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Distinguishing the Early and Late Transition States and Exploring the Validity of $\sigma \rightarrow \sigma^*\#$, $\sigma\# \rightarrow \sigma^*$, and $\sigma \rightarrow \pi^*_{C=O}$ Concepts in Diastereoselection from NBO Analysis

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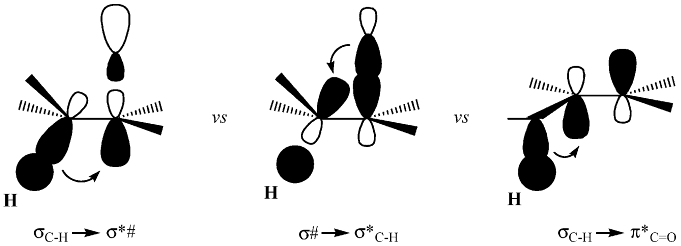

Natural bond orbital (NBO) analysis of several early TSs does not support the $\sigma \rightarrow \sigma^*\#$ hypothesis. The $\sigma \rightarrow \pi^*_{C=O}$ interaction controls the carbonyl pyramidalization that, in turn, controls the π-selectivity of a nucleophilic addition. In contrast, late TSs are devoid of $\sigma \rightarrow \pi^*_{C=O}$ interactions, and they benefit from $\sigma \rightarrow \sigma^*\#$ interactions that control π-selectivity. The evidence in favor of Anh−Felkin's $\sigma\# \rightarrow \sigma^*$ hypothesis is weak. The electron-withdrawing σ_{C-F} in the 2-fluoropropanal-LiCN TS did not align anti to the incipient bond even though there was complete conformational freedom. The initial guess for the TS in which σ_{C-F} was held anti to $\sigma\#$ optimized to what had lost the said geometrical relationship. Furthermore, in the TS for axial addition of LiCN to 2-ax-F-cyclohexanone, the net $\sigma \rightarrow \sigma^*\#$ interaction was considerably larger than the net $\sigma\# \rightarrow \sigma^*$ interaction. The relative TS energies require that the equatorial addition of LiCN to 2-ax-F-cyclohexanone be favored over the axial addition in good compliance with the available experimental results.

Introduction

After initial overwhelming support from a few laboratories,[1,2] Cieplak's $\sigma \rightarrow \sigma^*\#$ hyperconjugation hypothesis ($\sigma\#$ is the incipient bond)[3] soon turned controversial as it was considered to weaken the forming bond.[4] However, evidence neither in support nor contrary to it came forth until recently. Tomoda and co-workers have discovered a negative role of hyperconjugation in TSs for carbene insertion into methanol and cyclohexane from the study of 5-substituted-2-adamantanylidenes[5a] and from the addition of MeOH to 5-substituted-2-adamantyl cations.[5b] These authors have further argued that the Anh−Felkin model and the Cieplak model are not responsible for diastereoselection from the application of the frontier orbital extension model to the reduction of 1,3-hetran-5-ones by $LiAlH_4$.[5c,5d] We disclose herein our results from a thorough NBO analysis[6] of several TSs for nucleophilic additions to carbonyl function and demonstrate that the absence or presence of the Cieplak type σ-$\sigma^*\#$ interaction depends, respectively, on whether

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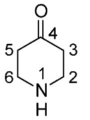
the TS in question is of early or late character. We also demonstrate from a combination of such studies and from the geometrical features of the TSs that the Anh−Felkin $\sigma\# \rightarrow \sigma^{*}$ hypothesis finds generally weak support.

The NBO analysis is based on optimally transforming a given wave function into localized forms that correspond to one-center (lone pair) and two-center (bond) elements in the Lewis structure regime. Donor−acceptor interactions related to hyperconjugation are estimated by the second-order perturbation theory analysis implemented in the NBO 5.0 program. Since the focus is on the interaction between the orbital of the forming bond and the vicinal bonds in both the Cieplak model and the Anh−Felkin model, Lewis resonance structures that have forming incipient bonds are chosen for the analysis.

We have studied the TSs from 4-piperidinone, **1**; 4-pyranone, **2**; 4-thiapyranone, **3**; 2-formyl-1,3-oxathiane, **4**; propanal, **5**; cyclohexanone, **6**; 2-fluoropropanal, **7**; and 2-ax-F-cyclohexanone, **8**. The choice of these substrates was made with a view to investigate diverse structural types to avoid substrate dependence, if any. All the calculations were performed using the Gaussian 98 suit of programs.[7] Every TS calculated in the present study was characterized by a single imaginary frequency. The discussion below has been divided according to the type of the TS (i.e., whether it is of early or late character).



