Electronic Control of Facial Selection in Additions to Sterically Unbiased Ketones and Olefins

Goverdhan Mehta*,†,‡,§ and Jayaraman Chandrasekhar*,‡,§

School of Chemistry, University of Hyderabad, Hyderabad 500046, India, Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India, Jawaharlal Nehru Centre for Advanced Scientific Research, Jakkur P.O., Bangalore 560064, India

Received August 19, 1998 (Revised Manuscript Received January 19, 1999)

Contents

I. Introduction

By definition, the two faces of a π bond are equivalent.[1] However, they are rendered nonequivalent in most molecules because of the absence of a plane of symmetry encompassing the double bond and the adjacent substituents. As a result, additions to trigonal centers from the two faces need not be equally facile. Exploiting this stereodifferentiation in a controlled manner represents one of the core problems in organic synthesis. Evidently, the factors which determine such diastereoselection need to be delineated in as much detail as possible.

Initial attempts at directing the facial approach of the reagent were understandably based on perturbing the immediate steric environment of the reaction center fairly strongly. The systems examined were generally acyclic compounds with inherent conformational flexibility. These data were used to generate conceptual models, empirical in nature and with steric factor as the basis. The classic work of Cram provided a fairly reliable framework for predicting the stereochemical outcome of additions to acyclic ketones.[2] In the transition state, the carbonyl group was assumed to be antiperiplanar to the largest of the three substituents, L, on the adjacent carbon. The sterically favored direction of approach of the nucleophile would then be from the face near the smallest substituent, S (Figure 1a).

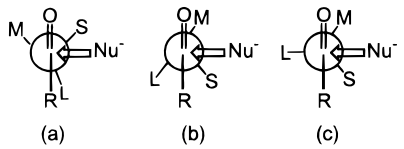
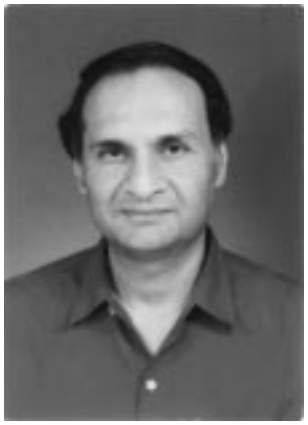


Figure 1. Conformational models for predicting the preferred direction of nucleophilic addition in acyclic ketones, proposed by (a) Cram, (b) Karabatsos, and (c) Felkin. The large, medium, and small groups are labeled L, M, and S, respectively.

In substrates containing oxygen, nitrogen, or polar groups, coordination and electrostatic interactions involving the bond dipoles were taken into account in arriving at the preferred conformation of the transition state, but the direction of approach of the reagent was predicted only on the basis of steric considerations.[3,4] Refinements to the Cram model were suggested by Karabatsos[5] and Felkin,[6] who proposed alternative torsional preferences for the idealized transition states (Figure 1b,c).

† University of Hyderabad.
‡ Indian Institute of Science.
§ Jawaharlal Nehru Centre for Advanced Scientific Research.

10.1021/cr980369v CCC: $35.00
Published on Web 04/07/1999



Goverdhan Mehta was born in Jodhpur, India, and obtained his Ph.D working at the National Chemical Laboratory, Pune, under the supervision of Dr. Sukh Dev. After postdoctoral research in the U.S., he started his independent academic career at the Indian Institute of Technology, Kanpur, and in 1977 moved to the University of Hyderabad as the Founder Professor of Chemistry. In 1998, he accepted an invitation to be a Professor of Organic Chemistry at the Indian Institute of Science, Bangalore. He has published over 300 research papers and received numerous awards and honors for his research accomplishments. in 1995, he was a recipient of the Humboldt Senior Scientist Award, and in 1996 received a Doctorate (*h.c.*) from the University of Marseilles, France. He is a Fellow of several Science Academies. Mehta's current research interests encompass total synthesis of natural products, design of aesthetically pleasing molecular entities, and devising incisive probes to study stereoelectronic control of diastereoselectivity.

Jayaraman Chandrasekhar graduated from Bangalore University and completed his M.Sc. at the Indian Institute of Technology, Madras. He obtained his Ph.D. at I. I. T., Madras, under the guidance of Professor S. Subramanian. He was a postdoctoral associate with Professor P. v. R. Schleyer at Erlangen, Germany. He was later associated with Professor W. L. Jorgensen at Purdue University, U.S.A. He joined the Department of Organic Chemistry, Indian Institute of Science, in 1985 and is currently a professor. He is an honorary faculty of the Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore. His research interests are in applications of computational methods for studying diverse chemical problems, particularly involving molecules of immediate experimental interest.

Nucleophilic additions to cyclohexanones formed the premise for additional models. From early results on hydride additions, Barton[7] pointed out that axial attack would be preferred in unhindered systems, but steric interactions would favor equatorial attack. Since the selectivity was dependent on the nature of the nucleophilic reagent, Dauben[8] postulated two different reaction types: steric approach controlled and product development controlled. The former was suggested to have reactant-like transition states and hence be subject to considerable steric encumbrance. The latter involve product-like transition states and the facial selectivities reflect product stabilities.

Felkin[9] suggested an alternative unified view of nucleophilic additions to cyclohexanones. The face selectivities were rationalized on the basis of relative torsional strain at reactant-like transition states. For equatorial attack, the transition state suffers eclipsing interaction between the newly formed bond and the adjacent C−H bonds. Axial attack was therefore predicted to be favored.

The possibility of an electronic factor playing a crucial role in face selectivity in additions to cyclohexanones and methylenecyclohexanes was first suggested by Klein.[10] He postulated distortion of the frontier orbitals due to σ-π mixing. The model was extended to cyclohexenone and related systems by Liotta.[11]

Computational methods are ideally suited for analyzing structural and electronic effects in a range of idealized conformations. The first ab initio calculations using the minimal STO-3G basis set on the conformational profiles of acyclic ketones were carried out by Anh and Eisenstein.[12] They used the computed data to evaluate the relative merits of the steric models of Cram, Karabatsos, and Felkin for predicting the direction of nucleophilic approach in acyclic ketones. Anh and co-workers also extended the analysis to cyclohexanones.[13] Their verdict was in favor of the Felkin model, but they took a further significant step by suggesting that an electronic factor was intertwined with the torsional model. It was argued that axial attack in cyclohexanone was favored because the corresponding transition state was stabilized, and not just because the equatorial attack transition state was destabilized. The stabilization of axial attack transition state was attributed to a two-electron interaction between the σ MO of the newly formed bond and the antiperiplanar C−H σ^* orbitals. Interestingly, the hyperconjugative interactions also promote torsional changes assumed in Felkin's model. Thus, the electronic and conformation-based structural proposals are interrelated.

An alternative to the involvement of the abovementioned electronic factor was suggested by Cieplak in a seminal paper in 1981.[14] The preferred axial approach of a nucleophile toward cyclohexanone was suggested to be due to a different two-electron stabilizing interaction, viz., that involving the antiperiplanar C−H σ bonds and the σ^* orbital associated with the newly formed bond.

Additional models of stereoselectivity, such as steric interactions involving other nonbonded contacts at the transition state,[15] as well as orbital twist due to differential hyperconjugation[16] and orbital distortion following lithium ion coordination,[17] have also been proposed. The problem of differentiating among these interpretations is quite complex.

While face selectivities in nucleophilic additions to cyclohexanones provided the impetus for most of the stereoelectronic models, these substrates do not represent the best means of distinguishing between steric, torsional, and various electronic factors. The distortions which can occur in the ring through substitution, especially near the transition state, are

vitiating factors. Rigid frameworks such as those provided by bicyclic systems may be useful. Studies on many substrates, such as substituted 2-norbornanones and 2-norbornenes, have proved to be ideal for confirming the role of steric interactions. Such studies[18] have also provided sufficient justification for discarding early models such as the concept of product development control. But in a majority of substrates, problems of interpretation were not eliminated. For example, steric,[19] torsional,[20] and orbital distortion[21] effects have been suggested to be responsible for the exo selectivity of electrophilic additions to norbornene.

A major advance occurred with the study of facial selectivity in specially chosen substrates in which the π bond was placed in an isosteric environment. The adamantane skeleton was exploited by le Noble to create a wide range of substrates with little or no intrinsic facial bias. The corresponding ketones and olefins bearing remote substituents were shown to undergo additions with small, yet remarkable selectivity.[22] Independent studies on several additional substrates by other workers added significantly to the body of experimental data on facial selectivity in sterically unbiased systems.

Much of the initial analyses of these data was based on qualitative arguments. At first, the single most important nonsteric factor contributing to face selectivity appeared to be obvious from these studies. But careful examination revealed that the results can be reconciled with several different models. Further, some of the factors which were sought to be eliminated by careful design of substrates, viz., steric bias at the reaction center, required critical reappraisal.

Subtle questions of interpretations are not easily resolved by qualitative arguments. The proponents of different models may not agree even on some basic premises, such as, for example, the relative donor abilities of C−H and C−C bonds. These, in turn, generate tautological arguments in favor of or against different models. It is therefore useful to have an independent procedure for evaluating some of the concepts in a quantitative manner. Computational procedures are very useful in this respect.

Numerous theoretical studies have been carried out on sterically unbiased substrates. The goals have been to obtain insights about the origins of face selectivity as well as to derive predictive models. Because of variations in rigor and methodology, the computed results have not always provided a uniform interpretation. Nevertheless, these studies have contributed significantly to the ongoing discussion on the electronic factors determining face selectivity.

From the above historical perspective, three major streams of development are evident in the research directed toward unraveling the origins of π-facial selectivity: (i) generation of a large body of experimental data on substrates designed with increasing sophistication to aid interpretation, (ii) identification of a variety of subtle factors by which face selectivity can be influenced and modulated, and (iii) development of reliable computational tools to predict selectivity as well as to extract the contributions of different factors. We present a critical overview of the insights obtained by the interplay of these developments about the electronic origins of diastereoselection.

Three reviews on the subject are of direct interest. Wigfield has provided an excellent summary of early models and results, especially on acyclic derivatives and cyclohexanones.[23] A more recent review by le Noble addresses in great detail the electronic factors contributing to facial selectivity.[24] Gung has included many additional experimental data and interpretations in his review on diastereoselection in nucleophilic additions.[25]

In the next section, various qualitative, semiquantitative, and quantitative models which have been proposed for interpreting facial selectivity in additions to sterically unbiased systems are summarized. A strategy for distinguishing between various models through combined experimental and theoretical studies on carefully chosen model substrates is then suggested. In the subsequent sections, results obtained for the additions to specific ketones and olefins in isosteric environments are presented and analyzed.

II. Models for Interpretation and Prediction of Facial Selectivity

Over the years, a number of factors have been identified as contributing to facial selectivity in additions to trigonal carbon centers. Many of these have been proposed to account for experimental results in sterically perturbed substrates such as those based on the cyclohexane skeleton. However, they have an important role in determining face selection in an isosteric environment which needs to be critically evaluated. We present below the key factors that may form the basis for interpreting and predicting selectivities. The concepts and models range from being qualitative to those with varying degrees of quantitative rigor.

We first discuss models of face selectivity which focus on the properties of the substrate in the ground state. These are obviously amenable to experimental and theoretical evaluation. We next consider approaches that are based on the molecular and electronic structures of the transition state. Because transition states are not directly characterizable experimentally, qualitative descriptions are often used. In addition, semiquantitative models of transition-state effects can be derived using computational methods. Later we describe computational models of face selectivity which are based on precisely determined transition state structures. Semiempirical MO or ab initio theory can be used to assess structures and electronic interactions of transition states.

A. Ground State Effects

1. Geometric Distortions

The presence of a clearly defined steric bias in a substrate offers conceptually the simplest interpretation for face selectivity. X-ray diffraction offers the best means of quantifying geometric distortions. Fairly accurate geometries for organic systems can

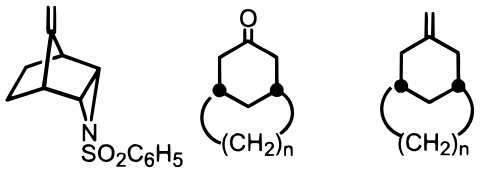
also be obtained through molecular mechanics methods (e.g., MM2, MMX, MM3),[26] semiempirical molecular orbital procedures (e.g., MNDO, AM1, PM3),[27] ab initio methods[28] with large basis sets (e.g., HF/6-31G*) and including electron correlation (MP2) as well as density functional approaches (e.g., B3LYP).[29] These methods are particularly useful in analyzing geometric preferences in conformationally flexible systems.

Exploiting the inherent steric bias in a substrate is one of the most common strategies for inducing diastereoselection, since the more accessible face for reagent approach is obvious in many cases. However, it is preferable to have precise structural data. A remarkable example of a totally unexpected geometric distortion is the pyramidalization found in a norbornene derivative, **1**. Neutron diffraction revealed out-of-plane bending by 7.4° of the olefinic hydrogens toward the endo side.[30] A similar distortion has been computed for the parent substrate, **2**, both using molecular mechanics[31a] and ab initio[31b] calculations. Thus, a simple geometric interpretation for the exo preference for electrophilic additions to norbornene is obtained.[19b,c] It has also been suggested that remote substituents may have an effect on the extent of out-of-plane bending of the olefinic hydrogen atoms, which in turn influences the facial selectivity.[19d] For example, 7-hydroxynorbornene, **3**, is computed to have a reduced degree of bending, which is consistent with the reduced exo selectivity in the electrophilic additions to the corresponding alkoxy derivative.

1 **2** **3**

It is now established that the olefinic hydrogen atoms of norbornadiene are also distorted toward the endo face by ca. 4°. This has been confirmed through microwave spectroscopy[32a] as well as by a recent accurate X-ray diffraction study.[32b] The distortion is accurately reproduced by ab initio calculations at the MP2/6-31G* level.[32b] The direction of out-of-plane bending offers a simple rationalization for the exo selectivity in electrophilic additions to norbornadiene.

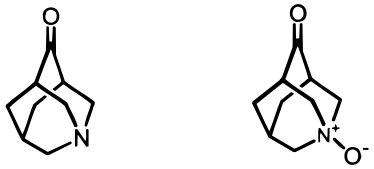
Studies of face selectivity should therefore begin with a thorough characterization of the ground-state geometry. A fine example of such analysis is provided by the study of Hoffmann and co-workers.[33,34] To interpret the syn-face selectivity in electrophilic additions[33] to a methylenenorbornane derivative, **4**, with an endo-fused aziridine ring, the X-ray structure of the substrate was determined. Besides reporting the usual bond lengths, angles, and torsion angles, the authors specifically examined[34] interplanar angles of direct relevance to face selection. While the tilt of the methylene bridge was less than 1°, the exo hydrogen atoms attached to the three-membered ring were distinctly oriented away from the reaction site. These clearly point to a more open access for the reagent from the syn face.



4 **5** **6**

Another interesting analysis of geometric effects is given by Paquette and co-workers.[35] The sterically less hindered face of the carbonyl group was identified in each of a series of *cis*-[*n*.3.1]bicyclic ketones, **5**. The observed variations in face selectivity in nucleophilic additions could then be readily rationalized. By assuming that the conformational effects are not altered on going to the corresponding olefins, the stereochemical outcome of electrophilic additions to **6** could be understood.

Geometric distortions may appear to be unimportant in the systems taken up for detailed examination in this review. However, this assumption has been questioned in a few cases,[36] such as in some heteroadamantane derivatives, **7** and **8**. An analysis of ground state distortions in supposedly sterically unbiased systems appears in an accompanying review.



7 **8**

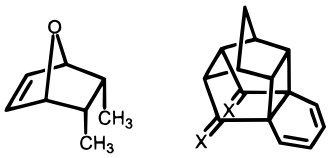
Critical assessment of ground-state geometric distortions is important for another reason. The most convincing proof for the existence of electronic factors is obtained if the facial preference is *opposed* to that of the inherent steric bias in the substrate in its ground state.

2. Product Stabilities

In many cases, face selectivities may be determined by relative product stabilities. This is valid not only in thermodynamically controlled reactions but also in highly endothermic processes with product-like transition states. Nucleophilic additions to carbonyl compounds and electrophilic additions to olefins usually do not belong to this category. Further, product energy differences are expected to be small in sterically unbiased systems. Nevertheless, kinetic control of product distribution should not be taken for granted. It is preferable to determine face selectivities from reactions occurring at low temperatures, which would preclude thermodynamic control.

Thermodynamic preferences can be assessed by equilibration studies. Energetics of products can also be obtained fairly reliably using computational methods such as molecular mechanics. Through such analysis, it has indeed been shown in a few cases that the observed product ratios do not necessarily follow the trends in thermodynamic preferences. For example, Vogel found that selectivity in cycloadditions to 7-oxa-2,3-dimethylnorbornene, **9**, could not be

explained on the basis of computed product stabilities.[37] Coxon also concluded that MMX relative energies of products of cycloaddition to a polycyclic 1,3-diene, **10**, were not compatible with the observed distribution.[38] These results imply the operation of stereoelectronic effects at the transition state which need to be explicitly taken into account.



9 **10** (X=O, H_2)

3. Orbital Effects

Several models invoke orbital interactions in the ground state of substrates which eventually determine the preferred direction of attack by reagents. The first proposal of this kind was given by Klein[10] who argued that the π^* MO of cyclohexanone should be distorted toward the axial face, making it more susceptible to nucleophilic attack. In contrast, the π HOMO of methylenecyclohexane was suggested to be distorted toward the equatorial face, favoring electrophilic attack from this face. The analysis was qualitative and emphasized interaction between the exocyclic π orbitals and β C−C orbitals in the ring (Figure 2). It was also noted that ab initio calculations of Anh supported the presence of these distortions.

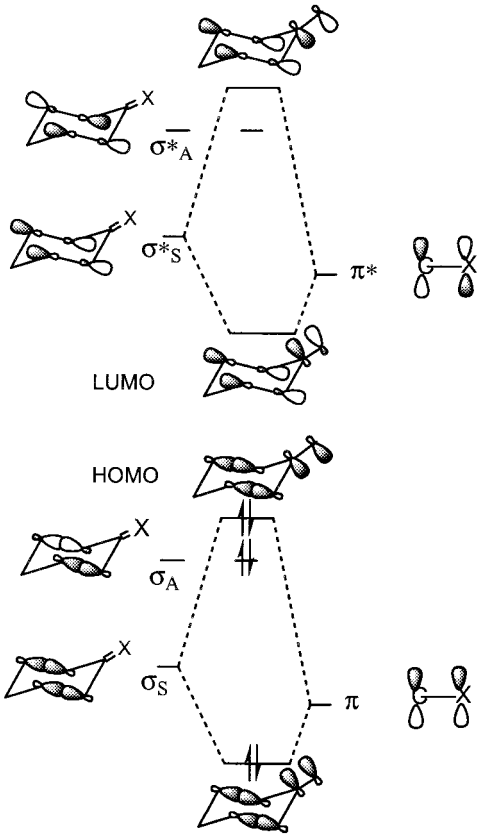
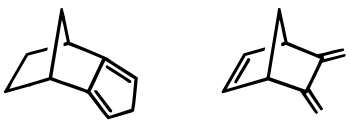


Figure 2. Distortion of π and π^* orbitals due to interaction with σ and σ^* orbitals of the β C−C bonds in cyclohexanone and methylenecyclohexane.

Orbital contours determined at ab initio levels with the 6-31G* basis set confirmed the axial face distortion of the π^* MO of cyclohexanone.[39] However, a similar distortion was also noted for the π MO of the corresponding olefin. It was pointed out that orbital distortions are also determined by interaction with the β C−H σ and σ^* orbitals, which were neglected by Klein. The need for evaluating qualitative proposals through high-level computations becomes evident from this study.

An alternative mode of orbital distortion in ketones was proposed by Hudec.[16] In an effort to interpret the changes in magnitude and sign in the circular dichroism (cd) of *n*-π^* transition in chiral carbonyl compounds, CNDO calculations were carried out on a number of substrates. The calculations revealed significant twist of *n* and π^* orbitals which were compatible with the observed cd changes. Hudec postulated that the mode of twist of the π^* orbital had a direct bearing on the preferred direction of approach of nucleophiles. The calculated twist angles were found to be consistent with the face selectivities in a number of cyclic and bicyclic ketones. The study was also extended to sterically unbiased substrates such as 5-haloadamantanones, for which experimental data were also generated. Thus, Hudec's work represents the first investigation on remote substituent effects on additions to ketones in a truly isosteric environment. The model is also remarkable in being a purely computational scheme with predictive capability and in connecting two disparate phenomena, viz., cd shifts and chemical reactivity. Unfortunately, some of the stereochemical assignments were shown to be incorrect,[22] raising doubts about the reliability of the computational model.

