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Using Perturbation and Frontier Molecular Orbital Theory To Predict Diastereofacial Selectivity

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I. Introduction

Several research groups have proposed simple procedures for predicting the preferred side of attack of unsymmetrical molecules, such as appropriately substituted ketones, leading to diastereofacial selectivity. Of reviews that have appeared, special attention should be given to those of Li and le Noble,[1] and Franck.[2] We shall consider those methods that are based entirely on electronic (as opposed to steric) analyses in this review. Molecular orbital studies of the transition states for several specific reactions leading to such selectivities have appeared in the literature. We shall not review these calculations on specific reactions.[3] We shall concentrate on those methods that only consider the nature of the locally planar molecule that is being attacked. We shall consider only selectivities based upon kinetic control of product formation. The attacking reagent is not specified, precluding analysis of the specific transition states. In such cases, one is forced to make qualitative and/or quantitative approximations of the relative rates of the similar reactions that occur on the different faces of the reagent. The attacking reagents for the two competing reactions are identical. The analysis, therefore, devolves upon prediction of the relative energies of the two diastereomeric transition states.

Because the purpose of this review is to present, discuss, and compare the bases of the procedures for predicting diastereofacial selectivity, rather than analyzing the experimental tests used for their verification, references to the experimental literature will be minimal.

Joseph Dannenberg, a native New Yorker, received his A.B. from Columbia College in 1962, and his Ph.D. from the California Institute of Technology in 1967. After postdoctoral fellowships at the Centre de Mécanique Ondulatoire Appliquée (Paris) and Columbia University, he joined the Faculty of The City University of New York at Hunter College and the Graduate School in 1968, where he is Professor of Chemistry. He has served in visiting appointments at the Université Pierre et Marie Curie (Université de Paris VI), Université de Bordeaux, Universitat Autonoma de Barcelona, and the National Research Council (Ottowa).

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A. Influence of Product Stability

Before proceeding further, we need to note the fact, initially recognized by Dauben,[4] that the relative energies of the two diastereomeric products can influence the activation energies of the two reactions. This can be understood from the Hammond postulate,[5] or more quantitatively from the Marcus equation.[6−10] The Hammond postulate simply states that the more exothermic a reaction, the more the TS resembles reactants. In this case the TS leading to the lower energy product should be preferred. The Marcus equation gives the activation enthalpy in terms of an intrinsic barrier and the enthalpy of reaction, as in eq 1,

$$\Delta H^{\ddagger} = \Delta H_i^{\ddagger} + \frac{\Delta H^{\circ}}{2} + \frac{(\Delta H^{\circ})^2}{16\Delta H_i^{\ddagger}} \qquad (1)$$

where $\Delta H^{\ddagger}$ is the enthalpy of activation, $\Delta H_i^{\ddagger}$ is the intrinsic enthalpy barrier, and ΔH° is the enthalpy of reaction (see Figure 1). Hence, the more exothermic of two reactions with the same intrinsic barrier will have a lower activation barrier. Thus, any truly unbiased test should involve formation of diastereomers whose energies are very close to equal.

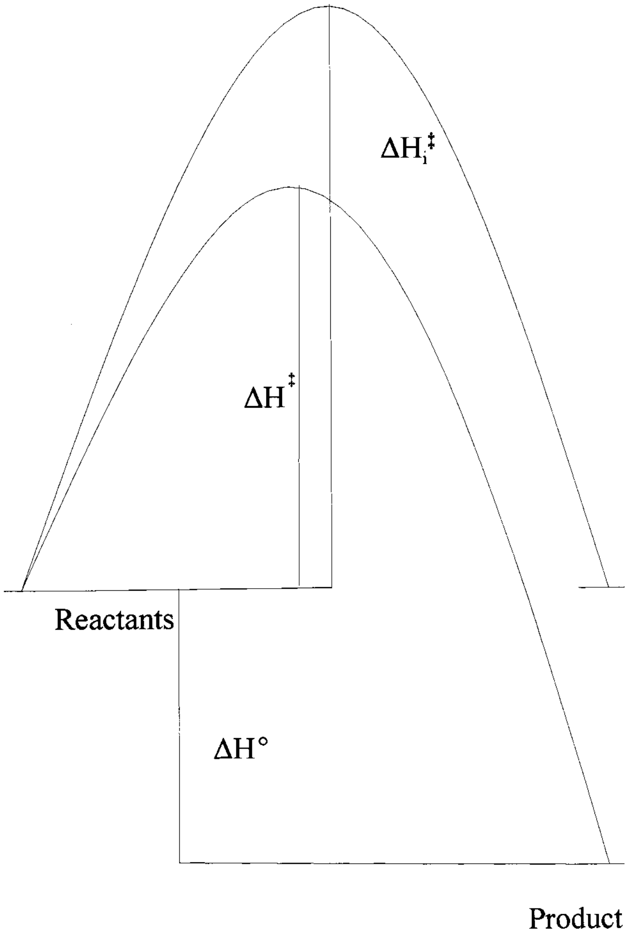


Figure 1. Illustration of how product stability can influence activation energies by means of the Marcus equation.

The Marcus equation can be used to estimate the difference in activation energies that are the direct result of the different exothermicities of the reactions that lead to the two diastereomers by assuming the intrinsic barrier to be the same for both reaction paths. The difference in the intrinsic barriers for each face can be approximated by subtracting the barrier difference due to the exothermicities from the measured difference in activation barriers. This would apply if the last term of eq 1 is small (as is often the case). Alternatively, one could calculate the intrinsic barrier for each diastereomeric reaction path from the activation enthalpies and enthalpies of reaction (if known).[11]

II. Perturbation Theory and Frontier Orbital Theory

Frontier molecular orbital (FMO) theory has played a central role in electronic analyses of regioselective reactivity. Clearly, diastereofacial selectivity falls in this category. For this reason, FMO theory is an attractive tool for predicting diastereofacial selectivity. However, a fundamental problem arises that prevents the use of FMO theory in its most common form: The coefficients of the local atomic p-orbitals that contribute to the frontier π-orbitals are the same for each face. Several clever schemes have appeared which remove the equivalence of the two faces, yet employ a variant of FMO theory. Others have roots in perturbation theory, from which FMO theory is derived. To properly appreciate the nature and the quality of the predictions made by the many methods in the literature, the organic chemist needs to understand (at least qualitatively) the basis for each method. The purpose of this review is to delineate and compare these bases.

A. Applying Perturbation Theory to Reactivity

To follow the analyses that will be presented, the reader needs at least a qualitative understanding of perturbation and FMO theory. A simple outline of perturbation theory and its application to transition states follows. More detailed and precise accounts that are useful for organic chemists can be found in several elaborations on perturbation theory.[12] We call particular attention to the analyses of Fukui,[13] Klopman,[14,15] Salem,[16] Hoffmann,[17] Sustmann and Binsch,[18] Dewar,[19] Hudson,[20] and Fleming.[21] Several of the authors of the methods discussed below have referred to one or more of these treatments, which differ somewhat in direction and in complexity. In the following discussion, the organic chemists' attention should be centered on the physical meanings of the various terms of perturbation theory. Mathematical development, while necessary, will be kept to a minimum.

Perturbation theory is based upon the idea that the interaction energy of several atomic or molecular systems can be described by an infinite series of perturbations of each by the others. Taken to its limit, perturbation theory should converge to the same result as molecular orbital (MO) theory at its limit. Clearly, we cannot hope to analyze an infinite quantity of terms (which, by the way, increase in complexity as we proceed). For our purposes, it is sufficient to limit the discussion to the consideration of two interacting systems. Let us consider only the first three terms of eq 2.

$$\Delta E = -\sum_{\mathrm{ab}}(q_{\mathrm{a}} + q_{\mathrm{b}})\beta_{\mathrm{ab}}S_{\mathrm{ab}} + \sum_{\mathrm{k}<\mathrm{l}}\frac{Q_{\mathrm{k}}Q_{\mathrm{l}}}{R_{\mathrm{kl}}} - \left(\sum_{\mathrm{s}}^{\mathrm{occ}}\sum_{\mathrm{r}}^{\mathrm{unocc}}\frac{2(\sum_{\mathrm{ab}}c_{\mathrm{ra}}c_{\mathrm{sb}}\beta_{\mathrm{ab}})^2}{E_{\mathrm{r}} - E_{\mathrm{s}}} + \sum_{\mathrm{r}}^{\mathrm{occ}}\sum_{\mathrm{s}}^{\mathrm{unocc}}\frac{2(\sum_{\mathrm{ab}}c_{\mathrm{ra}}c_{\mathrm{sb}}\beta_{\mathrm{ab}})^2}{E_{\mathrm{s}} - E_{\mathrm{r}}}\right) + \ldots \quad (2)$$

In this and the following equations, the interaction between two systems, A and B, is expressed via the interaction between atoms *k* (on A) and *l* (on B), where a and b are atomic orbitals on k and l; r (on A) and s (on B) are molecular orbitals obtained from the linear combination of atomic orbitals (LCAO) expansions; the *c* represents the appropriate coefficients in the LCAO expansions; the q_{a} and q_{b} represent the electronic populations in the atomic orbitals of a and b; the Q_{k} and Q_{l} represent the total charges on atoms k and l; R_{kl} represents the distance between k and l; β_{ab} and S_{ab} represent the appropriate resonance and overlap integrals between the atomic orbitals on a and b; and E_{r} and E_{s} represent the energies of the MOs r and s.

