

Face Selection in Addition and Elimination in Sterically Unbiased Systems

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1. Introduction

For the purpose of this review, addition processes are considered to include all of the reactions in which there is an increase in the number of ligands bound to a central atom, and elimination covers all of the chemistry in which there is a decrease. With so wide a range of such processes, there can be little doubt that they are among the most important in all of chemistry, not only because of the multitude of reactions that fit the definition but also, and perhaps especially, because of the stereogenesis that characterizes addition—that is where stereochemistry be-

gins. The question arises: when a new, additional ligand is going to be bound to the central atom, what will the preferred new configuration be? This question has created the need to know the factors that govern stereoselection.

Beyond any doubt, the best-documented and most powerful factor is the steric one, and for a long time, it was considered to be the only one. Even now, when the root mechanism of a successful new stereoselective reagent or catalyst is discussed, it is virtually always taken for granted that the selectivity is the result of a difference in steric hindrance between the two approaches the reagent may choose. Yet it has been known since the 1950s that products sometimes form as the consequence of reactions in which it is not intuitively obvious how steric crowding could have led to the result. A variety of suggestions have been offered for these observations, and they may be captured under the general description of stereoelectronic effects.

The obvious way to study these effects is to employ probe molecules in which the two faces eligible for addition are sterically equivalent. The power of that approach has been dramatically demonstrated by Hammett, who used *p*-substituents in phenyl rings to influence rate and equilibrium constants in ways which are impervious to steric effects. The 2-norbornyl cation has provided us with an equally dramatic example of the fact that failure to exclude possible steric effects where electronic influences are sought cannot lead to unassailable conclusions. The nonclassical ion controversy, in fact, was a study of face selection in an elimination reaction as well as of the stereochemistry of the final capture and addition step. In research of addition reactions involving neutral substrates, the most frequently used probes have been cyclohexanone and its derivatives, and from the beginning, there, too, arguments ensued about the degree and even direction of steric differences between the equatorial and axial approaches (to say nothing about the conformational nonrigidity). Thus, important though this simple ring system may be in organic chemistry, it should be recognized that studies employing it will never convincingly reveal the reasons for the observed selectivities.

Unfortunately, it is not possible to design a probe containing a planar atom with two faces which are absolutely indistinguishable sterically, yet different electronically. As we shall see, this ideal can only be

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Wen-Sheng Chung, a native of Hualien, Taiwan, received his B.S. degree from National Tsing-Hua University, Hsinchu, in 1982 with distinguished honors. After two years of army service and one year as a teaching assistant at Tsing-Hua, he went to Columbia University to study organic photochemistry and high pressure chemistry under the guidance of Professors N. J. Turro and W. J. le Noble. He received his Ph.D. degree and a Pegrarn award in 1991 from Columbia University. He then worked with Professor J. A. Berson at Yale University for one year on a study of non-Kekule biradicals. He returned to Taiwan to begin his present position in 1991, first as an Associate Professor, and since 1977, as Professor. His current research interests in physical organic chemistry include host-guest chemistry and molecular sensors. He enjoys playing volleyball, tennis, and table tennis with his many friends.

approached, and approached reasonably closely, but it cannot be reached. After all, electronic differences must be induced by means of one or more substituents, and while one can place these substituents at positions remote from the site of reaction, one cannot guarantee that they are remote enough to avoid subtle steric differences, through distortion, polarization, or other transmission. Indeed, a frequently raised point is whether the trigonal site to be added to is even planar, or whether the substitution has possibly induced pyramidalty.

In this article, we review results that have been obtained by means of studies employing several probes that come quite close to the ideal of zero steric



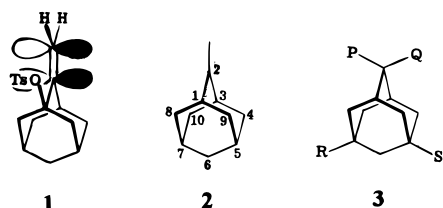
Bill le Noble is a native of Rotterdam, The Netherlands. He studied chemical engineering as an undergraduate in Dordrecht and then moved to the United States in 1949. After a stint in the U.S. Army, which included service in Korea, he attended the University of Chicago and received a Ph.D. degree in organic chemistry with Professor G. W. Wheland. Postdoctoral work at Purdue University with Professor N. Kornblum was followed in 1959 by an appointment at the then new State University of New York at Stony Brook, where he has stayed ever since. He has held Visiting Professorships at the Free University of Amsterdam and the University of Groningen, received Humboldt Senior Scientist and Mom-busho Special Professorship Awards, and he has served as senior editor of *The Journal of Organic Chemistry* and *Recueil* as well as in the Chair's position of his department. He is an avid swimmer and fisherman in his spare time.

bias. We did of course not attempt to incorporate a comprehensive listing of data which have been produced by colleagues who are also authors of papers in this issue, but we did refer to those of their experiments that were needed to produce a seamless account. For investigators planning their own research in this area, it is important to consult earlier reviews and/or accounts by Wigfield,¹ Ashby,² and Gung.³ Reviews are also available in more specialized areas of narrower focus; they include papers by Zimmerman⁴ and Pollack⁵ on keto-enol stereochemistry, by Fallis⁶ on pericyclic stereochemistry, by Franck⁷ on the stereochemistry of simple cyclohexanes, by Paddon-Row⁸ and by Bowden and Grubbs⁹ on the through-bond and through-space transmission of substituent effects, by Juaristi¹⁰ and Perrin¹¹ on the anomeric effect, and by Saunders¹² on carbocation chemistry. Each of these papers contains references to earlier summaries and seminal contributions to those topics. Excellent brief summaries may be found in the introductory paragraphs of recent research papers by Houk,^{13,14} Fraser,¹⁵ Fallis,¹⁶ Heathcock,¹⁷ Paddon-Row,¹⁸ Jorgensen,¹⁹ and Tomoda.²⁰ One of us has contributed reviews on the competing viewpoints of what lies behind nonsteric diastereoselection in addition²¹ and in solvolysis.²²

While addition to trigonal centers lies at the heart of stereogenesis, elimination to produce such centers revolves about relative rates. These two processes are, of course, closely related, as each is essentially the microscopic reverse of the other; however, the addition reaction has received far more attention (with carbocation chemistry the main exception), presumably because of its importance in synthesis.

Much of our own work in this field is based on the unique properties of the adamantane skeleton, such as its rigidity, a point which is elaborated further

below. Perhaps the first chemists to take advantage of these properties have been Schleyer²³ and Martin,²⁴ who showed in 1969 that the allylic ester **1** solvolyzes extremely *slowly*, thus demonstrating that when the leaving group is forced to depart in the plane perpendicular to the normally assisting π orbital, the vinyl group is an electron *withdrawing* one. Their work provided a dramatic example of the power of this probe to reveal insights that are hidden from view where nonrigid molecules are used.



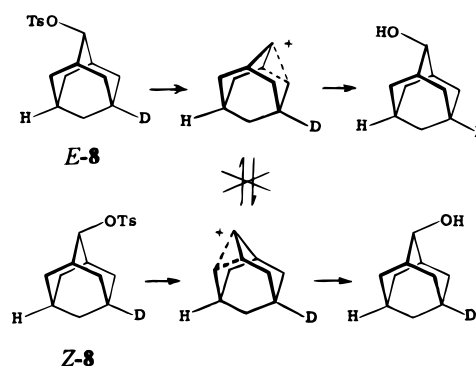
In the sections that follow, we discuss the most important addition processes and explain the observed configurational preferences by means of transition-state hyperconjugation, which we believe has proven to be the most successful theory to date for that purpose. In a final section, we mention the several alternative ideas to have emerged in the literature in recent years and their pros and cons. But first, we digress for a moment for two items of nomenclature. Throughout this paper and others already published, we have found it convenient to employ the numbering system shown in structure **2**, even though it is sometimes incorrect; thus, we refer to 1,4,4-trichloroadamantane as the 2,2,5-species, and so on. We also prefer to use the *E*- and *Z*-stereochemical designations; *E* if the higher priority substituent among P and Q in **3** is anti to the higher priority substituent among R and S, and *Z* if it is syn. This is, of course, exactly the same convention as that proposed by Blackwood et al.²⁵ and now in common use for olefins; we see no reason why it should not also be used for achiral cyclic molecules such as 1,3-disubstituted cyclobutanes, etc. We refer to the two faces of C-2 in **2** as the en and zu faces, where en describes the distal face with respect to the substituent at C-5, and zu represents the proximal one.²⁶ In a few instances, we shall mention research done with chiral molecules; in all of those cases, the substances used were racemic.

II. Cation Formation and Capture

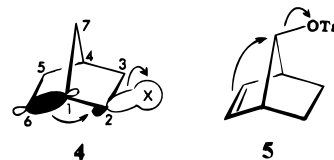
A. 5-Substituted 2-Adamantyl Cation

The stereochemistry of solvolysis went through a period of intense debate about the cause underlying often huge epimeric rate ratios.²⁷ The primary reason this dispute lasted for years without resolution was, as noted above, that the probes widely used to investigate the question, the *exo*-2-norbornyl esters **4**, generate cations with two sterically inequivalent faces, and hence it is not possible to offer rigorous proof that the cause of the 10³:1 *exo/endo* rate ratio is electronic in nature. In a few cases, unsaturated probes with sterically near-identical faces did find use, and the π -participation postulated to cause their

Scheme 1



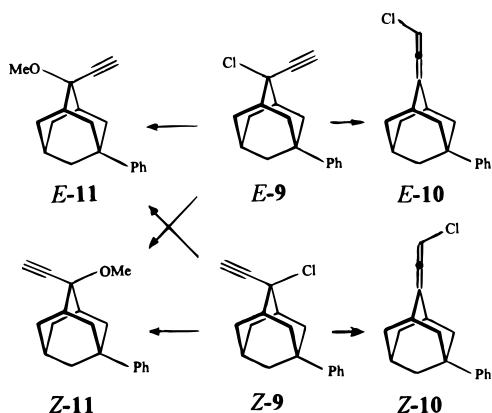
very large solvolysis rate ratios was not controversial; perhaps the best known example is the 7-norbornenyl tosylate **5**.²⁸ The phenomenon of σ -participation is now well-established as well, but it is interesting to speculate that it might have been studied, much earlier than it was, by means of 2-adamantyl esters or halides carrying a remote substituent to influence the ability of vicinal σ bonds to lend assistance in the heterolysis process. However, the parent 2-adamantyl ester was considered to provide the textbook case of unassisted solvolysis,²⁹ and thus, there was little or no incentive to study more elaborate specimens.



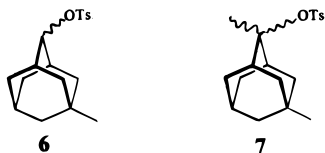
If one ignores this background, the 5-substituted adamantanes with a trigonal center at C-2 have much to recommend them as probes. The substituent, which is equatorial with respect to all three of the cyclohexyl rings converging at C-5, is remote enough from the trigonal center not to influence it sterically in any but the most extreme cases. There is virtually no conformational freedom in this rigid yet essentially strainless system, and Bredt's rule forbids the possibility of elimination as a competing process. In early applications, the assignment of configuration was an obstacle that could be overcome only by means of X-ray studies;³⁰ however, such assignments are now routinely based on NMR spectra.³¹

The first chemist to study the solvolysis of a 2-adamantyl ester carrying a 5-substituent was Whiting,³² who used a methyl group at that position to show that both secondary and tertiary esters **6** and **7** undergo acetolysis with predominant retention of configuration. The result was evidently surprising enough that the authors considered the possibility of an indirect steric effect, operating through the intervening axial hydrogen atoms, as the cause of the retention. Subsequent work in our own laboratory³³ showed that predominant (92:8) retention also characterized the hydrolysis of 5-deuterio-2-adamantyl tosylate *E*-**8** in 40% aqueous acetone (Scheme 1; note that *Z*-**8** was not studied experimentally since its retention may be taken for granted. To suppose otherwise is to postulate a δ deuterium isotope effect). That observation rules out the steric possibility,

Scheme 2



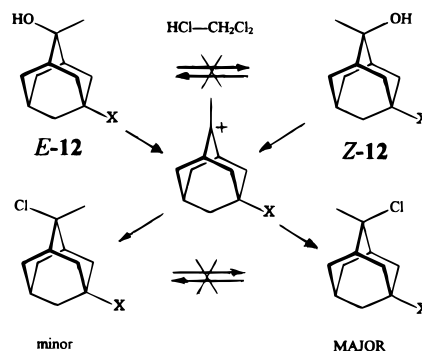
leaving assistance by the antiperiplanar vicinal bonds as the only reasonable explanation. One other possibility is sometimes mentioned as an alternative, namely, that the solvent molecule trapped between the cation and the leaving group in a solvent-separated ion pair might be a stronger nucleophile than bulk solvent by virtue of its proximity to the anion and thus produce retention. This explanation cannot apply, however, to the tertiary 2-adamantyl cations, as noted in the following paragraphs.



The first insight that a 5-substituent can influence face selection in the capture of a *free* 2-adamantyl cation derived from a study³⁴ of the 5-phenyl-substituted propargyl chlorides shown in Scheme 2. Dissolution of both the *E*- and *Z*-isomers **9** in methanol caused partial methanolysis and partial rearrangement to the chloroallenes **10**. The latter reaction is stereospecific, and hence there is evidently no crossover between or dissociation of the tight ion pair intermediates. In contrast, the methyl ethers **11** are produced in the same ratio from both epimers **9**; evidently, the free cation is a common intermediate. The composition of this common mixture is of special interest: the *Z*-ether predominates by a ratio of 3:1 over the *E*-isomer. The remote phenyl group clearly has a directive effect, which we attribute to σ -delocalization. Of the four C–C bonds vicinal to the cation center, the two proximal to the electron-withdrawing phenyl group are deactivated by it; the other two therefore are the bonds that stabilize the cation and control the stereochemistry. This clear evidence for delocalization is especially noteworthy because this cation is not just a tertiary species, but it is presumably stabilized by the triple bond. The conclusion that this stabilization is not enough to swamp the hyperconjugative interaction with the neighboring bonds is inescapable.

