Stereochemistry of Hydroboration of Methylenecyclohexanes

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Hydroboration of 3- and 4-methyl- and 3- and 4-*t*-butylmethylenecyclohexanes yielded, after oxidation, predominantly the axial–equatorial disubstituted cyclohexanes. Similar results were obtained when dichloroborane was used as the hydroborating agent. Dicyclohexylborane gave equal amounts of axial and equatorial products.

The addition of nucleophiles to unhindered cyclohexanones yields predominantly the more stable equatorial alcohols, whereas axial isomers are obtained in the reaction of hindered cyclohexanones.[2] These additions, and particularly hydride reductions, were discussed on the basis of empirical rules[3] named "product development control" and "steric approach control." Explanations of the stereochemistry of these reactions based on pure steric approach considerations[4] or on eclipsing effects[5] were also advanced. Recent kinetic work[6] had shown that hydride reductions yielding the more stable equatorial alcohol predominantly, and previously assumed to be determined by the stability of the products, are in fact kinetically controlled.

Methylenecyclohexanes have a structure similar to that of cyclohexanones. Reduction of the latter compounds with diborane was shown[7] to give a similar distribution of isomeric cyclohexanols to that found in the product of their reaction with metal hydrides. However, the mechanism of this reduction[7] is different from that of hydrogenation,[8] the last reaction being first order in diborane,[8] whereas the reduction is three-halves order in diborane. It was therefore of interest to compare the stereochemistry of the reduction of cyclohexanones with that of the hydroboration of methylenecyclohexanes. The stereochemistry of the hydroboration of the exocyclic olefins 3-methyl- (Ia) and 4-methylmethylenecyclohexanes (IIa) and 3-*t*-butyl- (Ib) and 4-*t*-butylmethylenecyclohexanes (IIb) was studied to this effect.

a, R = CH₃
b, R = C(CH₃)₃

I   II   III   IV   V   VI
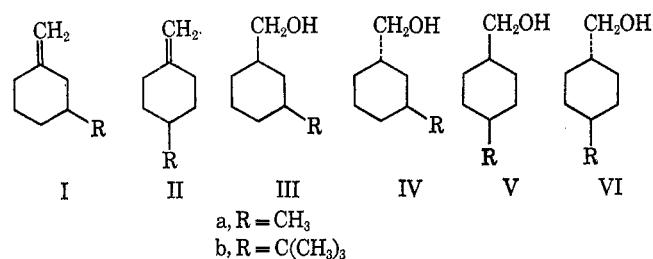
These compounds were prepared by the method of Corey[9] from the corresponding cyclohexanones.

The distribution of the isomeric alcohols III–VI,

obtained after oxidation of the products of hydroboration, is recorded in Table I.

The products of the reactions were analyzed by glpc and compared with samples of the alcohols IIIa, IIIb, IVa, IVb, Va, Vb, VIa, and VIb that were prepared by reduction of the methyl- or *t*-butylcyclohexanecarboxylic acids.

The less stable product was formed preferentially in the reaction of diborane with the compounds Ia, Ib, IIa, and IIb. The steric course of hydroboration was therefore different from the stereochemistry of the reduction of cyclohexanones,[7] as well as were their kinetics.[7,8] These results showed that the stability of the isomers did not determine the composition of the product of hydroboration and kinetic effect were apparently more important. The approach of diborane to the double bond was easier from the equatorial side, whereas the axial approach is generally preferred during the diborane or metal hydride reduction of unhindered cyclohexanones.

Possible reasons for the difference in approach in hydroboration and reduction, despite the fact that both reactions are kinetically controlled,[7,8] are the difference in the corresponding transition states[10] of the distances of the attacking molecules from the axial hydrogens on the carbons at positions 2 and 6 or 3 and 5, respectively (difference in steric interaction[4]), or from the C–H bonds at the positions 2 and 6 (eclipsing effects[5]). It seems, however, that different torsion effects derived from different points of attack by diborane in the hydroboration and reduction play an important role in the determination of their steric course. During the reductions of cyclohexanones it is the ring carbon that is attacked by diborane and the angle of torsion between the C–O bond and the two equatorial C–H bonds on the neighboring carbons diminishes and is close to zero in the transition state of an equatorial attack[11] (that gives the axial alcohol). This transition state is therefore less favorable than that for axial attack in reduction, where this angle of torsion increases to a more staggered conformation. On the other side, hydroboration proceeds by a four-center transition state in which the boron–carbon link is more developed than the forming carbon–hydrogen bond.[8,12] The boron atom begins to attach itself to the exocyclic carbon in the transition state of the hydroboration of methylenecyclohexanes, and the ring carbon retains its original trigonal geometry without appreciable change in torsion angles. Torsion effects should therefore discriminate very slightly between the two possible

