Can Tetramethylene Intermediates Be Intercepted?

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Thermal 2 + 2 cycloaddition reactions, in which two olefin molecules furnish cyclobutane derivatives, pose special mechanistic problems which have been summarized recently.[1] The suprafacial combination of two π-bonded systems, the process $[_{\pi}2_s + _{\pi}2_s]$, is forbidden to be concerted by the Woodward–Hoffmann rules.[2] It is generally assumed that this ban is by-passed in two-step reactions, in which the two new σ bonds are formed one after the other. The reverse type of process, the rupture of a four-membered ring to form two alkene molecules, should also occur in a nonconcerted fashion.

The Tetramethylene Species

There is ample evidence that thermal 2 + 2 cycloadditions or cycloreversions proceed via high-energy species which have been described either as zwitterionic tetramethylene derivative **2** or as singlet biradical **1**, as illustrated in Scheme I. The distance of about 3.1 Å between the termini b and d in the cis or gauche conformation of **1** and **2** still permits some bonding and electrostatic interaction. "Through-bond coupling" (see below) makes the terminal centers, even in the trans conformation **3**, "cognizant" of one another.

Are the 1,4-biradical **1** and the zwitterion **2** fundamentally different? The theorist's answer is an emphatic "no". Hoffmann et al.[3] assigned molecular orbitals to the tetramethylene; the relative magnitudes of the atomic orbital coefficients (their squares are the electron densities) at the termini indicate whether the biradical or the zwitterion is the more appropriate representation. Salem and Rowland[4] treated the tetramethylene by a linear combination of two terms, one for the biradical and the other for the zwitterion; **1** and **2** could thus be regarded as resonance structures. Their relative weights are determined by the substituents at the terminal centers; they decide where a given tetramethylene species has to be located on the *continuous scale between biradical and zwitterion.*

Experimental evidence for this continuum hypothesis is still lacking. The model reactions for which mechanistic criteria have been elaborated so far were tailor-made to fit either **1** or **2**. Bartlett's study of the mixed 2 + 2 cycloaddition of 1,1-dichloro-2,2-difluoroethylene and cis–trans isomeric butadiene derivatives[5] pertained to the prototype of a reaction via *biradical.* In contrast, cyclobutane formation by reaction of tetracyanoethylene (TCNE) with enol ethers proceeds according to numerous mechanistic criteria via a *zwitterion.*[1]

Is the Tetramethylene Species a True Intermediate?

An intermediate has a finite lifetime and is delineated by a dip in the energy profile. The trough must be

Scheme I
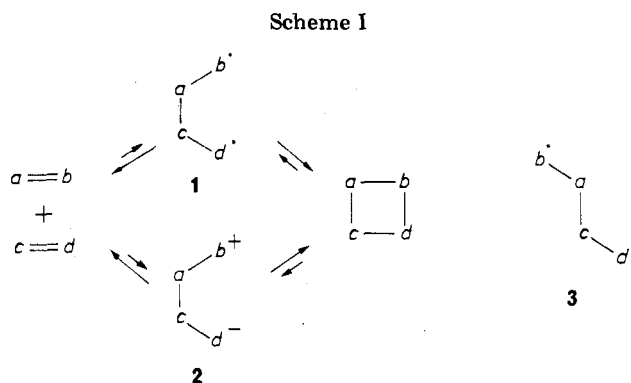
lower than $^1/_2 h\nu_0$, where ν_0 is the zero-point frequency of the stretching vibration which conveys the system "over the rim". Admittedly, the definition becomes shaky when one bears in mind that the usual energy profile is an idealized minimum potential-energy pathway, whereas in reality reacting systems cruise on a manifold of trajectories.

Based on thermodynamic estimates, Benson[6] placed the tetramethylene parent species into an energy well which lies ≥ 4 kcal/mol below the activation barrier of cyclobutane pyrolysis ($E_A = 62.5$ kcal/mol).[7] Hoffmann et al.[4] calculated the potential-energy surface between cyclobutane and two molecules of ethylene by extended Hückel (EH) theory. The tetramethylene does not emerge as a trough, but rather as a flat hypersurface. Whereas the gauche conformation **5** has to overcome a modest activation barrier for cyclization, **5** and **6** are not minima, but are unstable with respect to two ethylenes; the abyss of dissociation is open for all those conformations which, like **4–6** can form ethylene

4   *cis*   **5**   *gauche*   **6**   *trans*
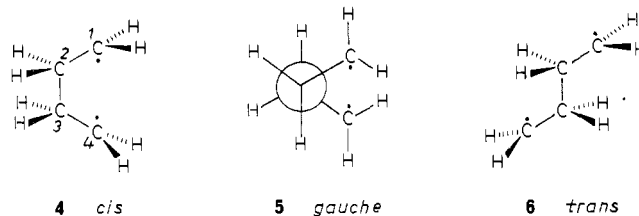
without substantial rotation about the C.1–C.2 or C.3–C.4 axis.

(1) R. Huisgen, *Acc. Chem. Res.*, **10**, 117 (1977).
(2) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).
(3) R. Hoffmann, S. Swaminathan, B. G. Odell, and R. Gleiter, *J. Am. Chem. Soc.*, **92**, 7091 (1970).
(4) L. Salem and C. Rowland, *Angew. Chem., Int. Ed. Engl.*, **11**, 92 (1972).
(5) P. D. Bartlett, *Science*, **159**, 833 (1968); *Q. Rev., Chem. Soc.*, **24**, 473 (1970).
(6) S. W. Benson and P. S. Nangia, *J. Chem. Phys.*, **38**, 18 (1963).
(7) C. T. Genaux, F. Kern, and W. D. Walters, *J. Am. Chem. Soc.*, **75**, 6196 (1953).

Segal[8] concluded from an ab initio calculation (SCF at STO-3G level, 15-dimensional configuration interaction) that there are two well-defined potential-energy minima for the gauche and trans conformations **5** and **6** on the "soft" surface of $(CH_2)_4$. The bond angles at C.2 and C.3 of the gauche form **5** are close to tetrahedral, while a slight pyramidalization at C.1 and C.4 maximizes residual C.1–C.4 bonding. The barrier of **5** to dissociation amounts to 3.6 kcal/mol and that to cyclization is ≥ 2.0 kcal/mol.

