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Diastereofacial Selection in Nucleophilic Additions to Unsymmetrically Substituted Trigonal Carbons

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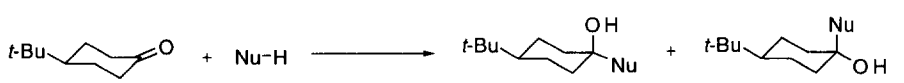
1. Introduction

Since the Cieplak model for nucleophilic addition to cyclohexanones was first introduced in 1981,[1,2] there have been active discussions in the literature concerning its validity. The on-going debate has stimulated many ingenious designs of experiments and theoretical studies, and the body of chemistry that has developed on this topic is both interesting and valuable. The results have improved our understanding of the relationships between stereoselectivity and various factors, such as conformational, electrostatic, hyperconjugative, torsional, and structural effects. Although supporters and critics of the Cieplak model still hold their respective views, they agree on many issues. The purpose of this Report is to present some of the interesting chemistry that has developed and to provide readers with an overview of this topic. Every effort has been made to include the latest relevant contributions, but the review is not meant to be exhaustive. Non-controversial issues, such as electrophilic reactions (epoxidation, osmylation, and Diels-Alder cycloadditions) and free radical reactions, are left out because: (1) there is a general agreement concerning the electronic nature of the transition state; (2) the Cieplak model was developed to rationalize the results from nucleophilic additions to cyclohexanones. Evidence supporting the Cieplak model is selected only if the original authors have clearly stated that their results are consistent with this model, and evidence against it is reviewed according to the same criteria.

2. Background

In nucleophilic additions to conformationally locked cyclohexanones, either equatorial attack (to give the axial alcohol) or axial attack (to give the equatorial alcohol) can occur (Figure 1). As generalized by Barton, axial attack of nucleophiles is favored when steric hindrance is negligible.[3] Experimental observations are as follows: Small nucleophiles (such as $LiAlH_4$ and $NaBH_4$) preferentially add to unhindered cyclohexanones from the axial side to give equatorial alcohol **B**.[4] In contrast, bulky nucleophiles add from the equatorial side to give axial alcohol **A**. Equatorial attack also predominates in ketones where axial approach is blocked by axial substituents at POSITIONS 3 and/or 5, such as in the case of 3,3,5-trimethyl-cyclohexanone.



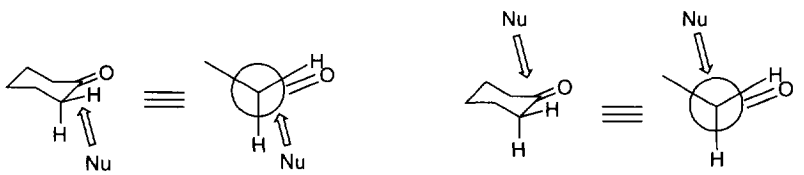
A **B**

Figure 1. Nucleophilic addition to 4-*tert*-butylcyclohexanone. Either equatorial attack (to give the axial alcohol **A**) or axial attack (to give the equatorial alcohol **B**) can occur.

There appears to be general agreement that preferential equatorial attack by bulky reagents or with hindered ketones is due to steric interference on the axial side.[5] However, numerous models have been

proposed to account for the fact that small nucleophiles add to unhindered ketones from the axial side. For these cases Dauben proposed that "product development control" dictates the outcome, so that axial attack produces the (more stable) equatorial alcohol in each case.[5] Klein,[6] Anh,[7,8] Liotta,[9] Ashby,[10] and Hudec[11] suggested in various ways that axial attack is preferred on account of distortion of the carbonyl π and π^* orbitals. That is, unequal distribution of electron or orbital density on the two faces of the carbonyl group leads to stereoselective attack. Wipke[12] and Muller[13] both developed force-field models that support the notion that stereoselectivity arises from a combination of torsional and steric effects. The steric approach-product stability control hypothesis has been further developed by Rei, who proposed to equate the difference in activation energies, ($\Delta\Delta G^{\neq}$), between formation of axial and equatorial alcohols with a linear combination of product stability (Δn) and steric strain ($\Delta\sigma$) terms: $\Delta\Delta G^{\neq} = a\Delta n + b\Delta\sigma$ (a and b are constants).[14]

The hypothesis most widely-accepted is the so called "Felkin-Anh" model, which is based on a combination of studies published by both Felkin[15] and by Anh.[8] Felkin suggested that the preference for axial attack on unhindered cyclohexanones is due to a greater torsional strain in the transition state for equatorial attack[15] (Figure 2). Attack on the carbonyl group along any chosen trajectory is more "eclipsed" from the equatorial direction. Anh and Eisenstein carried out calculations that generally support the Felkin model, but these authors also emphasized the importance of another factor, namely attack antiperiplanar to a vicinal bond.[8] The basis for this geometric requirement is electronic in origin. The transition state is stabilized in this arrangement by delocalization of electron density from the nucleophile to the antibonding orbital of the anti vicinal bond. This view implies that the transition state is electron-rich.



equatorial attack axial attack

Figure 2. The preference for axial attack on unhindered cyclohexanones is due to greater torsional strain in the transition state for equatorial attack.[15]

The Felkin-Anh model has received widespread acceptance among organic chemists and is often cited to rationalize stereochemical results.[16] At least two advanced textbooks have adopted the Felkin-Anh model.[17,18] However, in 1981, Cieplak challenged the Felkin-Anh model and proposed a conceptually different hypothesis.[1] The Cieplak model can be summarized in one statement: nucleophilic addition to a carbonyl group occurs preferentially in the direction antiperiplanar to the best electron-donor vicinal bond. According to Cieplak, the donor ability order of a σ-bond is C-S > C-H > C-C > C-O.[1] Thus, "the stereochemistry of nucleophilic addition to 4-*tert*-butylcyclohexanone is proposed to result from a

superposition of two effects: steric hindrance, which favors the equatorial approach, and electron donation from the cyclohexanone σ_{CC} and σ_{CH} bonds into the $\sigma^*_{\neq}$ (the anti-bonding orbital of the forming bond Nu-C) orbital, which favors the axial approach because the carbon-hydrogen bonds are better electron donors."[1]

axial approach equatorial approach

Figure 3. Electron donation from the cyclohexanone σ_{CC} and σ_{CH} bonds into the $\sigma^*_{\neq}$ orbital favors axial approach because carbon-hydrogen bonds are better electron donors.

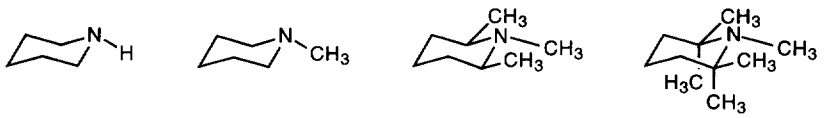
As described earlier, the Felkin-Anh model implies that the transition states of nucleophilic additions are electron-rich. In contrast to this implication, Cieplak argues that "the very definition of the incipient bond suggests that this bond is intrinsically electron deficient" and, electron donation from the antiperiplanar vicinal σ bonds into the incipient antibonding C-Nu orbital ($\sigma^*_{\neq}$) stabilizes the transition state and lowers the activation energy. The Cieplak model is based on the well known anomeric effect.[1] It is complicated by the fact that the theory of microscopic reversibility must be employed. Stereochemical studies of orthoester and orthoamide hydrolysis show that the most important factor in determining the direction of hydrolytic breakdown is the antiperiplanarity of the breaking σ bond with respect to the lone pairs on the adjacent heteroatoms.[19] Cieplak states that if alkoxide extrusion in orthoester breakdown is "facilitated by the antiperiplanar assistance of a lone pair, the reverse reactions of nucleophilic addition to a carbonyl group, hydride reduction, and water attack on carbonyl group in ester hydrolysis should be facilitated by this assistance as well."[1]

In one theoretical study of additions to cyclohexanone, the Cieplak model has been labeled "paradoxical"[20] because a bond-weakening process (electron-donation into the antibonding orbital $\sigma^*_{\neq}$) is being used to determine the Nu-C bond-forming process. However, in practice the Cieplak model is simple to apply: nucleophilic attack on carbonyl occurs anti to the better electron-donor vicinal bonds. The controversy appears to be that the applicability and relevance of microscopic reversibility to a process such as nucleophilic addition are not entirely clear.[21]

3. Which Is a Better Donor, the C-H or the C-C Bond?

One of the fundamental assumptions of the Cieplak model is that a CH bond is a better donor than a CC bond in hyperconjugative electron release. This assumption was first questioned by Rozeboom and

Houk in 1982.[22a] Their photoelectron spectra data and *ab initio* STO-3G calculations on methylpiperidines indicated that axial 2-methyl substituents lower the amine lone-pair ionization potential (IP) by ~0.26 eV, while equatorial 2-methyl (and 3- and 4-methyl) substituents lower the lone pair IP by < 0.1 eV.

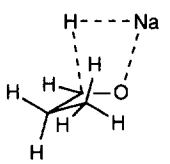


8.70 8.37 8.22 7.68

Figure 4. Ionization potentials (eV) of methylpiperidines.

They explained this observation by assuming the amine radical cation produced on ionization was stabilized by hyperconjugative electron release from the antiperiplanar vicinal bonds. Thus, a CC bond appeared to be a better donor than a CH bond.

In 1987, Wu and Houk reported a theoretical study of NaH addition to propanal.[22b] The transition state with the lowest energy had an anti CH bond and an inside methyl group. Although the result appears to be consistent with the Cieplak model, Houk concluded that: "The anti methyl group is disfavored relative to anti CH, because the former is a better donor and destabilizes the electron-rich transition structure."



Furthermore, Houk challenged the Cieplak model directly with the following comments: "Cieplak proposed that an anti CH stabilizes nucleophilic transition states by electron donation and that CH is a better donor than CC, contrary to much experimental evidence, which shows that CC is a better donor. We conclude that an anti methyl destabilizes the electron-rich transition state because it is a better donor than a CH bond." Thus Houk has raised doubt concerning two basic premises of the Cieplak model: (1) CH bonds are better donors than CC bonds; and (2) the transition state in nucleophilic addition to a carbonyl group is electron-deficient. The first issue will be the focus in this section, and the second point will be discussed later.

