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THE INFLUENCE OF STERIC AND TORSIONAL STRAIN ON THE STERIC COURSE OF ADDITIONS TO CYCLOHEXANONES. THE REACTION BETWEEN 4-T-BUTYLCYCLOHEXANONE AND T-BUTYLALLYL MAGNESIUM BROMIDE.

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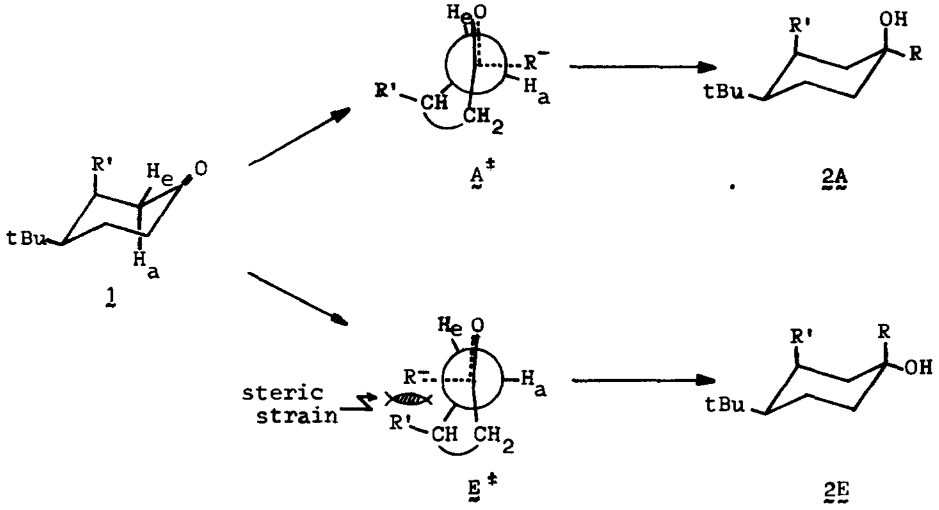
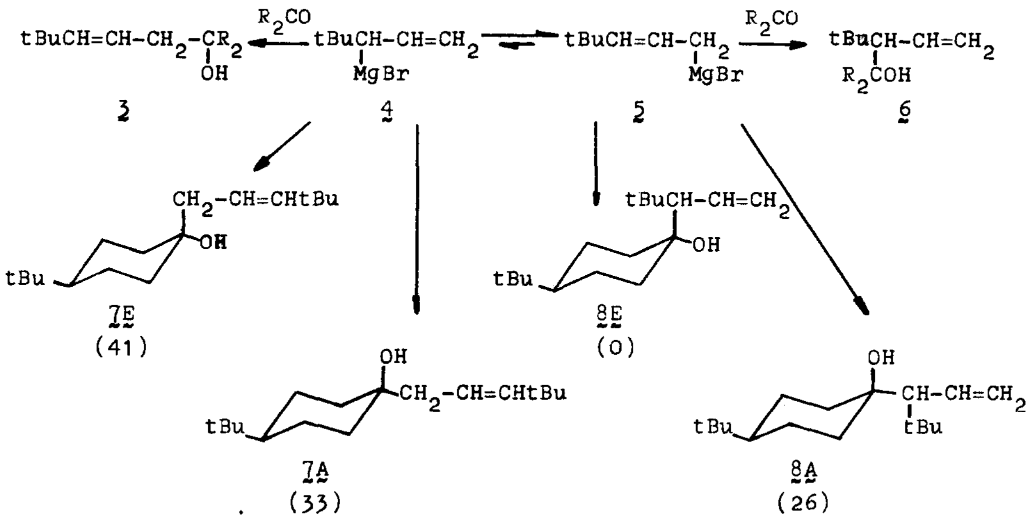
The steric outcome of the reactions of simple cyclohexanones (e.g., 1) with hydrides and Grignard reagents is governed by the relative magnitudes of the strains in the transition states A‡ and E‡, leading to the axial 2A and equatorial 2E alcohols respectively.[1,2]



It seems clear that the major factor which impedes the formation of the equatorial epimer 2E is steric strain (shown) in the transition state E‡: the bulkier R$^-$ and/or R', the smaller the product ratio 2E/2A ("steric approach control").[3] The factor which impedes the formation of the axial epimer 2A is, however, less obvious,[4] and different suggestions have been put forward at various times regarding the source of the strain in the corresponding transition state A‡: steric strain involving either O and R' ("product development control"),[3] or R^- and H_a;[5] *dipolar repulsion* between R^- and H_a;[6] *torsional strain* involving either R^- and H_a,[7] or O and H_e.[8] It was therefore of interest to find out whether or not the strain in the transition state **A**‡, leading to the axial epimer **2A**, is essentially steric in nature. The proportions of the isomeric tertiary alcohols obtained in the reaction between 4-t-butylcyclohexanone **1** (R' = H) and t-butylallyl magnesium bromide **4**-**5**, reported below, strongly support the view[6,7,8,9] that it is not.