It is a safe assumption that the wells for **5** and **6** should become deeper when the terminal carbon atoms bear substituents which stabilize radicals or zwitterions. Let us, however, seek experimental evidence for *energy troughs* of tetramethylene species. The fact that there are well-defined ratios of ring closure to rotation and to dissociation points to *intramolecular* competition phenomena typical for intermediates.[9]

Conceivably, various precursors produce one and the same intermediate in diverse conformations and with variant excess energies corresponding to different points on the hypersurface. Dervan and Uyehara[10] generated 1,2-dimethyltetramethylene (cis and trans forms) from both azo compound and 1,1-diazene precursors. The product ratios they observed are compatible with the same intermediates that are formed by thermolysis of *cis*- and *trans*-1,2-dimethylcyclobutanes.[11]

It is obvious that *intermolecular* competition reactions would provide superior evidence for the occurrence of intermediates.[9] Tetramethylenes turn out to be difficult to trap. In seeking to ensnare them, one would anticipate a greater chance of intercepting a zwitterionic tetramethylene rather than a biradical for two reasons: (a) well-solvated zwitterions have a longer lifetime than biradicals. In extreme cases such 1,4-dipoles become isolable and refuse to cyclize.[12,13]   (b) Tetramethylene zwitterions can be created at lower temperatures than biradicals. The unfavorable negative activation entropy of any bimolecular trapping reaction can be overcome more easily at low temperature.

Interception of the Zwitterions from TCNE and Enol Ethers with Alcohols

Both stereochemical and kinetic evidence suggest strongly the zwitterionic pathway for the smooth 2 + 2 cycloaddition of TCNE and enol ethers.[1] However, kinetic results can never give apodictic proof, but are at best consistent with a proposed pathway. A chemical confirmation by interception would be highly desirable.

Ethyl *trans*- and *cis*-propenyl ethers (**7** and **10**) afford with TCNE in aprotic solvents the cyclobutanes **8** and **11**, the nonstereospecific portion being increased with growing solvent polarity.[1,14] On running the reaction in *ethanol*—TCNE is sufficiently stable in cold pure

(8) G. A. Segal, *J. Am. Chem. Soc.*, **96**, 7892 (1974).

(9) Review on competition principle: R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **9**, 751 (1970).

(10) P. B. Dervan and T. Uyehara, *J. Am. Chem. Soc.*, **98**, 1262, 2003 (1976).

(11) H. R. Gerberich and W. D. Walters, *J. Am. Chem. Soc.*, **83**, 3935, 4884 (1961).

(12) Stable crystalline zwitterion from *N*-benzylidenemethylamine + SO₃: D. S. Breslow and R. Huisgen, University of Munich, 1965, quoted by R. Huisgen in ref 23c.

(13) Colored 1,4-dipoles from ketene *S,N*-acetals and polycyanoolefins: R. Gompper, W. Elser, and H.-J. Müller, *Angew. Chem., Int. Ed. Engl.*, **6**, 453 (1967).

(14) R. Huisgen and G. Steiner, *J. Am. Chem. Soc.*, **95**, 5054 (1973).

Scheme II
Kinetics of Acetal Formation from Propenyl Ethyl Ether (0.25 M) and TCNE (0.016 M) in Ethanol at 25 °C[15]

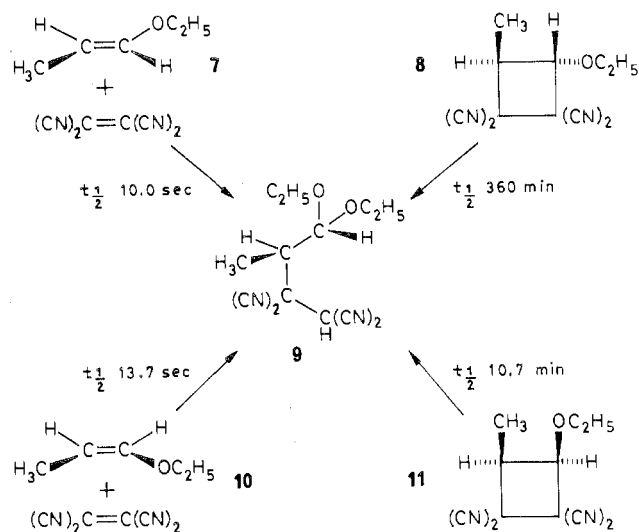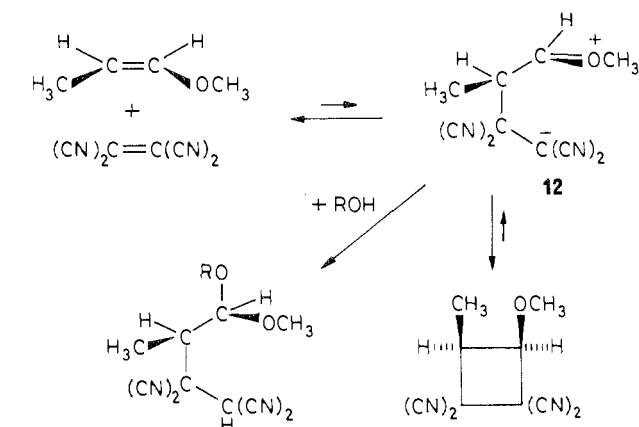**Table I**
Concurrent Formation of Acetal and Cyclobutane from TCNE and Methyl *cis*-Propenyl Ether in Various Alcohols at 0 °C[15,16]

R		
$-CH_3$	93 %	7 %
$-CH_2-CH_3$	84 %	16 %
$-C_{H}^{CH_3}{}_{CH_3}$	82 %	18 %
$-C{-CH_2-CH_3}^{CH_3}{}_{CH_3}$	59 %	41 %
$-CH_2CH_2OCH_3$	77 %	23 %

alcohols—one isolates the crystalline open-chain acetal **9** which is easily recognized as a 1:1:1 adduct of the three reactants (Scheme II).[15]

Does alcohol really intercept an *intermediate* or is **9** a product of ethanolysis of the cyclobutanes *after* cycloaddition? Actually, the cis,trans isomeric cyclobutanes, obtained in nonhydroxylic solvents, are converted in ethanol to the same acetal, but in much slower processes. The half-reaction times in Scheme II reveal that acetal formation from TCNE and the two enol

(15) R. Huisgen, R. Schug, and G. Steiner, *Angew. Chem., Int. Ed. Engl.*, **13**, 80 (1974).

ethers is faster by factors of 2200 and 47 (Scheme II) than that from the cyclobutanes.[15] The rate data exclude the cyclobutane as an intermediate on the pathway from TCNE + enol ether to the acetal. It is a tempting idea that the same zwitterion, produced *rapidly* from TCNE + enol ether and *slowly* by ring opening of the cyclobutane, is responsible for acetal formation.

A slow cis–trans equilibration of the cycloadducts, 8 ⇌ 11, in the polar aprotic solvent acetonitrile was attributed to rotation in the reversibly formed zwitterion.[1,14] Alcohols exceed acetonitrile in polarity and diminish further the energy distance between cyclobutane and the zwitterion. Additional evidence for the alcoholysis of cyclobutanes *via the zwitterion* is discussed below.

