12b: yield 95%; ^{1}H NMR 1.31–1.43 (several peaks, 2 H), 1.74–2.00 (several peaks, 5 H), 2.48 (m, 1 H), 7.56–7.67 (several peaks, 2 H), 7.88–8.00 (several peaks, 2 H), 7.99 (d, 1 H, *J* = 9.0 Hz), 8.31 (dd, 1 H, *J* = 1.8 Hz and 8.8 Hz), 8.84 (d, 1 H, *J* = 1.1 Hz).

Na₂S Reduction of Compounds 8a, 8b, 9, and 10a. Compounds **8a** and **8b** were treated with Na₂S·9 H₂O (20% aqueous) in an evacuated flask equipped with a septum and an addition funnel. The gaseous products were analyzed by GLC and compared with authentic samples.

Compound **9** (0.50 g, 1.0 mmol) was shaked thoroughly with ethyl ether (50 mL) and Na₂S·9 H₂O (20% aqueous, 50 mL). The organic phase was separated, dried (CaCl₂), and evaporated to give 0.38 g of a 1:1 mixture of 1-decene and 2,2′-dinaphthyl ditelluride: mp 117–118 °C (EtOH) [lit. 120–122 °C];[36] yield 96%.

Reduction of the deuterated analogue **10a** similarly gave only 1-(*E*)-deuterio-1-decene.

Synthesis of β-Chloroalkyltellurium Trichlorides (15–20). Typical Procedure. Freshly sublimed TeCl₄ (1.67 g, 6.2 mmol) and (*Z*)-2-butene (0.36 g, 6.4 mmol) were stirred in an ice-bath for 3 h in dry, ethanol-free chloroform (20 mL) when almost all the TeCl₄ had disappeared. Filtration and evaporation yielded 1.35 g of product (67%) as a mixture of isomers **15a** and **15b** (Table II). Recrystallization from acetonitrile afforded the pure threo isomer **15b** as a white crystalline material (Table I).

(*E*)-2-Butene required 3 h at 0 °C and stirring overnight at ambient temperature to give a 94% yield of isomers **15a/15b**. The cyclic and the terminal olefins reacted with TeCl₄ within 3 h at 0 °C to give the following yields of addition compounds: cyclopentene (98%), cyclohexene (99%), cyclooctene (83%), 1-decene (98%), and (*E*)-1-deuterio-1-decene (96%). The relative yields of isomers are shown in Table II and physical and analytical data are collected in Table I.

The experiments using *p*-benzoquinone were carried out as described in the typical procedure, but in the presence of 15–20 mol % of the quinone. Longer reaction times were frequently required and the reactions were not disrupted until all or most of the TeCl₄ had disappeared.

(*E*)-2-Butene again required stirring at ambient temperature overnight. This was also the case with cyclohexene.

Complementary ^{1}H NMR data for compounds **15–20** are given in the following (methine protons are reported in Table I): **15a**, 1.70 (d, 3 H), 2.30 (d, 3 H). **15b**, 1.76 (d, 3 H), 2.22 (d, 3 H). **16**, 0.89 (t, 3 H), 1.26–1.58 (several peaks, 12 H), 1.92 (m, 2 H), 4.42 (dd, 1 H, *J* = 11.1 and 4.9 Hz), 4.62 (t, 1 H, *J* = 11.1 Hz), 5.08 (m, 1 H). **17a** and **17b**, 0.89 (t, 3 H), 1.27–1.58 (several peaks, 12 H), 1.92 (m, 2 H). **18a** 1.90 (m, 1 H), 2.20–2.35 (several peaks, 3 H), 2.61 (m, 1 H), 3.55 (m, 1 H). **18b** 2.00–2.35 (several peaks, 4 H), 2.96 (m, 2 H). **19a** Could not be accurately determined. **19b** 1.43–1.68 (several peaks, 2 H), 1.79–2.00 (several peaks, 2 H), 2.09–2.29 (several peaks, 2 H), 2.51 (m, 1 H), 2.70 (m, 1 H). **20a** 1.45–1.88 (several peaks, 7 H), 2.16–2.40 (several peaks, 4 H), 3.32 (m, 1 H).

Registry No. 6, 39106-47-3; 7, 71578-23-9; 8a, 87099-35-2; 8b, 87099-36-3; 9, 87070-60-8; 10a, 87070-61-9; 11b, 87070-62-0; 12b, 87070-63-1; 15a, 87099-37-4; 15b, 87099-38-5; 17a, 87099-39-6; 17b, 87144-13-6; 18a, 87070-64-2; 18b, 87099-40-9; 19a, 87099-41-0; 19b, 87099-42-1; 20a, 87070-65-3; (*Z*)-2-butene, 590-18-1; (*E*)-2-butene, 624-64-6; cyclopentene, 142-29-0; cyclohexene, 110-83-8; cyclooctene, 931-88-4; TeCl₄, 10026-07-0.

(36) Petragnani, N.; de Moura Campos, M. *Tetrahedron* 1965, *21*, 13.

Computer-Assisted Mechanistic Evaluation of Organic Reactions. 7. Six-Electron Cycloadditions

Julia Schmidt Burnier and William L. Jorgensen*

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

An interactive computer program, CAMEO, is being developed to predict the products of organic reactions through the use of mechanistic reasoning. The program has been expanded to encompass six-electron cycloadditions, including reactions of 1,3-dipoles, as the first part of a general module for pericyclic chemistry. A review of the reaction components and their regiochemistry in six-electron cycloadditions is first presented. Next, the development and implementation of algorithms used to predict the likelihood and regio- and stereoselectivity of six-electron cycloadditions are described. The analyses are based on the frontier molecular orbital method. Consequently, it was necessary to devise efficient algorithms for predicting the energies and relative coefficients of frontier molecular orbitals. General empirical relationships were developed on the basis of experimental data and the results of quantum mechanical calculations. Sample sequences are provided that illustrate typical predictions made by the program.

I. Introduction

CAMEO is a computer program designed to predict the products of organic reactions given starting materials and conditions.[1-5] Two key features of the program are that its predictions are made via the simulation of reaction mechanisms and that it is interactive with the input and output of structures occurring at a graphics terminal. Following the input of reactants and conditions, the program enters a perception phase in which important structural features such as functional groups, rings, stereochemistry, and reactive sites are recognized. This in-

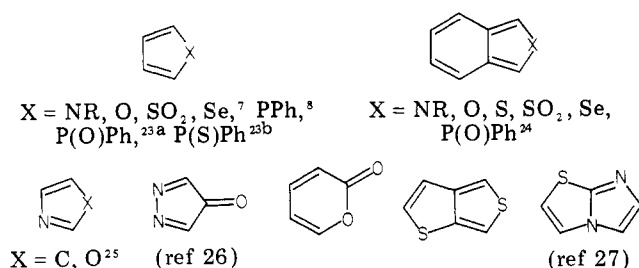(1) T. D. Salatin and W. L. Jorgensen, *J. Org. Chem.*, 45, 2043 (1980).
(2) T. D. Salatin, D. McLaughlin, and W. L. Jorgensen, *J. Org. Chem.*, 46, 5284 (1981).
(3) C. E. Peishoff and W. L. Jorgensen, *J. Org. Chem.*, 48, 1970 (1983).
(4) D. McLaughlin and W. L. Jorgensen, in preparation.

(5) B. L. Roos-Kozel, Ph.D. Thesis, Purdue University, 1981.

Chart I

X = NR, O, SO$_2$, Se,[7] PPh,[8]   X = NR, O, S, SO$_2$, Se,
P(O)Ph,[23a] P(S)Ph[23b]   P(O)Ph[24]

X = C, O[25]   (ref 26)   (ref 27)

formation is then used along with a knowledge of fundamental reaction steps in the reaction simulation phase, which creates mechanisms, considers competing processes, and generates products.

The first class of reactions implemented in CAMEO focused on base-catalyzed and nucleophilic chemistry consisting of substitution, elimination, addition, and proton-transfer steps.[1] Subsequently, this mechanistic class was expanded to incorporate reactions of ylides; the organometallic chemistry of Li, Cu, and Mg;[2] and organosilicon chemistry.[3] The program has also been broadened substantially by the addition of a module to oversee electrophilic processes involving carbonium ions as intermediates[4] and electrophilic aromatic substitution.[5]

The present paper describes the extension of CAMEO to cover another important group of reactions, six-electron cycloadditions including reactions of 1,3-dipoles. This represents the first part of a general module for pericyclic chemistry that will treat electrocyclic reactions and sigmatropic rearrangements as well as cycloadditions.

First, the reaction components and regiochemistry for six-electron cycloadditions are reviewed. The frontier molecular orbital method has been chosen as the framework for the prediction of the likelihood and the regiochemistry of cycloadditions.[6] The development of algorithms to predict the energies and polarization of the frontier orbitals and their implementation in CAMEO are then described. Finally, sample sequences that illustrate typical predictions made by the program are presented and discussed.
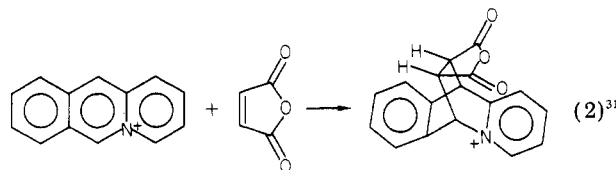
II. The Reaction Components

A. Dienes. A seemingly endless variety of dienes helps make the Diels–Alder reaction extremely versatile.[7,8] Acyclic dienes, with and without heteroatoms, have been considered extensively.[9,10] This category includes, to name but a few of the more common types, α,β-unsaturated carbonyls[9] and thiocarbonyls,[11–13] α-dicarbonyls,[9] some aza and diaza butadienes,[14–17] electron-poor azo systems,[9] and

a variety of hetero dienes.[9] Some less common alternatives like 1,4-disilabutadienes[18] and 1-oxaphosphabutadienes[9] emphasize the range of possibilities. Nonaromatic alicyclic dienes will usually be reactive in a Diels–Alder fashion if the 4π-electron system can achieve s-cis coplanarity. Eight- to eleven-membered-ring dienes are thus usually thermally unreactive.[19] It should be noted that although thiophenes[20] and pyrroles[21] are quite inert due to a high degree of aromaticity, their incorporation into polycyclic aromatic systems increases their reactivity markedly.[22] A variety of heterocyclic dienes is illustrated in Chart I.

