Origin of π-Facial Diastereoselection in Nucleophilic Addition to 1,3-Diheteran-5-ones (Heteroatom = O, S). Theoretical Evidence for the Importance of Ground-State Effects

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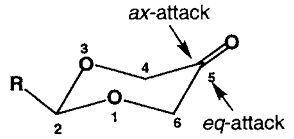
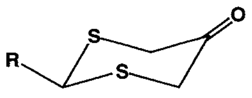
The exterior frontier orbital extension model (the EFOE Model) strongly suggested that reversal of π-facial diastereoselection in nucleophilic additions of 1,3-diheteran-5-ones (heteroatom = O or S) may originate from the unique ground-state conformation and the π-facial difference in the LUMO extension around the carbonyl carbon rather than from transition state effects.

The unique reversal of face selection in nucleophilic carbonyl additions of 2-phenyl-1,3-dioxan-5-one (**1a**) and 2-phenyl-1,3-dithian-5-one (**2a**) has been the subject of active debate since early 1980.[1] Jochims *et al.* reported $LiAlH_4$ reduction of **1a**.[2] The product ratio of the equatorial and axial alcohol was 94 : 6, indicating slightly higher axial selectivity than 4-*t*-butylcyclohexanone (ax : eq = 92 : 8).[3] Surprisingly the Grignard reaction of **1a** afforded almost exclusive equatorial alcohol *via* axial attack (*ax*-attack) (96–98%) even when bulky reagents, such as *i*-PrMgI or *t*-BuMgI, were employed. Jochims interpreted these unusual results in terms of reduced steric hindrance in the axial face of **1a** owing to the lack of two axial hydrogens at the 3- and 5-positions in the 6-membered ring. Interestingly, their subsequent studies using the sulfur analog **2a** indicated complete stereochemical reversal in nucleophilic additions of **2a** with $LiAlH_4$ and Grignard reagents (85–93%).[4]



1a : R = Ph
1b : R = H
1c : R = *t*-Bu



2a : R = Ph
2b : R = H
2c : R = *t*-Bu

Wu and Houk reported MM2 force field calculations of the parent compounds (**1b** and **2b**). They proposed the torsional strain to be responsible for the observed stereochemistry.[5] Cieplak interpreted these results according to his assumption of the order for the electron-donating abilities of the *anti*-periplanar bonds (C–S > C–H > C–C > C–O).[6] Wu and Houk disclosed criticism against Cieplak's hypothesis to propose again the torsional strain model combined with strong emphasis on the electrostatic solvent interaction.[7] Herein we show theoretical evidence which strongly supports our previous conclusions on the facial diastereoselection of cyclohexanone reduction.[11]

The transition states for the reduction of **1b** and **2b** with $LiAlH_4$ were calculated at the B3LYP/6-31+G(d) level.[8] Relative ZPVE(zero point vibrational energy)-corrected total electronic energies between the axial transition state (*ax*-TS) and the equatorial one (*eq*-TS) for **1b** and **2b** were 2.44 and –2.06 kcal mol^{-1}, respectively, in agreement with the experimental stereoselectivity for **1a** and **2a**. The difference in the total electronic energy of the bare 6-membered ring moiety (distorted 1,3-diheteran-2-one moiety) between *ax*-TS and *eq*-TS was found to be 5.89 kcal mol^{-1} for **1b** and 4.06 kcal mol^{-1} for **2b** (MP2/6-31+G(d)), indicating that the torsional strain is greater in *eq*-TS than in *ax*-TS in both cases. Substantially greater deformation of the 6-membered ring in *eq*-TS of **2b** (4.06 kcal mol^{-1}) is surprising because this is not consistent with the observed facial stereoselection of **2a**.[4] This clearly indicates that no logical basis can be found to single out the torsional strain of the substrate ketone moiety alone to discuss π-facial diastereoselection.

