termined from V_0, V_∞, and individual values of V_t and t) from the mean. This procedure is not strictly correct in that it assumes an equal uncertainty for all rate constants determined in a single run. However, the procedure is approximately correct if all rate constants are based on points taken between 20 and 80% reaction, and a rigorous treatment, if one were available, would not appreciably change the weighting factors and would have an even smaller effect on the best fit slopes and intercepts. The weighting factor, w, is given by the expression

$$w = (k_{obsd} - k_u)^4/(s^2_{k_{obsd}} + s^2_{k_u})$$

Activation Parameters for Acetolysis of the 1:1 Complex.—Least squares analysis of a plot of log k_c *vs.* $1/T$ led directly to ΔH_c and ΔS_c by the usual procedure (see above). Least squares analysis of a plot of $k_c k_u/K_T$ (initial slopes of plots of k_{obsd}/k_u *vs.* $[D]_0$) led to values for $(\Delta H_c^{\ddagger} + \Delta H^\circ - \Delta H_u^{\ddagger})$ and $(\Delta S_c^{\ddagger} + \Delta S^\circ - \Delta S_u^{\ddagger})$, together with standard deviations for these quantities. Combination with directly measured values of ΔH°, $\Delta H_u^{\ddagger}$, ΔS°, and $\Delta S_u^{\ddagger}$ led to $\Delta H_c^{\ddagger}$ and $\Delta S_c^{\ddagger}$. Standard deviations for the quantities were calculated in the usual way[23] from standard deviations in $(\Delta H_c^{\ddagger} + \Delta H^\circ - \Delta H_u^{\ddagger})$, ΔH°, and $\Delta H_u^{\ddagger}$.

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The Acid-Catalyzed Cyclization of Acyclic Dienes

BY H. E. ULERY AND J. H. RICHARDS[1]

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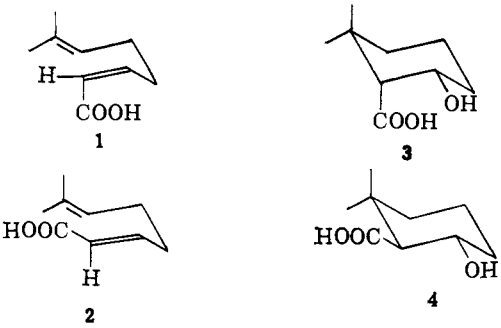
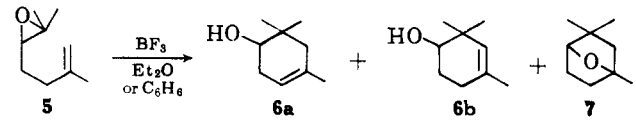
The acid-catalyzed cyclizations of *trans,trans*- and *cis,cis*-2,6-octadiene have been investigated utilizing deuterated acid to initiate cyclization. The stereochemistry of the products shows that the cyclization process is concerted with proton attack and follows the stereoelectronic predictions made for terpene biosynthesis. A small percentage of the time the acquisition of the nucleophile is clearly concerted with the preceding steps and leads, likewise, to the theoretically expected product.

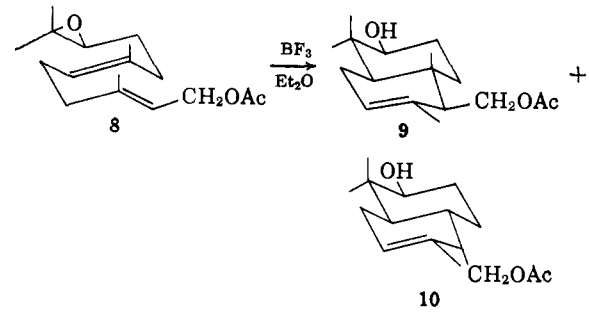
Introduction

The cyclization of acyclic polyolefins plays an important role in the biogenesis of many terpenoid compounds. For example, the cyclization of squalene to lanosterol[2] is an important step in the biosynthesis of cholesterol and other steroid hormones. The stereochemical implications of olefin cyclization have been elegantly discussed in a theoretical sense[3,4] and a large body of experimental studies on olefin cyclizations[5-8] has appeared. Though some of the systems studied gave those products expected to result from a concerted sequence of stereoselective events, these products could also have arisen by processes that were *not entirely* concerted, because it was not possible to examine the stereochemistry at *all* centers which were involved in the cyclization reaction, *i.e.*, had undergone rehybridization from sp^2 to sp^3. Another disadvantage with many of the systems studied hitherto is that they have utilized trisubstituted olefins which increase the possibility that classical carbonium ions might intervene as intermediates with resultant loss of stereospecificity. For example, the cyclization of *cis*- and *trans*-apogeranic acids (**1**) and (**2**) to the expected products **3** and **4**, respectively,[5,6] does not demand a totally concerted cyclization, but requires only a *trans* addition to the terminal double bond.