An interesting subset consists of the six-membered aromatic dienes. Although benzene, pyridines, and dinitrogen-containing aromatic rings are inert under Diels–Alder conditions, 1,2,4-[30] and 1,3,5-triazines[28] and 1,2,4,5-tetrazines as well as arsabenzene[29] have been found to be active dienes (eq 1):

(1)[30]

90%
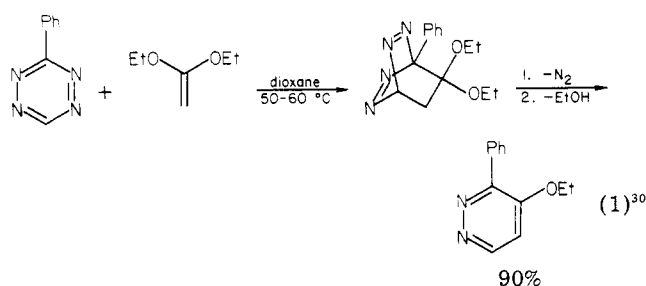
Naturally, the more aromatic a compound is, the less it is able to function as a diene. Although naphthalene and phenanthrene are inert under typical reaction conditions, the central ring(s) become less aromatic and more reactive as the fused ring system is expanded. Thus, anthracene, benzologues of anthracene and phenanthrene, and related compounds have been extensively used in Diels–Alder reactions (eq 2).[7] Styrene and its derivatives, in which

(2)[31]

(6) (a) K. N. Houk, *Acc. Chem. Res.*, **8**, 361 (1975); (b) W. C. Herndon, *Chem. Rev.*, **72**, 157 (1972).

(7) A. S. Onishchenko, "Diene Synthesis". Translation from the Russian by the Israel Program for Scientific Translations, Jerusalem, 1964.

(8) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **5**, 211 (1966).

(9) G. Desimoni and G. Tacconi, *Chem. Rev.*, **75**, 651 (1975).

(10) (a) K. B. Lipkowitz, S. Scarpone, B. P. Mundy, and W. G. Bornmann, *J. Org. Chem.*, **44**, 486 (1979); (b) G. Desimoni, P. Righetti, G. Tacconi, and R. Oberti, *J. Chem. Soc., Perkin Trans. 1*, 856 (1979); (c) P. Righetti, G. Tacconi, A. C. C. Piccolini, M. T. Pesenti, G. Desimoni, and R. Oberti, *ibid.*, 863 (1979); (d) M. O-oka, A. Kitamura, R. Okazaki, and N. Inamoto, *Bull. Chem. Soc. Jpn.*, **51**, 301 (1978).

(11) J. P. Pradere, Y. T. N'Guessan, H. Quiniou, and F. Tonnard, *Tetrahedron*, **31**, 3059 (1975).
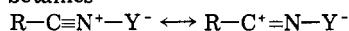
(12) K. B. Lipkowitz and B. P. Mundy, *Tetrahedron Lett.*, 3417 (1977).

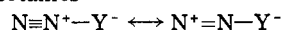(13) J. S. A. Brunskill, A. De, and D. F. Ewing, *J. Chem. Soc., Perkin Trans. 1*, 629 (1978).

(14) Y. Nomura, Y. Takeuchi, S. Tomoda, and M. M. Ito, *Chem. Lett.*, 187 (1979).

(15) A. E. Baydar, G. V. Boyd, P. F. Lindley, and F. Watson, *J. Chem. Soc., Chem. Commun.*, 178 (1979).

(16) R. Faragher and T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1*, 249 (1979).

(17) S. Somer, *Chem. Lett.*, 583 (1977).

(18) T. J. Barton and J. A. Kilgour, *J. Am. Chem. Soc.*, **98**, 7746 (1976).

(19) J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).

(20) H. Kotsuki, H. Nishizawa, S. Kitagawa, M. Ochi, N. Yamasaki, K. Matsuoka, and T. Tokoroyama, *Bull. Chem. Soc. Jpn.*, **52**, 544 (1979).

(21) A. P. Kozikowski, W. C. Floyd, and M. P. Kuniak, *J. Chem. Soc., Chem. Commun.*, 582 (1977).

(22) E. Chacko, J. Bornstein, and D. J. Sardella, *J. Am. Chem. Soc.*, **99**, 8248 (1977).

(23) (a) Y. Kashman and O. Awerbouch, *Tetrahedron*, **31**, 53 (1975); (b) Y. Kashman, I. Wagenstein, and A. Rudi, *ibid.*, **32**, 2427 (1976).

(24) T. H. Chan and K. T. Nwe, *Tetrahedron*, **31**, 2537 (1975).

(25) H. Takagaki, N. Yasuda, M. Asaoka, and H. Takei, *Chem. Lett.*, 183 (1979).

(26) P. J. Fagan, E. E. Neidert, M. J. Nye, M. J. O'Hare, and W.-P. Tang, *Can. J. Chem.*, **57**, 904 (1979).

(27) N. Abe, T. Nishiwaki, and N. Komoto, *Chem. Lett.*, 223 (1980).

(28) H. Neunhoeffer and M. Bachmann, *Chem. Ber.*, **108**, 3877 (1975).

(29) A. J. Ashe and H. S. Friedman, *Tetrahedron Lett.*, 1283 (1977).

(30) B. Burg, W. Dittmar, H. Reim, A. Steigel, and J. Sauer, *Tetrahedron Lett.*, 2897 (1975).

(31) I. J. Westerman and C. K. Bradsher, *J. Org. Chem.*, **44**, 727 (1979).

Table I[a]
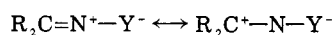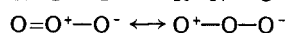
A. Dipoles with Internal Octet Stabilization

1. nitrilium betaines

$$R—C≡N^+—Y^- ⟷ R—C^+=N—Y^-$$

2. diazonium betaines

$$N≡N^+—Y^- ⟷ N^+=N—Y^-$$

3. azomethinium betaines

$$R_2C=N^+—Y^- ⟷ R_2C^+—N—Y^-$$

$$R—N=N^+—Y^- ⟷ R—N^+—N—Y^-{}^b$$

$$O=N^+—O^- ⟷ O^+—N—O^-{}^c$$

4. oxygen as central atom

$$R_2C=O^+—Y^- ⟷ R_2C^+—O—Y^-{}^b$$

$$R—N=O^+—Y^- ⟷ R—N^+—O—Y^-{}^b$$

$$O=O^+—O^- ⟷ O^+—O—O^-$$
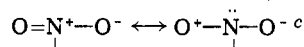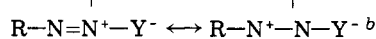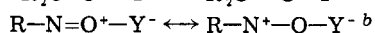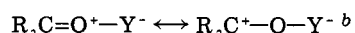
B. Dipoles without Internal Octet Stabilization

$$R—C—C=Y ⟷ R—C^+=C—Y^-$$

$$:N—C=Y ⟷ :N^+=C—Y^-$$
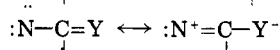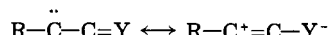
[a] $Y = CR_2$, NR, or O. [b] $RN=N^+—N^-R$, $R_2C=O^+NR^-$, $RN=O^+NR^-$, and $RN=O^+—O^-$ unknown. [c] Since the nitro group is exceptionally well stabilized by resonance, its tendency to undergo cycloadditions is very small (ref 33).

only one double bond of the diene belongs to the aromatic ring, can also function as dienes. The tendency of styrene to undergo polymerization sometimes gives yields too low to be used for preparative purposes. The 1:1 adduct either adds a second molecule of the dienophile or undergoes aromatization with a hydrogen shift.[7,8] In contrast, styrene derivatives such as 2-vinylnaphthalene give Diels–Alder adducts in high yields (eq 3).[32] Additionally, perylene and

(3)

95%
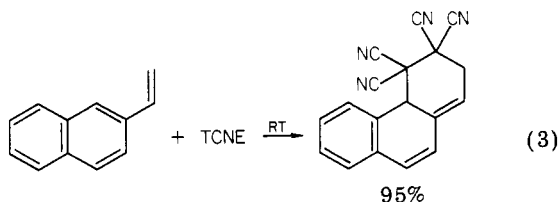
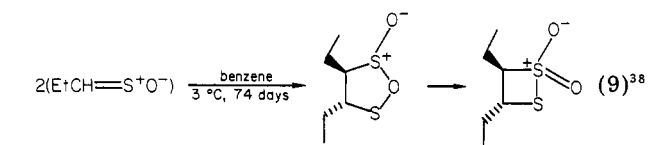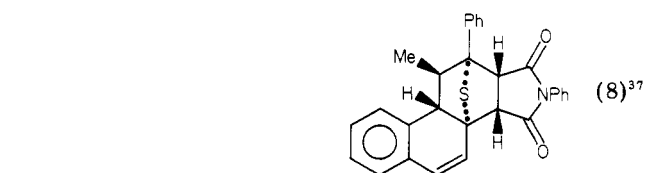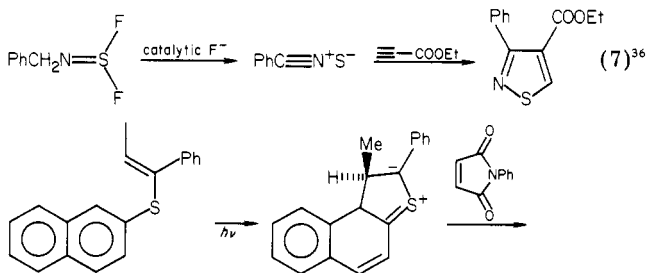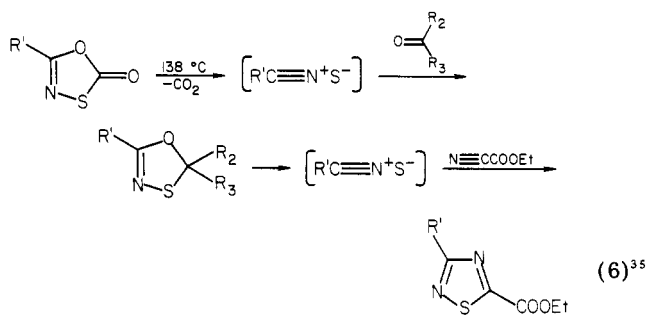its derivatives function as dienes (eq 4).[7]