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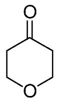

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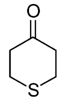

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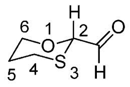
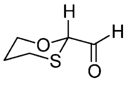


4a



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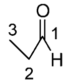

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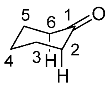

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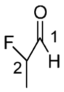

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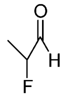

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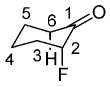

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Results and Discussion

(A) Early Transition States. (1) 4-Piperidinone, 4-Pyranone, and 4-Thiapyranone. Since the calculations of the TSs with LiH for carbonyl reduction have previously been demonstrated to reproduce the trends observed experimentally in reduction with $NaBH_4$,[8] several LiH-TSs were calculated. Species structurally similar to **1**−**3** have been found to undergo a predominantly axial attack in reduction with $NaBH_4$ and $Na(CN)BH_3$ in MeOH.[9] The $\sigma_{\mathrm{C3-Hax}}/\sigma_{\mathrm{C5-Hax}}$ had elongated by 0.28 and 0.18% in **1**-LiH, 0.18% each in **2**-LiH, and 0.18 and 0.0% in **3**-LiH at HF/6-31G* and B3LYP/6-31G* levels, respectively, in comparison to those in the parent ground-state molecules. The lengths of the incipient bonds were 1.96 and 2.58 Å in **1**-LiH, 1.98 and 2.73 Å in **2**-LiH, and 1.99 and 3.19 Å in **3**-LiH at the previous levels, in that order. It should be obvious from the long $\sigma_{\mathrm{C-H}}\#$ lengths that all these TSs are of early character. These TSs are shown in Figure 1 of the Supporting Information.

TABLE 1. Relevant σ-$\pi^{*}_{C=O}$ Interactions in the Axial 1/2/3-LiH-TSs

	HF/6-31G*		B3LYP/6-31G*	
substrate	$\sigma_{\mathrm{C3-Hax}} \rightarrow \pi^{*}_{C=O}$	$\sigma_{\mathrm{C5-Hax}} \rightarrow \pi^{*}_{C=O}$	$\sigma_{\mathrm{C3-Hax}} \rightarrow \pi^{*}_{C=O}$	$\sigma_{\mathrm{C5-Hax}} \rightarrow \pi^{*}_{C=O}$
1	7.86	7.86	5.77	5.77
1-LiH	13.2	13.2	9.04	9.03
2	7.87	7.87	5.68	5.68
2-LiH	13.2	13.2	8.59	8.58
3	6.91	6.91	5.22	5.22
3-LiH	12.6	12.6	7.03	6.86

NBO analysis did not reveal $\sigma_{\mathrm{C3-Hax}} \rightarrow \sigma^{*}\#$ and $\sigma_{\mathrm{C5-Hax}} \rightarrow \sigma^{*}\#$ interactions in any of the previous TSs. One may be encouraged to contemplate such interactions for the small increases in the $\sigma_{\mathrm{C3-Hax}}$ and $\sigma_{\mathrm{C5-Hax}}$ bond lengths. This, however, could as well be due to their enhanced interactions with $\pi^{*}_{C=O}$, Table 1, that has been rendered more electron-deficient by the coordination of lithium with the carbonyl oxygen. The axial **1**/**2**/**3**-LiH-TSs were more stable than the corresponding equatorial-TSs by 2.54, 2.91, and 2.36 kcal/mol at the HF/6-31G* level, respectively.

(2) 2-Formyl-1,3-oxathiane. Grignard additions to 2-acyl-1,3-oxathianes have been shown to proceed with high anti-to-S-selectivity.[10] The LiH-TSs from 2-formyl-1,3-oxathiane, **4**, were located for the anti-to-S and syn-to-S additions. The conformer **4a**, in which $\sigma_{\mathrm{C2-H}}$ is at a dihedral angle of 35.1−41.0° with the carbonyl oxygen, is 2.54 and 1.34 kcal/mol more stable than the conformer **4b**, in which the previous two maintain a dihedral angle of 117.2−120.6°, at the HF/6-31G* and B3LYP/6-31G* levels, respectively.