The first term, PT0 (eq 3), is a repulsive term that derives from filled orbitals interacting with each other. This is the kind of interaction that prevents two He atoms from bonding. The second term deals with Coulombic attraction (or repulsion) between the systems. In principle, this term will be near zero if at least one of the two systems is neutral. However, there is some ambiguity about this that will be treated later. The third term deals with interactions between filled orbitals on one system with empty orbitals on the other. These interactions are always attractive. They lead to bonding interactions. Each of these terms is usually expressed as a summation of all possible interactions. Thus, the first and third terms are sums of each possible interaction between pairs of filled orbitals, and filled and empty orbitals, respectively. The second term is sometimes considered as a sum over Coulombic interactions between all intermolecular pairs of atomic charges. The terms are often referred to as zeroth, first and second order.

$$\mathrm{PT0} = -\sum_{\mathrm{ab}}(q_{\mathrm{a}} + q_{\mathrm{b}})\beta_{\mathrm{ab}}S_{\mathrm{ab}} = \sum_{\mathrm{s}}^{\mathrm{occ}}\sum_{\mathrm{r}}^{\mathrm{occ}}\frac{2(\sum_{\mathrm{ab}}c_{\mathrm{ra}}c_{\mathrm{sb}}\beta_{\mathrm{ab}})^2}{E_{\mathrm{r}} - E_{\mathrm{s}}} \quad (3)$$

The third term, second order perturbation theory, PT2 (eq 4), is that which leads to FMO theory. The first (repulsive) term, PT0, is often said to cancel in comparisons of reactions that lead to regioselectivity. In fact, one might use it to explain selectivities based upon steric hindrance as in cases where the repulsive terms are dominant in prediction of the selectivities. The second term, PT1, is often considered to be zero for the reactions we are likely to consider (once again, see a later discussion).

$$\mathrm{PT2} = -\left(\sum_{\mathrm{s}}^{\mathrm{occ}}\sum_{\mathrm{r}}^{\mathrm{unocc}}\frac{2(\sum_{\mathrm{ab}}c_{\mathrm{ra}}c_{\mathrm{sb}}\beta_{\mathrm{ab}})^2}{E_{\mathrm{r}} - E_{\mathrm{s}}} + \sum_{\mathrm{r}}^{\mathrm{occ}}\sum_{\mathrm{s}}^{\mathrm{unocc}}\frac{2(\sum_{\mathrm{ab}}c_{\mathrm{ra}}c_{\mathrm{sb}}\beta_{\mathrm{ab}})^2}{E_{\mathrm{s}} - E_{\mathrm{r}}}\right) \quad (4)$$

Two different kinds of application of perturbation theory have been used to predict diastereofacial selectivities. One approach is to treat the two reactants as the systems that interact via perturbations. This led to the familiar FMO theory. The other is to treat prototype local group orbitals on the asymmetric molecule as perturbing each other. Thus, a prototypical C═O or C═C group would be assumed to have a plane of symmetry prior to the perturbation interaction with one or more localized σ-orbitals which break the symmetry. One must remember that if the correct MOs of the system are used, they are orthogonal to each other. Thus, they will not interact. However, prototype group orbitals are generally not the correct MOs, so they can interact. These two approaches involve a perturbation treatment of the *energy* or the *orbitals*, respectively. When the *orbital perturbation* approach is used to determine diastereofacial selectivities, the perturbed orbitals are genrally used for a *perturbation treatment of the energy*.

One should note that a particular order of perturbation on the orbitals implies a higher level of perturbation of the energy. The perturbation of prototypical orbitals mentioned above has involved second order perturbation theory on the orbitals in several cases. Hoffmann has shown that this level is necessary to reproduce certain orbital characteristics.[17] The work of Burgess and Liotta (described below) follows from Hoffmann's discussion. Fukui's work (also described below) follows from a similar treatment[22] known as the "orbital mixing rule." Despite the fact that such treatments imply higher order perturbations of the energy in order to obtain the perturbed orbitals, these orbitals (after perturbation) can be used for second order perturbation treatment of the energy. Only consideration of the energy can be useful for predicting the preferred transition state.

B. Perturbation Interactions between Prototype Group Orbitals

Perturbation interactions between prototype group orbitals on the same molecule can have various effects upon the energies of the orbitals as well as their polarizations (see Figure 2). Let us first consider the energies. When two localized orbitals interact, a new pair of orbitals is created that can be thought of as linear combinations of the two. Of the new orbitals, the lower will be lower in energy than the lower of the original pair. The linear combination will be weighted heavily toward the lower of the original orbitals (the coefficient in the linear combination will be much larger for the original lower orbital). Conversely, the higher of the two new orbitals will be higher in energy than the higher of the original pair, which it will resemble. The polarization will follow from maximizing the bonding interaction between the

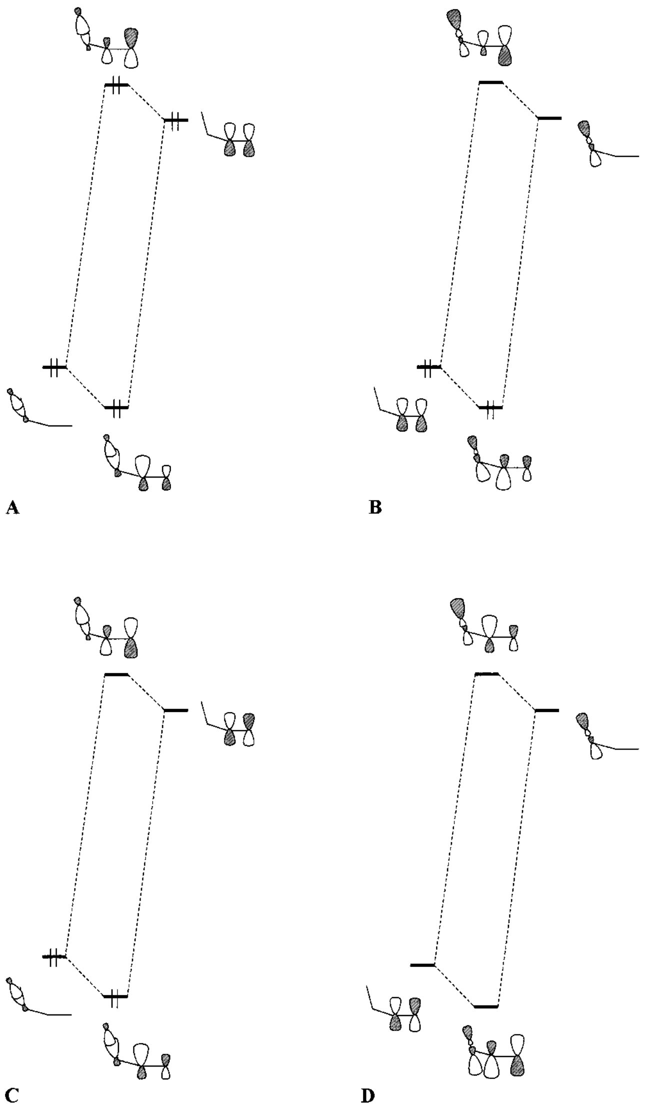


Figure 2. Four examples of perturbation interactions between idealized group orbitals within a molecule. (A) interaction between two bonding orbitals; (B) interaction between a bonding π-orbital and an antibonding σ^*-orbital; (C) interaction between a bonding σ-orbital and an antibonding π^*-orbital; (D) interaction between an antibonding π^*-orbital and an antibonding σ^*-orbital. A is an example of PT0 (first term of eq 2); B and C are examples of PT2 (third term of eq 2); while D does not affect the energy of the system (absent from eq 2) but could affect the FMO interaction with another system.

orbitals in the lower new orbital. The interactions[23] can be of four different types: (A) The first interaction we consider is between bonding orbitals (Figure 2A) where a σ-bonding orbital interacts with a π-bonding orbital. This would raise the energy of the π-bonding orbital (which may be the highest occupied molecular orbital (HOMO)). Because this orbital is the antibonding combination, it will be polarized away from the larger bonding lobes of the σ-bonding orbital, anti to the bond; (B) The second is between a bonding π-orbital and an antibonding σ^*-orbital (Figure 2B). This interaction will lower the energy of the π-orbital (which may be the HOMO). Because this orbital is the bonding combination, it will be polarized toward the larger lobes of the σ^*-orbital, anti to the bond; (C) The third interaction is between a bonding σ-orbital and an antibonding π^*-orbital (Figure 2C). This will raise the energy of the π^*-orbital (which can be the lowest unoccupied molecular orbital (LUMO)). Because this orbital is an antibonding combination, as in A it will be polarized away from the larger bonding lobes of the σ-bonding orbital, anti to the bond; (D) The last interaction is between an antibonding π^*-orbital and an antibonding σ^*-orbital (Figure 2D). This would lower the π^*-orbital (which could be the LUMO). Because this is a bonding interaction, like B it will be polarized toward the larger lobes of the σ^*-orbital, anti to the bond. For each of the above examples we have assumed that the σ-orbitals are more bonding and the σ^*-orbitals more antibonding than their π-counterparts. Note that the type A interaction comes from the first term of eq 2. Thus it is due to PT0. The type B and C interactions come from the third term. Thus they are due to PT2. Type D does not generally contribute directly to the energy of the interacting systems, as these orbitals are usually empty. However, this kind of interaction can play a role in a HOMO/LUMO FMO interaction with a nucleophilic reagent.

C. Frontier Molecular Orbital Theory

Each element in the summation of the PT2 term contains the square of the overlap of the two interacting MOs in the numerator and the energy difference between them in the denominator. The dominant element in the summation will usually be that with the smallest denominator and an appreciable numerator. Such a term will usually treat an interaction of the HOMO on one system with the LUMO on the other (eq 5). Of utmost importance (though often ignored) is the realization that the two systems will generally repel each other as they begin to move along the reaction path from reactants to TS. This is necessarily true if there is an activation barrier to overcome along the reaction path. Analysis of perturbation theory, as we have presented it so far, will not lead to the prediction of a transition state. Rather, it would lead to the prediction of a contact intermediate (if one exists). FMO theory predicts the relative energies of the transition states by approximating the slope of the reaction path diagram at the reactant. (See Figure 3). This can be thought

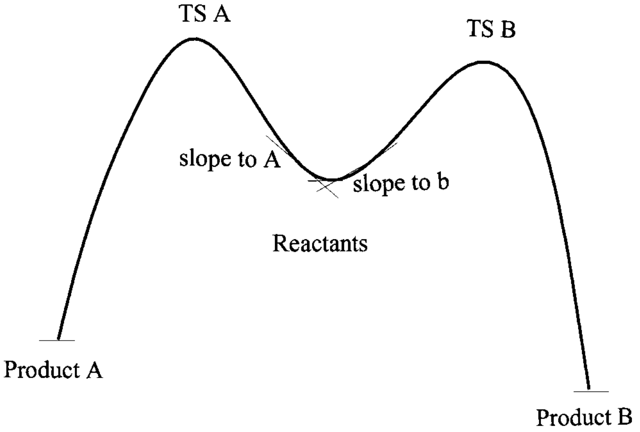


Figure 3. An illustration of how FMO theory can estimate the slope to the possible TSs at an early point along the reaction path.

of as the first derivative of the energy with respect to motion along the reaction path. No specific index of the reaction path occurs in the expression for PT2. However, we can consider increase in the overlap of the orbitals forming a bond as progress along the reaction path. If one takes the derivative of the energetic contribution of the HOMO/LUMO interaction with respect the overlap of the orbitals forming the bond, one obtains an expression (eq 6) that is now first order, specifically in the overlap of the active centers. In eq 6, all constants have been removed as they are assumed to be part of the proportional relationship.

$$\Delta E_{\mathrm{FMO}} \propto -\frac{2(c_{\mathrm{r(nuc)}}c_{\mathrm{s(elec)}}\beta)^2}{E^{\mathrm{LUMO}}_{\mathrm{(nuc)}} - E^{\mathrm{HOMO}}_{\mathrm{(elec)}}} \qquad (5)$$

$$\Delta E_{\mathrm{FMO}} \propto -\frac{c_{\mathrm{r(nuc)}}c_{\mathrm{s(elec)}}}{E^{\mathrm{LUMO}}_{\mathrm{(nuc)}} - E^{\mathrm{HOMO}}_{\mathrm{(elec)}}} \qquad (6)$$

From the earlier discussion of the perturbations of prototype group orbitals above, one can conclude that those interactions that raise the HOMO or lower the LUMO (Figure 2A, D) will facilitate the reaction, while those that lower the HOMO or raise the LUMO (Figure 2B, C) will inhibit the reaction.

