Reduction of Epoxides. II. The Lithium Aluminum Hydride and Mixed Hydride Reduction of 3-Methylcyclohexene Oxide[1,2]

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Received November 8, 1966

The previously reported anomalous behavior on reduction of 3-methylcyclohexene oxide has been clarified by examination of the nearly pure *cis* isomer and mixtures of *cis* and *trans* material. Lithium aluminum hydride reduction of the *cis* epoxide gives 89, 9, 0, and 2% of *cis*-2-methylcyclohexanol, *trans*-2-methylcyclohexanol, *trans*-3-methylcyclohexanol, and *cis*-3-methylcyclohexanol; the *trans* epoxide yields 0, 30, 61, and 9% of the same alcohols under these conditions. Aluminum hydride gives 94, 0, 0, and 6% and 0, 32, 68, and 0% of these alcohols from the *cis* and *trans* epoxide, respectively. The *trans* epoxide is unusual in that reduction by either reagent gives rise to a large percentage of equatorial alcohol product (methyl group equatorial). The mechanism of reduction is discussed.

In previous work[2] it has been shown that the bulky alkyl group in 4-*t*-butylcyclohexene oxide exhibits strong conformational control in hydride reduction processes. Thus, aluminum hydride[3] reduction of *trans*-4-*t*-butylcyclohexene oxide gives essentially pure *trans*-3-*t*-butylcyclohexanol. Lithium aluminum hydride reduction of this epoxide gives the same alcohol with about 10% of *cis*-3-*t*-butylcyclohexanol as the only detectable products. The formation of *cis* alcohol from *trans* epoxide was shown by deuterium incorporation to occur through a competing oxidative process in which 3-*t*-butylcyclohexanone was formed as an intermediate and subsequently reduced. These observations are consistent (for either reducing agent) only for reaction occurring by diaxial opening[4] and involving a transition state in which the *t*-butyl group strongly prefers the equatorial conformation. *cis*-4-*t*-Butylcyclohexene oxide behaves in an analogous manner, yielding exclusively *cis*-4-ol on reduction by aluminum hydride.[2]

The effect of the 4-methyl substituent is less easily predicted; evidence has been presented[5] which suggests that in 4-methylcyclohexene the equatorial conformation is preferred over the axial by approximately 1 kcal/mole. A preference of similar magnitude might be anticipated for *trans*-4-methylcyclohexene oxide which also exists in a half-chair conformation like that of cyclohexene.[6] The axial methyl epoxygen interaction in one conformer of *cis*-4-methylcyclohexene oxide is of undetermined magnitude, but in net effect should increase the preference for equatorial methyl in this isomer. Reduction of an approximately equal mixture of these stereoisomers by aluminum hydride gave a mixed product containing only 2% of equatorial alcohols,[5] showing that, like the *t*-butyl group, the 4-methyl group exhibits strong conformational control over the reduction process. This degree of control appears to be greater than anticipated from the conformational preference of the methyl group in the ground-state epoxide (particularly for the *trans* epoxide) and presumbly may be accounted for by added steric interactions in the transition state.

The oxidative inversion noted in the 4-*t*-butylcyclohexene oxide was also apparent in the lithium aluminum hydride reduction of 4-methyl- and *cis*-4,5-dimethylcyclohexene oxide,[5] and thus appears to be quite general for reductions of cyclohexene oxides by this reagent.

Results and Discussion

In a previous attempt[5] to determine the relative amounts of *cis* and *trans* epoxide formed in the reaction of 3-methylcyclohexene with per acid, the product mixture was subjected to both lithium aluminum hydride and aluminum hydride reduction. Both reagents gave substantial amounts of equatorial alcohol products; the aluminum hydride result was surprising in view of the high "axial" specificity found for this reagent and 4-alkylcyclohexene oxides. Since all four alcohol products were formed in both reductions, it was necessary to work with one isomerically pure epoxide to determine the product precursors. Using the method described previously for preparation of *trans*-4-*t*-butylcyclohexene oxide,[7] nearly pure *cis*-3-methylcyclohexene oxide was obtained in low yield. The results of reduction of this and other mixtures of *cis* and *trans* material are shown in Table I, along with the values (shown in parentheses) derived for the isomerically pure epoxides. The latter were obtained by plotting mole per cent of a given alcohol product *vs.* percentage of *cis* epoxide, and extrapolating to give the values shown for pure isomers.

