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RECENT CONTRIBUTIONS TO THE MECHANISM OF CONCERTED AND NON-CONCERTED CYCLOADDITIONS

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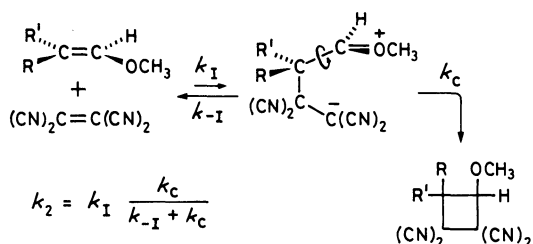
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Abstract – The Diels-Alder reactions of cyanoethylenes with cyclopentadiene and 9,10-dimethylanthracene are accelerated 10^7 and 10^{10} fold by the introduction of further cyano groups. In the 2 + 2 cycloaddition to isobutenyl methyl ether, however, acrylo- and fumaronitrile are inert, and the rate differences are small for 1,1-dicyano-, tricyano- and tetracyanoethylene. On the basis of PMO the data establish an early transition state for the concerted Diels-Alder reaction and a late one for the formation of a zwitterionic intermediate in the 2 + 2 cycloaddition. – 1,3-Dipolar cycloadditions proceed with retention of 1,3-dipole and dipolarophile configuration. Stereospecificities of >99.94 and >99.997 % were evaluated for the cycloadditions of diazomethane to methyl angelate and methyl tiglate, respectively. These data would impose improbably high barriers on the rotation of an intermediate in a hypothetical two-step mechanism. – The norbornene bond shows two exceptional characteristics : high cycloaddition rates and exo selectivity. The rate constants are too high to be ascribed to a release of ring strain in an early transition state. A nonequivalent π orbital extension was proposed by Fukui in 1976 to explain electrophilic exo additions to norbornene. Rate comparisons of norbornene with bicyclo(2.2.2)octene, bicyclo(2.1.1)hexene and tricyclo(3.3.0.0^{2,6})octene in 1,3-dipolar cycloadditions and Diels-Alder reactions would be in accordance with the Fukui effect. The rate data are discussed in the light of theoretical concepts and calculations.

A CRITERION FOR EARLY AND LATE TRANSITION STATES

Elucidating a reaction mechanism does not always involve a back-breaking effort. Often the comparison with an accepted reference system is sufficient. The addition of tetracyanoethylene to enol ethers may be

Scheme 1

$$k_2 = k_I \frac{k_c}{k_{-I} + k_c}$$
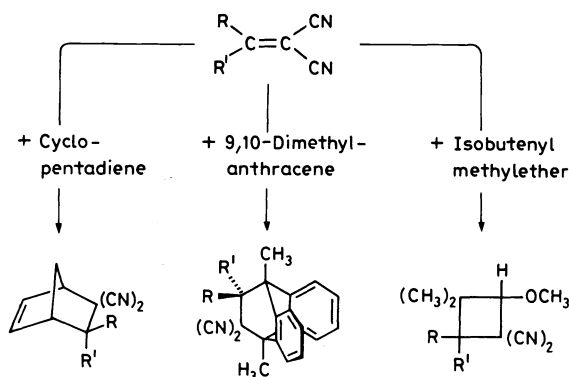
MECHANISTIC CRITERIA
Nonstereospecificity
Reversibility of Zwitterion Formation
Influence of Solvent Polarity on Rate
Structure-Rate Relationship
Activation Volume and Solvent Polarity
Trapping of Zwitterionic Intermediate
and its Steric Course

recommended as a model for 2 + 2 cycloadditions via a zwitterionic intermediate.

The whole arsenal of mechanistic criteria has been applied to this test case in the Munich Laboratory (Scheme 1, Ref. 1). The results are in harmony with the two-step mechanism via the zwitterion as a high-energy intermediate. The rate constants on structural variation of the enol ether reflect the stabilization of a carboxonium zwitterion which is formed in the slow step k_1 (Ref. 2).

Scheme 2

Some kinetic data may shed light on the fundamental mechanistic difference between the Diels-Alder reaction and the 2 + 2 cycloaddition of cyanoethylenes to enol ethers. Polycyanoethylenes combine with cyclopentadiene or 9,10-dimethylanthracene in 4 + 2 cycloadditions, whereas the cyclobutane derivative is obtained with isobutenyl methyl ether (Scheme 2). How do the rate constants depend on the number of cyano groups in the polycyanoethylene ?

Table 1.   Rate Comparison of 4 + 2 and 2 + 2 cycloadditions of polycyanoethylenes ;
$10^5 k_2$ (l mol^{-1} sec^{-1})
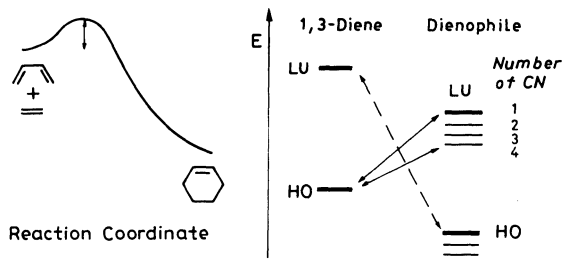
	Diels-Alder Reaction (Dioxane, 20°C)		2 + 2 Cycloaddition (Benzene, 25°C)
	Cyclo-pentadiene	9,10-Dimethyl-anthracene	Isobutenyl methyl ether
Acrylonitrile	1.04	0.89	0
Fumaronitrile	81	139	0
1,1-Dicyanoethylene	45 500	127 000	31.6 (16.0)
Tricyanoethylene	480 000	5 900 000	2.39 (1.2)
Tetracyanoethylene	43 000 000	13 000 000 000	3.97 (≡ 1.0)

The second-order rate constants of the Diels-Alder reactions were measured by J. Sauer et al. (Ref. 3). The stepwise introduction of cyano groups from acrylonitrile to tetracyanoethylene increases the rate constant versus cyclopentadiene 40 million-fold and that towards dimethylanthracene even by a factor of 15 billions (Table 1). 1,1-Dicyanoethylene is more active than 1,2-dicyanoethylene, but there is no doubt that also the third and fourth cyano group at the second olefinic carbon atom are strongly accelerating (Ref. 4).