Recently, the cyclization of epoxy olefins has received some attention.[9-11] Goldsmith[9] studied the cyclization of geraniolene monoepoxide (**5**) by boron trifluoride in benzene and ether solvent and observed the formation of two isomers of 2,2,4-trimethylcyclohexenol (**6a** and **6b**) and 2,2,4-trimethyl-1,4-endoxycyclohexane (**7**) in small yield. van Tamelen, *et al.*,[10] studied the reaction of the terminal monoepoxide of *trans,trans*-farnesyl acetate (**8**) also with boron trifluoride–ether and were able, after extensive chromatographic purification, to isolate a modest yield of bicyclic diol monoacetate which consisted of 85% of stereoisomer **9** and 15% of its epimer **10**. Attempted[11] cyclizations of monoepoxides of a number of 1,5-dienes in protic solvents led almost exclusively







(1) Alfred P. Sloan Fellow.

(2) T. T. Tchen and K. Bloch, *J. Biol. Chem.*, **226**, 921 (1957).

(3) L. Ruzicka in "Perspectives in Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1956, p. 265, *et seq.*

(4) J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959).

(5) R. Helg and H. Schinz, *Helv. Chim. Acta*, **35**, 2406 (1952).

(6) G. Gamboni, H. Schinz, and A. Eschenmoser, *ibid.*, **37**, 964 (1954).

(7) G. Stork and A. W. Burgstahler, *J. Am. Chem. Soc.*, **77**, 5068 (1955).

(8) P. A. Stadler, A. Nechvatel, A. J. Frey, and A. Eschenmoser, *Helv. Chim. Acta*, **40**, 1373 (1957).

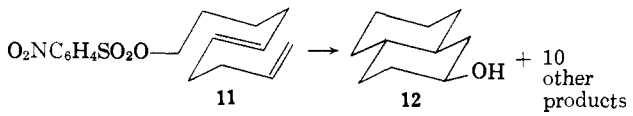
(9) D. J. Goldsmith, *J. Am. Chem. Soc.*, **84**, 3913 (1962).

(10) E. E. van Tamelen, A. Storni, E. J. Hessler, and M. Schwartz, *ibid.*, **85**, 3295 (1963).

(11) H. Ulery, Ph.D. Thesis, California Institute of Technology, 1963.

to formation of ketonic products; no cyclization was observed.

In an important recent paper on this general subject, Johnson[12] described some initial studies on cyclizations initiated by carbonium ions generated by ionization of tosylate esters. In the case of 5,9-decadienyl *p*-nitrobenzenesulfonate (**11**), reaction led to at least 11 products among which, in 6.4% yield, was that isomer (**12**) expected for a completely concerted process operating on an olefin chain folded in quasi-chair conformation.



11 12

The purpose of the work described here was to study the acid-catalyzed reactions of disubstituted 1,5-dienes in such a way that the stereochemical outcome of any cyclization could be examined at all four centers which are converted from trigonal to tetrahedral configuration. To this end, the cyclizations of *cis,cis*- and *trans,trans*-2,6-octadiene by deuteriosulfuric acid in deuterioformic acid were investigated. Disubstituted olefins were used to minimize loss of stereochemistry which is so often encountered when tertiary carbonium ions can intervene. The utilization of deuterio acids allows one to define the stereochemistry at the center of initial proton attack.

Results

Preparation and Identification of Isomeric 2,3-Dimethylcyclohexanols and 2,3-Dimethylcyclohexanones.—In order to establish the stereochemistry of the 2,3-dimethylcyclohexanols derived by cyclization of 2,6-octadiene, it was necessary to prepare the four isomeric 2,3-dimethylcyclohexanols. Three were prepared in pure form. The fourth isomer is much less accessible and was never isolated as a pure substance.

All-*cis*-2,3-dimethylcyclohexanol was prepared by the low pressure hydrogenation of 2,3-dimethylphenol over finely divided platinum.[13] This hydrogenation yielded a mixture of four alcohols which was analyzed by v.p.c. In order of increasing retention time the isomers were: A (9%), B (6%), C (3%), and D(82%). As similar reductions of 2,4-dimethylphenol[14] and 3,5-dimethylphenol[15] produced the all-*cis* isomers the assignment of an all-*cis* stereochemistry (2^e,3^e-dimethylcyclohexanol) to D is logical.

