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The Roles of 2- and 3-Axial Methoxy Groups in Determining the Stereochemistry of the Complex Metal Hydride Reduction of Cyclohexanones:
Examination of the Cieplak Model

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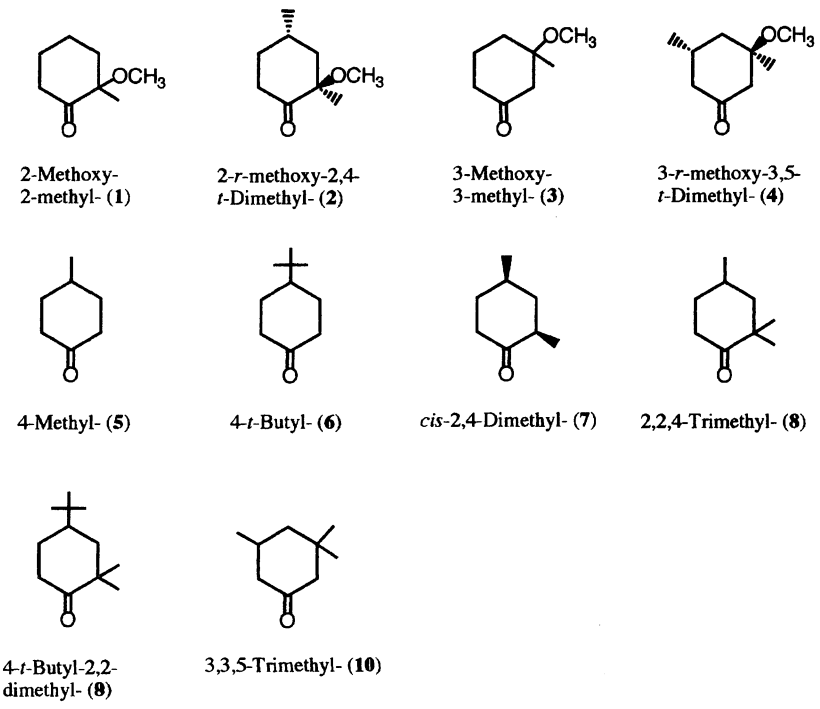
The 2- and 3-axially substituted methoxy groups in cyclohexanones exhibit steric hindrance similar to that of the methyl group in $LiAlH_4$ and $NaBH_4$ reductions. The chelate complex formation between the zinc ion and the two oxygens in the molecule was suggested in the zinc borohydride reduction. The relative reactivities of cyclohexanones in which the 2-axial position is substituted by the methyl or the methoxy group in the $LiAlH_4$ reduction strongly support Cieplak's proposal, which focuses on the importance of the stabilization of the transition state by *anti*-periplanar allylic bonds.

The stereochemistry of the complex metal hydride reduction of cyclohexanones has long been discussed, and many investigations have been published.[1] Among the discussions, Klein first introduced the concepts of orbital symmetry arguments, which control the stereochemistry of the reduction of unhindered cyclohexanones, such as 4-*t*-butylcyclohexanone.[2] Presently there is a great deal of discussion as to whether the stereochemistry of the nucleophilic reaction of the unhindered cyclohexanones is governed by molecular orbital overlap, which includes the carbonyl group. Cieplak focuses on the importance of the stabilization of the transition state by *anti*-periplanar allylic bonds.[3] He explained a large variety of substituent effects for nucleophilic addition stereoselectivities with this model. Steric effects are still one of the dominant factors in determining the stereochemistry of the reduction of hindered cyclohexanones.

In order to ascertain the effects of polar substituents at the 2- and 3-axial positions on the stereochemistry of complex



2-Methoxy-2-methyl- (**1**)
2-*r*-methoxy-2,4-*t*-Dimethyl- (**2**)
3-Methoxy-3-methyl- (**3**)
3-*r*-methoxy-3,5-*t*-Dimethyl- (**4**)
4-Methyl- (**5**)
4-*t*-Butyl- (**6**)
cis-2,4-Dimethyl- (**7**)
2,2,4-Trimethyl- (**8**)
4-*t*-Butyl-2,2-dimethyl- (**9**)
3,3,5-Trimethyl- (**10**)

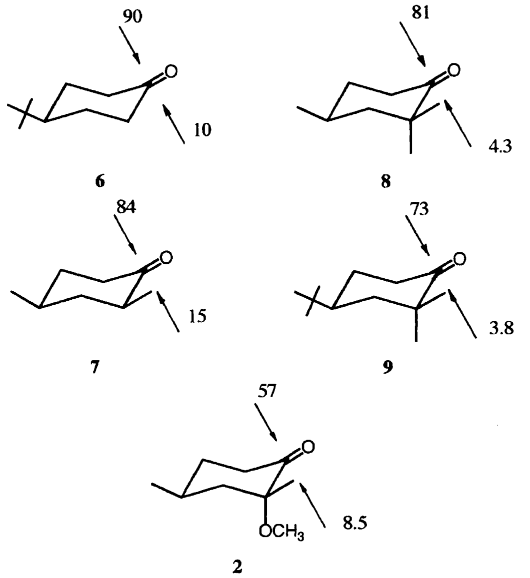
Fig. 1. Cyclohexanones.