Cieplak's assumption is based on the Baker-Nathan effect in which hyperconjugation is invoked to explain the rates of substitution of *p*-alkyl benzyl bromides. The observed order of reaction rates is methyl

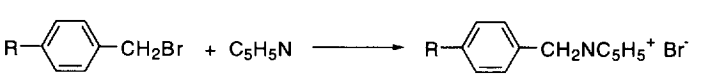


Figure 5. Reaction rates of pyridine with *p*-substituted benzyl bromides follows the order: methyl > ethyl > isopropyl > *tert*-butyl.[23]

> ethyl > isopropyl > *tert*-butyl.[23]

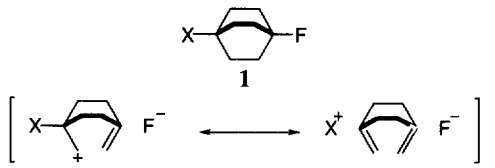
It has been disputed whether or not the origin of the Baker-Nathan effect is hyperconjugative. For example, differential solvation has been suggested as the reason for the observed rate trend.[24] Thus the order of hyperconjugation ability for alkyl groups was also questioned. The stereochemical results from some rigid cyclic ketones also cast doubt on the relative donor ability of CH versus CC bonds.[25]

However, recent evidence seems to indicate that hyperconjugative electron donation by σ_{CH} bonds is larger than that by σ_{CC} bonds. Laube has reported a theoretical study of hyperconjugation in substituted acetaldehydes.[26a] Based on X-ray structure data and *ab initio* calculations at the 4-31G* level, they obtained the potential energy curves for rotation about the C_{sp2}-C_{sp3} bond of substituted acetaldehydes. The least-squares adjustment of a truncated Fourier series allows a separation of the potential energy (V) into a onefold (dipolar and steric interactions), a twofold (hyperconjugative interactions), and a threefold term (bond electron repulsions). A comparison of the V2 coefficients gave the following order of hyperconjugation: CH > CC > CCl > CF. Based on the X-ray structure of the $SbCl_5$-complexed 5-phenyladamantanone, Laube also concluded that a CH bond is a better donor than a C_{sp3}-C_{sp2} bond.[26b]

In 1989 Cieplak[2] suggested an alternative explanation for the ionization potentials of the methylpiperidines reported by Houk, namely, there is a significant ring distortion in 2,2,6,6-tetramethylpiperidine due to the syn-diaxial interaction of the methyl groups. Since ionization potentials of amines and ethers are known to decrease when the ring size and the endocyclic valence angle increases,[26c] Cieplak believes this distortion to be the most likely reason for the marked decrease in the ionization potential of 2,2,6,6-tetramethyl-piperidine.[2]

However in a 1991 paper,[27] Houk *et al.* reiterated their position that CC bonds are better electron-donors than CH bonds. The main argument was based on theoretical studies of carbocation structures. In the case of the 1-propyl cation, their calculations showed that the methyl-bridged structure is more stable than a hydrogen-bridged structure by 1.4 kcal/mol.

Nevertheless, the most recent work with ^{19}F NMR probes indicate that CH_3 is a σ-electron withdrawing group compared to H.[28a] ^{19}F chemical shifts are found to be appropriate electronic probes for substituent effects and mode of transmission (Table 1). Polycycloalkyl fluorides, such as **1**, were found to respond sensitively to the extent of delocalization of electrons from neighboring antiperiplanar carbon-carbon bonds into the σ^* orbital of the C-F bond. The ^{19}F chemical shift data in Table 1 show that alkyl groups are electron-withdrawing compared to H. This conclusion is consistent with the study reported previously by Olah and Forsyth.[28c] The effect of methyl substitution for hydrogen on the charge distribution at the carbon undergoing substitution was discussed in relation to the deshielding of C_α observed in ^{13}C NMR spectra. The data of substituent-induced chemical shifts are consistent with the fact that methyl group has a negative inductive effect that increases in magnitude as the extent of electron donation from methyl increases via hyperconjugation.[28c]



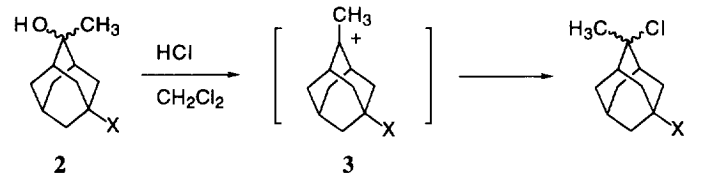
1

Table 1 ^{19}F Substituent Chemical Shifts (SCS)[a] of 4-Substituted Bicyclo[2.2.2] oct-1-yl Fluorides (**1**)

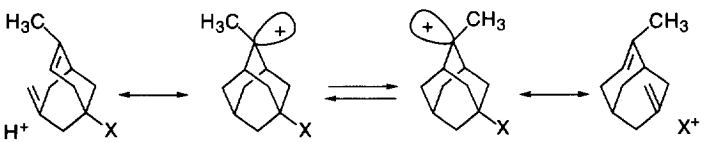
X	c-C_6H_{12}	$CDCl_3$	DMF	CF_3CO_2H
NO	-8.39	-9.89	-9.53	-17.45
CN	-4.15	-5.40	-4.79	-12.55
CF_3	-5.08	-6.05	-5.98	-10.12
COOH	-4.75	-5.68	-4.93	-10.57
$CONH_2$	—	-6.09	-4.87	-13.80
$COOCH_3$	-4.38	-5.29	-5.05	-10.19
$COCH_3$	-4.15	-5.11	-4.52	-10.56
CHO	-3.09	-4.10	-3.50	-9.92
OH	-8.06	-9.24	-7.47	-14.96
OCH_3	-6.40	-7.62	-7.15	-14.28
$OCOCH_3$	-6.08	-7.30	-7.11	-13.15
F	-8.90	-10.32	-10.19	-16.13
Cl	-6.97	-8.14	-8.07	-12.66
Br	-5.94	-7.07	-6.98	-11.50
I	-3.35	-4.29	-4.12	-8.22
NH_2	-6.60	-7.51	-6.28	—
$N(CH_3)_2$	-4.66	-5.84	-5.31	—
$NHCOCH_3$	-4.66	-5.82	-4.78	-14.86
$^+NH_3$	—	—	—	-17.97
$^+N(CH_3)_3$	—	-11.14	-9.34	-20.14
CH_3	-3.81	-3.92	-3.90	-4.08
C_2H_5	-2.79	-2.91	-2.93	-2.97
i-C_3H_7	-2.68	-2.79	-2.82	-2.72
t-C_4H_9	-3.11	-3.20	-3.23	-3.04
C_6H_5	-3.37	-3.94	-3.68	-5.29
p-$NO_2C_{63}H_4$	-4.12	-4.78	-4.15	-8.10
$Sn(CH_3)_3$	3.67	3.83	3.94	—

[a] Defined as the difference (in parts per million) between the ^{19}F chemical shift of the substituted compound and that of the parent compound (X = H). See original publication for further details.[28a]

The results from both hydrochlorination and fluorination of 5-substituted adamantan-2-ols reported by Adcock also support the conclusion that a C-H bond is a better donor.[28b] The additions (Table 2 and 3) were found to proceed through a pair of equilibrating carbocation intermediates (**3a** and **3b**), one of which, the anti-cation (**3**), is stabilized by hyperconjugative σ-electron donor groups, such as $SiMe_3$ and $SnMe_3$. It is significant that X = methyl was found to be electron-withdrawing compared to X = H.[28b]



2 **3**



3a **3b**

Table 2 Anti and Syn Product Distribution for the Hydrochlorination of 5-X substituted 2-Methyladamantan-2-ols (**2**).[a]

	Tertiary Chlorides				
X	%anti	%syn	X	%anti	%syn
F	27	73	$Si(CH_3)_3$	61	39
F	25	75	$Si(CH_3)_3$	60	40
Cl	30	70	C_6H_5	42	58
Cl	29	71	*p*-FC_6H_4	39	61
Br	39	61	*p*-BrC_6H_4	38	62
CH_3	41	59	*p*-$CH_3OC_6H_4$	43	57

[a] Product ratios are calculated from ^{13}C and ^{19}F or ^{13}C and ^{1}H spectra. See original publication for further details.[28b]

This evidence supports the view that CH bonds are better hyperconjugative donors than CC bonds. Same conclusion was reached in our own study of Lewis acid-complexed α,β-unsaturated esters.[29] Thus, due to lack of contrary evidence, we shall focus on other issues surrounding the Cieplak model.

Table 3 Product Distribution in the Fluorination (DAST) of Mixtures (*anti* and *syn* Isomers) of 5-Substituted (X) Adamantan-2-ols.[a]

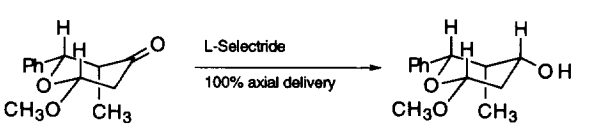
	Fluorides			Fluorides	
X	%anti	%syn	X	%anti	%syn
NO_2	5	95	$OCOCH_3$	21	79
	7	93	$N(CH_3)_2$	28	72
CN	11	89	CH_3	38	62
CO_2CH_3	30	70	$Si(CH_3)_3$	84	16
	30	70	$Sn(CH_3)_3$	100	0
F	10	90		>98	trace
	6	94	C_6H_5	41	59
Cl	15	85	*p*-$NO_2C_6H_4$	35	65
	16	84	*p*-CNC_6H_4	35	65
Br	18	82		35	65
	19	81	*p*-$CO_2CH_3C_6H_4$	39	61
I	35	65	*p*-FC_6H_4	41	59
	38	62	*p*-BrC_6H_4	36	64
OCH_3	34	66		38	62
	33	67	*p*-$CH_3OC_6H_4$	45	55
$OCOCH_3$	20	80	*p*-$(CH_3)_2NC_6H_4$	39	61

[a] Multiple results are based upon different methods of analysis, such as ^{13}C NMR, GC, ^{19}F NMR. See original publication for further details.[28b]

4. Studies Supporting the Cieplak Model

A. Hydride Reduction of 4-Tetrahydropyranones (4-THPN)

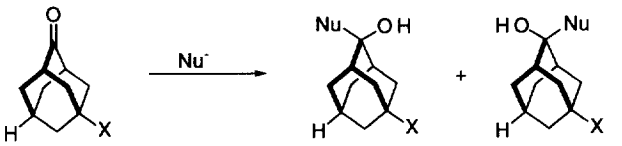
In 1985, Danishefsky and Langer found that reduction of pyranones with L-selectride led to predominantly equatorial alcohols.[30] The authors rationalized their results in terms of the Cieplak model. The results were suggested to be a case of electronic effect overriding steric approach. The argument is that oxygen substituents at C3 and C5 makes the C_α-C_β bonds electron-deficient, thus disfavoring equatorial



attack according to the Cieplak model. The accompanying equation illustrates the outcome for a substituted pyranone carrying a OCH_3 at C3. (However, for an alternative explanation of the pyranone results based on conformation, see Section 5. C.)

