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THE ROLE OF SECONDARY ORBITAL INTERACTIONS IN CONTROL OF ORGANIC REACTIONS

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The major thrust of our work on propellanes in recent years has acquainted us with "secondary orbital interactions" which we have invoked in order to explain the stringent regiospecificity which obtains in our reactions (see below). Upon reading papers that have appeared since the publication of Woodward and Hoffmann's book[1] (the Bible containing the blue and green orbitals) one almost gets the impression that any extraordinary reaction course with respect to the configuration of a product is explained by "secondary orbital interactions". Sometimes the explanation is (what we organic chemists like to call) "reasonable" but there are plenty of one-sentence statements referring to this concept, citing some important source, which have naught to do with the matter at hand. Since we are dealing with "Holy Writ", extensions and interpretations of the abovementioned Bible[1] abound, and since many referees were trained before its codification, incorrect statements have been allowed to stand.

Various effects may *a priori* be responsible for stereoselectivity, say, of the Diels–Alder reaction. The first rule formulated in this connection, the Alder rule, is more a statement of fact that an explanation. Its physical basis was assumed to be the lower activation enthalpy for *endo* addition.

Inductive forces of the van der Waals type or dipolar forces have been used to rationalize the stabilization of the *endo* transition state. Charge transfer has been invoked. Favorable geometry for overlap has been suggested as an explanation, "secondary binding forces", and secondary orbital interactions. A plethora of excuses. To complicate matters, experimental parameters have been shown to exert an important influence, e.g. solvent effects, Lewis acid catalysis. All of these factors will be mentioned in the discussion.

It has therefore been a challenge to write this Tetrahedron Report. In order to define the scope of the subject I perhaps foolishly confront, I quote from a reply to my letter to R. Hoffmann in which I asked for particular examples of secondary orbital interactions. He replied: "I will think about your request for instances of secondary orbital interactions controlling the course of chemical reactions. But I'm a little paralyzed by the request. *Every* paper we write, every instance of frontier control (and of course I'm prejudiced to think all reactions are so controlled) has built into the detailed analysis secondary effects. Isn't that how one could think of substituents affecting a reaction in general? Since I write many papers, I see too many cases . . .".[2]

The old Jewish sages have said: "If you grasp at too much, naught remains in your grasp". I had hoped I could include in this Report some cases, considered by Hoffmann to be outstanding, in which secondary orbital interactions exert the cardinal influence upon the reaction course. Although his broad view is understandable, I should not have undertaken to write within such context if only because of the constraints as to space imposed upon a Tetrahedron Report, not to speak of my own limitations in discharging so broad a task.

I have therefore chosen from the literature certain "case histories" which struck me as being apt for this discussion. I have probably missed very important cases, and for reasons of personal taste, may have overemphasized others, but no malice has been involved.

Since the term "secondary orbital interactions" is used rather loosely I shall try to define it as it is used in subsequent discussion:[3]

First order orbital interactions are the in-phase and out-of-phase relationships between the atomic orbital coefficients at the pertinent reaction centers. (At this stage it does not matter, for example, if an *exo* or an *endo* product is obtained, nor is the regiospecificity of any concern.)

Second order orbital interactions are those which are determined by the magnitudes of the atomic orbital coefficients and/or the shape of the wave function. (For example, the former determines regiospecificity, the latter, the efficacy of $\sigma - \pi$ mixing; see below.) These include substituent effects which cause polarization of π-systems and $\sigma - \pi$ mixing at the atoms where new bonds are formed, polar group effects, and secondary orbital interactions between atoms which are not involved in bond formation or cleavage. Yet these determine the configurations of products, e.g. *exo-endo*, *syn-anti*. We shall emphasize these secondary orbital interactions, but cannot avoid mentioning the additional factors involved.

Now let us get down to cases.

It is reasonable to list first the cases cited by Woodward and Hoffmann in their section called "secondary effects".[4] The first concerns the exclusive formation of the *endo* product when 1,3-butadiene adds to itself in a $[{}_{\pi}4_{s} + {}_{\pi}2_{s}]$ cycloaddition.[5] Later, $[{}_{\pi}6_{s} + {}_{\pi}4_{s}]$ were postulated and shown to occur.[6] A case of $[{}_{\pi}2_{s} + {}_{\pi}2_{s} + {}_{\pi}2_{s}]$ cycloaddition is then cited.[7]

For cyclobutadiene dimerization the possibilities of $[{}_{\pi}2_{s} + {}_{\pi}2_{s}]$, $[{}_{\pi}2_{s} + {}_{\pi}4_{s}]$ and $[{}_{\pi}4_{s} + {}_{\pi}4_{s}]$ cycloadditions may be predicted *a priori* if the double bonds are rather localized. The Woodward-Hoffmann prediction with respect to the $[{}_{\pi}2_{s} + {}_{\pi}4_{s}]$ *endo* reaction had been confirmed after the prediction was made but before their book was published.[8]

In the sense of the present discussion secondary orbital interactions predict that the *syn* cyclobutadiene dimer **1a** ought to be preferred to the *anti* dimer **1b** because *endo* addition is preferred over *exo* addition. In the event, reactions with various cyclobutadiene precursors afford some of the *anti* dimer as well but in those reactions where the formation of a free cyclobutadiene is more certain, the *syn* product is obtained.[9]

1,5-Hexadienes undergo [3,3]-sigmatropic rearrangement more readily through a quasi-chair transition state than through the quasi-boat.[10] A detailed explanation is given.[11] It is nevertheless true that when forced to do so a molecule can undergo [3,3]-sigmatropic rearrangement via a less favorable transition state without particular difficulty.[12]

Finally a [4 + 2] cycloaddition of butadiene to an allyl-cation is mentioned. The prediction that secondary interactions would cause an *exo* transition state to be preferred has been confirmed experimentally.[13]

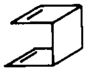
I had been unaware, while writing this Report, of an excellent critical review by Sauer and Sustmann of mechanistic aspects of the Diels–Alder rection. In it additional references may be found which deal with secondary orbital interactions.[13a]

In a 1967 paper,[14] Herndon and Hall, appeared to have reversed their previous stand in agreement with others,[15] that "*secondary attractive forces*" (my italics) operating between centers which are not bonded in the adduct account for the rule of "*endo*-addition" in Diels–Alder reactions. This is the famous rule of "maximum accumulation of double bonds"."[5a] This paper is typical of the perplexed condition of the pioneers in this field. In it they suggested that these "*secondary relationships*" (my italics) may be relatively unimportant and that the stabilities of *endo* and *exo* transition states are governed by the geometrical overlap of the π-orbitals at the (primary) centers only, where the bonds are actually made. They discussed both transition states for the concerted [4 + 2] cycloaddition of cyclopentadiene to itself and calculated the overlap integrals for the reactants in each transition state. The calculations indicated that the geometric relationship of the primary interactions is dominant as compared to the secondary ones, accounting for over 90% of the stabilization energy difference between the *endo* and the *exo* transition states.

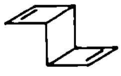
Perhaps we have a problem of semantics (italicized phrases above) and these phrases are not used in the same sense that I have defined secondary orbital interactions. Nevertheless, in another paper published in the same year, the authors say:[16] "The predominant formation of endo adducts is accounted for by *secondary interactions* (my italics) between atoms which do not become bonded in the adduct, just as suggested by Woodward and Hoffmann". (They refer to Ref. 16*a*). Later they say: "The major portion of the stabilization energy is due to the primary interaction, that between the highest occupied MO of the diene and the lowest vacant MO of dienophile". Thus, apparently the [4 + 2] cycloaddition of 1,3-butadiene to itself, cited above,[17] with its secondary orbital interaction still appears to be the guide to the perplexed,[18] those perplexed about certain cases of *endo*-addition, e.g. norbornene, cyclopentene and cyclopropene.

The looseness in terminology in some of the early discussion of the phenomenon we are confronting herein is probably purposeful. Life sometimes requires a certain befogging of the issues.[19] Woodward and Katz taked about *secondary attractive forces*[15] (my italics): "Conformational specificity about the newly-forming bond is determined by secondary attractive forces involving the electrons not directly associated with the primary bonding process".

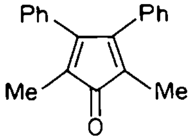
Houk pointed out, as did Herndon and Hall[14] before him, that dienophiles such as cyclopropene, cyclopentene and norbornene, in which no secondary orbital stabilization is possible, nevertheless give *endo* transition states.[20] Houk showed that 2,5-dimethyl-3,4-diphenylcyclopentadienone with cyclopentadiene gives at least 97% of the *endo* adduct. With cyclopentene, however, a mixture of *ca.* 56:44 of the *endo* and *exo* adducts is obtained. Similar results were obtained for the same dienophile with cycloheptatriene (*endo* adduct only) and cycloheptene (mixture of both), respectively.



Ia



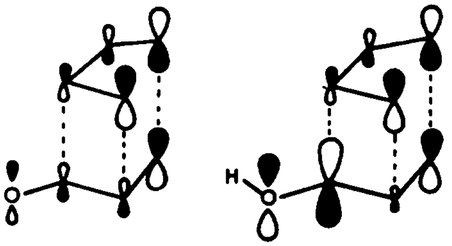
Ib



Houk points out that the second double bond, in going over from cyclopentene to cyclopentadiene, transforms a non-stereoselective reaction to a stereoselective one. This is a nice demonstration of the importance of secondary orbital interactions in the stabilization of an *endo* transition state. The stabilization afforded appears to be about 2.5–5.0 kcal/mol.

In another paper Houk discusses frontier orbital energies and the relative magnitude of the coefficients of 1- and 2-substituted dienes in terms of conjugating substituents, electron-releasing and electron-withdrawing groups.[21] The coefficients at the terminals C-1 and C-4 in the HOMO and LUMO of 1-substituted electron-deficient dienes are nearly the same. Although regioselectivity in reactions of such substrates would be expected to be less pronounced, this is not, in fact, the case.[22] Houk attributes this to the possible influence of secondary orbital interactions between substituents,[23] a procedure followed by many authors (see below). Houk has also explained the higher stereoselectivity under Lewis acid catalysis in terms of a "tighter" transition state resulting from greatly increased secondary orbital interactions, not ruling out that the conformational changes may also contribute.[24] As may be seen in Fig. 1 the secondary orbital interaction between the HOMO of the diene and the LUMO of the dienophile between the carbonyl carbon and C-2 of the diene is greatly increased in the coordinated carbonyl group for the coefficient at the carbonyl-carbon becomes very large.

Alston and Ottenbrite have subsequently made the point that in disubstituted dienes with similar terminal orbital coefficients, secondary orbital interactions would be more important in the



(a) (b)

Fig. 1. Diene HO-dienophile LU interactions in *endo* transition states with (a) acrolein and (b) protonated acrolein.

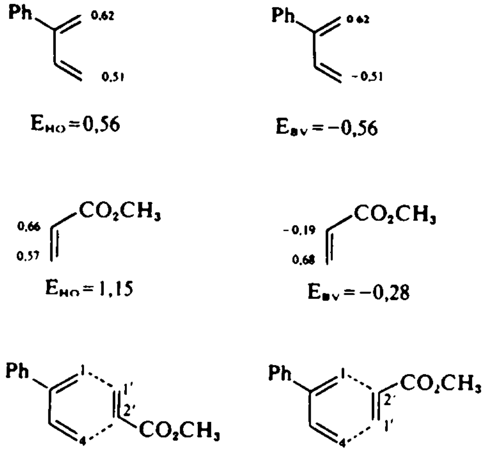


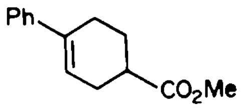
Fig. 2. Frontier orbitals of phenylbutadiene and methyl acrylate.

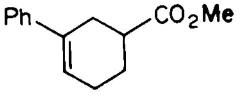
1,2-disubstituted case and least important in the 1,4-disubstituted case in Lewis acid catalyzed Diels–Alder reactions.[25]

In a very interesting paper Nguyên Trong Anh and Jacqueline Seyden-Penne, a powerful combination, discussed the Diels–Alder reaction of 2-phenyl-1,3-butadiene with methyl acrylate with and without the presence of aluminium chloride as a Lewis acid catalyst.[26] I have heretofore omitted explicit examples of how the coefficients at the terminals affect the regiospecificity of the reaction, for these are so well known. (Readers who require a didactically clear and detailed exploration of this subject are referred to the excellent monograph by Fleming[27].)

Since the ease of bonding is in the order $4\text{–}2' < 1\text{–}2' < 4\text{–}1' < 1\text{–}1'$, the major product is **2** rather than **3**.

2





3

Aluminium chloride catalysis accelerates the formation of **2** more than that of **3** [$\Delta E(1\text{–}1') = -0.02$; $\Delta E(4\text{–}1') = -0.01$]. In fact the **2**/**3** ratio in the uncatalyzed reaction is 80/20 and in the catalyzed one it is increased to 97/3. These calculations are in accord with the kinetic study of Inukai and Kojima.[28]

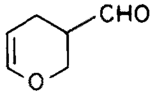
A further point of interest made in this paper concerns the postulate (in keeping with a paper discussed below[29]) that it is possible to apply the same arguments to asymmetric induction which is also governed by steric and orbital interactions. It had already been shown experimentally that the *endo* adduct of cyclopentadiene and (−)-menthyl acrylate at 0° was obtained in 9.1% optical yield. Addition of BF_3 at the same temperature increased the optical yield to 74%.[30]

It may be possible to exploit secondary orbital interactions in order to control the extent of stereoselectivity by introducing suitably interacting groups near a prochiral center adjacent to a chiral one and thus favor one diastereomeric transition state sufficiently over the other so as to get $\Delta\Delta G$ of over 3 kcal/mol, affording a suitably higher enantiomeric excess.[30a]

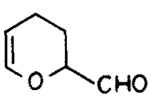
A very recent paper discussed the powerful catalysis of certain Diels–Alder cycloaditions by aminium cation radical salts, e.g. $Ar_3N^+/SbCl_6^-$ in the context of secondary orbital interactions. It is believed that these are enhanced in the cation radical transition state for the reaction.[30b]

A Japanese group has interpreted their findings with 1,4-disubstituted cyclopentadienes and various dienophiles in terms of rate: the faster the reaction, the higher the *endo*/*exo* ratio.[31] This too is laid at the door of secondary orbital interactions. From previous work on the effect of pressure on the Diels–Alder reaction they deduced that a faster reaction proceeds through a "tighter" transition state. "The tighter transition state implies the existence of a stronger secondary orbital interaction as well as a closer proximity of the reaction species. The extent of stabilization due to secondary orbital interactions must be responsible for the determination of the *endo*-*exo* isomer ratio". A figure is given showing a linear relationship between that ratio and the rate. "The correlation shown in Fig. 1 indicates that the more reactive dienophile is characterized by the possibility of the stronger secondary orbital interaction." Would that figures concerning experimental parameters indeed bear true witness to the (hidden) existence of secondary orbital interactions!

Anh *et al.* have published two interesting papers concerning the mode of simple prediction of the orientation of cycloaddition in Diels–Alder reactions by application of the "hard" and "soft" concept to the Woodward–Katz model,[32] and in thermal [2 + 2] cycloadditions.[33] They discuss the cyclodimerization of acrolein which may afford either **4** or **5** (only **5** is observed experimentally).

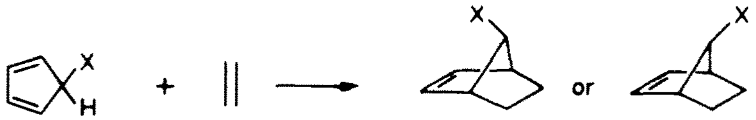


4



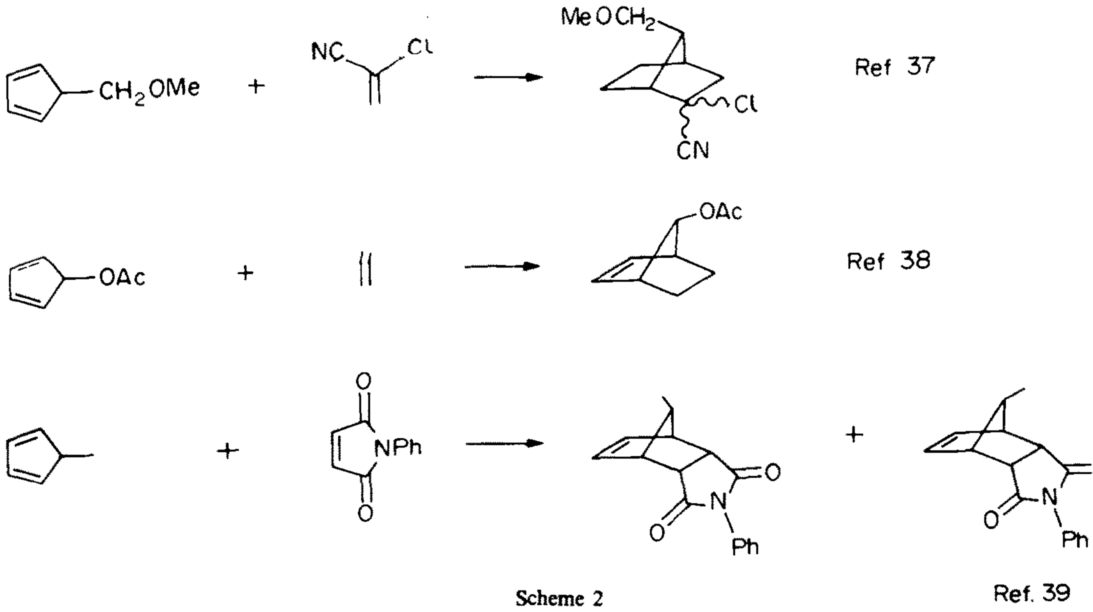
5

Salem found that both products are predicted by Hückel orbital interactions over the four reaction centers.[34] π SCF calculations including first order charge interactions and overlap yield the correct orientation. The major contribution to the stability of **5** vis-à-vis **4** therefore arises from electrostatic terms.[35] The Anh method considers only the orbital interactions of the terminal carbons and predicts **5** correctly. Alston showed that secondary orbital interactions (at non-reacting atoms, C-2 and C-3 of the diene) predict the wrong isomer **4**.[36] Quoth Anh: "That secondary orbital interactions sometimes predict the incorrect regioselectivity is to be expected". This need not be an unfriendly remark within the scope of this Report. Is there a concept of this type that does not "sometimes" predict incorrectly? ("Exceptions: there are none".) In fact, in an earlier paper Anh suggests that secondary orbital interactions "analogues à celles invoquées par Woodward et Hoffmann" with respect to the *endo* effect play in important role in the reaction of a 5-substituted cyclopentadiene with a double bond potentially leading to either a *syn* or an *anti* product (Scheme 1):



