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INTEGRITY OF ALKENE STEREOCHEMISTRY IN THE DIELS–ALDER REACTION

JOSEPH B. LAMBERT,* CHARLES D. MCLAUGHLIN and VICTOR MARK
Department of Chemistry, Northwestern University, Evanston, IL 60201, U.S.A. and Engineering Products Department, General Electric Co., Mt. Vernon, IN 47620, U.S.A.

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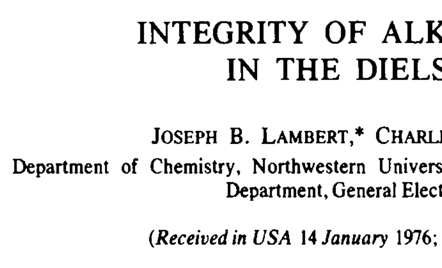
Abstract—The Diels–Alder reaction of hexachlorocyclopentadiene and α-methylstyrene produces both *exo*-phenyl and *endo*-phenyl adducts, with the latter in preponderance. A deuterium label at the β position of the alkene provides a probe for determining whether the vicinal stereochemical relationship between groups on the alkene is retained in the adducts. From the alkene labeled 77.6 ± 2.3% *E* and 22.4 ± 2.3% *Z* was produced the major (*endo*-phenyl) isomer with 79.4 ± 1.1% *exo-d* and 20.6 ± 1.1% *endo-d* and the minor (*exo*-phenyl) isomer with 78.9 ± 0.5% *endo-d* and 21.1 ± 0.5% *exo-d*. Thus both adducts are produced with complete retention of alkene stereochemistry.

In 1965, we reported on the stereochemistry of the Diels–Alder reaction of hexachlorocyclopentadiene and α-methylstyrene (Eqn 1).[2] The reactants were chosen to produce a potentially well-stabilized diradical intermediate, if the reaction should take place by a stepwise mechanism. One radical center would be tertiary and benzylic, the other tertiary, allylic and chlorine-stabilized (Scheme 1). A deuterium atom was placed stereospecifically at the β position of the alkene to serve as a probe of reaction stereochemistry. The Diels–Alder reaction can produce adducts with the phenyl group either *endo* (3) or *exo* (4) (Scheme 1). Although secondary orbital interactions suggest that the *endo*-phenyl product (3) will be dominant,[3] it is not uncommon that both isomers are formed.[4] In our original study, only the *endo*-phenyl isomer was isolated,[2] but later work[4] showed that both isomers are produced. The major isomer was originally assigned, with reluctance,[5] to the *exo*-phenyl structure (4) on the basis of then-available NMR correlations.[2] These correlations, however, proved to be faulty, and indeed the major isomer is the *endo*-phenyl (3).[4]

