STEREOCHEMISTRY OF THE DIELS–ALDER REACTION

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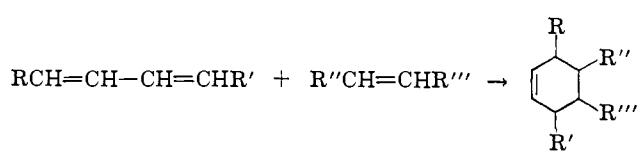
I. Introduction

The reaction between a conjugated diene and an olefin (the dienophile), also usually conjugated, to form a substituted cyclohexene was correctly formulated by Otto Diels and Kurt Alder in 1928 (139) and intensively investigated by them. In the intervening years it has become one of the most fundamental and useful reactions in the armamentarium of the synthetic organic chemist; in recognition of this importance, its discoverers were awarded the Nobel Prize in Chemistry in 1950.

The widespread utility of the reaction rests not only on its ability to form ubiquitous six-membered ring compounds and molecules otherwise difficultly accessible (such as bridged bicyclic compounds), but also on its remarkable stereospecificity. In the addition of a 1,4-disubstituted diene to a 1,2-disubstituted olefin,



for example, no less than eight racemic products could conceivably be formed; the number is doubled by considering, in addition, the alternate *structural* orientation. Yet the usual result of the reaction is the obtention of one, or at the most two, stereoisomers. Empirical rules which govern the selection of isomers were formulated by Alder and Stein (45). In recent years, the selectivity of diene addition has been exploited in stereospecific syntheses of a number of natural products, e.g., cholestanol (308), cortisone (260), reserpine (303), estrone (118), yohimbine (282), cantharidin (276), and conduritol-D (129).

A. SCOPE OF THE REVIEW

The purpose of this review is to focus attention on steric aspects of the Diels–Alder reaction. Purely synthetic and analytic uses of the reaction will not be discussed, nor will the arguments and evidence for the mechanism *per se*. (The reader may find leading references to and recent work on the mechanism in references 96, 290, and 306.)

The Diels–Alder reaction was last reviewed in this journal in 1942 (238), and other excellent reviews have appeared (3, 5, 112, 168, 186). Applications of the diene synthesis to the chemistry of natural products have been discussed (38). The most thorough previous review of the stereochemistry was the classic article by Alder and Stein in 1937 (45), while certain steric aspects of acyclic diene addition were briefly summarized by Alder in 1951 (4). For the present article the literature has been covered through late 1960, with emphasis on work since 1937.

B. FACTORS AFFECTING STEREOCHEMICAL CONCLUSIONS

Several pitfalls await the unwary investigator who attempts to draw conclusions about the stereochemical preferences of the Diels–Alder reaction which are based on the observed stereochemistry of isolated products.

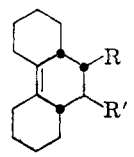
1. Epimerization of adducts

Cases have been reported in which the initial adduct was epimerized to a more stable stereoisomer by sufficiently severe reaction conditions. While maleic anhydride and its derivatives ordinarily add to 1,3-butadiene to give derivatives of *cis*-4-cyclohexene-1,2-dicarboxylic acid, in refluxing xylene mono- and diesters of maleic acid give trans adducts (192). 1-Phenyl-1,3-butadiene reacts with acrylyl chloride at room temperature to form only *cis*-2-phenyl-3-cyclohexenecarboxylic acid, but at reflux temperature the product is a mixture of stereoisomers, mostly the trans (207). 3-Ethoxy-1,3-pentadiene adds to ethyl 1-methyl-2,5-diketo-3-cyclohexenecarboxylate so slowly that the initial cis ring junction in the product has time to epimerize to the more stable trans (199).

Isomerization of the diene may occur before addition; Alder has reported that several cis 1-substituted dienes, on being heated to high temperatures with maleic anhydride, give adducts of the trans diene (35, 36). Epimerization may also occur during workup of the products: the 1-phenyl-1,3-butadiene–acrolein adduct isomerizes from cis to trans during purification with sodium bisulfite (54), and alkaline hydrolysis of the cis adduct of cyclopentadiene and dimethyl maleate gives the trans diacid (103).

2. Migration of the double bond

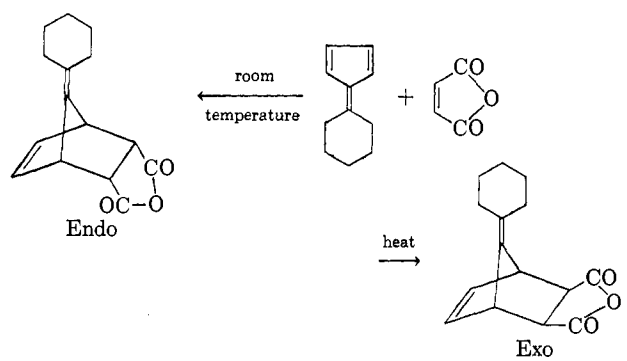
A possible cause for the obtention of isomeric adducts is migration of the cyclohexene double bond of the adduct. Wicks, Daly, and Lack have shown that the double bond of the sorbic acid–maleic anhydride adduct migrates at 160°C. to another position (294), and there is evidence for a similar double-bond shift in the addition of 3,4-dimethyl-1,3-butadiene to benzoylacrylic acid (170), in the addition of 1,3-butadiene to 1-cyano-1,3-butadiene (268), and in additions of 1-vinylcyclohexene (231). Migration of the double bond has been suggested as the explanation for the formation of two adducts from 1,1′-bicyclohexenyl and *trans*-cinnamic acid (93), but there is no evidence to negate the reasonable assumption that these are instead the two possible normal trans adducts, I and II.



I: R = C_6H_5, R′ = COOH
II: R′ = COOH, R′ = C_6H_5

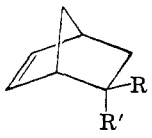
3. Reversibility of the Diels–Alder reaction

Diels–Alder adducts dissociate into their components on heating. One consequence of this reversibility is that if two stereoisomeric products are possible, the use of high temperatures and extended reaction times in carrying out additions may permit repeated dissociation and recombination, with the resultant formation of the thermodynamically more stable adduct at the expense of the kinetically favored stereoisomer. An example of this phenomenon was provided by Woodward and Baer (304), who found that at room temperature maleic anhydride added to 6,6-pentamethylenefulvene to form the endo adduct, but at higher temperatures or with longer reaction times, the product was the exo isomer. Similar results have been reported



for the addition of other fulvenes to maleic anhydride (10, 52, 128) and for the addition of furan to maleimide (194). Berson, Remanick, and Mueller (96) have reported recently that heating the optically active *endo*-methyl methyl methacrylate–cyclopentadiene adduct (III) at 170°C. for 3 hr. resulted in 7 per cent racemization and 5.6 per cent isomerization to the

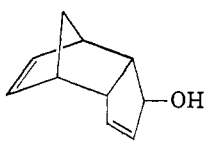
optically inactive *exo*-methyl adduct (IV), a result compatible with a dissociation–recombination mechanism.



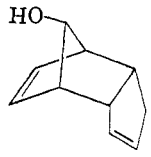
III: R = $COOCH_3$, R′ = CH_3
IV: R = CH_3, R′ = $COOCH_3$

On the other hand, there appears to be an internal process whereby Diels–Alder adducts can undergo thermal rearrangement to stereoisomers without complete separation of the two components. Craig first suggested this possibility for the thermal endo–exo rearrangement of the cyclopentadiene–maleic anhydride adduct (127), and later for the 1,1-dimethylfulvene–maleic anhydride adduct (128). Berson, Reynolds, and Jones (97) demonstrated through the use of a radioactively labeled endo adduct of cyclopentadiene and maleic anhydride that an internal process offered the more facile route for rearrangement, and that isotopic integrity was lost by the slower dissociation–recombination mechanism only after a longer time lapse than was required for initial endo–exo rearrangement. It has been argued that the furan–maleic acid endo–exo rearrangement may also take place through some internal process (98).

The remarkable and completely stereospecific thermal rearrangement of the formal Diels–Alder adduct (V) to a *structural* isomer (VI), which has an important bearing on the mechanism of Diels–Alder addition, was reported recently by Woodward and Katz (306). Although the results clearly rule out a solvent-caged mechanism for this rearrangement, such a description is still an attractive alternative for the endo–exo rearrangements described above.



V

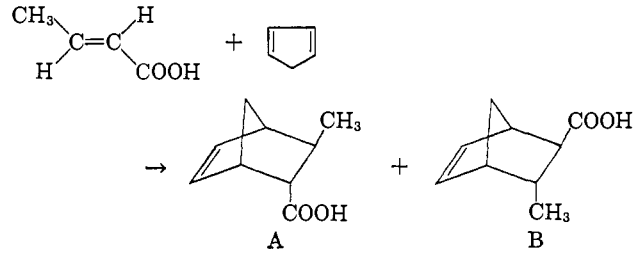


VI

Whatever the mechanism, the effect of temperature on the ratio of stereoisomeric adducts formed is very real and often pronounced; unfortunately, few workers have investigated the temperature factor thoroughly in carrying out Diels–Alder additions. A relevant example of the effect of temperature on the stereochemistry of the product, in the addition of cyclopentadiene to crotonic acid, is shown in table 1, taken from the work of Alder, Günzl, and Wolff (15). Similar changes in product ratios with temperature have been noted in the addition of cyclopentadiene to cinnamic acid (15) and

TABLE 1

Effect of temperature on stereochemistry of the product



Temperature	Yield of A	Yield of B
°C.	*per cent*	*per cent*
−10	85	15
80	70	30
110	60	40
170	40	60

methacrolein (209), and of 1-phenyl-1,3-butadiene to acrylic acid (54); other cases are cited in Section V,A.

4. Difficulty of separation and analysis of the product

The formation of stereoisomeric products offers the usual experimental problem of separation of substances of closely related properties, and there is no doubt that product ratios determined solely on the basis of isolated yields are often inaccurate and occasionally conflicting (15, 217). The development of gas chromatography has made possible the determination of many isomer ratios with a high degree of accuracy (123, 197), as has infrared analysis (106, 128, 131). In at least one instance, quantitative nuclear magnetic resonance analysis has been employed (183).

Errors may arise in the determination of adduct configuration. For example, the standard method of demonstrating the endo configuration of the adduct of a cyclic diene with an unsaturated acid is the interaction of the carboxyl group with the double bond, brought about by such reagents as strong acids or halogens, to form a lactone, sterically impossible in the exo adduct. Yet the reagent may cause skeletal rearrangement of these bridged adducts, and certain exo acids have been demonstrated to yield lactones by rearrangement when treated with sulfuric acid (46, 85, 86) or bromine (25, 286, 305). The milder procedure of iodolactonization (281) has been shown to be more reliable (253, 286), and the recently introduced method of anilinolactonization (15) should prove useful. For bicyclic adducts containing hydroxyl groups, the related chloromercuration and iodoetheration procedures have been employed (162, 178).

II. Steric Effect of Substituents on Rates and Adduct–Adduct Equilibria

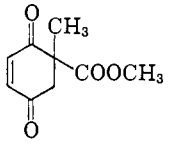
The first step in the addition of a diene to a dienophile is generally regarded as the formation of a loose

complex in which the addends lie one above the other in parallel planes (258). While steric effects are thus minimized, it is reasonable to expect that substituents which project much out of the plane of either addend might inhibit complex formation. A related factor is that bulky substituents in the diene or dienophile may be more compressed in the adduct than in the addend, and consequently shift the equilibrium in favor of the components.

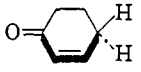
Such steric effects in the diene seem to be of minor importance. Dienes with bulky substituents, such as 1,3-di-*tert*-butyl-1,3-butadiene (79, 146), hexachlorocyclopentadiene (237, 242, 245, 273), and ergosterol (298) still form adducts fairly readily. 9,10-Dimethylanthracene and 9,10-diethylanthracene add maleic anhydride much faster than does anthracene (65, 220), and 9,10-diethyl-1,2-benzanthracene reacts more rapidly with maleic anhydride than does benzanthracene itself (74).

In the dienophile, however, substituents have a pronounced effect. Simple olefins containing two alkyl groups or halogen atoms on the same carbon atom do not add to hexachlorocyclopentadiene (205). Methyl 1-methyl-2,5-diketo-3-cyclohexenecarboxylate (VII), in spite of its resemblance to *p*-benzoquinone, is a fairly unreactive dienophile (199). Molecules of the type $RR'C{=}CHCOCH{=}CH_2$, which provide a built-in competition between substituted and unsubstituted dienophiles, add dienes only on the unsubstituted double bond (230). Pentamethyl- and hexamethylcyclopentadienes do not dimerize readily (287).

Cyclohexenones are disappointingly poor dienophiles (84, 171, 252); a possible reason is the presence of two hydrogen atoms at C-4 projecting out of the plane (see formula VIII), which interfere with complex formation.