Orbital distortion arising from σ-π mixing was proposed by Fukui[21] with implications for selectivity in a number of systems. The most thoroughly examined system in this category is norbornene, whose exo preference for electrophilic additions was attributed to π orbital distortion toward the exo face. Similarly, Gleiter and Paquette suggested an orbital tilting effect resulting from σ-π mixing, with ramifications for facial selectivity.[40] The product distributions in cycloadditions to isodicyclopentadiene, **11**, and the related triene, **12**, have been interpreted using this model. Such orbital effects can be identified only through calculations. Their relevance to facial selectivity in isosteric systems has not been examined critically.

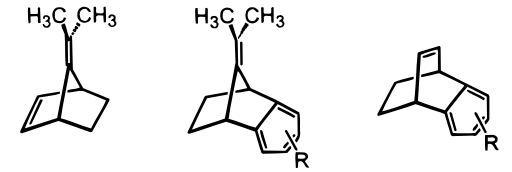


11 **12**

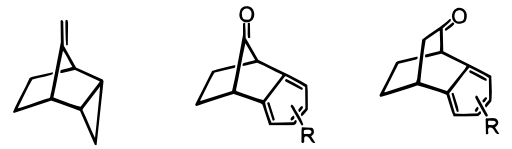
Rigid substrates which possess strained rings or multiple π bonds in close proximity are characterized by strong through-space and through-bond interactions.[41] The effects in the ground state may control the reactivity pattern too. The orbital effects can be quantified through photoelectron spectral methods and/or through calculations. The data can then be

used to rationalize the observed selectivities. Olefins based on bicyclo[2.2.1]heptane and bicyclo[2.2.2]-octane frameworks, **13**−**15**, have been thoroughly examined in this manner.[42−45] To reduce the filled orbital repulsions, the exocyclic double bond is polarized away from the etheno bridge. This, in turn, determines the preferred direction of approach of an electrophile. For example, singlet oxygen addition to these systems occurs preferentially anti to the unsaturated unit.

A similar interpretation involving the exocyclic double bond and one of the Walsh orbitals of the cyclopropyl ring has been employed to account for the anti preference in electrophilic additions to tricyclic olefin **16**.[34] The reversed selectivity in additions to **4** was attributed to the reduced magnitude of the orbital interaction, as revealed by PE data. Homoconjugative interactions have also been invoked to account for nucleophilic additions to the ketones, **17** and **18**.[46]

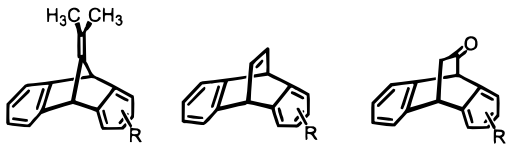


13 **14** **15**



16 **17** **18**

The diastereoselection in additions to the dibenzo derivatives **19**−**21** are particularly interesting in view of the removal of steric bias around the reaction center.[47] A detailed analysis of orbital effects and face selectivity in these systems is provided by Ohwada in an accompanying review.[48]



19 **20** **21**

4. Electrostatic Effects

The magnitude and directionality of weak intermolecular interactions are often accurately reproduced through models based on electrostatic interactions.[49] Therefore, it appears logical that the same effects may have a directing influence on reagents, especially charged ones, approaching a substrate. Field effects of substituents are known to extend over distances of several angstroms and have been quantified using a variety of empirical correlations.[50] Hammett type analyses have been used to model through-space electrostatic interactions (in addition to resonance effects). Heavy atom chemical shifts are particularly sensitive probes for assessing electrostatic contributions. Therefore, reasonable correlation between ^{13}C (or ^{19}F) chemical shift data of substrates and face selectivities implies the underlying similarity in the origins of these properties.[51] Hence, such analyses may be used as arguments favoring the electrostatic model of facial selection.

A more direct way of analyzing the electrostatic influence of substrates is to compute molecular electrostatic potentials (MESP). These can be derived at different computational levels, including using ab initio methods. The MESP surfaces show considerable topographical variation, with many minima, saddle points, and maxima. These can be correlated with well-known chemical bonding concepts and the analysis can be made quite quantitatively.[52] Every π bond has a local minimum of electrostatic potential on either face. Because the regions with large negative potentials should direct the initial approach of an electrophile, the relative depths of the two minima can be used to predict the preferred facial selectivity. Alternatively, integrated volumes of a certain negative potential can be obtained for the two faces. Electrophilic attack is predicted to be larger on the face with larger integrated volume. The approaches have been used effectively in a number of systems, qualitatively as well as rigorously.[17,44,53]

The complementary problem of predicting the preferred direction of nucleophilic approach toward a substrate using MESP is less straightforward, although it has been attempted for **18** (R = H).[54] While electronic charge distribution is diffuse in a molecule, nuclear charges are concentrated at specific points. Hence the maxima of MESP do not show the subtle variations as do the minima. Instead, the maxima are very large and localized at the nuclear centers. These provide no useful chemical information. To extract better insights concerning the preferred sites for nucleophilic attack from MESP data, a simple computational procedure has been suggested by Politzer.[55] The MESP values are generated on a surface enveloping the molecule at which the electron density is small and constant (0.002 electrons/bohr^3). The variations in the positive potentials on this surface are monitored to identify the preferred site and direction of nucleophilic attack. The procedure has been tested at the STO-3G level for a few representative systems.[55] It would be of interest to extend it to the study of electrostatic control of facial selectivity in sterically unbiased ketones.

5. Electron Density and Bond Properties

It is not necessary to use electronic models which focus on a few specific orbitals. Instead, the total electron density can also be analyzed. Variations in total electron density take into account compensating distortions which may occur in several filled orbitals. However, total density in the ground state may not be a sufficiently sensitive probe for assessing face selectivity. For example, it was noted that computed electron densities show very little variation in the axial and equatorial faces of cyclohexanone, unlike the LUMO or electrostatic potential minima.[56]

Alternatively, the properties of specific localized bonds in a molecule can be analyzed. Thus, the

characteristic topographical features of electron density maps may provide useful criteria for interpretation. For example, the electron density has critical points for each chemical bond. The density at the CP can be used as a measure of the donor ability of the bond in a hyperconjugative interaction. These are important in certain orbital interpretations involving model transition states, to be discussed in the next section.

B. Stereoelectronic Effects in Idealized Transition States and Intermediates

Features of chemical reactivity are primarily determined by structural and electronic effects at the transition state. Unless the reaction involves an early transition state and the stereoelectronic effects in the ground state are quite strong, it is unlikely that the models described in the previous sections will always be reliable. Alternative descriptions which focus on the transition state provide a firmer basis for rationalization, especially in substrates in which ground-state effects are minimized, if not eliminated, through design.

The major difficulty in deriving stereoelectronic models for the transition state is the absence of direct experimental information on the molecular and electronic structures of the transition state. However, this is not a problem for qualitative approaches. In certain classes of reactions which involve high-energy intermediates, the latter may be chosen as models for the transition state. For example, carbocations in solvolysis processes and halonium ions in halogen addition reactions serve as ideal handles for detailed analysis. The structural and electronic effects in these intermediates can be determined quite effectively through computational means.

Theoretical methods can also be used to generate semiquantitative models for transition states. One approach is to carry out MO calculations on a simple substrate to generate a force field for the transition state to be used in conjunction with a standard molecular mechanics scheme. Such hybrid MO/MM procedures have led to valuable insights concerning stereoelectronic effects in transition states involving complex substrates.[57] Alternatively, transition-state models can be constructed using some plausible geometric assumptions derived from available experimental and theoretical data. These can then be used in quantitative MO procedures to extract insights about electronic effects. One such approach is discussed in detail in a later section.

1. Torsional Effects

The changes in torsional interactions during the formation of the transition state have been suggested to be important in determining selectivity in a number of systems. Schleyer proposed this interpretation for the exo selectivity in electrophilic additions to norbornene.[20] The atoms attached to the olefinic centers suffer unfavorable eclipsing interactions with the groups at the bridgehead position for endo attack. On the other hand, the exo addition transition state does not involve such repulsions.

The torsional model has also been invoked for nucleophilic additions to cyclohexanones and electrophilic additions to methylenecyclohexanes by Felkin.[9] Addition from the equatorial face necessarily leads to eclipsing interactions between the newly formed bond and the β C−H bonds.

While differential torsional interactions may be quite important in general, they are unlikely to be determinants of diastereoselectivity in additions to sterically unbiased substrates, unless geometric changes occur at the transition state.

2. Orbital Effects

Two orbital interaction models have been proposed to account for diastereoselection which do not require detailed knowledge of the transition state. The focus is on specific stabilizing interactions involving the orbitals associated with the newly formed bond(s) and those which are aligned antiperiplanar at the β position. In the Felkin−Anh approach,[13] the interaction of the σ orbital of the newly formed bond with the antiperiplanar σ^* orbitals is considered (Figure 3). On the other hand, the Cieplak model invokes stabilizing interaction between the σ^* orbital associated with the newly formed bond and the antiperiplanar σ MO (Figure 4).[14] Both of the interactions are hyperconjugative in nature and, in principle, are not mutually exclusive (an additional four-electron destabilization between the two sets of σ MOs is also present, but it is unlikely to be important in determining facial selectivity). Facial selectivity is determined by identifying the direction of approach in which the proposed orbital interaction is maximized. In the Felkin−Anh model, the reagent is predicted to approach preferentially antiperiplanar to the more effective acceptor orbital. In contrast, Cieplak's proposal favors approach of the reagent antiperiplanar to the superior donor bond orbital.

The two orbital models emphasize different sets of hyperconjugative interactions. While both are qualitative, the Felkin−Anh model requires knowledge of the relative acceptor ability of the σ^* orbitals, which

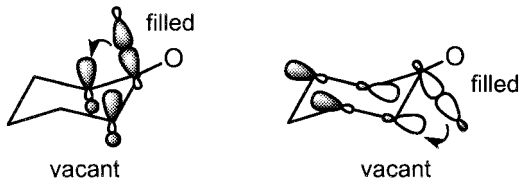


Figure 3. Stabilizing orbital interaction according to the Felkin−Anh model in the transition states for axial and equatorial nucleophilic additions to cyclohexanone. The interaction for the axial approach was suggested to be more effective.

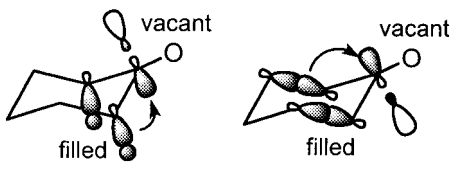


Figure 4. Stabilizing orbital interaction according to the Cieplak model in the transition states for axial and equatorial nucleophilic additions to cyclohexanone. The interaction for the axial approach was suggested to be more effective.

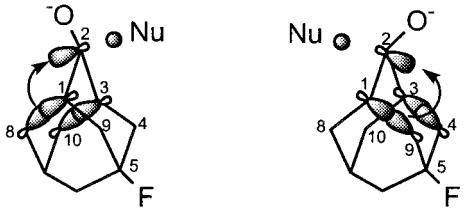


Figure 5. The stabilizing orbital interaction in the syn and anti nucleophilic addition transition states to 5-fluoroadamantanone according to the Cieplak model. The syn approach is stabilized to a greater extent because of the involvement of stronger donor orbitals.

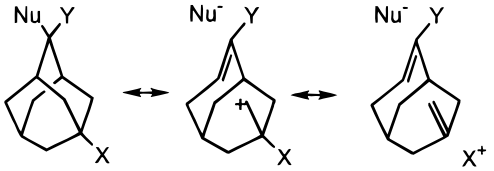
is usually not easy to predict. In contrast, the Cieplak model is particularly easy to use. Long range substituent effects can be readily predicted within this model, because the focus is on identifying the stronger set of donor orbitals. The inductive effect of the substituent is taken into account to identify the relative donor or acceptor strengths of the bonds β to the reaction center. The proposal is best clarified through an example, say 5-fluoroadamantanone (Figure 5). The C_1-C_9 and C_3-C_4 bonds are depleted of electron density by the inductive effect of the halogen. Compared to these, C_1-C_8 and C_3-C_{10} bonds are electron rich and can act as better donors. Within the Cieplak model, the differential hyperconjugative stabilization leads to diastereoselection. The nucleophile should preferentially approach antiperiplanar to the latter set of σ bonds to maximize the hyperconjugative interaction. Hence, nucleophilic addition should occur predominantly to the syn face with respect to the substituent. The major product should therefore be the (*E*) alcohol.

The second major feature of both of the qualitative models is their applicability in a wide variety of contexts. The proposals do not distinguish between various reaction types. Hence, the same selectivity is predicted for nucleophilic additions to a carbonyl compound and electrophilic additions to the corresponding olefin. The qualitative models additionally suggest how the face selectivity can be fine-tuned, e.g., by varying the σ and σ^* orbital energies and relative coefficients at the β bonds and the newly formed bond through electronegative perturbation.

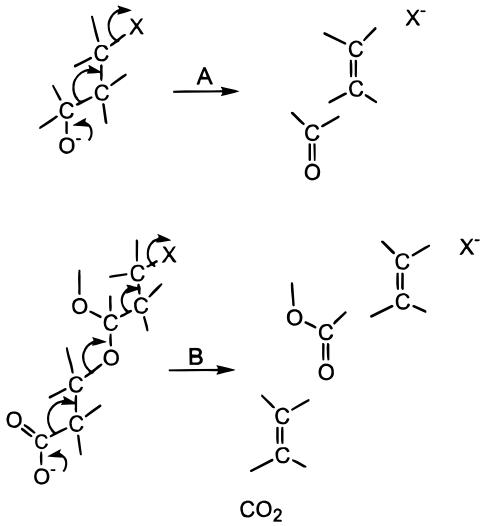
Numerous examples of experimentally observed face selectivities in a variety of electrophilic, nucleophilic, and cycloadditions have been interpreted in terms of these two orbital models.[58] The Cieplak proposal has been widely commended and also occasionally criticized.[59] In an accompanying review, Cieplak provides a detailed assessment of his model.[58c]

In an interesting variation of the Cieplak model, the possibility of double hyperconjugation involving a sequence of antiperiplanar units has been proposed to account for face selectivity in adamantyl derivatives.[60] In this model, the role of the substituent is not limited to perturbation through inductive effect. The group is included in a relay of hyperconjugative interactions along with the newly formed bond at the idealized transition state. The stabilization mode may be viewed in terms of the no-bond resonance as indicated in Scheme 1. The origin of syn selectivity for nucleophilic approach is then attributed to more effective interaction with the C−H bond compared

Scheme 1



Scheme 2. Grob (A) and Eschenmoser (B) Fragmentations



to C−F bond. The proposal has similarities to Eschenmoser[61] and Grob[62] fragmentations (Scheme 2) which also involve rupture of several antiperiplanar bonds. The high degree of alignment of the participating bond orbitals is therefore the stringent requirement of the double hyperconjugation model.

3. Counterion Effects

It is well-known that counterions can strongly influence structures, electronic effects, and mechanistic details in polar reactions. The possible role of metal coordination on π face selectivity has often been a concern. In nucleophilic additions to ketones, the first step may well be Lewis acid complexation to the carbonyl oxygen. The stereoelectronic changes that occur through such coordination have been analyzed by several groups.

Royer used CNDO calculations to suggest that the electrostatic potential around the carbonyl group in cyclohexanone becomes highly disymmetric through lithium ion complexation.[17] As a result, axial attack was predicted to be favored.

Significant geometric distortions also accompany counterion coordination. Distortions induced by chelation have been examined through X-ray crystallography for two cyclohexanone complexes with Li^+ and $SbCl_5$ as well as for an adamantanone complex with $SbCl_5$.[63] Additional coordination to ketones induces cationic character at the carbon center. This leads to characteristic geometric changes, generally to enhance hyperconjugation. The C=O bond becomes longer, the carbonyl group pyramidalizes, and additional bond length changes occur in the ring. The pyramidalization in the cyclohexanone complex making the axial face more open to attack is consistent with the face selectivity in nucleophilic additions.

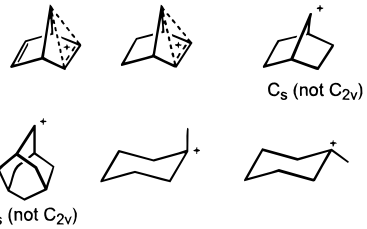


Figure 6. Schematic representations of calculated structures of carbocations which distort to maximize homoconjugation or hyperconjugation.

Yadav and co-workers have interpreted face selectivity in a number of acyclic ketones and cyclohexanones using ab initio calculations by considering the substrates complexed to a proton or a lithium cation.[64] The simple approach provides a means of rationalizing and even predicting face selectivities, without having to determine transition states precisely.

The effect of the counterion may be viewed in a different light. Instead of being a complicating factor, coordination seems to enhance the importance of various other stereoelectronic effects. Thus, Felkin's torsional model becomes more relevant in the distorted structure of the complex than in the parent substrate. Further, complexation reduces the carbonyl π^* orbital energy, making it more sensitive to differential hyperconjugative effects. Klein's model becomes more appropriate, as a result. As is well-known, a free carbocation or an intermediate with cationic character is highly susceptible to a variety of orbital interactions. While homoconjugative stabilization has been thoroughly established experimentally in systems such as the 7-norbornenyl and 7-norbornadienyl[65] cations, the significance of subtle distortions calculated in 7-norbornyl,[66] 2-adamantyl,[67] and cyclohexyl[68] cations has not been adequately appreciated (Figure 6). The distortion away from the expected C_{2v} geometry in the 7-norbornyl cation has been attributed to through-space stabilization with the C2−C3 σ bond. However, the presence of a similar distortion in the 2-adamantyl cation suggests that these ions evidently attempt to maximize hyperconjugative stabilization with one set of C−C bonds. Similarly, two stationary points have been computed for the 1-methylcyclohexyl cation, with a pyramidal tertiary cationic center. In one form, the distortion maximizes C−H hyperconjugation. In a marginally more stable conformer, the geometry changes enhance C−C hyperconjugative stabilization. It is very likely that the distortions in the cations will attain greater directional character in the presence of a substituent. These arguments imply that counterion complexation prepares the system for enhanced stereoelectronic control of facial selectivity.

Counterions can influence face selectivity by another mode. Complexation can occur directly with the substituent in some favorable cases.[69] The nucleophilic reagent would then necessarily be guided toward the carbonyl π face closer to the substituent. Such subtle mechanistic possibilities should not be overlooked, especially if exclusively syn face attack is observed. The problem is best resolved through comparative experimental studies with a variety of counterions, including noncoordinating counterions.

4. A Semiquantitative Predictive Model

Numerous qualitative models of face selectivity have been discussed in the previous sections. While these are very useful for interpretation and even for prediction, they may not always be correct. It is difficult to distinguish between two stereoelectronic effects if they both lead to the same predictions. Opposing contributions may be overlooked, because the magnitude of the effects examined are indeed small. Therefore, there is a clear need for semiquantitative models, which go beyond qualitative arguments.

We have developed a model for predicting and interpreting face selectivity in nucleophilic additions to ketones.[70] The features of the model were chosen with the following consciously adopted constraints. To enable the study of a large number of fairly complex substrates, the procedure should not be computationally demanding. The approach should lead to unambiguous predictions of facial selectivity. Importantly, the model should allow segregation of orbital and electrostatic effects, which seemed to be the key to face selectivity in isosteric environments.

With the above goals in mind, the MNDO method was chosen as the computational procedure and the electronic effects were probed in an idealized geometric model of the nucleophilic addition transition state. For each substrate, the ground-state geometry was first optimized. The differential electrostatic interaction between the nucleophile and the substrate on either face of the carbonyl group was estimated by two calculations. A full negative charge was placed on either face at a distance of 1.4 Å from the carbonyl carbon. The angle of approach of the charge with respect to the carbonyl group was fixed at 90°. The relative energies in this *charge model* calculation provide a measure of the facial preference resulting from primarily electrostatic interactions. It must be emphasized that the charge model includes additional electrostatic effects other than those obtained through MESP data of the ground-state substrate. Because the wave functions are recomputed in the presence of the test charge, electronic reorganization within the substrate due to the approaching reagent is also taken into account. Important polarization effects are thus included.

In another set of calculations, a hydride ion is used as a probe instead of a test charge. The geometrical assumptions remain the same as in the charge model. The use of the hydride ion has two consequences. The charge on the nucleophile becomes fractional, as it must be in the true transition state. Therefore, electrostatic effects are more realistically included in the *hydride model*. Importantly, the newly formed partial bonds can participate in all possible interactions with the substrate fragment orbitals. In particular, the hyperconjugative interactions represented by the Felkin−Anh and Cieplak models are incorporated in the hydride model. In principle, this computational procedure should lead to more reliable

predictions than either of the hyperconjugative models, besides having the advantage of being quantitative in nature.

