2a^{2+}, 72866-06-9; **2b**, 138878-63-4; **2b**$^{2+}$, 138878-65-6; **2c**, 29554-56-1; **2c**$^{2+}$, 63397-56-8; **3**, 63318-58-1; **3**$^{2+}$, 138878-66-7; **4a**, 35087-43-5; **4a**$^{2+}$, 63832-64-4; **4b**, 29212-88-2; **4b**$^{2+}$, 59227-70-2; **5**, 262-89-5; **5**$^{2+}$, 63397-57-9; **6**, 25835-57-8; **6**$^{2+}$, 109124-31-4; **7**, 14458-51-6; **7**$^{2+}$, 77966-08-6; **8**, 78038-55-8; **8**$^{2+}$, 68630-17-1; **9**, 65549-72-6; **9**$^{2+}$, 65583-97-3; **10a**, 104720-28-7; **10a**$^{2+}$, 112532-59-9; **10b**, 104701-63-5; **10b**$^{2+}$, 112532-58-8; **11**, 1448-74-4; **11**$^{2+}$, 60790-15-0; **12**, 2292-79-7; **12**$^{2+}$, 95531-36-5; SbF_5, 7783-70-2; triphenylene, 217-59-4; triphenylene dication, 138878-64-5; chrysene, 218-01-9; chrysene dication, 115949-55-8; picene, 213-46-7; picene dication, 60670-20-4; tetrabenzonaphthylene, 191-68-4; tetrabenzonaphthylene dication, 60670-18-0; coronene, 191-07-1; coronene dication, 62683-79-8; benz[*a*]anthracene, 56-55-3; benz[*a*]anthracene dication, 60670-19-1; pyrene, 129-00-0; pyrene dication, 60670-21-5; benzoperylene, 191-24-2; benzoperylene dication, 60829-72-3; perylene, 198-55-0; perylene dication, 60670-21-5; 9,10-dichloroanthracene, 605-48-1; 9,10-dichloroanthracene dication, 87517-70-2; 9,10-dimethylanthracene, 781-43-1; 9,10-dimethylanthracene dication, 75309-26-1; 9,10-diphenylanthracene, 1499-10-1; 9,10-diphenylanthracene dication, 70470-09-6; 9-chloro-10-methylanthracene, 19096-07-2; 9-chloro-10-methylanthracene dication, 87517-72-4; 1,4–dimethoxyanthracene, 13076-29-4; 1,4-dimethoxyanthracene dication, 87517-74-6; 2-methylanthracene, 613-12-7; 2-methylanthracene dication, 87517-75-7; 1,2,3,6,7,8-hexahydropyrene, 1732-13-4; 1,2,3,6,7,8-hexahydropyrene dication, 72287-34-4.

Computer-Assisted Mechanistic Evaluation of Organic Reactions. 20. Ene and Retro-Ene Chemistry

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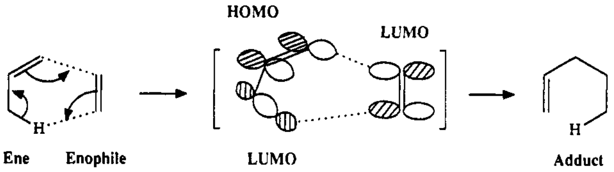
The pericyclic module of the computer program CAMEO has been expanded to encompass ene and retro–ene reactions. The implementation of ene chemistry required substantial modifications to the existing algorithm for the estimation of FMO energies as well as enhancements in the perception phase of the module for the recognition of additional π systems. New equations for computing the FMO energies of 2π and cumulene parent systems have been developed and implemented in the program. Ene reactions have been analyzed by using a frontier molecular orbital approach. Consequently, predictions of regiochemistry in ene additions are based on the relative magnitude of the terminal coefficients of the frontier orbitals and on the topological geometry of the reacting molecules. Analyses of retro-ene fragmentations are made by applying empirical rules derived from literature precedents. Several examples of synthetic sequences that demonstrate the current predictive capabilities of CAMEO are presented.

Introduction

CAMEO is an interactive computer program that predicts the products of organic reactions through the application of mechanistic logic.[1] Given the reactants and conditions, the program typically arrives at its predictions by simulation of reaction mechanisms. Recent extensions to the program include the mechanistic treatment of hydride reductions[2a] and the development of a reaction model that mimics free-radical chain processes.[2b,c] Other types of reactions that are currently handled by CAMEO include base-catalyzed and nucleophilic,[3] acid-catalyzed and electrophilic,[4] thermal pericyclic,[5] oxidative,[6] and heterocycle-forming reactions.[7] The incorporation of ene and retro-ene reactions into the pericyclic module of CAMEO is addressed in this paper.

Scheme I



The philosophy behind CAMEO's approach to reaction prediction is that diverse organic processes can be treated as a sequence of basic mechanistic steps. Thus, reaction analysis is greatly simplified by focusing on a small set of fundamental processes. Competitions between these processes are generally assessed by application of empirically-derived rules or known physical–organic principles. When available, a well-established theory behind a mechanistic process is applied in the analyses of reactions. Thus, the pericyclic module utilizes frontier molecular orbital (FMO) theory[8] in predicting both the feasibility and regiochemistry of thermal cycloadditions. The same approach has been utilized for the evaluation of ene reactions.

The implementation of ene chemistry in CAMEO entailed not only enhancements in the perception of π systems but

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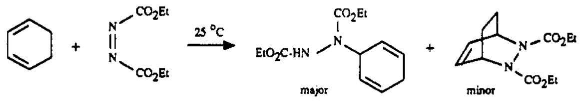
also modifications to the existing alogrithm for calculating FMO energies.[5a] New equations for estimating the FMO energies of 2π and cumulene parent systems have been devised and implemented in the program. These expressions can now accommodate (a) additional π systems such as $-\mathrm{C{\equiv}P}$, $>\mathrm{Si{=}Si}<$, $-\mathrm{P{=}P}-$, $>\mathrm{C{=}Si}<$, $>\mathrm{C{=}P}-$, and $-\mathrm{N{=}Si}<$, (b) a larger variety of heterocumulenes (e.g., $-\mathrm{N{=}S{=}N}-$, $-\mathrm{N{=}C{=}S}$, $-\mathrm{N{=}S{=}O}$), and (c) charged π systems such as $>\mathrm{C{=}N^+}<$, $>\mathrm{C{=}S^+}-$, $-\mathrm{C{\equiv}O^+}$, and $-\mathrm{C{\equiv}N^+}-$. Other refinements in the original algorithm include the differentiation of the FMO energies of substituted and unsubstituted bonds in monofunctional allenes and the modification of substituent constants. The present FMO algorithm has been validated by comparison of its predictions with experimental ionization potential (IP) and electron affinity (EA) data. This paper begins with a brief overview of ene and retro-ene chemistry focusing on aspects that are crucial to reaction implementation. The strategies used in analyzing and implementing these reactions are described next. The paper concludes with a presentation of sample synthetic sequences that demonstrate the program's predictive capabilities.

Overview of Ene and Retro-Ene Chemistry

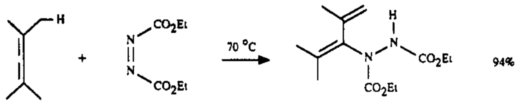
The Ene Synthesis. The scope, synthetic potential, and broad applicability of the ene reaction have been reviewed extensively.[9a-c] The reaction, as originally defined by Alder,[10] involves the addition of an olefin possessing an allylic hydrogen (ene) to a compound having an electron-deficient multiple bond (enophile). The mode of addition may be described as a suprafacial, three-component interaction among the HOMO of the ene, the LUMO of the allylic C–H bond of the ene, and the LUMO of the enophile (Scheme I).[11] The concerted nature of the ene process has been supported experimentally,[12] and the reaction can be designated as $[{}_{\sigma}2_{s} + {}_{\pi}2_{s} + {}_{\pi}2_{s}]$ in the Woodward–Hoffmann notation.[11] The definition of the ene reaction now includes other types of ene and enophilic systems and some nonprototropic migrations such as silatropic shifts and metallo-ene reactions.[9a] The present paper focuses only on thermal ene processes involving hydrogen transfers.

Ene Components. Enes are π-bonded molecules that contain at least one active hydrogen atom at the allylic, propargylic, or α-position. Possible ene components include olefinic,[13] acetylenic,[14] allenic,[15] aromatic,[16] cyclopropyl,[17] and carbon–hetero[18-20] bonds. With olefinic and acetylenic ene components, competition between cycloadditions and ene reactions can occur[14a,17b,21,22] (e.g., eq 1).[21a]

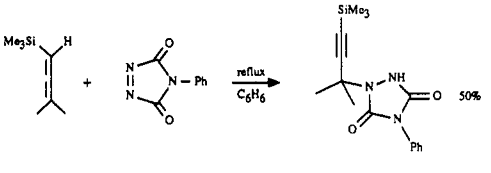


(1)

Allenic systems normally undergo ene reactions at the allylic hydrogen atoms (eq 2).[15] Exceptions are allenyl silanes which react at the allenic hydrogen atom α to the silicon substituent (e.g., eq 3).[23] This unusual behavior may be ascribed to some partial positive charge development on the central allene carbon which is stabilized by the β-silicon in the transition state.