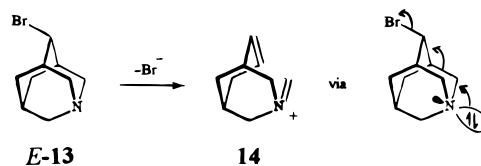
These conclusions were supported by means of extensions to other systems. First, it was found that other electron-withdrawing substituents such as chloro-, fluoro-, trifluoromethyl in the 5-position lead to a similar or even larger preference of the nucleo-

Scheme 3



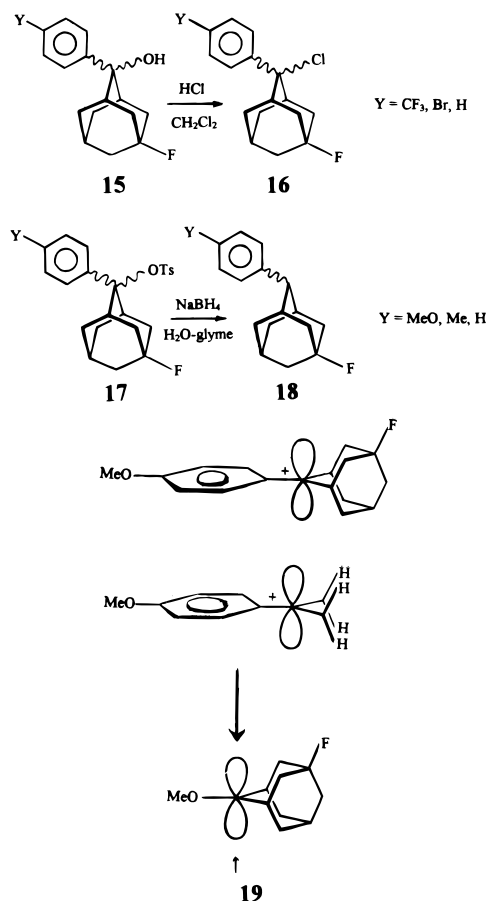
phile for the *zu* face; thus, exposure of either of the two tertiary alcohols **12** to hydrogen chloride in dichloromethane leads to identical mixtures of 2-chloroadamantanes in which the *Z*-isomers are present in severalfold excess.³³ Neither the alcohols nor the products interconvert under these conditions (Scheme 3).

When the rates of generation of the cations rather than the ratios of the products are measured, far larger effects are encountered.³⁵ Thus, a 5-fluoro substituent gives rise to an *E/Z* rate ratio of solvolysis of the secondary 2-adamantyl tosylates in aqueous acetone of less than 0.01. It was also found that if the 5-substituent is a donor such as trimethylstannyl, *E/Z* rate ratios far *larger* than unity result.³⁶ The most powerful donor effect was found by Grob,³⁷ who replaced C-5 by a nitrogen atom. The assistance in this case derives from the unshared pair. The reaction of *E*-**13** is some 10^5 times faster than that of 2-bromoadamantane and produces the ring-opened species **14** as the initial product.

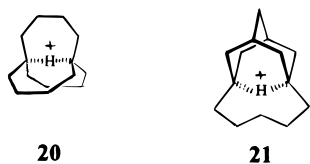


The remarkable persistence of the ability of antiperiplanar neighboring bonds to stabilize cations even if the positive center is bound to an ethynyl group led us to try to tune the product ratio in 2-phenyl-2-adamantyl cations by means of *p*-substitution. In one series of reactions, the cations were generated from mixtures of *E*- and *Z*-alcohols **15** by means of hydrogen chloride gas dissolved in methylene chloride to give chlorides **16**; in another, they were obtained by solvolysis of mixtures of *E*- and *Z*-tosylates **17** and captured with sodium borohydride to give reduction products **18**. In all instances, the products resulting from attack at the *zu* face predominated over their isomers by margins ranging narrowly and apparently randomly between 78:22 to 73:27. Evidently, the assistance is not even swamped by a *p*-anisyl group. It should be noted that these cations are essentially cumyl cations, the same species that provide the basis for the σ^+ constants! One is led to see that the stability of cumyl cations is derived in part from delocalization by the methyl C–H bonds. It is evident that the σp -applications

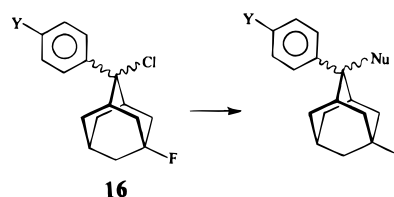
which have been used so often²⁷ to call the existence of σ -delocalization into question provide at best a shaky basis on which to build such conclusions. When the solid salt **19** is treated with sodium borohydride, even then, the *E*-ether is formed in excess over the *Z*-isomer by a margin of 83:17.³⁸ The conclusion is that σ -delocalization from vicinal bonds does not merely occur, but that it cannot be swamped by a substituent bearing unshared pairs.



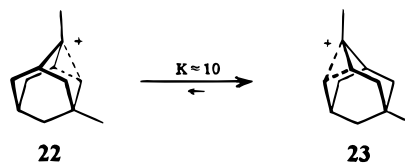
We take note here of the presumed difference between σ -delocalization and hyperconjugation. As we have argued elsewhere,²² when the participating or delocalizing bond is a vicinal one, there appears to be no difference; in fact, there is to our knowledge no clear definition of these two terms which addresses the difference in the literature (however, see Kirmse et al.:³⁹ "...there is no reason to mingle hyperconjugation with σ delocalization..."). The term σ -delocalization is perfectly descriptive and justified when the assistance is rendered through space by a more remote single bond; thus, McMurry's cation **20**⁴⁰ and Sorensen's cation **21**⁴¹ are good examples of σ -participation by a remote C-H bond. Yet, the two-electron three-center bonds, even in these species, are essentially hyperconjugative in nature.



We also note a paper by Liu⁴² in which he reports a decrease in the *E/Z* rate ratio of solvolysis of compounds **16** as Y changes from trifluoromethyl to methyl and claims that this shows our conclusion regarding the absence of swamping to be invalid. However, to "swamp" means to submerge completely, and Liu's data do not indicate that his phenyl groups have stopped the assistance of the vicinal bonds; in fact, the product mixtures reported in Liu's paper show that the capturing nucleophile preferentially attacked the *zu* face in every case, by margins between three and fifty to one.



The evidence that the 2-adamantyl cations are subject to stabilization by the vicinal bonds has been confirmed by Sorensen⁴³ in a dramatic way. He was able to study the 2,5-dimethyladamant-2-yl cation in superacid solution at low temperature by means of ¹³C NMR, and found it to be an equilibrating mixture of two structures, presumably **22** and **23**. The equilibrium constant for the reaction as written is about 10. At least equally pertinent in this respect are the several studies by Laube, who has been able to carry out X-ray diffraction studies on solid carbocation salts at low temperatures.⁴⁴ The structure of the 2-phenyl-2-adamantyl cation is of special interest.⁴⁵ The C₁-C₂ and C₂-C₃ bonds are shortened by nearly 0.1 Å; the C₁C₂C₃ bridge leans toward one side by 7.86°, and the phenyl group by an additional 5.6°. The vicinal bonds on that side are elongated by about 0.05 Å; all of this is consistent with strong hyperconjugation. Bond shortening in the C-CH₃ bonds has also been observed in the parent cumyl cation itself.⁴⁶ While one could also attribute the stereochemistry to the greater openness of the leaning bridge or the pyramidalicity at C-2, because both of these distortions are themselves due to hyperconjugation, these are not different explanations.



The question arises how the substituent at C-5 makes its influence felt in the intervening anti-periplanar vicinal bonds. Carrying the argument of hyperconjugation one step further, we suppose that the effect is ascribable to delocalization of electrons in these bonds into the σ^* orbital of the C-X bond, thus reducing their ability to assist at C-2. Strong support for efficient electron delocalization in this type of extended hyperconjugation has been reported by Grob,⁴⁷ Adcock,⁴⁸⁻⁵¹ Borden,⁵² Michl,⁵³ Verhoeven,⁵⁴ Vinkovic,⁵⁵ and Vögtle.⁵⁶

We summarize as follows. The physical properties of the 2-methyl- and 2-phenyl-2-adamantyl cations clearly show that they are subject to hyperconjugation. We therefore feel that the stereochemistry of capture of 5-substituted 2-adamantyl cations as well as the epimeric rate ratios observed in their generation are not merely conveniently explained by hyperconjugation, but are plainly a consequence of it.

B. 4-Substituted 2-Adamantyl Cation

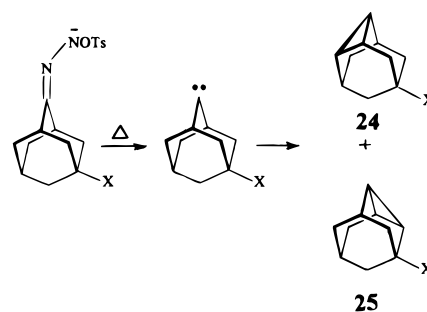
The preceding section gives rise to the intriguing question of how face selection in 2-adamantyl cations will be affected by a 4-substituent. If this substituent is axial (with respect to the cyclohexyl cation), it will obviously affect the stereochemistry in a steric way,⁵⁷ and hence we will limit this discussion to cases in which it is equatorial. While an electron-withdrawing group in that position will inductively reduce the ability of the C₃–C₄ bond to assist at C-2, it is not self-evident that this effect will be stronger than that exerted by the same substituent at C-5, the nature of the interaction being different.

Experimental data relevant to this question have been provided by Grob,^{58,59} who found the ability of substituents to affect solvolysis rates of 2-adamantyl esters weaker if they are in the equatorial 4-position than if they are located in the 5-position. He interpreted this fact as evidence that conflicts with the proposal that hyperconjugation is the reason why 5-substituents have such drastic effects as noted in the preceding section.⁵⁹ However, this conclusion is certainly debatable; 5-substituents affect *both* intervening bonds vicinal to C-2, whereas equatorial 4-substituents affect only one. Note also that all four of the bonds vicinal to C-2 are related differently to C-4. We presume that the extended antiperiplanarity of 5-substituents is the factor that renders them so effective in this reaction.

III. Carbene Capture

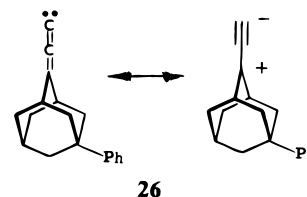
A. 5-Substituted 2-Adamantylidene Carbene

Carbenes in which neither of the two groups bound to the carbenic center carries unshared electrons behave as strongly electron-deficient species, and hence they may be expected to mimic carbocations in their stereochemical properties. We see the adamantylidene carbene as a species in which C-2 has a filled sp² orbital and a vacant p orbital. A report bearing out this expectation has been published by Majerski.⁶⁰ He studied the formation of dehydroadamantanes **24** and **25** in the Bamford–Stevens reaction shown below, and observed the product ratio to be 74:26 in favor of **24** when X is methyl, and 92:8 when it is chloro. These results signify that the secondary hydrogen atoms most remote from the substituent are the favored targets for carbene insertion, and that this preference becomes more pronounced the more electronegative the substituent.



B. 5-Substituted 2-Vinylideneadamantane

We referred in section IIA to the neutral solvolysis of the propargyl chlorides *E*- and *Z*-**9**. When these same compounds are exposed to a *basic* medium, the resulting anions⁶¹ jettison chloride ion to give carbene-anion pairs,⁶² which in part undergo retentive isomerization to the allenes **10** and in part dissociate to the common free carbene **26**. This carbene has a strongly dipolar character,^{63,64} and the dipole moment should increase because of induction as a nucleophile approaches. Carbenes such as **26** should therefore mimic the 2-adamantyl cation in their behavior, and indeed, **26** captures methanol with a 3:1 preference for *Z*-**11** as the product.⁶⁵

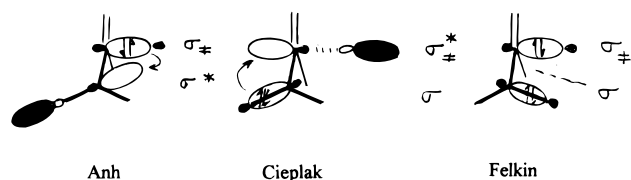


IV. Nucleophilic Addition to Ketones

The stereochemistry of addition to carbonyl groups in open-chain compounds is obviously sensitive to steric and thermodynamic factors, and simple, well-known rules have been developed to predict both the conformation of the necessary nearby chiral center, the least hindered face for the approach of the reagent, and the stability of the products. It was only when cyclohexanone stereochemistry began to be studied that awareness gradually set in that these three influences alone were insufficient to explain the observed results.

The alternative and additional factors that can play a role have been much debated, and there is still much disagreement about them. Because most of the experimental background fueling these discussions is in the area of nucleophilic addition to ketones and because much of the discussion in the literature concerns the relevance of through-bond interactions between substituents and the carbonyl center, a brief digression is inserted here to describe the arguments favoring such interactions, and thus to clarify the purposes of the experiments. Readers wishing to see a fuller discussion of the main schools of thought may consult ref 21, papers quoted in that account, section XII below, and other papers in this issue; suffice it here to say that the similarity in stereochemical behavior between carbenes and cations naturally led to the question whether ketones might not also fit this mold.

Chart 1



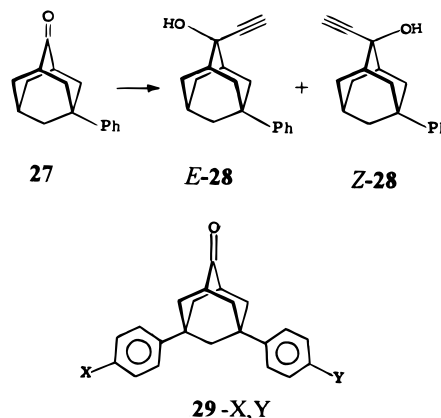
The π and π^* orbitals, which interact weakly with the vicinal σ and σ^* orbitals, evolve into the new σ and σ^* orbitals as the reaction coordinate is traversed. The electronic interaction of the incipient bond with vicinal bonds can take three forms: between σ_i and σ_v^* , between σ_i^* and σ_v , and between σ_i and σ_v , where *i* stands for incipient and *v* for vicinal. The first two of these, favored by Anh⁶⁶ and Cieplak,⁶⁷ respectively, are interactions between an empty and an antiperiplanar filled orbital, and, as such, they do in principle lower the transition-state energy; the third, favored by Felkin,⁶⁸ is a repulsive one between filled, synperiplanar orbitals and thus, it raises the barrier (Chart 1). The best Anh approach is clearly that which will donate electron density from the incipient bond into the most electron-deficient vicinal bonds; the best Cieplak approach is that which will donate electron density from the most electron-rich vicinal bonds. These two views therefore make clearly opposite predictions. The Felkin approach is least repulsive when the synperiplanar bond is electron deficient; hence, this interaction predicts the same stereochemistry as does the Cieplak model. All three have been successfully applied to cyclohexanone addition stereochemistry; however, the Anh and Felkin models also postulate various conformational distortions to account for the results. The Cieplak model postulates that C–H bonds are better donors than C–C bonds (in other words, that the Baker–Nathan order is correct) in order to explain the oft-observed axial approach of nucleophiles to cyclohexanones.⁶⁹

The 5-substituted adamantanone system is virtually ideal to test these models. The skeleton has two carbonyl faces which would be identical but for the remote 5-substituent; its rigidity avoids the distortions apparently important in the Anh and Felkin models, and the propriety of the Baker–Nathan order is immaterial because all four vicinal bonds are C–C bonds which are differentiated only by the remote substituent. This same remoteness is of course also a disadvantage: the product (or rate) ratios are generally quite modest. But, one could say this also about secondary isotope effects. The point of the experiments is not to find large effects, but insightful ones, and, if that is achieved, they are well-chosen.

