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STEREOCHEMICAL ASPECTS OF THE DIELS-ALDER REACTION

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The mechanism of the Diels-Alder reaction has been a subject of intense interest for many years (1) and yet there is still substantial ambiguity concerning the timing of formation of the various bonds. In the present work we have examined the stereochemical pathways of systems designed to favor the diradical intermediate which might be involved in a two-step mechanism. The Woodward-Katz mechanism (1) embraces the salient features of both concerted and stepwise processes, although the authors seem to imply that, under favorable circumstances, a second barrier may intervene during the formation of the second bond, thus causing the overall process to be truly stepwise and perhaps not wholly stereospecific. In this context, Hendrickson (2) has recently investigated the reaction between cyclopentadiene and the isomeric β-sulfoacrylic acids which may involve loss in the adduct of the stereochemical integrity of the alkene, but no clear conclusion was possible. Bartlett and co-workers (3) have demonstrated for the 1,4-cycloaddition between 2,4-hexadiene and 1,1-dichloro-2,2-difluoroethylene that a bifunctional

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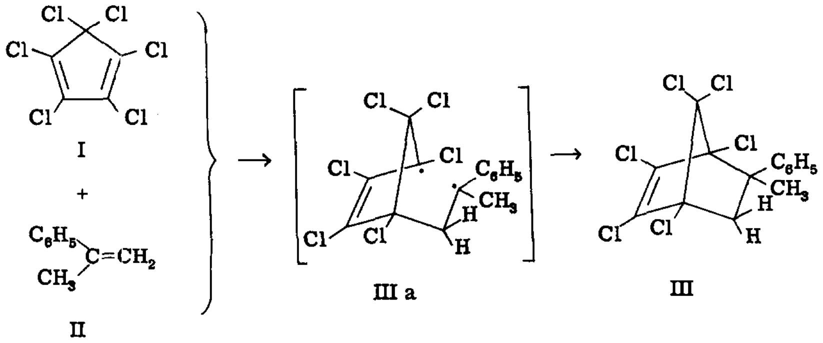
* Contribution No. 3210.

intermediate is sufficiently long-lived to permit internal bond rotation, with concomitant loss of the initial stereochemistry, about ten times as fast as ring closure to the four-membered ring. The proposed diradical intermediate for this case is stabilized as an allyl radical at one center and as a dichloromethyl radical at the other.

A similarly stabilized diradical intermediate could be involved in the Diels-Alder reaction of hexachlorocyclopentadiene (I) and α-methylstyrene (II).



At one center, the intermediate would be a tertiary and benzylic radical whereas at the other it would be an allylic radical, stabilized by a chlorine atom. We have followed the stereochemical course of this reaction by stereospecific introduction of deuterium into the vinyl position of the alkene and examination of the location of labeling in the adduct by n.m.r. spectroscopy.*

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* Another reason for choosing the particular system was to have two groups on the same carbon atom of the alkene in order to avoid the predominant *endo* or *exo* preference which a single group usually has. Phenyl and methyl have similar tendencies to give *endo*/*exo* products as compared to the carboxyl group, *cf.* J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).

α-Methyl-*trans*-β-deuteriostyrene* was prepared by hydrolysis (4) of the lithium reagent** of α-methyl-*trans*-β-bromostyrene with deuterium oxide. The bromide had been fractionally distilled until less than 2% of the *cis* isomer was present. The diene, a two-fold excess of the alkene, and a tenth molar portion of 2,6-lutidine were heated in a sealed glass ampoule at 130° for 3 hours.*** The unreacted alkene and the adduct, a high boiling oil, were purified by distillation (5).

Figure 1 displays the spectrum of the geminal protons of the adduct labeled predominantly *trans* to the phenyl group. The quartet

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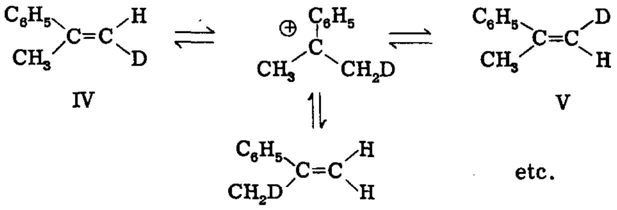
*"*Trans*" will always be with reference to the phenyl group.

**In subsequent experiments it was found that hydrolysis of the Grignard reagent afforded a more specifically labeled product, *e.g.*, 78% *trans* and 2% *cis* deuterium. There is extensive formation of methylphenylacetylene in the reaction of the bromide with lithium.

***The hindered base is required to trap small amounts of hydrochloric acid which are produced during the reaction. In the absence of base, the acid catalyzes a symmetrization of the alkene which scrambles deuterium between the methyl and vinyl positions:



The alkene itself was configurationally stable under the above reaction conditions, but after reaction with the diene at 130° for 20 hours in the absence of base, deuterium was distributed statistically among the five positions offered by the methyl and vinyl groups. This scrambling process provided a means of demonstrating the irreversibility of adduct formation, since the *endo*/*exo* ratio in deuterated III never approached unity, even when the *cis*/*trans* ratio in excess alkene had long since attained this value.

