CHAPTER

5

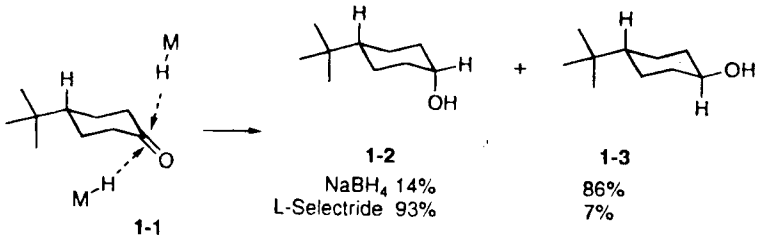
Stereoelectronic Effects in Six-Membered Rings

Richard W. Franck

5.1. Introduction

A working definition of the term *stereoelectronic effect* is required at the outset of this review. When a ground-state geometry or a stereochemical reaction of a molecule is observed that cannot be explained or rationalized by simple steric effects, then the force that is invoked as the explanation for the observation is stereoelectronic. Namely, a force due to molecular orbitals, viewed as bonding (or antibonding) interactions or as producing an electrostatic field, is considered to add to or subtract from the forces developed simply from the mechanical interaction of atoms as they become near neighbors. This is a related but somewhat more inclusive definition of stereoelectronic effects than that put forward by Deslongchamps in his pioneering book,[1] where he states "... many results indicate that the reactivity of most types of organic molecules depends upon relative *stereochemistry of particular electron pairs, bonded or non-bonded.*" Before identifying a stereoelectronic effect, one must first understand the size and direction of the steric effect to be expected in the absence of stereoelectronic influences. The tacit assumption of organic chemists is, in simple models where stereoelectronic effects are absent, that ground-state steric effects can be experimentally determined and that they can be successfully modeled by molecular-mechanics programs widely available for personal computers accessible to most organic research groups.

Whereas the determination of the steric effect of a group in the general case, known originally as its E_s value, now superseded as the upsilon steric parameter (υ) is based on a combination of experimental determinations and calculations of van der Waals radii,[2] the case of groups on six-membered rings is different. Here, the steric effect of an attached group has been defined as the $-\Delta G$ in kcal/mol of the K_{eq}, in favor of the equatorial conformational isomer over the axial of a substituted cyclohexane. The $-\Delta G$ is traditionally recorded as an A value with a positive sign, implying the higher potential energy of the group when it is axially positioned on the cyclohexane.[3] Although the data tables are often presented with the solvent in which the K_{eq} has been determined, it has been customary to assume that the steric effect of ordinary functional groups is not solvent dependent. However, as will be seen in the following on the anomeric effect, stereoelectronic behavior is often

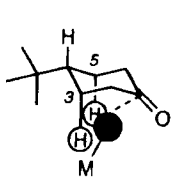


associated with solvent effects, which cannot be interpreted unambiguously in the absence of a knowledge of the solvent effect on pure steric effects.

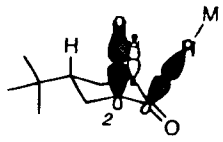
An encyclopedic review of all the important examples of stereoelectronic effects reported for six-membered ring compounds is beyond the scope of this chapter. The purpose of this chapter is to analyze critically some of the important and well-studied systems so that, as the reader examines the literature of stereoelectronic effects, she (he) will have a basis for evaluating the conclusions about the existence and the extent of the effects that are being described.

5.2. Carbonyl Group

An area that continues to produce discussion and contention is the nucleophilic addition of an organometallically delivered hydride or carbanion to a cyclohexanone carbonyl. The process and the stereoelectronic question is summarized by the illustration in Scheme 5.1. When *t*-butylcyclohexanone **1-1** is reduced with sodium borohydride, the two products, cis- and trans-*t*-butylcyclohexanol are produced in 14% and 86% yields, respectively. To produce the cis isomer **1-2,** the hydrogen atom must be delivered by its carrier from the upper face of the *t*-butylcyclohexanone shown; whereas the trans isomer **1-3** must have its hydrogen delivered by a carrier from below. There is a consensus that the angle of approach of the hydride from both faces is stereoelectronically controlled in that its trajectory toward the carbonyl carbon is the Burgi–Dunitz angle of 105° from the C–O axis. This angle was derived from X-ray crystallographic data of a series of amino ketones where the intramolecular distance between the tertiary amine and carbonyl affected the degree of carbonyl pyramidalization. It is presumed that the Burgi–Dunitz angle corresponds to the antibonding orbital of the C–O bond, the lowest-energy empty orbital that is available for attack by an electron-rich reagent.[4] Beyond this consensus, the differing interpretations begin. The question put simply is: What forces determine whether attack is from above or below, and are they stereoelectronic or purely steric? The steric forces that are considered to hinder attack from below are the repulsive interactions that develop between the axial hydrogen atoms at carbons 3 and 5 and

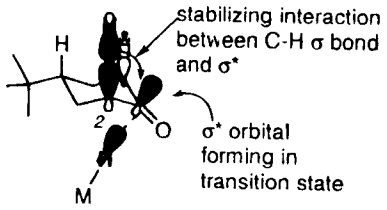


2-1 steric repulsion between reagent and axial hydrogens

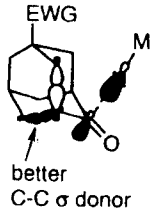


2-2 torsional repulsion between electrons in forming bond and vicinal bonds

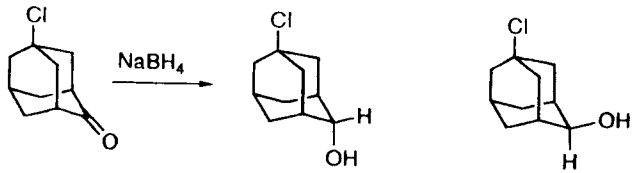
the hydride reagent, illustrated in Scheme 5.2, structure **2-1.** This steric interaction can be amplified by increasing the bulk of the reagent, for example, lithium tri-*s*-butylborohydride ("L-selectride") whereupon the fraction of below-plane attack is decreased to 7% from the 86% when sodium borohydride was used. The forces that hinder attack from above are postulated to be torsional repulsions between the axial sigma bonds at carbons 2 and 6 and the developing bond as the hydride–carbonyl carbon interaction emerges in the transition state, shown in structure **2-2.** Note that torsional repulsions, first described by Felkin,[5] are sometimes classified as stereoelectronic factors, not as simple steric repulsions. Using detailed theoretical analysis, Houk concluded that torsional effects suffice to rationalize the large data set of ketone reductions.[6] In fact, when these opposing steric and torsional interactions are modeled in a mechanical algorithm, most cyclohexanone results are correlated in a satisfactory manner.[7] There have been attempts to analyze transition-state bonding effects that focus on interactions with σ bonds vicinal to the forming bond at the carbonyl center. These effects, summarized in detail by le Noble[8] and Cieplak,[9] can be used to rationalize a great deal of cyclohexanone additions. The analysis most widely applied (and controversial) is due to Cieplak and postulates a bonding interaction between the antiperiplanar axial C–H sigma (σ) bond and the developing sigma antibonding orbital (σ*) of the bond forming between the nucleophile and the carbonyl carbon. In cyclohexanones, this interaction would favor axial delivery of the incoming nucleophile, pictured as structure **3-1** in Scheme 5.3 and in more detail in Scheme 5.4, structures **4-1** and **-2** for axial approach and **4-3** and **-4** for equatorial. If this Newman projection analysis is correct, then one of the disagreements about Cieplak's interpretation as to the better electron-donor capacity of C–H bonds compared to C–C bonds becomes moot. It is clear that early in the transition state **4-3** there can be very little interaction between the C–C bond or the C–H bond with the developing bond to the carbonyl carbon. This model is notable in that it does succeed in rationalizing the adamantanone addition chemistry,[10] where the stereochemically equivalent faces are differentiated only by the vicinal C–C σ bond donating ability, as depicted in **3-2.** According to the Cieplak model, the EWG (electron-withdrawing group) diminishes the donating ability of its proximal C–C bonds, hence favoring the distal C–C bonds as the donors antiperiplanar to the forming bond, thus rationalizing the major product, where attack has occurred syn to the EWG. As le Noble pointed out in a recent adamantanone paper,[11] the Cieplak



3-1 illustration of Cieplak concept



3-2 application of concept to adamantanones



3-3 **3-4** 67% **3-5** 33%

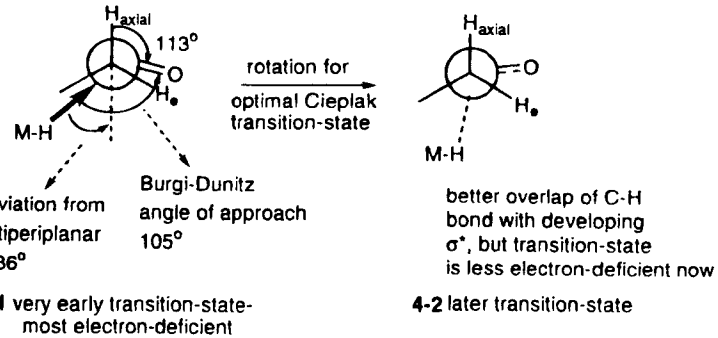
one of approx. 15 adamantanone cases consistent with the Cieplak rationalization

conceptualization works well in adamantanone systems unencumbered by steric complications (and, as pointed out, below-polar complications) so that only the weak hyperconjugative effects can be made manifest.

Despite its empirical success, not only in correlating the face selectivity of addition to cyclohexanones, but in other ring sizes and with other reaction types, the Cieplak analysis is often discounted. The reason that the Cieplak approach is not considered to be a good *explanation,* despite its usefulness, lies in the fact that it is an unorthodox application of FMO theory. The key interaction depicted in the qualitative picture of structure **3-1** in Scheme 5.3, as popularized by Cieplak, really requires three consecutive assumptions, shown in Scheme 5.5. Step 1 in an FMO analysis postulates a major interaction between the HOMO and LUMO of the reacting species, namely the electrons on the nucleophilic hydride donor and the carbonyl π^*, respectively. By FMO convention, this interaction would create a stabilized bonding orbital lower in energy than the starting HOMO and a destabilized antibonding orbital higher in energy than the original LUMO, this new HOMO–LUMO couple representing an early transition state. Step 2 (for the Cieplak effect) is a bonding interaction between the C–H σ orbital with the transition state. According to perturbational MO concepts, this interaction must be with the new antibonding level, which must be raised even higher in energy, while the σ orbital must be lowered in energy. Finally, step 3 in the logical chain assumes that the consequence of the raising of the antibonding orbital in step 2 and the lowering of the C–H bonding orbital, is to lower the total energy of the transition state compared to its energy in the absence of the interaction. And this lowering must be greater

Detailed Newman projection analysis of the Cieplak rationalization for cyclohexanone face selectivity

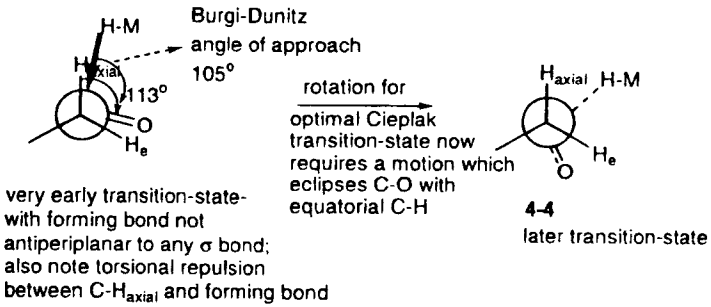
Attack leading to new axial C-H bond



4-1 very early transition-state-most electron-deficient

4-2 later transition-state

Attack leading to new equatorial C-H bond

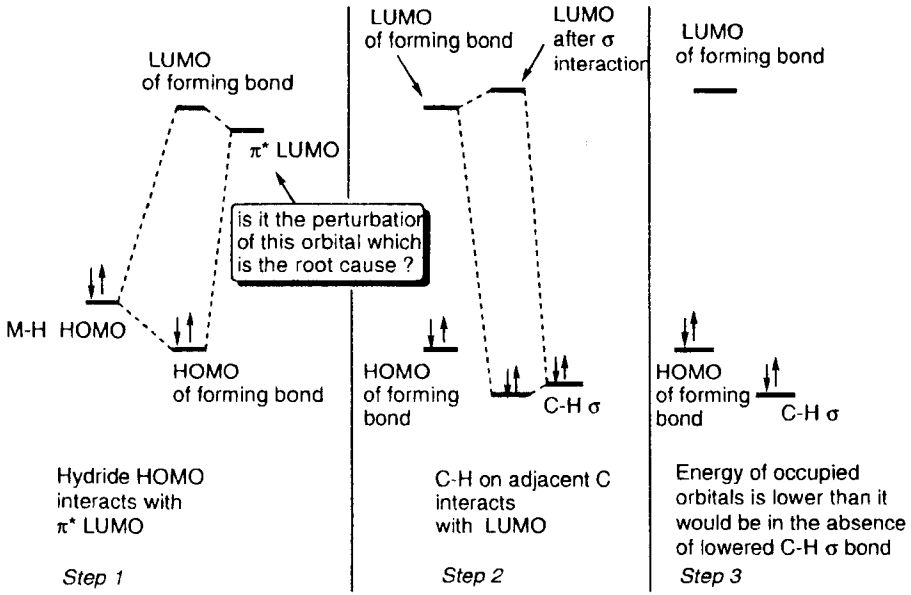


4-3 very early transition-state-with forming bond not antiperiplanar to any σ bond; also note torsional repulsion between C-H_{axial} and forming bond

4-4 later transition-state

for the diastereomeric transition state developing when the face antiperiplanar to the axial C–H bond is attacked. When one dissects out the series of assumptions on what is ultimately a diastereomeric perturbation of the carbonyl π^* component of the transition state, one concludes that a direct examination of this key orbital be undertaken. In terms of the energy separation from the filled orbitals, which are the perturbing influence, the carbonyl π^* is closer in energy than the developing antibonding orbital of the transition state; hence the magnitude of the perturbation should decrease as the transition state develops. Cieplak recognized this qualitative FMO argument as casting doubt on his theoretical approach, and therefore originally proposed that the transition state for metal hydride addition to a carbonyl that included the metal ion should have a low-lying unoccupied orbital. This postulated new LUMO could then interact with the C–H σ orbital with equal or greater strength in the transition state than the ground-state interaction with the carbonyl π^*. However, MO calculations have not borne out this assumption.[12]