VII



VIII

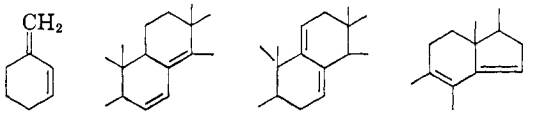
A long floppy chain in the dienophile is a powerful inhibitor of the Diels–Alder reaction, undoubtedly for the reasons mentioned at the beginning of this section. Perry (240) has found that, using standard conditions for the addition of simple dienes to a series of α,β-unsaturated acids, $RCH{=}CHCOOH$, the reaction fails if R is *n*-propyl or larger, and in the addition to $RCH{=}CHCOCH_3$, when R is larger than *n*-propyl.

Stereochemical preferences which appear to be due largely to steric effects are noted in Section V,B. Steric hindrance may affect structural orientation, too; dienes and dienophiles both substituted with bulky groups give increasingly higher proportions of adducts with the substituents separated as far as possible (232).

III. Cisoid Conformational Requirement of the Diene

A. Evidence from Cyclic Dienes

Since a trans double bond in a six-membered ring is geometrically impossible, Diels–Alder addition can occur only when the diene possesses a cisoid conformation. A number of transoid cyclic dienes have been shown to be inert to dienophiles; examples are 3-methylenecyclohexene (228) and β-phellandrene (157) with the diene system (IX), $\Delta^{6,8(14)}$-cholestadiene (X), $\Delta^{7,9}$-cholestadiene (XI), and $\Delta^{8,14}$-cholestadiene (XII) (143), all of which are unreactive to maleic anhydride. The use of addition of maleic anhydride to determine



IX X XI XII

whether a cyclic conjugated diene is cisoid or transoid has been exploited in structural studies on cholestadienes (95) and abietic acid (81, 295) among others (186).

B. Effect of Substituents on Conformation of Acyclic Dienes

Acyclic dienes are, of course, free to take the cisoid or

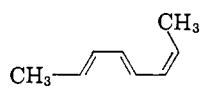
Cisoid Transoid

transoid conformation, but Diels–Alder reactions can take place only in the cisoid, or quasicyclic (4), orientation. Steric factors in the diene play a crucial role in determining the relative stability of these two forms, and repulsions which increase the strain energy of the cisoid conformation, relative to the transoid, have an adverse effect on diene addition. One such factor is a cis 1-substituent on the diene; the nonbonded interaction between the substituent R and the cis 4-hydrogen makes the cisoid conformation more difficult to achieve. Accordingly, it is uniformly true that a trans 1-substituted 1,3-butadiene reacts with dienophiles

Cisoid Transoid

much more readily than the cis isomer. Since the cis isomer usually polymerizes faster than the trans (151), many attempts to add dienophiles to cis 1-substituted dienes have led only to copolymers. Goldman has shown recently (156) that polymerization may often be avoided by carrying out the reaction under nitrogen, with 5–10 per cent by weight of added hydroquinone.

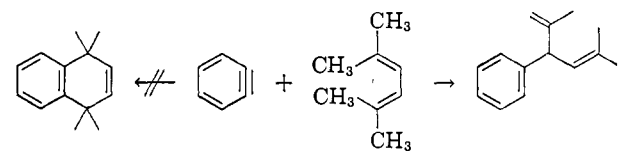
Even so, the difference in reactivity is so pronounced that addition of maleic anhydride can be used as a method of quantitatively separating the cis and trans isomers. *trans*-Piperylene forms adducts with acrylonitrile (151) and maleic anhydride (125), using conditions under which the cis isomer does not react. Craig has shown (126) that *cis*-piperylene can be induced to add maleic anhydride and fumaric acid, but only under much more drastic conditions than are required for the trans isomer. *trans*-1-Phenyl-1,3-butadiene gives a quantitative yield of the maleic anhydride adduct on refluxing in toluene for 4 hr., while the cis compound reacts to the extent of only 5 per cent (158). *cis*-1,3,5-Hexatriene adds maleic anhydride readily, while the trans isomer does not react (173). *trans*-1-Ethyl-1,3-butadiene forms a maleic anhydride adduct easily in boiling benzene, though the cis isomer is inert (7, 57); the same is true of the trans and cis isomers of 1-cyano-1,3-butadiene (270). Similar differences in reactivity have been observed for several pairs of trans,trans and cis,trans 1,4-disubstituted dienes: 1,4-dimethyl-1,3-butadiene (57), 1,2,3,4-tetramethyl-1,3-butadiene (130), 4-methyl-1-phenyl-1,3-butadiene (37), 1,4-diphenyl-1,3-butadiene (35), and 4-carbomethoxy-1-phenyl-1,3-butadiene (36). Alder and von Brachel have shown that several trans,trans,cis trienes, e.g., XIII, which contain both cis and trans 1-substituted diene systems to which addition could take place, add maleic anhydride only to the trans,trans end (7).



XIII

1,1-Disubstituted 1,3-butadienes, which must have a cis 1-substituent, add dienophiles with reluctance, and several early investigators were doubtful that addition occurred at all (72, 73, 80, 163, 198, 277). Under forcing conditions, however, adducts have been formed from 1,1-dimethyl-1,3-butadiene (156), 1,1,2-trimethyl-1,3-butadiene (156, 219), 1,1,3-trimethyl-1,3-butadiene (140, 179, 180, 200, 201), 1-methyl-2-vinylcyclohexene (156), and 1,3-dimethyl-2-vinylcyclopentene and cyclohexene (156). In the series 1,1,4,4-tetraphenyl-1,3-butadiene to 1,1,12,12-tetraphenyldodecahexaene, the terminal cis phenyl substituents inhibit the cisoid conformation of the terminal pairs of conjugated double bonds, preventing their addition to dienophiles; the interior diene systems are not affected by the substituents and react readily (34). Several texts (153, 165) have proposed that the difficulty in adding dienophiles to 1,1-disubstituted dienes is due to the direct steric repulsion of the dienophile by the substituents, but this factor appears to have only secondary significance, since other dienes similarly substituted but in fixed cisoid conformations, as in the ergosterol series (298), add dienophiles readily.

Cis substituents at both ends of an acyclic 1,4-diene further decrease the reactivity, to the point where the Diels–Alder reaction does not occur. Hexachloro-1,3-butadiene does not give adducts with maleic anhydride or benzoquinone (152), and *cis,cis*-1,4-diphenyl-1,3-butadiene is completely unreactive toward dienophiles (35). When conditions under which *trans,trans*-1,4-diacetoxy-1,3-butadiene adds quantitatively to juglone are employed, the cis,trans isomer reacts in only 47 per cent yield and the cis,cis isomer not at all (176). The 1,1,4,4-tetramethyl- and tetraethyl-1,3-butadienes do not add to α-naphthoquinone (150). Two further indications of the extreme unreactivity of the tetramethyl compound are (*a*) it reacts with maleic anhydride only at very high temperatures, after first rearranging to 4-isopropyl-2-methyl-1,3-butadiene (229), and (*b*) it reacts with the "benzyne" intermediate by substitutive addition rather than 1,4-addition (67).



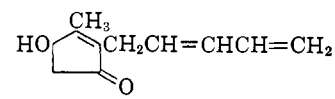
The difference in reactivity between cis and trans 1-substituted dienes with maleic anhydride has been utilized in the determination of the stereochemistry of a number of natural dienes and polyenes (38, 213). By this method dimorphecolic acid (XIV) was shown to be a trans,trans diene (266), the dehydration product (XV) of ricinelaidic acid ("Mangold's acid") was also shown to be a trans,trans diene (24), and the configuration of the diene substituent in the pyrethrolones (XVI) was shown to be trans (132). Configurations have also been assigned to the triene systems in α- and β-eleostearic acids (XVII) (24, 100) and their isomer punicic acid (144), α- and β-licanic acids (XVIII) (216), the isomers of the tetraene, parinaric acid (XIX) (184), allo- and neoalloöcimene (XX) (13, 117), and a series of simple trienes (7) by the use of the Diels–Alder reaction. This method was also of great utility in elucidating the structure and stereochemistry of irradiation products of ergosterol (149).

$CH_3(CH_2)_4CH{=}CHCH{=}CHCHOH(CH_2)_7COOH$

XIV

$CH_3(CH_2)_5CH{=}CHCH{=}CH(CH_2)_7COOH$

XV



XVI

$CH_3(CH_2)_3(CH{=}CH)_3(CH_2)_7COOH$

XVII

$CH_3(CH_2)_3(CH{=}CH)_3(CH_2)_4COCH_2CH_2COOH$

XVIII

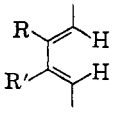
$CH_3CH_2(CH{=}CH)_4(CH_2)_7COOH$

XIX

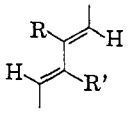
$(CH_3)_2C{=}CHCH{=}CHC(CH_3){=}CHCH_3$

XX

Bulky substituents at the 2- and 3-positions of a 1,4-diene also influence the conformational equilibrium in the diene and consequently the ease of Diels–Alder addition. It is seen that when R and R′ are large,



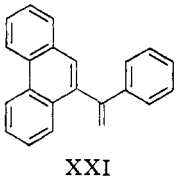
Cisoid



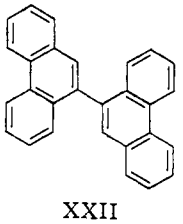
Transoid

steric repulsions are considerably lower in the transoid conformation than in the cisoid, and Diels–Alder reactions are accordingly difficult. 2,3-Di-*tert*-butyl-1,3-butadiene is the best example; it is completely inert to dienophiles (78), although the 1,3-isomer adds maleic anhydride (79, 146). 2,3-Dichloro-1,3-butadiene is reported not to react with maleic anhydride or naphthoquinone (89). 2,3-Dimethyl-1,3-butadiene, on the other hand, is a notorious partner in Diels–Alder reactions (238), and 2,3-diphenyl-1,3-butadiene, though sluggish, reacts with several dienophiles (62, 63), which may indicate that the phenyl groups can twist out of coplanarity. Both 1,2,3,4-tetraphenyl-1,3-butadiene and 1,2,4-triphenyl-1,3-butadiene add maleic anhydride under vigorous conditions (19).

Also falling in the category of bulkily 2,3-disubstituted dienes are 9-(α-styryl)phenanthrene (XXI) and 9,9′-biphenanthryl (XXII), which do not react with maleic anhydride, in contrast to simpler vinylphenanthrenes (90, 92).



XXI



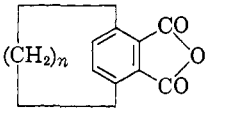
XXII

C. EFFECT OF RING SIZE IN HOMOANNULAR DIENES

A final factor which influences diene conformation is the ring size of homocyclic dienes. Cyclopentadiene and 1,3-cyclohexadiene, both containing fixed cisoid conformations, readily take part in Diels–Alder reactions, especially the former (238). It has been postulated that the dimers which result from attempts to prepare derivatives of cyclobutadiene are formed by Diels–Alder additions of the extremely reactive intermediates (115), and Cava and Mitchell have trapped benzocyclobutadiene as its adduct with *N*-phenylmaleimide (114). 1,3-Cycloheptadiene is less reactive than the five- and six-membered dienes, but still forms adducts easily (18, 25, 189).

With dienes having rings of medium size, however, the reaction suddenly fails. 1,3-Dienes in rings of eight to eleven members do not form adducts with maleic anhydride (102, 124, 147, 313). The reason for this seems clear: models reveal that a planar cisoid conformation of the diene in these rings is too highly strained to be stable, a conclusion reinforced by the low intensity of their ultraviolet absorption (102, 147). Two geometrical isomers of 1,3-cyclodecadiene are known, the cis,cis and cis,trans, but neither has a planar cisoid diene system and neither reacts with maleic anhydride (102). Cycloöctatetraene, which also lacks a planar diene system, reacts with maleic anhydride only after isomerization to bicyclo[4.2.0]-octa-2,4,7-triene, which adds the dienophile to the cyclohexadiene moiety (243).

Rings larger than eleven atoms again permit the cisoid diene conformation, and 1,3-dienes in 12-, 13-, 14-, and 18-membered rings add maleic anhydride, albeit in low yield (83, 174). The adducts of the latter three were dehydrogenated to interesting para-bridged phthalic anhydrides (XXIII) (174, 296).



XXIII

IV. The Cis Principle

The cardinal stereochemical principle of the Diels–Alder reaction was recognized early and formulated as the first of the classical Alder–Stein rules: the "cis" principle (45). Aside from the factors listed in Section I,B, which are independent of the reaction itself and its mechanism, no exceptions are known to the rule that the relative configuration of the starting materials is retained in the adduct; the reliability of the rule is one of the major factors in the importance of the Diels–Alder reaction in synthesis and in stereochemical studies.[1] An explanation for this behavior, in modern terms, is that after the diene and dienophile have been joined by one bond, the partial formation of the new bond and the secondary attractive forces in the transition state serve to prevent any rotation which might lead to inversion of the relative configurations at the termini of the addends (306).

[1] It is noteworthy that even when catalyzed by a molar equivalent of aluminum chloride, Diels–Alder addition of anthracene to maleic anhydride and dimethyl fumarate retains its stereospecificity (309).

