Orbital-Controlled Stereoselections in Sterically Unbiased Cyclic Systems

Tomohiko Ohwada

Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya, 467, Japan, and Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan

Received October 16, 1998 (Revised Manuscript Received March 16, 1999)

Contents

10.1021/cr980371m CCC: $35.00
Published on Web 04/28/1999

I. Introduction

The reactivities of most types of organic molecules depend on the three-dimensional interactions of particular orbitals occupied or unoccupied by electrons.[1] The orbital interactions may determine the course of attack of a reagent, particularly when the stereogenic center is free from steric bias.[2] Such an influence of electronic modifications of the inducing center has been demonstrated in studies on the π facial selectivities of cyclic systems (see Figures 1−5), such as methylenecyclohexanes,[3] 5-substituted 2-adamantanones,[4,5] 5-substituted 1,3-cyclopentadienes,[6] 2,2-diarylcyclopentanones,[7] and spirofluorenecyclopentanones,[8,9] in addition to the classic examples of anomeric effects of pyranose sugars[10] and the exo reactivities of norbornanones and norbornenes[11] and cyclohexanones.[12] Biased reactions in nucleophilic additions, electrophilic additions, and Diels−Alder cycloadditions of those systems are the phenomenologically reasonable results of the unsymmetrical π face of the carbonyl and the olefin groups, arising from nonequivalent substituents. This asymmetry is an intrinsic feature of the system and is not induced by the attack of a reagent. In terms of perturbation theory,[13] the asymmetry of the π face stems from orbital interactions between particular orbitals of the σ and π frameworks in the molecule. Thus, the unsymmetrical π face of the carbonyl and the olefin groups involves unsymmetrization of π orbitals (see section II). This review is restricted to the π facial selectivities of *sterically unbiased cyclic systems* of ketones (section III), olefins (section IV), Diels−Alder dienophiles (section V), Diels−Alder dienes (section VI), and 1,4-conjugate addition acceptors (section VII). Cyclic systems hitherto studied are based on norbornane, cycloalkane, and bicyclic systems. In these cyclic systems, unpredictable steric effects due to the conformational ambiguity inherent in open-chain systems can be minimized.[14−17] Some sterically biased cyclic systems are also mentioned as a refer-

Tomohiko Ohwada was born in Tokyo, Japan, in 1959. He graduated from the University of Tokyo, Faculty of Pharmaceutical Sciences in 1982. In 1987 he received his Ph.D. from the University of Tokyo under the direction of Professor Koichi Shudo. Before obtaining his Ph.D., in 1985, he was an Assistant Professor at the University of Tokyo, Faculty of Pharmaceutical Sciences. In 1998 he moved to the present position as Full Professor. From 1992 to 1994 he did a visiting study with Professor Koop Lammertsma (now Professor at Vrije University, Amsterdam, The Netherlands) at the University of Alabama at Birmingham in the area of ab initio calculations. His research interests include the chemistry of dications (superelectrophiles), stereoselections, theoretical calculations, and medicinal chemistry.

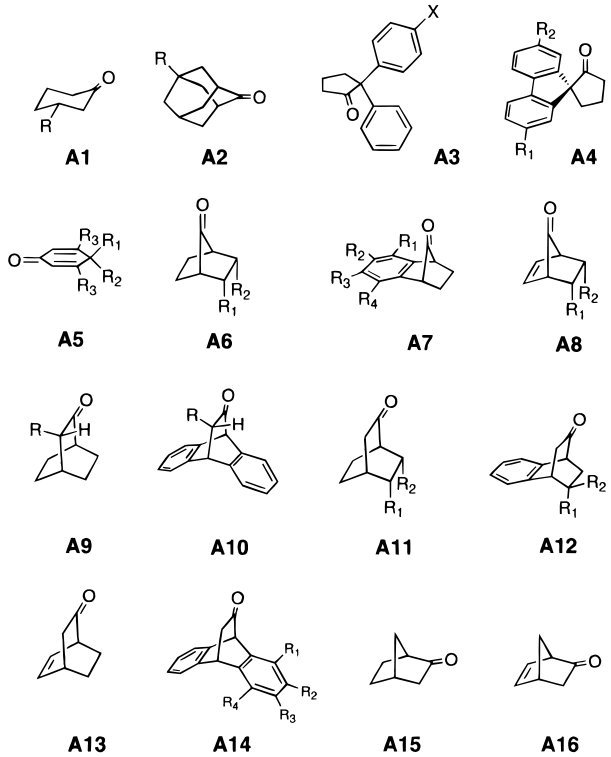


Figure 1. Facially biased ketones.

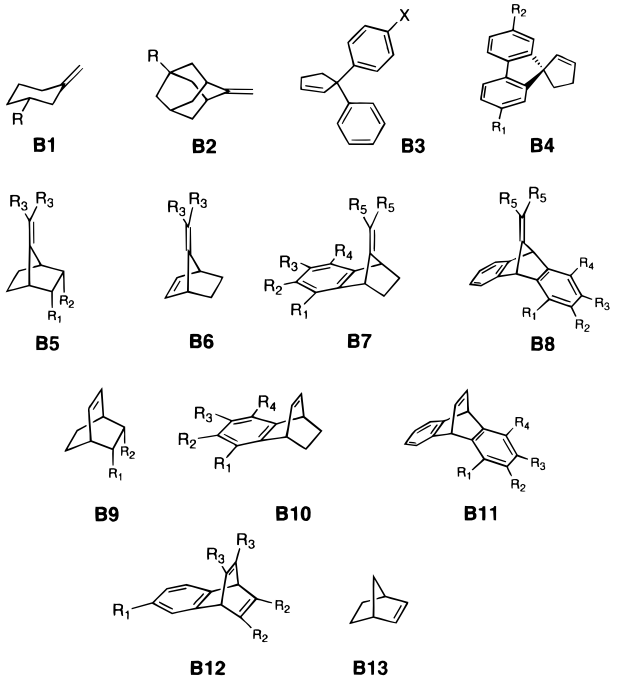


Figure 2. Facially biased olefins.

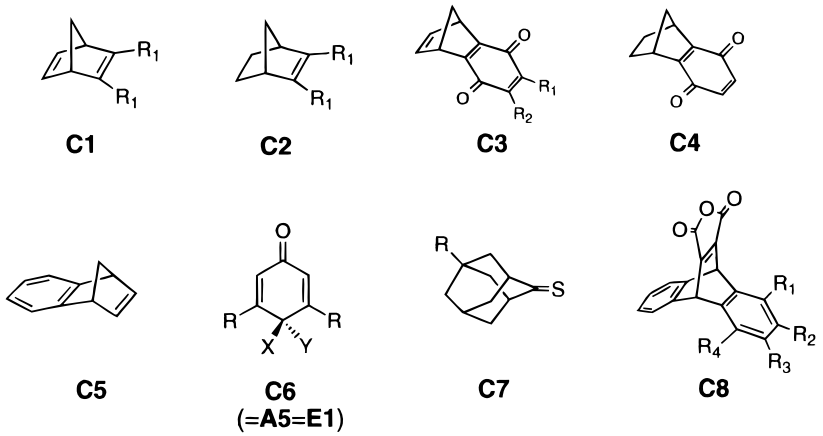


Figure 3. Facially biased Diels−Alder dienophiles.

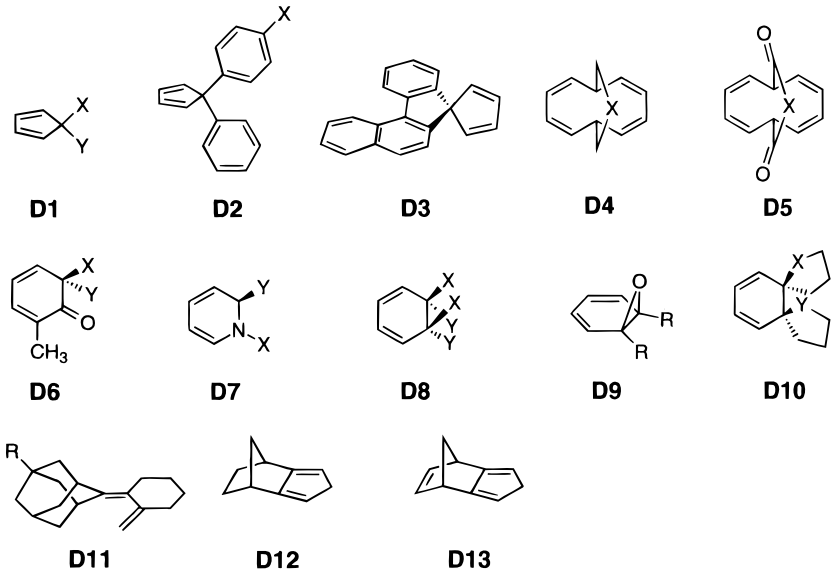


Figure 4. Facially biased Diels−Alder dienes.

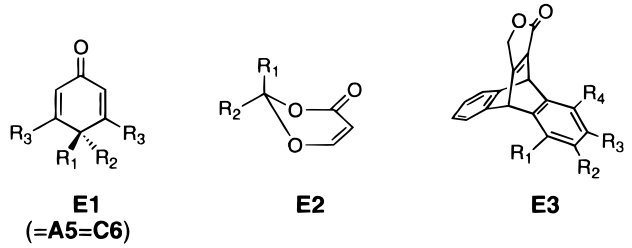


Figure 5. Facially biased Michael acceptors.

ence of a steric effect. Finally, the interaction leading to an unsymmetrical π face affects the interacting substituents in a reciprocal manner. These reciprocal perturbations are discussed in section VIII.

II. Unsymmetrization of π Orbitals

A. π-Facial Selectivities of Sterically Biased and Sterically Unbiased Systems

π Orbitals of trigonal carbon atoms of a carbonyl or an olefin group have a symmetric character, i.e., they are symmetric in magnitude and antisymmetric in sign. This nodal property constitutes a symmetric π face (π plane) of carbonyl and olefin groups. Sterically biased carbonyl and olefinic compounds afford a biased pair of reaction products. Steric bias can be amplified through coordinative association of reagents prior to the formation of the product. These sterically biased systems involve a different space environment with respect to the relevant π face, whether the π face remains intact to conserve the intrinsic symmetric nature of the π orbitals (Figure 6a) or is subject to geometrical distortions, such as pyramidalization of the trigonal carbon centers[18−23] or twisting of the C−O or C−C double bonds[24] (Figure 6b). Facially selective reactions do occur in sterically unbiased systems, and these facial selectivities can be interpreted in terms of involvement of an unsymmetrical π face (Figure 6c and 6d). Particular emphasis has been placed on the dissymmetrization of the symmetric magnitude of the orbital extension, i.e., *orbital distortions*, as an origin of the facial selectivities (Figure 6d).[25,26] There are two types of orbital distortions, orbital rehybridization (**2.1**, Figure 7a) and orbital tilting (**2.2**, Figure 7b), arising from p−s orbital mixing and p−p orbital mixing, respectively. The theoretical foundations and chemical applications of orbital distortions have been established by Fukui's group (Inagaki, Fujimoto, Fukui),[25−28] Hoffmann's group (Libit and Hoffmann),[29] and Imamura[30,31] on the basis of the perturbation

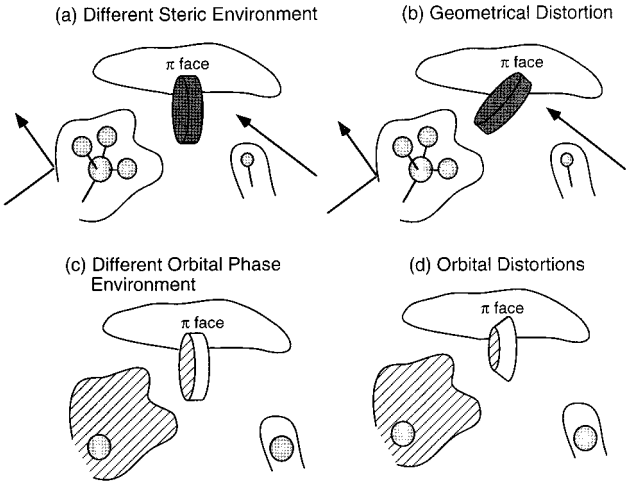


Figure 6. Unsymmetrization of the π face in sterically biased systems (a and b) and in sterically unbiased systems (c and d). (a) Steric difference unsymmetrizes the π face. (b) Steric difference may accompany the geometrical distortions such as pyramidalization and tilting of the π face. (c) Different orbital phase environment unsymmetrizes the π face. (d) Different orbital phase environment can induce orbital distortions such as orbital rehybridization and tilting (see also Figure 7).

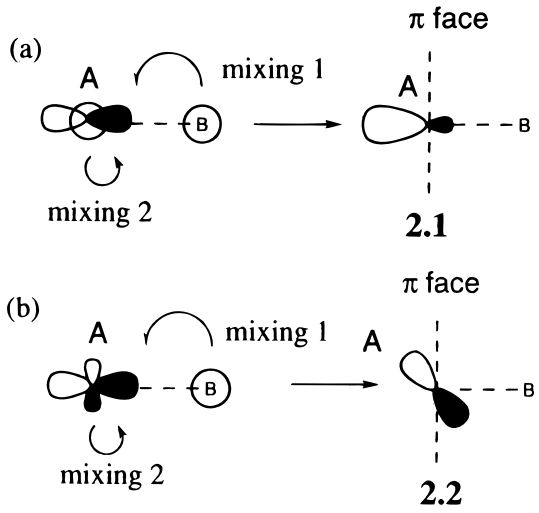


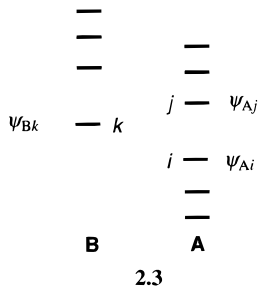
Figure 7. Orbital mixing: (a) orbital hybridization (b) orbital tilting. Mixing 1: first-order orbital mixing. Mixing 2: second-order orbital mixing.

theory of orbital interactions,[13,32] and the applicability of orbital distortions to the chemistry of cyclohexanone was proposed as early as 1973 by Klein.[12] Later, essentially the same generalization of orbital distortions was described by Burgess and Liotta.[33] Although orbital distortion, i.e., thorough orbital mixing, is essential in canonical molecular orbitals,[34] little attention was paid to the unsymmetrization of the orbital phase symmetry (i.e., antisymmetric in sign) of the relevant π orbitals, that is, *unsymmetrization of the orbital phase environment in the vicinity of the π reaction orbital* (Figure 6c).[9] The following section briefly presents orbital interction diagrams based on perturbation theory as an aid to understanding the unsymmetrization due to the orbital phase environment, as distinct from that of orbital extensions.[13]

B. Orbital Distortions

1. Formalism of Perturbation Theory and Orbital Mixing Rules

Orbital unsymmetrization of the π orbitals of reaction centers can be analyzed in terms of perturbation theory:[13] molecular orbitals of the whole molecule are considered to be constructed from orbitals of the composite subsystems, the carbonyl (or olefin) moiety, and the remaining framework. Such analysis can identify the intrinsic nature of unsymmetrization to which the π orbitals are exposed. The way in which the orbitals of a molecule (or a fragment) are modified by those of another molecule (or a fragment), when interaction is allowed, can be formulated on the basis of perturbation theory.[26−30] Orbitals of fragment A are represented by ψ_{Ai} and ψ_{Aj} and those of fragment B by ψ_{Bk}. (**2.3**). In most



2.3

cases, nondegenerate perturbation can be assumed. According to perturbation theory, modification of the orbital ψ_{Ai} of fragment A by other orbitals can be represented (eq 1) as a second-order perturbed orbital (ψ_{Ai}'), where ϵ is the orbital energy of the specified unperturbed orbital and h_{ab} is the resonance integral between the orbitals a and b. This formalism distin-

$$\psi_{Ai}' = \psi_{Ai} + t_{ki}^{(1)}\psi_{Bk} + t_{ji}^{(2)}{}_{Aj} \quad (1)$$

$$t_{ki}^{(1)} = \frac{h_{ik}}{(\epsilon_{Ai} - \epsilon_{Bk})} \quad (2)$$

$$t_{ji}^{(2)} = \frac{h_{ik}h_{jk}}{(\epsilon_{Ai} - \epsilon_{Aj})(\epsilon_{Ai} - \epsilon_{Bk})} \quad (3)$$

guishes the modification of the original wave function ψ_{Ai} arising from mixing-in of the orbital ψ_{Aj} on the same fragment (A) from that of the orbital ψ_{Bk} on the other fragment B. Thus, ψ_{Bk} mixes into ψ_{Ai} with the first-order mixing coefficient $t_{ki}^{(1)}$, and ψ_{Aj} also mixes into ψ_{Ai} within fragment A with the second-order mixing coefficient $t_{ji}^{(2)}$, when the orbitals ψ_{Ai} and ψ_{Ak} both interact with ψ_{Bk} of fragment B (see Figure 7). The energy $\epsilon_{Ai'}$ of the perturbed level ψ_{Ai}' that originates from ψ_{Ai} is given by expansion terms in perturbation theory as

$$\epsilon_{Ai'} = \epsilon_{Ai}^{0} + \epsilon_{Ai}^{(1)} + \epsilon_{Ai}^{(2)} + \epsilon_{Ai}^{(3)} + \ldots$$

The first-order energy $\epsilon_{Ai}^{(1)}$ vanishes since the geometry of fragment A and that of fragment B are assumed to be unaffected by intermolecular perturbation in the present approximation. Note that the

first-order mixing between ψ_{Ai} and ψ_{Bk} (i.e., $t_{ki}^{(1)}$) leads to the second-order energy change $\epsilon_{Ai}^{(2)}$. The second-order orbital mixing (i.e., $t_{ji}^{(2)}$) between ψ_{Ai} and ψ_{Ak} leads to a third-order energy correction $\epsilon_{Ai}^{(3)}$. Two modes of interactions are possible, with in-phase and out-of-phase combinations of orbital mixing (see Figure 9), depending on the signs of the resonance integrals (e. g., h_{ab}) and the relationship of the orbital energies. If we arrange the orbital phases of ψ_{Ai} and ψ_{Bk} such that a positive overlap integral represents bonding character and assume that resonance integrals (e.g., h_{ab}) are usually negative (according to the Wolfsberg−Helmholz formula[13]), the numerator of the first-order mixing coefficient $t_{ki}^{(1)}$ has a minus sign and that of the second-order mixing coefficient $t_{ji}^{(2)}$ has a plus sign. Thus, in the first-order orbital mixing, ψ_{Bk} mixes into ψ_{Ai} in an in-phase combination, i.e., in a bonding manner (i.e., $t_{ki}^{(1)} > 0$) if ψ_{Bk} lies higher in energy than ψ_{Ai} (i.e., $\epsilon_{Ai} - \epsilon_{Bk} < 0$), but in an out-of-phase combination, i.e., in an antibonding manner (i.e., $t_{ki}^{(1)} < 0$) if ψ_{Bk} lies lower in energy than ψ_{Ai} (i.e., $\epsilon_{Ai} - \epsilon_{Bk} > 0$). Similarly, the sign and magnitude of the second-order mixing coefficient are determined by the orbital energy order and overlap efficiency. All possible modes of orbital mixing in the second-order perturbation were presented by Inagaki et al.[26] Therefore, second-order orbital interactions involve mixing together of the orbitals of a molecule or the atomic orbitals of an individual atom, which are intrinsically orthogonal, through the interaction of an intervening orbital B. These authors interpret the observed unsymmetrical π face in electrophilic reactions of norbornene (**42**)[25,26] (see IV.F) and Diels−Alder reactions of 5-substituted cyclopentadienes (**50**)[35] in terms of the distorted shapes of orbitals due to second-order mixing (see VI.B). These distortions may stem from second-order orbital interactions but are essentially small and in some cases arbitrary or overestimated.[36] However, this second-order perturbation cannot be ignored, because the first-order perturbation should lead to second-order mixing. Furthermore, the effect of the first-order mixing may be amplified along the reaction coordinate.[37]

2. Klein's Model

Klein proposed that the axial preference of cyclohexanones (**A1**) originates in the nonequivalence of the two faces of the carbonyl group,[12,38,39] which is inherent to substituted cyclohexanones but not to acyclic ketones. The remainder of this paragraph is taken directly from the publication of Klein[12] (see Figure 8 essentially the same as Klein's originally figure). In the substituted cyclohexanones all the atoms and bonds are on one side of the carbonyl plane and particularly important are the β C−C bonds which enter into a hyperconjugation interaction with the π-electrons of the carbonyl group. The symmetrical bonding σ orbital of these bonds interacts with the π bond, forming two orbitals of different energy (Figure 8). A similar interaction exists between the antibonding symmetrical σ^* orbital of the β C−C bonds and the antibonding π^* orbital, again forming two orbitals of different energy. The bonding orbital of highest energy (**2.4** in Figure 8) has an out-of-phase combination (i.e., antibonding interaction)

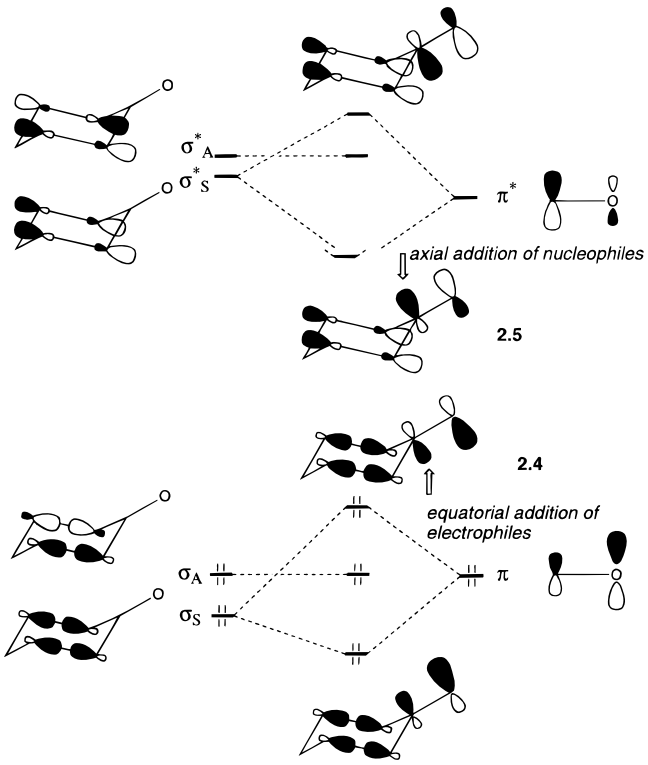


Figure 8. Klein's model.

of the carbonyl π_{CO} orbital with the orbitals of the C−C bonds (σ_{CC}), and the electron density at the carbonyl function on the side containing these bonds is diminished but the density on the other face would be therefore larger. This is the frontier orbital (HOMO) that will be attacked by electrophiles such as boranes or also a proton in the case of an enol, since a similar scheme can be established for the exocyclic C=C double bond of methylenecyclohexanes (**B1**). In fact, in the 3-substituted methylenecyclohexanes **B1** equatorial attack is therefore observed (see IV.A). Nucleophiles, on the other hand, will attack the lowest unoccupied orbital (LUMO, **2.5** in Figure 8). Here the situation is reversed, since the in-phase interaction with the symmetrical vacant C−C σ^* bond orbital makes the lobe of the orbital on the carbonyl carbon (π^*_{CO}) of the LUMO smaller on the face containing the C−C bonds, thus avoiding electron repulsion, and therefore the orbitals of the LUMO are larger on the side of the β C−C bonds. The attack of nucleophiles such as hydride ion by interaction with the LUMO will be therefore easier from the axial direction in the absence of steric effects. This is what is observed in the reduction of cyclohexanones **A1**.

Apparently the Klein's model is based on orbital distortions[12] (Figure 7a), i.e., orbital rehybridization of the carbon 2p and 2s atomic orbitals of the relevant carbon reaction center, although unsymmetrical first-order perturbation on the π orbital is suggested. Another important point in Klein's model is the orbital motifs of the LUMO of carbonyl molecules and the HOMO of olefinic molecules. That is, the former arises from in-phase combination of the orbital of the carbonyl π_{CO}^* and that of the remaining fragment while the latter arises from out-of-phase combination

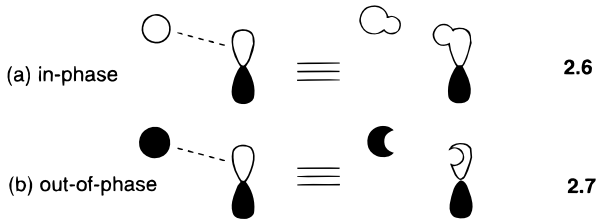


Figure 9. First-order unsymmetrization of π orbitals.

of the olefinic π_{CC} and the residual orbital.[40−42] This notion is based on the definition of frontier orbital theory.[1]

C. Unsymmetrized Orbital Phase Environment

1. Principles of Orbital Interactions

Although the second-order mixing of orbitals has been appreciated as a source of orbital unsymmetrization, the effect of the first-order mixing on the unsymmetrization of the π orbitals has been little discussed. The first-order interactions asymmetric to each π lobe of the carbonyl or olefin π orbitals are proposed to be the origin of the facial selectivities (Figure 9).[9] These first-order interactions involve two possible combinations, in-phase (**2.6**, Figure 9a) and out-of-phase combinations (**2.7**, Figure 9b) of the interacting orbitals, *although these mixings will not by themselves create a second-order hybridization* (Figure 7a) *or tilting* (Figure 7b) *of the* π *and* π^* *orbitals to one face of the* π *bond*. Unsymmetrization of the π orbitals arising from the first-order mixing is based on simple, well-defined principles of electron density perturbation along the internuclear region (Figure 10).[13] Principle 1: in-phase mixing of orbitals (of fragments A and B, for example, **2.8**) leads to buildup of bonding electrons along the internuclear region (of a combined molecule A−B); out-of-phase mixing of orbitals (A and B, **2.9**) depletes the bonding electrons from the internuclear region (A−B). To emphasize the electron density distribution of the internuclear region in addition to the phase relation of the interacting orbitals, we adopt the diagrams depicted in **2.6**, **2.7**, **2.8**, and **2.9** (Figures 9 and 10):[9] the buildup of the bonding electron is equivalent to delocalization of the electron into each bonding region along the bond axis (**2.8**, see also **2.6**); the removal of the bonding electron from the internuclear region can be regarded as virtual delocalization of the electron of each fragment into each antibonding region along the internuclear axis (**2.9**, see also **2.7**). In the case of orbital interactions of two vacant orbitals, the depletion and buildup of the orbital electron density (or the diffusion of the orbital into the internuclear region) are notional because there is no electron present. However, we can consider the virtual electron density which is to be attacked by electrons of an occupied orbital (e.g., the HOMO) of a reagent.[43] The bonding or antibonding delocalization depends on the energy difference and on overlap:[13] interactions of orbitals with a smaller energy gap or with a larger set of overlap integrals more significantly perturb the electron density distribution in the interacting region. All possible orbital motifs for facial selectivities are shown in Figure 11, motifs i and ii

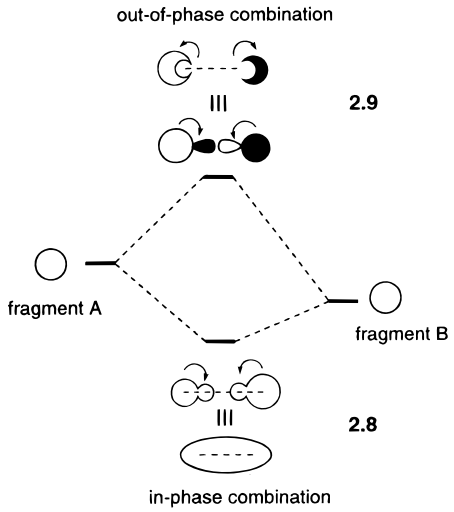


Figure 10. Principles of orbital interaction.

being for vacant reaction π orbitals such as those of ketones and motifs iii and iv being for occupied reaction π orbitals such as those of olefins.[44] Predicted preferred attack is based on the intrinsic unsymmetrization of the π (π^*) orbitals of the reaction centers (Figure 11). Reagents can recognize this asymmetry of the π orbital if the trajectory of additions permits. Houk et al. defined the orbital interaction between reagents and substrates along the trajectory of additions.[222] This can be regarded as an outcome of the orbital unsymmetrization inherent in the π reaction centers. In-phase combination of the π^*_{CO} orbital and the vacant peripheral orbital lowers the energy of the π^*_{CO} fragment, so activating it for attack of a nucleophile, and different amplitudes of the wave functions of the peripheral orbitals result in different build-up of the virtual bonding region between nuclei (**2.6**). A larger vacant bonding region captures the incoming electrons of a nucleophile more efficiently (motif i in Figure 11). Out-of-phase combination of π_{CC} with the occupied peripheral orbital raises the energy so as to activate the π_{CC} fragment of the olefin to the attack of an electrophile. The different overlaps with the peripheral orbital result in divergent amplitudes of the antibonding region between nuclei. The antibonding unsymmetrization (**2.7**), arising from the orbital bearing a larger coefficient, greatly reduces the electron-donating ability in response to the attack of the electron-deficient orbital of an electrophile (motif iv in Figure 11).