Calculations that reveal distortions of the carbonyl π and π^* orbitals have been carried out by Frenking in a convincing manner.[13] His thorough, ab initio calculations



[using MP2/6-31G(d)//HF/3-21G] basis sets demonstrate that the difference in energy between transition states for hydride delivery to axial and eqautorial faces are due to unequal interactions of the hydride donor and the substrate ground state. The calculations reveal that the π^* orbital of the carbonyl carbon, namely, the LUMO that is to undergo attack by the hydride, is clearly larger in size on the axial face (Figure 5.1). Interestingly, the HOMO is also larger on the axial face. Frenking's data validate an early deduction by Klein about nucleophilic addition.[14] It is also probably the case that the structural features that Cieplak had attributed to a transition-state bonding effect simply correlate with the Frenking–Klein ground-state effect. One interesting conclusion of the Frenking work is that, for cyclohexanone, the axial C–H does participate in the perturbation of the carbonyl π^*. Thus, Cieplak was intuitively correct in his identification of the importance of the C–H bond in this particular case, even if his conclusion was made on the basis of an unjustifiable assumption. It should be noted that Frenking reminds the reader that it is difficult to predict a priori which interactions are dominant without carrying out quantum-mechanical calculations. A different processing of similar high-level quantum calculations is reported by Boyd. Instead of focusing on the desymmetrization of orbital density in the axial and equatorial directions, he solved for charge density and found no significant difference in the electron deficiency on the two faces of the carbonyl carbon and thus discounted the unsymmetrical π orbital model. He attributes the differential reactivity to the difference in electrostatic fields surrounding the carbonyl, with the equatorial approach being destabilized by what appears to be commonly described as torsional repulsions.[15]

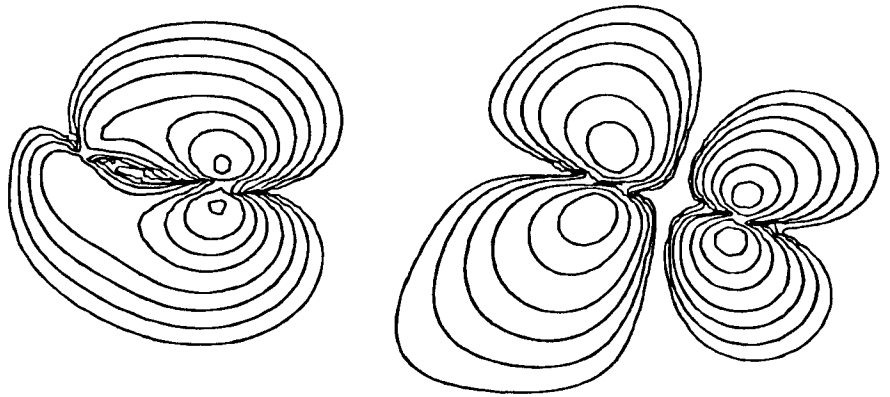
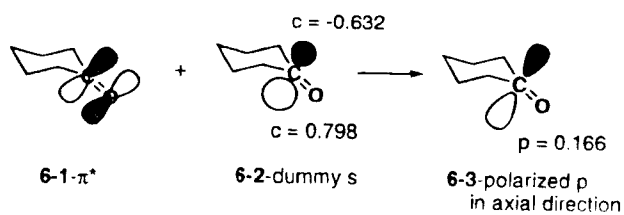


Figure 5.1. Plot of the C = 0 π orbitals of cyclohexanone. The atoms are shown as dots, carbon at the left, oxygen at the right [6-31G(d)//3-21G]. (a) $\pi_{C=0}$; (b) π_{C-0}^*. The contour lines correspond to electron densities of 0.001, 0.002, 0.004, 0.008, 0.02, 0.04, 0.08, 0.2 atomic units.
(Reprinted from Frenking et al., *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*(9), Fig. 3, p. 1148, with permission from the author and publisher.)

Since the Frenking level of calculation is not feasible for all the potential candidate carbonyl compounds with diastereotopic faces, simpler computational approaches that may reveal the same effect could become useful. The polarized-π-frontier molecular-orbital (PPFMO) approach describes a rapid calculation that measures the distortion of reacting π and π^* orbitals by comparing the coefficients of two independently variable "dummy" *s* orbitals whose centers are superimposed over the lobes of the *p* orbital of interest.[16] The separate *s* orbitals are sensitive to the molecule's inherent asymmetry and their different coefficients reflect the different "size" of the lobes of the *p* orbitals. The polarization of a reacting π^* orbital is defined as the absolute difference between the two computed coefficients of the dummy *s* orbitals. To compare similar but not identical molecules reacting under identical conditions so that the E_{HOMO} can be assumed to be constant, a normalization procedure, based on the conventions of FMO theory, is accomplished by dividing the polarization by the energy of the LUMO. As shown in Scheme 5.6, the cyclohexanone LUMO is polarized in the axial direction. The calculation is simpler than the Frenking method, which differentiates the *p* lobes by their electron-density contours computed



with high-level ab initio techniques. In the examples studied to date, the PPFMO method seems quite reliable. The crucial test of its usefulness awaits its packaging in commercially available programs so that the organic community can access the method and apply it to systems of interest.

An alternative computational approach that shows promise is the evaluation of the electrostatic potential of the carbonyl-containing molecule.[17] Then the simple prediction is that the negatively charged nucleophile will be attracted toward the more positive face (or repelled from the more negative face). The electrostatic potential can be computed using local-density-functional theory (LDF), which is claimed to be intrinsically faster than conventional Hartree–Fock ab initio techniques and is available in a commercial package. This technique has been applied to the benzobicyclooctenone in Fig. 5.2 and correctly rationalizes the delivery of nucleophiles to the carbonyl face anti to the more electrostatically negative benzo region. Semiempirical methods, including PM3, AM1, and MNDO, have also been used to compute electrostatic potentials, but have not been applied to the cyclic ketone question. It has not yet been demonstrated that the region of positive potential is a consequence of or directly correlates with the polarized empty orbital that undergoes nucleophilic attack. For many organic chemists schooled in the examination of localized orbital systems, the idea of a diffuse, nonlocal orbital field effect is hard to accept or internalize into one's viewpoint. Nevertheless, when a larger test sample of carbonyl systems has been computed, the electrostatic potential may turn out to be useful to practicing organic chemists.

To this reviewer, the pyranoside ketones of Scheme 5.7 make up a carbonyl system that is clearly governed by stereoelectronic effects and that could serve as a touchstone for the predictive power of the several different methodologies described. In the 2-keto isomer **7-1,** there is one nonvicinal and axial C–H bond serving as hindrance to axial attack of borohydride, while there are two axial and vicinal C–H bonds that, in the Cieplak hypothesis, should enhance antiperiplanar axial delivery of hydride. Nevertheless, equatorial delivery of hydride is favored.[18,19] In the 3-keto isomer **7-4,** there is an additional nonvicinal and axial C–H that should increase steric hindrance to axial attack, yet the converse, more axial attack is observed. Clearly, the vicinal bond–antiperiplanar hypothesis is an insufficient model in this case. For the α-glycoside series, the effect of the axial alkoxy is greater for the 3-ketone than for the 2-ketone. This suggests that its steric effect is more important than its polar effect. Data from the 4-keto series indicate no trends in the α-glycoside series, but a clear predominance of equatorial hydride delivery in the β-series is observed.[20,21] In addition to the borohydride data, there is a body of results in the C-branched carbohydrate literature where various organometallics have been added to these carbonyls with a range of stereochemical outcomes. These interesting test molecules have not been subjected to the computational models described. After the pyranose derivatives are treated by these theoretical approaches, the organic community might have a benchmark of their predictive power for "real" systems other than cyclohexanones. It is interesting to note that Miljkovic, two decades ago, anticipated the electrostatic explanation for face selectivity of attack in the 2-ketopyranose series.[22]

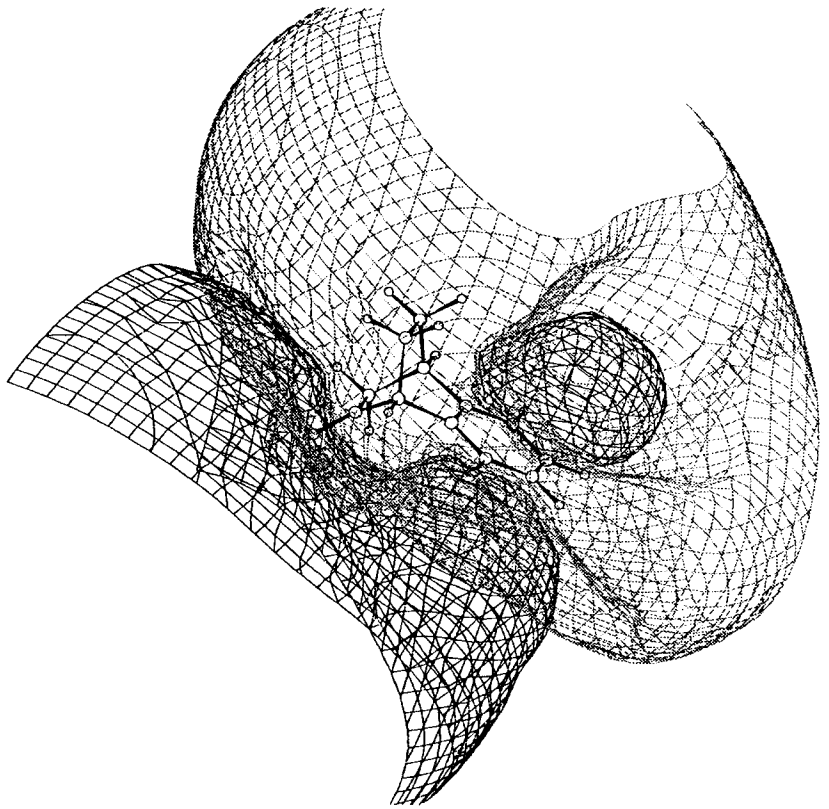
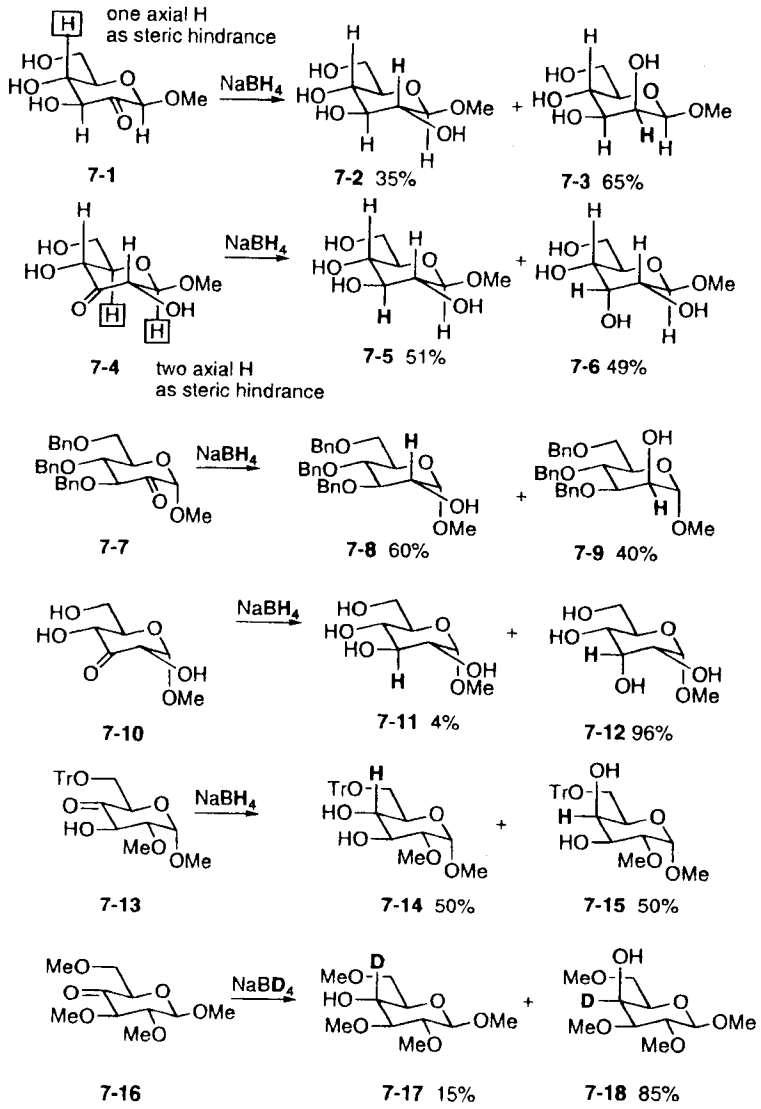
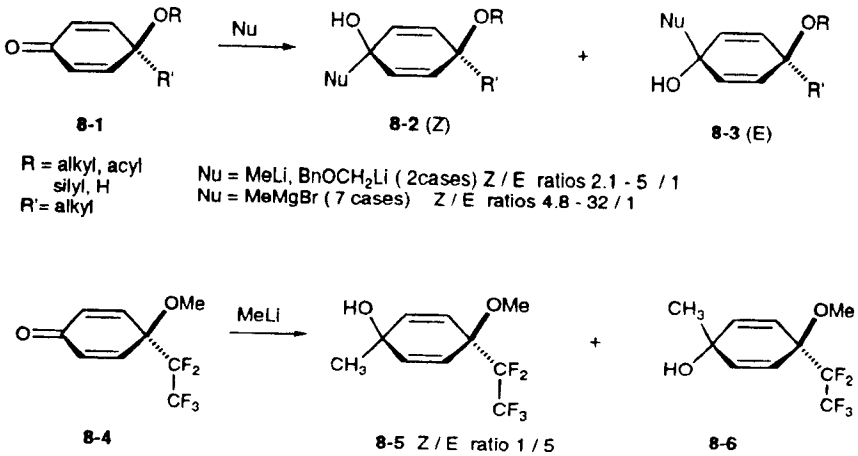


Figure 5.2. LDF/DND electrostatic potential map for 2-oxo-benzobicyclo[2.2.2]octane. The light and dark contours were taken at, respectively, −0.002 and +0.002 hartree (1.255 kcal/mol), the smallest increments on either side of zero at this contour level. The first few contours at higher absolute values of energy (e.g., ±0.004, ±0.006, and so on) continue to follow closely the shapes of the contours shown but enclose successively smaller volumes within them. Note that the molecule is oriented with its carbonyl group pointing to the lower left.
(Reprinted from Pudzianowski, A. T.; Barrish, J. C.; Spergel, S. H. *Tetrahedron Lett.* **1992,** *33,* 293–96, with kind permission from Elsevier Science Ltd., The Boulevard, Langford Lane, Kidlington OX5 1GB, U.K.)

