Role of the nitrogen atom in the complex metal hydride reduction of unhindered γ-azacyclohexanones

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Preferential hydride attack has been found to occur at the *en* face, which is the opposite side to the γ-nitrogen atom, of the carbonyl group in the $LiAlH_4$ reduction of 1-azaadamantan-4-one, whose n_N orbital is in an equatorial position. On the other hand, hydride attack occurred predominantly from the axial side of 1,2-dimethylpiperidin-4-one and 2-ketoquinolizidine whose n_N orbitals are in the axial position. The appreciable solvent effect apparent in the $NaBH_4$ reduction of 1-azaadamantan-4-one may be responsible for the hydrogen bond formation of the n_N orbital with the protic solvent. The stereochemistry of the complex metal hydride reduction of γ-azacyclohexanones could be explained by the difference in the non-bonding two electron stabilisation between the incipient σ_i^* bond and the antiperiplanar allylic σ_i bonds which were perturbed by the through-space and/or through-bond interaction with the remote heteroatom.

Klein first introduced the concept of orbital symmetry arguments, including those of the carbonyl group, which mainly control the stereochemistry of the reduction of unhindered cyclohexanones, *e.g.* 4-*tert*-butylcyclohexanone.[1] Among the theories of orbital overlap control, the Cieplak model focusses on the importance of transition-state stabilisation by antiperiplanar allylic bonds (Fig. 1).[2] He rationalised a large variety of substituent effects for nucleophilic addition stereoselectivity with this model. The nucleophilic reaction of cyclohexanones which contain heteroatoms such as oxygen and nitrogen in the ring system often shows different stereochemistry compared with alkyl-substituted cyclohexanones.

In order to investigate the orbital effects of the heteroatom which is placed at the γ-position to the carbonyl carbon in the hetero-cyclohexanone ring, the $LiAlH_4$ and $NaBH_4$ reductions of γ-azacyclohexanones, *e.g.* 1-azaadamantan-4-one **2**, 1,2-dimethylpiperidin-4-one **4** and 2-ketoquinolizidine **5** were examined. The nitrogen lone pair of **2** is fixed in an equatorial direction, whereas for **4** and **5** it is predominantly in the axial direction. Since the steric environment of both diastereofaces of the carbonyl group of **2** was found to be identical by the structure optimisation of the MO (MNDO/PM3)[3] calculation, the steric effect, which may contribute to the stereochemistry of the reduction, should be neglected (Fig. 2). The stereochemistry of the reduction of **2** indicated a slight preference for the *en*[4] (the opposite side to the nitrogen atom at the 1-position) approach of the hydride with $LiAlH_4$ and $NaBH_4$ in THF, while *zu*[4] (the same side as the nitrogen atom at the 1-position) attack was preferred by $NaBH_4$ in protic solvents (Table 1).

In order to obtain further quantitative information, a binary mixture prepared from equimolar amounts of adamantanone **1** and **2** was reduced with $LiAlH_4$ in THF, and the relative reactivity was determined during the early stages of the reduction. The conversion of the competitive reduction was controlled so as to be less than 10%. These results are shown in Table 2. The relative reactivity for the formation of adamantanol from **1** is arbitrarily set at 100. The relative reactivity for **2** was 83 and the reactivity of the *en* and *zu* diastereoface of the carbonyl group for **2** was 45 and 38, respectively. Compound **3**, could not be subjected to the competitive $LiAlH_4$ reduction because of its poor solubility in THF.

The substrates, **4** and **5**, which have functional groups in common with **2**, were reduced by $LiAlH_4$ and $NaBH_4$ and their stereoselectivity is also shown in Table 1. A preference for axial attack, which corresponds to the *zu* attack on **2**, was observed in the reduction of these compounds.