The unsymmetrized orbital interaction through the first-order mixing involves perturbation of the electron density along the internuclear axis, that is perturbation out of the nucleus, which is poorly described in the conventional nucleus-centered atomic orbital functions. Dannenberg et al. invented a method (polarized π-frontier orbitals, PPFMO) of breaking the symmetry of the π-orbitals of nonsymmetrical molecules with respect to their nodal planes.[45,46] To break the symmetry of the atomic p-function of the reactive π center, each new p-orbital is constructed from a normal p-function and two additional Gaussian s-type functions, the latter superimposed over each lobe of the p-function (Figure 12). These additional polarizable s-orbitals have

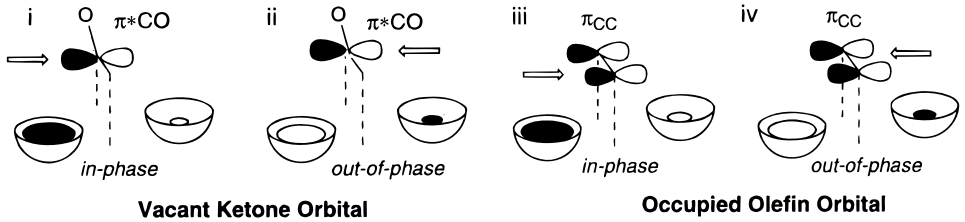


Figure 11. General orbital interaction motifs.

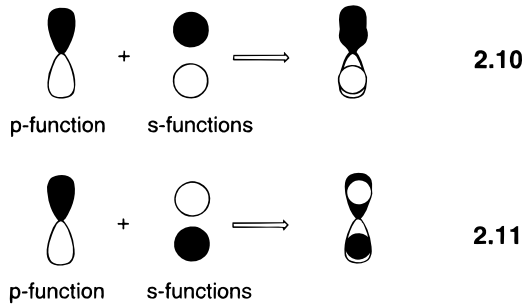


Figure 12. Combination of a p-orbital with two s-functions.

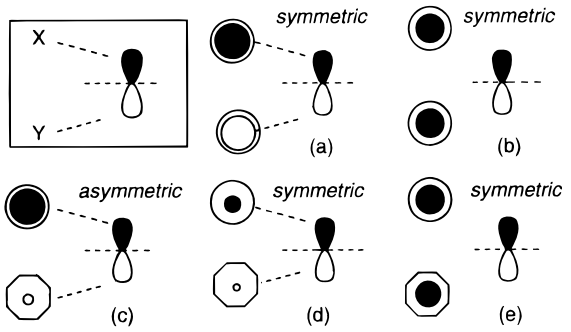


Figure 13. Unsymmetrization of π orbitals. Equivalent substituents on both sides (X = Y) do not perturb π face symmetry, regardless of whether an interaction is present (case a) or absent (case b). Nonequivalent substituents (X ≠ Y) do perturb the π face to be asymmetric (case c). When the nonequivalent interaction arising from the nonequivalent substituents (X ≠ Y) is small or negligible, the π face can still be symmetric (case d). When the interaction is absent, even in the case of the nonequivalent substituents (X ≠ Y), the π face is symmetric (case e).

different coefficients associated with each face of each π-center. These additional s functions on each lobe of the p_π orbital in in-phase (**2.10**) and out-of-phase (**2.11**) modes may represent the different first-order mixing imposed on each lobe of the π orbitals in the in-phase (**2.6**) and out-of-phase (**2.7**) motifs, respectively.[47]

Phenomenologically, the effects of substituents (in particular, those free from significant steric interference) on the π centers of carbonyl and olefin groups can be classified as follows (Figure 13):[48] equivalent substituents on both sides essentially do not perturb π face symmetry, regardless of whether an interaction is present (case *a*) or absent (case *b*). Nonequivalent substituents do perturb the π face and will produce a biased pair of products (case *c*). This is not always the case, however. Even in the presence of the interaction of nonequivalent substituents, the π face can still be equivalent when the interaction is symmetric or canceled (case *d*). When the interaction between the nonequivalent substituents and the π center is absent, of course, there is no perturbation of the π face (case *e*), which corresponds to orbital noninteraction as defined by Hoffmann et al.,[49] owing to symmetry disagreement. Precisely speaking, case *d* can be regarded as an extremely weak asymmetric interaction of nonequivalent substituents, which is, in fact, different from noninteraction (case *e*). Defining these three cases (*c*, *d*, and *e*) is of theoretical importance because chemical intuition will not distinguish them.

D. Orbital Interactions in the Transition State

There are several rationalizations of the experimental facial selectivities, the most significant discrepancies being in the assumptions concerning the orbital interactions involved in the reaction coordinate leading to the transition state. Formation of a chemical bond represents localization of electrons in the internuclear region, that is electron delocalization into the internuclear region from the nucleus.[43,50−53] It is, therefore, reasonable to assume that an in-phase bonding interaction between the carbonyl vacant π^*_{CO} and an occupied orbital of nucleophiles,[54,55] or between the occupied olefinic π_{CC} orbital and an unoccupied orbital of electrophiles,[51,56−59] is indispensable for the reaction to proceed along the reaction coordinate (Figure 14a).[60] The orbital phase relations depicted in Figure 11 all involve these bonding interactions between a pair of reaction centers. Furthermore, orbital phase relations between the paired reaction centers and the peripheral orbital region (Figure 11) may encourage electron accumulation into the forming bonds. [61]

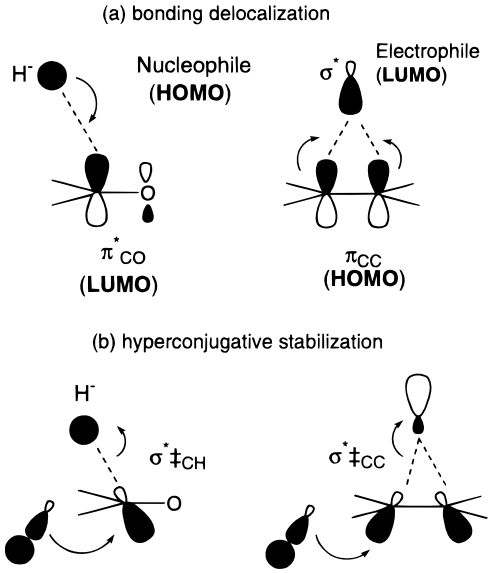


Figure 14. Orbital interactions in transition-state structures.

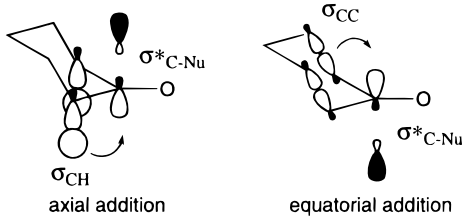


Figure 15. Cieplak model of hyperconjugation.

The ideas of Chérest and Felkin[62,63] and Anh and Eisenstein[64] are in line with the assumption that the incipient bond involves electron localization. They postulated that torsional repulsion between the resultant bonding incipient bond and eclipsing vicinal σ bonds destabilize the transition state. Felkin[62,63] attributed the developing eclipsing and resulting torsional strains to axial preference in the additions to cyclohexanones (**A1** in Figure 1), i.e., they proposed that the developing torsional strains of the bonding incipient bond formed on the equatorial side are more serious than the steric interference by the axial hydrogens in the three positions that occurs during attack on the axial side (see Figure 15). More recently, Houk et al. generalized the effects of torsional strain in determining facial selection in cyclic and acyclic systems.[65,66] Anh and Eisenstein introduced the concept of relief of exchange repulsion of the bonding incipient bonds,[64] that is, a hyperconjugative delocalization of the electrons in the incipient bond into their vacant antiperiplanar σ^* orbitals. This situation may correspond to motif ii in Figure 11.

On the other hand, Cieplak emphasized on the stabilizing effect on the transition-state structure arising from electron donation to the antibonding (i.e., vacant) incipient bond in an antiperiplanar manner (Figure 14b).[67] Hyperconjugative stabilization in the relevant orbital interactions should exist.[68] However, this stabilization is unlikely to result in accumulation of electron density in the internuclear region but rather should produce electron density transfer to the attacking reagent. This electron transfer resembles the orbital interaction involved in S_N2 nucleophilic substitution.[37,69]

III. Stereoselection of Ketones

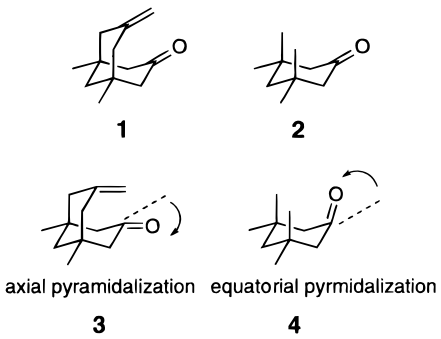
A. Cycloalkanone Derivatives

1. Cyclohexanones (A1)

Facial selectivities of cyclohexanone derivatives **A1** (Figure 1), i.e., axial or equatorial addition, have been intriguing to experimental and theoretical chemists for a long time. Although the facial selectivities of cyclohexanones **A1** depend to some extent on the nature of the nucleophiles, theoretical accounts of the axial addition of reducing reagents to cyclohexanones were proposed by Klein[12,38] and Cieplak et al.[67,70] A key observation concerning cyclohexanones **A1** is that hydride reduction of 4-*tert*-butylcyclohexanone gives the equatorial alcohol;[71] two reducing reagents ($LiAlH_4$ and $NaBH_4$) exhibit the same preference in favor of axial addition, i.e., axial addition:equatorial addition = 91−88.5:9−11.5 ($LiAlH_4$)[71,72] and axial addition:equatorial addition = 87−86:13−14 ($NaBH_4$).[71,73] Addition of acetylide anion, Na(Li or K)C≡CH, also showed a similar axial preference.[74] On the other hand, organolithium and Grignard reagents exhibited the reverse facial selectivity in favor of equatorial attack on 4-*tert*-butylcyclohexanone: axial addition:equatorial addition = 35:65 (CH_3Li)[72] and axial addition:equatorial addition = 31:69 (C_2H_5MgBr).[75] Similar facially selective behaviors are observed in 3-monoalkyl- and 3,5-dialkylcyclohexanones.[76]

Cieplak focused on the former axial preference (Figure 15)[67] and postulated that the axial approach is preferred in 4-*tert*-butylcyclohexanone because the stabilization energy arising through electron delocalization from σ_{CH} bonds into the $\sigma^*_{‡}$ orbital is greater than the stabilization energy from the corresponding interaction with σ_{CC} bonds, which occurs during the equatorial approach. This stabilization overwhelms the steric hindrance impeding the axial approach. There is great controversy as to whether CC or CH bonds are better donor/acceptors.

Laube and Hollenstein studied the single-crystal structures of conformationally defined cyclohexanone derivatives complexed with a Lewis acid.[77] They observed pyramidalization of the carbonyl group in **1** and **2**, the directions being in sharp contrast, that is, the pyramidalization is axially oriented in **1** (i.e., **3**) but equatorially oriented in **2** (i.e., **4**). Thus, the



axial pyramidalization in **3** causes the 2p C atomic orbital of $\pi C{=}O^*$ to approach the $C_\alpha{-}H_{ax}$ bond, acting as an electron donor, whereas the equatorial pyramidalization in **4** bends the carbonyl $\pi C{=}O^*$ orbital toward the $C_\alpha{-}C_\beta$ bond. Pyramidalization enhances bonding stabilization arising from the in-phase combination of the carbonyl π^* orbital with the σ_{CH} orbital in cyclohexanone **1** (**3.1** in Figure 16) or with the σ_{CC} orbital in **2** (**3.3** in Figure 17). The bicyclic ketone **1** serves as an example of pure axial attack, because the olefinic double bond behaves like an intramolecular nucleophile or it prevents the equatorial attack of other nucleophiles. Eliel and Senda showed that nucleophiles (such as H^- in the reaction with $LiAlH_4$) attack **2** with high preference from the equatorial direction.[71] Thus, the preferred direction of attack of the hydride nucleophile coincides with the preoriented geometrical pyramidalization, axial in **1** and equatorial in **2**. In this context, the geometric change is inherent to the ketone substrates, not induced by the attack of a reagent,

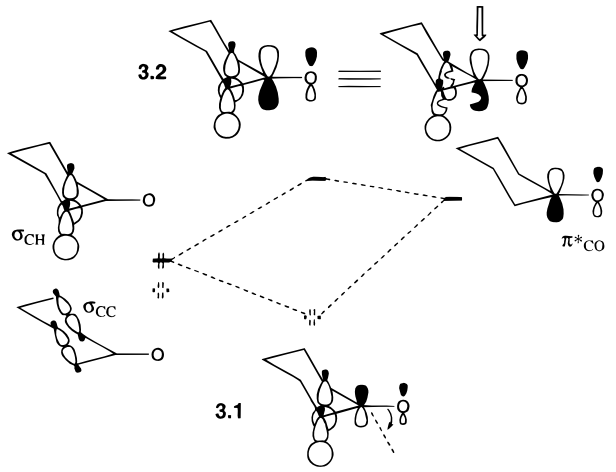


Figure 16. Orbital unsymmetrization of cyclohexanone.

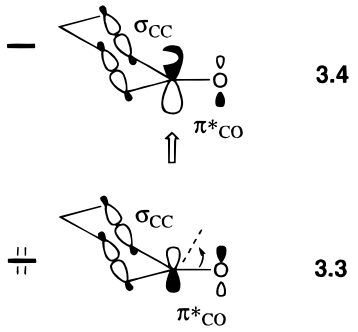
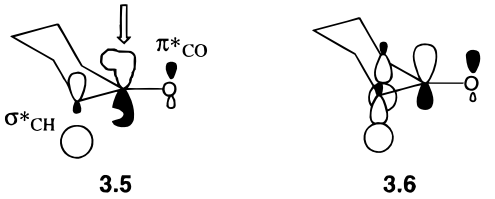


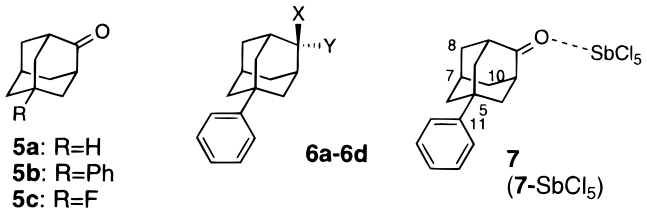
Figure 17. Orbital unsymmetrization in favor of equatorial addition.

supporting the intrinsic unsymmetrization of the carbonyl π^* orbital. In the reciprocal manner (Figure 16), the carbonyl π^* orbital, the orbital of the reaction center, is subject to out-of-phase combination with the relevant σ orbital, i.e., with the σ_{CH} orbital in **1** (**3.2** in Figure 16) and with the σ_{CC} orbital in **2** (**3.4** in Figure 17). The preferred direction of attack is consistent with the orbital unsymmetrization arising from this first-order unsymmetrization (motif ii in Figure 11). It is also plausible that the carbonyl π^* orbital (**3.5**) is unsymmetrized owing to the in-phase combination with the vacant σ^*_{CH} orbital (motif i in Figure 11), which would also favor axial addition. The orbital interaction diagram (Figure 16) is consistent with the recent computational work of Frenking et al. based on natural-bond-orbital (NBO) analysis[78] of the parent unsubstitued cyclohexanone,[79] the mixing of the β-σ_{CH} orbital being predominant over that of the β-σ_{CC} orbital in the LUMO of cyclohexanone. This is a reasonable outcome because of the more efficient orbital overlap with the carbonyl π^* orbital of the β-σ_{CH} orbital, which is aligned more parallel to the carbonyl π^* orbital rather than the β-σ_{CC} orbital, which is close to the carbonyl π plane. Frenking et al. also demonstrated orbital rehybridization of the carbonyl π^* orbital of cyclohexanone (**3.6**), resulting in a more diffused orbital amplitude in an axial direction.[79] This orbital distortion was also discussed in a quantitative manner by Tomoda and Senju.[68,80] This is superficially consistent with Klein's model (**2.5**, Figure 8). This orbital hybridization (**3.6**) is indicative of second-order mixing of the vacant 2s−2s σ^*CO orbital perpendicular to the carbonyl π^* orbital.



2. Adamantanones (*A2*)

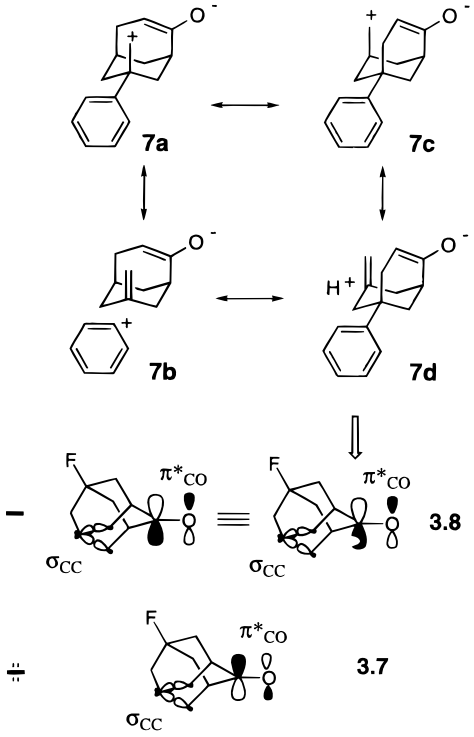
Adamantan-2-one (**5a**) can be regarded as a cyclohexanone derivative which is sterically and electronically symmetrized in both the axial and equatorial directions by means of additional bridging of the cyclohexanones (**A1**) and is also conformationally rigid. Facial selectivity of 5-substituted adamantan-



2-ones (**A2**) was initially studied by Giddings and Hudec,[4] followed by intensive studies by le Noble's group[5,81−83] on the adamantan-2-ones themselves and related analogues. Electron-withdrawing groups such as phenyl (**5b**), fluoro (**5c**), hydroxyl, and trifluoromethyl groups at the 5-position favored syn addition of the reducing agent ($NaBH_4$) (with respect to the substituent at the 5-position).[4,5] For example, in the hydride reduction with $NaBH_4$ of 5-phenyladamantan-2-one **5b**, syn addition was favored over anti addition (syn:anti = 58:42). The nucleophilic capture of the 5-phenyladamantyl cation corresponds well to the facial selectivity of 5-phenyladamantan-2-one:[5,84] syn addition is also favored, although the direction is rather dependent on the stereochemistry of the precursors. For example, while two precursors **6a** (X = −C═CH,Y═Cl) and **6b** (X = Cl,Y = −C═CH) gave the same preference (syn:anti = 75:25, for both precursors), another set of precursors **6c** (X = H, Y═ OTs) and **6d** (X = OTs,Y = H) gave a completely reversed preference: syn:anti = 25:75 (from **6c**) and syn:anti = 100:0 (from **6d**). Two different interpretations of the facial selectivities of adamantanones (**A2**) have been proposed, i.e., orbital tilting of the carbonyl carbon π^* orbital through the second-order orbital mixing of the perpendicular carbonyl carbon 2p orbital (Figure 7b)[4] and the Cieplak hyperconjugation model.[5] Cieplak himself[67] mentioned the applicability of his proposal to the results of Giddings and Hudec.

A comparison of the geometry of the symmetrized cage of the complex of 5-phenyladamantan-2-one-pentachloroantimony **7** (**7**-$SbCl_5$) (in order to average the disorder of the crystal structure of the adamantane skeleton) with the calculated structure of adamantanone was made by Laube and Stilz.[85] Bond length differences between the symmetrized adamantanone cage of **7** and the calculated structure (MM2) of adamantanone indicated a shortening of

the C7−C8 and C7−C10 bonds and a flattening of C7, which is consistent with the superior electron-releasing properties of the C7−H bond over the C5−C11 bond. This structural change can be interpreted in terms of preference for the resonance structures **7c** and **7d** over **7a** and **7b**, which is equivalent to the orbital interaction represented by **3.7**. This observed



structural character is consistent with the Cieplak model accounting for the observed syn addition of 5-phenyladamantan-2-one (**5b**) and 5-phenyladamantyl cation. In addition, the work of Laube explicitly demonstrated interaction of the σ_{CC} orbital and the carbonyl π^*_{CO} orbital, i.e., the observed geometrical change enforces the in-phase interaction of these relevant orbitals (**3.7**). In a reciprocal manner, the carbonyl π^* orbital of the 5-phenyladamantan-2-one (**3.8**) is unsymmetrized, arising from the first-order out-of-phase perturbation of the σ_{CC} orbitals, which is consistent with the observed syn preference. Thus, the carbonyl π face of the 5-phenyladamantan-2-one **5b** is intrinsically unsymmetrized even in the absence of the reagent, that is, prior to the formation of a "vacant incipient bond".

3. Cyclopentanones (A3)

The conformational nature of the six-membered cyclohexanone ring essentially contains a steric bias which predisposes the system toward axial attack. In fact, depending on the reagents, equatorial attack is favored, probably due to steric hindrance. The cyclopentyl framework eliminates much of the conformational ambiguity inherent in the freely rotating acyclic systems and also much of the inherent steric bias of rigid cyclohexane systems, where different approach trajectories of the nucleophile are not geometrically equivalent. Conformational flexibility of the five-membered ring (see Figure 18) allows for

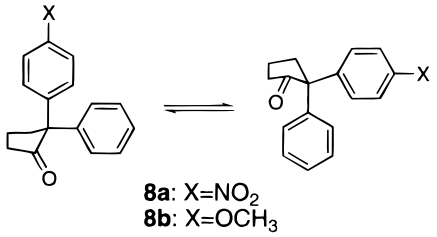
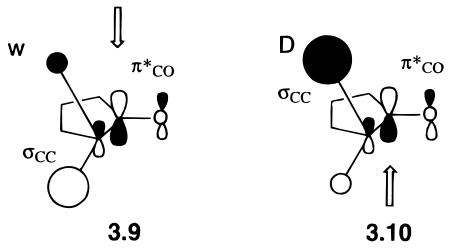


Figure 18. Puckering of the cyclopentane ring.

the geometric equivalence of the competing transition states. Halterman and McEvoy studied hydride reduction of a functionalized 2,2-diarylcyclopentanone **8** (Figure 18) containing an unsubstituted phenyl group and a *para*-substituted phenyl group, both geminal substituents being assumed to be sterically equivalent.[7] In this system, the two possible donating (or withdrawing) bonds are both carbon−carbon, so the dispute in the case of Cieplak and Johnson's cyclohexanones as to whether C−C or C−H bonds are better donors/acceptors can be avoided.[70] The stereoselective reduction with sodium borohydride of a functionalized 2,2-diarylcyclopentane was observed, the preferred direction being dependent on the aromatic substituent. In the case of the electron-withdrawing nitro group (**8a**), syn addition of the hydride ion was favored (syn:anti = 79:21), whereas the electron-donating methoxy group (**8b**, X = OCH_3) favored anti addition (syn:anti = 43:57). The addition opposite the more electron-rich aromatic ring was favored, which is in agreement with the Cieplak hypothesis.[7] The carbonyl π^* orbital is also assumed to be unsymmetrized, arising from the out-of-phase interaction of the σCC orbital attached to the more electron-donating aryl group (**3.9** and **3.10**). These

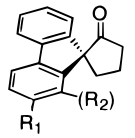


unsymmetrizations of the carbonyl π^* orbital correspond well to syn (**3.9**) and anti addition (**3.10**), respectively. The cyclopentane system was more sensitive to stereoelectronic effects, showing larger induced biases than the adamantanone system.[5]

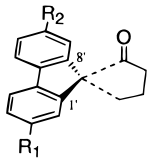
4. Spirocyclopentanones (A4)

As shown in the previous examples, the unsymmetric π face of carbonyl groups is postulated to be attributed to orbital interactions between a σ fragment and a π fragment. Possible interactions between two π fragments in a molecule are anticipated, wherein each of the interactive fragments would be subject to efficient reciprocal perturbations in its reactivity (see also section VIII).[8,9] As probes to pursue facial selectivities arising from π orbitals rather than from the σ orbitals, spiro[cyclopentane-1,9′-fluorene]-2-ones **9a**−**e** were designed and syn-

thesized and the facial selectivities of the carbonyl groups of **9a**−**e** are studied in this laboratory.[8,9] The



9a: R_1=H
9b: R_1=NO_2
9c: R_2=NO_2
9d: R_1=F
9e: R_1=OCH_3



10

carbonyl π orbital can interact with the aromatic π orbital of the fluorene in a manner similar to spiro conjugation.[86−90] The ketones **9** were reduced to the alcohols by the action of sodium borohydride in methanol at −43 °C. The anti alcohol, i.e., the syn addition of the reducing reagent with respect to the substituent, is favored in all cases irrespective of the substituent at C-2 or C-4 of the fluorene ring (2-nitro **9b** (syn:anti = 68:32), 4-nitro **9c** (syn:anti = 71:29), 2-fluoro **9d** (syn:anti = 72:28), and 2-methoxyl **9e** (syn:anti = 74:26) groups). This lack of substituent effect is in sharp contrast to the situation in the 2,2-diarylcyclopentanones **8**.[7]

A coordinative interaction of the substituent with the reducing agent can be excluded, in view of the great distances between the substituents and the carbonyl group. The distance between the fluorine atom at C-2 and the carbonyl carbon atom in **9d**, for example, is more than 5 Å on the basis of molecular models. The oxygen atoms of the nitro group at the 4-position (**9c**) are too far away to interact directly, or even in a coordinative manner, with the carbonyl group. Furthermore, the similar behavior of the two isomeric nitro fluorenes (2-nitro **9b** and 4-nitro **9c**) also excludes this possibility.

Simple considerations on the basis of electron delocalization theory allow us to predict a divergent reaction depending on the nature of the substituents, i.e., electron withdrawing (such as a nitro group) or electron donating (such as a methoxy group), as exemplified in the biased reductions of 2,2-diarylcyclopentanones **8**.[7] The result of the reduction of methoxy-substituted **9e** is, however, apparently in conflict with this idea. In the context of the Cieplak postulation, the electron-donating occupied orbitals, which may stabilize the incipient bond, will be the σ orbitals (C1′−C9/C8′−C9). However these σ orbitals are lower-lying in energy, as compared with the π orbitals of the fluorene. Thus, the electron donating arising from these σ orbitals is not effective.

In fluorenes bearing a spiro carbonyl group, π orbitals of fluorenes (**3.12**) and those of the carbonyl group (**3.11**) can interact predominantly through the *ipso* (C-1′ and C-8′) positions of the fluorene ring (**10**) (see also Figure 19). This type of interaction involves σ-type overlaps of the π orbitals in a spiro geometry, in a manner similar to spiro conjugation.[86,87] To reveal the perturbations arising from the spiro interaction, the molecular orbitals of the spiro ketone are considered to be constructed from orbitals of the composite subsystems, a fluorene and a carbonyl

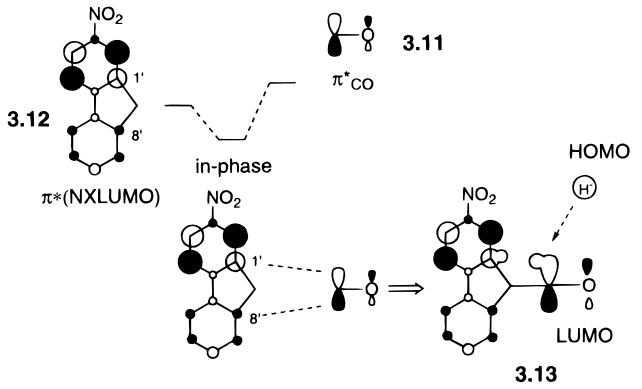


Figure 19. Orbital unsymmetrization of the carbonyl π* orbital.

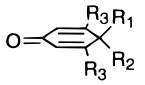
group. In accordance with the orbital phase agreement and similar energy, the π^*_{CO} orbital (**3.11**) interacts preferentially with the next-LUMO (NLUMO) (**3.12**) of the fluorene derivative, not with the LUMO: the LUMOs bear the orbitals at the *ipso* (C-1′ and C-8′) positions, symmetric in sign with respect to the plane passing through C-9 and the carbonyl group; the NLUMOs and π_{CO}* are antisymmetric in sign (Figure 19). The NLUMOs have coefficients largely localized on the one of the benzene rings, the one bearing the nitro, fluoro, or methoxyl substituent (for example at C-1′ rather than at C-8′). In addition, there are small energy separations between the NLUMO of the relevant substituted fluorenes and carbonyl π_{CO}*. In-phase combination of the NLUMO of the fluorene (for example, 2-nitrofluorene) and π^*_{CO} orbital (**3.13**, Figure 19) lowered the energy of the π^*_{CO} fragment, activating it for attack of a nucleophile. At the points of interaction (at C-1′ and C-8′), different amplitudes of the wave functions of the NLUMO of the fluorene result in different build-up of the virtual bonding region between nuclei.[21] A larger vacant bonding region captures the incoming electrons of a nucleophile more efficiently. Therefore, the π^*_{CO} fragment favors the interaction with the HOMO of the hydride ion on the side of the substituent, resulting in a biased reduction product (see Figure 11, motif i).