Oxidation of the above mixture of four alcohols, under nonisomerizing conditions, gave a mixture of two ketones E (15%) and F(85%) (in order of the retention times). Oxidation of the pure all-*cis* alcohol D gave only ketone F.

As ketone F is produced by oxidation of the all-*cis* alcohol under nonepimerizing conditions, its methyl groups must be *cis*, *i.e.*, one axial and one equatorial. This ketone should, therefore, be convertible to a ketone with *trans*-methyl groups by epimerization in strong base. Treatment of ketone F with a dilute solution of sodium methoxide in methanol for periods up to several days led to an equilibrium mixture of about 88% ketone E and 12% ketone F,[16] which confirms that ketone F is the *cis* isomer.

Reduction of ketone E with methanolic sodium borohydride gave alcohols A (46%) and B (54%) indicating that these are epimers at the hydroxyl group with a *trans* orientation of the two methyl groups. While sodium borohydride reductions generally lead to kinetically controlled products,[17] reduction with lithium aluminum hydride yields a mixture whose composition reflects product development control, *i.e.*, is closer to that expected from the thermodynamic stabilities of the isomeric possibilities.[18] Thus when ketone E was refluxed with a large excess of lithium aluminum hydride for 2 days the crude product was a mixture of 19% A and 70% B. In addition some epimerization of the α-methyl group has occurred as evidenced by the isolation of about 10% D and 1% C. Hence B is assigned the thermodynamically most stable all-equatorial configuration (2^t, 3^c-dimethylcyclohexanol) and A is considered to be the epimer 2^c,3^t-dimethylcyclohexanol. Alcohol C is, then, the remaining isomeric possibility 2^t,3^t-dimethylcyclohexanol.

Preparation of Stereochemically Pure Dienes.—The *trans,trans*-2,6-octadiene was prepared by coupling *trans*-crotyl chloride with nickel tetracarbonyl[19] which yielded the desired octadiene and 3-methyl-1,5-heptadiene in a ratio of about 3:1. Fractionation gave a sample which was at least 99% homogeneous as indicated by v.p.c. analysis.

The *cis,cis*-2,6-octadiene was obtained by reduction of the corresponding diacetylene over a Lindlar catalyst[20] whose selectivity had been enhanced by heavy poisoning with quinoline. Again the diolefin produced was at least 99% homogeneous by v.p.c. analysis.

The infrared spectral properties of these olefins are in accord with these assignments. The *trans,trans*-olefin showed a strong band at 963 cm.$^{-1}$ and the *cis,cis*-olefin exhibited a very strong absorption at 713 cm.$^{-1}$ and a band of medium intensity at 1658 cm.$^{-1}$, as expected.[21]

Cyclization of *trans,trans*-2,6-Octadiene.—Treatment of *trans,trans*-2,6-octadiene (13) with a mixture of formic and sulfuric acids[22,23] gave a 37–40% yield of 2^t,3^c-dimethylcyclohexyl formate (**14**) which gave no evidence of contamination with any other products on v.p.c. analysis (less than 0.1% impurities). There was also isolated a second higher boiling fraction

(12) W. S. Johnson, *Pure Appl. Chem.*, **7**, 317 (1963).

(13) For a discussion *cf.* (a) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 350; (b) E. H. Rodd, "Chemistry of Carbon Compounds," Vol. IIA, Elsevier Publishing Co., New York, N. Y., 1953, p. 124.

(14) W. Hückel and M. G. E. Ibrahim, *Ber.*, **91**, 1970 (1958).

(15) J. von Braun and E. Anton, *ibid.*, **60**, 2438 (1927); A. Skita and W. Faust, *ibid.*, **72B**, 1127 (1939).

(16) From these equilibrium data for 2,3-dimethylcyclohexanones, one calculates an energy difference between the *trans* and *cis* isomers of 1.2 kcal./mole. The free energy difference between an axial and an equatorial methyl group of cyclohexane is 1.5–1.9 kcal./mole but should be somewhat smaller for an axial 3-methylcyclohexanone because there is one less methyl–hydrogen interaction; *cf.* ref. 13.

(17) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953); N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p. 124.

(18) W. G. Dauben, G. J. Fonken, and D. S. Noyes, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

(19) I. D. Webb and G. T. Borcherdt, *ibid.*, **73**, 2654 (1951); *cf.* I. G. Farbenindustrie, Belgium Patent 448,884 (1943); *Chem. Abstr.*, **41**, 6576*a* (1947).

(20) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

(21) E. A. Braude and E. S. Waight, *Progr. Stereochem.*, **1**, 126 (1954); W. von E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).

(22) K. Bernhauer and R. Forster, *J. Prakt. Chem.*, **147**, 199 (1936).