Table 1. Stereochemistry of the Reduction of Substituted Cyclohexanones in Diglyme

Reducing reagent	$LiAlH_4$	$NaBH_4$	$Zn(BH_4)_2$
Cyclohexanone		Axial attack (%)	
1	53 (55)[a)]	37 (60)[b)]	48
2	91 (87)	92 (94)	57
5	85 (78)	78 (76)	86
6	89 (90)	93 (87)	92
7	84 (85)	85 (72)	80
8	95 (95)	95 (94)	94
9	95 (94)	94 (94)	92
10	42 (45)	34 (26)	33

a) In diethyl ether. b) In ethanol.

Table 3. Relative Reactivities of the Representative Cyclohexanones in the $LiAlH_4$ Reduction in Diethyl Ether



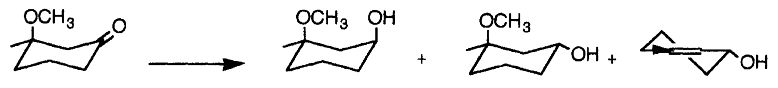
metal hydride reduction, the following methoxy substituted cyclohexanones were reduced with several complex metal hydrides, and the stereochemistries of the products were examined. The cyclohexanones employed were 2-methoxy-2-methyl- (**1**), 2-*r*-methoxy-2,4-*t*-dimethyl- (**2**), 3-methoxy-3-methyl- (**3**), and 3-*r*-methoxy-3,5-*t*-dimethylcyclohexanones (**4**). The stereochemical results were compared with those obtained from the corresponding alkyl substituted analogs: 4-methyl- (**5**), 4-*t*-butyl- (**6**), *cis*-2,4-dimethyl- (**7**), 2,2,4-trimethyl- (**8**), 4-*t*-butyl-2,2-dimethyl- (**9**), and 3,3,5-trimethylcyclohexanones (**10**) (Fig. 1).

The isomeric distribution of the products is summarized in Tables 1 and 2.

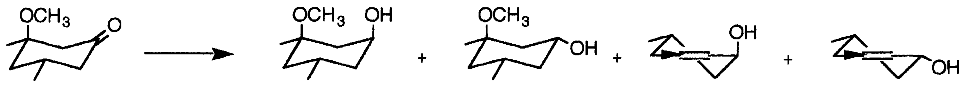
Lithium Aluminum Hydride Reduction. Ten percent of the equatorial and 90% of the axial attack of the hydride occurred on the carbonyl group of the unhindered and rigid **6**. The introduction of a methyl group to the 2-equatorial position (**7**) decreased the hydride attack from the axial side to 84%. On the other hand, the introduction of a methyl group to the 2-axial position (**8**, **9**) decreased the hydride attack from the equatorial side to 5%.[4)] The methoxy group at the 2-axial position (**2**) exhibited not as large an effect on the stereochemistry of the hydride reduction as the methyl group.

To obtain further quantitative information, the relative reactivities of these cyclohexanones were determined. Binary mixtures prepared from equimolar amounts of two of the five cyclohexanones: **2**, **6**, **7**, **8**, and **9** were reduced with $LiAlH_4$, and the relative reactivities were determined during the early stage of the reaction. The conversion of the competitive reduction was controlled to less than 10%. The results of the competitive reductions are shown in Table 3. The relative reactivities for the formation of 4-*t*-butylcyclohexanol from

Table 2. Stereochemistry of the Reduction of **3** and **4** in Diglyme



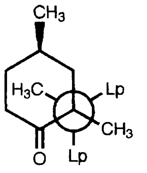
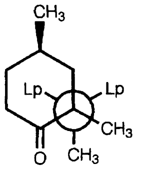
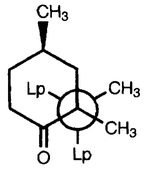
(**3**)	(**11**)[a)]	(**12**)	(**15**)
Reducing reagent			
$LiAlH_4$	68 (71)[b)]	24 (23)	8 (6)
$NaBH_4$	75 (72)[c)]	23 (24)	2 (4)
$Zn(BH_4)_2$	79 (81)[b)]	21 (19)	0 (0)



(**4**)	(**13**)	(**14**)	(**16**)	(**17**)
Reducing reagent				
$LiAlH_4$	0 (0)[b)]	19 (16)	78 (80)	3 (4)
$NaBH_4$	0 (0)[c)]	18 (15)	76 (79)	6 (6)
$Zn(BH_4)_2$	62 (68)[b)]	28 (27)	4 (1)	6 (4)

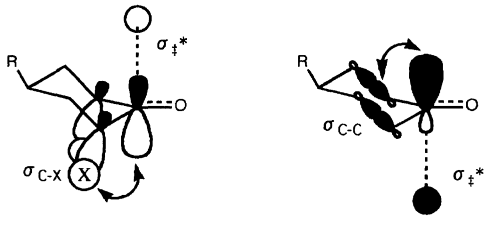
a) Probably exists in inverted conformation. b) In diethyl ether. c) In ethanol.