(4)

perylene
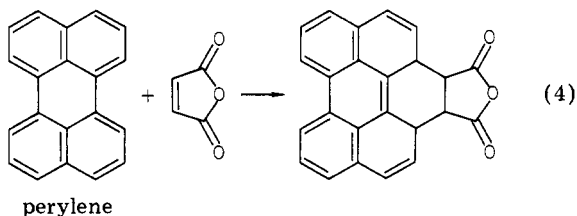
B. 1,3-Dipoles. As with dienes, the range of 1,3-dipoles is broad. In the 1960's, Huisgen and co-workers[33] explored many 1,3-dipoles and demonstrated that they readily undergo [4 + 2] cycloaddition reactions. Dipoles were classified into two major types: (1) those with internal octet stabilization, where a mesomeric formula can be drawn such that the central atom of the dipole has a positive charge and all centers have completely filled valences, and (2) those without internal octet stabilization, where each

mesomeric form has an electron sextet (see Table I).

By far the more common group of dipoles is the former, mainly because the dipoles in the second group are all unstable and must be generated in situ. Also, they often exhibit carbene chemistry to the exclusion of, or in competition with, 1,3-dipolar cycloadditions (eq 5).

(5)[34]
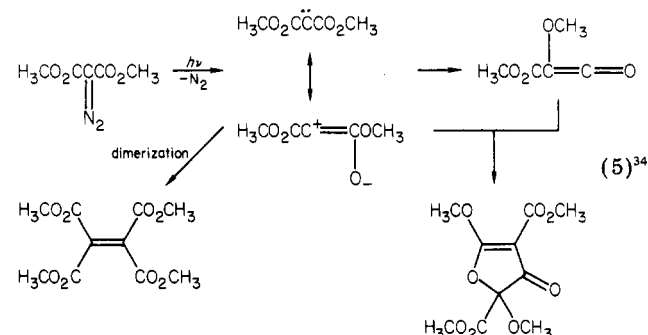
All the dipoles in Table I involve first-row elements. The inclusion of second-row elements such as sulfur or phosphorus would broaden the 1,3-dipole category considerably, but such species have received limited attention. A few reactions of novel sulfur containing 1,3-dipoles are shown in eq 6-9.

(6)[35]

(7)[36]

(8)[37]

(9)[38]

(32) W. J. Middleton, R. E. Heckert, E. L. Little, and C. G. Krespan, *J. Am. Chem. Soc.*, **80**, 2783 (1958).

(33) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).

(34) G. Maas, K. Eichhorn, R. Hoge, and M. Regitz, *Chem. Ber.*, **110**, 3272 (1977).

(35) R. M. Paton, F. M. Robertson, and J. F. Ross, *J. Chem. Soc., Chem. Commun.*, 714 (1980).

(36) M. J. Sanders, S. L. Dye, A. G. Miller, and J. R. Grunwell, *J. Org. Chem.*, **44**, 510 (1979).
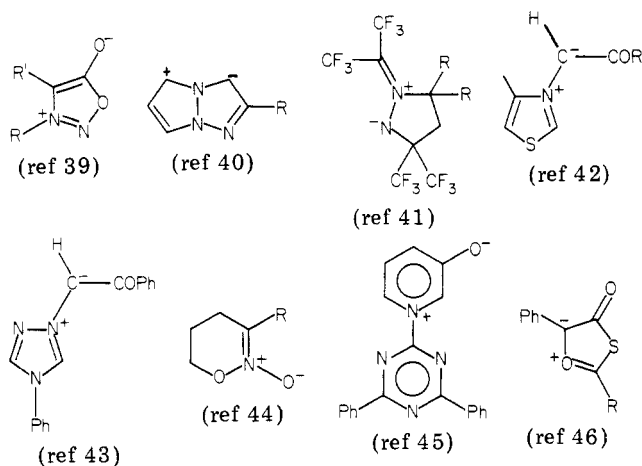
(37) A. G. Schultz and M. B. DeTar, *J. Am. Chem. Soc.*, **98**, 3564 (1976).

(38) E. Block, A. A. Bazzi, and L. K. Revelle, *J. Am. Chem. Soc.*, **102**, 2490 (1980).

<center>Chart II</center>

(ref 39) (ref 40)

(ref 41)

(ref 42)

(ref 43) (ref 44) (ref 45) (ref 46)

The incorporation of 1,3-dipoles into mesoionic five- or six-membered-ring heterocycles further extends the possibilities as shown in Chart II.[39-46]

There are a number of other possible 1,3-dipolar systems that form five-membered rings in the presence of dipolarophiles; however, the mechanisms for these species do not clearly involve six-electron cycloadditions. Some examples are given in eq 10–13.

C. The 2π-Electron Component. Options for the 2π-electron component in [4 + 2] cycloaddition reactions, referred to as the dienophile or dipolarophile, are also very diverse. Olefins, acetylenes (including benzynes[51]), and compounds with various hetero multiple bonds[52] including unusual systems with second-row elements such as Si,[53] P,[54] and S[55] can function in this capaciity (eq 14–16).

$(10)^{47}$

$(11)^{48}$

$(12)^{49}$

95%

$(13)^{50}$

68%

$(14)^{53c}$

68%

$(15)^{53d}$

$(16)^{54}$

Cumulated systems extend the set of dienophiles and dipolarophiles considerably. Numerous reviews are available.[56] Their reactivities vary widely (many are known more for their reactivity in [2 + 2] cycloadditions);
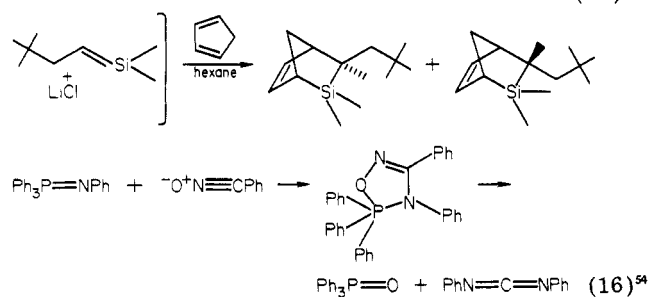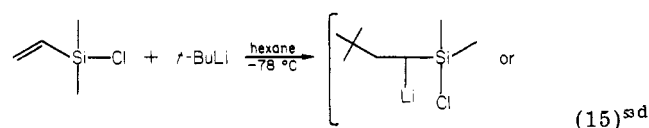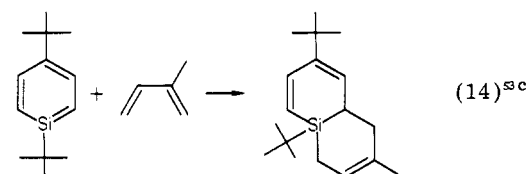
(39) H. Gotthardt and F. Reiter, *Chem. Ber.*, **112**, 1193 (1979).

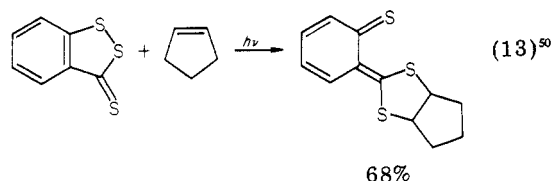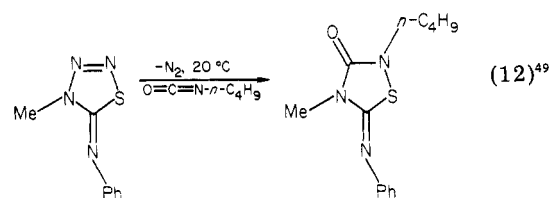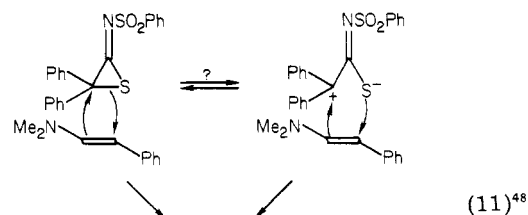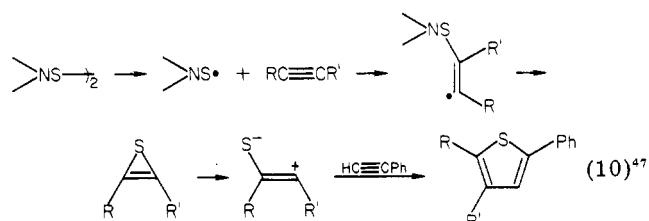(40) H. Koga, M. Hirobe, and T. Okamoto, *Tetrahedron Lett.*, 1291 (1978).