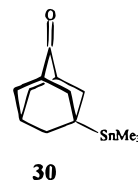
A. 5-Substituted Adamantanone

The first indication that the usefulness of the adamantanone probe was not limited to electron-deficient intermediates such as carbocations and carbenes came from the observation⁶⁵ that the ethynylation of 5-phenyladamantanone **27** did not give a 50/50 mixture as we had supposed; the *E*-isomer of **28** dominated by a margin of 2:1. In later work, we

learned that this deviation was general; the reduction of this ketone by means of the usual complex hydrides also produced *E*-alcohols in excess. Furthermore, other electron-withdrawing 5-substituents such as methoxycarbonyl,⁷⁰ bromo, chloro, fluoro, hydroxy, and trifluoromethyl³³ caused the same behavior; the margins, ranging from 70:30 to 55:45, seemed to reflect the electronegativity of the substituents. In the case of 5-phenyl, in fact, it was possible to tune the ratio by means of variations in the para substituent, although not as much as we at first reported.^{33,71,72} An electron-withdrawing substituent such as nitro tends to increase the tendency of the phenyl group to direct the nucleophile toward the *zu* face of the carbonyl carbon, whereas a *p*-amino group tends to diminish it. These effects can be most clearly seen in the 5,7-diphenyladamantan-2-ones **29-X,Y**.⁷³

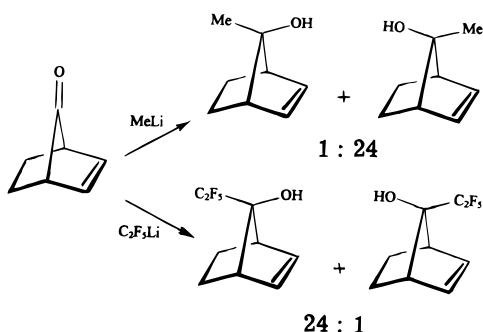


Upon reduction with sodium borohydride in 2-propanol, ketones **29-H**, **NO₂**, **29-H**, **NH₂**, and **29-NH₂**, **NO₂** produce the *E*- and *Z*-alcohols in the ratios of 1.30, 0.78, and 1.64, respectively. It is evident that the nitro group which deactivates the proximal vicinal bonds directs the nucleophile to the *zu* face and that the amino function activates the same bonds and directs the reagent to the *en* face; in **29-NH₂**, **NO₂**, both effects team up to give a ratio which is the quotient of the other two. The effects of a donor substituent are also observable in the 5-trimethylsilyl- and -stannyl-2-adamantanones; thus, treatment of **30** with methyllithium gave the tertiary *E*- and *Z*-adamantanols in a ratio of 36:64.⁷⁴

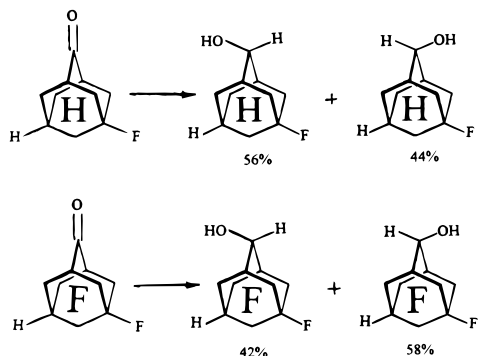


One might expect that the magnitude of the selectivity should be somewhat dependent on the nature of the nucleophile, but the variation is surprisingly small. The addition of 5-fluoroadamantan-2-one to six *p*-substituted phenylmagnesium bromides, with the *p*-substituent varying from trifluoromethyl to dimethylamino, gave *E/Z* ratios between 68:32 and 76:24, with no obvious trend or correlation.⁷⁵ In our search for such effects, we recalled a drastic case of nucleophile differentiation which had

Scheme 4



Scheme 5

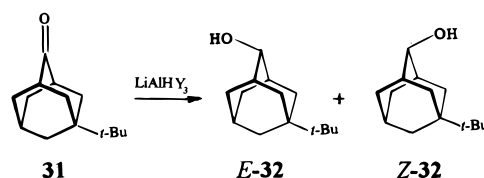


been reported by Gassman;⁷⁶ he had found a complete reversal of face selection in the two reactions in Scheme 4. When these two reagents were allowed to react with 5-fluoroadamantan-2-one, however, the *E/Z* ratios were found to be nearly identical (2.3 vs 3.0). Evidently, the double bond in norbornenone begins to play a role⁷⁷ when the ionic reagent pentafluoroethylolithium approaches the keto function.

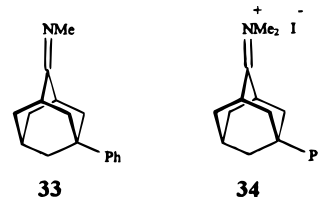
In any event, we now strongly suspected that transition-state hyperconjugation was driving the stereochemistry, and that the carbonyl group's selectivity was a consequence of its carbocation character. One possible test of this conjecture is to deactivate all four of its vicinal bonds completely. In pursuit of that notion, we studied the reaction of lithium borohydride dissolved in ether with 7-monohydrylperfluoroadamantan-2-one (Scheme 5), in which fluorine substitution abrogates the ability of the vicinal bonds to function as donors, and converts them into acceptors instead. As the scheme indicates, this ketone does indeed follow the prediction made on the basis of reverse electron flow.⁷⁸

The apparently predictable selectivity of the adamantanones led us to search for ways to control it; i.e., to reverse it or to augment it at will. One obvious way to reverse it (by means other than the perfluorination just mentioned) is by introducing a steric factor, for example, by the use of a bulky 5-substituent, or reagent, or both. Indeed, the data for **31**⁷⁹ show that *en face* can be favored in such cases:³³ while a 50/50 product distribution was observed when Y in the reagent is H, alcohol *Z*-**32** predominates by 58:42 when it is *tert*-butoxy. Even more effective approaches have been devised; they include the blocking of the normally preferred face by means of a catalyst (see section VA), and encapsulating the adamantanone in a cyclodextrin (an example is

discussed in section VIII).



There are two ways to enhance the selectivity. The first depends on rendering the substrate more "carbocation-like". This can be done by allowing the carbonyl oxygen atom to complex with a Lewis acid; we had already noted that with lithium aluminum hydride this selectivity was somewhat more pronounced than with sodium borohydride, and assumed that this was due to the complexation of the lithium ion as a Lewis acid. Indeed, the reduction of 5-phenyladamantan-2-one with sodium borohydride in the presence of a variety of Lewis acids such as aluminum chloride, boron trifluoride, stannic chloride, and so on⁸⁰ raised the *E/Z* ratio of alcohols by 15–30%. Antimony pentachloride was among the most effective of these acids; this is of special interest because the complex has been isolated and studied by means of X-ray diffraction.⁸¹ Laube found that the C=O bond and the C₃–C₄ and C₁–C₉ bonds in the complex are lengthened by 0.045 and 0.017 Å, respectively, while the C₁–C₂ and C₂–C₃ bonds are shortened by 0.031 Å, compared to the free ketone. Thus, complexation has the effect of increasing the need for hyperconjugative delocalization. The *E/Z* ratio (83:17) in the reduction of 5-fluoro-2-methoxy-2-adamantyl cation (**19**), as already noted, is about triple that of 5-fluoroadamantan-2-one (62:38); this may be seen as an extreme case of complexation of the latter ketone by a Lewis acid, the methyl cation. Interestingly, no increase was seen at all when the methylimine **33** was compared with the iminium salt **34**: under a variety of conditions, they showed identical *E/Z* ratios of about 2:1 in the reduction with sodium borohydride. We assume that the imine, the ratio for which seems abnormally large, is in fact in cationic form (protonated or complexed with lithium cation) during reduction.⁸⁰



Similar effects can be brought about by the introduction of charge at the site of the 5-substituent. Thus, the sodium borohydride reduction of 5-dimethylaminoadamantan-2-one in D₂O, which normally has an *E/Z* ratio of 65:35, may be compared with the trimethylammonium salt which weighs in at 86:14, a more than threefold increase.⁸⁰ The *E/Z* ratio for 5-hydroxyadamantan-2-one (58:42) is diminished after treatment with sodium hydride to 49:51 and that for 5-methoxycarbonyladamantan-2-one (57:43) may be compared with 45:55 for the carboxylate salt.⁸⁰ Even

Scheme 6

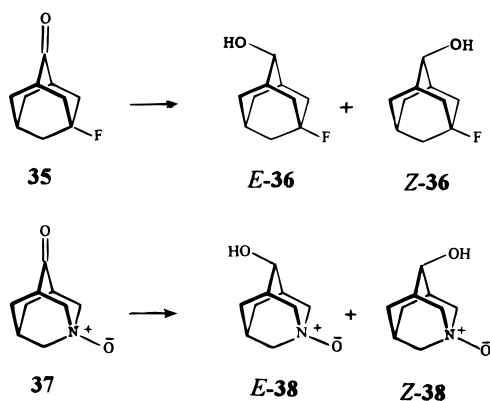
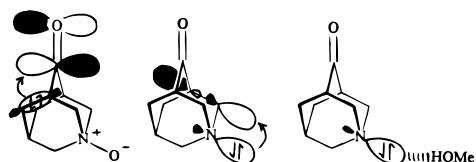


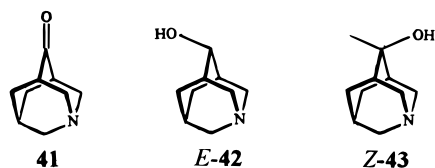
Chart 2



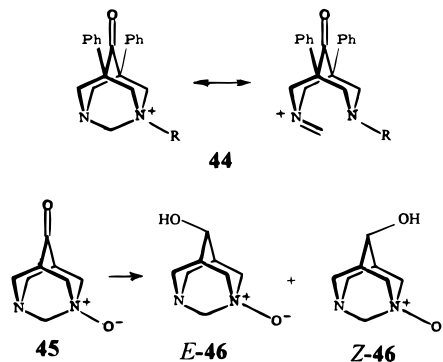
more drastic effects are observed if C-5 itself is replaced by positive nitrogen, as may be seen in Scheme 6. The *E/Z* product ratios in these two reactions are 60:40 and 96:4, respectively. This presents an increase in the ratio by a factor of 16, for two substrates which are isoelectronic! Similar results were obtained with iodide of cation **39** and betaine **40**.⁸² The same high ratio was found in methanol, water, and saturated aqueous sodium chloride (for an alternative interpretation, see section XII).



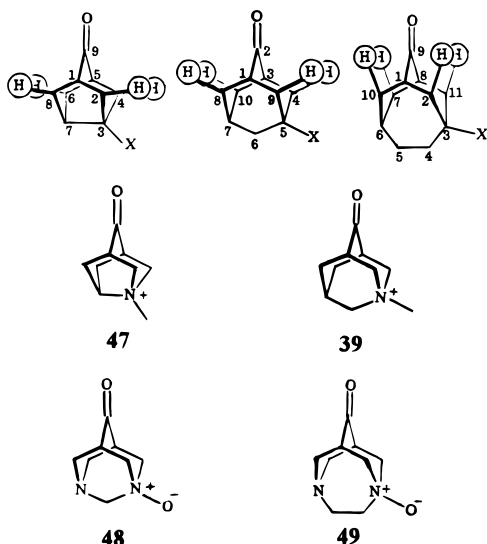
The behavior of the neutral aminoketone itself is also of interest. We found the secondary alcohol *E*-**42** to be in excess upon reduction in methanol (62:38), but a small excess of the tertiary alcohol *Z*-**43** (55:45) is obtained in the reaction with methyllithium in THF. We can readily account for this solvent effect; in the latter reaction, we assume that the syn vicinal bonds are activated by the nitrogen unshared pair and that this donation is prevented or thwarted in a hydrogen-bonding solvent (Chart 2). Senda⁸³ has measured the ratio of sodium borohydride reduction in several alcohols and in THF; in fact, an excellent linear correlation of the *E/Z* ratio was found when it was plotted against the Swain solvent-acidity parameter. The crossover in favor of *Z*-**42** found by Senda in THF was included in the plot.



The effects of initial-state hyperconjugation can be seen very clearly in compounds **44** (*R* = H or Me). Zefirov⁸⁴ determined the X-ray diffraction pattern of these cations. The N₅–C₆ bond was found to be more than 0.1 Å longer than the N₇–C₆ bond which clearly supports the contention that the alternative “no-bond structure” makes an important contribution. This type of hyperconjugation reduces the difference in donating power of the two sets of vicinal bonds, and the *E/Z* ratio of alcohols **46** in the sodium borohydride reduction of **45** in D₂O is observed⁸⁵ to be 7.3, compared to 24 for the monoaza analogue.



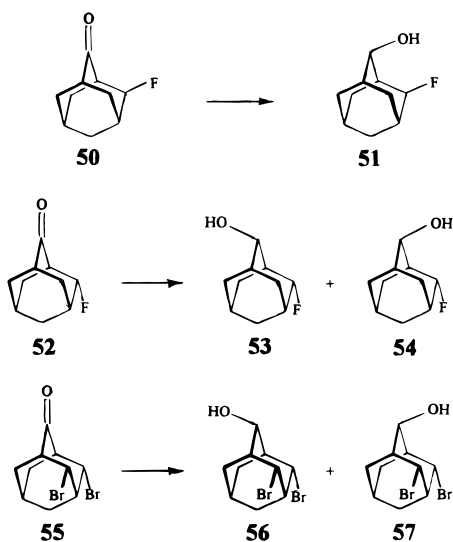
In discussions of face selection, questions about the approach angle are often raised. Indeed, if the rigidity of the adamantane skeleton and the location of the axial hydrogen atoms force an abnormal approach trajectory upon the nucleophile, one may argue that the adamantanone probe is not a good one. Conversely, the near-symmetry of the molecule should allow the angle to be the same at both faces and thus cancel it out as a matter of concern. Be that as it may, we sought to gain an insight into this aspect by adjusting the length of the bridge represented by C-6 in the adamantanone probe. As the structures drawn below suggest, a more favorable approach is possible in the noradamantan-9-ones and an even more crowded one seems unavoidable in the homoadamantan-9-ones. Studies of the reduction and alkylation product ratios did not show much difference between these ketones, and the small variations observed were not systematic. The quaternary bridgehead aza analogues, with their substantially larger ratios, were more informative; they suggest that the adamantanone structure provides the largest ratios. Thus, the *E/Z* ratios for the alcohols obtained by sodium borohydride reduction of **47** and **39** are 87:13 and 96:4, respectively, and those of **48** and **49** are 88:12 and 83:17, respectively. We assume that this trend is due to the more nearly perfect antiperiplanarity of the substituent with the bonds vicinal to it.⁸⁶ One additional point of interest is that both methylation and reduction of the azanoradamantanone show the same solvent dependence as does the azaadamantanone itself, and surely for the same reason: donation by the unshared nitrogen pair in THF, and electron withdrawal by the nitrogen in a hydrogen-bonding medium such as methanol.