Table 4. Conformational Distribution of **2** by MM2

		
2-a(a)	**2-gp(a)**	**2-gd(a)**
0.0%	95.2%	4.8%

6 are arbitrarily set at 100.

The methyl group at the 2-axial position of the cyclohexanone skeleton appreciably retarded the partial reactivity form the equatorial side. The relative reactivity from this direction decreased to less than one-half. The relative reactivity of **2** indicated that the steric hindrance of the 2-axial methoxy group on the hydride attack from the equatorial direction was not as serious as that of the 2-axial methyl group. There are three possible conformers depending on the orientation of the methyl of the axial methoxy group. The methyl of the methoxy group can take an *anti* and two *gauche* conformations, in which the methyl of the methoxy group is proximal and distal to the carbonyl group, with respect to the equatorial 2-methyl group. Because the methoxy group is in an axial position, conformations are represented as **2-a(a)**, **2-gp(a)**, and **2-gd(a)**, respectively. Other conformers which are given by the ring inversion are considered not to exist due to the severe diaxial interaction between the 2-methyl and the 4-methyl groups. The population of the conformers obtained by Allinger's MM2[5] calculations is 95.2% **2-gp(a)** and only 4.8% of **2-gd(a)** (Table 4).



axial attack. equatorial attack.

(X = H, CH$_3$, OCH$_3$)

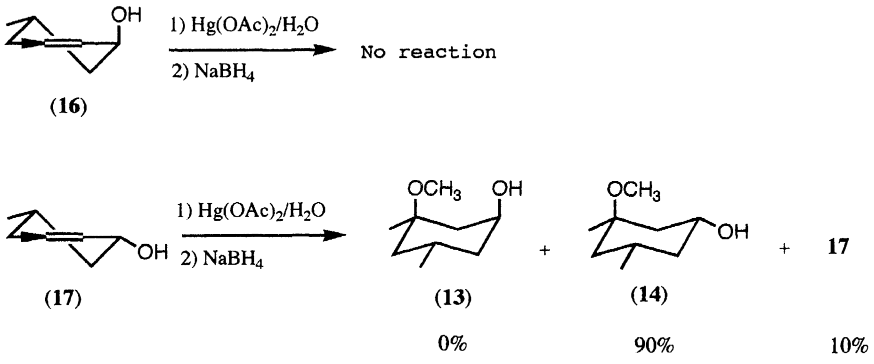
Fig. 2. The $\sigma_{\rm C-X}$, $\sigma_\ddagger^*$, and $\sigma_{\rm C-C}$, $\sigma_\ddagger^*$ interaction in the transition state.

The partial reactivity from the axial side of **7** slightly decreased compared to that of **6**. This indicates that the 2-equatorial methyl group restricted the hydride attack from the axial direction. Furthermore, the relative reactivities from the axial side diminished by the introduction of the methyl or the methoxy group at the 2-axial position of **7**. Since the steric environment of the axial side around the carbonyl group of **2**, **7**, and **8** seems to be virtually identical in the transition state, the decrease in the partial reactivity from this direction to the carbonyl group is mainly attributed to the electron-donating ability of the 2-axial substituents, the order of which is C–H > C–C > C–O.[3]

Table 5. Results of MO (MNDO/PM3) Calculation for Representative Cyclohexanones

Compound **2**[a] {**2gp(a)**}				Compound **7**[a]				Compound **8**[a]			
Bond length (Å)											
C1–C2 1.550		C1–C6 1.513		C1–C2 1.524		C1–C6 1.514		C1–C2 1.536		C1–C6 1.517	
β (eV)											
C1–C2 −3.960		C1–C6 −4.226		C1–C2 −4.146		C1–C6 −4.219		C1–C2 −4.059		C1–C6 −4.197	
No. of orbital	Orbital energy (eV)	Eigenvector (2pπ of)		No. of orbital	Orbital energy (eV)	Eigenvector (2pπ of)		No. of orbital	Orbital energy (eV)	Eigenvector (2pπ of)	
	$\sigma_\ddagger^{*\rm b)}$	(C1)[b]			$\sigma_\ddagger^{*\rm b)}$	(C1)[b]			$\sigma_\ddagger^{*\rm b)}$	(C1)[b]	
33	0.675	0.757		27	0.880	0.761		30	0.896	0.762	
	$\sigma_i^{\rm c)}$	(C2)	(C6)		$\sigma_i^{\rm d)}$	(C2)	(C6)		$\sigma_i^{\rm e)}$	(C2)	(C6)
30	−11.655	0.040	0.121	25	−11.745	0.064	0.121	28	−11.486	0.071	0.130
29	−12.064	0.070	0.079	24	−12.069	0.431	0.018	27	−12.022	0.246	0.088
28	−12.185	0.154	−0.005	23	−12.150	−0.058	0.109	26	−12.148	0.196	−0.057
27	−12.523	0.137	0.373	22	−12.392	0.111	−0.057	25	−12.442	0.051	0.352
26	−12.633	0.292	−0.151	21	−12.623	−0.035	0.385	24	−12.612	0.237	−0.109
25	−13.042	0.111	−0.110	20	−12.033	−0.030	0.138	23	−12.650	0.095	0.056
(SE)$_{\rm axial}$ (eV)			0.526				0.605				0.584
Relative reactivity[f]			57				84				81