The reactivity sequence is grossly different for the 2 + 2 cycloaddition model. Acrylonitrile and fumaronitrile do not react at all with isobutenyl methyl ether. Starting with 1,1-dicyanoethylene, the rate does not

profit from introducing further cyano groups, but rather decreases by a factor of 16 (Ref.5). The k_2 value of tetracyanoethylene has to be divided by a statistical factor of 2.

Scheme 3

Reaction Coordinate

The Diels-Alder reaction possesses an early transition state (Scheme 3) which is typical for concerted cyclo-additions and a prerequisite for the successful application of MO perturbation theory. The transition state still resembles the two-plane orientation complex of diene + dienophile. It was observed for the reaction of TCNE with dimethylanthracene in benzene at $25^{\circ}C$ that 86 % of $\triangle G^{\ddagger}$ is due to the entropy term whereas only 14 % for $\triangle H^{\ddagger}$ signifies little change in bond energy (Ref.6).

The discussed Diels-Alder reactions belong to the "normal" type which are HOMO(diene) - LUMO(dienophile) controlled. The stepwise introduction of the cyano groups is accompanied by a successive lowering of the orbital energies (Scheme 3). The diminishing frontier orbital separation corresponds to an increasing energy gain in the creation of the new MO's of the transition state. A dramatic increase of the rate constant is the result.
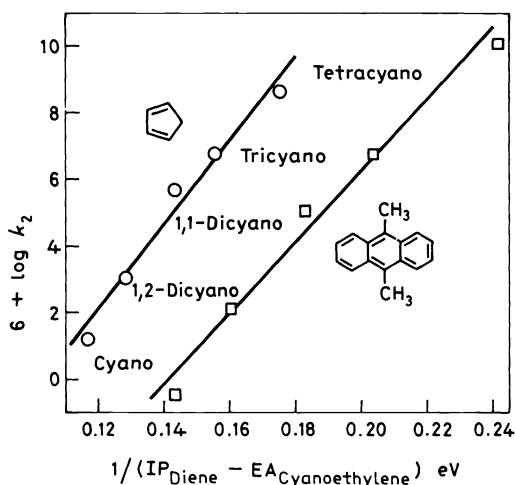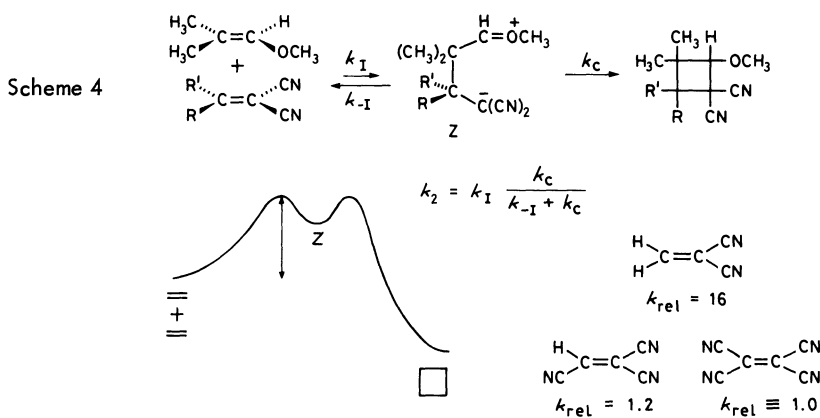

Fig. 1   PMO treatment of rate constants for Diels-Alder reaction of cyanoethylenes

In a crude approximation of the second-order perturbation term the energy gain in producing the MO's of the transition state should be inversely proportional to the mentioned frontier orbital separation. The ionization potential of the diene and the electron affinities of the dienophiles may serve as experimental quantities. Houk and Munchausen (Ref.7) made a sophisticated estimate of some electron affinities and indeed noticed a linear dependence of log k_2 on the reciprocal difference of ionization potential and electron affinity (Fig.1).

Scheme 4

In contrast, the slow step of the 2 + 2 cycloaddition furnishes a zwitterionic intermediate which is partitioned between cyclization and dissociation (Scheme 4). The experimental rate constants probably reflect the variation of k_I, the rate of zwitterion formation, rather than the partition coefficient. Under a special set of conditions the ratio of cyclization to dissociation of the zwitterion amounted to 1.0 corresponding to equal barrier heights surrounding the energy dip of the intermediate (Ref.8).

The late transition state structurally resembles the high-energy intermediate rather than the reactants. During the activation process the rehybridization of the carbon atoms involved reaches such an extent that the orbital energies of the reactants become irrelevant ; perturbation theory which inspects the first infinitesimal part of the reaction, is no longer applicable.

Nevertheless, the rate constants are meaningful. One nitrile group is not sufficient to stabilize the anionic portion of the zwitterion; therefore, acrylonitrile and fumaronitrile are unreactive. Two cyano groups at the terminal carbon atom are required to provide the zwitterion with the stabilization of the malodinitrile anion. Cyano groups at the other carbon atom decelerate the cycloaddition somewhat. The influence of the orbital energies of the cyanoethylenes in the ground state is overcompensated by two factors. One is the steric screening of the carbon atom which forms the first σ bond. The second factor concerns the conjugation energy of the additional cyano groups which is lost during the conversion of the trigonal to a tetrahedral carbon atom.

Thus, the grossly disparate influence of the cyano groups allows to conclude an early transition state for the Diels-Alder reaction and a late one for the 2 + 2 cycloaddition.
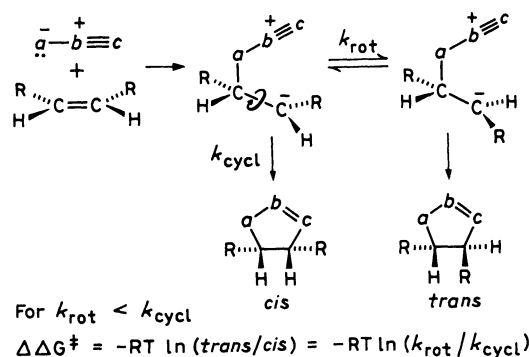
Indirectly, a valuable criterion for the presence or absence of concertedness is involved. The rate constants of the Diels-Alder reactions are larger by magnitudes than those of the 2 + 2 cycloadditions. The concerted 4 + 2 cycloaddition avoids the hardship of a high-energy intermediate which must be passed in the 2 + 2 cycloaddition due to the forbiddenness of the $_\pi 2_s + _\pi 2_s$ process. The data reveal what one has begun to understand 15 years ago : the magic of the symmetry-allowed concerted process (Ref.9).