Theoretical evidence against the Cieplak model[6] has been obtained by natural bond orbital (NBO) analysis.[9] The $LiAlH_4$ transition states of **1b** show significant difference in percent elongation[10] of the *anti*-periplanar bonds vicinal to the incipient bond (C4–H4ax/C6–H6ax for *ax*-TS or C4–O3/C6–O1 for *eq*-TS) due to the *anti*-periplanar hyperconjugative stabilization effect (hereafter called "the AP effect") between the *ax*-TS (+0.11%) and *eq*-TS (+0.62%) relative to the ground-state **1b** optimized at the same level. The relative magnitude of these AP effects is clearly inconsistent with the observed facial selection for **1a**.[4] In consonant with these results, the difference in NBO bond population (ΔBP)[9] for the *anti*-periplanar bonds between the transition state and the ground state was –0.0068 *e* (electrons) for *ax*-TS and –0.0081 *e* for *eq*-TS. The greater ΔBP for the latter is again consistent with the greater AP effect in *eq*-TS. Consequently, the Cieplak model cannot be employed to explain the observed facial stereoselection for **1**. The same arguments can be made for the sulfur analogs (**2**). The percent elongation[10] of the vicinal *anti*-periplanar bonds (C4–H4ax/C6–H6ax for *ax*-TS or C4–S3/C6–S1 for *eq*-TS) for *ax*-TS and *eq*-TS for **2b** were +0.25% and –0.11%, respectively. The values of ΔBP for the *anti*-periplanar bonds, calculated for the $LiAlH_4$ transition states of **2b**, were –0.0188 *e* for *ax*-TS and –0.0002 *e* for *eq*-TS. Hence, the AP effects are apparently operating against the observed stereoselectivities both in **1b** and **2b** as observed in the case of cyclohexanone reduction.[11] We emphasize here again that the AP effects are regarded as a major internal energy relaxation mechanism that operates against the direction of the bond formation process.

The above theoretical results strongly suggests that the facial differences in the transition state effects do not necessarily agree with observed stereoselectivities. Accordingly we propose here again[11,12] that the ground state conformational and electronic properties may be responsible for the unique stereochemical reversal observed for **1a** and **2a**. Table 1 shows the analysis based on our new theoretical model for π-facial stereoselection; "the exterior frontier orbital extension model" (the EFOE model)[13] using the $\pi_{C=O}{}^*$ orbitals of the three model compounds for each 1,3-diheteran-5-one series along with experimental stereoselectivities including the recent results of **1c**.[14] Both the EFOE density (π-plane-divided exterior frontier orbital electron

Table 1. EFOE Analysis of **1** and **2** and Observed Stereoselectivity [a]

Compd.	EFOE Density /% [b]		PDAS /au [3c]		δ /% [d]	Obs. /%		
	ax	*eq*	*ax*	*eq*		Compd	Reagent	*ax* : *eq*
1a [e]	1.279	0.245	67.6	26.5	40.7	**1a** [f]	$LiAlH_4$	94 : 6
1b	1.739	0.243	71.2	26.2	40.4	**1a** [f]	RMgI [h]	96~98 : 4~2
1c	1.750	0.241	70.2	26.2	40.2	**1c** [g]	$LiAlH_4$	89 : 11
						1c [g]	$NaBH_4$	97 : 3
2a [e]	0.299	0.882	17.9	55.4	–17.1	**2a** [f]	$LiAlH_4$	15 : 85
2b	0.277	0.834	18.4	54.6	–20.5	**2a** [f]	RMgI [h]	7~11 : 93~89
2c	0.278	0.854	19.0	54.1	–14.2			

[a] Calculated at the HF/6-31G(d) level using the EFOE program[13] after structure optimization with Gaussian 94[15] at the same level. [b] π-Plane-divided exterior frontier orbital electron density. [c] π-plane-divided accessible space. [d] Orbital distortion index.[12] Positive sign indicates distortion toward the axial direction. [e] LUMO+2. [f] Ref. 2 and 4. [g] Ref. 14. [h] R = Me, *i*-Pr, *t*-Bu.

density)[12] and the PDAS value (π-plane-divided accessible space)[13] predict correctly the experimentally observed stereochemical reversal of compounds **1a** and **2a**. In particular, the π-facial differences in the PDAS values between these substrates are significant, clearly indicating that the steric environment around the carbonyl carbons of these ketones (**1** and **2**) is opposite with each other. This is quite surprising because the two heteroatoms belonging to the same family in the periodic table exhibit exactly the opposite conformational property around the carbonyl.

Figure 1 depicts the side views of the conformations and the LUMOs of **1b** and **2b** optimized at the HF/6-31G(d) level. It is seen that the conformation of **1b** around the carbonyl is nearly planar (torsion angle along O=C5–C6–O1; τ = 158.5°) compared with cyclohexanone (torsion angle along O=C1–C2–C3; τ = 131.4°). The ring-flattening causes the enormous steric relaxation at the axial face (PDAS in the axial region = ~ 70 au^3). In contrast, the geometry of **2b** around the carbonyl is significantly puckered (torsion angle along O=C5–C6–S1; τ = 115.9°), which leads to considerable increase in the PDAS values at the equatorial face (~ 55 au^3). The PDAS values for the *ax*-face of **2** (~ 18 au^3), which lack the axial hydrogens at the 1- and 3-positions, are nearly the same as the axial PDAS of cyclohexanone (19.4 au^3). The LUMO of **1b** is more expanded into the *ax*-face than in the equatorial region, where significant out-of-phase (antibonding) contribution at H4ax and H6ax is observed with negligible contribution from the lone-pair orbitals in the *ax*-face. In sharp contrast, the LUMO of **2b** shows significant antibonding contribution of the lone-pair orbital in the *ax*-face with nearly zero contribution at H4ax or H6ax in the *eq*-face.

