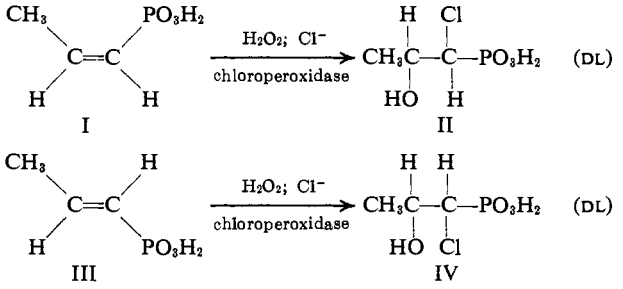
manner. To our knowledge, there is no exception in the literature[1] to this rule.

However, we wish to describe an instance of an *enzymatic synthesis of a chiral molecule in its racemic form from an achiral substrate.*




Hydrogen peroxide (0.055 *M*, 21 ml) was added over a period of 8 hr to a solution of *cis*-propenylphosphonic acid (I)[2] (1 mmol), potassium chloride (2 mmol), and 25 mg of chloroperoxidase preparation[3] in 20 ml of potassium phosphate buffer (pH 2.75). The solution was periodically assayed for enzymatic activity (Morris and Hager[3]) and when, after 6 hr, this diminished to 0.1 of the original value, an additional 28 mg of enzyme was added. The solution was concentrated *in vacuo* to 15 ml and passed through 30 ml of Dowex 50-X8 ($H^+$ form). The acidic eluate was concentrated *in vacuo* to a syrup which was then treated in methanol with diazomethane and concentrated again, and the residue chromatographed on a 100-g silica gel H dry column using a chloroform–isopropyl alcohol mixture (92:8, v/v) as solvent eluent. From the effluent was isolated 80 mg of *threo*-dimethyl 1-chloro-2-hydroxypropylphosphonate (dimethyl ester of II); $[\alpha]_D$ 0° (*c* 2, methanol).[4]

(1) M. Dixon and E. C. Webb, "Enzymes," 2nd ed, Academic, New York, N. Y., 1964, 205. The stereospecificity of reactions catalyzed by (isolated) enzymes is to be contrasted with transformations in cell systems which, in some cases, yield products with less than 100% optical purity, thus indicating stereoselective instead of stereospecific reaction; *e.g.*, fermenting yeast reduces ketones with variable and substrate-dependent (12–90%) stereoselectivity [R. MacLeod, H. Prosser, L. Fikentscher, J. Lanyi, and H. S. Mosher, *Biochemistry*, **3**, 838 (1964)]. However, the fact that actively fermenting yeast is capable of reducing ketones which are not reduced by the purified yeast ADH–DPNH enzyme (see MacLeod, *et al.*, p 844) suggests that the overlapping effect of more than one enzyme may be responsible for the lack of stereospecificity. For instance, yeast contains separate L-lactate and D-lactate dehydrogenases (J. Westley, "Enzymic Catalysis," Harper and Row, New York, N. Y., 1969, p 66).

(2) N. N. Girotra and N. L. Wendler, *Tetrahedron Lett.*, 4647 (1969).

(3) Prepared by Drs. R. F. White, T. A. Jacob, and F. W. Bollinger of these laboratories, employing the method of D. R. Morris and L. P. Hager, *J. Biol. Chem.*, **241**, 1763 (1966). The enzyme purification was carried to the second ethanol precipitate (29 units/mg). (Crystalline chloroperoxidase contains 1600 units/mg; see Morris and Hager.) We also wish to thank Professor L. P. Hager, University of Illinois, Urbana, Ill., for the gift of a similar enzyme preparation.

