Tetrahedron Letters No.18, pp. 2199-2204, 1968. Pergamon Press. Printed in Great Britain.

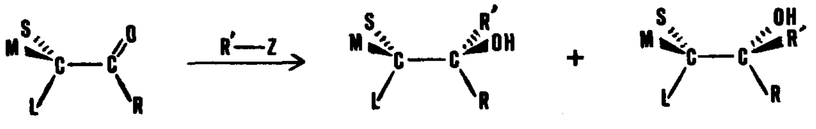
TORSIONAL STRAIN INVOLVING PARTIAL BONDS. THE STEREOCHEMISTRY OF THE LITHIUM ALUMINIUM HYDRIDE REDUCTION OF SOME SIMPLE OPEN-CHAIN KETONES

Marc Chérest, Hugh Felkin, and Nicole Prudent

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

(Received in UK 22 November 1967)

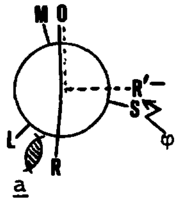
The reactions of hydrides and Grignard reagents with simple open-chain aldehydes and ketones I (L, M, S, and R being groups containing carbon and hydrogen only) are known to lead predominantly to the diastereoisomers IIA, as predicted by "Cram's rule" (1).



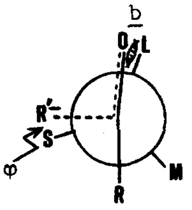
I IIA IIB

According to current theory, reactions of this type occur via "reactant-like" transition states, in which the nucleophilic part of the reagent (R'^-) (2) lies in the π-axis of the carbonyl carbon. Cram (1, 3) assumes that the preferred conformations of the transition states are such that, for steric reasons, R'^- is remote from the two bulkiest groups L and M, as in CA‡ and CB‡, and that CA‡ ["open-chain model" (1, 3)] is preferred over CB‡ because it only involves steric strain (a) between L and R, rather than between L and the allegedly bulkier metal-complexed and solvated carbonyl oxygen (b).

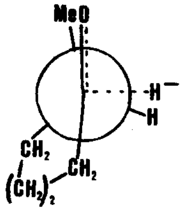
Karabatsos (4) has recently criticised this interpretation, and has sug-



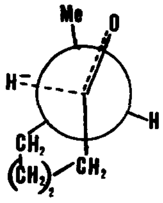
CA‡ (φ ~ 0°)
KA‡ (φ ~ 30°)



CB‡ (φ ~ 0°)
KB‡ (φ ~ 30°)



DA‡



DB‡

gested that the conformations of the preferred (reactant-like) transition states are the same as those of the corresponding aldehydes (5), with either M ($KA^{\ddagger}$) or L ($KB^{\ddagger}$) eclipsing the carbonyl oxygen; he assumes that, for steric reasons, the incoming R'^{-} group is closest to the smallest group S, as in $KA^{\ddagger}$ and $KB^{\ddagger}$, and that $KA^{\ddagger}$ is preferred over $KB^{\ddagger}$ because it involves smaller carbonyl-eclipsed group interactions. The correspondence between the magnitude of these interactions, as deduced from aldehyde n.m.r. data (5b), and the product ratios (IIA/IIB) is, in many cases, quite good.

Both these interpretations suffer, in our opinion (6), from two major shortcomings:

(a) It seems inconceivable that the mechanism of the hydride reduction of "unhindered" cyclohexanones can differ in any significant respect from that of simple open-chain ketones; and yet the reduction of 2-methyl-cyclohexanone, for example, leads preferentially to trans 2-methyl-cyclohexanol (via the allegedly product-like transition state $DB^{\ddagger}$), whereas it would have been expected to lead preferentially to the cis isomer via the reactant-like transition state $DA^{\ddagger}$ which, to within a very few degrees of dihedral angle, would be identical with the proposed transition states $CA^{\ddagger}$ and $KA^{\ddagger}$ [$LR = (CH_2)_4$] (7, 8).

