Origin of π-Facial Stereoselectivity in Nucleophilic Addition. Application of the Exterior Frontier Orbital Extension Model to Substituted Bicyclo[2.2.1]heptan-7-ones

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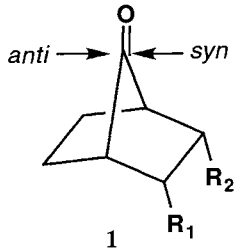
The exterior frontier orbital extension model (EFOE model) has shown that π–facial stereoselection in nucleophilic additions of 2,3-*endo,endo*-disubstituted bicyclo[2.2.1]heptan-7-ones (**1**) is dictated by the three terms of the Salem-Klopman equation – steric effect, electrostatic interaction and orbital interaction.

The origin of diastereoselection of addition reactions to unsaturated organic substrates continues to attract lively discussion.[1] Since Cieplak's proposal of his conceptual model in 1981,[2] most discussions are focused on the importance of transition state stabilization arising from the *anti*-periplanar hyperconjugative stabilization effect involving the incipient bond (hereafter called "the AP effect").[1,3]

Recently we reported quantitative analysis of the first transition states of carbonyl reduction with $LiAlH_4$ using the natural bond orbital (NBO) analysis[4] and proposed that the transition state effects, such as torsional strain and the AP effect, are not essential for π-facial diastereoselection of nucleophilic carbonyl additions of cyclohexanones and adamantanones.[5] It was found that the incipient bond is electron-deficient, showing the preponderance of the Cieplak effect[2] over the Felkin-Anh effect.[3] Surprisingly they often operate against observed facial stereoselectivity and their facial differences are generally marginal in transition state. To this end, we have recently proposed a new theoretical approach: the exterior frontier orbital extension model (EFOE model).[6] This model is designed to identify quantitatively the two terms – the first term (the exchange repulsion; steric effect) and the third term (the orbital interaction; donor-acceptor stabilizing interaction) – of the Salem-Klopman equation.[7]

In the present paper, we first show another example of a transition state where the relative magnitude of the AP effect does not explain observed π-facial stereoselection. We then show by applying the EFOE model[6] that the electrostatic interaction between reactants, represented as the second term in the Salem-Klopman equation,[7] may be another important factor for π-facial stereoselection of substrates carrying an electron-withdrawing substituent. The model compounds chosen are 2,3-*endo,endo*-disubstituted bicyclo[2.2.1]heptan-7-ones (**1**).



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Facial stereoselection of **1** has been extensively studied by Mehta (Tables 1; last column).[8] The *anti*-stereoselectivities were observed with the exceptions of compounds having electron-withdrawing groups, such as carbonyl, cyano, and ethynyl. When Mehta first reported these results in 1990, he rationalized the data in terms of the Cieplak model.[8b] This work was theoretically followed immediately by Houk, who showed by *ab initio* calculation that electrostatic interaction might be important in the system having CO_2Me groups.[9] In his later elaborate work, Mehta emphasized the importance of both orbital and electrostatic interactions.[8a]

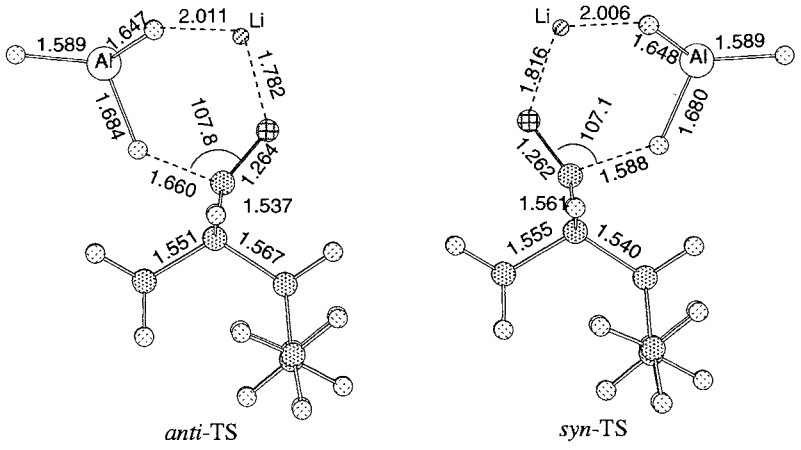

Figure 1. Transition states of $LiAlH_4$ reduction of 2,3-*endo,endo*-diethylbicyclo [2.2.1]heptan-7-one (**1a**) optimized at the B3LYP/6-31G(d) level. Distances are in Å and angles are in degree.