B. Hydride Reduction of 5-Substituted Adamantanones

Extensive studies by le Noble brought significant attention to the Cieplak model.[31-43] He and his co-workers pioneered syntheses and structural studies of adamantane derivatives,[31-35] and in 1986 published results of hydride reduction of 5-substituted-2-adamantanones (**4**) and of solvolysis of 2-adamantyl substrates.[36] The results of hydride reduction and CH_3Li addition are summarized in Table 4.



4 (syn) (anti)

Table 4. Stereochemical Course of Nucleophile Attack on 5-Substituted Adamantan-2-ones[a] (**4**)

			Alcohol	
5-Substituent	Nucleophile	Conditions	% Anti	% Syn
C_6H_5	$LiAlH_4$	Et_2O, rt	56	44
C_6H_5	$LiAl(O\text{-}t\text{-}Bu)_3H$	Et_2O, rt	49	51
t-Bu	$LiAlH_4$	Et_2O, rt	50	50
t-Bu	$LiAl(O\text{-}t\text{-}Bu)_3H$	Et_2O, rt	42	58
p-$C_6H_4NO_2$	$NaBH_4$	Me_2CHOH, rt	65	35
p-C_6H_4Cl	$NaBH_4$	Me_2CHOH, rt	60	40
C_6H_5	$NaBH_4$	Me_2CHOH, rt	58	42
p-$C_6H_4OCH_3$	$NaBH_4$	Me_2CHOH, rt	48	52
p-C_6H_4OH	$NaBH_4$	Me_2CHOH, rt	44	56
F	$NaBH_4$	Me_2CHOH, rt	62	38
Cl	$NaBH_4$	Me_2CHOH, rt	59	41
Br	$NaBH_4$	MeOH, 0° C	59	41
F	MeLi	Et_2O, 0° C	70	30
OH	$NaBH_4$	MeOH, 0° C	57	43
CF_3	$NaBH_4$	Me_2CHOH, 0° C	59	41
CF_3	MeLi	Et_2O, 0° C	72	28

[a] This is an updated table based on several of le Noble's articles. See original publications for further details.[36]

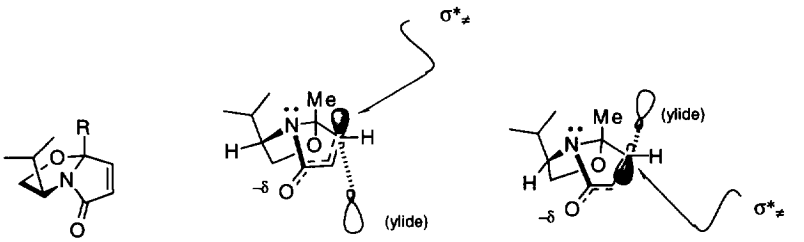
The stereoselectivity observed for these rigid molecules was best rationalized by the Cieplak model. At the time no other well known theory could explain these results. The widely-accepted Felkin-Anh model would predict stereochemistry opposite to that observed. A wide range of reactions was carried out by the le Noble group on the adamantane system.[37-43] This review, however, is limited to nucleophilic additions because there seems to be a general agreement on the transition state arrangement in electrophilic additions, namely, electrophilic addition to an sp^2 carbon should occur anti to electron-donor bonds.[44,45] The results from nucleophilic additions to 5-substituted-2-adamantanones (**4**) also appear to follow the same trend.

Part of the reason for wide-acceptance of the Cieplak model may be found in le Noble's influential paper published in 1986: "The principal advantage of Cieplak's proposal is that it recommends the very simple device of electron withdrawal or donation to predict preferred directions, and it appears to do so with success, at least in the cases reported here. Furthermore, it appears to be capable of extension to such additional features as the nucleophilicity of the reagent group, solvent effects, and the direction of approach in electrophilic addition of carbocations, carbenes, and alkylating agents to olefins and enolates."[36]

> Perhaps the most persuasive argument in terms of theory presented by le Noble is as follows: "---, there is a close connection between Cieplak's view of nucleophilic approach to carbonyl carbon and Winstein's concept of σ participation in the formation and hence capture of carbocations. The only distinguishing feature is that in the former theory, the delocalization of the neighboring σ electrons is into the σ^* orbital arising out of the combination of the high energy carbonyl π^* orbital and the unshared-pair orbital of the nucleophile; in Winstein's description of carbocations, these electrons are delocalized into the vacant p-orbital. As the bond formation progresses, the difference becomes smaller and finally vanishes as the carbonyl electrons become oxygen unshared electrons. It will be clear that the stabilization for carbocations will be greatest before the nucleophile begins to bind, whereas with the carbonyl compound, stabilization is more prominent in the transition state."[36]

To date, this analysis has met with little challenge (however, see footnote 21). A theoretical study on nucleophilic additions to 5-aza-2-adamantanone has recently appeared.[40] The authors of that study seem to acknowledge the importance of both torsional and hyperconjugative effects.

In 1988, Meyers *et al.*, convinced by le Noble's experimental results, applied the Cieplak model to rationalize the stereochemistry of ylide additions to lactam **5**.[46] Cyclopropanation proceeded with high selectivity from the sterically more hindered (concave) face to give an endo/exo ratio in a range of 96-99:1. These results were explained by comparison of transition states **C** and **D**, which clearly showed the essence of the Cieplak effect, namely, stabilization of the $\sigma^*_{\neq}$ by the adjacent electron donating methyl (**C**) or destabilization by the electronegative CO bond (**D**). This intriguing effect became a key component of Meyers' synthetic planning until later findings made him change his view.[47] For details, see Section 5. B.



5 C D

Figure 6 Stabilization of the $\sigma^*_{\neq}$ by the adjacent electron donating methyl (**C**) or destabilization by the electronegative CO bond (**D**)

C. Nucleophilic Additions to 3-Substituted Cyclohexanones

Cieplak and Johnson reported a systematic study of nucleophilic additions to 3-substituted cyclohexanones (Fig 7) and electrophilic additions to 3-substituted methylenecyclohexane in 1989.[2] The 3-substituent was varied from electron donating groups, such as Me_3Si, to electron withdrawing groups, such as F_3C, in an attempt to correlate π-facial selectivity and electron deficiency of the ring C_α-C_β bond. The results are listed in Table 5.

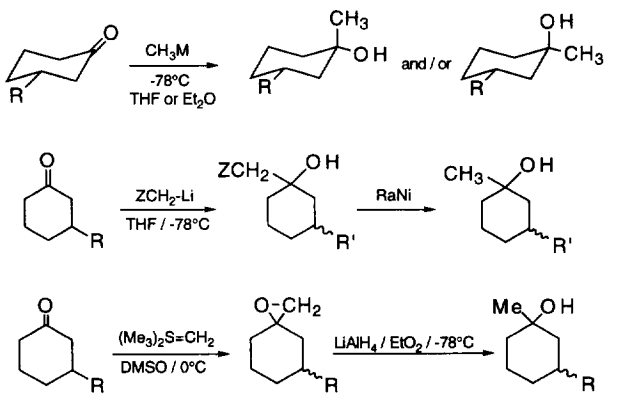


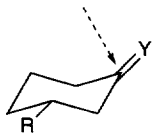
Figure 7. Nucleophilic additions to 3-substituted cyclohexanones.

Examination of the data reveals a consistent pattern of the C-3 substituent effect. As compared to 3-H and 3-phenyl groups, the electron-releasing 3-*tert*-butyl and 3-trimethylsilyl groups decrease the percentage of axial attack. The electron-withdrawing $C_6H_4CF_3$, C_6F_5, and CF_3 groups increase the proportion of axial attack.

In their article, other models of π-facial selection were also discussed extensively and led Cieplak and Johnson to the following conclusion: "The models that invoke the effects of ground-state distortions or

repulsive torsional interactions appear to fail this test. In contrast, the data reported here are consistent with the predictions of the Cieplak model, which attributes stereoelectronic control in cyclohexane-based systems to electron donation into the $\sigma^*_{\neq}$ orbital, the vacant orbital associated with the incipient bond."[2] However, for an alternative rational of the results in Table 5 based on electrostatic effects, see Section 5. D.

Table 5 Percentage of Axial Attack in Nucleophilic Additions to 3-Substituted Cyclohexanones and Electrophilic Additions to 3-Substituted Methylenecyclohexanes



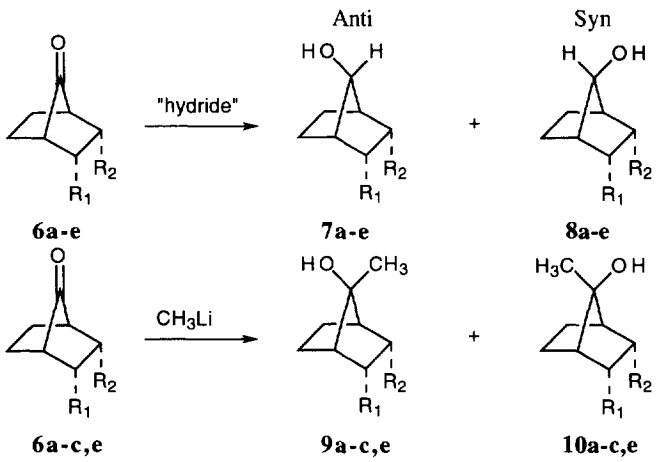
Y = O R	CH_3Li Ether -78 °C	$Li_2(CH_3)_3Cu$ Ether -78 °C	CH_3Li THF -78 °C	$PhSCH_2Li$ THF -78 °C	$PhSO(NMe)CH_2Li$ THF -78 °C	$Me_2S{=}CH_2$ DMSO 0° C
a $Si(CH_3)_3$	15	2	22	10	55	44
b *tert*-Bu	19	3	27	11	56	48
c H	21	6		17;20		80
d *p*-$MeOC_6H_4$	24	8	30	16	66	44
e *p*-MeC_6H_4	23	8	30	19	65	48
f C_6H_5	25	7	30	15	65	45
g *p*-$F_3CC_6H_4$	28	10	36	24	72	46
h C_6F_5	34	21	50	28	70	58
i CF_3	50	42	58	53	83	69

$Y = CH_2$ R	$Hg(OAc)_2$ H_2O 0 °C	mCPBA CH_2Cl_2 0 °C	OsO_4/Me_3NO THF/H_2O 25 °C
j $Si(CH_3)_3$	40	52	7
k t-Bu	58	60	
l H	69	69	14
m C_6H_5	67	70	15
n *p*-$F_3CC_6H_4$	70	75	14
o CF_3	92		

D. Nucleophilic Additions to 2,3-Endo, endo-disubstituted-7-norbornanones

By 1990, interest in the Cieplak effect was so great that several groups designed model systems to test its validity. Interestingly enough, if the molecules are rigid and sterically unbiased, the observed stereoselectivity usually follows the rule: nucleophiles attack anti to the best electron-donor bond. It should be noted, however, that the assumption that a CH bond is a better donor than a CC bond does not always apply, as we shall see from the following example.

