# On the Stereochemistry of the Reduction of Cyclic Ketones with Lithium Tri-*t*-butoxyaluminum Hydride

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The stereochemistry of the reduction of cyclic ketones by lithium tri-*t*-butoxyaluminum hydride has been examined. An explanation of these results, which is based solely on steric factors, is proposed.

The stereochemical results for the reduction of cyclic ketones by complex hydrides have generally been explained in terms of "steric approach control" and "product development control" as proposed by Dauben and his co-workers.[1] The necessity of the concept of product development control has always appeared doubtful to the author on the basis of the following reasons. (a) A stability factor is introduced in order to account for some of the stereochemical results obtained in the reductions of cyclic ketones; however, the additions to acyclic carbonyl groups are regulated only by steric factors such as Cram's rule[2] and Prelog's rule.[3] (b) In certain cases a stability factor is introduced in order to explain the relatively small amount of unhindered alcohols [3$\alpha$-cholestanol or *cis*-4-*t*-butylcyclohexanol (**1**)] formed; it is then surprising that in other cases highly hindered alcohols of low stability (isoborneol and 11$\beta$-hydroxy steroids) are produced in large amounts.

This paper reports the results obtained in the reduction of certain cyclic ketones by LiAlH(O-*t*-Bu)$_3$ (*cf.* Table I). An explanation of these results, which is based solely on steric factors, is proposed.[6]

TABLE I

REDUCTION OF SUBSTITUTED CYCLOHEXANONES

| Ketone | % of stable isomer[a] |
|---|---|
| Camphor | 5[b] |
| 2-Methylcyclohexanone | 63.2[c] |
| 3-Methylcyclohexanone | 86.0 |
| 4-Methylcyclohexanone | 82.6[d] |
| 4-*t*-Butylcyclohexanone (**2**) | 89.7 |
| 4-*t*-Butyl-2,2-dimethylcyclohexanone (**3**) | 100[e] |
| 3,3,5-Trimethylcyclohexanone | 12.2 |

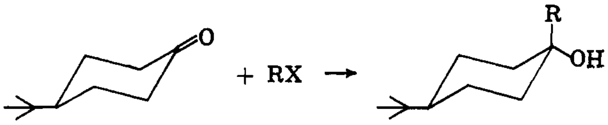
[a] Normalized per cents of alcohols. [b] This result does not vary even when the ketone is in excess. Dauben[4a] reports a value of 5% while Wheeler and Mateos[4b] report 75%. [c] Dauben[4a] reports 64%. [d] Wheeler and Mateos[4b] report 86%. [e] From Perrault's thesis.[5] With LiAlH$_4$-ether the amount of stable isomer formed is 95% while with NaBH$_4$–*i*-PrOH it is 92%. At equilibrium (aluminum isopropoxide–acetone) the amount of stable alcohol is 60%.

The concept of product development control was derived from the premise that an unhindered cyclic ketone [3-cholestanone or 4-*t*-butylcyclohexanone (**2**)] is symmetrical above and below the plane of the carbonyl group and should lead to the formation of a 50:50 mixture of isomeric alcohols, if steric factors only were concerned. Considering that the reductions of these ketones lead to the preferential formation (90:10) of the more stable isomer, a stability factor was introduced.

By examination of Table II, reporting the results for the addition of small (hydride and cyanide ions) or rod-like substituents ($^-CH_2NO_2$ and $^-C{\equiv}C{-}H$) to 4-*t*-butylcyclohexanone, a striking similarity between these results is observed and might indicate that an axial attack (by a small or rod-like substituent on an "unhindered ketone") should be favored (90:10) over an equatorial attack.

TABLE II

ADDITION REACTIONS TO 4-*t*-BUTYLCYCLOHEXANONE



| R | Reagent | % of *trans*-hydroxy product |
|---|---|---|
| $CN^-$ | HCN | 90[a] |
| $^-CH_2NO_2$ | $CH_3NO_2$ | 90[b] |
| $^-C{\equiv}C{-}H$ | Acetylene | 89[c] |
| $H^-$ | $LiAlH_4$ | 92[d] |
| $H^-$ | LiAlH(O-*t*-Bu)$_3$ | 89.7 |

[a] See ref. 7. [b] See ref. 8. [c] See ref. 9. [d] See ref. 10.