(1) Taken from the M.S. Thesis of D. Lichtenberg, The Hebrw University, 1967.

(2) For a review see A. V. Kamernitzky and A. A. Akhrem, *Tetrahedron*, **18**, 705 (1962).

(3) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, **78**, 2579 (1956).

(4) J. C. Richer, *J. Org. Chem.*, **30**, 324 (1965).

(5) M. Cherest and H. Felkin, *Tetrahedron Lett.*, 2205, (1968).

(6) J. Klein, E. Dunkelblum, E. L. Eliel, and Y. Senda, *ibid.*, 6127 (1968).

(7) J. Klein and E. Dunkelblum, *Tetrahedron*, **23**, 205 (1967).

(8) J. Klein, E. Dunkelblum, and M. Wolff, *J. Organometal. Chem.*, **7**, 377 (1967).

(9) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(10) J. A. Marshall and R. D. Caroll, *ibid.*, **30**, 2748 (1965).

(11) P. von R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 699, 701 (1967).

(12) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962.

TABLE I

PRODUCTS OF HYDROBORATION[a] OF
METHYLENECYCLOHEXANES

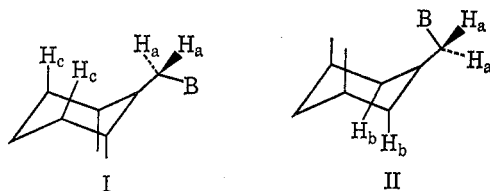| Starting material	Hydroboration agent	Yield, %, of alcohols	% cis in product	% trans in product
Ia	Diborane	76	37 IIIa	63 IVa
IIa	Diborane	82	66 Va	34 VIa
Ib	Diborane	78	33 IIIb	67 IVb
IIb	Diborane	75	68 Vb	32 VIb
Ia	Dicyclohexylborane	58	43[b] IIIa	42[b] IVa
IIa	Dicyclohexylborane	62	42[c] Va	45[c] VIa
Ia	Dichloroborane	68	34 IIIa	66 IVa
IIa	Dichloroborane	66	68 Va	32 VIa

[a] In THF. [b] 15% additional product was formed. [c] 13% additional product was formed.

modes of attack during hydroboration. A similar picture is obtained, when the formation of a complex[8,13] between borane and the olefin is the rate-determining step. However, torsion interactions alone could explain statistical distribution of the two products, but not the predominant formation of the axial isomer during hydroboration and an additional effect is necessarily present to account for this result. It seems to us that the concept of Zimmerman[14] on the favored protonation of exocyclic enols from the equatorial side can be applied in our case, and the protonation is a good model for reactions where torsion effects are small owing to a small degree of bond formation in the transition state and where steric interactions have a predominant influence. Equatorial approach of diborane is from the outside of the fold formed by the exocyclic methylene and the ring VII, whereas the axial attack is from the inside of the fold and is the more hindered of the two. The shift of the attacking reagent from the ring carbon toward the exocyclic carbon increases even more the difference in the energies of the two transition states in favor of the equatorial attack[15] owing to steric interaction of the reagent with the ring hydrogens. This

discussion assumes a structure of the methylenecyclohexane part of the transition state of hydroboration that is essentially similar to that of the olefin. This structure is supported by the strong steric interference during hydroboration of cyclohexenes having an axial methyl at the 4 position,[16-19] and even of an axial hydrogen geminal to a *t*-butyl group at this position.[19]

axial attack

equatorial attack

VII
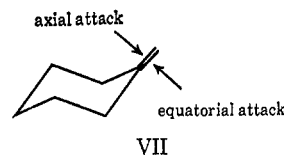
Only chair conformations of methylenecyclohexanes were considered in agreement with the nmr spectrum of the parent compound.[20,21]