STEREOSPECIFICITY AS A MECHANISTIC CRITERION

Stereospecificity concerns retention or inversion of reactant structure during the cycloaddition. Cis,trans isomeric ethylene derivatives as dipolarophiles should fully retain their configuration in a concerted cyclo-

addition. That may be different for a two-step addition. If a zwitterionic or biradical intermediate would occur, rotation about the former double bond of the dipolarophile should compete with the ring closure. Some product with inverted configuration is anticipated (Scheme 5).
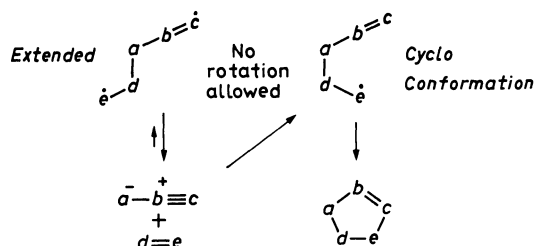
Scheme 5   Two-Step Cycloaddition via Zwitterion or Diradical

For $k_{rot} < k_{cycl}$

$\Delta\Delta G^{\ddagger} = -RT \ln (trans/cis) = -RT \ln (k_{rot}/k_{cycl})$
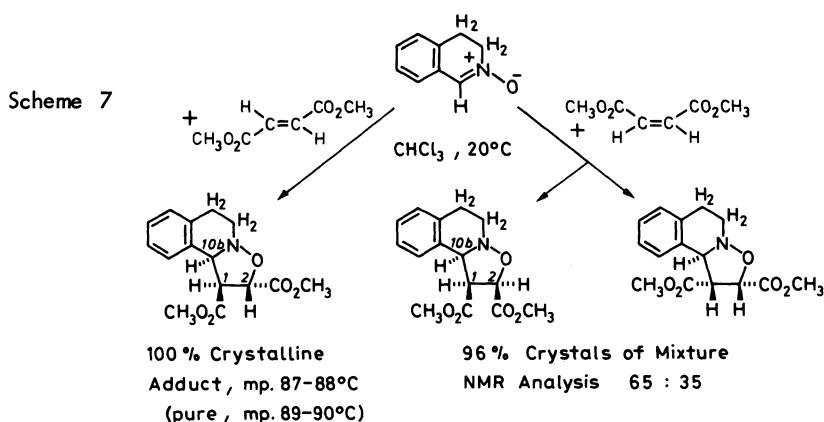
A violation of stereospecificity would establish a two-step mechanism. In such a case the ratio of products with inverted and retained configuration would approximate the rate ratio of rotation and cyclization of the intermediate.

Scheme 6   How is the Two-Step Mechanism Compatible with
                                           Stereospecificity ?
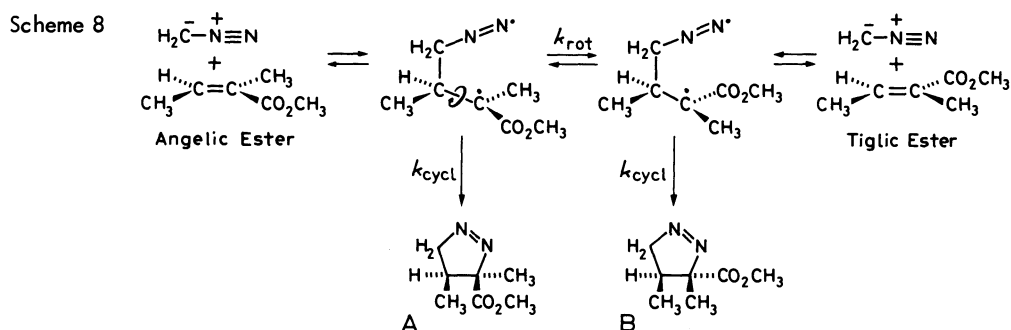
Stereospecificity is an indispensable, but not a conclusive criterion for concertedness. Two-step processes may also appear stereospecific, if the ratio of cyclization versus rotation of the intermediate is sufficiently large. The inherent weakness of a stereospecific two-step mechanism for 1,3-dipolar cycloadditions and Diels-Alder reactions should not be ignored. As shown in Scheme 6, the intermediate could initially be formed in an extended or a cyclo conformation as well as possibilities in between. Cyclization of the extended form requires a rotation about the bond a-d. Should one not anticipate a concomitant rotation about e-d from which nonstereospecific product would emerge ? One has to postulate that extended conformations dissociate into reactants like a shot, before rotation about e-d takes place. On the other hand, the cyclo conformation must undergo ring closure so fast that rotation has no chance.

Dozens of 1,3-dipolar cycloadditions have been examined and found stereospecific without exception (Ref.10). Nearly quantitative yields of stereospecific cycloadducts were isolated as crystalline material in the example of Scheme 7, the reaction of 3,4-dihydroisoquinoline N-oxide to dimethyl fumarate and dimethyl maleate (Ref.11). More frequently, only part of the product is isolated in a pure state and the mother liquor is scru-

Scheme 7

100 % Crystalline
Adduct, mp. 87–88°C
(pure, mp. 89–90°C)

96 % Crystals of Mixture
NMR Analysis   65 : 35

tinized by NMR for the nonstereospecific product. Now it is a necessity to test the analytical limits for the "wrong" isomer with artificial mixtures; these limits amount to roughly 2 % in favorable cases of NMR analysis. Thus, one can guarantee only for better than 98 % stereospecificity. In the framework of the two–step process of Scheme 5 this would be tantamount to a rotational barrier which is by more than 2.3 kcal mol^{-1} higher than the activation energy for the cyclization of the intermediate.

Which rate ratio of rotation versus cyclization and dissociation could be regarded as reasonable for the hypothetical intermediate of Scheme 5 ? We searched for an example in which gas chromatography of products permits the demonstration of a much higher stereospecificity than the NMR analytical limit of 2 %.