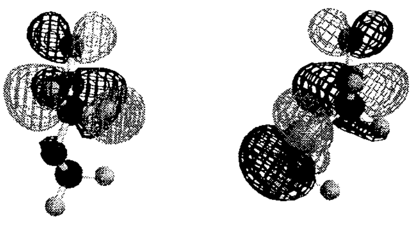

1b **2b**

Figure 1. Side views of the LUMOs of **1b**, and **2b**.

The EFOE data are consistent with the experimental facial stereoselectivity of sterically demanding Grignard reagents, such as *i*-PrMgI, which shows nearly the same selectivity as hydride reduction. It is evident from Table 1 that these theoretical results should not be affected by the substituent at C2 (Ph, H, or *t*-Bu) in 1,3-diheteran-5-ones. It is therefore concluded that marked conformational differences should be responsible for the reversal of facial stereoselection in these cases. Full details of its origin will be reported in due course.

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References and Notes

1 B. W. Gung, *Tetrahedron*, **52**, 5263 (1996).
2 J. C. Jochims, Y. Kobayashi, and E. Skrzelewski, *Tetrahedron Lett.*, **1974**, 571.
3 D. C. Wigfield and D. J. Phelps, *J. Am. Chem. Soc.*, **94**, 543 (1974); D. C. Wigfield and D. Phelps, *J. Org. Chem.*, **41**, 3789 (1976).
4 Y. M. Kobayashi, J. Lambrecht, J. C. Jochims, and U. Burkert, *Chem. Ber.*, **111**, 3442 (1978).
5 Y-D. Wu and K. N. Houk, *J. Am. Chem. Soc.*, **109**, 908 (1987).
6 A. S. Cieplak, *J. Am. Chem. Soc.*, **103**, 4540 (1981).
7 Y-D. Wu, K. N. Houk, and M. N. Paddon-Row, *Angew. Chem.*, **104**, 1087 (1992); *Angew. Chem., Int. Ed. Engl.*, **31**, 1019 (1992); Y-D. Wu and K. N. Houk, *J. Am. Chem. Soc.*, **115**, 10992 (1993).
8 Total electronic energy (*E*), imaginary frequency (v_i), and incipient bond distance (*d*) for the transition states calculated with GAUSSIAN 94[15] at the B3LYP/6-31+G(d) level: **1a** (*ax*-TS; *E* = -634.077257 au, v_i = -290.7 cm^{-1}, *d* = 1.8618 Å; *eq*-TS; *E* = -634.073362 au, v_{ii} = -340.3 cm^{-1}, *d* = 1.7156 Å); **2a** (*ax*-TS; *E* = -1280.023831 au, v_i = -234.6 cm^{-1}, *d* = 1.9522 Å: *eq*-TS; *E* = -1280.027120 au, v_i = -383.3 cm^{-1}, *d* = 1.5441 Å).
9 A. E. Reed, L. A. Curtiss, and F. Weinhold, *Chem. Rev.*, **88**, 899 (1988).
10 Percent Elongation = (Δr / r_S) × 100, where Δr = the difference in the bond lengths between the vicinal *anti*-periplanar (AP) bond in transition state (r_{TS}) and the corresponding bond of starting ketone (r_S); $\Delta r = r_{TS} - r_S$. Both structures were optimized at the same level of calculation method and basis set (B3LYP/6-31+G(d)).
11 S. Tomoda and T. Senju, *Chem. Commun.*, **1999**, 423.
12 S. Tomoda and T. Senju, *Tetrahedron*, **53**, 9057 (1997).
13 S. Tomoda, *Chem. Rev.*, **99**, 1243 (1999).
14 Y. Senda, H. Sakurai, and H. Itoh, *Bull. Chem. Soc. Jpn.*, **72**, 285 (1999).
15 GAUSSIAN 94 (Revision D.1 and E.2); Gaussian, Inc., Pittsburgh, PA, 1997.