In reactions of TCNE with enol ethers in alcohols for several minutes at 0 °C, acetalic trapping products and 2 + 2 cycloadducts were formed side by side as result of *kinetic control*,[15] as shown by NMR analysis. Addition of alcohol and cyclization compete for the zwitterion 12. Some data for methyl *cis*-propenyl ether and TCNE in Table I show the effect of variation of the alcohol. The portion of the zwitterion 12 which is intercepted drops from 93% in methanol ($\Delta\Delta G^{\ddagger}$ = 1.5 kcal/mol) to 59% in *tert*-amyl alcohol with its increased steric requirements and its reduced molar hydroxyl concentration. β-Methoxyethanol is less nucleophilic than ethanol and gives rise to a smaller percentage of acetal.

Alcohols intercept the zwitterionic intermediates from TCNE and a great variety of enol ethers.[15,16] Finding that they do was admittedly a stroke of luck. The addition of *p*-methoxystyrene to TCNE is slower than that of methyl vinyl ether; in this case, ethanol or acetic acid did not trap an intermediate.[17] Likewise futile were endeavors to intercept with alcohols the zwitterion from TCNE and tetramethoxyethylene;[16] the very fast cyclobutane formation[18] could not be suppressed.

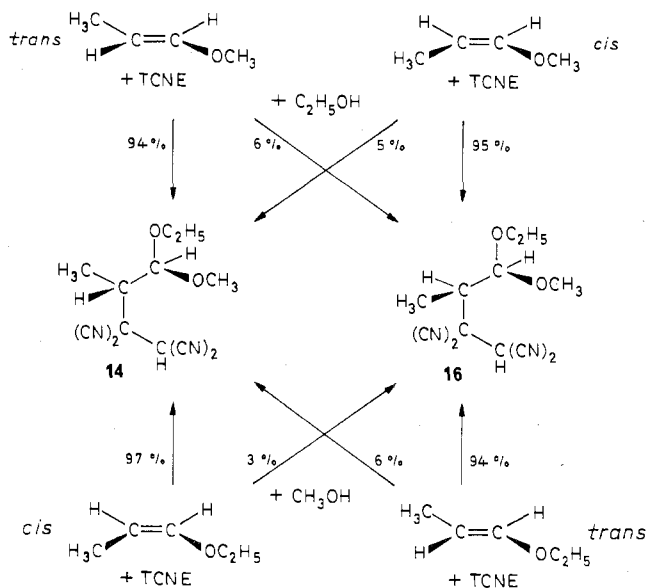## Stereoselectivity of the Trapping Reaction with Alcohol

The acetal 9 is chiral at C.2. If different alkoxy groups appear in the enol ether and in the intercepting alcohol, there is a second asymmetric center at C.1 of the acetal. The ratio of diastereomers should probe the stereochemistry of the trapping reaction.[19]

Ethyl cis-propenyl ether is converted by TCNE in *methanol* to 11% of the cyclobutane 11 and 89% of a mixture of diastereomeric ethyl methyl acetals; of the latter, 86% is 14 and 3% is 16, corresponding to a 97% stereoselectivity of acetal formation (Scheme III). When the alkoxy residues of enol ether and alcohol are exchanged, *methyl cis*-propenyl ether and TCNE produce in *ethanol* 4% 14 and 80% 16 besides 16% cyclobutane 17. That amounts to a 95% stereoselectivity in the trapping reaction, now in favor of 16. Both of the mixed ethyl methyl acetals were obtained pure and crystalline.
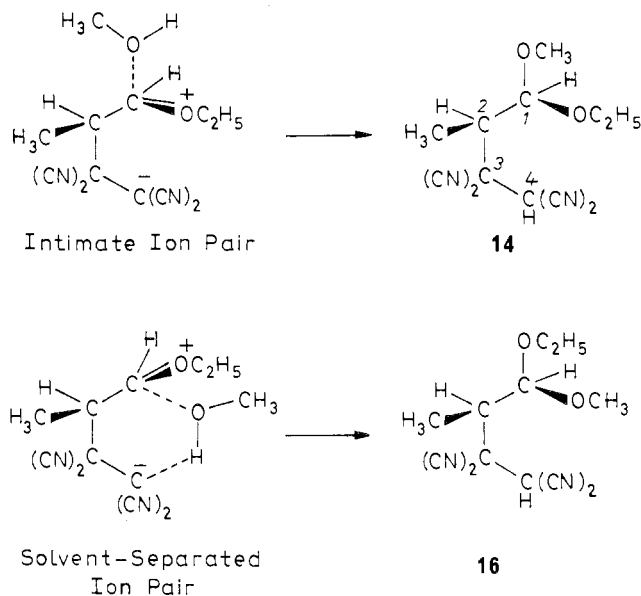
(16) R. Schug, Ph.D. Thesis, University of Munich, 1976.

(17) D. W. Wiley, unpublished; quoted by E. Ciganek, W. J. Linn, and O. W. Webster, "The Chemistry of the Cyano Group", Z. Rappoport, Ed., Interscience, London–New York, 1970, p 454.

(18) R. W. Hoffmann, U. Bressel, J. Gehlhaus, and H. Häusler, *Chem. Ber.*, 104, 873 (1971).

(19) R. Huisgen, R. Schug, and G. Steiner, *Angew. Chem., Int. Ed. Engl.*, 13, 81 (1974).

Scheme III
Reactions of Alkyl *cis*-Propenyl Ethers with TCNE in Alcohols at 0 °C (NMR Analysis)[19]
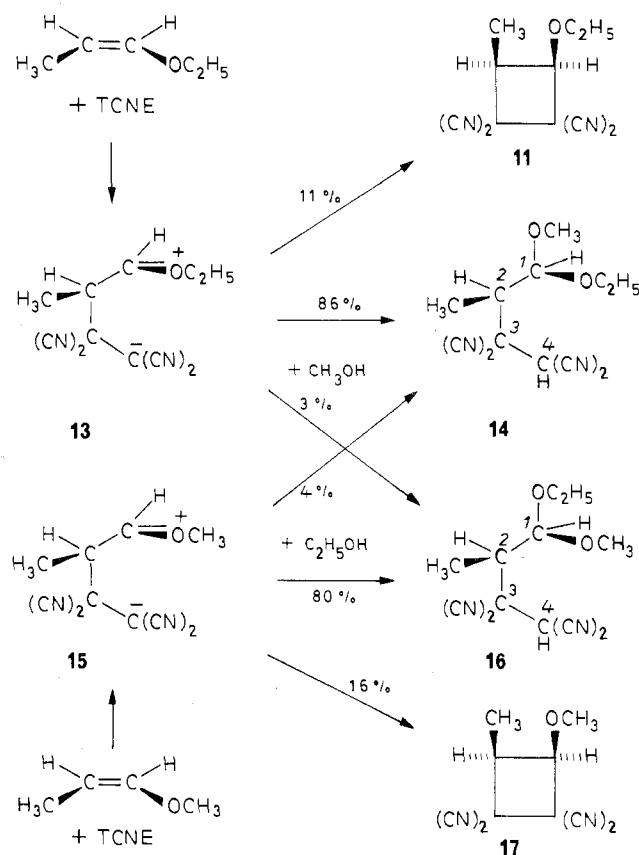
Scheme IV
Formation of Mixed Acetals from Alkyl *cis*- and *trans*-Propenyl Ethers with TCNE in Alcohol at 0 °C[19]