Scheme 8

Angelic and tiglic ester constitute a pair of cis,trans isomers which afford the diazomethane adducts A and B quantitatively. The reaction was first described by van Auken and Rinehart in 1962 (Ref.12). The adducts pass the capillary gaschromatographic column at 92°C with little decomposition. Scheme 8 provides the hypothetical reaction scheme involving biradical intermediates (Ref.13).

Double preparative gas chromatography gave the pure angelic and tiglic ester which did not show any mutual admixture. After diazomethane reacted with two equivalents of methyl tiglate, the excess of the latter was reisolated. The residual tiglate did not exhibit an angelate peak in the GC at highest attenuation ; the peak became recognizable after addition of 6 ppm methyl angelate. Thus, the isomerization of tiglic ester during the reaction with diazomethane must be smaller than 6 ppm. The less sensitive analysis of tiglic ester in angelic ester becomes manifest in a somewhat larger limit : below 80 ppm here (Table 2, Part a; Ref.14).

After reacting tiglic ester with diazomethane, the adduct B – its large peak is cut at high attenuation in Fig. 2 – is accompanied by unknown impurities in the ppm range, most of them originating from a slight
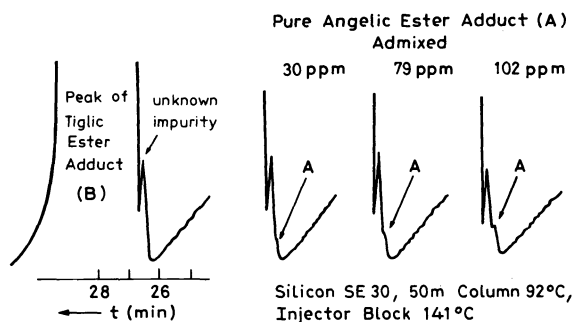
Fig. 2   Capillary chromatography of 1-pyrazolines A and B

pyrazoline thermolysis. The peak of the angelic ester adduct A is missing, but the analytical limit can be detected on admixing tiny amounts of pure adduct A. Whereas 102 ppm produced a discrete peak, as little as 30 ppm could be made out. Should some of the sterically wrong isomer arise from methyl tiglate and diazomethane, it would be in an amount smaller than 30 ppm (Ref. 14).

Table 2.   The reaction of diazomethane with methyl angelate and methyl tiglate as a test of the biradical hypothesis

a.   No cis,trans isomerization of unconsumed ester after reaction

In Experiment with Angelic Ester < 0.008 % (80 ppm) Tiglic Ester
                      Tiglic Ester   < 0.0006 % (6 ppm) Angelic Ester

b.   Stereospecificity of cycloadduct formation

Reaction with	Analyt. Limit	Stereospecificity	k_{cycl}/k_{rot}	$\Delta\Delta G^{\ddagger}$ (kcal/mol)
Angelic Ester	0.06 % B in A	> 99.94 %	> 1 700	> 4.4
Tiglic Ester	0.0030 % A in B	> 99.997 %	> 33 000	> 6.2

The analytical limit for the tiglic ester adduct B in the artificial mixture with angelic ester adduct A is somewhat higher. Thus, the stereospecificities of both cycloadditions must be greater than the percentages given in the second figure column of Table 2, Part b. If the intermediates of this hypothetical scheme were to occur, their cyclization would be more than 1,700 or 33,000 times faster than rotation.

Is this reaction model with biradical or zwitterionic intermediates reasonable ? We don't think so. Even if a $\Delta G^{\ddagger}$ of zero were assumed for the cyclization of the intermediates, rotational barriers of greater than 4.4 or 6.2 kcal mol^{-1}, respectively, appear to be excessive. Rotational barriers in alkyl radicals have been measured and are much smaller than those in alkanes (Ref. 15). The barriers range from close to zero kcal mol^{-1} for ethyl to 1.2 kcal mol^{-1} for the tetramethylethyl radical. The steric requirements at the single bond of our diradicals may be similar to the ones of the tetramethylethyl radical. Thus, our experiment imposes unjustifiably high rotational barriers on the biradical intermediates.

Moreover, the assumption of a cyclization barrier of zero for the intermediates is not meaningful, because such a mechanism would become indistinguishable from a concerted pathway. In addition, other features strongly militate against the biradical intermediates of Scheme 8. Diazo radicals eliminate N$_2$ very fast.

No nitrogen is evolved during these diazomethane cycloadditions. Whenever nitrogen elimination was obser-
ved in the interaction of diazomethane and unsaturated compounds, it was traced back to the decomposition
of an initially formed pyrazoline (Ref.16).

THE EXCEPTIONAL REACTIVITY OF THE BICYCLO(2.2.1) HEPTENE DOUBLE BOND

The reactivity of the norbornene double bond shows two exceptional characteristics : high exo selectivity
and increased rate constants in all addition reactions including cycloadditions.

[Mitteilungen aus dem Chemischen Laboratorium
der Universität Kiel.]

(Eingelaufen am 24. Dezember 1930.)
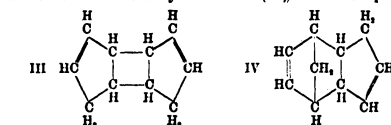
Über das abgestufte Additionsvermögen von
ungesättigten Ringsystemen;

von *Kurt Alder* und *Gerhard Stein.*

Gemeinsam mit Hugo Finzenhagen.

So tritt z. B. die Vereinigung von Styrol mit Phenylazid
bei Zimmertemperatur erst nach Wochen quantitativ ein.
Um so merkwürdiger erscheint die Vereinigung von
Phenylazid mit Dicyclopentadien, die bei gewöhn-
licher Temperatur unter beträchtlicher Wärme-
abgabe in ganz kurzer Zeit zu Ende geht. Die Ver-
mutung liegt nahe, daß die Ursache für diese Erscheinung
in einer konstitutionellen Eigentümlichkeit des Dicyclo-
pentadiens zu suchen ist.

Für den Kohlenwasserstoff sind zwei Strukturen[1] dis-
kutiert worden; eine symmetrische (III) mit Cyclobutan-
struktur und eine unsymmetrische (IV), die durch partielle

[1] Literatur vgl. nächste Arbeit.