The anti-to-S-TS from **4a** ($\sigma_{\mathrm{C2-S3}} \rightarrow \pi^{*}_{C=O} = 5.52$ kcal/mol and $\sigma_{\mathrm{C2-O1}} \rightarrow \pi^{*}_{C=O} = 0.0$ kcal/mol) was more stable than the corresponding *syn*-to-S-TS by 2.59 kcal/mol at the HF/6-31G* level and 1.23 kcal/mol at the B3LYP/6-31G* level. Likewise, the anti-to-S-TS from **4b** was more stable than the corresponding syn-to-S-TS by 5.69 kcal/mol at the HF/6-31G* level and 7.12 kcal/mol at the B3LYP/6-31G* level. However, importantly, the anti-to-S-TS from **4b** was more stable than the anti-to-S-TS from **4a** by 3.26 kcal/mol at the HF/6-31G* level and 5.66 kcal/mol more at the B3LYP/6-31G* level. The HF/6-31G*-TSs from both **4a** and **4b** are shown in Figure 2 of the Supporting Information.

The possible reason for the preference of the anti-to-S-TS from **4b** over the anti-to-S-TS from **4a** is the chelation of lithium (hard acid) with the carbonyl oxygen and the (hard) oxygen rather than the (soft) sulfur atom of the oxathiane ring. This explains the observed predominant anti-to-S addition, which was previously perceived by Eliel.[10e]

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(9) Unpublished results from our laboratories. See also: Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

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TABLE 2. Characteristics of LiH-TSs from 4a and 4b

TS	$\sigma\#$ length (Å)/$\sigma \rightarrow \sigma^{*}\#$ (kcal/mol) HF/6-31G*	B3LYP/6-31G*	B3LYP/6-31+G*
anti to S **4a**-LiH	2.14/0.0	3.03/0.0	2.99/0.0
anti to S **4b**-LiH	2.17/0.0	2.79/0.0	2.87/0.0

TABLE 3. Characteristics of TSs of 5a with LiH and MeLi

TS	$\sigma\#$ length (Å)/σ-$\sigma^{*}\#$ (kcal/mol) HF/6-31G*	HF/6-31+G*	B3LYP/631G*	B3LYP/6-31+G*
5a-LiH	2.06/0.0	2.08/0.0	2.93/0.0	3.17/0.0
5a-MeLi	2.39/0.0	2.37/0.0		

Irrespective of whether it was the syn-to-S- or anti-to-S-TS from **4a** or **4b**, the $\sigma \rightarrow \sigma^{*}\#$ interaction was absent. The length of $\sigma_{C-H}\#$ in the anti-to-S-TS from **4a** and **4b** was 2.14 and 2.17 Å at the HF/6-31G* level and 3.03 and 2.79 Å at the B3LYP/6-31G* level, respectively. These TSs are, therefore, early in character for the long $\sigma_{C-H}\#$ lengths. The relevant data on LiH-TSs formed from **4a** and **4b** are collected in Table 2.

(3) Propanal. Intrigued with the previous negative support for the $\sigma \rightarrow \sigma^{*}\#$ interaction and presuming, although without a genuine reason, that the rings in **1**−**4** may possibly have corrupted the NBO analysis in some manner, it was decided that an acyclic system such as propanal, **5**, should be studied. The conformer **5a** (dihedral angle O−C1−C2−C3 = ∼0.0°) was 1.14 kcal/mol more stable than the conformer **5b** (O−C1−C2−C3 = 126.0°) and 1.79 kcal/mol more stable than the conformer **5c** (O−C1−C2−C3 = 180.0°) at the HF/6-31G* level. We have, therefore, studied the TSs from **5a**.

The length of $\sigma\#$ in **5a**-LiH was 2.06 Å at the HF/6-31G* level and 2.93 Å at the B3LYP/6-31G* level. The $\sigma \rightarrow \sigma^{*}\#$ interaction was absent from each TS. Both these TSs are of early character for the long $\sigma_{C-H}\#$ lengths. Our presumption of the corruption of NBO analysis by the rings in **1**−**4** was, therefore, unfounded. The **5a**-LiH-TSs are collected in Figure 3 of the Supporting Information, and their structural characteristics are in Table 3.

Attention also turned to changing the nucleophile, and we employed MeLi. In the TS **5a**-MeLi, the $\sigma\#$ length was 2.39 Å at the HF/6-31G* level and 2.37 Å at the HF/6-31+G* level. The $\sigma \rightarrow \sigma^{*}\#$ interaction was absent. Again, these TSs are of early character for the long $\sigma_{C-C}\#$ lengths. The **5a**-MeLi-TS is shown in Figure 3 of the Supporting Information, and its structural characteristics are in Table 3.