(41) K. Burger and F. Hein, *Liebigs Ann. Chem.*, 133 (1979).

(42) K. T. Potts, D. R. Choudhury, and T. R. Westby, *J. Org. Chem.*, **41**, 187 (1976).

(43) M. Petrovanu, C. Luchian, G. Surpăteanu, and V. Bărboiu, *Rev. Roum. Chim.*, **24**, 733 (1979).

(44) V. M. Shitkin, I. E. Chlenov, V. A. Tartakovskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 211 (1977).

(45) N. Dennis, A. R. Katritzky, G. J. Sabounji, and L. Turker, *J. Chem. Soc., Perkin Trans. 1*, 1930 (1977).

(46) H. Gotthardt, C. M. Weisshuhn, and K. Dörhöfer, *Chem. Ber.*, **111**, 3336 (1978).

(47) F. M. Benitez and J. R. Grunwell, *Tetrahedron Lett.*, 3413 (1977).

(48) G. L'abbé, J.-P. Dekerk, S. Toppet, J.-P. Declercq, G. Germain, and M. Van Meerssche, *Tetrahedron Lett.*, 1819 (1979).

(49) G. L'abbé and G. Verhelst, *Angew. Chem., Int. Ed. Engl.*, **15**, 489 (1976).

(50) R. Okazaki, K. Sunagawa, K.-T. Kang, and N. Inamoto, *Bull. Chem. Soc. Jpn.*, **52**, 496 (1979).

(51) R. Huisgen and R. Knoor, *Tetrahedron Lett.*, 1017 (1963).

(52) (a) Yu. A. Arbuzov, *Russ. Chem. Rev.*, **33**, 407 (1964); (b) S. Patai, Ed., "Chemistry of Functional Groups, Supplement A, Chemistry of Double-Bonded Functional Groups" Wiley, Chichester, England, 1977, Part 1; (c) S. B. Needleman and M. C. Chang Kuo, *Chem. Rev.*, **62**, 405 (1962).

(53) (a) Y. Nakadaira, T. Kobayashi, T. Otsuka, and H. Sakurai, *J. Am. Chem. Soc.*, **101**, 486 (1979); (b) H. Sakurai, Y. Nakadaira, T. Kobayashi, *ibid.*, **101**, 487 (1979); (c) G. Markl and P. Hofmeister, *Angew. Chem., Int. Ed. Engl.*, **18**, 789 (1979); (d) P. R. Jones, T. F. O. Lim, and R. A. Pierce, *J. Am. Chem. Soc.*, **102**, 4970 (1980).

(54) A. Schmidpeter and T. von Criegern, *Chem. Ber.*, **112**, 3472 (1979).

(55) (a) K. Friedrich and M. Zamkanei, *Chem. Ber.*, **112**, 1873 (1979); (b) W. Bludssus and R. Mews, *J. Chem. Soc., Chem. Commun.*, 35 (1979).

(56) (a) L. Ghosez and M. J. O'Donnell, *Org. Chem.* (*N.Y.*), **35**, 79–140 (1977); (b) W. Reichen, *Chem. Rev.*, **78**, 569 (1978); (c) H. Ulrich, "Cycloaddition Reactions of Heterocumulenes", Academic Press, New York, 1967.

some of the more stable heterocumulenes such as CO_2, SCO, and SO_2 do not take part in [4 + 2] cycloadditions. CS_2, although generally considered to be inert, has been trapped with the extremely reactive dipole RC^+=CRS^-.[46] The following list summarizes the cumulenes that have been observed to react in cycloadditions:

C=C=X   X = C, N, O, or S

N=C=X   X = N, O, or S

C=S=X   X = C or O

C=SO_2

N=S=X   X = N or O

A few examples of charged dienophiles have also appeared in the literature (eq 17 and 18). Heteroaromatics as 2π-

(17)[57a]

73%   26%

R = COOMe
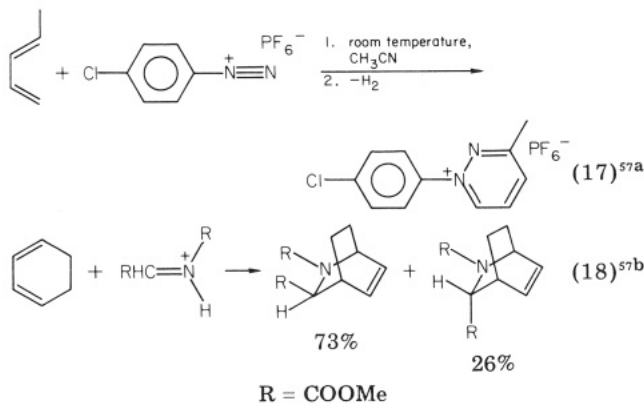
electron components in [4 + 2] cycloadditions are scarce. Although isolated examples of 1,3-dipolar cycloadditions may be found,[58] yields are generally low, mixtures are obtained, and the dipole must be generated in situ with the heteroaromatic as the solvent.

III. Theory of Concerted Cycloadditions

Frontier molecular orbital (FMO) theory has been applied with great success in the analyses of cycloadditions.[6,60,61] The theory, which was well developed by Fukui,[61] is also consistent with the orbital symmetry rules of Woodward and Hoffmann.[62,63] Briefly, the interaction energy between two conjugated molecules can be described by a second-order perturbation theory expression which contains terms for closed-shell repulsions, Coulombic interactions, and overlap stabilization.[59] For cycloadditions, the latter term is particularly significant and is dominated

by the interactions between the highest occupied and lowest unoccupied molecular orbitals (HOMO's and LUMO's) of the reactants. An allowed reaction can occur when constructive interactions exist between the HOMO of one component and the LUMO of the other as illustrated below for Diels–Alder and 1,3-dipolar cycloadditions.

Furthermore, the amount of stabilization is inversely proportional to the energy difference between the interacting FMO's: the smaller the gap, the more facile the reaction. So, the first step in applying the FMO approach in CAMEO is to determine the FMO energies of π systems. Computation of the resultant HOMO–LUMO gaps usually reveals one FMO pair to be dominant. Regiochemical predictions may be obtained subsequently by matching up the largest terminal MO coefficients for the controlling pair of FMO's.[6,64]

IV. Regiochemistry

Theoretical treatments of cycloadditions attempt ultimately to predict reactivity and the regiochemistry of the products. Studies on Diels–Alder reactions are so numerous that no attempt will be made to summarize them here.[6,8,65] 1,3-Dipolar cycloadditions, on the other hand, are not as well understood, so a brief overview of the current thinking about this reaction is in order.

The mechanism of 1,3-dipolar cycloadditions, in spite of numerous studies, remains controversial. On one side, Huisgen[66] and Houk[67] have argued consistently in favor of a concerted mechanism that features a "parallel planes" approach of the dipole and dipolarophile:

Several observations are consistent with this mechanism: the general stereospecificity of the reaction (cis or trans relationship of substituents on the dipolarophile is maintained), the insensitivity to solvent polarity, small activation enthalpies, and large negative activation entropies. Additionally, 1,3-dipolar cycloadditions are symmetry-allowed reactions, and time and time again frontier molecular orbital theory has been utilized successfully to rationalize the observed regioselectivities. On the other side, Firestone has argued strongly in favor of a diradical mechanism and has pointed out that low solvent dependence and large negative activation entropies are also consistent with this alternative.[68] He contended that Huisgen incorrectly calculated the energy of activation for a diradical mechanism and that his own recalculation gives

(57) (a) B. A. Carlson, W. A. Sheppard, and O. W. Webster, *J. Am. Chem. Soc.*, **97**, 5291 (1975); (b) G. R. Krow, C. Johnson, and M. Boyle, *Tetrahedron Lett.*, 1971 (1978).

(58) (a) P. Caramella, G. Cellerino, A. C. Coda, A. G. Invernizzi, P. Grünanger, K. N. Houk, and F. M. Albini, *J. Org. Chem.*, **41**, 3349 (1976); (b) B. Laude, M. Soufiaoui, and J. Arriau, *J. Heterocycl. Chem.*, **14**, 1183 (1977); (c) P. Caramella, G. Cellerino, P. Grunanger, F. M. Albini, and M. R. Re Cellerino, *Tetrahedron*, **34**, 3545 (1978).

(59) (a) L. Salem, *J. Am. Chem. Soc.*, **90**, 543 (1968); (b) *ibid.*, **90**, 553 (1968).

(60) (a) R. Sustmann and H. Trill, *Angew. Chem., Int. Ed. Engl.*, **11**, 838 (1972); (b) R. Sustmann and R. Schubert, *ibid.*, **11**, 840 (1972); (c) A. I. Konovalov and V. D. Kiselev, *J. Org. Chem., USSR (Engl. Transl.)*, **2**, 136 (1966); (d) A. I. Konovalov, V. D. Kiselev, and O. A. Vigdorovich, *ibid.*, **2**, 136 (1966).

(61) (a) K. Fukui and H. Fujimoto, *Bull. Chem. Soc. Jpn.*, **42**, 3399 (1969); (b) K. Fukui, *Fortschr. Chem. Forsch.*, **15**, 1–85 (1970); (c) K. Fukui, *Acc. Chem. Res.*, **4**, 57 (1971).

(62) R. Hoffmann and R. B. Woodward, *Acc. Chem. Res.*, **1**, 17 (1968).

(63) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie International, Deerfield Beach, FL, 1981.

(64) Ian Fleming, "Frontier Orbitals and Organic Chemical Reactions", Wiley, New York, 1976.

(65) O. Eisenstein, J. M. Lefour, Nguyên Trong Anh, and R. F. Hudson, *Tetrahedron*, **33**, 523 (1977).