By using two sets of models, it becomes possible to evaluate the roles of orbital and electrostatic effects. If both the charge and hydride models consistently make correct predictions of face selectivity, it may be concluded that there is no need to invoke orbital interactions. However, it is also possible that in such systems electrostatic and orbital effects act in concert. Proof of the importance of orbital effects in determining face selectivity can be claimed in systems for which the charge model yields an incorrect result but for which the prediction of the hydride model is consistent with experiment. In such cases, orbital effects overwhelm electrostatic contributions with the two factors opposing each other. Finally, any incorrect prediction of face selectivity by the hydride model, which incorporates orbital as well as electrostatic interactions, is indicative of the inherent deficiencies of the computational procedure.

The models do involve a number of assumptions which need justification. The geometric constraints appear to be too severe. Retaining the ground state structural parameters of the ketone in the model transition state is a gross approximation. Partial pyramidalization of the carbonyl unit would have allowed for realistic modeling of rehybridization effects. However, it is not obvious whether this has a role to play in face selectivity. By choosing a rigid model, the isosteric environment at the carbonyl group is left unchanged. Hence, torsional distortions at the transition state and orbital distortions which can occur through s,p mixing are not included. Success of the computational model would imply that these latter effects are relatively unimportant in determining facial selectivity in the sterically unbiased systems.

Use of a full negative charge leads to overestimation of electrostatic interactions. A value of −0.5 or less is indicated from population analyses data on representative ab initio transition states. However, the trends are not expected to be dependent on the precise magnitude of the charge. The interaction distance of 1.4 Å is perhaps too short. It was derived by constrained geometry optimizations on a number of test systems. With the substrate kept rigid, optimum interaction was noted at distances in the range of 1.35 to 1.45 Å with the O=C−H$^-$ angle being 91 to 94°. Idealized values were therefore used. As a result of these assumptions, large energy differences are obtained as facial preferences.

The use of a hydride ion to model a nucleophile is also an oversimplification. Hydride reductions do not involve a bare hydride anion. Experimental studies of nucleophilic additions often employ polar organometallics, such as alkyllithium or Grignard reagents, which may include additional steric components to facial discrimination. It is also possible that other nucleophiles respond to electrostatic and orbital effects of the substrates in different magnitudes. However, to the extent that the observed diastereoselectivity is insensitive to the precise choice of the nucleophilic reagent used, the hydride ion serves as a convenient model. Because the ion introduces just a pair of newly formed C−H σ and σ* orbitals into the model, it offers a simple means of taking into account Cieplak and Felkin−Anh hyperconjugative interactions, without any additional complicating orbital effect.

In summary, the semiquantitative model takes into account electrostatic effects, including polarization effects, and also hyperconjugative orbital interactions. It allows for an evaluation of relative contributions of orbital and electrostatic effects. However, the hydride model does not enable a distinction to be made between the Felkin−Anh and Cieplak proposals. The approach ignores the possible role of distortions at the transition state inducing facial selection. Counterion effects and the role of the solvent medium are also not taken into account. By the choice of the Hamiltonian, the deficiencies inherent in the MNDO methodology are also carried over into the model, although cancellation of errors may be expected to a large degree in comparisons of two related idealized transition states. The dependence of the predictions on the MO procedure employed can be assessed by carrying out the calculations at higher levels. Further validation of the models can be sought through comparisons with transition-state energetics computed using ab initio methods. The final verdict on the utility of the approximate models rests on concordance with experimental face selectivities in a number of substrates.

An alternative computational strategy has been proposed by Dannenberg for predicting face selectivities.[71] The approach called the Polarized Pi Frontier Molecular Orbital method probes the polarization of the frontier orbital induced by a test reagent.

C. Stereoelectronic Effects in Realistic Transition States

The most reliable approach to understanding stereoelectronic factors determining face selectivity is through examination of realistic transition states. It has become increasingly possible to locate saddle points on potential energy surfaces and to characterize them unambiguously. Efficient gradient minimization algorithms have been implemented with modern computational methods which enable geometry optimization of minima as well as transition states. Both types of structures have vanishing energy gradients. But minima with N atoms have 3N-6 positive force constants and real vibrational frequencies (3N-5 for linear systems). Saddle points have 3N-7 positive force constants but are characterized by one and only one negative force constant with an imaginary frequency. The vibrational mode associated with the imaginary frequency represents the reaction coordinate.

Semiempirical and ab initio calculations have been used to obtain transition-state structures and energetics for a number of reactions. However, there are practical difficulties in the study of nucleophilic additions to ketones and electrophilic additions to olefins. With many bare anionic model nucleophiles, such as H$^-$, OH$^-$, and OR$^-$, there are no transition

states on the potential energy surface for addition to a carbonyl group![72] This is not always an artifact of theoretical methodology. In the gas phase, many of the additions occur extremely rapidly.[73] Solution phase barriers result principally from solvation and counterions in these systems. However, transition states could be obtained for cyanide ion addition to carbonyl compounds.[74] Even with this model, inclusion of a lithium counterion led to complications. Attempts to locate transition states were unsuccessful, with geometry optimizations leading to products without activation.

The most commonly used models for nucleophilic additions to ketones are LiH and NaH.[75] These do not correspond to the reagents used experimentally. Further, the overall activation energy is calculated to be negative. A positive barrier is obtained only if solvation is included.[76] Nevertheless, the transition-state structures are likely to be realisitic. The relative energies may also not be affected by solvation. Hence, these structures form a suitable basis for evaluating stereoelectronic effects. Methanol has also been used as a model nucleophile by Coxon[77a] within the AM1 methodology. Coxon has used addition of AlH_3 to ketones as a representative nucleophilic addition reaction.[77b]

For electrophilic additions to olefins, intermediates derived from addition of H^+, Br^+, I^+, and Hg^+ have been used as models.[53] Borane addition provides a good model for attack by a neutral species. However, the PE surface is flat, with the relative energies of the π-complex and the subsequent transition state being method dependent. In recent years, CCl_2 addition has been used extensively. Even in this system, the reaction is calculated to proceed with no activation barrier at many levels of theory.[78] Transition states obtained at the AM1 level have generally been used for interpretation.

Once precise transition states are located, computations can be used for extracting a large amount of information. Geometric distortions can be analyzed in detail. Bond length changes on going from the reactant to the transition state can be used to verify the presence of hyperconjugative interactions. Bond orders provide further confirmation for such interpretations. Natural population analyses, which yield orbital interaction energies through a perturbative scheme, can be employed[79] to distinguish between Felkin−Anh and Cieplak models.

The contributions of geometric, orbital, electrostatic, and counterion effects can be quantified through additional calculations on various fragments of the transition state.[75] For example, the energy of the substrate fragment of the transition state can be computed and compared with its energy in the ground state. The increase provides a measure of the energy required to distort the substrate to reach the transition state. Similarly, orbital and electrostatic effects can be modeled by replacing the reagent at the transition state with a bare partial charge, without any associated basis functions which allow hyperconjugative interactions. Counterion effects can be estimated by recomputing the energy of the transition-state fragment in which the ion is removed. These additional handles for interpretation make computational studies quite valuable. Many studies which exploit these tools have been reported for understanding the origins of stereoselectivity in nucleophilic additions.[39,75]

Solvent effects can also be included in calculations by different procedures. The simplest strategy is to use the Self-Consistent Reaction Field (SCRF) model. It has been used to demonstrate the important role of solvents in determining face selectivity in one set of substrates.[80] More systematic studies may be anticipated in the future.

III. A Unified Strategy toward Unraveling the Electronic Origins of Face Selectivity

In view of the multiplicity of stereoelectronic factors which can determine face selectivity, a well designed strategy is needed to derive useful generalizations. It is highly desirable to keep steric influences to a minimum. Therefore, a series of sterically unbiased substrates need to be chosen for examination. Without affecting the isosteric nature of the reaction center, the effect of a large number and type of substituents must be studied. In addition, the number of intervening bonds separating the substituent and the reaction site must be varied. It will be useful to change the orientation of the substituent with respect to the line of attack of the reagents.

Since orbital and electrostatic models need to be distinguished, comparisons of selectivity in additions involving oppositely charged species would be revealing. Hence, studies of facial preferences for nucleophilic additions to sterically unbiased ketones should be complemented by parallel investigations of electrophilic additions to corresponding olefins. To obtain a fair comparison, reaction conditions within each class of substrates should be maintained constant or fairly similar.

While the experimental results can be interpreted in terms of a few plausible stereoelectronic models in a qualitative manner, a detailed computational analysis provides valuable additional insights. Again, it is important to compare results obtained using uniform theoretical levels.

In the following, the discussion is limited to studies which follow the above pattern. The substrates are presented in a sequence such that insights concerning different factors emerge. Some interesting experimental results which have been interpreted phenomenologically are not taken up for detailed analysis but are briefly mentioned. In particular, from the exhaustive series of studies by le Noble, only representative examples, which have been subject to theoretical analysis, are discussed. Full details are provided in an accompanying article.[81] In a few cases, systems with some steric bias are also included for discussion. These have been carefully chosen such that they reinforce the conclusions derived from related unbiased substrates.

IV. Nucleophilic Additions to Carbonyl Groups

A. Remote Substituent Effects in 7-Norbornanones, Adamantanones, and Related Systems

1. Interpretations Based on the Cieplak Model

In a remarkably simple experiment,[22] le Noble showed that a distal 5-fluoro substituent induces a low, but measurable face selectivity in the sodium borohydride reduction of adamantan-2-one, **22** (R=F). The major isomer was shown to be the (*E*) alcohol, implying preferred nucleophilic attack from the syn face (Scheme 3, Table 1).

To contrast the effect of the fluorine substituent, face selectivities were also determined with several other remotely placed groups.[82] A summary of the observed diastereoselectivities is provided in Table 1. Uniformly, acceptor substituents induce syn face attack, while inductive donor groups induce anti selectivity.

Subsequently, the study was extended to a variety of other substrates related to **22**.[83] Diastereoselectivity was also examined in other types of reactions, such as epoxidation and dichlorocarbene addition,[84] solvolysis,[85] thermal[86] and photocycloadditions,[87] cycloreversion,[88] oxidation,[89] oxy-Cope[90] and Claisen[91] rearrangements, protonation,[92] radical capture,[93] and iron tricarbonyl complexation.[94] The remote substituent effects in all of these diverse reactions were qualitatively similar.

Scheme 3

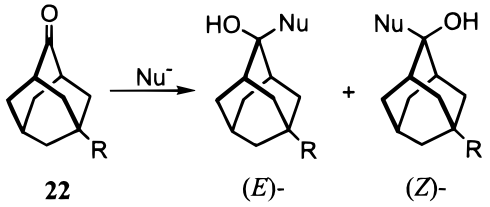


Table 1. Observed Product Ratios of Nucleophilic Additions to 5-Substituted Adamantan-2-ones (22)

substituent (R)	nucleophile	alcohol % (*E*)	alcohol % (*Z*)
$COOCH_3$	$NaBH_4$	57	43
	CH_3Li	55	45
CN	$NaBH_4$	69	31
	CH_3Li	68	32
t-Bu	$LiAlH_4$	50	50
F	$NaBH_4$	62	38
	CH_3Li	70	30
Cl	$NaBH_4$	59	41
	CH_3Li	62	38
Br	$NaBH_4$	59	41
	CH_3Li	60	40
I	$NaBH_4$	64	36
	CH_3Li	57	43
OH	$NaBH_4$	57	43
CF_3	$NaBH_4$	59	41
	CH_3Li	72	28
OCH_3	$NaBH_4$	64	36
	CH_3Li	63	37
$OCOCH_3$	$NaBH_4$	62	38
$N(CH_3)_2$	$NaBH_4$	65	35
	CH_3Li	63	37
CH_3	$NaBH_4$	51	49
	CH_3Li	54	46
$Si(CH_3)_3$	$NaBH_4$	50	50
	CH_3Li	49	51
$Sn(CH_3)_3$	$NaBH_4$	48	52
	CH_3Li	48	52

Scheme 4

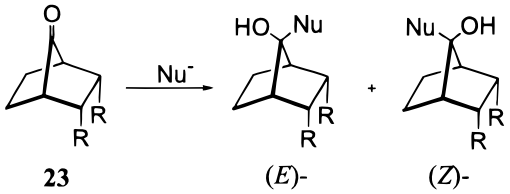


Table 2. Observed Product Ratios of Nucleophilic Additions to endo,endo-2,3-Disubstituted Norbornan-7-ones (23)[a]

substituent (R)	nucleophile	alcohol % (*E*)	alcohol % (*Z*)
$COOCH_3$	$NaBH_4$	84	16
	$LiAlH_4$	87	13
	$(t\text{-}BuO)_3LiAlH$	77	23
	CH_3Li	>90	<10
CH_2OCH_3	$NaBH_4$	40	60
	CH_3Li	34	66
$CH{=}CH_2$	$NaBH_4$	36	64
	$LiAlH_4$	35	65
	$(t\text{-}BuO)_3LiAlH$	34	66
	CH_3Li	27	73
CH_2CH_3	$NaBH_4$	20	80
	$LiAlH_4$	21	79
	$(t\text{-}BuO)_3LiAlH$	29	71
	CH_3Li	17	83

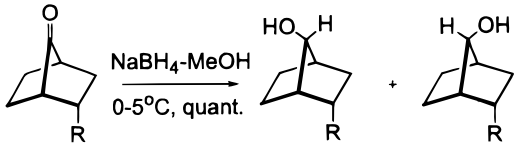
[a] The (*E*) and (*Z*) alcohols are obtained, respectively, by syn and anti face addition of the nucleophile.

The consistency of the results obtained for a wide variety of reactions carried out under different conditions (reagent, solvent, temperature, etc.) clearly favors a common electronic origin. The results were interpreted in terms of the Cieplak model.[14,58] The inductive effect of the substituent alters the donor ability of the C_1-C_9 and C_3-C_4 bonds, relative to C_1-C_8 and C_3-C_{10} bonds, to take part in hyperconjugative interaction with the σ^* orbital of the newly formed C−X bond at the transition state. The preferred direction of approach of the reagent is anti to the electron-rich bonds (Figure 5). Hence, electron withdrawing substituents induce syn addition, while inductive donors favor anti addition.

Independent studies on other sterically unbiased substrates supported the Cieplak proposal. For example, face selectivities in nucleophilic additions to 2,3-endo,endo-disubstituted 7-norbornanones, **23**, were shown to be highly sensitive to the nature of the distal substituents (Scheme 4).[95] The ratio of (*E*) and (*Z*) alcohols in sodium borohydride reduction was found to be 84:16 with ester substituents (Table 2). The ratio switched to 20:80 with ethyl groups. The pattern remained the same for reactions with other hydride reagents as well as for methyllithium.

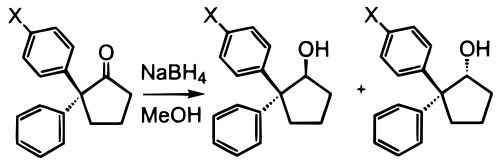
Even monosubstitution was found to be effective enough to induce diastereoselectivity in norbornanones, **24** (Scheme 5).[70] Furthermore, the same trend in selectivity was observed in the electrophilic additions to the corresponding 2,3-endo,endo-disub-

Scheme 5



24 R=CN	(*E*)-88%	(*Z*)-12%
R=$COOCH_3$	68%	32%
R=C≡CH	69%	31%

Scheme 6



25 R=NO_2	(*Z*)-21%	(*E*)-79%
R=Cl	37%	63%
R=Br	37%	63%
R=H	50%	50%
R=OCH_3	57%	43%
R=OH	70%	30%
R=NH_2	64%	36%

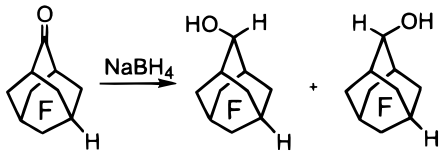
stituted 7-methylenenorbornanes.[96] Facial preference was found to be reversed on going from the diester to the dialkyl derivative in epoxidation, hydroboration, and oxymercuration reactions. The favored approach of the nucleophile or electrophile from the syn face in the case of inductively electron withdrawing groups and the opposite preference with donor substituents is entirely compatible with the Cieplak model.

In parallel investigations, Halterman and McEvoy found systematic variations in the diastereoselectivity in the borohydride reductions of a number of 2-phenyl-2-(4-X-phenyl)cyclopentanones, **25** (Scheme 6).[97] The (*E*)/(*Z*) alcohol product ratios could be switched from 79:21 to 30:70 by varying the para substituent on one of the aryl rings. Consistently, in all of the substrates, the hydride addition occurred preferentially from the carbonyl face opposite to the electron-rich aryl ring. Subsequently, the same pattern was demonstrated in the cycloaddition of 5,5-diarylcyclopentadienes[98] and in the osmylation of 3,3-diarylcyclopentenes.[99] These results are again in accord with the Cieplak model.

2. Interpretations Invoking Alternative Models

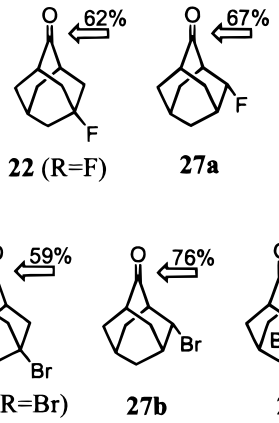
Despite the large body of evidence collected in favor of the Cieplak stereoelectronic theory, some doubts refused to disappear. For example, the assumption of an isosteric environment in heteroadamantanones, **7** and **8**, was criticized.[36] Even in other systems, a few facts did not strictly fit the Cieplak model. In particular, the endo vinyl groups were found to induce anti addition in 7-norbornanone when, on the basis of inductive effects, syn attack should have been favored.[95] Was there a novel interaction involving the

Scheme 7



26 (*E*)-58% (*Z*)-42%

Scheme 8



22 (R=F) **27a**

22 (R=Br) **27b** **28**

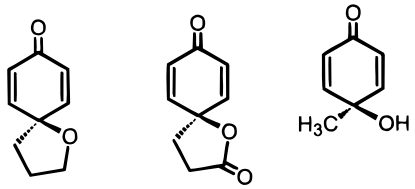
π-electron clouds of the double bonds which enhanced the donor abilities of the C_1-C_2 and C_3-C_4 σ bonds relative to C_1-C_6 and C_4-C_5 bonds, effectively making the vinyl group to act as a donor in the Cieplak sense?[95] Perhaps this is another manifestation of the double hyperconjugation model.[60] Of course, these refinements may appear to be ad hoc modifications made with an inordinate desire to retain the Cieplak model for interpretation.

Another system for which the Cieplak model was shown to be incorrect corresponds to the adamantanone derivative, **26**, in which the hydrogen and fluorine atoms were completely interchanged.[100] The major product during reduction of this interesting substrate is the one in which addition occurs syn to the hydrogen (Scheme 7). Because hydrogen is a better inductive donor than fluorine, the selectivity is incompatible with the Cieplak model. However, the observed selectivity is consistent with the Felkin–Anh hyperconjugative model. This is not surprising because polyfluorination lowers the energies of σ^* orbitals, making them more responsive to donor interaction with the σ orbital of the newly formed bond.

A puzzling trend, which suggests the need to go beyond the Cieplak theory, was noted in the diastereoselectivity in the reductions of adamantanones, **27a,b** and **28**, with 4- and 4,9-substitution (Scheme 8).[101] Despite greater perturbation of the stereodirecting σ bonds through closer proximity, the preference for syn addition was found to be only slightly greater than that observed in the corresponding 5-substituted derivatives, **22**. The results seemed to highlight the importance of orbital alignment in inducing face selectivity. Perhaps the double hyperconjugation model is operative, after all.[60]

More serious difficulties with the hyperconjugation approach were encountered in the interpretation of

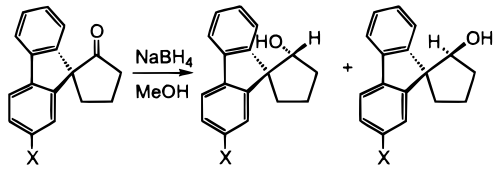
face selectivities in other sterically neutral substrates. Nucleophilic additions to a series of 4,4-disubstituted cyclohexadienones, **29a**−**c**, were shown to exhibit facial selectivity compatible with exclusively electrostatic interactions.[102] It was suggested that the dominant factor determining the preferred approach of the nucleophile was the bond dipoles of distal substituents. The observed product distributions were found to be consistent with AM1 calculated molecular dipole moment components. In these systems, hyperconjugative interactions are not likely to be operative. Cieplak and Felkin−Anh effects need to be transmitted through C=C π bonds, and their impact on the preferred direction of approach of the nucleophile can only be marginal.