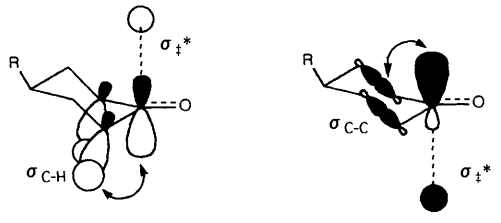
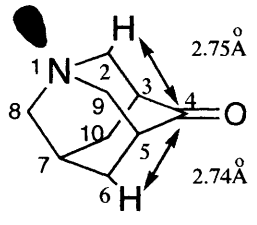


Fig. 1 Cieplak's model



Dihedral angle(O-C4-C3-C2)=122.2°
Dihedral angle(O-C4-C5-C6)=119.8°

Fig. 2 Optimised structure of **2** by MO calculations

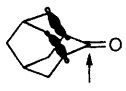
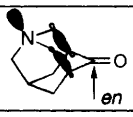
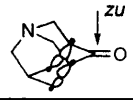
Based on UV and ^{13}C NMR studies of **2**. Dekkers *et al.*[5] found a certain amount of charge transfer from the n_N orbital to $\pi_{C=O}$ through the σ_{C2-C3} and σ_{C5-C9} orbitals. We also examined the IR and ^{13}C NMR spectra of **1**, **2** and 1,7-diazaadamantan-4-one **3**. These results, together with the electron densities of the carbonyl carbons obtained by the MO calculation are shown in Table 3. By increasing the number of nitrogen atoms in the molecule, the signal of the carbonyl carbon shifted upfield by 3–4 ppm and a 20–30 cm^{-1} decrease in the stretching frequency of the carbonyl group was observed. Since ^{13}C NMR shifts are known to be very sensitive to changes in charge density, this suggests that electron delocalisation occurred from the nitrogen atom, in other words, the interaction of the

Table 1 Stereochemistry of the $LiAlH_4$ and $NaBH_4$ reduction of γ-azacyclohexanones and corresponding carbocyclic ketones

Compounds	Reaction conditions	Acidity parameter of solvent[a]	*zu* or axial attack (%)
2	$LiAlH_4$ (0 °C in THF)	0.17	45
	$NaBH_4$ (0 °C in THF)		47
	$NaBH_4$ (0 °C in EtOH)	0.66	70
	$NaBH_4$ (25 °C in EtOH)		70
	$NaBH_4$ (25 °C in Pr^iOH)	0.59	65
	$NaBH_4$ (25 °C in Bu^tOH)	0.45	60
4	$LiAlH_4$ (0 °C in EtOH)		92
	$NaBH_4$ (0 °C in EtOH)		90
	$NaBH_4$ (0 °C in Pr^iOH)		90
	$NaBH_4$ (0 °C in Bu^tOH)		94
5	$LiAlH_4$ (0 °C in EtOH)		89
	$NaBH_4$ (0 °C in EtOH)		86
	$NaBH_4$ (0 °C in Pr^iOH)		86
	$NaBH_4$ (0 °C in Bu^tOH)		90
4-*tert*-Butylcyclohexanone	$LiAlH_4$ (0 °C in EtOH)		90
	$NaBH_4$ (0 °C in EtOH)		88
	$NaBH_4$ (0 °C in Pr^iOH)		88
	$NaBH_4$ (0 °C in Bu^tOH)		91
(*E*)-2-Decalone[b]	$LiAlH_4$ (0 °C in EtOH)		86
	$NaBH_4$ (0 °C in EtOH)		84
	$NaBH_4$ (0 °C in Pr^iOH)		84

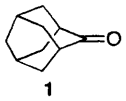
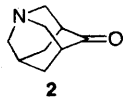
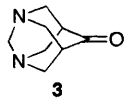
[a] Swain's parameter, ref. 6. [b] (*E*)-Decahydronaphthalen-2-one.

Table 2 Relative reactivities and results of MO(MNDO/PM3) calculations for representative adamantanones

	Compound			
				
Relative reactivity ($LiAlH_4$ in THF)[a]	50	45		38
$\pi^*_{C=O}$ Orbital energy (eV)	0.926		0.735	
$\pi^*_{C=O}$ Eigenvector of $C{=}O_{(2p_z)}$	0.761		0.758	
π_i Orbital energy (eV)	−11.325	−9.525		−11.729
π_i Eigenvector of $C\alpha_{(2p_z)}$	0.257	0.164		0.175
E_S/eV[b]	0.117	0.0563		0.0528

