Tetrahedron Letters No.18, pp. 2205-2208, 1968. Pergamon Press. Printed in Great Britain.

TORSIONAL STRAIN INVOLVING PARTIAL BONDS. THE STERIC COURSE OF THE REACTION BETWEEN ALLYL MAGNESIUM BROMIDE AND 4-T-BUTYL-CYCLOHEXANONE

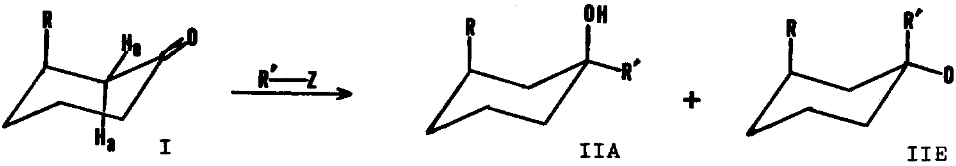
Marc Chérest and Hugh Felkin

Institut de Chimie des Substances Naturelles, C.N.R.S.,
91-Gif-sur-Yvette, France.

(Received in UK 22 November 1967)

It is generally assumed (1) that the steric course of the reactions of cyclohexanones with hydrides and with Grignard reagents (2) is governed by two factors:

(a) Steric Approach Control, which implies an essentially reactant-like transition state, and is used to explain the predominant "equatorial attack" (formation of axial alcohol IIA) observed in the reactions of hindered cyclohexanones (I, R = alkyl) with both hydrides (R' = H) and Grignard reagents;

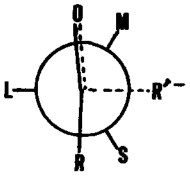


I IIA IIE

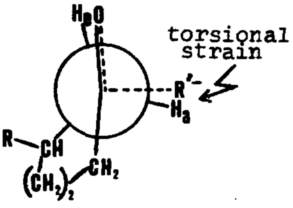
(b) Product Development Control, which implies an essentially product-like transition state, and is used to explain the predominant formation of the more stable alcohol, observed in the reactions of unhindered cyclohexanones (I, R = H): the axial alcohol (IIA, R' = alkyl) with Grignard reagents, and the equatorial alcohol (IIE, R' = H) with hydrides.

It seems most unlikely that, as this theory suggests, there can be any fundamental difference between the factors which determine the preferential steric outcome of these reactions in the case of open-chain ketones, on the one hand, and of cyclohexanones, on the other. It follows that the simple premises outlined in the accompanying communication (3) for open-chain carbonyl compounds should, if they are valid, be applicable to cyclohexanones. We propose to show that this is indeed so, and that there is no need to assume a change in the preferred transition state from one that is essentially reactant-like in the case of sterically hindered cyclohexanones, to one that is essentially product-like in the case of unhindered cyclohexanones (4).

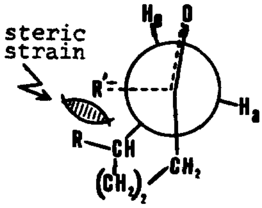
The alternative interpretation is based upon the fact that, whereas both torsional strain and steric strain can be simultaneously minimised in a reactant-like transition state when the substrate is acyclic, as in our sugges-



A1‡



A‡



E‡

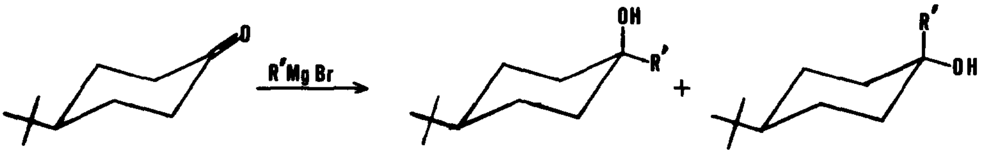
ted preferred transition state A1‡ (3), this is not possible in the cyclohexanone case: formation of the axial alcohol (IIA) ("equatorial attack") implies a partially eclipsed transition state A‡ involving some degree of torsional strain (3, 5), and formation of the equatorial alcohol (IIE) ("axial attack") implies an essentially staggered transition state E‡ involving some degree of steric strain. We suggest, therefore, that these reactions all proceed via reactant-like transition states, and that, in the absence of polar effects (6), their steric outcome is determined by the relative magnitudes of torsional strain in A‡ and of steric strain in E‡.

When both R' and R are small, as is the case in the reaction between hydrides (R' = H) and unhindered cyclohexanones (R = H), steric strain in transition state E‡ is expected to be small, smaller than the torsional strain in transition state A‡ (7), and this will result (as observed) in the predominant formation of the equatorial alcohol IIE. Although the product (IIE, R' = H) happens in this instance to be the more stable of the two, this, we suggest, is fortuitous; the predominant formation of the equatorial alcohol is due to torsional strain in the reactant-like transition state A‡, and not to the kind of steric strain implied by the term "product development control" (8).

Making R bulky (e.g., alkyl) will lead to increased steric strain in transition state E‡; the result is the observed formation of a regularly increasing proportion of axial alcohol IIA (via transition state A‡) as the number or bulk of the axial substituents is increased (2b).