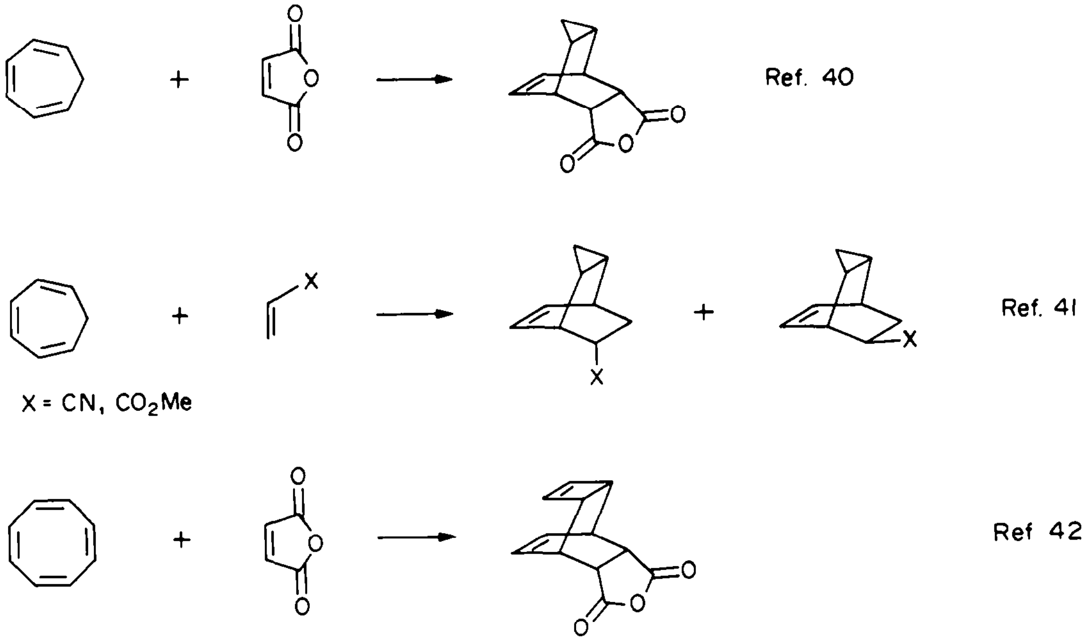
Scheme 1

Steric factors may cause preferential formation of the *syn* isomer but there are exceptions in which the *anti* isomer predominates due to an attractive interaction between the dienophile and the bridge substituent (Scheme 2):



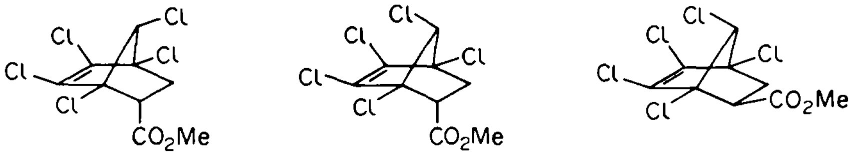
Scheme 2

When cycloheptatriene or cyclooctatetraene are used as dienes, only *syn* products are obtained (Scheme 3):



Scheme 3

Finally, perchlorocyclopentadiene gives with some 10 dienophiles mixtures containing both *syn* and *anti* isomers, with the latter varying from 31 to 91%.[43] In the case of methyl acrylate as dienophile, the following results are obtained (Scheme 4):[26]



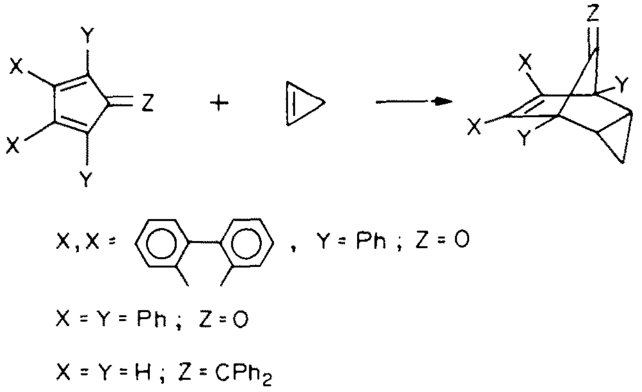
	anti-endo	*syn-endo*	*syn-exo*
Non-catalyzed	53.2%	36.6%	10.2 %
Catalyzed	69.1%	28 5%	2.4 %

Scheme 4

The configuration of the adducts formed in the reaction of cyclopropene (as the dienophile) with dienes is determined by secondary orbital interactions with participation of the methylene fragment.[44] Cyclopropene reacts with a wide range of dienes.[45]

Endo adducts are obtained with cyclopentadiene[46] and its derivatives,[47] with tropone and tropolone,[48] with cyclohexadiene,[49] and with dimethylfulvene.[50] With furan[51] and with diphenylisobenzofuran[52] a mixture of *exo* and *endo* adducts is obtained. In the opinion of the Russian authors, steric reasons are responsible for *endo* addition of cyclopentadienes and cyclohexadiene,[44] and they think that it remains an open question whether or not the Alder rule is operating. They therefore undertook a study of cyclopropene with dienes in which there is the same *a priori* probability for the formation of an *endo* or an *exo* adduct and in which orbital interactions may be the determining factor.

Only *endo* products were obtained owing to interaction of the π systems of the diene and the substituents at the double bond of the dienophile in the transition state. Although cyclopropene does not have a classic π system at the double bond, its methylene group has an occupied molecular orbital with π-symmetry (a bonding linear combination of the $2p_z$ atomic orbital of carbon with



Scheme 5

the antisymmetric linear combination of the 1s atomic orbitals of the hydrogens). The fixed position of the methylene group permits effective interaction between the cyclopropene π bond and the orbital with π-symmetry in the saturated part of the cyclopropene. The authors' Hückel calculations showed that overlap of the LUMO of cyclopropene with the HOMO of the diene, of the same symmetry, would be the same in both *exo* and *endo* transiton states. They therefore concluded that the reaction course would then be determined by overlap of the HOMO of cyclopropene with the LUMO of the diene of the same symmetry.

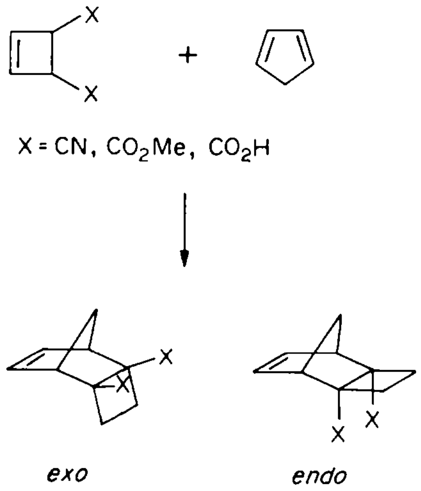
Sustmann and Binsch have published MINDO/1 calculations on the reaction of cyclopentadiene and cyclopropene, showing that the *endo* transition state should indeed be favored.[44b]

Mellor and Webb have published cases in which steric factors, repulsive non-bonding interactions, control *endo* selectivity. They emphasize that secondary orbital interactions cannot reasonably explain the reactions of cyclopentadiene with a large variety of dienophiles substituted at the double bond.[53] Papers such as these have quite a dampening, but salutory, effect on persons enthusiastic about secondary orbital interaction control of the course of chemical reactions and serve as a reminder that one must always tread warily in interpretations of this kind. There are many factors involved. Sometimes secondary orbital interactions play the overwhelming role, overcoming other factors, or appear to play an overwhelming role when they are merely buttressing additional factors in determining the reaction course. Sometimes, though they exist, they appear to be absent because other factors predominate. But even when they appear to be the determining factor, it may be that (an anthropomorphic) God above is smiling to Himself for *He* knows the truth and that secondary orbital interactions indeed do not necessarily predominate but rather, say, electrostatic ones.

The possibility has been discussed[54] that secondary orbital interactions between "non-bonded electrons on the hetero atoms" in N-phenylmaleimide and the "π electrons of a bridged carbonyl group" may be responsible for the formation of *exo*-adducts.[55] It turns out that testing this hypothesis with 2,3,4,5-tetraphenylcyclopentadienone did not give a result different from that obtained with 1,2,3,4-tetraphenylcyclopentadiene. Both give *endo*-adducts. This is ascribed to steric effects.

Belluš has presented a beautiful example in which secondary orbital interactions are at first disappointing.[56] The *endo* adduct of a cyclic diene with a dienophile containing an alkyl-substituted double bond was desired, specifically that between cyclopentadiene and cyclobutene-1,2-dicarbonitrile. Although a quantitative reaction occurs, an *exo*-*endo* mixture is obtained, for steric reasons, in a ratio of 20:1 (Scheme 6). Variation of temperature, solvent polarity and use of aluminium chloride catalysis did not significantly change this isomer distribution.

The yield of *endo* isomer was slightly increased for the corresponding dimethyl ester when polarity of the solvent was changed (*cf* Berson, Ref. 5*a*). However, when the free dicarboxylic acid was used, the isomer ratio changed dramatically, it was reversed and the *endo* isomer was obtained in 88% yield. The diacid was known to have a very low pK_1 (1.12) and a very high second dissociation constant (pK_2 7.63) due to a strong intramolecular hydrogen bond, enabling the latter to lie within the molecular plane. The authors suggest, also on the basis of the X-ray structural determination that the high dienophilicity is a consequence of this planarity which allows maximum

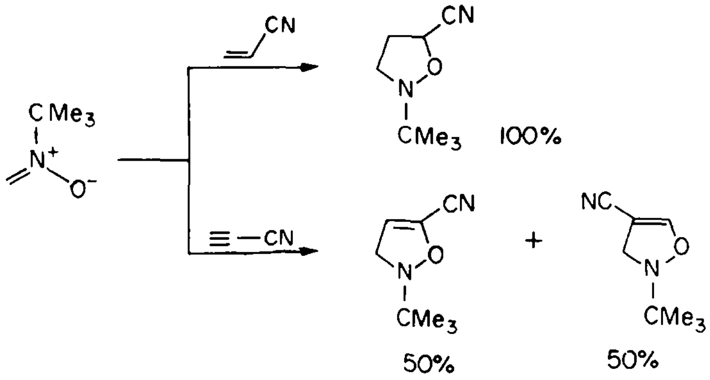


Scheme 6

conjugation between the carboxyls and the double bond. Dreiding models show for the potential *exo*-transition state a considerable repulsive-non bonding interaction between the out-of-plane hydrogens of cyclopentadiene and the hydrogen involved in the intramolecular hydrogen bond.[57] The methylene hydrogen of cyclopentadiene may no longer insert between the functional groups of the cyclobutene molecule as they could with the cyano or with the ester groups. Fixation of one carbonyl group (by the H-bond) in the *s-trans*-conformation provides unfavorable geometry for secondary orbital interactions between the lone pairs on the hydroxylic oxygen in this group and the π-electrons of the cyclopentadiene in the *endo* transition state. The secondary orbital interactions evidently become considerably less pronounced. Therefore the activation energy for *exo*-addition may become higher than that for *endo*-addition. The experimental results (88% *endo* adduct) support this explanation. Secondary orbital interactions have redeemed themselves!

The operation of secondary orbital interactions in 1,3-dipolar addition of N-*t*-butylnitrone and acrylonitrile has been suggested since a quantitative yield of only one of the possible regioisomers was obtained (Scheme 7). This is in contradistinction to the reaction with cyanoacetylene which gives both possible isomers.[58] The HOMO dipole–LUMO dipolarophile interactions in the concerted additions of N-methylnitrone to cyanoacetylene and to acrylonitrile are shown in Figs. 3 and 4.

The secondary attractive interactions in Fig. 3 between the 2pπ cyano carbon orbital and the approach 2pπ orbital of the nearest carbon atom of the nitrone (distance is only 0.86 Å when standard bond distances and angles are used and the dipole is projected onto the plane of cyanoacetylene, whilst that to the adjacent acetylene carbon, where a bond is formed, is only 0.52 Å). Similarly in Fig. 4 for acrylonitrile, considerably more differing values (1.29 and 0.45 Å) are obtained for primary–secondary and primary–primary distances, respectively.



Scheme 7

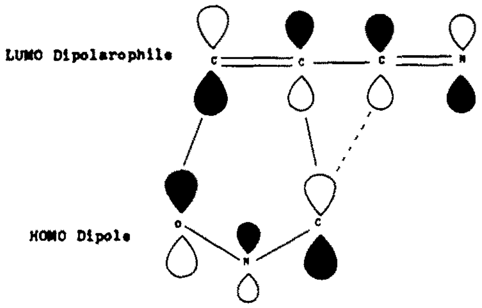


Fig. 3. HOMO dipole–LUMO dipolarophile interaction in the concerted addition of N-methylnitrone to cyanoacetylene.

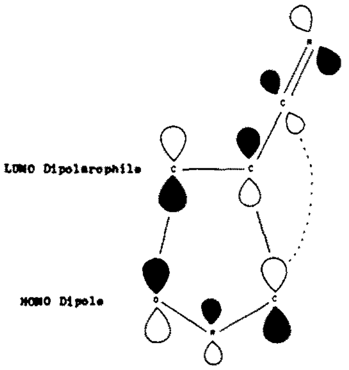
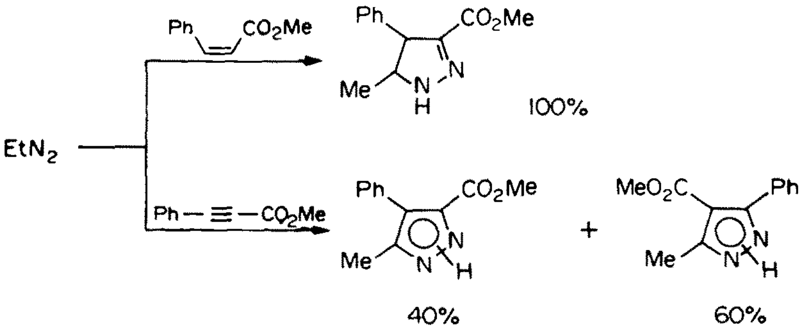


Fig. 4. HOMO dipole–LUMO dipolarophile interaction in the concerted addition of N-methylnitrone to acrylonitrile.

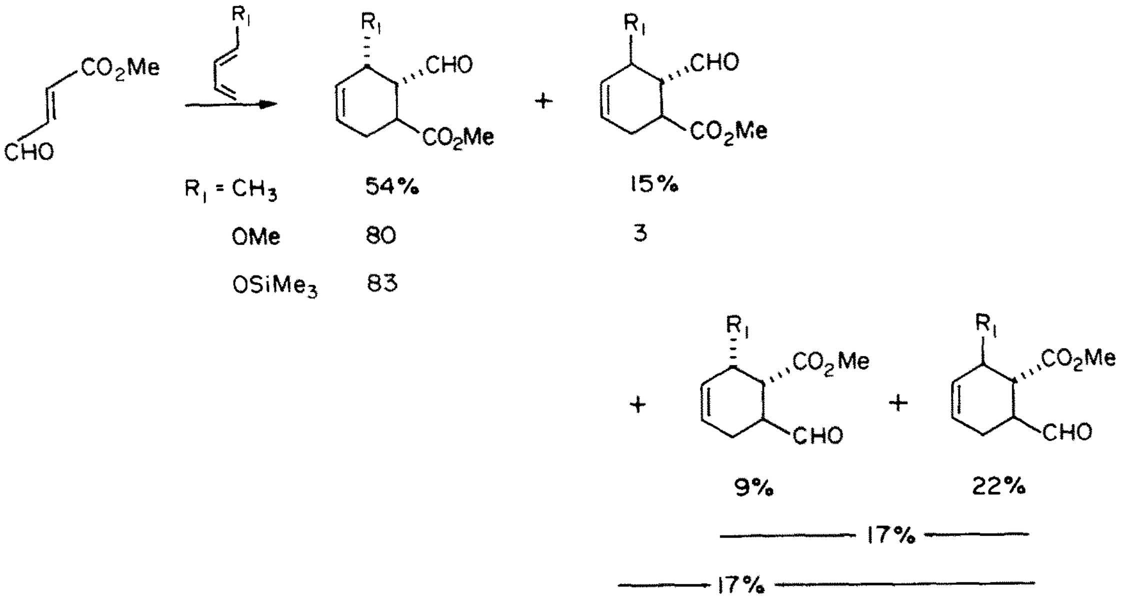
For consideration of the regionchemistry of the reaction, the primary–secondary interaction must be included in addition to the primary–primary one in an electron-deficient acetylenic compound. When the dipole has the same atom as its primary centers, the primary–secondary interaction will have nearly the same added stabilization for each concerted attack and will not differ much with respect to the behavior of the alkene. But in view of differing long-range bond characteristics of hetero-atoms the primary–secondary interaction can contribute disproportionately to transition state energies when the 1,3-dipoles have asymmetric primary centers. Therefore the authors attribute the loss in regioselectivity in the nitrone reaction with the electron-deficient acetylene to the fact that the primary–secondary C–C attraction will be much larger than the CO contribution at long distance, thereby counterbalancing the primary–primary orbital preferences which predominate in the corresponding olefins.