D. Coulombic Interactions

The second term, PT1, which is zero for the interaction of a neutral species with either another neutral or a charged species, can take on importance if one considers local charge distributions and polarization. Interactions of this nature have been considered in detail by Klopman.[12] These will be important in the analysis of those methods that predict diastereofacial selectivity based upon “electrostatic” considerations. Klopman’s analysis includes terms due to solvation and dielectric constant of the medium. However, these can be ignored for a purely theoretical gas-phase treatment. He assumes that the interaction between two reactive centers will be due to a Coulombic interaction between the atomic or orbital centers plus a second order term that is due to the intermolecular exchange between the reactive centers. These are analogous to the second and third terms of eq 2, where only the interactions between the reactive centers are considered. The analysis suggests that the Coulombic interaction will dominate when the HOMO/LUMO gap is large and the centers bearing the relevant charges are not very polarizable. These properties have been associated with “hard” centers by Pearson.[24,25] Hard centers retain their charge distribution under the influence of external interactions. Thus, they are not polarizable. Negative hard ions will have large ionization potentials and small electron affinities. The ideal hard anion is a point charge, which by definition is not polarizable and has infinite ionization potential and zero electron affinity. Because the ionization potential of a reagent can be considered to be the energy of an electron in a HOMO, one expects hard nucleophiles to create large HOMO/LUMO gaps. A large HOMO/LUMO gap suggests that charge transfer will be difficult. A low polarizability suggest that the Coulombic interaction will be approximately electrostatic (little reorganization of charge occurs under the influence of an applied electric field).

One might note that the change in an electrostatic attraction with distance, $\mathrm{d}(q_r q_s/r)/\mathrm{d}r$, can be replaced with an energetically equivalent expression where r is constant but q_s changes. The derivative $\mathrm{d}(q_r q_s/r)/\mathrm{d}q_s$, which defines the change in energy with respect to charge, can be used as a definition of hardness. Other possible definitions explored by Klopman are related to the ionization potential, I_{p}, minus the electron affinity, A.

Klopman concludes that the first term of eq 7 will dominate for hard/hard, while the second term will dominate for soft/soft interactions. Hard/soft and soft/hard interactions should not generally be large.

$$\Delta E = \frac{q_{\mathrm{r(nuc)}}q_{\mathrm{s(elec)}}}{\epsilon R_{\mathrm{rs}}} - \frac{2(c_{\mathrm{r(nuc)}}c_{\mathrm{s(elec)}}\beta)^2}{E^{\mathrm{LUMO}}_{\mathrm{(nuc)}} - E^{\mathrm{HOMO}}_{\mathrm{(elec)}}} \qquad (7)$$

Another consideration must be the nature of the Coulombic interaction when at least one species is neutral. The Klopman analysis considers the interaction of atomic or orbital charges at the reactive centers. However, the definition of these charges in a molecule is arbitrary. Compensating charges on adjacent atoms and/or orbitals can mask the effect of the interaction at the reactive centers.

E. Logical Considerations for Comparing Predictive Methods

We should devote special attention to the following conclusions from the discussion above: (1) Normal perturbation theory can give the interaction energy between two systems, A and B; (2) The lowest interaction energy leads to the most stable complex (or intermediate), not a transitions state; (3) Prediction of the preferred transition state comes from estimation of the slope of the energy as the specific reaction proceeds. This means, only the change in energy as a function of the overlap of the reacting centers is important; (4) Because the slope of the reaction path is estimated near the reactant, FMO theory should only be applicable to reactions with early transition states. These are generally reactions that are exoergonic; (5) Because only the orbital interaction energy has been considered, all analyses of this type can lead only to activation energies or enthalpies. Free energies of activation will be predictable only if the entropies play no decisive role in the *relative* reactivities; (6) We also need to remember that, according to transition state theory[26,27] and the Curtin−Hammett principle,[28,29] intermediates along the reaction path between reactants and the transition state have no effect upon the activation energy, and likewise the reaction rate; (7) However, if the reaction is a multistep sequence, consideration of the reactants will estimate the activation for the first step. If the first step is not rate determining, FMO theory may not estimate the rate correctly. Likewise, if the first step is not product determining, FMO theory should not estimate the product ratio correctly.

Table 1. General Comparison of the Methods Discussed in This Review

method	PT level	stabilization of GS or slope to TS	orbital energy (E), polarization (P), both (B), or neither (N)	specific perturbation (S) or all (A)	ref
Felkin/Anh	PT2	TS	E	S type D	36−40
Cieplak	PT2	GS[a]	E	S type C	30
Klein	PT2	TS	P	S types A or D	41, 42
Fukui	PT2	TS	P	S	22, 46
Gleiter/Paquette	PT2	TS	B	see text	48−51
Burgess/Liotta	PT0 and PT2	TS	B[b]	S type depends	47
Chandrasekhar/Mehta	PT1	GS	N	N/A	55
PPFMO	PT2	TS	B	A	52
Tomoda	PT2	GS/TS	B	A	54
Wipf	PT1	GS	N	N/A	58

[a] Does not adhere to Fukui's principle that "the bordering surface of the two parts between which the HOMO−LUMO interaction is considered should be crossed by the newly formed bonds." [b] Selects perturbation using E, decides selectivity using P.

In addition to determining their relationship to perturbation theory, we need to consider the accuracy of the predictions. Here, we encounter an important question: Should comparison be made to theoretical (e.g., MO calculations) or to experimental reports? Clearly, the experimental chemist needs a measure of experimental prediction more than a prediction of what to expect from MO calculations. Just as clearly, arguments based upon electronic (e.g., orbital) arguments of one reactant cannot reasonably be expected to allow for the influence of the myriad of additional factors that exist in the real experiment. Thus, *the best test of the orbital-based methods is comparison with good MO calculations*. If the simple predictions agree with the MO calculations, but they both disagree with the experimental results, the problem must lie elsewhere than in the simplification of the orbital analysis.

Several different effects have been used to predict selectivities. We shall use the following classifications to aid discussion and comparison of the various propositions found in the literature. Some use "electrostatic" arguments. These are related to the second term of eq 2, which represents first order perturbation theory, PT1. Others use PT2. Of those that use PT2, the interactions that are taken as dominant can either be directed toward the numerator, the denominator, or both of the PT2 theory. Second, a qualitative "rule of thumb" can be used to delineate one of many possible perturbation interactions as dominant, or the cumulative effect of several (or all) possible effects can be assessed. Third, the effect can be assessed either by qualitative argument or by calculation of the MOs and orbital energies.

We shall now individually consider each of several published methods for predicting diastereofacial selectivity. To simplify the following discussion, we will classify each method according to (a) whether it uses "electrostatic" or PT2; (b) considers stabilizations (GS) or slopes of stabilization along the reaction path (TS); (c) considers FMO orbital energies, orbital polarizations, or both; (d) focuses on a specific perturbation interaction or considers all; (e) the type of PT2 interaction between prototype group orbitals as defined in Figure 2. Table 1 summarizes this information while providing lead references to the development of the methods (not to reports using them). Other information in Table 1 is discussed below.

III. Methods for Predicting Diastereofacial Selectivity

Several methods have appeared in the literature that predict diastereofacial selectivities based upon purely electronic considerations. We present them individually and discuss their relationship with PT in this section.

A. Methods Based upon Second Order Perturbation Theory (PT2)

1. Cieplak's Method

Cieplak suggests that the dominant stabilizing interaction is that between the vicinal occupied orbital and the antibonding orbital of the incipient bond.[30] Cieplak requires that the incipient bond be considered a "very stretched and very polarized covalent bond." These requirements are said to ensure that σ^* will have a low orbital energy. The lowest orbital energy for σ^* will be that of the LUMO of the molecule being attacked when overlap is infinitesimal. These conditions are entirely consistent with the idea that the transition state will be very early. The stabilization energy is given by the expression of eq 8. The similarity between eq 8 and the third term (PT2) of eq 2 is obvious. The term selected from the summation is the interaction of the filled vicinal orbital and the incipient antibonding orbital.

$$SE(\sigma_{\mathrm{vic}},\sigma^*_{\ddagger}) = \frac{S^2\sigma_{\mathrm{vic}},\sigma^*}{\Delta\epsilon(\sigma_{\mathrm{vic}},\sigma^*)} \tag{8}$$

In the following discussion, one must pay careful attention to the terminology, which can be somewhat confusing. The *incipient bond* will be made from the lone pair of the nucleophile (HOMO) and the π^* of the C=O fragment (LUMO). At the start of the reaction, the nucleophile HOMO will be the σ-orbital of the incipient bond. The π^*-orbital of the carbonyl (LUMO) will be the σ^*-orbital of the incipient bond (see Figure 4). Thus, the interaction described by eq 8 will lower the energy of the vicinal bond and raise the LUMO (type C of Figure 2). Because there are three vicinal bonds per adjacent carbon (assuming saturated carbon centers), one must decide which has the most stabilizing interaction. The attack is said to come preferably at the face which allows the