If the zwitterions from the two enol ethers and TCNE were formed in random conformations, the stereoselectivity of the reaction with alcohol should be low. We must conclude from the observed stereoselectivity that most of the zwitterions arise in the cis or gauche conformations 13 and 15 which are favored by the Coulomb attraction between the charge centers and by a donor–acceptor interaction between the vacant and filled orbitals at C.1 and C.4. The gauche arrangement

Scheme V
Steric Course of the Reaction of
Zwitterion 13 with Methanol

Intimate Ion Pair

14

Solvent-Separated
Ion Pair

16

Scheme VI
TCNE and Methyl *cis*-Propenyl Ether in
(S)-(+)-2-Butanol[21]

17

15

Outside Attack of Alcohol

18

19

Scheme VII
Steric Course of the Methanolysis of Cyclobutane 11[19]

11   24 h 25°C

99 : 1
+ CH₃OH

14   **16**

+ CH₃OH
97 : 3

10   4 min 0°C

+ TCNE

would suffer less from conformational strain at the C.2–C.3 bond.

There is a second way to reverse the ratio of acetals 14 and 16: one keeps the nature of the alcohol constant, but shifts from the cis to the trans configuration of the enol ether. In Scheme IV the selectivities of acetal formation are compared; the formulas of the zwitterions and the concomitantly formed cyclobutanes are omitted.

How do we know the configurational assignments for the diastereomeric acetals 14 and 16? This implicates the question:

How Does the Zwitterion React with Alcohol?

In the gauche zwitterion from ethyl *cis*-propenyl ether and TCNE (Scheme V), the malononitrile anion group offers excellent "built-in solvation"[20] of the carboxonium ion from the inner side. The species may also be depicted as an intramolecular *contact ion pair* with substantial charge-transfer character. The nucleophilic methanol molecule should attack the carboxonium center of 13 *from outside*, furnishing the acetal 14, and causing the carbanionic group to recede.

A second alternative would be a *solvent-separated ion pair* in which one molecule of methanol connects the ionic centers in a cyclic hydrogen chelate. This species (Scheme V) would produce an acetal which is *epimeric* at C.1. X-ray structure analysis should provide a decision between reaction via intimate or solvent-separated ion pair.

Experimentally, zwitterion 15 was allowed to react with (S)-(+)-2-butanol in the expectation that the minor acetalic product—3–6% in Scheme IV—would remain in the mother liquor. If the optically active alcohol attacks the chiral zwitterion 15 from "outside", diastereomeric acetals 18 and 19 with the configurations *SRR* and *SSS* should be formed in comparable amounts (Scheme VI). Either would serve the purpose, because only the relative configurations at the former enol ether
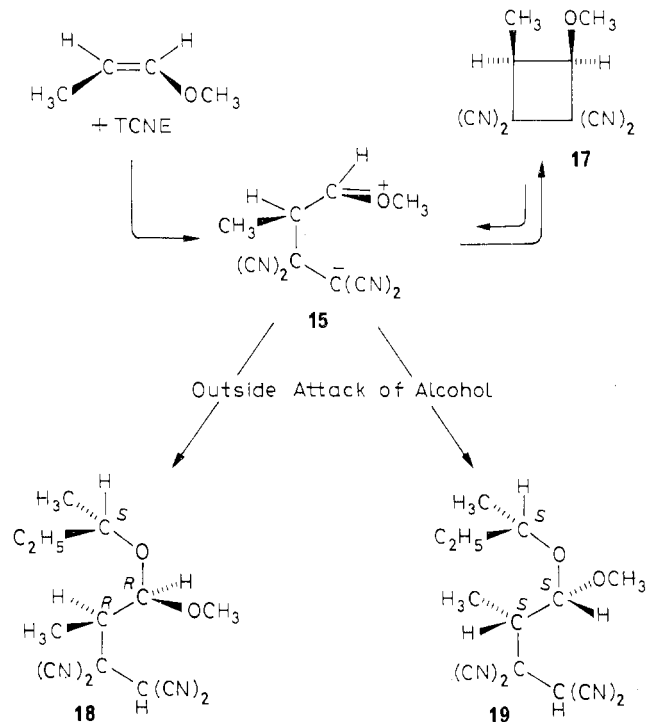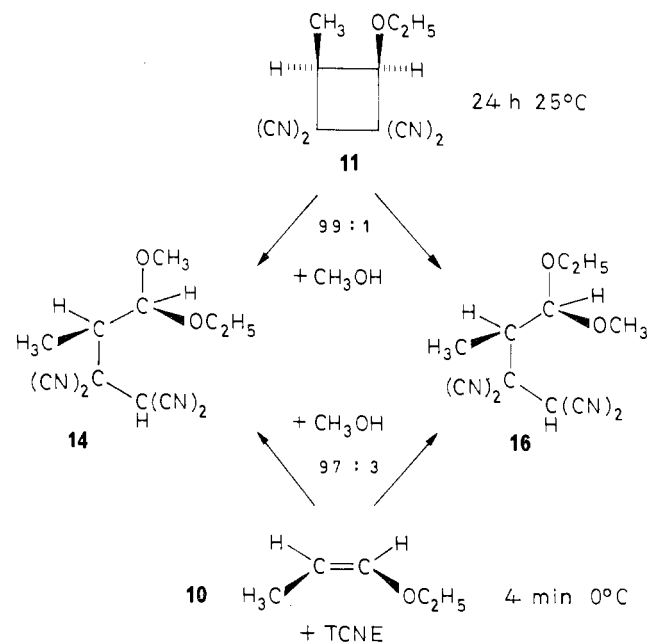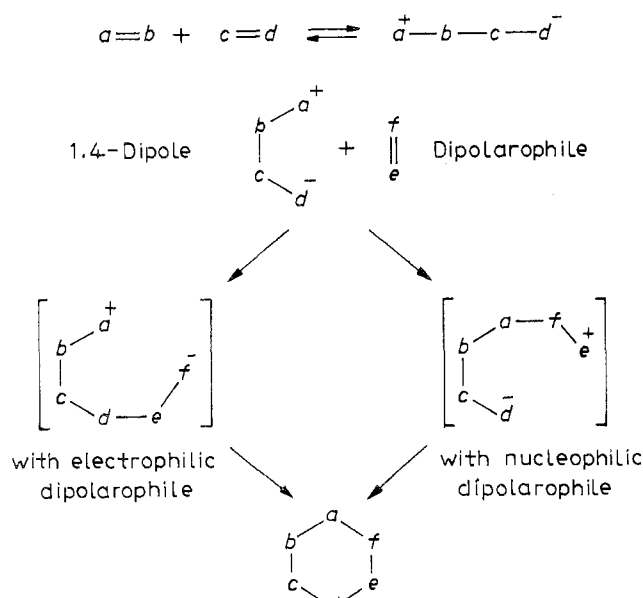
carbons are of interest. In the event, a mixture of diastereomeric acetals was obtained, but a single isomer was isolated by crystallization from (+)-2-butanol and shown by x-ray analysis, carried out by Karle and Flippen,[21] to have structure 18 (Scheme VI). Outside attack on the zwitterion by alcohol is thereby demonstrated.