(23) H. B. Knight, R. E. Koos, and D. Swern, *J. Am. Chem. Soc.*, **75**, 6212 (1953).

(50–52%) which contained a mixture of three formate isomers and which analyzed for $C_{10}H_{18}O_9$. Saponification and oxidation with chromic acid led to a mixture of three ketones whose infrared spectra possessed a single carbonyl absorption at 1715 cm.$^{-1}$. The isomers are present in the ratio of 1:2:1 and none of them corresponds to either of the two previously characterized 2,3-dimethylcyclohexanones (nor do the alcohols correspond to the 2,3-dimethylcyclohexanols). From these data and the n.m.r. spectrum of the mixture (methyl singlet at τ = 2.23, methyl triplet at τ = 1.14) we conclude that the second reaction product is a mixture of 2,7-, 2,6-, and 3,6-octadiyl diformate.

Interruption of the cyclization reaction before completion does not give rise to any new products, and there was no indication of isomerization of the unreacted *trans,trans*-2,6-octadiene. Also, the formates of all four 2,3-dimethylcyclohexanols were stable under the reaction conditions.[24]

When the reaction was carried out in deuterated acid, the 2,6-dimethylcyclohexyl formate possessed a C–D absorption at 2171 ± 4 cm.$^{-1}$. (There was no evidence of absorption near 2150 cm.$^{-1}$.) The axial C–D stretching mode of monodeuteriocyclohexane has been reported at 2146 cm.$^{-1}$ and the equatorial C–D stretch at 2174 cm.$^{-1}$.[25] We conclude, therefore, that the acquired deuterium occupies an equatorial position[26] such that the product is the *trans,anti,trans* isomer, $2^t,3^c$-dimethyl-4^t-deuteriocyclohexyl formate (**12**).

Cyclization of *cis,cis*-2,6-Octadiene.—Treatment of *cis,cis*-2,6-octadiene (**15**) with a mixture of formic and sulfuric acids at room temperature produced a noticeably exothermic reaction which gave a homogeneous solution within 1 hr. compared with the several hours required in the case of the *trans,trans*-diene. Under these conditions, the yield of 2,3-dimethylcyclohexyl formate was less than 3%. The yield was, however, increased to 11% by carrying out the reaction at 0° for several days. Under these conditions, there was also obtained about 23% of a mixture of cyclic monoformates (no spectral evidence for a double bond), all of whose retention times were significantly less than those of authentic samples of the four isomers of 2,3-dimethylcyclohexyl formate. The major product of the reaction (41%) was the same isomeric mixture of acyclic octadiyl diformates obtained previously.

The 2,3-dimethylcyclohexyl formate (obtained in 11% yield) was a mixture of two isomers, about 94% $2^t,3^c$-dimethylcyclohexyl formate (**16**) and 6% of the epimeric $2^c,3^t$-dimethylcyclohexyl formate (**17**).

Interruption of the reaction before completion gave no new products, though the unreacted diene was found to contain about 1.5% of two new components neither of which was *trans,trans*-2,6-octadiene.

After carrying out the reaction in deuterated acids, it was possible to isolate a sample of $2^t,3^c$-dimethylcyclohexyl formate by gas chromatography. The infrared spectrum of this substance had absorption at 2142 ± 8 cm.$^{-1}$ (no absorption observed in the region of 2175 cm.$^{-1}$), and the product was therefore assigned

(24) A similar observation was reported by R. Helg and H. Schinz, *Helv. Chim. Acta*, **35**, 2406 (1952).

(25) M. Larnaudie, *Compt. rend.*, **235**, 154 (1952).

(26) The experimental sensitivity to an axial C–D is such that we judge no more than 5% of the axial isomer could pass unobserved.