Careful examination of an unhindered cyclohexanone indicates that, contrary to what has been assumed,[1] the hydrogens in positions 2 and 6 are not disposed symmetrically above and below the plane of the carbonyl group. The equatorial hydrogens (or substituents) are in the "plane" of the carbonyl group[11] and will not interfere with a species approaching the carbonyl group either from its axial or equatorial side. On the other hand, the axial hydrogens are "perpendicular" to the plane of the carbonyl group and would interfere with a species approaching the carbonyl group from the equatorial side. It is evident then that the stereochemical results of all the additions on unhindered ketones by groups small enough not to interfere with the axial hydrogens in positions 3 and 5 will be directed exclusively by the presence of the axial hydrogens in positions 2 and 6 which hinder attack from the equatorial side.

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[1] W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

[2] D. J. Cram and F. A. Abd Elhafez, *ibid.*, **74**, 5828 (1952).

[3] V. Prelog, *Bull. soc. chim. France*, 987 (1956).

[4] (a) W. G. Dauben, R. E. Bozak, R. Ellis, and F. Willey, *Rev. Chim., Acad. Rep. Populaire Roumaine*, **7**, 803 (1962); (b) O. H. Wheeler and J. L. Mateos, *Can. J. Chem.*, **36**, 1431 (1958).

[5] G. Perrault, Mémoire de Maîtrise, Faculté des Sciences, University of Montreal, Sept. 1962.

[6] Most of the results and conclusions presented in this paper were reported at the 44th Annual Meeting of the Chemical Institute of Canada, Montreal, Aug. 1961.

[7] D. Gravel, Doctoral Thesis, University of Montreal, April 1962.

[8] H. Favre and D. Gravel, *Can. J. Chem.*, **39**, 1548 (1961).

[9] G. F. Hennion and F. X. O'Shea, *J. Am. Chem. Soc.*, **80**, 614 (1958).

[10] E. L. Eliel and R. S. Ro, *ibid.*, **79**, 5992 (1957).

[11] (a) R. N. Jones, D. A. Ramsay, F. Merling, and K. Drobiner, *ibid.*, **74**, 2828 (1952); (b) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, C. Djerassi [*ibid.*, **83**, 4013 (1961)] suggested that the angle between the carbonyl and equatorial hydrogens is 4°.

Application of the above all-steric proposal leads to the prediction that reduction of 4-*t*-butyl-2,2-dimethylcyclohexanone (**3**) should give more axial attack than its unmethylated analog **2** owing to the greater influence of the 2-axial methyl group over the influence of the 2-axial hydrogen. This prediction has been borne out (see Table I); the experimental result however is contrary to what would be predicted by product development control, since the 4-*t*-butyl-2,2-dimethylcyclohexanols give more axial OH at equilibrium than the 4-*t*-butylcyclohexanols.

In the preceding paragraphs the additions of small species to unhindered cyclohexanones have been shown to be governed by the axial substituents in positions 2 and 6. However as the size of the entering group becomes larger, more and more interactions with the 3 and 5 axial hydrogens are felt, favoring to a greater extent the equatorial (over the axial) attack on the unhindered ketone. For example, the axial introduction of a methyl group (from methylmagnesium iodide) on the unhindered 4-*t*-butylcyclohexanone would provoke in the transition state a 1a-$CH_3$–3a-H interaction which causes an attack from the equatorial side of the carbonyl group to the extent of 50%.[8,12] It is noteworthy that the axial introduction of a hydride ion (from $LiAlH_4$) on the 3,3,5-trimethylcyclohexanone which would provoke in the transition state a 1a-H–3a-$CH_3$ interaction also leads to a mixture of isomeric alcohols containing approximately equal parts of each.[13]

Although it is recognized that any extensive generalization on the stereochemistry of the hydride reductions will have to take into account such factors as solvent,[14] nature of the hydride ,[15] electrostatic effects,[16] internal complexes, the influence of added Lewis acids,[17] and the temperature,[18] it seems possible to explain all the stereochemical results of the hydride reduction of cyclic ketones on the basis of steric factors only. Extension of the concepts developed above to the field of other additions to cyclic $sp^2$ carbon atoms could be made and would, for example, help to bring about an understanding of the stereochemical results reported by Greene[19] in the field of free radicals.