A similar analysis of the direction of attack of cyclohexyl radicals in terms of torsion interactions was published recently.[22]

The ratio of the two isomers formed during the studied hydroboration reactions were not identical for all compounds, and the small differences in this ratio can be rationalized in terms of the relative proportions of various chair conformations in which the starting materials exist and the interference of axial substituents in the 3 position to hydrocarbon *cis* to them[16,19]

It is interesting that dichloroborane gave similar ratios of isomers to those formed in the reaction with diborane, but dicyclohexylborane gave almost equal amounts of the two isomeric products. The bulk of the hydroborating agent[23] appears to have an effect in this case, and this effect may be due to the interaction with the substituents on the carbons at positions 2 and 6. However, this evidence is not clear-cut, since the yield in this reaction is lower than in the previous reactions and, in addition, a third compound was formed. Its structure was not established, but it might be an isomer formed by addition, elimination, and a further addition of dicyclohexylborane. Since the elimination reaction could proceed with different rates from the two isomeric boranes formed in the first step, the final composition of the product might not reflect the steric course of the initial reaction.

Experimental Section

3-Methylcyclohexanone and 4-methylcyclohexanone were commercial products (Fluka). 3-*t*-Butylcyclohexanone[24] and 4-*t*-butylcyclohexanone[25] were prepared by published methods.

3-Methylmethylenecyclohexane (Ia).—NaH, 4.8 g of a 50% suspension in mineral oil, was washed with dry pentane. Dimethyl sulfoxide (DMSO) (50 ml) was then added and the mixture was heated for 1 hr at 70°[9] and then cooled in an ice bath, and a solution of 35.7 g of methyltriphenylphosphonium bromide[26] in 100 ml of DMSO was added dropwise. The red solution so formed was stirred for 15 min at room temperature; then 11 g of 3-methylcyclohexanone was added dropwise over 15 min.

(13) A. Streitwieser, Jr., L. Verbit, and R. Bittman, *J. Org. Chem.*, **32**, 1530 (1967).

(14) For a recent discussion see H. E. Zimmerman and P. S. Mariano, *J. Amer. Chem. Soc.*, **90**, 6091 (1968).

(15) A referee suggested a different explanation for the stereochemistry of these hydroborations: "When the reagent approaches the terminal carbon, the hydrogen atoms attached to the carbon are pushed out of the plane while little change occurs in the planar geometry of the inner carbon. Of the two possible approaches shown below, molecular models suggest that I is more favored by 0.2–0.6 kcal/mol because nonbonded hydrogen repulsions between H_a and H_c in I are smaller than those between H_a and H_b in II." We think that this explanation is not correct

I   II

for several reasons. It does not conform to what we know on the transition state of the hydroboration reaction, which has a structure similar to that of the starting olefin as shown by a ρ close to zero (hydroboration of substituted styrenes[5]) and the interference of axial substituents during hydroboration of cyclohexenes.[16] Even assuming the transition states I and II proposed by the referee, the repulsive interaction between H_a and the equatorial hydrogens in positions 2 and 6 in I will be greater than between H_a and H_b or H_c in I and II, respectively. It seems also that these interactions are rather of attractive than of repulsive nature. Our view is that it is the diborane which interferes differently with the ring at its both sides and not the hydrogens of the methylene group.

(16) J. Klein, E. Dunkelblum, and D. Avrahami, *J. Org. Chem.*, **32**, 935 (1967).

(17) M. Nussim, Y. Mazur, and F. Sondheimer, *ibid.*, **29**, 1120 (1964).

(18) G. Zweifel and H. C. Brown, *J. Amer. Chem. Soc.*, **86**, 393 (1964).

(19) D. J. Pasto and F. M. Klein, *J. Org. Chem.*, **33**, 1468 (1968).

(20) J. T. Gerig, *J. Amer. Chem. Soc.*, **90**, 1065 (1968).