Fig. 3   The classic paper of Alder and Stein in Liebigs Ann.Chem. of 1931

In 1931, Alder and Stein reported on the extraordinary ease with which dicyclopentadiene accepts <u>one</u> mole-
cule of phenyl azide ; this fact allows to decide in favor of the unsymmetrical structure of dicyclopentadiene
(Fig.3, Ref.17). Furthermore, the authors recommended the phenyl azide addition as a diagnostic tool for
bicyclo(2.2.1)heptene double bonds. All the adducts from cyclopentadiene and dienophiles belong to this
type.
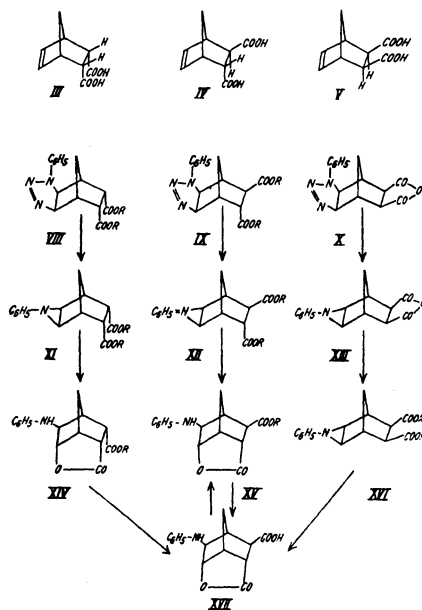
Scheme 9

Über den sterischen Verlauf
von Additions- und Substitutions-reaktionen. V.

Der sterische Verlauf der Phenylazid-reaktion;

von *Kurt Alder* und *Gerhard Stein.*

Gemeinsam mit Stephan Schneider.

In a masterly study, the same authors established in 1935 the exclusive exo addition of phenyl azide to the stereoisomeric norbornenedicarboxylic acids (Scheme 9, Ref.18). Alder was cautious enough not to offer an explanation for the two exceptional properties, high reactivity and exo selectivity.
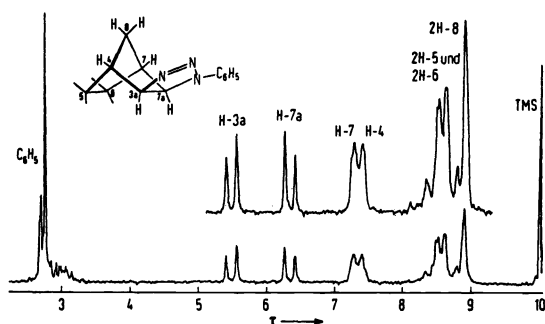

Fig.4 ^{1}H-NMR spectrum of the cycloadduct of phenyl azide to norbornene at 60 MHz in CDCl$_3$

Today the test of exo annellation of the phenyltriazoline ring to the norbornane skeleton is simple. Since F. Anet in 1961 discovered that the endo protons of norbornane do not couple with the bridgehead hydrogens (Ref.19), a quick glance at the ^{1}H-NMR spectrum of Fig.4 is required in order to differentiate exo and endo adduct (Ref.20). The endo protons in positions 3a and 7a form an AB spectrum ; the lack of coupling with the bridgehead protons is the result of a dihedral angle of 82° (Ref.21).

Table 3.   Relative rate constants for 1,3-dipolar cycloadditions of nitrilium and dia-
zonium betaines towards cycloalkenes

1,3-Dipole	Temp.	Cyclo-hexene	Cyclo-pentene	Norbor-nene	$\Delta\Delta G^{\ddagger}$ (kcal mol^{-1})
C$_6$H$_5$–C≡$\overset{+}{N}$–$\overset{-}{N}$–C$_6$H$_5$ Diphenylnitrilimine	80°C	≡ 1	10	210	3.8
C$_6$H$_5$–C≡$\overset{+}{N}$–$\overset{-}{O}$ Benzonitrile Oxide	0°C	1	85	6 100	4.7
$\overset{-}{H_2C}$–$\overset{+}{N}$≡N Diazomethane	25°C	1	69	5 400	5.1
C$_6$H$_5$–$\overset{-}{N}$–$\overset{+}{N}$≡N Phenyl Azide	25°C	1	56	5 700	5.1

Kinetic measurements of the sixties revealed that the phenyl azide addition is not a monopoly of the norbornene double bond. Common cycloalkenes react too, but much slower (Table 3, Ref.22). Other 1,3-dipoles of the propargyl-allenyl type likewise combine with norbornene 210 - 6,100 times faster than with cyclohexene corresponding to a decrease of the activation free energy by 4 - 5 kcal mol^{-1} (Ref.23).

What is the reason for the high norbornene reactivity ? The hydrogenation enthalpy of norbornene surpasses that of cyclohexene by 6 kcal mol^{-1}; R. Turner convincingly interpreted this with a diminution of ring strain in the conversion of norbornene to norbornane (Ref.24). In the early sixties we explained the high dipolaro-

philic activity of norbornene similarly, namely by a partial release of ring strain in the transition state of cycloaddition (Ref.25). This opinion was widely accepted and quoted ; nevertheless it is incorrect. In the last decade the evidence for <u>early transition states</u> of concerted cycloadditions accumulated. Experimental findings (Ref.10) as well as ab initio calculations of transition states (Ref.26) underline that the two new σ bonds are still long and weak and that the bond lenghts of the reactants haven't changed much. It is inconceivable that such transition states profit from 5 kcal mol^{-1} of strain release, if this release totals 6 kcal mol^{-1} in converting the norbornene into the norbornane type.

