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Reversal of π -facial diastereoselection in the hydride reduction of selenanones. Further application of the exterior frontier orbital extension model

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Abstract

Reversal of π -facial diastereoselection in the hydride reduction of 2-phenyl-4-selenanone (**1b**) and 6-phenyl-3-selenanone (**2b**) has been rationalized by the exterior frontier orbital extension model (EFOE model). © 2000 Elsevier Science Ltd. All rights reserved.

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It has long been known that replacement of C3 of a cyclohexanone ring with a sulfur atom causes diastereofacial reversal in nucleophilic carbonyl addition. Two remarkable examples have been reported.^{1,2} While common six-membered ketones containing one or two second-row heteroatom(s) (O, N) undergo preferential axial attack, a predominant equatorial attack has been observed for the nucleophilic addition to 3-thianones¹ and 1,3-dithian-5-one.² The unusual facial diastereoselection has been explained in terms of the transition state hyperconjugative stabilization model of Cieplak assuming the order of the electron-donating property of antiperiplanar bond(s) to be C–S > C–H > C–C.³

Recently, we proposed a new theoretical model (the exterior frontier orbital extension model; the EFOE model) to explain and predict π -facial diastereoselection of the nucleophilic carbonyl addition.⁴ The simple semi-quantitative model has been successfully applied to a variety of cyclic ketones⁵ including 1,3-diheteran-5-ones (heteroatom = O or S).⁶ Herein, we show by theory and experiment that facial diastereoselection of selenanone reduction is dictated by ground-state properties of the ketones rather than by transition state effects which have been emphasized in the previous intuitive models.^{3,7}

The model compounds chosen are 4-selenanones (**1**) and 3-selenanones (**2**). The EFOE model predicts opposite π -facial diastereoselection for the model selenanones: preferential axial attack

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for **1** and equatorial attack for **2** (RHF/6-31G(d) level⁸ using the Huzinaga basis set for selenium⁹). This model is based on the simple assumption that the π -facial difference in the reaction driving force must be the origin of the π -facial diastereoselection. It is assumed that the π -facial difference in frontier orbital (LUMO) and conformational (steric) properties of a ground-state ketone should be the origin of the facial selection. Two quantities corresponding to the first term (exchange repulsions; steric effect) and the third term (donor–acceptor stabilizing interactions) of the Salem–Klopman equation¹⁰ were defined in the exterior of the van der Waals surface of a ketone substrate: π -plane-divided accessible space (PDAS)¹¹ and π -plane-divided exterior frontier orbital electron density (EFOE density).¹²

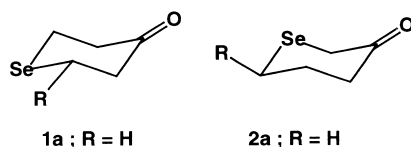


Table 1 collects the data of EFOE analysis for the model selenanones along with those of cyclohexanone for comparison. It is clear that both EFOE density and PDAS values of 4-selenanones (**1a**, **1b**) behave in a manner similar to those of cyclohexanone except that the former prefers greater equatorial attack than the latter due to larger values of EFOE density (0.482%, 0.470%) and PDAS (53.0 au³, 55.8 au³) in the equatorial face of **1** than those of cyclohexanone (EFOE density = 0.249%; PDAS = 47.2 au³). Hence, the diastereoselection of 4-selenanones is orbital-controlled rather than steric-controlled like that of cyclohexanone.¹² On the other hand, the magnitudes of the EFOE densities of 3-selenanones (**2a**, **2b**) over the axial face are lower (0.125%, 0.297%) than those of the equatorial face (0.568%, 0.459%). The origin of such reversal of the order of the values of the EFOE density compared with those of cyclohexanone may be due to significant out-of-phase (antibonding) mixing of the selenium lone pair orbital to the $\pi^*_{C=O}$ orbital thus causing appreciable reduction in the EFOE density over the axial face of the carbonyl plane of **2a**, whereas there is no such significant antibonding contribution in **1a** (Fig. 1). Furthermore, the equatorial faces of 3-selenanones (PDAS = 57.9 au³ for **2a**, 59.2 au³ for **2b**) are much

Table 1
EFOE analysis of the $\pi^*_{C=O}$ orbitals of 4-selenanones (**1**) and 3-selenanones (**2**)^a

Comps.	EFOE Density (%)		PDAS (au ³)		Hydride Reagents	Obs. ax : eq ^c
	ax	eq	ax	eq		
Cyclohexanone	1.940	0.249	19.4	47.2	LiAlH ₄	92 : 8 ^c
1a	1.960	0.482	14.4	53.0	–	–
1b ^b	1.722	0.470	11.7	55.8	LiAlH ₄	80 : 20 ^d
					LiBH ₄	81 : 19 ^e
					NaBH ₄	68 : 32 ^e
2a	0.125	0.568	13.0	57.9	–	–
2b ^b	0.297	0.459	12.2	59.2	LiAlH ₄	10 : 90 ^d
					LiBH ₄	12 : 88 ^e
					NaBH ₄	5 : 95 ^e

^a HF/6-31(d)//HF/6-31G(d) with Huzinaga basis set for Se. ⁹ LUMO corresponds to $\pi^*_{C=O}$ unless otherwise indicated. ^b LUMO+2 corresponds to $\pi^*_{C=O}$. ^c Data of 4-*tert*-butylcyclohexanone. D. C. Wigfield and D. J. Phelps, *J. Am. Chem. Soc.*, 1974, **94**, 543. ^d In diethyl ether at 0°. ^e In MeOH at 22°.