The tetracyano-substituted acetals dissolve in aqueous sodium carbonate and are by some 14 pK units more acidic than methanol or ethanol. Therefore, al-

(20) Definition: J. F. Bunnett and R. J. Morath, *J. Am. Chem. Soc.*, 77, 5051 (1955); J. F. Bunnett, R. J. Morath, and T. Okamoto, *ibid.*, 77, 5055 (1955).

(21) I. Karle, J. Flippen, R. Huisgen, and R. Schug, *J. Am. Chem. Soc.*, 97, 5285 (1975).

Scheme VIII

$$a = b \ + \ c = d \ \rightleftharpoons \ \overset{+}{a} - b - c - \overset{-}{d}$$

with electrophilic dipolarophile

with nucleophilic dipolarophile

cohol as a nucleophile will react with the carboxonium ion; C-protonation takes place subsequently.

Ring Opening of the Cyclobutanes in Alcohols

The slow conversion of the 1-alkoxy-2,2,3,3-tetra-cyanocyclobutanes by alcohols to the open-chain acetals was subjected to the same stereochemical probe used for acetal formation from TCNE and enol ether in alcohol. The acetal ratios in Scheme VII diagnose an even higher stereoselectivity for the methanolysis of the *cis*-cyclobutane 11. The corresponding reaction of the *trans*-cyclobutane 8 with methanol yields 2% 14 and 98% 16,[19] whereas ethyl *trans*-propenyl ether (7) + TCNE produces in methanol the acetals 14 and 16 in a 6:94 ratio.

The cis or gauche zwitterion is a logical intermediate of this ring-opening alcoholysis, essentially S_N1 type. Although the first step is the reversion of the zwitterion cyclization discussed above, an alternative S_N2-type displacement would not violate the principle of microscopic reversibility. Opening of the four-membered ring by nucleophilic alcohol attack would follow the same steric course, inversion. The activation volume tenders a welcome criterion: Le Noble and Mukhtar[22] measured the pressure dependence of methanolysis rate for *trans*-cyclobutane 8 up to 2 kbars and deduced from $\Delta V^{\ddagger} = -16.7 \ \text{cm}^3/\text{mol}$ an S_N1 solvolysis mechanism.

The somewhat smaller stereoselectivity of the reaction of TCNE with propenyl ethyl ether in methanol (Scheme VII) suggests a few percent more conformational stray shots, i.e., a tiny involvement of anti or other conformations besides the dominant cis or gauche.

1,4-Dipolar Cycloadditions of the Zwitterionic Intermediate

Ten years ago, 1,4-dipolar cycloaddition was introduced as a general principle for synthesis of six-membered heterocycles.[23] A nucleophilic double bond

(22) W. J. Le Noble and R. Mukhtar, *J. Am. Chem. Soc.*, **97**, 5938 (1975).

(23) (a) R. Huisgen and K. Herbig, *Justus Liebigs Ann. Chem.*, **688**, 98 (1965); (b) R. Huisgen, M. Morikawa, K. Herbig, and E. Brunn, *Chem. Ber.*, **100**, 1094 (1967); (c) review: R. Huisgen, "Topics in Heterocyclic Chemistry", R. N. Castle, Ed., Wiley-Interscience, New York, N.Y., 1969, p 223.

Scheme IX
Interception of the Zwitterion by 1,4-Dipolar Cycloaddition[24]
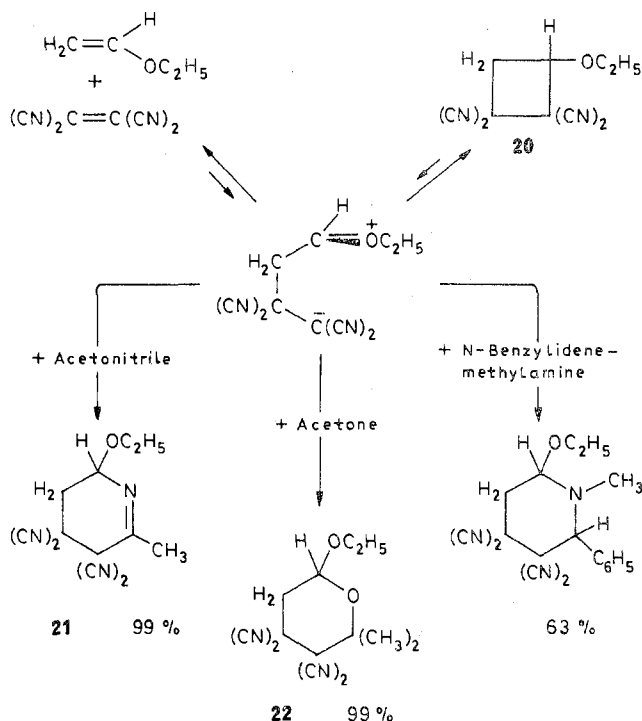
a=b reacts reversibly with an electrophilic c=d, creating the 1,4-dipole which is trapped by a third multiple bond system, the dipolarophile e=f (Scheme VIII). Probably, this cycloaddition takes place in a stepwise fashion.

The zwitterion from TCNE and enol ether is such a 1,4-dipole. Its cycloadditions escaped our attention for several years; the additions are slow, and their products are those of *thermodynamic control*. Ethyl vinyl ether and TCNE combine within a minute to give the cyclobutane 20 which in acetonitrile or acetone solution is converted slowly, but virtually quantitatively, into 21 and 22 in a week at room temperature (Scheme IX). The whole of the material is gradually siphoned off through a small equilibrium concentration of the zwitterion to afford six-membered-ring products which are thermodynamically more stable because they lack the ring strain of 20.[24]

Trapping the zwitterion by dipolarophiles is slower than by alcohols. The reaction of TCNE with ethyl vinyl ether in acetonitrile or acetone under conditions of *kinetic control* (10 min, 20 °C) rendered 4% 21 or 6% 22, respectively, besides 20.