29a **29b** **29c**

The selectivities obtained by Ohwada[103] in a sterically unbiased spiro system, **30**, with distal substitution were also not entirely consistent with the Cieplak model. While nitro substitution induced syn selectivity, a methoxy group unexpectedly yielded the same preference (Scheme 9). This was reconciled

Scheme 9

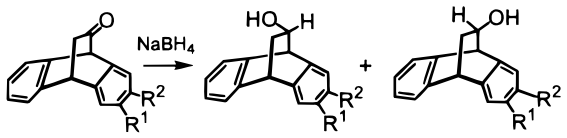


30 R=NO_2	(*E*)-68%	(*Z*)-32%
R=F	72%	28%
R=OCH_3	74%	26%

using electrostatic arguments on the basis of total charges on each aryl ring from STO-3G calculations. The problem of interpretation persisted in the electrophilic additions to the corresponding olefins. In these substrates, an orbital distortion model was proposed to account for the results. The model has also been applied to explain face selectivity in substituted dibenzobicyclo[2.2.2]octanone derivatives, **21** (Scheme 10).[47]

The validity of hyperconjugative models was questioned in a study of nucleophilic additions to bridged biaryl ketone, **31**.[104] The product distributions could not be reconciled with the Cieplak model, but were suggested to be consistent with through-bond interactions as well as through-space electrostatic effects at the transition state. It must, however, be recognized that while the substrates are conformationally rigid, the two π faces are not sterically equivalent. The steric perturbation is fairly close to the reaction center. Hence, the failure of the hyperconjugative

Scheme 10

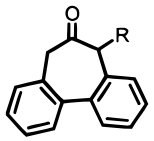


21 R_1=H; R_2=H	(*E*)-50%	(*Z*)-50%
R_1=NO_2; R_2=H	77%	23%
R_1=OCH_3; R_2=H	46%	54%
R_1=F; R_2=H	57%	43%
R_1=H; R_2=NO_2	77%	23%
R_1=H; R_2=OCH_3	49%	51%
R_1=H; R_2=F	61%	39%

Table 3. Ab Initio Calculated Energy Differences (kcal mol^{-1}) between Anti and Syn Addition Transition States for the Reaction of LiH with endo,endo-2,3-Disubstituted Norbornanones (23)

substituent (R)	6-31G*	MP2/6-31G*	exptl
CHO (eclipsed to CC)	3.0	4.0	
CHO (eclipsed to CH)	−0.2	−0.6	
$COOCH_3$ (eclipsed to CC)	2.8		0.9
$COOCH_3$ (eclipsed to CH)	1.0		
CH_2F	0.5	0.7	
CH_2OH	−0.1	−0.1	−0.2
$CH{=}CH_2$	−0.3	−0.4	−0.3
CH_3	−0.5	−0.6	−0.8
SiH_3	−0.8	−0.3	

models in these substrates cannot be construed to be serious.



31

Serious doubts about the importance of Cieplak model were also raised on the basis of ab initio calculations of LiH additions to a few endo-substituted 7-norbornanones, **23**.[105] Transition-state energetics were obtained for a number of derivatives and were found to be generally consistent with experimental data (Table 3). For the diester and diformyl derivatives, different conformations were obtained in which the carbonyl groups on the substituents were eclipsed either to adjacent C−C or to C−H bonds. The relative energies were sensitive to the orientation of the groups, hinting at the possibility of through-space field effects between the nucleophile and the substituent oxygen atoms. Such variations are clearly not compatible with orbital models in which differential hyperconjugation results from the inductive effect of the substituent.

To probe the role of electrostatic effects, the LiH unit was replaced by a partial negative charge (−0.5) and the transition-state energies were recomputed for the diformyl substrate. The trends were unchanged on going from realistic transition states to the charge model. It was therefore argued that electrostatic effects at the transition state exclusively

determined the face selectivities in this system. The conclusion was assumed to hold good for all other substituents as well.

3. Critical Evaluation of Different Interpretations

In many of the examples cited in the previous section, the reasons for the failure of the Cieplak model of diastereoselection can be readily recognized. In the polyfluoroderivative, **26**, the Felkin−Anh hyperconjugative model evidently comes into play because of low-lying C−F σ^* orbitals on the substrate.[100] In the substituted cyclohexadienones,[102] **29**, spiro derivatives,[103] **30**, and the dibenzobicyclo-[2.2.2]-octanones,[47] **21**, the scope of differential hyperconjugative interactions induced by the remote substituent is significantly curtailed by the intervening π units. Therefore, alternative electronic interactions become more important in these systems. The failure of the hyperconjugative models in **31** can also be understood in terms of the steric bias at the reaction center, although alternative interactions have been proposed to rationalize the observed trends.[104] Interestingly, the criticism of the Cieplak model has not been restricted to these substrates. Even in nucleophilic additions to adamantanones and norbornanones, electrostatic effects at the transition state have been suggested to be the primary factor determining facial selection. The generality of this conclusion, on the basis of ab initio calculations on select model systems,[105] needs critical evaluation. For this reason, a wider variety of substrates was examined using the semiquantitative MNDO model described in an earlier section by extensive study of face selectivities in a number of norbornanones and adamantanones.[70] Several useful insights have emerged from the data computed using the charge and hydride models.

First of all, the MNDO optimized geometries of a number of 5-substituted adamantanones as well as 2-endo-substituted and 2,3-endo,endo-disubstituted 7-norbornanones confirm that there is virtually no steric bias at the carbonyl center in the ground state. There is little pyramidalization or tilt of the carbonyl groups in any of these systems. The facial discrimination in these systems is achieved through nonsteric means.

The relative energies obtained with the hydride model for syn and anti approach of a test nucleophile in a set of 2,3-endo,endo-disubstituted 7-norbornanones, **23**, are given in Table 4. The experimentally observed preferences in borohydride reduction are given for direct comparison. Qualitatively correct predictions are made in all cases. The more stable model transition state corresponds to the major product obtained experimentally. The opposite face selectivities of diethyl and diester derivatives are correctly reproduced. More impressively, the preference for anti attack found in the divinyl derivative is obtained from the hydride model too.

The data for monosubstituted derivatives, **24**, are useful to eliminate the potential role of conformational variations due to intersubstituent interactions. The results for methyl and cyano derivatives remove conformational uncertainties altogether. The hydride model yields predictions consistent with experimental data in all systems for which comparisons are available (Table 5). A single ester or cyano group is correctly calculated to induce syn selectivity and with the expected reduction in preference compared to the diester substituents. In view of the surprisingly accurate predictions in virtually all of the sterically unbiased systems considered, the interpretations from the simple model are likely to be reliable. It is therefore instructive to consider the predictions of the charge model.

Table 4. Calculated Relative Energies (kcal mol^{-1}) of Idealized Transition States for Syn and Anti Nucleophilic Addition to endo,endo-Disubstituted 7-Norbornanones (23) with the MNDO Charge and Hydride models

	model					
	charge		hydride		exptl	
substituent (R)	anti	syn	anti	syn	anti	syn
CH_2CH_3	0	7.8	0	1.9	0	0.8
$COOCH_3$	0.8	0	2.2	0	0.9	0
CH_2OCH3	0	7.0	0	1.3	0	0.2
$CH{=}CH_2$	0	7.2	0	2.0	0	0.3
CH_3	0	7.2	0	1.9		
CN	3.3	0	2.6	0		
C≡CH	0	1.3	0.4	0		

Table 5. Calculated Relative Energies (kcal mol^{-1}) of Idealized Transition States for Syn and Anti Nucleophilic Addition to Mono-*endo*-substituted 7-Norbornanones (24) with the MNDO Charge and Hydride models

	charge model		hydride model		exptl	
substituent (R)	anti	syn	anti	syn	anti	syn
CH_2CH_3	0	3.9	0	0.9		
$COOCH_3$	0.1	0	1.0	0	0.4	0
$CH{=}CH_2$	0	2.8	0	0.4		
CN	1.8	0	1.4	0	1.1	0
C≡CH	0	0.9	0.1	0	0.4	0

The energy differences obtained with the charge model are substantially greater than those obtained with the hydride model for almost all of the 7-norbornanone derivatives. The only exceptions are the ester-substituted compounds and, to a certain extent, the cyano derivatives. The magnitude of the energy differences with the charge model may be attributed to the inherent assumptions of the approach. But it is indeed remarkable that the face selectivity predicted is identical to that of the hydride model and importantly, that which is observed experimentally in all cases. This implies that face selectivity in these substrates can be interpreted exclusively in terms of electrostatic effects. In particular, anti face selectivity in alkyl, methoxymethyl, and vinyl derivatives is suggested to have a common electrostatic origin. The ester and cyano derivatives are the only systems in which orbital interactions included in the hydride model seem to play a role in inducing a strong preference for syn face attack.

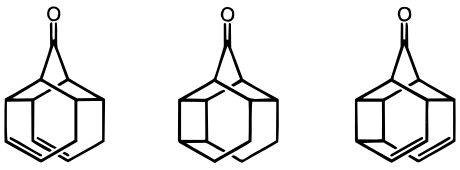
It may seem surprising that alkyl and vinyl groups can lead to large electrostatic destabilization for syn face approach of the nucleophile. The substituents are unlikely to polarize the exo face near the substituent in the same manner as to cause electrostatic

Table 6. Experimentally Observed Distribution of Products Derived from Syn and Anti Face Nucleophilic Additions to 32−34 and Relative Energies (kcal mol^{-1}) Obtained Using the MNDO Charge and Hydride Models

	32		33		34	
	anti	syn	anti	syn	anti	syn
exptl product ratios						
$LiAlH_4$	43	57	33	67	33	67
CH_3Li	39	61	33	67	32	68
model						
Charge	1.8	0				
Hydride	0.7	0				

repulsion. The most plausible interpretation is direct through-space interaction between the negatively charged nucleophile and the electron cloud of the substituents, as suggested earlier on the basis of ab initio calculations.[105] The MNDO models suggest that a similar repulsion which is possible in the ester and cyano derivatives is compensated by the attractive interaction of the nucleophilic charge with the strongly positively polarized exo face of the substrate and hence the facial selectivity is determined by hyperconjugative interactions in these substrates.

The experimental and computed face selectivity data in the endo-annulated norbornanones, **32**−**34**, enable additional evaluation of the above arguments. In the hexacyclic diene derivatives, the preferred direction of approach of the nucleophile is from the face syn to the double bonds (Table 6).[106] This result was originally interpreted in terms of the Cieplak model (invoking the inductive withdrawing nature of sp^2 centers). The charge model reveals that electrostatic repulsion of the approaching nucleophile with the sp^3 centers is greater relative to that with olefinic units, leading to the correct prediction of facial selectivity for **32**. The hydride model including hyperconjugative effects also yields the same selectivity, but it is difficult to estimate its importance in this system.



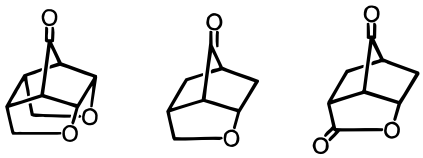
32 **33** **34**

The preferences found in other annulated derivatives, **35**−**37**, provide further tests for theoretical models of interpretation.[107] Experimentally, hydride approach from the face syn to the endocyclic ether oxygen is favored (Table 7). The MNDO hydride model reproduces the trends in all of the derivatives. On the other hand, the energy differences obtained with the charge model are negligible. The through-space repulsion that is possible between the charged nucleophile and the ether oxygen atom(s) seems to be nullified by attractive interaction with the positively polarized exo face. The observed face selectivities and calculated energy differences with the hydride model suggest the primacy of hyperconjugative control of facial selectivity in these systems. The

Table 7. Experimentally Observed Distribution of Products Derived from Syn and Anti Face Nucleophilic Additions to 35−37 and Relative Energies (kcal mol^{-1}) Obtained Using the MNDO Charge and Hydride models

	35		36		37	
	anti	syn	anti	syn	anti	syn
exptl product ratios						
$NaBH_4$	<15	>85	35	65	31	69
theor models						
MNDO (hydride)	0.8	0	0.5	0	0.4	0
MNDO (charge)	0	0.2	0.2	0	0	0.1
HF/3-21G	1.5	0	0.3	0	1.0	0
HF/6-31G*	1.4	0	0.3	0	1.0	0
HF/6-31G* (charge)	1.7	0	0.4	0	1.2	0
MP2/6-31G*	0.7	0	0	0.2	0.9	0
MP2/6-31G* (charge)	1.0	0	0.1	0	1.1	0

inductively electron withdrawing effect of the ether oxygen is superior to that of a methylene and even a carbonyl group. Therefore, attack from the syn side of the ether linkage is in accord with the Cieplak theory.



35 **36** **37**

Ab initio calculations at the HF/3-21G, HF/6-31G*, and MP2/6-31G* levels have been carried out on LiH addition transition states on these annulated ethers and lactone. The difficulty associated with accurately determining small energy differences of the order of 0.5 kcal mol^{-1} is noticeable in the method dependence of the predicted facial selectivity in the ether, **36**. But overall, the calculations yield qualitatively the correct preferences. Electrostatic contributions modeled by replacing the LiH unit with partial negative charge follow the same trends as the relative energies of the transition states. As in the earlier study on substituted 7-norbornanones, ab initio calculations seem to favor a dominant role for electrostatic effects in determining face selection, even in these substrates.

In light of the differences in interpretations of the origins of face selectivity in substrates related to 7-norbornanones, it is of interest to consider the results obtained for 5-fluoroadamantanone. On the basis of the MNDO charge model, electrostatic effects are indicated to favor anti face approach of the nucleophile in this substrate.[70] Despite the distal location of the electronegative substituent, through-space repulsions with the reagent are calculated to be quite significant. The inductive polarization of the carbon and hydrogen at C_4 and C_9 positions does not seem to be large enough to result in stabilizing coulombic interactions for the syn face attack. Interestingly, the preference dictated by electrostatic interactions is reversed by orbital interactions. The hydride model yields syn selectivity, consistent with experimental data.

The above interpretation of orbital control of face selectivity in 5-substituted adamantanone is sup-

ported by AM1 and ab initio calculations of transition states for AlH_3 additions.[108] The electrostatic effects are likely to be less important with this model nucleophile. The role of stereoelectronic factors was inferred from computed geometries of transition states. The distortions support the operation of hyperconjugative interactions and also the secondary role played by torsional changes.

The MNDO models as well as ab initio transition state calculations have also been applied to a number of heteroadamantanones.[70] The interpretations in these systems are complicated by the possible role of Lewis acid coordination to the free nitrogen lone pair in 5-azaadamantanone and potential ground-state geometric distortions.

Overall, the facial selectivities obtained from ab initio calculations on realisitic transition states and MNDO procedure with idealized structures are both generally concordant with experimental data. Besides predicting the correct preference in all of the substrates for which the qualitative Cieplak model is successful, the simple computational model offers a satisfactory resolution to the puzzling trend noted in the vinylnorbornanones. The dominant effect of electrostatic interactions is suggested to be responsible for the substituents to induce preferential anti attack by the nucleophile.

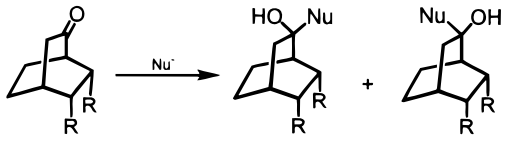
Ab initio results on LiH addition transition states and the MNDO charge model lead to different interpretations of the relative importance of electrostatic and orbital effects in some cases. The former points to a dominant role for electrostatic interactions in determining face selectivity in all of the substrates. While the models based on MNDO yield the same conclusion for a few norbornanones, orbital effects are suggested to reinforce electrostatic preferences in a significant manner in some systems. In endo-annulated ethers and lactones, the semiempirical procedures support dominant orbital control of face selectivity. For 5-substituted adamantanones, the semiempirical approach and ab initio calculations for AlH_3 additions yield the same conclusion supporting the importance of hyperconjugative interactions.

B. Electrostatic Control of Facial Selectivity: Substituted Bicyclo[2.2.2]octanones

In the majority of the systems considered above, the observed face selectivities can be reconciled by invoking either or both electrostatic and orbital models. It would be of interest to examine substrates in which the effects can be segregated. The study of facial selectivity in distally substituted cyclohexadienones, **29**, represents an interesting example.[102] In these substrates, vinylogous orbital interactions are unlikely to be important. The observed trends reflect the nature and magnitude of through-space interaction between the substituent and the approaching nucleophile. A more direct evaluation of the importance of electrostatic and orbital effects was achieved through another series of substrates, viz., substituted bicyclo[2.2.2]octan-2-ones, in which, through proper positioning of the substituent, the orbital interactions could be turned "on" or "off".

The face selectivities observed for 5,6-endo,endo-disubstituted derivatives, **38**, parallel the trends

Scheme 11

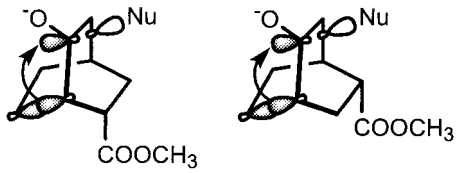


38 (*E*)- (*Z*)-

Table 8. Observed Product Ratios of Nucleophilic Additions to endo,endo-5,6-Disubstituted Bicyclo[2.2.2]octanones (38)[a]

		alcohol	
substituent (R)	nucleophile	% (*E*)	% (*Z*)
$COOCH_3$	$NaBH_4$	70	30
	$(i\text{-}Bu)_2AlH$	67	33
CH_2OCH_3	$NaBH_4$	52	48
$CH{=}CH_2$	$NaBH_4$	50	50
	$(i\text{-}Bu)_2AlH$	50	50
	CH_3Li	54	46
CH_2CH_3	$NaBH_4$	39	61
	$(i\text{-}Bu)_2AlH$	35	65
	CH_3Li	34	66

[a] The (*E*) and (*Z*) alcohols are obtained, respectively, by syn and anti face addition of the nucleophile.



39 **40**

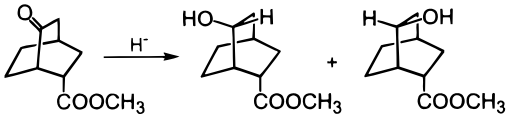
Figure 7. Cieplak interaction for syn face addition transition states in substrates **39** and **40**. Substituent effect is "on" in **39** but "off" in **40**.

noted in the corresponding norbornanones, **23**.[95,109] With ester substituents, nucleophilic addition occurs preferentially from the syn face (Scheme 11, Table 8). While methoxymethyl and vinyl groups do not induce any significant selectivity, ethyl substituents lead to preferential addition from the anti face of the carbonyl group. These results can be rationalized in terms of the Cieplak model, although the role of electrostatic effect cannot be discounted.

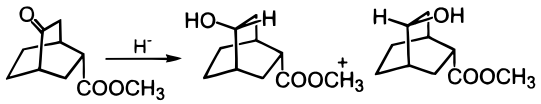
Crucial evidence in support of electrostatic contribution to the observed diastereoselectivity was obtained by studying the monosubstituted bicyclo[2.2.2]-octan-2-ones, **39** and **40**. In the former, the substituent is ideally placed to direct the approaching nucleophile through hyperconjugative interaction. In isomer **40**, the substituent is far removed from the reaction center. Cieplak-type interactions have been effectively turned off in this substrate (Figure 7). Interestingly, both **39** and **40** show the same selectivity when subjected to $NaBH_4$ and DIBAL-H reduction (Scheme 12). Even in the off position, the substituent has been effective in leading to syn face addition.

The interplay of orbital and electrostatic interactions in determining the diastereoselectivity in the addition to ketone **39** is supported by the MNDO-based charge and hydride model calculations (Table 9). A negative charge placed on the syn face of the carbonyl group is computed to be less favorable compared to that on the anti face by 3.3 kcal mol^{-1}.