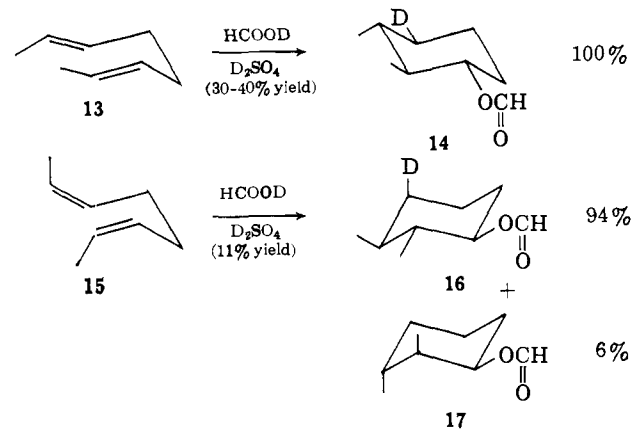


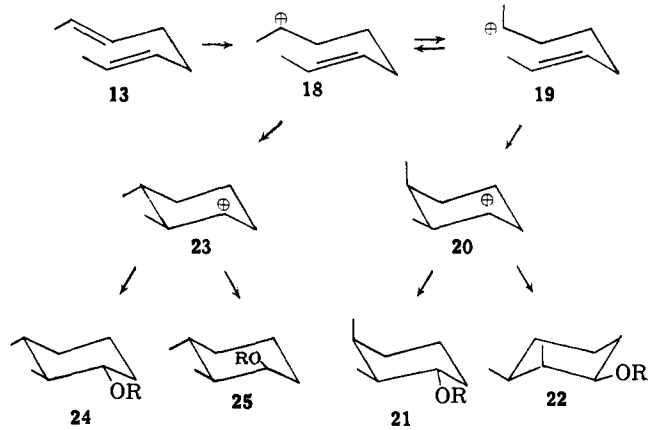
Figure 1.

the structure $2^t,3^c$-dimethyl-4^c-deuteriocyclohexyl formate (**16**). These results are summarized in Fig. 1.

Discussion

Cyclization of *trans,trans*-2,6-Octadiene.—In the cyclization of the *trans,trans*-diolefin, the steric course of the reaction is exceedingly specific, only one 2,3-dimethylcyclohexyl formate isomer being formed. The stereochemistry at all four centers involved in the reaction is just that anticipated on the basis of a process subject to complete steric control.

However, as the observed isomer is also thermodynamically the most stable, it may result from a nonconcerted process and be produced simply by virtue of thermodynamic control. That such thermodynamic control alone is operative is an unsatisfactory explanation and will be evident from an examination of the products expected from a stepwise process. Thus, proton addition to give the classical secondary ion **18** might be envisioned. Inversion of this ion could produce a species, **19**, which might cyclize to **20** which on neutralization could lead to either **21** or **22**. Or the intermediate **18** itself could cyclize to **23** which would be neutralized to **24** or **25**. If one assumes that the difference between the energy needed for the ion **19** to cyclize to **20** and the energy needed for the ion **18** to cyclize to **23** is approximated by the energy difference between an axial and equatorial methyl group (1.7 kcal.),[13] then one might anticipate about 5% of an



isomer with an axial methyl group. However, to within one part in one thousand, no such isomer is produced. Thus we conclude that those fractions of diene molecules which lead to cyclic products are con-

verted from an acyclic intermediate to a cyclic ion before inversion about a carbonium ion such as **18** is possible. With this time scale as the basis of the definition "concerted," the results require that the diene **13** accepts a proton and is converted to an intermediate such as **23** by a "concerted" process. A similarly

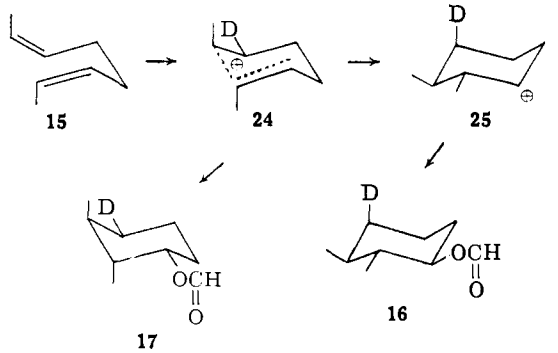
13 **23**

concerted acquisition of a nucleophile will give the observed product. However, thermodynamic considerations also favor equatorial attack[27,28] of the nucleophile on **23** though again the exclusive production of only one epimer suggests that this nucleophile acquisition may also be the result of a stereoelectronically concerted process.

To summarize: the stereochemistry of the product is that which would result from a completely concerted attack by proton, cyclization, and nucleophile acquisition, though the last step may be largely the result of thermodynamic control. In those cases where cyclization does occur, the aliphatic diolefin chain must be in a quasi-chair conformation. When the diolefin is not suitably oriented to facilitate concerted cyclization, the two double bonds act independently and octadiyl diformates are produced.

Cyclization of *cis,cis*-2,6-Octadiene.—In the cyclization of the *cis,cis*-diolefin (**15**) the product of complete steric control, 2^c,3^t-dimethylcyclohexyl formate (**17**), is formed only as 6% of the dimethylcyclohexyl product. (Because of the small yield, it was not possible to determine the stereochemistry of the deuterium.) The remaining dimethylcyclohexyl product (94%), 2^t,3^c-dimethyl-4^c-deuteriocyclohexyl formate (**16**), exhibits steric control at three of the four newly rehybridized carbons.

