A Probe of Cieplak's Proposal: Effect of 2-Axial Substitution on Reactivity in the $LiAlH_4$ Reduction of Cyclohexanones

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The relative reactivities of cyclohexanones in which the 2-axial position is substituted by methyl or methoxy group in $LiAlH_4$ reduction strongly support the Cieplak model which focuses on the importance of stabilisation of the transition state by antiperiplanar allylic bonds.

Stereochemistry in the complex metal hydride reduction of cyclohexanones has long been discussed and many investigations have been published.[1] Recently, orbital interaction arguments have been suggested.[1] Klein first introduced the concept of orbital symmetry arguments including the carbonyl group which controls the stereochemistry of the reduction of unhindered cyclohexanones such as 4-*tert*-butylcyclohexanone (**1**).[2] At present, there is much discussion as to whether the stereochemistry of nucleophilic reactions of unhindered cyclohexanones is governed by molecular orbital overlap control including the carbonyl group. Among the theories of orbital overlap control, the Cieplak model focuses on the importance of stabilisation of the transition state by antiperiplanar allylic bonds.[3] He rationalised a large variety of substituent effects for nucleophilic addition stereoselectivities with this model.

We performed $LiAlH_4$ reduction of cyclohexanones which are axially substituted with methyl, methoxy or hydroxy groups at the 2-position and obtained results which fully support Cieplak's proposal.

The reduction of 2,2,4-trimethylcyclohexanone (**4**) gave 95% equatorial alcohol and 5% axial. This isomeric product distribution is the same as that for 4-*tert*-butyl-2,2-dimethylcyclohexanone (**3**) previously reported.[4] By introduction of a methoxy group as the polar substituent at the 2-axial position, the reduction of 2,4-*t*-dimethyl-2-*r*-methoxycyclohexanone (**5**) produced more of the axial alcohol compared with **3** and **4**. The isomeric distribution of the products is summarised in Table 1.

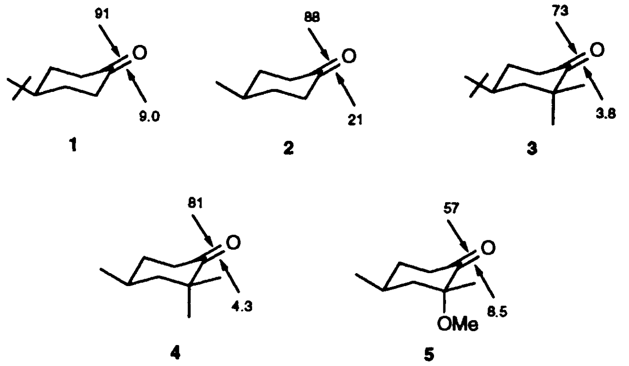
Binary mixtures prepared from equimolar amounts of two of the five cyclohexanones employed here were reduced and the relative reactivities were determined at an early stage of the reduction. The conversion of the competitive reduction was controlled to less than 10%. The results are shown in Table 2. The relative reactivities of 4-methylcyclohexanone (**2**) were less from the axial and more from the equatorial direction than those of **1**, which is considered to be structurally identical, because the former exists as a conformational mixture. Assuming that the conformational mixture of **2** consisted of 95% equatorial methyl species and 5% axial methyl species, the calculated relative rates are in good agreement with the observed value. The steric hindrance of the 2-axial substituents affected the relative reactivities from the equatorial direction. The replacement of the hydrogen at the 2-axial position of the cyclohexanone skeleton by a methyl group appreciably retarded the partial reactivity from the equatorial side. The relative reactivity from this direction decreased to less than one-half. No sizable decrease in the relative reactivity, however, was found on the replacement of the hydrogen at the 2-axial position with a methoxy group. Only 6% retardation of the partial reactivity was observed. It is most likely that the bond between the methoxy oxygen and methoxy methyl carbon can rotate to minimise the steric interaction with the incoming hydride, so that the apparent steric hindrance of the methoxy group is considered to be unexpectedly small.

Table 1 $LiAlH_4$ reduction of cyclohexanones[a]

Cyclohexanone	Axial attack (%)
4-*tert*-Butyl- (**1**)	91
4-Methyl- (**2**)	81
4-*tert*-Butyl-2,2-dimethyl- (**3**)	95
2,2,4-Trimethyl- (**4**)	95
2,4-*t*-Dimethyl-*r*-2-methoxy- (**5**)	87
2,4-*t*-Dimethyl-*r*-2-hydroxy- (**6**)	36

[a] Diethyl ether solution of $LiAlH_4$ (0.025 mmol) was added to the substrate (1 mmol) in the same solvent and was stirred for 15 min at 0 °C. After hydrolysis the products were analysed by GLC.

Table 2 Relative reactivities of the representative cyclohexanones in the $LiAlH_4$ reduction[a]



[a] Competitive reduction was performed as reported before (ref. 4). The relative reactivities are averaged values obtained from binary mixtures of several different pairs of cyclohexanones. Solution of $LiAlH_4$ (0.05 mmol in 2 cm^3 Et_2O) was added dropwise to a binary mixture of the substrates (2 mmol in 4 cm^3 Et_2O) and was stirred for 15 min at 0 °C. After hydrolysis, the products were analysed by GLC. The reactivity for formation of 4-*tert*-butylcyclohexanol from **1** is arbitrarily set at 100.

