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

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(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).

According to current theory, reactions of this type occur via "reactant-like" transition states, in which the nucleophilic part of the reagent (R') lies in the n-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-
gested that the conformations of the preferred (reactant-like) transit on states are the same as those of the corresponding aldehydes (5), with either M (KA$) or L (KB$) eclipsing the carbonyl oxygen; he assumes that, for steric reasons, the incoming R' group is closest to the smallest group S, as in KA$ and KB$, and that KA$ is preferred over KB$ 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$), whereas it would have been expected to lead preferentially to the cis isomer via the reactant-like transition state DA$ which, to within a very few degrees of dihedral angle, would be identical with the proposed transition states CA$ and KA$ [LR = (CH$_2$)$_4$] (7, 8).

(b) Making R progressively more bulky must introduce progressively more strain (a) into the transition states CA$ and KA$, and hence destabilise them with respect to the transition states (CB$ and KB$, respectively) with the "opposite" configuration. In other words, the bulkier R, the less stereose-

<table>
<thead>
<tr>
<th>L</th>
<th>R = Me</th>
<th>R = Et</th>
<th>R = iPr</th>
<th>R = tBu</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclohexyl</td>
<td>1.6 (-1.1)</td>
<td>2.0 (-1.1)</td>
<td>4.1 (-1.5)</td>
<td>1.6 (+0.1)</td>
</tr>
<tr>
<td>phenyl</td>
<td>2.8 (-1.0)</td>
<td>3.2 (-0.9)</td>
<td>5.0 (-0.3)</td>
<td>49 (-2.7)</td>
</tr>
</tbody>
</table>

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-
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 $L$).

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 \( A1^+ \) is not, however, strain free when \( R = tBu \) (see inset), and the drop in stereoselectivity probably reflects this, strain between \( L \) and \( R \) in \( A1^+ (R = tBu) \) becoming almost as severe as strain between \( L \) and \( R^- \) (and 0) in \( B2^+ \).

Polar effects modify this picture. Thus, the reactions of hydrides and Grignard reagents with \( \alpha \)-chloro aldehydes and ketones (I, \( L = \text{alkyl} \), \( M = \text{Cl} \), \( S = \text{H} \)), in which \( M \) is strongly electronegative, are known not to obey Cram's rule (14), and this is consistent with a stabilisation of \( B2^+ \), in which the separation between \( L \) and \( M \) is greatest, and a destabilisation of \( A1^+ \), in which the groups bearing a partial negative charge (0, \( M \) and \( R^- \)) are crowded together. Conversely, \( A1^+ \) is expected to be stabilised, and \( B2^+ \) destabilised, when \( L \) is electronegative. The reactions should therefore be more stereoselective when \( L \) is an electronegative group (\( L = \text{phenyl} \)) (15) than when it is not (\( L = \text{cyclohexyl} \)). 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 (\( B1^+ \)) leading to diastereoisomer IIB than it does into the transition state (\( A1^+, R = tBu \)) leading to diastereoisomer IIA.

Finally, it is interesting to note that steric strain in \( B1^+ \) will increase not only as \( R \) is made bulkier, but also as \( M \) is made bulkier. When there are no polar groups (e.g., \( L = \text{alkyl} \)), 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 \( A1^+ \) and \( B2^+ \). The situation is different, however, when \( L \) is an electronegative group (e.g., \( L = \text{phenyl} \)) because \( B2^+ \) is now destabilised by polar effects, and this explains the puzzling fact that the hydride reduction of the ketones (I, \( L = \text{Ph} \), \( S = \text{H} \)) 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 \( M = \text{Me} \) (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 (\( A1^+ \)) 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


2. "K⁺⁻" is to be taken as representing a nucleophilic entity being transferred from metal to carbon, rather than a free anion.


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. Pétizon, and W. Vetter, Bull. Soc. Chim. France, 3236 (1965); see also ref. 1]. The ΔΔH° values (= ΔH°IIA - ΔH°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.


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)].

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. Oua-nnes, and J. Jacques, Bull. Soc. Chim. France, in the press), and it also provides the basis for an alternative explanation of the preferred "anti-parallel 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. R. Kiew, Tetrahedron Letters, 1269 (1966)].

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


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)].

HIGHLY STEREOCONTROLLED REDUCTION OF α'-ALKOXYENONES TO GIVE EITHER THE THREO OR ERYTHRO ALLYLIC 1,2-DIOL. ASSIGNMENT OF THE THREO CONFIGURATION TO THE C-15,C-16 DIOL OF PUMILIOTOXIN B.¹

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Summary: Model studies indicate that the allylic diol of pumiliotoxin B has the threo configuration, and that this functionality can be prepared with excellent stereocontrol by reduction of an α'-t-butyldiphenylsilyloxyenone.