In an extension of a reaction used for a synthesis of aranorosin, Wipf studied the addition of various organolithiums and Grignard reagents to the carbonyl of 4-methyl-4-alkoxyoxy- and acyloxycyclohexadienones (Scheme 5.8). With the exception of hydride reagents and a propargylic reagent, the carbonyl face anti to the 4-oxy group is attacked preferentially. When the component of the dipole moment orthogonal to the dienone plane is reversed in the pentafluoroethyl analog, the face selectivity is also reversed. Whether this is a manifestation of electrostatic effects or carbonyl polarization remains to be sorted out.[23]



The conclusion to be drawn from the data on carbonyl reduction is that there are nonsteric forces that influence the direction of nucleophilic attack on carbonyl groups. But it appears that the entire molecular electronic assembly is the force that perturbs both the ground state of the carbonyl and, to some extent, the transition state, so as to favor bonding to one diasteretopic face. The propensity of organic chemists to attribute to one or two bonds, or one or two local interactions, the controlling electronic force in this face selection is an oversimplification put forward in the just cause of establishing a predictive rule.

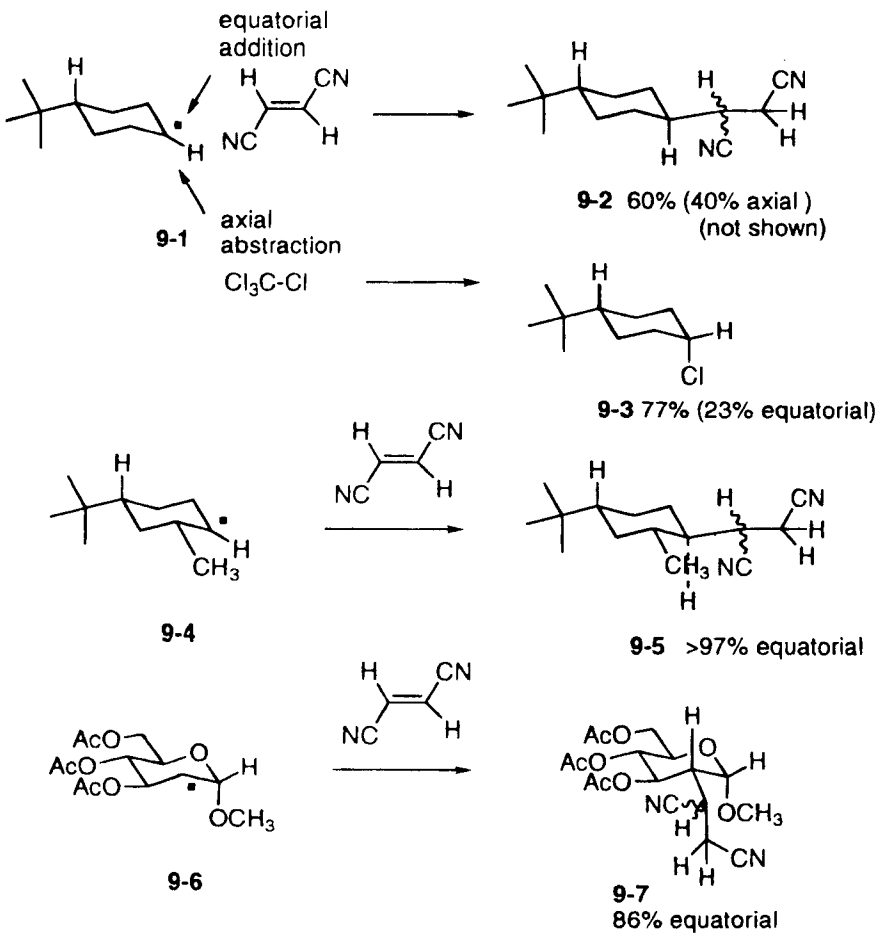


5.3. Free Radicals

Giese has reviewed the stereochemistry of six-membered cyclic radicals in detail.[24] The 4-*t*-butylcyclohexyl radical displays modest preferences for axial attack in four-atom abstraction reactions (HO, Cl, D, Br) and equally modest equatorial preferences in fiveout of six alkene additions. A balance between torsional and steric effects is invoked to explain the results. The effect of vicinal equatorial substituents in favoring equatorial attack is quite striking. The data shown in the scheme are representative and are suggestive of an effect other than steric. Houk and Giese have constructed a force field for radical additions based on a UHF/3-21G transition state computed for addition of alkyl radicals to acrylonitrile. An interesting feature of this transition state is the productlike geometry of the reacting carbons. Application of this force field to the cyclohexyl radical problem suggested that the stereoselectivity resulted from a balance between 1,3-diaxial repulsions and torsional effects. For example, the increased equatorial selectivity for **9-4** (Scheme 5.9) is attributed to one additional axial-like hydrogen on the vicinal methyl group blocking the axial face.[25] However, this rationale cannot be used for the effect of vicinal acetoxy groups in **9-6** and related compounds. The full range of calculations of the type described for carbonyl systems have not been applied to these radical systems.[26] In the section on anomeric effects, it will be seen that radicals are subject to powerful stereolectronic forces affecting their ground-state geometry; so it is not surprising that substituents would have a significant influence on their reaction stereochemistry as well. Whether the control factor is a result of pyramidalization, polarization, or transition-state stabilization effects remains to be determined.

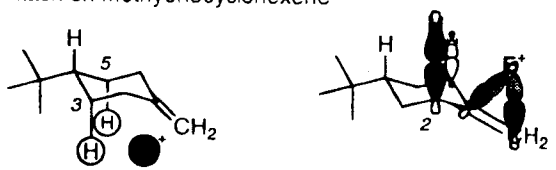
5.4. Alkenes

The scope of alkene chemistry is much greater than that for carbonyls. Diastereofacial selection has been observed in electrophilic addition, in cycloadditions, in radical



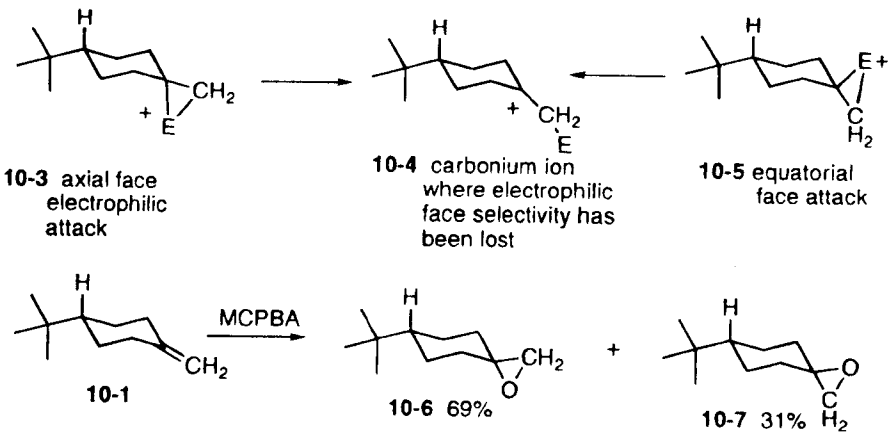
addition, and in nucleophilic additions (when the alkene is conjugated to a carbonyl). Again, the focus of this section will be on examples that illustrate the operation of stereoelectronic effects. Beginning with methylene cyclohexenes and electrophilic attack, one can postulate a similarity to the cyclohexanone analysis. One subtle difference is that the angle of approach of the electrophile, toward the midpoint of the π bond and quite different from the Burgi–Dunitz carbonyl approach, causes a reduction in both the steric repulsion on the axial face (**10-1,** Scheme 5.10) and the torsional repulsion on the equatorial face (**10-2**). The Cieplak conceptualization predicts that an attacking and bridging electrophile will approach the same axial face as observed in the ketone series since the same antiperiplanar C–H σ bonds will interact with the developing σ^* of the transition state, leading to the onium ion **10-3.** The final stereochemistry of the product after the nucleophile opens the onium species with inversion would be equatorial. Alternately, as is the case with

Electrophilic attack on methyenecyclohexene



10-1 steric repulsion is less severe than in carbonyl case

10-2 torsional repulsion is less severe than in carbonyl case



10-3 axial face electrophilic attack

10-4 carbonium ion where electrophilic face selectivity has been lost

10-5 equatorial face attack

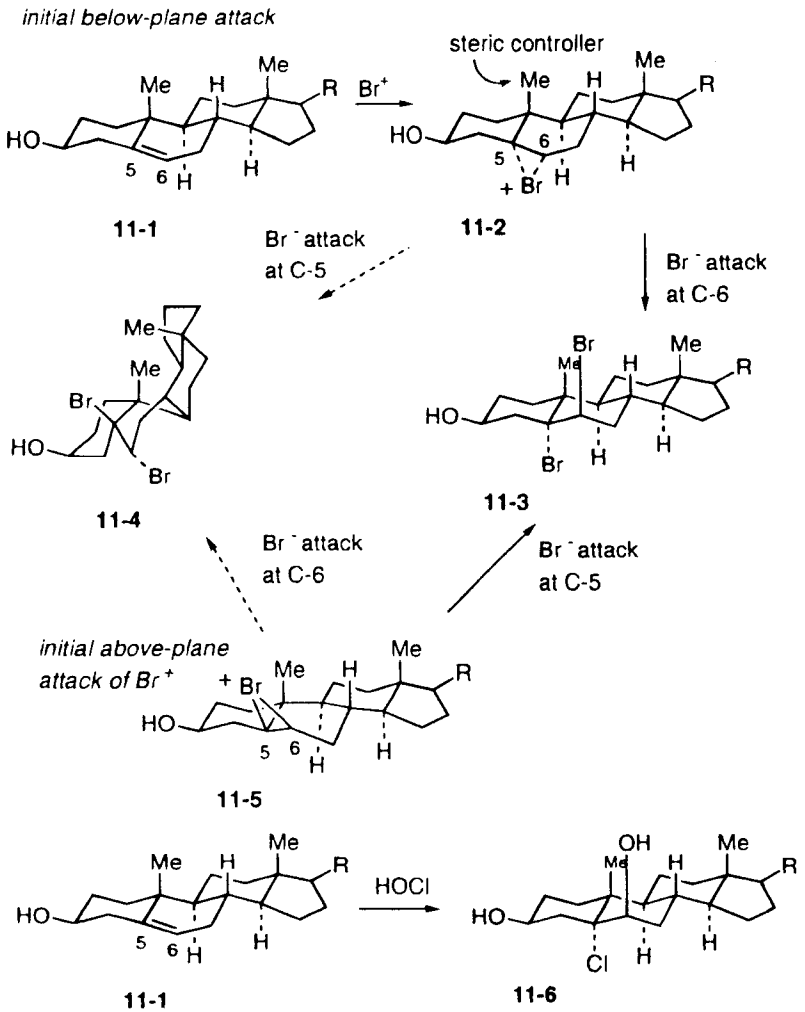
10-1

10-6 69%

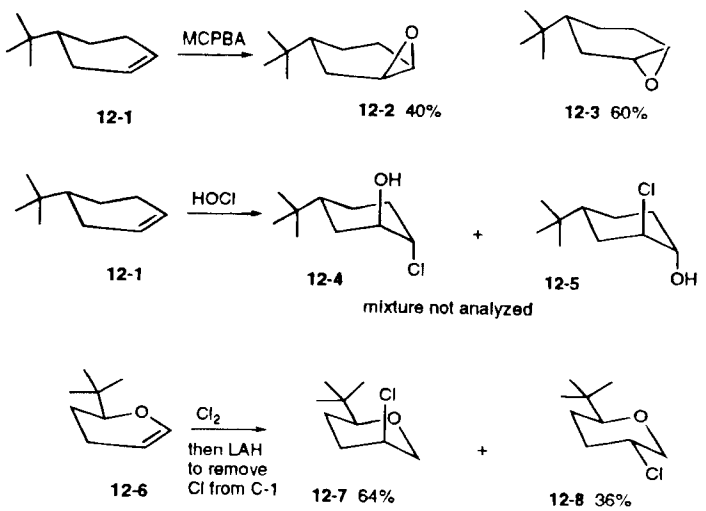
10-7 31%

oxymercuration, the two, diastereofacial intermediate mercurinium ions equilibrate rapidly, and the product stereochemistry is determined by which ion is more rapidly attacked by nucleophile. A third alternative can also be considered; if the intermediate onium species were to isomerize to the ring-opened carbonium ion **10-4** faster than nucleophilic trapping, the entrance of the nucleophile should be from the axial face. It must be noted that the same two products could be obtained from the intermediate **10-5** originating via equatorial attack. Johnson and Cieplak[9b] described experiments with peroxidation, mercuration, and osmylation with methylene cyclohexanes, which reveal weak axial preferences in the first two reactions and equatorial preference in the third. The effect of substituents at C(3) of the cyclohexane are in the direction rationalized by the Cieplak analysis. Osmylation is the exception presumably because it is certainly a different sort of mechanism. Again, the Frenking approach, computing the distortion of the HOMO π orbital, also predicts axial selectivity, and electrostatic arguments that describe ground states, although not yet reported for the methylene cyclohexane case, have been shown to predict the outcomes consistent with experiment.