(B) Late Transition States. (1) Propanal. Having failed to notice the σ-$\sigma^{*}\#$ interaction in the previous early TSs, we considered studying late TSs. Because the incipient bond formation has progressed in a late TS, the $\sigma \rightarrow \sigma^{*}\#$ interaction could be reasoned to exist like other vicinal $\sigma \rightarrow \sigma^{*}$ interactions. We studied first the TS **5a**-LiCN, wherein the length of $\sigma\#$ was 1.90, 2.00, and 1.99 Å at the HF/6-31G*, B3LYP/6-31G*, and B3LYP/6-31+G* levels, respectively. For the short $\sigma_{C-C}\#$ length, **5a**-LiCN-TS conforms to the late category, and the much anticipated σ_{C2-H}-$\sigma^{*}\#$ interaction measures 10.1, 7.41, and 7.62 kcal/mol at the previous computational levels, in that order. The corresponding opposite $\sigma\# \rightarrow \sigma^{*}_{C2-H}$ interaction measured 3.38, 2.65, and 2.69 kcal/mol, respectively. Importantly, the $\sigma_{C2-H} \rightarrow \sigma^{*}\#$ interaction is more energy-lowering than the opposite $\sigma\# \rightarrow \sigma^{*}_{C2-H}$ interaction. Also, the interacting σ_{C-H} is nearly anti to $\sigma\#$ (dihedral angle = 170.0−171.7°).

To assess the effect of the countercation of the nucleophile, we next investigated **5a**-NaCN. The length of $\sigma\#$ was, respectively, 1.90, 1.97, and 1.98 Å at the HF/6-31G*, B3LYP/6-31G*, and B3LYP/6-31+G* levels. Like **5a**-LiCN, **5a**-NaCN also conforms to the late character, and the $\sigma_{C2-H} \rightarrow \sigma^{*}\#$ interaction measures 9.23, 6.61, and 6.98 kcal/mol with the opposite $\sigma\# \rightarrow \sigma^{*}_{C2-H}$ interaction measuring 3.62, 2.83, and 2.85 kcal/mol at the previous levels, in that order. The interacting σ_{C-H} was again nearly anti to $\sigma\#$ (dihedral angle = 169.7−170.3°). The TS **5a**-LiCN is shown in Figure 4 of the Supporting Information. The $\sigma_{C2-H} \rightarrow \sigma^{*}\#$ and $\sigma\# \rightarrow \sigma^{*}_{C2-H}$ interactions are shown in Table 4.

TABLE 4. $\sigma\#$ Lengths and Orbital Interactions (kcal/mol) in TSs 5a-LiCN and 5a-NaCN

TS	HF/6-31G*//B3LYP/6-31G*//B3LYP/6-31+G* $\sigma\#$ (Å)	$\sigma_{C2\text{-}H} \rightarrow \sigma^{*}\#$	$\sigma\# \rightarrow \sigma^{*}_{C2\text{-}H}$
5b-LiCN	1.90//2.00//1.99	10.1//7.41//7.62	3.38//2.65//2.69
5b-NacN	1.90//1.97//1.98	9.23//6.61//6.98	3.62//2.83//2.85

σ_{C2-H} and σ_{C2-C3} occupied, respectively, the anti and inside positions in the TSs **5a**-LiCN and **5a**-NaCN as also noticed earlier by Houk[11] and supported later by others.[12] Since $\sigma_{C2-H} \rightarrow \sigma^{*}\#$ is always larger than $\sigma\# \rightarrow \sigma^{*}_{C2-H}$, $\sigma\#$ is electron-deficient, and the incipient bond will be expected to align anti to the more electron-donating group for stereoelectronic stabilization.[3] The argument of TS destabilization by an anti σ_{C-Me} for its presumed higher electron-donating ability than an anti σ_{C-H} need not be necessarily true.[11,12] The larger $\sigma_{C2-H} \rightarrow \sigma^{*}\#$ than $\sigma\# \rightarrow \sigma^{*}_{C2-H}$ interaction also raises questions about the Anh−Felkin hypothesis (vide infra) that treats $\sigma\#$ as electron-rich and, thus, favors placing $\sigma\#$ anti to the strongest acceptor bond to maximize stabilization through the $\sigma\# \rightarrow \sigma^{*}$ interaction.[13]

(2) 4-Azacyclohexanone, 4-Oxacyclohexanone, and 4-Thiacyclohexanone. The lengths of $\sigma\#$ are 1.88, 1.96, and 1.96 Å in **1**-LiCN, 1.88 , 1.95, and 1.95 Å in **2**-LiCN, and 1.88, 1.95, and 1.95 Å in **3**-LiCN at the HF/6-31G*, B3LYP/6-31G*, and B3LYP/6-31+G* levels, in that order. These TSs are of late character and possess $\sigma \rightarrow \sigma^{*}\#$ and $\sigma\# \rightarrow \sigma^{*}$ interactions. The TSs with LiCN are shown in Figure 5 of the Supporting Information, and their $\sigma \rightarrow \sigma^{*}\#$ and $\sigma\# \rightarrow \sigma^{*}$ interactions are collected in Table 5.