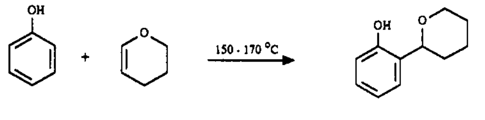


(2)



(3)

Carbon–carbon aromatic bonds can also act as ene components, as shown in the thermal reaction of phenol with dihydropyran (eq 4).[16] Other viable ene components include the fused cyclopropyl bonds in [1.1.0] or [2.1.0] ring systems and the nonfused cyclopropyl bonds in [n.1.0] (n > 4) fused rings. With small fused ring systems (e.g., [1.1.0] and [2.1.0]), enophilic attack occurs at the zero-bridge bonds which are associated with the HOMO (e.g., eq 5).[17b] For norcaradiene systems, enophilic attack occurs at the one-bridge bonds, i.e., at the 1,7- and 6,7-bonds in **2**.[17a] In these systems, the HOMOs are concentrated on the one-bridge bonds.[17a]



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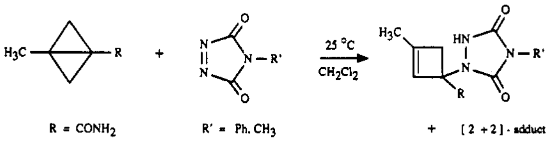
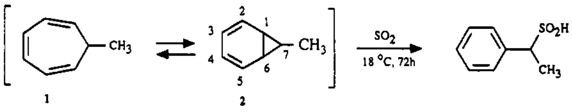


(5)



(6)

Eqs 7–9 illustrate the participation of C=O,[18] C=N,[19] and C=Si[20] bonds as ene components. Rate-determining tautomerization prior to ene addition is exemplified in eqs 7[18d] and 9,[20] while tautomerization of the initial ene adduct

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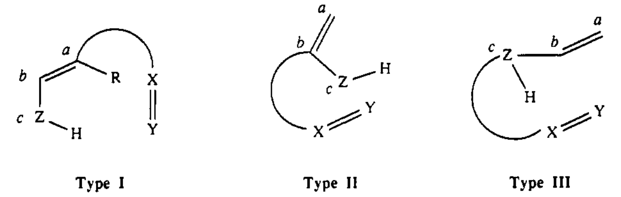
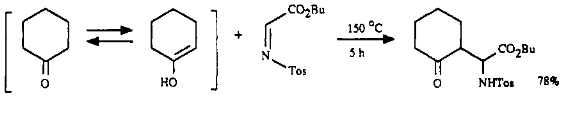
Chart I

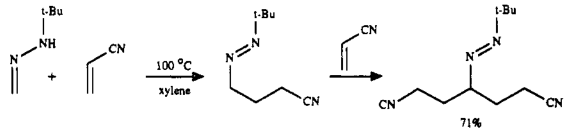


Type I Type II Type III

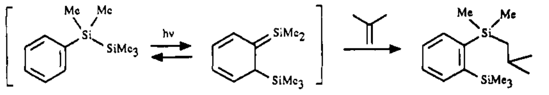
which promotes a second ene addition is depicted in eq 8.[19a]



(7)

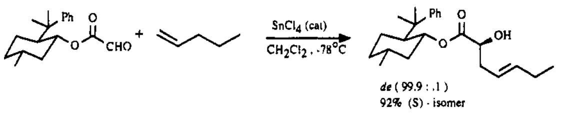


(8)

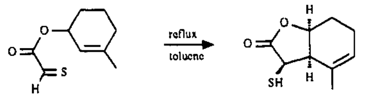


(9)

Enophile Components. Enophiles consist of π-bonded molecules having a characteristic low-lying LUMO. Reactive enophilic components include carbon–carbon multiple bonds (olefinic,[24] acetylenic,[25] benzyne[26]), carbon–hetero multiple bonds ($C=O$,[27] $C=N$,[28] $C=S$,[29] $C\equiv P$[30]), hetero–hetero multiple bonds ($N=N$,[31] $^1O=O$,[32] $Si=Si$,[33] $N=O$,[34] $S=O$[35]), cumulene systems ($N=S=O$,[36] $N=S=N$,[37] $C=C=O$,[22,38] $C=C=S$,[26] SO_2[39]), and charged π systems ($C=N^+$,[40] $C=S^+$,[41] $C\equiv N^+$,[42] $C\equiv O^+$).[43] The variety of enophiles makes ene reactions extremely versatile. The ene addition of chiral glyoxylates, for example, represents a powerful method for the synthesis of homoallylic alcohols with asymmetric induction levels of >90% (e.g., eq 10).[27a] Similarly, the stereoselective synthesis of homoallylic thiols is readily effected by the ene addition of thiocarbonyl compounds to alkenes (e.g., eq 11).[29a] The ene reaction of N-substituted imino esters also provides viable synthetic routes to γ,δ-unsaturated α-amino acids (eq 12).[28d] The versatility of ene reactions is further illustrated in the isomerization of olefins **3**[32c] and **4**[36c] and in the synthesis of β,γ-unsaturated ketones using a charged enophile (e.g., eq 15).[42]



(10)



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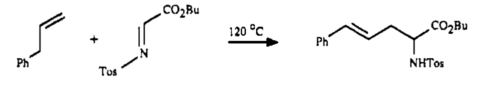

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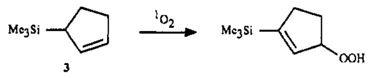

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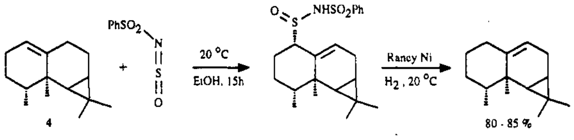

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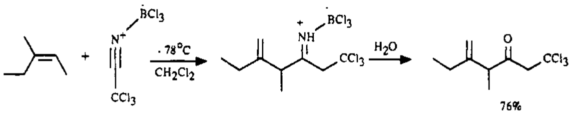

(15)

Intramolecular Ene Reactions. Intramolecular ene additions benefit from entropic advantage and allow nonactivated enophiles to react more readily. The high regio- and stereoselectivity exhibited by these reactions offer considerable control in the synthesis of intricate ring systems. Oppolzer and Snieckus[9b] have classified intramolecular ene processes into three types according to whether the enophile is linked to the ene unit by a bridge at terminal atom *a* (type I), at central atom *b* (type II), or at allylic atom *c* (type III), as illustrated in Chart I. For each type, two modes of intramolecular additions are possible since the terminal atom of the ene unit can be bonded to either atom of the enophile. The extent of interaction depends upon the potential orbital overlap between the two reaction components; hence, the orientation of addition is largely controlled by the geometry of approach of the components. For example, geometric considerations in eq 16 favor formation of the 5-membered ring over the 6-membered ring.[44a] In general, intramo-

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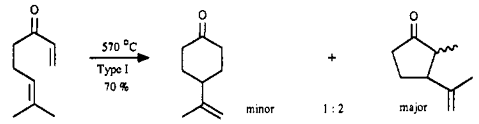
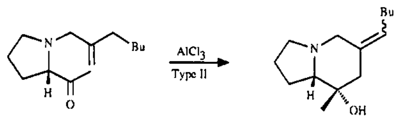


(16)

lecular ene reactions of type I favor σ-bond formation between the closest unsaturated centers; ene reactions of types II and III favor σ-bond formation to atoms X and Y, respectively, of the enophile.

Type I reactions occur predominantly in 1,6-dienes,[44] 1,7-dienes,[45] 1,7-enynes,[25a] and ene systems containing polarized enophiles.[46,47] Type II reactions proceed through a highly ordered bridged bicyclic transition state and occur less readily than the type I counterparts. These reactions usually occur in 1,6-dienes,[9b] 1,6-enones,[48,49] and 1,6-ene-nitroso[50] compounds (e.g., eq 17).[48a] Type III reactions result in the formation of medium or large rings and are entropically unfavorable and less common than type I and II reactions.[14a,51] An example of a type III ene addition is shown in eq 18.[51]



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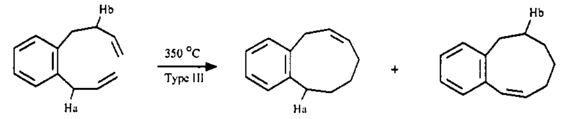
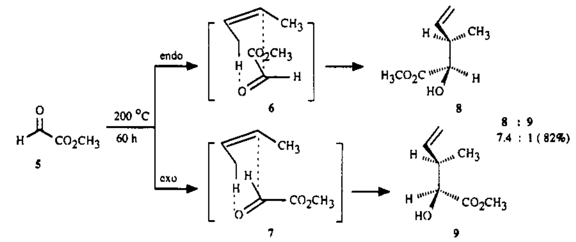


(18)

Stereo- and Regioselectivity. Ene and enophilic systems capable of inducing endo/exo discrimination can provide useful stereoselectivity.[28b,52a,b] For example, ene reactions of *cis*-alkenes with polarized enophiles[28b,52b] give diastereomers resulting predominantly from an endo transition state (e.g., eq 19).[52b] The inherent preference for an endoselectivity may be diminished by steric effects between substituents in the transition state. Thus, less endoselectivity is observed in the corresponding ene reactions of *trans*-alkenes.[52b]

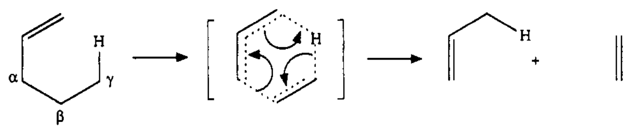


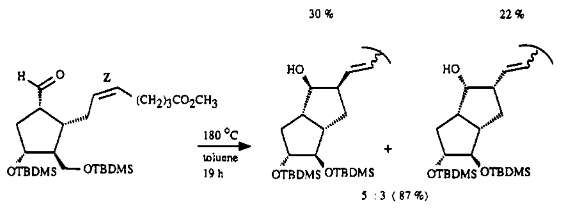
(19a)

(19b)