A. RETENTION OF CONFIGURATION OF DIENOPHILE SUBSTITUENTS

Table 2 gives a partial listing of Diels–Alder reactions for which there is sound experimental evidence that the relative configuration of the dienophile substituents is unchanged in the adduct. It is now tacitly assumed that all Diels–Alder reactions obey this rule, but only those cases for which some independent evidence of the stereochemistry of the adduct is available are included in the table.

TABLE 2

Retention of configuration of dienophile substituents

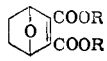
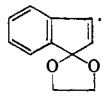
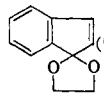
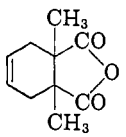
Dienophile	Diene and Reference
Acyclic:	
Maleonitrile	Cyclopentadiene (103)
Dimethyl maleate	Indene (27), anthracene (76)
Fumaric acid	1,3-Butadiene (191), anthracene (76), 1-vinylnaphthalene (77)
Dihydromuconitrile	Cyclopentadiene (26)
Dimethyl fumarate	1-Acetoxy-1,3-butadiene (193), anthracene (76)
Fumaronitrile	Cyclopentadiene (103)
Mesaconic acid and derivatives	Anthracene (76), cyclopentadiene (9, 224), 1,3-cyclohexadiene (9), 1-vinylnaphthalene (77), 1-vinylcyclohexene (222)
Diethyl glutaconate	1,3-Butadiene (164, 240)
Crotonic acid and isocrotonic acid	Cyclopentadiene (15)
Crotonaldehyde	1,3-Butadiene (140)
cis- and trans-Cinnamic acids	1,3-Butadiene (54), cyclopentadiene (15), 2-ethoxy-1,3-butadiene (171), 1,1′-bicyclohexenyl (93)
Benzalacetone	1,1′-Bicyclohexenyl (93), 2-ethoxy-1,3-butadiene (171)
Benzoylacrylic acid	Cyclopentadiene (217), 2,3-dimethyl-1,3-butadiene (170)
1-Nitropropene	Anthracene (236), cyclopentadiene (283)
β-Nitrostyrene	Anthracene (236), 1,3-butadiene (69), cyclopentadiene (292)
$C_6H_5SO_2CH{=}CHCOOH$	Cyclopentadiene (215)
β-Haloacrylic acids	Cyclopentadiene (16)
1,2-Diacetylethylene	1,3-Butadiene, 2,3-dimethyl-1,3-butadiene, cyclopentadiene, 1,3-cyclohexadiene (262)
Cyclic:	
Maleic anhydride	Anthracene (76), 1,3-butadiene (45), furan (305), cyclopentadiene (61), 1,3-cyclohexadiene (53), 1,3-cycloheptadiene (25), 1-vinylnaphthalene (77), 1-alkyl-1,3-butadienes (7, 126), hexa-, hepta-, and octatrienes (7), 1,4-dialkyl-1,3-butadienes (7, 13, 57), 1,4-diphenyl-1,3-butadiene (35), 4-methyl-1-phenyl-1,3-butadiene (37), methyl 4-phenyl-1,3-butadiene-1-carboxylate (36), alloöcimene (13), eleostearic acids (24), 1,2,4-triethylnaphthalene (188), 1-vinylcyclohexene (193), 1,2-dimethyl-1,3-butadiene (193)
Maleimide	Furan (194)
N-Phenylmaleimide	1,2-Dimethylene-3,5-cyclohexadiene (113)
Phenylmaleic anhydride	Cyclopentadiene (9, 218)
Dimethylmaleic anhydride	1,3-Butadiene (307)
Citraconic anhydride	Cyclopentadiene (9, 224), 1,3-cyclohexadiene (9), anthracene (76), 1-vinylnaphthalene (77), 3,4-dihydro-6-methoxy-2-vinylnaphthalene (75, 161), 1-acetoxy-1,3-butadiene (193)
Cyclopentadiene	Cyclopentadiene (47)
Vinylene carbonate	Cyclopentadiene (61), 1,4-diacetoxy-1,3-butadiene (129)
Cyclohexene-1-carboxaldehyde	1,3-Butadiene (91)
Cyclopentene-1-carboxaldehyde	1,3-Butadiene (91)
2-Methyl-2-cyclohex-1-enone	1,3-Butadiene (154)
Cyclohexen-2-one	1-Vinylcyclohexene (233)
3-Methyl-3-cyclopentene-1,2-dione	1,3-Butadiene (265), 3,4-dihydro-6-methoxy-1-vinylnaphthalene (265)
3,6-Dihydrophthalic acid	1,3-Butadiene (6)
Bicyclo[2.2.1]heptene	1,3-Butadiene (26)
p-Benzoquinone	1,3-Butadiene (42), cyclopentadiene (42), 1,3-cyclohexadiene(42), 1-vinylcyclohexene (249), vinylacrylic acid (303), 3,4-dihydro-6-methoxy-1-vinylnaphthalene (251), 3-ethoxy-1,3-pentadiene (99, 261)
4-Methoxytoluquinone	1,3-Butadiene (308), piperylene (104)
	1,3-Butadiene (196)
	1,3-Butadiene (276)
	1,3-Butadiene (172), 2-ethoxy-1,3-butadiene (171)
	1,3-Butadiene (172)

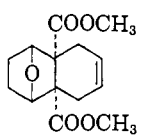
TABLE 2 (*Continued*)

In addition to the reactions cited in table 2, there are a number of cases in which stereoisomeric dienophiles lead to stereoisomeric adducts, but for which retention of configuration, while almost certain, has not been specifically proved. Among these are the addition of *cis*- and *trans*-dibenzoylethylenes to cyclopentadiene (1), the addition of maleic and fumaric acid derivatives to 2,5-dimethyl-3,4-diphenylcyclopentadienone (64) and di(1-cyclohexenyl)acetylene (111), the addition of *cis*- and *trans*-*o*-methoxycinnamic acids to 2,3-dimethyl-1,3-butadiene (2), and the addition of hexachlorocyclopentadiene to *cis*- and *trans*-cycloöctenes and *cis,cis*- and *trans,trans*-1,5-cycloöctadienes (311).

The butadiene–dimethyl maleic anhydride adduct (XXIV) was hydrogenated to desoxycantharidin (307), and the adduct (XXV) of 1,3-butadiene with dimethyl 3,6-epoxy-3,4,5,6-tetrahydrophthalate was the intermediate used by Stork, van Tamelen, Friedman, and Burgstahler in an ingenious synthesis of cantharidin itself (276). The use of vinylene carbonate as a



XXIV

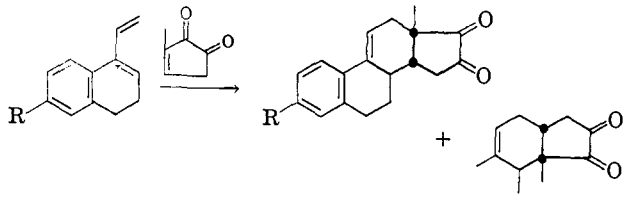


XXV

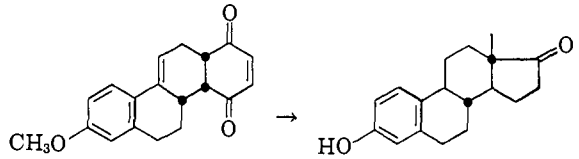
dienophile provides a new route to *cis*-1,2-glycols (61, 235) and sugar derivatives (129).

Numerous attempts have been made to synthesize members of the steroid family by Diels–Alder reactions. Earlier work, using 3,4-dihydro-1-vinylnaphthalenes

as the diene and five-membered dienophiles such as 3-methyl-3-cyclopentene-1,2-dione (75, 136, 265), was plagued by the obtention of both the wrong structural isomer and the wrong (C/D cis) stereoisomer:



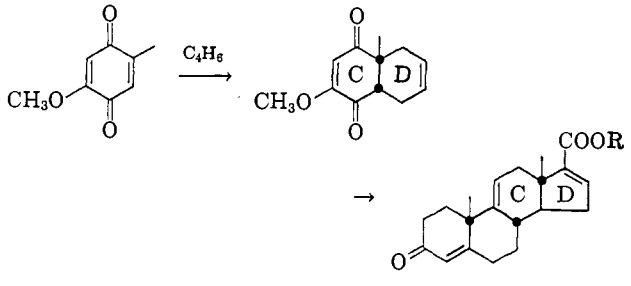
The adduct (XXVI) of *p*-benzoquinone with the above diene (R=OCH_3), however, has been successfully transformed into estrone (118). Recent applications of



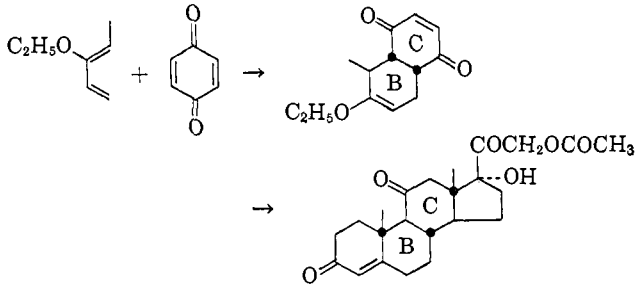
XXVI

the Diels–Alder reaction have made available non-aromatic steroids in unnatural configurations (*221*, 234).

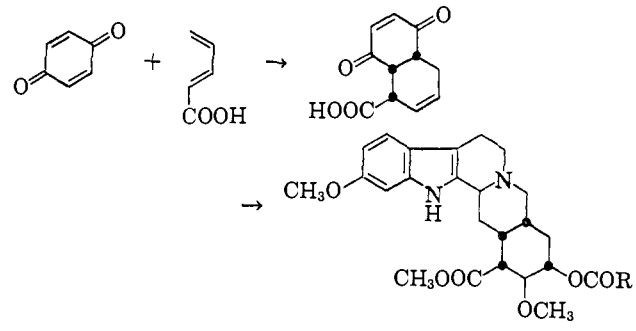
More modest uses of the Diels–Alder reaction in steroid synthesis, in constructing only two rings of the skeleton, have met with outstanding success. Both the Harvard synthesis (308) and the Monsanto synthesis (82, 274) utilize the adduct of 1,3-butadiene and methoxytoluquinone in building rings C and D:



while the Merck cortisone synthesis begins by constructing rings B and C by the addition of 3-ethoxy-1,3-pentadiene to benzoquinone (260, 261):



Finally, the benzoquinone–vinylacrylic acid adduct was the starting point of the elegant total synthesis of reserpine (303), and the quinone–1,3-butadiene adduct



served as a similar origin of the D and E rings of yohimbine (282).

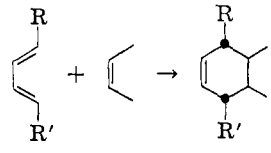
B. RETENTION OF CONFIGURATION OF DIENE SUBSTITUENTS

In contrast to the large number of substituted dienophiles which give adducts of known stereochemistry, relatively few cases have been investigated which provide unambiguous evidence for the configurational fate of diene substituents. Every reported example, however, substantiates the rule of cis addition and resulting retention of relative configuration of substituents on the 1- and 4-positions of the diene. These are listed in table 3. Cyclic 1,3-dienes in rings of medium

TABLE 3

Retention of configuration of diene substituents

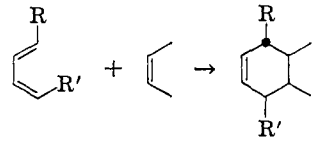
A. Trans,trans 1,4-disubstituted dienes



R and R′ cis

R	R′	References
C_6H_5	C_6H_5	(35)
CH_3	CH_3	(57)
C_6H_5	CH_3	(37)
C_6H_5	$COOCH_3$	(36)
$COOCH_3$	$COOCH_3$	(53, 145)
$-CH_2CH(CH_3)_2$	CH_3	(13)
$-CH=C(CH_3)_2$	CH_3	(13)
$-CH=CH_2$	CH_3	(7)
C_2H_5	CH_3	(7)
$-CH=CHCH_3$	CH_3	(7)
n-C_3H_7	CH_3	(7)
$OCOCH_3$	$OCOCH_3$	(129)
n-C_6H_{13}	$-(CH_2)_7COOH$	(24)
$-CH=CH(CH_2)_6CH_3$	$-(CH_2)_7COOH$	(24)
n-C_4H_9	$-CH=CH(CH_2)_7COOH$	(24)
n-C_4H_9	$-(CH_2)_9COOH$	(24)

B. Cis,trans 1,4-disubstituted dienes

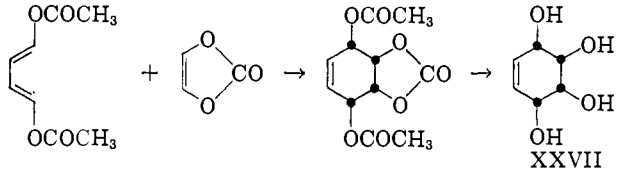


R and R′ trans

R	R′	Reference
C_6H_5	CH_3	(37)
CH_3	CH_3	(57)
C_6H_5	$COOCH_3$	(36)
$-CH=C(CH_3)_2$	CH_3	(13)

size lead to bridged bicyclic adducts in which the bridge must clearly be attached by cis linkages, and so need not be discussed further. Most of the evidence for the configuration of adducts of 1,4-disubstituted acyclic dienes comes from the careful work of Alder and his students.