(3) Cyclohexanone. Cyclohexanone, **6**, has been, by far, the most studied molecule for the discussion of diastereoselectivity. We also chose to study this molecule and, hence, calculated its ax-TSs with LiH and LiCN at the HF/6-31G*, B3LYP/6-31G*, and B3LYP/6-31+G* levels. The length of $\sigma\#$ in the TS with LiH was 1.97, 2.54, and 2.74 Å at the previous levels, in that order. Since these TSs are early for the long $\sigma_{C-H}\#$ lengths, the $\sigma_{C2-Hax} \rightarrow \sigma^{*}\#$ and $\sigma_{C6-Hax} \rightarrow \sigma^{*}\#$ interactions must be absent, as indeed they are, in keeping with the results discussed previously. On the contrary, the TSs with LiCN are late in character for the rather short $\sigma_{C-C}\#$ lengths of 1.88, 1.95, and 1.95 Å at the previous levels, in that order. Further, the $_{C2-Hax} \rightarrow \sigma^{*}\#$ (=$\sigma_{C6-Hax} \rightarrow \sigma^{*}\#$) and $\sigma\# \rightarrow \sigma^{*}_{C2-Hax}$ (=$\sigma\# \rightarrow \sigma^{*}_{C6-Hax}$) interactions are also present. The $_{C2-Hax} \rightarrow \sigma^{*}\#$ interaction measured 9.75, 6.97, and 7.40 kcal/mol, and the $\sigma\#$

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TABLE 5. $\sigma\#$ Lengths and Vicinal Orbital Interactions (kcal/mol) in the ax-TSs from 1−3 with LiCN

TS	$\sigma\#$ (Å)	$\sigma_{C3-Hax} \rightarrow \sigma^*\#$	$\sigma_{C5-Hax} \rightarrow \sigma^*\#$	$\sigma\# \rightarrow \sigma^*_{C3-Hax}$	$\sigma\# \rightarrow \sigma^*_{C5-Hax}$
	HF/6-31G*//B3LYP/6-31G*//B3LYP/6-31+G*				
1-LiCN	1.88//1.96//1.96	9.69//6.84//7.25	9.71//6.85//7.26	3.46//2.71//2.89	3.46//2.72//2.89
2-LiCN	1.88//1.95//1.95	9.63//6.77//7.13	9.63//6.77//7.13	3.53//2.77//2.94	3.53//2.77//2.94
3-LiCN	1.88//1.95//1.95	9.55//6.76//7.18	9.56//6.75//7.17	3.49//2.70//2.91	3.48//2.70//2.91

TABLE 6. $\sigma\#$ Lengths and Vicinal Orbital Interactions (kcal/mol) in ax-TSs 6-LiH and 6-LiCN

	HF/6-31G*//B3LYP/6-31G*//B3LYP/6-31+G*		
ax-TS	$\sigma\#$ (Å)	$\sigma_{C2-Hax} \rightarrow \sigma^*\#$	$\sigma\# \rightarrow \sigma^*_{C2-Hax}$
6-LiH	1.97//2.54//2.74	0.00//0.00//0.00	0.00//0.00//0.00
6-LiCN	1.88//1.95//1.95	9.75//6.97//7.40	3.57//2.75//2.98

$\rightarrow \sigma^*_{C2-Hax}$ interaction measured 3.57, 2.75, and 2.98 kcal/mol at the previous levels, in that order. The HF/6-31G*-TSs with LiH and LiCN are shown in Figure 6 of the Supporting Information, and their structural characteristics are in Table 6.

Our results are thus consistent across a range of molecules, both acyclic and cyclic. The TSs with LiH are early in character and do not exhibit $\sigma \rightarrow \sigma^*\#$ interactions. On the contrary, the TSs with LiCN and NaCN are late in character, and they exhibit significant $\sigma \rightarrow \sigma^*\#$ and $\sigma\# \rightarrow \sigma^*$ interactions. Since the $\sigma \rightarrow \sigma^*\#$ interaction is stronger than the opposite $\sigma\# \rightarrow \sigma^*$ interaction, $\sigma\#$ is electron-deficient in the late transition states. As the reaction trajectory moves onward from the late TS into the product domain, the $\sigma \rightarrow \sigma^*\#$ interaction will be expected to diminish and the $\sigma\# \rightarrow \sigma^*$ interaction to increase to allow take-over by the product-development regime.