Intramolecular ene cyclizations preferentially form cis-disubstituted five-membered rings and trans-disubstituted six-membered rings.[53] For example, type I cyclizations of 1,6-dienes[44b,54] and 1,6-enones[46,55] selectively lead to rings where the H-donor and H-acceptor sites are oriented in a cis fashion. For these systems, the cis configuration of the ene adducts has been shown to be independent of the stereochemistry of the reacting ene unit; i.e., the H-donor site may be trans (e.g., eq 20)[54] or cis (e.g., eq 21)[46b] with respect to the enophilic chain. Construction of molecular models has shown that ene reactions of the former proceed via an endo transition state, while reactions of the latter involve an exo transition state.[44b,56] Type I cyclizations of 1,7-dienes, on the other hand, lead to *trans*-cyclohexanes.[45] This stereoselectivity can be rationalized in terms of an exo-*E*-anti conformation of a cyclohexane-like transition state.[45a]

Scheme II

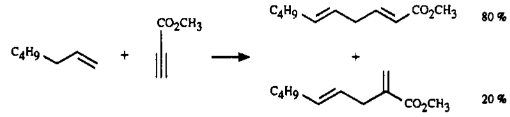




(20)

(21)

Regioselectivity in ene reactions refers to the preference of the ene or enophile to form a σ bond at either terminal atom of the π bond.[24a] This preference results from the best orbital overlap between atoms with the largest frontier MO coefficients.[57] The nature of the atoms comprising the ene or enophilic bonds as well as the nature and position of substituents influence both the extent and polarization of the orbitals and, consequently, the orientation of ene addition. The direction of ene addition can also be predicted from the relative stabilization of the developing partial charges in an unsymmetrical transition state with early formation of the σ bond.[57] Thus, the major regioisomer usually arises from a transition state in which the ene and enophile are oriented such that the substituents are best able to stabilize the transient charges.[13b] An example is shown in eq 22.[25a]



(22)

Prediction of regioselectivity can be complicated by geometric factors, particularly for intramolecular reactions. For example, the inherent regiochemical preference arising from the electronic effects of substituents may be overcome by conformational factors, as in eq 23.[29b] In this case, the transition state leading to the sulfide adduct is geome-

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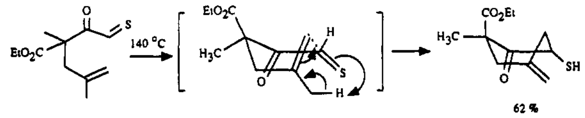
Table I. Ionization Potentials and Theoretical and Predicted FMO Energies (eV) for 2π Parent Systems

2π parent	–IP	3-21G HOMO	predicted HOMO	3-21G LUMO-3.3	predicted LUMO (EA)	ref (IP; EA)
$H_2C=CH_2$	–10.5	–10.3	–10.5	1.8	1.8 (1.78)	73; 74
$HC\equiv CH$	–11.4	–11.2	–11.4	2.8	2.6 (2.6)	75; 76
$H_2C=O$	–14.5	–14.3	–14.5	0.7	–0.1 (0.8)	77; 78
$H_2C=NH$	–12.5	–12.2	–12.4	1.5	1.2	79
$HC\equiv N$	–13.6	–13.6	–13.3	2.5	2.0 (2.3)	80; 81
$H_2C=S$	–11.8	–11.3	–11.8	–2.0	–1.9	82
$H_2C=PH$	–10.3	–9.85	–10.1	–1.4	–1.0	79
$HC\equiv P$	–10.8	–10.5	–11.0	–0.8	–0.2	83
$H_2C=SiH_2$	–8.8	–8.5	–9.0	–0.8	–0.3	84
$HN=NH$	–14.4	–10.9	–14.3	0.7	0.6	85
$HP=PH$	–9.8	–9.7	–9.7	–3.7	–3.8	86
$HN=PH$	–11.6	–10.1	–12.0	–1.8	–1.6	87
$H_2Si=SiH_2$		–7.6	–7.5	–2.2	–2.4	
$HP=SiH_2$		–8.7	–8.6	–2.8	–3.1	
$HN=SiH_2$		–9.9	–10.9	–1.0	–0.9	
$HP=O$		–12.8	–14.1	–2.7	–2.9	
$HP=S$		–11.0	–11.4	–4.4	–4.7	
$HN=S$		–12.4	–13.7	–2.9	–2.5	
$HN=O$		–1.58	–16.4	–0.6	–0.7	
$O=O$		–17.1	–18.5	–2.7	–2.0	

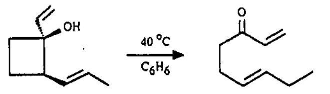
trically disfavored, thus leaving the alternate pathway leading to the mercaptan.



(23)

Retro-Ene Fragmentations. The formal reverse of an ene reaction, intramolecular transfer of γ-hydrogen atom to an unsaturated center via a six-electron cyclic transition state, can also occur thermally (Scheme II). The concerted nature of this process has received experimental support, and the reaction has been reviewed.[9a–c] Reactive π bonds for retro-ene fragmentations include olefinic,[9a–c] acetylenic,[58] allenic,[59] cyclopropyl,[60] carbon–hetero (e.g., C=O,[61] C=N,[62] C=Si[63]), and hetero–hetero (e.g., N=N[64]) bonds.

For olefinic substrates, the preferred geometry of the transition state for the ene and retro-ene reactions is an envelope conformation.[53,65] Some variation is possible since both the *cis*- and *trans*-2-vinyl-1-cyclobutanols are accommodated (eqs 24[66] and 25[67]).



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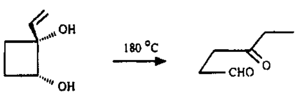
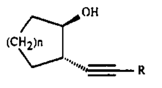
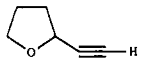


(25)

For acetylenic substrates, a planar transition-state geometry, which offers the least amount of distortion in the linear system, has been proposed.[65,68] The requirement for this geometry accounts for the reluctance of acetylenic substrates **10**[69] and **11**[58b] to undergo retro-ene fragmentations. It should be noted that the corresponding reactions of the olefinic analogs are feasible under the same conditions.[58b,69]

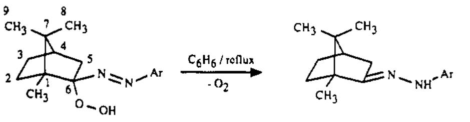


10a n = 1 : R = C_6H_{13}
b n = 2 : R = C_5H_{11}



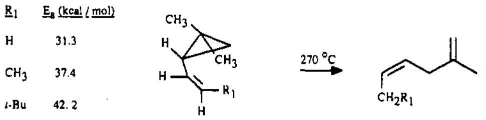
11

The rates of retro-ene reactions may be enhanced[62b,64] or diminished[70] by steric effects. For example, the steric hindrance between the methyl-8 and arylazo groups in **12** inhibits free rotation of the latter, thus resulting in a fixed conformation that is conducive to a retro-ene mechanism. Interestingly, a free-radical mechanism prevails in the absence of this methyl-8 group. In contrast, steric inhibition is possible as shown in eqs 27 and 28. In the former, *cis*-alkyl substitution at the reacting π bond causes a substantial decrease in the rate of retro-ene reaction.[70a] In the latter, the retro-ene reaction is completely inhibited



12 **13**

(26)



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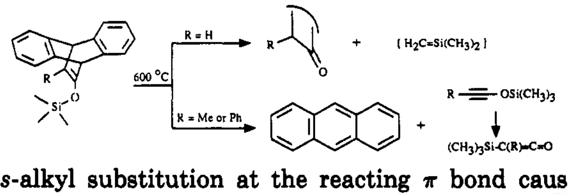

(28a)

(28b)

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Table II. Ionization Potentials and Theoretical and Predicted FMO Energies (eV) for Cumulene Systems

cumulene	−IP	predicted HOMO	3-21G LUMO-3	predicted LUMO (EA)	ref (IP; EA)
$CH_2{=}C{=}CH_2$	−10.2	−10.2	2.0	2.0 (2.0)	88; 81
$CH_2{=}C{=}O$	−9.8	−10.0	0.7	1.1	89
$CH_2{=}C{=}NH$	−9.7	−9.5	1.8	1.5	90
$CH_2{=}C{=}S$	−8.9	−10.6	−1.4	1.6	91
$HN{=}C{=}O$	−11.6	−11.4	3.9	3.2	92
$HN{=}C{=}NH$	−10.2	−10.5	2.7	3.6	93
$HN{=}C{=}S$	−9.9	−9.9	1.5	1.1	94
$O{=}S{=}O$	−13.2	−13.2	−3.6	−3.4	95
$O{=}S{=}NH$	−11.6	−11.6	−2.8	−2.8	96
$HN{=}S{=}NH$		−10.7	−2.3	−2.4	
$O{=}C{=}O$	−13.8	−13.8	2.7	2.6	97
$S{=}C{=}O$	−11.2	−10.8	0.2	0.7	98
$S{=}C{=}S$	−10.1	−10.6	−1.8	−1.8	99

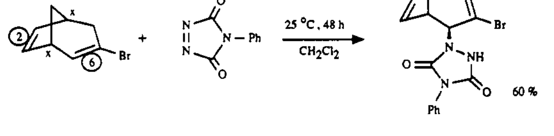
upon *cis*-methyl or *cis*-phenyl substitution, and an alternate retro-Diels–Alder pathway predominantes.[70b]

Implementation of Ene Chemistry in CAMEO. The pericyclic module in CAMEO oversees the processing of thermal pericyclic reactions. It analyzes the input reactants for all possible pericyclic pathways, forms the products, and evaluates periselectivity. The module currently treats cycloadditions, sigmatropic rearrangements, electrocyclic ring closures, and ring opening (e.g., reverse Diels–Alder, retro-cheletropic, electrocyclic) reactions.[5] Extension of the module to include ene and retro-ene reactions required the addition of two subroutines, each of which is responsible for the perception of reactants and evaluation of mechanisms. The following sections describe the general procedures for the implementation of ene and retro-ene reactions.