(b) Making R progressively more bulky must introduce progressively more strain (a) into the transition states $CA^{\ddagger}$ and $KA^{\ddagger}$, and hence destabilise them with respect to the transition states ($CB^{\ddagger}$ and $KB^{\ddagger}$, respectively) with the "opposite" configuration. In other words, the bulkier R, the less stereoselective these reactions should be. This is not borne out by experiment: in the lithium aluminium hydride reduction of two series of ketones (I, L = Ph and cyclohexyl, M = Me, S = H; R = Me, Et, iPr, tBu), the bulkier R, the more stereoselective the reactions become (see Table), the only exception being the fall in stereoselectivity in the cyclohexyl series on going from R = iPr to R = tBu. The stereoselectivity of the reduction in the phenyl se-

TABLE

Diastereoisomer ratios (IIA/IIB, M = Me, S = R' = H) in the alcohols from the $LiAlH_4$ reduction of the ketones (I) in ether at 35°, and (in parentheses) the activation enthalpy differences ($\Delta\Delta H^{\ddagger}$) (9).

L	R = Me	R = Et	R = iPr	R = tBu
cyclohexyl	1.6 (-1.1)	2.0 (-1.1)	4.1 (-1.5)	1.6 (+0.1)
phenyl	2.8 (-1.0)	3.2 (-0.9)	5.0 (-0.3)	49 (-2.7)

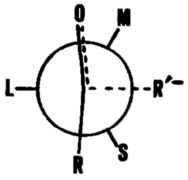
ries when R = tBu is, on the contrary, strikingly high: the threo isomer (IIA) is obtained 98% pure even at 35°, and the product is 99.8% pure threo when the reaction is carried out at -70°.

The purpose of this communication (6) is to show that a simple, internally consistent, interpretation of the steric outcome of these reactions, encompassing both open-chain carbonyl compounds and cyclohexanones (8), can be based upon the following four premises:

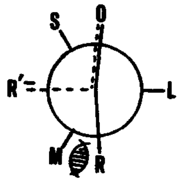
(1) The transition states in these reactions are, in all cases, essentially "reactant-like" (1, 3, 4), rather than "product-like" (10).

(2) Torsional strain (Pitzer strain) involving partial bonds (in transition states) represents a substantial fraction of the strain between fully-formed bonds, even when the degree of bonding is quite low (11, 12). In the case of open-chain carbonyl compounds, this implies preferred staggered conformations for the transition states, in which R'^{-} is approximately skew to two of the groups on the adjacent carbon atom (as in $A1^{\ddagger}$, $B1^{\ddagger}$, $B2^{\ddagger}$), rather than eclipsed ($CA^{\ddagger}$) or half-eclipsed ($KA^{\ddagger}$) with one of them, be it the smallest.

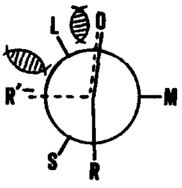
(3) The important steric interactions involve R'^{-} and R, rather than the carbonyl oxygen as assumed by Cram (1) and Karabatsos (4). On this basis, the least strained of the six possible staggered conformations is $A1^{\ddagger}$, followed by $B1^{\ddagger}$ and $B2^{\ddagger}$ (the other three all involve gauche interactions between R'^{-} and L, and, at the same time, between R and M or L).



$A1^{\ddagger}$



$B1^{\ddagger}$

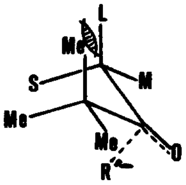


$B2^{\ddagger}$

(4) Polar effects stabilise those transition states in which the separation between R'^{-} and an electronegative group (L, M, or S) is greatest, and destabilise the others.

It follows from these premises that, in the absence of polar groups, the conformation of the preferred transition state in the case of open-chain ketones is $A1^{\ddagger}$, and that the stereoselectivity of the reactions is generally expected to increase as either L or R'^{-} is made bulkier since this increases the strain in $B2^{\ddagger}$ (relative to $A1^{\ddagger}$), and also as R is made bulkier since this increases the strain in $B1^{\ddagger}$ (13).