Complex formation of the reducing reagent, predominantly on the side of the nitro benzene moiety of **9b** and **9c**, might take place prior to the attack of reagents. This idea is based on a favorable electrostatic interaction, which may account for the observed facial selectivity. In this case, however, the nucleophile on the syn side is stabilized and less reactive and, therefore, the nucleophile would attack on the anti side. This is in disagreement with the observed bias. In fact, Wipf and Kim showed a retarded addition of a nucleophile arising from dipole−dipole stabilization of the reagent in the 4,4-disubstituted cyclohexadienone system **A5** (vide infra).[91]

5. 4,4-Disubstituted Cyclohexadienones (A5)

Wipf and Kim studied nucleophilic carbonyl additions of 4,4-disubstituted cyclohexadienones **A5** (Figure 1).[91] Addition of methylmagnesium bromide to the dieneone **11** in THF at −78 °C gave the alcohol,

the anti addition (with respect to the methoxy group) being favored with syn:anti = 17:83 (1:4.8). If complexation of the Grignard reagent to the oxygen substituent at the 4-position of the dienone **11a** has any influence on the stereochemical course of the nucleophilic addition, then such an effect would be expected to be more pronounced in the alcohol **11b** and significantly less effective in the silyl ether **11c**.



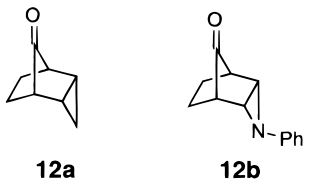
11a: R_1=OCH_3, R_2=CH_3, R_3=H
11b: R_1=OH, R_2=CH_3, R_3=H
11c: R_1=OTMS, R_2=CH_3, R_3=H

Treatment of **11c** with methylmagnesium bromide in THF led, however, to a considerable increase of anti addition, resulting in the facial selectivity of syn:anti (with respect to the silyl ether group) = 5:95 (1:17.7). In contrast, treatment of alcohol **11b** with an excess of Grignard reagent resulted in a reduced syn:anti selectivity (syn:anti (with respect to the methoxy group) = 11:89 (1:7.9)). In the reaction of **11b** with the Grignard reagent, a product arising from conjugate addition was formed, which showed exclusively syn preference with respect to the hydroxyl group. This syn preference is consistent with the observation of Liotta et al.,[92,93] who suggested ligand-assisted nucleophilic addition reactions of **11b** (see section VII). An excellent linear correlation of calculated dipole moments vs the logarithm of the facial selectivity (the larger the dipole moment of the oxygen function, the larger the anti preference (with respect to the oxygen function) was obtained in the case of 4,4-disubstituted cyclohexadienones, supporting the notion that the addition of a reagent on the side stabilized by dipole interactions will be retarded.

B. Bicyclic Systems

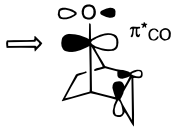
1. Bicyclo[2.2.1]heptane Systems (A6)

a. Small-Ring-Annulated Bicyclo[2.2.1]heptanones. Gassman et al. studied the facial selectivity of 7-norbornanone **12a** annulated with an *exo*-cyclopropyl group, i.e., tricyclo[3.2.1.$0^{2,4}$]octan-8-one.[94,95] Addition of methyllithium to **12a** gave predominantly the anti addition product with respect to the fused cyclopropane ring (syn addition:anti addition = 5:95).



12a **12b**

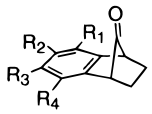
Similarly, addition of methylmagnesium iodide gave a 9:1 mixture of anti and syn adducts (syn addition:anti addition = 10:90). The carbonyl π^* orbital is subject to out-of-phase coupling with the bonding Walsh orbital (**3.14**).[34] This out-of-phase motif (**3.14**) is consistent with retardation of the syn addition with respect to the cyclopropyl group, that is, anti preference. On the other hand, the addition of lithium



3.14

dimethylcuprate to the ketone **12a** gave a reverse facial selectivity (syn addition:anti addition = 92:8), which occurs because this reagent has a different mechanism of methyl transfer, involving an initial electron-transfer process.[94] Sodium borohydride reduction of the 7-norbornanone **12b**, annulated with an *N*-phenyl aziridine ring, 3-phenyl-3-aza-*endo*-tricyclo[3.2.1.$0^{2,4}$]octan-8-one, was also studied by Gassman et al.,[95] who found a strong syn preference with respect to the aziridine group (syn addition:anti addition = 100:0). Replacement of the cyclopropyl ring with an aziridine ring diminished the contribution of the Walsh-type orbital to the LUMO of the molecule. Houk et al. rationalized the anti preference of a reducing reagent toward **12a** in terms of electrostatic repulsion due to the electron-donating cyclopropyl group.[96] Also, the reverse syn addition of **12b** was rationalized in terms of geometrical distortion of the ethano bridges arising from ring strain due to the aziridine ring, rather than the electrostatic interaction.[96]

b. 7-Benzonorbornenones (A7). Metal hydride reduction of 7-benzonorbornenones **13a** was studied by Okada et al.[97,98] Reducing agents such as $LiAlH_4$,



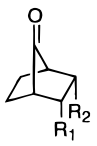
13a: R_1=R_2=R_3=R_4=H
13b: R_1=R_2=R_3=R_4=F
13c: R_1=R_2=R_3=R_4=Cl
13d: R_1=R_4=OCH_3, R_2=R_3=H

3.15

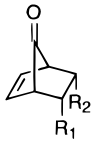
$NaBH_4$, B_2H_6, $BH(Sia)_2$, $LiAlH(O^tBu)_3$, and DIBAL-H favored anti addition (with respect to the ethano bridge) to the tetrafluoro (**13b**) and tetrachloro (**13c**) derivatives, for example, **13b**, syn addition:anti addition = 0:100 ($NaBH_4$); **13c**, syn:anti = 5:95. On the other hand, the 2,5-dimethoxy derivative (**13d**) also exhibited anti preference in the reduction with $LiAlH_4$ (in ether), $NaBH_4$ (in ethanol), B_2H_6, and $LiAlH(O^tBu)_3$, but a reverse syn selectivity was obtained in the reduction with $LiAlH_4$ (in THF), $BH(Sia)_2$, and DIBAL-H. Therefore, undefined effects such as solvent effects upon the aggregation of the reducing agents and chelation of the reducing agent to the carbonyl oxygen atom may influence the facial selectivity. A typical nonchelating reducing agent, sodium borohydride, highlights the intrinsic anti preference of the 7-benzonorbornanone **13a**. This anti preference is in disagreement with the Cieplak model,[67] although the syn preference (with respect to the ethano bridge) of the related bicyclic system, benzo[2.2.2]octene-2-one (**A12** in Figure 1; **19**), is compatible with the Cieplak prediction (*vide antra*).[99] The observed anti preference of **7a** can be rationalized in terms of steric hindrance due to the methylene

protons, in addition to the orbital unsymmetrization of the carbonyl π^* orbital arising from the in-phase combination of the aromatic π^* orbital (**3.15**).

c. 2,3-*endo,endo*-Disubstituted 7-Norbornanones (A6, A8). 2,3-*endo,endo*-Disubstituted 7-norbornanones **14a,b** are excellent substrates based on the 7-norobornanone system for probing nonsteric bias. Mehta and colleagues studied the facial selectivi-

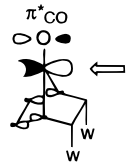


14a: $R_1=R_2=CO_2CH_3$
14b: $R_1=R_2=C_2H_5$



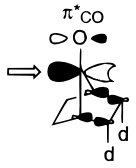
15a: $R_1=R_2=H$
15b: $R_1=R_2=CO_2CH_3$

ties of 2,3-*endo,endo*-disubstituted 7-norbornanones **14a,b**.[100−102] In the reduction of **14a,b** with sodium borohydride, lithium aluminum hydride, and the bulky lithium tri-*tert*-butoxyaluminum hydride, a very significant variation in face selectivity as a function of 2,3-*endo,endo* substitution was found, the most dramatic being the reversal in the syn:anti ratio (with respect to the substituent) in going from **14a** (bis(methoxycarbonyl), 84:16) to **14b** (diethyl, 20:80). The asymmetry of the π face of the 2,3-disubstituted 7-norbornanones **14a,b** arises from the first-order orbital unsymmetrization of the carbonyl π^* orbital (**3.16** in **14a** and **3.17** in **14b**), which is commonly involved in the facial unsymmetry of 5,6-*endo,endo*-disubstituted bicyclo[2.2.2]octan-2-ones (**A11** in Figure 1). Mehta et al. also studied the facial selectivities



w= electron-withdrawing group

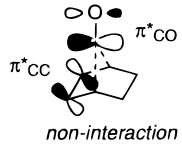
3.16



d= electron-donating group

3.17

of *endo*-substituted 7-norbornenones **15a,b**, which exhibit steric bias with respect to the anti side of the π face (with respect to the *endo* substituent).[103,104] In the reduction with sodium borohydride, high anti preference (more than 85%) was observed in the parent derivative **15a**. This is consistent with the facial preference of the reduction of 7-benzonorbornanone **13a**. Weak electron-withdrawing substituents (CH_2OCH_3, CH_2OAc, COONa) also showed anti preference, the magnitude being comparable to that in the case of the parent compound (**15a**), indicative of the steric bias of **15a**. In contrast to the 7-benzonorbornanone **13a** (like **3.15**), the relevant orbital interaction of the carbonyl π^* orbital with the unoccupied olefin π^* orbital (**3.18**) is disallowed in 7-norbornenone **15a** because of disagreement of orbital symmetry. In the case of a strong electron-withdrawing substituent (di- or mono-CO_2CH_3, CN), the syn preference of addition was increased, becoming predominant in some cases (di-CO_2CH_3 (**15b**), syn:anti = 55:45; mono-CO_2CH_3, syn:anti = 32:68; mono-CN, syn:anti = 56:44). This is consistent with the intrinsic



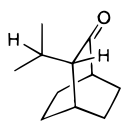
non-interaction

3.18

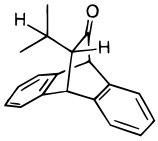
syn preference of 7-norbornanones **14a** substituted with potent electron-withdrawing groups. The syn preference of the strong electron-withdrawing groups is even greater in the addition of methyllithium: the diester derivative **15b** exhibited a high syn preference (syn:anti = 90:10), while anti preference was found in the parent (**15a**) and diether derivative (CH_2OCH_3) (syn:anti = 26:74). Electrostatic attraction was proposed as a rationale for the observed facial preferences of **14a,b** by Houk et al.[96] and Mehta et al.[102]

2. Bicyclo[2.2.2]octane Systems

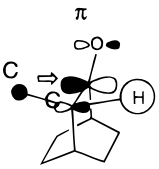
a. α-Alkyl-Substituted Bicyclo[2.2.2]octanones (A9, A10). The lithium aluminum hydride reduction of rigid bicyclic ketones, bicyclo[2.2.2]octan-2-ones **A9**[105] and dibenzobicyclo[2.2.2]octan-2-ones **A10**[106−108] (Figure 1), bearing an alkyl substituent at the α position of the carbonyl group was studied. A more hindered approach was preferred, i.e., an isopropyl group at the adjacent position of the ketone (R) seems to attract the hydride attack in **16a** and **17a**, syn addition:anti addition = 72:28 in **16a**; syn addition: anti addition = 80:20 in **17a**. This is analogous to



16a



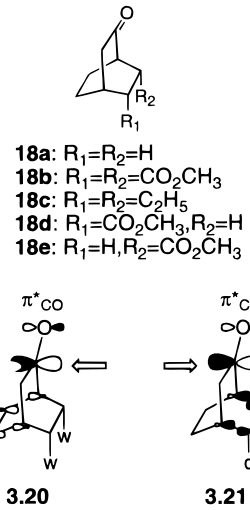
17a



3.19

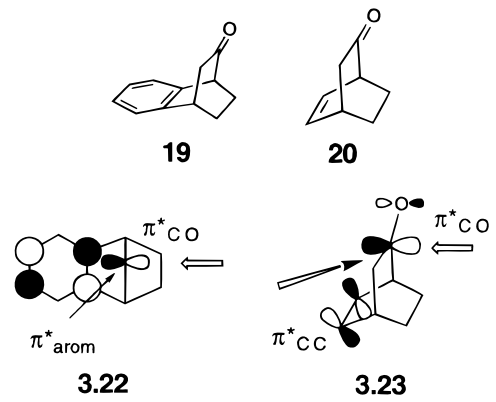
the predominance of the more hindered approach, that is, axial addition, in the lithium aluminum hydride reduction of 4-*tert*-butylcyclohexanone (**A1** (R = tBu)) (vide supra). As in the case of cyclohexanone (**3.2**), unsymmetrization of the carbonyl π^* orbital arising from the predominant interaction of the σ_{CH} orbital (**3.19**) may rationalize the syn preference.

b. 5,6-*endo,endo*-Disubstituted Bicyclo[2.2.2]-octan-2-ones (A11). Mehta et al. studied the facial selectivities of 5,6-*endo,endo*-disubstituted bicyclo-[2.2.2]octan-2-ones **A11** (Figure 1).[102,109] These systems are related to the 2,3-*endo,endo*-disubstituted 7-norbornanones **A6** (in Figure 1) but differ in the direction of the carbonyl π face (see Figure 25). Hydride reduction of 5,6-*endo,endo*-disubstituted bicyclo[2.2.2]octan-2-ones (**18**) with $NaBH_4$ and DIBAL-H and methylation with MeLi were studied.[102,109] The remote *endo*-substituents have a profound bearing on the face selectivity in nucleophilic additions to these ketones. The syn preference (with respect to the *endo* substituent) of the bis(methoxycarbonyl) substituents (**18b**) is completely reversed in favor of anti face addition in the diethyl substrate **18c**. On the other hand, relatively modestly inductive *endo*-substituents (R_1 and/or R_2 in **18**), such as



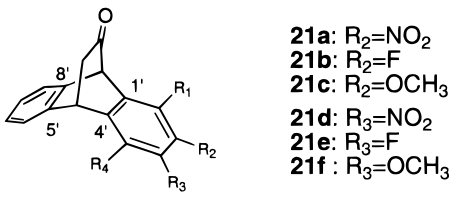
methoxymethyl and vinyl groups, exhibit no facial bias. These results are generally consistent with those obtained for the 2,3-*endo*,*endo*-disubstituted 7-norbornanone derivatives **14a,b**,[100,101] and therefore there seems to be no significant effect of bicyclic systems on the facial selectivities. The facial selectivities observed in both bicyclic systems (**14a,b** and **18b,c**) are compatible with the Cieplak model. These preferences can be also rationalized in terms of orbital unsymmetrization of the carbonyl π^* orbital arising from out-of-phase mixing of the vicinal σ_{CC} orbital of the bicyclo[2.2.2]octene systems **18** (**3.20** (for **18b**) and **3.21** (for **18c**)). The latter proposal is compatible with the observation that both **18d** ($R_1 = CO_2CH_3$, $R_2 = H$) and **18e** ($R_1 = H$, $R_2 = CO_2CH_3$) exhibit little difference in the face selectivity, i.e., syn selectivity when subjected to $NaBH_4$ (syn:anti = 65:35 in **18d**; 62:38 in **18e**) and DIBAL-H (syn:anti = 66:34 in **18d**; syn:anti = 61:39 in **18e**) reduction. That is, the facial selectivity is rather indifferent to whether the donating bond is precisely antiperiplanar or not with respect to the vacant incipient bond as defined in the Cieplak model (Figure 14b). Thus, Mehta et al. suggested the presence of significant electrostatic contributions from *endo*-electron-withdrawing groups, rationalizing the syn face selectivity in **18a,b**.[102] The behavior of **18d** and **18e** is also consistent with orbital unsymmetrization as in **3.20**.

c. Benzobicyclo[2.2.2]octan-2-ones (A12, A13). The facial selectivity of the parent benzobicyclo[2.2.2]-octan-2-one **19** (**A12**, $R_1 = R_2 = H$) (Figure 1), studied by Pudzianowski et al.,[99] is rather unexpected. Addition of organometallic reagents such as methyllithium and Grignard reagents exhibited syn preference (with respect to the ethano bridge), which is the more sterically hindered side. In the reduction of bicyclo[2.2.2]octenone **20** (**A13** in Figure 1) with $LiAlH_4$, syn addition is also favored (82:18 (syn:anti, with respect to the ethano bridge), the rate of syn attack being enhanced (in a ratio of 2.6) over that observed in the saturated derivative, bicyclo[2.2.2]-octanone **18a**.[11] This is in sharp contrast to the anti preference (with respect to the ethano bridge) of bicyclo[2.2.1]hepten-7-one **15a**[100] and 7-benzonorbornanone **13a**.[97,98] Therefore, the facial selectivities depend on the bicyclic systems. In the parent benzobicyclo[2.2.2]octan-2-one **19** and bicyclo[2.2.2]-octenone **20**, the carbonyl π^*_{CO} orbitals interact with the aromatic π^* orbital (**3.22**) or the olefin π^* orbital (**3.23**) in the in-phase manner, implying anti preferences in both systems. Thus, the predictions seem to



be in conflict with the observed syn biases. However, along the trajectory of attack of the nucleophile to the carbonyl group of the bicyclo[2.2.2]octane structures (indicated in **3.22** and **3.23**), out-of-phase interactions between the reagent and the substrate are involved, which is different from the situation in the bicyclo[2.2.1]heptane structures (**13a** and **15a**).[110−114] Thus, attack on the side opposite to the unsaturated moiety will be favored.

d. Dibenzobicyclo[2.2.2]octadienones Derivatives (A14). Dibenzobicyclo[2.2.2]octadienones (**A14** in Figure 1) bearing an aromatic substituent were designed to probe the unsymmetrization of the carbonyl π^* orbital arising from the aromatic π orbitals.[48,115] Aromatic substituents on the dibenzobicyclo-[2.2.2]octadienones **21** are unlikely to unsymmetrize the carbonyl π face sterically, because of their distance from the reaction center. Reduction of the carbonyl moiety of 2- ($R_2 \neq H$) and 3-substituted ($R_3 \neq H$) dibenzobicyclo[2.2.2]octadienones (**21**) was studied by using sodium borohydride in methanol at −43 °C. The 2- (**21a**) and 3-nitrodibenzobicyclo[2.2.2]-octadienones (**21d**) preferentially gave *anti* alcohols (with respect to the nitrobenzene moiety) on reduction with hydride ion, i.e., syn attack with respect to the nitrobenzene moiety (syn:anti = 77:23), with values of diastereomeric excess of 54% (**21a**) and 54% (**21d**), respectively. A fluoro substituent (in **21b** and



21e) also favors syn addition to give an *anti* alcohol (for **21b**. syn:anti = 57:43; for **21e**, syn:anti = 61:39). Substituent effects were found to be similar in both 2- and 3-substituted ketones, although the substituent is remote from the reaction center and different in direction. On the other hand, a methoxy group (in **21c** and **21f**) showed only a negligible

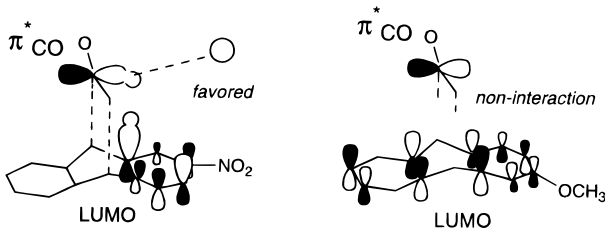


Figure 20. Orbital unsymmetrization of the carbonyl π^* orbital.

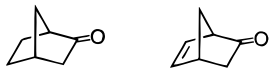
preference in the reduction reaction, giving a slight excess of the *anti* products.

The orbitals of the substituted dibenzobicyclo[2.2.2]-octadienones (**21**) are also assumed to be constructed from orbitals of subsystems, i.e., the substituted dihydroanthracene in convex geometry (**3.24**) and the carbonyl group (Figure 20). The low-lying vacant orbitals of the dihydroanthracene fragment bearing components at the *ipso* (C-1′,C-4′, C-5′, and C-8′) positions can participate in mixing with the π^*_{CO} orbital. An electron-withdrawing substituent such as a nitro or a fluoro group perturbs the π face of the carbonyl group. The lower-lying vacant aromatic π^* orbital of the dihydroanthracenes substituted with an electron-withdrawing nitro group (for example **3.24**) has coefficients largely localized on the benzene ring bearing the nitro group, because the relevant vacant aromatic π^* orbital (**3.24**) is predominantly derived from the LUMO of nitrobenzene, which is significantly lower in energy than the LUMO of benzene. Owing to orbital phase agreement and similar energy, the π^*_{CO} orbital mixes preferentially with the vacant aromatic π^* orbital of the dihydroanthracene (**3.24**) at the *ipso* position at C-1′ in an in-phase manner (**3.24** in Figure 20). This in-phase mixing lowers the energy of the π^*_{CO} fragment, activating it for attack of a nucleophile. Simultaneously, the in-phase overlap results in buildup of a virtual bonding region between nuclei (**3.24**). Therefore, the π^*_{CO} fragment favors the interaction with the HOMO of the hydride ion on the side of the substituent (motif i in Figure 11), resulting in the biased reduction product (syn alcohol) observed for the 2- and 3-nitro derivatives (**21a** and **21d**). On the other hand, the lowest-lying vacant aromatic π^* orbital (LUMO) of the dihydroanthracene substituted with an electron-donating hydroxyl group (**3.25**) has the orbital amplitudes at the *ipso* (C-1′ and C-4′; C-5′ and C-8′) positions that are approximately symmetric in sign and magnitude with respect to the plane passing through C-9 and C-10 (Figure 20). The NXLUMO of the hydroxy-substituted dihydroanthracene is also symmetric in sign. Therefore, the antisymmetric π^*_{CO} orbital does not interact significantly with these vacant π orbitals of **3.25**, resulting in an unperturbed π face of the carbonyl π^* orbital. This motif is regarded as an example of orbital *non*interaction,[49] designated as case *e* (Figure 13). Thus, the reduction of 2-methoxy and 3-methoxydibenzobicyclo[2.2.2]octadienones (**21c** and **21f**) should intrinsically show little or no bias, although the slight anti preference of **21c** is not explained by this model.

C. Classical Example of 2-Norbornanone (A15, A16)

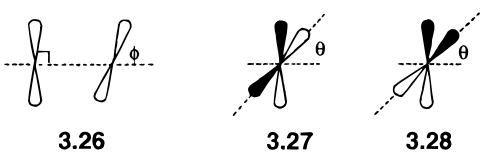
1. Unsymmetrization of the Carbonyl Orbital in 2-Norbornanone

Exo reactivity of 2-norbornanone **22** in nucleophilic addition (such as reduction with hydride) is a classical example of the facial selectivity of carbonyl groups.[11] Various theoretical interpretations of the



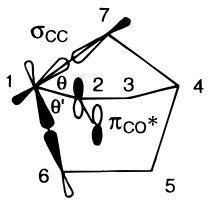
22 **23**

bias have been proposed. Two basic explanations have previously been given, that is, torsion-based arguments[116] and stereoelectronic arguments.[20,21,25,26,117,118] Intuitively, it seems likely that the asymmetry of the π orbital is an intrinsic feature of the nonequivalent environment around the trigonal center arising from the unsymmetrical substituents, *methano* and *ethano* bridges in norbornanone. It is still worthwhile to consider what is the difference between the orbital interaction of the carbonyl π^* orbital with the methano bridge and that with the ethano bridge.[119] In a manner similar to orbital unsymmetrization of the relevant bicyclic ketones (for example **A6** and **A11**, Figure 1), the π^*_{CO} of the carbonyl moiety of norbornanone **22** can interact with CC framework orbitals of the methano and ethano bridges, i.e., σ_{CC} orbitals of the vicinal CC bonds, judging from the small energy difference (see **3.29**). Owing to the higher energy level, the π^*_{CO} orbital mixes out-of-phase with the occupied σ_{CC} orbitals of the vicinal C−C bonds (C_1-C_6 and C_4-C_5 in the ethano bridge; C_1-C_7 and C_4-C_7 in the methano bridge) to give an energetically deactivated LUMO (**3.29**). This mixing involves a π-type overlap of these orbitals whose magnitude exhibits dihedral angle dependence. In the Wolfsberg−Helmholz formula,[13] the orbital interaction energy between two orbitals is approximated to be negatively proportional to the overlap integral. In a simple arrangement of two parallel 2p atomic orbitals (AOs) (**3.26**, $\phi = 90°$), the angular variation of π-type overlap of these 2p AOs is a sine function ($\sin\theta$) of the angle θ. Here θ is defined as the dihedral angle of the molecular planes (one of the planes is a π plane in these cases) rather than that of the orbitals as in **3.27** and **3.28**; overlap greatly increases as the angle (θ) increases ($0° \leq \theta \leq 90°$). In out-of-phase mixing, the greater the angle,

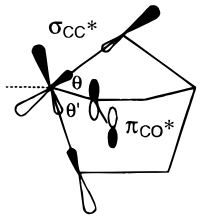


3.26 **3.27** **3.28**

the stronger the interaction (**3.27**) and, thus, the larger the depletion of the virtual bonding electrons. Owing to symmetry agreement, the C−C bond orbitals take part in this π-type overlap with vacant 2p orbitals of the carbonyl moiety (**3.29**). Because of the less acute angle of the σ bonds of the ethano bridge



3.29

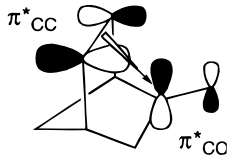


3.30

(θ (dihedral angle, $\angle C_7C_1C_2$ C_3 or $\angle C_7C_4C_3C_2$) > θ' (dihedral angle $\angle C_6C_1C_2C_3$ or $\angle C_5C_4C_3C_2$) in **3.29**, out-of-phase mixing of the σ_{CC} orbital of *the ethano bridge* more markedly depletes the virtual electron density of the π_{CC} orbital of the carbonyl group on the *endo* face, favoring *exo* addition of nucleophiles. This unsymmetrical π face character will be conserved during the attack of a reagent.

Another mechanism of unsymmetrization of the carbonyl π^* orbital was also proposed, arising from the in-phase combination of the vacant σ^*_{CC} orbitals.[119] Because of the small difference in energy, the π^* orbital can interact with the vacant C−C σ^* orbitals (i.e., σ^*_{C-C} bond orbitals) of the methano and ethano bridges (see **3.30**). Thus, the lower-lying π^*_{CO} is perturbed by in-phase mixing of the σ^* orbitals of the vicinal C_1-C_7 and C_1-C_6 bonds to give an energetically activated LUMO (**3.30**). In this case, however, owing to the antibonding nature of the σ^*_{C-C} orbitals, the overlap effect of the π^* orbital of the carbonyl group is canceled. Instead, the π^*_{CO} orbital can interact with the backside lobes of the σ^*_{C-C} orbitals centered on the bridgehead carbon atom (C_1) in an in-phase manner. This interaction motif bears a close resemblance to orbital interactions in the transition state associated with a backside nucleophilic attack (S_N2) on a tetrahedral carbon center.[69,120] Owing to symmetry agreement, these interactions can be approximated to the π-type overlap of the π^*_{CO} orbital with 2p AO components of these σ^*_{C-C} orbitals. The magnitude of the interaction is also dihedral angle dependent: the greater the angle (θ), the greater the overlap of the orbitals (**3.28**). Thus, the in-phase mixing with less acute orbitals (θ') of *the ethano bridge* involves larger build-up of the virtual internuclear bonding region on the *exo* face which is to be attacked by electrons of an occupied orbital of a nucleophilic reagent. This orbital distortion is consistent with the experimental *exo* reactivity of norbornananone **22**.

2-Norbornenone **A16** (Figure 1) undergoes reduction by sodium borohydride under kinetic conditions to produce 5% *exo*- (i.e., *endo* attack) and 95% *endo*- (i.e., *exo* attack) 2-norborneol. This leads to the partial rate constants of 11.4 for *exo* and 0.6 for *endo* attack (relative rate with respect to the rate of $LiAlH_4$ reduction of cyclopentanone (1.00)).[11] In the saturated 2-norbornanone **22**, the values are 4.55 for *exo* and 0.74 for *endo* attack. Thus, the introduction of the double bond enhances the *exo* attack while the *endo* attack is rather unaffected. The carbonyl π^* orbital is subject to in-phase combination with the vacant olefinic π^* orbital (**3.31**), and the orbital level is lowered, which is consistent with the acceleration of the reduction. However, the trajectory of the addition



3.31

again involves unfavorable out-of-phase orbital interaction in a manner similar to **3.22** and **3.23**, and thus, the *endo* addition is not encouraged.