(66) (a) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963); (b) R. Huisgen, *J. Org. Chem.*, **41**, 403 (1976).

(67) (a) K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.*, **95**, 7287 (1973); (b) K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *ibid.*, **95**, 7301 (1973).

(68) (a) R. A. Firestone, *J. Org. Chem.*, **33**, 2285 (1968); (b) R. A. Firestone, *J. Chem. Soc. A*, 1570 (1970); (c) R. A. Firestone, *J. Org. Chem.*, **37**, 2181 (1972); (d) R. A. Firestone, *Tetrahedron*, **33**, 3009 (1977).

a better fit for a diradical mechanism than a concerted one. Exceptions to 100% stereospecificity and examples of experimentally observed non-symmetry-allowed reactions are used as arguments against a concerted mechanism.

Nitrone cycloadditions illustrate how either mechanism can be used to rationalize the observed regiochemistries. Before 1973, nitrones were believed to add exclusively to yield the 5-substituted adduct, independent of the nature of substituent X (eq 19). Since then, exceptions have been

$$\text{(19)}$$
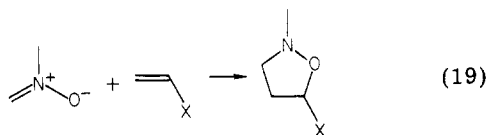
reported. Notably, C-phenyl N-methyl nitrone reacts with methyl propiolate to give a mixture of regioisomers[69] (eq 20). Diradical proponents rationalize the regiochemistry

$$\text{(20)}$$

42:58
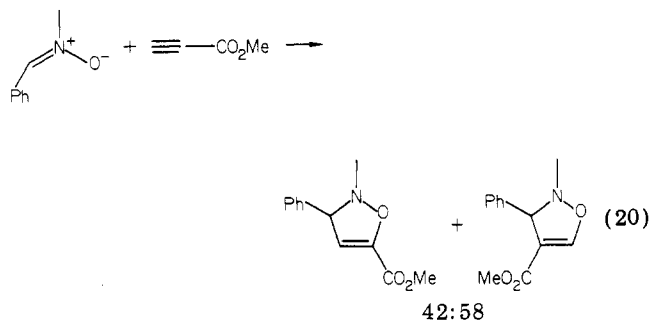
of most nitrone cycloadditions in terms of the more stable diradical **1**. The mixture of products obtained with methyl

1   **2**   **3**
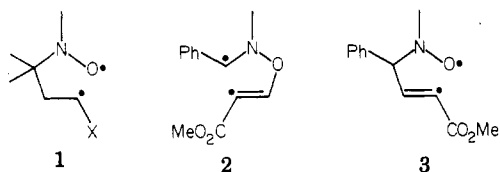
propiolate is explained as being due to greater π delocalization energy in **2** than in **3**.[68d] In FMO theory, the usual 5-substituted orientation is a result of LUMO control of the dipole with a gradual switch to HOMO control when the dipolarophile's LUMO energy is particularly low, as with methyl propiolate.

To deal with the regiochemistry of 1,3-dipolar cycloadditions, Sustmann classified dipolar cycloaddition reactions into three types: HO controlled (main interaction is between the HOMO of the dipole and the LUMO of the dipolarophile), HO–LU controlled (both interactions are significant), and LU controlled (LUMO dipole–HOMO dipolarophile).[60b] Houk has also shown how generalized frontier molecular orbitals within the framework of qualitative perturbation theory can be used as a key to understanding 1,3-dipolar regiochemistry, relative reactivity, and periselectivity.[67] Because of the success of FMO theory in this area, it has been chosen as the framework for the treatment of thermal cycloadditions in CAMEO.

V. Implementation

A. Program Flow. The relationship of subroutines in the pericyclic phase of CAMEO and a simplified flowchart of the program are shown in Figures 1 and 2. The pericyclic executive, PREXEC, oversees the processing in this mechanistic module. CYCLST finds all $2n$ electron sets (n
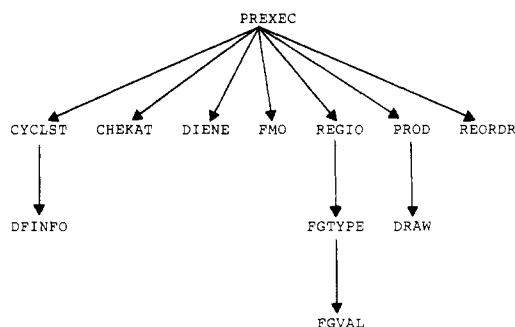
(69) K. N. Houk, *Top. Curr. Chem.*, **79**, 1 (1979).

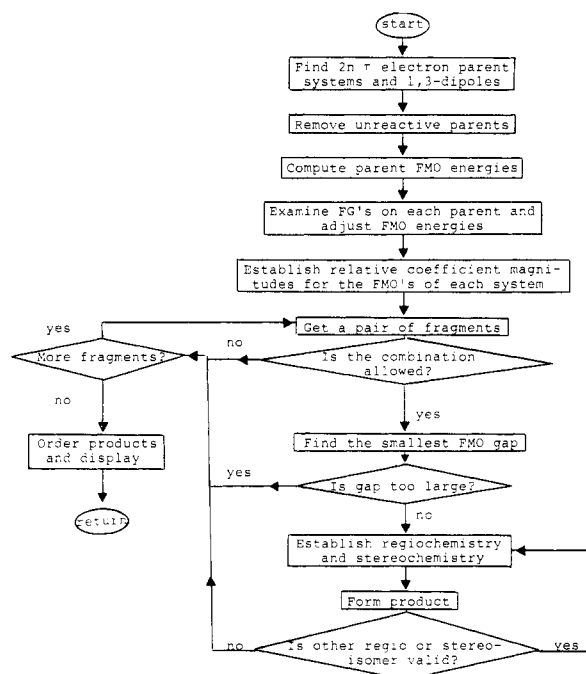**Figure 1.** Subroutines in the pericyclic module.

Figure 2. Simplified flowchart for six-electron cycloadditions.

> 1) and 1,3-dipoles; DFINFO finds all suitable dienophiles, and CHEKAT and DIENE then weed out unsuitable dienes. The parent frontier orbital energies are estimated by FMO followed by refinement of these energies by REGIO, which takes into account the functionality attached to each parent system. The necessary functional group perception is carried out by FGTYPE and FGVAL. Once all this information is tabulated, PREXEC decides which reagent combinations will yield allowed products. For each possible product, PROD is called to form the product with the correct regio- and stereochemistry. DRAW reconstructs the products more aesthetically, and REORDR serves to display them on the graphics terminal from most to least favorable. The different parts of the procedure will now be described in more detail.

B. Perception of Reaction Components. In a program designed to be as general and as predictive as possible, the selection of suitable reaction components (in this particular case dienes, 1,3-dipoles, and 2π-electron components) is best achieved by initially perceiving all possible candidates and then "weeding-out" unsuitable ones. Figure 1 outlines the general flow of the pericyclic phase of CAMEO and illustrates in what order each of the main subroutines is called. The routine CYCLST is responsible for the identification of all reaction components, including 10π-, 8π-, and 6π-electron systems, dienes, and 1,3-dipoles.

1. Dienes. For a 1,3-diene to be reactive in a Diels–Alder reaction it must be able to attain the s-cis conformation.[7] Subroutine DIENE eliminates all 1,3-dienes that
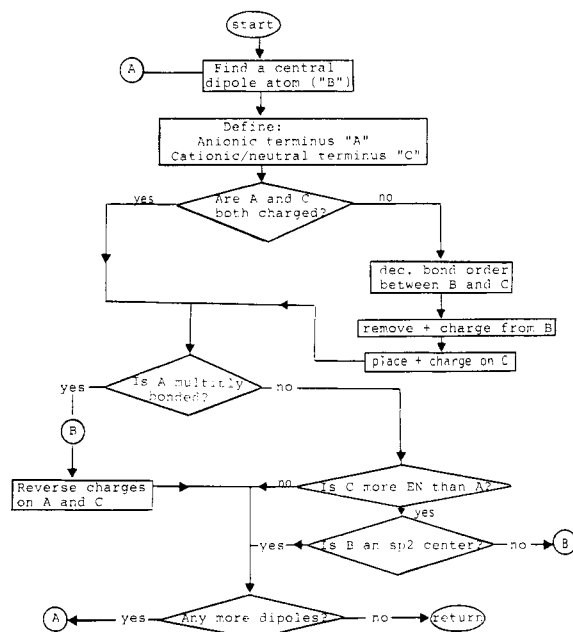
Figure 3. Flowchart for dipole resonance.

**Table II. Vertical Ionization Potentials of Parent Systems Relative to 1-Substituted Parents (eV)**[a]

| | | ΔIP | | | |
parent	IP (parent)	X = Me	X = Et	X = Br	X = OMe
$H_2C=CH_2$	10.5	−0.5	−0.8	−0.7	−1.4
$HC\equiv CH$	11.4	−1.0	−1.2	−1.2	
$H_2C=O$	14.5	−1.1	−1.8		−2.8
$HC\equiv N$	13.6	−1.4	−1.5	−1.7	
$H_2C=CHCH=CH_2$	9.0	−0.2			−0.8

[a] The IP's for hetero parents are those corresponding to the highest occupied π orbital. Data are from ref 82.

have geometrical restraints which prevent them from achieving the *s*-cis form. These include dienes in which an exocyclic double bond is conjugated to a double bond in the ring as in **4** and **5**, 1,3-dienes in 8–11-membered

4   **5**
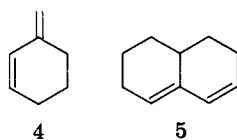
rings, acyclic bulky cis-1-substituted dienes, and acyclic bulky 2,3-disubstituted dienes. DIENE allows *s*-cis-1-substituted dienes only if the substituent is a primary atom, a triply bonded functional group such as cyano, a nitrogen, oxygen, or sulfur with a single primary atom attached (e.g., a methyl group), or if the substituent is part of the ring containing the diene. Additionally, dienes are allowed if the cis-1-substituent is part of a ring system ($\leq$6 membered) as in **6** and **7**. Acyclic cis,cis-1,4-disubstituted

6   **7**
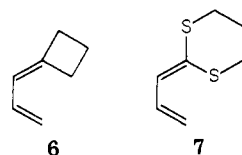
dienes are not presently allowed. If the acyclic diene is 2,3-disubstituted and both substituents are quaternary centers or both are halogens other than fluorine, it is removed from the set of allowed dienes. Some of the above rules are illustrated in reactions 21–25.