The partial reactivity from the axial side of **3** and **4** decreased to around 80–90% of that of **1**. Moreover, the relative reactivity from the axial direction of **5** became less than those of **3** and **4**. In order to provide structural information on the cyclohexanones employed here, Allinger's molecular mechanics calculations[5] were carried out and the optimised three dimensional geometries were obtained. Assuming that the incoming nucleophile approaches the carbonyl carbon along the vertical line of the carbonyl plane, the incoming hydride may be placed at 2.0[1] or 2.3 Å[6] perpendicular to the carbonyl carbon in the transition state. The distances between this incoming hydride and the hydrogen atoms at the 3-positions in the cyclohexanone molecule indicate that the steric environment of the axial side around the carbonyl group of the substrates here looks virtually

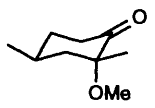
Table 3 Results of MO(MNDO/PM3) calculation for representative cyclohexanones[a]

Compound	**1**	**4**	**5**-a	**5**-gp	**5**-gd
Conformational population (%)	100.0	100.0	13.8	40.2	46.0
Orbital energy/ev					
$\pi^*_{C=O}$	0.870	0.896	0.700	0.675	0.800
$\sigma_{C2-X(axial)}$	−11.495	−11.486	−11.541	−11.655	−11.758
Energy gap	12.365	12.382	12.241	12.330	12.558
Eigenvector of $C2_{2pz}$[b]	0.116	0.070	0.112	0.041	0.037
Square value	0.013	0.0049		0.0030[c]	
Relative reactivity from axial side[d]	100	89		63	

[a] The MO calculation shows that **1** and **4** practically exist as one conformer, while **5** acts as the mixture of three conformers depending on the orientation of the methoxy methyl group. The methoxy methyl group and 2-equatorial methyl can take *anti* and two *gauche* conformations in which the methoxy methyl group is proximal and distal to the carbonyl group. These are represented as **5**-a, **5**-gp and **5**-gd, the ratios of which are evaluated to be 13.8, 40.2 and 46.0%, respectively (see below).

1

4



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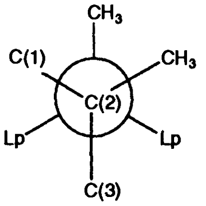
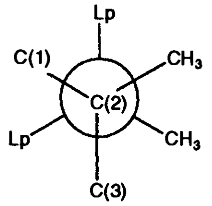
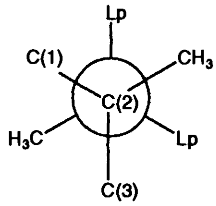


5-gp

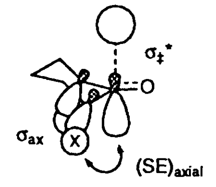


5-gd



5-a

[b] When the carbonyl group is on the *xy* plane, the eigenvector of $C2_{2pz}$ is the component of that of $\sigma_{C2-X(axial)}$ interacting with $\pi^*_{C=O}$. [c] Weighted average. [d] Experimental results.



X = H, CH3, OCH3

Fig. 1 The σ_{C-X}, $\sigma_{\ddagger}^*$ interaction in the transition state

identical in the transition state. The decrease in the partial reactivity from the axial side of the carbonyl group is attributed to the electron-donating ability of the 2-axial substituents, the order of which is C–H > C–C > C–O.[3]

According to Cieplak's proposal, the stereoselectivity in the complex metal hydride reduction of unhindered cyclohexanones was determined by the difference in the nonbonding 2pπ–2pπ interaction between the antibonding orbital of the incipient bond ($\sigma_{\ddagger}^*$) and the antiperiplanar allylic σ orbitals (Fig. 1). The transition state stabilisation energy (SE) for the axial and equatorial approach can be expressed as follows:

$$(SE)_{axial} = S^2(\sigma_{C-X}, \sigma_{\ddagger}^*)/\Delta\varepsilon(\sigma_{C-X}, \sigma_{\ddagger}^*)$$

$$(SE)_{equatorial} = S^2(\sigma_{C-C}, \sigma_{\ddagger}^*)/\Delta\varepsilon(\sigma_{C-C}, \sigma_{\ddagger}^*) \quad (X\text{: H, CH}_3\text{, OCH}_3)$$

in which the denominator and the numerator represent an energy separation of the two MOs and a square of their overlap, respectively.

Since the steric environment of **1**, **4** and **5** seems identical, we evaluated the correlation of the relative reactivity of this direction with the $(SE)_{axial}$ values. In order to obtain information about $\sigma_{C-X(axial)}$, semiempirical MO(MNDO/PM3) calculations were performed on these compounds.[7] At present, the values of the energy and eigenvectors of σ* cannot be obtained by the MO calculation, but these values are predicted to be smaller than but close to, those of $\pi^*_{C=O}$, since the $LiAlH_4$ reduction proceeds *via* a reactant-like transition state. We tentatively used the values of $\pi^*_{C=O}$ as the maximum of those of the corresponding $\sigma_{\ddagger}^*$ for the calculation. The results are tabulated in Table 3. It should be noted that the replacement of the 2-axial hydrogen with the methyl or methoxy group caused a reduction in the eigenvector of $\sigma_{C-X(axial)}$ interacting with $\pi^*_{C=O}$. Since the potential energy differences between $\pi^*_{C=O}$ and $\sigma_{C-X(axial)}$ are nearly equal, $(SE)_{axial}$ is dependent on the square of their overlap. The order of $(SE)_{axial}$, **1** > **4** > **5**, is identical with that of the relative reactivities from this direction. This indicates that the results of the MO treatments also support Cieplak's proposal that the orbital overlap control plays one of the most important roles in determining the stereochemistry of the nucleophilic reaction.

The relative reactivity of **4** and **5** from the equatorial side must be controlled mainly by the steric hindrance of the 2-axial substitution.

In summary, the competitive reduction of cyclohexanones and the molecular orbital calculation are consistent with Cieplak's proposal that the stereochemistry of the nucleophilic addition to unhindered cyclohexanones is governed by orbital overlap control.

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