TABLE I

Epoxide, % *cis*	Hydride	*cis*-2-Ol	*trans*-2-Ol	*trans*-3-Ol	*cis*-3-Ol
(100)[a]	$LiAlH_4$	(89)	(9)	. . .	(2)
96.6	$LiAlH_4$	87	10	1.4	3.1
55.1	$LiAlH_4$	49	20	26	5.6
38.8	$LiAlH_4$	32	21	40	6.4
(0)[b]	$LiAlH_4$	. . .	(30)	(61)	(9)
(100)[a]	AlH_3	(94)	. . .	. . .	(6)
96.6	AlH_3	93	1.0	2.0	5.6
55.1	AlH_3	51	17	29	3.4
38.8	AlH_3	32	20	44	2.6
(0)[b]	AlH_3	. . .	(32)	(68)	. . .

[a] Extrapolated values are shown in parentheses. Estimated error in the alcohol distribution from *cis* epoxide is ±1%. [b] Owing to the greater extrapolation necessary for alcohol distribution from *trans* epoxide, the estimated error is ±2%.

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(1) Support by the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

(2) Part I: B. Rickborn and J. Quartucci, *J. Org. Chem.*, **29**, 3185 (1964).

(3) The term "aluminum hydride" is used here to describe the material that is formed in ether on mixing lithium aluminum hydride and aluminum chloride in a 3:1 molar ratio.

(4) A. Furst and P. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).

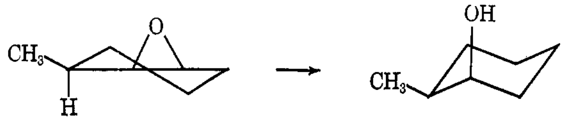
(5) B. Rickborn and S. Lwo, *J. Org. Chem.*, **30**, 2212 (1965).

(6) B. Ottar, *Acta Chem. Scand.*, **1**, 283 (1947).

(7) B. Rickborn and J. Quartucci, *J. Org. Chem.*, **29**, 2476 (1964).

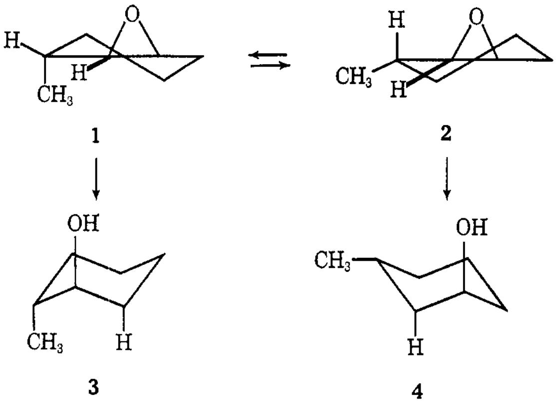
The oxidative inversion noted with other cyclohexene oxides is also evident in the present system, accounting for the formation of *trans*-2-methylcyclohexanol (from *cis* epoxide) and *cis*-3-methylcyclohexanol (from *trans* epoxide). Approximately 10–15% of the reduction occurs by this pathway.[8,9] In agreement with previous observations, aluminum hydride reduction yields alcohols in which the carbon–oxygen bond has fully retained its initial configuration. Thus, as seen from the data in Table I, *cis* epoxide leads, within experimental error, to *cis* alcohols only, while the converse is true of the *trans* epoxide.

cis-3-Methylcyclohexene oxide behaves in a normal manner on reduction with either reagent, although the 6% of equatorial alcohol formed on aluminum hydride reduction is higher than observed with 4-alkylcyclohexene oxides. The major reduction pathway thus appears to involve diaxial opening through the presumed more-stable quasi-equatorial methyl half-chair conformer.



cis

The *trans* epoxide, however, is unusual in that a substantial amount of equatorial alcohol is formed on reduction. Assuming, again on the basis of past experience with other alkyl-substituted cyclohexene oxides, that the reduction process involves a *trans*-diaxial transition state, two reasonable mechanisms are available. In one of these, the two reduction products may be viewed as arising from the two rapidly interconverting half-chair conformers of the *trans* epoxides 1 and 2.



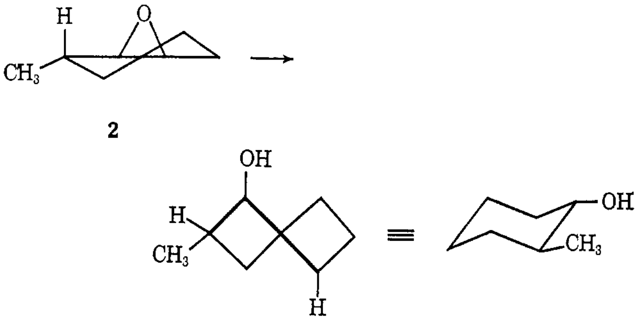
1 **2**

3 **4**

This mechanism has several attractive features. Although it is not possible to relate the reduction product distribution quantitatively to the ground-state conformational equilibrium, a kinetic effect is anticipated. If the equatorial alcohol product arises from half-chair 1, there must be more of this conformer present in the equilibrium than would be expected on the basis of the *cis*-epoxide reduction. Indeed, models suggest that the 2 proton in conformer 2 is nearly eclipsed with the quasi-equatorial 3-methyl group. It may be argued that the destabilization of 2 owing to this interaction increases the contribution of 1 to the conformational equilibrium.