(4) Chromatography was monitored by tlc (silica gel plates, 92:8 $CHCl_3$–*i*-$C_3H_7OH$); all the product-containing fractions were combined before checking for optical activity, thus excluding the possibility of losing optically active material by inadvertent separation. None of the *erythro* isomer (dimethyl ester of IV) was detected in this product by gas–liquid chromatography [QF-1 (20%) 1/4 in. × 10 ft at 180°; injection at 230°]. In an artificial mixture of 0.5% *erythro* and 99.5% *threo* (both of nonenzymatic origin) the presence of the *erythro* isomer was detectable, retention times 13.8 and 16.2 min, respectively. The infrared and pmr spectra of product were identical with those of authentic material prepared from I by reaction with *t*-butyl hypochlorite followed by esterification with diazomethane.[2] Authentic (+)-II[2] with diazomethane gave the corresponding (+) antimer, $[\alpha]_D$ 10.3° (*c* 2, methanol); $[\alpha]_{250}$ 83° (*c* 6, acetonitrile). The optical activity of an artificial mixture of the latter compound with (nonenzymatically made) racemate (0.3% of active ester mixed with 99.7% racemate, $\Sigma c$ 6.3, in acetonitrile at 250 nm) was clearly detectable (Cary 60 spectropolarimeter). Under similar conditions (*c* 6.26, acetonitrile, 250 nm) the enzymatically prepared material was found optically inactive. For the ORD measurements, we thank Dr. J. J. Wittick of these laboratories.

Enzymatic hydroxychlorination of *trans*-propenylphosphonic acid (III) was performed in a similar way, to give *erythro*-dimethyl 1-chloro-2-hydroxypropylphosphonate[5] (dimethyl ester of IV), also optically inactive.

Subjecting optically active *threo*-1-chloro-2-hydroxypropylphosphonic acid[6] to the action of the same enzymatic system, the isolated *threo*-dimethyl 1-chloro-2-hydroxypropylphosphonate displayed full optical activity, thus excluding the possibility of subsequent racemization of an initially formed optically active chlorohydrin. According to the chlorodimedon assay (see Morris and Hager, ref 3), our enzyme preparation lost its activity on exposure for a few minutes to a pH 8.01 phosphate buffer. In another control—with omission of the enzyme—I was found to be unreactive with the $H_2O_2$–$Cl^-$ system at pH 3.

Chloroperoxidase has been found to be an active catalyst for halogenation of several classes of compounds, *e.g.*, cyclic β-diketones,[7a] β-keto acids,[7b] anisole,[7c] and unsaturated steroids.[7d] However, a stereochemical definition of the reaction is impossible in these cases because the products are either achiral or, as in the case of 9(11)-dehydrosteroids,[7d] the configurations of the products are influenced by asymmetric induction.

According to Hager,[8] the mechanism of chloroperoxidase action involves an enzyme–halogenium ion complex,[7c] the reaction of which, with the acceptor molecule, yields the halogenated product with regeneration of the free enzyme. Surprisingly, this intimate involvement of the enzyme in the halogen transfer does not assure the asymmetric course of the reaction.

(5) This product gave identical infrared and pmr spectra with those of an authentic preparation, prepared from *trans*-propenylphosphonic acid, by the method under ref 2. $CH_3$–CH in this compound is a doublet at 1.42 ppm (TMS, $CDCl_3$), $J$ = 6 cps; the methyl protons in the *threo* isomer appear as double doublets at 1.36 ppm, $J$ = 6.5 and 1.5 cps.

(6) See ref 2.

(7) (a) L. P. Hager, D. R. Morris, F. S. Brown, and H. Eberwein, *J. Biol. Chem.*, **241**, 1769 (1966); (b) P. D. Shaw and L. P. Hager, *ibid.*, **236**, 1626 (1961); (c) F. S. Brown and L. P. Hager, *J. Amer. Chem. Soc.*, **89**, 719 (1967); (d) S. L. Neidleman and S. D. Levine, *Tetrahedron Lett.*, 4057 (1968).

(8) L. P. Hager, "Mechanism of the Peroxidase Halogenation Reaction," Abstracts of Papers, V, Symposium, Membrane Function and Electron Transfer to Oxygen, Jan 20–24, 1969, University of Florida, Fla.