## Experimental

The reduction reported in Table I were carried out in tetrahydrofuran with hydrides from a commercial source or prepared *in situ*. The reaction times at room temperature were about 3.5 hr. The normalized percentages of the isomeric alcohols formed were estimated from vapor phase chromatograms using the peak height times half-width band method. These chromatograms were recorded on a Burrel K-2 apparatus. Except for the reduction products of the cyclohexanones **2** and **3**, the conditions used for chromatography were a 1.5-m. column of 20% glycerol on Kromat FB and temperatures from 110–120°. The cyclohexanones **2** and **3** were analyzed on a 2.5-m. column of 20% Carbowax 20M on Kromat FB at 160°.

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[12] (a) B. Cross and G. H. Whitham, *J. Chem. Soc.*, 3892 (1960); (b) C. H. Depuy and R. W. King, *J. Am. Chem. Soc.*, **83**, 2743 (1961); (c) W. J. Houlihan, *J. Org. Chem.*, **27**, 3860 (1962).

[13] E. L. Eliel and H. Haubenstock, *J. Am. Chem. Soc.*, **84**, 2363 (1962).

[14] G. Just and R. Nagarajan, *Can. J. Chem.*, **39**, 548 (1961).

[15] D. M. S. Wheeler and J. W. Huffman, *Experientia*, **16**, 516 (1960).

[16] D. M. S. Wheeler and M. Wheeler, *Chem. Ind.* (London), 463 (1961).

[17] (a) J. C. Richer and E. L. Eliel, *J. Org. Chem.*, **26**, 972 (1961); (b) E. L. Eliel and M. N. Rerick, *J. Am. Chem. Soc.*, **82**, 1367 (1960).

[18] P. T. Lansbury and R. E. MacLeay, *J. Org. Chem.*, **28**, 1940 (1963).

[19] F. D. Greene, C.-C. Chu, and J. Walia, *ibid.*, **29**, 1285 (1964).

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# 2:3-Benzo-1-silacycloalkenes. II. Improved Syntheses and Reactions

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The di-Grignard reagents of 3-(*o*-bromophenyl)propyl bromide and 2-(*o*-bromophenyl)ethyl bromide reacted with dichlorosilanes to give benzosilacycloalkenes. The six-membered ring compound, 2:3-benzo-1,1-diphenyl-1-silacyclohex-2-ene, was readily brominated by N-bromosuccinimide to give the 4-derivative. This compound coupled when allowed to react with magnesium and was converted into the ketone, 2:3-benzo-1,1-diphenyl-1-silacyclohex-2-en-4-one.

Previously we reported the preparation of some 2:3-benzo-1-silacycloalkenes by ring closure of (*o*-chlorophenyl)alkylsilanes with molten sodium in refluxing toluene.[1] A possible use of these compounds is as precursors to larger ring systems.[1b] An independent synthesis of 2:3-benzo-1,1-diphenyl-1-silacyclohex-2-ene (I) was realized by allowing 3-(*o*-bromophenyl)propyl bromide to react with magnesium in an ether–tetrahydrofuran mixture and subsequently treating the organomagnesium compound with dichlorodiphenylsilane. Although the yield of I was low, the method of synthesis suggested the presence of an aralkyl di-Grignard reagent hitherto unknown.[2] This paper reports improved yields of the di-Grignard reagent, its reaction with carbon dioxide and dichlorosilanes, and some reactions of the resulting cyclic silanes.

When 3-(*o*-bromophenyl)propyl bromide was allowed to react with magnesium in tetrahydrofuran and the resulting organomagnesium compound was treated with dichlorodiphenylsilane, 2:3-benzo-1,1-diphenyl-1-silacyclohex-2-ene (I) was obtained in a good yield. The di-Grignard reagent II was also characterized by carbonation to 4-(*o*-carboxyphenyl)butyric acid.[3] The di-Grignard compound also reacted with diphenyltin dichloride to give 2:3-benzo-1,1-diphenyl-1-stannacy-

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[1] (a) H. Gilman and O. L. Marrs, *Chem. Ind.* (London), 208 (1961); (b) *J. Org. Chem.*, **29**, 3175 (1964).

[2] I. T. Miller and H. Heaney, *Quart. Rev.* (London), **11**, 109 (1957).

[3] P. D. Gardner, *J. Am. Chem. Soc.*, **78**, 3421 (1956). A sample of the acid was kindly furnished by Dr. Gardner.