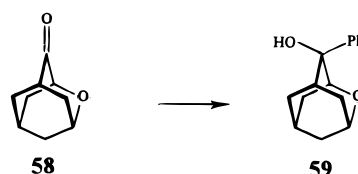
B. 4-Substituted Adamantanone

As noted in section IIB, a 4-substituent, to be useful at all, should be in the equatorial position because otherwise it will affect the stereochemistry sterically; but even then, it has the disadvantage of being poorly aligned and of affecting only one of the vicinal bonds. Nonetheless, its greater proximity to the trigonal center renders such probes interesting.

The steric effect of an axial substituent makes itself felt with even the smallest, namely fluoro: sodium borohydride attacks probe **50** exclusively at the en face to give the pure diequatorial alcohol **51**, whereas with the equatorial fluorine substitution in **52**, the diequatorial alcohol **53** is formed with a 67:33 preference over its isomer **54**.⁸⁷ Similar data were found for the two bromoketones. In one instance, we were able to prepare a diequatorial species, namely, 4,9-dibromoadamantan-2-one **55**. Sodium borohydride reduction in that case gave the two alcohols **56** and **57** in a ratio of 86:14.⁸⁷ This ratio is substantially but not spectacularly larger than that observed with 5-bromoadamantan-2-one (59:41), which reinforces our impression that the effect of the bromine atom in the latter case is effectively transmitted via extended hyperconjugation.



Another interesting question is what might happen if C-4 and/or C-9 are replaced by nitrogen, but these compounds are not known. However, the oxa derivative **58** has been prepared. Here we must deal with an uncertain difference in size between an axial hydrogen atom and an axial unshared pair and the ability of the oxygen to withdraw electrons vs its ability to participate with its unshared pair. In methylation, phenylation, and reduction, all of the reagents attack exclusively at the *zu* face⁸⁸ to give alcohols such as **59**, but whether this is due to reduced hindrance, oxygen electronegativity (or both), or even chelation is unsettled.



C. Other Carbonyl Probes

The face selection studies possible with 2,3-bis-endo-disubstituted 7-norbornanones **60** have been conducted principally by Mehta. Here also, the two faces are sterically equivalent; **60** differs from the 5-substituted adamantanones principally in that, the substituents being closer to the trigonal center, the product ratios are larger. A more minor consideration is that **60** is not as rigid, and the torsional motion possible in the C₂–C₃ and C₅–C₆ bonds was once considered⁸⁹ as a contributor to the high exo/endo solvolysis rate ratios of 2-norbornyl esters.

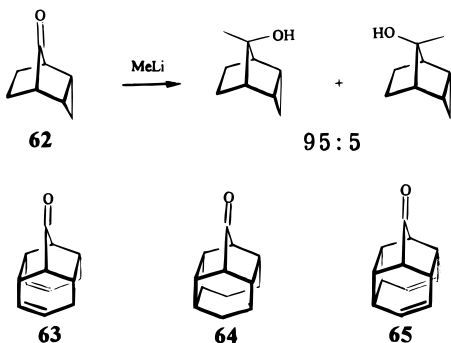


Mehta's first report⁹⁰ revealed that the *E*-alcohol formed preferentially when X and Y are both methoxycarbonyl groups, both in reduction with complex hydrides (margins of 3:1 to 6:1) and in the reaction with methyllithium (>10:1). Rather surprisingly, however, when X and Y are both methoxymethyl, ethyl or vinyl, the *Z*-alcohols predominate, by margins of 1.5 to 4:1 in the reduction and 5 in the methylation. Thus, if hyperconjugation in the Cieplak sense is expected, these substituents should be functioning as acceptors compared to the endo hydrogen atoms at C₅ and C₆. Similar findings were reported⁹¹ in instances in which the C₂–C₃ bond was annelated with a five-membered ring on the endo side. In a later paper,⁹² Mehta attempted to correlate the observed ratios with those calculated on the basis of the assumption that the selectivity has an electrostatic origin, with partial success. This explanation was also advanced for the product ratios in the reduction of a number 2-phenyl-substituted norbornanones in which the phenyl ring itself was also substituted.⁹³ However, as we pointed out above, a 2-substituent alone affects all four of the vicinal bonds differently, making it difficult to predict what

will happen as a result of hyperconjugation. The tetracyclic bis-ether **61** undergoes reduction at the zu face to give the *E*-alcohol by a margin of more than 85:15; the result is reproduced by both MNDO and ab initio calculations, but these techniques suggest different reasons for the result (orbital and electrostatic effects, respectively).⁹⁴

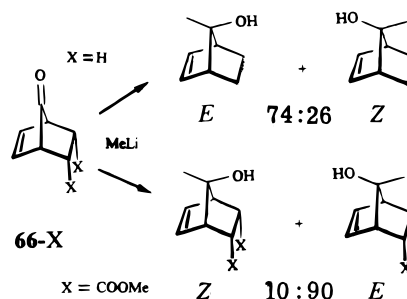


An intriguing contribution by Gassman⁹⁵ concerns the tricyclic ketone **62**. The methylation of this compound occurs with an *EZ* ratio which is strongly dependent on the reagent: lithium dimethylcuprate, which operates via an initial electron transfer, reverses to 8:92 the ratio attained with methyllithium (95:5) or methylmagnesium iodide (90:10). It will be of great interest to learn whether a similar reversal occurs in the 4,9-didehydroadamantan-2-one (the ethylene ketal of which is known.⁸⁷) No reversal of stereochemistry was observed with 5-phenyladamantanone; the ratio was exactly the same as with sodium borohydride.⁹⁶ In the case of the more complex norbornanones **63–65**, both sodium borohydride and methyllithium preferentially attack the zu face,⁹⁷ by margins ranging from 57:43 to 68:32. In this case, at least, the norbornanones appear to behave as expected on the basis of transition-state hyperconjugation, which points up the need to use rigid probes in these studies.

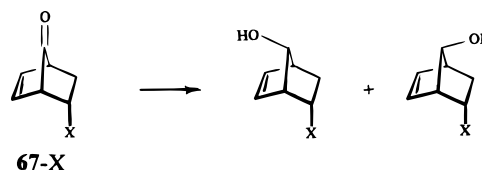


5,6-Bis-endo-disubstituted norbornenones have also been studied by Mehta. While the two faces differ sterically in these cases, one can look for trends as a function of the substituents. Thus, while the parent ketone **66-H** reacts with methyllithium to give the tertiary *E*-alcohol by a margin of 74:26, two methoxycarbonyl groups cause a reversal⁹⁸ to 90:10 (note that the *E*- and *Z*-descriptors must be reversed too! See Scheme 7). In the case of **66-COOMe**, the authors were able to obtain X-ray data, which allow several important conclusions to be drawn. One that is particularly pertinent is that there is no significant pyramidalization in this molecule: the three angles at the carbonyl carbon add up to 360°. On the other hand, the carbonyl bridge leans somewhat in the direction of the C₅–C₆ bond. Thus, whatever the reason for this distortion, the reagent seeks out the

Scheme 7



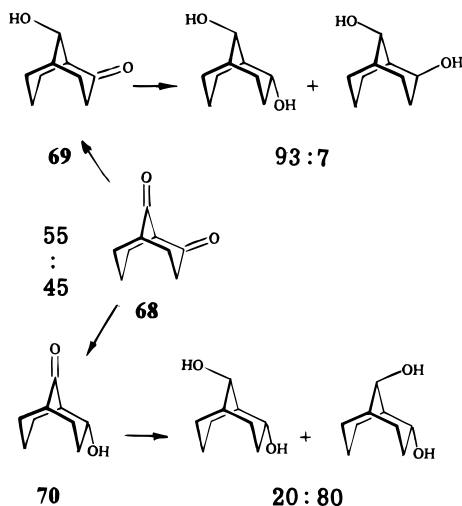
more hindered face.⁹⁹ Some of the 5-monosubstituted substrates **67-X** also furnish interesting data; they seem in reasonable agreement with transition-state hyperconjugation, but they also vividly demonstrate the advantage of probes in which each face is anti-periplanar to only a single kind of vicinal bond. Thus, with **67-CN**, **-COOMe**, and **-COO⁻**, sodium borohydride attacks the carbonyl face remote from the double bond by margins of 44:56, 68:32, and >90:10, respectively.



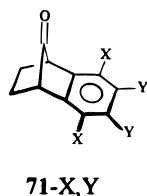
Mehta also found interesting changes in the reduction product ratio if β -cyclodextrin is present.¹⁰⁰ with both 7-norbornenones and 7-norbornanones, the amount of *Z*-alcohol rises. Thus, the *EZ* ratio for the reduction of **66-COOMe** declines from 55:45 in methanol to 8:92 if β -cyclodextrin is added. Neither the α - nor γ -cyclodextrins have much effect. The interpretation is that the methoxycarbonyl groups become complexed in the β -cyclodextrin cavity, thus leaving the en face more exposed. The α - and γ -cyclodextrins do not provide a good fit, and thus affect the ratio less or not at all. This experiment is similar to one reported earlier (see section VIII below).

Berg and co-workers have reported¹⁰¹ interesting data on the sodium borohydride reduction of dione **68**. Both carbonyl groups react at nearly equal rates, and both do so stereospecifically: only syn attack occurs in both branches. Both ketols **69** and **70** thereafter undergo a second reduction, the former mostly on the syn side, but the latter on the anti side. This latter result is unexpected in terms of hyperconjugative donation to an electron-deficient incipient bond; a good explanation cannot be given at this time.

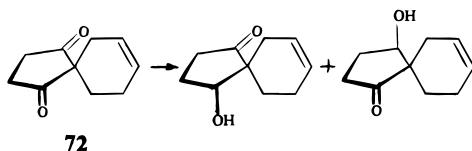
Okada et al.¹⁰² have described their results with several 7-benzonorbornenones **71-X,Y**. The carbonyl faces are not sterically equivalent, but the variation in product distribution as a function of the benzo substitution is significant. These authors report that in the reduction with lithium aluminum hydride, the percent *E*-alcohol equals 100 with **71-F,F**; 92 with **71-Cl,Cl**; 62 with **71-H,H**; and 45 with **71-COOMe,H**. Similar data were obtained with five other common reducing agents. While transition-state hyperconjugation in the Cieplak sense would seem to account for these data, one could also maintain that the



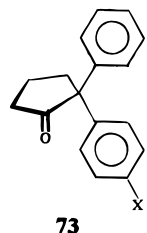
nucleophile forms a complex with the benzo face and then attacks the carbonyl group on that side; such a complex would be expected to be strongest when the benzo substituents are the most electron-withdrawing.



Burnell has reported¹⁰³ the reactions of ketone **72** with sodium borohydride and methyllithium, both of which take place at the carbonyl face closest to the double bond. The margins were about 5:1. This finding is readily interpreted in terms of the Cieplak model, and the authors did so.



A closely related experiment was carried out by Halterman.¹⁰⁴ The reduction and methylation of ketones **73** gave rise to products resulting from addition of the nucleophile opposite the more electron-rich phenyl rings; a linear relationship was found between the logarithm of the ratio versus the σ constant of substituents varying from amino to nitro.



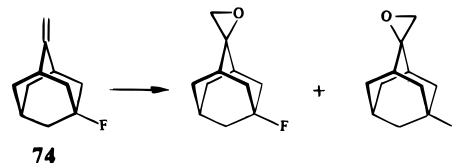
V. Electrophilic Addition to Olefins

A. 5-Substituted 2-Alkylideneadamantane

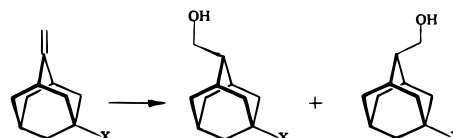
One of the interesting questions that may be raised for theories that purport to correctly interpret the

stereochemistry of nucleophilic addition to carbonyl groups is whether they can be used to predict the stereochemistry of electrophilic addition. If the σ_i^* orbital is indeed the recipient of electron donation by the antiperiplanar vicinal bond(s), the stereochemistry in the two types of reaction should be the same. In this view, it is immaterial whether the electrons that will populate the σ_i orbital are contributed by the reagent nucleophile or by the substrate; the important feature is the σ^* component and its acceptance of electrons from the richest available vicinal bond(s). The prediction is therefore that the stereochemistry should be the same. To put it in different words: hyperconjugative assistance will lower the transition-state energy in the same way whether the probe molecule is the substrate or the reagent (the nucleophile or the electrophile).¹⁰⁵

Two early reports addressing this question appeared simultaneously in 1987. In one of them,¹⁰⁶ 5-fluoro-2-methyleneadamantane **74** was treated with several electrophiles, and indeed, syn attack was observed in every case. Thus, epoxidation by means of *m*-chloroperbenzoic acid gives the *Z*- and *E*-oxiranes in a ratio of 66:34, respectively; similar results were obtained in the capture of dihalocarbenes and in the anti Markovnikov hydroboration. Much larger ratios were seen in those cases in which the reagent becomes bound to the methylene carbon, leaving C-2 in cationic form to scavenge anions; in the reaction of **74** with hydrogen chloride in dichloromethane, for example, the *E*-dihalide product is almost undetectable (0.05%). The other paper just mentioned¹⁰⁷ describes a study of electrophilic additions to monocyclic methylenecyclohexanes; the conclusions were the same, although these are of course subject to the same objections which have so often been raised against cyclohexanones as probes.

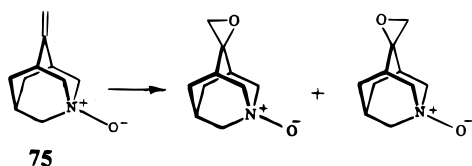


Burgess¹⁰⁸ has published an interesting extension of our study with 5-substituted 2-methyleneadamantanes, using the hydroboration reaction to show not only that syn approach is favored if the substituent is fluoro or phenyl, but also that anti attack predominates if it is trimethylsilyl. The *E/Z* product ratios were found to be 64:36, 53:47, and 47:53, respectively. Furthermore, all of the results are reversed when a rhodium catalyst is added; the ratios then are 46:54, 42:58, and 75:25, respectively. No solvent effects worth mentioning were encountered. The catalyst apparently affects the outcome of the reaction through prior complexation at the normally favored face.