Does the product **17** expected for a reaction subject to complete steric control result, in fact, from a concerted process, *i.e.*, **15** → **24** → **17** or, rather, from a random neutralization of a classical carbonium ion intermediate such as **25**? In the case of the cyclization of the *trans,trans*-diolefin **13** the acquired nucleophile was *entirely* equatorial (less then 0.1% axial attack). Therefore, we deem it most improbable that the presence of 6% axial product in the cyclization of the *cis,cis*-diolefin **15** can be the result of a nonstereospecific neutralization of an ion such as **25**. Rather, we conclude that the 2^c,3^t,-dimethylcyclohexyl formate (**17**) is, indeed, the result of a *completely concerted process, i.e.*, the cyclization proceeds from the diene **15** to **24** which acquires a nucleophile yielding **17** before it has a chance to undergo conformational inversion. The other, major product (94%) is formed as a result of a process in which proton attack and cyclization are concerted, giving **24**, which inverts to **25** (an inversion for which there is much thermodynamic driving force) before acquisition of a nucleophile with equatorial stereochemistry yielding **16**.



15 **24** **25** **17** **16**

The simplest description of the process is, therefore, one in which cyclization occurs only when the electrophile and both double bonds are oriented in such a way as to facilitate a concerted process. Some of the time (6%) the nucleophile is also properly positioned for the completely concerted reaction leading to 2^c,3^t-dimethylcyclohexyl formate (**17**). Most of the time, however, the nucleophile is not acquired until the intermediate **24** has had an opportunity to undergo a conformational inversion which brings two axial methyl groups into equatorial positions. The resulting major product is then 2^t,3^c-dimethyl-4^c-deuteriocyclohexyl formate (**16**). It is again clear that the observed products are formed only if the cyclizing diene is folded in the thermodynamically more stable, chair conformation before the cyclization commences.

These results thus confirm the theoretical expectations and demonstrate, further, that these *in vitro* systems are subject to a capriciousness that is absent in their biological counterparts where enzymatic influences organize the geometrical relationships of the reactants.

Experimental

Microanaylyses were performed by Spang Microanalytical Lab., Ann Arbor, Mich. Melting points are uncorrected.

2^c,3^c-Dimethylcyclohexanol (D).—Low pressure hydrogenation (30–35 lb.) of 50 g. (0.408 mole) of 2,3-xylenol (m.p. 72.5–74.5°, Aldrich) over platinum in glacial acetic acid at room temperature gave a quantitative yield of 2,3-dimethylcyclohexanols; v.p.c. analysis indicated that the crude mixture was about 82% D. Fractional distillation using a 56-cm. stainless steel spinning band column gave 24.7 g. (48%) of pure D isomer, b.p. 103° (38 mm.), n^{25}D 1.4675.

Anal. Calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.84; H, 12.51.

This alcohol gave a solid *p*-nitrobenzoate, m.p. 62.5–63.0°.

***cis*-2,3-Dimethylcyclohexanone (F).**—Alcohol D (6.5 g., 0.051 mole) was oxidized with 3.75 g. (0.037) of chromium trioxide using the method of Hückel and Ibrahim.[14] A yield of 5.7 g. (87%) of ketone F was obtained, b.p. 99° (57 mm.), n^{25}D 1.4523.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.86; H, 11.28.

This ketone gave a solid semicarbazone, m.p. 174.5–175.5°.

***trans*-2,3-Dimethylcyclohexanone (E).**—A mixture of 10 g. of the *cis*-ketone F in 50 ml. of 0.025 *M* sodium methoxide in methanol was allowed to equilibrate at room temperature for periods of 8 hr. to 3 days at room temperature. The ketone was recovered by ether extraction and then distilled, yielding 8.8 g. (88%), of a liquid which v.p.c. analysis indicated was 88% E and 12% F. Further fractional distillation gave material which was 98% E, b.p. 96° (57 mm.), nD 1.4475.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.89; H, 11.18.

This ketone gave a solid semicarbazone, m.p. 205.5–206°.

A similar mixture is obtained[29] by the high temperature reduction of 2,3-dimethyl-2-cyclohexenone. Preparation of a ketone by the method of Colonge, Dreux, and Thiers,[30] gave a product

(27) W. G. Dauben, R. C. Tweit, and C. Mannerskantz, *J. Am. Chem. Soc.*, **76**, 4420 (1954).

(28) A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957).

(29) D. Capon, M. Claudon, R. Cornubert, H. Lemoine, R. Malzieu, and G. Vivant, *Bull. soc. chim., France*, 837 (1958).