IV. Stereoselection of Olefins

A. Methylenecycloalkane and Cycloalkene Derivatives

1. Methylenecyclohexanes (B1)

Klein showed that axial reaction of the parent methylenecyclohexane **24a** (**B1** (R = H) in Figure 2) is preferred in hydroboration.[38] This axial preference is consistent with Klein's model,[12] based on the orbital distortion of the olefin π orbital (Figure 8). However, the experimental data on the parent methylenecyclohexanone **24a** accumulated by Senda et al.[121] and the more recent systematic studies by Cieplak et al.[3,70] on π-facial selectivities of 3-substituted methylencyclohexanes **24** characterized the intrinsic features of the facial selection of methylenecyclohexanes. That is, axial preference of unsubstituted and 3-substituted methylenecyclohexanes was observed in oxymercuration[121] and epoxidation reactions.[122] There is also an increase in the proportion of axial attack with increase in the electronegativity of the remote 3-equatorial substituent (R).[3,70] On the other hand, in the dihydroxylation with osmium tetroxide,[123] equatorial preference was observed in the parent and 3-aryl-substituted methylenecyclohexanes in a manner similar to the hydroboration. It is still worthwhile to try to rationalize the dependence of facial selectivities on the reactions.The inherent axial preference can be rationalized in terms of orbital unsymmetrization arising from first-order mixing (Figure 21). Because of more efficient overlap, the olefin π orbital interacts with the σ_{CH} orbitals to a greater extent than with the σ_{CC} orbitals. The HOMO of methylenecyclohexanone is, thus, generated by out-of-phase combination of the olefin π orbital and the σ_{CH} orbitals (**4.2**), the composition being similar to **3.2** of cyclohexanone but the occupation of electrons being different.[124] This asymmetry of the olefin π orbital is consistent with the

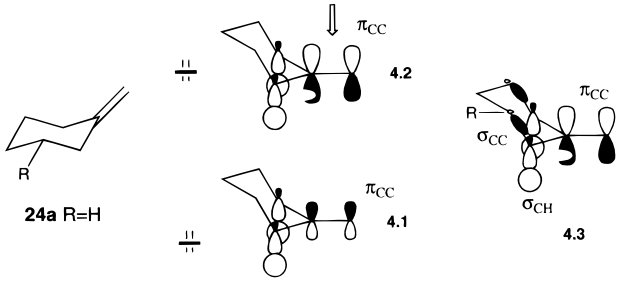
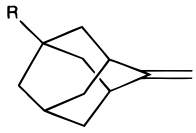


Figure 21. Orbital unsymmetrization in methylenecyclohexane.

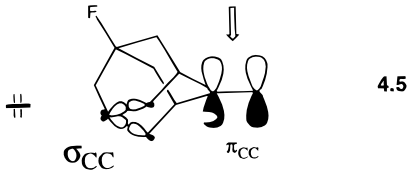
axial preference of methylenecyclohexane **24a** (motif iv in Figure 11). The HOMO of methylenecyclohexane **24a**, in fact, involves out-of-phase combinations of the olefin π orbital with the σCH orbitals and the σCC orbitals (**4.3**), the former component being larger. Electron-withdrawing substitution at C−(3), which attenuates the contribution of the σCC orbitals in **4.3**, thereby increases the percentage of the axial approach. Cieplak et al. also emphasized the better donating ability of the σCH orbitals rather than the σCC orbitals which stabilize the vacant incipient bond in the axial addition.[70]

2. 2-Vinylideneadamantanes (*B2*)

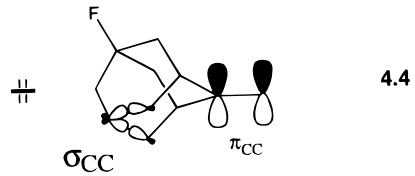
Srivastava and le Noble reported facial selectivities arising from remote substituents in the case of 2-vinylideneadamantane derivatives **B2** (Figure 2).[125] Epoxidation of 5-fluoro-2-methyleneadamantane **25a** with mCPBA gave a mixture of epoxy products (syn:anti (with respect to the fluoro group) 66:34). A 60/40 ratio was obtained in the addition of dichlorocarbene. Similar syn preference was obtained in the addition of dibromocarbene and in hydroboration. Oxymercuration of **25a** with mercuric acetate favored syn addition (>95% syn alcohol), while addition of trifluoroacetic acid furnished >99% syn ester, and HCl gas gave ≫99% syn dihalide. These syn preferences of **25a** are consistent with the Cieplak model. The olefin π orbital of 5-fluoro-2-methyleneadamantane **25a** is also subject to unsymmetrization arising from out-of-phase combination of the relevant σ_{CC} orbitals (**4.5**), addition on the side of the fluorine being encouraged.



25a R=F



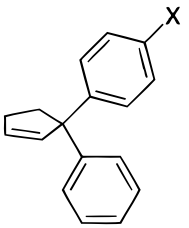
4.5



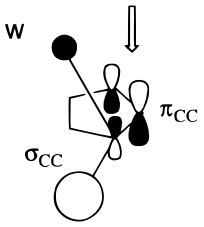
4.4

3. Cyclopentenes (*B3*)

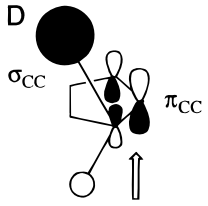
The stereoselective osmium-catalyzed dihydroxylation of a functionalized 2,2-diarylcyclopentene **B3** (Figure 2) containing an unsubstituted phenyl group and a *para*-substituted phenyl group were also examined by Halterman and McEvoy.[126] A similar trend of facial selectivity to that in the case of the reduction of the relevant cyclopentanone derivatives **A3** (Figure 1)[7] was obtained in the reaction of the corresponding olefin **26**. The electron-withdrawing nitro substituent (**26a**, X = NO_2) favored syn addition with respect to the substituted benzene ring (syn:anti = 70:30), whereas the electron-donating *N*,*N*-dimethylamino group (**26b**, X = $N(CH_3)_2$) favored anti addition with respect to the substituted benzene ring (syn:anti = 36:64). The addition opposite the more electron-rich aromatic ring was favored, which appears to be in agreement with the Cieplak hypothesis.



26a: X=NO$_2$
26b: X=N(CH$_3$)$_2$



4.6

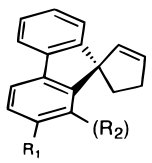


4.7

The olefin π orbitals are essentially unsymmetrized due to the unequal contributions of the relevant σCC orbitals in an out-of-phase manner (**4.6** and **4.7**). This out-of-phase motif with respect to the olefin π orbital is in agreement with the observed facial selectivities (syn with respect to the electron-withdrawing group (**4.6** in **26a**) and anti with respect to the electron-donating substituent (**4.7** in **26b**).

4. Spiro[Cyclopentane-1,9′-fluorene]-2-enes (*B4*)

Epoxidation of substituted spiro[cyclopentane-1,9′-fluorene]-2-enes **27** with a peroxidic reagent was studied.[9] The spiro olefins react with *m*-chloroperbenzoic acid (mCPBA) in chloroform at 3 °C to give a mixture of the epoxides. In all cases (2-nitro (**27b**), 4-nitro (**27c**), 2-fluoro (**27d**), and 2-methoxyl (**27e**) groups), the *syn*-epoxides, i.e., the syn addition of the peroxidic reagent with respect to the substituent, is favored. For example, for **27b**, syn:anti = 63:37; for **27c**, syn:anti = 65:35. Thus, a similar bias is observed in both the reduction of the carbonyl derivatives of **A4** (Figure 1) and the epoxidation of the derivatives of **27**.



27a:R_1=H
27b:R_1=NO_2
27c:R_2=NO_2
27d:R_1=F
27e:R_1=OCH_3

In the epoxidation of an olefin with a peracid, the occupied π orbital of the olefin group (π_{CC}, HOMO)

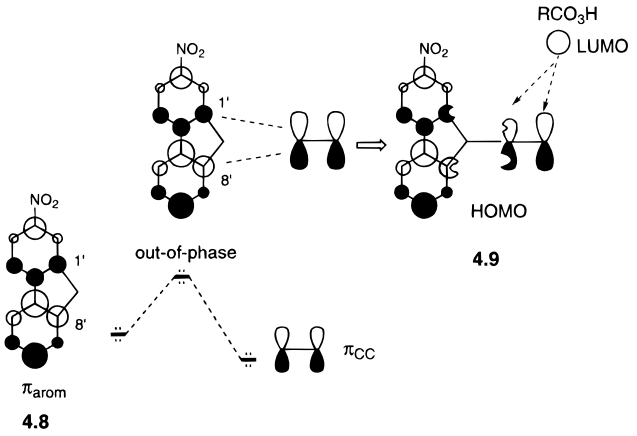


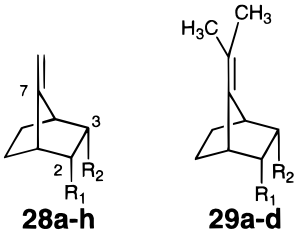
Figure 22. Orbital unsymmetrization of the olefin π orbital.

interacts with the vacant orbital (LUMO) of the peracid.[56,57] The higher-lying aromatic π orbital of the substituted fluorenes (**4.8**) can interact with the π_{CC} orbital in a manner similar to spiro conjugation (Figure 22). Out-of-phase combination of π_{CC} with the aromatic π orbital (**4.8**) of the substituted fluorene raises the energy so as to activate the π_{CC} fragment of the olefin to the attack of an electrophile. The relevant aromatic π orbital of substituted fluorenes, for all substituents studied, has biased orbital coefficients at the points of interaction: the coefficient of C-8′ is larger than that of C-1′ (see **4.8**). These different overlaps result in divergent amplitudes of the antibonding region between nuclei (**4.9**). The antibonding unsymmetrization, arising from the orbital bearing a larger coefficient, greatly reduces the electron-donating ability toward the attack of the electron-deficient orbital of an electrophile (motif iv in Figure 11). Thus, the π_{CC} fragment favors the attack of an electrophile on the side of the substituent, providing a reasonable interpretation of the observed biased epoxidation of the olefin.

B. Unsaturated Bicyclo[2.2.1]heptane Derivatives

1. 2,3-endo,endo-Disubstituted Bicyclo[2.2.1]heptane Derivatives (B5)

Mehta et al. studied 2,3-*endo*,*endo*-disubstituted 7-methylenenorbornanes **28** [127] and 2-*endo*-monosubstituted 7-isopropylidenenorbornanes **29**.[104,128] The



28a-h

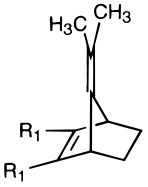
29a-d

a: $R_1=R_2=H$
b: $R_1=R_2=CO_2CH_3$
c: $R_1=R_2=CH_2OCH_3$
d: $R_1=R_2=C_2H_5$
e: $R_1=H$, $R_2=CN$
f: $R_1=H$, $R_2=CO_2CH_3$
g: $R_1=R_2=CN$
h: $R_1=R_2=CH_3$

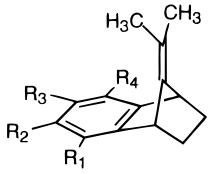
7-methylenenorbornanes **28** bearing *endo*-electron-withdrawing substituents were subject to epoxidation, hydroboration, and oxymercuration reactions, which showed consistent syn facial selectivities (with respect to the *endo* subsitutent). In the case of disubstitution of methoxycarbonyl groups (**28b**), syn addition of the reagent is favored, for example, in epoxidation syn:anti addition = 74:26. The dimethoxymethyl compound **28c** showed anti preference, and the diethyl substrate **28d** showed a greater anti preference, for example, in epoxidation syn:anti addition = 30:70. Owing to electron-donating methyl groups on the olefin, the isopropylidene derivatives **29** undergo the addition of dichlorocarbene as well as singlet oxygen addition, epoxidation and reaction with the bromine (I) cation. A single *endo*-electron-withdrawing substituent, as in **29e** (R_2 = CN) and **29f** ($R_2 = CO_2CH_3$), also favored syn addition (with respect to the *endo* substituent) in all the reactions studied. Thus, the substituent effects on the facial selectivity of the olefin **28** and **29** are consistent with those of the carbonyl counterparts (**A6**; **14**). Orbital unsymmetrization of the olefin π orbital of 7-methylenenorbornane **28** and 7-isopropylidenenorbornane **29** is involved, as in the case of bicyclo[2.2.2]octenes (**B9** in Figure 2) (*vide antra*).

2. 7-Isopropylidenenorbornenes and 7-Isopropylidenebenzonorbornenes (B6, B7)

Okada and Mukai studied facially selective addition of singlet oxygen to 7-isopropylidenenorbornene derivatives **30**.[129] 7-Isopropylidenenorbornene **30a** was photooxidized in acetonitrile, followed by reduction with dimethyl sulfide in methanol to give a mixture of 7-alcohols. 7-Isopropylidenenorbornene **30a** showed syn preference with respect to the ethano bridge (syn:anti = 83:17). Similar syn preference (with respect to the ethano bridge) was observed in the addition of singlet oxygen to 7-isopropylidenebenzonorbornene **31a** (syn:anti = 74:26). The facial selectivity of these reactions seems to overwhelm the steric interference of the methylene groups, that is, the out-of-phase motif of the exocyclic olefin π orbital arising from the endocyclic olefin π orbital (**4.10** for **30a**) or the aromatic π orbital (**4.11** for **31a**) retards the addition on the side of the π group.[130] Houk also



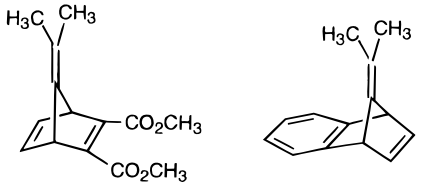
30a: R_1= H
30b: R_1= CO_2CH_3



31a: $R_1=R_2=R_3=R_4=H$
31b: $R_1=R_4=OCH_3$, $R_2=R_3=H$
31c: $R_1=R_2=R_3=R_4=F$
31d: $R_1=R_2=R_3=R_4=Cl$

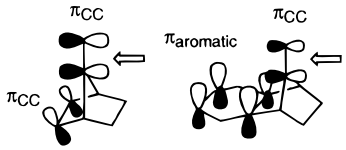
suggested repulsive orbital interaction of the relevant orbital motif **4.10** with a reagent.[96] On the other hand, disubstitution of methoxycarbonyl groups on the olefin moiety of 7-isopropylidenenorbornene (that is **30b**) showed rather small syn preference (syn:anti = 54:46) (with respect to the ethano bridge) under the same reaction conditions, that is, an increase of anti addition. This substituent effect provides supporting evidence for the intervention of the endocyclic olefin π orbital in retardation of the anti addition. Substitution with the diester groups (**30b**) significantly lowers the energy level of the olefin π orbital, leading to a weak interaction with the olefin π orbital of the exocyclic olefin (see **4.10**).

Similar stereoselectivity was also observed in the case of the logicyclic compounds,[130−133] 7-isopropylidenenorbornadiene **32**, wherein one of the olefin groups is disubstituted with methoxycarbonyl groups.[129] Only the syn hydroperoxide (with respect

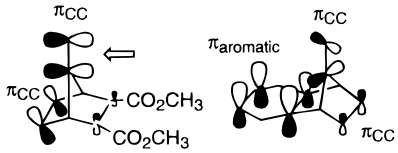


32 **33**

to the substituted olefin moiety) was formed in the photooxidation. This facial selectivity can be rationalized in terms of the out-of-phase motif of the *exo*-olefinic π orbital (**4.12**) in a manner similar to **4.10**.



4.10 **4.11**



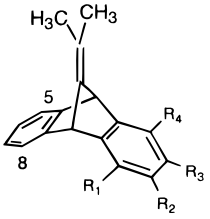
4.12 **4.13**

On the other hand, the facial selectivity of 7-isopropylidenebenzonorbornadiene **33** is unexpectedly anti with respect to the olefin moiety (syn:anti = 38:62). The olefin π orbital of the exocyclic olefin was mixed with the aromatic π orbital to a larger extent than with the olefin π orbital, in an out-of-phase motif (**4.13**). This unsymmetrization of the olefin π orbital predicts syn addition (with respect to the olefin moiety) in a manner similar to 7-isopropylidenebenzonorbornene **31a**. The olefin orbital of **33** also exhibits second-order orbital distortion, orbital tilting (**4.13**) (see also **2.2** in Figure 7b), which also predicts syn addition. However, the experimental preference is anti. Similar orbital tilting was proposed in the case of 7-isopropylidenebenzonorbornene **31a** (**4.10**), which is compatible with the observed syn preference.[129]

Hertel and Paquette[134] and Gleiter et al.[135] also independently studied the facial selectivities of electrophilic additions to 7-isopropylidenebenzonorbornenes **31**. They described the effect of aromatic substitution on the facial selectivities. The parent (**31a**) and dimethoxy-substituted derivatives (**31b**) of 7-isopropylidenebenzonorbornadienes are attacked by $^1O_2$ predominantly from the syn direction (with respect to the ethano bridge), but this stereoselectivity is appreciably reversed in the case of the tetrafluoro (**31c**) and tetrachloro derivatives (**31d**), that is, anti preference is observed. This reverse facial selectivity is relevant to the increase of the anti addition of 7-isopropylidenenorbornene **30b** upon disubstitution with the electron-withdrawing ester groups at the olefin moiety of **30a**. On the other hand, in the epoxidation with mCPBA, a constant syn preference (with respect to the ethano bridge) was observed among the 7-isopropylidenebenzonorbornenes **31a**−**d**. These syn preferences are compatible with the orbital unsymmetrization **4.13**. Close scrutiny showed that the syn preference is decreased upon substitution of halogen atoms into **31a** (**31a**, syn:anti = 83:17) to afford **31c** (**31c**, syn:anti = 63:37). This is consistent with the attenuation of the contribution of the aromatic π orbital to the HOMO of the molecule (**31c**) upon substitution of electron-withdrawing groups. Electrostatic interactions were proposed to account for these facial selectivities by Houk et al.[136]

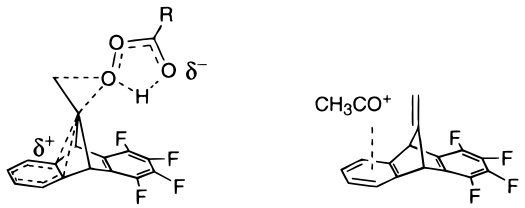
3. 11-Isopropylidenedibenzonorbornadienes (B8)

Electrophilic additions of 11-isopropylidenedibenzonorbornadienes **34** were studied by Paquette et al.[137] In the epoxidation with mCPBA, the tetrafluoro derivative (**34a**) and tetrafluoro-5,8-dimethoxy derivative (**34b**) favored syn addition (with respect to the tetrafluoro substituents)—**34a**, syn:anti = 77:23; **34b**, syn:anti = 77:23—while the 5,8-dimethoxy derivative **34c** itself showed a small syn preference (syn:anti = 55:45, with respect to the substituted benzene). Paquette et al. interpreted these observed



34a: $R_1=R_2=R_3=R_4=F$
34b: $R_1=R_2=R_3=R_4=F$,$OCH_3(5)$,OCH_3(8
34c: $R_1=R_4=OCH_3$, $R_2=R_3=H$

facial preferences in terms of electrostatic stabilization.[137] Long-range homoaromatic stabilization has been shown to be important in transition states involving 9-isopropylidenebenzonorbornenes **34** (see **4.14**) and weak electrophiles.[134,135,138] The unsym-



4.14 **4.15**

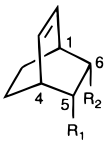
metrical transition state for the syn addition involves charge dispersal to the unsubstituted benzene ring (**4.14**), while that for the anti addition created a positive charge on the tetrafluorobenzene ring.[137] The former (**4.14**) is favorable in terms of stabilization of the formal positive charge, and thus, the syn addition is favored. In addition, electrostatic stabilization of the formally negatively charged peracid moiety to the electron-deficient benzene ring may also participate

(**4.14**). Facial selectivities in the reactions which involve more discrete positively charged electrophiles were also studied.[137] Strong electrophiles such as the Friedel−Crafts acylium cation and that in the Prins reaction (paraformaldehyde in dioxane containing concentrated sulfuric acid) showed the reverse anti preference (**34a,b** with respect to the tetrafluorobenzene moiety, **34c** with respect to the unsubstituted benzene moiety) in all the substrates studied (**34a**−**c**). That is, the additions on the side of the more electron-rich benzene ring are preferred. Thus, the observed preference can be rationalized in terms of the cation−π-type complexation of the reagents (**4.15**) on the side of the more electron-rich benzene ring.[139,140] This complexation is compatible with the observed preference.

C. Bicyclo[2.2.2]octene Derivatives

1. 5-exo-Substituted Bicyclo[2.2.2]octenes (B9)

Jones and Vogel recently investigated the substituent effect of a 5,6-bis(methoxycarbonyl) group in bicyclo[2.2.2]octene (**35i**).[141] The substituent effect of



35

a: $R_1=R_2=H$
b: $R_1=CN, R_2=H$
c: $R_1=CO_2CH_3, R_2=H$
d: $R_1=CO_2NHPh, R_2=H$
e: $R_1=CO_2H, R_2=H$
f: $R_1=CH_2OCH_3, R_2=H$
g: $R_1=CH_2OTs, R_2=H$
h: $R_1=CH_3, R_2=H$
i: $R_1=R_2=CO_2CH_3$
j: $R_1=R_2=CN$
k: $R_1=R_2=CH_3$

a single 5-*exo* substituent on the facial selectivities of bicyclo[2.2.2]octenes **35b**−**h** was also characterized by our group.[142] Epoxidation and dihydroxylation of the olefin moiety of 5-*exo*-substituted bicyclo[2.2.2]-octenes (**35b**−**h**) were investigated. 5-*exo*-Cyanobicyclo[2.2.2]octene **35b** underwent preferential syn addition (with respect to the face of the cyano group) of peroxidic reagents, i.e., *m*-chloroperbenzoic acid (mCPBA) and osmium tetroxide. In the epoxidation of **35b** with mCPBA, the syn epoxide is favored over the anti epoxide. In the dihydroxylation with osmium tetroxide, the syn diol is also favored over the anti diol. Values of diastereomeric excess observed in these reactions ranged from 70% (syn:anti = 85:15) to 72% (syn:anti = 86:14). Direct intervention of the *exo* substituent at the reaction center, such as a coordinative interaction, can be ruled out because of the rigid structure of the bicyclo[2.2.2]octene system and the dangling position of the *exo* substituent. 5-*exo*-Methoxycarbonylbicyclo[2.2.2]octene **35c** also preferentially gave the *syn* epoxide (de 36%) (syn:anti = 68:32) and the *syn* diol (de 68%) (syn:anti = 84:16). The electron-withdrawing nature of the substituent is important for syn preference, as judged from the findings that benzanilide (**35d**) and carboxylic acid (**35e**) substituents distorted the olefinic π face similarly to the methoxycarbonyl group, whereas the methoxymethyl group (**35f**) imparted reduced (in the case of dihydroxylation, de 20%) or absent (in the case of epoxidation) selectivity. Tosylation of the methyl alcohol functionality (**35g**) restored the *syn* selectivity to some extent in hydroxylation and particularly in the epoxidation. On the other hand, the 5-methyl derivative **35h** showed a negligible preference in both reactions.

The syn preference arising from the electron-withdrawing groups is consistent with the preference observed in the case of the bis(methoxycarbonyl) group (**35i**) (de 46% in the epoxidation; de 66% in the dihydroxylation). A single substituent is sufficient to perturb the π face in the bicyclo[2.2.2]octene system **35**. This observation is consistent with the case of vinylidenenorbornanes **29**.[104,127] Furthermore, the bicyclo[2.2.2]octane system **35** exhibited the same preference as those found in 7-methylidene- (**28**) and 7-isopropylidenenorbornanes (**29**), except for the effect of electron-donating alkyl groups: in 7-vinylidenenorbornane (**29d**) the ethyl substituent favored anti addition in the epoxidation with mCPBA.

In the bicyclo[2.2.2]octene system **35**, the olefin π orbital can interact with the σ framework of the cyclohexane fragment and four possible types of σ fragment orbitals of cyclohexane moiety can participate, i.e., parallel C−C bonds (a), vicinal C−C bonds (b), *exo*-C−H bonds (c), and *endo*-C−H bonds (d) (Figure 23).[142] The nodal property of the σ bonds excludes the contribution of parallel C−C bonds in the bicyclo[2.2.2]octene system (Figure 23a), and inefficient overlap (owing to unfavorable directions and small amplitudes of orbitals) disfavors *endo*-C−H bonds (Figure 23c) and *exo*-C−H bonds (Figure 23d). Therefore, the π orbital of the olefin should interact exclusively with the vicinal C−C σ orbitals (Figure 23b) in the bicyclo[2.2.2]octene system **35**. This is because the vicinal σ_{C-C} orbitals are aligned to overlap distinctly with the π orbital of the olefin in a π-type fashion. Thus, the HOMO of unsubstituted bicyclo[2.2.2]octene **35a** is intrinsically comprised of the π orbital of the ethylene and the σ orbitals of the

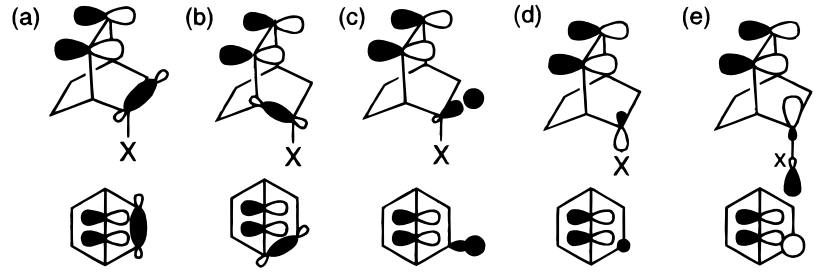
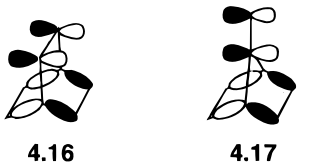
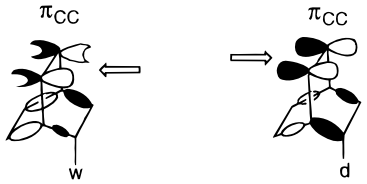


Figure 23. σ-Components of bicyclo[2.2.2]octenes: (a) parallel σ_{C-C}, (b) vicinal σ_{CC}, (c) *exo*-σ_{CH} (σ_{CX}), (d) *endo*-σCH (CX), (e) *exo*-σ^*_{CX}.

ethano bridges, the coupling being in an out-of-phase fashion (**4.16**). Essentially the same motif was found

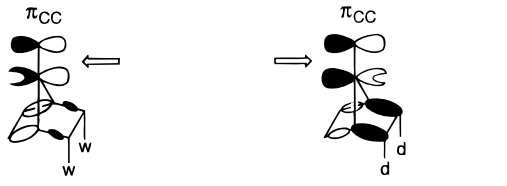


4.16 **4.17**



4.18 **4.19**

in the HOMO of unsubstituted vinylidenenorbornane **28a,** but in a different arrangement (**4.17**). Thus, the orbital is selected by symmetry *not* by the order of the energy level. The π orbitals of the olefins of **35a** (**4.16**) and **28a** (**4.17**) are symmetric because of equivalent $\sigma-\sigma$ coupling with respect to the π plane. Asymmetric $\sigma-\pi$ coupling is postulated to be a cause of unsymmetrization of the π face. A substituent modifies the orbital energy level of the vicinal bonds. An electron-withdrawing group significantly lowers the energy of the vicinal σ orbital (Figure 23b). Changing the substituent from a cyano to a methoxycarbonyl, carboxylic acid, hydroxymethyl, or methyl group causes the energy of the σ_{C-C} orbital of the substituted ethane to rise, in the case of the hydroxymethyl group, to an energy level comparable to that of the σ_{C-C} orbital of the parent ethane. Thus, substitution of an electron-withdrawing group at the C_5 position (R_1) of **35** decreases the contribution of the vicinal σ_{C-C} orbital (C_4-C_5 bond) to the HOMO of the whole bicyclo[2.2.2]octene molecule (**4.18**). Therefore, antibonding nature is weakened on the side of the substituent: the antibonding orbital on the side of the substituent is less diffused. σ-Type reagents having an early transition state (such as mCPBA (the σ^*_{OO} orbital) and OsO_4 (the vacant diffused $3d_z$ orbital)) favor attack on the side of the less diffused antibonding region. Therefore, the syn addition is favored. A similar orbital interaction diagram is also valid in the case of 5-substituted 7-methylidenenorbornane **28** (**4.20** for electron-withdrawing groups; **4.21** for electron-donating groups). The outcome of orbital unsymmetrization by

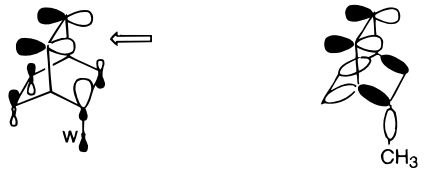


w= electron-withdrawing group d= electron-donating group

4.20 **4.21**

the unsymmetrical $\sigma-\pi$ coupling coincides with the result predicted by the Cieplak model because orbitals antiperiplanar with respect to the π orbital are selected to interact with the π orbital due to orbital symmetry rather than orbital energy level.

