Origin of π-Facial Diastereoselection in Hydride Reduction of Piperidones. The Importance of Ground-State Effects

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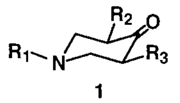
The exterior frontier orbital extension model (the EFOE Model) strongly suggested that the ground-state conformation (steric effects) and the anisotropic frontier orbital (LUMO) extension over π-faces may be the origin of the π-facial diastereoselection in hydride reductions of substituted piperidones.

The origin of π-facial diastereoselection in nucleophilic carbonyl reactions has been intensively discussed for these two decades.[1] Replacement of one carbon atom in the cyclohexanone ring with an electronegative element has long been known to result in intriguing stereochemistries. Possible participation of heteroatoms in reactions across 6-membered ring or further along acyclic chain has been the subject of numerous studies.[2]

Hydride reduction of nitrogen-containing heterocyclic ketones has been studied kinetically by using alkyl-substituted 4-piperidones (**1**) and 3-piperidones (**2**) as model compounds.[2] 4-Piperidone (**1a**) is about 6.2 times more reactive than cyclohexanone in $NaBH_4$ reduction despite that the LUMO levels remain unchanged.[2a-c] **1a** is 320 times more reactive than the acyclic analog, 4-dimethylamino-2-butanone. Replacement of the ring NH group in **1a** with an alkyl group causes 1.5 times rate enhancement. However, substitution at the ring carbons at C-2 and C-6 reduces the rate. The rate enhancement has been explained by transannular dipolar stabilizing interaction between positively charged C-3 and C-5 and the negatively charged carbonyl reaction center in the transition state.[3] Cieplak interpreted these data in terms of his conceptual model involving remote anchimeric assistance of nitrogen lone pair with the electron-deficient carbonyl center.[4] However, his interpretation is questionable since transannular participation of the nitrogen lone pair of **1a** should require an enormous amount of ring-deformation energy (torsional strain), which should be far greater than that gained by the Cieplak mode of anchimeric hyperconjugation. Furthermore, selectivity changes with alkyl substitution at various ring carbons cannot be easily rationalized by his model.



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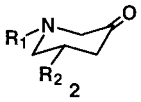

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We have recently shown that the π-facial differences in the transition state effects, such as the torsional strain[5] and the anti-periplanar hyperconjugative stabilization effects,[4,6] should not be responsible for facial stereoselection[7] and proposed a new theoretical model.[8] The new model is based on the simple assumption that the ground-state properties of unsaturated substrates (ketones) should be responsible for facial stereoselection in hydride reduction. Based on the Salem-Klopman equation,[9] the steric effect and the donor-acceptor orbital interactions were quantitatively evaluated as HF/6-31G(d) level. Both quantities were calculated in the exterior area of substrate molecular surface, where reactants initially meet each other.

Table 1 collects the two quantities calculated[10] with the EFOE model at the HF/6-31G(d) level together with the experimental product ratios for methyl-substituted 4-piperidones (**1**). The observation that methyl substitution at the ring carbon(s) (**1a**→**1b**→**1c**; **1d**→**1e**→**1f**) decreases the ratio of axial attack can be rationalized by the steady decrease in the EFOE density over the axial face (*ax*-face) as well as by the steady increase in the EFOE density over the equatorial face (*eq*-face) in this order. Considerable reduction in the PDAS values in the ax-face are evident again in this order, while the corresponding equatorial values show only marginal change. In contrast, methyl substitution at the nitrogen (R_1) (**1a**→**1d**; **1b**→**1e**; **1c**→**1f**) causes: (a) slight increase in the axial PDAS (*ax*-PDAS) value, (b) decrease in the equatorial PDAS (*eq*-PDAS) value, (d) increase in orbital distortion index and (d) reduction in the LUMO level, all of which are consistent with the rate enhancement upon alkyl substitution at the nitrogen. As shown in Figure 1, the experimental facial selectivity (ln(*ax*/*eq*)) of these compounds (**1**) shows a remarkable linear relationship with the λ values ($\lambda = \mathrm{EFOE}(eq)^2 - \mathrm{EFOE}(ax)^2$)[8a,c] calculated according to the EFOE model. Therefore it is not necessary to assume the dipolar interaction mechanism involving the nitrogen lone pair[2a] nor the Cieplak's remote anchimeric hyperconjugation.[4]

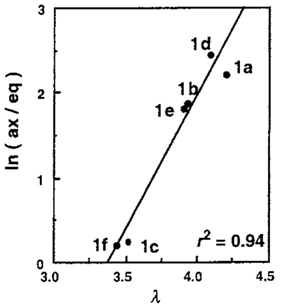


Figure 1. The EFOE plot of **1**.

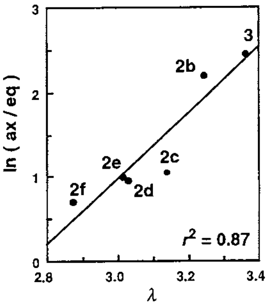


Figure 2. The EFOE plot of **2** and **3**.