ENERXN is the executive routine for evaluating ene additions. The program flow involves (1) identification of all possible reactive ene and enophile components, (2) estimation of HOMO and LUMO energies of the reaction components, which is critical to the prediction of the facility of the reaction, (3) determination of regiochemistry, and (4) execution of the ene mechanism and construction of products with the proper stereochemistry. Each of these steps is expanded on as follows.

Identification of Reaction Components. A current list of ene/enophile parent systems that are recognized in CAMEO is provided in Tables I and II. In perceiving the ene units, the following rules governing the reactivity of C–H bonds have been implemented in CAMEO.

(a) Bridgehead allylic hydrogen atoms in small bridged systems are unreactive[22,29b,31c,36b,40,71] (e.g., eqs 29[31c] and 30[36b]). In eq 29, the ene unit containing bond 2 is deleted from consideration.



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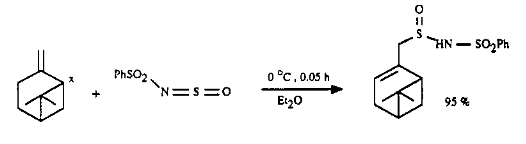
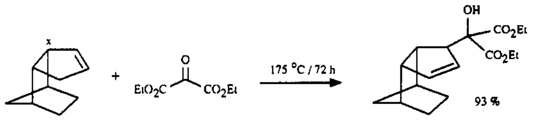
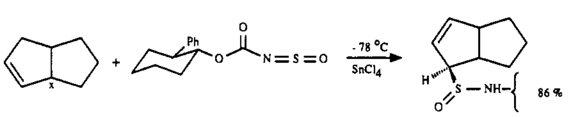


(30)

(b) Allylic hydrogen atoms at ring fusions are unreactive if the ene double bond is incorporated in a ring with size ≤5 (e.g., eqs 31[27b] and 32[36a]). As for the bridgehead hydrogens, the preferred envelope conformation for the transition state with the migrating hydrogen eclipsing the π-orbital is difficult to achieve in this case.



(31)



(32)

Estimation of FMO Energies of the Reaction Components. The most critical step in the evaluation of ene reactions is the calculation of the FMO energies of the reacting π systems. This consists of two substeps, namely: (a) estimating the FMO energies of the parent (unsubstituted) π systems, and (b) estimating the effects of substituents on the calculated FMO energies.

The algorithm for predicting the FMO energies of the parent π systems utilizes approximate expressions derived from a regression analysis of experimental ionization potential (IP) data and theoretical LUMO energies obtained from ab initio calculations using the 3-21G basis set with fully optimized geometries.[72] From Koopmans' theorem, IP's can be equated to the HOMO energies and EA's (electron affinities) to the LUMO energies. Since the experimental EA's are scarce, ab initio results were utilized in deriving empirical expressions for the LUMO energies. The following equations for calculating the FMO energies of 2π and cumulene systems have been devised and implemented in CAMEO. For 2π systems

$$E_{\mathrm{HOMO}} = -10.5 - (4N_{\mathrm{O}} + 1.9N_{\mathrm{N}} + 1.3N_{\mathrm{S}} + 0.9N_{\mathrm{tb}} - 0.4N_{\mathrm{P}} - 1.5N_{\mathrm{Si}}) \quad (33)$$

$$E_{\mathrm{LUMO}} = 1.8 - (1.9N_{\mathrm{O}} + 0.6N_{\mathrm{N}} + 3.7N_{\mathrm{S}} + 2.8N_{\mathrm{P}} + 2.1N_{\mathrm{Si}} - 0.8N_{\mathrm{tb}}) \quad (34)$$

where N_{X} is the number of atoms of type X and N_{tb} is unity if a triple bond is present or null if absent. For cumulene systems

$$E_{\mathrm{HOMO}} = -10.2 - (0.4N_{\mathrm{CS}} + N_{\mathrm{CN}} + 1.2N_{\mathrm{SN}} + 2.8N_{\mathrm{SO}} + 3.4N_{\mathrm{CO}} + 0.2A_{\mathrm{O}} - 0.7A_{\mathrm{N}}) \quad (35)$$

$$E_{\mathrm{LUMO}} = 2.0 - (0.9A_{\mathrm{O}} + 0.5A_{\mathrm{N}} + 3.4A_{\mathrm{S}} - 1.5T_{\mathrm{O}} - 2.1T_{\mathrm{N}} + 0.4T_{\mathrm{S}} + 6.0C_{\mathrm{S}}) \quad (36)$$

where N_{XY} is unity if the X=Y bond is the π-HOMO, A_{Z} is unity if atom Z is adjacent to either atom X or atom Y, T_{Y} is unity if terminal atom Y in the π-HOMO is present, and C_{S} is unity if the central atom in the cumulene is a sulfur atom; otherwise, each parameter is zero. For example, in $O{=}S{=}NH$, the S=N bond is the π-HOMO and nitrogen is a terminal atom in the π-HOMO. Hence, both N_{SN} and T_{N} are equal to 1. Since an oxygen atom is adjacent to one of the atoms in the π-HOMO, A_{O} is 1. C_{S} is also equal to 1 since the central atom in this cumulene is a sulfur atom. Thus, $E_{\mathrm{HOMO}} = -10.2 - 1.2 - 0.2 = -11.6$ eV; $E_{\mathrm{LUMO}} = 2.0 - 0.9 + 2.1 - 6.0 = -2.8$ eV. The results for the other parent π systems are summarized in Tables I and II.

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Using ethylene and allene as reference standards for 2π and cumulene systems, respectively, the decrease in the HOMO energy produced by replacing carbon atoms with heteroatoms is known experimentally.[73-99] However, the experimental IP's for some hetero–hetero systems are not available. Therefore, the algorithm has been devised to provide reasonable estimates for the HOMO energies of the parent systems with either experimentally known or unknown IP's. Results in Tables I and II show that the predicted HOMO energies are in good agreement with both experimental and theoretical data. It should be noted that "relative" LUMO energies obtained via 3-21G calculations were employed in the least-squares fit, i.e., the energy values were corrected by 3.3 and 3.0 eV for 2π and cumulene systems, respectively. These corrections were made in order to match the experimental results for ethylene and allene. The predicted LUMO energies are also in reasonable agreement with the "relative" theoretical LUMO energies.

Table III. Substituent Constants τ for Common Functional Groups

FG	τ	FG	τ	FG	τ
$N(CH_3)_2$	44	SCl	18	F	0
$NHCH_3$	42	Et	18	H	0
C_6H_5	42	CH_2SiH_3	16	CCl_3	0
SCH_3	40	CH=S	16	$CONH_2$	−3
NH_2	36	OAc	16	CH_2F	−4
$CH{=}CHCH_3$	36	$SC{\equiv}N$	14	CO_2Me	−6
O-*i*-Pr	35	Br	13	NF_2	−6
OEt	34	CH_3	12	COEt	−7
$SSCH_3$	33	CH_2NMe_2	12	CO_2H	−8
OCH_3	32	CH_2SMe	11	$POMe_2$	−8
$CH{=}CH_2$	30	$SiMe_3$	11	SOMe	−9
OH	26	Cl	10	COMe	−9
I	23	CH=NH	9	$C{\equiv}N$	−10
$N{=}CH_2$	21	CH_2NH_2	9	CH=O	−12
CH_2TMS	21	CH_2I	9	COF	−12
t-Bu	21	CH_2OH	6	CF_3	−12
CH_2OMe	20	CH_2Br	6	COCl	−14
i-Pr	20	CH_2Cl	4	N=O	−16
NHCl	20	N=NH	4	SO_2Me	−27
$C{\equiv}CH$	18	SiH_3	2	NO_2	−36

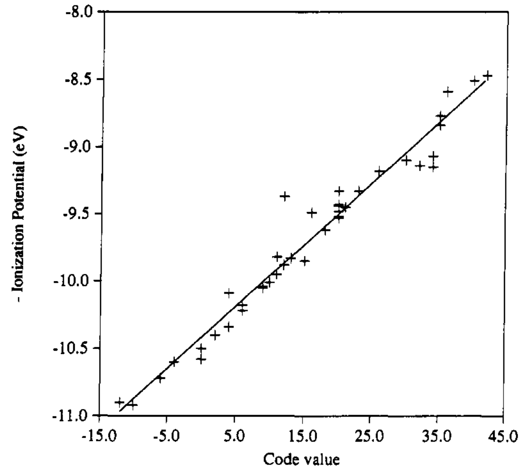

Figure 1. IP's of monosubstituted alkenes vs code values, τ.

The calculated FMO energies of the parent systems are then modified to account for the effects of substituents. The strategy used for estimating the HOMO energies of mono- and polysubstituted systems is discussed first.

HOMO Energies of Monosubstituted Systems. Using ethylene as the reference system, the effect of a given functional group (FG) on the HOMO energy of ethylene can be known if the experimental IP of the FG-substituted ethylene is known. For example, the change in IP produced by an ethyl group on ethylene can be computed from the experimental IP's of ethylene (−10.5 eV)[73] and 1-butene (−9.62 eV),[75b] i.e., $\Delta IP = (-9.62) - (-10.5) = 0.88$. Thus, any given FG has an associated substituent constant τ which reflects the change in HOMO energy relative to the reference system. For convenience, a scale was chosen such that a change in IP of 0.5 eV is equivalent to a change in τ of 10 units, i.e., $\tau = (IP_H - IP_{FG})20$, where IP_H and IP_{FG} are the ionization potentials of ethylene and FG-substituted ethylene, respectively. In the above example, the computed τ_{exptl} for the ethyl group is 0.88(20) or 17.6.