Additional $\sigma^*-\pi$ coupling (see **4.22**) can also participate in the facial selectivities.[142] That is, substitution of an electron-withdrawing group (W) makes the relevant carbon atom (C−W) more electronegative, which leads to a situation where the σ bonding orbitals are weighted more heavily on the atom W and *the σ antibonding orbitals* are weighted more heavily on the relevant carbon atoms (**4.22**).[30] The π



4.22 **4.23**

orbital of the olefin in **35b**−**e** can interact efficiently with the *exo*-σ^*_{CW} orbital in an in-phase manner (Figure 23e), which provides a more extended bonding region on the side of the substituent (**4.23**) in the cases of electron-withdrawing substituents. This in-phase region corresponds to motif iii of Figure 11. This reinforces the syn preference.[31]

2. Comparison of Norbornane and Bicyclo[2.2.2]octene Systems

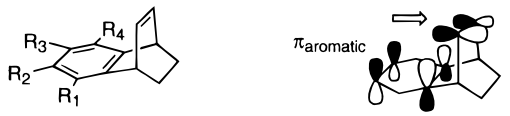
Owing to the energetic perturbation arising from the methyl substituent on the substituted ethane, the contribution of the vicinal orbital bearing the methyl group will be increased in the $\sigma-\pi$ coupling in the bicyclo[2.2.2]octene (as in **4.19**) and 7-methylidenenorbornane (as in **4.21**) and, therefore, anti preference should exist. This is indeed observed in 7-methylidenenorbornane (2-ethyl-7-methylidenenorbornane **28d**),[127,128] but no definite bias was detected in the case of bicyclo[2.2.2]octene **35h**.[142] Despite the energetically perturbing effect of the methyl group, evaluation of the orbital interaction may be exaggerated due to the neglect of the effect of overlap: because of the equal contribution of the two σ_{C-C} orbitals as in (**4.23**), the coefficient of each σ_{C-C} orbital in real bicyclic systems is decreased to compensate for the energetic effect.

To shed light on the different behavior of the two bicycles (bicyclo[2.2.2]octenes **35** and 7-methylidenenorbornanes **28**), Bader topological one-electron density analysis[143] was performed on the HF/6-31G* optimized geometries.[142] Due to symmetrical benefit and the anticipated similar substituent effects, the molecules bearing two substituents (**28a**, **28g**, **28h** and **35a**, **35j**, **35k**), imposing C_s symmetry, were calculated. The topological one-electron density analysis was previously carried out in the former bicyclic system by Mehta et al.[104] The parent bicyclo[2.2.2]-octene (**35a**) is a cage structure, characterized by the presence of three ring critical points on each convex six-membered ring and also containing a cage critical point. 7-Methylidenenorbornane (**28a**) is an open structure with two curved five-membered ring surfaces with one common carbon (C_7). Therefore, the two bicyclic systems have different electron networks as pointed by Wiberg et al.[144−146] One-electron densities (ρ) at the bond critical points indicated that the methyl substituent did not increase the electron

density of the vicinal bond (C_1-C_2 and C_3-C_4 in **28h**; C_4-C_5 and C_1-C_6 in **35k**) but rather decreased it as compared with the vicinal bond (C_1-C_6 and C_4-C_5 in **28h**; C_4-C_8 and C_3-C_7 in **35k**) opposite the methyl group. Unexpectedly, this was the case for both 5,6-*exo*,*exo*-dimethylbicyclo[2.2.2]octene **35k** and 2,3-*exo*,*exo*-dimethyl-7-methylidenenorbornane **28h** in the present calculations. On the other hand, an electron-withdrawing group such as the cyano group of **28g** and **35j** decreases the electron density of the adjacent vicinal bond. Wiberg et al. also defined the strain energy of the bicyclic molecules in terms of the Bader charge[143] of the bridgehead carbon atoms and found that as strain (or strain energy) is increased on going from the bicyclo[2.2.2]octene system to the norbornane system, the bridgehead carbon atoms increase in both electronegativity and stability.[144] Therefore, a charge flow from the peripheral methylene groups to the bridgehead carbons in the norbornanes **28** is encouraged as compared with the bicyclo[2.2.2]octene **35**.[142] Thus, the electron donation of the methyl group is enhanced to refill the electron deficiency of the peripheral methylene group in the norbornanes (**28a**). This electron shift is supported by slightly smaller values of ρ and $\nabla^2\rho$ and ellipticity (ϵ) of the C_2-CH_3 (C_3-CH_3) bonds in the dimethylnorbornane (**28h**) as compared with those of dimethylbicyclo-[2.2.2]octene (**35k**) (i.e., C_5-CH_3 (C_6-CH_3) bonds). Even in terms of Mulliken charges (based on the HF/6-31G* optimized geometries), while in the bicyclo-[2.2.2]octene system **35** the carbon atoms (C_5 and C_6) bearing the methyl groups (**35k**) tend to obtain a slightly more positive charge as compared with the parent bicyclo[2.2.2]octene (**35a**), the C_2 (C_3) carbon atom shows lower positive charge on substitution of the methyl groups in the vinylidenenorbornane system (**21h**), indicating enhanced electron donation of the methyl groups of **28h**.[142]

3. Benzobicyclo[2.2.2]octadienes (*B10*)

Paquette et al. studied the effect of the aromatic substituent on facial selectivities of benzobicyclo-[2.2.2]octadiene derivatives **B10** (Figure 2).[147] Anti preference of the parent **36a** was observed with respect to the ethano bridge. This is in contrast to



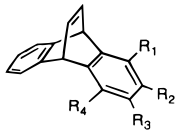
36a: $R_1=R_2=R_3=R_4=H$
36b: $R_1=R_4=OCH_3, R_2=R_3=H$
36c: $R_1=R_2=R_3=R_4=F$

4.24

the syn preference (with respect to the ethano bridge) of the vinylidenebenzonorbornane **31a**. Again, facial selectivities are divergent, depending on the bicyclic systems, that is the arrangement of molecular fragments. Furthermore, the magnitude of the anti preference in epoxidation was increased upon substitution either of an electron-donating (**36b**) or an electron-withdrawing group (**36c**): in the parent **36a**, syn:anti = 41:59; in **36b**, syn:anti = 37:63; in **36c**, syn:anti = 24:76. This result suggests that the out-of-phase motif (**4.24**) of the olefin π orbital with the aromatic π orbitals is not of major importance. Paquette et al.[147] pointed out the orbital tilting of the olefin π orbital of **36**, but the syn face of **36** is sterically biased arising from the methylene protons. Because of the trajectory of the addition onto the olefin moiety, the syn preference of **31** is orbital-controlled and the anti preference of **36** is sterically determined. Furthermore, it is important to notice that the facial selectivity of the olefin **36** is reversed as compared with that of the carbonyl counterpart **19**. This is also true in the cases of **30a** and **15a** and **31a** and **13a**.

4. Dibenzobicyclo[2.2.2]octatrienes (*B11*)

Epoxidation and dihydroxylation of the olefin moiety of 2-substituted dibenzobicyclo[2.2.2]octatrienes (**B11**, Figure 2) were studied.[48,115] 2-Nitrodibenzobicyclo[2.2.2]octatriene **37a** undergoes preferential syn addition (with respect to the nitro group) of peroxidic reagents, i.e., *m*-chloroperbenzoic acid, osmium tetroxide, and potassium permanganate. In the epoxidation



37a-c

a: $R_2=NO_2$; **b**: $R_2=F$; **c**: $R_2=OCH_3$
$R_1=R_3=R_4=H$

of **37a** with mCPBA, the syn epoxide is favored over the anti epoxide. In the dihydroxylation with osmium tetroxide or potassium permanganate, the syn diol is also favored over the anti diol. The epoxidation with mCPBA at high reaction temperature (20 °C) did not significantly alter the ratio of syn to anti isomers. Values of diastereomeric excess observed in these reactions ranged from 54% to 76%. 2-Fluorodibenzobicyclo[2.2.2]octatriene **37b** also preferentially gave the *syn* epoxide and the *syn* diol. On the other hand, the 2-methoxy substrate **37c** showed only a small preference in the reactions, giving a slight excess of the *anti* products. Direct interaction of oxidative electrophilic reagents with the electron-rich benzene ring (like **4.15**) is unlikely to participate in the facial selectivities of **37**.

To reveal the perturbation of the π orbital of the ethylene arising from the nonequivalent substituents in the substituted dibenzobicyclo[2.2.2]octatrienes (**37**), the molecules are assumed to be constructed from the orbitals of the convex-substituted dihydroanthracene (like **4.25**) and the ethylene (**4.26**) (Figure 24). The π orbitals of the dihydroanthracene can also be further analyzed as a combination of π orbitals of the two benzene moieties. A similar orbital combination was suggested in barrelene on the basis of the photoelectron spectra.[148] The HOMO of the unsubstituted dihydroanthracene in convex geometry (like **4.25**) is essentially derived from the in-phase combination of the HOMOs of the two benzene nuclei. The level ordering was modified by the through-bond coupling of the two aromatic π orbitals through the pseudo π orbital (π_{CH2}) of the insulating methylene group:[24] the in-phase combination of the HOMOs of

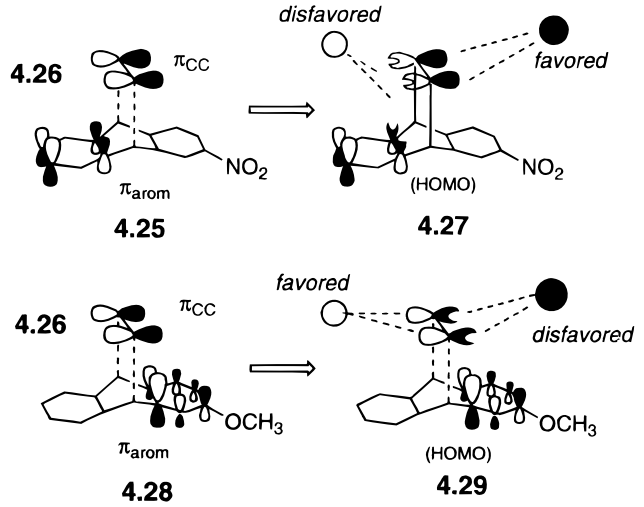
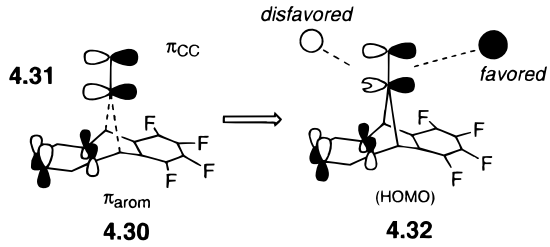


Figure 24. Unsymmetrization of the olefinic π orbital.

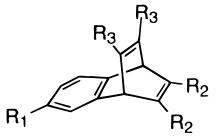
the two aromatic rings is higher in energy than the out-of-phase combination. A substituent destroys the symmetrical arrangements of the HOMO and the NXHOMO of the dihydroanthracene. The HOMOs of substituted dihydroanthracenes in convex geometry (for example, **4.25** (nitro) and **4.28** (methoxyl)) are energetically higher-lying than that of the ethylene (**4.26**, π_{CC}). The lower-lying HOMO of the ethylene can mix with the higher-lying aromatic π orbital of the aromatic component (**4.25** and **4.28**) in an out-of-phase fashion to give the energetically activated HOMO of the whole molecules, which will determine the direction of attack of the vacant orbital of the oxidative reagent. The HOMO (**4.25**) of 2-nitrodihydroanthracene is essentially localized on the unsubstituted benzene moiety, stemming predominantly from the HOMO of the benzene, which is higher in energy than the HOMO of the nitrobenzene. The orbital phase agreement favors the interaction of the ethylene (HOMO) with the HOMO of 2-nitrodihydroanthracene. The out-of-phase overlap of these π orbitals raises the energy of the olefin moiety, involving the depletion of the electron density in the internuclear region (**4.27**), i.e., antibonding orbital diffusion.[3] Therefore, electrophilic oxidative reagents attack the olefinic π lobe opposite the depleted region, that is, from the same side as the substituent (motif iv in Figure 11). In the case of an electron-donating hydroxyl group, an out-of-phase combination of π_{CC} of the olefin with the HOMO of hydroxydihydroanthracene (**4.28**) raises the energy so as to activate the π_{CC} fragment to the attack of an electrophile. The HOMO of 2-hydroxydihydroanthracene (**4.28**) also has biased orbital amplitudes localizing on the phenol moiety, not on the benzene moiety, because of the higher level of the HOMO of phenol than that of benzene. A larger overlap results in greater amplitude of the antibonding region between nuclei. The depleted region (**4.29**), arising from the orbitals on the phenol moiety, disfavors the attack of the electrophile (Figure 24). Therefore, the π_{CC} fragment intrinsically favors the attack of an electrophile on the side opposite the hydroxyl group. However, the HOMO of hydroxydihydroanthracene (**4.28**) increases the energy separation from the HOMO of ethylene (**4.26**) by 13.63 kcal/mol (PM3) as compared with the case of the nitro substituent (**4.25**). The large energy gap of these interactive fragments would decrease the effect of asymmetrization in **4.29**. Thus, the reactions of 2-methoxydibenzobicylo[2.2.2]octatriene **37c** with mCPBA and osmium tetroxide showed a slight distortion of the π face of the olefin moiety. The small but consistent preference for *anti* attack of the reagents in these two reactions is also compatible with the orbital unsymmetrization model. Thus, the 11-isopropylidenedibenzonorbornadienes **34**[137] and the dibenzobicyclo[2.2.2]octenes **37** exhibited similar substituent effects (see section IV.B.3.): a "frontier-electron-withdrawing" nitro or fluoro group gave a large to moderate bias (preferred syn attack with respect to the substituents) whereas an electron-donating methoxyl substituent exhibited a small or negligible bias. Syn preference of 11-isopropylidenedibenzonorbornadiene (for example, the tetrafluoro derivative **34a**) can also be rationalized in terms of the out-of-phase motif (**4.32**) exposed on the π orbital (**4.31**) of the exocyclic olefin arising from the higher-lying aromatic π orbital of the tetrafluorodihydroanthracene in the convex geometry (**4.30**).



D. Orbital Size Effect on the Magnitude of Facial Selectivity (B12)

The dibenzobicyclo[2.2.2]octatriene system (**37**) essentially involves orbital interaction of three composite π orbitals, i.e., the olefinic π orbital as the reaction center and two aromatic π orbitals. We are interested in a simplified interaction network, i.e., *two π-component systems free from steric bias*. In this context, the facial selectivities of benzobicyclo[2.2.2]-octatrienes (**B12** (Figure 2); **38** and **39**) bearing two electron-withdrawing groups at one of the olefin groups were studied.[149] Remote substituents do not change facial preference but do change the magnitude of the selectivity.

Unsubstituted benzobicyclo[2.2.2]octatriene **38a** bearing two methoxycarbonyl groups at the C_2 and C_3 positions exhibited strong anti preference (with respect to the benzene moiety) with two oxidative electrophilic reagents, *m*-chloroperbenzoic acid (mCPBA) and osmium tetroxide.



R_2	R_3	R_1=H	R_1=NO_2
CO_2CH_3	H	**38a**	**39a**
CO_2tBu	H	**38b**	**39b**
CN	H	**38c**	**39c**
CO_2CH_3	CH_3	**38d**	**39d**

The diastereomeric excess (de) of **38a** reached 72% (epoxidation) and 98% (dihydroxylation). Nitro substitution on the aromatic ring (as in **39a**) significantly

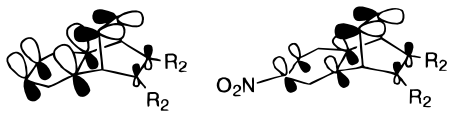
reduced the selectivity (increased the syn proportion), although anti preference was still conserved in epoxidation (20% de) and in dihydroxylation (68% de).

The anti face, i.e., the syn side with respect to the diester groups, seems to suffer from steric congestion owing to the out-of-plane conformations of the proximate diester functional groups. This is supported by the results with the bis(*tert*-butoxycarbonyl) compound **38b**: the sterically demanding *tert*-butyl groups did reduce the selectivity in both epoxidation (26% de) and dihydroxylation (90% de). However, anti preference survived, indicating that the intrinsic nature of the benzobicyclo[2.2.2]octatriene motif is as proposed. An aromatic nitro group (**39b**) also reduced (46% de in dihydroxylation) or almost abrogated (8% de in epoxidation) the selectivity. Therefore, the selectivity is determined by nonsterical bias. In the case of dicyanodibenzobicyclo[2.2.2]octatriene **38c** and its nitro substrate **39c**, a similar effect on the magnitude of selectivity is observed in the epoxidation reaction. These results exclude a contribution of electrostatic attraction of the reagent to the anti side, owing to the electronegative oxygen atoms of the ester groups of **38a,b** and **39a,b**.

Dimethyl substitution (R_3) on the olefin moderately activates reactivity, as in the case of **38d**. Epoxidation occurred readily even at 3 °C. In this case, the observed anti preference of **38d** was also reduced upon substitution of a nitro group on the aromatic ring (as in **39d**).

These substituent effects on the selectivity might be accounted for in terms of the Cieplak model:[70] the nitro substituent reduced the electron-donating effect of the vicinal C−C σ bond, which is relevant to stabilization of the electron-deficient incipient bond in the anti addition transition state. However, comparison of the ^{13}C NMR chemical shifts of the olefinic and bridgehead carbon atoms of the unsubstituted and nitro-substituted substrates, **38a** (139.1 ppm; 50.3 ppm) and **39a** (139.1 and 138.4 ppm; 50.1 ppm) and **38c** (138.0 ppm; 51.7 ppm) and **39c** (138.6 and 138.0 ppm; 51.9 ppm), indicated some shielding shifts upon nitration, tending to rule out significant transmission of the inductive effect of the nitro group to the bridgehead and to the olefin moieties.

Within the framework of perturbation theory, the HOMO of dibenzobicyclic **37** can be represented as a combination of the three π orbitals, i.e., $\Psi_{HOMO} = a\pi_{olefin} + b\pi_{aromatic} + c\pi_{aromatic}$. However, owing to the low energy of the π orbital (π_{R2}) of the ethylene substituted with electron-withdrawing groups, the HOMO of **38** and **39** can be approximated as a two π interacting system (see **4.33** and **4.34**): the orbital components are assumed to involve the π orbital (π_{olefin}) of the ethylene (as the reaction center) and that (π_{arom}) of the aromatic ring. In this system, the remote nitro substituent significantly modifies the magnitude of selectivity by causing the *anti* orbital side of the HOMO π olefin to be unsymmetrized (**4.33**). Unsymmetrization of the olefin π orbital (**4.33**) on the side of the π_{R2} is much smaller than that on the side of the aromatic π orbital because the π_{R2} orbital is lower-lying in energy due to the electron-withdrawing groups. In the substitution of the nitro



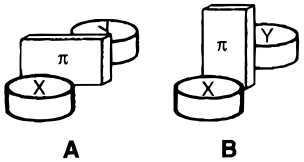
4.33 **4.34**

group, unsymmetrization of the olefin π orbital on the side of the aromatic π orbital is smaller than that of the unsubstituted case but there is still bias. Thus, the amplitude of the out-of-phase region exposed to the π reaction center can determine the magnitude of facial selectivity.

E. Effects of Different Arrangements of Composite Molecules

The spiro[cyclopentane-1,9′-fluorene] **27**[8,9] 11-isopropylidenedibenzonorbornadienes **34**[137] essentially involve the interactions of three composite π functional groups, i.e., the olefinic π group as the reaction center and the two aromatic π orbitals. In these systems, the π faces of the olefins are subject to unsymmetrization due to the difference of the aromatic groups (arising from a remote substituent) with respect to the π plane. In terms of the interactions, spiro[cyclopentane-1,9′-fluorene] **27** and dibenzobicyclo[2.2.2]octatrienes **37** contain similar composite fragments but the connectivity of these fragments, i.e., the topology of the π systems, is different (**A** and **B**, Figure 25). This divergent three-dimensional connectivity might modify chemical behaviors such as facial selectivity.

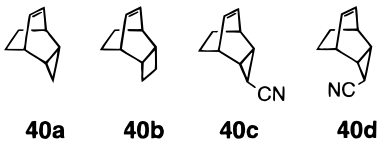
While substitution of an electron-withdrawing group such as a nitro group on an aromatic ring of the olefins (**27b** and **37a**) and the ketones (**9b,21a**, and **21d**) favors the syn attack of reagents, the perturbation arising from a methoxyl group on the aromatic ring shows appreciably divergent effects on the facial selectivity depending on the bicyclic system: in the cases of the olefin (**27e**) and ketones (**9e**) in the spiro system, the aromatic methoxy group favors the syn addition of the reagents while in the dibenzobicyclo[2.2.2]octane system the methoxy group shows no influence on the facial selectivities of the olefin **37c** and the ketone **21c** and **21f**. Recently, a reverse perturbation effect of a cyclopropyl group on facial selectivities was described in two bicyclic systems, bicyclo[2.2.2]octane **40** and norbornane (bicyclo[2.2.1]heptane) **41**.[150] Bicyclo[2.2.2]octene **40a**, annulated with an *exo*-cyclopropyl group, i.e., *exo*-tricyclo[3.2.2.0^{2,4}]non-6-ene, and 7-methylenenorbornane **41a**, annulated with an *endo*-cyclopropyl group, i.e., 8-methylene-*endo*-tricyclo[3.2.1.0^{2,4}]octane, are isomers wherein the olefin group is faced with the same structural units while the orientations of the olefin are different (**40** as in **A**, and **41** as in **B**, Figure



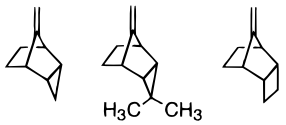
A **B**

Figure 25. Different arrangements of composite molecules.

25). The annulated cyclopropyl group introduces no



40a **40b** **40c** **40d**



41a **41b** **41c**

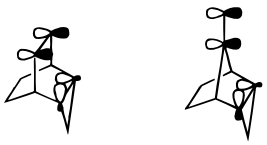
direct steric bias in either of these bicyclic systems.[151,152] Thus, the reactivities of the olefin, in particular the facial selectivities, are expected to be similar. However, experimentally this is not the case.[150] Dihydroxylation of **40a** with osmium tetroxide in pyridine and epoxidation of **40a** with *m*-chloroperbenzoic acid (mCPBA) both showed high syn preference of the addition (OsO_4, syn:anti = 95:5; mCPBA, syn:anti = 92:8). This preference is in sharp contrast to the anti preference of **41a** (syn:anti = 12:88), observed under similar dihydroxylation conditions with osmium tetroxide in pyridine. While the facial selectivity of **41a** has been examined previously,[153−156] that of **40a** has been little studied[157] and the topology-dependent behavior described here has not previously been documented or characterized.

The anti facial preference of the norbornane **41a** was previously found in the additions of dichlorocarbene (syn:anti = 44:56)[153,155] and 9-BBN (syn:anti = 11:89).[153,155] The anti preference was also observed in the reactions of methylidenebicyclo[2.2.1]heptane (**41b**) bearing an *endo*-dimethylcyclopropyl group[153,155] with dichlorocarbene (syn:anti = 34:66) and 9-BBN (syn:anti = 5:95). Therefore, we can conclude that the anti preference, induced by a cyclopropyl group, is intrinsic to the 7-methylidenenorbornane **41a**. The anti preference was also observed in alkyl-substituted **28d** ($R_1 = R_2 =$ Et), supporting the idea that a cyclopropyl group behaves as an electron-donating substituent.[109]

On the other hand, the observed syn preference of **40a** is consistent with the previous study of hydroboration of **40a** with diborane by Schueler and Rhodes,[157] who obtained a mixture of the monoalcohols (syn:anti = 74:26) upon oxidative workup. A similar magnitude of the syn preference was found (syn:anti = 73:27) in the hydroboration with a bulkier borane, 2,3-dimethyl-2-butylborane (thexyl borane).[157] This lack of effect of the bulk of the reagent in the hydroboration of **40a** is consistent with the idea that the π face of **40a** is free from steric bias[157] and that the syn preference of **40a** found in dihydroxylation and epoxidation is nonsterically determined.[151]

The syn preference of **40a** is concluded to be attributed to the fused cyclopropyl ring, based on the observation that the bicyclo[2.2.2]octene (**40b**) fused with a cyclobutane ring changes the preference to the anti direction in both the dihydroxylation (syn:anti = 40:60) and epoxidation (syn:anti = 42:58). The anti preference of the 7-methylenenorbornane **41a** is also diminished when the cyclopropyl ring is replaced with a cyclobutane ring (**41c**); in the attack of diphenylketene, the syn:anti ratio is 45:55.[154,156]

A cyclopropyl group is known to act as a strong π donor due to a high-lying occupied Walsh orbital,[158] which is frequently regarded as an equivalent of a double bond.[154,159−166] Photoelectron spectra of the olefins **40a** and **41a** were previously measured and the signals assigned.[154,163−166] Vertical ionization potentials of the olefin π orbitals of **40a** and **41a** were found to be higher than those of the unsubstituted parent bicyclo[2.2.2]octene **35a** ($R_1 = R_2 =$ H) and 7-methylenenorbornane **28a** ($R_1 = R_2 =$ H), respectively, indicating a sizable interaction of the π orbital of the double bond with the occupied Walsh orbital of the fused cyclopropane ring. The previous account of the observed anti facial preference of **41a** was based on this interaction, in particular, out-of-phase interaction of the relevant orbitals (**4.36**).[153−156] How-



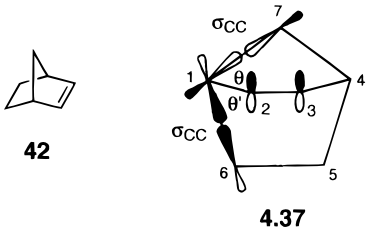
4.35 **4.36**

ever, the corresponding out-of-phase interaction of the olefinic π orbital with the Walsh orbital of the cyclopropyl group (**4.35**) does not seem to be relevant to **40a** because of the observed reverse syn preference. This view is consistent with the following observation. Because substitution of a cyano group on the cyclopropane ring lowers the energy of the Walsh orbital of the cyclopropyl group, the resultant attenuation of the interaction of the olefin orbital with the Walsh orbital, if this interaction is indispensable, would reduce the facial selectivity. However, substitution of a cyano group on the cyclopropyl group as in *exo*-cyano **40c** and *endo*-cyano **40d** essentially does *not* modify the syn preference in dihydroxylation and epoxidation but even increases the syn preference (**40c** (98:2) and **40d** (>99:<1)) in the case of dihydroxylation.

Phenomenologically, the effect of the cyclopropyl group observed in the bicyclo[2.2.2]octene (**40a**) is equivalent to that of an electron-withdrawing substituent, such as a cyano (**35b**) or a methoxycarbonyl (**35c**) group, which shows syn preference in dihydroxylation and epoxidation.[149] Thus, a cyclopropyl group can produce a reverse facial selectivity, strongly depending on the orientation of the olefin group. In terms of facial selective behavior, the cyclopropyl group embedded in the bicyclo[2.2.2]octene (**40a**) seems to be equivalent to a substitution with an electron-withdrawing group, although this is in sharp contrast to the conventional understanding of this group as strongly electron-donating.[96,167,168]

F. Classical Example of 2-Norbornene (B13)

Exo reactivity of norbornene **42** (**B13** in Figure 2) has been rationalized in terms of the torsional strain[116,169] and orbital distortion of the olefin π orbital.[20,21,25,26,117,118] Fukui et al.[25,26] proposed that the



42 **4.37**

π orbital extension of the olefin in **42** is unsymmetrical due to the second-order orbital distortion (Figure 7a) with the σCC bond of the olefin skeleton through the intervention of the σ orbital of the methano bridge. This mixing leads to hybridization of the π orbital of the olefin. Another orbital distortion was also previously proposed,[117] namely, π orbital tilting (Figure 7b) due to the combination of 2pπ−2pσ orbitals on the same regional carbon atom through the intervention of the π-type group orbital of the methylene group (πCH_2) of the methano and ethano bridges in **42**.[118,170] In norbornene **42**, the πCC of the olefin moiety can interact with CC framework orbitals of the methano and ethano bridges (**4.37**), i.e., σCC orbitals (rather than σCC* orbitals) of the vicinal CC bonds, judging from the small energy difference. Owing to the higher energy level, the πCC orbital mixed out-of-phase with the occupied σCC orbitals (equivalently, σCC bond orbitals) of the vicinal C−C bonds (C1−C6 and C4−C5 in the ethano bridge; C1−C7 and C4−C7 in the methano bridge) to give an energetically potent HOMO (**4.37**). This mixing involves a π-type overlap of these orbitals whose magnitude exhibits dihedral angle dependence.[119] In out-of-phase mixing, the greater the angle, the stronger the interaction and thus the larger the depletion of the bonding electrons. Owing to symmetry agreement, the C−C bond orbitals take part in this π-type overlap with p orbitals of the olefin moiety. Because of the less acute angle of the σ bonds of the ethano bridge (θ (dihedral angle, $\angle C_7C_1C_2$ C_3 or $\angle C_7C_4C_3C_2$) > θ' (dihedral angle $\angle C_6C_1C_2C_3$ or $\angle C_5C_4C_3C_2$) in **42**, out-of-phase mixing of the σ_{CC} orbital of *the ethano bridge* more markedly depletes the electron density of the π_{CC} orbital of the olefin on the *endo* face, favoring *exo* addition of electrophiles. This unsymmetrical π face character would be conserved during the attack of a reagent.