Not only 1,3-dipolar cycloadditions and Diels-Alder reactions of bicycloheptene and its derivatives occur on the exo side. Virtually all reactions display this exo preference: catalytic hydrogenation, permanganate oxidation, polar additions of hydrogen chloride and acetic acid etc.
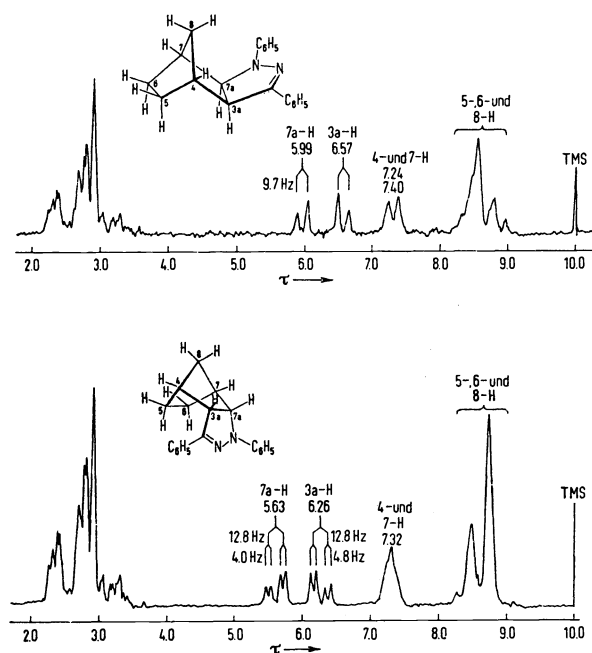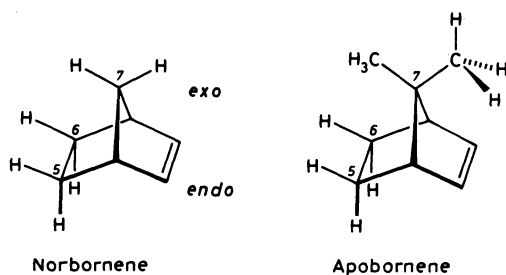

Fig.5 ^{1}H-NMR spectra of the exo- and endo-annelated pyrazolines from diphenyl-
nitrilimine and norbornene in CCl$_4$

The exo adduct of diphenylnitrilimine and norbornene , shown in Fig.5, was dehydrogenated by chloranil to the aromatic pyrazole derivative. In the reduction with sodium and alcohol the hydrogen came from the exo side and squeezed the 2-pyrazoline ring into the endo position (Ref.27). The availability of the endo adduct made a controlled search in the original product from norbornene and diphenylnitrilimine feasible. No endo adduct was found and one could rule out more than 0.3 % alongside with 97 % isolated crystalline exo adduct (Ref.28). Is the reason for the exo selectivity, the second exceptional feature of norbornene, clearer than the high rate constants ?

In 1967 H.C. Brown et al. made a steric hindrance of the endo attack by the 5-H and 6-H (Scheme 10) responsible (Ref.29). In apobornene a methyl group above the double bond massively obstructs the exo access. 1,3-Dipolar cycloadditions of diphenylnitrilimine and benzonitrile oxide to apobornene are slowed down by

Scheme 10

Norbornene   Apobornene

several magnitudes; nevertheless, only the exo adducts were found (Ref.28). We hardly dare to assume that the 5- and 6-endo-hydrogens impair the transition state of endo attack more strongly than the 7-methyl group does with regard to the exo attack.
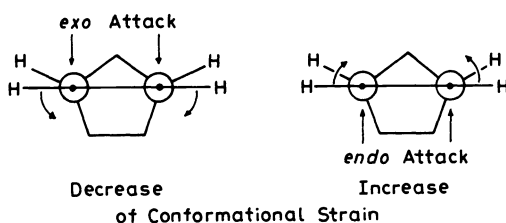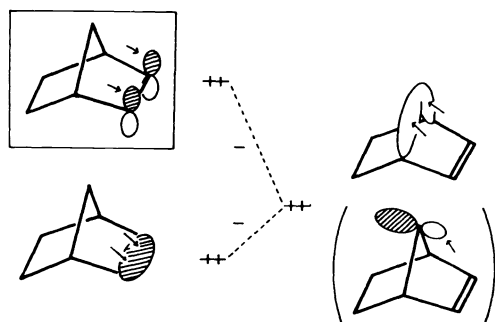

Fig. 6   The "torsional effect" in norbornene

An ingenious explanation was promoted by P.v.R. Schleyer (Ref.30). The structure of norbornene shows a di-hedral angle of $22°$ between the olefinic CH bonds and the bridgehead hydrogens. On exo attack the dihedral angle is increased, i.e., the conformational strain is diminished. During the endo attack, however, the former olefinic hydrogens pass eclipsed positions (Fig.6).
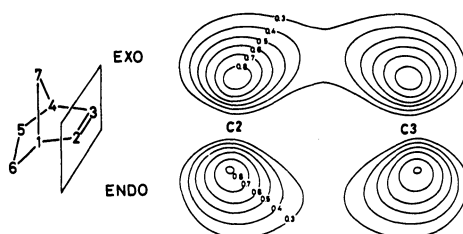
What is this "torsional effect" worth energy-wise ? The maximal difference of two pairs of staggered and eclipsed CH bonds amounts to 2.0 kcal mol^{-1} and could be responsible for an exo/endo ratio of 30. Ratios of 300 (Ref.28) or even higher cannot be defrayed by this effect. H.C. Brown et al. reported an exo/endo ratio of 5 000 for the addition of trifluoroacetic acid to norbornene (Ref.31).

Scheme 11

In 1976 S. Inagaki, H. Fujimoto, and K. Fukui (Ref.32) applied the "orbital mixing rule", based on MO per-turbation theory, to norbornene. Extended Hückel and CNDO/2 calculations led to the concept of "nonequi-valent orbital extension" for the π bond as a result of hyperconjugative interactions (Scheme 11).
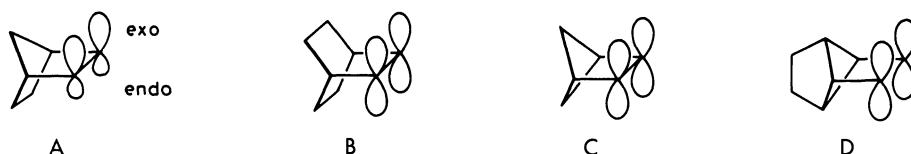
Scheme 12

A change of the normal olefinic hybridization brings about an electron distribution for the π HOMO which indicates larger orbital lobes in the exo position (Scheme 12, Ref.32). Fukui et al. wanted to clarify the exo preference in the addition of electrophilic reagents to norbornene and found an explanation of fascinating simplicity.