Are Stepwise Cycloadditions Subject to Orbital Control?

In the cis or gauche zwitterion from TCNE and enol ether, the π orbitals at the termini are waiting to form the σ bond and thus close the cyclobutane ring. These π orbitals are at a distance where a weak σ overlap is possible. On second thought, is it not surprising that the cyclization rate can be exceeded by *intermolecular* interception reactions?

All bond-making and -breaking processes are subject to orbital control which, however, becomes evident in

(24) R. Schug and R. Huisgen, *J. Chem. Soc., Chem. Commun.*, 60 (1975).
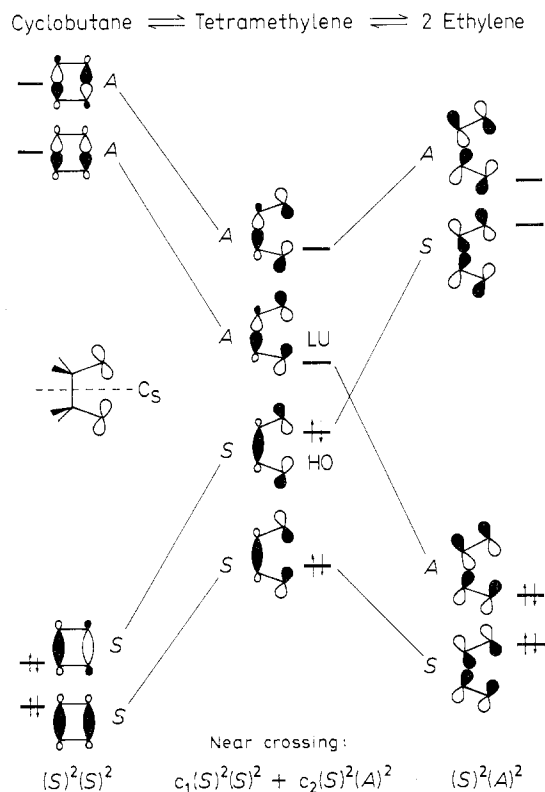
Figure 1. MO symmetry correlation diagram for the two-step interconversion cyclobutane $\rightleftharpoons$ 2ethylene.

rate and steric course only if two or more bonds are made or broken in concert. The tacit assumption that one can forget orbital control in discussion of two-step cycloadditions is fallacious in the opinion of this author. In the following discussion the Woodward–Hoffmann formalism[2] is used, although the Evans–Zimmerman–Dewar approach[25,26] gives similar results. The qualitative reasoning will pertain to the *tetramethylene species* without particular emphasis on whether it is biradical or zwitterion.

Let us start with the symmetry-forbidden *concerted* splitting of cyclobutane into two molecules of ethylene, the process $[_\sigma 2_s + {}_\sigma 2_s]$. The delocalized σ orbitals of cyclobutane are classified as symmetric (S) or antisymmetric (A) with respect to two symmetry planes.[2] After Woodward and Hoffmann, correlation of the AS highest occupied orbital of cyclobutane with the likewise AS antibonding LUMO of two oriented ethylene molecules is banned. One crosses the line of nonbonding in the MO symmetry correlation diagram.

The molecular state correlation diagram[27] reveals that the ground state of cyclobutane, $(SS)^2(AS)^2$, is symmetry-connected with the second excited state of the two oriented ethylene molecules. This correlation line crosses a second one which links the likewise symmetric ground state of two ethylenes, $(SS)^2(SA)^2$, with a higher excited state of cyclobutane. Configuration interaction decrees noncrossing. The two ground states now become connected, not directly "through the ground floor", but rather over a substantial energy barrier which constitutes the "forbiddenness" of concerted

bond cleavage. Near the crest of the barrier the system is described by a wave function to which both configurations, $(SS)^2(AS)^2$ and $(SS)^2(SA)^2$, contribute.

Now let the two σ bonds of cyclobutane be broken *one after the other* and the tetramethylene intermediate be inserted. All MO's in Figure 1 are defined with respect to the remaining plane of symmetry which cuts orthogonally the projection plane. As for the construction of the MO's of tetramethylene, the σ hybrid orbitals of the C.2–C.3 bond and the terminal π orbitals are sufficient for examination of dissociation and cyclization.[3] The two occupied σ MO's of cyclobutane furnish two likewise symmetric MO's of tetramethylene. For the second bond-breaking step, however, the electrons of the symmetric HOMO of tetramethylene must be transferred into the bonding antisymmetric MO of two oriented molecules of ethylene.

Thus, in the MO correlation diagram of the *two-step reaction* one also faces the energy-consuming crossing of MO correlation lines. Near the crossing point the molecular state is portrayed by a linear combination of two electronic configurations. As in the concerted process, the ground state of cyclobutane glides continuously over to the ground state of the two oriented ethylenes. As in the concerted process, this is accomplished by configuration interaction, but not for nothing. An extra energy barrier also reflects the "symmetry forbiddenness" of the two-step process.

What makes the two-step process energetically less painful than the concerted scission of cyclobutane?[28] The first bond-breaking step profits from the loss of most of the 26-kcal/mol strain energy of cyclobutane, whereas the rectangular transition state of the concerted splitting still harbors most of the ring strain. Furthermore, substituents at C.1 and C.4 can interact with the π orbitals of the tetramethylene species, i.e., terminal substituents stabilize the "biradical" and "zwitterion", respectively, to a higher extent than the transition state of the concerted process.

The Question of the Tetramethylene HOMO

Can one be sure that the symmetric MO is the HOMO of tetramethylene, as illustrated in Figure 1? One cannot be certain. One of the striking results of Hoffmann's EH calculation[3] is that the energy levels of the second and third MO (S and A) of tetramethylene approach each other in the process cyclobutane → tetramethylene and cross, when the angle at C.2 and C.3 becomes 116°. The intact C.2–C.3 σ orbital plus bonding "through-space interaction" in the symmetric MO is compensated in the antisymmetric MO by "through-bond coupling" (TBC).[3,29] This concept, due to Hoffmann, can be depicted by a π-type overlap between the terminal p orbitals and the sp^3 hybrid orbitals at C.2 and C.3. TBC has developed to a fruitful general principle, reaching far beyond tetramethylene chemistry.[30]

Impeded rotation about the C.1–C.2 and C.3–C.4 bond of tetramethylene is an important corollary. While C.2–C.3 rotation does not impair TBC, it is

(25) H. E. Zimmerman, *Acc. Chem. Res.*, **4**, 272 (1971).
(26) M. J. S. Dewar, *Angew. Chem., Int. Ed. Engl.*, **10**, 761 (1971).
(27) H. C. Longuet-Higgins and E. W. Abrahamson, *J. Am. Chem. Soc.*, **87**, 2045 (1965).