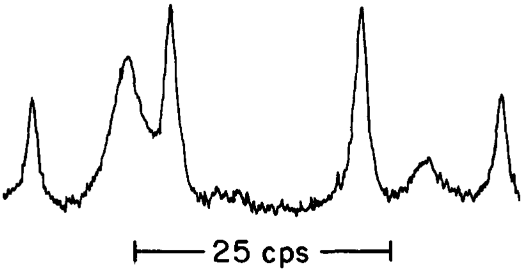
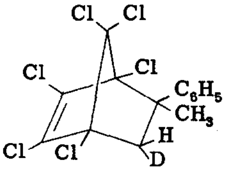


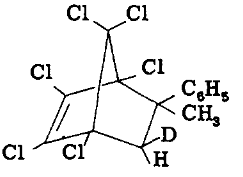
FIG. 1.

Proton spectrum of the methylene group of the adduct of hexachlorocyclopentadiene and α-methylstyrene partially deuterated in the beta position (III, VII, and VIII). The field increases from left to right.

resonance arises from III. The low-field peaks, in accordance with an



VII



VIII

abundance of empirical data (5-7), are assigned to the exo protons, which are approximately in the plane of the anisotropic double bond. The distributions of deuterium in the adduct and in the starting material, as derived from their proton spectra, are listed in Table I. The exo/endo ratio and the cis/trans ratio are identical within the experimental error.

The predominance of protons in the exo portion in the adduct coupled with knowledge that the deuterium in the starting alkene was largely trans indicates that the adduct has the phenyl group exo (III). The only

TABLE I

Distribution of Deuterium Labeling

	trans	cis
Starting alkene[a,b]	43.4±1.5	16.6±1.5
	endo	exo
Adduct[a,c]	41.8±2.0	17.0±1.0

[a] The percentages are the average of at least 5 upfield and 5 downfield sweeps.

[b] The integrals of the vinyl protons were obtained by comparison with a standard of 3 protons provided by the methyl group.

[c] The percentages were obtained by direct integration of the components of the methylene group.

alternative would be to have a complete reversal of stereochemistry in the addition; i.e., the phenyl coming in so as to be exclusively endo, but cis to deuterium to precisely the same extent that it was trans in the starting alkene.* This is rather improbable. These data therefore show that, even in this case, heavily weighted toward a diradical pathway, the stereochemical relationship between the groups on the alkene is maintained in the adduct. Nonstereospecificity to the extent of 2-3% would have gone undetected.

Since, in a two-step mechanism, the initially formed bond would presumably be that to the methylene group, bond rotation would only

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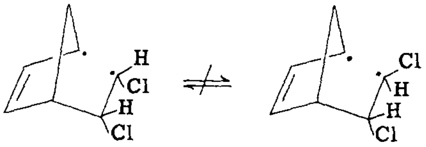
* This conclusion would obviously not follow if a mixture of isomers were formed. However, the sharp melting point (5) and the presence of only a single quartet resonance for the methylene group excludes this possibility. The phenyl group must therefore be completely exo or completely endo.

affect the stereochemistry of the tertiary carbon. If the reaction were subject to thermodynamic control and if the diradical IIIa were more stable than the corresponding endo-phenyl diradical, the observed high degree of specificity would also be expected. Because the reaction is irreversible, this is unlikely; however, the possibility cannot be logically excluded without demonstration of complete retention of stereochemical relationships in the missing endo-phenyl isomer. To clarify this point, a second system, for which both isomers were available, was investigated. The stereospecificity of the addition of cis- and trans-1,2-dichloroethylene to cyclopentadiene was examined by gas chromatography, an analytical tool of much higher sensitivity than n.m.r. spectroscopy. The cis and trans alkenes were obtained from commercial mixtures, each containing about 80-90% of the respective isomers, by distillation through an 80-cm column with Heli-Pak packings, and when purified contained 99.99% cis (b.p. 60.0°) and 99.5% trans (b.p. 47.5°), respectively. The additions were carried out for 24 hours at 180° in a sealed glass tube, and the adducts (8) were characterized by their retention times and n.m.r. spectra. In each case, when pure alkene was used, the product of nonstereospecific addition was not present in a concentration greater than that of the impurity in the starting material ($< 0.5\%$), as ascertained by flame-ionization gas chromatography. The reaction mixtures were examined directly without purification in order to avoid preferential losses during isolation procedures. Clearly, if diradical intermediates such as IX and X are actually formed, they show no significant tendency to interconvert even though the steric strain in IX might tend to favor its conversion to X. The high degree of specificity in these reactions seems best accounted for on the basis of a one-step, concerted mechanism (9).



IX X

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(9) The apparent *exo* orientation of phenyl in III is surprising, in view of the Alder rule. If future empirical evidence indicates a reversal of assignment, i.e., *endo* protons resonate at lower field, the stereochemistry of III will be altered, but the conclusion that the reaction is stereospecific will not be affected.