Unfortunately, IP data are not available for many FG's. Therefore, it was necessary to develop an algorithm that predicts a substituent constant τ for any FG.[5a] The formulated algorithm has two key features: (1) it utilizes a simple three-layer approach to functional group recognition, and (2) it operates on a small data base of experimentally-derived ionization potentials. The functional group approach adopted for CAMEO allows the recognition

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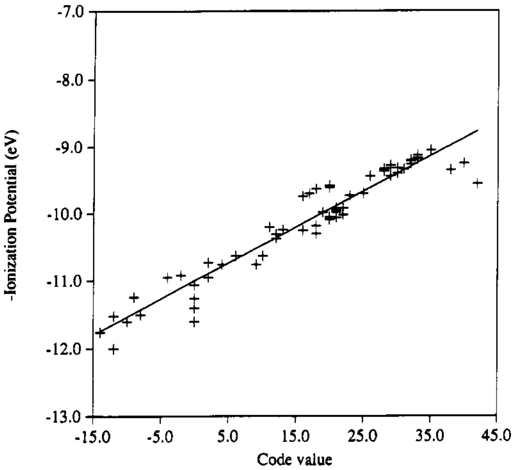


Figure 2. IP's of substituted alkynes vs code values, τ.

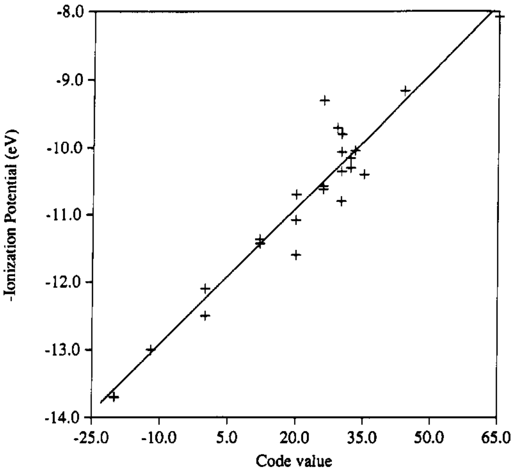
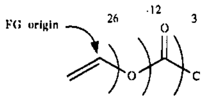


Figure 3. IP's of substituted imines vs code values, τ.

of any FG by treating it as a layer of atoms or groups of atoms. A small set of basic units was selected such that any FG can be constructed from them.[5a] To illustrate the computation of τ values in conjunction with the above strategy, consider the substituent $OCOCH_3$. In the algorithm, this substituent is partitioned into three layers, as shown in **14**. Starting from the FG origin, as the first unit is encountered, a constant that reflects the change in IP produced by the unit is assigned to it. In this case, the first unit is an oxygen atom, and its corresponding constant derived from the data base of IP's is 26. [Note: $\Delta IP = IP_{OH} - IP_H = (-9.18)^{100} - (-10.5)^{73} = 1.32$; $\tau_{OH}(\text{exptl}) = \Delta IP(20) = 26.4$]. As each subsequent unit is encountered, the assigned value is adjusted to account for both electronic and resonance effects. The effect of a unit decreases with its distance from the origin. In **14**, the electron-donating effect of oxygen is diminished by the electron-withdrawing effect of C═O. In the present example, the corresponding unit constants for C═O and CH_3 are −12 and 3, respectively. The τ for $OCOCH_3$, as shown in **14**, is computed from the expression τ = code1 + code2 + 2/3code3, where code*n* refers to the unit constant in the *n*th layer.



14

$$\tau_{calc} = \text{code1} + \text{code2} + 2/3\text{code3}$$

$$\tau_{calc} = 26 \bullet (-12) + 2/3(3) = 16$$

$$\tau_{expt} = (IP_{OAc} - IP_H) \times 20$$

$$\tau_{expt} = [(-9.85) - (-10.5)] \times 20 = 13 \text{ (refs 73, 101)}$$

Table III gives an updated list of τ's for common functional groups. Note that hydrogen atoms have a τ value of zero, while electron-donating and electron-withdrawing FG's have positive and negative τ values, respectively. The present table has been expanded to include 15 more functional groups (cf. ref 5a). Additionally, the τ's for 14 substituents (e.g., Cl, Br, I, OH, and SCH_3) have been modified to better fit the experimental IP data. For example, the substituent constant for Cl was changed from 6 to 10. The outcome is a general improvement in the HOMO predictions of Cl-substituted systems such as CH_2═CHCl, HC≡CCl, N≡CCl, P≡CCl, CH_3COCl, Cl_2C═S, and Cl_2C═C═O.

The estimated τ values can be plotted against the experimental IP's of a variety of monosubstituted parents. A few examples of these plots are provided in Figures 1–3. The different slopes, $\gamma(P)$, obtained from these plots suggest that each 2π parent system has an inherent sensitivity toward a given functionality. The previous algorithm that estimates this sensitivity has been updated and is now represented by eq 37. In addition, a new

$$\gamma(2\pi) = 0.01N_{tb} + 0.06N_O + 0.02N_N + 0.03N_S - 0.01N_P + 0.05 \tag{37}$$

$$\gamma(\text{cumulene}) = 0.06T_O + 0.02T_N + 0.03T_S + 0.05 \tag{38}$$

$$E_{HOMO} = \gamma(P) \times \tau(FG) + E_{HOMO}(P) \tag{39}$$

equation for computing $\gamma(P)$ for cumulene systems has been developed (eq 38). To illustrate, the computed slopes from eq 38 for H_2C═C═NH and NH═C═O are 0.05 and 0.07, respectively. In the former, C═C bond is the π-HOMO; in the latter, N═C bond is the π-HOMO, and T_N is 1. Once $\gamma(P)$ and $\tau(FG)$ are known, the HOMO energy of any monosubstituted 2π system can be computed using eq 39. For example, in ClCH═C═O, γ is 0.05, τ(Cl) is 6 (Table III), and $E_{HOMO}(CH_2{=}C{=}O)$ is −10.0 eV (Table II). Therefore, the predicted E_{HOMO} for the above cumulene is −9.7 eV, which is in close agreement with the experimental −IP value (−9.5 eV).[102]

HOMO Energies of Polysubstituted Systems. An algorithm for predicting the HOMO energies of polysubstituted π systems based on collective τ values was previously implemented.[5a] The symbol τ_C represents the net effect of all FG's attached to the parent and is given by the equation

$$\tau_C = \tau_{max} + 2\tau_{sum}/(1 + \text{NFG}) \tag{40}$$

where τ_{max} is the maximum absolute τ for systems with all-donating or all-withdrawing FG's or the sum of the τ values of the most electron-donating and the most electron-withdrawing FG's; τ_{sum} is the sum of the τ values of the remaining FG's; the NFG is the total number of FG's attached to the parent system. The HOMO energy of any polysubstituted system can then be calculated from eq 41.

$$E_{HOMO} = \gamma(P)\tau_C + E_{HOMO}(P) \tag{41}$$

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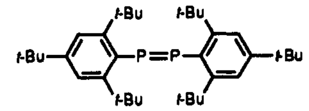
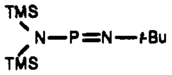
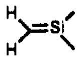
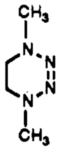
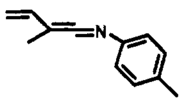
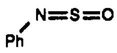
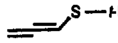
Table IV. Examples of HOMO Energies Predicted by the CAMEO Program

entry no.	substrate	exptl -IP (eV)	predicted HOMO (eV)	ref[a]
1		-7.27	-7.2	105
2		-8.48	-8.3	99
3		-7.98	-8.0	106
4		-8.11	-7.6	107
5		-7.73	-7.6	88
6		-9.12	-8.7	108
7		-8.32[b] -9.56[c]	-8.1 -9.5	109 109

[a] For experimental IP values. [b] HOMO energy for substituted C=C bond in allene. [c] HOMO energy for unsubstituted C=C bond in allene.

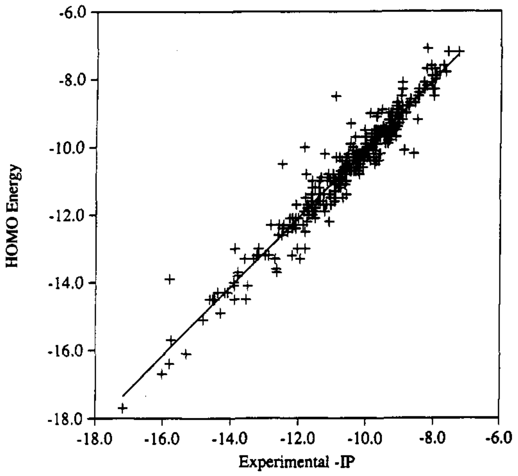
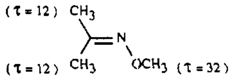


Figure 4. Predicted HOMO energies vs experimental IP's (eV).

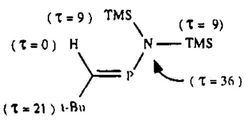
Sample calculations of HOMO energies are illustrated below.