(21) F. R. Jensen and B. H. Beck, *ibid.*, **90**, 1066 (1968).

(22) F. R. Jensen, L. H. Gale, and J. E. Rodgers, *ibid.*, **90**, 5793 (1968).

(23) H. C. Brown and G. Zweifel, *ibid.*, **82**, 3222 (1960); **83**, 1241 (1961).

(24) J. Sicher, F. Sipos, and M. Tichy, *Collect. Czech. Chem. Commun.*, **27**, 2907 (1962).

(25) M. Tichy, F. Sipos, and J. Sicher, *ibid.*, **26**, 847 (1961).

(26) A. Maercker, *Org. Reat.*, **14**, 1270 (1965).

The mixture was stirred for an additional hour and the product was distilled directly from this solution at 58° (25 mm). Redistillation gave 8.4 g (77%) of pure Ia: bp 118° ; ir (liquid film) 890 cm⁻¹ (C=CH₂).

Anal. Calcd for C₈H₁₄: C, 87.27; H, 12.73. Found: C, 87.55; H, 12.90.

4-Methylmethylenecyclohexane.[27]—Similar treatment of 4-methylcyclohexanone gave IIa: 78% yield; bp 120°; ir (liquid film) 890 cm⁻¹ (C=CH₂).

3-*t*-Butylmethylenecyclohexane (Ib) was prepared analogously, in 63% yield from 3-*t*-butylcyclohexanone. However, the product was not distilled directly from the reaction mixture, but water (1 l.) and pentane (250 ml) were added, and the mixture was stirred for 15 min and filtered from the precipitate. The layers were separated, the aqueous layer was extracted twice with pentane, and the combined pentane solutions were washed twice with a saturated aqueous solution of NaCl and filtered through a column containing 25 g of alumina. The solvent was removed and the residue was distilled giving Ib: 63% yield; bp 78° (15 mm); ir (liquid film) 886 cm⁻¹ (C=CH₂).

Anal. Calcd for C₁₁H₂₀O: C, 86.84; H, 13.15. Found: C, 86.71; H, 12.98.

4-*t*-Butylmethylenecyclohexane (IIb).—Similar treatment of 4-*t*-butylcyclohexanone gave IIb: 65% yield; bp 90° (25 mm);[28,29] ir (liquid film) 888 cm⁻¹ (C=CH₂).

3-Methylcyclohexanecarboxylic acids were prepared by known procedures.[30] The *cis* acid (mp 28°) was obtained pure, but the *trans* was contaminated with the *cis* product.

***cis*-4-Methylcyclohexanecarboxylic acid** had mp 28° (lit.[31,32] 28–30°). The *trans* isomer was obtained after equilibration of the mixture of isomers[33] and had mp 109° [lit.[31,32] 110°].

***cis*-3-*t*-Butylcyclohexanecarboxylic Acid.**[31]—Dehydration of 3-*t*-butylcyclohexaneonecyanhydrine[34] followed by acid hydrolysis of the nitrite and hydrogenation of the formed unsaturated carboxylic acid gave, after equilibration and two recristalizations from hexane, the pure acid, mp 95° [lit.[31] 95°]. The *trans* isomer was not isolated pure but was contaminated with the *cis* acid.

***cis*-4-*t*-Butylcyclohexanecarboxylic acid,** mp 117°, and its *trans* isomer, mp 175°, were separated by thiourea.[33,35]

***cis*-3-Methylcyclohexylmethanol (IIIa).**—A solution of 1 g of *cis*-3-methylcyclohexanecarboxylic acid in 10 ml of dry ether was added dropwise to 0.5 g of LiAlH₄ in 20 ml of dry ether. The reaction mixture was refluxed for 1 hr; the excess hydride was decomposed with water then 4 N H₂SO₄, and extracted twice

with 10-ml portions of ether. The combined ethereal solutions were washed with water, aqueous KOH, and then again with water. Distillation gave 0.6 g of IIIa, bp 110° (20 mm).