What stabilizes an early TS? We have noticed previously the $\sigma \rightarrow \pi^*_{C=O}$ interactions in all the early TSs but none in those of late character. The vicinal σ bond that contributed the most was the one that was parallel to $\pi_{C=O}$. This assists carbonyl pyramidalization, necessitated by the coordination of the countercation with the carbonyl oxygen, in the early course of the reaction in a manner that the larger coefficient of the electron-deficient $p_{C=O}$ orbital aligns anti to the better electron-donating $\sigma_{vicinal}$ bond. It is this $\sigma \rightarrow \pi^*_{C=O}$ controlled orientation of the electron-deficient $p_{C=O}$ that determines the facial preference.[14] Vicinal $\sigma \rightarrow \pi^*_{C=O}$ interactions, expected to intensify, en route, from the reactant to the TS as a function of the strength of coordination of the carbonyl oxygen with the cation end of the nucleophile, are therefore important. The $\sigma \rightarrow \sigma^*\#$ interaction does not exist along this segment of the reaction pathway.

Comments on the Anh−Felkin $\sigma\# \rightarrow \sigma^*$ Hypothesis. The $\sigma\# \rightarrow \sigma^*$ interaction observed previously is reminiscent of the Anh−Felkin interpretation of diastereocontrol. The observation that the $\sigma\# \rightarrow \sigma^*$ interaction was always less intense than the $\sigma \rightarrow \sigma^*\#$ interaction led us to examine the Anh−Felkin interpretation in detail. We have studied 2-fluoropropanal, **7**, wherein a full conformational mobility around σ_{C1-C2} during TS formation is allowed, and 2-ax-F-cyclohexanone, **8**, wherein only a little conformational change is required for the anti arrangement of $\sigma\#$ and σ_{C-F} in the ax-TS.

(1) 2-Fluoropropanal. The two main ground-state conformers of **7** are **7a** and **7b** that possess σ_{C-F} syn and anti to the carbonyl function, respectively. The conformer **7b** is more stable than the conformer **7a** by 2.87 kcal/mol at the HF/6-31G* level, due possibly to the reduced dipole−dipole interactions. The calculated dipole moments of **7a** and **7b** are, respectively, 4.07 and 1.34 D. We have investigated the TSs formed from both **7a** and **7b** with LiCN at the HF/6-31G* level.

The length of $\sigma\#$ in **7a**-LiCN was 1.96 Å, and it showed no σ-$\pi^*_{C=O}$ interaction. Significantly, σ_{C-F} did not turn anti to $\sigma\#$ as required for the Anh−Felkin proposal; the dihedral angle was 63.0°. It was rather σ_{C2-C3} that had disposed anti to $\sigma\#$ (dihedral angle = 178.6°). The $\sigma_{C2-C3} \rightarrow \sigma^*\#$ and $\sigma\# \rightarrow \sigma^*_{C2-C3}$ interactions measured, respectively, 4.93 and 4.39 kcal/mol.

The length of $\sigma\#$ in **7b**-LiCN, wherein σ_{C2-H} was anti to $\sigma\#$ with a dihedral angle of 178.1°, was 1.98 Å. It possessed $\sigma_{C2-H} \rightarrow \sigma^*\#$ and $\sigma\# \rightarrow \sigma^*_{C2-H}$ interactions measuring 10.50 and 3.03 kcal/mol, respectively. The $\sigma \rightarrow \pi^*_{C=O}$ interaction was absent. The $\sigma\# \rightarrow \sigma^*_{C2-F}$ interaction measured 0.60 kcal/mol, and the dihedral angle between $\sigma\#$ and σ_{C2-F} was 63°. Further, in **7b**-LiCN wherein σ_{C2-C3} was nearly anti to $\sigma\#$ (dihedral angle = 141.5°), $\sigma\#$ was 1.98 Å long. The interactions $\sigma_{C2-C3} \rightarrow \sigma^*\#$ and $\sigma\# \rightarrow \sigma^*_{C2-C3}$ measured, respectively, 5.61 and 3.85 kcal/mol. The TSs from **7a** and **7b** are shown in Figure 7 of the Supporting Information, and the structural characteristics are in Table 7.

Neither **7a**-LiCN- nor **7b**-LiCN-TS favored the Anh−Felkin argument of a predominant $\sigma\# \rightarrow \sigma^*$ interaction. Specifically, σ_{C-F} did not turn anti to $\sigma\#$ even though the molecule enjoyed full conformational mobility. Wong and Paddon-Row have previously studied the TSs formed from CN^- and 2-fluoropropanal and reported that σ_{C-F} was anti to $\sigma\#$ in the best TS structure.[12] Why then did σ_{C-F} not move anti to $\sigma\#$ in **7**-LiCN? When the ground-state geometry was searched from an initial guess having σ_{C-F} orthogonal to the carbonyl function, it had converged to **7b**. Thus, the conformer with σ_{C-F} orthogonal to the carbonyl function must, at best, be a transition structure between **7a** and **7b**. The construction of a TS on such a transient ground-state conformer deserves possibly a separate treatment.