Scheme 12



39 $NaBH_4$ (*E*)-65% (*Z*)-35%
DIBAL-H (*E*)-66% (*Z*)-34%



40 $NaBH_4$ (*E*)-62% (*Z*)-38%
DIBAL-H (*E*)-61% (*Z*)-39%

Table 9. Calculated Relative Energies (kcal mol^{-1}) of Idealized Transition States for Syn and Anti Nucleophilic Addition to Mono-*endo*-substituted Bicyclo[2.2.2]octanones, 39 and 40, with the MNDO Charge and Hydride Models

	model					
	charge		hydride		exptl	
ketone	anti	syn	anti	syn	anti	syn
39	0	3.3	0.6	0	0.3	0
40	1.4	0	1.5	0	0.3	0

This implies the presence of electrostatic repulsions between the approaching nucleophile and the distal substituent. The repulsions are indicated to be overcome by orbital interactions. When the latter are included, as in the hydride model, syn face addition is calculated to be preferred, in agreement with the experimental trends.[109]

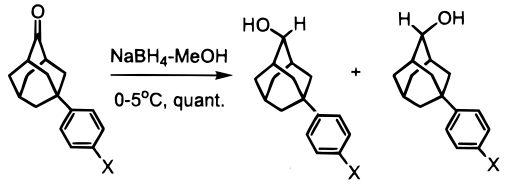
The computed results for ketone **40** are also revealing. The charge model leads to the syn face preference observed experimentally. The use of the hydride ion probe makes little difference to the relative energies and results in the same selectivity. Thus, syn face preference is induced exclusively through electrostatic interactions without contributions from hyperconjugation. The reversal in the predicted face selectivity with the charge model for **39** and **40** is also understandable. Through-space electrostatic repulsions between the approaching nucleophile and the substituent are dominant only for the syn face addition to **39**. These interactions are absent in the corresponding transition state involving **40**, because the substituent is placed away from the trajectory of the approaching nucleophile. However, the residual attractive interaction between the nucleophile and the positively polarized exo face hydrogen atoms would lead to a small preference for syn face addition.[109]

The results discussed in this section confirm that it is possible to achieve diastereoselection in nucleophilic additions even in substrates which do not offer scope for differential hyperconjugative interactions. Facial discrimination is induced exclusively through electrostatic means. Interestingly, electrostatic control of facial selectivity has been invoked in two different modes. In the monosubstituted bicyclo[2.2.2]-octan-2-one, **40**, the mild positive polarization of the exo face by the inductively withdrawing substituent is implicated for the favored approach of the nucleophile from the syn side. In the cyclohexadienones, **29a**−**c**, studied by Wipf and Kim,[102] direct field effect between the substituent and the nucleophile is held responsible for the preferred addition from the anti face. We turn next to the possibility of proving the importance of these effects individually and of quantifying them.

C. Through-Space Electrostatic Interactions: 2-Aryl-7-norbornanones

The aryl group has proved to be of great value in isolating through-bond and through-space effects in a number of contexts. By introducing additional substituents on the ring at different positions, probes with varying electron demand can be constructed.[110] Two such sets of substrates have been studied to determine the origin of facial selectivity in nucleophilic additions to sterically unbiased ketones. Adcock and co-workers evaluated the diastereoselectivity in nucleophilic additions to a number of 5-aryladamantanones, **41**, with substituents at the para position of the aryl ring (Scheme 13).[51a] A larger set

Scheme 13



41 (*E*)- (*Z*)-

of 2-*endo*-aryl-norbornan-7-ones, **42**, was studied by Mehta and co-workers.[51b,111] The corresponding derivatives have been subject to detailed computational analysis at both semiempirical and ab initio levels, providing a basis for interpretations.

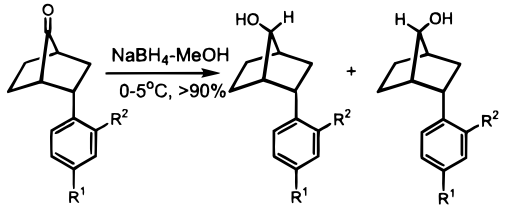
The observed diasteroselectivity with the unsubstituted phenyl group is itself interesting (Table 10 and Scheme 14). Reduction of the adamantanone derivative[51] leads to a mixture of alcohols in which

Table 10. Observed Product Ratios of Nucleophilic Additions to 5-(*p*-substituted) Aryladamantan-2-ones (41)[a]

		Alcohol	
substituent (X)	nucleophile	% (*E*)	% (*Z*)
H	$NaBH_4$	58	42
	CH_3Li	62	38
NO_2	$NaBH_4$	68	32
CN	$NaBH_4$	66	34
	CH_3Li	72	28
$COOCH_3$	$NaBH_4$	64	36
	CH_3Li	68	32
F	$NaBH_4$	63	37
	CH_3Li	67	33
Br	$NaBH_4$	64	36
	CH_3Li	68	32
OCH_3	$NaBH_4$	59	41
	CH_3Li	59	41
$N(CH_3)_2$	$NaBH_4$	57	43

[a] The (*E*) and (*Z*) alcohols are obtained, respectively, by syn and anti face addition of the nucleophile.

Scheme 14



42a	R^1=R^2=H	(*E*)-45%	(*Z*)-55%
b	R^1=CH_3; R^2=H	45%	55%
c	R^1=NO_2; R^2=H	58%	42%
d	R^1=H; R^2=NO_2	47%	53%
e	R^1=F; R^2=H	46%	54%
f	R^1=NH_2; R^2=H	40%	60%
g	R^1=H; R^2=NH_2	43%	57%

the (*E*) isomer is the major product. However, the (*Z*) alcohol is formed to a greater extent in the reduction of the corresponding norbornanone.[111] This trend is the same as that found earlier for the vinyl derivative.[95] Although donor interaction involving the π units and the norbornyl unit can be postulated, through-space repulsions between the electron-rich substituent and the negatively charged nucleophile offer the most convincing interpretation, as indeed supported by MNDO model calculations. Because the phenyl ring is further removed from the reaction center in the adamantanone derivative, the field effect is weaker. The preference for syn face attack by the nucleophile is therefore governed by differential hyperconjugative interactions produced by the inductively electron withdrawing phenyl ring.

The variations in face selectivities in the series of substituted aryladamantanones (Table 10) as well as arylnorbornanones (Scheme 14) are consistent with the above proposals. When a donor substituent, such as the amino group, is introduced, syn face addition becomes less favored. The opposite trend is observed with an acceptor group at the para position. The effect of a nitro group is particularly significant. An electron deficient aryl ring promotes syn face addition in two ways. Through-space repulsion with the nucleophile is reduced. Cieplak-type interactions also become more effective. The variations in selectivity, though small, are internally consistent.[111]

A striking demonstration of the through-space intersubstituent interaction is provided by the observed face selectivity for the *o*-nitrophenylnorbornanone, **42d**. The substituent is expected to deplete electron density from the aryl ring as effectively as in the para isomer, **42c**. Cieplak-type orbital interactions must also be equally strong. However, instead of favoring syn face addition, the (*Z*) alcohol is obtained as the major product on reduction. The observed trend can only be reconciled by invoking repulsion between the nitro group and the approaching nucleophile for syn face addition in **42d**.

Calculated transition-state energetics for the various arylnorbornanones (Table 11)[111] are of interest for several reasons. The face selectivity for the parent phenylnorbornanone, **42a**, is not reproduced at ab initio levels employing geometries optimized using the 3-21G basis set. The failure highlights the difficulty in making accurate predictions of small energy differences, especially when the substrates possess conformational flexibility. Perhaps fortuitously, the MNDO method yields anti face selectivity for hydride addition to phenylnorbornanone in agreement with the experimental data. At all theoretical levels, the effect of additional substituents on the relative face selectivity is correctly reproduced. In particular, the *p*-nitro group is calculated to enhance syn face addition. The large destabilization of the syn face addition transition state for the *o*-nitro derivative due to electrostatic repulsions is also correctly predicted.

Table 11. Calculated Energy Differences (kcal mol^{-1}) of Syn and Anti Addition Transition States for the Reaction of LiH with Arylnorbornanones, 42[a]

ketone	MNDO	HF/3-21G	HF/6-31G*	MP2/6-31G*	exptl
42a	0.21	−0.59	−0.04	−0.21	0.1
b	0.20	−0.53	−0.05	−0.13	0.1
c	−0.16	−1.24	−0.59	−0.67	−0.2
d	1.18	7.73	5.84	5.03	0.7
e	0.27				0.9
f	0.30				0.2
g	0.19				0.2

[a] A positive value indicates preference for anti face addition.

D. The Role of Hyperconjugative Interactions: Substituted Norsnoutanones and Snoutanones

As pointed out in section IVB, unambiguous evidence for electrostatic control of face selection in nucleophilic additions could be obtained by using probes in which differential hyperconjugative interactions are effectively eliminated. Conversely, proof for orbital control can be obtained by designing substrates in which electrostatic interactions are minimized. In particular, through-space interaction between the substituent and the nucleophile can be reduced by enhancing their spatial separation. This is achieved in 4-substituted norsnoutan-9-ones, **43**. The substrates offer several interpretive advantages. The ketones are rigid and sterically unbiased. While there is a formal similarity to the endo-substituted norbornanones, **23**, the substituent is further removed from the reaction center. The separation is even larger than in 5-substituted adamantanones, **22**, as is evident from the overlay diagram of the corresponding cyano derivatives (Figure 8). The presence of three-membered rings is an additional point of interest, because the strained bonds may transmit orbital interactions more effectively.

The observed diastereoselectivities in the reductions of a number of norsnoutanones reveal the profound effect of distal substituents (Scheme 15).[112] Electron withdrawing groups such as the cyano and ester substituents lead to a high percentage of (*E*) alcohols. The preference for syn face addition in the cyano derivative is significantly larger than in the adamantanone and is comparable to that in the norbornanone. The ethyl derivative yields a marginal preference for anti face addition. Interestingly, the vinyl and acetylide substituents induce syn selective addition. All of these trends are clearly consistent with the Cieplak model of stereoselection.

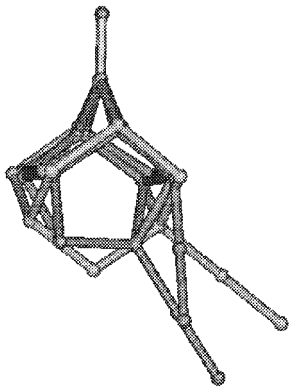
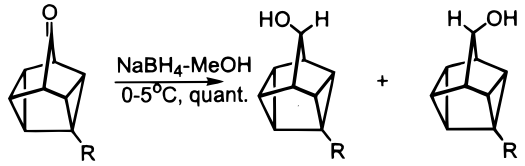


Figure 8. Overlay diagram of the optimized structures of cyano substituted norbornanone, adamantanone, and norsnoutanone.

Scheme 15



43	R=CN	(*E*)-84%	(*Z*)-16%
	R=$COOCH_3$	79%	21%
	R=C≡CH	76%	24%
	R=$CH=CH_2$	60%	40%
	R=CH_2OCH_3	56%	44%
	R=CH_2CH_3	48%	52%

Table 12. MNDO and Ab Initio Energy Differences (kcal mol^{-1}) for LiH Addition Transition States to the Syn and Anti Faces of 4-Substituted Norsnoutan-9-ones, 43[a]

substituent (R)	MNDO	HF/3-21G// HF/3-21G	HF/6-31G*// HF/3-21G	MP2/6-31G*// HF/3-21G	exptl
CN	0.5	1.0	0.9 (0.4)	1.0 (0.5)	0.9
$CH=CH_2$	0.1	0.1	0.0 (0.2)	−0.1 (0.1)	0.2

[a] Values in parantheses correspond to relative energies obtained by replacing LiH by a point charge at the location of the hydride. A positive value implies preference for syn face addition.

Because the geometry of a cyclopropyl unit is quite sensitive to substituents, especially π acceptor groups, the possibility of an inherent structural bias in these substrates needs to be considered. However, single-crystal X-ray structure of **43** (R = $COOCH_3$) confirms the isosteric nature of the reaction center.[112b] There is neither pyramidalization nor tilt of the carbonyl group in this substrate.

For confirming the electronic interpretation of facial selectivity in **43**, semiempirical and ab initio calculations were carried out for LiH addition to the cyano and vinyl derivatives (Table 12). The observed syn selectivity for nucleophilic approach for the cyano derivative is reproduced at these levels of theory. Additional model calculations were performed to isolate the electrostatic component in determining face selectivity. In the ab initio procedure, a partial negative charge was placed in place of LiH to estimate the electrostatic effect at the transition-state geometries. For the cyano derivative, the magnitude of the energy difference is smaller in this model, but the predicted direction of preferential approach is the same.

Table 13. MNDO Relative Energies (kcal mol^{-1}) for Syn and Anti Face Addition Calculated Using the Charge and Hydride Models as well as with LiH Addition Transition-State Geometries for Substituted Adamantanones (22), Norbornanones (23), and Norsnoutanones (43)[a]

ketone	charge	hydride	transition state	exptl syn:anti
22 R = CN	1.3	0.9	0.2	68:32
23 R = CN	1.8	1.4	0.5	88:12
43 R = CN	3.5	1.7	0.5	84:16
22 R = $CH=CH_2$	−1.0	0.0	0.0	
23 R = $CH=CH_2$	−2.8	−0.4	−0.2	36:64
43 R = $CH=CH_2$	1.0	0.5	0.1	60:40

[a] A positive value implies preference for syn face addition.

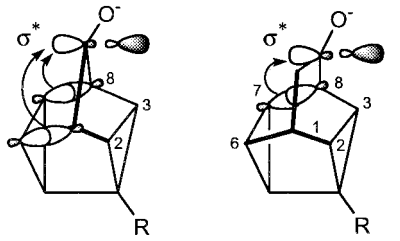
The charge and hydride model calculations (Table 13) using the MNDO approach also suggest that the observed diastereoselectivity can be reconciled using a combination of both electrostatic and orbital effects. Interestingly, the results for the vinyl derivative confirm that through-space repulsion between the substituent and the nucleophile is absent in the norsnoutanone. In this system, electrostatic interaction is calculated to be favorable for syn face addition, in contrast to the corresponding norbornanone.

The above results suggest that the strained cyclopropyl unit effectively communicates the orbital interactions induced by the substituent. The polarization of the exo face is also more pronounced in these systems, resulting in an electrostatic component to the observed face selectivity.

To segregate the above contributions to face selectivity, a modified substrate was examined.[113] The 4-substituted snoutanones, **44**, retain the same four-bond separation between the substituent and the reaction center as the corresponding norsnoutanones, **43**. Hence, direct interaction between the substituent and the nucleophile should be absent in this series too. Further, the electrostatic interaction between the nucleophile and the exo face hydrogen may be expected to be as effective as in the norsnoutanone, because the trajectory of the nucleophile is more directly above this atom. However, Cieplak-type orbital interactions should be reduced to a significant extent in the snoutanones. Differential hyperconjugation is possible only through one set of C−C bonds (Figure 9). A direct comparison of the diastereoselectivity in the snoutanone and norsnoutanone series would therefore provide a useful basis for interpretation.

Reductions of the snoutanones, **44**, uniformly led to a mixture of alcohols in which the (*E*) isomer was the major product (Scheme 16). All of the substituents induce syn face selective additions. However, the selectivity is consistently lower than in the corresponding norsnoutanones.

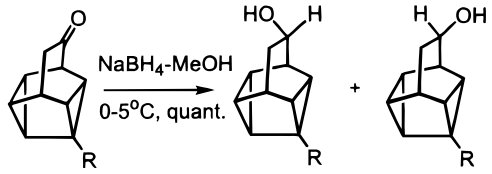
Ab initio calculations on the transition states for LiH addition to the cyano derivative reveal a lower energy difference in favor of syn addition in the snoutanone compared to 4-cyanonorsnoutanone (Table



43 44

Figure 9. Cieplak interactions in the syn addition transition states of **43** and **44**. Hyperconjugative stabilization is possible with two antiperiplanar β C−C bonds in **43** and only one in **44**.

Scheme 16



44 R=CN	(*E*)-59%	(*Z*)-41%
R=$COOCH_3$	59%	41%
R=C≡CH	57%	43%
R=$CH=CH_2$	57%	43%
R=CH_2OCH_3	53%	47%

Table 14. Relative Energies (kcal mol^{-1}) for the Syn and Anti LiH Addition Transition States for Cyano-Substituted Snoutanone and Norsnoutanone[a]

	snoutanone		norsnoutanone	
	anti	syn	anti	syn
HF/6-31G*//HF/3-21G	0.4 (0.5)	0.0 (0.0)	0.9 (0.4)	0.0 (0.0)
MP2/6-31G*//HF/3-21G	0.4 (0.5)	0.0 (0.0)	1.0 (0.5)	0.0 (0.0)

[a] Data using the charge model are in parantheses.

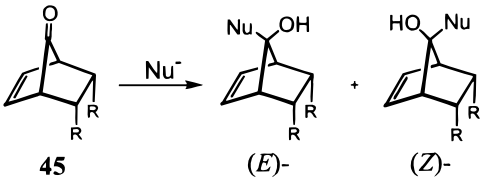
14). Interestingly, additional calculations using fractional charge in the place of LiH support the expectation that electrostatic preferences are roughly of the same magnitude in the two substrates. The reduction in the observed face selectivity can therefore be taken as a measure of the more effective Cieplak-type orbital interactions operating in the norsnoutanones.

The recently observed face selectivities for noradamantanones are interesting in this regard.[114] Reduced facial preferences have been obtained compared to adamantanones. The results have not been subject to detailed interpretations.

E. Overcoming Steric Bias through Electronic Effects: Substituted Norbornenones and Other Geometrically Perturbed Substrates

The substrates considered above have the reaction center in essentially an isosteric environment. These are ideal for evaluating different modes of electronic control of face selectivity. However, it is possible to derive information about electronic effects in substrates with a steric bias by more detailed examination. For example, by using nucleophiles which make varying steric demands at the transition state, the presence of additional factors can be discerned. The most striking demonstration of electronic effects would be through examples in which the steric bias is fully overcome. The face selectivity observed in the reduction of endo-substituted norbornenones, **45**, belongs to this class and hence is discussed here.

Scheme 17



45 (*E*)- (*Z*)-

Table 15. Experimentally Observed Product Ratios in the Reduction of Norbornenones, 45

		alcohol	
substituent (R)	nucleophile	% (*E*)	% (*Z*)
H	$NaBH_4$	85	15
	CH_3Li	74	26
	CH_3MgBr	96	4
	CH_2CHLi	29	71
	C_6H_5Li	28	72
	C_6H_5MgBr	74	26
	CH_2=$CHMgBr$	80	20
	C_2F_5Li	0	100
	C_2F_5MgBr	4	96
$COOCH_3$	$NaBH_4$	45	55
	CH_3Li	10	90
CH_2OMe	$NaBH_4$	88	12
	CH_3Li	74	26
CH_2OCOCH_3	$NaBH_4$	87	13

The diastereoselectivity in nucleophilic additions to the parent norbornenone (Scheme 17, Table 15) has been a long standing problem. The carbonyl face closer to the olefinic unit is sterically less encumbered. However, for approach of a reagent from this face, the possibility of through-space interaction with the etheno bridge has to be taken into account. Coordination of the counterion to the C=C bond may also influence the outcome of the reaction. Experimentally, widely varying product distributions have been observed,[115] depending on the reagent and the reaction conditions used. Ab initio calculations have also shown that the predicted face selectivity is sensitive to the model nucleophile employed.[116] Thus, different selectivities are computed for the addition of LiH and methyllithium.

Despite the above caveats, it is possible to demonstrate the role of orbital and electrostatic interactions in determining the face selectivity in this substrate. Using the same reagent and conditions, the preferred direction of nucleophilic addition has been reversed through distal substitution.[117]

The ratios of diastereomeric alcohols obtained by sodium borohydride reduction of a series of endo-substituted norbornenones, **45**, are provided in Table 15. The parent substrate shows a strong preference for nucleophilic addition from the anti face (with respect to the ethano bridge bearing the distal substituents). The preference is not significantly altered by methoxymethyl and acetoxymethyl substituents. However, a single ester group reduces the anti selectivity. In the corresponding cyano and diester derivatives, a complete reversal of facial

Table 16. Calculated Relative Energies (kcal mol^{-1}) for Anti and Syn Approach of Test Charge and Nucleophile to endo,endo-Disubstituted 7-Norbornenones, 45

	charge		hydride		exptl	
substituent (R)	anti	syn	anti	syn	anti	syn
H	0	6.0	1.3	0	0	0.9
CH_2OCH_3	0	8.5	0.5	0	0	1.1
CH_2CH_3	0	12.7	0	0.2		
$COOCH_3$	0	5.2	4.1	0	0.1	0

preference is achieved. The alcohol formed by nucleophilic attack from the syn face is the major product in these systems.

The endo substituents do not alter the steric environment around the carbonyl group. Optimized geometries obtained at the MNDO level lead to similar structures for the parent and substituted derivatives. In all of the substrates, the syn face is more sterically encumbered. In addition to the exo hydrogen atoms of the ethano bridge, the keto fragment is also calculated to be tilted away from the C═C bond. The single-crystal X-ray structure of the diester derivative confirms the presence of the tilt (6°).[118] Thus, nucleophilic addition occurs preferentially from the less open face in the norbornenones with strongly electron withdrawing groups. A simple interpretation of these trends is in terms of the Cieplak stereoelectronic theory.