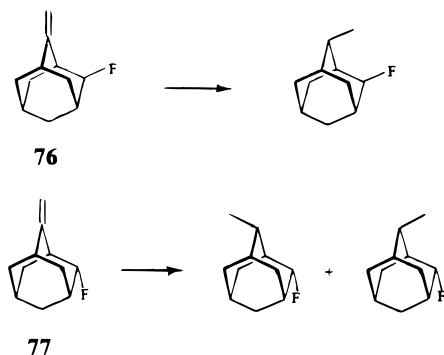
A similar explanation may apply to the biohydroxylations described by Bailey¹⁰⁹ and by Davis.¹¹⁰ Bailey found that the resulting 2-hydroxy-5-substituted adamantanes all had the *E*-configuration in a group of eight substrates, each with an electron withdrawing substituent; on the other hand, Davis reported that with the bridgehead substituted azidoadamantane, the resulting 5-azidoadamantan-2-ol was a mixture with a 10:1 predominance of the *Z*-isomer. Because these oxygenations undoubtedly take place in an environment involving other complex biomolecules, no mechanistic conclusions can be drawn from these observations, interesting though they are.

As was the case in nucleophilic addition, replacing C-5 with positive nitrogen magnified the ratio considerably. To mention one example,¹¹¹ the epoxidation of amine oxide **75** gives the *Z*- and *E*-epoxides in a ratio of about 5:1. Additional instances may be found in the same paper.



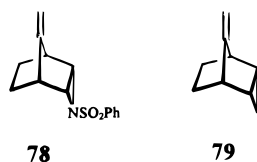
B. 4-Substituted 2-Alkylideneadamantane

The only example appears to be Duddeck's report¹¹² which describes the catalytic hydrogenation of the 4-fluoro-2-methyleneadamantanes **76** and **77**; however, the presence of an axial fluorine in one case and that of a heterogeneous catalyst in both reactions rules out the possibility of a mechanistic interpretation.

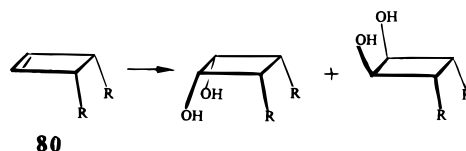


C. Other Olefinic Probes

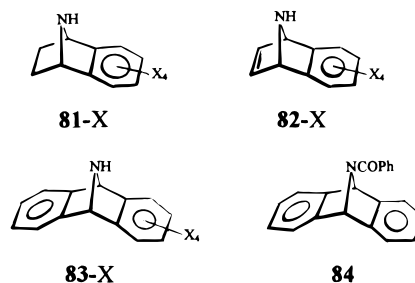
An early paper by Hoffmann¹¹³ describes his group's results obtained with compounds **78** and **79** in the addition of dichlorocarbene and in hydroboration with 9-BBN. As would be expected, while the former compound directs these reagents to the syn face, a reversal occurs in the latter. It is possible that in the reaction of **79**, electron donation from the cyclopropyl group's bent C–C bond plays a significant role.



Mehta^{114–116} and Ohwada¹¹⁷ have made contributions to our knowledge and understanding of electrophilic addition to 7-methylenenorbornanes as well; these are discussed elsewhere in this volume. Gandolfi¹¹⁸ has made good use of the 3,4-disubstituted cyclobutenes **80**. The osmium tetroxide mediated dihydroxylation of these compounds is of course determined in part by steric interactions; nevertheless, a trend can be seen as a function of the substituents which hints at an electronic contribution. The syn products dominate with R = OSO₂Me (8:1); the ratio is much smaller with R = Cl (3:2), and only anti product is formed when R,R = (CH₂)₄.

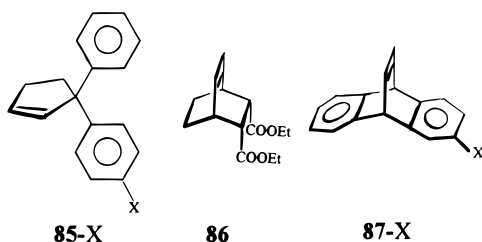


Malpass has been able to study¹¹⁹ the chlorination of 7-azabenzonorbornenes **81-X** and -norbornadienes **82-X**, no small feat if one considers that the *N*-chloroamine products are configurationally stable only up to –50°. This instability has the advantage, however, that the thermodynamic ratios are also available. In this case also, the two faces differ sterically, but the effect of benzo substitution tells the story. Thus, while the parent compounds react with *N*-chlorosuccinimide to give the *E*-chloro compounds, the introduction of electron-withdrawing substituents on the benzo ring leads to a clear shift in favor of the *Z*-isomers. With tetrafluoro substitution as in **82-F**, the *Z*-isomer is the principal product. This is what the Cieplak model predicts; however, as Malpass pointed out, an increasing interaction between the benzo ring and the succinimide anion being released could also be responsible. Furthermore, there is a fair correlation between the ratios under kinetically and under thermodynamically controlled conditions, so that product stability may also have influenced the transition-state barriers. In **83-X**, where steric differences should be absent, syn chlorination predominates by a 3:1 margin.¹²⁰ But one other reservation must be expressed for these studies: Ohwada¹²¹ has found that even amide **84** has a distinctly pyramidal nitrogen atom, and this is surely also the case with Malpass' amines.



Haltermen has used 3,3-diphenylcyclopentenes **85-X** very effectively to study both the osmium-catalyzed cis-dihydroxylation¹²² and the epoxidation mediated by peracetic acid.¹²³ In both cases, excellent correlations were obtained in plots of the logarithm of the ratio versus the σ constants, with *p*-nitro

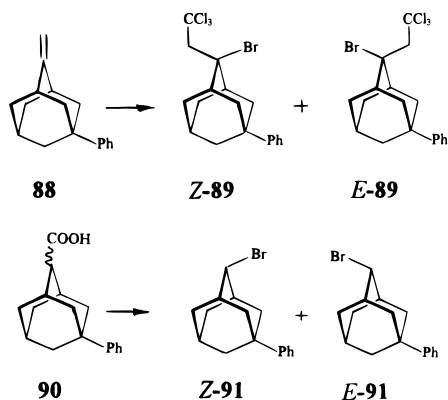
promoting the largest amount of syn attack and *p*-amino or *p*-methoxy the largest amount of anti attack. These observations provide strong evidence for the notion that transition-state hyperconjugation is driving the face selection. The same reactions take place with bicyclo[2.2.2]octenes **86**, and again, the preferred approach is syn in both of these cases.¹²⁴ In the analogous compound **87-X**, Ohwada^{125,126} found a strong preference for syn attack if X is nitro; however, he attributed this to π lobe unsymmetrization.¹²⁷



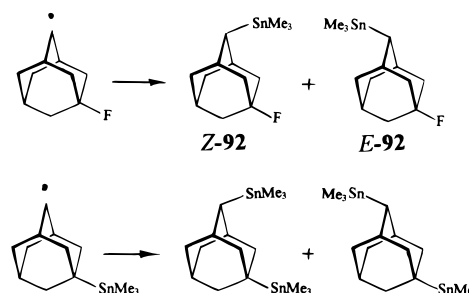
VI. Radical Capture

In all of the foregoing sections, the newly forming bond can easily be argued to be an electron-deficient one, at least in the transition state, as either the reagents or the substrate atoms undergoing addition are electron-deficient from the start. The intriguing question arises whether the rules will be different in radical abstraction reactions, which are more electroneutral. An important starting point¹²⁸ is that 2-adamantyl has a planar C-2 radical center, while 2-methyl-2-adamantyl has a shallow pyramidal configuration with a barrier to inversion of perhaps 5 kcal/mol.

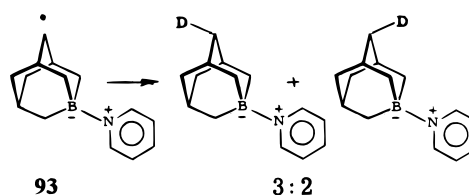
Two reactions have been reported¹²⁹ as favoring the capture of 5-substituted 2-adamantyl radicals at the face syn to the electron-withdrawing substituent. In the first, the radical was generated in a chain process involving an initiator, bromotrichloromethane solvent and 2-methylene-5-phenyladamantane **88**. Bromide **Z-89** is then the principal product (64:36). The other study concerned the Hunsdiecker decarboxylation of acid **90** and bromine abstraction by the secondary radical; here also, syn capture predominates, by a margin of 57:43. Thus, the radical behaves the same way as do the carbocation and the carbene, albeit with more modest ratios; we attributed these observations to transition-state hyperconjugation.¹²⁹



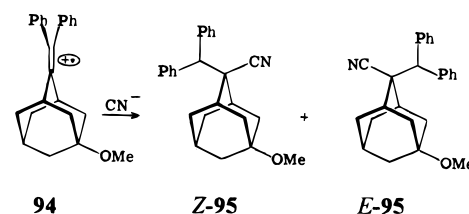
A subsequent study by Adcock¹³⁰ poses a serious question for this interpretation: it was found that, while 5-fluoro-2-adamantyl does react with trimethylstannyl lithium to give an excess of **Z-92**, the trimethylstannyl-2-adamantyl radical produces only 50/50 mixtures of products; in other words, the 5-trimethylstannyl group fails to exhibit the strong donor properties so obvious in the 2-adamantyl cation. For this reason, Adcock prefers electrostatic control as the cause of the modest directive effects by 5-phenyl- and -fluoro substituents, and by extension, to nucleophilic addition to ketones and electrophilic addition to olefins as well (see also section XII). One is reminded of Bartlett's search¹³¹ for evidence bearing on the question whether the formation of 2-norbornyl radicals is subject to the σ -assistance then so strongly suspected in the corresponding cation.



In still more recent work, we defended our original proposition by means of a study of radical **93**, which is isoelectronic with 5-phenyladamantyl but has a powerful remote donor instead of an electron-withdrawing group.¹³² This radical abstracts deuterium from tri-*n*-butyltin deuteride at the zu face by a margin of approximately 3:2 (note that with the boron at the 5-position having a lower priority than the carbon at the 7-position, the en and zu faces are opposite in location to where they normally are).



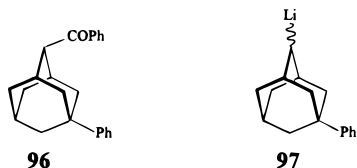
A recent study by Pincock¹³³ has shown that radical cation **94** is captured by cyanide anion to give primarily the *Z*-nitrile (58:42).



VII. Carbanion Capture

Little has been done about this topic with sterically unbiased probes. Attempts to study the enolate of

ketone **96** were unsuccessful;⁹⁶ it resisted bromination, and protonation and methylation gave only the enol and enol ether, respectively. However, the 5-phenyl-2-adamantyllithium **97** derived from either of the two bromides gave the *Z*-carboxylic acid and the *Z*-bromide in excess over the *E*-products upon carboxylation and bromination, respectively.⁹⁶ Thus, as noted earlier, newly forming bonds tend to be electron-deficient in the transition state, regardless of which of the two reactants is contributing the two electrons.



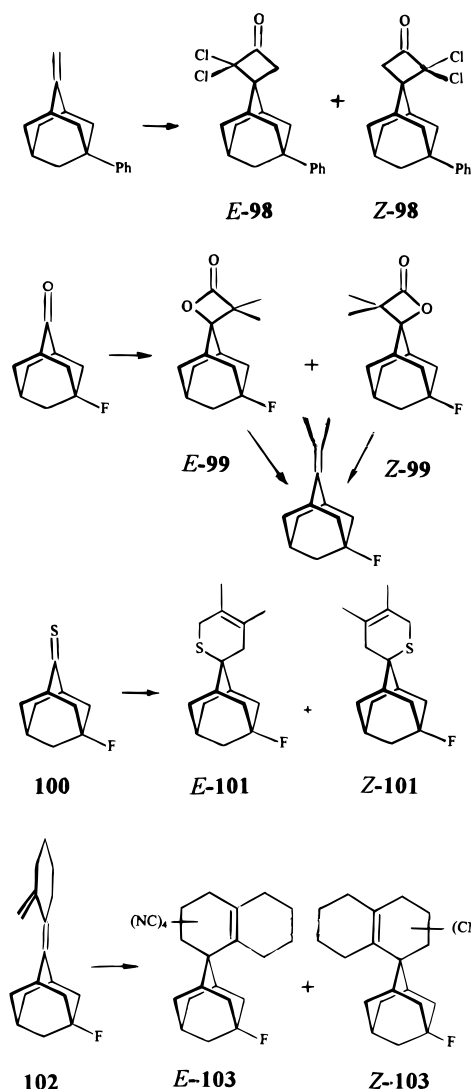
VIII. Cycloaddition

Cycloadditions are perhaps the most important examples of pericyclic reactions, in which doubly bound atoms of the first row undergo addition, and others, singly bound, undergo simultaneous elimination. While the Woodward–Hoffmann rules in symmetry-allowed cases successfully specify whether these reactions occur suprafacially or antarafacially, they are silent about *which* faces will be presented for reaction. When it appeared that transition-state hyperconjugation could account for face election in both nucleophilic and electrophilic additions, it occurred to us that pericyclic chemistry might also prove to be predictable by means of this device.

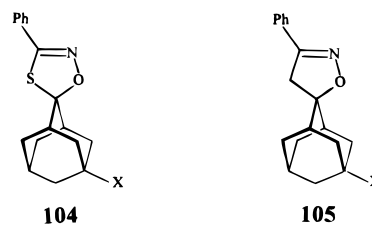
Several thermal cycloaddition processes have been studied with this objective.¹³⁴ It should be noted that the concerted or stepwise nature of these reactions is not an issue in these studies: if transition-state hyperconjugation is a valid predictor of configuration in pericyclic chemistry, the face selection will not be affected by the simultaneity or even the sequence of the bonding steps.

The [2+2] cycloaddition of dichloroketene and 2-methylene-5-phenyladamantane gives *E*- and *Z*-**98** in a 44:56 ratio. The enolate of methyl isobutyrate adds to 5-fluoroadamantan-2-one to give lactone *E*-**99** in a 60:40 excess over isomer *Z*-**99**, and the latter product eliminates carbon dioxide six times faster than the former. 5-Fluoro-adamantan-2-thione **100** undergoes the Diels–Alder reaction with 2,3-dimethylbuta-1,3-diene; the adduct *E*-**101** is in excess by a margin of 67:33. Furthermore, the more elaborate but still mostly rigid substrate **102** reacts with tetracyanoethene to give *E*- and *Z*-**103** in a 42:58 ratio.¹³⁴ Thus, all of these cycloaddition processes exhibit face selectivities in accord with the notion of transition-state hyperconjugation;¹³⁵ in fact, the Diels–Alder reactions mentioned show this principle to apply to both diene and dienophile.