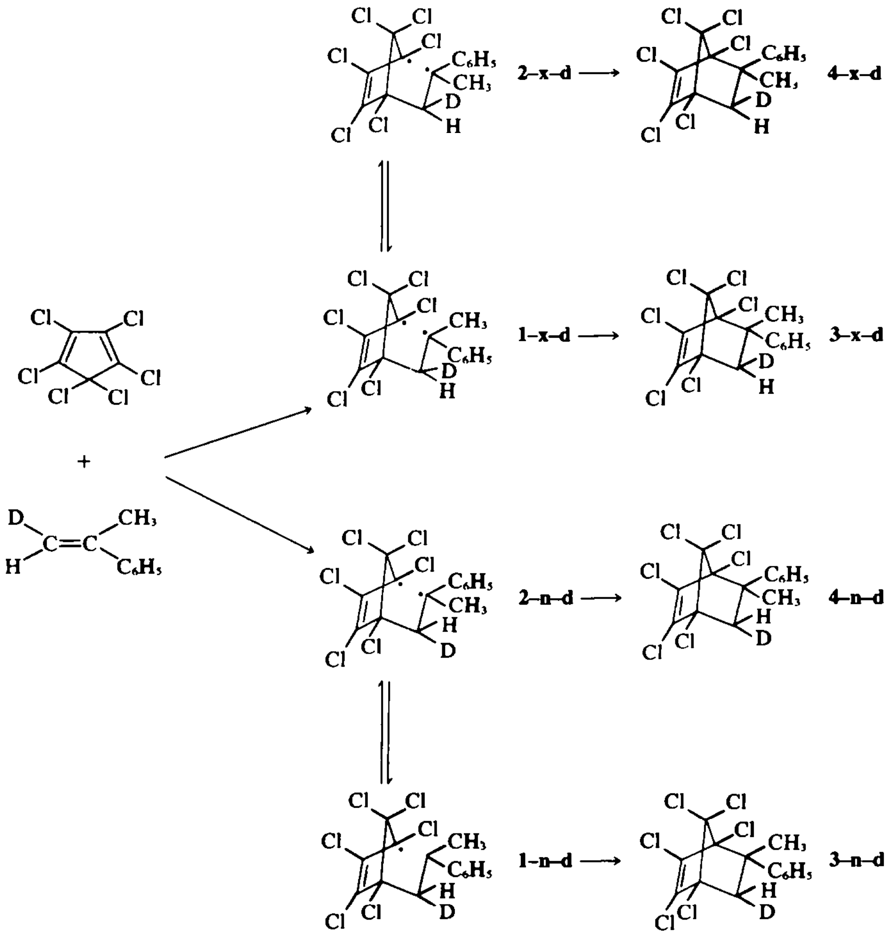


(1)

In our earlier study, we showed that the vicinal stereochemical relationship between groups on the deuterium-labeled alkene is completely retained in the *endo*-phenyl adduct.[2] Because the minor adduct was not isolated, however, the analysis suffered from a major drawback. In a hypothetical two-step mechanism, the first bond to be formed would undoubtedly be that between the diene and the methylene carbon of the alkene, in order to produce the more stable diradical (**1**-*x*-*d* or **2**-*n*-*d* in Scheme 1). The stereochemistry of the –CDH– center is thereby frozen. Any number of rotations could take place about the $CH_3C_6H_5C$–CHD bond *without loss of the original alkene stereochemistry*, so long as a phenyl group that begins in the endo position (**1**-*x*-*d*) also ends up there (**3**-*x*-*d*). In order to produce loss of *cis-trans* stereochemistry, the *endo*-phenyl diradical **1**-*x*-*d* would have to rotate an odd number of times to give **2**-*x*-*d* and ultimately the less stable *endo*-methyl isomer **4**-*x*-*d*. Thus loss of stereochemistry in the *endo*-phenyl diradical **1** could only be observed in the labeling pattern of the minor *endo*-methyl isomer **4**, which was not isolated in the original study.[2] The previously observed retention of alkene stereochemistry in the major *endo*-phenyl isomer **3** only demonstrated that rotation does not occur in an initially formed minor *endo*-methyl diradical (**2**-*n*-*d* $\nrightarrow$ **1**-*n*-*d*). Without knowledge of the stereochemical result in both the major *endo*-phenyl and the minor *endo*-methyl adducts, however, the *cis-trans* stereospecificity of the reaction has not been rigorously tested. This fallacy in the analysis was pointed out in the original paper,[2] and control experiments were run to strengthen the case. In the later study,[4] which did not utilize deuterium labeling, the minor isomer was finally isolated. The critical experiment therefore is to examine the minor isomer, suitably labeled with deuterium, for *cis-trans* stereochemical scrambling. Any loss of stereochemical integrity in the favored diradical **1** would be reflected in the stereochemistry of the less favored product **4**. We report herein the preparation of α-methylstyrene with improved stereoselectivity of the β-deuterium label, compared to that in the original study.[2] We have isolated both the *endo*-phenyl and the *endo*-methyl products and determined the location of the deuterium label. Both products are formed with complete stereospecificity.

RESULTS AND DISCUSSION

Quenching of the Grignard reagent from *trans*-β-bromo-α-methylstyrene in deuterium oxide produced β-deuterio-α-methylstyrene, which by NMR integration had a composition of 77.6 ± 2.3% *E* and 22.4 ± 2.3% *Z*.[6] This label is somewhat more specific than that used in the previous study[2] (72.3 *E*, 27.7 *Z*), which utilized an organolithium preparation.[7] The Diels–Alder reaction was carried out by heating the labeled alkene with hexachlorocyclopentadiene and a small amount of 2,6-lutidine in a sealed container at 127–133° for 3 hr. The hindered base was used to scavenge small amounts of acid that could



Scheme 1.

cause alkene isomerization.[2] The alkene was configurationally stable under the reaction conditions.[8] The distilled reaction mixture could be analyzed directly by NMR integration, or the *endo*-phenyl and *endo*-methyl isomers could be separated by column chromatography and analyzed separately by NMR.