A similar explanation is given for the reaction of diazoethane with methyl cinnamate where only one regioisomer is obtained and β-phenylmethyl propiolate where a mixture of both is formed (Scheme 8).[59]



Scheme 8

The relative behavior of methyl E-4-oxobutenoate[60] and E-4-nitrobutenoate[61] have been compared by Kakushima and Scott.[60] The product on the left is the major one (Scheme 9):



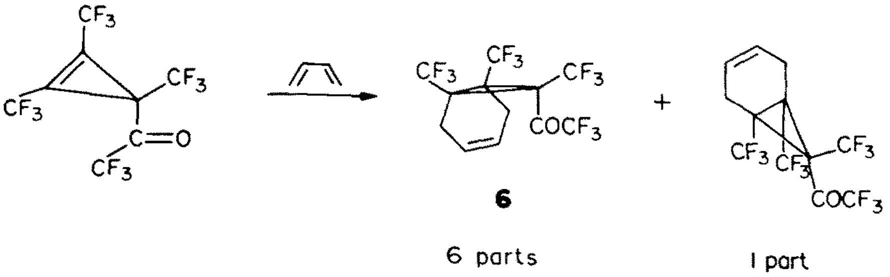
Scheme 9

In the corresponding nitro compound the regionselectivity is completely controlled by the nitro group; the magnitudes of the LUMO coefficients at C-2 and C-3 of both the formyl and nitro compounds agree with the observed selectivity. But though the formyl group also controls *endo* stereoselectivity, the nitro group does not. Although the magnitudes of the LUMO coefficients at C-1 and at the nitrogen in the latter are larger than those at the C-1 and C-4 terminals of the former, leading to a prediction that the nitro group would give *endo* selectivity owing to secondary attractive interaction, closed-shell repulsion at nitrogen counteracts this attraction. The exclusion-shell at the formul group is much smaller than at the nitro group and since in the latter case the experimental results show that closed-shell repulsion and secondary attractive interaction are about the same (*endo*/*exo* ~ 1:1), the secondary attraction in the case of the formyl compound overcomes closed-shell repulsion and an *endo* isomer is formed more than the other *exo*-isomers.

Tris(trifluoromethyl)trifluoroacetylcyclopropene gave with dienes mainly the adduct of type **6** in which the trifluoroacetyl group is *syn* to the newly-formed ring, owing to secondary orbital interactions between the carbonyl group and the dienic component; an *endo* transition state therefore predominates.[62]

For example, the reaction with butadiene is shown in Scheme 10.

In other cases the *syn* product may not be isolated but reacts further to yield a cage-product. The product distribution with 2,3-dimethylbutadiene is *syn* (8): *anti* (1) whilst cyclopentadiene, furan, and pyrrole afford the *syn* isomer exclusively.



Scheme 10

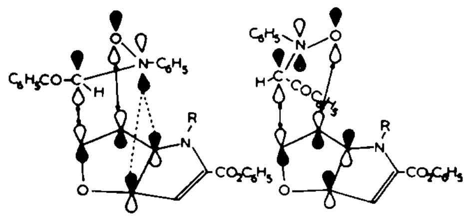
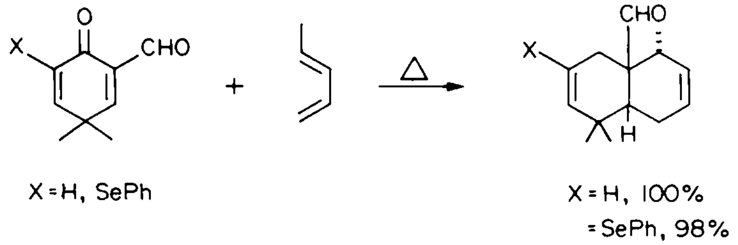


Fig. 5. *Endo* and *exo* transition states.



Scheme 11

Peculiarly, a paper which cites many structures which would be helpful for its understanding, does not formulate this graphically but its gist is that C-benzoyl-N-phenyl nitrone slowly undergoes 1,3-dipolar cycloaddition with benzofuran to yield only one adduct in 35% yield.[63] Figure 5 shows the difference between the *endo* and *exo* transition states in an analogous reaction.

The Diels–Alder reactions of cross-conjugated dienones has been studied.[64] When the formyl dienone (X = H) shown in Scheme 11 was reacted with excess of piperylene, only a single adduct was formed. The X-ray structure was determined for the derivative with X = SePh. Reaction occurred at the more activated double bond of the dienophile and the expected "ortho" product was obtained in which the vicinal substituents are *trans-* to one another. The latter observation is surprising because the transition state required to produce the *trans*-configuration is more hindered than the one leading to the *cis*-isomer (Fig. 6). This is understood when one examines the LUMO coefficients of the hypothetical formyl dienone (hydrogens instead of methyls). These clearly show (Fig. 7), that the transition state at the left in Fig. 6 incorporates larger stabilizing secondary orbital interactions than the one on the right. Other analogous examples are given.

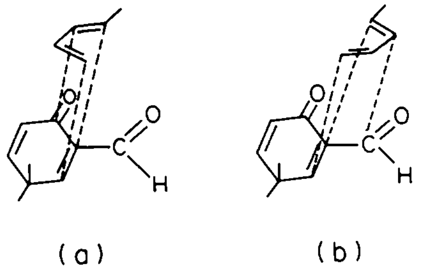


Fig. 6. (a) Transition state involving secondary orbital interactions between the ketone carbonyl carbon and the diene. (b) Transition state involving secondary orbital interactions between the aldehyde carbonyl carbon and the diene.

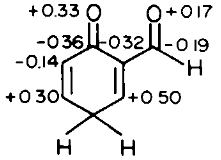
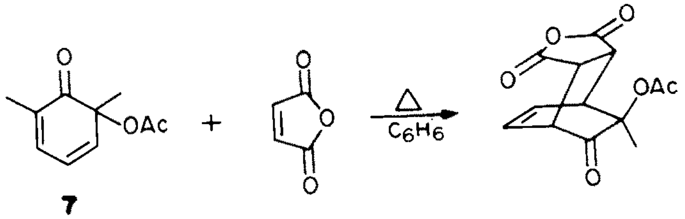
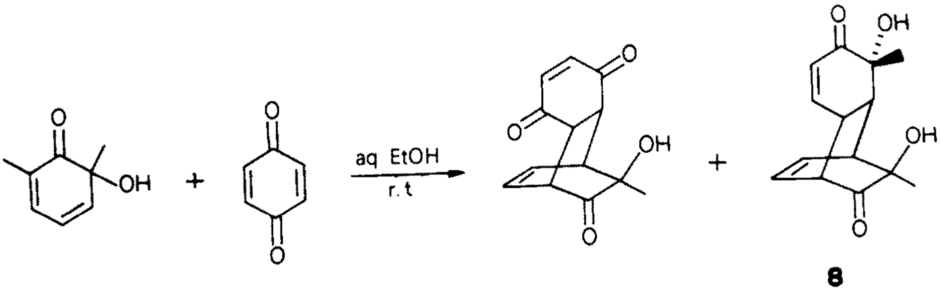


Fig. 7. LUMO coefficients of formyl dienone as determined by MINDO/3 calculations.



Scheme 12



Scheme 13

The stereochemistry and regiochemistry of the Diels–Alder reactions of 6-acetoxy-2,6-dimethyl-2,4-cyclohexadienone **7** has also been studied (Scheme 12) and a more conservative interpretation placed on the results.[65] A single adduct was obtained with maleic anhydride in boiling benzene, whose structure was established by analysis of NMR spectra of the product and some of its derivatives. Yates refers to similar stereoselectivity in the corresponding 6-hydroxy compound with *p*-benzoquinone[66] which also gives a single adduct accompanied, however, by a dimer **8** of the dienone and refers to previous interpretations of formation of *endo*-adducts in terms of secondary orbital overlap and closed-shell repulsion (Scheme 13). But he points out that the high stereoselectivity involves attack on that face of the dienone which bears the acetoxy or the hydroxy group. This may be interpreted in terms of a combination of steric, London–van der Waals and secondary orbital overlap factors. Indeed this conservative approach has much to say for itself. The assessment of the importance of these and of other factors is clearly difficult in general and also in this specific reaction. The variegated contrapuntal tapestry which may be woven in order to explain the course of a chemical reaction may be compared in complexity, if not in sheer sensual beauty, to the Bach B minor Mass. In its entirety it commands our awe for its apparent simplicity just as does the Fukui and Woodward–Hoffmann edifice which stands as the foundation of our modern explanations in this field.

Yates points out that the very much greater rate of dimerization of the 6-hydroxy-dienones as compared to their 6-acetoxy analogs, reflects both a reduced steric effect and enhanced secondary orbital overlap with the unshared electron pairs on the oxygen atom. Presumably, though a pictorial representation is not given, what is meant is shown in Fig. 8.

Dicyanoacetylene affords a mono-adduct with tetramethylfuran. Only one *bis*-adduct is obtained with a second mole of the diene, the *exo-endo*-adduct **9** (Scheme 14), owing to a secondary orbital interaction.[66] The *endo* approach in the transition state for formation of **9** is shown in Fig.

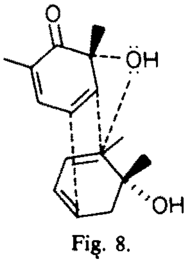
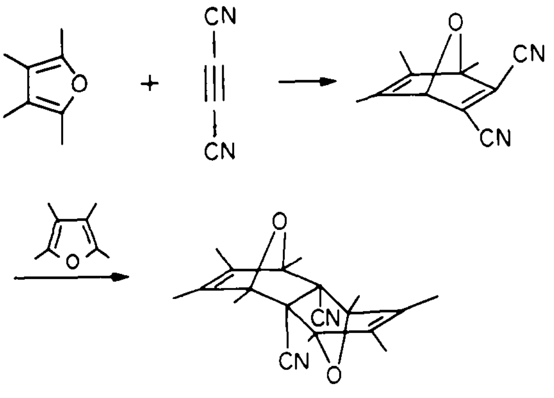


Fig. 8.



9

Scheme 14

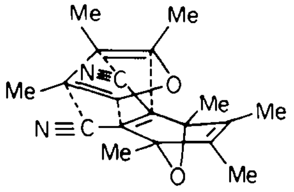


Fig. 9.

9. The furan approaches the mono-adduct from the less hindered side concomitantly avoiding oxygen–oxygen repulsion. The structure of **9** was confirmed by X-ray determination.

Although a full discussion of two recent communications is not possible, it ought to be mentioned that a suggestion has been made that though alkenes and carbonyls are normally planar, in cases where substituents are asymmetric with respect to the local symmetry plane of such unsaturated bonds, small but chemically significant pyramidalizations are caused.[68] The direction of pyramidalization is predictable when the alkenes are attacked by a nucleophile or by an electrophile. Evidently there is a relationship between this distortion and stereoselectivity of addition reactions. These ideas were then used to apply the *anti*-periplanar effect proposed by Felkin[69] (and treated theoretically by Anh[70] for nucleophilic addition to carbonyl groups) also to electrophilic and radical attacks on π systems. It is a large effect and influences both the stereoselectivity and reactivity of unsaturated compounds.[71] The authors proposed a general rule of stereoselectivity: "Attack of a reagent at an unsaturated site occurs such as to minimize antibonding secondary orbital interactions between the critical frontier molecular orbital of the reagent and those of the vicinal bonds". This rule affords the same predictions as the "orbital distortion rule"[72] but the new formulation attributes unequal orbital density on the two sides of an asymmetric π orbital to substituent orbital overlap with the π orbital whereas the earlier one[72] attributes this to sp mixing. Figure 10 gives an example of electrophilic attack of propene. The top drawing in Fig. 10 represents attack by an electrophile *syn*-periplanar to an allylic bond. Secondary

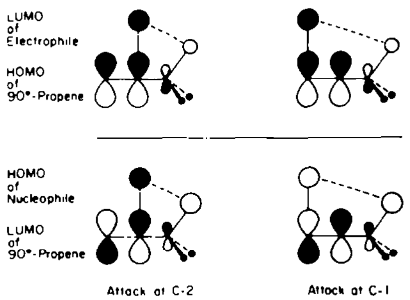
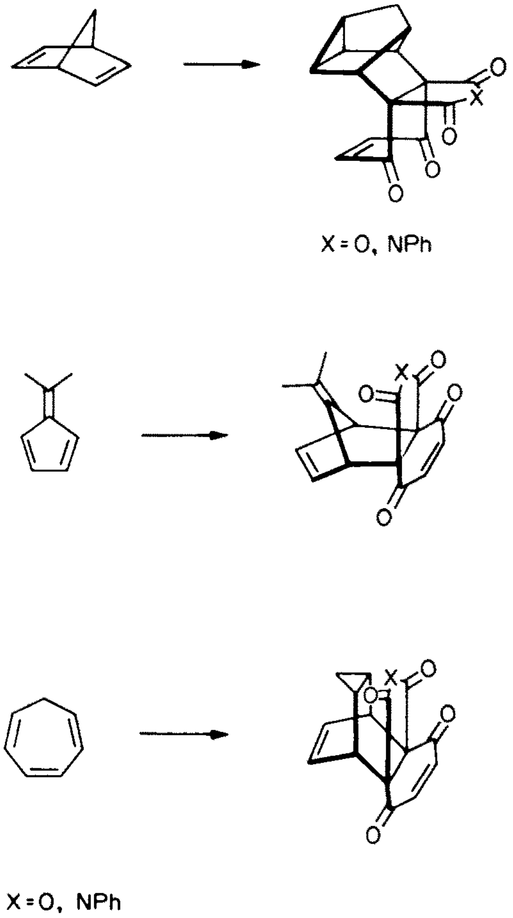


Fig. 10. Top: Interaction of the LUMO of an electrophile with the HOMO of 90° propene at C-2 and C-1. Bottom: Interaction of the HOMO of a nucleophile with the LUMO of 90° propene. Solid lines represent primary bonding interactions. Dashed lines represent secondary orbital interactions.

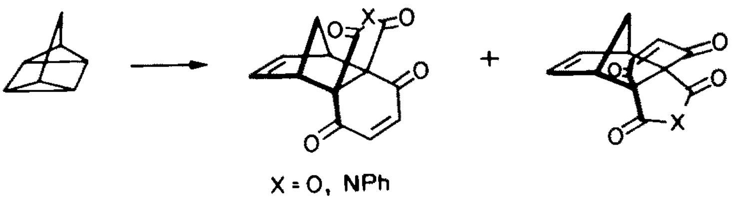
orbital interactions diminished HOMO–LUMO overlap in this case more than in *anti*-periplanar attack both at C-1 and at C-2. The lower drawings in Fig. 10 show that *syn*-periplanar nucleophilic attack is favored at C-1 but disfavored at C-2 due to secondary orbital interactions. Interaction of a radical SOMO with either HOMO or LUMO is stabilizing. Both favor *anti*-attack at C-2 but at C-1 they favor opposite configurations. Calculations for the reaction of 1,3-pentadiene with an H atom support the secondary orbital explanation. There is no steric preference for either C-1 or C-2 but attack at C-3 or C-4 of pentadiene is analogous to the results for attack at C-1 or at C-2 of propene.

p-Benzoquinone derivatives, the 2,3-anhydride and the 2,3-N-phenylimide were reactive towards electron-rich dienes and trienes such as norbornadiene, 6,6-dimethylfulvene and cycloheptatriene.[73] The *endo* 1:1 homo Diels–Alder products shown in Scheme 15 were formed exclusively. The LUMO's of the dienophiles have the highest coefficients at C-2 and C-3 and the propellanes are therefore formed regioselectively.

In the other cases the *endo* products were also obtained. The quadricyclane, however, gives the adducts shown in Scheme 16.



Scheme 15



Scheme 16

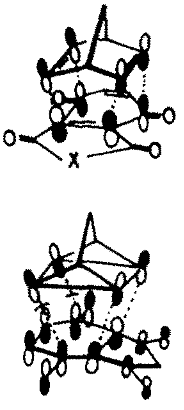
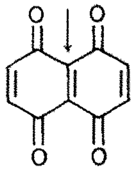


Fig. 11.

Figure 11 explicitly shows the secondary orbital interactions which explain the selectivities in the first and fourth examples.

This study was extended to that of 1,4,5,8-naphthodiquinone **10** and its 2,3-dichloro-derivative as well as to 1,4,9,10-anthradiquinone.[74] Reactions with electron-rich dienes again give propellanes by exclusive reaction with the internal double bond (e.g. arrow in **10**). This appears extraordinary in view of earlier results of the reaction of **10** with 1,3-butadiene in which case the disubstituted



10

double bonds reacted more readily than the tetrasubstituted one.[75] In the present example **10** reacted with cyclopentadiene, quadricyclane and anthracene at the central double bond, affording the propellanes in 95, 85 and 75% yield, respectively, with no further products reported in the experimental section (!). This is surprising despite the fact that the authors' calculations show the largest LUMO coefficients at the terminals of the internal double bond, just where it is required by the experimental results. Even if isomers or 2:1 and 3:1 adducts by reaction at the disubstituted double bonds had been isolated from the mother liquors, the yields of propellanes reported above are surprising even for a fan of secondary orbital interactions.

Kanematsu invoked secondary orbital interactions in frontier-controlled reactions of phenylcyclone with electron-rich dienophiles.[76] Spectroscopic evidence leads the authors to interpret the reaction as occurring via a charge transfer complex in the reaction mixture.

Figures 12 and 13 show the coefficients (MINDO/3) and possible transition states for the reaction of cyclopentadienone with methyl vinyl ether. The predominant formation of an *endo* [4 + 2] cycloadduct is attributed to a secondary orbital interaction (Fig. 13).

Thus, for example, phenylcyclone **11** and isobutyl vinyl either give the *endo* adduct in 75% yield (Scheme 17).

Roush[77] and White[78] have shown in intramolecular Diels–Alder reactions of acyclic dienes that both *endo* and *exo* adducts may be formed. In a Lewis acid catalyzed intramolecular reaction of

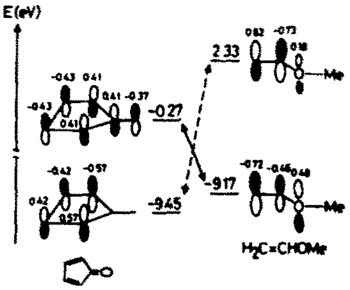


Fig. 12. Calculated FMO energies and coefficients by the MINDO/3 MO method.