a) We selected the closest six σ_i orbitals to the $\pi^*_{\rm C=O}$ in energy. b) The value of $\pi^*_{\rm C=O}$ was used. c) Orbital No. 32 and 31, which are attributable to $n_{\rm C=O}$ and $n_{\rm OMe}$, respectively, were omitted. d) Orbital No. 26, which is attributable to $n_{\rm C=O}$, was omitted. e) Orbital No. 29, which is attributable to $n_{\rm C=O}$, was omitted. f) Experimental evidence.



Scheme 1.

According to Cieplak's proposal, the predominance of the axial approach of the hydride to unhindered cyclohexanones was explained by the difference in the nonbonding 2pπ–2pπ interaction between the antibonding orbital of the incipient bond ($\sigma^{*}_{\ddagger}$) and the *anti*-periplanar allylic σ orbitals (Fig. 2, X = H). The transition state stabilization energy (SE) for the axial and equatorial approach can be expressed as follows:

$$(\mathrm{SE})_{\mathrm{axial}}=2(\sigma_{\mathrm{C2\,(and\ C6)-H(axial)}}\cdot\sigma^{*}_{\ddagger}\cdot\beta)^{2}/|\Delta\varepsilon(\sigma_{\mathrm{C2\,(and\ C6)-H(axial)}}-\sigma^{*}_{\ddagger})|, \tag{1}$$

$$(\mathrm{SE})_{\mathrm{equatorial}}=2(\sigma_{\mathrm{C2\,(and\ C6)-C(equatorial)}}\cdot\sigma^{*}_{\ddagger}\cdot\beta)^{2}/|\Delta\varepsilon(\sigma_{\mathrm{C2\,(and\ C6)-C(equatorial)}}-\sigma^{*}_{\ddagger})|, \tag{2}$$

in which the denominator and the numerator represent an energy separation of the two MO's and the square of their overlap, respectively.

We evaluated the correlation of the relative reactivity of this direction with the $(\mathrm{SE})_{\mathrm{axial}}$ values for **2**, **7**, and **8**. Because it is obvious that unsymmetric substitution at the 2 and 6 positions caused the significant deviation of the bond lengths of these axial C–X (X=H, Me, and OMe), the orbital energies of $\sigma_{\mathrm{C-X(axial)}}$, and the eigenvectors of $C_{2\mathrm{pz}}$[#] between C2 and C6, Eq. 1 should be rewritten as follows:

$$(\mathrm{SE})_{\mathrm{axial}}=2\sum_{i}[\{(\sigma_i)_{\mathrm{C2-X(axial)}}\cdot(\sigma^{*}_{\ddagger})\cdot\beta_{\mathrm{C1-C2}}+(\sigma_i)_{\mathrm{C6-X(axial)}}\cdot(\sigma^{*}_{\ddagger})\cdot\beta_{\mathrm{C1-C6}}\}^{2}/|\Delta\varepsilon\{(\sigma_i)-(\sigma^{*}_{\ddagger})\}|], \tag{3}$$

in which *i* is the *i*th occupied σ orbital, and β is the resonance integral.

The information about the $\sigma_{\mathrm{C-X(axial)}}$ of **2**, **7**, and **8** was obtained from the semiempirical MO (MNDO/PM3)[6] calculations. The calculation of **2** was performed only for **2-gp(a)** because of its predominance (>95%) over **2gd(a)** and **2a(a)**. The replacement of the 2-axial H of **7** by the methyl and the methoxy groups results in an elongation of the C1–C2 bond length from 1.524 to 1.536 and 1.550 Å, respectively. This results in the increase in β from −4.146 for **7** to −4.059 for **8** and −3.960 eV for **2**.[7] This means that the stabilization energy for **2** is ca. 10% smaller than that of **7** (Table 5). At present, the values of the energy and the eigenvector of $\sigma^{*}_{\ddagger}$ cannot be obtained by the MO calculation. These values are predicted to be smaller, but are close to those of $\pi^{*}_{\mathrm{C=O}}$, because the LiAlH$_4$ reduction proceeds via a reactant-like transition state. We tentatively used the values of $\pi^{*}_{\mathrm{C=O}}$ as the maximum of those of the corresponding $\sigma^{*}_{\ddagger}$ for the calculation. Calculated parameters responsible for the stabilization of the axial approach are also collected in Table 5. It should be noted that the replacement of the 2-axial hydrogen with the methyl or the methoxy group caused a reduction in the eigenvector of the $\sigma_{\mathrm{C-X(axial)}}$ interacting with $\sigma^{*}_{\ddagger}$. Because the potential energy differences between $\sigma^{*}_{\ddagger}$ and $\sigma_{\mathrm{C-X(axial)}}$ are nearly equal, the $(\mathrm{SE})_{\mathrm{axial}}$ is dependent on the square of their overlap. The order of the $(\mathrm{SE})_{\mathrm{axial}}$, **7**>**8**>**2**, 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 the equatorial attack of the hydride decreased in the order H>OMe>Me at the 2-axial position, which is the same trend as the amounts of the conformational free energies of these substituents. This shows that the steric bulk plays a major role in determining the attack of the hydride from the equatorial side in the reduction of 2-axially substituted cyclohexanones.