As shown in table 3, all trans,trans 1,4-disubstituted dienes which have been investigated form adducts (mostly with maleic anhydride) in which the 1- and 4-substituents are cis to each other. These include such simple dienes as the 1,4-diphenyl- and 1,4-dimethyl-1,3-butadienes and dimethyl muconate, as well as alloöcimene and β-eleostearic acid. Criegee and Becher (129) utilized the retention of configuration of both diene and dienophile substituents in a stereospecific synthesis of conduritol-D (XXVII) from *trans,trans*-1,4-diacetoxy-1,3-butadiene.



XXVII

Similarly, dienes in which the substituents are trans to each other, i.e., cis,trans 1,4-disubstituted dienes, give adducts in which the substituents remain trans, as shown in part B of table 3.

V. Stereochemical Orientation of the Addends

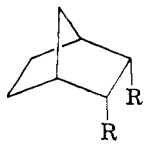
Three features of the reaction process determine the stereochemical relationship in the adduct among the substituents originating in the addends. Briefly, these are: (A) endo addition, (B) steric control of approach of the diene to the dienophile, and (C) steric control of approach of the dienophile to the diene. As opposed to the fundamental nature of the rules of cis addition and cisoid conformation of the diene, these three considerations are more relative, and frequently exhibit a dependence on the competition between various forces, often subtle in nature. For this reason, conclusions based on these effects may be speculative in some cases, to which attest the frequent reports in the literature of Diels–Alder adducts unexpected on the basis of analogy to prior reactions.

A. Endo Addition

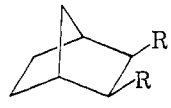
The title given to this section is derived from the strong propensity of most dienophile substituents to orient in the endo configuration in the bridged bicyclic adducts formed from cyclic dienes. Although the term endo is a misnomer in referring to reactions of acyclic dienes, it is useful for describing certain orientational preferences with cyclic and acyclic dienes alike. Endo addition thus involves the tendency for dienophile substituents to be so oriented in the favored transition state that they lie directly above the residual unsaturation of the diene, whether for reasons of spatial orbital overlap or for reasons of steric accommodation. That transition state which is best stabilized by spatial orbital overlap and simultaneously least destabilized by unfavorable steric repulsions has the lowest free energy of all possible transition states, and consequently predominates in the kinetically determined product. The concept of the fairly rigid transition state, with secondary attractive forces preventing conformational inversions of either component (306), underlies the preservation, in the adduct, of the orientation of the addends in the transition state.

1. Cyclic dienes: endo vs. exo orientation

The original rule of Alder and Stein concerning endo addition of dienes to dienophiles (45) was based on results of addition of several dienophiles to cyclopentadiene, and this diene has continued to be the most widely used for stereochemical investigations. In table 4 are summarized results of analyses of kinetically controlled addition of simple monosubstituted and cis 1,2-disubstituted olefins to cyclopentadiene to give adducts in which the substituent may be endo or exo. With one exception, that of 2,5-dihydrofuran (for which it is not clear that the adduct is the kinetically



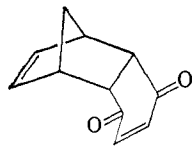
Endo



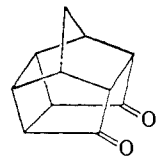
Exo

favored one), the endo adduct predominates, bearing out the conclusion of Alder and Stein. The endo:exo ratio at the lowest temperature employed for the reaction is given where that is known.

Several of the examples listed in table 4 merit further comment. The adduct of cyclopentadiene with benzoquinone (XXVIII), as well as that with chloranil, was shown to be endo by ultraviolet irradiation to the pentacyclic diketone (XXIX) (121). This remarkable reaction was used to demonstrate the endo orientation



XXVIII



XXIX

TABLE 4

Adducts of cyclopentadiene with monosubstituted and cis 1,2-disubstituted olefins

A. Monosubstituted olefins, CH_2=CHX

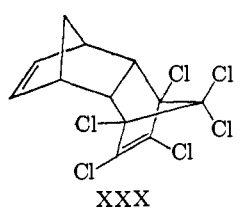
X	Endo:Exo	References
COOH	75:25	(286)
	70–75:5–10	(248)
$COOCH_3$	76:24	(123)
$CONH_2$	10:1	(106)
CHO	Only endo	(49, 51)
CN	60:40	(22)
CH_2OH	80:20	(58, 178)
CH_2Cl	Only endo	(58)
CH_2Br	Only endo	(58)
CH_2NH_2	Only endo	(58)
CH_2CN	Only endo	(58)
CH_2COOH	Only endo	(58)
CH_2O-phthaloyl	Only endo	(58)
NO_2	Mostly endo	(29, 247)
$OCOCH_3$	81:19	(247)
	17:2	(289)
OCHO	Mostly endo	(28)
Br	Mostly endo	(248)
Cl	Mostly endo	(248)
—CH=CHCN	Only endo	(269)

B. Cis 1,2-disubstituted olefins, RCH=CHR′

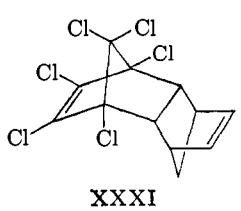
R	R′	Endo:Exo	References
COOH	CH_3	85–90:10–15	(15)
COOH	C_6H_5	90–92:5	(15)
COOH	$SO_2C_6H_5$	91:9	(215)
COOH	Cl, Br, I	80:10	(16)
COOH	$=CH_2$	Only endo	(131)
CH_2OH	CH_2OH	Only endo	(30)
Br	Br	1:8*	(197)
Cl	Cl	Mostly endo	(246)
—COOCO—		Only endo	(46)
—CONHCO—		Only endo	(103, 160)
—CH=$CHCH_2$—		Only endo	(43, 131)
—$CH_2CH_2CH_2$—		98:2	(131, 297)
—CH_2OCH_2—		Mostly exo	(107, 134)
—CH_2SCH_2—		Only endo	(101)
—OCOO—		Mostly endo	(61, 195)
—COCH=CHCO—		Only endo	(26, 121)
—COCH=CH—		Only endo	(138)
—CH_2—		Only endo	(293)
Bicyclo[2.2.1]heptadiene		Only endo	(275)
Hexachlorobicyclo[2.2.1]heptadiene		Only endo	(120)

* The product was mostly exo in a preparative run in a steel bomb at 190°C., but data in the experimental section of reference 197 suggest that the endo isomer predominates when the reaction is run in a glass-lined vessel.

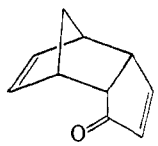
of other adducts which contain two double bonds suitably placed for ring closure (120, 121): the adducts of benzoquinone with hexachlorocyclopentadiene, cycloöctatetraene, and dichlorobicyclo[4.2.0]octadiene; the adduct of the latter diene with hexachlorobicyclo[2.2.1]heptadiene; and the important insecticide isodrin (XXX), the adduct of hexachlorobicyclo[2.2.1]heptadiene and cyclopentadiene (211). The isomeric insecticide aldrin (XXXI), formed from hexachlorocyclopentadiene and bicyclo[2.2.1]heptadiene, is also a product of endo addition. Compound XXXII is formed at room temperature from cyclopentadiene and the transient dienophile cyclopentadienone (138, 159) and has been identified as the endo isomer by synthesis from *endo*-dicyclopentadiene.



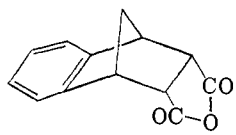
XXX



XXXI

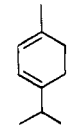


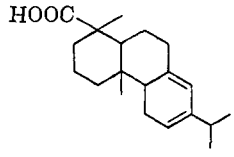
XXXII



XXXIII

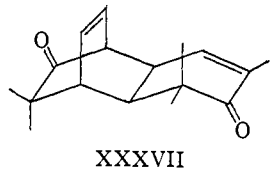
In addition to the reactions of cyclopentadiene cited in table 4, a number of other cyclic dienes have been demonstrated to give almost exclusively endo adducts. Ethyl 2,4-cyclopentadiene-1-carboxylate (46) and 1,1,2-trimethyl-2,4-cyclopentadiene (60) both give endo adducts with maleic anhydride, as shown by lactonization experiments. Indene reacts with maleic anhydride via a quinodimethylene tautomer to yield the endo adduct (XXXIII) (27). 1,3-Cyclohexadiene gives a totally endo adduct with maleic anhydride (46, 53) and a 10:1 ratio of endo to exo adducts with ethyl acrylate (106), but only a 1:1 mixture with the poorly orienting acrylonitrile (22). The 1,3-cyclohexadiene systems in α-terpinene (XXXIV) (142) and levopimaric acid (XXXV) (66, 259) both give endo adducts with maleic anhydride, as does the bicycloöctadiene tautomer (XXXVI) of cycloöctatetraene and several of its derivatives (71, 243).


XXXIV



XXXV


XXXVI



XXXVII

Cyclohexadienones react readily with dienophiles (119, 135, 182, 212), and several observations support endo addition in these reactions. 6-Dichloromethyl-6-methyl-2,4-cyclohexadien-1-one reacts with maleic anhydride to give an endo adduct (122), and 2,2,6-trimethylcyclohexadienone forms a dimer assigned the endo configuration (XXXVII) on the basis of its dipole moment (108).

1,3-Cycloheptadiene also forms an endo adduct with maleic anhydride (25), and the maleic anhydride

adducts of several cycloheptatrienones have been assigned endo configurations on the basis of bromolactonizations; these include tropone (239), 2-bromotropone (239), and 4-methoxytropone (116).

Aside from the rigorous generality of endo addition demonstrated in these reactions, certain other noteworthy features are evident. Listing those reactions from table 4 for which accurate analyses of the product ratio are available, in order of decreasing endo content, with the derived free-energy difference, $\Delta\Delta F^{\ddagger}$ (in kcal./mole), favoring endo vs. exo transition states, one arrives at the following:

Dienophile	$\Delta\Delta F^{\ddagger}$	Dienophile	$\Delta\Delta F^{\ddagger}$
	kcal./mole		*kcal./mole*
Cyclopentene	2.37	Br(Cl)CH=CHCOOH	1.3
C_6H_5CH=CHCOOH	1.76	CH_2=CHOCOCH$_3$	0.88
$C_6H_5SO_2CH$=CHCOOH	1.41	CH_2=CHCH$_2$OH	0.84
CH_2=CHCONH$_2$	1.4	CH_2=CHCOOR	0.67
CH_3CH=CHCOOH	1.34	CH_2=CHCN	0.25

Alder and Stein proposed that the overriding tendency for endo addition was due to spatial orbital overlap of unsaturated centers of the diene and dienophile in the transition state (45). However, of the dienophiles in the above list, only one, acrylamide, appears far out of order in a series which otherwise shows simply the steric bulk of the substituents. The fact that the cyano group is the poorest endo director in additions to both cyclopentadiene and 1,3-cyclohexadiene agrees well with its small size and linearity. The exceptional endo tendency shown by cyclopentene is difficult to account for on the basis of "overlap of unsaturation" and appears more likely to result from steric compression between the methylene hydrogen and trimethylene bridge in the exo transition state; the addition of cyclopentene to a substituted furan has been reported (301) to afford both endo and exo products in a ratio of 3–4:1. From a calculation of differences in activation energy for endo and exo addition of cyclopentadiene to methyl acrylate and methyl methacrylate, Berson, Remanick, and Mueller (96) concluded recently that the attractive forces of spatial orbital overlap are weak, and easily overweighed by the demands of structural changes in the dienophile.

Several dienophiles in table 4 are reported to yield only endo products. An estimate of thermodynamic data would be hazardous, but to the extent that "only" can be assumed to mean 99:1 to 95:5 ratios, the differences in activation energy for exo and endo addition range from 1.8 to 2.8 kcal./mole. Such dienophiles as maleic anhydride, maleimide, and cyclopentadiene probably approach or exceed the upper value.