Mehta and co-workers published a series of papers describing reactions of 2,3-disubstituted-7-norbornanones (Figure 8).[48-50] When compounds **6a-6e** were subjected to nucleophilic addition reactions, the ratio of anti- and syn- alcohols varied according to the endo substituents R_1 and R_2. As shown in Table 6, the anti-alcohols predominate when R_1 and R_2 are the electron-withdrawing acetoxy groups (CH_3CO_2), whereas the syn-alcohols are the major product when R_1 and R_2 are ethyl groups (CH_3CH_2).



6a: $R_1 = R_2 = CO_2CH_3$ **b**: $R_1 = R_2 = CH_2OCH_3$
c: $R_1 = R_2$ = vinyl **d**: R_1 = vinyl; R_2 = ethyl **e**: $R_1 = R_2$ = ethyl

Figure 8. Nucleophilic additions to 2,3-endo, endo-disubstituted-7-norbornanones

The results in Table 6 were said to be "fully consonant" with the Cieplak model. However, the authors acknowledged that it was unexpected that the methoxymethyl and the vinyl groups also acted as electron donating substituents, while traditionally they are considered electron-withdrawing. This contradiction was further discussed by Mehta and le Noble in a joint paper published in 1991.[25] It was suggested that "the origin of these difficulties may lie in the conformational freedom of these substituents of **6**. There are many discussions in the literature of the connection between hyperconjugation and conformation, and it may be best at present to restrict discussions of electronic effects of face selection to

probes in which not only the carbonyl-flanking groups but also distant face-differentiating groups are held in rigid and well-known positions."[25]

Table 6. Product Ratios in Metal Hydride Reductions and Methyllithium Additions to 2,3-disubstituted-7-norbornanones (**6a-e**)

	anti:syn distribution			
substrate	$NaBH_4$	$LiAlH_4$	$(t\text{-}BuO)_3LiAlH$	CH_3Li
6a	84:16	87:13	77:23	>90:<10
	(**7a**) (**8a**)	(**7a**) (**8a**)	(**7a**) (**8a**)	(**9a**) (**10a**)
6b	40:60			34:66
	(**7b**) (**8b**)			(**9b**) (**10b**)
6c	36:64	35:65	34:66	27:73
	(**7c**) (**8c**)	(**7c**) (**8c**)	(**7c**) (**8c**)	(**9c**) (**10c**)
6d	25:75			
	(**7d**) (**8d**)			
6e	20:80	21:79	29:71	17:83
	(**7e**) (**8e**)	(**7e**) (**8e**)	(**7e**) (**8e**)	(**9e**) (**10e**)

E. Nucleophilic Additions to 2,2-Diarylcyclopentanones

Halterman and McEvoy studied the sodium borohydride reduction of 2,2-diarylcyclopentanones.[51] The percentage of cis versus trans attack is as high as 79:21 (Table 7), which surpasses those ratios on 5-substituted 2-adamantanones.[36] A Hammett plot of log (cis/trans) versus the σ para parameter produced a linear relationship with a correlation coefficient of 0.98. According to these researchers, "the diastereoselective reduction of these 2,2-diarylcyclopentanones provides strong evidence for the involvement of stereoelectronic control in carbonyl reductions as postulated by Cieplak." For an alternative rational based on electrostatic effects, see Section 5. D.

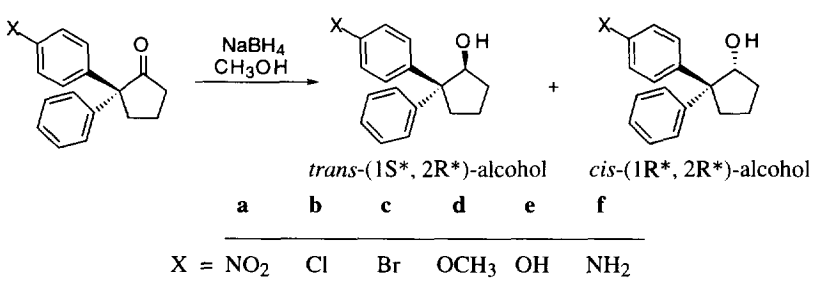


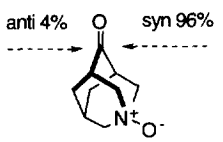
Table 7. Product Ratios in Sodium Borohydride Reduction of 2,2-diarylcyclopentanones

X	Alcohol	σ_p	% trans	% cis	log (cis/trans)
NO_2	**a**	0.778	21	79	0.575
Cl	**b**	0.227	37	63	0.231
Br	**c**	0.232	37	63	0.231
(H)	**g**	0.0	(50	50)	0.0
OCH_3	**d**	-0.268	57	43	-0.122
O^-	**e**	-0.52	70	30	-0.368
NH_2	**f**	-0.66	64	36	-0.301

F. Nucleophilic Additions to 5-Azaadamantanones

In 1992, le Noble disclosed results from the reduction of 5-aza-2-adamantanone (**11**) derivatives. The π-facial selectivity reached 96:4 (syn:anti) in the case of 5-aza-2-adamantanone N-oxide (**12**).

11



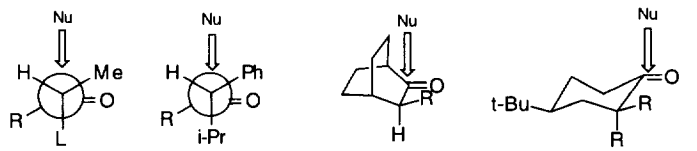
12

This high selectivity has been viewed as an excellent example of the Cieplak model in operation.[42] The possibility of an alternative reason for the high selectivity, such as an electrostatic interaction bringing the borohydride anion preferentially to the syn face, was excluded by solvent studies. The ratio of alcohols did not change with a change from methanol to water or even to saturated aqueous sodium chloride. To support the argument that **11** and **12** are free from skeletal distortion, three references to crystal structures of related compounds were cited.[42] However, *ab initio* molecular orbital calculations at the 6-31G** level indicate significant distortions in the structure of **12**.[43]

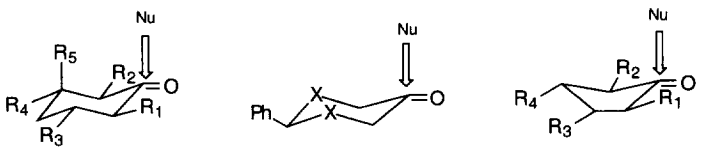
5. Studies Opposing the Cieplak Model

A. Modified MM2 Force Field and the Reduction of Benzocycloheptanone

In 1987, Wu and Houk reported computational results on hydride reduction of α-substituted cyclohexanones using a modified version of Allinger's MM2 force field, which incorporates the results from *ab initio* molecular modeling of the LiH reduction of acetone.[22] This model quantitatively accounts for the stereoselectivity of $LiAlH_4$ reductions. Houk incorporated the conformational preferences of the α-substituent into the model by redefining the torsional parameters for dihedral angles about the C_α-CCO bond. A comparison of predicted and experimental results for $LAlH_4$ reductions and some methyl Grignard additions to ketones **13-19** are shown in Table 8. There is an outstanding agreement for acyclic, cyclic, and bicyclic ketones. Houk concludes: "In the absence of steric hindrance, axial attack is preferred in order to minimize torsional repulsion."



13 **14** **15** **16**

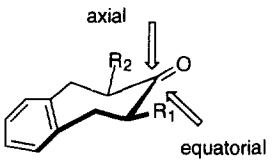


17 **18** **19**

In 1988, Houk's team reported experimental results that support the predictions of their modified MM2 model.[52] Derivatives of benzocycloheptenone **20** were synthesized and subjected to $LiAlH_4$ reduction. The products from equatorial attack are favored from both **20b** and **20c**. From **20b**, the ratio of equatorial/axial attack is 60:40, just as predicted, whereas only the product of equatorial attack can be detected from **20c**. According to the crystal structure of **20c**, equatorial attack can seemingly occur with less eclipsing than axial attack.

Table 8 Observed (Experiment) and Calculated Diastereofacial Selectivity (Axial: Eq) for Nucleophilic Additions to Various Ketones

Compound		Reagent	Stereochemistry	
			Expt.	Calc.
13a.	L = C_6H_{11}, R = Me	$LiAlH_4$	62 : 38	69 : 31
b.	R = Et	$LiAlH_4$	67 : 33	72 : 28
c.	R = i-Pr	$LiAlH_4$	80 : 20	79 : 21
d.	R = t-bu	$LiAlH_4$	62 : 38	80 : 20
e.	L = Ph, R = Me	$LiAlH_4$	74 : 26	60 : 40
f.	R = Et	$LiAlH_4$	76 : 24	67 : 33
g.	R = i-Pr	$LiAlH_4$	83 : 17	79 : 21
h.	R = t-Bu	$LiAlH_4$	98 : 2	94 : 6
14a.	R = Me	$LiAlH_4$	97 : 3	93 : 7
b.	R = H	MeMgBr	45 : 55	36 : 64
15a.	R = Me	$LiAlH_4$	50 : 50	35 : 65
b.	R = Et	$LiAlH_4$	68 : 32	46 : 54
c.	R = i-Pr	$LiAlH_4$	72 : 28	58 : 42
d.	R = t-Bu	$LiAlH_4$	15 : 85	30 : 70
e.	R = Ph	$LiAlH_4$	5 : 95	7 : 93
16a.	R = H	$LiAlH_4$	88-91 : 12- 9	88 : 12
b.	R = Me	$LiAlH_4$	95 : 5	90 : 10
17a.	R_1 = Me, $R_2 = R_3 = R_4 = R_5$ = H	$LiAlH_4$	60-82 : 40-18	82 : 18
b.	$R_1 = R_2$ = Me, $R_3 = R_4 = R_5$ = H	$LiAlH_4$	62 : 38	73 : 27
c.	R_3 = Me, $R_1 = R_2 = R_4 = R_5$ = H	$LiAlH_4$	84-87 : 16-13	88 : 12
d.	$R_3 = R_4 = R_5$ = Me, $R_1 = R_2$ = H	$LiAlH_4$	20-48 : 80-52	30 : 73
18a.	X = CH_2	$LiAlH_4$	91 : 9	89 : 11
b.	X = O	$LiAlH_4$	94 : 6	96 : 4
c.	X = S	$LiAlH_4$	15 : 85	9 : 91
a.	X = CH_2	MeMgI	45 : 55	68 : 32
b.	X = O	MeMgI	98 2	94 : 6
c.	X = S	MeMgI	7 : 93	3 : 97
19a.	R_1 = Me, $R_2 = R_3 = R_4$ = H	$LiAlH_4$	74-84 : 26-16	70 : 30
b.	R_3 = Me, $R_1 = R_2 = R_4$ = H	$LiAlH_4$	40-27 : 60-73	46 : 54
c.	$R_1 = R_2$ = Me, $R_3 = R_4$ = H	$LiAlH_4$	----	93 : 7
d.	$R_3 = R_4$ = Me, $R_1 = R_2$ = H	$LiAlH_4$	90 : 10	73 : 27

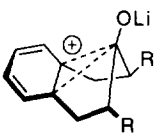


20a: $R_1 = R_2 = H$ **b**: $R_1 = Me$, $R_2 = H$ **c**: $R_1 = R_2 = Me$

Calculations with the modified MM2 methods predict that the transition structure for equatorial-like attack is 0.2 kcal/mol more stable than that for axial-like attack. This model disregards the metal cation but includes the hydride as the nucleophile in the transition state.[22,52] According to Houk, the similarity of the local environment of **20** to cyclohexanone suggests that the Cieplak model would predict a preference for axial attack. Axial attack is more or less anti to two CH bonds, whereas equatorial attack is anti to two CC bonds.