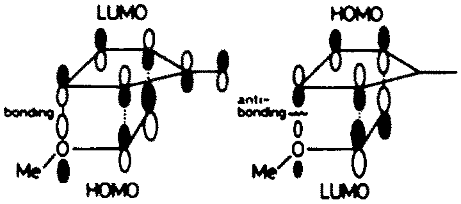
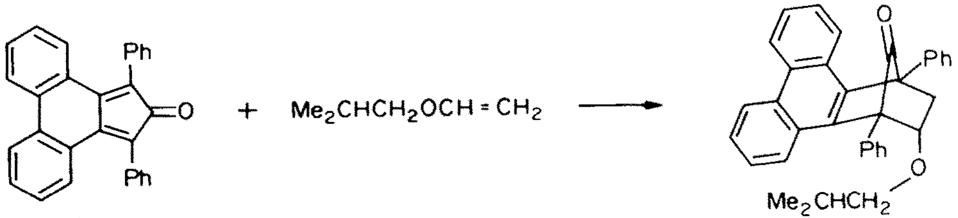


Fig. 13. Transition states in *endo*-addition.

this kind of terminally activated trienic esters the *endo* cycloadducts were formed preferentially.[79] This is explained by the increased secondary orbital interaction caused by Lewis acid activation.

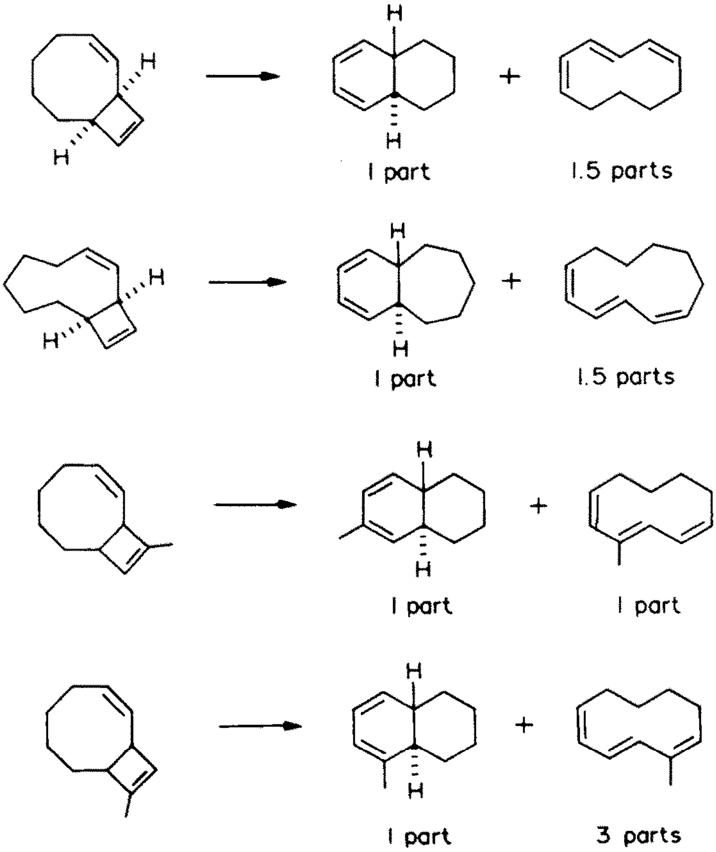
A beautiful study of orbital symmetry control in thermal valence isomerization of *cis*-fused bicyclic cyclobutenes has recently appeared.[79a] Subtle secondary orbital interactions have been invoked in evaluating the product distributions in the thermal reactions of several substrates shown in Scheme 18.

It is believed that these subtle interactions in the non-conjugated dienic substrates cause an orbital distortion in the π-system. The orbital topology obtained causes the σ framework to open in such a way that preferential overlap of the large centers of electron density occurs, affording a *cis*, *trans*, *cis* configuration of the double bonds (Fig. 14).



11

Scheme 17



Scheme 18

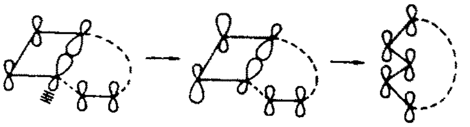


Fig. 14.

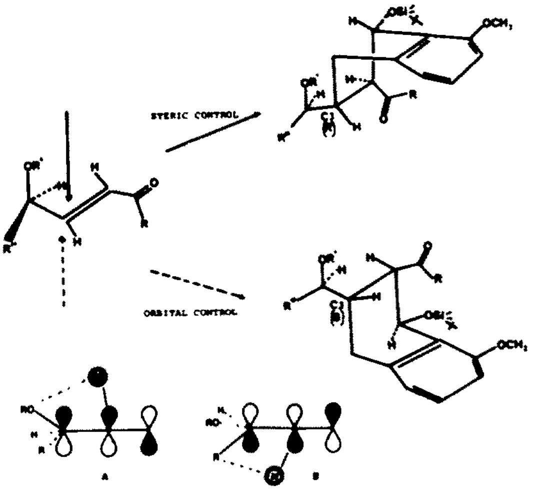


Fig. 15.

Another example of the Diels–Alder reaction of an acyclic dienophile, this time intermolecular,[80] successfully applied the stereoselectivity rule discussed above. The assumption was made in accord with the rule that the LUMO–HOMO interaction of a *syn*-alkoxy group in transition state A is more unfavorable than the *syn*-alkyl interaction in transition state B (Fig. 15).

The incoming group should therefore bond to the face opposite to the allylic oxygen function, i.e. to the si face, in order to minimize secondary orbital antibonding effects. In the event, the diene precursor **12** on heating gives **13** which reacts in a sealed tube with the sugar derivatives **14** or **15**. Two adducts were obtained, **16** and **17**, in a ratio of 4:1, respectively. NMR analysis suggested that *endo* control by the ester function had prevailed. X-ray structural determination of **18** showed that the major adduct indeed was of the *S*-configuration, and that addition had therefore indeed occurred on the si face of the dienophile (Scheme 19).

Mulzer has discussed the high diastereoselectivity in obtaining the *threo*-product as compared to the *erythro*-isomer in the system shown in Fig. 16. He had already reported on the reaction of preformed enolates with carbonyl compounds.[80a] Figure 16 shows the aldol addition of metallated carboxylic acids to aldehydes forming chelated aldol adducts. Two opposing effects, that of the metal template and a second order orbital interaction play a role, the latter more important than the former. We are indebted to Dr. Mulzer for Fig. 16 which indicates both effects and gives the *threo*/*erythro* product ratio for different metal cations.

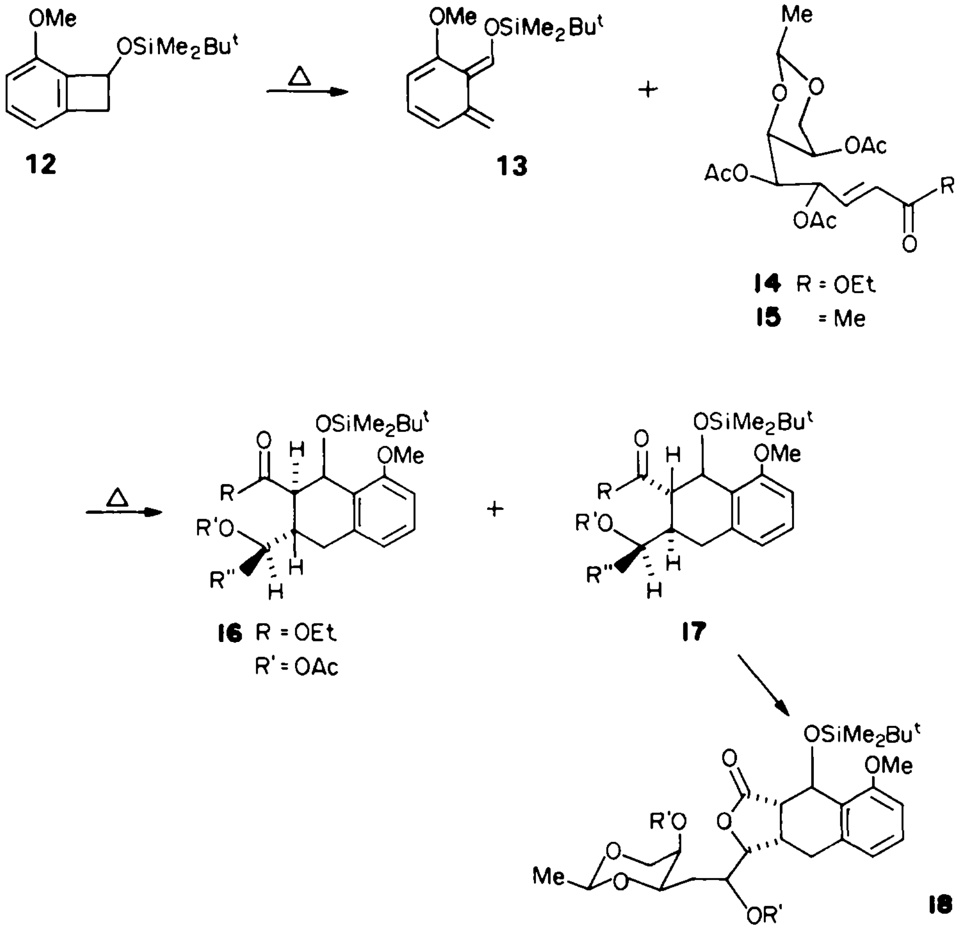
Mukaiyama has made the interesting observation when stereoselective synthesis of tricyclic compounds was studied using an intramolecular Diels–Alder pathway, that internal coordination with magnesium affords predominantly *exo*-cyclization leading to *trans*-fused cycloadducts.[80b] Magnesium salts of N-(2,4-alkadienyl)-N-(2-hydroxyphenyl)cyclopent-1-ene carboxamides, **19**, were employed (Scheme 20).

When there is no magnesium salt the *exo–endo* ratio approaches 1:1, somewhat favoring the *endo* isomer but when chelation is employed, the ratio varies from 88:12 to, at worst, 60:40, favoring the *exo* product.

The chelates are shown in Scheme 21. The *endo* chelate is more strained.

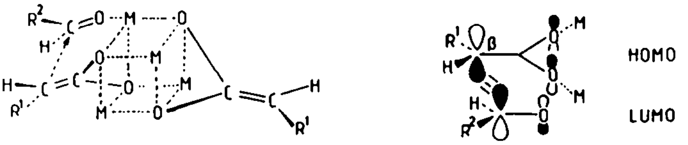
The template was employed to overcome secondary orbital control of the stereoselectivity. This discovery will, of course, be applied to further natural products synthesis.

One cannot help wondering whether the structure and packing arrangement of the 2:1 adduct of 9,10-diazaphenanthrene and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone is influenced by secondary orbital interactions within the crystal, three stacks being involved.[81] The packing mode is rather extraordinary. It consists of sheets of "dimerized" donors (diazaphenanthrene) which alternate with relatively flat layers of acceptor. The latter is thus enclosed in a "vise" formed by two nearly coplanar donors with the mean molecular planes of donor and acceptor being nearly perpendicular to one another. There are short contacts (2.85–2.92 Å) between the nitrogen atoms of the donor and the quinonoid ring of the acceptor, the charge transfer interaction is probably of the n-π^* type



Scheme 19

Cation-Effects and threo-Diastereoselectivity

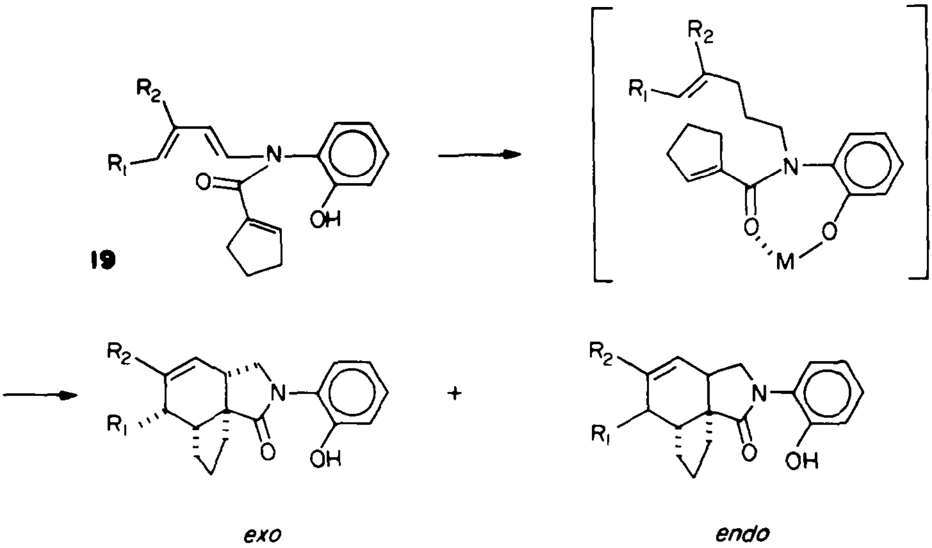


Template-Effect short O-M-distance: high threo-selectivity

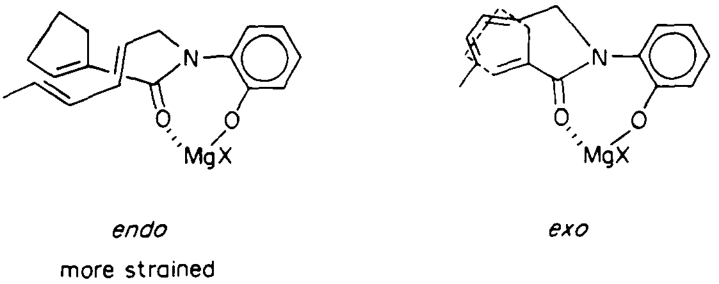
Frontier-Orbital-Effect: high c(β), high HOMO-energy high threo-selectivity

M	O-M-distance	covalent character of O-M-bond	HOMO-energy and c(β)	threo:erythro(R^1=Ph,R^2=tBu)
Mg	increases ↓	decreases ↓	increases ↓	52 : 48
Li				66 : 34
Na				79 : 21
K				86 : 14
K + 18-Crown-6				95 : 5

Fig. 16.



Scheme 20



Scheme 21

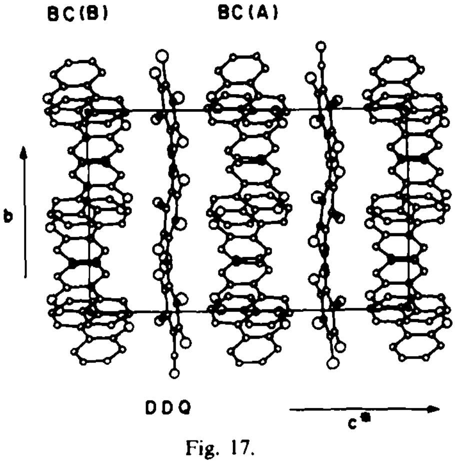
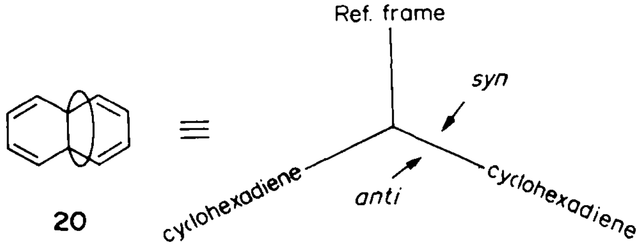


Fig. 17.

(reminiscent of the propellane cases discussed below).[121,124] This is a significant donor–acceptor interaction which may be due to the interactions shown in Fig. 17.

We were particularly struck with this crystal structure in view of our own work on secondary orbital interactions.

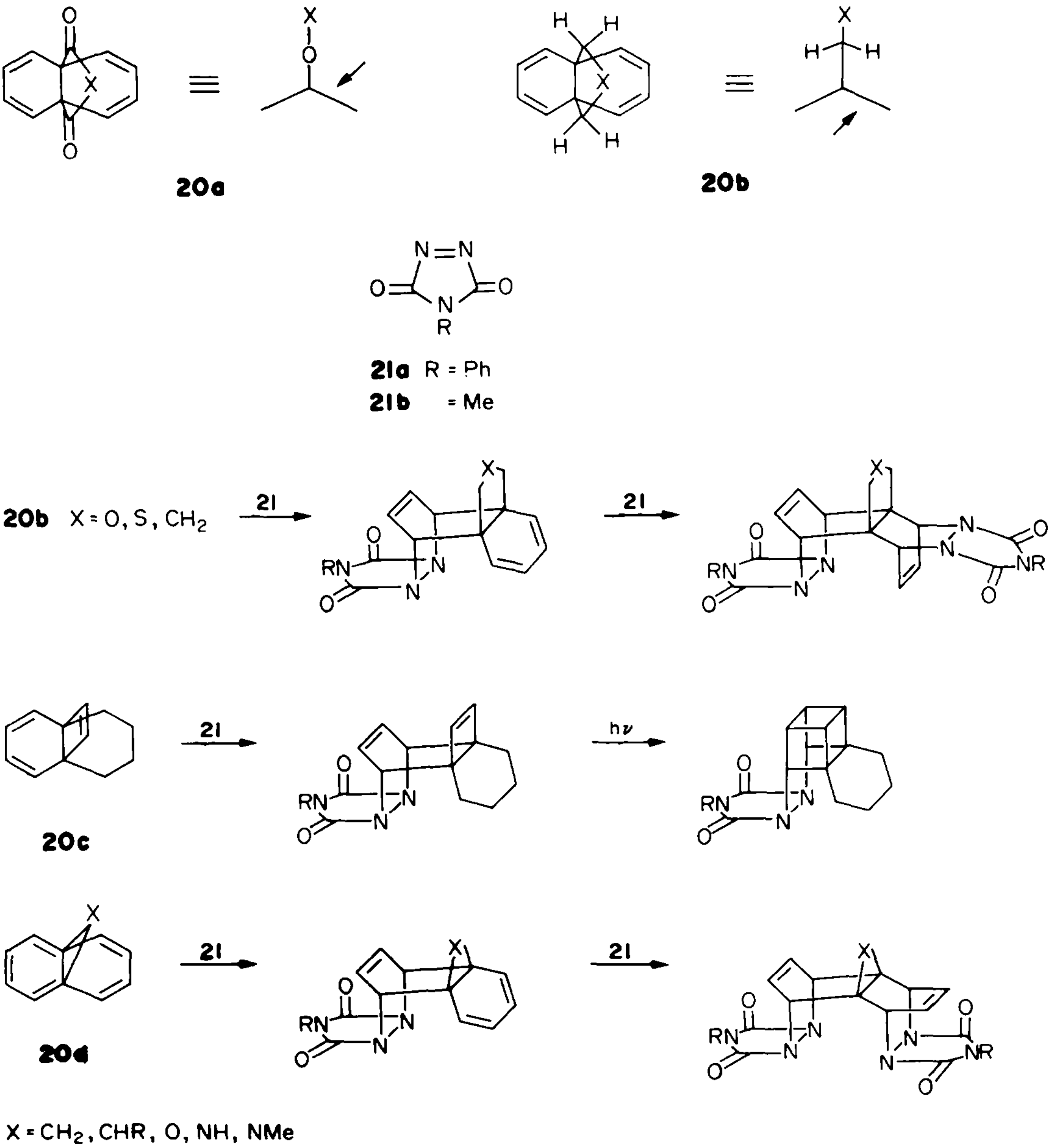
With the advent of propellanes,[82] substrates became available for the study of the Diels–Alder reaction, the likes of which had not previously existed. A compound of type **20**, having C_{2v} symmetry may react with a dienophile from either the side *syn* to the notional ring which serves as reference-frame for the two others, the latter being capable of such reaction, or from the side *anti* to it (Scheme 22).