MNDO calculations using the charge and hydride models were employed to obtain additional support for the above interpretation.[70,118] The results obtained for the parent substrate (Table 16) are inconsistent with experimental results for borohydride reduction. While the observed preference for approach from the etheno bridge is predicted with the charge model, the opposite selectivity is obtained with the hydride model, which includes orbital effects as well. The computational procedure is evidently inadequate for sterically biased systems. However, the variations in selectivity induced by electron withdrawing groups are correctly reproduced with the hydride model. These results were seen as strong proof for the importance of orbital interactions in reversing the diastereoselectivity in the reduction of norbornenone through distal substitution.

In an independent study,[119] bromomethyl substituents were shown to lead to preferential addition from the syn face (with respect to the substituents). The result was interpreted in terms of molecular electrostatic potential maps derived using the AM1 method. However, the ability of semiempirical procedures to accurately describe electrostatic interactions is questionable, especially in sterically nonequivalent substrates. Ab initio calculations are likely to be more reliable.

The relative energies of syn and anti addition transition states have been calculated for a number of norbornenones using LiH and methyllithium as model reagents.[116] The data (Table 17) show a fairly strong dependence on the level of theory employed. The computed energy differences are also much larger than those corresponding to the observed product ratios. Nevertheless, some internally consistent interpretations do emerge.

Table 17. Calculated Energy Differences (kcal mol^{-1}) of Transition Structures for Syn and Anti Face Additions of Lithium Hydride and Methyllithium to endo,endo-Disubstituted Norbornenones, 45[a]

	substituent				
	SiH_3	CH_3	H	CH_2OH	CN
LiH additions					
3-21G	0.52	1.32	1.65	2.09	6.78
6-31G*	0.91	1.12	1.87	1.56	6.41
MP2/6-31G*	2.42	1.99	2.96	1.87	8.31
point charge 6-31G*	0.25	0.28	1.07	0.76	5.88
MeLi additions					
3-21G	−4.90	−3.94	−2.94	−2.95	0.31
6-31G*	−4.62	−4.13	−2.77	−3.63	−0.60
MP2/6-31G*	−3.48	−3.36	−1.88	−2.70	−1.72
exptl			−0.95	−1.09	

[a] A positive value implies preference for addition to the face syn with respect to the substituent.

For all of the derivatives, addition syn with respect to the endo substituent is predicted to be favored. Although this result is contrary to observed diastereoselectivity in borohydride reductions for most substrates, it was argued that the computed preferences represent the *intrinsic* facial selectivity of the ketones, in reactions with sterically nondemanding reagents. Further, electron donor groups were computed to lead to slightly reduced preference, while electron withdrawing groups strongly enhance syn selectivity. These trends follow the observed variations in selectivity. Interestingly, the changes were interpreted in terms of electrostatic interactions, based on the relative energies obtained using a fractional point charge in place of LiH. The data imply that the nucleophile suffers electrostatic repulsion with the C═C π cloud, thus leading to favored attack from the syn face. The preference is enhanced with electron withdrawing groups, which polarize the exo face hydrogen atoms in such a way that the interaction is attractive for syn face addition.

To account for the anti selectivity observed in many of these substrates, it was argued that steric effect also has an important role to play. Using methyllithium as the model, it was found that anti face addition is uniformly favored in almost all of the systems. With a bulkier nucleophile, the nonbonded repulsions with the exo hydrogens become more pronounced. However, the effect of the *endo* substituents on the relative energies remains the same. The role of the solvent was suggested to be unimportant on the basis of SCRF calculations. Overall, the observed variations in face selectivities in norbornenones were attributed to the interplay of steric and electrostatic factors. No compelling reason was found to invoke the Cieplak model in these systems.

A critical evaluation of the computed data suggests that much as the earlier study using the MNDO methodology erred in overemphasizing the orbital effect,[70,118] the ab initio investigation[116] seems to have given excessive importance to the electrostatic factor. With the exception of the dicyano derivative (for which experimental results are not available), the magnitude of the energy difference in the charge calculation represents only a small fraction of the

overall preference (Table 17). The similarity in trends cannot be taken as conclusive proof of the absence of other factors, in particular hyperconjugative interactions. It would be of interest to quantify the orbital contributions to face selectivity, for example through natural bond orbital analysis, in these systems.

V. Electrophilic Additions to Olefins

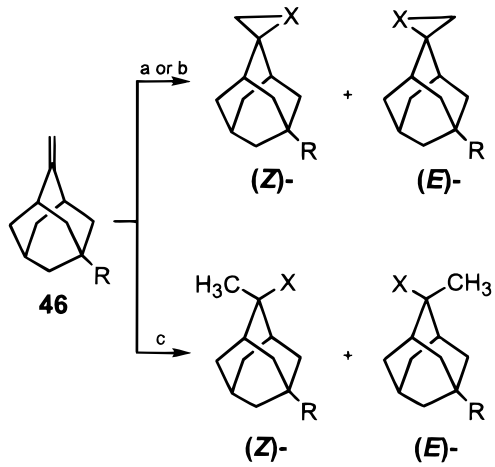
A. Remote Substituent Effects in Methyleneadamantanes and methylenenorbornanes

The previous sections confirm that the interpretation of π-face selectivities in nucleophilic additions to sterically unbiased ketones is not quite straightforward. In many cases, the results can be reconciled in terms of orbital or electrostatic effects. To complicate matters, the latter has both attractive and repulsive components, depending on whether the interaction of the nucleophile is with the polarized atoms near the reaction center or directly with the substituent. The resolution of these difficulties requires the study of a variety of carefully crafted substrates and use of computational data.

An additional strategy to derive unambiguous interpretations is to consider complementary processes in which the charge requirements are altered or even reversed. Diastereoselectivities in electrophilic additions in sterically unbiased olefins would therefore provide useful insights. A number of such studies are considered in this section. The substrates bear considerable resemblance to the ketones analyzed in the previous sections.

Epoxidation of 5-fluorosubstituted methyleneadamantane, **46**, revealed a preference (66:34) for syn face attack of the electrophile (Scheme 18, Table 18).[84] Addition of neutral dichlorocarbene was also shown to favor the same facial approach.

Scheme 18[a]



[a] Reagents and Conditions: (a) *m*-CPBA; (b) $CHCl_3$; (c) HCl.

Addition of HCl to a number of 5-substituted methyleneadamantanes has also shown systematic variations in disatereoselectivity (Table 18).[92] While the halogen is added to the syn face in most of the substrates, anti addition is favored for the trimethylsilyl derivative. A strong inductive donor is evidently needed to induce anti addition.

Table 18. Observed Product Distributions in Electrophilic Additions to 5-Substituted Methyleneadamantanes, 46

substituent (R)	reagent	X	product ratio % (*Z*)	product ratio % (*E*)
F	$:CCl_2$	CCl_2	60	40
	m-CPBA	O	66	34
	HCl	Cl	>99	trace
CN	HCl	Cl	87	13
$COOCH_3$	HCl	Cl	72	28
Cl	HCl	Cl	83	17
Br	HCl	Cl	78	22
I	HCl	Cl	66	34
OCH_3	HCl	Cl	86	14
C_6H_5	HCl	Cl	65	35
CH_3	HCl	Cl	61	39
$Si(CH_3)_3$	HCl	Cl	35	65

Table 19. Observed Product Distributions in Electrophilic Additions to 2,3-endo,endo-Disubstituted Methylenenorbornanes, 47

substituent (R)	reagent	product ratio % (*Z*)	product ratio % (*E*)
$COOCH_3$	m-CPBA	74	26
	B_2H_6	41	59
	$Hg(OAc)_2$	>95	trace
CH_2OCH_3	m-CPBA	45	55
	B_2H_6	56	44
	$Hg(OAc)_2$	40	60
CH_2CH_3	m-CPBA	30	70
	B_2H_6	62	38
	$Hg(OAc)_2$	17	83

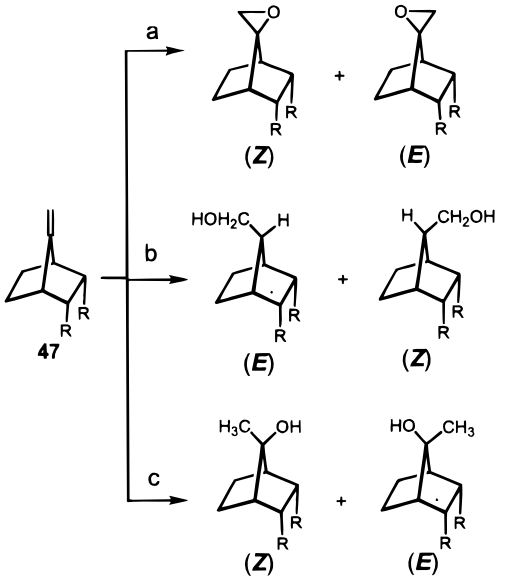
The facial preferences observed in epoxidation, hydroboration, and oxymercuration of endo-substituted methylenenorbornanes, **47**, also follow the same general trends (Table 19).[96] Electrophilic addition occurs preferentially from the syn face for the diester, but the selectivity is reversed on going to the dimethoxymethyl and diethyl derivatives.

Halterman and McEvoy also examined electrophilic additions to diaryl cyclopentenes, **48**,[99] complementing their earlier investigations on nucleophilic additions to the corresponding cyclopentanones.[97] Osmium tetroxide catalyzed cis-hydroxylation of the olefins yielded diasteromeric diols in substrates with dissimilar aryl groups (Scheme 20). In these systems also, addition was found to occur predominantly from the face anti to the electron-rich aryl ring. In the series of substrates examined, the variations in the relative transition-state energies span a range of 1.1 kcal mol^{-1}, a substantial value considering the subtle nature of perturbation.

Jones and Vogel mustered further examples of facial selectivity which followed the trends mentioned above.[120a] Electrophilic additions to substituted bicyclo[2.2.2]octene, **49**, were found to occur preferentially from the face of the double bond syn to the ester substituents (Scheme 21). Gandolfi et al. obtained similar selectivities in electrophilic additions of related derivatives.[120b]

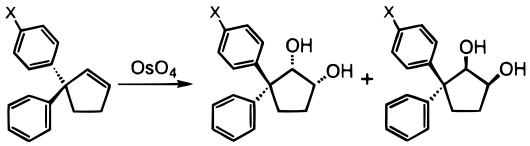
In view of the similarity in the facial selectivity in the nucleophilic additions to ketones and electrophilic

Scheme 19[a]



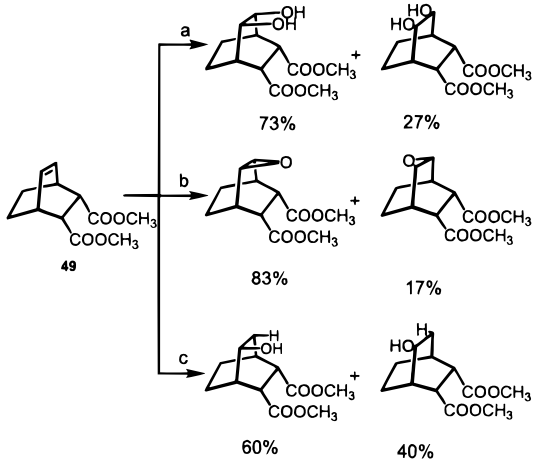
[a] Reagents and Conditions: (a) *m*-CPBA, CH_2Cl_2, 0−5 °C; (b) B_2H_6-THF, H_2O_2-aq·NaOH; (c) $Hg(OAc)_2$, aq·THF, $NaBH_4$-NaOH.

Scheme 20



48	X=H	(*E*)-50%	(*Z*)-50%
	X=NO_2	30%	70%
	X=Cl	43%	57%
	X=Br	45%	55%
	X=OCH_3	57%	43%
	X=$N(CH_3)_2$	64%	36%

Scheme 21[a]



[a] Reagents and Conditions: (a) OsO_4, Et_3NO, acetone-H_2O, 0 °C, 3 h; (b) *m*-CPBA, CH_2Cl_2, rt, 10 h; (c) BH_3, Et_2O, rt, 3 h; $NaBO_3$, H_2O, 10 h.

additions to the corresponding olefins, a common electronic origin was envisaged.[84,96,99] The preference for syn face approach of the reagent with electron withdrawing groups and its reversal in donor-substituted substrates was readily accounted for in terms of Cieplak stereoelectronic theory. However, a few mechanistic details need to be first taken into account before accepting this general conclusion.

Table 20. Calculated PM3 ΔH_f Values (kcal mol^{-1}) for Complexes between endo,endo-Disubstituted Methylenenorbornane 47 and Electrophile E

	R = F,F		R,R = -CH_2-	
reagent (E)	syn	anti	syn	anti
H^+	139.03	139.85	256.10	255.69
I^+ (cyclic)	151.42	150.06	268.60	269.23
I^+ (classical)	149.44	149.88	265.01	264.69
$Hg(OH)_2$	−130.36	−134.00	−11.56	−9.36
$Zn(OH)_2$	−118.47	−122.30	1.59	0.93
BH_3	−50.93	−50.66	85.11	84.88
BH_3 transition state	−39.49	−38.45	95.46	95.31
CCl_2 (attack at C7)	−7.36	−5.36	120.87	120.02
(attack at C8)	−10.41	−11.01	116.58	116.26

The mechanism of HCl addition surely involves an initial protonation step to form a tertiary cation, which captures the halide ion to form the eventual product. Therefore, the face selectivity must arise in the second step. Being a nucleophilic addition to a trigonal carbon, this process is governed by the same factors which were considered in the previous sections. Therefore, the product distribution must be dictated by a combination of orbital and electrostatic interactions.

The reactions involving perbenzoic acid and mercuric acetate are also likely to proceed through carbocationic intermediates. The product stereochemistry may be derived from the initial direction of approach of the electrophile or from the subsequent reaction with a nucleophile. Therefore, invoking Cieplak-type orbital interactions in these systems without a detailed mechanistic analysis remains debatable.

Semiempirical PM3 calculations were used to show that the preferred initial approach of the electrophile in these substrates can be controlled by orbital or electrostatic effects.[53] Molecular electrostatic potentials of methylenenorbornanes, **47**, with electron withdrawing endo substituents (such as COOMe and F) were suggested to prefer attack of the electrophile from the anti face. Consistently, the anti isomers of the π-complex intermediates formed by addition of I^+, $Hg(OH)_2$, and $Zn(OH)_2$ were calculated to be more stable than the syn forms (Table 20). The face selectivities of the final product in these systems were suggested to be determined by the subsequent rate-limiting nucleophilic attack by water which should occur anti to the complexed electrophile. Thus, it was argued that preferential formation of the (*Z*) epoxide cannot be taken as proof of syn selectivity in electrophilic addition.

In contrast to the above interpretation, hyperconjugative interactions were invoked in other systems. If classical carbocations are formed (by addition of H^+ or even I^+), the charge is localized on a carbon atom. Hence, electrostatic effects would be unimportant in determining face selectivities. Calculated energies revealed syn selectivity in a few representative species (Table 20), attributable to hyperconjugative stabilization. The strongest evidence for orbital interactions was obtained for addition of neutral

electrophiles such as borane and CCl_2. For the difluoro derivative, syn addition was calculated to be favored, while the selectivity was reversed with alkyl substituents.

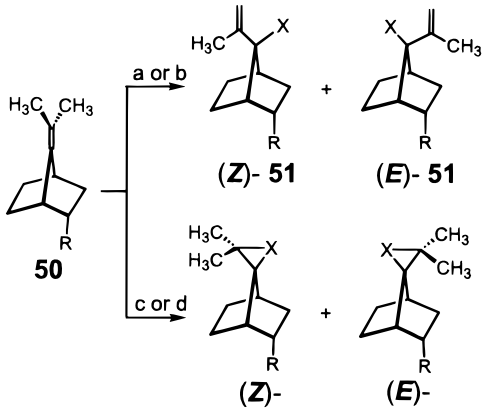
While the issues raised by Broughton et al.[53] are highly relevant to the interpretation of facial selectivity in electrophilic additions, the mechanistic speculations may not be fully justified. For example, the calculated MESP for 5-fluoromethyleneadamantane showed very little variation on either π face. Hence, electrostatic control was suggested to be less important in this substrate. Hydroboration, which is orbital controlled was predicted to show greater diastereoselection than an electrostatically controlled process such as oxymercuration. For the latter reaction, greater than 95% (*Z*) alcohol is obtained,[84] completely undermining the proposal. As pointed out by le Noble, oxymercuration presumably occurs with an initial interaction of the electrophile with the methylene carbon and the face selectivity is determined by the addition of the nucleophile.[84] Consistently, the selectivity is similar to those obtained with trifluoroacetic acid (>99% of (*Z*) ester) and HCl (>99% of (*Z*) halide), both of which proceed with initial rapid electrophilic addition to the methylene carbon, followed by a slower capture of the nucleophile.

It is perhaps pertinent to point out a series of studies carried out by Vogel et al.[120c] exploiting subtle variations in the electronic structures of intermediates formed through electrophilic addition to norbornene derivatives. In the first step in the reaction, electrophilic addition occurs preferentially to the exo face of the double bond. Depending on the nature of the electrophile, a bridged or classical ionic intermediate is formed. However, a distal substituent is suggested to determine the site with maximum positive charge and consequently the regiochemical outcome of the nucleophilic addition in the second step of the reaction. Thus, a carbonyl group homoconjugatively stabilizes a cationic center, while a cyano substituent has a destabilizing field effect at the same center. Hence, the regioselectivity differs in the two cases under conditions of kinetic control. The generality of the results has been confirmed in a number of substrates.[120c] Although these examples are not directly related to facial selectivity in an isosteric environment, the results are important from the point of view of recognizing nuances in reaction mechanisms.

B. Removing Mechanistic Ambiguities: Orbital Control of Facial Selectivity in Isopropylidenenorbornanes

The computational study[53] on the relative roles of orbital and electrostatic interactions discussed in the previous section raised several important issues which need to be critically evaluated while interpreting face selectivity in electrophilic additions. If charged species are involved, a detailed assessment of the molecular electrostatic potential of the substrate needs to be made to identify the intrinsic electrostatic preference. Mechanistic doubts should also be eliminated. Further, orbital effects are best evaluated using neutral electrophiles. All of these factors were taken into account in a study[121] using endo-substituted 7-isopropylidenenorbornanes, **50**.

Scheme 22[a]



[a] Reagents and Conditions: (a) $^1O_2$, hν, methylene blue, $NaBH_4$; (b) NBS, DME-H_2O, 0−5 °C; (c) $CCl_3COO^-Na^+$, DME-TCE; (c) *m*-CPBA, Na_2CO_3, CH_2Cl_2, 0−5 °C.

Table 21. Observed Product Distributions in Electrophilic Additions to 50

	Br^+		CCl_2		$^1O_2$		*m*-CPBA	
substituent (R)	% (*Z*)	% (*E*)	% (*Z*)	% (*E*)	% (*Z*)	% (*E*)	% (*Z*)	% (*E*)
CN	72	28	78	22	78	22	77	23
$COOCH_3$	59	41	60	40	61	39	62	38

The chosen substrates offer a number of advantages. The double bond is made more reactive, enabling carbene additions to be studied experimentally. The site of initial electrophilic attack is likely to be C7 (and not C8 as computed for the methylene derivatives, **47**), which is more sensitive to the differential hyperconjugative interactions arising from the distal substituent. Hence, the substrates serve as ideal models for probing orbital effects.

Mono-endo-substituted 7-isopropylidenenorbornanes, **50**, react with a variety of electrophiles, such as dichlorocarbene, singlet oxygen, bromine (I) cation, and perbenzoic acid (Scheme 22). The observed product distributions are given in Table 21. In all of the systems, the major product corresponds to syn addition. While this is obvious for the carbene adduct, there is also no ambiguity in the case of Br^+ reaction. The nucleophilic attack on the bromonium ion is followed by an elimination to yield (*Z*) and (*E*) isomeric olefins, **51**. The position of the halogen corresponds exactly to the initial direction of approach of the electrophile toward the substrate, **50**. In view of the overall similarity in the product distributions in the epoxidation and singlet oxygen addition, a common electronic origin can be postulated for all of the reactions.