Prior to the examples with moncyclic alkenes, research on steroids established the concept of diaxial opening of the bridged onium species or epoxides formed upon electrophilic attack of steroidal alkenes (the Furst–Plattner rule),[7] and because



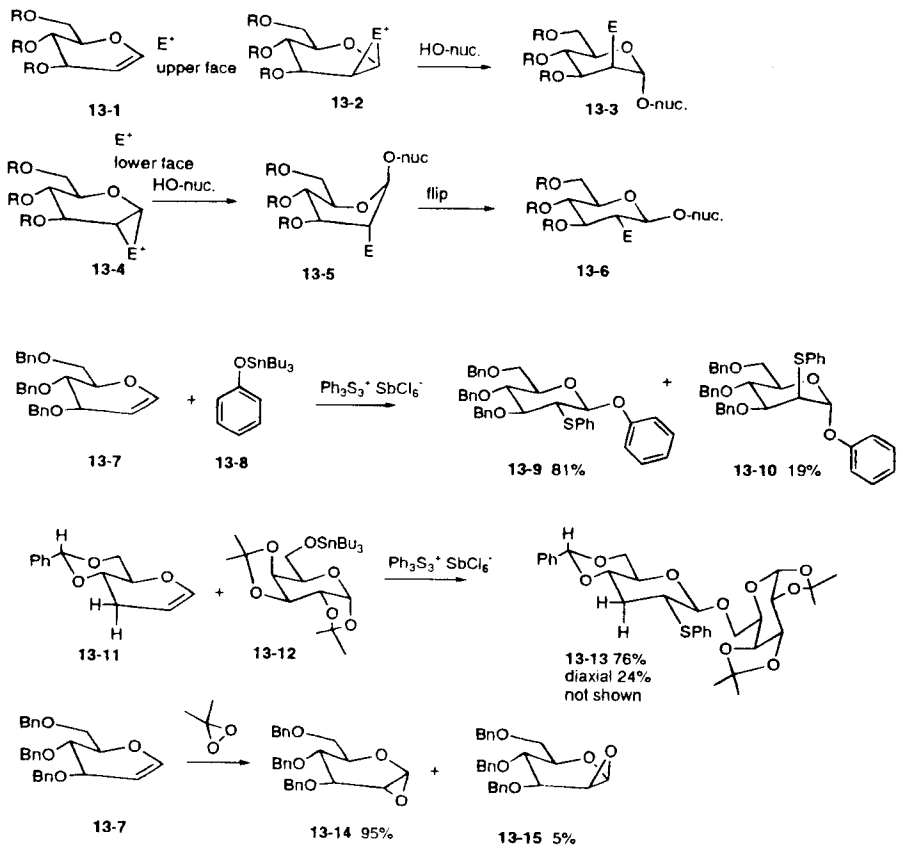
of the rigidity of most steroid frameworks, there was never much ambiguity as to which face had been attacked. Furthermore, straightforward steric effects were usually assigned as controlling the face selectivity (Scheme 5.11). However, it must be noted that in bromination, Br^+ attack at either face of cholesterol can yield the observed dibromide. Also, "diaxial" opening of either intermediate bromonium ion **11-2** or **11-5** (Scheme 5.11) can occur at either end, with either "Markovnikov or anti-Markovnikov" addition. Probably the isomer **11-3,** from Markovnikov opening of **11-2,** is not a kinetic product because the intermediate formation of a boat conformer is endothermic compared to the formation of chair form **11-4.** Diequatorial compounds derived from **11-3** are observed, but are not the products of kinetic control, and only appear after equilibration. Experimental differentiation between



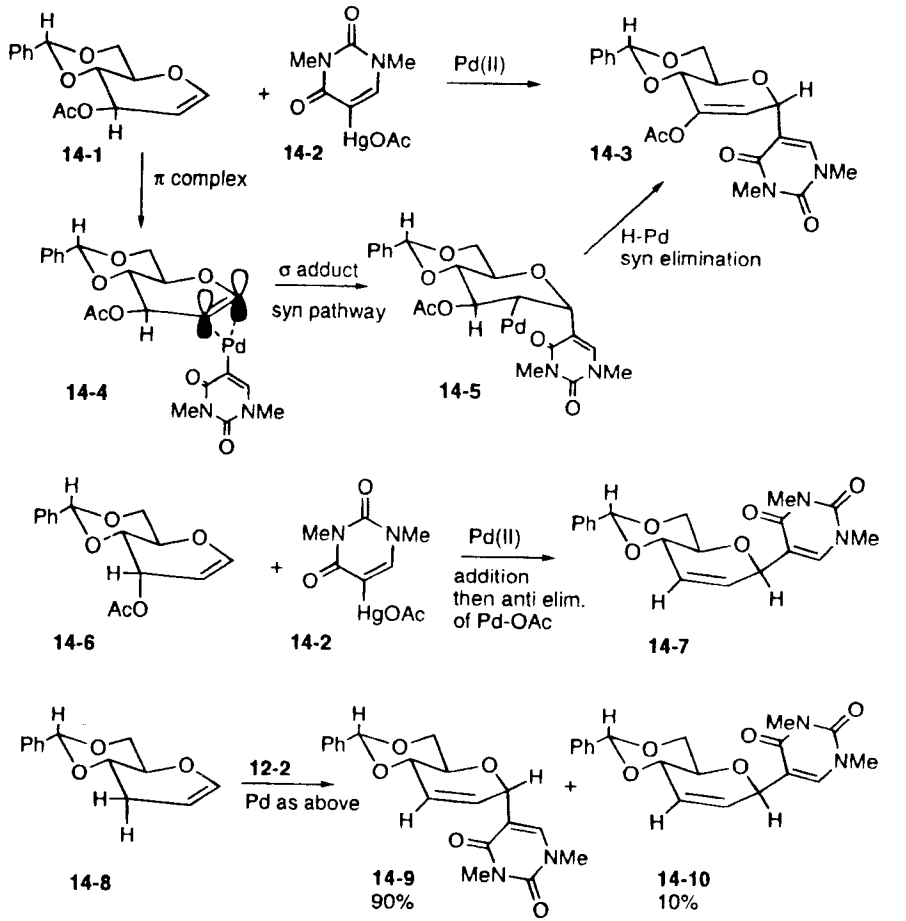
diastereofacial intermediates such as **11-2** and **11-5** can only occur when the three-membered ring is stable (epoxidation or cyclopropanation) or when electrophile and nucleophile are not identical. In the specific example shown, it is interesting that the diaxial opening of an epichloronium intermediate via a chairlike conformer (i.e., the Furst–Plattner mode via a stereoelectronic force) overrides the Markovnikov regiochemistry to yield chlorohydrin **11-6.** The observation also proves what most chemists have surmised, that the initial electrophilic attack on the double bond was from below the plane, presumably because of top-side hindrance by the angular methyl group. This outcome is the usual case in these steroidal systems.[28]

Similar conformational analyses can be expressed for simple cyclohexenes, and the literature does not reveal an obvious stereoelectronic facial bias in electrophilic attack for simple systems, as the examples (MCPBA,[29] HOCl[30]) in Scheme 5.12 reveal. The substitution of an oxygen in the ring effects a small change in the selectivity from cis (lower face) to trans (upper face),[31] but the reagents are not identical in these simple test cases so that any conclusions about inherent preference are suspect.

Facial selectivity in the electrophilic chemistry of glycals is observed in an unambiguous way because the tetrahydropyranyl ring oxygen confers a bias on the opening of onium intermediates so that the initial electrophilic bond formation is always at C(2) and the nucleophile is at C(1). Hence the detection of a product with a below-plane electrophile at C(2) implies a below-plane onium ion, which, in order to maintain a "diaxial" opening pathway, must proceed via a boatlike intermediate (**13-5**) before relaxing to the observed chair (Scheme 5.13). The ring opening via a boat, although endothermic compared to a chair process, occurs subsequent to the stereochemistry-establishing electrophilic attack. If the stereochemistry-determining step is not reversible, then "diequatorial" products, having arisen via a diaxial–boat sequence will be observed. Some authors depict a flipped-chair form in place of

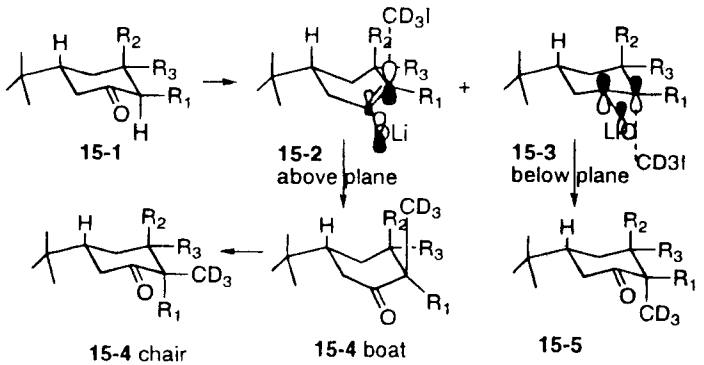


the boatlike intermediate **13-5.** This flipped chair would place all the remaining groups in axial positions, and furthermore, would not be possible when the 4 and 6 positions of the sugar are bridged in an acetal ring. Hence, this reviewer believes it is preferable to use boat forms as intermediates in these cases. In fact, in every example known to this reviewer, save electrophilic iodine species and selenium in some cases, electrophiles do attack glucals from below the plane. A typical example is shown in the conversion of **13-7** to products **13-9** and **13-10** with the diequatorial product favored.[32] When **13-11** is a substrate, below-plane attack is again favored in a case where neither "diaxial" opening nor initial attack of the electrophile can occur on a flipped-chair form because of the restriction of the bridging acetal. A further example of below-plane selectivity comes from Danishefsky's group, where dioxirane oxidation gives a very clean formation of the indicated epoxide **13-14,** which in subsequent chemistry is ring opened to yield diequatorial products.[33] This series of observations cannot be rationalized by the antiperiplanar C–H σ bond stabilization of the transition-state (Cieplak) scenario, which would predict exactly the opposite of what is observed. In fact, the only successful rationalization of the



below-plane activity comes from PPFMO work, which calculated that both *p* orbitals in glucal are polarized below the plane. For glycals with differing ring substitution patterns, the PPFMO results were in agreement with the observed selectivities of a D^+ and PhS^+ study. In order to obtain a correlation, the reasonable assumption was made that the D^+ attack did not involve bridging between C(1) and C(2) so that only the polarization of C(2) was considered. For the PhS^+ intermediate, the assumption was made that the attack did require bridging to both C(1) and C(2); hence polarization of both *p* orbitals was considered.[34] It would be interesting to know if an electrostatic field that would be negative below the plane would also account for the face selectivities observed.

An organometallic syn addition to glycals, shown in Scheme 5.14, displays the same selectivity as electrophilic attack.[35] In these examples, the face selected by the Pd is revealed by the ultimate attachment of the pyrimidine nucleophile, since the Pd is lost in the ultimate step of the reaction. It is interesting that the face selectivity

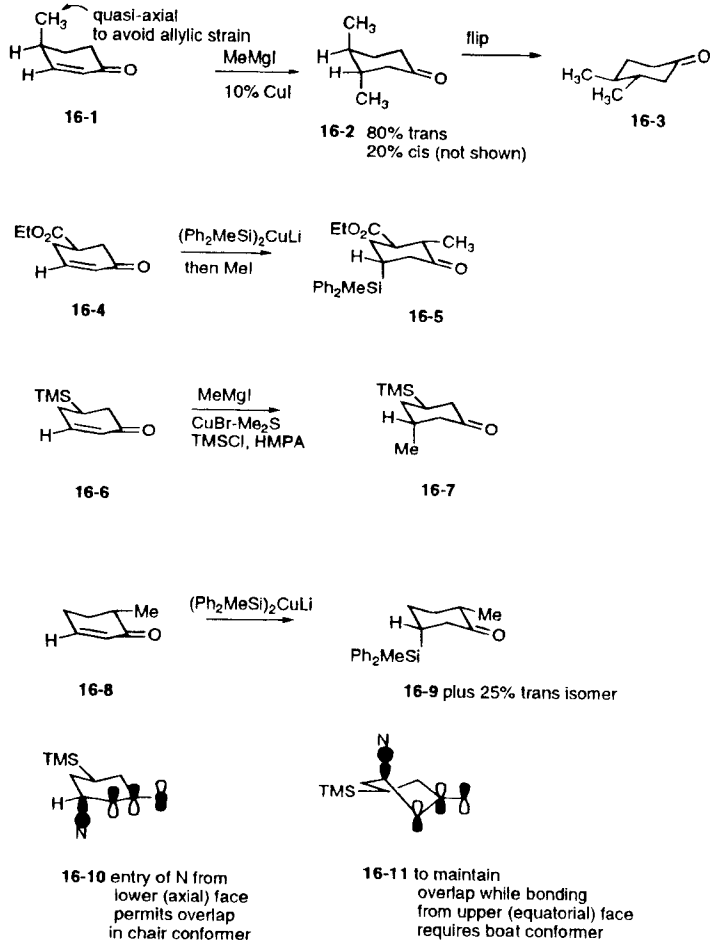


R1	R2	R3	15-4	15-5
H	H	H	32	68
Me	H	H	17	83
H	Me	H	4	96
H	H	Me	75	25

of alkene attack cannot be entirely due to a steric or electronic effect of the allylic group since in glycal **14-8,** an allylic acetate is not present, yet the bottom face attack is still preferred. Although the exact orbital details of the organometallic transfer via Pd bonding to an alkene are not necessarily identical to the electrophiles described in the preceding paragraph, it appears that the polarizing forces within the glycal influence face selectivity independent of the attacking species.