20

Scheme 22

It turned out that compounds of type **20** reacted in accordance with the nature of the notional ring shown in its structure. Compounds having the structure **20a** gave Diels–Alder mono-adducts with 4-substituted-1,2,4-triazoline-3,5-diones **21**, resulting from (so far as it is possible to discern chemically) exclusive *syn* attack by these very reactive beautiful red dienophiles. On the other hand compounds **20b–d** (and others) afforded only *anti* mono-adducts. The reactions of the five-membered containing compounds of type **20b** have been reported in a number of papers;[83] [85a]



20a

20b

21a R = Ph
21b = Me

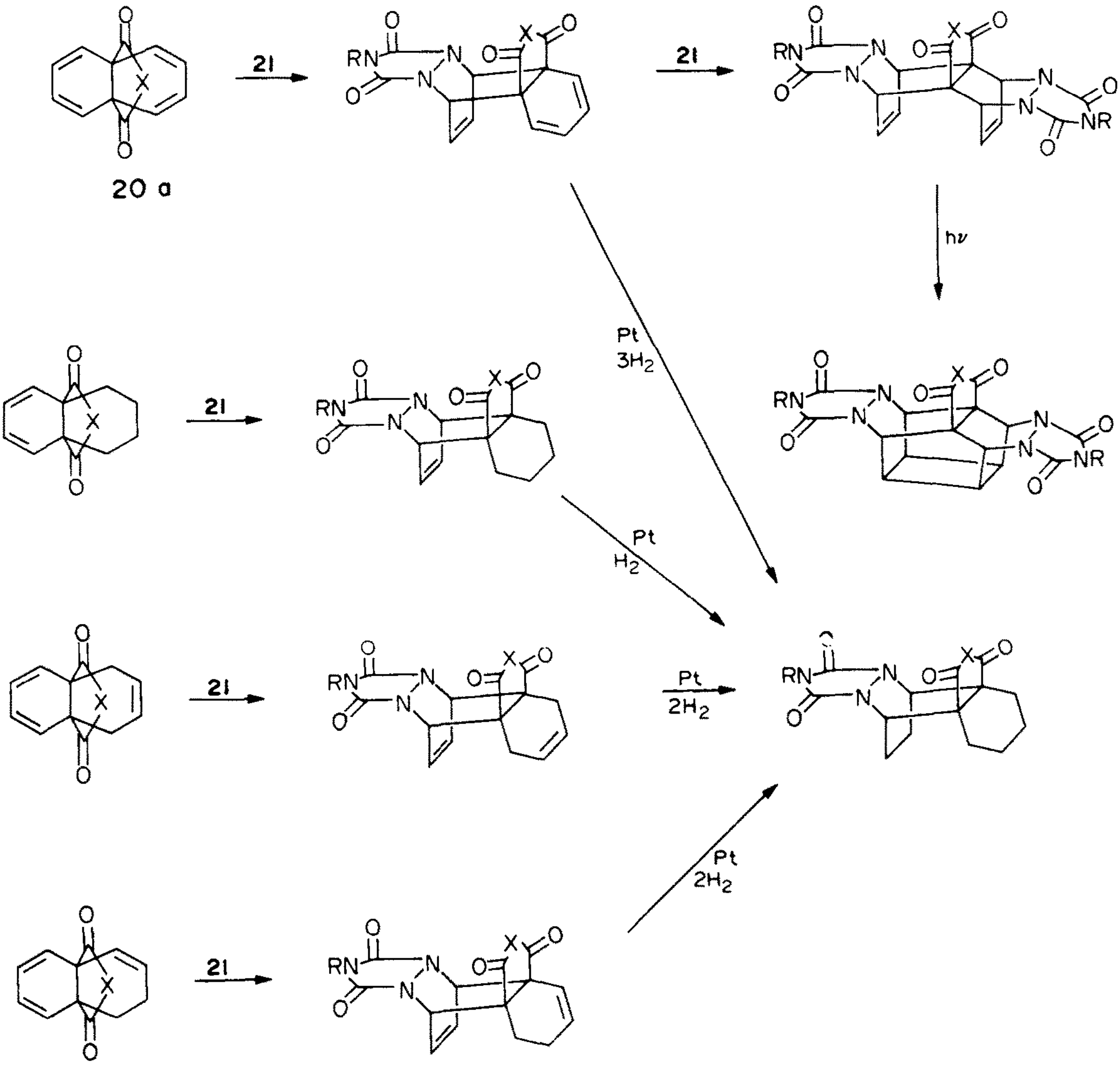
20b X = O, S, CH$_2$

20c

20d

X = CH$_2$, CHR, O, NH, NMe

Scheme 23



Scheme 24

four membered ring containing compounds of type **20c** have been correlated [85b] and a series of papers has been published regarding the bridged [10] annules of type **20d**.[86] Scheme 23 shows that **20b** give an *anti-syn-bis*-adduct, so do the tetraenic cyclobutane-containing propellanes of type **20c** and several other propellanes[85b] but the bridged annulenes of type **20d** give *anti-anti-bis*-adducts.[86]

All of the propellanes of type **20a** give a *syn-syn-bis*-adduct as may be seen in Scheme 24. In many cases the tetraenic propellane behavior has been correlated with that of the corresponding diene and triene(s) of the same family (same X; Scheme 24).

Since we could never isolate even a small amount of isomeric adduct in each of the above cases, this apparently absolute stereoselectivity required explication; the yields of *syn-* or *anti*-mono adduct, as the case may be, were always nigh quantitative for the examples **20a–c**. It is not surprising that **20d** often gave only a *bis*-adduct for the cyclohexadienic mono-adduct being a diene reacts much faster than its aromatic precursor. Nevertheless it was sometimes possible to isolate the mono-adduct.[86] Perhaps, had we been Swiss, we might have been able to isolate a second mono-adduct in negligible yield, but we nevertheless doubt it. (Tetraenic propellanes of C_{2v} symmetry, of course, may in principle give two mono-adducts, the *syn* and the *anti* isomers.)

We have explained the behavior of **20b–d** by invoking steric grounds whether at the stage of mono-adduct formation or the *bis*-adduct formation.[87]

But we have invoked the secondary orbital interactions shown in Fig. 18 to explain the attraction that the dienophile finds on the *syn* side of substrates of type **20a**. This attractive

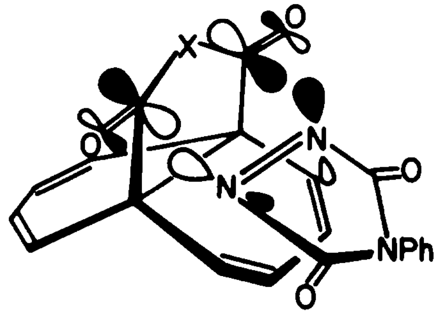


Fig. 18.

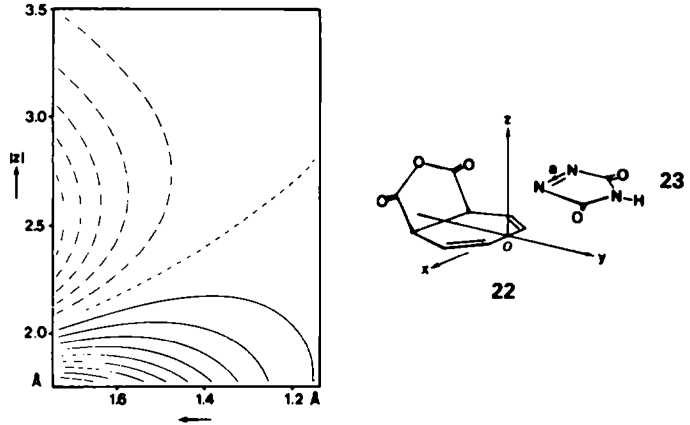


Fig. 19. Contour diagram of the EH potential surface for the addition of **23** to **22**. The contours are drawn every 0.2 eV and represent the difference in energy between *syn*-addition (+ z) to the anhydride group and *anti* (− z) to it. The broken lines correspond to situations where *syn*-addition is favored; the full lines indicate *anti*-addition.

interaction between the π^* orbitals (LUMO) of the carbonyls in the reference-ring and the n_--antisymmetric combination of nitrogen lone pair orbitals stabilizes the *syn* transition state for dienophile attack at the *syn* cyclohexadiene face rather than at the *anti* face which is preferred only when the dienophile encounters the repulsive *millieu* at the *syn* faces of substrates **20b–d**. Part of the potential surface for the reaction of the models **22** with unsubstituted triazolinedione **23** was investigated by the EH method. Fig. 19 shows the energy difference map for *syn* approach of **23** to the plane of the butadiene moiety along the + z axis and the *anti* approach along the − z axis. The y component of the O-a vector is given along the abscissa.[87b,c]

The calculation suggests overall attraction in the region between $y = -1.1$ Å and $z = +1.75 - 2.0$ Å. In principle we must consider the primary interaction between the HOMO of the butadiene moiety with π^* of **23** and a secondary orbital interaction between the π system of

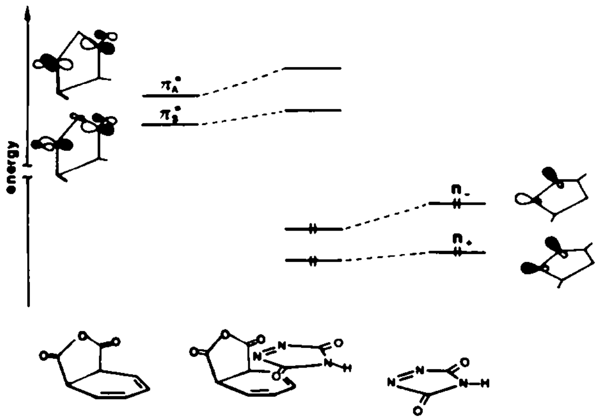
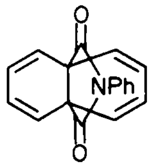
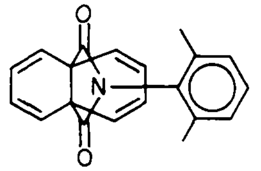


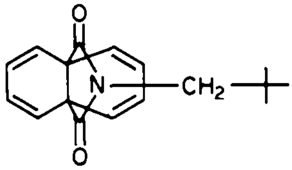
Fig. 20. Qualitative interaction diagram for the *syn*-approach of **23** to **22**. Only the interaction between lone pairs on nitrogens in **23** and π^* carbonyl orbitals is shown. The interaction between π orbitals of carbonyls and the n orbitals in **23** is omitted.



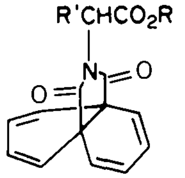
20a X = NPh



X = 2, 6-dimethylphenyl



X = neopentyl

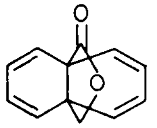


X = N − CHR'CO_2R

22 and the n orbitals of the nitrogens in **23**. The former clearly exists when **23** approaches from either cyclohexadiene face but the second effect is only present in *syn* attack. Figure 20 shows the interaction between the nitrogen lone pairs and the π^* orbitals of the two carbonyls. A strong interaction exists between n_- and π^*_A, stabilizing the transiton state for *syn* approach.

Various experiments were conducted in order to support or deny this thesis. We superimposed a steric factor upon the electronic (secondary orbital interaction) one in the hope that less *syn* attack would occur and more concomitant *anti* attack would occur. Thus, for **20a**, X = NPh we still could discern no *anti* mono-adduct but for the cases where X = N-neopentyl, or N-2,6-dimethylphenyl, N–CHR'CO_2R where R' > H and R = Me or isobornyl, respective mixtures of syn and *anti* mono adducts were indeed obtained. It roughly appears that the larger the effect of steric repulsion superimposed on the electronic one, the more *anti* product is present in the *syn-anti* mixture.[88]

We studied the tetraenic lactone **24** in its reaction with triazolinediones.[89] Consider this within the context of the corresponding anhydride **20a**, X = 0 and the corresponding ether **20b**, X = 0.

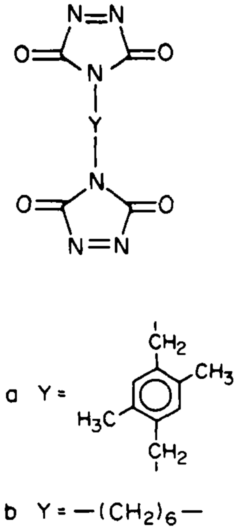


24

It may be viewed as intermediate between the anhydride (which gives only *syn* attack) and the ether (which gives only *anti* attack). It is as though we have exchanged one carbonyl of the anhydride for a methylene group, i.e. we have superimposed the steric effect of two hydrogens upon the electronic effect of the carbonyl. Indeed here too we obtained a *ca* 1 : 1 mixture of the *syn* and *anti* mono-adducts of **24**.

A story is told about Napoleon riding *en route* to Paris at the head of his (for once) bedraggled army returning from the disastrous Russian campaign. Nevertheless, as they passed through each small French village the churchbells rang; in all but one! M. le Maire hastened to greet his Emperor and said: "M. l'Empereur, there are 72 reasons why our churchbells do not ring; firstly, our church has no bells . . .". If we apply the moral to the case at hand, we may compare the behavior of 4-methyl- or 4-phenyltriazolinedione to N-methyl- or N-phenylmaleimide in which it appears that the N=N bond has been exchanged for a CH=CH double bond. The maleimides react with **20a** type compounds from the *anti* side in contradistinction to the triazolinediones which attack from the *syn* side.[90] The maleimides do not have churchbells, they do not have lone pairs on the double bond carbon atoms. Repulsive steric interaction at the *syn* side causes reaction to occur on the *anti* side. The triazolinediones have churchbells in the form of nitrogen lone pairs which cause the secondary orbital interaction with the carbonyl groups of **20a** followed by *syn* attack.

The most exciting case of apparent secondary orbital interactions controlling the course of reaction stem from the use of "double" triazolinediones **25**. Four substrates of type **20a** (X = O, NH, NMe, NPh) reacted with **25**, affording cyclic oligomers containing the two substrates in ratios of 3 : 3, 4 : 4; 5 : 5; 6 : 6; 7 : 7; 8 : 8.[91] Irradiation of these (the 4 : 4 compound **26** serves to illustrate this point) affords the products of [2 + 2] photocycloaddition, e.g. **86** in this case, proving that all of the dienophile molecules can discriminate and react with the *syn* face of the cyclohexadiene rings in the propellanes. All of the vinylic protons of **26** disppear and are replaced by cyclobutyl protons in **27**.