The LiAlH$_4$ reduction of **3** yielded a 68% axial hydroxy product, 3-*c*-methoxy-3-*t*-methyl-1-*r*-cyclohexanol (**11**), and a 24% equatorial hydroxy product (**12**), accompanied by 8% allylic cyclohexenol, *cis*-3-methyl-2-cyclohexenol (**15**) in diglyme. In the reduction of **4**, 19% 3-*t*-methoxy-*c*-3,*c*-5-dimethyl-1-*r*-cyclohexanol (**14**) was obtained along with 78% 3,*trans*-5- (**16**) and 3% 3,*cis*-5-dimethyl-2-cyclohexenols (**17**) in diglyme; however, no *c*-3-methoxy-*t*-3,*t*-5-dimethyl-1-*r*-cyclohexanol (**13**) was obtained (Table 2).

The methoxymercuration–demercuration of **17**, which was obtained from 3,5-dimethyl-2-cyclohexenone with LiAlH$_4$ reduction,[8] produced no **13**, but 90% **14**, and 10% **17** was recovered. Similarly, the methoxymercuration–demercuration of **16** gave no product; however, the starting material was recovered unchanged (Scheme 1). These results suggest that the primarily obtained **13**, which has both the 1-hydroxy and 3-methoxy group in the axial position, may be converted to

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[#] When the carbonyl group and the adjacent two carbons are on the *xy* plane, the eigenvectors of $C2_{2\mathrm{pz}}$ and $C6_{2\mathrm{pz}}$ are the components of those of the corresponding $(\sigma_i)_{\mathrm{C-X(axial)}}$ interacting with $\sigma^{*}_{\ddagger}$.

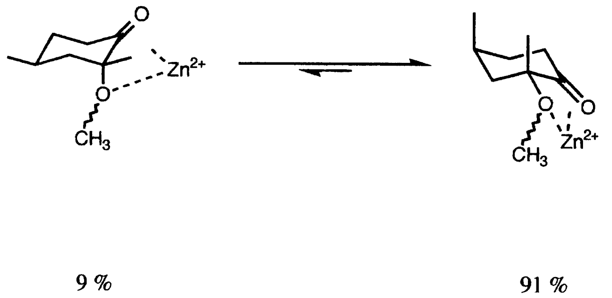

Fig. 3. Zinc chelate complex of **2**.

16 by the elimination of methanol during the $LiAlH_4$ reduction of **4**. Because the ring conformation is fixed by the 5-methyl group in **13**, all the diaxial epimeric products might be decomposed to cyclohexenol, while most of the hydroxy group can take the equatorial direction to release the steric interaction between the substituents by ring inversion in **11**, and the methanol elimination may be limited.

Keeping in mind the above assumption, the attack of the hydride might be estimated at around 80% from the opposite side of the methoxy group to the carbonyl of **3** and **4**, in which the methoxy groups are introduced at the 3-axial position.

The reduction of **10** occurred a 42% axial attack, while that of **4** occurred around 20% in diglyme. This appears as if the methoxy group at the 3-axial position is sterically bulkier than the methyl group; even the conformational free energy of the former is smaller than that of the latter.

The $NaBH_4$ reduction gave stereochemical results similar to the $LiAlH_4$ reduction.

Zinc Borohydride Reduction. The stereochemistry of the reductions of alkyl substituted cyclohexanones with $Zn(BH_4)_2$[9] was similar to that with $LiAlH_4$ and $NaBH_4$. However, the attack of the hydride from the same side of the methoxy group at the 2-axial position increased in **2** compared to the case of the methyl substituted analog, **8**.

In the $Zn(BH_4)_2$ reductions of ketones, which contain a hetero atom such as oxygen or sulfur other than the carbonyl oxygen in the molecule, the formation of zinc-mediated cyclic intermediates has been suggested.[10] The formation of such cyclic intermediates should be taken into consideration in the reduction of **1** and **2**.

There are six possible zinc-coordinated conformations for **2**, which are given by the rotation of the methoxy oxygen–C2 bond in each of the two conformers: One is with the axial methoxy group, and the other is with the equatorial methoxy group by ring inversion. Structure optimization by MO calculation was performed for these twelve zinc-coordinated conformers which were supposed to form during the reduction. For simplification, calculations were performed for the structure coordinating with the Zn^{2+}, not with $Zn(BH_4)_2$. If it is possible to neglect the entropy change, the enthalpy differences obtained in the conformational isomers of **2** indicated the presence of approximately 91% zinc chelate conformers with the 2-equatorial methoxy group making the five-membered cyclic structure including zinc ion, and 9% with the 2-axial methoxy group (Fig. 3). This results in the loss of stereoselectivity in the reduction. A similar discussion is possible in the reduction of **1**.