$\tau_C = 32 + 2(24)/(1+3) = 44$

$E_{HOMO} = -12.4 + (.07)(44) = -9.3$

$-IP = -9.16$ eV (ref 103)

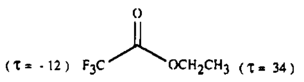


$\tau(N(TMS)_2) = 36 + 2(18)/3 = 48$

$\tau_C = 48 + 2(21)/(2+1) = 62$

$E_{HOMO} = -10.1 + (.04)(62) = -7.6$ eV

$-IP = -8.01$ eV (ref 104a)

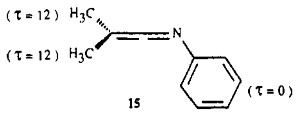


$\tau_C = 34 - 12 = 22$

$E_{HOMO} = -14.5 + (.11)(22) = -12.1$ eV

$-IP = -11.81$ eV (ref 104b)

Although the majority of the calculations are straightforward, special conformational considerations have been afforded to some π systems. The previous HOMO algorithm has been modified to account for a few of these cases. For example, the phenyl ring at the N-terminus of ketene imine **15** is not supposed to exhibit any conjugation with the C=N bond since the ring lies in a plane perpendicular to the C–C–C–N plane.[90] Hence, it does not affect the energy of the π-HOMO of ketene imine, i.e., $\tau(\text{Phe}) \approx 0$. In contrast, the phenyl ring in **16**, which is bonded to the C-terminus, is coplanar with the H–C–C–N moiety; hence, its π MO can interact with the π-HOMO of ketene imine, thereby raising its energy.[90] It should be noted that in **16** the cyclohexane ring contributes only half of its total electronic effect ($\tau_{\text{effective}} = 22/2$) to the π-HOMO since it is not directly attached to the C=C bond which is associated with the HOMO. In general, the effective τ value of a remote FG on π_{XY} in cumulene X=Y=Z—FG is about half its calculated τ value.

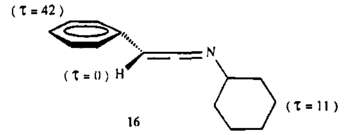


15

$\tau_C = 12 + 2(12)/3 = 20$

$E_{HOMO} = -9.5 + (.05)(20) = -8.5$ eV

$-IP = -8.02$ eV (ref 90)



16

$\tau_C = 42 + 2(11)/3 = 45.6$

$E_{HOMO} = -9.5 + (.05)(45.6) = -7.2$ eV

$-IP = -7.6$ eV (ref 90)

It should be realized that the CAMEO program must be able to predict the products of organic reactions rapidly even for complicated molecules. Therefore, it is not practical to perform quantum mechanical calculations for complex systems. Rather, it is necessary to develop an efficient algorithm that estimates rapidly the FMO energies such that the values are accurate enough to allow correct predictions of reactivity. The new FMO algorithm is efficient and generally accurate; its validity has been established by comparison with experimental data, i.e., with 319 IP values and 36 EA values. Figure 4 gives a plot of the predicted HOMO energies versus the experimental IP's. The standard deviation and coefficient of linear correlation for this plot are 0.472 and 0.964, respectively. A few outliers such as those corresponding to CF_3CO_2H, $H_2NC{\equiv}N$ and $CH_3OCH_2CH{=}NN(CH_3)_2$ have higher predicted HOMO energies. For these π systems, the resonance effects of oxygen and nitrogen electron lone pairs have been overestimated in the HOMO algorithm. Table

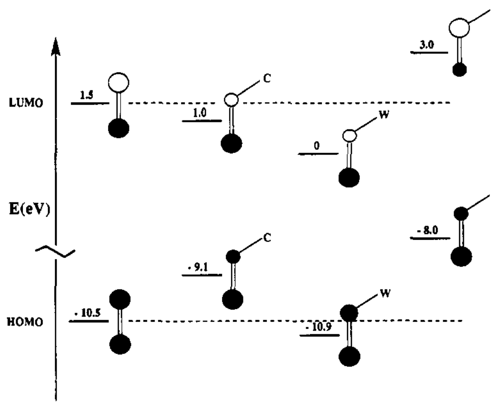
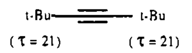


Figure 5. Estimated frontier orbital energies and coefficients for substituted ethylenes.

IV contains examples of typical predictions of HOMO energies for some complex π systems.

LUMO Energies of Substituted Systems. Once the effects of functional groups on the HOMO energies are known, the corresponding effects on the LUMO energies are roughly estimated based on known relationships between the effects of FG's on the HOMO and LUMO energies. A pictorial overview of these relationships has been given by Houk[110] (Figure 5) and is summarized as follows: (i) a conjugating FG lowers the LUMO energy of the parent about one-third to one-half as much as it raises the HOMO energy; (ii) a withdrawing FG lowers the HOMO energy about one-third as much as it lowers the LUMO energy; and (iii) a donating FG raises the HOMO energy about twice as much as it raises the LUMO energy. For convenience, the γ values for the parent systems are kept constant, while the τ values for the HOMO energies are adjusted to give the corresponding τ values for the LUMO energies. For polysubstituted systems, an equation similar to eq 41 is used except that τ_C now corresponds to the total effect of all FG's on the LUMO energy of the parent system. Sample calculations of LUMO energies are provided below.

$$E_{LUMO} = \gamma(P) \times \tau_C + E_{LUMO}(P) \qquad (42)$$

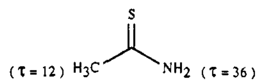


τ_C (HOMO) = 21 + 2(21)/3 = 35

τ_C (LUMO) = 35/2 = 17.5

E_{LUMO} = 2.6 + (.06)(17.5) = 3.65 eV

EA (experimental) = 3.1 eV (ref 111)



τ_C (HOMO) = 36 + 2(12)/3 = 44

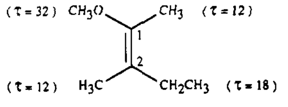
τ_C (LUMO) = 44/2 = 22

E_{LUMO} = -1.9 + (.08)(22) = 0.14 eV

EA (experimental) = 0.4 eV (ref 112)

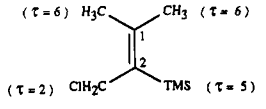
Determination of Regiochemistry. As mentioned above, regiochemical orientation in ene reactions can be predicted from the sizes of the coefficients of the frontier orbitals. If the relative magnitudes of the orbital coefficients at the reacting termini are known, the direction of addition can be predicted. Results of quantum chemical calculations show that for unsymmetrical π bonds, the larger HOMO coefficient resides on the more electronegative atom. Conversely, the larger LUMO coefficient resides on the less electronegative atom. For example, the starred atoms in the following enophiles represent the atoms with the larger coefficients in the π LUMO's: $>C^*{=}O$, $>C^*{=}N-$, $-N^*{=}O$, $>C^*{=}S^+-$, $-C^*{\equiv}N^+-$, $>C{=}C^*{=}O$, $O{=}S^*{=}N-$.

For symmetrical π bonds such as olefinic, allenic, azo, and diphosphene bonds, the extent and direction of polarization of the MO coefficients depend on the substituents. Figure 5 shows the effects of the different types of functional groups on the terminal coefficients of substituted ethylenes.[110] To summarize, all functional groups attached to the terminal positions increase the magnitudes of the HOMO coefficients on the opposite termini. The same relationships hold for the LUMO coefficients, except when the functional groups involved are electron-donating, in which case the direction of polarization of the orbitals is reversed. Thus, the calculated τ values of the substituents are used to evaluate the regiochemistry. Examples of calculations of the relative magnitude of the MO coefficients are provided as follows:



$|32| + |12| > |12| + |18|$

larger HOMO coefficient at atom 2



$|6| + |6| > |2| + |5|$

larger LUMO coefficient at atom 1

In the first example, each electron-donating group increases the MO coefficient at the opposite terminus. The contributing effects of methoxy and methyl groups overrides those of methyl and ethyl groups; hence, the larger MO coefficient resides on atom 2. In the second example, each electron-donating group increases the MO coefficient of the terminal atom to which it is attached. Since TMS and CH_2Cl have smaller electronic effects on the π bond than methyl, the larger MO coefficient is located at atom 1.

In the algorithm that evaluates regiochemistry, the atoms with the larger HOMO and LUMO coefficients are labeled as the KEYHOMO and KEYLUMO atoms, respectively. Naturally, symmetrical π components will have the same MO coefficients at the reacting termini. In this case, both termini are considered for σ-bond formation. In addition, when the differences in the sums of absolute values for FG's fall within a 0.4-eV range, both regioisomers are allowed to form; i.e., both termini are labeled as the KEYHOMO and KEYLUMO atoms.

Formation of Ene Adducts. Before performing the ene mechanism, a few preprocessing steps are undertaken. First, the viability of each ene/enophile pair is established by computing the FMO gap of the reacting components. If the ene or enophile is symmetric, only one equivalent atom is processed further to avoid formation of duplicate products. Next, the feasibility of an intramolecular ene reaction is assessed if the ene and enophile components are in the same fragment. The correct stereochemistry in intramolecular ene reactions is then assigned. Rules for implementing the stereochemistry for intramolecular ene reactions are as follows: (a) the type I cyclizations leading to 5-membered ring formation, the H-donor and the H-acceptor sites are denoted with a cis configuration;[44b,46,53–55] (b) for type I cyclizations leading to six-membered ring formation, a trans configuration is assigned to the H-donor and H-acceptor sites.[45,53] The reaction temperature range is then estimated based on the computed FMO gap (e.g., T = 100–200 °C for ene reactions with an FMO gap that lies between 10.5 and 13.5). Finally, the ene mechanism is performed, and the atoms with the largest MO coefficients, i.e., the KEYHOMO and the KEYLUMO atoms,

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(110) (a) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092. (b) Houk, K. N.; Sims, J.; Duke, R. E., Jr.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287.

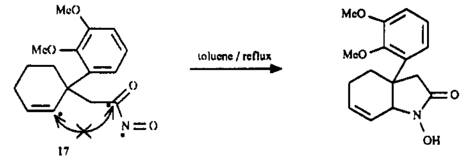
(111) Ng, L.; Jordan, K. D.; Krebs, A.; Ruger, W. *J. Am. Chem. Soc.* **1982**, *104*, 7414.