(30) J. Colonge, J. Dreux, and M. Thiers, *Compt. rend.*, **243**, 1425 (1956) *ibid.*, 450 (1959).

which by v.p.c. analysis contained only 7–8% of ketones E and F.

2^c,3^t-Dimethylcyclohexanol (A).—Sodium borohydride (8.0 g., 0.21 mole) was added in 1-g. portions to a solution of 25.2 g. (0.20 mole, 4-fold excess) of *trans*-ketone E in 100 ml. of absolute methanol. The mixture was allowed to stand 4 hr., and the bulk of the methanol was removed by evaporation. The solid was decomposed in 700 ml. of 1 *M* ammonium sulfate and the resulting alcohol was extracted with ether. The ether was dried and removed at reduced pressure. The crude product (23.8 g., 93%) was 46% isomer A and 54% B according to v.p.c. analysis. Fractional distillation gave 7.1 g. of material which was 83% A, b.p. 92.5–93° (38 mm.), n^{25}D 1.4578. Repeated fractionation gave pure A, b.p. 93° (38 mm.), n^{25}D 1.4583.

Anal. Calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.87; H, 12.57.

This alcohol yielded a solid *p*-nitrobenzoate, m.p. 83–83.5°.

2^t,3^c-Dimethylcyclohexanol (B).—To a refluxing solution of 4 g. (0.1 mole) of lithium aluminum hydride in 300 ml. of absolute ether was added dropwise a solution of 12.6 g. (0.1 mole) of *trans*-ketone (E) in 50 ml. of ether. After addition was complete, reflux was maintained for 2 days. After work-up the crude alcohol (11.2 g., 89%) was found to have the composition: A (19%), B (67%), C (0–1%), and D (10%). Fractional distillation gave 9.1 g. (72%) of material which was 79% isomer B, b.p. 94–96° (38 mm.). Repeated fractionation yielded B, b.p. 95–96° (38 mm.), n^{25}D 1.4561.

Anal. Calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.81; H, 12.42.

This alcohol gave a solid *p*-nitrobenzoate, m.p. 61.0–61.5°; mixture m.p. with the *p*-nitrobenzoate of alcohol isomer D, 47–54°.

2^t,3^c-Dimethylcyclohexyl Formate.—A mixture of 60 ml. of pyridine, 6 g. (0.13 mole) of 98–100% formic acid, and 3 g. of alcohol isomer B was cooled to −35° in a Dry Ice–acetone bath. Phosgene (5 g., 0.05 mole) was condensed in a small Schlenk tube immersed in the cooling mixture. The Schlenk tube was inverted, and the phosgene added dropwise to the reaction mixture over a period of about 30–45 min. It is necessary to stir the contents vigorously during this time. After all the phosgene has reacted, the mixture was stored at −10° for 12 hr. (Caution: If all the phosgene has not been consumed, the reaction may become violently exothermic upon removal from the coolant. This is best avoided by not overcooling the mixture during the addition of the phosgene.)

The semisolid material was poured into a slight excess of 6 *N* sulfuric acid containing crushed ice. The cold acid solution was extracted immediately with ether, the extract washed with 2 *N* sodium carbonate solution, and dried. Removal of the solvent, followed by distillation, gave 2.56 g. (71%) of 2^t,3^c-dimethylcyclohexyl formate, b.p. 86–88° (30 mm.), n^{25}D 1.4381.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.17; H, 10.30. Found: C, 68.91; H, 10.16.

***trans,trans*-2,6-Octadiene (1).**—The method of Webb and Borcherdt[19] was used to couple 125 g. (1.4 moles) of crotyl chloride (K. & K. Labs; mostly *trans* isomer according to its infrared spectrum). Fractional distillation gave 11.3 g. (15%) of material which was largely 3-methyl-1,5-heptadiene, b.p. 92–121°, and 48.1 g. (62%) of quite pure *trans,trans*-2,6-octadiene, b.p. 121–122.5° (744 mm.), n^{24}D 1.4284. In the infrared, this exhibited a band at 963 cm.$^{-1}$.

***cis,cis*-2,6-Octadiene (5).**—A solution of 20 g. (0.19 mole) of 2,6-octadiene (Farchan) in 50 ml. of cyclohexane containing 0.8 g. of 90% quinoline (Eastman, Practical Grade) was hydrogenated over 2.0 g. of Lindlar catalyst[20] at 5 lb. pressure and room temperature. Gas uptake virtually ceased after 7 hr. when 2 mole equivalents had been absorbed. Fractional distillation gave 18.5 g. (89%) of the *cis,cis*-diene, b.p. 124–124.2° (744 mm.), n^{24}D 1.4351. In the infrared, this exhibited a band at 713 and 1658 cm.$^{-1}$.