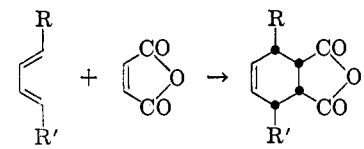
2. Orientation in addition to acyclic dienes

Translating the rule of endo addition into the reactions of acyclic dienes requires that the adducts of trans 1- and 4-substituted dienes with simple dienophiles be completely cis-substituted cyclohexenes. In table 5 are collected the results of additions of acyclic

TABLE 5

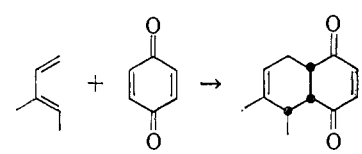
Addition of trans-substituted acyclic dienes to dienophiles

A. Addition to maleic anhydride



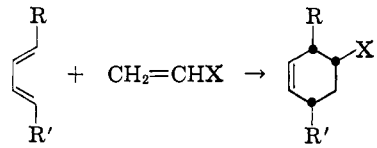
R	R′	References
CH_3	H	(126)
C_2H_5	H	(7, 57)
n-C_3H_7	H	(7)
n-C_4H_9	H	(7)
—CH=CH_2	H	(7)
—CH=$CHCH_3$	H	(7)
—CH=CHC_2H_5	H	(7)
CH_2OH	H	(133)
$OCOCH_3$	H	(193)
C_6H_5	H	(54)
3,4-$(CH_3O)_2C_6H_3$	H	(68)
α-Naphthyl	H	(68)
CH_3	CH_3	(57)
C_2H_5	CH_3	(7)
n-C_3H_7	CH_3	(7)
—CH=$CHCH_3$	CH_3	(7)
$CONHCH_2CH(CH_3)_2$	CH_3	(133)
C_6H_5	CH_3	(37)
CH_2Br	CH_2Br	(145)
COOR	COOR	(53, 145)
C_6H_5	$COOCH_3$	(36)
C_6H_5	C_6H_5	(35)
1,2-Dimethyl-1,3-butadiene		(193)
1,2-Diphenyl-1,3-butadiene		(20)
2-Methyl-1-phenyl-1,3-butadiene		(20)
2-Ethyl-1-phenyl-1,3-butadiene		(20)
Methyl 1-phenyl-1,3-butadiene-2-carboxylate		(20)
1-Methyl-3-phenyl-1,3-butadiene		(11)
1-Isopropyl-3-methyl-1,3-butadiene		(7)
1-Isopropenyl-3-methyl-1,3-butadiene		(7)
Alloöcimene		(13, 117)
Eleostearic acids		(24)
1-Vinylcyclohexene		(193, 223)
1-Anilino-2,4-diethyl-1,3-butadiene*		(267)
$\Delta^{1,4}$-Hexahydro-6,9-dimethyl-1-vinylnaphthalene†		(225)

B. Addition to *p*-benzoquinone



Diene	References
1-Vinylcyclohexene	(234, 249, 250)
3-Ethoxy-1,3-pentadiene	(261)
Methyl vinylacrylate	(303)
3,4-Dihydro-6-methoxy-1-vinylnaphthalene	(118, 251)
6-Keto-9-methyl-1-vinyl-$\Delta^{1,2}$-octalin	(221, 234)
Piperylene‡	(104)
1-Acetoxy-1,3-butadiene§	(177)

TABLE 5 (*Continued*)
C. Addition to acrylic acid and its derivatives



R	R′	X	References
CH_3	H	COOH	(55)
CH_3	H	$COOCH_3$	(208)
CH_3	H	CHO	(55, 169)
CH_3	H	CN	(208)
C_6H_5	H	COOH	(35, 54, 105, 256)
C_6H_5	H	COCl	(207)
C_6H_5	H	CHO	(54)
p-BrC_6H_4	H	COOH	(257)
$OCOCH_3$	H	COOH	(33)
COOH	H	COOH¶	(39)
COCl	H	COCl	(39)
COOH	H	CH=CHCOOH	(56)
CH_3	CH_3	COOH	(57)
C_6H_5	CH_3	COOH	(40, 54)
COOH	CH_3	COOH	(40)
$COOC_2H_5$	CH_3	$COOC_2H_5$	(40)
C_6H_5	COCl	COCl	(40)
C_6H_5	C_6H_5	COOH	(35, 54)
3-Methyl-1-phenyl-1,3-butadiene		COOH	(11)
1-Vinylcyclohexene		$COOCH_3$	(226)
1-(α-Acetoxyvinyl)-1-cyclohexene		$COOCH_3$	(227)
2-Ethyl-1-phenyl-1,3-butadiene		COOH	(20)
1,2-Diphenyl-1,3-butadiene		COOH	(20)

* This is the tautomeric form in which the phenylimine of α-ethyl-β-*n*-propylacrolein reacts with maleic anhydride.

† Reaction with citraconic anhydride gives a mixture of four products, in which the two with the three new asymmetric centers all-cis predominate.

‡ The quinone used was *p*-methoxytoluquinone.

§ The quinone used was 5-hydroxy-1,4-naphthoquinone.

¶ When the sodium salts are used, the reaction gives mixtures of both cis and trans and ortho and meta products (21).

dienes to three main dienophiles: maleic anhydride, *p*-benzoquinone, and acrylic acid and its derivatives. Most of the examples are provided by the thorough investigations of Alder and his collaborators, and clearly show that the principle which determines the orientation of addition to cyclic dienes also operates in acyclic dienes.

One difficulty previously mentioned is that the all-cis adducts are prone to isomerize to their more stable trans isomers under vigorous conditions. Some original reports of trans adducts from acyclic dienes have been corrected in recent years by showing that, at low temperatures and in the absence of equilibrating catalysts, the cis isomer predominates (54, 55, 207, 208). Exceptions to the rule that cis adducts are formed are the *trans*-2-phenylcyclohexenecarboxylic acid derivatives resulting from the addition of *trans*-1-phenyl-1,3-butadiene to acrylonitrile and acrylamide (207), and of methyl 1-phenyl-1,3-butadiene-2-carboxylate to acrylic acid (20).

A corollary of this rule is that cis 1-substituted butadienes should form adducts in which the diene substituent is trans to the dienophile substituent. This has been found to be the case in the adducts of maleic anhydride with *cis*-1-ethyl-1,3-butadiene (7), *cis,trans*-1,4-dimethyl-1,3-butadiene (57), *trans,cis*-4-methyl-1-phenyl-1,3-butadiene (37), methyl *trans,cis*-1-phenyl-1,3-butadiene-4-carboxylate (36), and neoalloöcimene (13).

3. Quasitheoretical calculations

In an attempt to reduce the principle of "maximum overlap of double bonds" to a more quantitative basis, Butz and Butz (110) developed a method of geometrical analysis, which they applied to the reaction of 1,3-cyclohexadiene with 5-acetoxytoluquinone. Employing accurate scale drawings of the diene superimposed on the dienophile in four possible prereaction orientations, they measured the distances between all combinations of the centers of all the double bonds present, assuming an interplanar separation of 1.39 A. (a more reasonable estimate of 2.5–3.0 A. would not alter the results appreciably). They assumed that the angle of rotation of the acetoxy substituent permitting the minimum sum of distances for each of the four diene orientations would be the best approximation of that angle, and that the prereaction orientation which had the smallest resulting sum of distances would produce the major adduct isomer. The properties of the two isolated products were consonant with the structures predicted by this analysis. This method was applied to a number of reported adducts of unknown structure and configuration (110), and in at least one case (265) their predictions have been confirmed experimentally.

Mousseron, Winternitz, and Rouzier (218) extended this approach by deriving a linear equation for T_1, the percentage of a given isomeric adduct, as a function of X_1, the relative double-bond accumulation of the prereaction orientation corresponding to this isomer compared with other possible orientations. This "relative accumulation" was given by $X_1 = C_1/(C_1 + C_2 \ldots C_n)$, where C_1 is the reciprocal of the minimum sum of distances in the orientation involved and C_2 through C_n refer to the other isomers. The constants in the final equation, $T_1 = aX_1 + b$, were evaluated by substituting the T and X values obtained for the cyclopentadiene–maleic anhydride addition, assumed to yield 100 per cent endo adduct. T_1 values for the per cent of adduct with exo carbonyl groups were calculated for five reactions and showed remarkable agreement with experimental results then available (see table 6).

More recent analyses of the products of three of these reactions at lower temperatures indicate, however, that the agreement is not as good with results more kinetically controlled, and that the close comparison with the available data may have been fortuitous. The reaction between cyclopentadiene and cinnamic acid, which gave 85 per cent exo carboxyl at 170°C.

TABLE 6

Results of calculations of Mousseron, Winternitz, and Rouzier (218)

Reaction	T_1		Reference
	Calculated	Experimental	
Cyclopentadiene + benzoylacrylic acid	61	60	(217)
Cyclopentadiene + cinnamic acid	80	85	(217)
Cyclopentadiene + phenylmaleic anhydride	70	70	(218)
Dimethylfulvene + maleic anhydride	56	60	(45)
1,3-Cyclohexadiene + 5-acetoxytoluquinone	35 (a)*	39*	(110)
	42 (b)	55	
	5 (c)	0	
	18 (d)	6	

* a, b, c, and d refer to the four isomeric adducts. The French authors listed 39 per cent of isomer a as found experimentally, although the paper referred to (110) reported the isolation of only a "trace."

(217), produces only 57 per cent exo at 55°C. (253). Two reports claim that cyclopentadiene and phenylmaleic anhydride, at 50°C., give only the endo anhydride (9, 214). At 0°C., the lowest temperature reported for the addition of dimethylfulvene to maleic anhydride, the result is a 3:2 mixture favoring the endo isomer (32). Thus, though this treatment may indicate a profitable mathematical approach, it has certain shortcomings. The neglect of directional characteristics of the attractive interactions between the unsaturated centers, the implication that an increase in stabilization with decreasing distance between double bonds is continuous at small distances, and the nonconsideration of steric repulsions appear to be the most important of these.

A qualitative analysis of spatial relationships of substituents in the transition state proposed by Woodward and Katz (306) has emphasized that, in addition to the secondary attractive forces held responsible for endo addition, steric repulsions between substituents on the diene and dienophile may be of equal or greater importance in determining both stereochemical and structural orientation of the addends (203). Generally, both overlap forces and steric repulsions act in concert to join the addends first at the less substituted carbon atoms and to direct endo addition; in the following section, cases will be considered in which these forces may oppose each other.

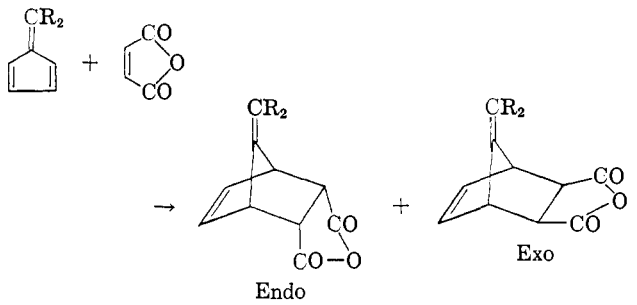
4. Competing effects in dienes and dienophiles

(a) Dienes

The earliest deviations noted from the strict adherence to the rule of endo addition were the fulvene–maleic anhydride adducts (10, 32, 45, 128), in which considerable amounts of exo products accompanied the endo isomers. It was argued, in explanation, that the fulvene possessed two centers of unsaturation which competed for overlap with the dienophile (45, 52, 110). Shown in table 7 are the most recent product analyses

TABLE 7

Stereochemistry of fulvene–maleic anhydride adducts



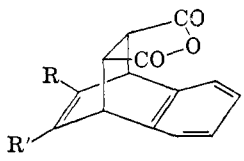
R	Temperature	Endo	Exo	Reference
	°C.			
CH_3	0	1.3	1	(32)
	15	1	1.1	(128)
	38	1	1.3	(32)
	80	1	8.9	(32)
C_6H_5	25–80	Only	—	(10)
	110	2.5	1	(10)
	142 (15 min.)	1.5	1	(10)
	(5 hr.)	1	2.5	(10)

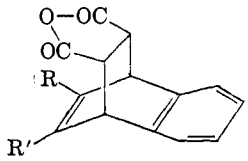
for the addition of maleic anhydride to dimethyl- and diphenylfulvenes, and the striking influence of temperature on the stereochemistry of the product. In both cases the endo isomer is favored at low temperature, while heat favors the exo adduct; the same temperature effect has been noted for the addition of maleic anhydride to 1,1-pentamethylenefulvene (304). Steric effects in the transition state should be slight, since the fulvene carbon atoms are trigonally hybridized, and the kinetic preference for endo addition appears to indicate the greater involvement of the π electrons of the diene ring in complex formation than those of the exocyclic double bond (304).

Another cyclic diene which gives appreciable amounts of both endo and exo adducts is furan. The addition of maleic anhydride in water gives the endo adduct (141), too unstable to be isolated except as its bromolactone, while the adduct formed with maleic anhydride in ether is the exo isomer (305). It, too, forms a bromolactone, which results from molecular rearrangement (305). Berson and Swidler (98) developed a method of analysis which enabled them to follow the course of the aqueous reaction. The endo adduct was initially formed more rapidly, but the addition appeared to be easily reversible, and the more stable exo isomer gradually accumulated at the expense of the endo. The suggestion was made that hydrogen bonding or solvation effects in the aqueous medium may play a part in the preference for endo addition.

In ether at 25°C. maleimide and furan form an endo adduct, which isomerizes on heating or irradiation to the exo isomer (194). 1-Methylfuran adds maleic anhydride in ether to yield almost quantitatively the exo adduct (244). Considering the extreme ease of reversibility of additions to furan, the apparently slight difference in activation energies for endo and exo addition, and the possibility of solvent influences on stereochemistry, it seems unwise to assign configurations to other furan adducts without strong supporting evidence.