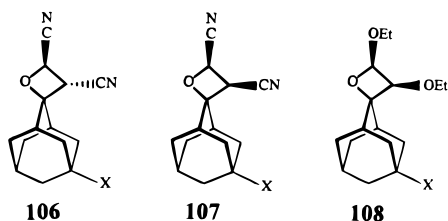
Similar findings¹³⁶ have been reported for several 1,3-dipolar cycloadditions: benzonitrile oxide adds to



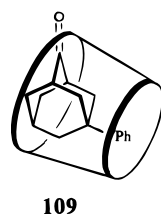
5-halo- and 5-phenyladamantanethiones and -2-methylene-adamantanes to give, respectively, the *E*- Δ^2 -1,4,2-oxathiazolines **104** and the *Z*- Δ^2 -isoxazolines **105** in excess, by margins ranging from 69:31 to 56:44.



Several photocycloaddition studies have also been published. Adamantanones carrying a variety of electron-withdrawing 5-substituents were found¹³⁷ to undergo the Paterno–Büchi reaction with electron-poor olefins such as fumaro- and maleonitrile as well as with electron-rich alkenes such as *Z*-diethoxyethene to give moderate but clear excesses of the oxetanes **106**–**108**, respectively.¹³⁸ An especially interesting observation¹³⁹ was that a trimethylsilyl group behaves in the same fashion (i.e., as a syn director) as do known electron-withdrawing groups, which poses the question whether this group in the excited ketone functions as an acceptor group.

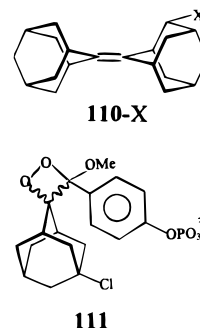


As noted earlier, an interesting protocol has also been devised by one of us (W.-S.C.) for reversing face selections in the reactions of adamantanone derivatives: if β -cyclodextrin is present during the addition reaction, it complexes the substrate in such a way as to protect the favored face and leave the alternative site open to attack. Models show that the cavity in α -cyclodextrin is too small to form such a complex and that γ -cyclodextrin can accommodate both substrate and reagent; indeed, neither of these additives strongly affects the ratio of the isomers during the photocycloaddition of fumaronitrile to 5-substituted adamantan-2-ones, whereas β -cyclodextrin causes clear reversals from syn to anti attack. In a typical example, 5-phenyladamantan-2-one in aqueous solution gives a syn/anti approach product ratio of 62:38; this is reduced somewhat to 58:42 if either α - or γ -cyclodextrin is present, but with 1.5 equiv of β -cyclodextrin present, the ratio is reversed to 23:77. Complex **109** is clearly responsible.¹⁴⁰ In later work, even larger effects were reported;¹⁴¹ in the presence of β -cyclodextrin, 5-trimethylsilyladamantan-2-one suffers as much as 98% attack at the face anti to the silicon. A molecular mechanics calculation by Jaime¹⁴² has confirmed our interpretation.

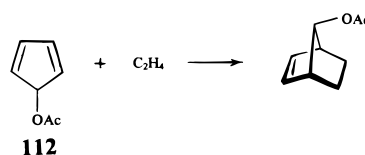


Another interesting extension that should be mentioned in this section is the use of substituted adamantylideneadamantanes **110-X**. Hummelen¹⁴³ reported an early instance of face selectivity in **110-NHCOC₂H₅**: singlet oxygen addition furnished a 3:2 excess of the dioxetane resulting from syn attack. A much more drastic example was later found by Nelsen,¹⁴⁴ who found that the preference for syn approach at -78° was as large as 25:1 in this reaction with **110-Cl**. The active species in this chain reaction is the radical cation; an interesting perspective on this process derives from the observation¹⁴⁵ that the radical cation of the parent hydrocarbon **110-H** has an ESR spectrum revealing strong coupling of the signal with the four remote bridgehead hydrogen atoms. In more recent work, Nelsen has measured the ratios with other halogen derivatives in epoxidation, dioxetane formation, and cycloaddition to *N*-methyltriazolinedione, but although they found syn attack to be predominant in all cases,

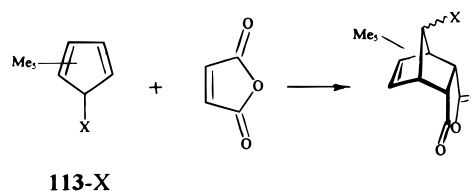
they also argued that there were small variations that were difficult to square with the Cieplak hypothesis alone.¹⁴⁶ The chemiluminescent dioxetane fission to give excited adamantanones should also be of interest, but although one example of a kinetic study has been reported,¹⁴⁷ the authors made no mention of having separated the isomers of their substrate **111**.



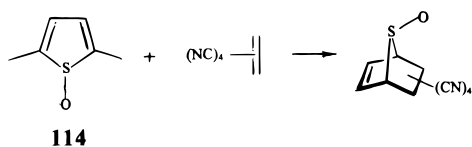
A large amount of work has been lavished on the Diels–Alder reactions of 5-substituted cyclopentadienes which are not free of steric bias but with which variations in product composition as a function of the substituent suggest that the steric factor alone cannot account for all of the data. An early example was reported by Woodward, who found that 5-acetoxycyclopentadiene **112** adds ethylene on its syn side.²⁸ The same contrasteric prejudice has been observed with 1,2,3,4,5-pentachlorocyclopentadiene,¹⁴⁸ but 5-iodocyclopentadiene undergoes Diels–Alder cycloaddition at its en face;¹⁴⁹ evidently, if the 5-substituent is bulky enough, the reaction becomes subject to steric control.



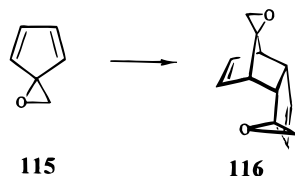
A systematic study by Fallis¹⁵⁰ showed that the reaction of 5-substituted pentamethylcyclopentadienes **113-X** with maleic anhydride gave only the syn adduct when X = OH, OMe, NH₂, or NHAc; there is a small excess of syn adduct if X = SH but a large excess of anti adduct if X = SMe, and this becomes the only product with X = SOMe or SO₂Me. The authors initially briefly summarized the several explanations that had been offered in the literature for these and similar observations; in their subsequent view, the stereochemistry of these reactions can be understood in terms of transition-state hyperconjugation tempered or even negated by sterically demanding substituents.¹⁵¹



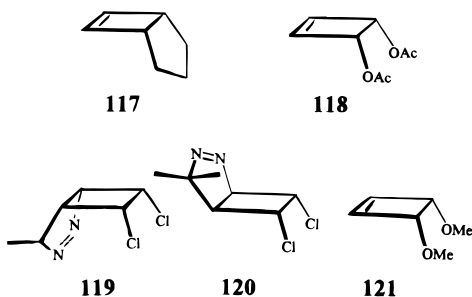
Another remarkable observation by Fallis¹⁵² concerns the Diels–Alder reactions of 2,5-dimethylthiophene oxide **114**, generated in situ from the thiophene by peracid oxidation. Several dienophiles were used; in all instances, the cycloaddition occurred exclusively in syn fashion.



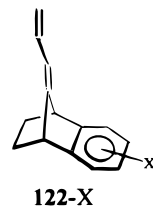
Other rather stark examples have been published by Ishida,¹⁵³ who reported that *N*-phenylmaleimide attacks 5-cyanopentamethylcyclopentadiene exclusively at the zu face and the 5-hydroxymethyl analogue equally exclusively at the en face, and by Trost,¹⁵⁴ who found that the dimerization of **115** gives primarily compound **116**; in this case, the same compound furnishes both the diene and the dienophile, and in both roles, the face syn to the oxygen is the reactive one. Burnell¹⁵⁵ and his group have also contributed much valuable information derived from 5-substituted cyclopentadienes; although their data tend to be in general harmony with those quoted above, these authors have stressed mostly the steric aspect of these reactions.



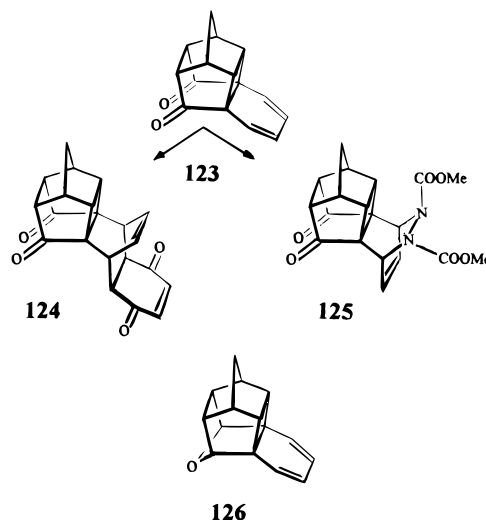
Gandolfi and co-workers have used *cis*-3,4-disubstituted cyclobutenes to study the stereochemistry of 1,3-dipolar cycloadditions,¹⁵⁶ and here also, a remarkable dichotomy was observed. With all of the eight dipoles, cycloaddition occurs exclusively trans to the trimethylene bridge of **117**; however, in cyclobutene **118**, the same dipoles add predominantly (and in a few cases, exclusively) to the zu face. Similar findings were reported by H.-D. Martin;¹⁵⁷ thus, *cis*-3,4-dichlorocyclobutene reacts with diazoethane to give predominantly the adduct **119**, but 2-diazopropane gives mostly product **120**. Clearly, syn addition is induced by the chlorine atoms unless the dipole makes this process sterically prohibitive. With dimethoxycyclobutene **121**, the syn stereochemistry is predominant even with 2-diazopropane.



Paquette has contributed¹⁵⁸ a study of the Diels–Alder reaction of *N*-methyl-triazolidinedione with dienes **122-X**; while the approach to the diene is in favor of the face anti to the benzo ring (75:25) when X = H, the ratio is reduced to 49:51 when X = F.

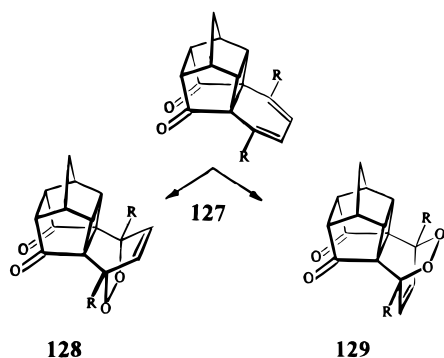


The hexacyclic structure **123** and its reaction with more than twenty dienophiles has been studied by Coxon,¹⁵⁹ Pandey,¹⁶⁰ and Marchand.¹⁶¹ In most cases, the cycloaddition occurred exclusively at the “carbonyl face” to give adducts such as **124**. In a few instances, mixtures were obtained, and in one, with diethyl azodicarboxylate, cycloaddition took place exclusively syn to the cyclobutane ring to give product **125** (with the nitrogen atoms pyramidal and in *s*-trans conformation). Except for the azo derivatives, all of the dienophiles appear to add in accordance with expectations based on the Cieplak mode of transition-state hyperconjugation. Coxon also reported¹⁶² sharply divergent results for ether **126**, which reacts primarily at the face syn to oxygen with maleic anhydride but at the opposite face with dimethyl acetylenedicarboxylate and *N*-phenyltriazolidinedione, and attributed the latter results to repulsion between one of the oxygen unshared pairs and the π electrons of these dienophiles.

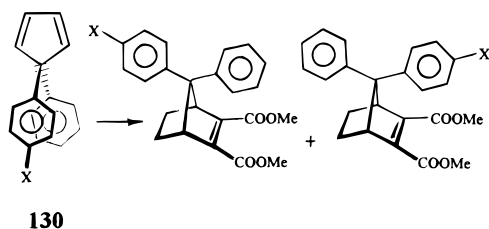


An interesting finding by Mehta¹⁶³ concerns the contrast between diene **123** and its derivatives **127**. When R = H, **128** is the principal product (78:22), but when R = OMe or OAc, only **129** is formed. Mehta attributed the behavior of the disubstituted dienes to twisted conformations at the 1,4-positions due to these substituents.

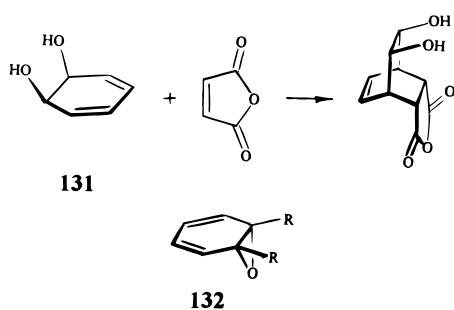
Halterman¹⁶⁴ has used a version of his probe (**130**) to good effect in the Diels–Alder reaction with



dimethyl acetylenedicarboxylate: the zu face was selected when the ring substituent was nitro or chloro, and the en face when it was dimethylamino. A fair correlation of the logarithm of the ratio versus σ was again obtained; the authors attributed their results to the Cieplak mode of transition-state hyperconjugation.

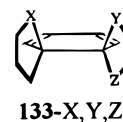


Burnell¹⁶⁵ has contributed valuable results with *cis*-5,6-dihydroxycyclohexadiene **131** and several derivatives, which capture maleic anhydride principally at the zu face. In contrast, benzene oxide **132** suffers attack by dimethyl acetylenedicarboxylate exclusively anti to oxygen. But this appears to be primarily a steric effect; as Burnell points out, the C–O–C fragment is almost perpendicular to the cyclohexadiene part.¹⁶⁶

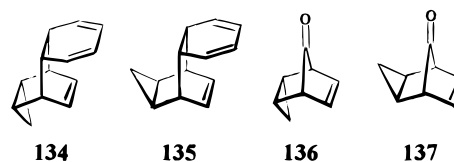


Paquette and Gleiter¹⁶⁷ have reported a massive study of the dispirodiene system **133**-XYZ. With *N*-phenylmaleimide, attack occurred exclusively or nearly exclusively at the face syn to the oxygen atom(s) with **133**-OOC, -OCC, -SOC, and -OCS. No cycloaddition occurred with **133**-SSC, but it would presumably have been about 50/50 because that was the case with **133**-SCC. It is, at any rate, clear that the dienophile is strongly directed syn to the oxygen, and that with sulfur, this preference is essentially gone. The other striking result is that with *N*-methyltriazolidinedione, attack occurs largely to

exclusively anti to the oxygen and/or sulfur (only with **133**-OCS is the ratio approximately 50/50). The exceptional behavior of the N=N double bond as the dienophile was already mentioned; the authors attribute this to the likely formation of an aziridinium imide zwitterion intermediate which then rearranges to the Diels–Alder adduct. In such an intermediate, particularly in the relatively nonpolar solvents generally used in Diels–Alder reactions, electrostatic effects may well play a more important, even dominant role.