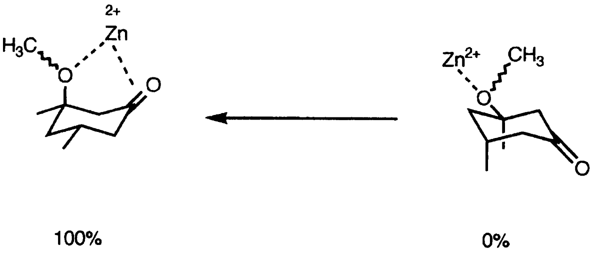

Fig. 4. Zinc chelate complex of **4**.

The methoxy group which is placed at the 3-axial position appeared only to be a steric hindrance similar to the case of the $LiAlH_4$ and $NaBH_4$ reduction. In the reduction of **4**, 62 and 68% hydride attack apparently occurred from the equatorial side in diglyme and diethyl ether, respectively (Fig. 4). Cyclohexenols (**16**) were detected in the reduction, but their amounts were rather small compared to the $LiAlH_4$ and $NaBH_4$ reductions. Taking into account that **16** comes from the reduction product **13**, by the elimination of methanol, the hydride attack predominantly occurred from the side opposite to the methoxy group to the carbonyl of **4**.

Similar to the case of **2**, the structure optimization of twelve possible zinc-coordinated intermediates of **4** was performed by MO calculation. The optimized structure suggested the presence of only a chelate intermediate with the axial methoxy group. The optimized structure, together with the stereoselectivity of reduction, seems to indicates that the chelated zinc borohydride moiety does not intramolecularly supply the hydride, but is only the steric hindrance. In this situation, the hydride attack occurs intermolecularly from the opposite side of the methoxy group.

In summary, the competitive reduction of cyclohexanones and the MO calculation strongly support Cieplak's proposal that the stereochemistry of the nucleophilic addition to unhindered cyclohexanones is governed by molecular orbital overlap. The stereochemistry of the $Zn(BH_4)_2$ reduction of cyclohexanones with the methoxy substituent suggests the formation of a zinc-mediated cyclic intermediate which includes the ether and carbonyl oxygens.

Experimental

Materials. *cis*-2,4-Dimethylcyclohexanone (**7**),[11] 2,2,4-trimethylcyclohexanone (**8**),[12] and 4-*t*-butyl-2,2-dimethylcyclohexanone (**9**)[13] were prepared by the methods in the literature.

2-Methoxy-2-methylcyclohexanone (1):[14] A mixture of $Hg(OAc)_2$ (26.5 g, 80 mmol) and 2-methylcyclohexenol (4.5 g, 40 mmol) which was prepared by the $Hg(OAc)_2$ oxidation[15] of 1-methylcyclohexene in AcOH at 100 °C followed by hydrolysis, was stirred for 90 min at room temperature. Sodium hydroxide (3.0 M, 40 cm^3) (1 M=1 mol dm^{-3}) and $NaBH_4$ (1.52 g, 40 mmol) in aq NaOH (3.0 M, 40 cm^3) were added at 0 °C. The precipitated Hg was removed by filtration. The product was isolated by diethyl ether extraction. After drying over Na_2SO_4 and evaporation, 2-methoxy-2-methylcyclohexanol[16] (4.0 g, 28 mmol, 69%) was obtained; bp 92—102 °C (25 mmHg, 1 mmHg=133.322 Pa); ^{1}H NMR ($CDCl_3$) δ=1.23 (3H, s), 1.31—2.13 (8H, m), 2.42 (1H, bs), 3.18 (3H, s), and 3.30 (1H, m). The PCC oxidation of 2-methoxy-2-methylcyclohexenol in $\mathrm{CH_2Cl_2}$ gave **1** (2.75 g, 19 mmol, 70%); bp 76—80 °C (25 mmHg); IR (film) 1700, 1420, and 1060 $\mathrm{cm^{-1}}$; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=1.11 (3H, s), 1.20—2.42 (8H, m), and 3.24 (3H, s).

2-*r*-Methoxy-2,4-*t*-dimethylcyclohexanone (2): 2,4-Dimethyl-2-cyclohexenol (5.0 g, 40 mmol) which was obtained by chlorination and subsequent dehydrochlorination[17] of 2,4-dimethylcyclohexanone followed by $\mathrm{LiAlH_4}$ reduction, was methoxymercurated and demercurated to give 2-*r*-methoxy-2,4-*t*-dimethylcyclohexanol (4.15 g, 29.2 mmol, 73%); bp 88—90 °C (20 mmHg); ^{1}H NMR ($\mathrm{CDCl_3}$) δ=0.85 (3H, d, *J*=5.4 Hz), 1.10—2.00 (7H, m), 1.13 (3H, s), 2.10 (1H, bs), 3.10 (3H, s), and 3.40 (1H, m), which was oxidized by PPC to give **2** (1.9 g, 12 mmol, 31% from 2,4-dimethyl-2-cyclohexenol) including a small amount of 2-*r*-methoxy-2,4-*c*-dimethylcyclohexanone. The product, **2**, was purified as semicarbazone; bp 76—80 °C (27 mmHg); IR (film) 1710, 1450, 1180, 1120, and 1080 $\mathrm{cm^{-1}}$; ^{1}H NMR ($\mathrm{CDCl_3}$) 0.83 (3H, d, *J*=5.6 Hz), 1.02 (3H, s), 1.21—2.83 (7H, m), and 3.11 (3H, s); Semicarbazone; mp 168 °C (Found: C, 56.11; H, 8.71; N, 19.81%; Calcd for $\mathrm{C_{10}H_{19}N_3O_2}$: C, 56.31; H, 8.98; N, 19.70%). The steric configuration was tentatively assigned by the reaction mechanism of oxymercuration.[18]