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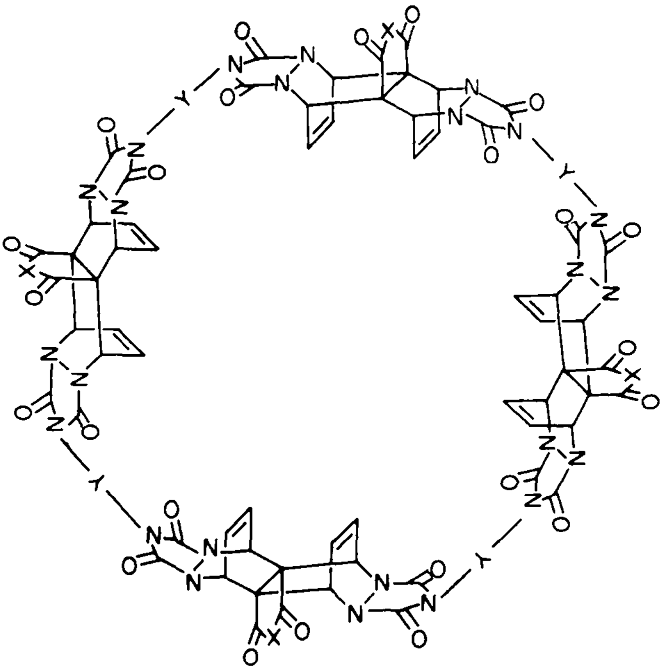
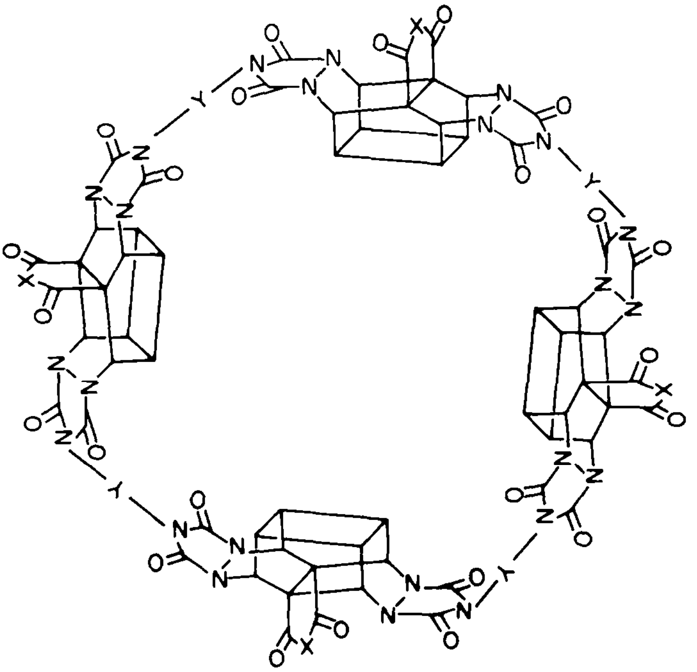


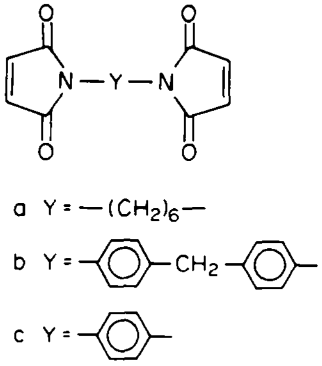
26 X = O, NH, NMe, NPh; Y as in **25**



27 X as in **26**; Y as in **25**

As stated above maleimides attack **20a** from the *anti* side.[90] It is therefore not surprising that **20a**, X = NMe reacts with **28**, a "double" maleimide to afford the 2:1 product **29**. This then with **25** gives the cyclic [4 + 2 + 2] oligomer **30**.[92]

Singlet oxygen which is also able to interact in an antisymmetric manner with propellanes of type **20a**, X = O, NMe (see **31**), indeed attacks these from the *syn* side, **20b**, X = O from the *anti* side and the lactone **24** from both sides. The compounds obtained in each series were correlated and their structures proved.[93]



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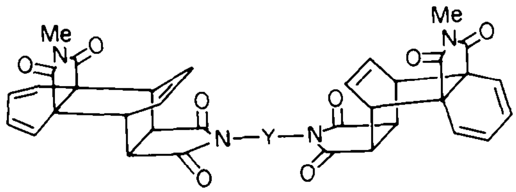
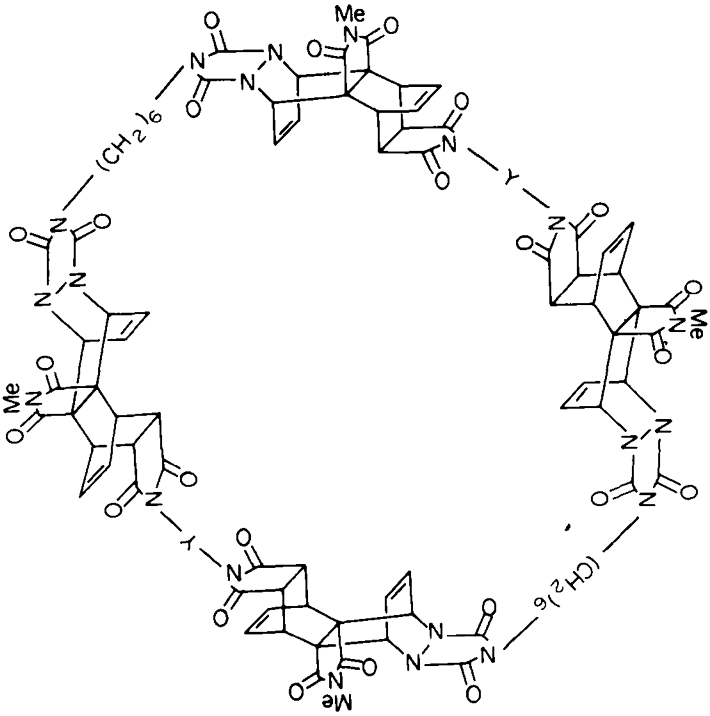
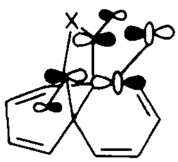


29 Y as in **28**



30 Y as in **28**



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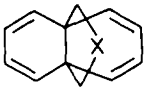
It has been calculated that such a secondary orbital interaction may be worth 4–6 kcal/mol in lowering the activation energy of the reaction from the *syn* side.[87c] Böhm and Gleiter have also calculated that when the *syn* transition state is formed and stabilized by the abovementioned secondary orbital interaction, variation of the angle α shows that there is a minimum at $\alpha = 35°$ (choosing varying parameters for the y and z distances). This minimum corresponds to the most effective possible overlap between the p orbitals of the dienophile and of the cyclohexadiene which then undergo the [4 + 2] cycloaddition on the *syn* side.[87c]

Finally, in the propellane story, it should be mentioned that although in **20b**, X = S, attack is on the *anti* side but when the corresponding sulfone is used (**20b**, X = SO_2), attack is 97% *syn* and 2% *anti*. The *syn* attack in this case cannot be justified by a secondary orbital interaction nor can that of the sulfoxide (**20b**, X = SO) which gives a more complex mixture of *syn* and *anti* products because of the lesser symmetry of the sulfoxide group as compared to the sulfone.[94] The behavior of these substrates has been explained in terms of polar group effects.

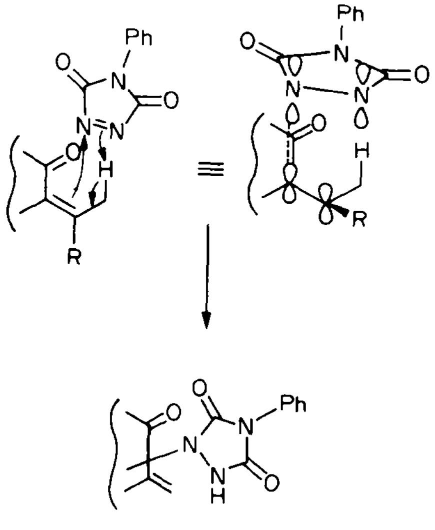


20b X = SO, SO_2

It is rationalized as due to a stabilizing Coulomb attraction between the strongly deficient S atom in the SO and SO_2 group and the electron-rich –N = N-group in the dienophile. In addition one must consider the area of high electron density around the oxygen centers of the SO_2 group and the charge deficient region on each side of the π plane of the dienophile.[3,87]

Instead of adding further modulations we have carried out in the propellane framework in connection with operation or non-operation of secondary orbital interactions with the dieniophile, I shall discuss a somewhat related case, in that it involves PTAD, albeit in a reaction with an α,β-unsaturated ketone.[95] Both groups invoke secondary orbital interactions "between the PTAD imidic O=C–N unit and the enone carbonyl group" to account for the very high regioselectivity in the reaction [95a] or "between the carbonyl group of the enone and the carbonyl-nitrogen system of the PTAD"[95b] when the s-*cis* conformation of the enone **32** is involved. The interactions described are not identical with those invoked in carbonyl-containing propellanes. If the authors had noted the propellane work, they may perhaps have formulated the interactions more in keeping with those. As may be seen, a formulation is given involving p-orbitals on the nitrogen (Scheme 25).

Human beings are by their natures prejudiced. Although we feel that the propellane substrates of type **20a** constitute a beautiful example in which secondary orbital interactions control the



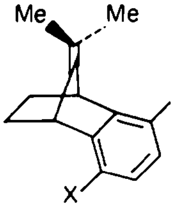
Scheme 25

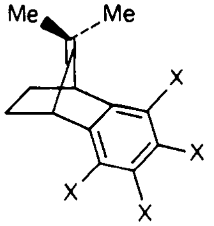
regiospecificity of the reaction course, we must, since we are human beings, be humble. Thus although we cry our belief from the rooftops, we know that in contradistinction to a rigorous proof of structure a mechanism or an interpretation can never be rigorously proven. And since God always knows better, perhaps He also knows of a better alternative interpretation than the one that we have given.

Paquette *et al.* have published a growing series of papers in which Gleiter and Böhm have become involved and which appears to be a much more complex example of secondary orbital interaction control of the steric course of reactions. The substrates incorporate dienic units adjacent to various σ-frameworks.

Paquette has found that in compounds **33a** and **33b** singlet oxygen attacks predominantly from the direction *anti* to the methylene bridge whereas in **34a** and **34b** the stereoselectivity is appreciably reversed.[96] Thus the variability in the stereoselectivity cannot be due to a steric effect but is presumed to be electronic.

33a X = H
33b = OMe





34a X = F
34b = Cl

The predominant *anti* addition for **33** was explained in terms of a large coefficient for the wave function at the *exo*-methylene group. Considerable mixing with a high lying σ orbital distorts the π-orbital so that overlap with one approaching from the *anti* side is favored (Fig. 21).

But when electron-withdrawing halogens are present (**34**), the more dominant factor results from reduced electron density above and below the aromatic ring. Calculation of the electrostatic fields shows that there are indeed intensely positive regions there and a transition state for electrophilic attack gains added stabilization when singlet oxygen comes from the *syn* side. N-Bromosuccinimide and N-methyltriazolinedione also afford more *syn* attack for **34a** and **b**. Peracids with olefins show less propensity for the formation of charge-separated transition states and indeed attack both **33** and **34** mainly from the *anti* direction.[96]

This was the start of the Paquette–Gleiter collaboration attempting to sort out the predominant factors responsible for stereoselectivity of attack in compounds having a σ-framework.

The second paper in the series[97] reported that exclusively *syn*-attack occurs on acetylation of **33a**, **33b** and **34b** with $CH_3COCl/AlCl_3$ at − 10° in CH_2Cl_2 or with $Ac_2O/ZnCl_2$ at r.t. They undergo the Prins reaction with similar stereoselectivity. *t*-Butyl hypochlorite with **33a** gives 85% *anti* attack in methyl formate solution but admixture with formic acid the yield of the *syn*-isomer increases to 42% or even to 80% when a 1:1 mixture of the solvents is used. Similar trends were observed for **33b** and **34b**. This is attributed not merely to a solvent effect but to increased protonation (so

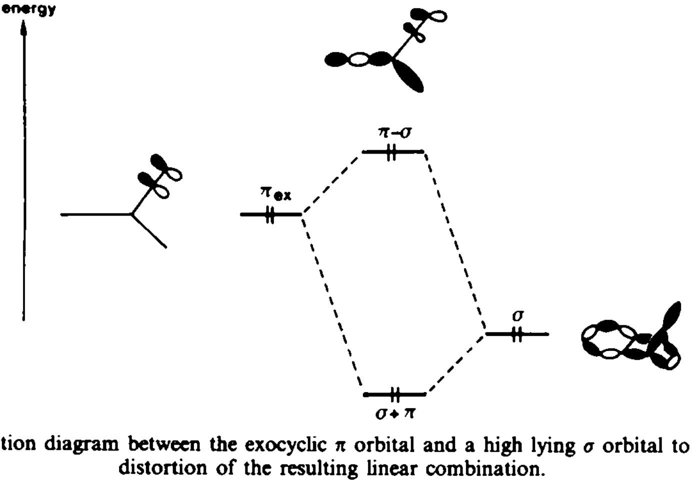
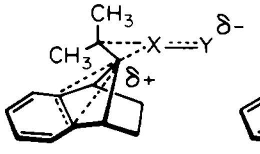


Fig. 21. Interaction diagram between the exocyclic π orbital and a high lying σ orbital to visualize the distortion of the resulting linear combination.

that the attacking species is a protonated hypochlorite) rather than to determination of electrophilicity, i.e. whether the electrophilic reagent needs assistance from the π-bond for adequate polarization (**35**) or for disengagement from its anionic component (**36**). If so, an *anti* sterically congested transition state forms, which is electronically favored and kinetically preferred. If π-bond assistance is not necessary due to increased electrophilicity, steric factors and thus *syn* attack, predominate.



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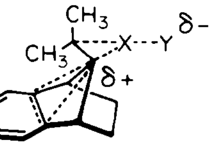

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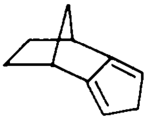
In the next paper of the series[98b] Paquette ties in with Bartlett's work on sesquinorbornenes and that of Vogel (see below). Substrates **37**–**39** were investigated. The first two give with methyl acrylate in sealed tubes at 42° *anti-exo* adducts (with respect to the methylene bridge), **40** and **41** as exclusive products (94 and 88%, respectively). Earlier work [98a] had shown *syn* preference of **23** for methyl acrylate and methyl propiolate and both steric and electronic factors were discussed in explaining the results.



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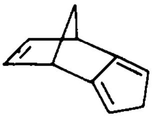

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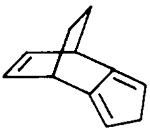

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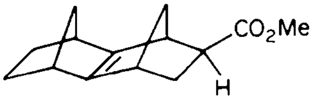
Methyl propiolate added analogously but maleic anhydride with **37** gave a mixture of *anti-exo* **42** and *anti-endo* **43** isomers as a 2:1 mixture. With **38** it gave exclusively the *syn* adduct.



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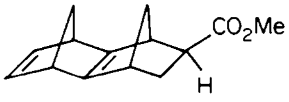

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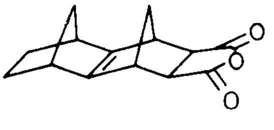

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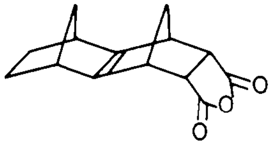

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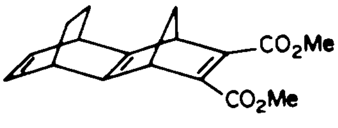
p-Benzoquinone and MTAD afforded only one *syn* adduct with both **37** and **38**, as does phenyl vinyl sulfone.

After all this stereoselectivity, **39** with an ethano bridge gives an *anti* (14%)-*syn* (86%) mixture, **44** and **45** with dimethyl acetylenedicarboxylate. Benzyne behaves analogously: *anti* (·19%)-*syn* (81%). These results are rationalized in the full paper,[99] in terms of σ-orbital mixing with the π_s



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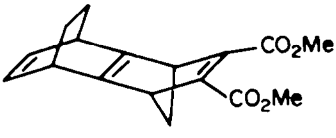


45

diene orbital. Such interactions serve to tilt the diene orbitals in a disrotatory manner, resulting in minimization of the level of antibonding interaction on the *anti* face of **37** and of **38** as compared to the *syn* face. Calculations were made on the simpler model systems **46** and **47**.

46

47

The results of the calculations were compared to the corresponding photoelectron spectral data. HOMO (π_A) of these compounds don't interact significantly with the σ frame. The π_s orbital of the butadiene moiety, however, admixes substantially with it. The terminal atom π lobes move in disrotatory fashion enhancing electron density *syn* to the CH_2 bridge while the π orbitals of the central butadiene atoms rotate in the opposite manner (Fig. 22). The rotation leads to significant differences in electron distribution on the *syn* and *anti* sides. One would predict that for **46** and **47** a dienophile would add *anti* to the bridge because the destabilizing interactions between π_s of the butadiene moiety and the HOMO of the dienophile is smaller for *anti* attack than for *syn* attack (Fig. 23).

Figure 22 shows the rotation of the terminal p_x-lobes for π_s of **46**. This rotation leads to significant differences in electron distribution on the *syn* and *anti* sides. The precise sequencing of π_s (above or below) with respect to σ_s is crucial. MINDO/3 differs from the other methods in

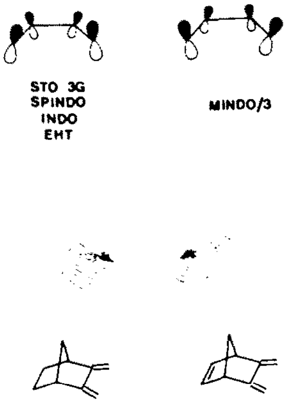


Fig. 22. Top: Schematic representation of the π_s orbital in **46** and **47** obtained by the indicated methods (left) and the MINDO/3 method (right). Bottom: Contour diagram for **46** showing the deformation of the two terminal π-lobes.

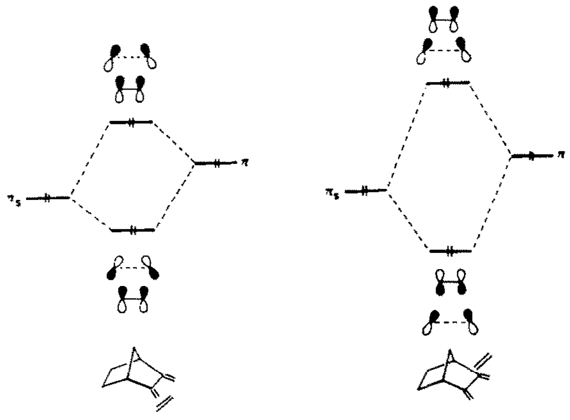
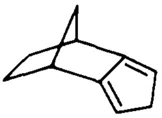
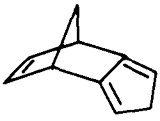


Fig. 23. Qualitative diagram of the interaction between π_s of the butadiene unit of **46** and **47** and a π bond. Left: The situation of the approach of the ethylene *anti* to the methylene group. Right: Corresponding *syn* approach.

predicting the rotation. It gives a result opposed to that predicted by the other methods. Fortunately, reliability of the calculations may be checked against the pertinent PE spectra. As in **37** and **38**, the π/σ interaction encountered in **46** and **47**, leads to an enhancement of the amplitudes *syn* to the CH_2 bridge.

In their review Gleiter and Böhm[3] give a table which shows the four electron destabilization energies ΔE_{ij} for **37** and **38**.[3]





	37	**38**
ΔE_{ij}^{exo}[kcal/mol]	9.9	7.0
ΔE_{ij}^{endo}[kcal/mol]	5.45	4.0
$\Delta\Delta E_{ij}$[kcal/mol]	4.5	3.0

Clearly *anti* attack is favored. The relatively large energy differences explain why only the *anti*-product is obtained.

The authors mention Anh's alternative rationalization[29] with which they do not agree.