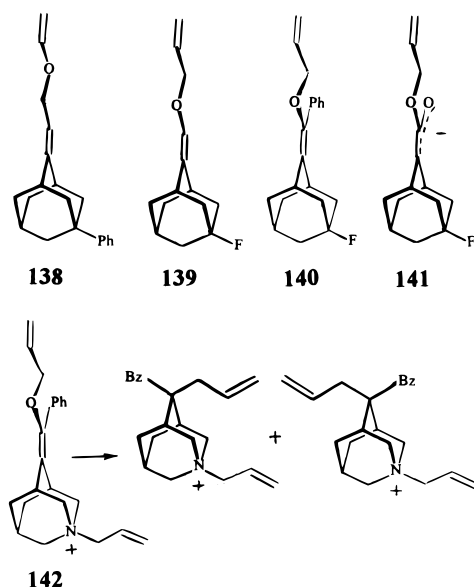


Warner has described¹⁶⁸ a retro-Diels–Alder reaction of interest in this connection; in such cases, one depends on relative rates rather than on product ratios. The reactions studied were the fission of benzene from substrates **134** and **135**, and of carbon monoxide from substrates **136** and **137**, respectively. The diene left behind in all four reactions is norcaradiene. It was found that **134** reacts faster than **135** by a factor of about 10^4 , and **136** was faster than **137** by a factor of 10^5 . The authors ascribed the fast rates to better homoaromatic delocalization; one could also say that the bond fission is assisted by the electron-rich cyclopropane bonds.



IX. Sigmatropic Shifts

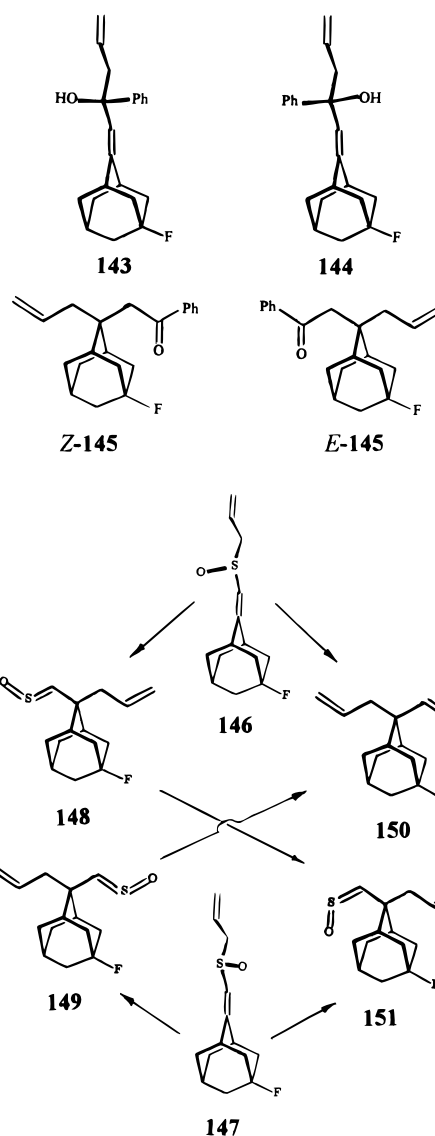
Several examples of 3,3-sigmatropic shifts have been examined in our laboratory, among them those of structures **138**–**141**.¹⁶⁹ In all four, the zu face of C-2 was preferred by the migrating group; the ratios varied in a minor way, from 1.35 to 1.65. Two facts are worthy of note in this group. First, **138** and **139** show that the same factor is responsible for face selectivity at both the allyl and vinyl termini of ethers undergoing the Claisen rearrangement. Second, compound **141** shows that no significant change is observed when the C-2 terminus bears a partial negative charge; as we noted in section VII, we had not succeeded in finding many examples of face selection in addition to such carbon atoms. Another noteworthy example is furnished by the cationic substrate **142**; the *E*-salt product predominates over the *Z*-isomer by a margin of 93:7. This is yet another demonstration of the powerful ability of positive nitrogen at the 5-position to differentiate the donating abilities of the syn and antiperiplanar vicinal bonds.¹¹¹



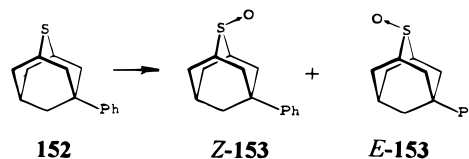
A somewhat more complex case is encountered^{170,171} with the oxy-Cope rearrangement of hexadienols **143** and **144**; because the hexadiene fragment contains a chiral center, this substrate occurs in the form of two diastereomers. These isomers rearrange via chair-shaped transition states, the first of which has the phenyl group in an axial position while the second has it in an equatorial position. The consequence is that in **143**, a steric difficulty opposes the electronic factor normally expected to operate, while in **144**, both factors reinforce one another. And indeed, the ratios reflect this circumstance; while **143** gives mostly the *Z*-isomer of ketone **145** (64:36), compound **144** leads to a substantial excess of *E*-**145** (81:19). Simple arithmetic then shows that the steric factor alone in this reaction would cause a factor of 2.75, while that caused by the electronic one amounts to 1.54. An even more complex situation arises with sulfoxides **146** and **147** (Scheme 7), first, because we were unable to separate mixtures of these two substrates, and second, because under the conditions of the 3,3-sigmatropic shift, the *E*-sulfine products **148** and **149** undergo further rearrangement to the *Z*-sulfines **150** and **151**. Nevertheless, it proved possible to analyze the reaction mixtures by means of their ¹H NMR spectra and by numerical approximation of the rate laws;¹⁷² the final result was that the steric factor alone (axial versus equatorial oxygen in the pseudo-chair transition states) is a bit larger (68:32 in favor of equatorial oxygen) than the electronic one alone (60:40 in favor of attack at the *zu* face).

X. Other Addition Processes

The oxidation of divalent sulfur compounds to the pyramidal sulfoxides is a stereogenetic process which has been examined by means of 5-phenyl-2-thiaadamantanes **152**.¹⁷³ Isomer *Z*-**153** is in excess when the oxidation is carried out by means of sodium periodate or *m*-chloroperoxybenzoic acid; a 50/50 mixture is encountered with nitrogen tetroxide and the *E*-product

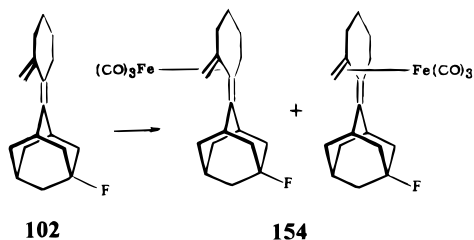


is predominant when oxone or *tert*-butyl hypochlorite is used. The 50/50 result is simply an equilibrium mixture; either isomer is quickly converted into it when exposed to nitrogen tetroxide.¹⁷⁴ The reaction with the hypochlorite begins with chlorination of the sulfur atom, preferably at the *zu* face; this step is followed by ion-pair collapse with the *tert*-butoxide anion and, finally, elimination of chloride ion and 2-methylpropene.¹⁷⁴ This sequence of events leaves the oxygen atom at the *en* face, giving *E*-**153** as the main product. This reaction therefore follows the general rule of attack at the face opposite the more electron-rich antiperiplanar vicinal bonds. While the mechanism of the oxone reaction is unknown, a process similar to that of the hypochlorite oxidation is easily conceivable.

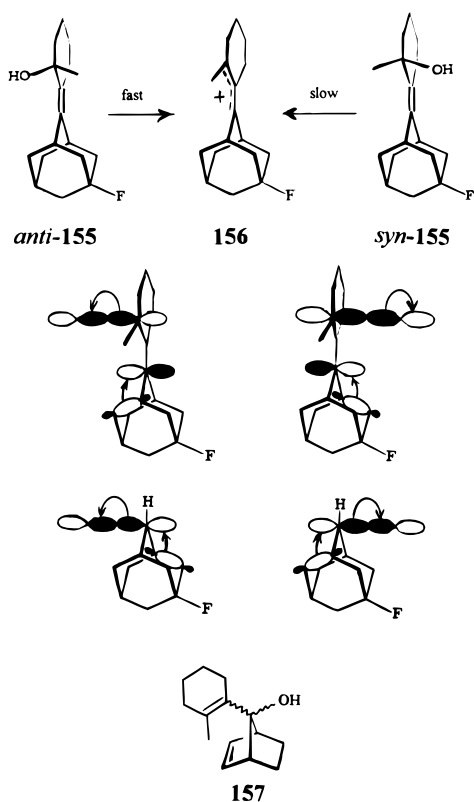


The diene-iron tricarbonyl complexation has also been studied.¹⁷⁵ When the conjugated diene **102** is

exposed to iron pentacarbonyl in refluxing *n*-butyl ether, the anti and syn complexes **154** are obtained in a 2:3 ratio; the structures were proved by means of X-ray diffraction.



An interesting observation was made¹⁷⁶ with the epimeric alcohols **155**. When treated with dilute acid in methylene chloride, both isomers eliminate water to give a mixture of dienes via the common allylic cation **156**, but the anti isomer does so an order of magnitude faster than does the syn isomer. This stereochemistry is opposite that observed in the solvolyses of 5-fluoro-2-adamantyl tosylate: we interpret this reversal as evidence that the vicinal σ bonds can assist even in the formation of an allylic cation, albeit resulting in the opposite stereochemistry, and that the symmetry of the allyl orbital is the cause of change in stereochemistry. By contrast, we found that the allylic alcohols **157** react at the same rate; in this reaction, evidently, π -assistance is not accepted by the stable cation.¹⁷⁷

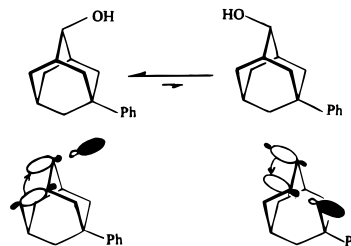


XI. Equilibrium vs Kinetic Ratios

There are good reasons why it is desirable (when-ever possible) to determine what the equilibrium ratio would be for the two stereoisomers formed

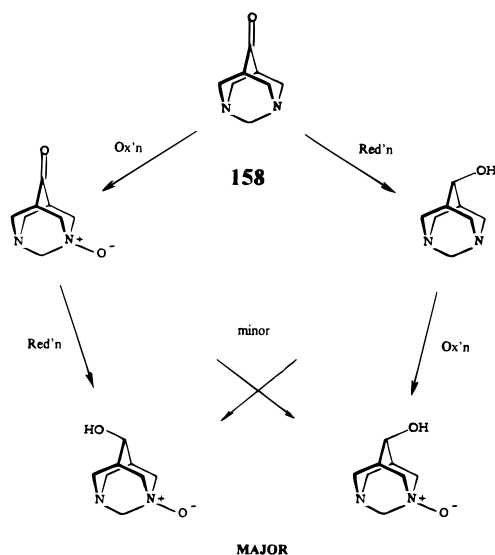
in the addition reactions. First, it should be established that the observed ratio results from kinetic control rather than simply by equilibration; second, one needs to determine whether product stability, foreshadowed in the transition state, is determining the result. It is usually not feasible to equilibrate the products directly, which of course provides the answer to the first question, but in a few cases, we were able to determine the equilibrium position. Thus, as mentioned in section X, the *E*- and *Z*-sulfoxides **153** undergo rapid equilibration catalyzed by dinitrogen tetroxide; as noted that ratio is exactly 50/50. In that case, the answer to the second question is thus also available, and negative.

An equilibrium constant of unity does not apply in each case, however. The secondary 5-phenyl-adamantan-2-ols can be equilibrated by prolonged exposure to aluminum isopropoxide at 130°; *K* is found to be 1.310 in favor of the *Z*-isomer! Thus, the formation of the *E*-isomer is predominant not because of product stability, but despite product instability; to the extent that this factor plays a role, the ratio in the reduction would have been larger if the relative stabilities had not mitigated against it.³³ We suspect that hyperconjugation is behind the equilibrium position as well: the favored isomer has the acceptor and donor bonds antiperiplanar, in a zigzag pattern. While in the reduction transition state, the incipient C-H bond is electron deficient; that same bond, once fully formed, functions as a donor. The electron deficiency of all incipient and breaking bonds is really the heart of the Cieplak proposal.

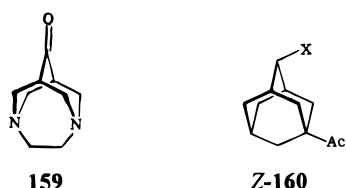


An interesting extrapolation can be derived from this insight, namely, that if the hydrogen atom at C-5 in secondary 2-adamantyl derivatives is at one end of a W-conformation with an electron-withdrawing substituent at the other, then that atom should be more reactive than its cousin at C-7. Indirect evidence for this suggestion was found in the oxidation-reduction chemistry of ketone **158**. The evidence may be described with the aid of Scheme 8. Both of the reductions displayed there were carried out under identical conditions; the same was true for the two oxidation reactions.⁸⁵ Reduction of the keto-*N*-oxide to the alcohol *N*-oxides favored the *E*-species by a ratio of 88:12, whereas the oxidation of the diaza alcohol favored the *Z*-isomer by a ratio of 69:31. An entirely similar set of data was later reported⁸⁶ for ketone **159**. Also along this line is the information uncovered by Fukunishi¹⁷⁸ that adamantanes with an electron-withdrawing

Scheme 8



2-substituent give primarily the 5-acetyl derivative **Z-160** upon irradiation of a solution containing biacetyl.



XII. Interpretations

A. Concerted vs Multistep Bonding Changes

It is important to recognize that bond formation and cleavage may in some cases be processes more complex than we realize. Experimental evidence is available in some instances in which these apparently simple reactions may involve one or more energy minima on the way to the transition state; perhaps the best known example is that of heterolysis, in which one or more types of ion pairs intercede as intermediates. However, in most types of addition, such as radical abstractions, nucleophilic and electrophilic additions, Woodward–Hoffmann allowed reactions, and so on, there is no such evidence, and in those cases, it seems safe to claim that the stereochemistry is purely a transition-state phenomenon. That is to say that the reactions producing the two stereoisomers have equal energy (or even identical) initial states, and that the energy profiles begin to diverge only on the way to the transition state. The energy difference presumably reaches a maximum there.