It struck me that this phenomenon might also be responsible for the second exceptional characteristic of norbornene, its anomalously high reactivity. According to the second-order term of the perturbation equation, the energy gain in creating the MO's of the transition state should be proportional to the square of the products of the atomic orbital coefficients, i.e., the relative electron densities. Thus, the interaction with the larger exo lobes of norbornene should result in a greater gain of bond energy than the interaction with the endo lobes. An attractive solution of the puzzle comes within reach, namely a common reason for both exceptional features of norbornene reactivity.

Scheme 13

A   B   C   D
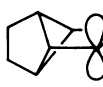
The proof should be straightforward and requires a comparison of the cycloaddition constants of norbornene (A) with those of bicyclic alkenes which due to symmetry cannot display nonequivalent π orbital extension. This is true for bicyclo(2.2.2)octene (B), bicyclo(2.1.1)hexene (C) as well as for the better accessible tricyclooctene (D) in which the bicyclohexene skeleton is incorporated. A symmetry plane which is absent in norbornene cuts the π orbitals of the three other bicycloalkenes in halves (Scheme 13).

Table 4.   Heats of formation and strain energies of cycloalkenes and cycloalkanes calculated by MM2

	Cycloalkene		Cycloalkane	
	ΔH_f^o	Strain	ΔH_f^o	Strain
Cyclohexene	− 1.88	2.76	− 29.53	2.61
Bicyclo[2.2.2]octene	+ 5.59	15.15	− 22.41	14.64
Bicyclo[2.2.1]heptene	+ 19.40	23.20	− 12.84	18.46
Bicyclo[2.1.1]hexene	+ 51.41	49.45	+ 13.95	39.49
Tricyclo[3.3.0.0^{2,6}]octene	+ 49.86	52.82	+ 13.45	43.91

For a quantitative evaluation it is mandatory to know the strain energies of the bicycloalkenes and bicycloal-kanes. On our request, N. L. Allinger extended his improved force field for molecular mechanics calculations, MM2 (Ref.33), to alkenes. The calculated standard heats of formation for cyclohexene, bicyclo(2.2.2)octene, norbornene and their hydrogenation products agree well with experimental ΔH_f^o values (Ref.34). The strain energy of bicyclo(2.2.1)heptene more than doubles in bicyclohexene and its tricyclic derivative (Table 4).

Table 5.   Loss of ring strain (in kcal mol^{-1}) on hydrogenation of cycloalkenes
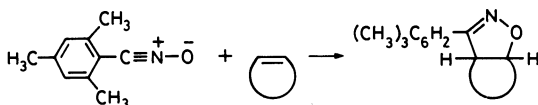
Cyclohexene	Bicyclo[2.2.2]-octene	Bicyclo[2.1.1]-hexene	Tricyclo[3.3.0.0^{2,6}]-octene	Bicyclo[2.2.1]-heptene
calcd. 0.15	0.51	10.0	8.9	4.7
exp. ≡ 0	1			6

The same is true for the difference in strain energy of the cycloalkenes and cycloalkanes (Table 5). The cal-culated strain release of 4.7 kcal mol^{-1} for the conversion of norbornene to norbornane compares well with Turner's experimental value of 6 kcal mol^{-1}. The loss of ring strain on hydrogenation of bicyclohexene and the tricyclic derivative amounts to 10 and 9 kcal mol^{-1}, respectively. For bicyclo(2.2.2)octene the strain release totals 0.5 kcal mol^{-1} calculated versus 1 kcal mol^{-1} derived from the heat of hydrogenation.
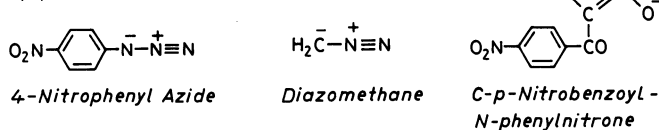
Should the rate increase of norbornene over cyclohexene originate only from strain release in the transition state, then one would anticipate the cycloadditions of bicyclohexene and tricyclooctene to show a diminu-tion of the activation free energy, which is roughly twice as large as that for norbornene. An example: Dia-zomethane adds to norbornene 5,000 times faster than to cyclohexene. The reaction with bicyclohexene should be 5,000^2, i.e., 25,000,000 times faster, if $\Delta\Delta G^{\ddagger}$ were double as large.

Scheme 14
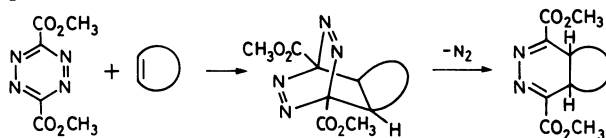
1,3-Dipolar Cycloadditions

2,4,6-Trimethylbenzonitrile Oxide

4-Nitrophenyl Azide   Diazomethane   C-p-Nitrobenzoyl -
                                                N-phenylnitrone
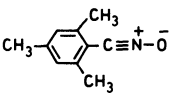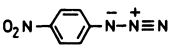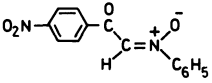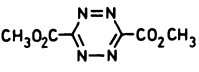
Diels-Alder Reaction

Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate

The test reactions are four 1,3-dipolar cycloadditions and one Diels-Alder reaction (Scheme 14); they differ in the relative share of the two frontier orbital interactions. The diazomethane additions are HOMO(1,3-dipole) – LUMO(cycloalkene) controlled, whereas both HO-LU interactions contribute to the additions of trimethylbenzonitrile oxide, 4-nitrophenyl azide and an acylnitrone. The last formula line pertains to a Diels-Alder reaction of inverse electron demand. The interaction of LUMO(tetrazinedicarboxylic ester) and HOMO (cycloalkene) dominates; the initial addition is followed by nitrogen loss to give a dihydropyridazine derivative (Ref.35). The rate measurements were preceded by preparative experiments which gave virtually quantitative yields; the structures of the cycloadducts were spectroscopically secured.