To assess the potential role of electrostatic effects, the MESP for the cyano and ester derivatives were computed at the ab initio level. A topographical analysis of the MESP revealed two critical points, one on each face of the π bond. While a slight asymmetry was noted (the anti CP has a more negative value), the magnitudes of the minima were relatively low (−0.022 au for the anti face in the cyano derivative,

Table 22. Calculated Relative Energies (kcal mol^{-1}) for Syn and Anti Addition Bromonium Ion Intermediates and CCl_2 Addition Transition States for Mono-endo-substituted Isopropylidenenorbornanes, 50

		Br^+		$:CCl_2$	
substituent (R)	site of attack	anti	syn	anti	syn
CN	C-8	0.3	0	0	0
	C-7	0.8	0	0.8	0
$COOCH_3$	C-8	0.1	0	0	0
	C-7	0.2	0	0.6	0

compared to −0.038 au in ethylene). Electrostatic control of face selectivity is unlikely to be important in these systems.[121]

The computed energies of bromonium ion intermediates provide evidence for the orbital control of face selectivity in these systems. At the PM3 level, classical carbocationic structures are obtained for Br^+ addition. The tertiary cations formed by addition to C7 are significantly more stable than those derived from attack at C8. While the syn adducts are more stable in both sets of intermediates, the preference is larger for the ions derived from attack at C7 (Table 22). Hyperconjugative interactions offer a simple means of accounting for these trends.

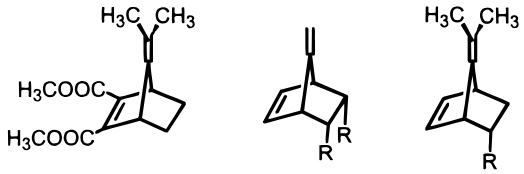
The energetics obtained at the AM1 level for CCl_2 addition transition states are even more convincing. Carbene additions follow a nonleast-motion pathway.[122] As a result, four saddle points are possible with unsymmetrical olefins such as **50**. The initial site of attack can be C7 or C8, and in each case syn and anti addition is possible. At the AM1 level, initial attack at C7 is computed to be favored. For this mode, the transition state for syn addition is calculated to be more stable for both substrates studied (Table 22). In these structures, hyperconjugative interaction with the newly formed σ^* orbital can effectively determine the preferred direction of approach of the electrophile. In the higher energy saddle points corresponding to initial approach of the carbene to C8 in which this discrimination is not possible, no facial selectivity is computed.

Overall, the detailed experimental results and the supportive MO calculations on electrophilic additions to 7-isopropylidenenorbornanes provide strong support for the Cieplak stereoelectronic theory.

C. Through-Space Orbital Effects and Electrostatic Interactions: Methylene- and Isopropylidene-norbornenes and Related Systems

Facial selectivities in electrophilic additions to the exocyclic double bond in 7-alkylidenenorbornenes have been studied in great detail over the last 20 years.[42−44] The substrate possesses an intrinsic steric bias, with the face above the ethano bridge being more crowded. However, the presence of two double bonds in close proximity allows for the possibility of homoconjugation.[123] The effect in the ground state has been quantified through photoelectron spectroscopy.[124] Because of through-space repulsion, the π orbital of the exocyclic double bond is expected to be polarized unsymmetrically, such that approach of an electrophile from above the ethano bridge is favored.

The diastereoselectivity in the singlet oxygen addition to isopropylidene-norbornene, **13**, seemed to confirm the orbital distortion model. The major product resulted from addition to the face anti to the double bond.[42] Consistent with the proposal, the facial selectivity was found to be reduced in the benzo analogue, **14**, as well as in the derivative with ester substituents on the norbornene double bond, **52**, in which through-space interaction is expected to be lower. However, the possibility of repulsion between the approaching singlet oxygen and the endocyclic double bond for syn addition was not ruled out.



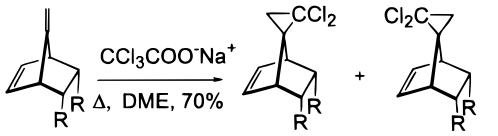
52 **53** **54**

Additional studies on other reactions confirmed the dependence of the facial selectivity on the nature of the electrophilic reagent. Paquette and Gleiter proposed[43,44] that weak electrophiles form cyclic adducts as intermediates which can take advantage of homoconjugation possible in the substrate. In such cases, the preferred product is derived from addition from the sterically congested ethano face. On the other hand, strong electrophiles react via stable classical intermediates which do not require homoconjugative stabilization. The corresponding reagents approach from the etheno bridge, perhaps because of initial coordination.

An alternative interpretation for the variation in diastereoselectivity in 7-alkylidenebenzonorbornenes, **14**, was offered by Houk and co-workers.[125] On the basis of computed electrostatic potential maps on simple models, it was proposed that the face selectivity was determined by reagent-sensitive electrostatic interactions.

It is therefore of considerable interest to check whether diastereoselection in these substrates, which result from a complex interplay of several factors, can be modulated through distal substitution. Interestingly, dichlorocarbene addition to endo-substituted methylenenorbornene, **53**, shows a subtle dependence on the nature of the substituent (Scheme 23).[126] With

Scheme 23

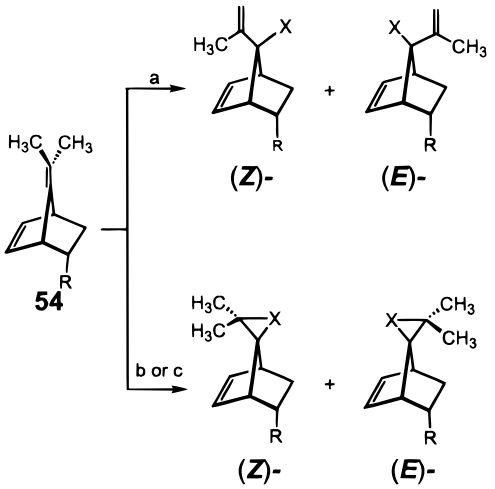


53 R=CH_2OCH_3 (*Z*)-11% (*E*)-89%

R=$COOCH_3$ 23% 77%

ester substituents, the extent of addition from the less crowded etheno bridge is reduced. As in the corresponding methylenenorbornanes, **47**, electron withdrawing groups enhance addition to the face syn to the substituents.

Scheme 24[a]



[a] Reagents and Conditions: (a) $^1O_2$, hν, methylene blue, CH_2Cl_2, $NaBH_4$, MeOH; (b) $CCl_3COO^-Na^+$, DME-TCE; (c) *m*-CPBA, Na_2CO_3, CH_2Cl_2, CH_2Cl_2, 0−5 °C.

Table 23. Observed Product Distribution in Electrophilic Additions to 5-endo-Substituted 7-Isopropylidenenorbornenes, 54

substituent (R)	reagent	X	product ratio % *Z*	product ratio % *E*
H	$^1O_2$	OH	86	14
	$CCl_3COO^-Na^+$	CCl_2	12	88
	m-CPBA	O	66	34
CN	$^1O_2$	OH	96	4
	$CCl_3COO^-Na^+$	CCl_2	35	65
	m-CPBA	O	>90	trace
$COOCH_3$	$^1O_2$	OH	92	8
	$CCl_3COO^-Na^+$	CCl_2	34	66
	m-CPBA	O	>85	<15

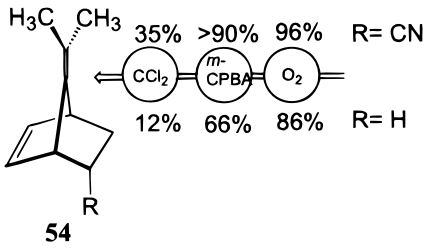


Figure 10. Variations in the preferred direction of electrophilic addition induced by a cyano group in **54**.

The results obtained for the endo-substituted 7-isopropylidenenorbornenes, **54**, confirm the above trend (Scheme 24).[126] As in the parent substrate,[43,44] the preferred direction of approach of the electrophile varies with the nature of the reagent employed (Table 23). However, in all cases, the presence of an electron withdrawing group at the endo position increases the percentage of the product formed by addition to the face syn to the substituent. The dramatic but consistent changes in the facial selectivity induced by a single cyano group are illustrated in Figure 10.

To determine the origin of the variations induced by remote substituents, a topographical analysis of ab initio MESP was carried out. Both methylene- and isopropylidene-norbornenes show interesting features. A minimum is found on either side of the two π bonds. The negative contours due to the two double bonds show considerable overlap, suggesting strong through-space interaction. On purely electrostatic grounds, approach of an electrophile from the etheno face should be favored, reinforcing the steric bias of the substrates. Interestingly, the MESP critical points are strongly affected by endo-cyano substituents. The minima become shallow. Facial differentiation due to electrostatic effects can therefore be ruled out in the substituted derivatives.

Table 24. Observed Selectivities and the Calculated Energy Differences (kcal mol^{-1}) between Syn and Anti CCl_2 Addition Transition States for 53 and 54

cmpd	obsd syn:anti ratio	site of attack	ΔE[a]
53 R=CH_2OCH_3	11:89	C-8	−0.77
		C-7	0.15
53 R=$COOCH_3$	23:77	C-8	−0.48
		C-7	1.88
54 R=H	12:88	C-7	0.28
		C-8	−0.45
54 R=CN	35:65	C-7	1.08
		C-8	−0.42
54 R=$COOCH_3$	34:66	C-7	0.84
		C-8	−0.46

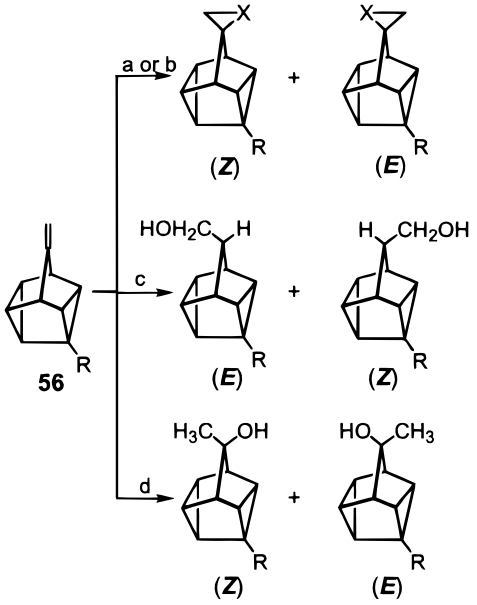
[a] A positive value implies preference for addition to the face syn with respect to the substituent.

Transition-state energies for CCl_2 addition calculated at the AM1 level provide support for the role of orbital effects in 7-isopropylidenenorbornenes (Table 24). Four sets of transition states are obtained for each substrate. The initial site of attack can be at C7 or C8, while the facial approach can be syn or anti with respect to the substituent. The computed energies do not lead to unambiguous predictions of face selectivity, because opposite preferences are obtained for transition states corresponding to attack at C7 and C8. However, the overall effect of the substituent is correctly reproduced. For initial attack at C8, there is a uniform preference for addition from the anti face with respect to the substituent. The magnitude of the selectivity does not depend on the distal substituent. However, for CCl_2 attack at C7, addition syn to the substituent is preferred. The magnitude of the preference is much larger with cyano and COOMe groups. The net effect would be enhanced syn selectivity. The results confirm that the remote substituent effect is primarily derived from the energetics of the C7 attack transition states, which are ideally suited for responding to differential hyperconjugative interactions induced by the substituent. Thus, even in these substrates for which interpretations are fairly complex, the role of Cieplak effect can be demonstrated.[126]

D. The Dominant Role of Hyperconjugative Interactions: Methylenenorsnoutanes

Orbital distortion due to through-space repulsions and related homoconjugative interactions are not limited to systems containing multiple nonconjugated C=C double bonds. The cyclopropyl unit has a pair of high energy HOMOs.[127] The Walsh orbital of the right symmetry can have through-space interactions with distal double bonds. The orbital energy splitting in a system such as **16** has been quantified through photoelectron spectroscopy. This effect has been

Scheme 25[a]



[a] Reagents and Conditions: (a) $CHCl_3$, aq NaOH, Et_3BnNCl, rt, 75−80%; (b) *m*-CPBA, CH_2Cl_2, Na_2CO_3, 5−10 °C, 75%; (c) B_2H_6-THF, H_2O_2-NaOH, 80%; (d) $Hg(OAc)_2$, aq THF, $NaBH_4$-NaOH, 80%.

invoked to rationalize the anti selectivity in the electrophilic additions to this substrate. The selectivity can also be attributed to Cieplak-type interactions resulting from the donor ability of the electron-rich cyclopropyl unit. However, the latter interpretation has been questioned.[128] The presence of an endo-cyclopropyl unit in bicyclo[2.2.2]octene, **55**, has been shown to yield predominantly syn addition in a variety of electrophilic reactions. Interestingly, PE studies reveal strong through-space interactions between a cyclopropane Walsh orbital and the π MO of the olefin, even in this system.[129]

55

A convenient model substrate to assess the relevance of the orbital distortion model as well as possible electrostatic interactions due to a cyclopropyl ring, but without any inherent steric bias, is provided by 4-substituted 9-methylenenorsnoutanes, **56**. The diastereoselectivity in the electrophilic additions in these systems complements the results obtained for the nucleophilic additions to the corresponding norsnoutanones.

Substrates **56** undergo a variety of electrophilic addition reactions (Scheme 25).[130] The diastereoselectivity is quite insensitive to the nature of the reagent employed (Table 25), unlike in the case of alkylidenenorbornenes.[43] Uniformly, addition from the syn face is preferred. The selectivity is quite substantial, considering the subtle mode of perturbation.

The nature of through-space interactions in methylenenorsnoutane was examined using MESP maps

Table 25. Observed Product Distribution in Electrophilic Additions to 4-Substituted 9-Methylenenorsnoutanes, 56

			product ratio	
substituent (R)	reagent	X	% *Z*	% *E*
CN	$:CCl_2$	CCl_2	61	39
	m-CPBA	O	66	34
	$Hg(OAc)_2$		>90	trace
$COOCH_3$	$:CCl_2$	CCl_2	60	40
	m-CPBA	O	57	43
	B_2H_6		40	60
	$Hg(OAc)_2$		>90	trace
CH_2OCH_3	$:CCl_2$	CCl_2	56	44
	B_2H_6		46	54
	$Hg(OAc)_2$		76	24

Table 26. AM1 Calculated Activation Energies (kcal mol^{-1}) for Syn and Anti CCl_2 Addition Transition States for 4-Substituted 9-Methylenenorsnoutanes, 56

	activation energy							
	R = CN		R = CO_2CH_3		R = CH_2OCH_3 (C_s)		R = CH_2OCH_3 (C_1)	
site of attack	syn	anti	syn	anti	syn	anti	syn	anti
C-9	13.59	13.90	13.55	13.85	13.61	13.22	13.19	13.48
C-10	7.02	7.02	6.92	6.92	6.56	6.39	6.41	6.52

computed at the ab initio level. While the double bond leads to a (3,+3) critical point on either face, the presence of the cyclopropyl rings results in additional features.[131] Each ring leads to a CP near an edge. Reflecting the strong interactions between the cyclopropyl units and the double bond, large negative contours are seen in the MESP map connecting the fragments. Introduction of a cyano substituent has a large effect on the MESP maps. The minima around the C=C bond are substantially reduced from −0.047 au in the parent to −0.029 au in the cyano derivative. Electrostatic interactions can be of little importance in determining the preferred direction of an electrophile in this substrate.

The induction of facial selectivity by the remote substituent must therefore have a different origin. Calculated activation energies for CCl_2 addition obtained at the AM1 level (Table 26) reveal the possible electronic factor operating in these systems. As in related structures involving methylenenorbornane and isopropylidenenorbornene, no facial preference is computed for the transition states in which the initial attack is at the distal olefinic center, C10. However, attack at C9 is calculated to lead to syn preference in substrates containing a strong electron withdrawing group. These results confirm that a relay of hyperconjugative interactions at the transition state is responsible for the observed diastereoselectivity. The study validates the Cieplak stereoelectronic model of face selectivity in electrophilic additions in these systems.

VI. Concluding Remarks

There is no doubt that more than one factor contributes to face selectivity in additions to sterically unbiased systems. Through a combination of experimental studies on carefully designed substrates and semiquantitative computational models, a set of

factors which need to be taken into account have been identified. In particular, orbital interactions operate in conjunction with electrostatic interactions in a large majority of substrates, including endo-substituted 7-norbornanones and 5-substituted adamantanones.

Electrostatic effects influence the relative stability of the transition state for syn face addition in two ways. Because of the inductive effect of the distal substituent, atoms on the syn face are polarized, resulting in electrostatic interaction with the approaching reagent. This component is attractive for nucleophilic additions in substrates having electron withdrawing substituents. The reagent also experiences a direct through-space electrostatic interaction with the substituent. This is repulsive for nucleophilic additions in which the substituent bears considerable electron density.

Evidence for both components of electrostatic control of facial selectivity has been obtained by several means. The experimental and computed data on the bicyclo[2.2.2]octanones, especially in the substrate with the Cieplak effect turned off, confirm that it is possible to induce diastereoselection exclusively through polarization of the exo face. On the other hand, results obtained for 2-aryl-7-norbornanone specifically point to the existence of a through-space field effect between the substituent and the reagent. The selectivities observed in cyclohexadienones as well as the dependence of the computed preferences on the conformation of the substituent offer independent evidence for through-space interactions.

The role of orbital effects in nucleophilic additions is most clearly seen from the diastereoselectivities observed for norsnoutanones and snoutanones. In these substrates, through-space interaction between the reagent and the substituent is effectively eliminated. The variations in the selectivities in the two sets of ketones provide an independent measure of orbital and electrostatic attractive components of face selectivity.

The overall similarity in the selectivities for nucleophilic additions to ketones and electrophilic additions to the corresponding olefins provides particularly convincing support for the importance of orbital interactions in these systems. In many olefinic substrates which show significant selectivity, the absence of a strong electrostatic bias has been explicitly demonstrated through topological analyses of MESP maps, providing further evidence for the orbital effect. These results imply that the principal conclusions based on nucleophilic and electrophilic additions may be valid in a wider context.

In general, the orbital effects are small in magnitude and are easily overwhelmed by steric factors. However, in at least a few substrates, electronic effects have been shown to swamp inherent geometric bias.

The studies carried out so far have helped delineate various subtle interactions which determine diastereoselection, even in an isosteric environment. However, the individual contributions need to be quantified so that the insights can be used in a predictive manner in synthetic applications. This requires additional experiments as well as modeling studies. In particular, further experimental examination on a wider variety of carefully designed substrates is needed. Systematic investigations of the dependence of diastereoselectivities on reagents and solvents are clearly warranted. In particular, electrostatic effects can be effectively monitored by using a greater range of nucleophiles.[102,132] The double hyperconjugation model and through-space participation of the C2−C3 bond in the norbornyl systems need closer analysis.

Computational studies have so far focused on estimating the electrostatic contributions to face selectivity, especially in nucleophilic additions, with some simple model reagents. Additional studies on a range of reagents would throw light on how the interplay of electrostatic and orbital effects can be manipulated. Quantitative estimation of the orbital effects through perturbative schemes would also be valuable.[79] Such studies would be useful in another important context. As can be seen from the discussions of theoretical studies presented in this review, the emphasis has been on the Cieplak model or on the combined effect of all of the hyperconjugative interactions at the transition state. The Felkin−Anh model has not been examined in sufficient detail, primarily because of difficulties in isolating the corresponding contribution and quantifying it, not because the model is unimportant per se. Perturbation analysis using natural orbitals offers a convenient procedure for critically assessing the relative importance of the Cieplak and Felkin−Anh models.

Eventually, a hierarchical arrangement of all of the key factors determining diastereoselection has to be aimed at. This would enable approaching the goal of predicting selectivity in more complex situations, e.g., in reactions involving a general substrate with an inherent steric bias. Reactions carried out in organized media,[133] such as micelles, solid state, and cyclodextrins, offer additional interpretive challenges.

In summary, the electronic factor is small but is indeed a useful handle for inducing diastereoselection. A consistent pattern which emerges from the studies carried out so far is that, in the absence of a strong steric bias, a distal electron withdrawing group is syn directing and a donor substituent is anti directing. These trends are strongly modulated by through-space interactions between a charged reagent and the substituent. As a result, a remote perturbation may be more effective in inducing facial selectivity in a predictable manner than a substituent closer to the reaction center. This proposal needs to be evaluated in greater depth in order to exploit the role of distal substituents as stereodirectors in synthesis.[134]

VII. Acknowledgments

We thank F. A. Khan, C. Ravikrishna, B. Ganguly, I. N. N. Namboothiri, and P. Kalyanaraman for their enthusiastic participation and contributions to the work on π face selectivity in sterically unbiased systems. Professor S. R. Gadre, R. N. Shirsat, and C. H. Suresh are gratefully acknowledged for providing molecular electrostatic potential data.