One could conceive of the possibility that the energy difference continues to widen beyond that stage to reach a maximum in the final state; indeed, it was at one time proposed that the axial reduction and alkylation of cyclohexanones to give equatorial alcohols were the result of product stability control.¹⁷⁹ But as noted in the preceding section, in the few cases where we were able to study the direct equilibration of the addition products from adamantanones and

their analogues, the equilibrium positions were either at 50/50 or even favoring the “wrong” isomer. We therefore assume that the explanation of the observed stereochemistry should focus on the transition state.

But before we do so, let us consider what may happen if the reaction is not concerted. If the reagent or catalyst becomes bound to the exocyclic doubly bound atom in the plane perpendicular to the symmetry plane, then there will be only a single (C_s) intermediate. Such an intermediate has actually been proposed for the sodium borohydride reduction of cyclohexanones,¹⁸⁰ and we have found some evidence for the binding of a proton or counterion by the nitrogen atom in the reduction of imines⁸⁰ (see section IVA). Such an intermediate may enhance the difference between the two faces, but it does not create a steric bias. If a catalyst is used which acts by engaging the trigonal carbon atom in the symmetry plane, the picture changes more drastically. There will then be two isomeric intermediates, each on the way to its “own” stereoisomer. The energies of these two intermediates then clearly have a role to play; one intermediate will be preferred over the other, and it must be established whether the departure of the catalyst and the arrival of the reagent occur with retention or inversion. These features may apply in the case of the *catalytic* hydroboration reaction reported by Burgess,¹⁰⁸ which gave the normally disfavored isomer regardless of the nature of the 5-substituent (see section VA). A second example is furnished by the oxidation of 5-phenyl-2-thiaadamantane which gives the normally expected *Z*-product with several oxidizing agents, but the *E*-isomer is the principal product with *tert*-butyl hypochlorite.¹⁷³ In that case, at least, the reason is clear (see section X); the first step is the delivery of positive chlorine to the sulfur atom at the syn face. *tert*-Butoxide then becomes bound at the opposite face; finally, chloride ion and isobutylene are eliminated, leaving the oxygen atom bound at the anti face.

Chelation has provided the basis of stereogenetic control in some instances: if a substituent which is able to form a complex with the addition reagent prior to the main reaction can be arranged to be present, one may be able to manipulate the outcome. Several impressive examples of this approach have been reported.¹⁸¹ In the case of the probe molecules discussed in this paper, however, the substituents used have been too innocuous and too remote to play such a role.

B. Distortion

It is common knowledge that the introduction of substituents causes small changes in nearby parts of the skeleton: bond angles and bond lengths are affected in minor ways. The investigators who used distant substituents to study face selection have generally taken it for granted that these changes and their effects on the addition stereochemistry are too minuscule to account for the often surprisingly large product ratios.¹⁸² However, when a particularly large

ratio was observed⁸² by replacing C₅–F in 2-adamantanone by N–O (see section IVA), this assumption, considered but dismissed by the authors, was challenged by Gung,¹⁸³ on the basis of calculations suggesting that this replacement causes fairly major changes in the geometry of the carbonyl domain. The principal alteration was concluded to be the “leaning” of the carbonyl bridge away from the nitrogen, by about two degrees in the amine and about four degrees in the amine oxide. These distortions were then held to be responsible for the observed strong preference of the *N*-oxide and for a reduced one in the free amine.

However, the argument has two weaknesses. First, while the borohydride reduction of the aminoketone in methanol does indeed show a much smaller preference for the *en* face, the methyllithium reaction in THF gives rise to attack at the *zu* face. The *ab initio* calculation therefore predicts the wrong result for this probe unless an acidic (i.e., H-bonding) solvent is used. Senda's results leave no doubt that, in a noninvolved solvent, borohydride also attacks the *zu* face. This weakens the argument that *ab initio* computation can account for the selectivity, as no mention was made of any influence by the medium. As we have noted above (section IVA), this solvent dependence can be readily accounted for on our alternative basis.

The second problem is that the cause of the distortion was not addressed in Gung's paper. Our view on this point, qualitative though it may be, is that if it is real, it may well be caused by initial-state hyperconjugation of vicinal bond electron density into the π^* orbital. The C1–C8 and C3–C10 bonds, being remote from the N–O group, are best placed for such an interaction, the result of which may well be the sort of leaning Gung described. In the amine, the availability of the nitrogen unshared pair would reverse this situation unless a hydrogen bond ties it down. How such an initial-state distortion would subsequently develop into the transition state is addressed further below.

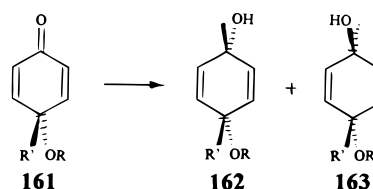
Various other or additional distortions have been mentioned in the literature; pyramidalities of the trigonal carbon function,¹⁸⁴ nonplanarity of certain strained olefins,¹⁸⁵ and orbital deformations¹⁸⁶ are prominent among them. Although there is no doubt that such distortions can and do occur, there is no experimental evidence that they play a significant role in the selectivity of the unstrained probe molecules that are the subject of this paper. It is also important to note here that, while pyramidalities may hinder the approach “inside” the pyramid, the “outside” approach lacks the element of rearside displacement of the assisting bond(s), if such assistance does occur. The retentive solvolysis process is a vivid demonstration of the importance of this element. Proposals of pyramidalities have generally not included any discussion of the possibility of two equilibrating pyramidal structures (e.g., as in Malpass' amines; see section VC). Curtin–Hammett considerations apply then, and transition-state energies determine the outcome.

C. Electrostatic Effects

Westheimer's computation of the acid strength of chloroacetic acid, which was based on the interaction of the C–Cl and O–H dipoles,¹⁸⁷ was an impressive achievement, but at the same time, it became an early indication of how difficult it would be to extend such equilibrium calculations to more complex molecules and to reaction rates. The obstacles to extension include conformational questions, uncertainty of the transition-state “location”, and above all, what values to assign to the dielectric constant. As a result, just so as steric hindrance was at one time described as “the last refuge of the puzzled organic chemist”, so are electrostatic effects now sometimes mentioned as the cause of diastereoselection simply because other plausible explanations appear to fail!

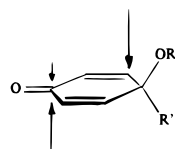
It should be added at once that extensive and promising efforts have been made in the past few years¹⁸⁸ to fortify the foundations on which these claims are made, and three of them are briefly mentioned here. Adcock et al. have published¹⁸⁹ extensive sets of NMR chemical shift data for 5-substituted 2-adamantanones and 2-methyleneadamantanes, and in turn, used these data to distinguish between expectations based on electrostatic and hyperconjugation effects. Although the authors concluded that the former correlation is superior, the argument is not convincing as yet. It may become exactly that if solvent effects are found which can be demonstrated to be in harmony with predictions based on electrostatic considerations. To date, however, such data are not available. We recall that the sodium borohydride reduction of 5-azaadamantan-2-one-*N*-oxide, which had produced the largest selectivity yet seen,⁸² is indifferent to medium changes varying from methanol to saturated aqueous sodium chloride; this result may be contrasted with the huge effects seen by Haberfield^{82,190} in rate studies in which the solvent was varied from moist *p*-dioxane to water.

The second instance is one in which Wipf reported that several cyclohexadienones of the general type **161** react with methylmagnesium bromide to give the two products **162** and **163** in ratios varying from about 5:1 to more than 30:1, respectively.¹⁹¹ These ratios correlated very well indeed with dipole moments calculated for the dienones, and the implication is that the favored product configuration is a consequence of electrostatic steering. Wipf noted that this behavior is also seen with pentafluoroethyl-lithium as the nucleophile (3:1), but there is a reversal (1:5) if the group OR is methoxy and R' is pentafluoroethyl, and this reversal is accounted for by the dipole moment.

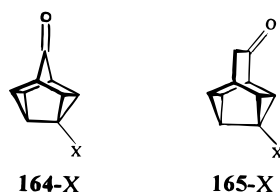


However, the apparently excellent agreement leaves several questions unanswered. Thus, it is not clear

why one of the substrates ($R = R' = \text{Me}$) has a much reduced sensitivity to the nature of the nucleophile (with three of them, the selection can only be described as random). More important, and as Wipf conceded, the extra double bond between the carbonyl carbon and the substituent could lead to an inversion of the normal effect (see section X). It is interesting that in two instances in which conjugate addition dominates, the attack occurs exclusively at the *zu* face.



Finally, an interesting recent paper by Mehta¹⁹² reports a comparison of the reductions with sodium borohydride in methanol of norsnoutan-9-ones **164-X** and snoutan-9-ones **165-X**. The *Z*-alcohols were favored in all cases when *X* is cyano, methoxycarbonyl, ethynyl, vinyl, and methoxymethyl; however, the ratios were systematically somewhat larger for **164** than for **165**. The authors noted that this was expected on the basis of the hyperconjugative model because **164** has two vicinal bonds through which to transmit the remote substituent effect, whereas **165** has only one (see also section IIB). Their additional postulate that an electrostatic component is also operating is unnecessary, in our opinion.



D. Hyperconjugative Effects

Hyperconjugation (or no-bond resonance) has a long and tumultuous history, some aspects of which were mentioned in an earlier paper by one of us.²¹ As noted in the text describing Chart 1, three types of hyperconjugative interactions are possible between an incipient bond *i* resulting in addition and a vicinal bond *v*: $\sigma_i - \sigma_v^*$, $\sigma_i^* - \sigma_v$, and $\sigma_i - \sigma_v$. The first two of these interactions, which are attractive (energy-lowering) in nature, are associated with the names of Anh and Cieplak, respectively, while the third and repulsive one has been advocated by Felkin.

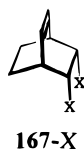
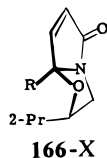
The experimental results described in this paper provide strong evidence for the following points. First, the Anh model predicts that the electrons of the newly forming bond will delocalize into the more electron-poor antiperiplanar σ^* orbital, thus favoring product configurations exactly opposite to those observed. We conclude that this model, whatever its merits in predicting the stereochemistry of the reactions of open-chain or monocyclic compounds, fails as an explanation for addition and elimination with the more rigid polycyclic compounds. Second, both the Cieplak and Felkin models are in accord with the observed facts. However, the latter view, so far as

we know, has never been seriously considered as an explanation for the huge rate ratios so often encountered in heterolysis. Because the stereochemistries of the reactions discussed here and of the heterolytic process are invariably the same, we feel that it is unreasonable to accept one model for the one set and a different one for the other. The unified Winstein–Cieplak view is a powerful tool for explaining the stereogenesis (or -demise) in all addition (or elimination) chemistry. The principal distinction between the Winstein and Cieplak models is that the former depends on the possibility of delocalization into an empty *p* orbital, whereas the latter rests on the availability of a vacant σ_i^* orbital.

This picture has gradually become persuasive to us because of the multitude of reactions the stereochemistry of which was found to be predictable on that basis; they include not only solvolysis and nucleophilic addition to carbonyl compounds but also the capture of carbocations, carbenes, radicals and carbanions, the electrophilic addition to olefins, the full variety of cycloadditions, sigmatropic shifts, metalation of dienes, and sulfide oxidation. It accounts for the effect of introducing remote charge centers, for the solvent effect observed with 5-azaadamantan-2-one, and for the changeover in configuration of the sulfoxides formed from 2-thiaadamantanes depending on the choice of reagent. It helped us find a literature error in the assignment of a ¹³C chemical shift in a case where the model appeared to fail.¹³⁴ It allowed us to predict the stereochemistry depicted in Scheme 8; we know of no other basis on which such a prediction could have been made with confidence.

One of the objections occasionally raised against the Cieplak model is the apparent contradiction of stabilizing a transition state by delocalizing bonding electrons into the *antibonding component* of a newly forming bond.¹⁹³ However, as we have commented elsewhere,⁸² "... by virtue of microscopic reversibility, the transition states for bond formation and cleavage are the same. The explanation is paradoxical only if one attributes too literal a meaning to the term 'antibonding'. The proposition that electronic energy is lowered by delocalization into a vacant orbital of *higher energy* is a fundamental tenet of quantum chemistry."

To be sure, there are a number of ends that need to be accounted for. One of these concerns some intriguing experiments by Meyers et al. The unsaturated bicyclic amide **166-Me** undergoes cyclopropanation predominantly at its more hindered endo face, leading these authors to attribute their finding to transition-state hyperconjugation with the bridgehead methyl group functioning as the donor.¹⁹⁴ However, it was later found that compound **166-C₂F₅** is also subject to endo cyclopropyl formation,¹⁹⁵ yet one would hardly expect the pentafluoro group to have donor properties. One possible explanation⁷⁸ might be that with the alkoxy and pentafluoroethyl functions serving as the vicinal bonds, the transition-state polarization is opposite to what it normally is, and the incipient bond becomes the donor (as in the Anh model; see Scheme 5).



Another problem is the peculiar failure of the trimethylstannyl group to assist in radical abstraction by the en face,¹³⁰ another, the interesting reversal of the trimethylsilyl group, which appears to function as a donor in ground-state chemistry, but as an acceptor in a photocycloaddition.¹³⁹ Also problematic is the behavior of olefin **167-X**. While most reactions with the double bond occur syn to the electron-withdrawing substituents if these are cyano or mesylate, cycloaddition with diazomethane occurs mostly anti.¹⁹⁶ Finally, it needs be mentioned that nitroxylation of adamantanes carrying an electron-withdrawing group at C-2 occurs primarily at C-5 (syn), but if the substituent is alkyl, it takes place mostly at C-7 (anti). Thus, alkyl groups would have to be considered electron donors if located at C-2 even though they behave as acceptors at C-5.¹⁹⁷ But regardless of which explanation will eventually be agreed upon as the correct one, the data do seem to tell us that the addition to trigonal centers is assisted by electron-rich antiperiplanar vicinal bonds, and there is no reason to suppose that this principle is limited to highly symmetrical, rigid polycyclic molecules.

One may ask whether the efforts to understand the nature of the electronic effect in face selection in addition and elimination, as detailed in the papers in this issue, will bear any fruit, given the fact that so much controversy continues to surround the various proposals to explain it. Our feeling is that the information uncovered by the use of cyclic and polycyclic probe molecules can be summarized by the simple statement that the reagent tends to approach (or depart from) that face which is anti to the more electron-rich antiperiplanar vicinal bonds. Whatever factor is behind this experimental observation, it must surely also play a role in the chemistry of open-chain molecules. This means that there is a conformation for such molecules which has an electronic advantage over all others. That factor may of course be offset or even swamped by steric considerations; however, predictions of the stereochemistry of addition processes based *only* on estimates of which substituents are small, medium, or large will never be as successful as they could be.

XIII. Acknowledgments

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