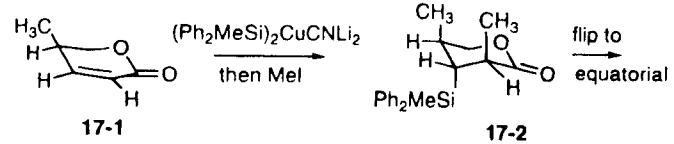
Electrophilic attack of cyclohexanone enolate species has been an important reaction for synthetic chemists. In simple, monocyclic enolates, there is a small preference for attack leading to axial products. The standard explanation for this result is that bonding in the transition state for axial product **15-3** (Scheme 5.15) leads naturally to a chair conformer, while the maintenance of overlap leading to the eventual equatorial product proceeds via a twist–boat **15-2** of higher energy. Since the selectivity is quite low, the argument follows that the transition state is so early that the differences between the two paths in their ring geometry is not very influential.[36] Whereas the effect of an added methyl on the enolate or the vicinal axial methyl are easily rationalized, it is interesting and somewhat puzzling that vicinal substitution with an equatorial methyl reverses the face selectivity. This equatorial effect is reminiscent of the radical additions described earlier.

Nucleophilic addition to double bonds conjugated to carbonyl groups is an important synthetic operation. In the cyclohexenone series, the influence of substituents at the allylic position [C(4)] is considered to be steric; hence the incoming group is trans to the group (Scheme 5.16), as shown in **16-1.** It is noteworthy that when substituents at carbons 5 and/or 6 are present, the incoming group in organometallic additions, with few exceptions, enters from the "axial" face. This class of reactions seems to be the most highly "stereoelectronically" controlled series in carbocyclics.[37–40] The rationale has been that, independent of the details of the organometallic group transfer, the bond-forming step at the β-carbon requires

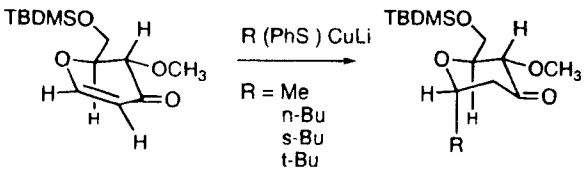


maximum overlap with the residual π system as the β-carbon pyramidalizes. As the pyramidalization occurs toward axial product, the ring system can remain chair-like. As the geometric reorganization develops for the group entering from the soon-to-become equatorial face, the ring must become boatlike, a higher-energy form that is less likely to offer a lower-energy transition state. In the cases shown, the electronegativity and polarity of the groups at 5 and 6 are diverse, and it seems unlikely that a polarization or electrostatic argument would be useful in organizing these data.

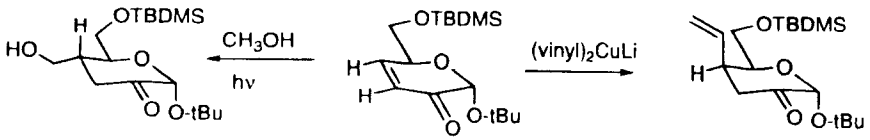
When the enones are part of a pyranoid ring, high selectivity of organometallic addition is also observed.[41] In an exception to the axial attack "rule," the photoaddition of methanol is equatorial. The reactive species is presumed to be the $HOCH_2\cdot$ free radical, but it is not easy to rationalize its addition to the unaltered unsaturated ketone to give a stereochemical outcome opposite to other reagents.[42] An explanatory



17-1 17-2



17-3 17-4



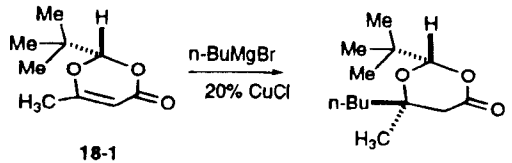
17-7 88%
axial hydroxymethyl
(not shown) 12%

17-5 17-6

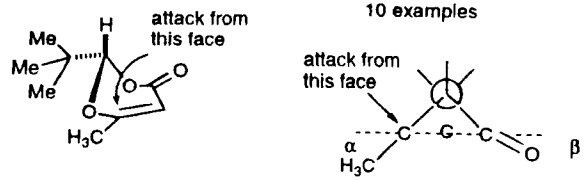
theoretical analysis of the selectivity in this reaction would be well received, (Scheme 5.17).

Seebach has studied the selectivity of addition in the interesting heterocyclic systems shown (Scheme 5.18).[43] His explanation for the observed selectivity arises from a correlation with a pyramidalization of the π system. Careful analysis of X-ray crystallography data on a series of related dioxenones revealed that the carbon undergoing nucleophilic addition was not planar, but was pyramidalized in the range of 0.9° to 2.6° in the direction from which attack occurs. This is sketched in **18-4,** where the pyramidalization of the reacting carbon is conceived as being opposite in direction to the deviation from planarity of the attached methyl group. Seebach suggested that this distortion away from planarity reflects the orbital forces that favor a transition state with attack at the lobe of the antibonding orbital "pointing" in the direction of the pyramidalization. It is interesting that the direction of pyramidalization is the same as the direction of polarization that comes from PPFMO theory.[16] Would this direction also be reflected in a Frenking orbital density analysis or an electrostatic calculation? Are all these different methods of explanation really finding the same molecular effect?

In related work, the same stereochemical outcome was reported for the dioxinone with a methyl group in place of the quasiaxial hydrogen.[44] However, dioxinones whose "sofa" structure is similar to the Seebach compounds showed completely opposite face selectivity. The X-ray data did not reveal the small pyramidalization,

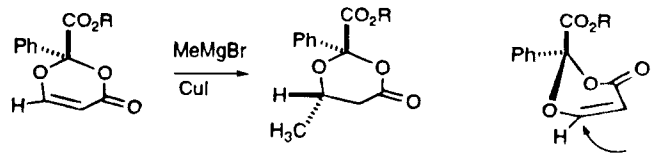


18-1 18-2
10 examples



18-3
note large group is far removed from reacting center and does not interfere

18-4
note α and β are not 0° and deviate opposite to small group at acetal center.



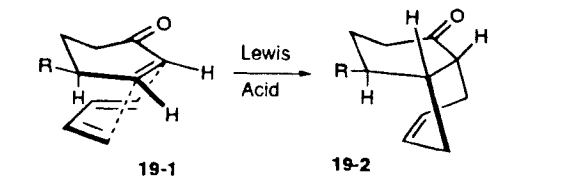
18-5
R = l-menthyl
R = Me

18-6
7 examples

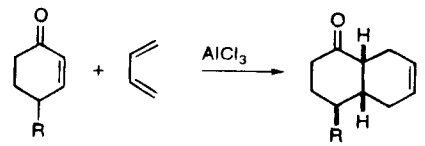
18-7
note that axial CO_2R is much larger than H in **18-3** above: hence attack is now from below

and the authors propose that the outcome can be explained simply by the organometallic approaching from the less hindered face; in this series, the susceptible face is opposite the axial alkoxy carbonyl group.[45] The two systems cannot be easily compared because the alkoxycarbonyl group has a different polarity from the proton or methyl in the other examples. Thus one cannot conclude whether polarization, pyramidalization, or simple steric arguments will be most satisfactory for explaining these results.

Diels–Alder cycloaddition to simple cyclohexene dienophiles has been important in the synthesis of decalin ring systems ever since Lewis acid catalysis was first shown to improve the dienophilicity of cyclohexenone. There is a recent thorough review of the field that includes a discussion of the effects of substituents on the face selectivity.[46] The working hypothesis has been that the compact endo transition state **19-1** (Scheme 5.19) is less congested when the diene approaches anti to the cyclohexenone substituent. When the 4-substituent is methyl or acetoxy, the selectivity is greatly reduced. The exception to this generalization is that of the 4-TBDMSO derivative **19-7,** which undergoes cycloaddition with very high syn selectivity.[47]

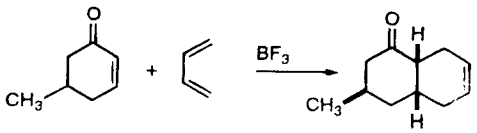


19-1 19-2



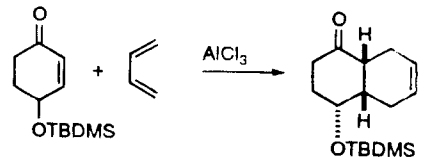
19-3
R = Me
R = t-Bu

19-4
R = Me 55% anti
R = t-Bu 100% anti



19-5

19-6
96% anti

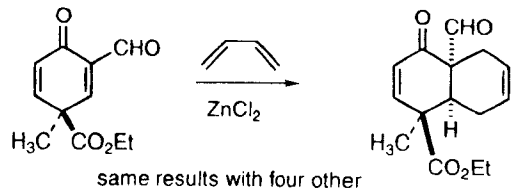


19-7

19-8
6% anti
76% syn

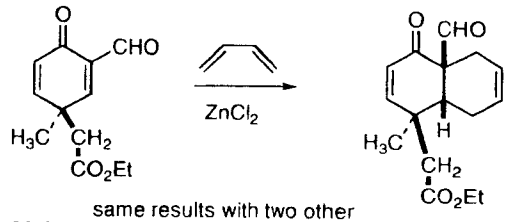
Perhaps this result hints that the steric rationale is too simple, and that a stereoelectronic effect can be uncovered if the electronegativity or polarity of substituents at the 4, 5, and 6 positions of cyclohexenones is systematically varied. Since in essentially every successful cycloaddition a Lewis acid catalyst is used, it comes as no surprise that the extent of face selectivity is often dependent on catalyst choice.

Cyclohexadiene derivatives seem to be sensitive to stereoelectronic effects, as illustrated in Scheme 5.20. No convincing explanation of the observed selectivities has been presented.[48] Since Diels–Alder reactions of the type shown are essentially nonpolar, an orbital polarization scheme or a transition-state stabilization model will probably be preferred over that of a ground-state electrostatic effect. Interestingly, powerful effects have been observed in pyranoid, unsaturated carbonyl dienophiles, which must be stereoelectronic in nature (Scheme 5.21). Here, the limited data set suggests that an undiagnosed effect exists for compounds **21-5** and **21-6** in that



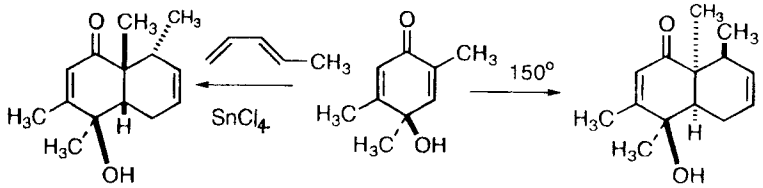
20-1 20-2

same results with four other simple dienes;also Lewis acid or thermal reactions give same face selectivity



20-3 20-4

same results with two other simple dienes;also Lewis acid or thermal reactions give same face selectivity



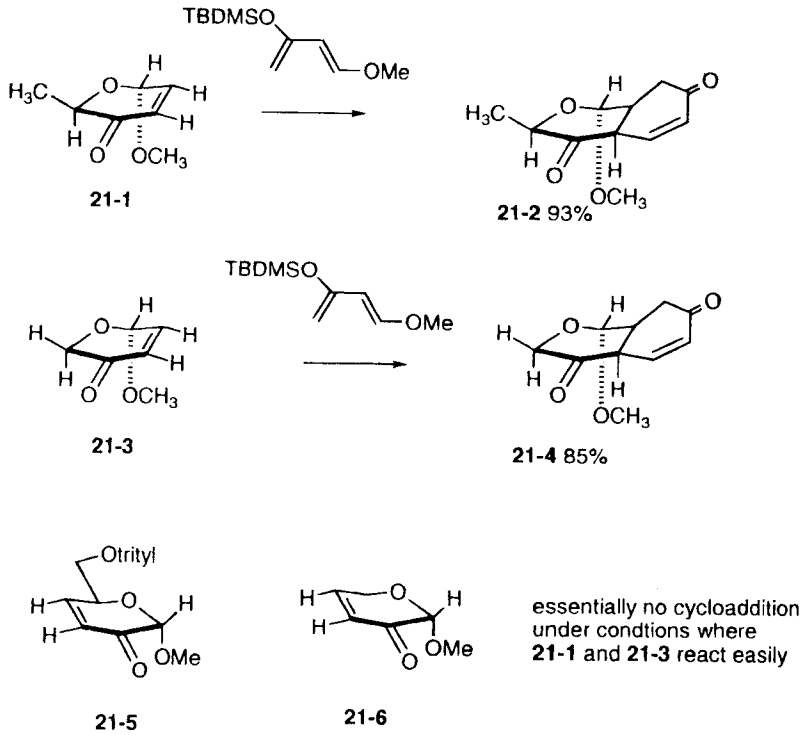
20-7 20-5 20-6

reaction at both faces is quenched.[49] One wonders what the effect would be of an equatorial alkoxy group at C(2)?

Inverse-electron-demand cycloadditions have also been observed in unsaturated pyrans.[50–52] In the examples shown (Scheme 5.22), the below-plane selectivity obtained might be stereoelectronic and linked to the same forces that favor the below-plane electrophilic attack noted in Scheme 5.13. Or the compact transition state of the apparent Diels–Alder cycloadditions may be sensitive to the same steric influences described for the cyclohexenones. Since both forces would operate in the same direction, the extremely high selectivities observed are understandable.