(112) Modelli, A.; Jones, D.; Rossini, S., Distefano, G. *Tetrahedron* **1984**, *40*, 3257.

are joined by a σ bond. For allenyl silanes, the mechanism involves the abstraction of a hydrogen at the terminal cumulene atom bearing the silyl substituent. For carbonyl ene components, tautomerization is carried out first before executing the ene mechanism.

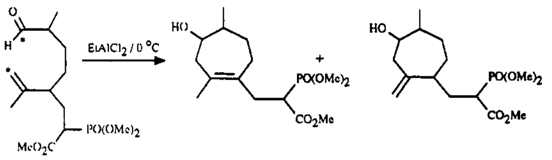
In evaluating the feasibility of intramolecular ene reactions, the following rules based on a survey of literature precedents have been implemented.

(a) Cyclizations leading to three- and four-membered rings are energetically disfavored (e.g., four-membered ring closure in 17 does not occur).[47] Formation of rings with sizes ranging from five to 10 is permitted (see eqs 21,[46b] 17,[48a] 44,[113] and 18[51] for 5, 6, 7, and 9 ring closures, respectively). Cyclizations leading to rings larger than 10-membered are currently ruled out since they are entropically unfavorable.



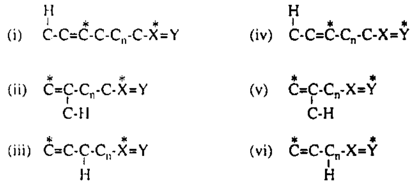
(43)

(b) For five-membered ring cyclizations, six cases may be envisioned. Cases ii–vi ($n = 1$) occur via small bridged



(44)

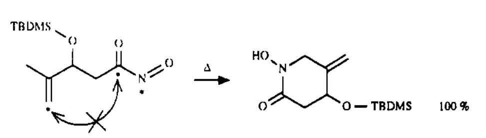
bicyclic ([2.*n*.1], $n = 1$–3) transition states and are not allowed. Cases ii and iii are exemplified in eq 45,[50] which leads to six-membered ring formation. The starred atoms in all cases refer to the KEYHOMO and KEYLUMO atoms that are to be joined by a σ bond.



(i) $\overset{\mathrm{H}}{\mathrm{C}}\text{-C=}\overset{*}{\mathrm{C}}\text{-C-}\mathrm{C}_n\text{-C-}\overset{*}{\mathrm{X}}\text{=Y}$ (iv) $\overset{\mathrm{H}}{\mathrm{C}}\text{-C=}\overset{*}{\mathrm{C}}\text{-}\mathrm{C}_n\text{-C-X=}\overset{*}{\mathrm{Y}}$

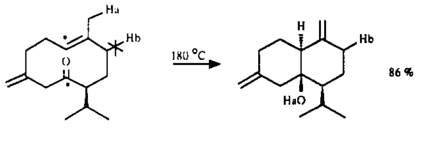
(ii) $\overset{*}{\mathrm{C}}\text{=}\underset{\text{C-H}}{\mathrm{C}}\text{-}\mathrm{C}_n\text{-C-}\overset{*}{\mathrm{X}}\text{=Y}$ (v) $\overset{*}{\mathrm{C}}\text{=}\underset{\text{C-H}}{\mathrm{C}}\text{-}\mathrm{C}_n\text{-X=}\overset{*}{\mathrm{Y}}$

(iii) $\overset{*}{\mathrm{C}}\text{=C-}\underset{\mathrm{H}}{\mathrm{C}}\text{-}\mathrm{C}_n\text{-}\overset{*}{\mathrm{X}}\text{=Y}$ (vi) $\overset{*}{\mathrm{C}}\text{=C-}\underset{\mathrm{H}}{\mathrm{C}_n}\text{-X=}\overset{*}{\mathrm{Y}}$

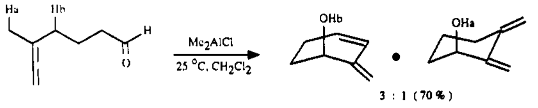


(45)

(c) For six-membered ring cyclizations, six cases may also be envisioned. Cases i, ii, and iv ($n = 2$) are allowed; cases iii, v, and vi ($n = 2$) which proceed via small bridged bicyclic transition states are not allowed (e.g., eqs 17[48a] and 46[49] for case iii). An exception to case iii is found when the ene or enophile component is part of a cumulene system, as in eq 47.[48a]



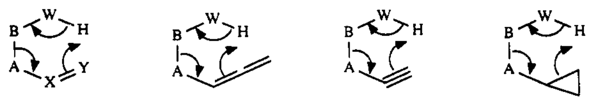
(46)

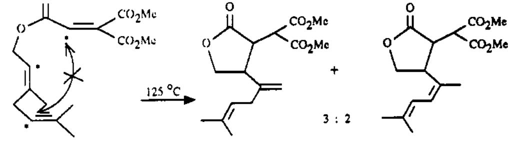


(47)

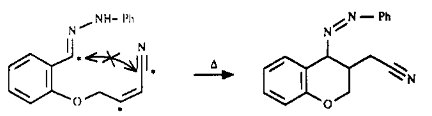
(d) Five- and six-membered ring cyclizations that do not violate rules b and c are more favored than seven to nine-membered ring closures (e.g., eqs 48[54] and 49[19b]).

Chart II





(48)

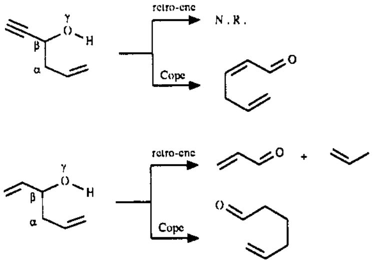


(49)

Implementation of Retro-Ene Chemistry in CAMEO. RETENE is the executive subroutine for evaluating retro-ene fragmentations. Its major functions include (1) preception of all possible reactive paths in a molecule, (2) evaluation of competition among viable paths, and (3) implementation of the retro-ene mechanism and periselectivity.

Perception of Reactive Paths. A reactive path is defined as the string of atoms involved in the 6e$^-$ cyclic transition state. In perceiving potentially reactive paths, the molecular frameworks in Chart II are searched for. A path is perceived by sequential examination of the atoms comprising the path starting with the atoms of the multiple or cyclopropyl bond. The multiple bonds that are considered include carbon–carbon bonds, aromatic or nonaromatic carbon–hetero bonds, and hetero–hetero bonds. The following rules for weeding out unreactive paths have been devised and implemented in the program.

(a) An acyclic path is unreactive if an acetylenic carbon is attached to the β-position; in this case, the competing Cope rearrangement predominates (e.g., eq 50).[65] Note that β-olefin substitution does not hinder retro-ene fragmentation (eq 51).[65]



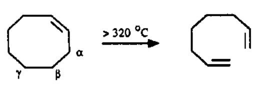
(50)

(51a)

(51b)

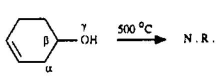
(b) Transannular retro-ene fragmentation is not allowed in a cyclic path if the ring size is ≤7 (e.g., compare eq 52[114a] and eq 53[9c]).

(52)



(53)

≤ 6 (e.g., eq 54).[114b]



(54)

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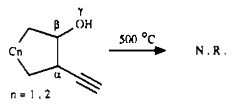
(113) Snider, B. B.; Phillips, G. B.; *J. Org. Chem.* **1983**, *48*, 3685.

(114) (a) Arnold, R. T.; Smolinsky, G. *J. Am. Chem. Soc.* **1959**, *81*, 6443. (b) Arnold, R. T.; Smolinsky, G. *J. Org. Chem.* **1960**, *25*, 129.

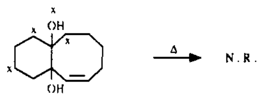
(c) A path is rejected if three bonds along the path are contained in a nonbridged ring of size ≤6 (e.g., eq 54).[114b]

(d) A path that contains an acetylenic bond is unreactive if it is incapable of achieving the required planar transition-state structure (e.g., eq 55).[69]

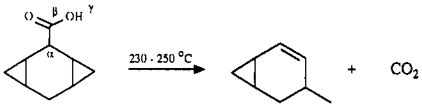


(55)

(e) A path is not allowed if one or more atoms along the path is part of a fused ring system (e.g., eq 56).[115] An exception is when a fused three-membered ring is involved, as in eqs 57[60b] and 58.[116]

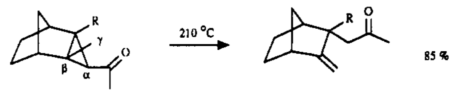


(56)

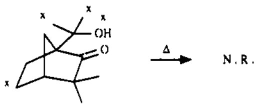


(57)

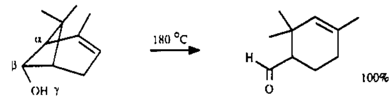
(f) A path is not allowed if a double bond to a bridgehead atom in a small bridged ring system will be formed in the process (eq 59[117]). If the multiple bond is part of a bridged system and the required transition-state structure is attainable, retro-ene reaction is permitted to occur (e.g., eq 60).[118]



(58)



(59)

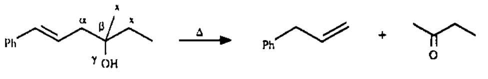


(60)

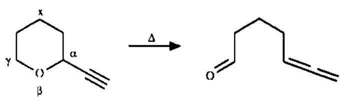
Once an acceptable path is found, it is assigned to a group that reflects its reactivity, as described below. The atoms along the path are then stored sequentially in an array for later retrieval during path evaluation.