The latter trend is indeed found in our cyclohexyl series for R = Me, Et, iPr, but it is followed by a sharp drop on going from R = iPr to R = tBu (see Table). The preferred transition state $A1^{\ddagger}$ is not, however, strain free when R = tBu (see inset), and the drop in stereoselectivity probably reflects this, strain between L and R in $A1^{\ddagger}$ (R = tBu) becoming almost as severe as strain between L and R'^{-} (and O) in $B2^{\ddagger}$.



$A1^{\ddagger}$ (R = tBu)

Polar effects modify this picture. Thus, the reactions of hydrides and Grignard reagents with α-chloro aldehydes and ketones (I, L = alkyl, M = Cl, S = H), in which M is strongly electronegative, are known not to obey Cram's rule (14), and this is consistent with a stabilisation of $B2^{\ddagger}$, in which the separation between R'^{-} and M is greatest, and a destabilisation of $A1^{\ddagger}$, in which the groups bearing a partial negative charge (O, M and R'^{-}) are crowded together. Conversely, $A1^{\ddagger}$ is expected to be stabilised, and $B2^{\ddagger}$ destabilised, when L is electronegative. The reactions should therefore be more stereoselective when L is an electronegative group (L = phenyl) (15) than when it is not (L = cyclohexyl). This is indeed what is observed (see Table), and the effect is especially marked when R is very bulky (R = tBu), because this introduces far greater steric strain into the other transition state ($B1^{\ddagger}$) leading to diastereoisomer IIB than it does into the transition state ($A1^{\ddagger}$, R = tBu) leading to diastereoisomer IIA.

Finally, it is interesting to note that steric strain in $B1^{\ddagger}$ will increase not only as R is made bulkier, but also as M is made bulkier. When there are no polar groups (e.g., L = alkyl), this is not expected to lead to an increase in stereoselectivity, since the bulkier M, the more it is like L, and therefore the less difference there is between the transition states $A1^{\ddagger}$ and $B2^{\ddagger}$. The situation is different, however, when L is an electronegative group (e.g., L = phenyl) because $B2^{\ddagger}$ is now destabilised by polar effects, and this explains the puzzling fact that the hydride reduction of the ketones (I, L = Ph, S = H) becomes more stereoselective not only as R is made bulkier (see above), but also as M is made bulkier [with R = iPr, the IIA/IIB ratio increases from 5 when M = Me (see Table) to 10 when M = iPr (16)].

To sum up, it seems that an interpretation of the steric course of these reactions based upon a preferred staggered conformation ($A1^{\ddagger}$) for the transition state is consistent with the available experimental data. It has the added advantage that the same simple premises upon which it is based can also be used to interpret the steric course of the reactions of cyclohexanones with the same reagents (8).

Acknowledgements.- The views presented in this and the accompanying communication (8) (and their appearance in print) have benefited by the valuable comments (and encouragement) of a number of colleagues, particularly Drs. J. Jacques, J.McKenna, M.J.T.Robinson, and Mlle B.Tchoubar.