[a] Since the relative reactivity of **1** is arbitrarily set at 100, the relative reactivity from the one side of the carbonyl group of **1** becomes 50. [b] As an overlap integral, $\Delta\beta_{C(2p\pi-2p\pi,1.5\text{ Å})}$, 4.323 eV was employed.[13]

Table 3 Chemical shift, stretching vibration and atom electron density of carbonyl carbons of **1**, **2** and **3**

Compound	 **1**	 **2**	 **3**
Chemical shift (ppm) (in $CDCl_3$)	217.88	213.98	210.82
$\nu_{C=O}$/cm^{-1} (KBr)	1720	1700	1670
Atom electron density	3.714	3.716	3.719

n_N orbital with the σ_{C2-C3} and σ_{C5-C9} orbitals enhances the electron-donating abilities of these σ_{C-C} orbitals towards the carbonyl function in the ground state.

According to Cieplak's proposal, nucleophilic addition at the diastereoface of the carbonyl function was influenced by the difference in the non-bonding two electron stabilisation between the antibonding orbital of the incipient bond (σ_t^*) and the antiperiplanar allylic σ_i orbitals. The transition-state stabilisation energy (E_S) can be expressed by eqn. (1) in which

$$E_S = S^2(\sigma_i, \sigma_t^*)/\Delta\varepsilon(\sigma_i, \sigma_t^*) \quad (1)$$

the denominator and the numerator represent an energy separation of the two MOs and the square of their overlap, respectively. At present, the values of the energy and eigenvectors of σ_t^* cannot be obtained from the MO calculations, 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. As a consequence, eqn. (1) is approximated by eqn. (2). When the carbonyl carbon and the

$$E_S = S^2(\sigma_{C-X}, \pi^*_{C=O})/\Delta\varepsilon(\sigma_{C-X}, \pi^*_{C=O}) \quad (X: H \text{ or } C) \quad (2)$$

adjacent two α-carbons are in the *xy* plane, it can be approximated that the *z*-components of the antiperiplanar allylic σ_{C-X} bonds interact with that of the $\pi^*_{C=O}$. The calculation using eqn. (2) indicated that the total stabilising energy for **1** is larger than that (*en* plus *zu* side) for **2**. These results are entirely consistent with the evidence of the relative reactivities for **1** and **2** (Table 2).

The relative reactivity of **2** towards reaction from the *en* side was larger than that from the *zu* side. The MO calculation suggests that electron delocalisation on the σ_{C2-C3} and σ_{C5-C9}, and the n_N orbital, which is fixed in the equatorial direction, increases the electron-donating ability of these σ_{C-C} orbitals.

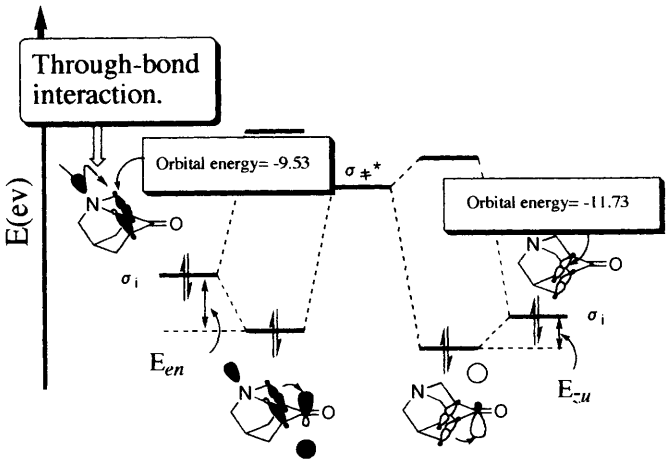


Fig. 3 Qualitative interaction diagram for the $\sigma_{\ddagger}^*$ and σ_i orbital of **2**

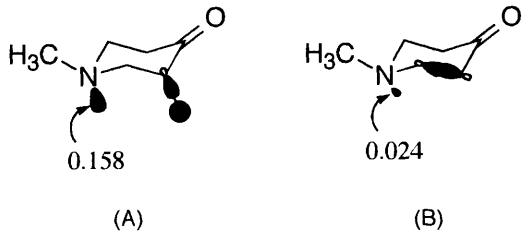


Fig. 4 Eigenvector values of the n_N orbital component interacting with the $\sigma_{C3(5)-H(axial)}$ and $\sigma_{C2(6)-C3(5)}$ orbitals. No. 21 (−12.42 eV) orbital (A) and no. 18 (−12.79 eV) orbital (B) are characterised to the $C_{3(5)}$–$H_{(axial)}$ and $C_{2(6)}$–$C_{3(5)}$ of N-methylpiperidin-4-one in which the n_N orbital is in the axial position, respectively. The values are the eigenvectors of the n_N orbital which contributes to $C_{3(5)}$–$H_{(axial)}$ and $C_{2(6)}$–$C_{3(5)}$.