$(21)^{70}$

$(22)^{71}$

50%

formation of tars   (23)

$(24)^{72}$

$(25)^{73}$
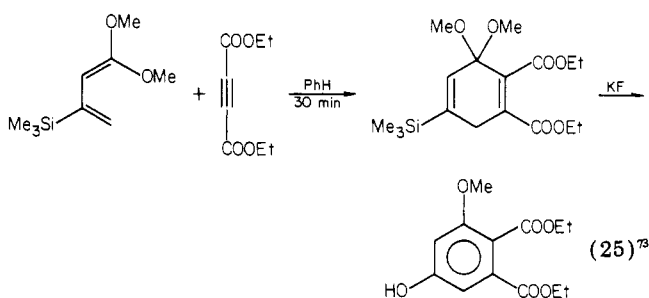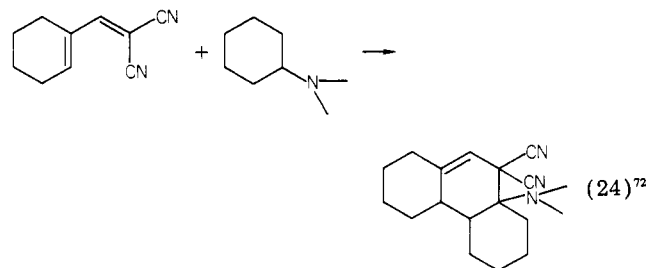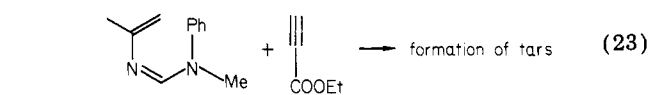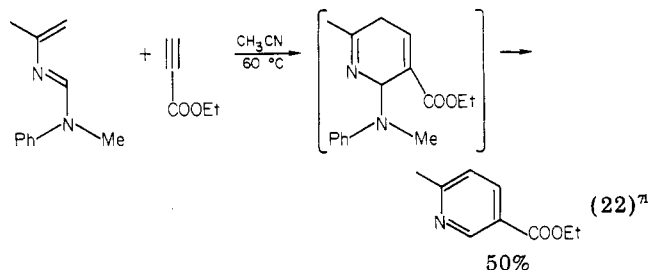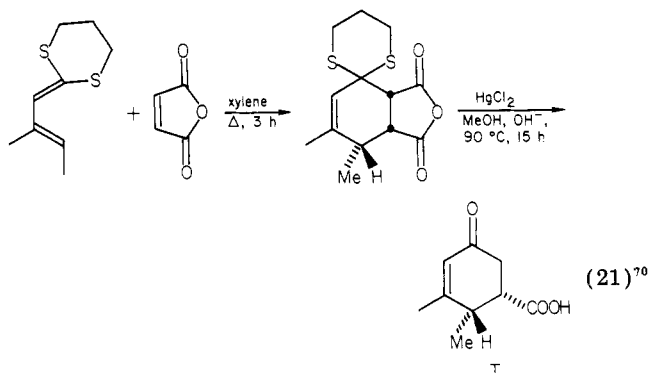
The set of viable dienes is further restricted by the heteroatoms that comprise the diene itself. The subroutine CHEKAT eliminates unsuitable dienes in this category. Conjugated nitroso and azo compounds appear to be active dienes only if the conjugated bond is a polarized multiple bond (note also that 1,2-cycloadditions are often competitive).[9] Similarly, a conjugated cumulene is an active

(26)
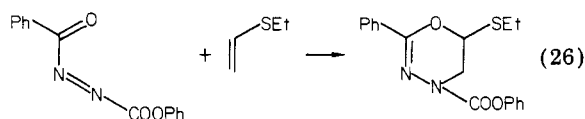
diene only when the cumulene terminus is an oxygen or sulfur atom and when it is conjugated to a polarized

(70) F. A. Carey and A. S. Court, *J. Org. Chem.*, **37**, 4474 (1972).
(71) F. Sainte, B. Serckx-Poncin, A.-M. Hesbain-Frisque, and L. Ghosez, *J. Am. Chem. Soc.*, **104**, 1428 (1982).
(72) R. Gompper, *Angew. Chem., Int. Ed. Engl.*, **8**, 312 (1969).
(73) S. Danishefsky, R. K. Singh, and R. B. Gammill, *J. Org. Chem.*, **43**, 379 (1978).

multiple bond, another polar cumulene, or an aromatic ring (eq 27–29).

(27)[56c]

(28)[9,56c]

(29)[56c]
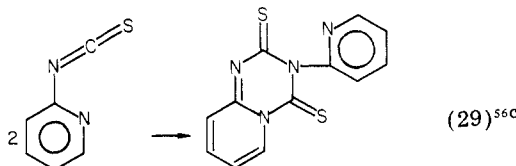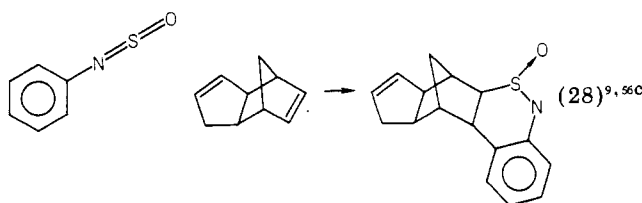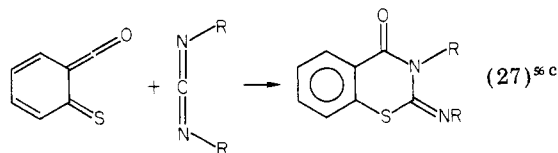
Aromatic dienes also examined by CHEKAT. Pyrroles and thiophenes are not allowed unless they exist in an extended aromatic system like **8**. Dienes in six-membered aromatic

8
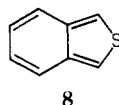
rings are considered only if the ring is fused to two other aromatic rings in the manner of the central ring in anthracene. For example, the starred rings below contain active dienes:
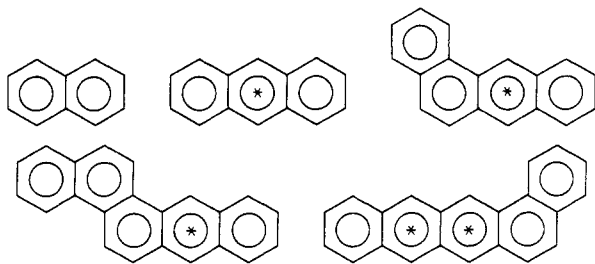
It should be noted that vinyl cyclopropanes and nitro compounds like **9** may also function as dienes (eq 30).

(30)[74]

9
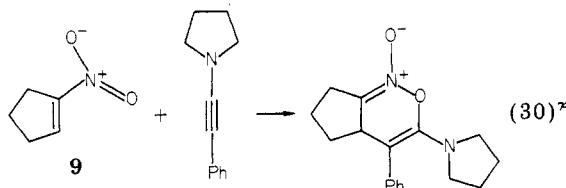
2. 1,3-Dipoles. 1,3-Dipoles require less screening than dienes. The major complication in their recognition is that a dipole can be represented in a variety of resonance forms:

The algorithm for the perception of 1,3-dipoles must be able to recognize the dipole in any resonance form and then modify it into the "appropriate" form. For the present

purposes, this form has the negative charge on the terminal atom with the larger coefficient in the HOMO and the positive charge on the terminal atom with the largest coefficient in the LUMO, e.g., the last structure above. Figure 3 illu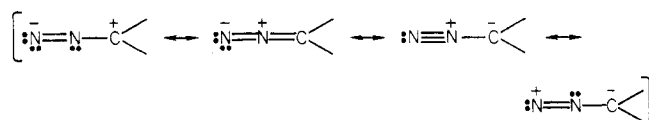strates how, in a concise fashion, any 1,3-dipole can be resonated into its "appropriate" form. This is convenient for eventual product formation; all that is left to do is to remove the charges from the terminal positions and form the bonds to the dipolarophile.

Recognition of 1,3-dipoles begins by identification of possible central atoms. Such atoms have a positively and a negatively charged neighbor or they are positively charged atoms that are adjacent to a negatively charged atom. The 1,3-dipole must also have a conjugated π system with 4π electrons. A central atom that is doubly bonded to an atom that is not part of the dipole as in **10**[49] or one

10   **11**
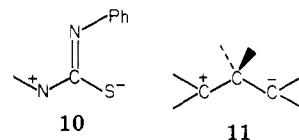
that is tetrasubstituted as in **11** is not allowed. Additionally, nitro groups are excluded as 1,3-dipoles since they are known to be unreactive in dipolar cycloadditions.[33]

It should also be noted that unless complex mesoionic dipoles are entered in the resonance form indicated in **12** or **13**, they are currently not perceived as 1,3-dipoles as they require somewhat complex manipulations.