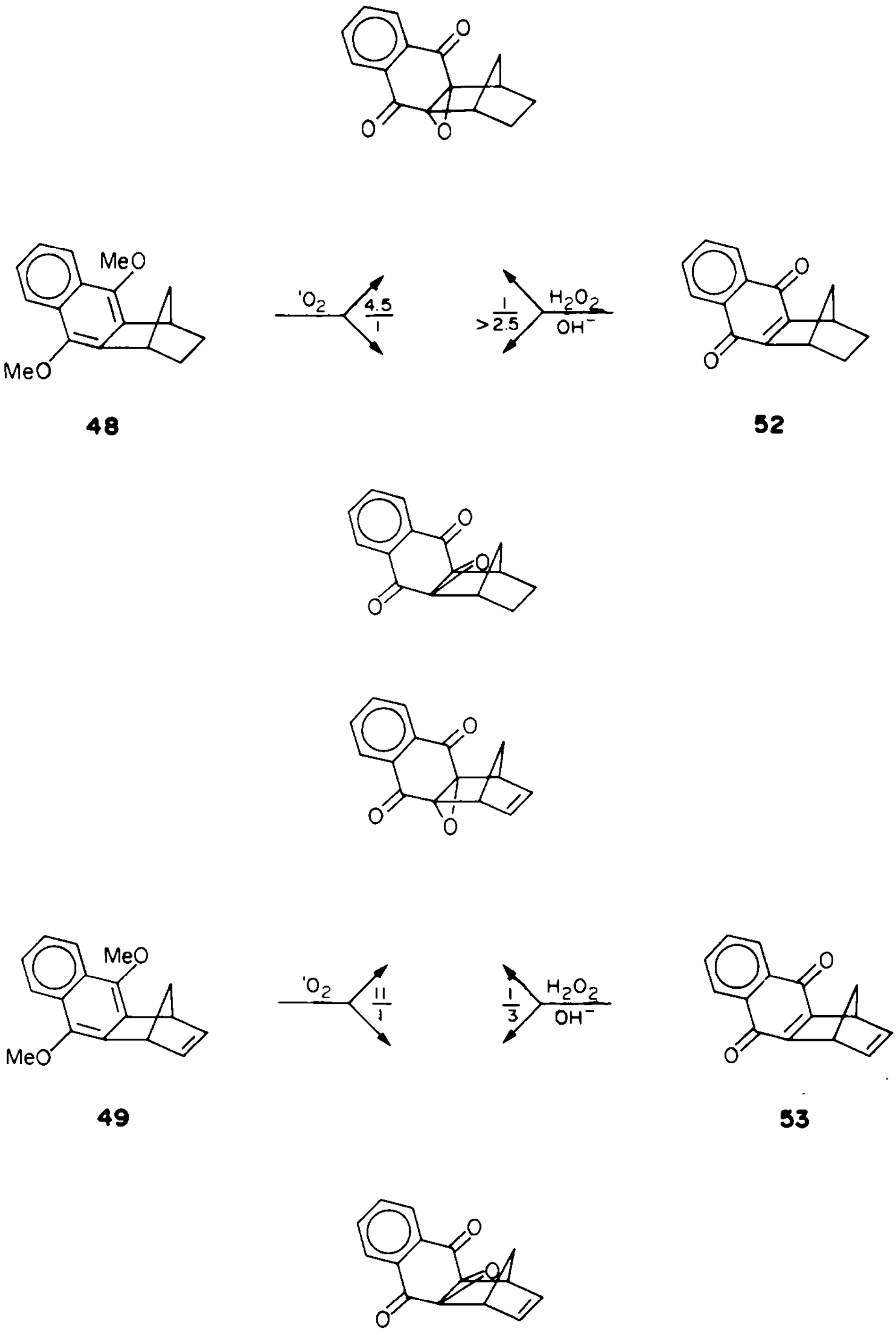
Singlet oxygen reactions of **37** and **38** proceed with only moderate stereoselectivity in favor of *anti* attack,[100] in contrast to the behavior described above for other dienophiles. This is attributed to energetic factors arising from the ionization potential of $^1O_2$ (16.12 eV) which differ considerably from the $\pi_1(s)$ energies of normal dienophiles (10.5–11.5 eV) and the $\pi_1(s)$ energies of the diene substrates (9.6–10.0 eV). I cannot agree with this explanation, for in another case, when $^1O_2$ attacks propellanes of differing structure it is capable of discriminating whether to attack a *syn* or an *anti* face of a cyclohexadiene, or both faces, depending upon the specific nature of the propellane (see above).[93]

Another paper employs substrates **48–51** in reactions with $^1O_2$ and **52–55** in oxidation reactions with H_2O_2.[101] The results are summarized in Scheme 26. π-Interactions with the σ frameworks are used to rationalize the results which, as may be seen in the scheme, are still not consistently all that stereoselective, again in contradistinction to the propellane reactions with $^1O_2$, instigated by Prof. Gleiter, which paid splendid dividends.

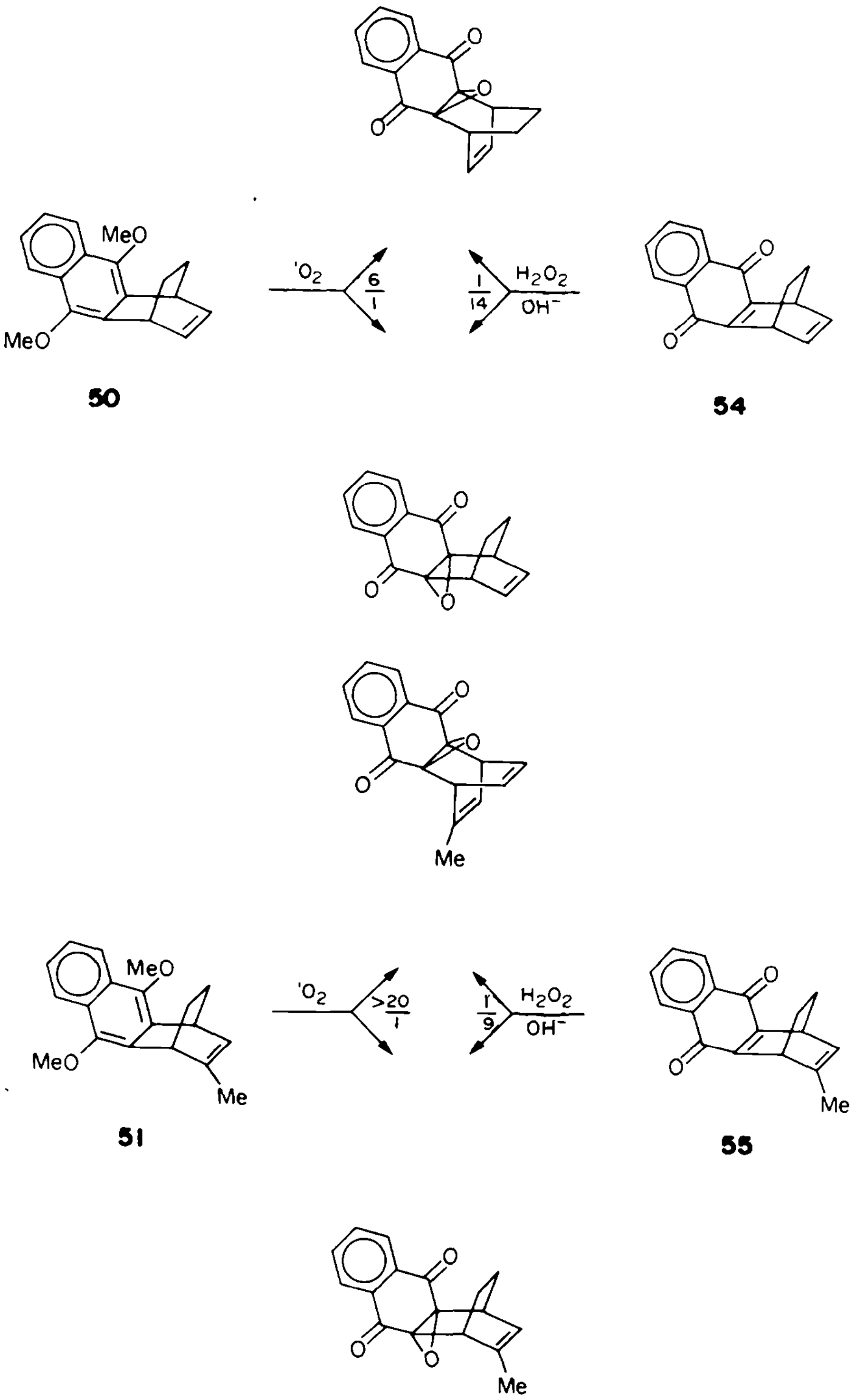
The seventh paper in the series[102] returns to substrates **37–39**, this time in reactions with MTAD. Here preference is overwhelmingly in favor of *anti* attack. The strain in the bicyclic system is transmitted and is recognized at more distant sites in the respective cyclopentadiene rings but this time **39** behaves similarly to **37** and **38** (*anti* rather than *syn* to the ethano bridge of **39**). Jacobson, in 1973, reported on the Diels–Alder reactions of *cis*-9,10-dihydronaphthalene **56** and its related derivatives **57** and **58** with PTAD, TCNE and diethyl fumarate, all of which are attacked from the less hindered face.[103] The selectivity was attributed to steric effects with secondary orbital interactions not being considered important. In the present paper,[102] the origin of the stereoselectivity is not yet completely understood though it resides in the "heretofore incompletely appreciated electronic character of strained bicyclic frameworks".

Next, a paper appeared on electrophilic additions to aryl-substituted 9-isopropylidenebenzonorbornenes.[104] The substrates **59–62** were tested for their behavior with $^1O_2$, *m*-CPBA, NBS, MTAD and TBH (*t*-butyl hypochlorite). Product distributions of all of these reactions favored *anti* addition for **59** and **60** but as in the earlier cases **33a** and **33b** vis-à-vis **34**, also **61** and **62** exhibit a reversal and *syn* attack either is favored or predominates. The explanation, similar to the one given for **33** vs **34**, invokes formation of bridged ions with the weak electrolytes, development of long range homoaromatic charge delocalization for the aromatic ring, causing consequent *anti* attack to dominate kinetically (**63**). With more powerful electrophiles this phenomenon is unimportant and transient aryl-complex formation appears to be the controlling factor. The latter operates through an "open ion" such as **64**.

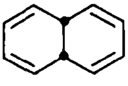
The *syn-anti* stereoselectivity is less impressive in electrophilic attack of aryl substituted benzobicyclo[2.2.2]octadienes.[105] The *syn* product is usually preferred in contrast with the



Scheme 26



Scheme 27



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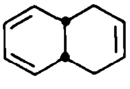
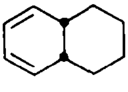
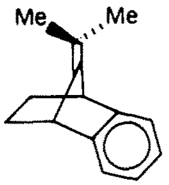


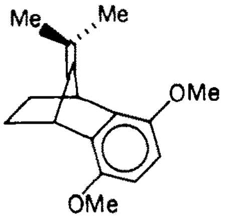
57



58



59



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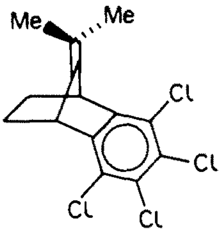

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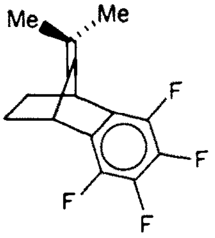
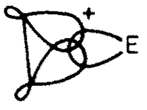
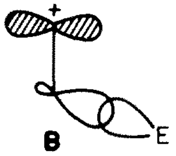


62



A

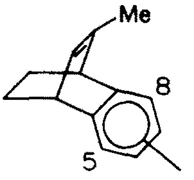
63



B

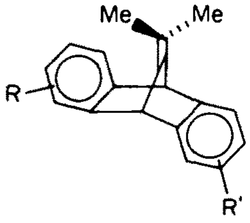
64

9-isopropylidenebenzonorbornenes. The substrates were of type **65**. The cause for this reversal of stereoselectivity is not clear.



65 R = H; 5,8-di-OMe; 5,6,7,8-tetra F

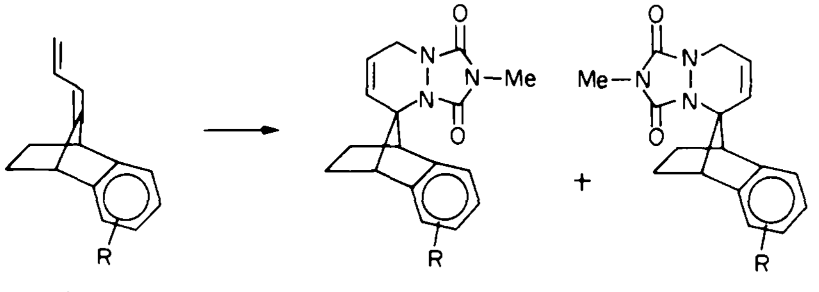
It appears to be that the substrates confronted in the tenth paper of the series are typical of the optimism which has led Prof. Paquette to many successes for the modulations are relatively subtle. 11-Isopropylidenedibenzonorbornadienes **66** were employed in which each of the aromatic



66

rings carried different functional groups. The authors have deduced that *syn-anti* ratios for epoxidation correlate well with the relative abilities of the two competing aromatic rings to participate in homoaromatic charge delocalization. With strong electrophiles (Friedel–Crafts and Prins reactions), these cases too fit in with the interaction of π complexes.

The long range modulation of stereoselectivity in Diels–Alder reactions with MTAD was studied with 9-butadienylidenebenzonorbornenes, **67**, yielding **68** and **69**, in varying ratios.[106]

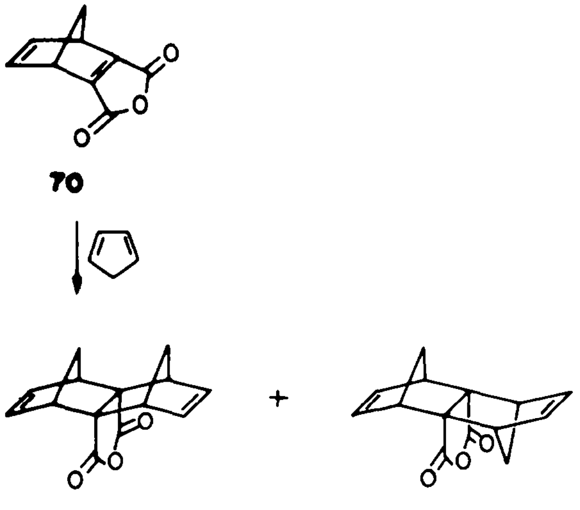


67 **68** **69**

Bartlett[107] cited previous work with respect to norbornadiene-2,3-dicarboxylic anhydride **70** which gives **71** and **72** in the ratio shown (Scheme 28).[108] But Bartlett showed that for norbornene-2,3-dicarboxylic anhydride (the disubstituted double bond missing from **70**), the corresponding ratio is 3:2 rather than 60:1. These sets of adducts were correlated through hydrogenation. Thus a double bond remote from the scene of action in **70** has an influence reminiscent of Paquette's abovementioned findings. But it is not surprising that Bartlett with his tradition for painstaking work and wary interpretation says that such a double bond "would not be expected to be effective in either a polar (secondary orbital interactions?—my comment!) or a steric sense. Work is continuing on this problem".

Bartlett explained the preferred attack on the *syn* side of *syn*-sesquinorbornene **73** (i.e. *syn* to the methano bridges and *anti* to the ethano bridges) on simple steric grounds. Also in the light-initiated acetone addition the *syn* adduct **74** was the exclusive product. Excited triplet acetone presumably transfers energy to **73** and in two successive captures of hydrogen from the solvent, the *anti-anti* dihydro-compound **75** is also formed.[109] Scheme 29 details the proposed mechanism.

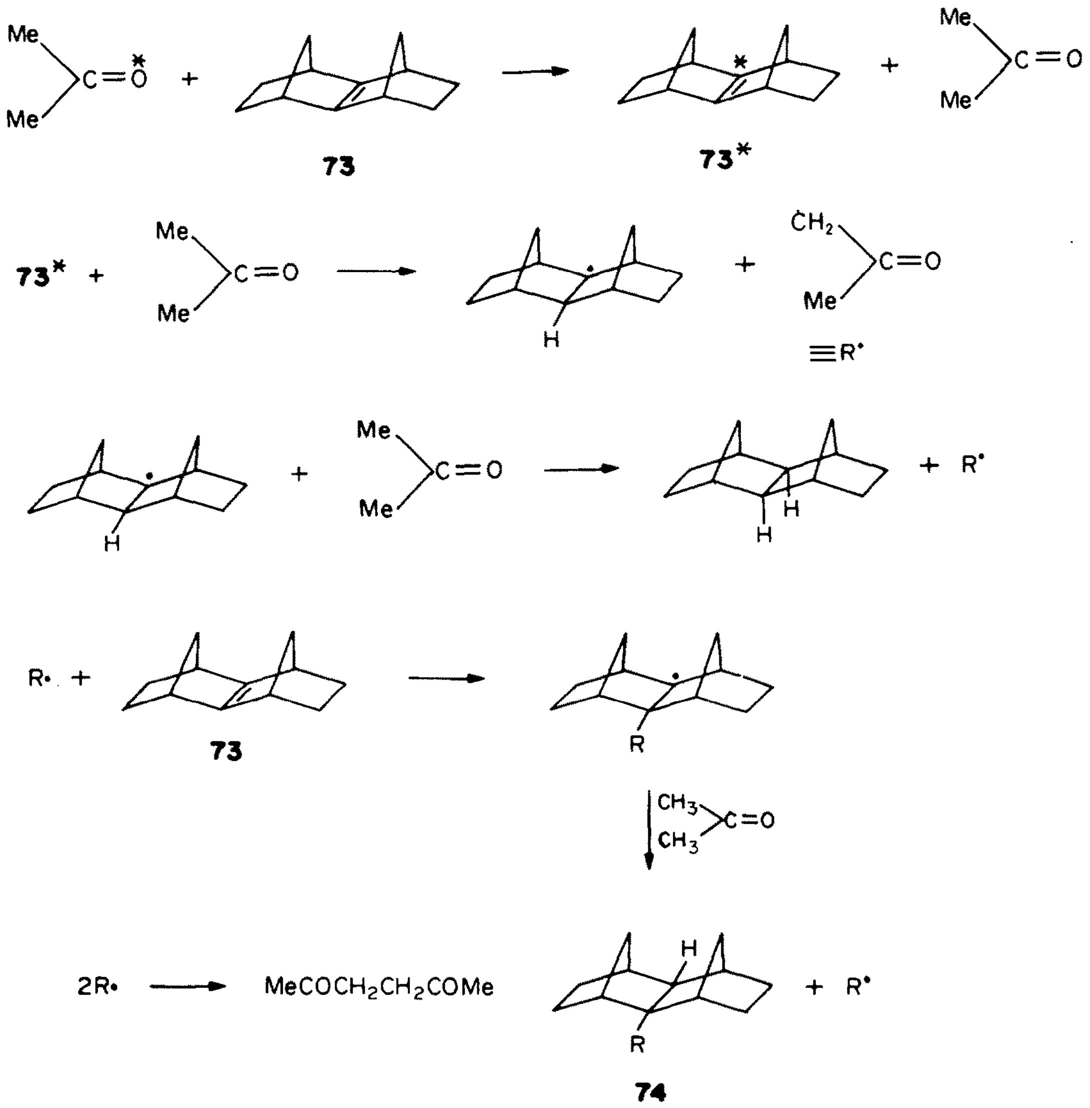
Gleiter[110] points out in a discussion of the ground and excited states of *syn*-sesquinorbornene **73** that given that a reduction of hyperconjugative interactions is the driving force for the observed ground state bend in these compounds, it may then be understood why NDO methods fail to predict this. Hyperconjugation involves interaction between filled π and σ orbitals and constitutes a net destabilizing effect. But repulsion between closed shells in a second order overlap effect isn't reproduced by NDO methods. The simple EH model based on explicit treatment of orbital overlap is therefore superior to the more sophisticated NDO method.