Increasing the "effective bulk" of the reagent should lead to the same trend, since torsional strain in transition state A‡ is expected to remain essentially unchanged (9); and the proportion of axial alcohol IIA is indeed always larger from alkyl Grignard reagents (R' = alkyl), for example, than it is from hydrides (R' = H) (2b). The "effective bulk" of the reagent is, however, not always easy to assess, since it must depend not only upon the "intrinsic bulk" of R', but also upon such things as solvation, the length of the $R'^{-}...C$ bond in the transition state, and the mechanism whereby "R'^{-}" is being transferred from metal to carbon. For instance, despite its similar "intrinsic bulk", allyl magnesium bromide, which reacts with electrophilic substrates by an S_E2' mechanism (10), is expected to behave as an "effectively" *less* bulky reagent than propyl magnesium bromide, because in the S_E2' transition state the magnesium and the carbonyl carbon are not bonded to the same carbon atom; there should therefore be *less* steric strain in the transition state $E^{\ddagger}$, and hence *more* of the equatorial alcohol in the product, when R' = allyl than when R' = propyl.

This has been found to be the case: propyl magnesium bromide and allyl magnesium bromide were allowed to react (at 0° in ether) with 4-t-butyl-cyclohexanone, and the product ratios (IIIE/IIIA) were respectively 0.35 (R' = propyl) and 1.06 (R' = allyl) (11). It is important to note that this steric outcome is predicted neither by "product development control", since the predominant epimer IIIE (R' = allyl) is certainly the *less* stable, nor by "steric approach control" since the predominant epimer is the *equatorial* alcohol, formed by "axial attack".



IIIA IIIE

In conclusion, the postulate that partial bonds in transition states can be the source of considerable torsional strain has been made the basis of an internally consistent interpretation of the steric course of the reactions between carbonyl compounds and nucleophilic reagents such as hydrides and Grignard reagents. It seems, moreover, not unlikely that this postulate will be found useful in other areas.

Footnotes

1. W.G.Dauben, G.J.Fonken, and D.S.Noyce, *J.Amer.Chem.Soc.*, **78**, 2579 (1956); G.Just and R.Nagarajan, *Experientia*, **18**, 402 (1962); H.C.Brown and H.R. Deck, *J.Amer.Chem.Soc.*, **87**, 5620 (1965); see also H.C.Brown and J.Muzzio, *ibid.*, **88**, 2811 (1966).
2. (a) The stereochemistry of these reactions has been reviewed: (b) A.V. Kamernitzky and A.A.Akhrem, *Tetrahedron*, **18**, 705 (1962).
3. Accompanying communication: M.Chérest, H.Felkin, and N.Prudent, *Tetrahedron Letters*, 2199 (1968).
4. We are not the first to draw attention to the somewhat contradictory and

ad hoc character of current theory regarding the steric course of these reactions. "Product development control", in particular, has already been the subject of a certain amount of adverse comment [refs. 5 and 6; see also D.Cabaret, G.Chauvière, and Z.Welvart, *Tetrahedron Letters*, 4109 (1966)].

5. The possible role of the axial hydrogens (H_a) on carbons 2 and 6, which are partially eclipsed with R'^- in transition state $A^‡$, has already been pointed out: Kamernitzky (ref. 2b) has suggested a polar interpretation, involving "the uncompensated dipole moments of the carbon-hydrogen bonds", which might tend to destabilise transition state $A^‡$ with respect to $E^‡$, whereas J.C.Richer [*J.Org.Chem.*, **30**, 324 (1965)] has put forward an "all-steric proposal" involving steric strain, in transition state $A^‡$, between R'^- and the axial hydrogens. See also J.A.Marshall and R.D.Carroll, *J.Org. Chem.*, **30**, 2748 (1965).

6. The influence of polar groups on the steric course of hydride reductions [M.G.Combe and H.B.Henbest, *Tetrahedron Letters*, 404 (1961); H.Kwart and T.Takeshita, *J.Amer.Chem.Soc.*, **84**, 2833 (1962); J.C.Jacquesy, R.Jacquesy, and J.Levisalles, *Bull.Soc.Chim.France*, 1649 (1967)] has been convincingly interpreted by D.M.S.Wheeler and M.M.Wheeler [*J.Org.Chem.*, **27**, 3796 (1962)] in terms of a *reactant-like* transition state.

7. Torsional strain involving the partial $R'^- \ldots C$ bond may be particularly large in transition state $A^‡$, since this bond is "wedged in" between two axial hydrogens (buttressing effect).

8. "Equatorial" torsional strain (as in $A^‡$) also provides an alternative interpretation for the preferred "axial attack" of certain *electrophilic* reagents upon cyclohexane derivatives with exocyclic double bonds; e.g., the preferred "axial" epoxidation of unhindered exocyclic olefins by peracids [R.G.Carlson and N.S.Behn, *J.Org.Chem.*, **32**, 1363 (1967)]. Similarly, the preferred "axial" protonation of exocyclic enolates [S.K.Malhotra and F.Johnson, *J.Amer.Chem.Soc.*, **87**, 5493 (1965)] may not be limited to cases in which there is a bulky axial group in the 2-position.

9. Torsional strain is known to be relatively insensitive to the bulk of the groups involved; the rotational barrier of propane, for example, is barely larger than that of ethane [J.Dale, *Tetrahedron*, **22**, 3373 (1966)].

10. H.Felkin and G.Roussi, *Tetrahedron Letters*, 4153 (1965); M.Gielen and J.Nasielski, *Ind.Chim.Belge*, **29**, 767 (1964).

11. Analyses were by gas chromatography. The IIIE/IIIA (R' = allyl) ratios were 1.14 at -40°, and 0.99 at 35°. When diallylmagnesium was used, the ratio at 0° was 1.25 [cf. H.Felkin, C.Frajerman, and Y.Gault, *Chem.Commun.*, 75 (1966)].