In an unlabeled run, the *endo*-phenyl adduct produces an AB quartet with the doublets at about $\delta 3.1$ and 2.6 for the geminal protons at the 6 position. In the labeled material, these doublets become singlets, whose relative intensities can easily be obtained by NMR integration. Similarly, the AB quartet of the minor isomer at about $\delta 3.6$ and 2.1 becomes a pair of singlets in the labeled adduct. In the *endo*-phenyl isomer, the *endo* proton resonates at lower field; in the *endo*-methyl isomer, the *exo* proton is at lower field.[4] It was this unexpected inversion of resonances that originally caused the misassignment of isomer structure.[2] Integration showed that the *endo*-phenyl isomer had 79.4 ± 1.1% *endo* proton (*exo* deuterium) and 20.6 ± 1.1% *exo* proton. The *endo*-methyl isomer had 78.9 ± 0.5% *exo* proton and 21.1 ± 0.5% *endo* proton. Thus there is no experimentally observable change in the stereorelationship between the deuterium label and the phenyl group in either the *endo*-phenyl or the *endo*-methyl isomers during the Diels–Alder reaction.

The observation of complete retention of alkene stereochemistry in both isomers is consistent either with an essentially concerted reaction or with the formation of diradicals (**1**-*x*-*d* and **2**-*n*-*d*) that do not rotate to the complementary diradicals (**2**-*x*-*d* and **1**-*n*-*d*), which have the same structures but different labeling stereochemistry. Although complete stereospecificity is possible in fully diradical (two-step) reactions, the anticipated structural stability of **1** and **2** makes the possibility unlikely.[8] The best qualitative picture of the "essentially concerted" reaction is the Woodward–Katz two-stage mechanism,[11] in which bond formation occurs simultaneously at both ends of the alkene, but to a different extent. Whatever the details, the stereospecificity of formation of both major and minor adducts indicates that molecular alignment in the transition state is extremely rigid.

EXPERIMENTAL

β-Deuterio-α-methylstyrene. In a 300 ml, 3-necked flask, flamed out and filled with N_2, a Grignard reagent was prepared from 0.02 mol of EtBr and 0.17 mol of Mg in 70 ml of THF. The mixture was refluxed for 0.5 hr and cooled to 0°, and 0.147 mol of β-bromo-α-methylstyrene in 40 ml of THF was added dropwise. The dark green soln was refluxed for 2.5 hr and cooled to 0°. With rapid stirring, 0.4 mol of D_2O was added dropwise. The soln was decanted from the Mg salts, which were washed several times with additional THF. Distillation yielded 9.2 g (52%) of the desired product: b.p. 63° (30 mm).

Diels–Alder reaction. In a 50 ml, pear-shaped flask sealed with a neoprene stopper, 0.084 mol of β-deuterio-α-methylstyrene, 0.04 mol of hexachlorocyclopentadiene, and 0.005 mol of 2,6-lutidine were heated at 127–133° for 3 hr. The cooled mixture was filtered and distilled at 120° (0.06 mm). The residue could either be examined directly by NMR spectroscopy, since the resonances of the *endo*-phenyl and *endo*-methyl isomers do not overlap,[4] or be chromatographed on neutral Al_2O_3 (Carmag 507-C) with pentane as the eluent. The reported integrations are the average of at least four sweeps in both the upfield and the downfield directions.

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[5] See footnote 9 of Ref. 2.

[6] Because there was some completely unlabeled material, the full label distribution was $d_1(E)$64.4, $d_1(Z)$18.6, $d_0$17.0%.

[7] When the amount of unlabeled material is taken into account, the Grignard procedure[6] is seen to be much superior. The lithium procedure originally gave $d_1(E)$43.4, $d_1(Z)$16.6, $d_0$40%.[2]

[8] The loss of stereospecificity encountered at the higher (~160°) temperatures required by less reactive *trans* dienophiles is apparently due to the incursion of alkene isomerization reactions.[9,10] To what extent these processes may involve diradicals or highly efficient radicals, e.g. Cl· or C_5Cl_5·, yielding end products that escape detection by proton NMR,[9] has not yet been determined. Until such work is done, the observed[9] loss in stereospecificity should best be considered as only a *de facto* and not a *de jure* violation of the *cis* principle.

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