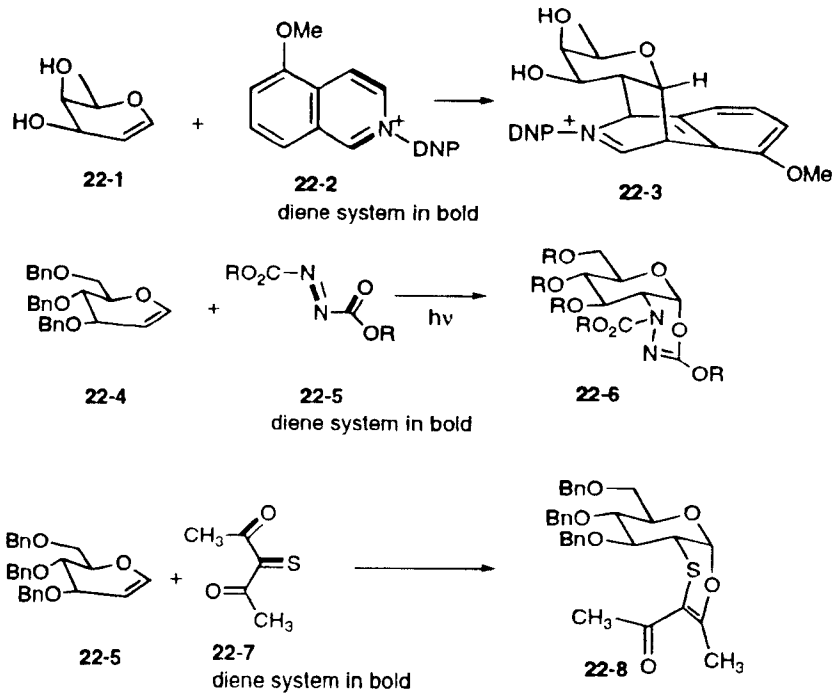
5.5. Anomeric Effect

The grandfather of all stereoelectronic effects is the anomeric effect.[53–55] It was first recognized in the conformational analysis of carbohydrates, where pyranose



diastereomers with their electronegative groups at the anomeric carbon being axial were found to be more populated or more stable than would have been predicted on the basis of the groups' *A* values as determined in cyclohexanes. Before an analysis of the causative forces of the anomeric effect can be undertaken, it is necessary to have a consistent definition of "more stable" for these axial groups. Although the following discussion is limited to tetrahydropyrans, many of the concepts can be generalized to other heterocycles and have been thoroughly reviewed by Juaristi.[53]

It has been recognized for some time that the energies of axial/equatorial preferences of groups in heterocycles could not be directly equated with cyclohexane *A* values.[56] The bond lengths and angles of heterocycles are not identical to those in cyclohexane; hence the nonbonded repulsions (or attractions) of axial groups in two different ring systems cannot be the same. Thus, to estimate the actual stereoelectronic effect of axially disposed electronegative groups in heterocycles, it has become customary to scale the *A* value of the group from cyclohexane to a new value for the heterocycle in question.[57] The scaling method simply assumes that the concatenation of bond angle and bond length adjustments in the heterocycle is essentially constant for the ring, compared to cyclohexane, independent of the of the axial functions. Then the proportionality constant that relates cyclohexane to the heterocycle is determined by comparing *A* values of simple alkyl groups and



other nonpolar carbon functions assumed to have no stereoelectronic effect. Thus a plot of *A* values in the heterocycle versus cyclohexane for these simple groups is assumed, in fact, to represent the scaling factor and predicts the *A* value of a group on the heterocycle if there were no stereoelectronic effect. Then the magnitude of the stereoelectronic effect is represented by the observed deviation from the predicted value of the energy corresponding to the observed axial/equatorial equilibrium composition of the functional group in the heterocycle. As graphically represented in Figure 5.3 for anomerically substituted tetrahydropyrans, the region below the line corresponds to greater axial preferences (i.e., the anomeric effect), whereas the region above the line reveals groups with greater than expected equatorial preference (i.e., the reverse anomeric effect).

With this operational definition it can be safely concluded that groups such as alkoxy, nitro, carbomethoxy, carboxamide in DMSO and dimethylphosphonate do have an unusual axial prefence in tetrahydropyrans that require some explanation. It is interesting that the scaling factor for tetrahydropyranyl *A* values has been used to rationalize the conformational behavior of idose and altrose derivatives that seemed inconsistent when cyclohexane *A* values had been applied.[58]

The two major conceptual approaches for explaining the anomeric effect and related phenomena are (1) a *stabilizing* effect of bonding interactions between *n* electrons on the oxygen (or other heteroatom) and the σ^* orbital of the bond connecting the electronegative axial bond and the anomeric carbon[59] and (2) a

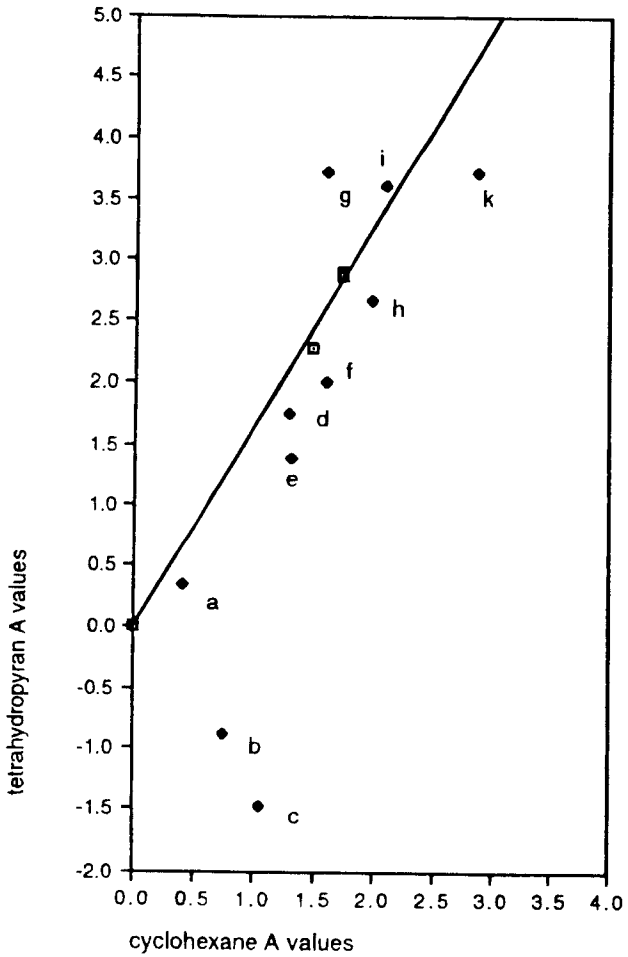


Figure 5.3. A correlation plot of *A* values of groups on cyclohexane versus tetrahydropyran. The line was created from data points for H, vinyl, CH_3, and CH_2OH. Legend for off-line points: larger anomeric effects, *b* = OMe, *c* = NO_2, smaller anomeric effects, *e* = CO_2Me, *f* = $CONH_2$ in DMSO, *h* = $(MeO)_2PO$, *k* = phenyl (pyridinium?), very small or no effect, *a* = ethynyl, *d* = Me_2N, *i* = imidazolyl H^+, reverse anomeric effect, *g* = $CONH_2$ in $CDCl_3$.

destabilizing dipole–dipole repulsion between the the two electronegative atoms and their associated electron pairs (Figure 5.4).[60] The bonding electron pair in rationale (1) is often depicted as coming from an axially oriented sp^3 hybrid on oxygen, in spite of a body of evidence that suggests that the four electrons on oxygens of this type are distributed between an orbital of predominantly *p* character and one of *s* character (see the following). Most workers in the area accept concept (1) since bond shortening of the internal C–O bond and lengthening of the exocyclic C–O bond consistent with the hypothesis has been reported for some, but not all,

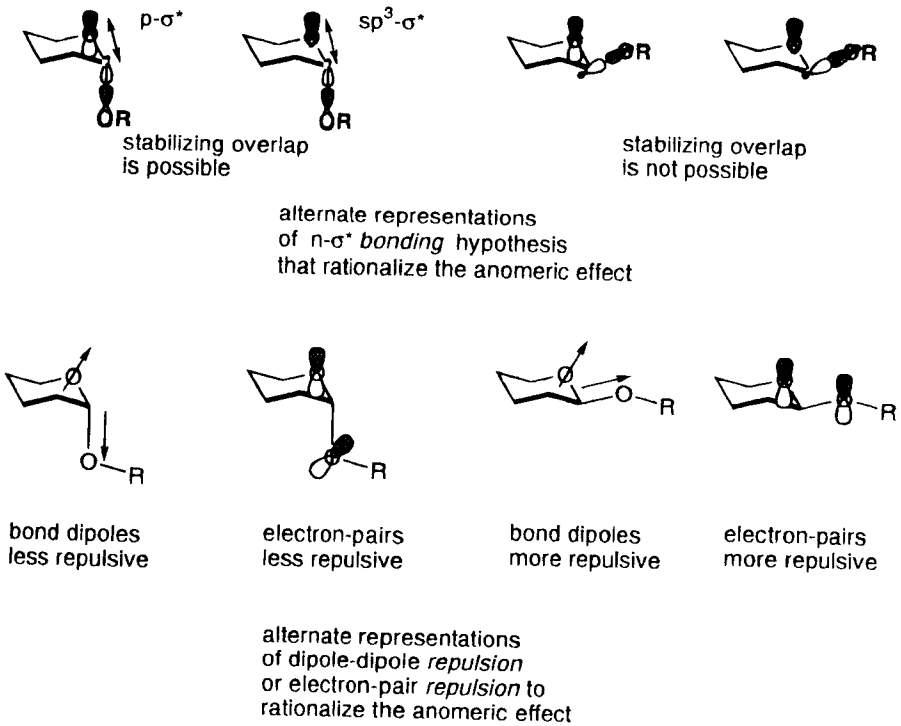
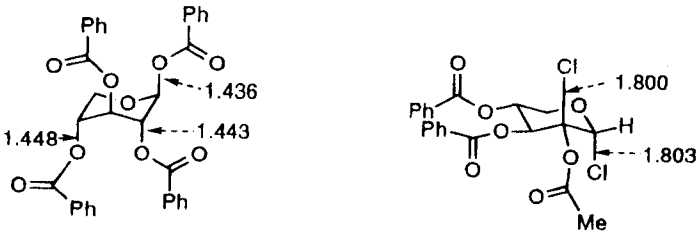


Figure 5.4. Representations of the principal rationalizations of the anomeric effect: First row, bonding; second row, repulsion.

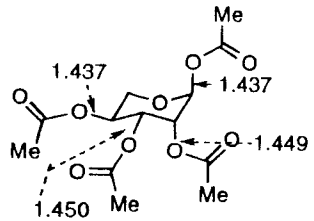
crystal structures.[61] However, Box has argued cogently that bond lengthening and shortening are also observed for bonds not at the anomeric carbon, thus casting doubt on the existence of significant n–σ^* bonding interactions as being confirmable by X-ray data. A representative sample of data (Figure 5.5), taken from the Cambridge Crystallographic Database by Box, illustrates the point that anomeric bonds are not unusual and differences observed are typical for all axial bonds versus equatorial bonds independent of their proximity to the ring oxygen.[62] To focus on one specific example, the axial anomeric bond in TALYXP is longer than the corresponding equatorial bond in TAXYLR, but it is not longer than a "normal" axial bond. Hence no special anomeric bond lengthening can be invoked as an indicator of n–σ^* bonding. It is interesting that high-level quantum-mechanical calculations for simple systems do confirm the stability of the conformers where the anomeric effect is found. But, when the molecular orbitals corresponding to the conformer of interest are analyzed so as to dissect out the specific bonding interactions, the results are *not* powerfully confirming for approach (1), the most widely accepted explanation.[63]

It is noteworthy that the concept of unfavorable dipole–dipole interaction or electron-pair repulsions explains much of the data related to the anomeric effect

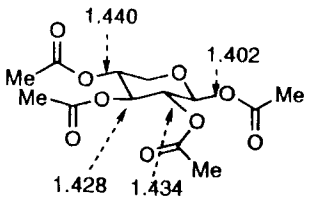


OBZXYP10
note axial anomeric CO is no longer than other axial CO

TBCXPC
note anomeric Cl is no longer than axial Cl which is geminal to electron-poor oxygen



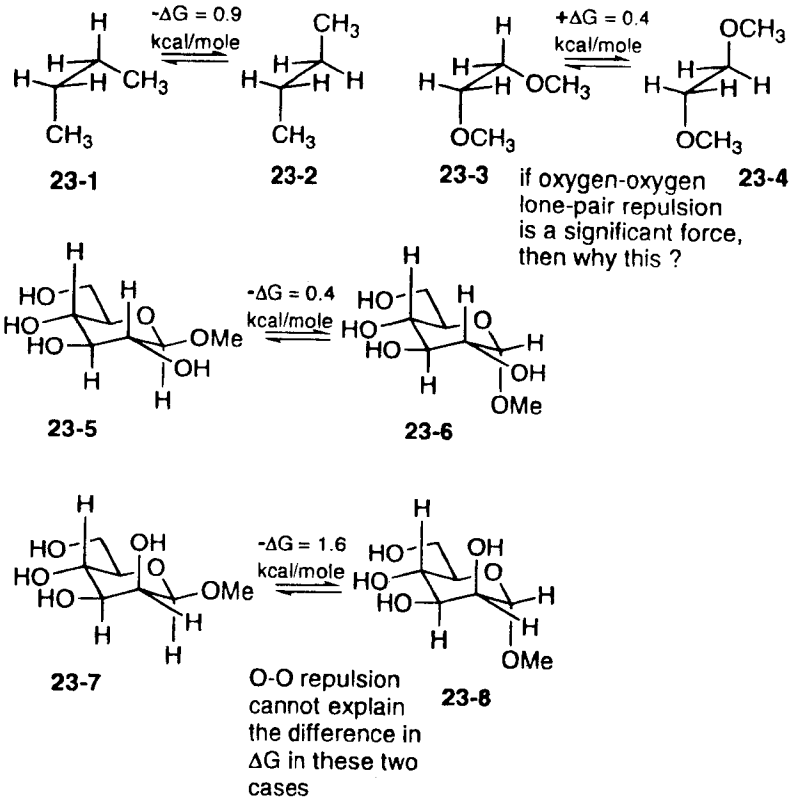
TALYXP
note axial anomeric CO is no longer than other axial CO but is longer than equatorial anomeric epimer TAXYLR



TAXYLR
note short equatorial anomeric CO even though n-σ* exo-anomeric effect can't be invoked

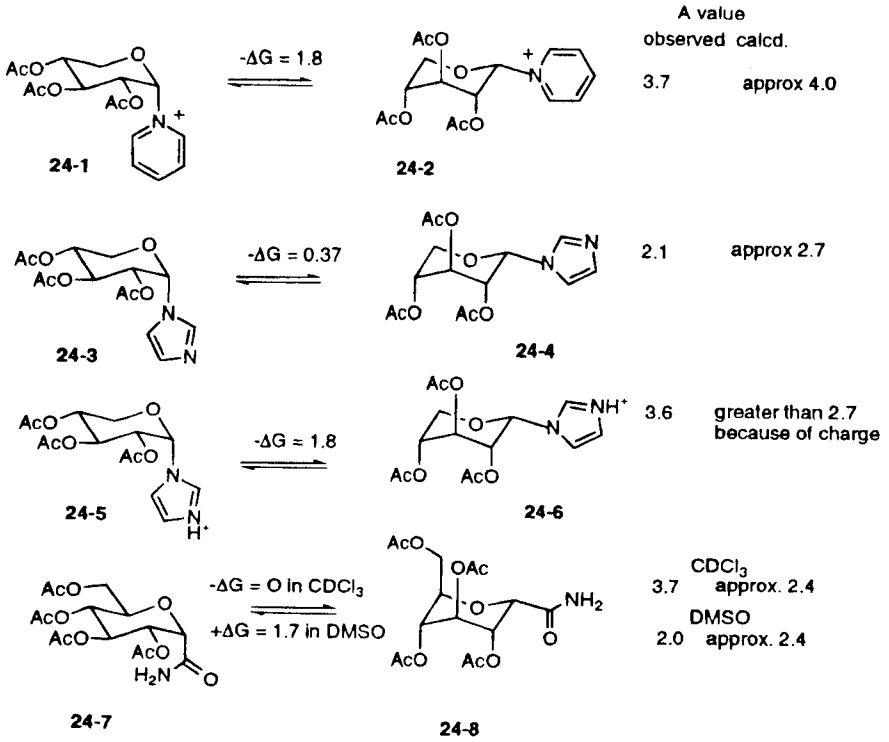
Figure 5.5. Bond lengths of four carbohydrates obtained from the Cambridge Crystallographic Data Base.