Furthermore, Houk contends: "Once the ground-state conformation is known, Felkin's model also predicts that the equatorial attack is favored, because the staggering in the transition state of equatorial attack is better." Houk's conclusion: " ··· we have demonstrated that the stereoselectivity of $LiAlH_4$ reductions of benzocycloheptanones can be correctly predicted by our quantitative calculational model and by Felkin's torsional strain model but not by other models."[52]

With regard to that conclusion, le Noble has argued that the authors failed to consider π-bond participation. A structure with lithium cation coordinating to the carbonyl oxygen and π-bond bridging to the carbonyl carbon (see **21**), was suggested.[35]



21

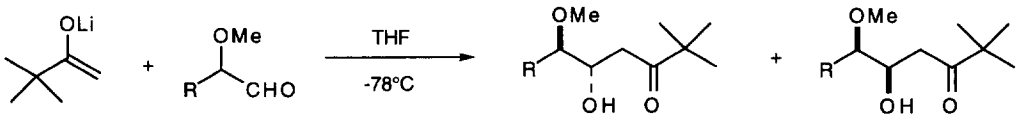
In their 1989 publication Cieplak and Johnson also provided a rebuttal to Houk.[2] They found no basis for the claim that Houk's results support the Felkin hypothesis of torsional strain and stated: "According to Felkin, the major contribution to the energy difference between the axial and equatorial transition states would be a destabilizing interaction in the latter due to eclipsing of the incipient bond and the axial CH bonds." They found this contribution to be negligible in Houk's model. Furthermore, they found that nearly the entire energy difference in favor of the axial transition state is produced by two unprecedented torsional interactions, which are introduced by unusual parameterization.

This unusual gauche-type parameterization stabilizes the axial transition state. According to Cieplak: "Stabilization of that kind, although of different origin, has been postulated by Cieplak, ···, and not by Felkin. ··· Therefore, even accepting the premise that MM2 results provide any clues as to what is the

physical nature of the effect in question, we cannot see how the Houk and Wu results can be interpreted as supportive of the torsional strain hypothesis."[2]

B. Acyclic Asymmetric Induction

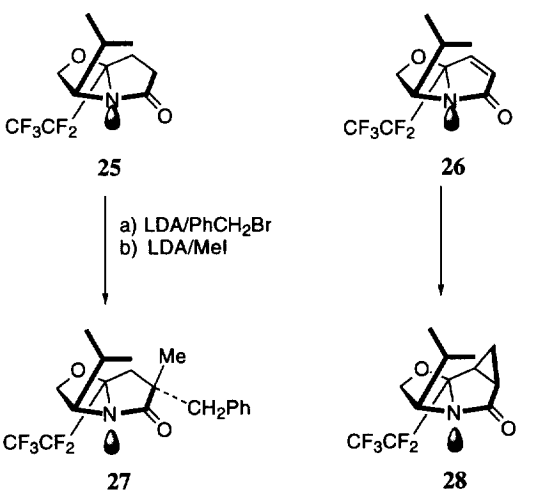
In 1987, Heathcock and Lodge studied the addition of the lithium enolate (**22**) of pinacolone to a series of α-chiral aldehydes.[53] The stereochemical results are consistent with a combination of steric effects and with the Felkin-Anh model but cannot be explained by the Cieplak hypothesis.



22 **23** **24**

a: R = Me; **b**: R = Et; **c**: R = *i*-Pr; **d**: R = *t*-Bu; **e**: R = Ph

In early 1989, Meyers changed his earlier support of the Cieplak model based on subsequent experimental results with lactams **25** and **26**, which have a strongly electronegative pentafluoroethyl group.[47] The cyclopropanation of **26** favors the endo product **28** by 20:1, a result of "anti Cieplak" stereoselectivity. Alkylation of the enolate from **25** also follows the same facial selectivity, namely, the electrophile enters from the face anti to the electronegative pentafluoroethyl group.



Based on these results, Meyers concluded "··· that the stabilization of the σ* orbital in the transition state, in order to direct stereochemical events, is not a major player for the system discussed here. Had the Cieplak rule held, we would have seen the opposite, or at least less selective, stereochemical behavior in the reactions of **25** and **26**."

C. Conformational Studies of 4-Tetrahydropyranones

With regard to Danishefsky's result (Section 4a), our research team studied the conformational profile of 4-tetrahydropyranones (THPN) by molecular mechanics,[54a] by variable temperature NMR,[54b] and for 2-hydroxy-THPN by *ab initio* MO methods.[54c] Danishefsky's presumption that the ground-state conformation of cis-2-methoxy-6-phenyl-4-THPN is a diequatorial chair appears to be inaccurate (see Figure 9). The equatorial phenyl orientation is opposed by an anomeric effect involving the OCH_3. Indeed, according to an MM2 calculation, the C2-methoxy prefers to be axial in the 4-pyranone system.

Our *ab initio* calculations reveal a direct relationship between the C-X distance and the endocyclic torsional angle ϕ in 4-X substituted cyclohexanones. Namely, the ϕ angle decreases as the C-X bond length becomes shorter.

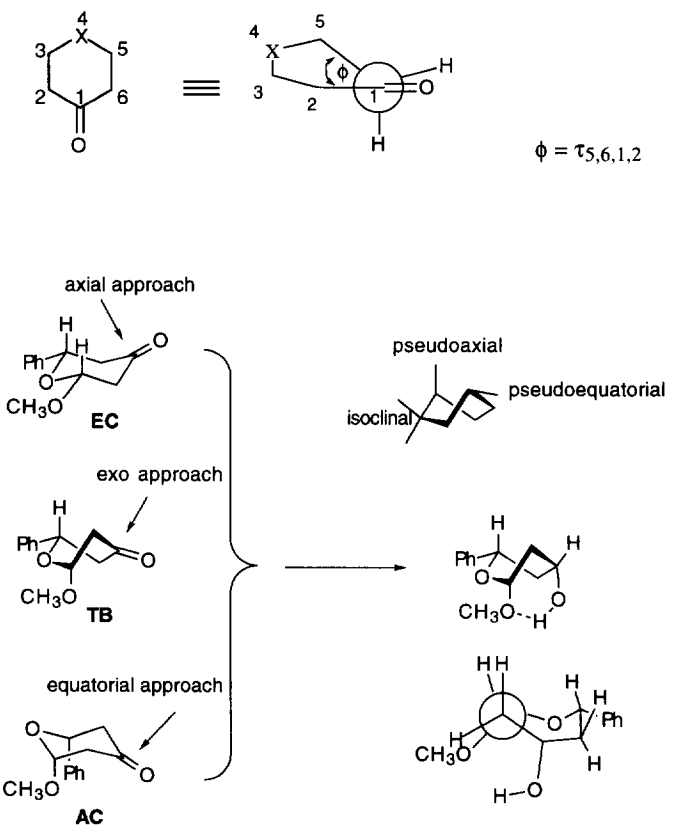


Figure 9. Three different conformations can result in the same π-facial selection.

The following increasing order of ϕ was found: 4-THPN (X = O, ϕ = 44.5 °) < 4-piperidinone (X = N, ϕ = 47.1°) < cyclohexanone (X = C, ϕ = 49.1 °) < 4H-thiopyran-4-one (X = S, ϕ = 53.6 °). A small ϕ indicates a flatter ring. A flattened ring reduces the barrier for ring inversion and also reduces the difference in energy between axial and equatorial additions on the basis of nucleophile trajectory. Our variable temperature NMR study indicates that the 4-THPN derivatives have rapid equilibrating conformations (diequatorial and diaxial) in solution. According to the Curtin-Hammett principle,[55] product ratios depend only on the energy difference of the diastereomeric transition states. Since we have shown that both the diaxial and the diequatorial conformers (**AC** and **EC**) are present, the product (equatorial alcohols) in the L-Selectride reduction[30] could have come from equatorial attack on the diaxial isomer (**AC**, Figure 9). Consequently, the high stereoselectivity in the hydride reduction of 4-THPN does not require a transition state resembling **EC**.

D. Theoretical Studies Suggesting Electrostatic Effects

Although there are disagreements about the validity of the theory behind the Cieplak model, no alternative explanations are available for the stereoselectivity of hydride reductions of sterically unbiased ketones, such as 5-substituted 2-adamantanones and 2,2-diarylcyclopentanones until recently. The direction of π-facial selection is consistent with the hyperconjugative effects proposed by Cieplak and is opposite to the prediction based on the widely-accepted Felkin-Anh model. However, in 1991 calculations on model systems,[56-57] as well as experiments and calculations with 5-substituted 2-decalones and cyclohexanones,[58] indicated that direct electrostatic interactions between remote polar groups and the nucleophile could influence the stereoselectivities of hydride reductions.

Wong and Paddon-Row calculated the transition structures for nucleophilic addition of both cyanide anion and LiH on four α-substituted aldehydes (Figures 10 & 11), in which the electronegativity of the substituent increases along the series SiH_3, CH_3, CN, F. Conformations of the free aldehydes and the transition structures for cyanide anion attack and for lithium hydride attack were fully optimized by use of the HF/3-21G and HF/6-31G(d) theoretical models.

