → **95** is quantitative. The racemization of **91**, Ar = $C_6H_4OCH_3$-*p*, is 110 times faster than its ring enlargement to **95** at 101°,[175] i.e., the diradical intermediates are often created from **91** before the pyrroline **95** is irreversibly formed. The lack of any dissociation of the 1,5-diradical intermediates is at variance with their alleged behavior.[22]



Ar = $C_6H_4NO_2$-*p*

Benzonitrile *p*-nitrobenzylide (**97**) combines with styrene to produce the pyrrolines **98** and **99** in 79% yield (at 20°).[177] The cis,trans isomeric *N*-cyclopropylazomethines **100** and **101** yield the same pyrrolines **98** and **99** quantitatively at 70°. Three arguments allow one to reject a common manifold of diradical intermediates in the two processes.

(1) The diradicals from **100** and **101** rotate and reclose the three-membered ring with a similar rate as they suffer ring expansion at 65°.[178] Though the azomethines **100** and **101** are stable at 20°, they do not occur as products in the cycloaddition of **97** + styrene at room temperature.

(2) The azomethine **100** (**101**) yields via rotameric diradicals the pyrrolines **98** and **99** in a 11:89 (22:78) ratio at 70°.[177,179] With a ratio of 66:34 of **98** and **99** at 70°,[180] however, the concerted cycloaddition of **97** to styrene shows a well-understood preference for the *cis isomer*.

(3) The conversion of the azomethines **100** and **101** into **98** + **99** is quantitative, even in methyl acrylate as solvent. That rules out any dissociation of diradical intermediates into **97** + styrene because methyl acrylate exceeds styrene $\geqslant$20-fold in dipolarophilic activity toward **97**.[180]

Calculation of the Transition State. Polanski and Schuster[181] used HMO to calculate the transition state energy for the concerted addition of diazomethane to ethylene. In a more refined study Fukui et al.[182] applied a semiempirical SCF including CI to the same reaction. They found the formation of the new σ bonds concerted, but nonsynchronous in the sense of CC < CN distance in the transition state due to the predominant HO(1,3-dipole)–LU(dipolarophile) interaction.

Recently Leroy and Sana[183] calculated the hypersurface of the reaction diazomethane + ethylene by an ab initio method. The transition state of the concerted cycloaddition was found at the following distances: CC 2.27 Å and CN 2.24 Å; the results excluded a secondary energy minimum. In agreement with PMO, there is a net flow of charge (6% of an electron charge) from diazomethane to ethylene in the transition state.

Conclusion

All mechanistic criteria underline the superiority of the concerted mechanism over the diradical hypothesis. My main concern, however, was not just to refute the arguments for diradical intermediates, but rather to point out how well the large bulk of data on 1,3-dipolar cycloadditions complies with the expectations for the concerted process $[{}_{\pi}4_{s} + {}_{\pi}2_{s}]$. The MO perturbational treatment provides a deeper insight and promises a solution of remaining problems in the near future.

Acknowledgment. I express my gratitude to Professors Paul D. Bartlett, Albert T. Bottini, Clair J. Collins, Paolo Grünanger, Kendall N. Houk, Paul v. R. Schleyer, and Reiner Sustmann for critical comments and illuminating discussions. I am especially grateful to A. T. Bottini and P. v. R. Schleyer for their help in preparing the English manuscript.

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Halocyclopropanes

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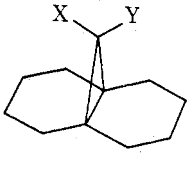
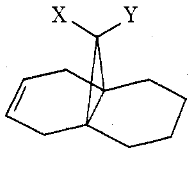
The chemistry of the tricyclic monobromides **4**, **5**, **6**, and **7** has been examined. Evidence is presented which implicates a partially opened cyclopropyl cation as a reaction intermediate.

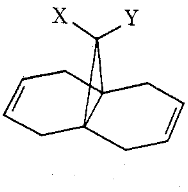
The chemical properties of various tricyclic cyclopropyl halides have been of interest to us and several others for some time now.[2] We recently reported on the silver ion assisted solvolysis of the *gem*-dibromides **1**, **2**, and **3**.[3] A continued interest in this area led us to examine the corresponding monobromo compounds **4**, **5**, **6**, and **7**. The chemistry of these monobromo derivatives differed significantly from that observed for the aforementioned dibromo systems. We now wish to report on these differences, and we attempt to offer reasonable explanations as to their origins.



1, X = Y = Br
4, X = H; Y = Br



2, X = Y = Br
5, X = H; Y = Br
6, X = Br; Y = H



3, X = Y = Br
7, X = H; Y = Br