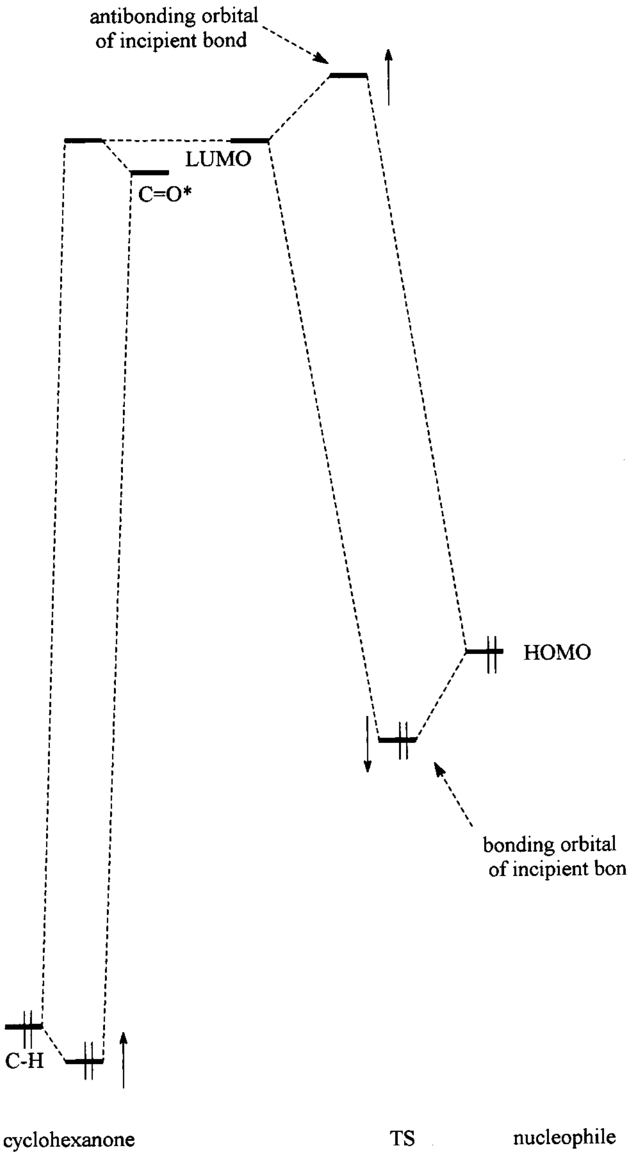


Figure 4. Significant orbital interactions for reduction of cyclohexanone using the Cieplak approach. On the left is depicted the orbital interaction between the filled C−H orbital and the empty carbonyl C=O*. This leads to a stabilization of the C−H bonding electrons and an increase in the energy of the LUMO. The LUMO interacts with the HOMO of the nucleophile (on the right side of the figure) to form the incipient σ and σ^* orbitals. Because the LUMO is raised by the interaction on the left, the HOMO/LUMO interaction with the nucleophile is decreased. As the reaction proceeds, the three solid arrows indicate the direction in which the orbitals will move. It can be seen that the stabilization of the C−H bonding electrons will decrease as the reaction proceeds. This will also increase the activation energy.

greatest possible interaction with this center. Cieplak assumes that an antiperiplanar interaction of the antibonding orbital of the incipient bond with the filled vicinal orbital will be best, as the antibonding σ^*-orbital will have larger lobes away from the bond being formed. Thus, this proposal removes the symmetry of attack on the π-system by assuming unequal changes in the LUMO energy as the reaction proceeds at the two different faces.

Reduction of cyclohexanone by nucleophilic addition of a hydride to the carbonyl was considered a model reaction. This reduction occurs preferentially on 4-*tert*-butylcyclohexanone with initial attack at the *more* hindered axial position leading to formation of the *more* stable product. However, the difference in product stability (about 0.5 kcal/mol by MMX molecular mechanics method[31]) is insufficient to explain the product ratio.[32] Substituting this value in the second term of the Marcus equation (eq 1) and neglecting the relative effect of the third term would predict a 0.2−0.3 kcal/mol difference in activation enthalpies if the intrinsic barriers for attack at each face were the same. Wigfield has estimated the enthalpy of activation to be 1.2 kcal/mol less for axial than for equatorial attack by $NaBH_4$.[33] Thus, this reaction is a leading candidate for a diastereofacial selective reaction that is not directed by steric considerations. There are two possible vicinal orbitals on each carbon adjacent to the carbonyl that can interact with the *incipient* σ^**-orbital*: the axial C−H bond, or the C−C bond of the ring. The equatorial C−H bond will have little overlap as it is near the nodal plane of the carbonyl π-system. Cieplak suggests that the C−H bond has a stronger interaction than the C−C bond based upon the Baker−Nathan effect[34] which compares rates of electrophilic aromatic substitution at the para positions of toluene and *tert*-butylbenzene. This leads to the prediction of the experimental result.

There are some problems here, as previously noted by Franck.[2] As mentioned above, the *SE* of eq 8 represents the stabilization of the electrons in the vicinal σ-bond with the antibonding σ^*-orbital of the incipient bond (see Figure 4). This interaction is of type C (Figure 2) and thus should *retard* the reaction. Let us follow this interaction along a hypothetical reaction path in some detail. We shall use the reduction of cyclohexanone as our example. Because the σ^*-orbital of the incipient bond (i.e., the π^*-orbital of the C=O) is empty, the interaction represents a stabilization of the reagent cyclohexanone, as the vicinal electrons are localized on this entity throughout the reaction. Correspondingly, the energy of the empty σ^*-orbital of the incipient bond increases. As mentioned above, at the beginning of the reaction the overlap between the nucleophile and the cyclohexanone will be infinitesimal. At this point, the σ^*-orbital of the incipient *bond* is equivalent to the LUMO (π^*) of cyclohexanone; the σ-orbital of the incipient bond is equivalent to the HOMO of the nucleophile. The interaction (see eq 5) is inversely proportional to the HOMO/LUMO energy gap. We see that the energy of the σ^*-orbital of the incipient bond has been raised because of the interaction which stabilized the electrons in the vicinal bond. Thus, the HOMO/LUMO energy gap is larger than it would have been without the Cieplak interaction. As the reaction proceeds, the two FMOs will increase their interaction. This will result in a decrease in the energy of the σ- and an increase in the energy of the σ^*-orbitals of the incipient bond. However, an increase in the σ^*-orbital of the incipient bond energy will decrease the original stabilization of the vicinal bonding pair (type C interaction). Thus, this stabilization will *decrease* as the reaction proceeds. What we see is that the Cieplak interaction results in a stabilization of the ground state that (1) decreases the HOMO/LUMO stabilization of the initial reagents as it raises the LUMO; and (2) the Cieplak ground-state stabilization, itself, dissipates as the reaction proceeds.

From a different perspective, one can consider the effect of increasing the electron donating capacity of the C−H bond. This can be imagined as the result of the effects of substituents which might raise C−H σ-bond energy or lower the C=O π*-orbital energy. From Figure 4, one can imagine that either of these effects should retard the reaction, contrary to the Cieplak prediction. Thus, the Cieplak effect should work in the opposite direction from how it was originally presented.

Furthermore, the Cieplak interaction for nucleophilic attack on cyclohexanone does not obey the principle enunciated by Fukui,[10] that "the bordering surface of the two parts between which the HOMO−LUMO interaction is considered should be crossed by the newly formed bonds." The orbital interactions specified by Cieplak are entirely confined to one of the reactants. The HOMO/LUMO interaction is between the C−H and C=O orbitals on the cyclohexanone, clearly not traversing a surface between the cyclohexanone and the nucleophile.

Additionally, experimental and computational evidence indicates that C−C bonds hyperconjugate better than C−H bonds in the absence of solvent effects (see detailed discussion below). Clearly, the Cieplak analysis should not depend on solvent effects.

le Noble[35] has reported that the Cieplak approach predicts the diastereofacial selectivities of electrophilic attack despite its formulation specifically for nucleophilic attacks. It is interesting to consider the Cieplak formalism when the attack is by an electrophile (see Figure 5). Here, the σ*-orbital of the incipient bond at the outset of the reaction is the LUMO of the electrophile. Because the reactants are separated, the overlap of the vicinal bond with the LUMO is zero at the beginning of the reaction. As the electrophile approaches, it interacts with the HOMO of the organic reagent forming the σ- and σ*-orbitals of the incipient bond. As the reaction proceeds, the overlap between the vicinal bond and the σ*-orbital increases, stabilizing the bonding electrons in the vicinal bond. At the same time, the energy gap between this bonding orbital and the σ*-orbital increases. This second effect will tend to decrease the interaction. However, because the interaction was zero at the reactant stage, it must be larger during reaction and specifically at the TS. Nevertheless, the inversion of the C−H and C−C bonds tendency to hyperconjugate still remains a problem.

Despite the fact that Cieplak's argument seems seriously flawed, it has been applied with some success. How can this be explained? There are several factors to consider: (1) There is a statistical 50:50 chance of predicting the correct selectivity. A high level of reliability is needed to confirm a causality (see below); (2) Most of the predictive methods discussed agree in many instances. Thus, they may be related (see below); (3) From the above discussion, we see two likely inconsistencies in Cieplak's argument. Each of them would reverse the predicted selectivity. Remarkably, taken together, they can be used to arrive at Cieplak's prediction because of a double reversal in logic!; (4) finally, the effect may be of limited importance; therefore, of little consequence.

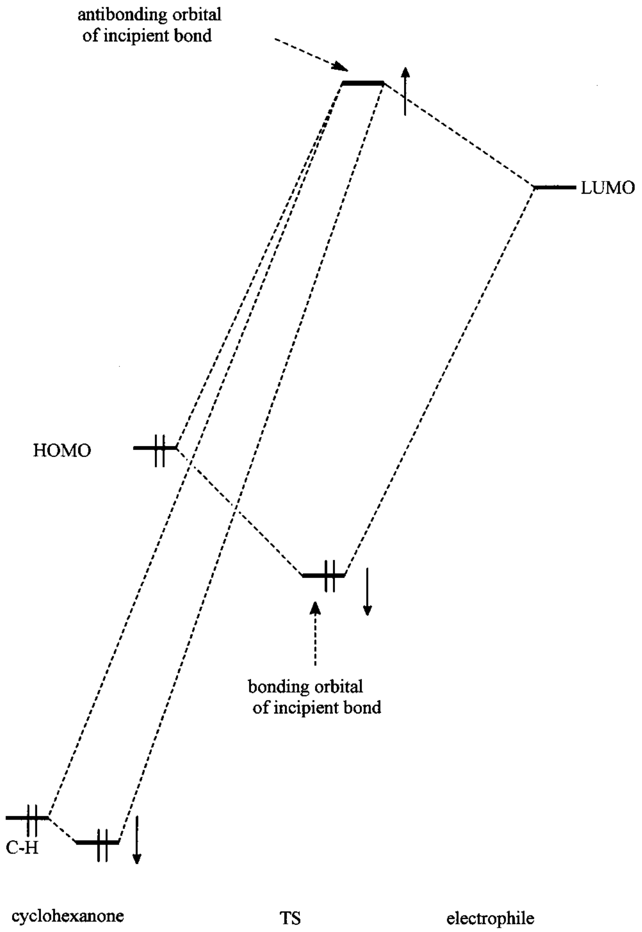


Figure 5. The Cieplak approach applied to an electrophilic attack. The interaction of the C−H bond with the incipient σ*-orbital is initially nil as the incipient σ *-orbital is the LUMO of the electrophile. As the reaction progresses, HOMO/LUMO overlap will increase, thereby increasing the interaction between the incipient σ*-orbital of the incipient bond with the C−H bonding orbital. In this manner, the C−H bonding pair of electrons will become increasingly stablized as the reaction progresses.