Another diene system which offers a competition between two alternate unsaturated centers for orbital overlap is that of unsymmetrical polycyclic aromatic compounds. Reaction of β-naphthol with maleic anhydride produces two isomeric adducts, XXXVIII and XXXIX (in the corresponding keto forms), the former predominating (280); configurations are assigned on the basis of dipole moments. Since steric effects should again be at a minimum, this is taken to



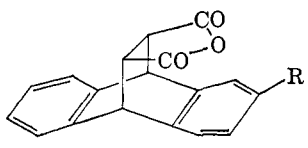


XXXVIII: R = H, R′ = OH
XL: R = R′ = CH_3
XLII: R = R′ = H

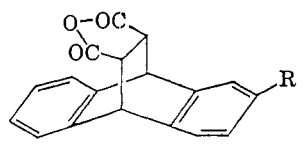
XXXIX: R = H, R′ = OH
XLI: R = R′ = CH_3
XLIII: R = R′ = H

indicate that the dienophile is attracted more strongly to the aromatic ring than to the enol double bond. The addition of maleic anhydride to 2,3-dimethylnaphthalene, however, with (309) or without (187) catalysis by aluminum chloride, yields predominantly the other adduct (XLI). Naphthalene itself gives both adducts XLII and XLIII (187, 278, 279), but in very low yield.

An experiment devised by Conroy and Kaplan (183) to assess the responsibility of electronic effects for endo orientation utilized the addition of maleic anhydride to 2-substituted anthracenes. It was argued that the change in the ratio of adducts XLIV and XLV, as the substituent R was varied from the strongly electron-releasing dimethylamino group to the strongly electron-attracting nitro group, should reflect the importance of polar attractive forces between the diene and dienophile in the transition state. The ratios of XLIV to XLV found were: R = NO_2, 40:60; R = $NHCOCH_3$, 50:50; R = $N(CH_3)_2$, 55:45. Although the results are qualitatively in the expected order, the



XLIV



XLV

free energies of activation of the transition states in each case differ by only about 0.2 kcal./mole; the conclusion was reached that polar effects are of minimal significance in determining the stereochemistry of Diels–Alder addition.

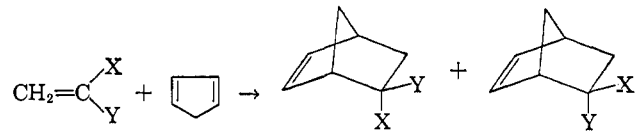
(b) Dienophiles

Possibly the most revealing indication of the delicate balance among the forces which encourage and oppose endo orientation comes from the use of dienophiles with substituents on opposite sides of the double bonds, where groups are pitted against each other in their ability to control the stereochemistry. Table 8 summarizes the results of reactions of cyclopentadiene with 1,1- and trans 1,2-disubstituted, trisubstituted, and tetrasubstituted olefins. Where independent studies of the same reaction are available, only the results of the more reliable analytical data are included if such a choice can be made. The mildest reaction conditions used are chosen, since it is the intention of this table to

TABLE 8

Adducts of cyclopentadiene with unsymmetrical 1,1-disubstituted olefins, trans 1,2-disubstituted olefins, and tri- and tetrasubstituted olefins

A. 1,1-Disubstituted olefins



endo-X endo-Y

X	Y	Endo-X	Endo-Y	Reference
COOH	H	75	25	(286)
COOH	CH_3	35	65	(15)
		24	46	(209)
COCl	CH_3	47.5	46.5	(15)
		60	40	(209)
$COOCH_3$	CH_3	—	Mostly	(86)
$CONH_2$	CH_3	—	Only	(209)
CN	CH_3	—	Only	(264)
CHO	CH_3	Major	Minor	(209)
		Minor	Major	(86)
COOH	C_2H_5	—	Only	(106)
CN	C_2H_5	—	Only	(264)
COOH	C_6H_5	60	40	(15)
COCl	C_6H_5	60	40	(15)
COOH	Cl	30	65	(16)
COOH	Br	30	70	(16)
$OCOCH_3$	CH_3	91.5	8.5	(202)
COOH	CH_2COOH	25	75	(284)
CO	CH_2CO	—	Only	(166)
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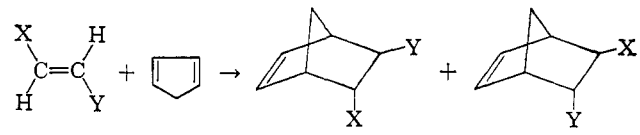
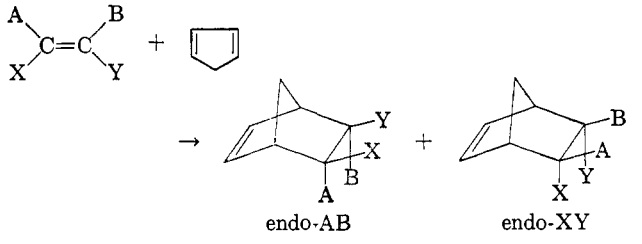
B. Trans 1,2-disubstituted olefins



endo-X endo-Y

X	Y	Endo-X	Endo-Y	Reference
COOH	CH_3	85	15	(15)
COCl	CH_3	Only	—	(49)
COOH	CF_3	33	66	(204)
COOH	Br	80	10	(16)
COOH	Cl	80	10	(16)
COOH	COC_6H_5	40	60	(217)
COOH	$SO_2C_6H_5$	39	61	(215)
$COOC_2H_5$	$CH_2COOC_2H_5$	—	78	(185)
SO_2Cl	C_6H_5	59	41	(255)
SO_2Cl	p-$O_2NC_6H_4$	74	26	(255)
SO_2CH_3	p-$O_2NC_6H_4$	65	35	(254)
$SO_2N(C_2H_5)_2$	p-$O_2NC_6H_4$	54	46	(255)
NO_2	C_6H_5	Only	—	(292)
COCl	C_6H_5	95	5*	(15)
		67	33†	(253)
COCl	p-$CH_3OC_6H_4$	66	34	(253)
COCl	p-ClC_6H_4	67	33	(253)
COCl	p-$O_2NC_6H_4$	64	36	(253)
COOH	C_6H_5	43	57	(253)
COOH	p-$CH_3OC_6H_4$	47	53	(253)
COOH	p-ClC_6H_4	40	60	(253)
COOH	p-$O_2NC_6H_4$	30	70	(253)
$COOCH_3$	C_6H_5	44	56	(253)
$COOCH_3$	p-$O_2NC_6H_4$	28	72	(253)
$CONH_2$	C_6H_5	34	66	(253)
$CONH_2$	p-$O_2NC_6H_4$	25	75	(253)

C. Trisubstituted and tetrasubstituted olefins



endo-AB endo-XY

A	B	X	Y	Endo-AB	Endo-XY	References
CO—O—CO		CH_3	H	Only	—	(9)
CO—O—CO		C_6H_5	H	Only	—	(9, 214)
CO—O—CO		Br, Cl	H	Only	—	(8)
CO—O—CO		Cl	Cl	Mostly	Some	(310)
CO—O—CO		Br	Br	Only	—	(8)
CO—O—CO		CH_3	Br	≥85	—	(9)
COCl	Cl	H	COCl	Only	—	(8)
COCl	CH_3	H	COCl	Only	—	(9)
COCl	CH_3	Br	COCl	—	≥75	(9)
CH_3	COOH	CH_3	H	Mostly	Some	(190)
				47	48	(31)
CH_3	CH_3	H	COOH	55	27	(85)
CH_3	CH_3	H	COCl	62	30	(17)
COOH	CH_3	Br, Cl	H	80	15	(16)
COOH	H	CH_3	Br	—	Only	(16)
COOH	H	Br	Br‡	26	28	(16)
COCl	H	Br, Cl	CH_3	Mostly	—	(16)
COOH	H	Cl	Cl‡	25	25	(16)

* At −10°C.
† At 55°C.
‡ Configuration of β-halogen not known with certainty.

evaluate kinetic control of the stereochemistry; for information on the effect of temperature on the endo–exo ratio, reported in many cases, and for experimental and analytical methods, reference should be made to the sources cited.

Although much of the data is only of approximate validity and may not reflect the true kinetic ratios accurately, a number of semiquantitative observations can be made and trends cited from the results in table 8.

1. As an α-substituent on acrylic acid increases in size from hydrogen to methyl, halogen, phenyl, carboxymethyl, and ethyl, the percentage of endo carboxyl in the adducts progressively decreases, to the point where α-ethylacrylic acid gives exclusively the exo adduct. The same is true for the series of α-substituted acrylonitriles, where even the substitution of methyl for hydrogen shifts the products completely to exo nitrile. The same behavior is exhibited in additions to 1,3-cyclohexadiene; methacrylic acid gives a nearly 1:1 ratio of endo and exo adducts (106), while methacrylonitrile yields exclusively the exo cyano isomer (264). In general, every α-substituent, whether saturated or unsaturated, lowers the amount of endo carboxyl in the product, compared to the unsubstituted case (a striking exception is the addition of isopropenyl acetate, which inexplicably affords an even higher endo:exo acetoxyl ratio than does vinyl acetate). These results represent probably the most compelling evidence for the presence of a strong steric factor in the determination of the stereochemistry of Diels–Alder adducts.

Table 9 presents a summary of activation energies

TABLE 9

Differences in activation energies for addition of α-substituted acrylic acids to cyclopentadiene

α-Substituent (R)	$\Delta\Delta F^{\ddagger}$ (endo R − exo R)	$\Delta\Delta F^{\ddagger}$(R) − $\Delta\Delta F^{\ddagger}$(H)
	kcal./mole	*kcal./mole*
H	−0.68	0
C_6H_5	−0.24	0.44
CH_3	0.47	1.15
Cl	0.47	1.15
Br	0.52	1.20
CH_2COOH	0.82	1.50

involved in the cases cited. The first column shows the difference in activation energies for the transition states leading to endo and exo substituents, while the final column is the difference between this figure and that for the unsubstituted acid, giving a measure of the efficacy of the substituent in overcoming the endo-directing tendency of carboxyl. It must be remembered, in comparing these figures, that the activation energies are not all calculated for the same temperature. Even with this reservation it is evident that, with the possible exception of phenyl, the success of a substituent in opposing the directional influence of carboxyl roughly parallels its size.

2. In the series of trans 2-substituted acrylic acids, the results are much less consistent. Phenyl and carboxymethyl have approximately the same effect in changing the product ratio as they do in the α-position, but, surprisingly, methyl and halogens actually increase

the proportion of endo carboxyl as compared with the parent acid.

An interesting case is the trifluoromethyl substituent. In the reactions of trifluorocrotonic acid with acyclic dienes, such as isoprene, it is the carboxyl which apparently determines the structural orientation (206), probably owing to its greater conjugative ability to stabilize the transition state. With cyclopentadiene, however, the adduct with endo trifluoromethyl predominates 2:1 over that with endo carboxyl. Interpretation of the result is complicated by the finding that the adduct of this dienophile with furan is entirely that with endo carboxyl (204).

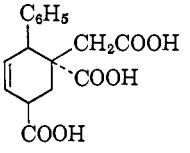
The apparent inconsistencies in the additions of trans 1,2-disubstituted olefins to cyclopentadiene are undoubtedly due largely to the fact that four possible transition states must be considered for each reaction, and these may not differ appreciably in activation energy. Using the transition state proposed by Woodward and Katz (306) for the Diels–Alder reaction and the addition of cyclopentadiene to cinnamic acid as an example, two transition states are derived by first joining the diene to the dienophile carbon attached to phenyl, in each of two possible stereochemical orientations, and the other two result from forming the primary bond to the dienophile carbon attached to carboxyl, again in two orientations. Which of these transition states is the one of lowest energy will depend upon a combination of several factors: (*a*) the relative capacity of each dienophile substituent to interact with the electron freed by primary bond formation, (*b*) the relative strength of the secondary attractive forces between the diene and each of the dienophile substituents, and (*c*) the relative magnitude of nonbonded steric repulsions between the dienophile substituents and the diene in each orientation. Quite clearly, the magnitude and relative weight given to each of these factors are difficult to assess, and the delicate balance among the forces which govern the orientation of the addends makes any prediction tenuous.

3. Nevertheless, in a restricted series of closely related compounds, electronic effects are clearly evident. The careful analysis of the reactions of cyclopentadiene with a series of derivatives of *trans*-cinnamic acid carried out by Rondestvedt and Ver Nooy (253) gives an evaluation of the effect of polar substituents on the steric course of addition. They found that, as the electron-withdrawing power of a *p*-substituent in the aromatic ring increases, the ability of the aryl group to interact with the electrons of the diene increases, and this is reflected in the increasing percentage of endo aryl isomer formed. Quantitatively, however, the change from *p*-methoxy to *p*-nitro increases the per cent of endo aryl from 53 to 70, which corresponds to a difference in activation energy of only 0.48 kcal./mole, so that polar interactions across space in the transition state are relatively feeble. In the cinnamoyl chlorides, changing the *p*-substituent has no effect on the endo:exo ratio.