3-Methoxy-3-methylcyclohexanone (3):[19] 3-Methylcyclohexenol[20] (4.5 g, 40 mmol) was methoxymercurated and demercurated to give 3-methoxy-3-methylcyclohexanol (4.1 g, 29 mmol, 72%); ^{1}H NMR ($\mathrm{CDCl_3}$) δ=0.91—2.22 (8H, m), 1.12 (3H, s), 1.85 (1H, bs), 3.03 (3H, s), and 3.06 (1H, m), which was oxidized by PCC to give **3** (3.3 g, 24 mmol, 82%) in $\mathrm{CH_2Cl_2}$; bp 85—87 °C (17 mmHg); IR (firm) 1690, 1420, and 850 $\mathrm{cm^{-1}}$; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=1.12 (3H, s), 1.23—2.02 (8H, m), and 3.24 (3H,s).

3-*r*-Methoxy-3,5-*t*-dimethylcyclohexanone (4): 3,5-Dimethylcyclohexanone (37.2 g, 0.3 mol) was transferred to 1-bromo-2,2-ethylenedioxy-3,5-dimethylcyclohexane. Dehydrobromination with sodium methoxide in DMSO,[21] followed by hydrolysis of ethylene ketal, gave 3,5-dimethyl-2-cyclohexenone, (10.1 g, 81 mmol, 27%), which was reduced with $\mathrm{LiAlH_4}$. The resulting 3,5-dimethyl-2-cyclohexenol[8] (3.32 g, 27 mmol) was methoxymercurated and demercurated to give 3-methoxy-3,5-dimethylcyclohexanol (3.15 g, 20 mmol, 75.7%); ^{1}H NMR ($\mathrm{CDCl_3}$) δ=0.98 (3H, d, *J*=5.4 Hz), 1.14 (3H, s), 1.25—2.60 (6H, m), 1.85 (1H, bs), 3.06 (3H, s), and 3.45 (1H, m). The product was oxidized by PCC to give **4** including a small amount of 3-*r*-methoxy-3,5-*c*-dimethylcyclohexanone (2.32 g, 15 mmol, 55% from 3,5-dimethyl-2-cyclohexenol). The compound, **4**, was purified as semicarbazone; bp 108 °C (21 mmHg); IR (firm) 1710, 1232, and 1038 $\mathrm{cm^{-1}}$; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=0.95 (3H, d, *J*=6.1 Hz), 1.16 (3H, s), 1.46—2.56 (6H, m), and 3.05 (3H, s). Semicarbazone; mp 179.5—181 °C (Found: C, 56.18; H, 8.99; N, 19.84%. Calcd for $\mathrm{C_{10}H_{19}N_3O_2}$: C, 56.31; H, 8.98; N, 19.70%). The steric configuration was tentatively assigned by the reaction mechanism of oxymercuration.[18]

Reduction with Complex Metal Hydride. $\mathrm{LiAlH_4}$ and $\mathrm{NaBH_4}$ Reduction. The solution of $\mathrm{LiAlH_4}$ or $\mathrm{NaBH_4}$ (0.02 M, 5 $\mathrm{cm^3}$) in dried solvent was added dropwise to 0.4 mmol of the substrate in 5 $\mathrm{cm^3}$ of the same solvent over a period of 10—15 min at 0 °C and the mixture was stirred for 5 min. Water and crushed ice were added and the organic layer was separated, dried over $\mathrm{Na_2SO_4}$, and analyzed by GLC.

$\mathrm{Zn(BH4)_2}$ Reduction. The solution of $\mathrm{Zn(BH_4)_2}$ (0.01 M, 5 $\mathrm{cm^3}$) in dried solvent was added dropwise to 0.4 mmol of the substrate in 5 $\mathrm{cm^3}$ of the same solvent over a period of 10—15 min at 0 °C and the mixture was stirred for 60 min. Water and crushed ice were added and the organic layer was separated, dried over $\mathrm{Na_2SO_4}$, and analyzed by GLC.