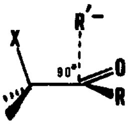
Footnotes

1. D.J.Cram and F.A.Abd Elhafez, J.Amer.Chem.Soc., 74, 5828 (1952); D.J. Cram and F.D.Greene, ibid., 75, 6005 (1953).
2. "R'^-" is to be taken as representing a nucleophilic entity being transferred from metal to carbon, rather than a free anion.
3. D.J.Cram and D.R.Wilson, J.Amer.Chem.Soc., 85, 1245 (1963); and most textbooks.
4. G.J.Karabatsos, J.Amer.Chem.Soc., 89, 1367 (1967).
5. (a) S.S.Butcher and E.B.Wilson, J.Chem.Phys., 40, 1671 (1964); L.S.Bartell, B.L.Carroll, and J.P.Guillory, Tetrahedron Letters, 705 (1964); M.J.T.Robinson, Chem.and Ind., 932 (1964); (b) G.J.Karabatsos and N.Hsi, J.Amer.Chem.Soc., 87, 2864 (1965).
6. The gist of this and the accompanying communication has been presented orally in a number of places during the past few years: see, e.g., 19th IUPAC Congress, Abstracts A, p.135 (1963); Chem.and Ind., 121 (1967).
7. This point has already been made by A.V.Kamernitzky and A.A.Akhrem, Tetrahedron, 18, 705 (1962).
8. The steric course of the reactions of hydrides and Grignard reagents with cyclohexanones is discussed in the accompanying communication: M.Chérest and H.Felkin, Tetrahedron Letters, 2205 (1968).
9. Analyses were by gas chromatography [Y.Gault and H.Felkin, Bull.Soc.Chim. France, 742 (1965)]; the ratios for L = Ph, R = Me and Et, and for L = cyclohexyl, R = Me, agree well with those found in the pre-GC era (ref.1). The configurations of the alcohols (II, L = cyclohexyl) were determined by synthesis [hydrogenation of the alcohols (II, L = Ph), the configurations of which are known: J.Sicher, M.Chérest, Y.Gault, and H.Felkin, Coll.Czech.Chem.Comm., 28, 72 (1963); E.Audier, H.Felkin, M.Fétizon, and W.Vetter, Bull.Soc.Chim.France, 3236 (1965); see also ref.1]. The $\Delta\Delta H^{\ddagger}$ values (= $\Delta H^{\ddagger}_{IIA}-\Delta H^{\ddagger}_{IIB}$, in $kcal.mol^{-1}$) were calculated from reductions run at -11.5 and -43°; the Arrhenius plots (log IIA/IIB vs. 1/T) gave good straight lines, indicating that these reactions all involve a single mechanism [cf. D.M.S.Wheeler and J.W.Huffman, Experientia, 16, 516 (1960)].

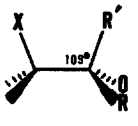
The results reported [Y.Gault and H.Felkin, Bull.Soc.Chim.France, 1342 (1960)] for the reduction of I (L = Ph, M = R = Me, S = H) were obtained by a faulty technique and are slightly in error.

10. J.McKenna, "Conformational Analysis of Organic Compounds", R.I.C.Lecture Series, London, n°1 (1966); H.C.Brown and J.Muzzio, J.Amer.Chem.Soc., 88, 2811 (1966).

11. In other words, we are postulating that the "percentage-torsional strain" in a transition state is greater than the "percentage-bonding". In an eclipsed reactant-like transition state (i), the partial bond is "bent forwards" (towards X) with respect to a fully formed bond (ii), and this bending could be compensating (and even, conceivably, over-compensating) for the lower electron-density in the partial bond [conversely, bonds which are "bent backwards" give rise to reduced torsional strain: J.Dale, Tetrahedron, 22, 3373 (1966)].



i



ii

12. This postulate may turn out to be quite useful. In particular, it has already been used for cases of 1,3-asymmetric induction (M.J.Brienne, C. Ouannes, and J.Jacques, Bull.Soc.Chim.France, in the press), and it also provides the basis for an alternative explanation of the preferred "antiparallel attack" of many reagents upon cyclohexenes and cyclohexenones [J.Valls and E.Toromanoff, Bull.Soc.Chim.France, 758 (1961); E.Toromanoff, ibid., 708 (1962); N.L.Allinger and C.K.Riew, Tetrahedron Letters, 1269 (1966)].

13. Buttressing effects are to be expected, especially when L, M, R, and R'^- are fairly bulky.

14. J.W.Cornforth, R.H.Cornforth, and K.K.Mathew, J.Chem.Soc., 112 (1959); H.Bodot, E.Dieuzeide, and J.Jullien, Bull.Soc.Chim.France, 1086 (1960).

15. The polar effect of the phenyl group also increases the rates of these reactions [H.C.Brown, R.Bernheimer, and K.J.Morgan, J.Amer.Chem.Soc., 87, 1280 (1965)]; it is probably responsible for the sometimes puzzling steric course of a number of stereoselective reactions in which a phenyl group is involved [e.g., E.P.Burrows, F.J.Welch, and H.S.Mosher, J.Amer.Chem.Soc., 82, 880 (1960)].

16. D.J.Cram, F.A.Abd Elhafez, and H.L.Nyquist, J.Amer.Chem.Soc., 76, 22 (1954).