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## Nature of the Skeletal Change in a Metal-Catalyzed Diene Rearrangement

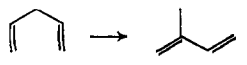
*Sir:*

The skeletal rearrangements of 1,4-dienes by a nickel-based homogeneous catalyst[1] are particularly interesting from a mechanistic standpoint. The observed transformations require the accomplishment of five fundamental changes common to many transition metal catalyzed olefin oligomerization reactions,[2] namely C–H bond cleavage and formation, C–C π bond cleavage and formation, and C–C σ bond formation. In addition they require a sixth process, much less common in homogeneous catalysis, the fission of a C–C σ bond.

(1) (a) R. G. Miller, *J. Amer. Chem. Soc.*, **89**, 2785 (1967); (b) R. G. Miller and P. A. Pinke, *ibid.*, **90**, 4500 (1968).

Katz and Cerefice have recently reported another instance where evidence indicates the accomplishment of all of these processes in a transition metal catalyzed transformation.[3] The recently discovered olefin "metathesis" or "disproportionation" reactions also provide examples of transformations afforded by homogeneous transition metal based catalysts, which involve the cleavage and formation of C–C bonds.[4] They do not involve hydrogen transfer. This class of reactions is not mechanistically related to the 1,4-diene rearrangements.

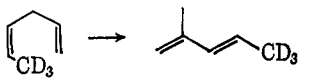
Two types of rearrangement are afforded by the nickel-based catalyst; these are exemplified by the transformation of (1) 3-methyl-1,4-pentadiene to 1,4-hexadiene[1a] and (2) 1,4-pentadiene to 2-methyl-1,3-butadiene.[1b] We wish to report results which define the nature of the latter skeletal change (eq 1).



(1)

In a series of experiments, three carbons in the 1,4-pentadiene skeleton were labeled with $CH_3$ or deuterium and the position of each label in the rearrangement product was determined. With the exception of the 3,3-dimethyl-1,4-pentadiene case, the formation of the skeletal rearrangement product in each experiment was accompanied by the production of lesser amounts of conjugated dienes, formally derived from migration of a terminal double bond in the 1,4-diene precursor.

The conversion of *cis*-1,4-hexadiene to *trans*-2-methyl-1,3-pentadiene at 25° in toluene solution was reported earlier.[1] The relatively high yields (>60%) of rearrangement product prompted us to examine this transformation in the greatest detail. The reaction of 1,4-pentadiene afforded only a 24% yield of 2-methyl-1,3-butadiene and *ca.* 8% of a mixture of *trans*- and *cis*-1,3-pentadienes at 34% conversion. The skeletal reorganization of *cis*-1,4-hexadiene was found to be related to the transformation in the parent system (eq 1) in the following manner. *cis*-1,4-Hexadiene-6-$d_3$ (98.5 ± 2.0% *d* at C-6) was synthesized[5] and, on reaction with the catalyst,[6] it was converted to *trans*-2-methyl-1,3-pentadiene-5-$d_3$ (98 ± 2% *d* at C-5) (eq 2)




(2)

(2) See R. Cramer, *Accounts Chem. Res.*, **1**, 186 (1968), for a recent discussion.

(3) (a) T. J. Katz and S. A. Cerefice, *J. Amer. Chem. Soc.*, **91**, 2405 (1969); (b) T. J. Katz and S. A. Cerefice, *ibid.*, **91**, 6519 (1969).

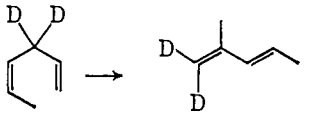
(4) For leading references, see (a) N. Calderon, E. A. Ofstead, J. P. Ward, W. A. Judy, and K. W. Scott, *ibid.*, **90**, 4133 (1968); (b) E. A. Zuech, W. B. Hughes, D. H. Kubicek, and E. T. Kittleman, *ibid.*, **92**, 528 (1970); (c) W. B. Hughes, *ibid.*, **92**, 532 (1970).