The ratio of products (**3**/**6**) formed in the reaction between ketones and this allylic Grignard reagent has been shown to be an extremely sensitive measure of steric hindrance in the neighbourhood of the carbonyl group: the greater the steric strain between the Grignard and ketone moieties in the transition state, the greater the ratio **3**/**6**.[10] In the case of t-butylcyclohexanone, there can be two epimeric pairs of alcohols, **7E** and **8E** (equatorial OH) and **7A** and **8A** (axial OH); the equatorial product **7E**/**8E** will reflect the magnitude of the steric strain [involving R' (= H) and R^-] in the transition state **E**‡, and the axial product ratio **7A**/**8A** the magnitude of the steric strain (involving H_a and R^-) in the transition state **A**‡. Steric hindrance on the axial and equatorial "sides" of the carbonyl group may thus be directly compared.

The proportions of alcohols obtained are shown (in parentheses) in the scheme.[11] As expected, the equatorial ratio **7E**/**8E** is large (> 100), thus confirming the reality of steric strain in the transition state **E**‡. The axial ratio **7A**/**8A**, however, is extremely small (1.3), smaller in fact than the ratio [**3**/**6** (R = Me) = 3.4] found with acetone;[10] it follows that the factor which impedes the formation of the axial epimer **2A** cannot be steric strain involving

R^- and H_a in the transition state $A^{\ddagger}$. Nor can it be "product development control" (steric strain involving O and R'), since the less stable γ-t-butylallyl epimer 7E is formed predominantly (7E/7A = 1.2).[12]

It seems, therefore, that the steric outcome of the reactions of simple cyclohexanones with hydrides and Grignard reagents is best ascribed to the net difference between the steric strain in the transition state ($E^{\ddagger}$), leading to the equatorial alcohol, and the torsional strain in the transition state ($A^{\ddagger}$), leading to the axial alcohol.

Footnotes

1. "R^-" is to be taken as representing a nucleophilic entity being transferred from metal to carbon, rather than a free anion.
2. These reactions are reviewed in refs 6 and 9b.
3. W.G.Dauben, G.J.Fonken, and D.S.Noyce, J.Amer.Chem.Soc., 78, 2579 (1956).
4. There must be some such factor, since the hydride (R^- = H^-) reduction of unhindered cyclohexanones (e.g., 1, R' = H) predominantly affords the equatorial alcohols 2E.
5. J.C.Richer, J.Org.Chem., 30, 324 (1965); J.A.Marshall and R.D.Carroll, J.Org.Chem., 30, 2748 (1965).
6. A.V.Kamernitzky and A.A.Akhrem, Tetrahedron, 18, 705 (1962).
7. M.Chérest and H.Felkin, Tetrahedron Letters, 2205 (1968).
8. J.Klein and D.Lichtenberg, J.Org.Chem., 35, 2654 (1970).
9. (a) J.Klein, E.Dunkelblum, E.L.Eliel, and Y.Senda, Tetrahedron Letters, 6127 (1968); (b) E.L.Eliel and Y.Senda, Tetrahedron, 26, 2411 (1970).
10. Accompanying communication: M.Chérest, H.Felkin, and C.Frajerman, Tetrahedron Letters, 5, 379 (1971)
11. For reaction conditions, see ref. 10. Gas chromatography was used to determine the proportions of the products, which were isolated by a combination of column and thin-layer chromatography. The three major products had n.m.r., i.r. and mass spectra consistent with the structures assigned to them: trans-7E, mp 75-76° (39.5%); trans-7A, mp 101-102° (32.5%); and 8A, liquid (26%). Cis-7E (1.5%) was identified by its i.r. and mass spectra, and a small peak in the gas chromatogram was assumed, from its retention time, to be cis-7A (0.5%). No trace of the sixth isomer (8E)

could be found; in particular, none of the intermediate fractions from column chromatography on alumina had an i.r. spectrum consistent with the structure **8E** (-CH=CH_2 *and* equatorial C-O), and the gas chromatogram of the total reaction product showed no peak having the expected retention time. We thank Dr. B.C.Das, of this Institute, for the mass spectral data and interpretations referred to in this and the accompanying communication.

12. This ratio (**7E**/**7A** = 1.2) is very similar to the ratio [**2E**/**2A** (R' = H, R = allyl) = 1.06] obtained with allyl magnesium bromide (ref. 7). As we have already pointed out [H.Felkin and C.Frajerman, *Tetrahedron Letters*, 1045 (1970)], this similarity is evidence that the γ-alkylallyl products (**7E** and **7A**) must be formed via a rearrangement mechanism from the secondary isomer **4** of the reagent, as shown in the scheme. If these products (**7E** and **7A**) were formed via a direct S_E2 displacement mechanism from the primary isomer **5**, as has been recently suggested [B.Gross and C.Prévost, *Bull.Soc.Chim.*, 3610 (1967); see also R.A.Benkeser, W.G.Young, W.E.Broxterman, D.A.Jones, and S.J.Piaseczynski, *J.Amer.Chem.Soc.*, *91*, 132 (1969)] the ratio **7E**/**7A** would be similar to the ratio [**2E**/**2A** (R' = H, R = propyl) = 0.35] obtained with propyl magnesium bromide (ref. 7).