7-LiCN, wherein σ_{C2-F} was constrained anti to $\sigma\#$ (dihedral angle = 179.9° and $\sigma\# = 1.94$ Å), was less stable than **7b**-LiCN, wherein σ_{C2-H} was anti to $\sigma\#$, by 2.40 kcal/mol. The $\sigma_{C2-F} \rightarrow \sigma^*\#$ and $\sigma\# \rightarrow \sigma^*_{C2-F}$ interactions measured, respectively, 3.76 and 5.44 kcal/mol. From the relative energy considerations, the Anh−Felkin transition structure is obviously less likely. The $\sigma\# \rightarrow \sigma^*_{C2-F} > \sigma_{C2-F} \rightarrow \sigma^*\#$ relation indicates that σ_{C-F} is possibly more electron-deficient than $\sigma\#$.

(2) 2-ax-Fluorocyclohexanone. The ax-TS formed from 2-ax-F-cyclohexanone, **8**, and LiCN was studied next at the HF/6-31G* level to understand the state of affairs when σ_{C-F} was geometrically constrained anti to $\sigma\#$. The corresponding eq-TS was also studied to strike a comparison and also to assess the

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TABLE 7. **HF/6-31G* Geometrical Parameters and Vicinal Interactions in 7a-LiCN and 7b-LiCN**

TS	$\sigma\#$ (Å)	$\sigma_{C2-C3} \rightarrow \sigma^*\#$ (kcal/mol)	$\sigma\# \rightarrow \sigma^*_{C2-C3}$ (kcal/mol)	$\sigma_{C2-H} \rightarrow \sigma^*\#$ (kcal/mol)	$\sigma\# \rightarrow \sigma^*_{C2-H}$ (kcal/mol)	$\sigma\# \rightarrow \sigma^*_{C2-F}$ (kcal/mol)
7a-LiCN[a]	1.96	4.93	4.39			1.17
7b-LiCN[b]	1.98			10.5	3.03	0.60
7b-LiCN[a]	1.98	5.61	3.85			0.68

[a] $\sigma\#$ was antiperiplanar to σ_{C2-C3}. [b] $\sigma\#$ was antiperiplanar to σ_{C2-H}.

TABLE 8

HF/6-31G* vicinal orbital interactions (kcal/mol) in the ax-TS from 2-ax-F-cyclohexanone with LiCN

	HF/6-31G*//B3LYP/6-31G*			
TS	$\sigma_{C2-F} \rightarrow \sigma^*\#$	$\sigma_{C6-Hax} \rightarrow \sigma^*\#$	$\sigma\# \rightarrow \sigma^*_{C2-F}$	$\sigma\# \rightarrow \sigma^*_{C6-Hax}$
7-LiCN	3.68//2.68	10.98//7.46	5.29//4.52	3.21//2.55

HF/6-31G* vicinal orbital interactions (kcal/mol) in the eq-TS from 2-ax-F-cyclohexanone with LiCN

	HF/6-31G*//B3LYP/6-31G*			
TS	$\sigma_{C2-C3} \rightarrow \sigma^*\#$	$\sigma_{C5-C6} \rightarrow \sigma^*\#$	$\sigma\# \rightarrow \sigma^*_{C2-C3}$	$\sigma\# \rightarrow \sigma^*_{C5-C6}$
7-LiCN	6.44//4.88	7.55//5.90	3.35//2.57	3.53//2.73

possible electrostatic effects arising from the interactions of fluorine with lithium.

The length of $\sigma\#$ in the ax-TS was 1.91 Å. The $\sigma_{C2-F} \rightarrow \sigma^*\#$ and $\sigma_{C6-Hax} \rightarrow \sigma^*\#$ interactions measured, respectively, 3.68 and 10.98 kcal/mol. The reverse $\sigma\# \rightarrow \sigma^*_{C2-F}$ and $\sigma\# \rightarrow \sigma^*_{C6-Hax}$ interactions measured 5.29 and 3.21 kcal/mol, respectively. Since the net electron-flow from the ring bonds to $\sigma^*\#$ measures $[(3.68 + 10.98) - (5.29 + 3.21)] = 6.16$ kcal/mol, the Anh−Felkin argument of diastereocontrol through $\sigma\# \rightarrow \sigma^*$ interaction appears untenable.[15] After all, the $\sigma\# \rightarrow \sigma^*_{C6-Hax}$ interaction is also present along with the $\sigma\# \rightarrow \sigma^*_{C2-F}$ interaction. The difference of these interactions, 2.08 kcal/mol, is possibly due to the difference in the $-I$ effects of the two elements, namely, H and F. The previous TS is shown in Figure 8a of the Supporting Information, and the orbital interactions are in Table 8.