(5) Prepared according to the procedure of W. R. Roth and J. König, *Justus Liebigs Ann. Chem.*, **688**, 28 (1965). The *cis*-1,4-hexadiene-6-$d_3$ was isolated by preparative glpc.

(6) In a typical experiment, a deoxygenated, dry toluene solution, 0.0109 *M* in *trans*-dichlorobis(tri-*n*-butylphosphine)nickel(II) and 0.133 *M* in 1,4-diene, was treated with a toluene solution of diisobutylaluminum chloride (Al:Ni mole ratio = 4:1). The amber reaction mixture was stirred at 24–26° under a nitrogen atmosphere. The progress of the reaction was followed by periodic removal of aliquots which were quenched with 2-propanol and then analyzed by glpc on a 20 ft 20% β,β′-oxydipropionitrile on Firebrick column. The reactions were terminated at the desired conversion and the product mixture was fractionally distilled, affording diene-rich toluene solutions. The diene products were then collected *via* preparative glpc and were identified by their pmr and infrared spectra. The mass spectra were recorded by Morgan-Schaffer Corp., Montreal, Canada.

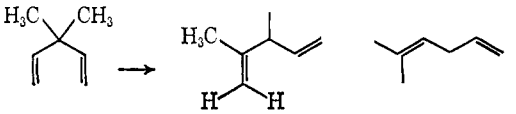
and deuterio-*cis,cis*-2,4-hexadiene and -*cis-trans*-2,4-hexadiene. The 2,4-diene pmr integrations were consistent with $d_3$ compositions and the deuterium appeared to reside at C-1. This latter tentative conclusion was based on comparisons of the pmr spectra with those of authentic samples of the nondeuterated 2,4-dienes. The position of the deuterium in the rearrangement product was established by the absence of the doublet proton resonance, present at $\tau$ 8.2 ($CCl_4$) in the spectrum of *trans*-2-methyl-1,3-pentadiene (the low-field signal in the doublet overlaps with the 2-methyl proton resonance at 60 MHz, but the high-field peak is free from overlap), and by the simplification of the complex C-4 olefinic proton resonance to the high-field half of an apparent AB quartet. The pmr spectrum of recovered starting material failed to show any deuterium scrambling or H–D exchange within the detection limitation of the spectrometer.

*cis*-1,4-Hexadiene-3-$d_2$ (0.3% $d_0$, 2.0% $d_1$, 97.7% $d_2$ by mass spectrometry) was synthesized.[7] It was treated with the catalyst and the reaction was terminated after 55% conversion of starting material to products. The resonance at $\tau$ 5.2, present in the spectrum of *trans*-2-methyl-1,3-pentadiene (signal of the C-1 alkene protons), was almost undetectable in the spectrum of the isolated rearrangement product. The ratio of residual proton at C-1 to total proton present at other positions was 1:260 by pmr integration. The sample contained 0.1% $d_0$, 1.6% $d_1$, 93.1% $d_2$, and 5.2% $d_3$ by mass spectrometry. Although the specific location of deuterium in the *cis,trans*- and *cis,cis*-2,4-hexadiene products could not be determined, the ratio of methyl:vinyl proton peak areas in the spectrum of a mixture of the two compounds was 2.04:1.00. The pmr spectrum of recovered starting material was essentially identical with that of the original *cis*-1,4-hexadiene-3-$d_2$. However, the mass spectrum of the sample indicated that *ca.* 10% of the molecules contained excess deuterium (9% $d_3$, 0.5% $d_4$).




(3)

3,3-Dimethyl-1,4-pentadiene was converted to 2,3-dimethyl-1,4-pentadiene (15% yield) and 5-methyl-1,4-hexadiene (47%) at 58% conversion of diene precursor to products. These were the only isomeric hydrocarbon products detected and were derived from the two types of skeletal change which the catalyst has been observed to afford.