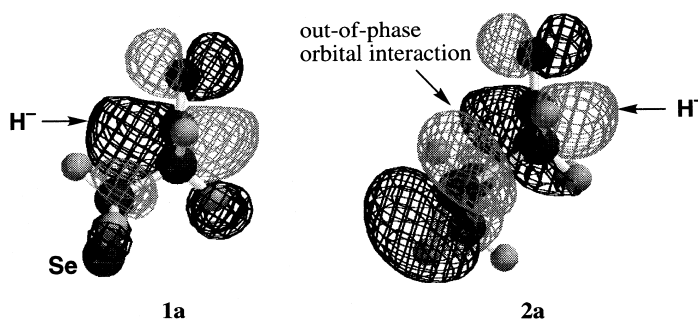
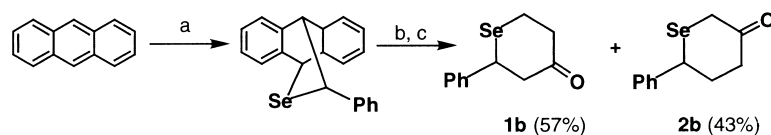


Figure 1. Side views of the LUMOs of 4-selenanone (**1a**) and 3-selenanone (**2a**) (HF/3-21G*)

more sterically relaxed than the axial faces (PDAS = 13.0 au³ for **1a**, 12.2 au³ for **1b**). Consequently, the facial diastereoselection of 3-selenanones is both orbital- and steric-controlled. It is noted that phenyl substitution at C4 does not affect this conclusion. Hence, the EFOE model predicts moderate axial preference for **1** and high equatorial preference for **2**. The following experimental results strongly support the above conclusions drawn from the EFOE analysis.

The syntheses of conformationally anchored selenanones (**1b** and **2b**) began with the synthesis of the Diels–Alder adduct between anthracene and selenobenzaldehyde generated using bis-(dimethylaluminum)selenide¹³ in the presence of benzaldehyde (Scheme 1). The labile selenoaldehyde, thermally generated by the retro-Diels–Alder reaction of the adduct, was trapped in situ with 2-trimethylsiloxy-1,3-butadiene to afford **1b** and **2b** in a 57:43 ratio after hydrolysis with trifluoroacetic acid. Each ketone was reduced with three common hydride reagents (LiAlH₄, LiBH₄, NaBH₄). Their diastereoselectivities were determined by ¹H NMR at 500 MHz.¹⁴ The last column of Table 1 shows the results. It is interesting to note that 4-selenanone (**1b**) behaves normally to undergo predominant axial hydride attack (68–81%), whereas an equatorial hydride attack is favored for 3-selenanone (**2b**) (88–95%). The latter observation is surprising since one might a priori expect steric relaxation owing to the lack of one of the axial hydrogens at C3 and C5 of the cyclohexanone moiety. Among the three hydrides employed, NaBH₄ seems the most sterically demanding (less axial attack).



Scheme 1. Synthesis of **1b** and **2b**. (a) PhCHO, (Me₂Al)₂Se, toluene–dioxane, 100°C, 5 h (82% yield); (b) 2-trimethylsiloxy-1,3-butadiene, toluene, 100°C, 5 h (78% yield); (c) CF₃CO₂H, 25°C, 30 min (95% yield).

To evaluate whether or not the antiperiplanar hyperconjugative stabilization effects (hereafter called ‘the AP effect’) in the transition state might dictate in the facial diastereoselection in these systems, transition structures of LiAlH₄ reduction were located using the two parent selenanones (**1a** and **2a**) at the B3LYP/6-31G(d) level⁸ using the Huzinaga basis for Se.¹⁵ The transition states (TS) of **1a** show significant differences in percent elongation (%BE)¹⁶ of the antiperiplanar bonds