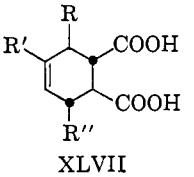
A somewhat greater response is elicited by altering the character of the carboxyl group in cinnamic acid; a trend of increasing endo carboxyl from 34 per cent to 67 per cent is noted as the electronegativity of the group increases from amide to methyl ester, acid, and acid chloride. This corresponds to a difference in activation energy of 0.9 kcal./mole, still slight.

4. In the addition of tri- and tetrasubstituted olefins to cyclopentadiene, it is again hard to deduce a consistent pattern. Evidently the cyclic anhydride moiety is a powerful endo director, giving endo anhydride adducts no matter what the other substituents; the same is true in additions to 1,3-cyclohexadiene (9, 312). In the other cases listed, it is generally, though not totally, true that the side of the dienophile which is substituted by the larger pair of groups tends to lie endo in the adduct, through there are hardly sufficient cases to permit a generalization.

A corresponding study of competing effects of substituents in unsymmetrical dienophiles in additions to unsymmetrical acyclic dienes would be valuable, but few cases of this sort have been reported. The addition of itaconic acid to 5-phenyl-2,4-pentadienoic acid gave the adduct XLVI, in which the carboxymethyl group appears to be cis to the diene substituents (155); this result is consistent with the stereochemistry of the itaconic acid–cyclopentadiene adduct (284).



XLVI



XLVII

1-Acetoxy-1,3-butadiene and fumaric acid give a mixture of both possible adducts in unspecified yield (193); their configurations have been assigned on the basis of conformational arguments. Fumaric acid reacts with *trans*-piperylene to give a 3:1 mixture of the two possible adducts, and with *cis*-piperylene to yield a 1:3 mixture of the same products, but there is no experimental evidence for their configurations (126). 1-Phenyl-1,3-butadiene and 4,4,4-trifluorocrotonic acid afford a 1:1 ratio of stereoisomeric adducts (206). The reaction of fumaryl chloride with several 2-substituted 1-phenyl-1,3-butadienes has been shown (20) to give adducts of configuration XLVII (R = C_6H_5; R″ = H; R′ = CH_3, C_2H_5, and $COOCH_3$), but its addition to 1,2-diphenyl-1,3-butadiene appears to yield the other possible configuration.

Alder and his coworkers studied the addition of fumaric acid derivatives to several unsymmetrically-1,4-disubstituted dienes. Methyl 5-phenyl-2,4-penta-

dienoate (36), 1-phenyl-1,3-pentadiene (37), and *trans, cis*-2,4-hexadiene (57) all gave mixtures of both adducts in unequal amounts, but only in the last case was it possible to show their configurations; the major product of this addition was XLVII (R = R″ = CH_3; R′ = H).

B. STERIC APPROACH CONTROL

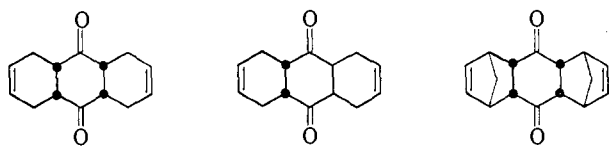
The final principle which governs the configuration of Diels–Alder adducts arises in additions of asymmetric dienes and dienophiles, i.e., addends in which the plane of the double bonds is not a plane of symmetry. A simple rule based on steric hindrance appears to apply to these cases; it may be expressed by stating that those faces of the addend planes which offer the least nonbonded repulsion will be juxtaposed in the favored preliminary complexes and transition states. The rule simply enunciates the natural expectation that the diene should add from the less hindered side of the dienophile, where such a choice exists, and that the dienophile should likewise approach the less hindered face of the diene. The term "steric approach control," coined by Dauben, Fonken, and Noyce (137) to describe a similar consideration in hydride reductions, is appropriate to express this principle here.

1. Steric control of approach to dienophiles

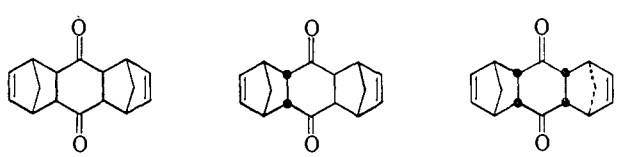
Two principal types of adducts illustrate the operation of steric approach control in the dienophile. These are the bisdiene–quinone adducts and the adducts formed by bridged bicyclic olefins related to norbornene.

(a) Bis adducts of quinones

p-Benzoquinone readily adds two moles of dienes to form bis adducts (14, 41, 42, 94, 179, 309). The first investigation of their stereochemistry was made by Alder and Stein (42) in the cases of adducts with 1,3-butadiene, cyclopentadiene, and 1,3-cyclohexadiene. They proved that all ring junctions in these adducts were cis, but could not decide between the two structures XLVIII and XLIX possible for the bis(1,3-butadiene) adduct or among the six possible configurations (L–LV) for the biscyclopentadiene adduct [six similar formulas are also possible for the bis(1,3-cyclohexadiene)adduct]. Based on the ease of isomerization of the adducts, however, tentative assignments were made to the adducts of the cis,syn,cis structures, XLVIII and L (42).



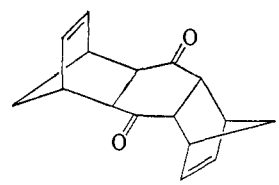
XLVIII XLIX L



LI LII LIII

LIV LV

Recently it was shown that the bis(1,3-butadiene) adduct is the cis,anti,cis compound (XLIX); the proof involved desulfurization with Raney nickel of the bis-ethylenethioketal to *cis,anti,cis*-perhydroanthracene (167). Using a particularly ingenious approach, de Vries, Heck, Piccolini, and Winstein (288) elucidated the configuration of the biscyclopentadiene adduct. The tetrahydro adduct could be isomerized by base to two additional isomers, and all three were oxidized to the same quinone. Two of the three isomers were partially reduced to monoalcohols which could be resolved, thus placing the adduct within the group LIII–LV. Since the monocyclopentadiene–quinone adduct is endo (26, 121), the bis adduct must have at least one endo junction, eliminating LV. The order of stepwise isomerization and the recognition that the adduct is the least stable of the three isomers were taken to show that the adduct is LIV, the endo-cis,anti,endo-cis isomer.



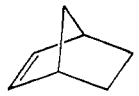
LIV

Thus the bisdiene adducts obey the rules of cis addition and endo orientation, and in addition illustrate the principle of steric approach control in giving cis,anti,cis products. It is known that the addition of dienes to quinone is stepwise, the first molecule adding some one hundred times more rapidly than the second (42, 291). These results show that the second diene molecule, in approaching the 1:1 adduct, prefers the less hindered side *opposite* that of initial addition.

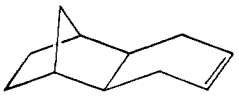
(b) Norbornene and related dienophiles

The strained double bond in norbornene (LVI) and its derivatives makes them good dienophiles. The principle of steric approach control leads to the expectation that dienes, like other reagents (61), should add preferentially from the exo side, with the hindrance due to the single methylene considered to be less than

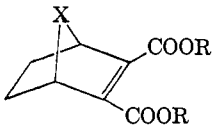
that caused by the ethylene bridge. This expectation has been confirmed by practically all additions in this series.



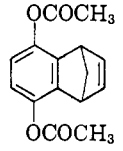
LVI



LVII



LVIII

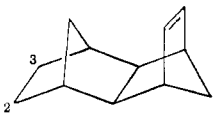


LIX

Alder, Mönch, and Wirtz (26) recently described the addition of 1,3-butadiene to norbornene and several of its relatives. The parent adduct (LVII) was shown to be exo by ozonolysis to a dicarboxylic acid which was synthesized by homologation of *exo*-norbornane-1,2-dicarboxylic acid. The adducts of 1,3-butadiene with norbornadiene, acetoxynorbornene, and with the cyclopentadiene–maleic anhydride adduct were all related to the parent, and thus shown to involve exo addition. 1,3-Butadiene adds to the bridged dienophiles LVIII (X = CH_2 or O) to yield adducts in which the new ring is exo (45, 276); the latter (XXV) was an intermediate in a stereospecific synthesis of cantharidin. Addition of 1,3-butadiene to LIX and bis addition to norbornadiene have been shown to occur completely exo (285).

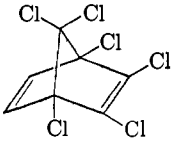
The use of cyclopentadiene in additions to norbornenes gives more complicated adducts in which four new asymmetric centers have been created. Alder and his coworkers early demonstrated that the skeleton formed has the same configuration, no matter what the substituents on the dienophile: the adducts of cyclopentadiene with the isomeric 5-norbornene-2,3-dicarboxylic acids (43), the adducts formed from two molecules of cyclopentadiene and vinyl acetate (28), vinyl formate (28), and acrolein (59), and the two cyclopentadiene trimers (43, 50) were all degraded to a common diacid which contained the four new asymmetric centers. The parent adduct of cyclopentadiene and norbornene was reported in 1952 by Soloway (271), who elegantly demonstrated it to have the configuration shown in formula LX. The reasonable assumption was made that the adducts of norbornene and acetoxynorbornene have the same stereochemistry; this has since been verified by Stille and Frey (275), who related the cyclopentadiene–norbornadiene adduct (LXI) to both Soloway's adduct and the adducts prepared by Alder. Hexachlorocyclopentadiene adds to 7-*anti*-hydroxynorbornene to afford an adduct of the same skeletal configuration (299).

Thus, the addition of cyclopentadiene to norbornenes is highly stereospecific, and exemplifies the principles of endo addition of the dienophile to cyclopentadiene and exo addition of the diene to the norbornene system. The important insecticides aldrin and isodrin (211) are further examples of the operation of these principles. Synthesis of aldrin (XXXI) involves endo addition to the diene, hexachlorocyclopentadiene, and exo addition to the dienophile, norbornadiene. Isodrin (XXX) represents the first violation of the rule of exo addition to norbornenes, but there appears to be good reason. In the dienophile LXII the methylene bridge is substituted by two bulky chlorine atoms, while the two-carbon chain has both carbon atoms trigonally hybridized, so the usual order of steric hindrance is reversed and the diene adds from the endo side (272).



LX

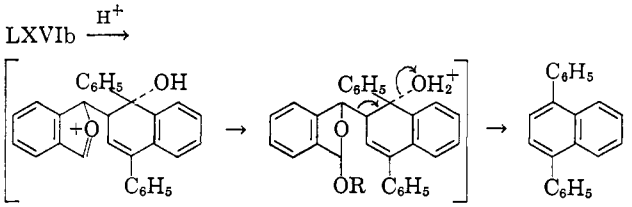
LXI (2,3-double bond)



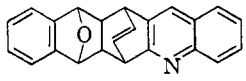
LXII

Two adducts of structure LXIII are formed in the reaction of acridine with the bridged oxide LXIV; they were regarded as resulting from addition of the diene both endo and exo to LXIV (302). From the prevalence of endo–exo mixtures in additions to cyclic dienes and the scarcity of endo addition to norbornenes, it seems more probable that the adducts are LXIIIa and LXIIIb, both formed by exo addition to LXIV. If the isomerism were only that due to endo and exo orientation with respect to the oxygen-bridged ring, then addition of anthracene to the same dienophile should also give two products; only one is reported (302). Two other unsymmetrical dienes, phenazine and 2,5-diphenyl-3,4-benzofuran (LXV), also give two stereoisomeric adducts with LXIV, which are undoubtedly of the same type.[2]

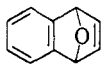
[2] Structures LXVIb and LXVIc were assigned to the latter adducts (302), but the experiments reported in the paper serve to exclude LXVIc and support LXVIa and LXVIb, the two isomers expected on the basis of the preceding arguments. Treatment of one of the adducts with acid gave 1,4-diphenylnaphthalene; this is consistent with configuration LXVIb, in which the bonds labeled x and y have the trans-anti-parallel relationship required for ready cleavage:



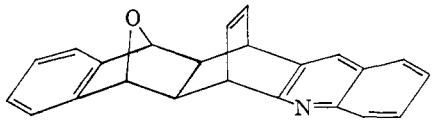
The other adduct, when treated with acid, formed 1,4-diphenyl-2,3-benzanthrone (LXVII), requiring a trans-anti-parallel alignment of the central hydrogen atoms and the C—O bridge for simple elimination. LXVIc does not meet this requirement (and in addition, has its two fused benzene rings prohibitively close together), but LXVIa does.