(4)

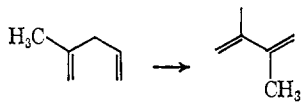
(7) An ether solution of ethyl *cis*-2-butenoate was treated with aluminum trideuteride to afford *cis*-2-buten-1-ol-1-$d_2$ in 84% yield using the general procedure of Jorgenson.[8] Treatment of the butenol with thionyl chloride in the presence of tri-*n*-butylamine[9] (ether solution) gave the chloride in 67% yield. Coupling of 1-chloro-*cis*-2-butene-1-$d_2$ with vinylmagnesium chloride[10] in tetrahydrofuran afforded a mixture of *cis*-1,4-hexadiene-3-$d_2$ (27%), 3-methyl-1,4-pentadiene-1-$d_2$ (13%), and a small amount of *trans*-1,4-hexadiene-3-$d_2$. The pure compounds were separated and isolated *via* glpc.

(8) M. J. Jorgenson, *Tetrahedron Lett.*, 559 (1962).

(9) W. G. Young, S. H. Sharman, and S. Winstein, *J. Amer. Chem. Soc.*, **82**, 1376 (1960).

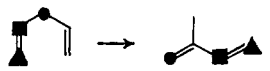
(10) H. Normant, *C. R. Acad. Sci.*, **239**, 1811 (1954).

The reaction of 2-methyl-1,4-pentadiene gave 2,3-dimethyl-1,3-butadiene (26%) and *trans*-2-methyl-1,3-pentadiene (24%) at 54% conversion, as isomeric products.



(5)

The results from these experiments indicate that each carbon with its label assumes the position in the product as described in eq 6. These data effectively eliminate a number of mechanistic possibilities from



(6)

consideration. They require a reaction path that can account for the transfer of hydrogen to and from carbons originally present in a terminal vinyl group in the 1,4-diene precursor. They are entirely consistent with a mechanism that would involve the intervention of a cyclopropylcarbinylmetal derivative.[1b]

**Acknowledgments.** Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the University of North Dakota grant-in-aid program for support of this research. We are grateful to the National Science Foundation for a departmental equipment grant (No. GP-8280).

(11) (a) Petroleum Research Fund Predoctoral Fellow, 1969; (b) NDEA Predoctoral Fellow, 1965–1968.

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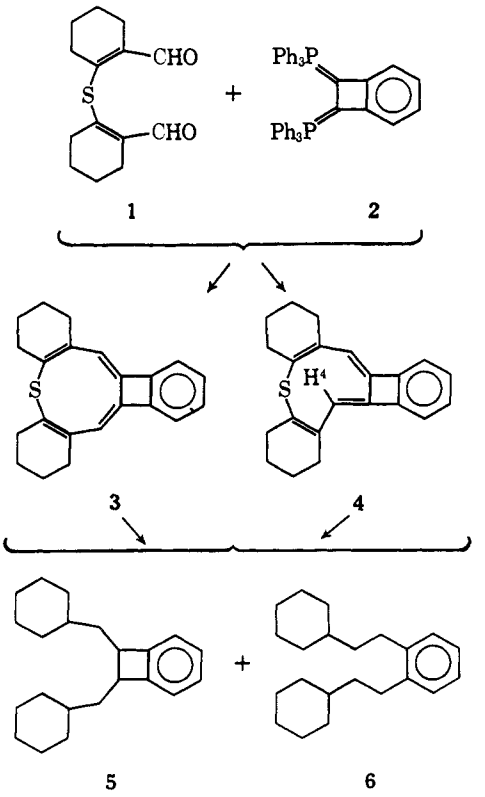
## The Synthesis of Benzo[3,4]cyclobuta[1,2-*e*]dicyclohexeno[*b*,*h*]thionin, an Analog of Biphenylene Containing a Thionin Ring

*Sir:*

We report the synthesis of two isomers of benzo[3,4]cyclobuta[1,2-*e*]dicyclohexeno[*b*,*h*]thionin (**3**, **4**), analogs of biphenylene[1] in which one of the benzene rings has been replaced by an alkylated, potentially aromatic thionin ring.[2] Isomer **4** is also of interest in that it represents the first isolated case of a fully unsaturated nine-membered-ring system containing a *trans* double bond.[3]

A solution of 2,2′-thiodi-1-cyclohexene-1-carboxaldehyde (**1**)[6] in tetrahydrofuran was added to an equimolar solution of preformed 1,2-bis(triphenylphosphoranyl)benzocyclobutene (**2**)[7] in ether under nitrogen at room temperature. Chromatography on alumina gave a mixture (*ca.* 1:2) of **3** and **4**, and these compounds were then separated by preparative tlc on alumina.