Table 1. EFOE Analysis of the LUMO of 2,3-*endo,endo*-R^1,R^2-Bicyclo[2.2.1]heptan-7-ones (**1**) [a]

R^1, R^2	EFOE Density / %		PDAS / au^3		ω / au^{3c}	Obs. / %[d] $NaBH_4$	Obs. / %[d] MeLi
	anti	*syn*	*anti*	*syn*		*anti* : *syn*	*anti* : *syn*
H, H	1.206	1.209	17.2	17.2	0.0	–	–
Me, Me	1.282	0.753	16.5	12.9	3.6	55 : 45	–
Et, Et (**1a**)	1.371	0.765	17.0	12.8	4.2	80 : 20	83 : 17
CH_2=CH–, CH_2=CH–	0.821	0.239	16.5	13.0	3.5	64 : 36	73 : 27
$MeOCH_2$–, $MeOCH_2$–	1.316	0.806	15.6	14.3	1.3	60 : 40	66 : 34
MeO_2C–, MeO_2C–[b]	1.217	0.385	15.4	14.3	1.1	16 : 84	<10:>90
MeO_2C–, H	0.855	1.456	16.3	16.1	0.2	32 : 68	–
CN–, H	1.179	0.986	16.5	16.5	0.0	18 : 82	–
HC≡C–, H	1.217	0.974	16.9	15.9	1.0	31 : 69	–
$-CH_2-$	1.441	0.900	17.0	18.7	–1.7	–	95 : 5
$-CH_2CH_2CH_2-$	1.326	0.885	16.3	12.8	3.5	76 : 24	86 : 14
$-CH_2CH$=CH–	1.166	0.434	16.6	14.0	2.6	63 : 37	78 : 22
–NPh–	0.892	1.271	15.8	22.4	–6.6	–	0 : 100[e]
–NH– (H-in)	1.227	0.880	18.1	18.2	–0.1	*anti*[f]	
–NH– (H-out)	1.394	1.181	16.3	21.9	–5.6	*syn*[f]	
–O–	0.947	1.202	16.7	22.7	–6.0	*syn*[f]	
F, F	1.269	1.569	15.7	18.6	–2.9	*syn*[f]	

[a]HF/6-31G(d). [b]Calculated using the (in,in) conformer. [c]ω = PDAS (*anti*) – PDAS(*syn*). [d]Reduction with hydride unless otherwise specified. Ref. 8 unless otherwise noted. [e]P. G. Gassman, J. H. Shaffhousen, and P. W. Raynolds, *J. Am. Chem. Soc.* **1982**, *104*, 6408 (1982). [f]Predicted by transition state calculation at the HF/6-31G(d) level.

Figure 1 depicts the two transition states (TS) of the reduction of 2,3-*endo,endo*-diethyl-bicyclo[2.2.1]heptan-7-ones (**1a**) with $LiAlH_4$ (LAH) optimized at the B3LYP/6-31G(d) level. The *anti*-TS (ν_t = –358.7 cm^{-1}) is more stable by 0.6 kcal mol^{-1} than the *syn*-TS (ν_t = –352.4 cm^{-1}) in agreement with experiment (*anti* : *syn* = 79 : 21).[8b] The % elongation of the *anti*-periplanar bonds relative to the ground-state **1a** optimized at the same level was 0.46% and 0.50% for *anti*- and *syn*-TS, respectively. Since the experimental facial selection of LAH reduction of **1a** was considerably different from unity,[8b] practically the same magnitude of the AP effects for both TS implied that the AP effect may not be responsible for facial stereoselection. In agreement with this, NBO analysis of these TS showed that the reduction in the bond populations of the *anti*-periplanar bonds were 0.012*e* (*anti*-TS) and 0.014*e* (*syn*-TS).

Table 1 collects the data of the two new quantitative parameters of the EFOE model for **1** – π-plane-divided accessible space (PDAS)[5] as the steric effect term and the exterior frontier orbital extension density (EFOE density of LUMO; lowest unoccupied molecular orbital) as the orbital interaction term – obtained at the HF/6-31G(d) level.[10] It is apparent that although **1** is assumed to be sterically unbiased, facial differences in the PDAS parameters are considerable. The *anti*-face is commonly less sterically congested (ω = PDAS(*anti*) – PDAS(*syn*) > 0) than the *syn*-face except for the three membered cases and the last example (F,F) (ω < 0). The data of EFOE densities often agree with the observed stereoselection and the importance of steric effect may be seen by comparing the relative magnitude of the PDAS values with observed stereoselection. However, the four cases involving electron-withdrawing substituents (CO_2Me, CN, C≡CH) uniformly show stereoselectivity against the prediction of the theory. It is seen that all other cases agree with the prediction from the PDAS values except for the two cases of three-membered substituents (CH_2 and NH(H-in)), the facial stereoselection of which may be orbital-controlled.

In agreement with the proposals of Mehta[8] and Houk,[9] the EFOE model predict correctly many cases of substituents except for electron-withdrawing ones, indicating that the electrostatic interaction of an electron-withdrawing substituent may be an important factor in facial stereoselection when the substituent is located close to the carbonyl – in these systems (**1**), only two bonds away from the reaction center. The importance of the electrostatic interaction between substrate and reagent is explicitly taken into account in the second term of the Salem-Klopman equation[7] as a Coulombic interaction, although identification of its detailed mechanism as to whether it is really the Coulomb, the Keesom or the Debye interaction is presently impeded by the absence of sufficient information.

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