2. Felkin/Anh/Eisenstein Methods

Felkin, Anh, and Eisenstein[36−40] have developed the first method of predicting diastereofacial selectivity based entirely on electronic (although steric effects play a role) considerations. They used PT2 to focus upon the interaction of the antibonding σ*-orbital of a σ-bond vicinal to the reactive center with the σ-orbital of the incipient bond. This orbital is the binding combination of the (π*) LUMO of the C=O and the lone pair (HOMO) of the nucleophile. We, again, use nucleophilic attack (reduction) on cyclohexanone as our model reaction (see Figure 6). From the FMO point of view, the σ-orbital of the incipient bond is equivalent to the HOMO of the nucleophile at the reactant stage of the reaction path. At this

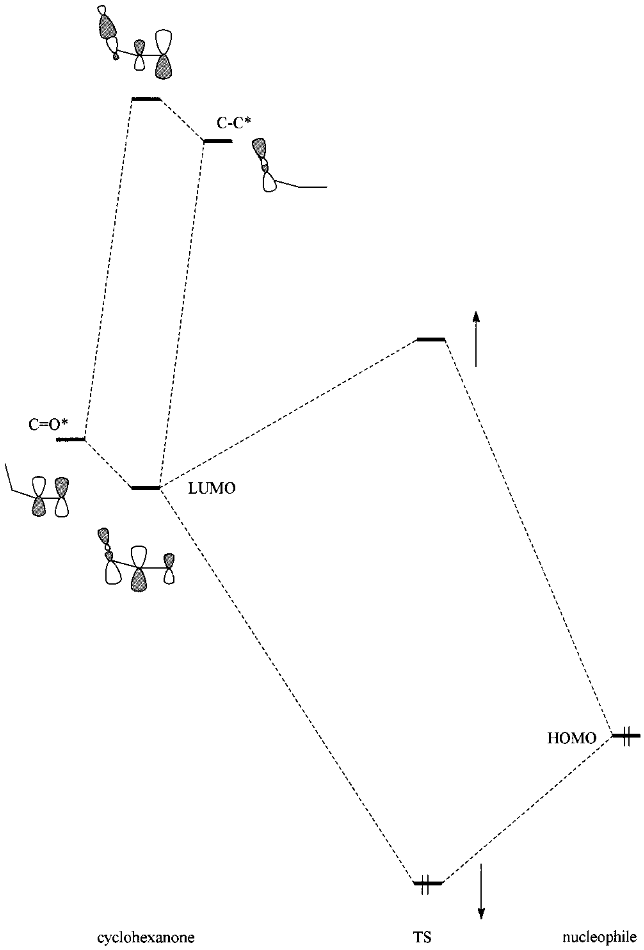


Figure 6. Significant orbital interactions for reduction of cyclohexanone using the Felkin/Anh/Eisenstein approach. The interaction of the antibonding σ*-orbital of the vicinal C−C bond with the π*-orbital of the C=O lowers the LUMO (type D interaction). Along the reaction path, the nucleophile HOMO increases interaction with the LUMO (which has a component of the antibonding σ*-orbital of the vicinal C−C bond mixed in). The original type D interaction has no effect upon the energy, as both orbitals involved are empty. However, as the reaction progresses, the incipient bonding orbital acquires more character of the original LUMO, thereby increasing the influence of antibonding σ*-orbital of the vicinal C−C bond upon the energy. The solid arrows indicate the direction of the orbital energies as the reaction progresses.

point, the overlap between the two orbitals in question is nil. Examination of the interaction between the σ*-orbital of the vicinal bond with the LUMO (π*) of the C=O reveals a type D interaction. This will lower the energy of the LUMO. As the LUMO is empty there will be no effect upon the ground-state energy. However, the HOMO/LUMO gap becomes smaller, facilitating the reaction. As the reaction proceeds (the overlap between the antibonding σ*-orbital of a σ-bond vicinal to the reactive center with the σ-orbital of the incipient bond orbitals), which is mediated via the HOMO/LUMO interaction, increases, leading to augmented stabilization.

The suggestion is straightforward. The interaction has no effect upon the GS energy. Stabilization clearly increases with progress along the reaction path, indicating that it will influence the slope of the reaction coordinate. Thus, this is a TS method. The effect is entirely upon the energy of the incipient orbital. The symmetry of the π-system is broken by considering which vicinal bond will have the best interaction. This will depend upon the σ*-energies of the vicinal bond orbitals and their relative orientations. Antiperiplanar is considered the preferred orientation to maximize overlap of the antibonding σ*-orbital of the vicinal bond with the incipient σ-orbital (via the LUMO of the C=O) during progress along the reaction path (see Figure 6). This analysis follows Fukui's principle[10] (see above).

3. Klein's Method

Klein[41,42] also considered the reduction of cyclohexanones. His analysis predicts correspondingly different distortions of the π-frontier orbitals due to interactions with the β-C−C bonds. The analysis considers the interactions (a) between the bonding orbital of a pure C=O with the bonding orbital of the C−C (type A) and (b) between the antibonding orbital of the C=O with the antibonding orbital of the C−C (related to, but different from, type D, see below). The first interaction creates two new orbitals, the higher of which will be a bonding C=O HOMO with a bit of the bonding C−C mixed in to it. The face of the C=O closest to the C−C bond will interact more strongly with the lower orbital, but less strongly with the higher (HOMO), resulting in a larger π-density on the face anti to the C−C bond in the HOMO. The second interaction, between the antibonding C−C σ*-orbital and the antibonding C=O π*-orbital, raises the C−C σ*-orbital and stabilizes the empty C=O π*-orbital through a bonding interaction. The lower orbital in the second interaction is the LUMO. It is the result of the bonding combination of the two orbitals. According to what is expected for type D, its π*-orbital should be polarized toward the face nearer the higher overlap. However, Klein used somewhat different logic to predict that the π*-orbital would be polarized toward the C−C bonds (the face of lower overlap). Essentially, he suggests that the LUMO polarization should be the opposite of the HOMO polarization. Thus the HOMO will be a π-orbital polarized away from the face nearest the C−C bond, while the LUMO will be a π*-orbital polarized toward this bond. Klein did not specifically discuss the effects upon the energies of the orbitals. The implication is that the reaction will occur at the larger face of the relevant FMO. Thus, nucleophilic attack on cyclohexanone will be axial, while electrophilic attack should be equatorial.

This analysis is very similar to that of Anh discussed above. However, it focuses upon the polarization of the π-orbitals rather than the effect on the HOMO/LUMO gap. It uses PT2 by implication, as the face with the higher density would have the larger overlap with the other reagent in the FMO treatment. The relative effect of overlap with the attacking reagent on each side will be qualitatively similar for the slope of the interaction energy with S or for the interaction energy of the particular interaction that leads to the product. Thus, this approach will lead to a qualitative prediction of the slope toward the TS. Like Anh and Cieplak, Klein focuses on a single perturbation interaction which is assumed to be dominant. Note how the Klein argument about the C−C interaction with the C═O in the LUMO parallels Cieplak's interaction. However, while Klein takes the C−C interaction to be directing, Cieplak needs the C−H interaction to be prevalent in order to agree with the experimental result.

One should note that accurate MO calculations on cyclohexanone by Frenking[43] predict that both the HOMO and LUMO of cyclohexanone should be polarized in the same direction.[44] This strongly suggests that the specific perturbation chosen by Klein is insufficient to determine the polarization of both orbitals. One should also note two errors: (1) Klein states that another approach would consider that the vacant antibonding π^*-orbital of the C═O in cyclohexanone should be stabilized by interaction with the occupied σ-orbital. In fact, it is the occupied orbital that should be stabilized while the empty π^*-orbital is destabilized by this interaction (type C interaction); (2) The LUMO is shown polarized opposite to the analysis of Figure 2D as it should be (structure II of ref 41, see discussion above).

A similar analysis of electronic control at double bonds[45] led to the conclusion that the polarization of the HOMO of 1-butene was in the direction of the C−C vicinal bond in all conformations, while that of the LUMO is conformationally dependent.

4. Fukui's Analysis

Fukui[46] has applied arguments similar to Klein's to account for the endo/exo selectivity of reactions at C═C bonds, particularly of norbornene. Here the reduction of carbonyl groups is not considered. However, the analysis is contemporary and somewhat similar to the original analysis of Klein (who later similarly considered diastereofacial reaction at C═C bonds).[45] This analysis similarly depends upon specific PT2 arguments, which will be qualitatively valid for a the slope toward the TS.

Fukui[22] has also elaborated the "orbital mixing rule," which has been applied the endo/exo selectivity of electrophilic attack at norbornene, bicyclo[2.1.0]-pentene, and other olefenic compounds. The perturbation treatment that he uses to rationalize the selectivities and the polarizations of the HOMOs is based upon second order perturbation on the *orbitals*. The basic treatment is somewhat similar to that of Hoffmann,[17] but applied to diastereofacial selectivity.