The transition structures for attack by cyanide anion (Fig. 10) are consistent with the Anh-Eisenstein prediction. The SiH_3 and CH_3 donor groups prefer the inside conformation (**29b, 30b**) to either the outside or anti conformations, whereas the CN and F acceptor groups have the strongest preference for the anti conformation (**31a, 32a**). Electrostatic interactions between the C-X and C=O bonds could account for the energetic distinction between the inside and outside conformations in much the same way that they influence the conformational energies of the free aldehydes. For example, **32c** is much more stable than **32b**.

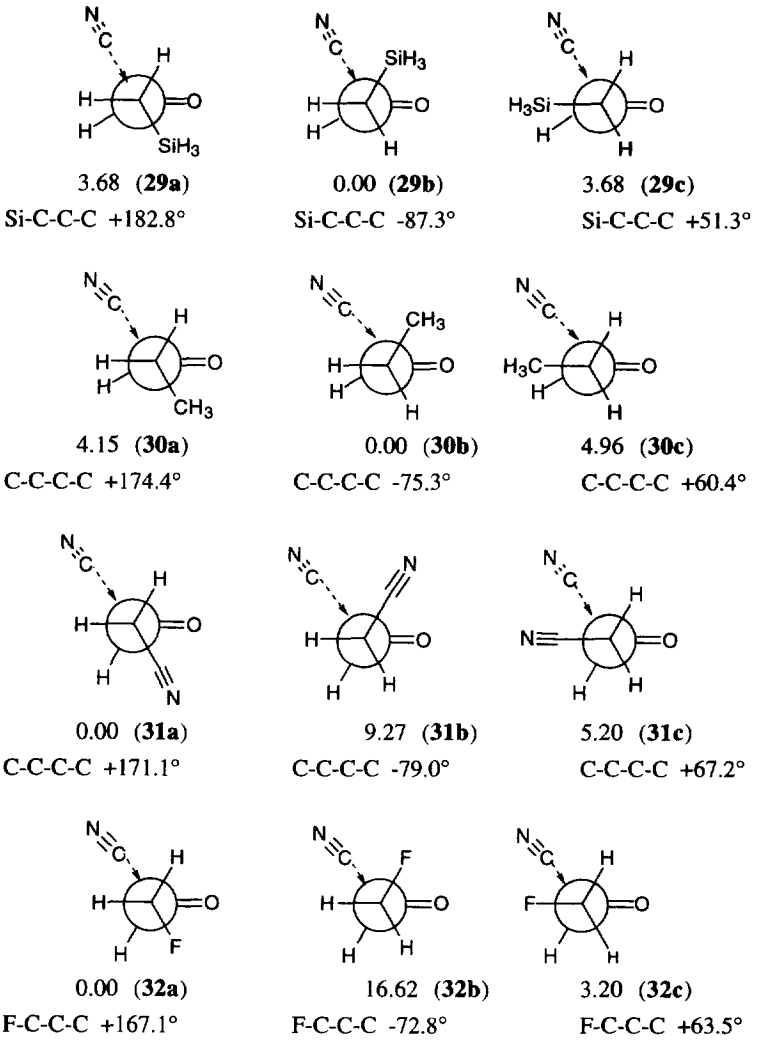
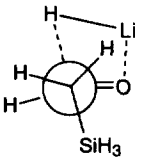


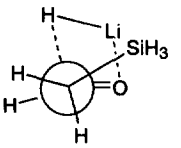
Figure 10 HF/6-31G(d) optimized transition structures (**29**)-(**32**) for cyanide anion attack. Relative energies (vibration-less) computed by MP2(FC)/6-31G+G(d)//HF/6-31G(d) are in kJ/mol. Dihedral angles (degrees) are defined according to the following sequence: α-substituent-C2-C1-nucleophile.



(33a)

3.41 (16.01)

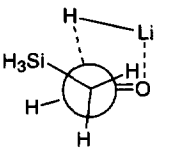
Si-C-C-H +172.6°



(33b)

6.75 (19.77)

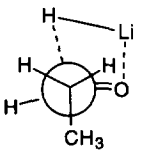
Si-C-C-H -80.8°



(33c)

0.00 (0.00)

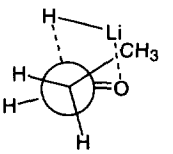
Si-C-C-H +32.2°



(34a)

5.93 (2.70)

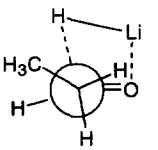
C-C-C-H +168.0°



(34b)

0.00 (0.00)

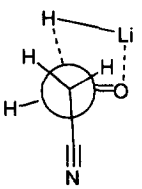
C-C-C-H -77.6°



(34c)

5.12 (8.11)

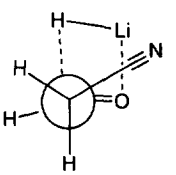
C-C-C-H +59.1°



(35a)

1.31 (0.00)

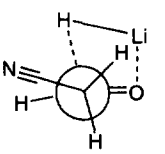
C-C-C-H +157.1°



(35b)

0.00 (36.25)

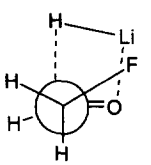
C-C-C-H -83.2°



(35c)

7.61 (24.02)

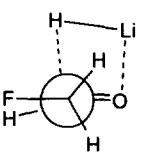
C-C-C-H +81.0°



(36b)

0.00 (18.01)

F-C-C-H -69.7°



(36c)

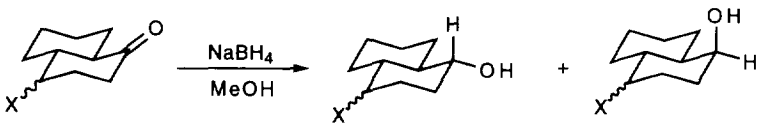
6.64 (0.00)

F-C-C-H +79.9°

Figure 11 HF/6-31G(d) optimized transition structures (**33**)-(**36**) for lithium hydride attack. Relative energies (vibration-less) computed by MP2(FC)/6-31+G(d)//HF/6-31G(d) are in kJ/mol. Relative energies with Li^+ removed are in parentheses. Dihedral angles (degrees) are defined according to the following sequence: α-substituent-C2-C1-nucleophile.

The transition structures (**33-36**, Fig. 11) for attack by LiH are in clear contrast to those involving attack by cyanide. The inside conformation is now preferred over the anti conformation when X = CN or F. This contra Anh-Eisenstein effect is explained in terms of an overriding attractive electrostatic interaction between X and Li, since removal of Li alters the energetic preference to favor the anti conformation (**35a**) for X=CN, and to favor the outside conformation (**36c**) for X = F. In conclusion, the results suggest that electrostatic effects, as well as Anh-Eisenstein effects, influence conformational preferences in the transition structure.

In 1991, Houk and co-workers published a combined experimental and theoretical study.[58] Transition structures for axial and equatorial additions of lithium hydride to cyclohexanone were located with full optimization with the 3-21G basis set. The axial transition structure is more stable than the equatorial transition structure by 1.0 kcal/mol at the 3-21G basis set level. This difference increases to 1.8 kcal/mol when the calculations are performed with the 6-31G* basis set on the 3-21G geometry. Torsional strain was evident for equatorial attack . Substituent effects were studied by calculations with substituents at



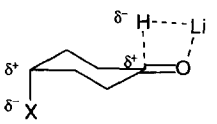
37/38 **A** **B**

Table 9 Stereoselectivities of Reductions of 4-Substituted *trans*-Decalones with Excess $NaBH_4$ in Methanol at 25 °C

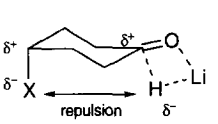
Compd.	X	% A	% B
37a	H	60	40
37b	eq OH	61	39
37c	eq OAc	71	29
37d	eq Br	66	34
37e	eq Cl	71	29
38b	ax OH	85	15
38c	ax OAc	83	17
38e	ax Cl	88	12
38f	ax F	87	13

the C4 position in the transition structure. The effects of OH and NH_2 substitution on stereoselectivity were shown to be dependent upon group orientation. This orientation dependence was explained in terms of long-range electrostatic effects.

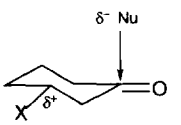
Experimentally, a series of nine 4-substituted trans-2-decalones (**37** and **38**) were synthesized and submitted to hydride reduction by $NaBH_4$. Equatorial electron-withdrawing substituents have very little effect on the stereoselectivity, whereas axial substituents have a large effect (Table 9). This outcome was consistent with the theoretical study and was rationalized by electrostatic or dipole effects. Equatorial attack



39



40

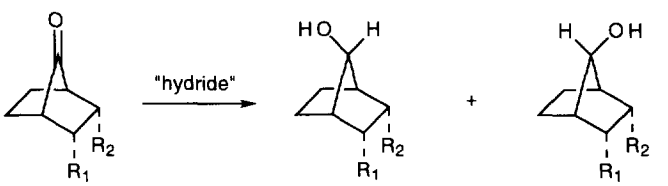


41

by the nucleophile is destabilized by an electrostatic repulsive interaction with the axial substituent (**40**), whereas axial attack is favored by the interaction **39**. The strong orientation preferences of OH and NH_2 groups in the calculated transition structures support this assessment.

Electrostatic effects, according to Houk,[58] also explain the variation in stereoselectivity reported by Cieplak and Johnson for 3-substituted cyclohexanones (Table 5), by Halterman *et al.* for 2,2-diarylcyclopentanones (Table 7), and by Mehta for 1,2-endo, endo-disubstituted-7-norbornanones (Table 6). For example, with 3-substituted cyclohexanones, an electron-withdrawing substituent induces positive charge at C3, which stabilizes axial attack of a negatively charged nucleophile, as shown in **41**.

In 1992, Paddon-Row, Wu, and Houk performed *ab initio* molecular orbital calculations on the transition structures of LiH addition to 1,2-disubstituted-7-norbornanones optimized with the 6-31G* basis set.[59] The energies were also evaluated with MP2/6-31G* calculations. The calculated energy differences for syn and anti attack of LiH on **6** are shown in Table 10. These calculated stereoselectivities agree with the experimental observations.