Furthermore, the increased contribution of 1 and the steric interaction between the attacking hydride donor and the quasi-axial methyl is expected to lead to a net decrease in rate of reduction of *trans*-3-methylcyclohexene oxide.[10] This has, in fact, been demonstrated in a qualitative manner, by examining the partial reduction of mixed epoxide by lithium aluminum hydride; *cis*-3-methylcyclohexene oxide is reduced somewhat more rapidly than the *trans* isomer (see the Experimental Section).

An alternate mechanism for reduction, involving reaction through quasi-equatorial methyl half-chain (2) to give product initially formed in the twist conformation (5), is considered less probable. The same process is available to *cis*-3-methylcyclohexene oxide and to the 4-alkylcyclohexene oxides examined previously, none of which give appreciable amounts of equatorial alcohol by direct reduction. However, as it is not possible to estimate accurately the ground- and transition-state conformational interaction energies in any of these systems, this mechanism cannot be rigorously excluded.



2

5

Although the reactions of isomeric 3-methylcyclohexene oxides have not been studied previously, it is of interest to compare the present results with those from similar systems. Lemieux and his co-workers[11] have examined the hydroxide opening of *cis*- and *trans*-3-methoxycyclohexene oxides.[12] The *cis* isomer gave predominately (*ca.* 80%) the product of attack at C-1, *i.e.*, the material that corresponds to diaxial opening through the quasi-equatorial methoxy conformation. The *trans* epoxide gave almost exclusively the product of C-1 attack, corresponding to diaxial opening through the quasi-axial methoxy conformer. Although the selectivity is different from that noted in this study, the greater involvement of the quasi-axial conformation in the *trans* substituted epoxide is evident in both systems. Although Lemieux has suggested that the directive influences found in the isomeric 3-methoxy-

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[8] N. A. Le Bel and G. G. Ecke [*J. Org. Chem.*, **32**, 4316 (1965)] reported a similar degree of oxidative inversion in the lithium aluminum hydride reduction of 1-methyl-4-*t*-butylcyclohexene oxide.

[9] Under the reaction conditions employed in this study, lithium aluminum hydride reduction of 2-methylcyclohexanone gives 72% *trans*-2-methylcyclohexanol and 3-methylcyclohexanone gives 91% *cis*-3-methylcyclohexanol, in good agreement with the values reported by Eliel [*Rec. Chem. Prog.*, **22**, 129 (1961)].

[10] It should be noted that this interaction cannot be too energetically unfavorable, as very little of product **3** would be formed under these conditions.

[11] R. U. Lemieux, R. K. Kullnig, and R. Y. Moir, *J. Am. Chem. Soc.*, **80**, 2237 (1958).

[12] J. A. McRae, R. Y. Moir, J. W. Haynes, and L. G. Ripley, *J. Org. Chem.*, **17**, 1621 (1952).

cyclohexene oxides are primarily electronic in nature, the similarities in the analogous 3-methyl compounds suggest that conformational effects may be controlling the ring-opening reactions in both systems. The lower conformational preference of methoxy (relative to methyl) in cyclohexane derivatives is in keeping with greater participation of quasi-axial conformers in the reactions of 3-methoxycyclohexene oxides.

A few studies have been carried out involving lithium aluminum hydride reduction of 3-substituted cyclohexene oxides of known configuration. Lemieux[11] has reported that the *trans*-3-methoxycyclohexene oxide yields predominantly *trans*-2-methoxycyclohexanol, in agreement with the direction of opening by other nucleophiles. Henbest and Wilson[13] found that *cis*-3-hydroxycyclohexene oxide gives over 90% *cis*-1,2-cyclohexanediol on reduction. Although the data are less exact, it appears that *trans*-3-hydroxycyclohexene oxide gives predominantly 1,3-diol. These two examples fit well with the conformational control argument if it is assumed that a rapid initial reaction between the hydroxyl function and the hydride donor occurs to give a solvated, bulky alkoxyaluminum group which prefers the quasi-equatorial position.[14] Interestingly, similar directive influences have been demonstrated by Cope and his co-workers[15] in the hydride reduction of the isomeric 3-hydroxycycloheptene oxides.