LXIII



LXIV



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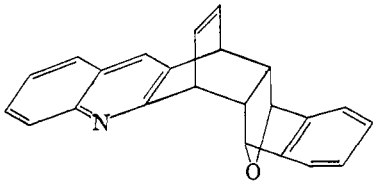

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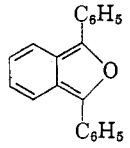
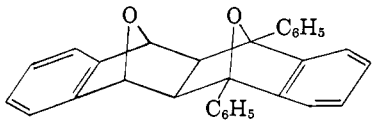
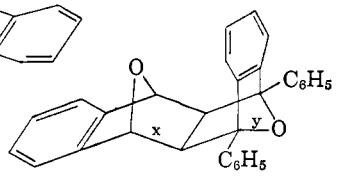


LXV



LXVIa



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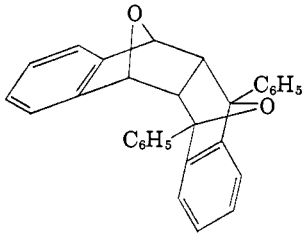
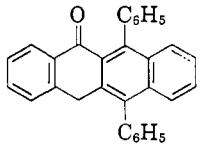


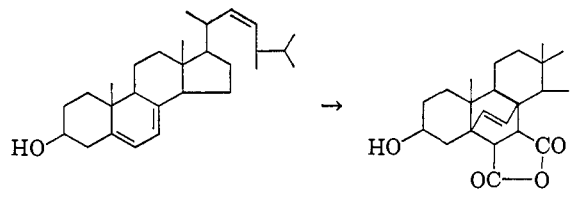
LXVIc



LXVII

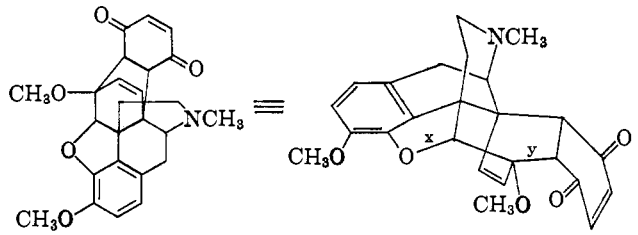
2. Steric control of approach to dienes

Two examples, both reactions of natural products, are recorded in the early literature of the Diels–Alder reaction, in which the stereochemistry of the products is interpretable in terms of steric control of approach to the diene. Maleic anhydride, in reacting with ergosterol (LXVIII), adds from the α (or less hindered) side (148) of the sterol (298). The evidence for the configuration of the adduct is the resistance of the 6,7-double bond toward hydrogenation (175), which indicates that not only is the double bond on the hindered β side of the molecule, but also that the anhydride added endo to the diene system. A similar result would be anticipated for the maleic anhydride–levopimaric acid adduct, for which there is some evidence (66, 259).



LXVIII

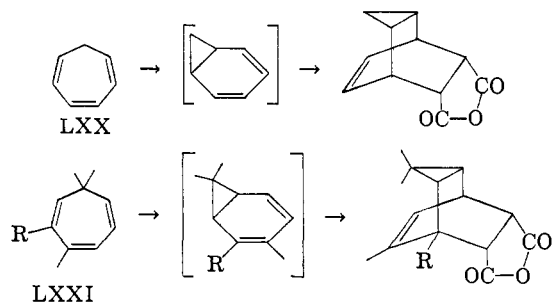
Not long after, the adducts of thebaine with dienophiles were assigned the configuration shown for the benzoquinone adduct (LXIX) (263), the dienophile having added from the less hindered side of the diene and oriented endo. The evidence for this configuration is (*a*) the resistance to hydrogenation of the nonconjugated double bond, (*b*) enolization to a hydroquinone whose properties show that one oxygen is close in space to the nitrogen, and (*c*) the trans-anti-parallel arrangement of the bonds labeled x and y which permits the facile rearrangement of the hydroquinone (210). Other adducts of thebaine, among them those with acrylonitrile, methyl vinyl ketone, and phenyl vinyl ketone (87, 88), appear to have the same configuration.



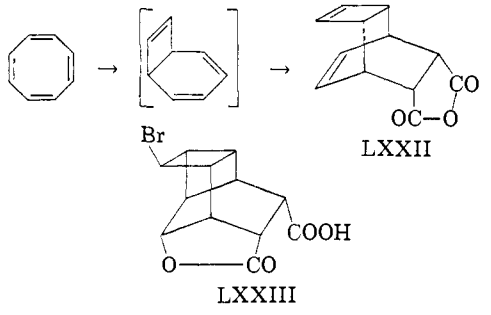
LXIX

Resistance to hydrogenation has been exploited effectively in determining the stereochemistry of other adducts. Cycloheptatrienes tautomerize to bicyclo-[4.1.0]heptadienes before adding maleic anhydride; since the double bond in the adducts of the substituted trienes (LXXI: R = H, CH_3, C_6H_5) is much more unreactive to hydrogenation or oxidation than that in the adduct of the parent triene (LXX), it was concluded that the adducts have the configurations shown (23). The maleic anhydride–cycloöctatetraene adduct has been shown recently to have the structure LXXII (71). This was uniquely demonstrated by conversion with bromine to the pentacyclic lactone LXXIII. Similar skeletal configurations are formed in adducts with cycloöctatetraene dibromide and epoxide and cycloöctatriene, and in the addition of fumaryl chloride and acetylenedicarboxylic ester to the tetraene (71). In all these additions the dienophile approaches from the less hindered side of the bicyclic diene.

In another example, the bis addition of maleic anhydride to 3,3-dianisyl-1,1-diphenylallene was reported



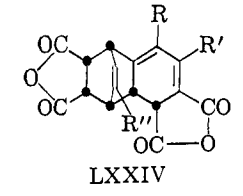
LXXI



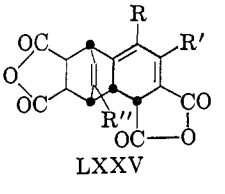
LXXII

LXXIII

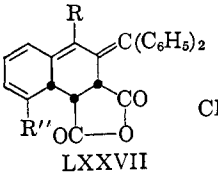
to give two adducts, LXXIV and LXXV (12). Both compounds, after hydrolysis of the enol ether, formed different lactones (LXXVI) on esterification. The lactones isomerized upon vigorous hydrolysis to produce the same keto tetraacid. These results are consistent only with the configuration shown. The major adduct was resistant to hydrogenation and was consequently assigned the endo configuration (LXXIV), while the minor adduct (LXXV) readily formed a dihydro compound. It can be seen that the adducts differ only in the endo and exo orientation of the anhydride ring, and both result from addition of the second molecule of maleic anhydride to the less hindered side of the 1:1 adduct (LXXVII). Tetraphenylallene gave similar results (12). The bis(maleic anhydride) adduct of anethole has been subjected to similar transformations (109), showing it to have the related structure LXXVIII.



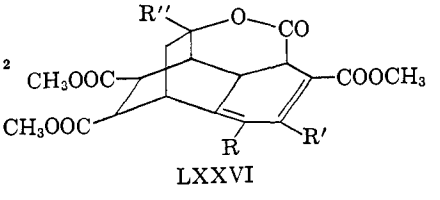
LXXIV



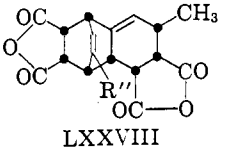
LXXV



LXXVII



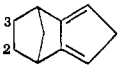
LXXVI



LXXVIII

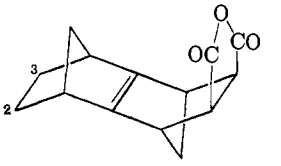
R = *p*-$CH_3OC_6H_4$; R′ = $CH(C_6H_5)_2$; R″ = OCH_3.

The interesting dienes "isodicyclopentadiene" (LXXIX) and "dehydroisodicyclopentadiene" (LXXX) were prepared by Alder, Flock, and Janssen (14) and found to add dienophiles readily. The maleic anhydride adducts were assigned configurations LXXXI and LXXXII on the basis of the principles discussed. A reservation to the acceptance of this configuration is that the adducts form addition products with phenyl azide, and this reagent has never been observed to add from the endo or hindered exo side of norbornenes (44, 48, 60), as structure LXXXI would require.



LXXIX

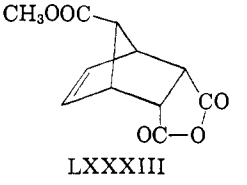
LXXX (2,3-double bond)



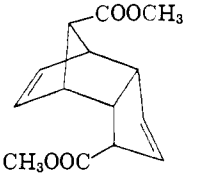
LXXXI

LXXXII (2,3-double bond)

Finally, mention should be made of conflicting results with a few simple monosubstituted cyclopentadienes. The principle of steric approach control predicts that a 5-substituted 1,3-cyclopentadiene should react with a dienophile to give a syn-7-substituted norbornene. This appears to be the case in the addition of maleic anhydride to methyl 2,4-cyclopentadiene-1-carboxylate (44), since the adduct (LXXXIII) is inert to phenyl azide. The dimer of this diene, however, apparently has the 7-anti configuration (LXXXIV), since it readily adds phenyl azide.

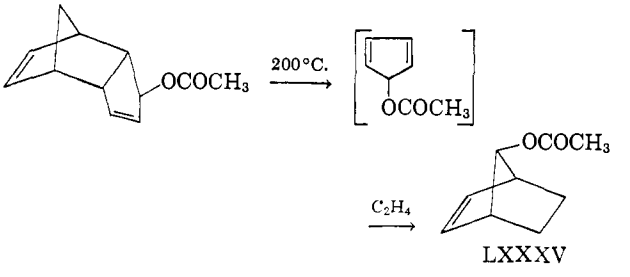


LXXXIII



LXXXIV

1-Acetoxy-2,4-cyclopentadiene, generated by the thermal decomposition of 1-α-acetoxydicyclopentadiene,[3] adds ethylene *in situ* to provide 7-*anti*-acetoxynorbornene (LXXXV) (300). Study of additional cases of this sort would clearly be worthwhile.



LXXXV

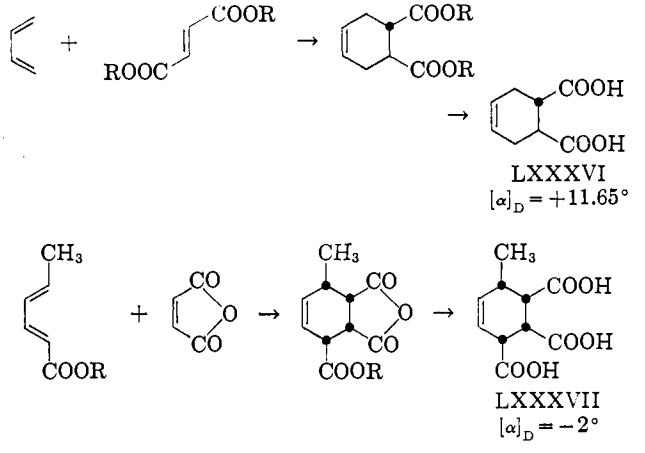
3. *Asymmetric induction in the Diels–Alder reaction*

Embodied in the principle of steric approach control is the corollary of asymmetric induction, the addition of a planar addend to an asymmetric one to create a new asymmetric center in nonstatistical ratio. An interesting Russian report bears out this possibility with simple optically active dienes and dienophiles.

Korolev and Mur (192) found that after adding 1,3-butadiene to the mono- or di-*l*-menthyl esters of

[3] The *Ring Index* name is 1-acetoxy-3*a*,4,7,7*a*-tetrahydro-4, 7-methanoindene.

fumaric acid (or the corresponding esters of maleic acid, which rearranged to fumarates under the reaction conditions), saponification of the adducts gave optically active 4-cyclohexene-1,2-dicarboxylic acid (LXXXVI). Similarly, the reaction of maleic anhydride with *l*-menthyl sorbate, followed by hydrolysis, afforded the partially active triacid LXXXVII. Neither the optical purity nor the absolute configuration of the products is known. The reaction represents a potentially powerful method for the determination of absolute configurations of a variety of adducts, comparable to the atrolactic acid method of Prelog for assigning absolute configurations to alcohols (241).



R = *l*-menthyl.

It may be noted that an example of asymmetric induction in a related reaction, the substitutive addition of dienophiles to olefins, has been reported (70) in the addition of maleic anhydride and its derivatives to β-pinene.

VI. Conclusions

It is impossible to complete a review of the stereochemistry of the Diels–Alder reaction without being impressed by the tremendous contributions, over many years, of Kurt Alder and his students, who have given the reaction probably the most thorough investigation that any organic reaction has ever received. Based on their work and that of many other investigators, the principles which appear to govern the stereochemistry of Diels–Alder addition may be summarized as follows:

1. The diene must be oriented in the "cisoid" conformation before addition. Substituents which interfere with the attainment of this conformation hinder or prevent addition.

2. With the reservation that the product isolated from a Diels–Alder reaction may not always be the initially formed adduct, no exceptions have been found to the rule that the orientation of substituents in the diene and dienophile is unchanged in the adduct.

3. Substituents in the dienophile prefer to lie above the unsaturated system of the diene, leading to endo addition. The experimental data support the suggestion that this is partly due to secondary attractive forces in the transition state, though the magnitude of these forces appears to be quite small. To a degree not heretofore considered, steric repulsions in the transition state appear to be largely responsible for endo addition.

4. The diene and dienophile tend to approach each other from the less hindered side of each.

It is a pleasure to acknowledge helpful discussions with Professor Gilbert Stork and his courtesy in making available some unpublished results.

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