5. Burgess and Liotta's Method

Burgess and Liotta[47] used perturbation of prototypical orbitals as their starting point. In their report, they use the terms "first order" and "second order" to indicate perturbative interactions on *orbitals*, not energies (in this they follow the usage of Hoffmann[17]). In their development, they consider two systems, A and B. The orbitals on A will interact with those on B through an *inter*molecular perturbation which they call "first order". *Inter*molecular "first order" interactions can be between pairs of filled orbitals or between filled and empty orbitals. These include contributions from the first and third terms of eq 2. The newly perturbed orbital on A can now interact with another orbital on A through an *intra*molecular process, which they call second order. When A and B are atoms (as in the original development) the s and p atomic orbitals on A are orthogonal to each other. Thus, these orbitals have no interaction until they are perturbed by the interatomic interaction with B. When A and B are molecules, the system is more complex. Burgess and Liotta refer to the π-orbitals as if they contained a plane of symmetry as in ethylene. The σ-orbitals will perturb the symmetry of the π-orbitals to change their polarization perpendicular to the nodal plane of the π-system. This polarization allows greater overlap on one face of the π-system which favors reaction on that face. The new π-orbital, $\psi_{\pi 1}'$, is described by eq 9, where the C_1's are the coefficients of the first order (*inter*-molecular) perturbations and the C_2's are the coefficients of the second order (*intra*molecular) perturbations. $\psi_{\rm p}$ refers to the orbital on the other system (B); $\psi_{\pi 2}$ refers to another bonding π-orbital on the same system (A); and ψ_σ refers to a σ-orbital on the same system (A). Other terms in bonding and antibonding orbitals can be added. Only the interactions with the σ-type orbitals provide polarization perpendicular to the plane of the prototype π-system. "Stereochemical inspection of a reactant determines" the interaction that "will provide the maximum energy level splitting after mixing with the π-system." Thus, one interaction is assumed to be predominant.

$$\psi_{\pi 1}' = \psi_{\pi 1}^0 + C\psi_{1\rm p}^0 + C_2^\pi \psi_{\pi 2}^0 + C_2^\sigma \psi_\sigma + ... \qquad (9)$$

The development is somewhat confusing. The necessity of interatomic interaction before the (formerly orthogonal) s and p orbitals can interact is clear for the case of *atoms*. When transferred to a molecular basis, the description loses clarity. The π-orbitals in an unsymmetric molecule have necessarily lost the symmetry properties of those in ethylene, as they are determined by the molecular symmetry. If one considers these orbitals on A, they are already polarized before intermolecular interaction with those on B. Thus, the first order intermolecular interaction is not necessary for the polarization. Alternatively, if one considers group orbitals on A, such as pure ethylenic π-orbitals, they are not orthogonal to the σ-orbitals as they are not the true MOs of A. Thus, the pure σ and π group orbitals can mix without the need for the intermolecular perturbation. Either of these two considerations leads to polarization of the π-system without the need for intermolecular perturbation. Nevertheless, intermolecular perturbation can contribute to the polarization.

Furthermore, the criterion of choosing the dominant interaction is based upon the energetic splitting upon mixing with the π-orbital, while the selectivity is determined by the polarization of the relevant π-orbital. The HOMO/LUMO interaction is based upon the overlap of these orbitals (numerator) and their energy difference (denominator). Lowering the energy of a LUMO will reduce the energy difference, thereby enhancing the interaction. Lowering the energy of a HOMO will increase the energy difference, thereby attenuating the interaction. Also, what happens in a case where a greater π-polarization can be achieved with a smaller energy splitting?

This method has the advantage of considering all possible interactions that can polarize the π-system, not just those between filled and empty orbitals. However, only one interaction is considered to be dominant. Like Klein, they consider both type A and D interactions (Figure 2).

6. Gleiter and Paquette's Method

Gleiter and Paquette used PT2 to estimate the ground-state interactions of a π-system with an unsymmetrical σ-bonding environment.[48] The interactions of the two lead to loss of the symmetry plane of the π-system with consequent loss of local planarity. The p-orbitals that contribute to the π-system are seen to be slightly tilted. This tilting can be observed experimentally by careful study of crystal structures[49] and electron densities.[50] These effects are clearly related to the polarization of the π-system, consequently to the numerator of eq 5. In a later paper,[51] Paquette showed that the diastereofacial selectivity could also be influenced through para substituents on a phenyl group attached directly to the π-system. This effect is explained by changes in the FMOs of the system. This factor is linked to the HOMO/LUMO gap, consequently to the denominator of eq 5. Thus, by combining the two effects, one has a reasonable approach to predicting the diastereofacial selectivities. The experimentally observed distortion is not specifically attributed to a single kind of perturbation. However, the modulation of the para substituents can be understood as a perturbation interaction with the FMOs. This can be considered a PT2 method as (a) the orbital polarization is implied by the distortion; and (b) the FMO energies are a function of substituent. Unlike the studies mentioned above that concentrated upon nucleophilic attacks, Paquette has concentrated on the diastereofacial selectivity of cycloadditions.

7. Polarized π-Frontier Molecular Orbital (PPFMO) Theory[52]

This approach differs from those described above in several ways. First, it does not attempt to identify a specific dominant perturbation. Rather, it depends on a simple MO calculation to obtain the data relevant to a proper FMO treatment. The polarization of the π-system is obtained by adding two Gaussian functions (similar to 1s functions) to the atomic p-orbital(s) of the reactive center(s), one on either face. These functions are aligned along the axis of the relevant p-orbital at a distance from the nucleus previously determined to provide a large effect. A normal MO calculation is then performed in which the coefficients of the added Gaussian functions are allowed to vary freely. The algebraic sum of the coefficients (which generally have opposite signs) of the two Gaussians provides a measure of the polarization, p, of the orbital. The polarization, p, is given by eq 10, where c_+ and c_- are the coefficients on the s-type basis functions χ_+ and χ_-, respectively. The ± notations correspond to the sign of the lobe of the p-orbital on which the new basis function is superimposed. A positive value of p signifies polarization in the direction of the positive lobe of the p-orbital. The same calculation gives orbital energies for the HOMO and LUMO (as well as all of the other orbitals). The polarization and orbital energies are both used to calculate the FMO interaction. The derivative with respect to overlap of the interaction energy for each face is given by eq 11, which is analogous to eq 6. Clearly, the difference in the derivatives at the two faces will be proportional to p and to the HOMO/LUMO gap (eq 12, 13). Appropriate FMO (HOMO for electophilic or LUMO for nucleophilic attack) energy of the reagent can be inserted into eq 11 to obtain the predicted diastereofacial selectivity for an attacking reagent with known FMO energy.

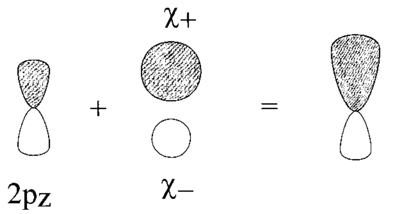


Figure 7. A combination of a p-orbital with 2 s-type Gaussians is used to break the symmetry.

$$p = c_+\chi_+ + c_-\chi_- \tag{10}$$

$$\Delta E^{\ddagger}{}_{\text{interaction}} \propto \frac{\sum_i c^{\text{HOMO}}{}_i c^{\text{LUMO}}{}_i}{E^{\text{LUMO}} - E^{\text{HOMO}}} \tag{11}$$

$$\Delta\Delta E^{\ddagger}{}_{\text{face}} \propto \frac{\sum_i p_i^{\text{LUMO}} c_i^{\text{HOMO}}}{E^{\text{LUMO}} - E^{\text{HOMO}}} \tag{12}$$

$$\Delta\Delta E^{\ddagger}{}_{\text{face}} = K\,\frac{\sum_i p_i}{k - E^{\text{HOMO}}} \tag{13}$$

Because the attacking reagent is not generally specified, some assumptions are made. As the same attacking reagent would attack either face, the FMO energy of the attacking reagent in eq 13 is a constant. For nucleophilic attacks, this will be the HOMO of the nucleophile. Reactions with early transition states are generally considered to be best treated by FMO theory. The more exothermic a nucleophilic attack, the higher will be the HOMO. The energy of a bonding orbital must be less than zero (taken as the energy of a free electron). Thus, the extreme case of an active nucleophile leads to eq 14 where E^{HOMO} is simply set to zero. The difference in reactivity at the faces simply becomes Kp/E^{LUMO} at each reactive position (one for a reduction of a carbonyl, two for a Diels−Alder reaction, etc.), where K is a constant that includes all of the parameters that are common to both faces.

$$\Delta\Delta E^{\ddagger}{}_{\text{face}} = K \sum_i \frac{p_i}{E^{\text{LUMO}}} \tag{14}$$

Using similar reasoning, an electrophilic reaction would lead to eq 15. If one arbitrarily considers the electrophile LUMO as zero, eq 15 becomes eq 16. While taking the electrophile LUMO as zero is less justifiable than taking the nucleophile HOMO as zero, it leads to a similar simple expression. More refined treatments could substitute known HOMO or LUMO energies for the attacking nucleophile or electrophile.

$$\Delta\Delta E^{\ddagger}_{\text{face}} = K \sum_{\text{i}} \frac{p_{\text{i}}}{E^{\text{LUMO}} - E^{\text{HOMO}}} \qquad (15)$$

$$\Delta\Delta E^{\ddagger}_{\text{face}} = -K \sum\nolimits_{\text{i}} \frac{p_{\text{i}}}{E^{\text{HOMO}}} \qquad (16)$$

Three other points should be mentioned. The molecule under study should be in its correct optimized geometry. This is generally obtained by optimizing the molecule using a simple semiempirical MO method such as AM1.[53] The orbital energies can be taken from this calculation. The ab initio calculation with the added Gaussian function must use a small basis set (for example, STO-3G). The larger the basis set, the less the effect of the added Gaussians. If the basis set is complete (Hartree–Fock limit), the added Gaussians will have no effect, resulting in $p \cong 0$. Last, the geometric optimization must *not* be performed using the basis set containing the added Gaussians, as they will perturb the spherical symmetry of an atom to which they are added. This will lead to incorrect geometric optimization.

The advantages of this method for obtaining the relative FMO interactions of the two faces are clear: All perturbations, both large and small, of the π-orbital polarizations *and* the FMO energies are explicitly included in the MO calculation. The calculation itself takes only a few seconds or minutes using readily available programs and computers.

The primary stated disadvantage lies in the inclusion of all of the effects that give it its advantages: one cannot easily identify a single qualitative effect as the principle cause of the predicted selectivity.

8. Exterior Frontier Orbital Extension (EFOE) (Tomoda)

The EFOE method,[54] like the PPFMO method, is based upon MO calculations on the reagent. However, it differs from PPFMO in several important respects. First of all, the full LUMO is considered, not simply an index of polarization. As Tomoda points out, the LUMO distortion will be more clearly manifest with larger basis sets. This must be true as the larger the basis set, the more flexible it will be to distortion. We noted in the discussion of PPFMO above, that a complete basis set would negate the effect of adding the extra Gaussians. This is because the complete basis set contains all of the polarization, while the small one does not.