In a similar manner we prepared *trans*-3-methylcyclohexylmethanol (IVa) (contaminated with the *cis* isomer), bp 110° (20 mm); *cis*-4-methylcyclohexylmethanol[32,36] (Va), bp 100° and (15 mm), and its *trans* isomer[32,26] (VIa), bp 108° (20 mm); and *cis*-4-*t*-butylcyclohexylmethanol[32](Vb), mp 56° (ethanol 80%), and its *trans* isomer[36] (VIb), bp 130° (20 mm).

***cis*-3-*t*-Butylcyclohexylmethanol (IIIb).**—To a stirred solution of 0.2 g of *cis*-3-*t*-butylcyclohexanecarboxylic acid in 5 ml of THF was added dropwise 3 ml of a 2.5 M solution of borane in THF. The solution was stirred for 2 hr and 3 ml of water was added; then the solution was stirred for 1 hr, the layers were separated, the aqueous layer was extracted three times with 10-ml portions of ether, and the combined ether layers were washed twice with 10 ml of saturated sodiumbicarbonate solution, dried over magnesium sulfate, and distilled, giving 130 mg of IIIb, bp 130° (20 mm).

Hydroboration Reactions.—A solution of 0.1 mol of the olefin in 100 ml of THF was added dropwise to a cooled solution of 0.25 mol of borane in THF. The reaction mixture was stirred 1 hr at 0°, then 2 hr at room temperature. Excess diborane was decomposed by dropwise addition of water (100 ml). A 3 N solution of NaOH (100 ml) was then added, followed by dropwise addition of 30% H₂O₂ (100 ml). The reaction mixture was stirred for 1 hr at room temperature and K₂CO₃ (20 g) was then added. The layers were separated, the aqueous solution was extracted three times with 100 ml of ether, and the combined organic layers were washed with water, dried over magnesium sulfate, then distilled, and analyzed by glpc.

In the dichloroborane reactions, only 0.1 mol of this hydroboration agent was used for each 0.1 mol of olefin. Dichloroborane was prepared by dissolution of 0.1 mol of BCl₃ in 20 ml of THF at 0° followed by addition of 0.05 mol of a solution of borane in THF. This solution was left at 0° for 10 hr before use.

Dicyclohexylborane was prepared by addition of 10 g (¹/₃ mol) of cyclohexene to 26 ml of 2.5 M solution of borane in THF (¹/₆ mol). The solution was left for 16 hr at room temperature before use.

Gas chromatography of the methylenecyclohexanes was carried out on a 3 m × ¹/₈ in. column of Porapak Q. The products of hydroboration were analyzed on a 3 m × 0.25 in. column of 10% Ucon Polar on Chromosorb P at 140°, or on 4 m × 0.25 in. column of 10% polyneopentyl glycol succinate or Chromosorb P at 170°. The ketones I and II were used as internal standards in the reaction mixture for quantitative determination of yields. The yields of the reactions were also determined directly by distillation of the products. The analyses of the obtained mixtures of isomers were in agreement with their formulas.

(27) J. F. Sauvage, R. H. Baker, and A. S. Hussey, *J. Amer. Chem. Soc.*, **82**, 6090 (1960).

(28) R. G. Carlson and N. S. Behn, *J. Org. Chem.*, **32**, 1363 (1967).

(29) B. Cross and G. H. Whitham., *J. Chem. Soc.*, 3892 (1960).

(30) L. H. Darling, A. K. Macbeth, and J. A. Mills, *ibid.*, 1364 (1953).

(31) M. Tichy, J. Jonas, and J. Sicher, *Collect. Czech. Chem. Commun.*, **24**, 3434 (1959).

(32) H. Van Bekkum, A. A. B. Kleis, A. A. Massier, D. Medema, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim. Pays-Bas*, **80**, 595 (1961).

(33) H. H. Lau and H. Hart, *J. Amer. Chem. Soc.*, **81**, 4897 (1959).

(34) L. Manday, *J. Chem. Soc.*, 1413 (1964).

(35) H. Van Bekkum, P. E. Verkade, and B. M. Wepster, *Proc. Kon. Ned. Akad. Wetensch. Ser*, *B62*, No. 3, 147 (1959); *B64*, 161 (1961).

(36) N. Mori, *Bull. Chem. Soc. Jap.*, **34**, 1299 (1961).