The length of $\sigma\#$ in the eq-TS was 1.97 Å. The $\sigma_{C2-C3} \rightarrow \sigma^*\#$ and $\sigma_{C5-C6} \rightarrow \sigma^*\#$ interactions measured, respectively, 6.44 and 7.55 kcal/mol. The reverse $\sigma\# \rightarrow \sigma^*_{C2-C3}$ and $\sigma\# \rightarrow \sigma^*_{C5-C6}$ interactions measured, respectively, 3.35 and 3.53 kcal/mol. The net $\sigma \rightarrow \sigma^*\#$ interaction outweighed the net $\sigma\# \rightarrow \sigma^*$ interaction by 7.11 kcal/mol. The eq-TS is shown in Figure 8b of the Supporting Information, and the orbital interactions are in Table 8.

It is indeed interesting to note that the eq-TS was 1.22 kcal/mol more stable than the ax-TS. The higher stability of the eq-TS with respect to the corresponding ax-TS is likely to be due to (a) the reduced dipole−dipole interaction in the eq-TS for the anti relationship of σ_{C-F} and σ_{C-O} and (b) the stereoelectronic destabilization of the ax-TS for the anti relationship of the electron-deficient $\sigma\#$ with the electron-deficient σ_{C-F}. It is equally interesting to note that the energy difference between the lithium salts of 2-ax-F-1-eq-CN-cyclohexanol (to be formed from eq-7-LiCN) and 2-ax-F-1-ax-CN-cyclohexanol (to be formed from ax-7-LiCN) is 3.72 kcal/mol at the HF/6-31G* level. These geometries are shown in Figure 9 of the Supporting Information.

Rosenberg et al. have reported an increased eq-attack to 4-*t*-butyl-2-ax-fluorocyclohexanone in reduction with $LiAlH_4$ in comparison to 4-*t*-butylcyclohexanone and its 2-ax-MeO/Me/Br/Cl derivatives, in decreasing order.[16] These authors have emphasized that the previous ordering was consistent with both the electrostatic model and the Anh−Felkin formulation after minor adjustments. The authors have observed further that the hyperconjugative effects were unable to account for the previous ordering, regardless of the adjustments. Our results differ from those stated previously. The hyperconjugative interactions are important in the late transition states. Also, the possibility of electrostatic interactions between fluorine and lithium is likely to be little over the >4.40 Å separation between the two in the eq-TS.

Conclusions

The hyperconjugative electron-donation from the vicinal σ bonds to the incipient $\sigma^*\#$ does not exist in the early TSs. The σ-$\pi^*_{C=O}$ interactions control the pyramidalization at the carbonyl carbon that, in turn, possibly controls the facial selectivity of nucleophilic additions. In contrast, the late TSs are devoid of $\sigma \rightarrow \pi^*_{C=O}$ interactions. This void, however, is compensated by the $\sigma \rightarrow \sigma^*\#$ interactions that control the facial selectivity. For the reason that all the TSs with LiH belong to the early category, they are devoid of $\sigma \rightarrow \sigma^*\#$ interactions, and hence, they could not be used to model the Cieplak's hyperconjugation hypothesis. The Cieplak's hyperconjugation hypothesis, however, appears applicable to those reactions that proceed through late TSs. This result differs partly from the results of Tomoda et al. who have argued for absolute inapplicability of the Cieplak model by studying carbene and cation substrates.[5]

The evidence in favor of the Anh−Felkin hypothesis is weak for the following reasons: (a) the electron-attracting σ_{C-F} in 2-fluoropropanal-LiCN-TS did not turn anti to $\sigma\#$ even though there was a complete conformational mobility; (b) the TS in which σ_{C-F} was constrained anti to $\sigma\#$ was less stable than when it was otherwise; (c) in the ax-TS for the addition of LiCN to 2-ax-F-cyclohexanone, the net $\sigma \rightarrow \sigma^*\#$ interaction was significantly larger than the net $\sigma\# \rightarrow \sigma^*$ interaction; and (d) the eq-TS formed from 2-ax-F-cyclohexanone and LiCN was more stable than the corresponding ax-TS.

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Supporting Information Available: Optimized geometries of ground-state substrates and transition states and the 3- D structures of various transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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