V. Stereoselection of Diels–Alder Dienophiles

A. Outlook

Although there have been many experimental and theoretical studies on the behavior of facially perturbed dienes (vide infra), only a few systematic experiments have been carried out to characterize facially perturbed dienophiles. Dienophiles embedded in the norbornane or norbornene motif have been rather intensively studied.[171−174] In most cases, steric effect controls selectivity, but in some cases (Figure 3), the reactions are considered to be free from steric bias and the selectivity has been explained in terms of other factors such as orbital effects.[175,176] In particular, the validity of the Cieplak model is the subject of lively debate. According to Cieplak, reactions such as polar addition (nucleophilic and electrophilic), radical addition or recombination, cycloaddition, etc., show unified facial selectivity in related systems.[3] However, this is not always the case.[175]

Within the framework of the frontier orbital theory,[2,177,178] Diels−Alder reactions involve electron delocalization through the orbital interaction between the HOMO of the diene and the LUMO of the dienophile, and this coincides with the geometric change along the reaction coordinate, i.e., weakening of the double bonds involved in diene and dienophile and strengthening of the internal bond of the diene. Orbital interaction of the LUMO of the diene and the HOMO of the dienophile also contributes cooperatively to bonding of the reagents.[177]

B. Dienophiles Based on Norbornane Structure

1. Maleic Anhydride Embedded in Norbornadiene Derivative (C1, C2)

Edman and Simmons[171] synthesized bicyclo[2.2.1]-hepta-2,5-diene-2,3-dicarboxylic anhydride **43** (Figure 26) as a facially perturbed dienophile on the basis of the norbornadiene motif, and its top selectivity in Diels−Alder reactions with cyclopentadiene (top-*exo*: top-*endo* = 60−70:1) was observed by Bartlett (Figure 26).[172] The most preferred addition was top-*exo* addition, along with the minor addition modes, top-*endo* ≫ bottom-*endo* addition (Figure 26). The addition of butadiene to this anhydride preferentially afforded the top adduct (top:bottom = 6:1). In the addition of anthracene, a top adduct was formed exclusively. Cycloaddition of bicyclo[2.2.1]hept-2-ene-2,3-dicarboxylic anhydride **44** (Figure 2b) with cyclopentadiene was also studied by Bartlett et al., who found exclusive top addition, the top-*endo*/top-*exo* ratio being 3:2.[172] The *endo*/*exo* ratio is significantly different from that of **43** (60−70:1). The observed top selectivity in norbornadiene (**43**) and norbornene (**44**) derivatives is consistent with the inherent top reactivity of norbornanone **22** and norbornene **42**. Orbital unsymmetrization of the dienophile vacant π orbital arising from out-of-phase $\sigma-\pi^*$ coupling (**5.1**) may participate in the top preference.

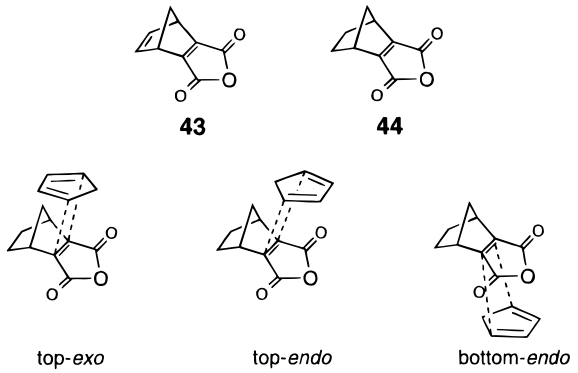
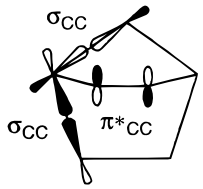


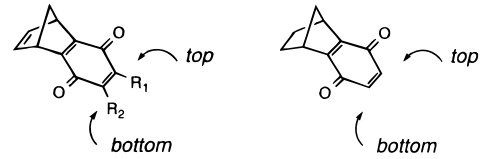
Figure 26. Addition modes of cyclopentadiene.



5.1

2. Norbornyl- and Norborneyl-Fused p-Benzoquinones (C3,C4)

Mehta et al. reported a systematic investigation of the reactions of norborneno- **45a** and norbornanobenzoquinones **46**.[173] Diels−Alder reactions of 2,3-nor-



45a: R_1=R_2=H
45b: R_1=(s)S-SOTol; R_2=H

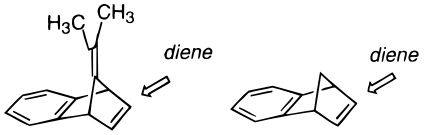
46

bornenobenzoquinone (**45a**, NPBQ) and 2,3-norbornanobenzoquinone (**46**, DNPBQ) with various dienes such as cyclopentadiene, cyclohexadiene, cyclooctatriene, isobenzofuran, and tetrachlorocyclopentadiene were studied. Both examples concern vinylogous π systems of a norbornadiene skeleton as dienophiles. Compared to **45a**, **46** has a uniformly greater preference for cycloaddition to the top face. Top or bottom preference was observed, depending on the structure of the diene. For example, **45a** with cyclopentadiene showed bottom preference (top:bottom = 35:65), while **33** with cyclopentadiene showed top preference (top:bottom = 78:22); NPBQ with 5,5-dimethoxytetrachloro-1,3-cyclopentadiene showed top preference (top:bottom = 77:23), while **46** with 5,5-dimethoxytetrachloro-1,3-cyclopentadiene showed top preference (top:bottom = 100:0). The diene dependence of the steroselectivities ruled out any important role for ground-state structural or electronic effects or orbital effects inherent to **45a** and **46** alone. This observation is consistent with the idea that steric interactions essentially determine the π facial selectivity in the cycloadditions of **45a** and **46**.

Carreño studied the effect of an additional tolylsulfinyl group on the benzoquinone (**45b**) and observed reverse top facial selectivity of **45b** with a high selectivity (top:bottom = 90:10) in the reaction of cyclopentadiene, in contrast to the bottom preference of **45a**.[174] In the presence of Lewis acid ($ZnBr_2$), the reaction is accelerated and the facial selectivity completely changes to bottom preference (top:bottom = 0:100). These reactions are of synthetic interest.[179−181]

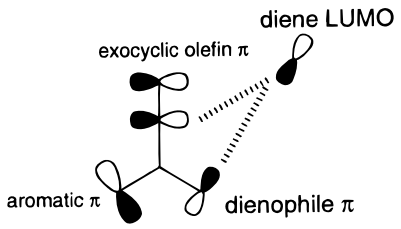
3. Benzonorbornadienes (C5)

Diels−Alder cycloadditions involving norbornene **42** (**C1** in Figure 3) and benzonorbornene (**C5** in Figure 3), 7-isopropylidenenorbornadiene, 7-isopropylidenebenzonorbornadiene (**33**), and benzonorbornadiene (**47**) as dienophiles are characterized as inverse-electron-demand Diels−Alder reactions.[132,133] These compounds react with electron-deficient dienes such as tropone. Exclusive top reactivities are found in a manner similar to the electrophilic reactions of norbornene **42**. In the inverse-electron-demand Diels−Alder reaction, orbital interaction between the HOMO of the dienophile and the LUMO of the diene is important. Thus, the orbital unsymmetrization of the olefin π orbital of norbornene (**4.37**) is assumed to be involved in these top selectivities in the Diels−Alder cycloaddition. Furthermore, large rate acceleration was encountered in these Diels−Alder cycloadditions of 7-isopropylidenebenzonorbornadiene (**33**) as compared with benzonorbornadiene (**47**) in the reaction of tropone.[132] As pointed out by

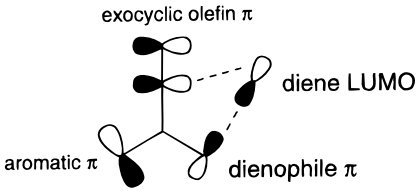


33 **47**

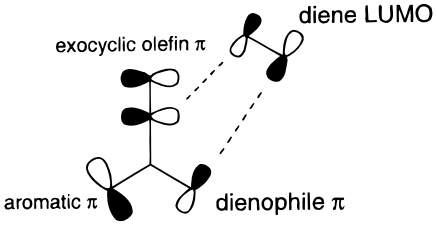
Haselbach and Rossi,[133] the initial orbital interaction of the HOMO of **33** and the LUMO of the diene is a noninteracting one (**5.2**) because of the orbital symmetry disagreement, leading to decreased reactivity of **33**. Thus, the observed large acceleration and high



5.2



5.3



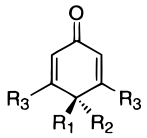
5.4

exo-selectivity of **33** can be rationalized in terms of favorable π* back-lobe interaction of the diene (the LUMO) with the HOMO of **47** (**5.3**), the interactions being late-developing. The secondary orbital interactions (**5.4**),[132] though sterically congested, may attenuate the initial unfavarable orbital interaction at the reaction centers.

C. Cyclohexanone Derivatives and Adamantane-2-thiones

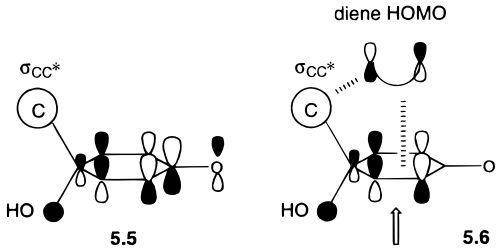
1. 2,5-Cyclohexadienones (C6)

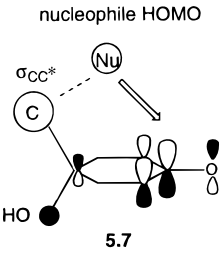
Liotta et al. studied the Diels−Alder reaction of 4-hydroxy-4-methyl-2,5-cyclohexadienone **11b** (**C6**, Figure 3, see also **A5** in Figure 1; **E1** in Figure 5) as a dienophile with *trans*-1,3-pentadiene, which gave a single adduct at 150 °C, the syn addition with respect to the hydroxyl group being favored.[182] This



11b: R_1=OH,R_2=CH_3, R_3=H
11d: R_1=OH,R_2=CH_3, R_3=CH_3

facial selectivity corresponds well to the syn preference (with respect to the oxygen group) of the Diels−Alder reaction of the isomeric cyclohexadienone, 6-acetoxy-2,4-cyclohexadien-1-one **57** (**D6** in Figure 4) with maleic anhydride, wherein the cyclohexadienone system works as a diene. Therefore, the oxygen substituent seems to enforce the addition of the dienophile or diene on the same side as the substituent. While the diene seems to react preferentially with the dienophile **11b** on its less hindered face; the orbital interaction **5.6**, which disfavors the anti side, can also participate. On the other hand, the reverse

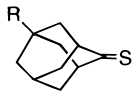




addition (i.e., anti addition with respect to the hydroxy group) of methylmagnesium reagent to the carbonyl group of **11b** has also been reported.[91] Different trajectories of addition between the Diels−Alder cycloaddition to the olefin moiety of **11b** and the nucleophilic addition to the carbonyl moiety of **11b** recognize different orbital environments of the LUMO (**5.5**) of **11b**.[222] In the latter case, the trajectory will favor the orbital interaction responsible for the syn addition (**5.7**). Furthermore, complete reversal of facial selectivities was observed in the Diels−Alder cycloadditions of 4-hydroxy-3,4,6-trimethyl-2,5-cyclohexadienone **11d** with *trans*-1,3-pentadiene, depending upon whether the process was done thermally (syn with respect to the hydroxyl group) or under Lewis acid conditions, $SnCl_4$-catalyzed (anti with respect to the hydroxyl group).[182] For the catalyzed process, the observed diastereoselectivity presumably results from complexation of the hydroxyl group by $SnCl_4$, thereby transforming it into the larger of the two geminal substituents.

2. 5-Substituted Adamantane-2-thiones (C7)

le Noble et al. studied the Diels−Alder reaction of 5-fluoroadamantane-2-thione **48a** with 2,3-dimethylbuta-1,3-diene.[183] The cycloaddition in toluene at



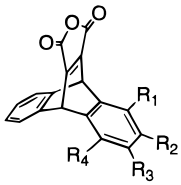
48a: R=F
48b: R=Br

reflux for 3 days gave a mixture of adducts which showed that a favored approach is syn with respect to the fluoro group (syn:anti = 67:33). A 5-bromo substituent (**48b**) also showed syn preference (syn:anti = 59:41). Photocycloaddition of fumaronitrile to 5-X-substituted adamanta-2-ones **5** (X = F, Cl, Br, OH) also showed syn preference. The observed preference is consistent with the Cieplak model. The preferred addition of the dienophile is the same as that observed in other types of reactions, such as reduction of the ketone (**5**) and electrophilic oxidation of the olefin (**25**). The observed bias is compatible with the relevant orbital unsymmetrization of the π^* orbital of the dienophile (like **3.8**).

D. Dienophiles Based on Dibenzobicyclo[2.2.2]-octatriene Structure

1. Maleic Anhydride Embedded in Dibenzobicyclo[2.2.2]-octatriene (C8)

The Diels−Alder reactions of anhydrides based on a dibenzobicyclo[2.2.2]octatriene motif **49**, as nonsterically biased dienophiles, were studied in this laboratory.[175] This system is a dienophile involving π facial nonequivalence arising from a remote substituent. Substituents in the dienophiles (**49b**−**e**) are far from the reaction center, providing a sterically equivalent π face. However, the substituents can

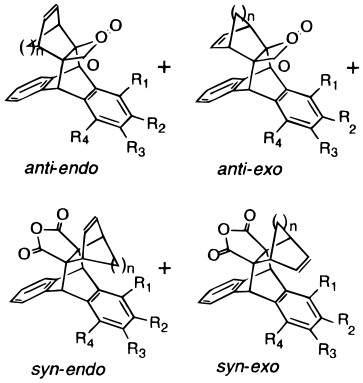


49a: R_1=R_2=R_3=R_4=H
49b: R_2=OCH_3, R_1=R_3=R_4=H
49c: R_2=NO_2,R_1=R_3=R_4=H
49d: R_1=R_2=R_3=R_4=F
49e: R_1=R_4=H,R_2=R_4=CF_3

modify the π face of the dienophiles through π^*-(anhydride)−π^*(aromatic) orbital interactions. The cycloaddition reactions of the anhydrides (**49a**−**e**) with acyclic dienes (butadiene and 1,4-dimethylbuta-1,3-diene) were conducted at 23 °C in dichloromethane as a cosolvent. Both of the dienes exhibited a similar substituent effect: while the electron-donating methoxy-substituted dienophile **49b** showed no facial selectivity in the cycloaddition, the nitro-substituted

49c did exhibit facial selectivity, i.e., anti addition (with respect to the substituted benzene ring) is favored over syn addition. The perturbing effect of an electron-withdrawing substituent is larger in 1,2,3,4-tetrafluoro- (**49d**) and 2,3-bis(trifluoromethyl)-substituted anhydrides (**49e**). Both substrates (**49d** and **49e**) also favored anti addition over syn addition: the tetrafluoro compound (**49d**) exhibited a similar bias (syn:anti = 36:64) to the nitro compound, and the bis(trifluoromethyl) compound (**49e**) exhibited a bias as large as 25:75 (syn:anti). Even when a mixture of the isolated *anti* adduct of 1,4-dimethylbuta-1,3-diene and 1,4-dimethylbuta-1,3-diene in toluene was subject to heating at 80 °C for 15 h, no isomerization was observed and the *anti* adduct was recovered unchanged. Therefore, the product distribution was determined kinetically.

Diels−Alder reactions of the anhydride (**49**) with the cyclic diene (cyclopentadiene) also proceeded at 23 °C in dichloromethane as a solvent. The four possible adducts (*anti-endo*, *anti-exo*, *syn-endo*, and *syn-exo* adducts) were formed in these reactions. The

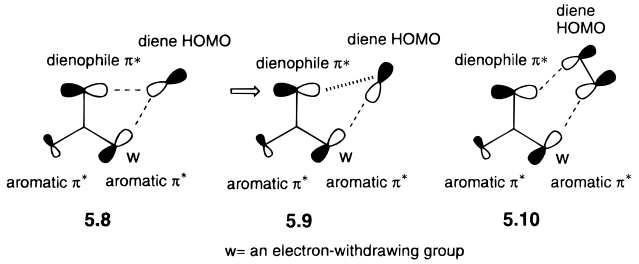


exo adduct of **49a** with cyclopentadiene did not change into any other stereoisomer, even on heating at 80 °C for 15 h in the presence of cyclopentadiene in toluene, indicating that the distributions of products are also kinetically controlled. Cycloadditions with cyclopentadiene exhibited a similar substituent effect to that in the cases of the reactions with the open-chain dienes (butadiene and 1,4-dimethylbuta-1,3-diene), i.e., the methoxy-substituted derivative (**49b**) reacted with cyclopentadiene without facial discrimination (anti/syn = 51:49), although **49b** showed an *endo* preference (*endo*/*exo* = 2:1) on both the anti and *syn* sides. A similar *endo*/*exo* ratio was found in the case of the parent substrate (**49a**). In the reactions of the substrates (**49c**−**e**) bearing electron-withdrawing groups, anti addition is favored over syn addition in both the *endo*- and *exo* adducts (except the *endo* adducts of **49d**). The anti/syn ratios increased from the tetrafluoro (**49d**) to the nitro (**49c**) and the bis(trifluoromethyl) case (**49e**); the ratios of **49e** were 23:77 (syn:anti, in the *endo* adducts) and 35:65 (in the *exo* adducts). Apparently the anti/syn ratios in the *endo* adducts are larger than those in the *exo* adducts. Close scrutiny of the results indicated that substrates **49c**−**e** favored *endo* additions over *exo* addition in the *anti* adducts and the *endo*/*exo* ratios are within the range of 1.4−1.6, quite close to the values obtained in the cases of unbiased **49a** (1.8) and **49b** (2.0). Thus, the *endo* preference observed in the *anti* adducts seems inherent in the 9,10-dihydro-9,10-ethenoanthracene motif. On the other hand, in the *syn* adducts **49c**−**e** the *endo*/*exo* ratios are divergent (0.68−1.2): the *endo*-*exo* preference was upset in the cases of **49d** and **49e**. When the reactions were carried out at 80 °C in toluene, the essential anti preference in the *endo* adducts was conserved in the substrates **49c**−**e**. However, the anti/syn selectivity is lower than those found at 23 °C. There is also a remarkable increase of syn addition in the *exo* addition of **49d** and **49e**, resulting in loss of the anti preference.

The relative rates of cycloaddition of **49b**−**e** were measured in comparison with that of the parent **49a** as a reference. A solution of an equimolar mixture of one of the substituted dienophiles (**49b**−**e**) and **49a** in CD_2Cl_2 was treated with a 2-fold molar excess of 1,4-dimethylbuta-1,3-diene, and the reaction was monitored in terms of disappearance of the proton signals of the substrates by ^1H NMR spectroscopy. The methoxy substituent has practically no effect on the reaction rate. However it is apparent that electron-withdrawing substituents (**49b**, **49c**, and **49e**) accelerate the anti addition significantly, whereas in syn addition the acceleration is not as large; the rate is comparable to that of the reference compound (**49a**). In the reactions of the tetrafluoro-substituted dienophile **49d**, we found significant rate acceleration on both sides, though the *anti* side addition was still substantially favored.

Therefore, the preference of the cycloadditions is opposite in direction to the biases observed in nucleophilic additions of 2-substituted 9,10-dihydro-9,10-ethanoanthracen-11-ones (**A10** in Figure 1; **21**) (dibenzobicyclo[2.2.2]octadienones) and in electrophilic additions of 2-substituted 9,10-dihydro-9,10-ethenoanthracenes (dibenzobicyclo[2.2.2]octatrienes) **37** (**B11** in Figure 2).[48] This example and the case of cyclohexadieneone **11b** observed by Liotta et al.[182] (see section V.C.1.) bring into question the general applicability of the Cieplak model.

The retardation at the syn face was proposed to stem from unfavorable orbital interaction developing along the syn attack trajectory:[175] as the diene approaches the anhydride moiety (either in *endo* or *exo* fashion), initially favorable in-phase interaction of the π lobes at C_1 and C_4 of the diene with the π^* lobes of the aromatic moiety of the dienophile occurs (**5.8**), in addition to the primary in-phase orbital interaction of the anhydride with the diene, as in the case of the attack of the hydride anion on the ketone (**3.24**). However, this interaction will start to be



counteracted by the emergence (or increase) of out-

of-phase interaction of the π-*back lobe* of the diene with the aromatic π^* orbital of the dienophile (**5.9**). This situation can be regarded as a type of noninteraction, as depicted in Figure 13e with some simplification. It is known that primary HOMO (diene)−LUMO (dienophile) interaction does not provide stabilization at the incipient stage of the Diels−Alder cycloaddition because of narrowing of the interfrontier level separation (orbital narrowing), i.e., raising the energy level (i.e., destabilization) of the HOMO and lowering the energy level of the LUMO.[184] However, the driving force of the cycloadditions depends significantly on the stabilization of the in-phase-combined π orbitals (of HOMO (diene)−LUMO (dienophile)), generating stable σ bonds, i.e., the conjugated π bonds of butadiene are transformed into two σ bonds in the product.[184] This stabilization emerges at a relatively late stage on the reaction coordinate, although an early transition state would be consistent with the exothermicity of the cycloaddition. Therefore, this late-developing orbital phase disagreement may modify the trajectory of the addition (probably causing an upward shift of the diene) on the syn side, leading to destabilization.[65] In the *exo* mode, the syn addition can also involve attractive secondary orbital interaction (**5.10**) (between the C_2 and C_3 π lobes of the diene and the aromatic π^* orbital of the dienophile), which will cancel the effect of the above out-of-phase interaction. This is partially compatible with the observed rather small change in the rate ratios of the *syn-exo* mode upon substitution.

VI. Stereoselection of Diels–Alder Dienes

A. Outlook

Although there have been many experimental and theoretical studies on the behavior of facially perturbed dienes, the number of sterically unbiased dienes available to probe the factors that determine the facial selectivities is still limited. In most cases (Figure 4), the steric effect controls selectivity. Facial selectivities of some dienes have been accounted for in terms of hyperconjugative,[185−187] electrostatic,[15,188] torsional,[189,190] or orbital effects.[25,26,35,118,147,191−196] The general applicability and predictive value of the proposed explanations are not obvious at the present stage.

B. Cyclopentadiene Motifs

1. 5-Substituted 1,3-Cyclopentadienes (D1)

One of the classical issues in the facial selectivity of Diels−Alder dienes is concerned with 5-substituted 1,3-cyclopentadienes. Woodward and co-workers established that ethylene added syn (with respect to the acetyl group) to 5-acetoxycyclopentadiene **50a**.[197]

50a:X=OAc, Y=H
50b:X=OH, Y=H

Recent studies using other 5-acetoxy- (**50a**) and 5-hydroxycyclopentadiene (**50b**) systems revealed a similar bias.[198] A systematic study of the facial selectivity of 5-substituted 1,3-cyclopentadines **50** as Diels−Alder dienes was carried out by Fallis and Macaulay.[6,185] Heteroatom substituents (X in **50**) of the first row (F, NH_2, OH, OAc) lead overwhelmingly to reaction onto the diene face syn to the hetereoatom. Dienes with a heteroatom substituent from the second row (Cl, SPh) afforded both syn and anti adducts, but for those with a substituent from the third or fourth row (Br, SePh, I), the anti addition occurs exclusively.

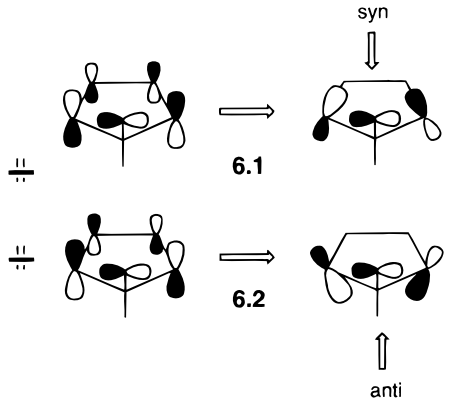
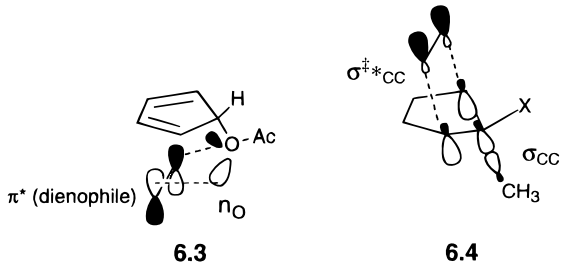


Figure 27. Orbital distortions of 5-substituted 1,3-cyclopentadienes.

The first theoretical rationalization of the facial selectivities of 1,3-cyclopentadienes was based on second-order orbital distortion, i.e., orbital tilting (Figure 7b), proposed by Inagaki et al.[26,35,191,192] The observed syn and anti preferences were rationalized in terms of the involvement of **6.1** and **6.2**, respectively (Figure 27). Regarding the preference of C-5-oxygen-substituted cyclopentadiene (**50a**), Anh pointed out the beneficial interaction (**6.3**) of the nonbonding oxygen orbital with the dienophile (LUMO).[199] However, the HOMO (π orbital) of the cyclopentadiene is subject to out-of-phase interaction of the n (π) orbital of the halogen atom attached to the 5-position (**6.1**). This out-of-phase motif, even when orbital tilting takes place, seems essentially to disfavor the syn addition. In fact, in the cases of substituents such as Br, SePh, and I, the anti preference is observed.



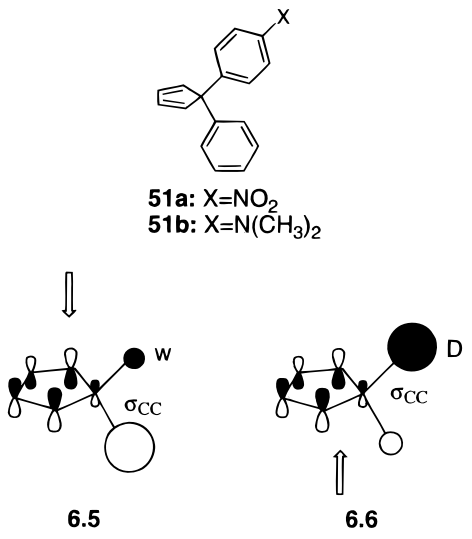
6.3 **6.4**

As an extension of the Cieplak model, Diels−Alder reactions of cyclopentadiene would be predicted this to occur anti to the adjacent C5 σ-bond, which is a better hyperconjugative donor.[185−187] According to orbital symmetry, only combination **6.4** can participate. Coxon and McDonald analyzed the AM1-calculated transition structures for the cycloaddition of ethylene and 5-chloro-5-methyl-1,3-cyclopentadiene[186] and showed that the most notable feature of

the transition-state geometry for the reaction of ethylene at each face of the diene is that the C−Cl or C−Me bond length for the anti addition of the dienophile is longer than the comparable bond length when the substituent is syn to the approaching dienophile. Lengthening of the C−X bond for anti addition is consistent with hyperconjugative stabilization involving the donation of electron density from the σ bond of an anti substituent to the forming σ^* orbital.

2. 5,5-Diaryl-1,3-cyclopentadienes (D2)

The sterically unbiased dienes, 5,5-diarylcyclopentadienes **51** (**D2** in Figure 4) wherein one of the aryl groups is substituted with NO_2, Cl, and $N(CH_3)_2$, were designed and synthesized by Halterman et al.[200] Diels−Alder cycloaddition with dimethyl acetylenedicarboxylate at reflux (81 °C) was studied: syn addition (with respect to the substituted benzene) was favored in the case of the nitro group (**51a**, X = NO_2) (syn:anti = 68:32), whereas anti addition (with respect to the substituted benzene) is favored in the case of dimethylamino group (**51b**, X = $N(CH_3)_2$) (syn:anti = 38:62). The facial preference is consistent with those observed in the hydride reduction of the relevant 2,2-diarylcyclopentanones **8** with sodium borohydride and in dihydroxylation of 3,3-diarylcyclopentenes **26** with osmium trioxide. Thus, the major product results from approach of the dienophile from the face opposite the better electron donor, compatible with the prediction of Cieplak's model. Unsymmetrization of the diene π orbitals is inherent in **51**, which is consistent with the observed facial selectivities (**6.5** for **51a**; **6.6** for **51b**).