vicinal to the incipient bond (C3–H_{ax}/C5–H_{ax} for ax-TS or C3–C2/C5–C6 for eq-TS) due to the AP effect between the ax-TS (%BE = +0.04%) and eq-TS (%BE = +0.05%) relative to the ground-state **1a** optimized at the same level. The magnitudes of the AP effects are virtually the same over both π -faces. This is not consistent with the observed facial selection of **1a**. In consonant with these results, the difference in NBO bond population for the antiperiplanar bonds between the transition state and the ground state (Δ BP)¹⁷ was $-0.0076 e$ (electrons) for ax-TS and $-0.0074 e$ for eq-TS (B3LYP/6-31G(d)). Fig. 2 shows the LiAlH₄ transition structures of 3-selenanone (**2a**). In agreement with the experiment, the ZPVE-corrected total electronic energy of the eq-TS is indeed lower by 1.2 kcal mol⁻¹ than that of the ax-TS. The AP effects evaluated by %BE and Δ BP, averaged for the two antiperiplanar bonds (C2–H_{ax}/C4–H_{ax} for ax-TS or Se1–C2/C4–C5 for eq-TS), are +0.21%/+0.20% and $-0.0150 e$ / $-0.0170 e$ for ax-TS and +0.13%/+0.03% and $-0.0075 e$ / $-0.0057 e$ for eq-TS. Evidently, the AP effects operate against the observed diastereoselection in **2a**. Hence, the AP effects cannot account for the observed facial stereoselectivity of **1b** and **2b**.

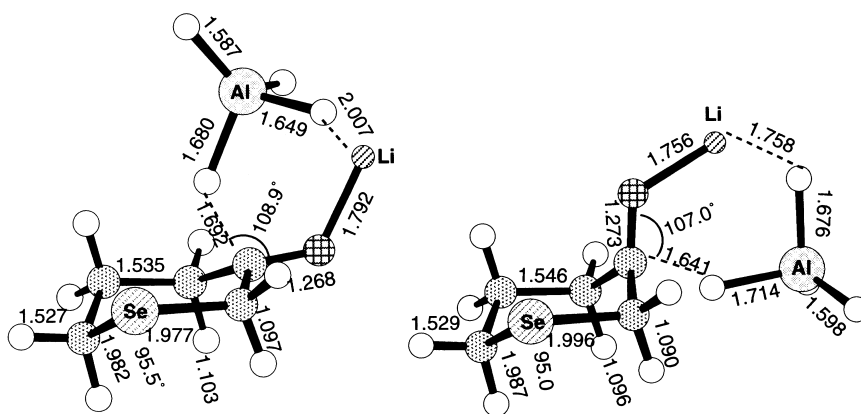


Figure 2. Transition structures of LiAlH₄ reduction of 3-selenanone (**2a**) (B3LYP method with Huzinaga basis for Se⁹ and 6-31G(d) basis sets for other elements). (Left: ax-TS; Right: eq-TS; bond lengths in Å and bond angles in degrees)

These conclusions are entirely consistent with our previous ones for the LiAlH₄ reductions of cyclohexanone, adamantan-2-ones, 1,3-diheteran-4-ones (heteroatom = O, S).^{5,6,18} It should be stressed here again that the AP effects are regarded merely as a major internal energy relaxation mechanism that operates against the direction of the bond formation process.³

In conclusion, it is demonstrated that the ground-state steric and frontier orbital properties must be responsible for π -facial diastereoselection in the reduction of selenones.

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11. PDAS (expressed in au; atomic unit = 0.529 angstrom) is defined as the π -plane-divided exterior space nearest to the carbonyl carbon. Integration is carried out up to 5.0 au from the van der Waals surface of the molecule. Tomoda, S.; Senju, T. *Chem. Commun.* **1999**, 621.
12. EFOE density is defined as the π -plane-divided exterior electron density of the frontier orbital (FMO; in the present case $\pi^*_{C=O}$) integrated over the subspace Ω satisfying the following condition: the absolute total value of the wave functions belonging to the carbonyl carbon makes a maximum contribution to the total value of the FMO wave function at the point so that the driving force vector on hydride is maximally directed toward the reaction center. The values of the EFOE density are expressed in percentages by normalizing the FMO wave function (Ψ_{FMO}) to 100:

$$\text{EFOE density (\%)} = 100 \times \int \Psi_{FMO}^2 d\Omega$$
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14. Stereochemical assignments were made by the chemical shift of the axial proton at C2 (equatorial alcohol: $\delta = 4.21$, axial alcohol: $\delta = 4.60$ for **1b**, and equatorial alcohol: $\delta = 2.71$, axial alcohol: $\delta = 2.79$ for **2b**).
15. Total electronic energy (E), imaginary frequency (ν_i), and incipient bond distance (d) for the transition states calculated with Gaussian 94¹¹ at the B3LYP/6-31G(d) level; **1a**: ax-TS; $E = -2922.449418$ au, $\nu_i = -351.6$ cm⁻¹, $d = 1.523$ Å; eq-TS; $E = -2922.448321$ au, $\nu_i = -380.0$ cm⁻¹, $d = 1.584$ Å; **2a**: ax-TS; $E = -2922.446505$ au, $\nu_i = -369.1$ cm⁻¹, $d = 1.692$ Å; eq-TS; $E = -2922.448385$ au, $\nu_i = -221.5$ cm⁻¹, $d = 1.641$ Å.
16. Percent bond elongation (%BE) = $(\Delta r/r_S) \times 100$, where Δr = the difference in the bond lengths between the vicinal antiperiplanar bond in the transition state (r_{TS}) and the corresponding bond of starting ketone (r_S); $\Delta r = r_{TS} - r_S$.
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