VIII. References

(1) Levine, I. N. *Quantum Chemistry*; Prentice-Hall: Englewood Cliffs, N. J., 1991.
(2) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5821.
(3) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748.
(4) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245.
(5) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367.
(6) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.
(7) Barton, D. H. R. *J. Chem. Soc.* **1953**, 1027.
(8) Dauben, W. G.; Fouken, G. J.; Noyce, D. S. *J. Am. Chem. Soc.* **1956**, *78*, 2579.
(9) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205.
(10) (a) Klein, J. *Tetrahedron Lett.* **1973**, 4307. (b) Klein, J. *Tetrahedron* **1974**, *30*, 3349.
(11) Liotta, C. L. *Tetrahedron Lett.* **1975**, 519.
(12) Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, 155.
(13) (a) Huet, J.; Bernard, Y.-M.; Anh, N. T.; Seyden-Penne, J. *Tetrahedron Lett.* **1976**, 159. (b) Anh, N. T.; Eisenstein, O. *Noveau J. de Chemie* **1977**, *1*, 61. (c) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.
(14) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.
(15) (a) Richer, J. C. *J. Org. Chem.* **1965**, *30*, 324. (b) Wigfield, D. C.; Gowland, F. W. *J. Org. Chem.* **1977**, *42*, 1108.
(16) Giddings, M. R.; Hudec, J. *Can. J. Chem.* **1981**, *59*, 459. For a recent contribution, see: Hudec, J.; Huke, J.; Liebeschuetz, J. W. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1129.
(17) Royer, J. *Tetrahedron Lett.* **1978**, 1343.
(18) (a) Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1977**, *42*, 264. (b) Arjona, O.; Fernandez, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1991**, *56*, 6227.
(19) (a) Brown, H. C.; Hammer, W. J.; Kawakami, J. H.; Rothberg, I.; Jugt, V. D. *J. Am. Chem. Soc.* **1967**, *104*, 6381. (b) Huisgen, R.; Ooms, P. H. J.; Mingin, M.; Allinger, N. L. *J. Am. Chem. Soc.* **1980**, *102*, 3951. (c) Huisgen, R. *Pure Appl. Chem.* **1981**, *53*, 171. (d) Alston, P. V.; Ottenbrite, R. M. *Heterocycles* **1977**, 1443.
(20) Schleyer, P. v. R. *J. Am. Chem. Soc.* **1967**, *89*, 701.
(21) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4057.
(22) Cheung, C. K.; Tseng, L. T.; Lin, M.-H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598.
(23) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449.
(24) Li, H.; le Noble, W. J. *Recl. Trav. Chim. Pays-Bas* **1992**, 199.
(25) Gung, B. W. *Tetrahedron* **1996**, *15*, 5263.
(26) Burkert, R.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982.
(27) Stewart, J. J. P. *J. Comput.-Aided Mol. Des.* **1990**, *4*, 1.
(28) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley: New York, 1986.
(29) Seminario, J. M., Politzer, P., Eds. *Modern Density Functional Theory. A Tool for Chemistry*; Elsevier: Amsterdam, 1995.
(30) Ermer, O.; Bell, P.; Mason, S. A. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1239.
(31) (a) Ermer, O. *Tetrahedron* **1974**, *30*, 3103. (b) Houk, K. N.; Rondan, N. G.; Brown, F. K.; Jorgensen, W. L.; Madura, J. D.; Spellmeyer, D. C. *J. Am. Chem. Soc.* **1983**, *105*, 5980.
(32) (a) Knuchel, G.; Grassi, G.; Vogelsanger, B.; Bauder, A. *J. Am. Chem. Soc.* **1993**, *115*, 10845. (b) Benet-Buchholz, J.; Haumann, T.; Boese, R. *J. Chem. Soc., Chem. Commun.* **1998**, 2003.
(33) Hoffmann, R. W.; Hauel, N.; Landmann, B. *Chem. Ber.* **1983**, *116*, 389.
(34) Massa, W.; Birkhahn, M.; Landmann, B.; Hoffmann, R. W. *Chem. Ber.* **1983**, *116*, 404.
(35) Paquette, L. A.; Underiner, T. L.; Gallucci, J. C. *J. Org. Chem.* **1992**, *57*, 86.
(36) Gung, B. W.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 232.
(37) Pinkerton, A. A.; Schwarzenbach, D.; Birbaum, J.-L.; Carrupt, P.-A.; Schwager, L.; Vogel, P. *Helv. Chim. Acta* **1984**, *67*, 1136.
(38) (a) Coxon, J. M.; Maclagan, R. G. A. R.; McDonald, D. C.; Steel, P. J. *J. Org. Chem.* **1991**, *56*, 2542. (b) Coxon, J. M.; Fong, S. T.; McDonald, D. Q.; Steel, P. J. *Tetrahedron Lett.* **1993**, 163.
(39) Frenking, G.; Kohler, F.; Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1146.
(40) Gleiter, R.; Paquette, L. A. *Acc. Chem. Res.* **1983**, *60*, 328.
(41) Gleiter, R.; Schafer, W. *Acc. Chem. Res.* **1990**, *23*, 369.
(42) Okada, K.; Mukai, T. *J. Am. Chem. Soc.* **1978**, *100*, 6509.
(43) Paquette, L. A.; Hertel, L. W.; Gleiter, R.; Bohm, M. C. *J. Am. Chem. Soc.* **1978**, *100*, 6510.
(44) (a) Paquette, L. A.; Hertel, L. W.; Gleiter, R.; Bohm, M. C.; Beno, M. A.; Christograph, G. C.; *J. Am. Chem. Soc.* **1981**, *103*, 7106. (b) Paquette, L. A.; Beliamy, F.; Wells, G. J.; Bohm, M. C.; Gleiter, R. *J. Am. Chem. Soc.* **1981**, *103*, 7122.
(45) (a) Ohwada, T.; Tsuji, M.; Okamoto. I.; Shudo, K. *Tetrahedron Lett.* **1996**, *37*, 2609. (b) Ohwada, T.; Uchiyama, M.; Tsuji, M.; Okamoto, I.; Shudo, K. *Chem. Pharm. Bull.* **1996**, *44*, 296.
(46) (a) Okada, K.; Tomita, S.; Oda, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2342. (b) Okada, K.; Tomita, S.; Oda, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 459.
(47) Ohwada, T.; Okamoto, I.; Haga, N.; Shudo, K. *J. Org. Chem.* **1994**, *59*, 3975.
(48) Ohwada, T. *Chem. Rev.* **1999**, *33*, 1337.
(49) (a) Scrocco, E.; Tomasi, J. *Top. Curr. Chem.* **1973**, *42*, 75. (b) Scrocco, E.; Tomasi, J. In *Advances in Quantum Chemistry*; Lowdin, P.-O., Ed.; Academic: New York, 1975; Vol. 11. (c) Politzer, P., Truhlar, D. G., Eds. *Chemical Applications of Atomic and Molecular Electrostatic Potentials*; Plenum: New York, 1980. (d) Pullman, B. *Int. J. Quantum Chem. Quantum Biol. Symp.* **1990**, *17*, 81. (e) Tomasi, J.; Bonaccorsi, R.; Cammii, R. In *Theoretical Models of Chemical Bonding*; Maksic, Z. B., Ed.; Springer: Berlin, 1991. (f) Naray-Szabo, G.; Ferenczy, G. G. *Chem. Rev.* **1995**, *95*, 829. (g) Murray, J., Sen, K. D., Eds. *Molecular Electrostatic Potentials: Theory and Applications*; Elsevier: Amsterdam, 1996.
(50) Bromilow, J.; Brownlee, R. T. C.; Lopez, V. O.; Taft, R. W. *J. Org. Chem.* **1979**, *44*, 4766.
(51) (a) Adcock, W.; Cotton, J.; Trout, N. A. *J. Org. Chem.* **1994**, *59*, 1867. (b) Mehta, G.; Khan, F. A.; Adcock, W. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2189.
(52) Bader, R. F. W. *Atoms in Molecules, A Quantum Theory*; Clarendon: Oxford, 1990.
(53) Broughton, H. B.; Green, S. M.; Rzepa, H. S. *J. Chem. Soc., Chem. Commun.* **1992**, 998.
(54) Pudzianowski, A. T.; Barrish, J. C.; Spergel, S. H. *Tetrahedron Lett.* **1992**, 293.
(55) Sjoberg, P.; Politzer, P. *J. Phys. Chem.* **1990**, *94*, 3959.
(56) Shi, Z.; Boyd, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 9614.
(57) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, J. *Science* **1986**, *231*, 1108.
(58) (a) Johnson, B. R.; Tait, B. D.; Cieplak, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 5875. (b) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447. (c) Cieplak, A. S. *Chem. Rev.* **1999**, *33*, 1265. (d) Macaulay, J. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1990**, *112*, 1136. (e) Nagao, Y.; Goto, M.; Ochiai, M. *Chem. Lett.* **1990**, 1507. (f) Coxon, J. M.; McDonald, D. Q. *Tetrahedron Lett.* **1992**, 651. (f) Vinkovic, V.; Majerski, K. M.; Marinic, Z. *Tetrahedron Lett.* **1992**, 7441.
(59) (a) Meyers, A. I.; Wallace, R. H. *J. Org. Chem.* **1989**, *54*, 2509. (b) Vedejs, E.; Dent, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 6861.
(60) Adcock, W.; Trout, N. A. *J. Org. Chem.* **1991**, *56*, 3229.
(61) Sternbach, D.; Shibuya, M.; Jaisli, F.; Bonetti, M.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 634.
(62) Grob, C. A.; Schiess, P. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1.
(63) (a) Laube, T.; Stilz, H. U. *J. Am. Chem. Soc.* **1987**, *109*, 5876. (b) Laube, T.; Hollenstein, S. *J. Am. Chem. Soc.* **1992**, *114*, 8812.
(64) (a) Jeyaraj, D. A.; Yadav, V. K. *Tetrahedron Lett.* **1997**, *38*, 6095. (b) Jeyaraj, D. A.; Yadav, A.; Yadav, V. K. *Tetrahedron Lett.* **1997**, *38*, 4483.
(65) Winstein, S.; Shatavsky, M.; Norton, C.; Woodward, R. B. *J. Am. Chem. Soc.* **1955**, *77*, 4183.
(66) Musaki, A. F.; Matsumoto, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 16.
(67) Dutler, R.; Rauk, A.; Sorensen, T. S.; Whitworth, S. M. *J. Am. Chem. Soc.* **1989**, *111*, 9024.
(68) Rauk, A.; Sorensen, T. S.; Maerker, C.; Carneiro, J. W. M.; Sieber, S.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1996**, *118*, 3761.
(69) Lin, M.-H.; Silver, J. E.; le Noble, W. J. *J. Org. Chem.* **1988**, *53*, 5155.
(70) Ganguly, B.; Chandrasekhar, J.; Khan, F. A.; Mehta, G. *J. Org. Chem.* **1993**, *58*, 1734.
(71) Huang, X. L.; Dannenberg, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 6017.
(72) (a) Bürgi, H. B.; Dunitz, J. D.; Shaffer, E. *J. Am. Chem. Soc.* **1973**, *95*, 5064. (b) Alagona, G.; Scrocco, E.; Tomasi, J. *J. Am. Chem. Soc.* **1975**, *97*, 6976.
(73) (a) Bowie, J. H.; Williams, B. D. *Aust. J. Chem.* **1974**, *27*, 1923. (b) Asubiojo, O. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1979**, *101*, 3715.
(74) (a) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1990**, 456. (b) Wong, S. S.; Paddon-Row, M. N. *Aust. J. Chem.* **1991**, *44*, 765.
(75) (a) Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560. (b) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908. (c) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018. (d) Wu, Y.-D.; Houk, K. N.; Paddon-Row, M. N. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1019. (e) Frenking, G.; Kohler, F.; Reetz, M. T. *Tetrahedron* **1991**, *47*, 9005.
(76) Madura, J. D.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1986**, *108*, 2517.
(77) (a) Coxon, J. M.; McDonald, D. Q. *Tetrahedron* **1992**, *48*, 3353. (b) Coxon, J. M.; Luibrand, R. T. *Tetrahedron Lett.* **1993**, 7097.
(78) Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 1919.

(79) Senju, T.; Tomoda, S. *Chem. Lett.* **1997**, 431.
(80) Cieplak, A. S.; Wiberg, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 9226.
(81) le Noble, W. J. *Chem. Rev.* **1999**, *33*, 1387.
(82) (a) Xie, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 3836. (b) Li, H.; le Noble, W. J. *Tetrahedron Lett.* **1990**, *31*, 4391.
(83) (a) Hahn, J. H.; le Noble, W. J.; *J. Am. Chem. Soc.* **1992**, *114*, 1916. (b) Lau, H.; Gonikberg, E. M.; Hung, J.-T.; le Noble, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 11421. (c) Gonikberg, E. M.; le Noble, W. J. *J. Org. Chem.* **1995**, *60*, 7751. (d) Gonikberg, E. M.; Picart, F.; le Noble, W. J. *J. Org. Chem.* **1996**, *61*, 9588. (e) Jones, C. D.; Kaselj, M.; Salvatore, R. N.; le Noble, W. J. *J. Org. Chem.* **1998**, *63*, 2758.
(84) Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 5874.
(85) (a) Lin, M.-H.; Cheung, C. K.; le Noble, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 6562. (b) Xie, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 3839. (c) Song, I. H.; le Noble, W. J. *J. Org. Chem.* **1994**, *59*, 58. (d) Adcock, W.; Head, N. J.; Lokan, N. R.; Trout, N. A. *J. Org. Chem.* **1997**, *62*, 6177.
(86) (a) Chung, W.-S.; Turro, N. J.; Srivastava, S.; Li, H.; le Noble, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 7882. (b) Chung, W.-S.; Tsai, T.-L.; Ho, C.-C.; Chiang, M. Y. N.; le Noble, W. J. *J. Org. Chem.* **1997**, *62*, 4672.
(87) Chung, W.-S.; Turro, N. J.; Srivatsava, S.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 5020.
(88) Li, H.; Silver, J. E.; Watson, W. H.; Kashyap, R. P.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 5932.
(89) Mukherjee, A. K.; le Noble, W. J. *J. Org. Chem.* **1993**, *58*, 7955.
(90) Lin, M.-H.; Watson, W. H.; Kashyap, R. P.; le Noble, W. J. *J. Org. Chem.* **1990**, *55*, 3597.
(91) Mukherjee, A.; Wu, Q.; le Noble, W. J. *J. Org. Chem.* **1994**, *59*, 3270.
(92) Bodepudi, V. R.; le Noble, W. J. *J. Org. Chem.* **1994**, *59*, 3265.
(93) Bodepudi, V. R.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2001.
(94) Mukherjee, A.; Venter, E. M. M.; le Noble, W. J.; Watson, W. H.; Kashyap, R. P. *Tetrahedron Lett.* **1992**, *33*, 3837.
(95) Mehta, G.; Khan, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 6140.
(96) Mehta, G.; Khan, F. A. *J. Chem. Soc., Chem. Commun.* **1991**, 18.
(97) Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 6690.
(98) Halterman, R. L.; McCarthy, B. A.; McEvoy, M. A. *J. Org. Chem.* **1992**, *57*, 5585.
(99) Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 980.
(100) Kaselj, M.; Adcock, J. L.; Luo, H.; Zhang, H.; Li, H.; le Noble, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 7088.
(101) Kaselj, M.; le Noble, W. J. *J. Org. Chem.* **1996**, *61*, 4157.
(102) Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678.
(103) (a) Ohwada, T. *J. Am. Chem. Soc.* **1992**, *114*, 8818. (b) Tsuji, M.; Ohwada, T.; Shudo, K. *Tetrahedron Lett.* **1998**, *39*, 403.
(104) Fraser, R.; Faibish, N. C.; Kong, F.; Bednarski, K. *J. Org. Chem.* **1997**, *62*, 6164.
(105) Paddon-Row, M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638.
(106) Li, H.; Mehta, G.; Padma, S.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2006.
(107) Mehta, G.; Khan, F. A.; Ganguly, B.; Chandrasekhar, J. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2275.
(108) Coxon, J. M.; Houk, K. N.; Luibrand, R. T. *J. Org. Chem.* **1995**, *60*, 418.
(109) Mehta, G.; Khan, F. A.; Ganguly, B.; Chandrasekhar, J. *J. Chem. Soc., Chem. Commun.* **1992**, 1711.
(110) Gassman, P. G.; Fentiman, A. F. *J. Am. Chem. Soc.* **1970**, *92*, 2549.
(111) Mehta, G.; Khan, F. A.; Mohal, N.; Namboothiri, I. N. N.; Kalyanaraman, P.; Chandrasekhar, J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2665.
(112) (a) Mehta, G.; Ravikrishna, C.; Ganguly, B.; Chandrasekhar, J. *J. Chem. Soc., Chem. Commun.* **1997**, 75. (b) Mehta, G.; Ravikrishna, C. Unpublished.
(113) Mehta, G.; Ravikrishna, C.; Kalyanaraman, P.; Chandrasekhar, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1895.
(114) Kaselj, M.; Gonikberg, E. M.; le Noble, W. J. *J. Org. Chem.* **1998**, *63*, 3218.
(115) (a) Brown, H. C.; Muzzio, J. *J. Am. Chem. Soc.* **1966**, *88*, 2811. (b) Erman, W. F. *J. Org. Chem.* **1967**, *32*, 765. (c) Warkentin, J. *Can. J. Chem.* **1970**, *48*, 1391.
(116) Williams, L.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1994**, 353.
(117) Mehta, G.; Khan, F. A. *Tetrahedron Lett.* **1992**, *33*, 3065.
(118) Kumar, V. A.; Venkatesan, K.; Ganguly, B.; Chandrasekhar, J.; Khan, F. A.; Mehta, G. *Tetrahedron Lett.* **1992**, 3069.
(119) Keserü, G. M.; Kajtár-Peredy, M.; Náray-Szabó, G. *Tetrahedron Lett.* **1994**, *35*, 9255.
(120) (a) Jones, G. R.; Vogel, P. *J. Chem. Soc., Chem. Commun.* **1993**, 769. (b) Gandolfi, R.; Amadé, M. S.; Rastelli, A.; Bagatti, M. *Tetrahedron Lett.* **1996**, *37*, 1321. (c) Vogel, O.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173 and references therein.
(121) Mehta, G.; Khan, F. A.; Gadre, S. R.; Shirsat, R. N.; Ganguly, B.; Chandrasekhar, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1390.
(122) (a) Hoffmann, R.; *J. Am. Chem. Soc.* **1968**, *90*, 1475. (b) Houk, K. N.; Rondan, N. G.; Mareda, J. *Tetrahedron* **1985**, *41*, 1563.
(123) (a) Gleiter, R.; Hoffmann, R. *J. Am. Chem. Soc.* **1968**, *90*, 5457. (b) Hoffmann, R. W.; Kurz, H. R. *Chem. Ber.* **1975**, *108*, 119.
(124) Heilbronner, E.; Martin, H.-D. *Helv. Chim. Acta* **1972**, *55*, 1490.
(125) Wu, Y.-D.; Li, Y.; Na, J.; Houk, K. N. *J. Org. Chem.* **1993**, *58*, 4625.
(126) Mehta, G.; Gunasekaran, G.; Gadre, S. R.; Shirsat, R. N.; Ganguly, B.; Chandrasekhar, J. *J. Org. Chem.* **1994**, *59*, 1953.
(127) Jorgensen, W. L.; Salem, L. *The Organic Chemists' Book of Orbitals*; Academic: New York, 1972.
(128) Tsuji, M.; Ohwada, T.; Shudo, K. *Tetrahedron Lett.* **1997**, *38*, 6693.
(129) (a) Martin, H.-D.; Heller, C.; Haider, R.; Hoffmann, R. W.; Becherer, J.; Kurz, H. R. *Chem. Ber.* **1977**, *110*, 3010. (b) Hoffmann, R. W.; Kurz, H. R.; Becherer, J.; Martin, H.-D. *Chem. Ber.* **1978**, *111*, 1275. (c) Hoffmann, R. W.; Schuttlen, R.; Schweig, A. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 512.
(130) Mehta, G.; Ravikrishna, C.; Gadre, S. R.; Suresh, C. H.; Kalyanaraman, P.; Chandrasekhar, J. *J. Chem. Soc., Chem. Commun.* **1998**, 975.
(131) Gadre, S. R.; Pundlik, S. S. *J. Am. Chem. Soc.* **1995**, *117*, 9559.
(132) Cieplak, A. S. *J. Org. Chem.* **1998**, *63*, 521.
(133) (a) Toda, F.; Kiyoshige, K.; Yagi, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 320. (b) Chung, W.-S.; Turro, N. J.; Silver, J.; le Noble, W. J. *J. Am. Chem. Soc.* **1990**, *112*, 1202. (c) Mehta, G.; Khan, F. A.; Lakshmi, K. A. *Tetrahedron Lett.* **1992**, 7977.
(134) Wipf, P.; Kim, Y. *J. Org. Chem.* **1993**, *58*, 1649.

CR980369V