3. Spiro-1,3-cyclopentadienes (D3)

Benzo[*a*]- (**a**), benzo[*b*]- (**b**), and benzo[*c*]fluorenes (**c**) bearing a carbonyl (**52**), an olefin (**53**), or a diene group (**54**) in spiro geometry are three possible combinatorial isomers wherein the direction of fusion of the naphthalene is different (Figure 28).[201] The π reaction centers of the carbonyl, olefin, and diene groups are subject to spiroconjugation[86,87,90] with the planar aromatic π system. The effect of perturbation arising from spiroconjugation on the chemical reac-

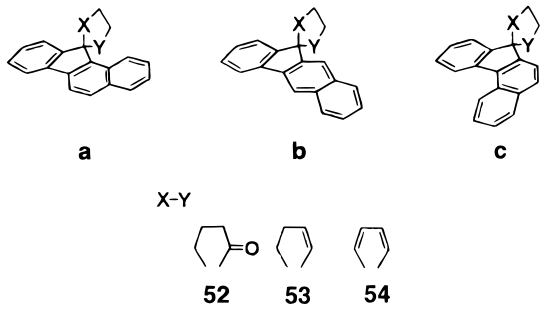


Figure 28. Possible combinatorial isomers.

tivities, in particular the facial selctivities, was investigated. With respect to the π faces of the relevant reaction centers, the first aromatic system is sterically biased (i.e., sterically unsymmetrical) while the latter two systems are assumed to be free from steric bias. These dienes react as Diels−Alder dienes with several dienophiles (maleic anhydride, *N*-phenylmaleimide, and *N*-phenyl-1,3,5-triazoline-2,4-dione). *Endo* isomers of the adducts were predominantly formed. The direction of fusion of the aromatic ring changes the facial preference. The diene (**54b**) bearing benzo[*b*]fluorene favored syn addition of the dienophiles (syn:anti = 62:38 (for maleic anhydride)) with respect to the naphthalene ring, whereas the diene **54c** (benzo[*c*]fluorene) showed a reverse anti preference for the additions (syn:anti = 28:72 (for maleic anhydride)). In contrast to the behavior of the dienes, spiro ketones and spiro olefins bearing a benzofluorene (except **52c** in the case of $NaBH_4$ reduction (syn:anti = 60:40)) showed little or no π facial selectivity in the absence of a steric influence (that is, **52a** and **53a**). The lack of interaction of the spiro π substituents (π fragments) can be explained in terms of the large energy gap of these fragments (Figure 29).[201] In the case of the ketone, the unoccupied carbonyl π^* orbital is perturbed by the lower-lying unoccupied aromatic π^* orbitals of the benzofluorenes, while in the cases of the olefins, the occupied olefin π orbital is perturbed by the high-lying occupied aromatic π orbitals of the benzofluorenes. In the case of the ketone **52c**, the relevant energy gap is apparently smaller than that of **52b**, leading to effective interaction, which is consistent with the observed selectivity of **52c** (no selectivity in the case of **52c**) in the reaction with $NaBH_4$. In the cases of the sterically unbiased olefins (**53b** and **53c**), there are consistently large energy gaps. The diene systems involve complete spiroconjugation, leading to an effective overlap of the diene π orbital and the aromatic π orbital. Furthermore, the HOMO of the diene is close to that of the aromatic benzofluorenes (Figure 29). Nonequivalent orbital interactions of the π reaction center with the aromatic π orbitals at the *ipso* positions are thought to be crucial for facial preference of aromatic spiro systems. In the case of the occupied π reaction center, reactions on the opposite side of the out-of-phase motif may be favored, while in the case of the unoccupied π^* reaction center, those on the side of the additional in-phase motif may be favored (Figure 30).[9] The observed preferences of the diene (syn (**54b**) and anti (**54c**)), in addition to the ketone **52c** (syn), seem to be

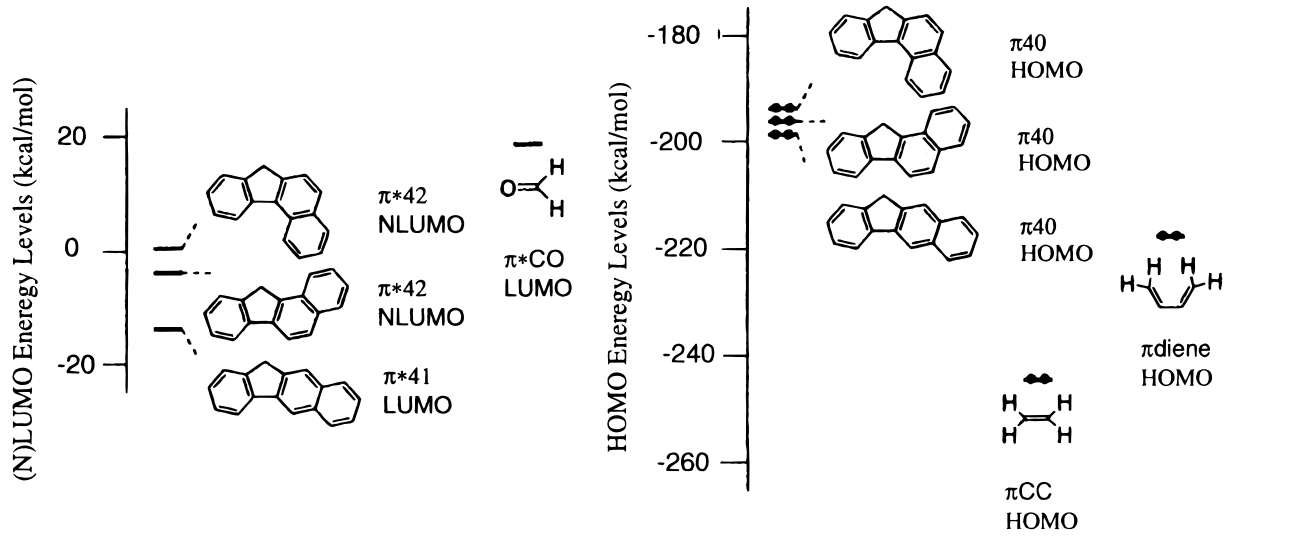


Figure 29. Energy gaps of the π fragment orbitals (PM3 (kcal/mol)).

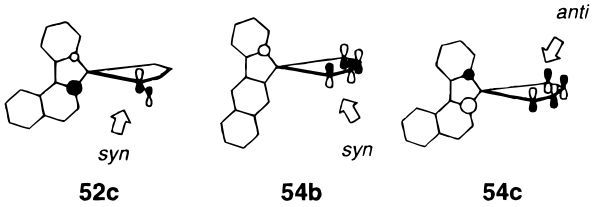


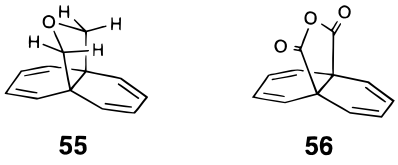
Figure 30. Relevant orbital interactions and predicted preferences.

consistent with this idea. This observed diversity of the facial selectivities of **54c** and **52c** may be in conflict with the Cieplak model.

C. Cyclohexadiene Motifs

1. Heterocyclic Propellanes (D4, D5)

The cycloaddition reaction of heterocyclic propellanes **55** (X = O and S) (**D4** in Figure 4) with *N*-phenyltriazolinedione (**N**) (Figure 31) affords the anti adduct with respect to the bridge.[193,194,202] Replacement of the α-CH_2 groups by carbonyls (that is **56**), instead, resulted in the formation of only syn products. Secondary orbital interactions (not second-order orbital mixing in Figure 7) were considered to be responsible for the reverse syn addition of triazolinediones to anhydride and imide-bridged [4.4.3]-propellane dienes **56** (Figure 31). When the carbonyl groups are present, the transition state for syn attack is stabilized by interactions between the out-of-phase combination of the NN lone pairs and the antisymmetric π^* orbital of the CO−X−CO bridge. Although the secondary effect operates only during syn approach and contributes added stabilization to this transition state, the primary orbital interaction (see **6.10**) between the HOMO of the cyclohexadiene moiety of **55** and the π^* orbital of the dienophile (**N**, Figure 31) is differentiated with respect to the direction of attack, i.e., syn or anti, of triazolinedione (**N**, Figure 31).



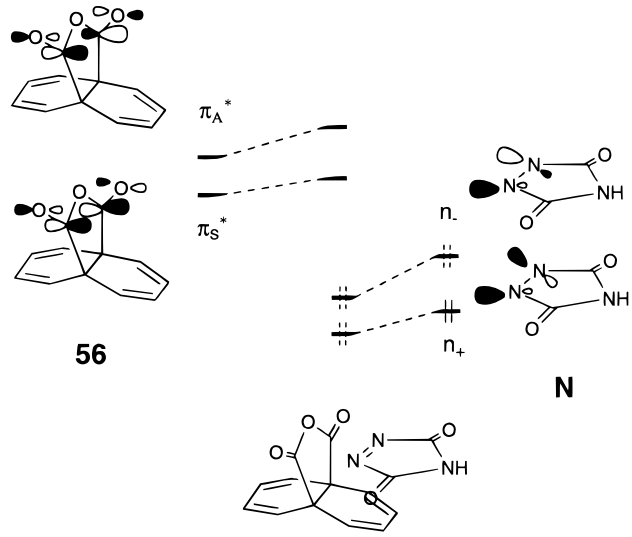
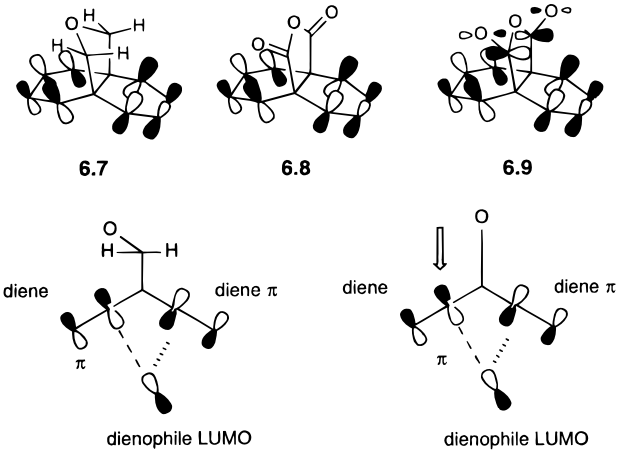


Figure 31. Secondary orbital interaction.

The stereochemical course of the first reaction of **55** can be rationalized in terms of the relative steric contributions of the flanking bridge, in particular of methylene protons and the puckering oxygen atom (see **6.7** and **6.10**). In terms of orbital interactions, both systems, **55** and **56**, involve the essential out-of-phase orbital interaction motif between two π components of the two butadiene units (**6.7** and **6.8**), and therefore, the anti addition is intrinsically unfavorable in these systems. Replacement of the flanking methylenes with the trigonal planar carbon atoms as in **56** retrieves the genuine steric unbias (**6.8** and **6.11**), exhibiting the inherent syn addition arising from the orbital unsymmetrization. Contribution of the in-phase motif of the vacant carbonyl π^* orbital of the anhydride moiety (**6.9**) to the HOMO of the molecule **56** also encourage syn addition of **56**.

2. 6-Acetoxy-2,6-dimethyl-2,4-cyclohexadienone (D6)

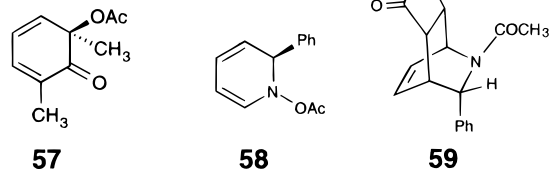
6-Acetoxy-2,6-dimethyl-2,4-cyclohexadienone **D6** (Figure 4), **57** (X = OAc,Y = CH_3), and maleic



anhydride or propiolic acid in boiling benzene give a single Diels−Alder adduct,[203] which is formed with high stereoselectivity by attack on the acetoxyl-bearing face of the dienone, i.e., syn:anti = 100:0 with respect to the acetyl group. *Endo* adducts are formed, as frequently observed with dienophiles such as maleic anhydride and *p*-benzoquinone. Since the reaction occurs under mild conditions, it is most probable that the facial selectivity is determined kinetically. This high syn preference is comparable with those observed in the Diels−Alder reactions of 5-acetoxy-1,3-cyclopentadiene **50a** and ethylene (syn:anti = 100:0),[197] or of 5-hydroxy- (**50b**) or 5-methoxy-1,2,3,4,5-pentamethyl-1,3-cyclopentadienes and maleic anhydride (syn:anti = 100:0).[6,185] Therefore, the 2,4-cyclohexadienone system **57** can be regarded as a β-vinylogous π system of the 1,3-cyclopentadiene system **50**.

3. 2-Phenyl-1,2-dihydropyridine (D7)

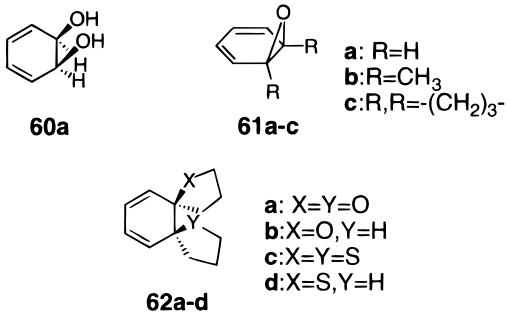
Diels−Alder cycloaddition reactions utilizing *N*-acyl-1,2-dihydropyridines **D7** (Figure 4) offer a convenient pathway to isoquinuclidines, substituted at 7- and/or 3,7-positions, which are of synthetic interest as versatile intermediates in natural product synthesis.[204] Reaction of *N*-acetyl-2-phenyl-1,2-dihydropyridine **58** (X = OAc, Y = Ph) with maleic anhydride afforded exclusively the 3-*exo*-phenyl adduct **59**. That



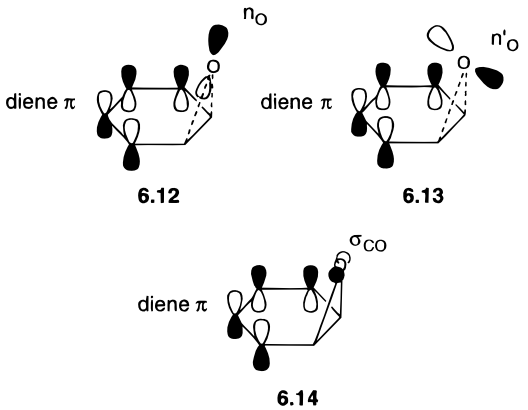
is, the face opposite the 2-phenyl substituent of N-acyl-1,2-dihydropyridine **58a** was favored. This facial selectivity is concluded to be determined kinetically, and the bias is reasonable due to the sterically hindered face with respect to the phenyl group.

4. cis-Cyclohexa-3,5-diene-1,2-diol (D8, D9)

Cycloaddition of *cis*-cyclohexa-3,5-diene-1,2-diol **60a** with *N*-phenylmaleimide in chloroform at room temperature for 24 h showed a syn preference of addition with respect to the oxygen substituents (syn:anti = 94:6).[205] Substitution on the oxygen atoms with



acetyl, trimethylsilyl, (dimethylsilylene)bis(oxy), and isopropylidenedioxy groups essentially did not change the syn preference, only the magnitude and the reaction rates being modified. In contrast to the syn preference of **60a**, 1,3,5-cyclohexatriene-1,2-dioxide (benzene oxide) **61a**, an epoxide analogue, showed exclusive anti preference in the Diels−Alder reaction with *N*-phenylmaleimide. 1,2-Dimethyl-1,3,5-cyclohexatriene 1,2-oxide (**61b**) and 10-oxatricyclo[4.3.1.0]-deca-2,4-diene (**61c**) also showed anti preference.[206] Therefore, despite the much larger size of two methyl or methylene groups compared to two hydrogens, the cycloaddition still exhibited complete π-facial selectivity. The geometry of the benzene oxides **61** is such that the oxygen is almost perpendicular to the plane of the diene moiety, whereas the oxirane substituents (two hydrogens, two methyls, and methylene) are roughly coplanar with the diene moiety. Therefore, there is a significant steric interaction between the oxygen and an incoming dienophile on the syn face. Superficially, the observed anti preference is in contrast to the syn preference of Diels−Alder reactions of 5-hydroxy-1,3-cyclopentadiene **50b**.[6,185] However, due to orbital symmetry, the HOMO of the diene is intact to interact with n orbitals of the oxygen atom (**6.12** and **6.13**), unlike that of the 5-hydroxy-1,3-cyclopentadiene **50b** (see **6.1**). The



HOMO of the diene interacts with the σ_{CO} orbitals in an out-of-phase motif (**6.14**), which is also relevant to the anti preference with respect to the out-of-phase motif.

5. Dispiro[4.0.4.4]tetradeca-11,13-dienes (D10)

Paquette et al. examined the facial selectivities of a series of dispiro[4.0.4.4]tetradeca-11,13-dienes **62**

(**D10** in Figure 4)[188] in a study which is closely related to the work of Gillard and Burnell[205] on the Diels−Alder reactions of *cis*-cyclohexa-3,5-diene-1,2-diols **60** (**D8** in Figure 4). These systems (**D10**) provide fixation of the direction of the substituent, in particular of the n(π) orbitals of the heteroatoms, and minimize steric bias. Heating a benzene solution of the *syn*-dioxa diene **62a** (X = Y = O) with *N*-phenylmaleimide or with maleic anhydride at reflux or with *N*-methyltriazolinedione at low temperature afford the syn adduct in all cases (with respect to the heteroatom). *p*-Benzoquinone and 1,4-naphthoquinone were less reactive, and the cycloaddition required high pressure. These dienophiles also gave exclusively syn adducts with **62a**. The mono-oxygen-containing diene **62b** (X = O, Y = H) also gave the syn adduct. In contrast, the cycloaddition reaction of the *syn*-dithiadiene **62c** (X = Y = S) is retarded. The cycloaddition with *N*-methyltriazolinedione gave the anti adduct exclusively. The monothia-containing substrate **62d** (X = S, Y = H) gave a 1:1 mixture of adducts with *N*-phenylmaleimide, and with *N*-methyltriazolinedione, anti addition is also favored (syn:anti = 1:10). These electrostatic properties were suggested by the authors[188] to be important in order to explain the π facial selectivities. *N*-Phenyl maleimide is suggested to have a positive partial charge on the hydrogen and carbon atoms of the carbon−carbon double bond, whereas *N*-methyltriazolinedione has a slight positive charge density on the doubly bonded nitrogen but a negative charge density in the region where the lone pairs are located (see **N** in Figure 31). Because oxygen bears a negative charge and sulfur bears a positive charge which is larger than that of the methylene group, the observed selectivity is consistent with electrostatic interaction between the diene and dienophile.

6. Adamantane Diene (*D11*)

The cycloaddition of 1,3-diene **D11** (Figure 4) based on adamantanes is also studied by le Noble et al.[232] Although the magnitude of facial selectivity is small in the reaction of the fluoro derivative **63a** with tetracyanoethene, syn preference (with respect to the fluoro group) was observed (syn addition:anti addition = 58:42). This syn preference is compatible with

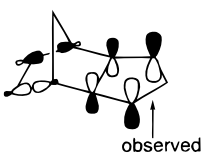
63a: R=F **64** **65**

the case of 5-fluoroadamantane-2-thione **48** as a Diels−Alder dienophile.

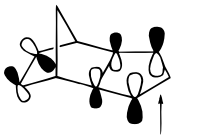
D. Norbornane Motifs (D12, D13)

1. Isodicyclopentadiene

It is noteworthy that Diels−Alder cycloaddition of isodicyclopentadienes (**64**, **D12** (Figure 4) and **65**, **D13** (Figure 4)) with methyl acrylate, maleic anhydride, and *p*-benzoquinone showed *endo* preference, which is in strong contrast to the inherent *exo* preference of the norbornene toward electrophilic reagents.[189,195,196,207,208] The cause of this behavior cannot be steric in origin since the reacting centers actually experience bond formation on the diene surface that is syn to the large ethano bridge. The observed facial selectivity can be interpreted in terms of σ/π interaction.[195] However, the magnitude of the destabilization energy arising from the four-electron−two-orbital repulsion is independent of the energy gap between the fragment orbitals involved.[13,175,209] Thus, the effect of the relevant interaction of the higher-lying occupied orbitals can be canceled by similar interactions between the lower-lying occupied orbitals. Houk and Brown postulated a role of torsional strain, which is relevant to the transition structures of the diene in the Diels−Alder cycloaddition.[189] The orbital interaction of isodicyclopentadiene (**6.15** and **6.16**) is reminiscent of the syn preference of 5-hydroxy-substituted 1,3-cyclopentadiene (**6.1**), which favors addition on the side of the more diffused out-of-phase motif.



6.15



6.16

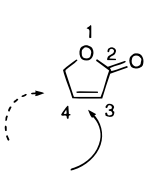
VII. Stereoselection of Michael Acceptors (E1–E3)

In the viewpoint of orbital interactions, 1,4-conjugate additions to enones (Michael additions) involve π^* orbitals of the olefin portions of the enones while the occupied π orbitals of the olefins contribute to the electrophilic reactions of the olefins (section IV). Therefore, the effects of occupied and unoccupied orbitals of the same functional group, i.e., olefins on facial selectivities, can be evaluated. Although facial selectivities of 1,4-conjugate additions (Michael additions) to enones are one of the fundamental issues in connection with stereoselective reactions,[210] the potential for facial selectivity arising from sterically unbiased Michael acceptors (Figure 5) does not seem to have been well evaluated. Liotta et al. studied the conjugate addition to γ-hydroxyenones **E1** (Figure 5) (**A5**, **C6**) of organometallic reagents (Figure 5).[92,93] They found that deprotonated *p*-quinols and 4-hydroxyenones undergo diasterofacially specific Michael additions with reagents which typically react intermolecularly in a 1,2-fashion, that is, syn addition with respect to the hydroxyl group is favored. This process appears to require the presence of alkoxide ion. If the oxygen is protonated with a trimethylsilyl group **11c**, no directing effects are observed. Thus, the syn preference is due to the initial complexation of the nucleophilic reagent by the alkoxide group, followed by intramolecular delivery of the bound nucleophile to the adjacent electrophilic center. This rationalization seems reasonable because the complementary anti addition was observed when metallocarbanionic reagents in which the metal is coordinatively saturated are employed. These observations are of synthetic significance.[93]

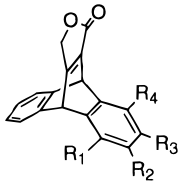
Seebach et al. studied the facial selectivity of the 2,6-disubstituted 1,3-dioxin-4-ones (**E2** in Figure 5)

in the Michael additions of organocuprate reagents.[23] The results can be rationalized in terms of steric hindrance.[211] Fixation of the conformations of 2,6-disubstituted 1,3-dioxin-4-ones does not seem to be the source of selectivities, because equilibrium is rapid in solution, even though the crystallographic structures suggested the conformation (see also Figure 18).[212]

In 1,4-conjugate additions toward cyclic unsaturated lactones, facial selectivity is generally determined by the stereochemistry of the substituents on the ring. Other effects such as stereoelectronic effects are also important in some cases.[212,213] To exclude a contribution of the classical steric effect or precoordination of reagents, several lactones with 2(5*H*)-furanone (**66**) embedded in a dibenzobicyclo[2.2.2]-octatriene frame (**67a**−**c**) (**E3** in Figure 5) were designed and synthesized.[214] In this system, the



66



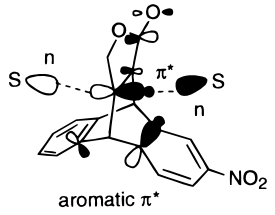
67 **a**: $R_1=R_2=R_3=R_4=H$
b: $R_1=R_2=R_4=H$, $R_3=NO_2$
c: $R_1=R_3=R_4=H$, $R_2=NO_2$

aromatic substituent is far from the reaction center and the π-face is considered to be free from conventional steric effects. Furthermore, the use of the cyclic lactone moiety fused to the bicyclo skeleton avoids complexity arising from cis/trans protonation of the intermediate adduct. Thus, these compounds should be substrates with minimal bias close to the reacting sp^2 carbon, allowing us to separate steric, torsional, and stereoelectronic variables.[214]

The base-catalyzed 1,4-addition of ethanethiol to **67a**−**c** in a variety of aprotic solvents at 23 °C for 75 h was studied. The 3-nitrolactone (**67b**) favors syn addition rather than anti addition in all cases (with respect to the nitro group). The 2-nitro lactone (**67c**) also favors syn addition, though the ratio obtained in a neat condition is smaller than that of **67b**. The *anti* adduct of **67c** did not change into the *syn* adduct at 23 °C during 94 h in a mixture of ethanethiol and sodium thioethoxide without solvent. In DMF as a solvent, the isomerization was observed to only a small extent (*anti* adduct:*syn* adduct = 93:7 (**67c**)). These results indicate that the distributions of products are kinetically determined. In both cases (**67b** and **67c**) it was found that the magnitude of the syn preference increased with increasing solvent polarity: the syn/anti ratio of **67b** and **67c** reached 79:21 and 75:25 in DMF, respectively. On the other hand, the reaction in a nonpolar solvent such as *n*-hexane showed a smaller selectivity than that in polar solvents, though syn preference was still observed. These results indicate intrinsic syn preference of attack of the nucleophilic reagent on **67b** and **67c**.

The syn preference of **67b** and **67c** is similar to those observed in the reduction of the related ketones, **A14** (Figure 1), and in the epoxidation and dihydroxylation of the related olefins **B11** (Figure 2).[48] Although the trajectories of the attacking reagents are considered to be different in these reactions,[55,65,110−114,215] all three types of reactions favor syn addition, which excludes a predominant role of divergent trajectories in these dibenzobicyclic systems.

The substituent effect of the aromatic nitro group can be accounted for in terms of π orbital unsymmetrization. The LUMO of the dibenzobicyclic lactone (**7.1**) can be analyzed as an in-phase combination of three vacant π^* orbitals, i.e., those of benzene, nitrobenzene, and the 2(5*H*)-furanone moiety. The energetically lower-lying π^* orbital of the nitrobenzene fragment contributes significantly to the LUMO of the whole molecule rather than the π^* orbital of the nonsubstituted benzene. Thus, the LUMO of 2(5*H*)-furanone is unsymmetrized (**7.1**). Therefore the



7.1

syn attack of the nucleophilic reagent is favored because of the additional *in-phase* interaction of the π^* lobe of the nitrobenzene motif.

The predominant component of the LUMO of the whole molecule is the π^* orbital of the nitrobenzene fragment rather than that of the reaction center. However, the orbital being perturbed to generate the syn preference is the LUMO and not the next-LUMO, which contains the π^* orbital of the reaction center as a main component.

VIII. Reciprocal Interactions

Interactions between two fragments (i.e., two functional groups) in a molecule would be subject to efficient reciprocal perturbations, reminiscent of "action and reaction" in dynamics. Few works payed attention to such reciprocal interactions which can modify the reactivities inherent to the respective functional groups. The following example will highlight the significance of the reciprocal interactions which is envisioned in the nitration of the fluorene ring of spiro ketones **9a**.

In the spiro systems **A4** (Figure 1), the aromatic orbitals unsymmetrized the carbonyl orbital. Simultaneously, the carbonyl group can perturb the orthogonal aromatic ring. Nitration of the fluorene derivatives (**9a**) bearing a spiro substituent was studied (Figure 32).[8,9]

The reactivities of **9a** can be interpreted in terms of the reciprocal perturbation of the aromatic ring arising from the bisected carbonyl group. Fluorene **68** exhibits more nucleophilicity at C-2 than at C-4, due to increased conjugation of the aromatic rings and steric congestion at C-4. In the nitration of the parent fluorene **68** at −43 °C with acetyl nitrate, the isomer distribution was observed to be 67% at C-2

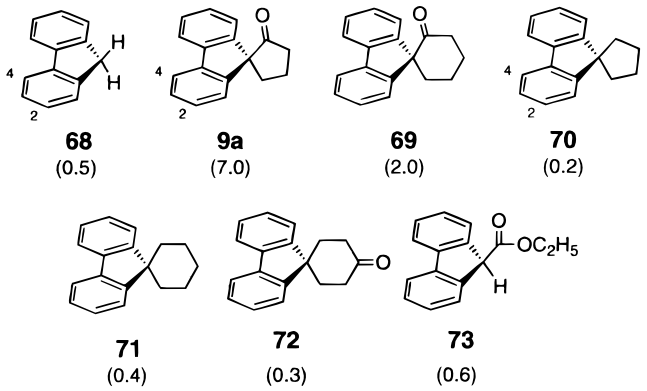


Figure 32. Reciprocal perturbations in nitrations. Ratios of 4-/2-nitration are shown in parentheses.

and 33% at C-4. Figure 32 also shows the 4-/2-nitration ratios. A spiro-substitution, on the other hand, was found to have a large effect on the nitration, resulting in a great change of the distribution of products: instead of the 2-nitro derivative (11%), spiro[cyclopentane-1,9′-fluorene]-2-one **9a** predominantly gave the 4-nitro derivative (77% yield) with the nitrating reagent at −75 °C. The use of a higher temperature, −43 °C, did not alter the result. A similar divergence in the distributions of nitrated compounds was also observed in the case of the reactions of the spiro fluorene bearing a six-membered ring, spiro[cyclohexane-1,9′-fluorene]-2-one **69**. The bisected carbonyl group of **9a** and **69** plays a significant role in these divergent nitrations: the nitration of spiro[cyclopentane-1,9′-fluorene] **70** and spiro[cyclohexane-1,9′-fluorene] **71**, the decarbonylated compounds, resulted in the commonly expected distributions of nitrated fluorenes. Judging from the ratios of 4-/2-nitration, a less flexible conformation, i.e., a more rigid planarity of the five-membered ring of **9a** and **70**, strongly perturbed the nitration. Neither the cyclohexane ring nor the cyclopentane ring, in the spiro geometry, encouraged the nitration at C-4, or rather both enhanced the reactivities at the C-2 position of the fluorene ring. These results also exclude possible steric congestion around the C-2 position owing to the spiro-substitution of the C-9 position. Moreover, the nitration of spiro[cyclohexane-1,9′-fluorene]-4-one **72** also favored the 2-nitro derivative (65%) rather than the 4-nitro derivative (17%), suggesting that proximity is requisite for interaction between the carbonyl and the aromatic moieties. An indirect effect on the nitration reaction arising from a carbonyl substituent at the C-9 position of the fluorene was indicated by the nitration of 9-ethoxycarbonylfluorene **73**. The 4-/2-ratio (0.6) is very similar to that of fluorene **68** (0.5). All the results, therefore, indicate perturbation of the fluorene ring arising from the bisected carbonyl group of **9a**.