To obtain the polarity of the LUMO, the integrated “hole density” is calculated above and below the plane of the carbonyl with the two restrictions noted below. The hole density is defined as the square of the LUMO, $\psi^{\text{LUMO}}(x, y, z)^2$. The two restrictions are that (1) only the regions exterior to the repulsive surface approximated by the van der Waals radii of the relevant atoms but within 2.65 Å (5 au) of this surface, are considered in the integration; (2) The points considered are assigned to the carbonyl only if basis functions assigned to the carbonyl account for the maximum contribution to the LUMO. The result of the integration is the EFOE density of the particular face of the LUMO. The difference in the enthalpy of activation, $\Delta\Delta H^{\ddagger}$, for the two faces is taken to be proportional to λ, where $\lambda = \text{EFOE}_{\text{ax}}^2 - \text{EFOE}_{\text{eq}}^2$.

As can be easily seen from the discussion above, EFOE theory is based upon a PT2 argument. The difference in the numerators of the third term of eq 2 for the two faces leads directly to λ. The analysis seems to be based upon a hybrid of GS and TS arguments. The part of the electron density considered is exterior to the van der Waals radius of the reagent. Clearly, this part of the electron density will be operative in determining the better contact intermediate rather than TS. At the TS, the attacking reagent must have traversed the repulsive barrier related to the van der Waals radius. Second, the square of the EFOE is used rather than the EFOE itself. This indicates that the PT2 interaction, rather than its derivative with respect to the reaction path, is considered. Both of the considerations imply evaluation of the GS interactions. On the other hand, the EFOE analysis is restricted to the LUMO and the contribution of the carbonyl to it. These are characteristics of a TS analysis.

The effect upon the energy of the LUMO is not expressly considered. Tomoda presents a linear plot of experimental $\Delta\Delta H^{\ddagger}$ vs λ, not vs λ/E^{LUMO} for reduction of 10 different substituted cyclohexanones.

The EFOE method does not appear sufficiently simple for regular use by organic chemists. It requires a reasonably accurate ab initio MO calculation, followed by integrations of the LUMO under some fairly sophisticated constraints. It does, however, provide a definable method for analyzing the polarization of π-wave functions, other than by simple inspection.

B. Methods that Emphasize Coulombic Interactions

We recall, at this point, Klopman’s description of the Coulombic interactions between reactants. In particular, eq 5 gave the intermolecular interaction in terms of a Coulombic and an FMO term. The Coulombic term should dominate when the interaction is between a hard nucleophile and a hard electrophile, while a soft/soft interaction implies FMO domination. Hard/soft and soft/hard interactions are small.

1. Chandrasekhar and Mehta’s Method

Chandrasekhar and Mehta[55] suggested predicting the diastereofacial selectivity by measuring the stabilization of a point charge (negative for nucleophiles) at a fixed distance, generally 1.4–1.5 Å from the reactive center, perpendicular to the plane of the π-system on either side. The energies of the systems are calculated using the MNDO MO method. The geometries are kept fixed at the optimized geometry for the reagent. The charge is approximated using the “sparkle” option of the MOPAC program, which provides a point charge and a radius but no orbitals. They were originally conceived to approximate metal ions in MO calculations of organic salts. Alternatively, hydride ions were used in place of sparkles. The predictive effect is said to be due to electrostatic interactions. Furthermore, the authors conclude that the success of this method illustrates the unimportance of torsional effects and orbital distortion.

Analysis of this method is rather complex. Important questions are: (1) Are the interactions calculated truly electrostatic? (2) Does any of this have to do with perturbation theory? (3) Are the properties evaluated related to the reagent (GS) or the TS? (4) Are the conclusions about the unimportance of orbital distortion supportable? Let us consider the questions individually.

True electrostatic interactions are between static charges. MO calculations of a molecule in the presence of a point charge (or a hydride ion, for that matter) allow for polarization even when the geometry is fixed. The interaction between two point charges separated by 1.4 Å is about 250 kcal/mol. If one considers that the density in the proximal lobe of the π-orbital is closer than that distance, the interaction might easily be considerably greater than that. Electric fields of this magnitude are sufficiently strong to induce polarization even beyond first order (hyperpolarizabilities). Furthermore, real nucleophiles are neither bare charges nor hydride ions. In fact, they are rarely charged. Rather they are (sometimes highly) polarized neutral reagents, ion-pairs, or ions with rather delocalized charges. A proper treatment of electrostatic interactions between neutral molecules might take the form of a multipolar expansion. This, of course, would not lead to a TS but to a contact intermediate, as it does not restrict the interaction to what occurs at the reactive site.

As discussed above, Klopman has shown that hardness is an important consideration for the PT1 term. Coulombic interactions will dominate when the nucleophile/electrophile interaction is hard/hard. Nothing can be harder than a point charge. A negative point charge has infinite ionization potential, I_p, and no electron affinity, A. It is not polarizable. An isolated hydride anion, H^-, is relatively soft. Its I_p is equivalent to the electron affinity of an H atom (17.4 kcal/mol). Not surprisingly, Mehta observed important differences when he compared the results obtained with a sparkle (point charge) and a hydride ion. The C=O group would generally be considered a soft electrophile as its LUMO is relatively low. By Klopman’s analysis, Mehta’s point charge probe ought not to provide the important interaction, as only hard/hard and soft/soft interactions can be dominant. Furthermore, the calculated properties are of a species that is neither the reagent GS (it is polarized differently) nor the TS (no attempt is made to optimize the TS). We performed a sample MNDO calculation on formaldehyde with a hydride anion positioned 1.4 Å from the carbon along the axis of the carbon p-orbital as specified. Only about half (0.49) the negative charge remained on the hydride.[56]

The MO calculations performed by Chandrasekhar and Mehta were at the restricted Hartree–Fock (RHF) level. In calculations of this type, all electrons are confined to be paired. Given the low I_p of H^-, it is likely that an electron transfer could and would take place from it to a typical carbonyl compound. This would produce the radical anion of the carbonyl compound and an H atom. The paired electron requirement of the RHF calculations would mask this process. At this point, a nucleophilic attack would no longer be an appropriate view of the reaction.

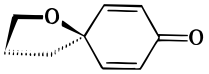
Does the calculated interaction have anything to do with perturbation theory? The calculations themselves are variational, but they are designed to probe the manner in which the GS will be transformed with progress along the reaction coordinate. Perturbation theory essentially does the same for an infinitesimal step along the reaction coordinate. As we have seen above, the perturbation due to a point charge at close range is hardly an infinitesimal perturbation. However, let us consider probing the two faces of the molecule with a more appropriate smaller partial charge. In this case, the energy profile would map out something similar to the LUMO. If the reagent were to capture an electron to form an anion, the LUMO would be the first order approximation of where it would reside.

Paddon-Row and Houk have similarly correlated diastereofacial reactivity with electrostatic interactions.[57] They optimized MO calculations of TSs for LiH addition to various substituted 7-norbornanones. They then replaced the LiH in the optimized TS with a point charge of −0.5 electrons at the position of the hydride. They found the energetic ordering of the TSs to be reproduced with this procedure, but not if the charge was absent. While this paper does not present a “method” as it requires optimization of the TS, we mention it because of its similarity to the work described immediately above.

2. Wipf’s Method

Wipf[58] has recently suggested that the component of the dipole moment perpendicular to the plane of the π-system, $\mu_\perp$, be the factor that controls the preferred direction of nucleophilic addition to carbonyls. This interaction does not specifically depend on the local charges at the reactive centers, as it is a molecular property. Thus, this interaction should lead to a GS interaction of a contact intermediate. One would expect that $\mu_\perp$ should become less useful as the reagent becomes increasingly large and complex. If the dominant contribution to $\mu_\perp$ is unrelated to the electron density near the reactive carbonyl group, it should completely lose its significance. This will be the probable result as one considers molecules of increasing complexity.

Wipf uses mostly reactions of organometallic reagents such as RLi or Grignard reagents at the carbonyls of compounds such as **I** for determining the diastereofacial selectivities.[59] Each of the examples treated has at least one oxygen positioned relative to the C=O as indicated in **I**. This procedure leaves some ambiguity with respect to the exact nature of the species being attacked. Organometallic reagents are known to aggregate with ethers. They could complex with lone pairs on the substituents of the distal ring. These interactions could change the dipole moment significantly as well as prejudice the diastereoselectivity in other (including steric) ways. To properly analyze the electronic effects upon the diastereofacial selectivities for the reactions reported by Wipf, one would need to know the structure(s) of the intermediate(s) being attacked by the nucleophile, as well as their relative concentrations in the reaction mixture.



I

IV. Comparative Discussion

A. Possible Linear Relationships between Methods

It is clear that a random prediction of facial selectivity on any system has a statistical 1:1 probability of being correct. Since there are many more predictive methods than possible results for any single system, there must be agreement between the various methods at least some of the time. It is highly probable, and highly reasonable, that many of the methods may have a significant component of linear dependence. That is to say that if a particular method makes a certain prediction, the likelihood that others will predict the same qualitative result is greater than 1:1. Considering this, the abundant arguments that purport to prove that the diastereofacial selectivities predicted are clearly due to the author's method and are unrelated to other effects are likely to be simple hyperbole. No fewer than four methods (PPFMO,[60] EFOE,[54] $\mu_\perp$,[61] and Paquette[51]) are confirmed by quantitative agreement with experimental results in the form of a linear relationship between calculated and experimental activations. Thus, rather than simply seeking the most apt method, it is prudent to try to understand why the predictions from methods that are apparently diverse resemble each other to such an extent.

Let us begin with a discussion of the differences in what we have called the GS and TS methods. Transition state theory and the Curtin–Hammett principle[28,29] tell us that the relative energies of intermediates do not determine the energies of related transition states. However, this does not mean that there may not be a correlation between them. In all likelihood, a correlation might be *expected* despite the fact that one is not logically *required*. There is a difference between an expected correlation and logical causality. Tall people can be expected to be better basketball players than short ones, on average. Yet, there is no logic that proves that a particular randomly chosen tall person will be a better player than a particular randomly chosen shorter one. Similarly, the rate laws can be logically linked by causality to the activation free energies, yet the energetic interactions that lead to intermediates along the same reaction paths might be expected, on average, to influence the TS energies, although this is not a logical requirement. Thus, GS interactions, although logically unpersuasive, can have an important correlative relationship with TS properties that are logically on firmer ground. In considering FMO theory, no actual construct of the TS is made. Only the concept of the slope of the reaction path from the reactants to competitive TSs is invoked. This approach is also correlative, not logically conclusive. Nevertheless, a direct attempt at correlation with the TS is more persuasive than one with a GS intermediate which then needs to be correlated a second time.