The gross structure of pumiliotoxin B (1) was reported by Daly and coworkers in 1980,² and last year our laboratory described³ the first total synthesis of a member of this alkaloid class, toxin 251D (2). As a prelude to a total synthesis of pumiliotoxin B, we have been investigating stereocommanded methods for assembling the allylic diol functionality of this toxin. In this Letter, we report that the allylic diol of pumiliotoxin B has the threo configuration, and moreover relate that the reduction of α'-alkoxyenones can be accomplished to give either threo or erythro allylic 1,2-diols with excellent (>95%) stereocontrol.

Since 1,2-addition to an enone is expected to occur via a skewed⁴ backside⁵ trajectory which should accentuate interactions of an entering hydride with a chiral α'-carbon, we chose to explore the preparation of the pumiliotoxin B diol functionality by relative 1,2-asymmetric induction⁶ as illustrated in eq 1. The model (2S,4E)-enones 3 and ⁴ were prepared from ethyl (S)-(+)–lactate in 30–40%
overall yield as summarized in the Scheme. Reduction of 3 with 2 equiv of diisobutylaluminum hydride (toluene, rt) gave a 3:2 mixture of diastereomeric alcohols in 80% yield. Separation by HPLC gave pure samples of 5 (major isomer) and 6, which were reductively debenzylated (Na/NH₃, -78°C) in essentially quantitative yields to give the threo diol 7 (δ 3.78, m, C₂-H; δ 3.72, broadened d, J = 7.0 Hz, C₃-H; δ 81.0, C₂; δ 68.8, C₂) and the erythro diol 8 (δ 3.91, broadened d, J = 5.2 Hz, C₃-H; δ 3.85, m, C₂-H; δ 83.1, C₂; δ 69.2 C₂) respectively. The stereochemical assignments for 7 and 8 were made on the basis of intramolecular nuclear Overhauser experiments. Thus, the threo d₆-acetonide 9 (δ 3.8-3.9, m, C₂-H and C₃-H) showed a strong signal (δ 3.87, d, J = 3.7 Hz) for the C₃-hydrogen in the difference NOE spectrum when the methyl doublet at δ 1.21 was irradiated, while the erythro d₆-acetonide 10 (δ 3.48, d, J = 5.2 Hz, C₃-H; δ 4.38, m, C₂-H) showed no detectable signal for the C₃-hydrogen under identical conditions. The 250 MHz ¹H NMR spectrum of pumiliotoxin B² (broadened d for the C₁₅-H at δ 3.66, J = 8 Hz; m for the C₁₆-H at δ 3.75) most clearly resembles the model threo diol 7.¹¹

The reduction of α'-alkoxyenones of this type can be controlled to give either the threo or erythro allylic diol by the proper choice of reducing agent and alcohol protecting group; a few of the combinations examined are summarized in the Table. The high erythro selectivity (98%) obtained from the reaction of

**Scheme**

<table>
<thead>
<tr>
<th>5, R = CH₂OCH₂Ph</th>
<th>6, R = CH₂OCH₂Ph</th>
</tr>
</thead>
<tbody>
<tr>
<td>7, R = H</td>
<td>8, R = H</td>
</tr>
<tr>
<td>11, R = SiPh₂Bu⁺</td>
<td></td>
</tr>
</tbody>
</table>

(a) PhCH₂OCH₂Cl or Ph₂Bu⁺SiCl; (b) 5% KOH, MeOH, rt; 2-pyridinethiol, DCC, rt; (c) CH₃CH=PPPh₃, THF, rt; (d) CH₃CH₂CHO, 50°C; (e) CD₃COCD₃, TsOH, rt.
Table Stereoisomer Ratios\textsuperscript{a} from Reduction of 2-Alkoxy-4-methyl-4E-hepten-3-ones