(28) An ab initio calculation of the concerted least-motion path results in an activation energy of 156 kcal/mol: J. S. Wright and L. S. Salem, *J. Am. Chem. Soc.*, **94**, 322 (1972).
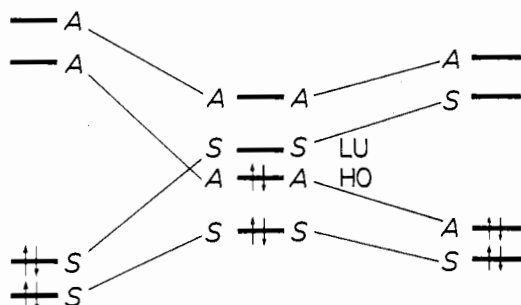(29) R. Hoffmann, A. Imamura, and W. J. Hehre, *J. Am. Chem. Soc.*, **90**, 1499 (1968).
(30) Reviews: (a) R. Hoffmann, *Acc. Chem. Res.*, **4**, 1 (1971); (b) R. Gleiter, *Angew. Chem., Int. Ed. Engl.*, **13**, 696 (1974).

Cyclobutane $\rightleftharpoons$ $\overline{\text{Tetramethylene}}$ $\rightleftharpoons$ 2 Ethylene

1. Level Ordering S below A for HO of Tetramethylene
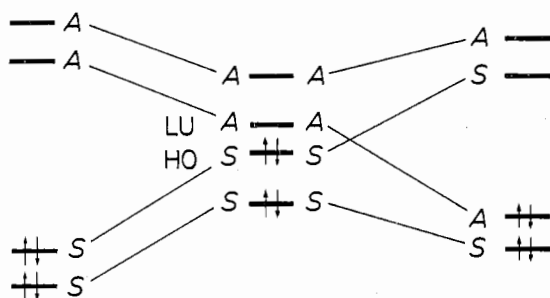
2. Level Ordering A below S for HO of Tetramethylene

Figure 2. MO correlation diagrams for the two-step interconversion cyclobutane $\rightleftharpoons$ 2ethylene via tetramethylene.

destroyed by a C.1–C.2 and C.3–C.4 rotation of 90°. *Without* TBC, the rotational barrier about the C.1–C.2 and C.3–C.4 bond should amount to 0–1.2 kcal/mol, as observed for alkyl radicals from ethyl to tetramethylethyl.[31] The barrier to C.2–C.3 rotation is normally 3–6 kcal/mol. 2 + 2 cycloadditions which initially generate the anti conformation of the tetramethylene should consequently (without TBC) be accompanied by a complete loss of stereochemistry of the reactants. However, the experimentally observed losses—greater for "1,4-biradicals"[5] than for "1,4-zwitterions"[1]—are far from complete.

The barrier heights of the C.1–C.2 and C.3–C.4 bonds are of great significance for the steric course of 2 + 2 cycloaddition. The EH calculation yields 13 kcal/mol for this barrier to rotation in the tetramethylene parent,[32] which is probably too high, not to mention the INDO calculated value of 45 kcal/mol.[33]
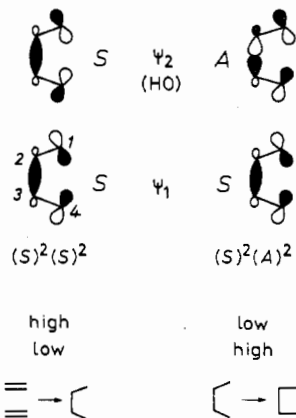
Segal's ab initio calculation[8] did not include C.1–C.2 rotation but underlines the conclusion of Hoffmann et al.[3] that the relative energies of the S and A orbitals of tetramethylene (Figure 1) respond sensitively to changes in bond angles, bond length, and substitution pattern.

Thus, two MO correlation diagrams for the two-step thermolysis of cyclobutane are imaginable (Figure 2). In the first, the level ordering S below A makes dissociation of the tetramethylene species the "forbidden step". In the second, A has assumed the role of HOMO, and the crossing of the correlation lines is pushed into the cyclization step.

(31) P. Krusic, P. Meakin, and J. Jesson, *J. Phys. Chem.*, **75**, 3438 (1971).
(32) Professor R. Gleiter, Darmstadt, private communication.
(33) L. M. Stephenson and T. A. Gibson, *J. Am. Chem. Soc.*, **94**, 4599 (1972).

	Ψ_2 (HO)	
S		A
	Ψ_1	
S		S

Electronic Configuration	$(S)^2(S)^2$	$(S)^2(A)^2$
Stereoselectivity in		
2 + 2 Cycloaddition	high	low
Cyclobutane Thermolysis	low	high
A–S Crossing	$\overset{=}{=} \rightarrow \lceil$	$\lceil \rightarrow \square$

Figure 3. Occupied MO's of tetramethylene and stereoselectivity in thermal 2 + 2 cycloaddition and cyclobutane cleavage.

$\underline{\qquad}$ $(S)^2(S)^2$

$----$ $(S)^2(A)^2$

$\cdots\cdots$ $0.71(S)^2(S)^2$ $+ 0.71(S)^2(A)^2$
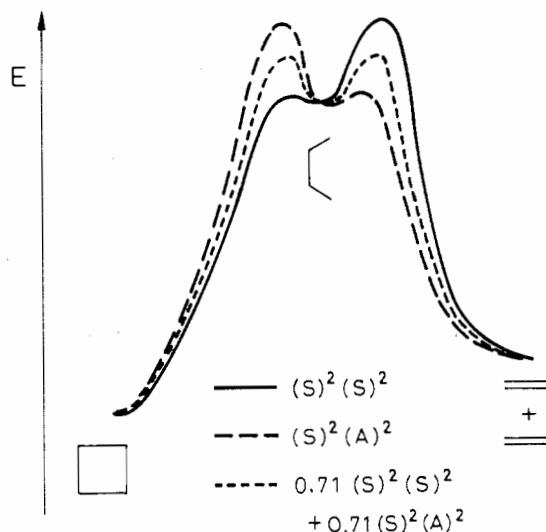
Figure 4. Energy profiles for two-step interconversions cyclobutane $\rightleftharpoons$ 2ethylene dependent on the mixing of electronic configurations in the tetramethylene ground state.

Electronic Configuration of Tetramethylenes and Steric Course

A general concept begins to emerge, linking the amount of stereoselectivity found in cyclobutane thermolyses and in 2 + 2 cycloadditions with the location of the crossing point of A and S correlations along the reaction coordinate.