Other correlations might work because there might exist linear relationships between factors. For example, a likely correlation between people with big feet and the ability to play basketball might exist. The size of one's foot has little to do directly with basketball prowess. Yet, we can imagine that people with big feet are likely to be taller than those with small feet. We have already supposed that tall people (on average) will be better basketball players than short ones. So a plot of foot size versus basketball ability might be expected to show a trend.

What linearities among the factors for predicting diastereofacial selectivities discussed above might exist? One obvious example might be that between polarization of the LUMO and the electric field. The LUMO is where a captured electron would be expected to reside in the radical anion of the reactant. If the LUMO is polarized so that it has more amplitude on one face of the molecule, the added electron would be expected to have a higher density on that face. Thus, one might logically expect the electric field about the reactant to be polarized to better accommodate a negative charge near the face with the higher LUMO amplitude. Thus, the electrostatic-based methods will probably be linearly related to the polarized LUMO methods in much the same way that foot size is related to height. This is the likely significance of the several reported linear relationships between quantitative predictions and experimental results. While the same experimental results were not used in each report, the likelihood that the predictions of the various methods would give linear relations when plotted against each other is high.

Nevertheless, several papers claim that the apparent agreement of their methods with experiment or calculation proves other methods to be incorrect. In view of the above discussion, we suggest that all such claims are simple hyperbole. It is not sufficient to show that a method correlates with experimental or MO results to discredit others. Rather, it is necessary to show that the other methods do not work. If big feet will correlate with basketball prowess, one might expect big toes to also correlate.

Clearly correlation and causality are different. Each can be useful. What knowledge do we seek? If we wish to predict the qualitative diastereofacial selectivity with reasonable frequency, then correlative ability will be sufficient. However, if we seek to understand the physical basis for these selectivities, correlative ability, by itself, will not help. While we cannot (at this point) clearly point to one qualitative effect that is causative, we can, nevertheless, delineate those methods that follow logical developments from those that wander from the logical path. Thus, those developments that violate the Curtin–Hammett principle are logically suspect. Those electrostatic methods that disregard the hard/soft principle clearly delineated by Klopman are also suspect. Methods that make clear predictions based upon perturbation arguments that are contradicted by properly conceived and accurate MO calculations must also be suspect.

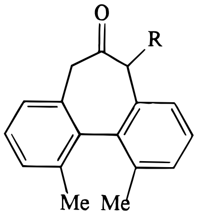
B. Energetic Considerations of C–H and C–C Hyperconjugative Interactions

Many of the PT2 arguments based upon prototype group orbitals, as depicted in Figure 2, depend on identifying the effect that is most important to reactivity. The Baker–Nathan effect was first believed to indicate C–H to be stronger than C–C hyperconjugation. Today this effect is more usually attributed to steric hindrance of solvation.[62–71] Only one report based upon NMR evidence seems to support the original Baker–Nathan order hyperconjugation interpretation.[72] In the work reported, Cooney and Happer studied the effect of different alkyl substituents at the para position of several differently β-substituted styrenes. They concluded that the small deviations in C^{13} chemical shifts follow the Baker–Nathan order in four solvents (CCl_4, $CDCl_3$, EtOH, and Me_2SO). However, they make no compelling argument that their observations are not due to steric hindrance to solvation.

If C–C bonds are assumed to hyperconjugate better than C–H bonds, as predicted by MO calculations, the Cieplak hypothesis predicts the reverse diastereofacial selectivity. We noted that the Baker–Nathan order of electrophilic substitution at the para positions of toluene and *tert*-butylbenzene (where the C–H bond is thought to hyperconjugate better than the C–C) has been experimentally shown to be a solvation effect. It is easier to solvate a charge adjacent to a methyl group than adjacent to a *tert*-butyl group. MO calculations confirm that the para-protonated *tert*-butylbenzene is more stable than the analogous protonated toluene. For example, it easier to protonate *tert*-butylbenzene than toluene by 1.3 (AM1) or 2.3 (HF/6-31G*) kcal/mol at the para position.[73] Is the situation different for the FMOs of carbonyl compounds? A comparison of the HOMOs and LUMOs of formaldehyde, acetaldehyde, and *tert*-butyl aldehyde indicates that the effect of either alkyl group upon the energies of these orbitals can be large. The alkyl groups raise the energy of the HOMOs and LUMOs in both cases. Once again, the effects are greater for *tert*-butyl than methyl. The HOMO is raised more by *tert*-butyl by 9.8 or 7.7 kcal/mol using AM1 and HF/6-31G*, respectively; while the LUMO is raised more by 2.3 and 1.0 kcal/mol using the same methods.

However, the nucleophilic attack might not occur directly on the carbonyl. In all likelihood, the oxygen of the C=O is first complexed with an electrophile. This would create additional positive character at the carbonyl C. Interaction of the vicinal alkyl groups would acquire more of the character of interactions with carbocations.

Of the various authors who have considered hyperconjugative interactions, only Cieplak requires that the C–H be stronger than the C–C interactions. His most recent publication on the subject still maintains this position.[74] The Felkin/Anh/Eisenstein and Klein formulations both require the C–C interaction to be the stronger. Cieplak needed to reverse the order so that his procedure would correctly predict the (known) diastereofacial selectivity of the reduction of cyclohexanone. However, Franck[2] has noted that the interaction he suggested would retard rather than facilitate the reaction on the experimentally preferred face (we have elaborated on his argument above). Because the interaction of the C–H bond should be weaker than that of C–C, one can conclude that the C–H interaction would retard the reaction less than the C–C interaction. Cieplak has interpreted the above as a stabilization of the transition state rather than a destabilization of the reactants. A recent experimental report by Fraser et al.[75] on face-specific $LiAH_4$ reductions of the ketone **II** is completely consistent with our analysis. They found that R = methyl decreases, while R = chloro and R = methoxy both increase antiperiplanar reactivity. Because C–C hyperconjugates better than C–H, R = methyl would stabilize the ground state more than C–H, thus decreasing the reactivity. However, C–O and C–Cl both should hyperconjugate less than C–H which would *destabilize* the ground state and, consequently, *increase* reactivity. However, there are many subtle effects discussed in this paper that cannot simply be attributed to hyperconjugative effects.



II

C. Comparison of Orbital Energies and Orbital Polarization

Clearly, the FMO interaction between the reacting molecules initially depends only upon orbital polarization as the FMOs are the same for attack on either face (see PPFMO discussion above). Thus, the orbital energy consideration can only differentiate between the faces if the interaction changes during the reaction coordinate in a different manner for attack at each face. Both the Cieplak and the Felkin/Anh/Eisenstein models do this. They do not consider polarization of the π-system. The Klein and Fukui proposals depend only upon the polarization of the π-system. Burgess and Liotta predict the selectivity based upon polarization, but decide the dominating interaction to be based upon energetics. The Gleiter/Paquette, PPFMO, and EFOE approaches use both polarization and energetics. However, the diastereofacial selectivity is the result of the polarization as the change in energy of the orbitals due to the PT2 interactions of the prototype group orbitals during the reaction is not considered.

D. Specific Interactions vs All Interactions

Organic chemists generally feel a need to be able to qualitatively identify a result with a particular effect. MO calculations are complex. Among several schemes that have been devised to analyze the results of MO calculations in terms of qualitative effects, the Morokuma analysis[76] and the Natural Bond Order (NBO) analysis of Weinhold[77] are most popular. Nevertheless, they must necessarily depend on some arbitrary definitions. They often are too complex for the generalized discussions that organic chemists prefer. The ability to define an observed result in terms of a readily identifiable effect is very attractive. Thus, we can say the ethyl cation is more stable than the methyl cation because of hyperconjugation. However, the magnitude of the energy difference between methyl and ethyl cations is much greater than the energetic differences leading to most observed electronically determined diastereofacial selectivities. These latter differences are generally less than 1 kcal/mol, often significantly less. Because the systems are necessarily more complex (they must be unsymmetrical), there are more possible interactions. Is it possible in such a case to unambiguously determine which interaction will be dominant by simple inspection of the molecular geometry? Burgess and Liotta suggest that one should decide which is the dominant interaction by inspection of the molecular geometry, but they give no definitive rules for making the selection. Cieplak seems to have inverted his logic twice. Only the Felkin/Anh/Eisenstein, Klein, and Fukui schemes present us with clearly reasoned pictures of what to expect. While the distortion predicted by Klein for the LUMO of cyclohexanone has been confirmed by MO calculations, that predicted for the HOMO of the same molecule was shown to be in error by the same MO calculation.[43] The polarization of the LUMO of cyclohexanone is opposite from the observed diastereofacial selectivity as well as the calculated polarization for each of the interactions in Figure 2 (A and D) that lower the LUMO. This is another indication that individual interactions can be misleading.

The apparent inability of one qualitative effect to dominate all others leads to the conclusion that several, if not all, interactions need to be considered for consistently accurate predictions of diastereofacial selectivity. Only the PPFMO method was methodically tested against all available relevant data at the time of its publication.[60] Other PPFMO results were discussed subsequently.[78,79] It would be useful to apply all of the methods discussed here to a similar data set brought up to date with the most current results. In such a comparison, methods that included all interactions would necessarily prevail, as whatever dominant interactions might exist would necessarily be considered. The inclusion of other, unimportant, interactions should not prejudice the results. However, the relative importance of individual interactions (at least to the correlation with the data) could be better judged.

V. Conclusions

Understanding and predicting diastereofacial selectivity remains an important subject of investigation. While several groups have had success *predicting* these selectivities, we do not have a reasonable general *explanation* for these selectivities that corresponds to those effects that organic chemists prefer to consider. Because of the small differences involved in the activation energies leading to the observed selectivities and the myriad of possible interactions that might contribute to these differences, it is unlikely that any satisfactory explanation of this type will emerge. Probably the best approach lies in the examination of the orbital energies and polarizations that result from MO calculations on the reactive substrates. While these calculations do not provide an organic chemist's explanation, they do contain the contributions of all possible effects.

VI. Acknowledgment

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