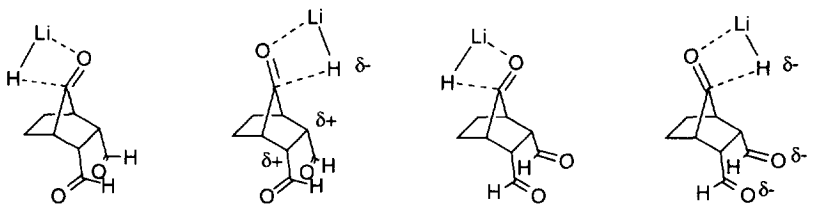


6 **7** **8**

Table 10 Calculated Relative Energies (kcal/mol) of Transition Structures for the Reaction of Lithium Hydride with **6a-g**, and Experimental Data for $NaBH_4$ Reductions

		$E_{(anti)} - E_{(syn)}$		
Compd.,	R1, R2	6-31G*	MP2/6-31G*	Experimental
6a	CHO (CC)	3.0	4.0	—
	CHO (CH)	-0.2	-0.6	—
6b	CO_2Me (CC)	2.8	0.9	—
	CO_2Me (CH)	1.0	—	—
6c	CH_2F	0.5	0.7	—
6d	CH_2OH	-0.1	-0.1	-0.2
6e	$CH{=}CH_2$	-0.3	-0.4	-0.3
6f	CH_3	-0.5	-0.6	-0.8
6g	SiH_3	-0.8	-0.3	-1.6

A notable feature is the dependence of calculated stereoselectivity upon the conformation of substituents, as found earlier for 4-substituted cyclohexanones. Figure 12 shows four transition structures for the reaction of LiH with **6a**. The syn addition is more stable than the anti by 4 kcal/mol when the two



	42	**43**	**44**	**45**
TS	4.0	0.0	5.6	6.0
TS, no LiH	0.0	0.8	2.4	2.6

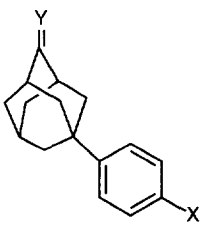
Figure 12 Transition structures of lithium hydride addition to 2,3-diformyl-7-norboranone. Relative energies (kcal/mol, MP2/6-31G*) of the transition structures, and TS without LiH (TS, no LIH).

C=O bonds eclipse the C-C bonds (**43** vs **42**). There is essentially no geometrical distortion about the carbonyl group in the ground states of **6**, and the orientation of the (remote) substituents at C2 and C3 has little effect on geometrical distortion. Therefore, torsional effects are not important factors for stereoselectivity in these systems. The calculated orientation dependence of stereoselectivity also cannot be explained by hyperconjugative effects, because the orientations of the substituents do not influence significantly the electron-donating ability of the allylic bonds.

To evaluate electrostatic interactions between substituents and nucleophile, the relative stabilities of the four transition states with distorted carbonyls were calculated by removal of the LiH from **42-45**. The calculated relative energies resemble those of ground states. This result clearly indicates that the relative stabilities of the syn and anti additions of LiH are largely determined by electrostatic interactions. As shown in **42-45**, the most favorable transition structure (**43**) has the hydride nearer the positively-charged atoms. The two anti transition structures (**42** and **44**) have much weaker stabilizing interactions with the positive carbon centers; and structure **45** suffers somewhat from destabilizing interactions with the carbonyl oxygen. In summary, Paddon Row et al, showed that electrostatic effects of remote substituents could have a significant influence on the stereoselectivities of nucleophilic additions.

E. Experimental Studies Suggesting Electrostatic Effects

The ^{13}C NMR chemical shifts of a series of 5-aryl-2-adamantanones were recorded by Adcock and co-workers.[28b] The carbonyl and ethylenic ^{13}C substituent chemical shifts are shown to be proportional to substituent field effects. By use of the polar field susceptibility parameter (ρ_F) for the carbonyl shifts, polar field parameters (σ_F values) have been calculated for a series of p-XC_6H_4 substituents. π-Facial diastereoselectivities for the reduction ($NaBH_4$) and methylation (MeLi) of para-substituted phenyl derivatives of **4** (Y = O) and, as well, for the hydrochlorination of similarly substituted alkenes **4** (Y = CH_2), have been determined and correlated successfully against polar field parameters ($\Delta\sigma_F$ values).



4

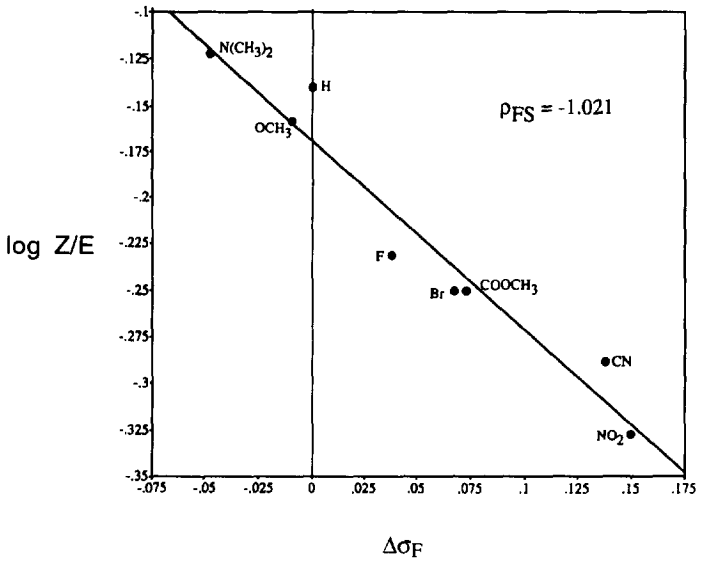


Figure 13 Plot of $\log_{10}[Z]/[E]$ for the $NaBH_4$ reduction of *para*-substituted 5-phenyl-2-adamantanones **4** (Y = O) versus $\Delta\sigma_F$

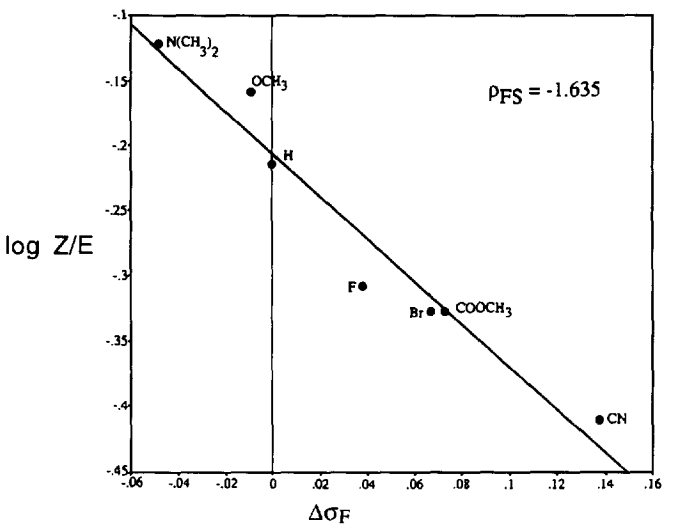


Figure 14 Plot of $\log_{10}[Z]/[E]$ for the methylation (CH_3Li) of *para*-substituted 5-phenyl-2-adamantanones **4** (Y = O) versus $\Delta\sigma_F$

The plots in Figures 13 and 14 show that the logarithms of [Z]/[E] correlate linearly with the respective $\Delta\sigma_F$ values and thereby suggest that the stereochemical outcome of these nucleophilic additions

is governed by the electrostatic field influence of the remote substituent. The relative stability of the two diastereomeric transition states for *syn* and *anti* additions is determined predominantly by electrostatic interactions.

By use of the Hammett-type equation (log [syn/ [anti] = $\rho_{FS}\sigma_F$), polar-field induced π-facial selectivities were calculated for the nucleophilic addition reactions of **4** (Y = O). These are listed in Tables 11 and 12 and compared with the experimentally observed product ratios. The data for nucleophilic additions are in good agreement with the calculated results. According to Adcock, the Me_3Sn group is a powerful electron donor in hyperconjugation. However, the selectivity exerted by this group (Tables 11 and 12) is very small, in accord with expectations based purely on electrostatic grounds. Thus, transition-state hyperconjugation is unimportant according to Adcock.[28b]

Table 11 Calculated Polar-Field Induced π-Facial Selectivities vs Observed Product Distributions for $NaBH_4$ Reduction of 5-Aryl-Adamantan-2-ones (**4**, Y = O)

		Obsd		Calcd[a]	
para-X	σ_F	% Anti	% Syn	% Anti	% Syn
NO_2	0.62	75	25	81	19
CN	0.54	69	31	78	22
CF_3	0.42	59	41	73	27
$COOCH_3$	0.29	57	43	66	34
F	0.41	59	41	72	28
Cl	0.43	63	37	73	27
Br	0.44	60	40	74	26
I	0.41	64	36	72	38
OCH_3	0.30	64	36	67	33
$OCOCH_3$	0.37	62	38	70	30
$N(CH_3)_2$	0.28	65	35	66	34
C_6H_5	0.17	58	42	60	40
CH_3	0.03	51	49	52	48
$C(CH_3)_3$	0.02	50	50	51	49
$Si(CH_3)_3$	0.01	50	50	50	50
$Sn(CH_3)_3$	-0.04	48	52	48	52

[a] log [syn]/[anti] = $\rho_{FS}\sigma_F$; ρ_{FS} = -1.01.

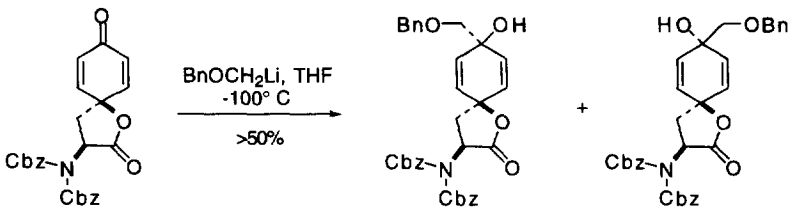
Table 12 Calculated Polar-Field Induced π-Facial Selectivities and Observed Product Distributions for Methyllithium Addition to 5-Aryl-Adamantan-2-ones (**4**, Y = O).

		Obsd		Calcd[a]	
X	σ_F	% Anti	% Syn	% Anti	% Syn
CN	0.59	68	32	90	10
CF_3	0.44	72	28	84	16
$COOCH_3$	0.22	55	45	69	31
F	0.39	66	34	81	19
Cl	0.43	62	38	83	17
Br	0.44	60	40	84	16
I	0.42	57	43	83	17
OCH_3	0.19	63	37	67	33
$N(CH_3)_2$	0.12	63	37	61	39
C_6H_5	0.15	62	38	64	36
CH_3	0.05	54	46	55	45
$Si(CH_3)_3$	0.00	49	51	50	50
$Sn(CH_3)_3$	-0.04	48	52	46	54

[a] $\log [syn]/[anti] = \rho_{FS}\sigma_F$; $\rho_{FS} = -1.01$.

Adcock concludes: "The results ... strongly suggest that it is unnecessary to invoke transition-state hyperconjugation in terms of Cieplak's model to explain π-facial selectivity for the reduction and methylation of 5-substituted (X) 2-adamantanones **4** (Y = O). For the most part, the results appear to be accommodated by an electrostatic field model."