<table>
<thead>
<tr>
<th>Enone R</th>
<th>Reductant</th>
<th>Temp, °C</th>
<th>Threo:Erythro</th>
</tr>
</thead>
<tbody>
<tr>
<td>R=CH\textsubscript{2}OCH\textsubscript{2}Ph (3)</td>
<td>Bu\textsubscript{3}\textsuperscript{i}Al, pentane</td>
<td>25\textdegree</td>
<td>70:30</td>
</tr>
<tr>
<td></td>
<td>Bu\textsubscript{3}\textsuperscript{i}Al, pentane</td>
<td>-22\textdegree</td>
<td>55:45</td>
</tr>
<tr>
<td></td>
<td>LiAlH\textsubscript{4}, THF</td>
<td>-10\textdegree</td>
<td>30:70</td>
</tr>
<tr>
<td></td>
<td>LiAlH\textsubscript{4}, Et\textsubscript{2}O</td>
<td>-10\textdegree</td>
<td>2:98</td>
</tr>
<tr>
<td>R=H</td>
<td>LiAlH\textsubscript{4}, THF</td>
<td>-10\textdegree</td>
<td>40:60</td>
</tr>
<tr>
<td>R=Ac</td>
<td>Bu\textsubscript{3}\textsuperscript{i}Al, pentane</td>
<td>25\textdegree</td>
<td>45:55</td>
</tr>
<tr>
<td>R=SiMe\textsubscript{3}</td>
<td>Bu\textsubscript{3}\textsuperscript{i}Al, pentane</td>
<td>25\textdegree</td>
<td>43:57</td>
</tr>
<tr>
<td>R=SiPh\textsubscript{2}But (4)</td>
<td>Bu\textsubscript{3}\textsuperscript{i}Al, pentane</td>
<td>25\textdegree</td>
<td>94:6</td>
</tr>
<tr>
<td></td>
<td>LiAlH\textsubscript{4}, THF</td>
<td>-20\textdegree</td>
<td>95:5</td>
</tr>
</tbody>
</table>

\textsuperscript{a} From 250 MHz \textsuperscript{1}H NMR analysis of crude products.

Enone 3 with LiAlH\textsubscript{4} in ether is consistent with reduction of a chelated\textsuperscript{6} intermediate. With many reducing agent-protecting group combinations, bad mixtures of threo and erythro diols were obtained, presumably resulting from competitive reduction of both chelated and non-chelated intermediates. When the extremely bulky t-butyldiphenylsilyl ether\textsuperscript{12} was employed, chelation was apparently prevented, and excellent (>94%) threo selectivity was observed with both LiAlH\textsubscript{4} and triisobutylaluminum. On a preparative scale, reduction of the t-butyldiphenylsilyloxyenone 4 with Bu\textsubscript{3}\textsuperscript{i}Al\textsuperscript{13} followed by chromatographic purification of 11 and desilylation (Bu\textsubscript{4}NF)\textsuperscript{12} gave the pure chiral\textsuperscript{14} threo diol 7 in 75\% overall yield.

The excellent erythro and threo selectivities obtained from LiAlH\textsubscript{4} reduction of \(\alpha\)-alkoxyenones 3 and 4 are higher than selectivities recorded in the literature\textsuperscript{6,15} for hydride reductions of \(\alpha\)-alkoxy (and \(\alpha\)-hydroxy)ketones, and may reflect the skewed trajectory illustrated in eq 1.\textsuperscript{16} Since enones 3 and 4 should be effectively locked in s-trans conformations,\textsuperscript{17} we note that the unusually high "Cram" selectivity observed with 4 may reflect also destabilization of the minor "Felkin-Ahn"\textsuperscript{18} transition state as a result of steric interactions between the \(\alpha\)-methyl group and the \(\beta\)-hydrogen of the enone system.\textsuperscript{16}
Acknowledgment. We particularly wish to thank Dr. John Daly and Dr. Takashi Tokuyama for generously providing a sample of pumiliotoxin B and information concerning their parallel studies. Financial support from the National Institutes of Health (HL-25854), the Camille and Henry Dreyfus Foundation (teacher-scholar award to L.E.O.), and the NSF (instrument program) is gratefully acknowledged.

References and Notes

7. All new compounds showed IR, 250 MHz 1H NMR (CDCl3), 63 MHz 13C NMR (CDCl3), and mass spectra which were fully in accord with their assigned structures.
8. A DuPont Zorbax PSM-60 column, G:1 hexane:ethyl acetate eluent, and 2.0 mL/min flow rate were used for this analysis.
9. This signal was simplified to a doublet with the same coupling constant as the C3-H when the methyl group (C5-H) was decoupled.
11. A nice comparison of a related series of phenylboronides is described in ref 1.
14. 250 MHz 1H NMR analysis of the (R)-MTPA ester of 11 indicated an enantiomeric excess of 90% for 11.
16. Experiments to specifically test this suggestion are underway in our laboratory.

(Received in USA 12 March 1982)