This results in an increase in E_S for the *en* attack of the nucleophile compared with that for the *zu* attack at the transition state (Table 2 and Fig. 3). If it is possible to neglect the entropy change in this reduction, the ratio of the specific rate for attack at the *en* side to that from the *zu* side can be obtained by eqn. (3) in which k_{en} and k_{zu} represent the rate

$$k_{en}/k_{zu} = \exp[(E_{S,en} - E_{S,zu})/RT] \qquad (3)$$

constants for the reaction at the *en* and *zu* face, respectively. Since the E_S difference in the *en* and *zu* side is 0.08 kcal mol^{-1} (see Table 2), the ratio becomes 1.16. This value is in good agreement with the experimental evidence, 1.18 (45/38).

A preference for axial attack was observed during the reduction of **4** and **5**, and the diastereoselectivity was more pronounced than in the corresponding carbocyclic compounds. We can find a sizable eigenvector value of the component of the n_N orbital which can overlap with the $\sigma_{C3-H(axial)}$ and $\sigma_{C5-H(axial)}$ orbitals, whereas that which can overlap with the σ_{C2-C3} and σ_{C5-C6} orbitals is relatively small according to the MO calculation of *N*-methylpiperidin-4-one, as a model compound whose n_N orbital exists mostly in an axial direction (Fig. 4). As a consequence, the transannular electron delocalisation from the n_N orbital to the allylic $\sigma_{C-H(axial)}$ orbitals appears to play an important role in determining the stereochemistry of the reduction of **4** and **5**.

The $LiAlH_4$ and $NaBH_4$ reductions of **2** in THF afforded the product owing to a slight preference for the *en* approach, while the preferred attack of the hydride was reversed and the *zu* attack was *ca.* 60–70% for the $NaBH_4$ reduction in protic solvents. The stereoselectivity varied depending on the protic solvent.

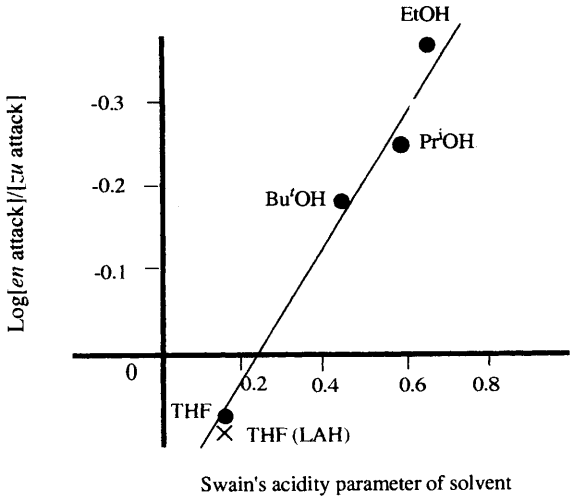


Fig. 5 Correlation between the stereoselectivity of the $NaBH_4$ reduction of **2** and the Swain's acidity parameter of solvent

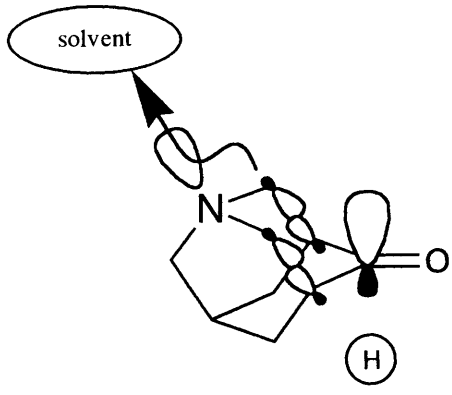


Fig. 6 Withdrawal of the electrons from the allylic σ_{C-C} orbitals by the hydrogen bond formation with the solvent