Isomer **3** (0.7%, mp 184–186°) had the molecular formula $C_{22}H_{22}S$,[8] and the nmr spectrum ($CCl_4$) showed signals at $\tau$ 2.91 (broad s, 4 H, aromatic), 4.44 (broad s, 2 H, olefinic), 7.1–8.1 (m, 8 H), and 8.1–8.7 (m, 8 H), in accord with the assigned structure. The uv spectrum [$\lambda_{max}^{EtOH}$ 223 sh nm ($\epsilon$ 14,500), 268 (31,000), 375 (6200)] was also consistent with formulation **3**.[9]

Isomer **4** (1.4%, mp 96–97°) also had the molecular formula $C_{22}H_{22}S$,[8] and the nmr spectrum ($CCl_4$) showed signals at $\tau$ 2.92 (broad s, 4 H, aromatic), 4.17 (broad s, 1 H, olefinic), 4.38 (broad s, 1 H, olefinic), 7.3–7.9 (m, 8 H), and 7.9–8.6 (m, 8 H). This spectrum reveals that the two olefinic protons are nonequivalent, indicative of the mono-*trans* structure **4**. The signal at $\tau$ 4.38 is assigned to H-4, since the solvent dependence of the position of this signal differs from that observed for the olefinic protons in **3**, whereas the signal at $\tau$ 4.17 has a similar solvent dependence.[10] The uv spectrum of **4** [$\lambda_{max}^{EtOH}$ 224 sh nm ($\epsilon$ 17,800), 285 sh (6600), 314 (11,400)] differs considerably from that of **3** and other 1,2-dimethylenebenzocyclobutenes,[9] presumably

(1) For the synthesis of other biphenylene analogs, see (a) M. P. Cava, K. Narasimhan, W. Zeiger, L. J. Radonovich, and M. D. Glick, *J. Amer. Chem. Soc.*, **91**, 2378 (1969); (b) C. S. Baxter, P. J. Garratt, and K. P. C. Vollhardt, *ibid.*, **91**, 7783 (1969); (c) P. J. Garratt and K. P. C. Vollhardt, *Chem. Commun.*, 109 (1970).

(2) The only previously known thionin derivative is 4,5:6,7-dibenzothionin: A. P. Bindra, J. A. Elix, P. J. Garratt, and R. H. Mitchell, *J. Amer. Chem. Soc.*, **90**, 7372 (1968).

(3) The existence in solution at low temperatures of the mono-*trans*-cyclononatetraenyl anion[4] and probably also of mono-*trans*-oxonin[5] has recently been reported.

(4) G. Boche, D. Martens, and W. Danzer, *Angew. Chem., Int. Ed. Engl.*, **8**, 984 (1969).

(5) S. Masamune, S. Takada, and R. T. Seidner, *J. Amer. Chem. Soc.*, **91**, 7769 (1969).

(6) M. Weissenfels and M. Pulst, *Tetrahedron Lett.*, 3045 (1968).

(7) A. T. Blomquist and V. J. Hruby, *J. Amer. Chem. Soc.*, **89**, 4996 (1967).

(8) Satisfactory elemental analyses and mass spectral data have been obtained for all new crystalline compounds.

(9) The uv spectra of all of the 1,2-dimethylenebenzocyclobutene derivatives examined by us show a high-wavelength maximum above 325 nm.

(10) The olefinic proton signals in **3** move downfield in $CD_2Cl_2$ and $C_6D_6$ as compared to $CCl_4$, whereas H-4 in **4** is unchanged in $CD_2Cl_2$ and moves upfield in $C_6D_6$.