Let us consider a cycloaddition via a tetramethylene which fits with S below A the upper part of Figure 2, i.e., its electronic configuration, $(S)^2(S)^2$, corresponds to that of the cyclobutane. The symmetry-forbidden step is the first one; the subsequent ring closure should not need much activation. The $(S)^2(S)^2$ tetramethylene is a sort of "precyclization" stage in which the second bond can just snap shut (Figure 3).

The pertinent energy profile in Figure 4 suggests that the $(S)^2(S)^2$ tetramethylene, once formed from the unsaturated reactants, does not offer much chance for rotation or trapping to occur before cyclization takes place. A high stereoselectivity of the 2 + 2 cycloaddition should be the result. Incorporation of a C.1–C.2 or C.3–C.4 rotation into the step for formation of the tetramethylene is improbable, because it would further increase the altitude of the highest mountain pass.

On the other hand, if combination of the olefinic reactants leads to a tetramethylene of the configuration

$(S)^2(A)^2$, the orbital-symmetry-imposed barrier has to be overcome in the second step (Figures 3 and 4). The tetramethylene will dissociate and recombine again; it has ample opportunity for rotation and interception before surmounting the cyclization barrier. The stereoselectivity of such a cycloaddition should be lowered.

The opposite relations hold for cyclobutane dissociation. The $(S)^2(A)^2$ configuration of the tetramethylene is a "predissociation" stage which rapidly goes on to two molecules of olefin over a low barrier. A high retention of the cyclobutane stereochemistry should characterize this scission. The contrasting steric courses predicted for 2 + 2 cycloaddition and cycloreversion pose a fascinating problem to the experimenter.

The picture, however, is more colorful than sketched so far:

(1) The two symmetric electronic configurations are not rigid alternatives, but can be mixed by linear combination. Specifically substituted tetramethylenes may possess any blend of $(S)^2(S)^2$ and $(S)^2(A)^2$. Segal[8] calculated that the gauche minimum of the parent $(CH_2)_4$ consists of 56% $(S)^2(S)^2$ and 44% $(S)^2(A)^2$. The energy trough of the tetramethylene becomes a more symmetrical mountain valley as the third profile in Figure 4 exhibits.

(2) It would be a gross simplification to ascribe the energy barriers which surround the intermediate to orbital control alone. Electronic and steric substituent effects will modify the energetics.

(3) If the tetramethylene is initially generated in the trans conformation, a second potential-energy minimum is added to the profile. This becomes less likely the greater the zwitterionic character of the intermediate.

Thus, it might seem promising for the experimenter to compare stereoselectivities and trapping reactions for 2 + 2 cycloadditions and cycloreversions via zwitterionic intermediates. The stereospecific additions of maleo- and fumaronitrile to tetramethoxyethylene,[18] even in the polar solvent acetonitrile,[16] as well as the lack of interceptability of the zwitterion from tetramethoxyethylene and TCNE[16] present a striking contrast to the behavior of enol ethers vs. polycyanoethylenes. In the latter case, the zwitterion possibly has more $(S)^2(A)^2$ character than in the first. It would be desirable to correlate experimental stereoselectivities with quantum mechanically calculated configurations of substituted tetramethylenes.

Further Comments on Tetramethylene Structures

Dewar et al.[34] introduced a topological distinction of isomers based on HOMO–LUMO crossing in their interconversion. Cyclobutane and two oriented ethylenes are "lumomers" with an increased activation energy for the "forbidden" interconversion. According to MINDO/3 results, Dewar and Kirschner[35] regard the *trans*-tetramethylene biradicaloid **6** (with terminal outward pyramidalization) as "homomeric" with two

oriented ethylenes, whereas the cis conformation **4** (pyramidalized inward) and cyclobutane constitute another homomeric pair. The rotation **4** ⇌ **6** with inversion at the terminal methylene groups is presumed to be "forbidden".

In his "orbital correspondence analysis in maximum symmetry", Halevi[36] orients the reactant and product molecules in a common point group of high symmetry and then considers how the symmetry is reduced during "allowed" reactions. Only the trans conformation **6** can be generated from two similarly oriented (C_{2h}) ethylene molecules without further reduction of symmetry. To be consistent with this finding, TCNE and enol ether should start their interaction in the trans arrangement; they would then rotate under the influence of developing charge separation and come close to the gauche conformation at the transition state of zwitterion formation. There is no experimental evidence for this contortion.

Gleiter et al.[37] found by EH calculation of the hypothetical 1,4-dipole from 1,1-dicyanoethylene and hydroxyethylene still a small energetic advantage for the trans over the gauche conformation; the EH procedure neglects Coulomb attraction. Restricted Hartree–Fock calculations of the transition state for cis and trans approach of hydroxyethylene and acrylonitrile favor the trans arrangement.[38] We agree with Epiotis that this contrasts with experimental results, but we do not regard *pericyclic* a proper description for the cis reaction course with the energy dip of an intermediate. Although not strictly comparable, it may be mentioned that the crystalline zwitterion from benzenesulfonyl isothiocyanate and N-isobutenyldimethylamine exists in a gauche conformation.[39]

To explain the retention of configuration in the 2 + 2 cycloaddition of donor and acceptor systems, Inagaki and Fukui[40] proposed an initial cyclic three-centered interaction between the two carbon atoms of the donor and the more electrophilic center of the acceptor. The stereoselectivity of TCNE cycloadditions was probably overestimated.

The notion "clarification of a reaction mechanism" has no absolute meaning, but reflects at best the present state of experiment and theory. There is no reason to doubt that the development of novel techniques and a deeper understanding of the reaction event will further modify and detail the mechanistic picture of 2 + 2 cycloadditions.

(34) M. J. S. Dewar, S. Kirschner, and H. W. Kollmar, *J. Am. Chem. Soc.*, 96, 5240 (1974).

(35) M. J. S. Dewar and S. Kirschner, *J. Am. Chem. Soc.*, 96, 5246 (1974).

(36) E. A. Halevi, *Helv. Chim. Acta*, 58, 2136 (1975); *Angew. Chem., Int. Ed. Engl.*, 15, 593 (1976).

(37) P. Hoffmann and R. Gleiter, *Tetrahedron Lett.*, 159 (1975).

(38) N. D. Epiotis, R. L. Yates, D. Carlberg, and F. Bernardi, *J. Am. Chem. Soc.*, 98, 453 (1976).

(39) X-ray analysis: E. Schaumann, A. Röhr, S. Sieveking, and W. Walter, *Angew. Chem., Int. Ed. Engl.*, 14, 493 (1975).

(40) S. Inagaki and K. Fukui, *Bull. Chem. Soc. Jpn.*, 46, 2240 (1973); S. Inagaki, H. Fujimoto, and K. Fukui, *J. Am. Chem. Soc.*, 97, 6108 (1975).