IX. Conclusions

This review contends that throughout the known examples of facial selections from classic to recently discovered ones, a key role is played by the orbital unsymmetrization of π reaction centers arising from the first-order perturbation, that is, the unsymmetrization of the orbital phase environment of the relevant π orbitals. This asymmetry of the π orbitals, if recognized along the trajectories of additions, is proposed to be generally involved in the facial selections of sterically unbiased systems. Experimentally, carbonyl and related olefin compounds, which bear a similar structural motif, exhibit the same facial preference in most cases, particularly in the cases of adamantanes. This feature seems to be compatible with the Cieplak model. However, this is not always the case for other types of molecules and in reactions such as Diels−Alder cycloaddition.

There have been several studies to characterize other facial selections of organic reactions, in particular, of sigmatropic reaction,[216,217] oxy-Cope rearrangement,[218] Claisen rearrangements,[219] and 1,3-dipolar cycloadditions,[220−224] which we did not mention here. le Noble and other groups also carried out extensive studies of the facial selective behavior of adamantane motifs, for example, captures of carbene,[225] radicals,[226] carbocations[227] and carboanions,[216] sulfur oxidation,[228] olefin−metal complexation,[229] and thermal[230] and photo cycloadditions.[231] Nevertheless, as Figures 1−5 suggest, the number of structural motifs of sterically unbiased substrates is limited. Further advances in our understanding of facial selections may require the design of new structural motifs, which can be used to test the general applicability of the relevant rationalizations and also to provide a basis for new and more general rationalizations. This process will be assisted by a combinatorial approach in experimental and theoretical studies.

X. References

(1) Fukui, K. *Science* **1982**, *218*, 747−754.
(2) Fukui, K. *Theory of Orientation and Stereoselection*; Springer-Verlag: Heidelberg, 1975.
(3) Johnson, C. R.; Tait, B. D.; Cieplak, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 5875−5876.
(4) Giddings, M. R.; Hudec, J. *Can. J. Chem.* **1981**, *59*, 459−467.
(5) Cheung, C. K.; Tseng, L. T.; Lin, M.-H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598−1605.
(6) Macaulay, J. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1988**, *110*, 4074−4076.
(7) Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 6690−6695.
(8) Ohwada, T.; Shudo, K. *Chem. Pharm. Bull.* **1991**, *39*, 2176−8.
(9) Ohwada, T. *J. Am. Chem. Soc.* **1992**, *114*, 8818−27.
(10) Lemieux, R. U.; Koto, S. *Tetrahedron* **1974**, *30*, 1933.
(11) Brown, H. C.; Muzzio, J. *J. Am. Chem. Soc.* **1966**, *88*, 2811−2822.
(12) Klein, J. *Tetrahedron Lett.* **1973**, *44*, 4307−4310.
(13) Albright, T. A.; Burdett, J. K.; Whangbo, M.-H. *Orbital Interactions in Chemistry*; John Wiley & Sons: New York, 1985.
(14) Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650−663.
(15) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 663−671.
(16) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 666−671.
(17) Chamberlin, A. R.; Mulholland, R. L.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672−677.
(18) Rondan, N. G.; Paddon-Row, M. N.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2436−2438.
(19) Burkert, U. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 572−573.
(20) Spanget-Larsen, J.; Gleiter, R. *Tetrahedron Lett.* **1982**, *23*, 2435−2438.
(21) Spanget-Larsen, J.; Gleiter, R. *Tetrahedron* **1983**, *39*, 3345−3350.
(22) Houk, K. N.; Rondan, N. G.; Brown, F. K.; Jørgensen, W. L.; Madura, J. D.; Spellmeyer, D. C. *J. Am. Chem. Soc.* **1983**, *105*, 5980−5988.

(23) Seebach, D.; Zimmermann, J.; Gysel, U.; Ziegler, R.; Ha, T.-K. *J. Am. Chem. Soc.* **1988**, *110*, 4763−4772.
(24) Beck, A.; Gompper, R.; Polborn, K.; Wagner, H.-U. *Angew. Chem., Int. Ed.* **1993**, *32*, 1352−1354.
(25) Inagaki, S.; Fukui, K. *Tetrahedron Lett.* **1974**, 509−514.
(26) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4054−4061.
(27) Fukui, K.; Nagata, C.; Yonezawa, T.; Kato, H.; Morokuma, K. *J. Chem. Phys.* **1959**, *31*, 287−293.
(28) Fukui, K.; Morokuma, K.; Yonezawa, T.; Nagata, C. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 963−973.
(29) Libit, L.; Hoffmann, R. *J. Am. Chem. Soc.* **1974**, *96*, 1370−1383.
(30) Imamura, A. *Mol. Phys.* **1968**, *15*, 225−238.
(31) Imamura, A.; Hirano, T. *J. Am. Chem. Soc.* **1975**, *97*, 4192−4198.
(32) Levine, I. *Quanatum Chemisty*, 4th ed.; Prentice-Hall: Englewood Cliffs, NJ, 1991.
(33) Burgess, E. M.; Liotta, C. L. *J. Org. Chem.* **1981**, *46*, 1703−1708.
(34) Jorgensen, W. L. *The Organic Chemist's Book of Orbitals*; Academic Press: Inc.: London, 1973.
(35) Ishida, M.; Beniya, Y.; Inagaki, S.; Kato, S. *J. Am. Chem. Soc.* **1990**, *112*, 8980−8982.
(36) Werstiuk, N. H.; Ma, J.; Macaulay, J. B.; Fallis, A. G. *Can. J. Chem.* **1992**, *70*, 2798.
(37) Fujimoto, H.; Inagaki, S. *J. Am. Chem. Soc.* **1977**, *99*, 7424−7432.
(38) Klein, J. *Tetrahedron* **1974**, *30*, 3349−3353.
(39) Eisenstein, O.; Klein, J.; Lefour, J. M. *Tetrahedron* **1979**, *35*, 225−228.
(40) Aubort, J. D.; Hudson, R. F. *J. Chem. Soc., Chem. Commun.* **1970**, 937−938.
(41) Fillippini, F.; Hudson, R. F. *J. Chem. Soc., Chem. Commun.* **1972**, 522−523.
(42) Cowan, D. O.; Gleiter, R.; Hashmall, J. A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 401−402.
(43) Fujimoto, H.; Koga, N.; Hataue, I. *J. Phys. Chem.* **1984**, *88*, 3539−3544.
(44) Ohwada, T.; Shudo, K. *Yuki Gosei Kagaku Kyokaishi* **1994**, *52*, 596−607.
(45) Huang, X. L.; Dannenberg, J. J.; Duran, M.; Bertrán, J. *J. Am. Chem. Soc.* **1993**, *115*, 4024−4030.
(46) Huang, X. L.; Dannenberg, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 6017−6024.
(47) Ohwada, T. *Kagaku* **1993**, *48*, 646.
(48) Ohwada, T.; Okamoto, I.; Haga, N.; Shudo, K. *J. Org. Chem.* **1994**, *59*, 9, 3975−84.
(49) Hoffmann, R.; Mollère, P. D.; Heilbronner, E. *J. Am. Chem. Soc.* **1973**, *95*, 4860−4862.
(50) Fukui, K.; Koga, N.; Fujimoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 196−197.
(51) Fukui, K.; Fujimoto, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1989−1997.
(52) Fujimoto, H.; Koga, N.; Fukui, K. *J. Am. Chem. Soc.* **1981**, *103*, 7452−7457.
(53) Fujimoto, H. *Acc. Chem. Res.* **1987**, *20*, 448−453.
(54) Perlberger, J.-C.; Müller, P. *J. Am. Chem. Soc.* **1977**, *99*, 6316−6319.
(55) Stone, A. J.; Erskine, R. W. *J. Am. Chem. Soc.* **1980**, *102*, 7185−7192.
(56) Singleton, D. A.; Merrigan, S. R.; Liu, J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 3385−3386.
(57) Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147−10152.
(58) Jørgensen, K. A.; Hoffmann, R. *J. Am. Chem. Soc.* **1986**, *108*, 1867−1876.
(59) DelMonte, A. J.; Haller, J.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Strassner, T.; Thomas, A. A. *J. Am. Chem. Soc.* **1997**, *119*, 9907−9908.
(60) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363−368.
(61) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4693−4701.
(62) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199−2204.
(63) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205−2208.
(64) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61.
(65) Houk, K.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108−1117.
(66) Coxon, J. M.; Houk, K. N.; Luibrand, R. T. *J. Org. Chem.* **1995**, *60*, 418−427.
(67) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540−4552.
(68) Senju, T.; Tomoda, S. *Chem. Lett.* **1997**, 431−432.
(69) Dedieu, A.; Veillard, A. *J. Am. Chem. Soc.* **1972**, *94*, 6730.
(70) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447−8462.
(71) Eliel, E. L.; Senda, Y. *Tetrahedron* **1970**, *26*, 2411.
(72) Rei, M.-H. *J. Org. Chem.* **1979**, *44*, 2760.
(73) Wigfield, D. C.; Phelps, D. J. *J. Org. Chem.* **1976**, *41*, 2396.
(74) Hennion, G. F.; O'Shea, F. X. *J. Am. Chem. Soc.* **1958**, *80*, 614.
(75) Meakins, G. D.; Percy, R. K.; Richards, E. E.; Young, R. N. *J. Chem. Soc. C* **1968**, 1106.
(76) Rickborn, B.; Wuesthoff, M. T. *J. Am. Chem. Soc.* **1981**, *92*, 6894.
(77) Laube, T.; Hollenstein, S. *J. Am. Chem. Soc.* **1992**, *114*, 8812−8817.
(78) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *83*, 1736−1740.
(79) Frenking, G.; Köhler, K., F.; Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1146−1149.
(80) Tomoda, S.; Senju, T. *Tetrahedron* **1997**, *53*, 9057−9066.
(81) Lin, M.-h.; Boyd, M. K.; le Noble, W. J. *J. Am. Chem. Soc.* **1989**, *111*, 8746−8748.
(82) Lau, J.; Gonikberg, E. M.; Hung, J.-t.; le Noble, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 11421−11425.
(83) Kaselj, M.; le Noble, W. *J. Org. Chem.* **1996**, *61*, 4157−4160.
(84) Lin, M.-H.; Cheung, C. K.; le Noble, W. J. *J. Am. Chem. Soc.* **1988**, *1988*, 6562−6563.
(85) Laube, T.; Stilz, H. U. *J. Am. Chem. Soc.* **1987**, *109*, 5876−5878.
(86) Simmons, H. E.; Fukunaga, T. *J. Am. Chem. Soc.* **1967**, *89*, 5208−5215.
(87) Semmelhack, M. F.; Foos, J. S.; Katz, S. *J. Am. Chem. Soc.* **1973**, *95*, 7325−7336.
(88) Tajiri, A.; Nakajima, T. *Tetrahedron* **1971**, *27*, 6089−6099.
(89) Bischof, P.; Gleiter, R.; Haider, R. *J. Am. Chem. Soc.* **1978**, *100*, 1036−1042.
(90) Gordon, M. D.; Fukunaga, T.; Simmons, H. E. *J. Am. Chem. Soc.* **1976**, *98*, 8401−8407.
(91) Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678−11688.
(92) Solomon, M.; Jamison, W. C. L.; McCormick, M.; Liotta, D. *J. Am. Chem. Soc.* **1988**, *110*, 3702−3704.
(93) Swiss, K. A.; Hinkley, W.; Maryanoff, C. A.; Liotta, D. C. *Synthesis* **1992**, 127−131.
(94) Gassman, P. G.; Schaffhaausen, J. G.; Raynolds, P. W. *J. Am. Chem. Soc.* **1982**, *104*, 6408−6411.
(95) Gassman, P. G.; Schaffhausen, J. G.; Starkey, F. D.; Raynolds, P. W. *J. Am. Chem. Soc.* **1982**, *104*, 6411−6414.
(96) Paddon-Row, M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638−10639.
(97) Okada, K.; Tomita, S.; Oda, M. *Tetrahedron Lett.* **1986**, *27*, 2645−2648.
(98) Okada, K.; Tomita, S.; Oda, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 459−468.
(99) Pudzianowski, A. T.; Barrish, J. C.; Spergel, S. H. *Tetrahedron Lett.* **1992**, *33*, 293−296.
(100) Mehta, G.; Khan, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 6140−6142.
(101) Mehta, G.; Praveen, M. *Tetrahedron Lett.* **1992**, *33*, 1759−1762.
(102) Ganguly, B.; Chandrasekhar, J.; Khan, F. A.; Mehta, G. *J. Org. Chem.* **1993**, *58*, 1734−1739.
(103) Mehta, G.; Khan, F. A. *Tetrahedron Lett.* **1992**, *33*, 3065−3068.
(104) Mehta, G.; Khan, F. A.; Gadre, S. R.; Shirsat, R. N.; Ganguly, B.; Chandrasekhar, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1390−1392.
(105) Varech, D.; Jacques, J. *Tetrahedron Lett.* **1973**, 4443−4446.
(106) Brienne, M. J.; Varech, D.; Jacques, J. *Tetrahedron Lett.* **1974**, 1233−1236.
(107) Chérest, M. J.; Felkin, H.; Tacheau, P.; Jacques, J.; Varech, D. *Chem. Commun.* **1977**, 372.
(108) Varech, D.; Brienne, M. J.; Jacques, J. *J. Chem. Res. Synop.* **1979**, 319.
(109) Mehta, G.; Khan, F. A.; Ganguly, B.; Chandrasekhar, J. *J. Chem. Soc., Chem. Commun.* **1992**, 1711−1712.
(110) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065−5067.
(111) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563−1572.
(112) Bürgi, H. B.; Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974,** *96*, 1956−1957.
(113) Bürgi, H.-B. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 460−473.
(114) Cieplak, A. S. C. In *Structure Correlation*; Bürgi, H.-B., Dunitz, J. D., Eds.; VCH: Weinheim, 1994; Vol. 1.
(115) Haga, N.; Ohwada, T.; Okamoto, I.; Shudo, K. *Chem. Pharm. Bull.* **1992**, *40*, 3349−51.
(116) Schleyer, P. v. R. *J. Am. Chem. Soc.* **1967**, *89*, 701.
(117) Ito, S.; Kakehi, A. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1869−1873.
(118) Mazzocchi, P. H.; Stahly, B.; Dodd, J.; Rondan, N. G.; Domelsmith, L. N.; Roseboom, M. D.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1980**, *102*, 6482−6490.
(119) Ohwada, T. *Tetrahedron* **1993**, *49*, 7649−56.
(120) Anh, N. T.; Minot, C. *J. Am. Chem. Soc.* **1980**, *102*, 103.
(121) Senda, Y.; Kamiyama, S.; Imaizumi, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 530.
(122) Carlson, R. G.; Behn, N. S. *J. Org. Chem.* **1987**, *32*, 1363.
(123) Patrick, D. W.; Truesdale, L. K.; Biller, S. A.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2628.
(124) Lessard, J.; Saunders: J. K.; Viet, M. T. P. *Tetrahedron Lett.* **1982**, *23*, 2059−2062.

(125) Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 5874−5875.
(126) Halterman, R.; McEvoy, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 980−985.
(127) Mehta, G.; Khan, F. A. *J. Chem. Soc., Chem. Commun.* **1991**, 18−19.
(128) Mehta, G.; Gunasekaran, G.; Gadre, S., R.; Shirsat, R. N.; Ganguly, B.; Chandrasekhar, J. *J. Org. Chem.* **1994**, *59*, 1953−1955.
(129) Okada, K.; Mukai, T. *J. Am. Chem. Soc.* **1978**, *100*, 6509−6510.
(130) Heilbronner, E.; Martin, H.-D. *Helv. Chim. Acta* **1972**, *55*, 1490−1502.
(131) Goldstein, M. J.; Hoffmann, R. *J. Am. Chem. Soc.* **1971**, *93*, 6193.
(132) Pfaendler, H. R.; Haselbach, E. *Helv. Chim. Acta* **1974**, *42*, 383−394.
(133) Haselbach, E.; Rossi, M. *Helv. Chim. Acta* **1976**, *59*, 278−290.
(134) Hertel, L. W.; Paquette, L. A. *J. Am. Chem. Soc.* **1979**, *101*, 7620−7622.
(135) Paquette, L. A.; Hertel, L. W.; Gleiter, R.; Böhm, M. *J. Am. Chem. Soc.* **1978**, *100*, 6510−6512.
(136) Wu, Y.-D.; Li, Y.; Na, J.; Houk, K. N. *J. Org. Chem.* **1993**, *58*, 4625−4628.
(137) Paquette, L. A.; Klinger, F.; Hertel, L. W. *J. Org. Chem.* **1981**, *46*, 4403−4413.
(138) Paquette, L. A.; Hertel, L. W.; Gleiter, R.; Böhm, M. C.; Beno, M. A.; Christoph, G. G. *J. Am. Chem. Soc.* **1981**, *103*, 7106−7121.
(139) Dougherty, D. A. *Science* **1996**, *271*, 163−168.
(140) Kumpf, R. A.; Dougherty, D. A. *Science* **1993**, *261*, 1708−1710.
(141) Jones, G.; Vogel, P. *J. Chem. Soc., Chem. Commun.* **1993**, 769−771.
(142) Ohwada, T.; Uchiyama, M.; Tsuji, M.; Okamoto, I.; Shudo, K. *Chem. Pharm. Bull.* **1996**, *44*, 296−306.
(143) Bader, R. F. W. *Atoms in Molecules—A Quantum Theory*; Oxford University Press: New York, 1990.
(144) Wiberg, K. B.; Bader, R. F. W.; Lau, C. D. *J. Am. Chem. Soc.* **1987**, *109*, 985−1001.
(145) Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312−322.
(146) Wiberg, K. B.; Bader, R. F. W.; Lau, C. D. H. *J. Am. Chem. Soc.* **1987**, *109*, 1001−1012.
(147) Paquette, L. A.; Bellamy, F.; Wells, G. J.; Böhm, M. C.; Gleiter, R. *J. Am. Chem. Soc.* **1981**, *103*, 7122−7133.
(148) Haselbach, E.; Heilbronner, E.; Schröder, G. *Helv. Chim. Acta* **1971**, *54*, 153−162.
(149) Ohwada, T.; Tsuji, M.; Okamoto, I.; Shudo, K. *Tetrahedron Lett.* **1996**, *37*, 2609−12.
(150) Tsuji, M.; Ohwada, T.; Shudo, K. *Tetrahedron Lett.* **1997**, *38*, 6693−6696.
(151) Calculated geometries of **64a** and **65a**, optimized with HF/6-31G* basis sets, show that *both* compounds exhibit tilting of the olefin plane toward the ethano bridge bearing the cyclopropyl group (data not shown). These geometrical perturbations do not appear to determine the facial selectivity of **64a** and **65a**, because the reverse facial preference was observed. An X-ray determination of the related aziridine derivative of 7-methylidenenorbornane was reported: Maasa, W.; Birkhahn, M.; Landmann, B.; Hoffmann, R. W. *Chem. Ber.* **1983**, *116*, 404−408. See also: Laube, T. *J. Am. Chem. Soc.* **1989**, *111*, 9224−9232.
(152) Broughton, H. B.; Green, S. M.; Rzepa, H. S. *J. Chem. Soc., Chem. Commun.* **1992**, 998−1000.
(153) Hoffmann, R. W.; Hauel, N.; Landmann, B. *Chem. Ber.* **1983**, *116*, 389−403.
(154) Hoffmann, R. W.; Kurz, H. R.; Becherer, J.; Reetz, M. T. *Chem. Ber.* **1978**, *111*, 1264−1274.
(155) Hoffmann, R. W.; Hauel, N. *Tetrahedron Lett.* **1979**, 4959−4962.
(156) Becherer, J.; Hoffmann, R. W. *Tetrahedron* **1978**, *34*, 1193−1197.
(157) Schueler, P. E.; Rhodes, Y. E. *J. Org. Chem.* **1974**, *39*, 2063−2069.
(158) Hoffmann, R.; Davidson, R. B. *J. Am. Chem. Soc.* **1971**, *93*, 5699−5705.
(159) Srinivasan, R.; Ors, J. A.; Brown, K. H.; White, L. S.; Rossi, A., R. *J. Am. Chem. Soc.* **1980**, *102*, 5297−5302.
(160) Rhodes, Y. E.; Schueler, P. E.; DiFate, V. G. *Tetrahedron Lett.* **1970**, 2073−2076.
(161) Günther, H.; Herrig, W.; Seel, H.; Tobias, S. *J. Org. Chem.* **1980**, *45*, 4329−4333.
(162) Haywood-Farmer, J. S.; Pincock, R. E. *J. Am. Chem. Soc.* **1969**, *91*, 3020−3028.
(163) Martin, H. D.; Heller, C.; Haider, R.; Hoffmann, R. W.; Becherer, J.; Kurz, H. R. *Chem. Ber.* **1977**, *110*, 3010.
(164) Bischof, P.; Heilbronner, E.; Prinzbach, H.; Martin, H. D. *Helv. Chim. Acta* **1971**, *54*, 1072−1080.
(165) Bruckmann, P.; Klessinger, M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 524−525.
(166) Hoffmann, R. W.; Schüttler, R.; Schäfer, W.; Schweig, A. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 512−513.
(167) Christl, M. *Chem. Ber.* **1975**, *108*, 2781−2791.
(168) Christl, M.; Herbert, R. *Chem. Ber.* **1979**, *112*, 2022−2027.
(169) Koga, N.; Ozawa, T.; Morokuma, K. *J. Phys. Org. Chem.* **1990**, *3*, 519−533.
(170) Hoffmann, R. *Acc. Chem. Res.* **1971**, *4*, 1−9.
(171) Edman, J. R.; Simmons, H. E. *J. Org. Chem.* **1968**, *33*, 3808−3816.
(172) Bartlett, P. D.; Blakeney, A. J.; Kimura, M.; Waatson, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 1383−1390.
(173) Mehta, G.; Padma, S.; Pattabhi, V.; Pramanik, A.; Chandrasekhar, J. *J. Am. Chem. Soc.* **1990**, *112*, 2942−2949.
(174) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717−1760.
(175) Okamoto, I.; Ohwada, T.; Shudo, K. *J. Org. Chem.* **1996**, *61*, 3155−66.
(176) Paddon-Row, M. N.; Patney, H. K.; Warrener, R. N. *J. Org. Chem.* **1979**, *44*, 3908−3917.
(177) Fujimoto, H.; Inagaki, S.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 2670−2671.
(178) Hoffmann, R.; Woodward, R. B. *J. Am. Chem. Soc.* **1965**, *87*, 4388−4389.
(179) Carreño, M. C.; Ruano, J. L. G.; Urbano, A.; López-Solera, M. I. *J. Org. Chem.* **1997**, *62*, 976−981.
(180) Carreño, M. C.; Ruano, J. L. G.; Remor, C. Z.; Urbano, A.; Fisher, J. *Tetrahedron Lett.* **1997**, *38*, 9077−9080.
(181) Carreño, M. C.; Urbano, A.; Fischer, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1621−1623.
(182) Liotta, D.; Saindane, M.; Barnum, C. *J. Am. Chem. Soc.* **1981**, *103*, 3224−3226.
(183) Chung, W.-S.; Turro, N. J.; Srivastava, S.; Li, H.; le Noble, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 7882−7883.
(184) Fukui, K.; Fujimoto, H. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3399.
(185) Macaulay, J. B.; Fallis, G. *J. Am. Chem. Soc.* **1990**, *112*, 1136−1144.
(186) Coxon, J. M.; McDonald, D. Q. *Tetrahedron Lett.* **1992**, *33*, 651−654.
(187) Poirier, R. A.; Pye, C. C.; Xidos, J. D.; Burnell, D. J. *J. Org. Chem.* **1995**, *60*, 2328−2329.
(188) Paquette, L. A.; Branan, B. M.; Rogers, R. D.; Bond, A. H.; Lange, H.; Gleiter, R. *J. Am. Chem. Soc.* **1995**, *117*, 5992−6001.
(189) Brown, F. K.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 1971−1978.
(190) Houk, K. N.; González, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81−90.
(191) Ishida, M.; Aoyama, T.; Beniya, Y.; Yamabe, S.; Kato, S.; Inagaki, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3430−3439.
(192) Ishida, M.; Kakita, S.; Inagaki, S. *Chem. Lett.* **1995**, 469−470.
(193) Gleiter, R.; Paquette, L. A. *Acc. Chem. Res.* **1983**, *16*, 328−334.
(194) Böhm, M. C.; Eiter, R. G. *Tetrahedron* **1980**, *36*, 3209−3217.
(195) Böhm, M. C.; Carr, R. V. C.; Gleiter, R.; Paquette, L. A. *J. Am. Chem. Soc.* **1980**, *102*, 7218−7228.
(196) Paquette, L. A.; Carr, R. V.; Böhm, M. C.; Gleiter, R. *J. Am. Chem. Soc.* **1980**, *102*, 1186−1188.
(197) Winstein, S.; Shatavsky, M.; Norton, C.; Woodward, R. B. *J. Am. Chem. Soc.* **1955**, *77*, 4183.
(198) Jones, D. W. *J. Chem. Soc., Chem. Commun.* **1980**, 739.
(199) Anh, N. T. *Tetrahedron* **1973**, *29*, 3227−3232.
(200) Halterman, R.; McCarthy, B. A.; McEvoy, M. A. *J. Org. Chem.* **1992**, *57*, 5585−5589.
(201) Tsuji, M.; Ohwada, T.; Shudo, K. *Tetrahedron Lett.* **1998**, *39*, 403−406.
(202) Gleiter, R.; Ginsburg, D. *Pure Appl. Chem.* **1979**, *51*, 1301−1315.
(203) Auksi, H.; Yates, P. *Can. J. Chem.* **1981**, *59*, 2510−2517.
(204) Krow, G. R.; Carey, J. T.; Zacharias, D. E.; Knaus, E. E. *J. Org. Chem.* **1982**, *47*, 1989−1993.
(205) Gillard, J. R.; Burnell, D. J. *J. Chem. Soc., Chem. Commun.* **1989**, 1439−1440.
(206) Gillard, J. R.; Newlands, M. J.; Bridson, J. N.; Burnell, D. J. *Can. J. Chem.* **1991**, *69*, 1337−1343.
(207) Alder, K.; Flock, F. H. *Chem. Ber.* **1956**, *89*, 2689.
(208) Kobuke, Y.; Sugimoto, T.; Furukawa, J. *J. Org. Chem.* **1976**, *41*, 1457.
(209) Ishida, M.; Inagaki, S. *Yuki Gosei Kyoukaishi* **1994**, *52*, 649−657.
(210) *Comprehensive Organic Synthesis*; Semmelhack, M. F., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, Chapter 1.
(211) Organ, M. G.; Froese, R. D. J.; Goddard, J. D.; Taylor, N. J.; Lange, G. L. *J. Am. Chem. Soc.* **1994**, *116*, 3312−3323.
(212) Sato, M.; Murakami, M.; Sunami, S.; Kaneko, C.; Furuya, T.; Kurihara, H. *J. Am. Chem. Soc.* **1995**, *117*, 4279−4287.
(213) Gung, B. W.; Francis, M. B. *J. Org. Chem.* **1993**, *58*, 6177−6179.
(214) Okamoto, I.; Ohwada, T.; Shudo, K. *Tetrahedron Lett.* **1997**, *38*, 425−428.
(215) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738−741.
(216) Bodepudi, V. R.; le Noble, W. J. *J. Org. Chem.* **1994**, *59*, 3265.
(217) Mukherjee, A.; Wu, Q.; le Noble, W. J. *J. Org. Chem.* **1994**, *59*, 3270.
(218) Lin, M.-h.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 997−998.
(219) Mukherjee, A.; Wu, Q.; le Noble, W. J. *J. Org. Chem.* **1994**, *59*, 3270−3274.
(220) Gandolfi, R.; Amade, M. S.; Rastelli, A.; Bagatti, M.; Montanari, D. *Tetrahedron Lett.* **1996**, *1996*, 517−520.

(221) Burdisso, M.; Gandolfi, R.; Lucchi, M.; Rastelli, A. *J. Org. Chem.* **1988**, *53*, 2123−2125.
(222) Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438−2440.
(223) Caramella, P.; Albini, F. M.; Vitali, D. *Tetrahedron Lett.* **1984**, *25*, 1875−1878.
(224) Huisgen, R.; Ooms, P. H. J.; Mingin, M.; Allinger, N. L. *J. Am. Chem. Soc.* **1980**, *102*, 3951−3953.
(225) le Noble, W. J.; Chiou, D.-M.; Okaya, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3244.
(226) Bodepudi, V.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2001.
(227) Xie, M.; le Noble, W. *J. Org. Chem.* **1989**, *54*, 3839.
(228) Mukherjee, A. K.; le Noble, W. J. *J. Org. Chem.* **1993**, *58*, 7955−7957.
(229) Adcock, W.; Coope, J.; Shiner, V. J.; Trout, N. A. *J. Org. Chem.* **1990**, *55*, 1411.
(230) Li, H.; Silver, J. E.; Watson, W. H.; Kashyap, R. P.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 5932.
(231) Chung, W.-S.; Turro, N. J.; Srivastava, S.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 5020.
(232) Li, H.; Silver, J. E.; Watson, W. H.; Kashyap, R. P.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 5932.

CR980371M