70

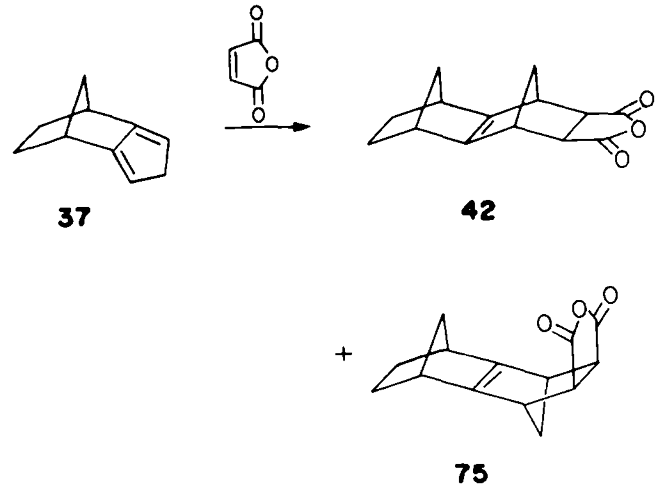
71 (1%) **72** (60-70%)

Scheme 28

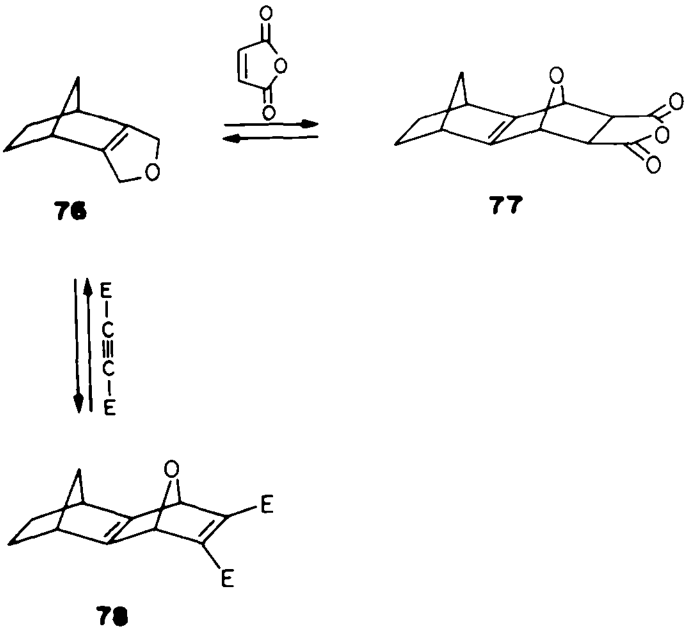


Scheme 29

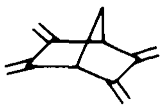
A paper has been submitted with respect to maleic anhydride addition to **37** in which **42** and **75** were formed in ratios of 55:45 to 35:65 depending upon temperature and solvent (Scheme 30).[111a] P. Vogel[111b] (Scheme 31) showed that the furan analog **76** with maleic anhydride and MDAD gave **77** and **78**, respectively. These are both *anti* adducts with respect to the methylene bridge. No trace of any isomer of each could be detected. The authors[111b] use the oxygen atom originating in the furan as the frame of reference and attribute the stability of the *syn*-oxasesquinorbornenes **77** and **78** with respect to the *anti*-oxa isomers (reverse position of anhydride and oxygen bridge and the maleate moiety and the oxygen bridge in **77** and in **78**, respectively), to a "synergic" effect of the polarization of the double bond π-electron density on the "*exo*" face of the norbornene (I have used "syn" terminology for this face, *syn* to the methylene bridge) and oxanorbornene moiety joined by the same double bond. "The kinetic *endo* (I have used "*anti*", with respect to the CH_2 bridge) stereoselectivity leading to **63** and **64** is parallel to the thermodynamic stereoselectivity." The message is loud, if not clear. P. Vogel does not believe the Paquette–Gleiter explanation of secondary orbital interaction control in these systems. Such resistance may be expected from a man stemming from a long line of independent vintners who produce fine Vaudois wines. I have found six more papers on this subject which have appeared prior to the time of writing this Report. The first has to do with the reactions of 2,3,5,6,-tetramethylidinenorbornane **79** and its 7-oxa analog **80** with TCNE.[112] Both reacted much faster than did their corresponding mono-adducts (364 and 375 times faster at 25°, respectively).



Scheme 30



Scheme 31



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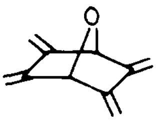

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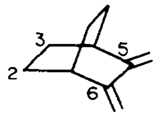


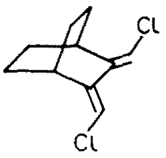
81

The next substrates compared to these were of the **71** type, substituted at the 2- and 2,3-positions.[113] The reactivity differences were not large on an absolute scale but are significant considering that the skeleton is similar and that remote effects are involved. There still appears to be a weak interaction between the homoconjugated olefinic chromophores and the Diels–Alder reactivity.

Additions of several new substrates of this type were examined.[114] The corresponding 2-norbornanone was "para" regioselective in its reactions with methyl propiolate and methyl vinyl ketone. The 2-bicyclo[2.2.2]octanone exhibited smaller "para"-regioselectivity. No regioselectivity was observed in the 2-*exo*-norbornanol, the 2-*exo*-acetate and the 2-*exo*-bicyclo[2.2.2]octanol.

Unpredictable "para" and "meta" stereoselectivities were found for the *endo*-norbornanol and its acetate and the corresponding 2-*endo*-bicyclo[2.2.2]octanol. Such geometric factors and steric factors should not *a priori* play a dominant role in determining the regioselectivities because the exocyclic s-*cis*-butadienes are grafted on rigid skeletons. The substitution is remote. If dipole–dipole (hard) interactions between the reactants were dominant, "para"-regioselectivity should have been expected for *all* of the reactions! Obviously other factors are taking part, e.g. hydrogen bonding OH ... ester in alcohols, charge transfer AcO ... C=O, etc. I should have thought that some of these factors might have been termed by others as "secondary orbital interactions" but the authors explain their results for the 5,6-dimethylidene-2-norbornanone by the hyperconjugative interactions $n(CO)/\sigma[C_1, C_2]/\pi[C_5, C_6]$ overriding the usual electron withdrawing effect $\pi^*(CO)/\pi[C_5, C_6]$ interactions. The other cases are not explained.

In the next paper of the series,[115] P. Vogel reviewed (before me!) the subtle factors that appear to influence regioselectivity in cycloadditions with the substrates discussed above in his work and in that of Paquette. Amen! as to their subtlety. Thus various bicyclo[2.2.2]octane derivatives were examined (**82–87**), and different behavior of different substrates is still manifest.



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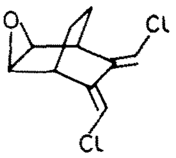

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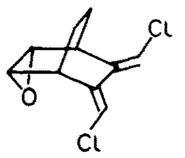

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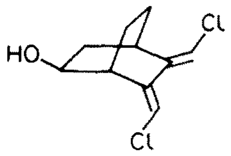

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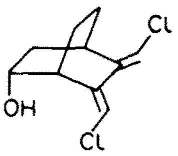

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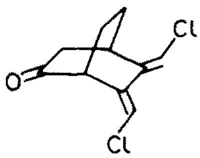


87

In a later paper concerning Diels–Alder reactions of 7-oxabicyclo[2.2.1]heptanes,[116] P. Vogel lists five factors which play a role in the face selectivity of cycloadditions upon the bicyclic substrates discussed heretofore: (1) steric hindrance; (2) differential dipole effects and (3) polarizability effects of the O-7 and C-5, C-6 bridges on the Diels–Alder transition; (4) π-anisotropy due to diene-O-7 interactions; (5) coordination (formation of charge transfer complexes) of the dienophiles by O-7. Still there is no explicit mention of secondary orbital interactions; perhaps fair enough since this is only one amongst, indeed, many factors. Rates of photooxidation of these substrates have been measured.[117] They correlate with the rates of the corresponding Diels–Alder reactions.

There are further interesting and exciting studies, not yet published by Paquette in this connection, which I have in preprint form.[118-125] I shall not detail this material but should like to quote several operational sentences from them: "Without question, the general relationship between electronic perturbation and stereoselection requires considerable additional study. For the present at least, the deductions arrived at here serve as a useful guide for predicting the possible influence on stereoselection which variations in the bridge segments of bicyclic moieties fused to exocyclic 1,3-dienes might induce".[119]

Paquette has his own list of "at least five phenomena that could seriously becloud the overall influence of electronic factors". These are: (1) possibility that the cycloadditions are reversible; (2) steric factors; (3) possible intervention of weak π complexes; (4) changes in transition state timing may not be a sensitive probe of subjacent orbital tilting effects; (5) a parallelism exists between kinetic and thermodynamic control as the result of fortuitous adherence to the Bell–Evans–Polanyi principle.

In short, though the Vogel and Paquette lists are not identical (so that even more than five factors may be involved) more work will have to be done with these substrates before secondary orbital interaction control will be generally accepted.

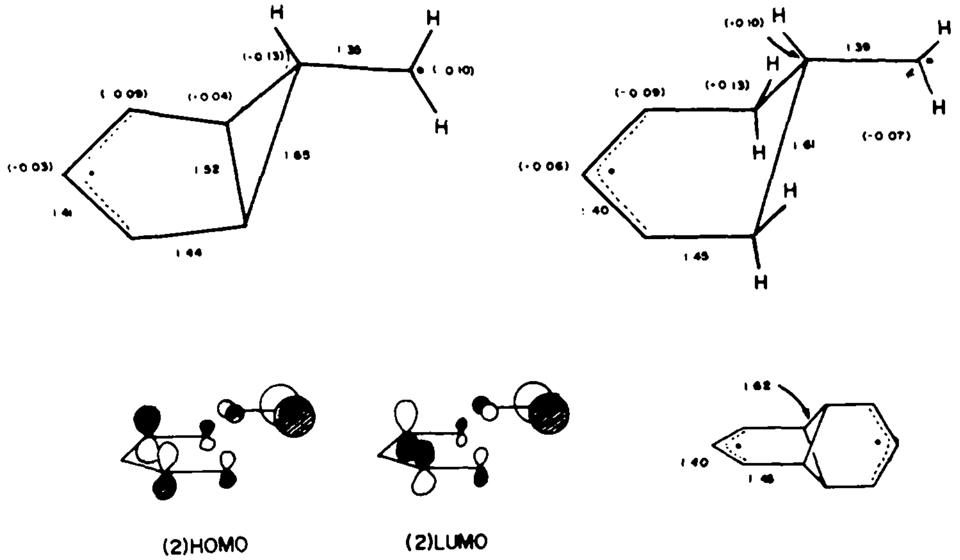
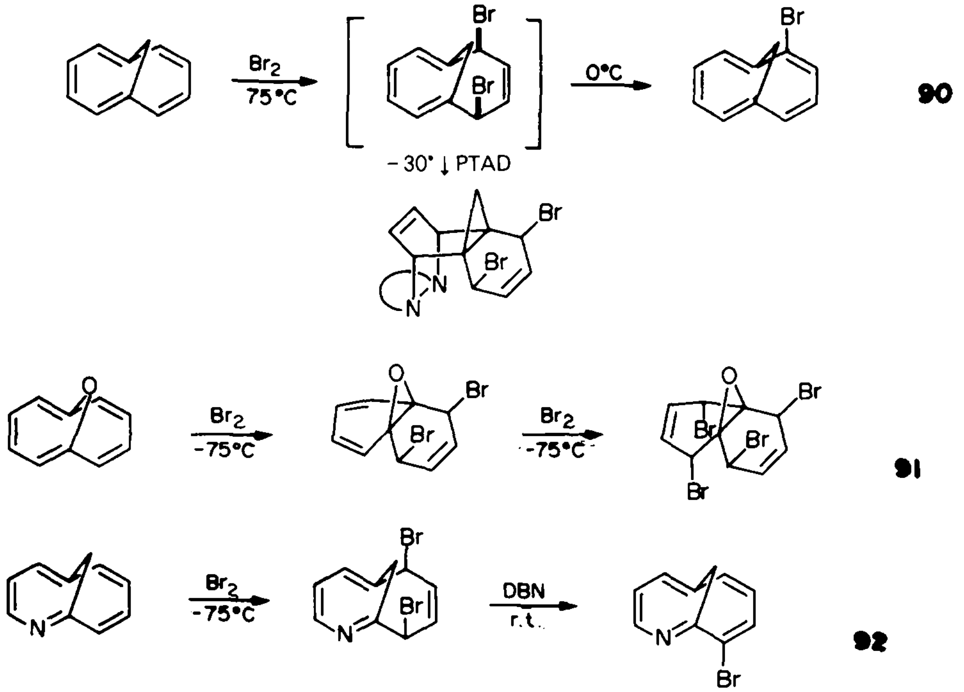


Fig. 24. The formula on the left is **88**, on the right is **89**.

Alder and Grimme[126] discussed 1,5-sigmatropic shifts of vinyl and related groups which occur by a mechanism in which σ-bond making is almost complete before bond breaking begins. MINDO/3 calculations were performed on several cyclopentadienes and on the C_s transition state or intermediate which is the mid-point in their 1,5-shift. Figure 24 shows that the HOMO and LUMO for **88** and **89** are antisymmetric with respect to the symmetry plane and this treatment may be reconciled with the attribution of the substrate behavior to secondary orbital interactions. In these rearrangements formation of the new σ-at the expense of π bonding is the major process occurring *en route* to the transition state. The authors cite several other papers explaining sigmatropic shifts in terms of secondary orbital interactions.[127-129]

Gleiter invokes a second order orbital interaction to explain E. Vogel's extraordinary results of bromination of 1,6-methano[10]annulene, **90**,[130] and of 1,6-oxa[10]annulene, **91** (Scheme 32).[131] The same holds for 2,7-methano-1-aza[10]annulene, **92**.[131]



Scheme 32

I think it is worthwhile borrowing a summary from Prof. Gleiter's recent manuscript.[3]

There are first order orbital interactions—in phase relations between the atomic orbitals where the bonds are made.

There are *second order orbital interactions* which may be subdivided into *secondary orbital interactions* (which have been the main theme herein but which could not be discussed *in vacuo*; they are emphasized along with the further effects in this subdivision), *substituent effects*, and *polar group effects*.

I believe that secondary orbital interactions are indeed important in determining the course of various chemical reactions. Sometimes these are masked by other factors which also influence the reaction course. I anticipate that in the near future my belief will be supported by a growing body of evidence and hope that this Report may be instrumental in catalyzing such growth.

Acknowledgements—I am indebted to Dr. Pnina Ashkenazi for making available to me her collection of reprints concerning secondary orbital interactions. I have learned much in this field from Prof. Dr. R. Gleiter. Collaboration with him since the inception of our work described herein began at the Minerva-Sponsored 1974 Elmau meeting, and has provided throughout a source of inspiration. I am also indebted to him and to Prof. Leo A. Paquette for frank criticism of the manuscript. I am grateful to Prof. Dr. H. A. Staab for providing Abraham-like hospitality at the Max-Planck-Institut für Medizinische Forschung in Heidelberg and for making it possible for me with the additional support of the Minerva Komitees für die wissenschaftliche Zusammenarbeit zwischen deutschen und israelischen Forschungsinstituten to write this Tetrahedron Report in the town which simulates Paradise, where Gleiter lives, and wo ich mein Herz verloren habe. The God of Abraham (and of others) has, however, taken steps to keep the inhabitants of Heidelberg from committing the sin of (over) pride; He has given them the climate of the Rhine valley.

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[4] Ref. 1, pp. 145–151.
[5a] For Alder rule of "maximum accumulation of double bonds" see K. Alder and G. Stein, *Angew. Chem.* **50**, 514 (1937); K. Alder, *Liebigs Ann. Chem.* **571**, 157 (1951); K. Alder and M. Schumacher, *Fortschr. Chem. org. Naturstoffe* **10**, 1 (1953). Exceptions to the rule: for solvent effects on the stereoselectivity *cf* J. A. Berson and W. A. Mueller, *Tetrahedron Lett.* 131 (1961); J. A. Berson, Z. Hamlet and W. A. Mueller, *J. Am. Chem. Soc.* **84**, 297 (1962). [b]For general discussion: K. Fukui, In *Molecular Orbitals in Chemistry, Physics and Biology* (Edited by P.-O. Lowdin and B. Pullman), p. 525. Academic Press, New York (1964). L. Salem, *J. Am. Chem. Soc.* **90**, 543, 553 (1968). [c]Inductive effects: A. Wasserman, *J. Chem. Soc.* 825, 1511 (1935); 432 (1936); *Trans. Faraday Soc.* **35**, 841 (1939). [d]Electrostatic forces: R. B. Woodward and H. Baer, *J. Am. Chem. Soc.* **66**, 645 (1944).
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