Evaluation of Competition among Reactive Paths. Reactive paths are classified into five groups according to reactivity. The types of substrates under each category are provided as follows: group I, acetylenic ethers, *cis*-hydroxyvinylcycloalkanes, *cis*-alkylcyclopropane carbonyl systems; group II, β,γ-unsaturated acids, *cis*-alkylvinylcyclopropanes, β,γ-cyclopropyl carboxylic acids; group III, β-hydroxyolefins, β-hydroxyacetylenes, *trans*-cyclooctene; group IV, allylic ethers, propargylic ethers; group V, alkenes, cycloalkenes, allenes, cycloallenes, vinyl ethers, vinyl esters, silyloxyenol ethers, alkylsilanes, silenes, etc.

Relative reactivity follows the order I > II > III > IV > V. Competition among viable paths is evaluated by considering only those paths belonging to the group with the highest reactivity. Thus, if reactive paths are present in group I, paths in groups II–V are not processed. Competition may occur within a given group depending on the geometry of the reacting molecule, e.g., reflecting steric acceleration and inhibition. Examples illustrating path competitions are shown in eqs 61[114] and 62.[58b]

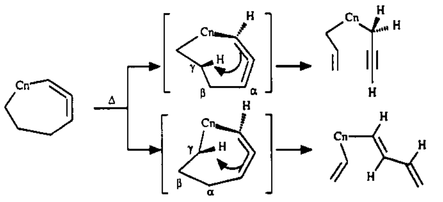


(61)



(62)

Implementation of the Mechanism and Periselectivity. After the various paths have been evaluated, the concerted retro-ene mechanism is implemented (see Scheme II). For cyclic allenes, two modes of ring fragmentation are carried out, one leading to enynes and the other to enedienes (eq 63).[59] With the former, the reactive path perceived is of the type C=C=A-B-W-H. This path presents a unique case since the α atom is usually singly-bonded to the terminal atom of the reacting π bond (see Chart II).



(63a)

(63b)

The retro-ene products formed are then compared with those obtained from the other pericyclic pathways. The comparison is based on the predicted temperature ranges for the reactions.[5b] Various procedures for estimating the reaction temperatures have been employed depending on the nature of the pericyclic process and the availability of kinetic and thermodynamic data. For example, for Diels–Alder, 1,3-dipolar cycloadditions, electrocyclic closures, and certain sigmatropic rearrangements (e.g., [3,3]-, [1,5]-, and [1,7]-carbon and -hydrogen shifts), the reaction temperature is calculated using the Arrhenius equation.[5b] For concerted [2 + 2] cycloadditions and ene reactions, the calculated FMO gaps are utilized to gauge reactivities and estimate temperature ranges. Since there are few kinetic and thermodynamic data on retro-ene reactions, assignment of temperature blocks are based on the group categories. This was made possible by a thorough survey of experimental reaction temperature and reactivity data. Reactants belonging to groups 1 and 2 were assigned the temperature ranges of 100–200 °C and 200–300 °C, respectively. Those belonging to groups 3–5 were assigned a temperature range of >300 °C. Overall, the algorithm for periselectivity gives reasonable estimates of the relative feasibility of pericyclic pathways. Consequently, pericyclic products are output from the most to the least favorable, i.e., from the lowest to the highest predicted temperature range requested by the user.

Sample Reaction Sequences. The CAMEO program successfully predicts the outcome of a wide variety of ene and retro-ene reactions including the examples in eqs 1–63. Additional examples of synthetic sequences that are predicted by the program are illustrated in the following schemes.

Scheme III illustrates a tandem Claisen–ene sequence, recently reported as the key transformation in the asymmetric total synthesis of (+)-9(11)-dehydroestrone methyl ether **23**.[13b] Submission of enol ether **18** to the pericyclic module of CAMEO affords ketone **19** via a Claisen rearrangement. Resubmission of this product to the same

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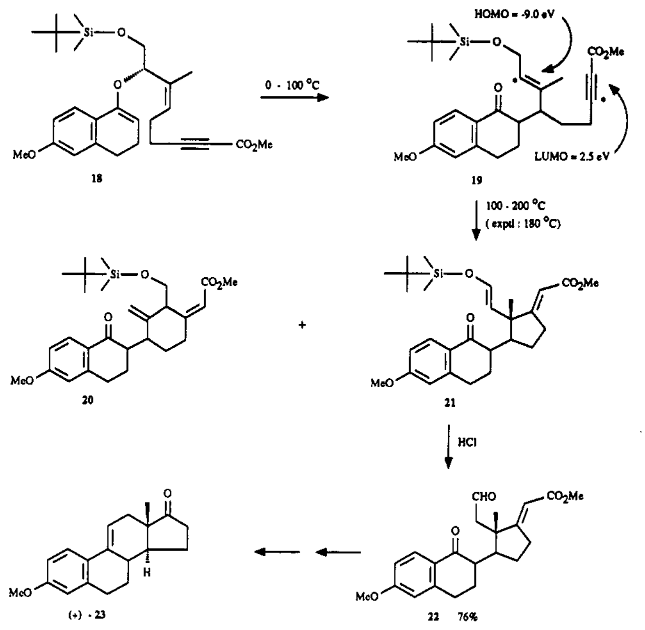
(115) Marvell, E. N.; Cheng, J. C. P. *J. Org. Chem.* **1980**, *45*, 4511.

(116) Creary, X.; Hudock, F.; Keller, M.; Kerwin, J. F., Jr.; Dinnocenzo, J. P. *J. Org. Chem.* **1977**, *42*, 409.

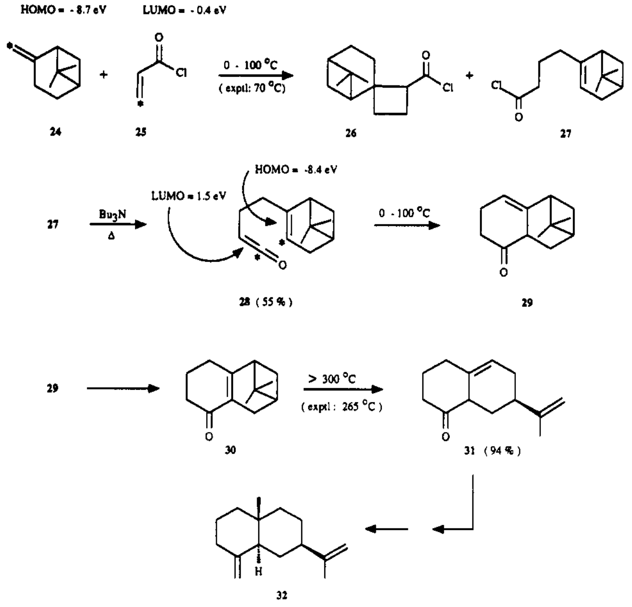
(117) Smith, G. G.; Yates, B. J. *J. Org. Chem.* **1965**, *30*, 2067.

(118) (a) Joulain, D.; Rouessac, F. *J. Chem. Soc., Chem. Commun.* **1972**, 314. (b) Ohloff, G. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 743.

Scheme III



Scheme IV



module gives two intramolecular ene adducts, **20** and **21**. The regiochemical preference in **19** is denoted by the starred atoms, i.e., the atoms with the larger frontier orbital coefficients, as predicted by the CAMEO program. Although ene cyclization to **20** is electronically preferred, it proceeds via a less favorable bridged bicyclic transition state (viz., eq 51). In contrast, ene cyclization to **21** involves a fused bicyclic-endo transition state and is geometrically favored. Finally, resubmission of **21** to the acidic module with HCl as the reagent gives the "tandem Claisen–ene" product **22**, a precursor to the desired estrogen compound **23**. In the present scheme, the calculated FMO energies of the reacting π components are given along with the predicted temperature ranges and experimental yields.

The ability of the CAMEO program to simulate the conversion of (−)-β-pinene (**24**) to a precursor of (+)-β-selinene (**32**) is outlined in Scheme IV.[22] The strategy used to effect this transformation involves an ene–ene–retro-ene synthetic route. Submission of (−)-β-pinene and acryloyl chloride (**25**) to the pericyclic module yields two products **26** and **27**. The former arises from a [2 + 2]-cycloaddition process, while the latter results from an intermolecular ene reaction. Note that the preferred regiochemical orientation in the latter is predicted by the program. Processing of **27** using the basic/nucleophilic module gives ketene **28**. The reaction occurs via an E1cb mechanism with tri-*n*-butylamine as the reagent. Submission of **28** to the pericyclic module affords nonconjugated ketone **29**, which undergoes base-catalyzed isomerization to conjugated ketone **30**. Formation of **29** involves an intramolecular ene reaction of type III. Finally, resubmission of tricyclic ketone **30** to the pericyclic module gives bicyclic ketone **31** as the sole product (experimental yield: 94%). The retro-ene fragmentation of ketone **30** to form **31** is presumably due to the strategic placement of one of the two methyl groups such that it is easily accessible by the π orbital of the carbon–carbon double bond. The predicted FMO energies of the reacting π systems as well as the estimated reaction temperature ranges are provided in the present scheme.

Conclusion

The capabilities of the pericyclic module of the CAMEO program have been enhanced by the inclusion of ene and retro-ene chemistry. A frontier molecular orbital approach has been utilized in the analyses of ene additions. Concomitant with this is the development of an efficient algorithm for the calculation of FMO energies. The new algorithm has been demonstrated to accurately predict the HOMO energies of a wide variety of π systems, as shown in Table IV and Figure 4. It should be mentioned that the FMO approach can also be applied to other classes of reactions. Recently, FMO energies have been utilized in the redox module for the determination of chemo- and regioselectivities in the hydride reductions of various olefinic systems.[2a] Similarly, HOMO energies are currently used in the carbene module to gauge the relative reactivity of alkenes toward electrophilic carbenes. Application of the FMO approach to photochemical cycloadditions is also envisioned as part of future expansion of the pericyclic module. Finally, refinements in the latter module with regard to periselectivity are anticipated as more kinetic and thermodynamic data become available.