Table 6.   Rate constants k_2 in $l\ mol^{-1}\ sec^{-1}$ for concerted cycloadditions

1,3-Dipole or 1,3-Diene	Solvent, Temp.						
CH_3-benzonitrile oxide (trimethyl) $C\equiv N-O$	CCl_4 25°C	$10^6 k_2$	1.2	5.7	3 150	2 300	2 280
O_2N-phenyl $N-N\equiv N$	DMF 50°C	$10^5 k_2$		1.3	112	126	
$H_2C-N\equiv N$	DMF 25°C	$10^7 k_2$	0.4		2 020	960	
O_2N-phenyl acylnitrone $C=N$ C_6H_5	Dioxan 25°C	$10^7 k_2$		5.9	6 340	6 420	1 010
CH_3O_2C-tetrazine-CO_2CH_3	Dioxan 25°C	$10^3 k_2$	1.27	113	11 700	5 370	
	IP(eV)		9.18	9.05	8.97	8.63	

The cycloalkenes are ordered in Table 6 by growing strain loss. Instead of reacting 3 - 4 powers of ten times faster than norbornene, the rate constants of bicyclohexene and tricyclooctene are similar or somewhat smaller than those of norbornene (Ref.34). Trimethylbenzonitrile oxide reacts 5 times faster with bicyclooctene than with cyclohexene, whereas norbornene displays a 2,500 fold acceleration; the k_2 values of the two highly strained alkenes are somewhat lower than that of norbornene. The other rate sequences show similar characteristics. E.g., in the Diels-Alder reaction of tetrazinedicarboxylic ester, norbornene reacts 9,200 times faster than cyclohexene and exceeds bicyclooctene 100 fold. The rate constant of tricyclooctene decreases to half the norbornene value.

One must conclude that the release of strain energy in the transition state can – at the most – be only partially responsible for the high rate constants of norbornene. The additional rate increase is attributed to a factor x which could be Fukui's nonequivalent orbital extension.

The numerical evaluation of the two factors rests on three simplifying assumptions. 1. The transition state is located at the same spot of the reaction coordinate, i.e., percentagewise, the strain release is the same for all the bicycloalkenes. 2. The steric requirements and activation entropies are equal. 3. The total rate difference between bicyclo(2.1.1) hexene and bicyclo(2.2.2)octene, the two symmetrical models, is accounted ted for by strain release in the transition state. The third is the most daring assumption.

Table 7.   Numerical evaluation of the factors contributing to the high norbornene reactivity ; energies in kcal mol^{-1}

2,4,6-Trimethylbenzonitrile Oxide

$10^6 k_2$ (25°C)	5.7	3 150	2 300	2 280
$\Delta\Delta G^{\ddagger}$ $\dfrac{\text{(Cycloalkene)}}{\text{(Bicyclooctene)}}$		3.8	3.6	3.6
Δ(Strain) calcd.	0.51	4.7	8.9	10.0
Additional Strain Loss		4.2	8.4	9.5
38% of " " "		1.6	3.2	3.6
i.e. % of $\Delta\Delta G^{\ddagger}$		42 %	90 %	100 %
Factor x in %		58 %		
in kcal mol^{-1}		2.2		

Trimethylbenzonitrile oxide adds to bicyclohexene with an activation free energy which is by 3.6 kcal mol^{-1} lower than that of the addition to bicyclooctene (Table 7). The strain release of bicyclohexene on hydrogenation exceeds that of bicyclooctene by 9.5 kcal mol^{-1}. The assumption of 38 % strain release in the transition state of cycloaddition brings the loss for bicyclooctene to 3.6 kcal mol^{-1}, i.e., 100 % of the $\Delta\Delta G^{\ddagger}$. The hydrogenation heat of norbornene surpasses that of bicyclooctene by 4.2 kcal mol^{-1}. If the transition state of the cycloaddition to norbornene were to profit again from 38 % strain release (1.6 kcal mol^{-1}), this would amount only to 42 % of $\Delta\Delta G^{\ddagger}$ = 3.8 kcal mol^{-1}, and 58 % could be attributed to factor x (Table 7). A similar distribution is achieved for the four other cycloadditions measured ; factor x participates with 51 – 73 % in norbornene reactivity.

Is Fukui's nonequivalent orbital extension in the norbornene π bond a reality ? Here comes the surprise: P.v.R. Schleyer (Ref. 36) and R. Gleiter (Ref. 37) carried out MNDO and MINDO/3 calculations of norbornene and did not find the nonequivalence of the π orbital extension. The hybridization of the olefinic carbon atoms was normal. One can either doubt the value of semiempirical calculations or look for another interpretation of factor x. Gleiter's calculation gave a valuable hint: The overlap integrals for endo and exo approach of the reagent are different in the sense of favoring the exo attack. In a conceivable alternative, factor x does not operate in the ground state, but rather affects the transition state energy. Further theoretical studies will be necessary.

Our analysis of the contributing effects was based on the presumption that all the rate increase of bicyclohexene over bicyclooctene is ascribed to strain release in the transition state. The presumption that 38 % of the total strain release between bicyclohexene and bicyclohexane becomes effective in the transition state of the nitrile oxide cycloaddition, is rather unlikely. The author would prefer a zero value for strain release in the very early transition state.

A theoretical concept begins to emerge – still somewhat foggy – that allows a description of cycloalkene and bicycloalkene reactivity which is consistent with the early transition states of concerted cycloadditions. The hyperconjugative interaction of the σ bonds of the one-carbon bridge of norbornene with the π orbitals plays an important role in Fukui's as well as in Gleiter's calculation. The same structural element is present

in bicyclohexene and tricyclooctene ; both hydrocarbons could profit in their cycloadditions from the same hyperconjugation as norbornene does, if factor x were no longer a ground state, but a transition state phenomenon. The similarity of the rate constants of norbornene and the more strained bicycloalkenes (Table 6) is conspicuous.

It may be recalled that cyclopentene exceeds cyclohexene 10 - 100 fold in cycloaddition rate (Table 3). Cyclopentene has an envelope structure with C-4 serving as the flap. Conceivably, its transition state of cycloaddition benefits from the same factor x as norbornene, though to a smaller degree.

New effects which control reactivity are no longer abundant. In the case of the Fukui phenomenon, the combined efforts of experimenter and theorist are needed to learn about origin and scope.

ACKNOWLEDGEMENT

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