The plots of Swain's acidity parameter of solvent[6] *vs.* stereoselectivity shown in Fig. 5 indicate a good correlation between the stereoselectivity and the solvent acidity. As has been previously mentioned, the preferential *en* attack of the hydride on **2** in THF can be explained in terms of the through-bond interaction between the n_N orbital and the allylic σ_{C-C} orbitals. The reversal of the stereoselectivity in protic solvents compared with the case in an aprotic solvent suggests hydrogen bond formation of the n_N orbital in an equatorial position with the solvents. This will cause withdrawal of the electrons from the allylic σ_{C-C} orbitals by a through-bond interaction (Fig. 6).

No appreciable solvent dependence on the stereochemistry of the $NaBH_4$ reduction of **4** and **5** in protic solvents, as observed in the corresponding carbocyclic ketones. This suggests that the hydrogen-bond formation between the protic solvents and the n_N orbital in an axial direction inhibits the through-space interaction between the n_N orbital and the allylic $\sigma_{C-H(axial)}$ orbitals. The stereochemistry of the reduction of **4** and **5** was similar to that of the corresponding carbocyclic ketones.

In summary, the stereochemistry of the nucleophilic reaction at the carbonyl group of **2** with the lone pair orbital at the γ-equatorial position is controlled by electron delocalisation from the n_N orbital to the allylic σ_{C2-C3} and σ_{C5-C9} bonds at the transition state. On the other hand, the axial attack is dominant for the reaction with **4** and **5** in which the through-space interaction between the n_N orbital at the axial position with the allylic $\sigma_{C-H(axial)}$ orbitals is possible. The hydrogen bond formation of the n_N orbital with the protic solvents results in a decrease in the electron-donating ability of the allylic σ_i bonds to the forming $\sigma_{\ddagger}^*$ at the transition state. Finally, it should be

emphasised that the stereochemistry and the relative rate for the nucleophilic addition to the carbonyl group in γ-azacyclohexanones could be explained by the difference in the non-bonding two-electron stabilisation between the incipient σ_t^* bond and the antiperiplanar allylic σ_i bonds which were perturbed by the through-space and/or through-bond interaction with the remote heteroatom. Thus, so called remote substituent effects in the reduction of γ-hetero-cyclohexanones can be reasonably correlated with Cieplak's proposal.

Experimental

Materials

The substrate ketones were prepared by the procedures previously reported: **2**,[7] **3**,[8] **4**[9] and **5**.[10]

$LiAlH_4$ and $NaBH_4$ reduction

A solution of $LiAlH_4$ or $NaBH_4$ (0.02 mol dm^{-3}, 5 cm^3) in dried solvent was added dropwise to 0.4 mmol of the substrate in 5 cm^3 of the same solvent over a period of 10–15 min at the temperature shown in Table 1 and the mixture was stirred for 30 min. Water and crushed ice were added and the organic layer was separated, dried (Na_2SO_4) and analysed by GC. Authentic samples of the products (from **2**,[4] **4**[9] and **5**[10]) were prepared by the methods previously reported.

Competitive reduction with $LiAlH_4$[11]

A calculated amount (0.1 equivalent) of a hydride solution in THF (0.01 mol dm^{-3}) was added to a mixture of **1** and **2** in 3 cm^3 of diethyl ether over a period of 10–15 min at 0 °C. The reaction mixture was stirred for 15 min. Water and crushed ice were added and the organic layer was separated, dried (Na_2SO_4) and analysed by GC. The competitive reduction was performed three times for the set of ketones and the averaged value was shown as the relative reactivity.

^{13}C NMR and GC analyses

^{13}C NMR spectra were obtained with a JEOL JNM FX-90-Q instrument operating at 22.53 MHz or a JNM α-400 instrument operating at 100.13 MHz in the pulse Fourier mode. GC analyses were performed on a Shimadzu model GC-8AIF with carbowax 20M and OV-1 chemical bonded silica capillary column (0.25 mm × 25 m) at 120 and 110 °C, respectively.

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