12

13
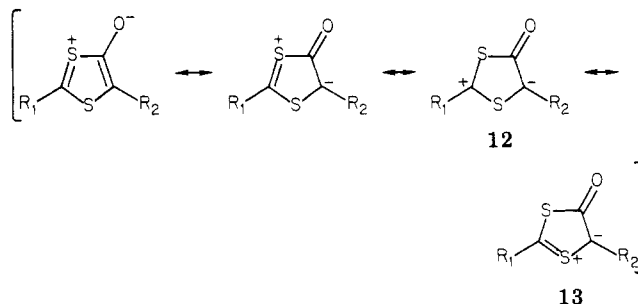
If the unsubstituted dipole is symmetrical, the substituent pattern will dictate the "appropriate" resonance form. This aspect is dealt with further in the program once functional groups on the parents have been perceived.

major resonance
contributor
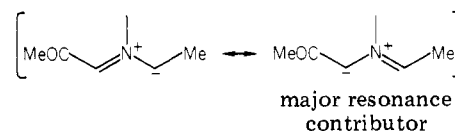
3. 2π-Electron Components. Initially, all multiple bonds are perceived as potential dienophiles/dipolarophiles. The screening process begins by elimination of all bonds in six-membered aromatic rings (except for the triple bond of benzynes). Double bonds in five-membered aromatic rings do not act as dienophiles, but they are known to react as dipolarophiles, e.g., furans,[58a] benzofurans,[75] thiophenes,[58c] and *N*-methylindoles[58b,76] (eq 31). Next,

(31)[58a]

99:1

(74) M. L. M. Pennings and D. N. Reinhoudt, *Tetrahedron Lett.*, 1781 (1980).
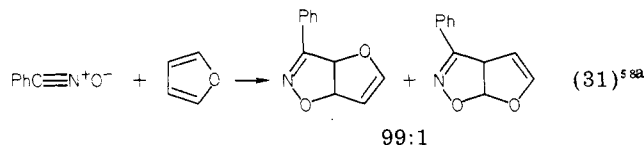
(75) P. Caramella, G. Cellerino, K. N. Houk, F. M. Alvini, and C. Santiago, *J. Org. Chem.*, **43**, 3006 (1978).

(76) M. Ruccia, N. Vivona, G. Cusmano, M. L. Marino, and F. Piozzi, *Tetrahedron*, **29**, 3159 (1973).

cumulenes are examined. Those with the central atom bound to two oxygens (CO_2 and SO_2) or an oxygen and a sulfur (SCO) are inert and are eliminated. If a C=S bond is part of the cumulene, it usually acts as the dienophile component, otherwise the reactive bond is the bond that includes the least electronegative cumulene terminus. If symmetrical, both bonds are considered. The examples in eq 32–35 illustrate some reactions with cumulenes as the 2π-electron component.

(32)[9]

(33)[77]

(34)[78]

(35)[79]
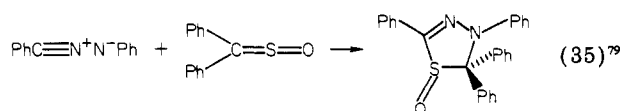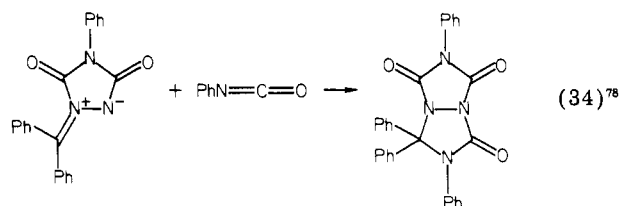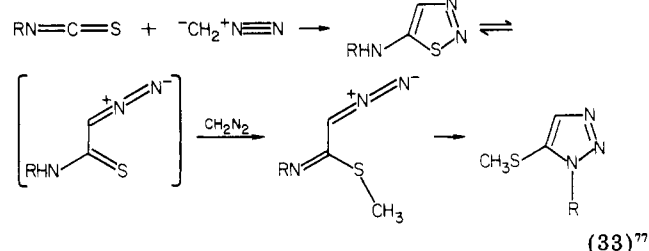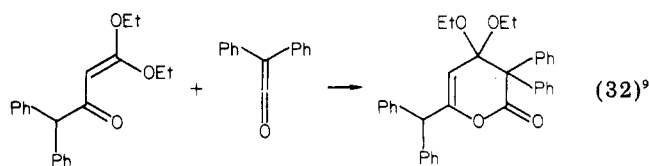
C. Estimation of Frontier Molecular Orbital Energies. 1. Overview.

The estimation of frontier orbital energies is a critical aspect of the pericyclic phase of CAMEO. It is important to realize that because CAMEO must predict products rapidly for even complex systems, it is not desirable to perform quantum mechanical calculations on the reactant molecules. Rather, it is necessary to develop an algorithm based upon reliable data that will yield energies that are accurate enough to allow correct prediction of the likelihood and regiochemistry of cycloadditions. Furthermore, in view of the enormous variety of possible combinations of reactants, the algorithm must be applicable to virtually any diene, 1,3-dipole, or 2π-electron component.

The initial task is to develop an algorithm that predicts the FMO energies of unsubstituted parents (section V.C.2). Next, the effect of monosubstitution on the parent systems must be treated (section V.C.3). Then, polysubstituted systems are considered in section V.C.5. If ionization potentials (IP's) of monosubstituted parents are examined, it is evident that the change in IP produced by a substituent depends upon the nature of the parent (see Table II). In other words, each parent has its own inherent sensitivity toward attached functionality. If this can be

determined and an index can be found which reflects the donating or withdrawing ability of functional groups, then, together with the parent FMO energies, the FMO energies of the substituted systems may be estimated.

2. FMO Energies of Parent Systems.

It is well-known that as heteroatoms replace carbon in a π system, the FMO's decrease in energy. An attempt has been made to quantify these effects by using ethylene as a standard for 2π-electron systems, 1,3-butadiene for 4π-electron systems, and a theoretical all carbon 1,3-dipole as a reference point for 1,3-dipoles.

The change in IP, which can be equated with the change in energy of the HOMO produced by substituting heteroatoms for carbon atoms is known experimentally for many parent systems. LUMO energies, on the other hand, present a number of problems. First of all, the extension of Koopmans' theorem to equate electron affinities with LUMO energies has been shown to be inaccurate.[80] In addition, reasonable LUMO energies are inherently difficult to calculate theoretically; the predicted energies are usually too high. To compound the problem, accurate electron affinities (EA's) are difficult to obtain experimentally and substantial variation is found in reported values.[80b]

The following approach was taken: for parent dienes and dienophiles with known IP's, ab initio calculations were carried out with the STO-3G and 3-21G basis sets by using fully optimized geometries reported previously.[81] In Table III, the experimental IP's[82] and the theoretical HOMO energies are recorded for each of these compounds. Likewise, Table IV lists known EA's[83] along with theoretical LUMO energies. In each table, the energy change relative to the corresponding carbon parent was computed. The experimental IP values and the HOMO energies obtained via 3-21G calculations agree most closely. In Table IV, although the theoretical LUMO energies are much higher than the experimental EA values, the energy changes relative to the corresponding carbon parent appear to be more reliable. Thus it was decided to utilize the *relative* LUMO energies obtained via 3-21G calculations in the development of the algorithm for the prediction of parent FMO energies. Note, however, that the well-known EA values[83] for ethylene and butadiene will be used as reference energy values.

The ab initio results for dienophiles and diene FMO energies (in eV's) were then fit to the following simple expressions, where N_X is the number of atoms of type X and N_{tb} is the number of triple bonds in the parent. The labels c and t refer to central and terminal atoms in the dienes:

for dienophiles

$$E_{HOMO} = -N_{tb} - 4N_O - 2N_N - N_S - 10.5 \quad (36)$$

$$E_{LUMO} = N_{tb} - N_O - 0.5N_N - 4N_S + 1.8 \quad (37)$$

for dienes

$$E_{HOMO} = -2N_O - N_{Nt} - 0.2N_{Nc} - 0.5N_{St} - N_{Sc} - 9.0 \quad (38)$$

$$E_{LUMO} = -N_O - 0.5N_N - 2N_{St} + 1.5N_{Sc} + 0.6 \quad (39)$$

(77) S. Hoff and A. P. Blok, *Recl. Trav. Chim. Pays-Bas*, **93**, 317 (1974).

(78) K. Ramakrishnan, J. B. Fulton, and J. Warkentin, *Tetrahedron*, **32**, 2685 (1976).

(79) B. F. Bonini, G. Maccagnani, G. Mazzanti, L. Thijs, G. E. Veenstra, and B. Zwanenburg, *J. Chem. Soc., Perkin Trans. 1*, 1218 (1978).

(80) (a) T. A. Koopmans, *Physica (Amsterdam)*, 1, 104 (1933); (b) J. M. Younkin, L. J. Smith, and R. N. Compton, *Theor. Chim. Acta*, 41, 157 (1976).

(81) R. A. Whiteside, M. J. Frisch, J. S. Binkley, D. J. DeFrees, H. B. Schlegel, K. Raghavachari, and J. A. Pople, "Carnegie-Mellon Quantum Chemistry Archive", 2nd ed., 1981.

(82) C. N. Rao, P. K. Basu, and M. S. Hegde, *Appl. Spectrosc. Rev.*, 15, 1–193 (1979).

(83) K. D. Jordan and P. D. Burrow, *Acc. Chem. Res.*, 11, 341 (1978).