One synthetically useful phenomenon that is nicely explained is the increased nucleophilicity of the anomeric β-alkoxide of pyranose sugars compared to the α-alkoxide.[64] Two very recent studies, one involving an experimental comparison of gas-phase and solution thermodynamics of a 2-methoxytetrahydropyran,[65] and the other a Monte Carlo study of solvent effects on the anomeric equilibrium,[66] also conclude that "a large component of the anomeric effect is the electrostatic interaction between the C–O dipoles. . . ." A puzzle that arises with the otherwise useful and general idea of dipole–dipole repulsions as a complete explanation is that the forces are not clearly demonstrable in a pivotal case where the anomeric effect cannot be invoked. Thus, 1,2-dimethoxyethane, a system where, a priori, one would predict that electron–electron repulsion would provide an enhancement of the anti conformer population compared to butane, actually favors the gauche conformation.[67] With this experimental fact in hand, it is hard to rationalize as simply a repulsion effect the well-known observation that the axial preference for mannose glycosides is greater than the comparable glucose case (Scheme 5.23). The generally accepted argument is that a gauche repulsion is avoided in the mannose case, but not in the glucose case. A



adjustment of this reasoning is required to become consistent with the dimethoxyethane data.

Another interesting data set that is not entirely consistent with the oxygen nonbonding electron-pair repulsion theory comes from work of Pierson and Runquist.[68] Their experiments with alkoxytetrahydropyrans showed that increasing the electron-withdrawing power of the alkoxy group increased the axial conformer mole fraction. The electron-withdrawing substituents would *decrease* the electron density on the alkoxy oxygen, hence decreasing any lone-pair repulsions. On the other hand, the electron-withdrawing alkoxy substituents would increase the dipole moment of the bond, thus increasing the dipolar repulsions in the equatorial conformer. Since the electron-withdrawing substituent would also lower the energy of the σ* orbital invoked in the *n*–σ* model, and stabilize the axial conformer, the data can be construed as supporting the bonding model. Similar conclusions buttressing the bonding model can be drawn from the data on the anomeric effect of para-substituted phenoxytetrahydropyrans. Thus Ouedraogo and Lessard showed that the magnitude of the axial preference of the phenoxy group was directly proportional to its pK_a; that is, phenols with electron-withdawing groups had a greater axial preference than phenols with electron-donating groups.[69] Most recently, Perrin has undertaken a



closely analyzed comparison of the anomeric effect of 2-methoxy-1,3-dioxane and 2-methoxy-1,3-dimethylhexahydropyrimidine and has concluded, for those systems, that the dipole–dipole repulsion effects are more significant than the n–σ^* bonding effect.[70]

Recently, Kishi and Houk have postulated the existence of a force similar to the anomeric effect for O–C–C–C fragments. Kishi's work on C-disaccharides unveiled conformational preferences quite analogous to those in O-disaccharides related to the exo-anomeric effect.[71] Houk has performed MO calculations that also find these same preferences.[72]

5.5.1. Reverse Anomeric Effect

There has been a small data set of pyranose derivatives whose conformational equilibria, shown in Scheme 5.24, traditionally have been taken as examples of the existence of a "reverse" anomeric effect. It is assumed that the group at the anomeric carbon, in its effect on the conformational population, is exerting a force "larger" than its steric, mechanical force is expected to be (i.e., larger than its "normal" A value), so as to stabilize the conformer where the other groups are axial. In a recent paper, Perrin has shown that the reverse anomeric effect does not exist for the simple

protonated amino group.[73] He further argues that the NMR data used to determine the equilibrium constants for the orignal systems is suspect so that the evidence for the reverse effect is inconclusive.[74] The problem with the pyridinium salt data is that the cyclohexane A value for pyridinium is not known. A simple approximation would be to assume a range between 2.5 and 3 kcal/mole comparable to that for phenyl. Hence its value in a tetrahydropyran, using the generally accepted amplification factor of 1.5,[75] would be approximately 3.7 to 4.5 kcal/mole. Since the observed $-\Delta G$ favoring the equatorial derivative in this case shown is about 1.75 kcal/mole, one can derive the A value for pyridinium as 3.7 kcal/mol, calculated by assuming OAc–OAc axial of 1.5, OAc–OAc gauche of 0.35, OAc–H axial of 0.45. Thus there is no necessity for invoking a reverse anomeric effect for the pyridinium group, and, in fact, it might have a small "normal" anomeric effect.

The conversion of the imidazole pyranoside **24-3** to its salt form **24-5** changes the apparent A value of imidazole from about 2.1 to 3.5 kcal/mole for the imidazolium salt. We estimate that neutral imidazole should have an A value of about 2.7 kcal/mole in tetrahydropyran since a PCModel calculation[76] in cyclohexane suggests a value of 1.9, and we then apply the amplification factor of 1.5. Hence there may be a normal anomeric effect for neutral imidazole. The reverse anomeric effect is supposed to become operative in the protonated species since it has been assumed that protonation does not change the size of the group. However, this assumption of "no size change upon protonation" is suspect. Certainly the counterion and the required solvation of the positive charge could quite easily affect apparent group size, as Perrin has shown. An examination of the standard table of A values for cyclohexanes[3] reveals that, in every case, the charged partner of a neutral and charged pair is larger, for example, NH_2 1.5, NH_3^+ 1.9; Me_2N 2.1, Me_2NH^+ 2.4; CO_2H 1.35, CO_2 1.9; SH 0.9, S^- 1.3 (kcal/mole). These data have been explored further, including the differences between cationic and anionic solvation shells by Perrin for the cyclohexane series.[77] Thus the existence of the "reverse anomeric effect" has not been properly established in the imidazole series.

Interestingly, the same absence of baseline data is found in the carboxamide study, where a reverse effect is claimed.[78] Here the apparent A value of the carboxamide in the pyranose **24-7** must be about 3.5 kcal/mol in chloroform solvent, whereas a simple PCModel calculation for carboxamido in cyclohexane is 1.6, which could be extrapolated to 2.4 for a tetrahydropyran. In the hydrogen-bond-accepting DMSO, the apparent size drops to about 2 kcal/mole. It appears that some special hydrogen-bonding features are affecting the observed equilibria, and the parent structures in the cyclohexane and tetrahydropyran series must be studied before firm conclusions can be drawn about the reverse anomeric effect of the carboxamido group.

5.5.2. Kinetic Anomeric Effect

Perhaps the area of greatest confusion about the anomeric effect is the interaction of the nonbonded electrons of the oxygen in bond-forming and bond-breaking reactions at the anomeric carbon. The most common picture used by organic chemists

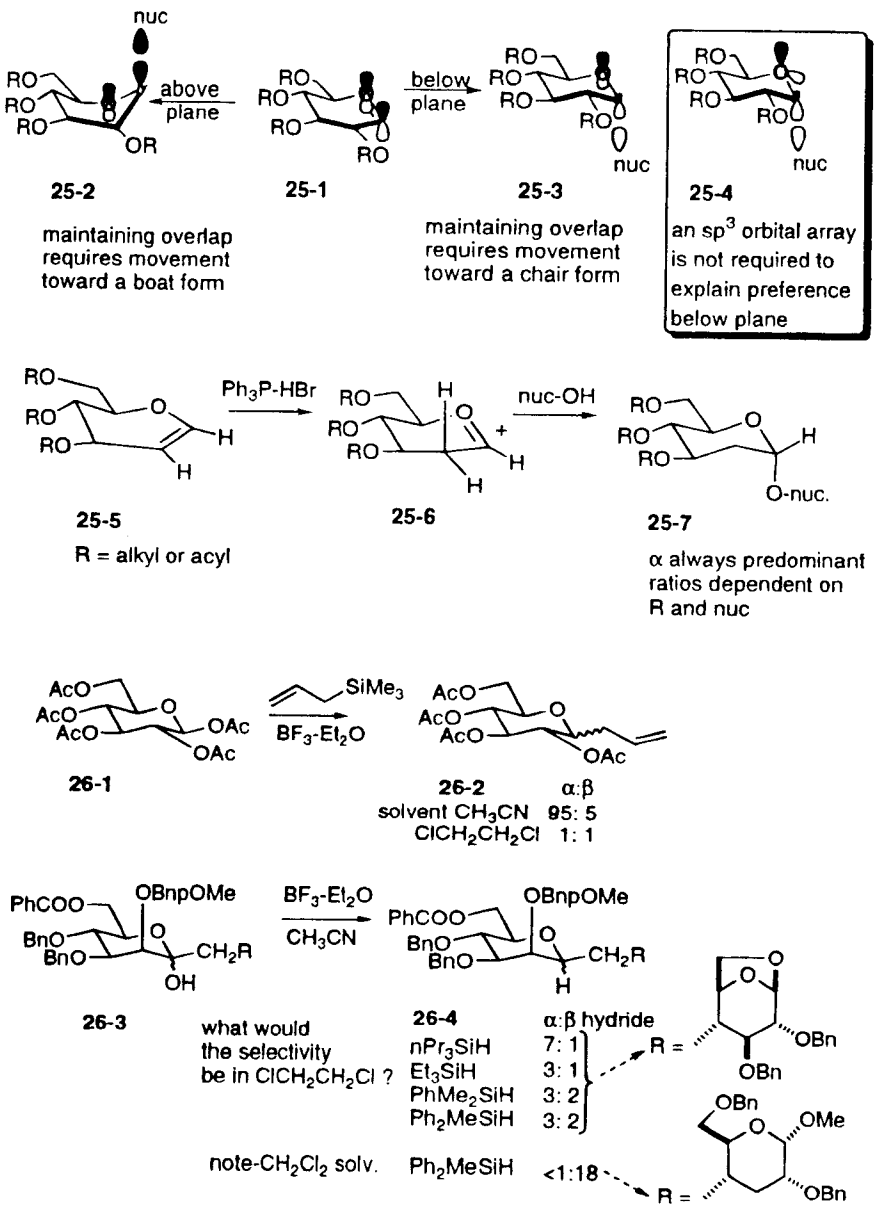
to visualize these interactions is that of an axial-like pair of electrons participating in an antiperiplanar manner with an electron-deficient incipient bond in the transition state for a reaction.[1] Thus the conventional reasoning is that a reaction in either direction, bond forming or bond breaking, must require an axial approach (departure) antiperiplanar to the putative axial sp^3 orbital.

It is certainly true that, in the ground state, the two orbitals bearing the four nonbonded electrons on an ether oxygen are really degenerate in energy and the postulation of two equienergetic sp^3 orbitals or one low-lying *s* orbital and one higher *p* orbital is equivalent since there is just a volume of electron density on the oxygen in the space where there are not bonds. The problem with the convenient picture of two degenerate sp^3 orbitals is that both theoretical work and photoelectron spectroscopy data reveal that when an electron is removed from the system, the more stable cation–radical state clearly does not have sp^3 orbitals, but has a higher-energy *p* orbital with one electron and a low-lying *s* orbital with two electrons.