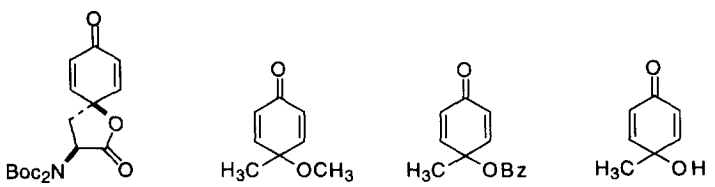
The latest study concerning π-facial selectivity in sterically unbiased systems was reported by Wipf and Kim.[60] In the course of their total synthesis of the anti tumor antibiotic aranorosin, they observed an intriguing selectivity in the 1,2-addition of organometallic reagents to 4,4-disubstituted dienones.[60] Treatment of spirolactone **46** with ((benzyloxy) methyl)lithium provided the bis-allylic alcohols **47** and **48** in a 5:1 ratio and in >50% yield.



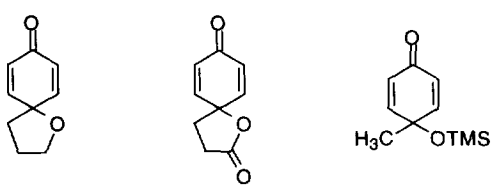
46 **47α** **48β**

5:1

Subsequently, they prepared model dienones **50-55** as sterically unbiased model systems in which the impact of any electronic effects on facial selectivity could be detected.

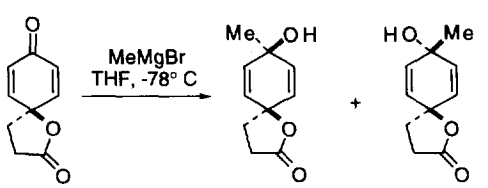


49 **50** **51** **52**



53 **54** **55**

The aranorosin intermediate **46** undergoes nucleophilic attack by an α-alkoxy organolithium reagent preferentially from the α-face of the dienone opposite the 4-alkoxy substituent. The data outlined in Table 13 confirmed this behavior as a general trend for 4,4-disubstituted cyclohexadienones.



54 **56α** **57β**

32 : 1

Table 13 Facial Selectivity in Nucleophilic Additions to Dienones

Entry	**Dienone**	Nucleophilic	Product % yield	α/β Selectivity
1	**46**	$BnOCH_2Li$	>50	5:1
2	**49**	MeMgBr	84	6:1
3	**50**	MeMgBr	86	4.8:1
4	**50**	$NaBH_4$ or $LiAlH_4$	100	1:1
5	**50**	HC≡CMgBr	70	1:1
6	**50**	$C_4H_9C{\equiv}CLi$	26	1.1:1
7	**50**	PhMgBr	83	3.6:1
8	**50**	MeLi/THF	87	2.1:1
9	**50**	$MeLi/Et_2O$	77	3.3:1
10	**50**	$BnOCH_2Li$	84	3:1
11	**51**	MeMgBr	75	8.6:1
12	**52**	MeMgBr	>61	10.1:1
13	**53**	MeMgBr	79	32:1
14	**54**	MeMgBr	81	7.9:1
15	**55**	MeMgBr	93	17.7:1

According to Wipf, whereas the Anh-Eisenstein model can account for the general increase in selectivity from 4-alkoxy to 4-acyloxy dienones, that theory does not easily lend itself to an explanation of the significant differences between monocyclic and spirocyclic systems or to the high selectivity in the case of the 4-silyloxy dienone **55**. "Similar problems arose in the consideration of a 'vinylogous Cieplak effect', e.g. the stabilization of the transition state by hyperconjugation of the newly forming σ*-bond by the σ-orbital of the 4-alkyl substituent *via* a σ-π*-σ* interaction."[60]

Wipf and Kim observed a qualitative correlation of the observed α-face selectivity with the expected dipole moment of dienones **50-55** (Figure 15). Thus they calculated the dipole moments of dienones **50**, **51**, and **53** with the semiempirical AM1 parameter set. The vector components of the calculated dipole moments orthogonal to the plane of the dienones were correlated to the natural logarithm of the observed facial selectivities and were linearly extrapolated. Based on this extrapolation and the calculated dipole moment of dienone **58**, the observed selectivity for nucleophilic attack on the fluorinated substrate **58** was indeed closely matched (Figure 16). According to Wipf this is the first example of a quantitative correlation between dipole moments and kinetic selectivities. The linearity of the plot indicates the importance of electrostatic control in polar addition reactions to sterically unhindered carbonyl groups.

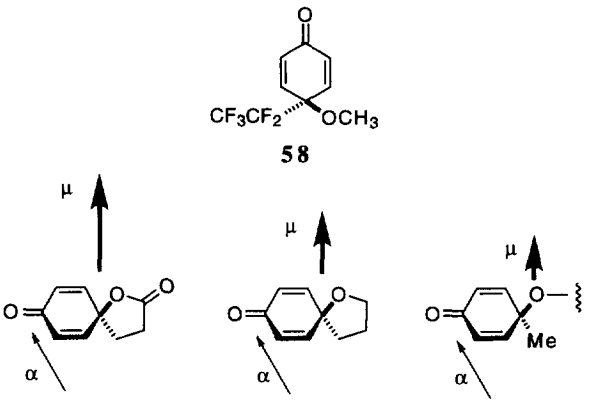


Figure 15 Qualitative order of dipole moments of dienones. The experimentally observed α-face selectivity decreases from left to right.

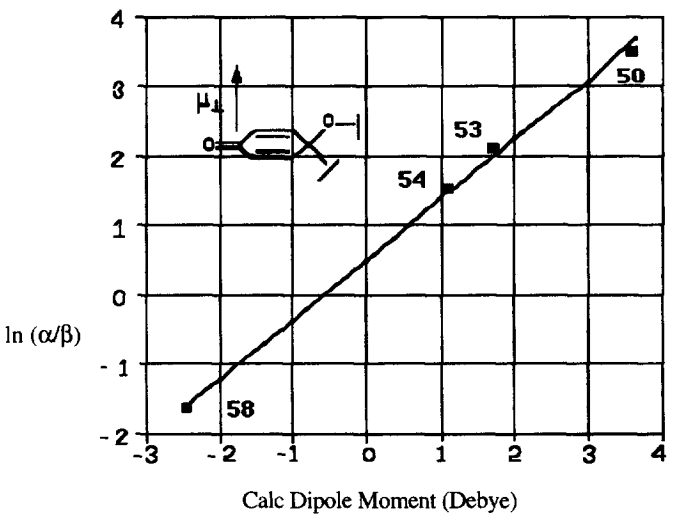


Figure 16 Least squares linear regression correlation of calculated dipole moments of dienones **50**, **53**, **54**, and **58** vs the logarithm of the experimentally observed facial selectivities in nucleophilic carbonyl additions. The values of the components of the dipole moments orthogonal to the dienone plane ($\mu_\perp$) are given in debye [D]. Correlation coefficient R = 0.998.

The conclusion from Wipf's investigation is that the facial selectivity of nucleophilic attack of 4,4-disubstituted dienones provides experimental evidence for dominant dipolar control in these carbonyl

addition reactions. Hyperconjugative orbital stabilization in the Felkin-Anh-Cieplak sense and orbital distortion effects appear to be of secondary importance. The excellent linear correlation of calculated dipole moments vs. the logarithm of the facial selectivity supports the notion that, in the absence of steric hindrance, the kinetic selectivity of irreversible C-C bond formation is strongly influenced by dipole-dipole interactions between reagent and substrate.

6. Concluding Remarks

With regard to the continued debate about the Cieplak model, it is interesting to note that there have been two shifts of opinions within the past 15 years. The first one arose from the accumulation of experimental data that cannot be explained with the widely-accepted Felkin-Anh model of π-facial selectivity but are consistent with the Cieplak model. These include the nucleophilic additions to 5-substituted-2-adamantanones, to 2,3-endo, endo-disubstituted-7-norbornanones, and to 2,2-diarylcyclopentanones. The second shift of opinion represents a renewed recognition of electrostatic effects in the control of diastereofacial selectivity. Cram's chelation model was developed more than 40 years ago.[61] However, long range electrostatic effects did not gain widespread recognition until recently. Kahn and Hehre have developed a model of π-facial selectivity based on electrostatic effects.[62] Unfortunately, their model depends on sophisticated computer modeling and is therefore difficult to apply intuitively in analysis of observed π-facial selectivity. The recent publications by Paddon-Row, Wu, and Houk, by Adcock, and by Wipf, allow one to use dipole-dipole interactions in the consideration of transition state arrangement. It appears that the stereochemical results from these sterically unbiased substrates are consistent with long range electrostatic effects.

However, many questions are still left unsettled. For example, is the transition state for nucleophilic addition to carbonyl group electron deficient or electron rich?[21] From the theoretical studies of Paddon-Row and Wu, it appears that the charge density of the transition state depends on the characteristics of the incoming nucleophile. When cyanide anion is the nucleophile the transition state is electron rich, and the most electronegative α-substituent assumes the anti position. When a counter ion is included, for example, Li^+, the transition state is electron deficient and the favored arrangement is changed. What is the role of the solvent? A recent theoretical study by Cieplak and Wiberg shows a decrease of electrostatic interactions on passage from the gas phase to the condensed phase.[63] Can electrostatic effect explain the stereochemical observations that have traditionally been rationalized by the Felkin-Anh model?

In cases where the substrates are not sterically unbiased, such as 4-tetrahydropyranones and 5-aza-2-adamantanone, conformational and structural effects must be taken into account in the consideration of diastereofacial selectivity. Long range electrostatic effects and secondary molecular orbital interactions in the transition state represent a relatively small influence (a few tenths of a kcal/mol) when compared to structural factors.

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21. In a private communication, Professor Houk has provided the following comments concerning microscopic reversibility and transition states of nucleophilic additions.

(1) About microscopic reversibility: "Marcus theory is one elegant way to talk about the fact that both thermodynamic factors (heats of reaction) and transition state stabilization are involved in determining activation energies. Microscopic reversibility does not require both forward and reverse rates to be accelerated by a substituent effect, unless the heat of reaction is constant. The lone pair of an oxygen speeds up formation of a cation at an adjacent center, but it also slows down the reverse reaction, because a cation is more stabilized by the lone pair donation than the transition state."

(2) About transition states of nucleophilic additions: "--- that electron donors slow down nucleophilic additions is ample proof that the transition states are electron rich with respect to reactants. Cieplak model would predict that amides react fastest, then esters, then ketones, then aldehydes, which is wrong."

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