Experimental Section

3-Methylcyclohexene.—This olefin, shown by vpc (di-*n*-butyl tetrachlorophthalate column) to be free of isomeric materials, was prepared from 3-bromocyclohexene and methylmagnesium iodide, bp 101–102.[16]

3-Methylcylohexene Oxide.—In a typical preparation, 35 g (0.29 mole) of 3-methylcyclohexene in 150 ml of anhydrous ether was treated with a 10% *M* excess of *m*-chloroperbenzoic acid at 0°. The reaction mixture was kept at ice temperature for 14 hr, washed with dilute base and ferrous sulfate solutions, and dried over magnesium sulfate, after which the solvent was evaporated. Distillation of the residue gave 27.4 g (70%) of epoxide, bp 75° (6 mm).[17]

Isomer composition was determined by vpc, using an 8-m 20% triscyanoethoxypropane column at 90°. The *cis* epoxide has the shorter retention time on this column. The *cis/trans* ratio was found to be variable when the conditions for epoxidation were changed, with increased *trans* content being associated with longer reaction times and lower over-all yields. Apparently the *cis* epoxide is opened more rapidly by *m*-chlorobenzoic acid to give hydroxy ester. To verify this, an equal mixture of *cis*- and *trans*-3-methylcyclohexene oxide was treated with insufficient lithium aluminum hydride at room temperature. Approximately 15% reduction to alcohol occurred, and the remaining epoxide was distinctly richer in *trans* isomer. The greater reactivity of the *cis* epoxide is in keeping with the conformational arguments presented in the text.

In order to determine the ratio of epoxide isomers initially formed in the peracid reaction, samples were removed from an olefin–peracid mixture in ether and analyzed directly by vapor phase chromatography. From about 5% through essentially complete reaction the product contained 50 ± 1% of each isomer. Loss of the *cis* epoxide occurred only if the reaction mixture was allowed to stand several hours at room temperature.

***cis*-3-Methylcyclohexene Oxide.**—Using a previously described procedure,[7] the mixed epoxide was converted into the chloro-*p*-nitrobenzoate derivative. Repeated recrystallization from methanol gave (in low yield) a solid, mp 109–110°, which was cleanly converted to epoxide by hydrolysis with potassium carbonate in aqueous methanol. Analysis by vpc showed 97% of the isomer with shorter retention time, along with 3% of the other isomer. Identification of the major product as the *cis* epoxide rests on the reduction data, *i.e.*, the expectation that *cis* alcohols should strongly predominate on treatment of this material with hydride.

Analysis of Reduction Products.—All reductions were carried to completion using a large excess of hydride. The mixture of alcohols was isolated in the normal manner; controls were run to show that no fractionation of product occurred. Numerous vapor phase chromatography columns were used in an attempt to obtain complete separation of the four alcohols (or their acetates). The best separation was obtained using an 8-m triscyanoethoxypropane column, 0.25 in., at 80–90°. Under these conditions complete peak separation was observed for *cis*-2-methylcyclohexanol (shortest retention time) and *cis*-3-methylcyclohexanol (longest retention time), allowing direct calculation of their percentage contributions to the mixture. The two *trans* alcohols were incompletely separated, allowing only an approximate calculation of the amount of each present (*trans*-3-methylcyclohexanol has a slightly longer retention time).

Chromic acid oxidation of the product mixture led to a mixture of 2- and 3-methylcyclohexanone, easily separable on the same column, and shown to be free of starting alcohols. Analysis of the ketone composition coupled with the known *cis* alcohol values allowed calculation of the contribution of each *trans* alcohol to the mixture. Controls were run with known alcohol and ketone mixtures, and it was found that no corrections were needed to obtain accurate date and that neither ketone is selectively further oxidized under these conditions (acetone, 0°).

Registry No.—*cis*-3-Methylcyclohexene oxide, 7443-69-8; *cis*-2-ol, 7443-70-1; *trans*-2-ol, 7443-52-9; *cis*-3-ol, 5454-79-5; *trans* isomer of **1**, 7443-54-1; *trans*-3-ol, 7443-55-2; 3-methylcyclohexene, 591-48-0.

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(13) H. B. Henbest and R. S. Wilson, *J. Chem. Soc.*, 1958 (1957).

(14) A large conformational preference would seem reasonable in view of Eliel's results [*Rec. Chem. Prog.*, **22**, 129 (1961)] on equilibration of alcohols with mixed hydride.

(15) A. C. Cope, J. K. Heeren, and V. Seeman, *J. Org. Chem.*, **28**, 516 (1963).

(16) R. T. Arnold, G. G. Smith, and R. M. Dodson, *ibid.*, **15**, 1256 (1950).

(17) M. Mousseron, G. Manon, and G. Combes, *Bull. Soc. Chim. France*, 396 (1949).