Table 6. Chemical Shifts for Carbinyl Carbons of the Products (δ)

Cyclohexanone	C–OH *cis*	C–OH *trans*
	(Relation between $\mathrm{OH–OCH_3}$)	
1	74.9	74.6
2	76.6	71.0
3	71.2	70.8
4	71.1	65.9

Competitive Reduction with $\mathrm{LiAlH_4}$.[22] The calculated amount (0.025 molar amount) of a hydride solution in diethyl ether (0.01 M) was added to a mixture of two ketones (**6** with **2**, **5**, **7**, **8** or **9**, and **2** with **5**, **7** or **8**, 0.5 mmol of each) in 3 $\mathrm{cm^3}$ of diethyl ether over a period of 10—15 min at 0 °C. The reaction mixture was stirred for 5 min. Water and crushed ice were added and the organic layer was separated, dried over $\mathrm{Na_2SO_4}$, and analyzed by GLC.

NMR and Gas Chromatographic Analyses. ^{13}C NMR and ^{1}H NMR spectra were obtained with a JEOL JNMFX-90Q instrument in the pulse Fourier mode. Gas chromatographic analyses were performed on a Shimadzu model GC-8AIF with carbowax 20M chemical bonded silica capillary column (0.25 mm×25 m) at a column temperature of 120 °C.

The configuration of 2-methoxy-2-methylcyclohexanol was known in the literature.[17] The configuration of other reduction products were determined by the comparison of ^{13}C NMR and gas chromatographic analyses. It has been reported that the signals of the carbinyl carbons with the axial hydroxy group on the cyclohexane ring appeared at a higher field than those of the corresponding equatorial analogs.[23] The results of the quantitative analyses by chromatography and the integrated peak area of spectra with sufficient pulse intervals were compared and determined the configuration of the respective isomers. The carbon chemical shifts for the carbinyl carbons of the stereoisomers are tabulated in Table 6.

References

1) B. W. Gung, *Tetrahedron*, **52**, 5263 (1996), and references cited therein.

2) J. Klein, *Tetrahedron*, **29**, 4307 (1973); **30**, 3349 (1974).

3) A. S. Cieplak, *J. Am. Chem. Soc.*, **103**, 4540 (1981).

4) J. M. Fang, S. F. Sun, and M. H. Rei, *J. Chem. Soc., Perkin Trans. 2*, **1989**, 747.

5) N. L. Allinger and D. Y. Chung, *J. Am. Chem. Soc.*, **99**, 6798 (1976); N. L. Allinger, *J. Am. Chem. Soc.*, **99**, 8127 (1977); N. L. Allinger and Y. Yuh, *Quantum Chem. Program Exch.*, **11**, 1395 (1979).

6) MOPAC Ver. 6, J. J. P. Stewart, *QCPE Bull.*, **9**, 10 (1989); revised as Ver. 6.01 by Tsuneo Hirano, University of Tokyo, for HITAC and UNIX machines, *JCPE Newsletter*, **1**, 10 (1990); Revised as Ver. 6.02 by Makoto Funamizu.

7) J. -C. Wu, K. N. Houk, and B. M. Trost, *J. Am. Chem. Soc.*, **109**, 5560 (1987).

8) K. Kikuchi, "Bunshikidoho," Kodansha, Tokyo, Chap. 3, p. 137; K. N. Houk, J. Sims, C. R. Watts, and L. J. T. Luskus, *J. Am. Chem. Soc.*, **95**, 7301 (1973).

9) W. J. Gensler, F. Johnson, and A. D. B. Sloan, *J. Am. Chem. Soc.*, **82**, 6074 (1960).

10) M. Shimagaki, M. Shiokawa, K. Sugai, T. Teranaka, T. Nakata, and T. Oishi, *Tetrahedron Lett.*, **29**, 959 (1989), and references cited therein.

11) B. J. Armitage, G. W. Kenner, and M. J. T. Robinson, *Tetrahedron*, **20**, 747 (1964).

12) D. C. Wiegfield, S. Feiner, and D. J. Phelps, *J. Org. Chem.*, **40**, 2533 (1975).

13) J. C. Richer and G. Perrault, *Can. J. Chem.*, **43**, 18 (1965).

14) T. Sakakibara, Y. Ikeda, and S. Sudoh, *Bull. Chem. Soc. Jpn.*, **55**, 635 (1982).

15) W. Treibs and M. Weissenfels, *Chem. Ber.*, **93**, 1374 (1960).

16) S. N. Merchant, S. C. Sethi, and H. R. Sonawane, *Indian J. Chem., Sect. B*, **14B**, 460 (1976).

17) *Org. Synth.*, Coll. Vol. 4, 162 (1963).

18) D. J. Pasto and J. A. Gontarz, *J. Am. Chem. Soc.*, **93**, 6909 (1971).

19) T. Sato, S. Yosiie, T. Inamura, K. Hasegawa, M. Miyahara, S. Yamamura, and O. Ito, *Bull. Chem. Soc. Jpn.*, **50**, 2714 (1977).

20) W. Crowyn and G. H. Hiesser, *J. Am. Chem. Soc.*, **76**, 1666 (1953).

21) E. W. Garbisch, Jr., *J. Org. Chem.*, **30**, 2109 (1965).

22) E. L. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1970).

23) J. D. Roberts, F. J. Weigert, J. T. Kroschwitz, and H. J. Reich, *J. Am. Chem. Soc.*, **92**, 1338 (1970).