Quantitative Analyses of Cieplak *vs*. Felkin-Anh Effects in Hydride Reduction of Cyclohexanone

Takatoshi Senju and Shuji Tomoda*

Department of Life and Environmental Sciences, Graduate School of Arts and Sciences, The University of Tokyo,
Komaba, Meguro, Tokyo 153

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Transition structures of LiH addition to cyclohexanone have been optimized at the B3LYP/6-31G* level. The bond lengths of the incipient bond become substantially elongated compared to the previous results at the HF/3-21G level. It has been revealed that both torsional effects and hyperconjugative stabilization are of less importance for the π-facial diastereoselectivity.

The origin of diastereofacial stereoselectivity of hydride reduction of carbonyl compounds has attracted significant interest. Although two transition state models, namely the Felkin-Anh model[1,2] and the Cieplak model,[3] seem to have general acceptance, they have completely different theoretical basis. The former places importance on the torsional strain exerted on the substrate ketones upon the approach of incoming nucleophile and hyperconjugative orbital interaction between the filled orbital of the newly forming bond and the vacant orbital of the *anti*-periplanar vicinal bonds, whereas the latter stresses the importance of hyperconjugation between the filled orbital of the vicinal bond and the vacant orbital of the incipient bond. Apparently, the mechanism of hyperconjugative energy stabilization is reversed between the two models. In spite of the fact that both hypotheses have been supported by a number of experimental and theoretical studies,[4] the question as to which model is more appropriate in general in describing the fundamental factor(s) of π-facial diastereoselection has not been resolved yet.

To gain detailed insight into the origin of π-facial stereoselectivity of hydride reduction of cyclohexanone, we have carried out *ab initio* MO studies of the two transition states of LiH addition to cyclohexanone, for which no correlated level results have been reported to date. The axial and equatorial transition state structures were fully optimized at the B3LYP[5] level using 6-31G* basis sets[6] (Figure 1). Both transition states were characterized with vibrational frequency analyses performed at the same theoretical level, which showed only one imaginary frequency in each transition structure.[7]

Table 1. Calculated total energy, ZPVE,[a] and relative energy between the axial and equatorial transition states

	E / au	ZPVE[a]	ΔE_{rel}[b]
ax-TS	−318.00896	99.05	1.70 (1.85)
eq-TS	−318.00626	99.21	

[a]Zero-point vibrational energy in kcal mol^{-1}. [b]$\Delta E_{\mathrm{rel}} = E_{\mathrm{eq}} - E_{\mathrm{ax}}$ in kcal mol^{-1}. Relative energy with ZPVE energy correction using the recommended scale factor 0.9806 for ZPVE energy correction[14] is shown in parenthesis.

The calculated energy difference of the axial and equatorial transition states is 1.70 kcal mol^{-1}, in very good agreement with the experimental product ratio of $LiAlH_4$ reduction of 4-*tert*-butylcyclohexanone (90:10) (Table 1).[8] In marked contrast to the previous results at the HF/3-21G level reported by Frenking[9] and Houk,[10] the bond length of the incipient H···C bond is significantly elongated to be 2.542 Å in the axial TS (ax-TS) and 2.403 Å in the equatorial TS (eq-TS), indicating the transition state appear much earlier than previously predicted. The angles of attack of hydride with the carbonyl π-plane become closer to the right angle (ax-TS: 89.8°, eq-TS: 92.4°), suggesting that the notion of non-perpendicular attack[2] would not be valid when the transition state becomes much earlier.

Difference of total energies computed with removal LiH from the optimized transition structures, with the cyclohexanone moiety being fixed, would give rough estimate of the torsional strain exerted into the cyclohexanone ring. The calculated relative torsional energy is 0.85 kcal mol^{-1}, favoring the axial transition state. However, this is only just half of the total energy difference between the two transition states. In order to delineate the fundamental cause of the π-facial

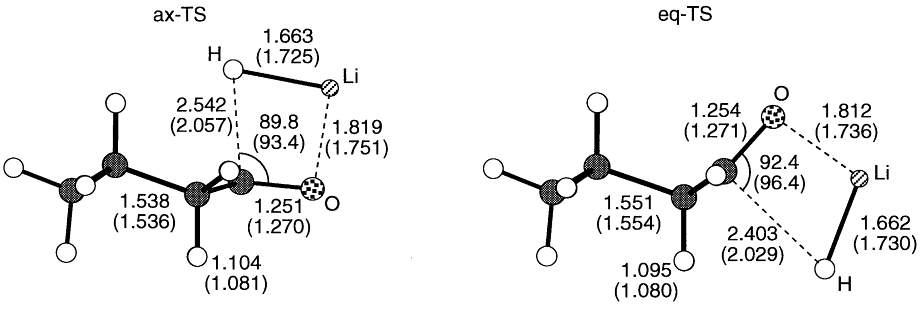

Figure 1. Transition structures of LiH addition to cyclohexanone optimized at the B3LYP/6-31G* level. Selected bond lengths are shown in Å and angles in degree. Data obtained at the HF/3-21G level are shown in parenthesis.

Table 2. Hyperconjugative orbital interaction energy (E_2) corresponding to the Felkin-Anh and the Cieplak model analyzed with NBO method[12]

	E_2 / kcal mol^{-1}	
	Felkin-Anh	Cieplak
ax-TS	0.00	0.66
eq-TS	0.00	0.81

stereoselectivity, the origin of the other half must be accounted for.

Therefore, the hyperconjugative stabilization energy was evaluated with the Natural Bond Orbital (NBO) method of Weinhold et al.[11] implemented on Gaussian 94[6] (Table 2). It is surprising that the Felkin-Anh effect is only marginal in both transition structures. This is due to the significant low electron population of the incipient bond orbital (ax-TS: 0.165, eq-TS: 0.161), which directly related to the second order perturbation energy.[12] On the other hand, the Cieplak effect has significant values, as the donor orbitals are almost filled with two electrons. Therefore, it may be concluded that the Cieplak effect is generally greater than the Felkin-Anh effect when the transition state is earlier and is significantly electron deficient. It should be noted, however, the calculated energy difference in the equatorial TS is somewhat greater than that in the axial TS, indicating hyperconjugative interaction in both sense may be unimportant to the π-facial stereoselectivity of cyclohexanone reduction.

In summary, we have shown that the torsional strain in the cyclohexanone ring alone may not be responsible for the stereoselectivity since its contribution to the total energy difference is no more than half of the total value. Hyperconjugative stabilization in Felkin-Anh sense seems to have nothing to do with the selectivity if the incipient bond was significantly electron deficient. Hyperconjugation in Cieplak sense, which have been shown to have marginal values, are not capable of explaining the remaining part of the energy difference between the axial and equatorial transition states. Therefore, it is clear that some other factors should be taken into account to describe the origin of π-facial stereoselectivity observed in cyclohexanone-related systems properly. Frenking[9] and Dannenberg[13] suggested that the importance of the π^*_{CO} orbital distortion and suggested that the selectivity can be explained with the frontier molecular orbital theory. We are currently investigating the LUMO effect quantitatively, and the results will be reported in a full paper shortly.

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$$E_2 = q_i \frac{F(i,j)^2}{\varepsilon_j - \varepsilon_i}$$

where q_i is the electron population of the ith donor orbital, ε_i and ε_j is the energy level of the ith and jth orbital, and $F(i,j)$ is the (i,j) element of the Fock matrix.[11]

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