Substituted 3-piperidones (**2**) present an intriguing system to test whether or not the remote anchimeric participation of the nitrogen lone pair may operate, since the lone-pair is located closer to the reaction center than that in **1**. Table 2 collects the data of EFOE analysis for **2**. As the size of the substituent in the 6-membered ring becomes larger (Me→*i*-Pr→*t*-Bu), the EFOE densities, the PDAS values,

Table 1. EFOE analysis of 4-piperidones (**1**) [a]

Compds	R_1	R_2	R_3	EFOE Density /%		PDAS /au^3		δ	LUMO[a]	Obs/%[c]
				ax	*eq*	*ax*	*eq*	/%[b]	/eV	*ax* : *eq*
1a	H	H	H	2.069	0.284	22.4	44.6	53.1	4.372	90 : 10
1b	H	H	Me	2.009	0.312	17.3	46.7	52.6	4.368	86 : 14
1c	H	Me	Me	1.906	0.332	14.1	46.4	52.4	4.370	56 : 44
1d	Me	H	H	2.038	0.269	23.0	44.5	53.4	4.324	92 : 8
1e	Me	H	Me	1.997	0.287	17.6	46.3	52.9	4.323	86 : 14
1f	Me	Me	Me	1.879	0.302	14.3	45.4	52.6	4.327	55 : 45

[a]HF/6-31G(d). [b]Orbital distortion index. Positive sign indicates distortion toward the axial direction.[8a] [c]Ref 2a. $NaBH_4$ reduction using substituted 3,5-*eq*,*eq*-diphenyl-4-piperidones.

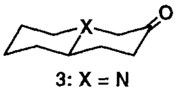
Table 2. EFOE analysis for the hydride reduction of alkyl-substituted 3-piperidones (**2**), 3-oxoquinolizidine (**3**), and *trans*-2-decalone (**4**) [a]

Compds	R_1	R_2	EFOE Density /%		PDAS /au^3		δ	LUMO	Obs/%[c]
			ax	*eq*	*ax*	*eq*	/%[b]	/eV	*ax* : *eq*
2a	H	H	1.851	0.171	42.8	33.4	55.3	4.395	–
2b	Me	Me	1.816	0.237	40.1	34.4	49.7	4.484	90 : 10
2c	Et	Me	1.786	0.233	39.5	34.4	50.9	4.545	74 : 26
2d	*i*-Pr	Me	1.755	0.261	34.0	35.1	49.2	4.569	73 : 27
2e	*t*-Bu	Me	1.754	0.255	36.6	33.8	50.5	4.549	72 : 28
2f	*t*-Bu	*t*-Bu	1.710	0.231	36.3	32.9	50.4	4.567	67 : 33
3	–	–	1.864	0.211	38.2	35.2	51.8	4.430	92 : 8[d]
4	–	–	1.820	0.289	18.9	46.9	51.0	4.466	79 : 21[d]

[a]HF/6-31G(d). [b]Orbital distortion index. Positive sign indicates distortion toward the axial direction.[8a] [c]$NaBH_4$ Ref. 2. [d]$NaBH_4$ in 2-propanol. Ref.11.

and the *eq* : *ax* ratio are all reduced. The PDAS values in the *ax*-face of **2** (36.3 – 42.8 au^3) are much greater than those for 4-piperidones (**1**) (14.1 – 23.0 au^3) because of the lack of one of the axial hydrogens at C-3 and C-5 in the 6-membered ring. Consequently the magnitude of the EFOE density over the *ax*-face for **2** (1.710 – 1.851%) is slightly smaller than those for **1** (1.879 – 2.069%). A reasonable linear relationship between the λ values derived from the EFOE model[8] and the experimental product ratio (ln(*ax*/*eq*)) was again obtained (Figure 2).

The linear correlations for both 3- and 4-piperidones (Figures 1 and 2) indicate that neither the dipolar interaction mechanism[2a] nor the Cieplak model[4] might be necessary to explain the observed trends of the reaction rates and the product ratios. Recently Senda reported intriguing kinetic and stereochemical studies of 3-oxoquinolizidine (**3**).[11] **3** is 1.3 times or 4 times more reactive than its carbon analog *trans*-2-stereoselection for the reduction with $NaBH_4$. The significant increase both in the EFOE density (1.846%) and in the PDAS value (38.2 au^3) in the *ax*-face of **3** compared with those of the corresponding π-face of **4** (1.820%; 18.9 au^3) is in good agreement not only with the rate enhancement (**3**/**4** = 1.3 – 4) but with the enhanced facial diastereoselection of **3** (*ax*/*eq* = 92/8 for **3** and 79/21 for **4**; $NaBH_4$ in 2-propanol). Interestingly, the EFOE plot shown in Figure 2 nicely accommodates the data of **3** (r^2 = 0.87).



3: X = N
4: X = CH

In conclusion, the EFOE model strongly suggests that subtle changes in the kinetic behavior of a compound may arise chiefly from a marginal ground-state deformation, which results in unignorable changes in surface molecular orbitals (frontier orbitals) and steric effects.

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