Anal. Calcd. for C_8H_{14}: C, 87.20; H, 12.80. Found: C, 87.18; H, 12.88.

Cyclization of *trans,trans*-2,6-Octadiene (1).—A solution of 20 ml. of 98–100% formic acid and 1.2 ml. of concentrated sulfuric acid was added to 10.0 g. (0.09 mole) of the *trans,trans*-diene 1, and the 2-phase system was stirred for 36 hr. at room temperature. After a few hours the reaction mixture was homogeneous and deep violet in color. The mixture was poured into 300 ml. of water containing 200 g. of crushed ice and 50 g. of sodium carbonate. The yellow basic solution was extracted completely with ether while still cold. After washing and drying, the ether was removed and the residue distilled. The first fraction, 5.2 g. (37%), was pure 2^t,3^c-dimethylcyclohexyl formate, b.p. 90–93° (34 mm.), n^{25}D 1.4389. This substance was also identified by: (1) comparison of v.p.c. retention time with an authentic sample; (2) nondepressed melting point with authentic α-naphthylurethan of alcohol B: and (3) the infrared spectrum of this formate was identical with that of an authentic sample.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.17; H, 10.30. Found: C, 68.99; H, 10.22.

A second fraction, 7.4 g. (52%), of an isomeric mixture of octadiyl diformate was obtained, b.p. 142–146° (30 mm.), n^{25}D 1.4300.

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97. Found: C, 59.31; H, 8.99.

Cyclization of *cis,cis*-2,6-Octadiene (5).—This procedure was the same as for the *trans,trans*-diene except that the reaction was stirred for 4 days at 0°. Distillation of the reaction product gave a mixture of cyclic monoformates, 4.8 g. (34%), b.p. 46–61° (5 mm.), which contained 11% of 2,3-dimethylcyclohexyl formate according to v.p.c. analysis. Of this 94% was the 2^t,3^c-yl isomer while the remaining 6% was the C-1 epimer.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.17; H, 10.30. Found: C, 68.88; H, 10.19.

A higher boiling fraction, b.p. 94–97° (5 mm.), n^{21}D 1.4306, afforded 7.5 g. (41%) of isomeric octadiyl diformates.

Cleavage of 2^t,3^c-Dimethylcyclohexyl Formate with Lithium Aluminum Hydride.—To a mixture of 100 mg. (27 mmoles) of lithium aluminum hydride in 50 ml. of absolute ether was added dropwise 1.0 g. (6.4 mmoles) of 2^t,3^c-dimethylcyclohexyl formate obtained from the cyclization of the *trans,trans*-diene. After 1 hr. the excess hydride was decomposed by cooling and adding carefully 20 ml. of saturated ammonium sulfate solution. The colorless oil obtained from the ether solution was shown by v.p.c. analysis to be pure isomer B. Distillation gave 0.63 g. (76%), b.p. 55° (6 mm.), n^{25}D 1.4561.

Anal. Calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.69; H, 12.61.

The α-naphthylurethan was prepared and crystallized from absolute methanol; m.p. 156.5–157.0°.

2^t,3^c-Dimethyl-4^t-deuteriocyclohexyl Formate (12).—A solution of 2.5 g. of anhydrous formic acid-*d* (HCOOD, Merck) and 0.20 ml. of concentrated deuterium sulfate was stirred with 0.75 g. (6.8 mmoles) of *trans,trans*-2,6-octadiene as previously described. Distillation of the reaction product gave 0.36 g. (34%) of 2^t,3^c-dimethyl-4^t-deuteriocyclohexyl formate, b.p. 46–47° (8 mm.), n^{25}D 1.4383, and 0.63 g. (46%) of isomeric dideuteriooctadiyl diformate, b.p. 65–68° (8 mm.), n^{25}D 1.4298. The infrared spectrum (CCl_4) of the former possessed a C–D absorption at 2171 ± 4 cm.$^{-1}$.

2^t,3^c-Dimethyl-4^c-deuteriocyclohexyl Formate (14).—The *cis,cis*-diene was treated exactly as above except that the reaction mixture was stirred for 7 days at 0°. On distillation there was obtained, following a small forerun, 0.18 g. of isomeric formates, b.p. 48–53° (8 mm.), n^{25}D 1.4376. A small amount of 2^t,3^c-dimethyl-4^c-deuteriocyclohexyl^c formate was recovered from this material by use of gas chromatography (Carbowax-1500 column at 115°). The infrared spectrum (CCl_4) of this ester displayed a C–D absorption band at 2142 ± 8 cm.$^{-1}$.

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