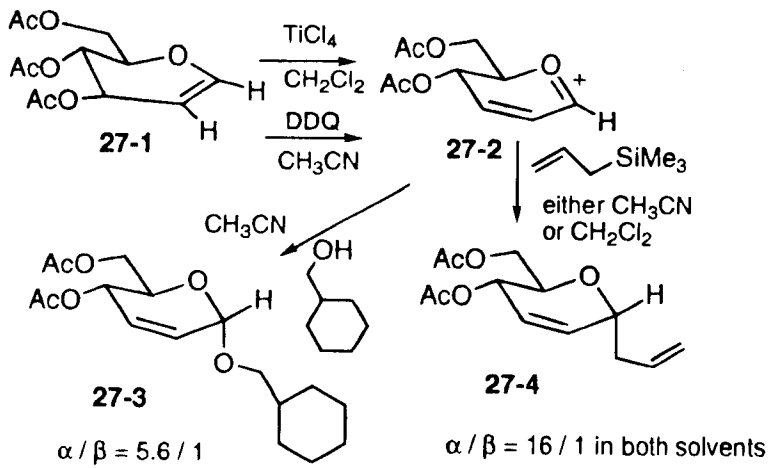
It seems reasonable to assume, therefore, that in transitions from ground states to electron-deficient states, even if an electron is not fully expelled as in the cation–radical case, the degeneracy in the distribution of the original four nonbonded electrons must be lifted in the direction of a *p* orbital, *not* in the direction of an orbital with *s* character.[79] Hence, the simplest model of bonding is that when the system is electron deficient, either in breaking a bond at the anomeric center or forming a bond, the interacting orbital on the oxygen is a *p* orbital and can overlap with forming or breaking bonds either above or below the plane. An analysis similar to this has also been published by Sinnott.[80]

Clearly, the fundamental reason for the so-called antiperiplanar lone-pair effect has nothing to do with *anti* periplanarity. It is true that the newly forming bond, as shown in **25-2** and **25-3** (Scheme 5.25) should be collinear with the orbital having *p* character, but the axial preference must emerge from the fact that collinear attack at one face leads toward a boat structure, which is higher in energy than collinear attack on the other face, where a chair conformer is forming. One unambiguous example of this preference is acid-catalyzed glycosidation (in the absence of participating groups) via protonation of glycals, shown in **25-5** to **25-7** via **25-6.** The authors were careful to rule out the possibility that there had been equatorial attack by triphenylphosphine followed by displacement with the alcohol to give the observed axial attack.[81]

This axial preference is found in other types of ionic reactions at the anomeric center, including C-glycoside formation (**26-1** to **26-2,** Scheme 5.26) via allyl silane alkylation[82] and via hydride transfer (**26-3** to **26-4**).[83] In a very suggestive series of experiments, Giannis found that the stereoselectivity of allyl silane alkylation was dependent on solvent. Thus, only in acetonitrile was the high axial selectivity obtained in the glucose series. Interestingly, the axial hydride transfer was also performed in acetonitrile. Furthermore, the selectivity of hydride transfer to **26-3** is very sensitive to the size of the alkyl groups on the hydride-bearing silane. To cloud the situation further, when the C-glycosidic moiety of **26-3** is changed from a bridged sugar to an unbridged case and methylene chloride is the solvent, the stereoselectivity of hydride transfer is reversed. This suggests that stereoelectronic



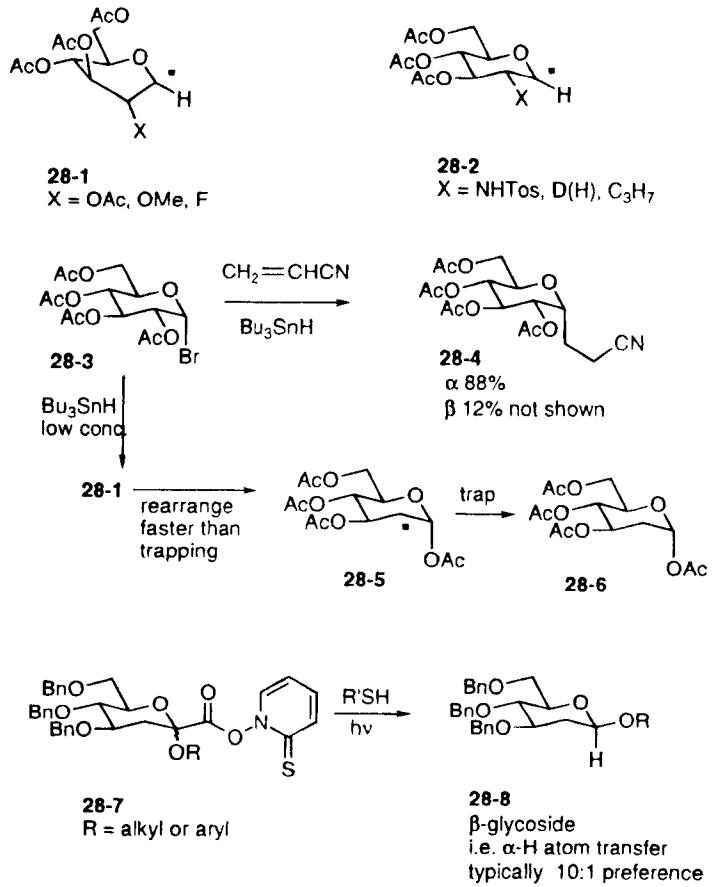
effect for axial attack at anomeric oxonium ions is very weak. Recently, Schmidt has suggested that acetonitrile actually reacts with anomeric carboxonium ions to form equatorial isonitrilium species, which could then undergo displacement with inversion to give the observed axial attack.[84] One reasonable explanation of the solvent effect can be that an equatorial isonitrlium salt is the most stable and does



not revert to an axial isomer, which is the kinetic product at very low temperature.[85] A second plausible assumption is that axial and equatorial isonitrilium ions in acetonitrile solvent are in rapid equilibrium; thus the observation of axial attack implies that the equatorial isonitrilium intermediate reacts more easily than the axial in the allyl silane transfer step or the silyl hydride transfer. This would be a novel stereoelectronic effect if true.

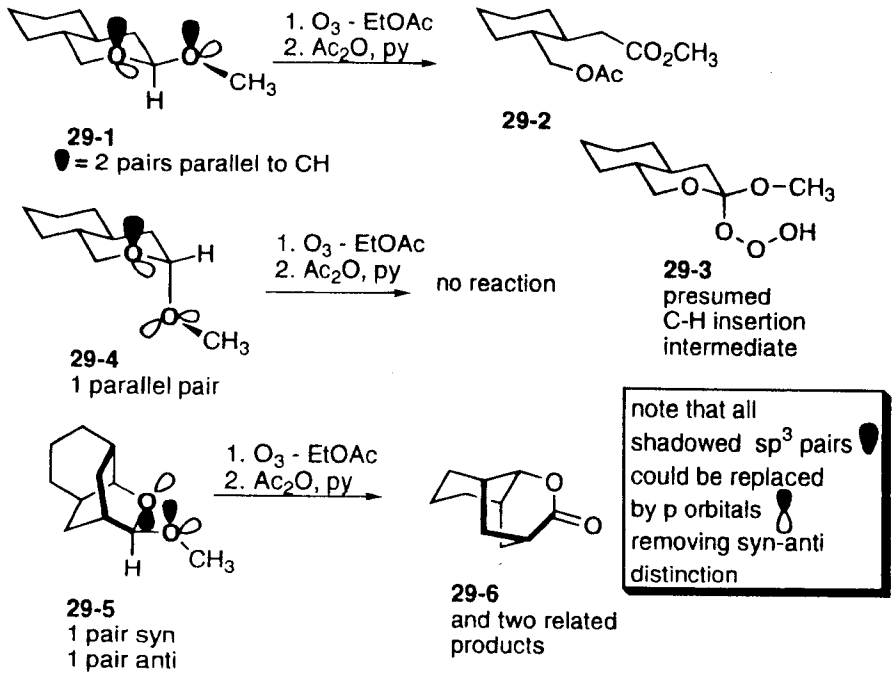
When the unsaturated oxonium ion **27-2** (Scheme 5.27) is generated, either by treatment of glucals with DDQ in acetonitrile or with $TiCl_4$ in methylene chloride, very clean axial C-allylation is observed in both instances and also reasonable axial O-glycosidation is obtained with the former catalyst.[86,87] Thus the erstwhile kinetic anomeric effect is more apparent in the more nearly planar ring system of **27-2** than in **26-1.** When the results of an examination of orbital polarization studies and/or transition-state calculations for a series of oxonium ions becomes available, then we might be able to draw some conclusions about the long-held intuition about the kinetic anomeric effect.

Stereoelectronic effects are quite pronounced in anomeric radicals. Remarkably, several glucosyl radicals have been shown by ESR spectroscopy to exist in the boat conformation **28-1** (Scheme 5.28). Using FMO theory to explain this geometry, Giese has proposed that the SOMO of the radical is raised in energy by its interaction with the ring oxygen lone pairs, but it is stabilized by interacting with the σ* orbitals of the adjacent C–*X* bond when it is electron withdrawing, hence with a low LUMO. This LUMO–SOMO interaction is only accessible if the glucose ring distorts to a boat. In the mannose series where the 2-acetate is axial and aligned for an interaction with the SOMO, the pyranose ring remains in a chair.[88] The preferred boat conformation of the glucosyl radical presents us with an interesting paradox. One common thread in the rationalization for the normally favored axial-like attack on unsaturated cyclohexyl species has been that axial approaches can proceed via chair forms, whereas approaches from the face that would eventually afford equatorial products



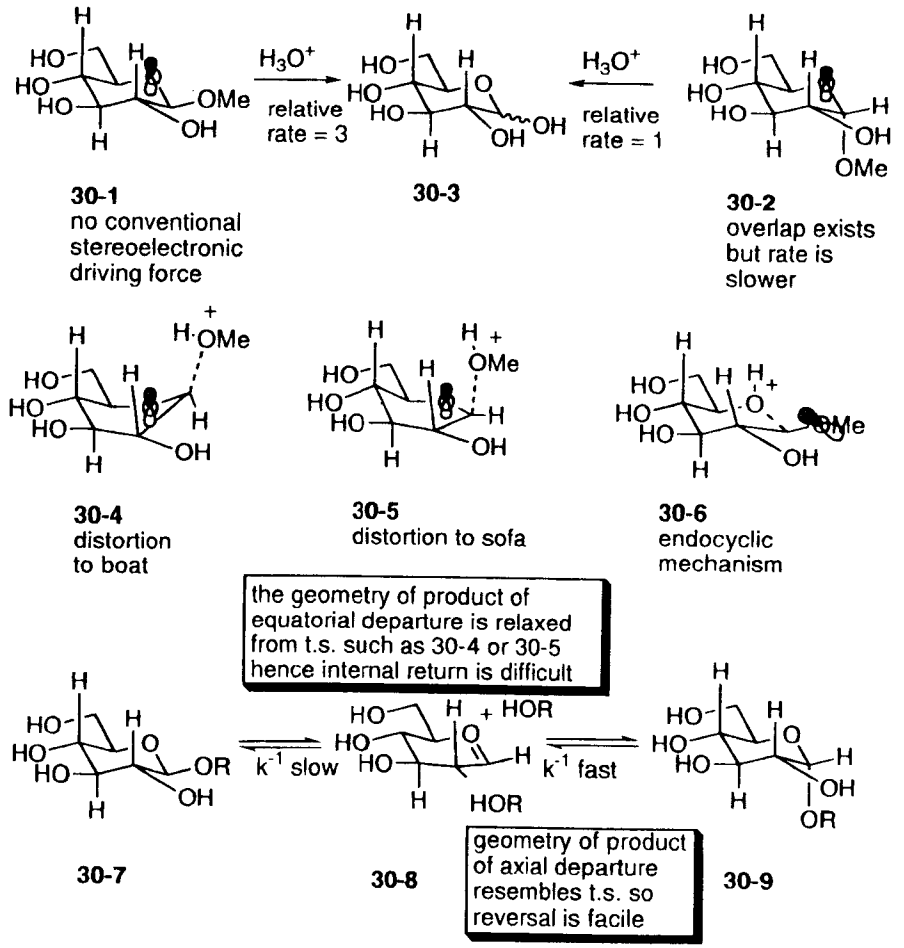
must go via higher-energy boats. Here, we have a lower-energy boat, yet it still prefers axial (below-plane) trapping. The effect causing this preference is not clear. Perhaps the chair conformer where the radical is unstabilized reacts faster, or, in the boat conformer, the above-plane face is somewhat blocked by the quasiaxial acetoxy at C(3). Or the radical *p* orbital is polarized. The eventual explanation will be most interesting. A second interesting feature of radical **28-1** is its rearrangement to **28-5.** It must be the case that the stabilization of an anomeric radical is less than the stabilization of an anomeric acetate.[89] A synthetically valuable application of the axial attack of anomeric radicals is the hydrogen transfer to obtain β-glycosides shown in the conversion of **28-7** to **28-8.**[90]

The ozonolytic oxygen insertion into the axial anomeric C–H bond was one of the key observations leading to the Deslongchamps scheme for antiperiplanar lone-pair effects. As illustrated, the argument for the totally selective cleavage of the axial C–H bond was that there were two such antiperiplanar lone pairs (APP) to activate the C–H bond and stabilize the transition state. Clearly, when the C–H bond



is equatorial, only one APP interaction is present; hence the reaction fails. It is equally clear that the same arguments would hold if the interacting orbitals were simply *p* and collinear. Hence, if the *p* character of the participating electrons on anomeric oxygen is accepted, then the claim of uniqueness for a syn-periplanar C–H bond cleavage is not really correct (Scheme 5.29) and the observation is easily understood as being a consequence of the boatlike nature of the material where there is a cleavable σ bond collinear with a potential *p* orbital on oxygen.[91] The same critique can be made for the claim of syn-periplanar C–O bond hydrolysis in a related structure.[92]

No rationalization of preferred axial attack (or axial cleavage) can explain the well-known kinetic preference of the acid-catalyzed hydrolysis of equatorial methyl glucoside over its axial anomer (Scheme 5.30). Explanations include the intervention of twist–boat-like forms,[93] half-chair or sofa forms,[94] prior endocyclic oxygen bond cleavage,[95] and least-motion arguments;[80] the first three do recognize the necessity for some sort of parallel overlap of the cleaving bond and a directional orbital on oxygen, whereas the last does not; and none of these has found wide acceptance in the organic community. Quite recently, DeShong has suggested that the higher observed rate for equatorial cleavage might be an artifact of the higher rate of internal return of the axial isomer.[96] Thus it is proposed that the axial bond cleaves faster than the equatorial. But the initially cleaved materials have different rates of internal return (k^{-1}) so that the equatorial intermediate goes forward to the detectable



product without any internal return. On the other hand, if the axial intermediate has a significant k^{-1}, then its expected faster rate of formation would not be directly observable. This argument is depicted in Scheme 5.30. If the product **30-8** is the ion that either reverses or traps water to give the observed product, it could be argued that reversal to **30-9** would be the more facile since reversal to **30-7** might require a distortion back to a nonchair geometry. Experimentation will be necessary to establish the validity of this new proposal.

5.6. Conclusion

That there are stereoelectronic effects is certain beyond doubt. However, a close analysis has revealed that the molecular basis for an observed effect is often difficult

to pinpoint. It is clear that the finely tuned intuition of pioneers in the field has given us valuable tools for thinking about reactivity and stereochemistry even though some of the explanatory hypotheses put forward have not withstood the close scrutiny of later investigators.

Acknowledgement

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