Table III. Experimental IP's and Theoretical HOMO Energies (eV)[a]

system	−IP	3-21G	STO-3G	−IP + 10.5	3-21G + 10.3	STO-3G + 9.1
$H_2C=CH_2$	−10.5	−10.3	−9.1	0.0	0.0	0.0
$HC≡CH$	−11.4	−11.2	−9.9	−0.9	−0.9	−0.8
$H_2C=S$	−11.8	−11.3	−8.7	−1.3	−1.0	−0.4
$H_2C=NH$	−12.5	−12.2	−10.6	−2.0	−1.9	−1.5
$HC≡N$	−13.6	−13.6	−12.0	−3.1	−3.3	−2.9
$HN=NH$	−14.4	−14.1	−12.1	−3.9	−3.8	−3.0
$H_2C=O$	−14.5	−14.3	−12.1	−4.0	−4.0	−3.0
$HN=O$	−17.7	−15.8	−13.3	−7.2	−5.5	−4.2

system	−IP	3-21G	STO-3G	−IP + 9.0	3-21G + 8.9	STO-3G + 7.5
$H_2C=CHCH=CH_2$	−9.2	−8.9	−7.5	0.0	0.0	0.0
$H_2C=CHN=CH_2$[b]		−9.2			−0.3	
$H_2C=CHCH=S$[b]		−9.4			−0.5	
$H_2C=CHCH=NH$[b]		−9.9			−1.0	
$H_2C=CHCH=O$	−10.9	−10.8	−9.0	−1.9	−1.9	−1.5
$H_2C=CHN=O$[b]		−11.0			−2.1	
$H_2C=CHHS=O$[b]		−12.1			−3.2	
$O=CHCH=O$	−13.9	−14.1	−11.3	−4.9	−5.2	−3.8

[a] IP's and HOMO energies refer to the highest occupied π orbital. Experimental data from ref 82. [b] In these cases, standard geometries rather than fully optimized geometries were used.

Table IV. Experimental Electron Affinities and Theoretical LUMO Energies (eV)[a]

system	−EA	3-21G	STO-3G	−EA − 1.8	3-21G − 5.1	STO-3G − 8.9
$H_2C=CH_2$	1.8	5.1	8.9	0.0	0.0	0.0
$HC≡CH$	2.6	6.1	11.2	0.8	1.0	2.3
$H_2C=S$		1.3	5.9		−3.8	−3.0
$H_2C=NH$		4.8	8.0		−0.3	−0.9
$HC≡N$		5.8	9.5		0.7	0.6
$HN=NH$		4.0	6.5		−1.1	−2.4
$H_2C=O$	0.9	4.0	7.7	−0.9	−1.1	−1.2
$HN=O$		2.7	5.9		−2.3	−3.0

system	−EA	3-21G	STO-3G	−EA − 0.6	3-21G − 3.4	STO-3G − 6.9
$H_2C=CHCH=CH_2$	0.6	3.4	6.9	0.0	0.0	0.0
$H_2C=CHN=CH_2$[b]		2.9			−0.5	
$H_2C=CHCH=S$[b]		0.7			−2.7	
$H_2C=CHCH=NH$[b]		2.9			−0.5	
$H_2C=CHCH=O$	<0.0	2.6	6.2	<−0.6	−0.8	−0.7
$H_2C=CHN=O$		1.6			−1.8	
$H_2C=CHSH=O$[b]		4.0			0.6	
$O=CHCH=O$		1.5	5.4		−1.9	−1.5

[a] Experimental data from ref 83. [b] In these cases, standard geometries rather than fully optimized geometries were used.

Table V. Comparison of Experimental IP's and Theoretical LUMO Energies with Estimated FMO Energies (eV)[a]

system	−IP(exptl)	HOMO algorithm	LUMO (3-21G) − 3.3	LUMO algorithm
$H_2C=CH_2$	−10.5	−10.5	1.8	1.8
$HC≡CH$	−11.4	−11.5	2.9	2.8
$H_2C=S$	−11.8	−11.5	−2.4	−2.2
$H_2C=NH$	−12.5	−12.5	1.5	1.3
$HC≡N$	−13.6	−13.5	2.5	2.3
$HN=NH$	−14.4	−14.5	0.7	0.8
$H_2C=O$	−14.5	−14.5	0.7	0.8
$HN=O$	−17.7	−16.5	−0.8	0.3

system	−IP(exptl)	HOMO algorithm	LUMO (3-21G) − 2.8	LUMO algorithm
$H_2C=CHCH=CH_2$	−9.0	−9.0	0.6	0.6
$H_2C=CHN=CH_2$		−9.2	0.1	0.1
$H_2C=CHCH=S$		−9.5	−2.1	−1.4
$H_2C=CHCH=NH$		−10.0	0.1	0.1
$H_2C=CHCH=O$	−10.9	−11.0	−0.2	−0.4
$H_2C=CHN=O$		−11.2	−1.2	−0.9
$H_2C=CHSH=O$		−12.0	1.2	1.1
$O=CHCH=O$	−13.9	−13.0	−1.3	−1.4

[a] IP's and HOMO energies refer to the highest occupied π orbital.

Table V compares the experimental IP values and the theoretical LUMO energies with the HOMO and LUMO energies calculated from the above algorithms. Note that the theoretical LUMO energies for 2π systems are corrected by −3.3 eV so that the value for ethylene will match its EA value. Likewise, theoretical LUMO energies for 4π

Chart III

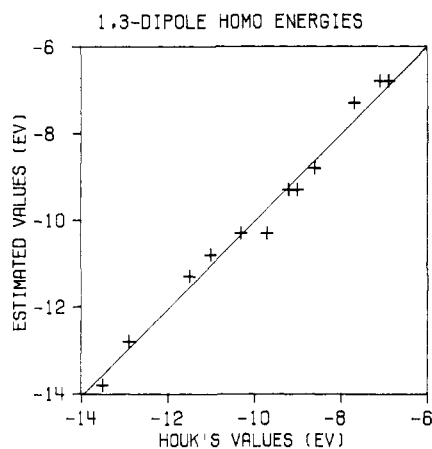| parent	slope (γ)	Y intercept	coefficient of determination	standard deviation of Y
ethylene	0.05	−10.4	0.91	0.20
acetylene	0.06	−11.1	0.89	0.15
carbonyl	0.11	−14.0	0.83	0.57
carbonyl without bulky alkyl	0.11	−14.4	0.98	0.22
nitrile	0.08	−13.1	0.81	0.50
butadiene	0.03	−9.1	0.92	0.14

Figure 4. Comparison of literature and estimated HOMO energies for 1,3-dipoles.

systems are corrected by −2.8 eV so that the value for butadiene will match its EA value.

Up to this point, nothing has been said about parent 1,3-dipole FMO energies. Because of the general absence of experimental data, Houk estimated the FMO energies by using experimental data wherever possible (spectroscopic data, reduction potentials, charge-transfer energies, and UV spectral data) and theoretical calculations only to fill in gaps.[67a] The LUMO of 1,3-dipoles is often an in-plane π^* orbital, while the NLUMO is a π^* orbital that is perpendicular to the plane of the molecule. It is the latter orbital that is relevant for the dipolar cycloadditions.

A similar algorithm has been developed for 1,3-dipoles, where t and c stand for terminal and central atoms in the 1,3-dipole, respectively. For the E_{HOMO}, N_{Nc} does not pertain to the azomethinium betaines:

$$E_{HOMO} = -3.5N_{Ot} - 2.0N_{Nt} - 0.5N_{Nc} + 0.5N_{Sc} - 6.8 \quad (40)$$

$$E_{LUMO} = \\ -1.4N_{Ot} - 0.5N_{Nt} + 4.4N_{Nc} + 4.4N_{Sc} + 3.9N_{Oc} - 3.4 \quad (41)$$

The energies reported by Houk and those calculated by the above algorithm are contrasted in Table VI and shown graphically in Figures 4 and 5. The correlation coefficient is better for HOMO energies (0.959) than for LUMO energies (0.797). This is not surprising since the former are known more accurately.

3. Monosubstituted Parent Systems.

It has been noted that each parent appears to have a characteristic sensitivity toward functionality. Ideally, a number, $\tau(Y)$, could be found for each functional group (FG), Y corresponding to its donating or withdrawing ability such that eq 42 would yield a reasonable estimate of the HOMO

$$E_{HOMO} = \gamma(P)\tau(Y) + E_{HOMO}(P) \quad (42)$$

energy of the substituted system (PY) where $\gamma(P)$ is a measure of the sensitivity of the parent P.

To test this idea, it is necessary to obtain some initial τ values for functional groups in order to test them for a variety of parent systems. Since IP data are most available
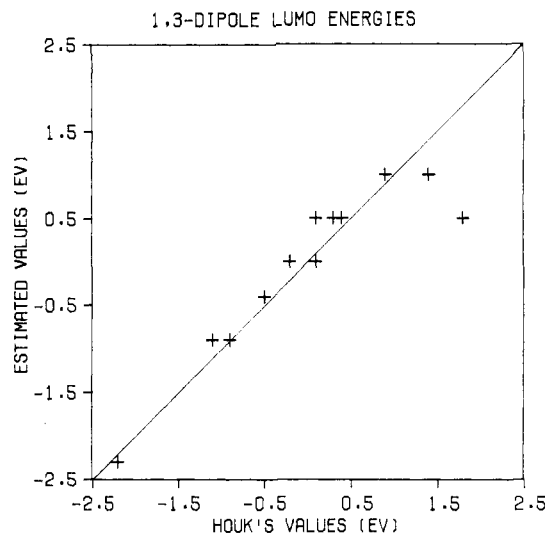

Figure 5. Comparison of literature and estimated LUMO energies for 1,3-dipoles.

1. −H	11. −NHMe	21. −SMe	31. −CHCl$_2$
2. −Me	12. −N(Me)$_2$	22. −F	32. −CCl$_3$
3. −Et	13. −OH	23. −Cl	33. −CH$_2$Br
4. −nPr	14. −OMe	24. −Br	34. −CH=CH$_2$
5. −iPr	15. −OEt	25. −I	35. −CH=CHMe
6. −nBu	16. −OiPr	26. −CH$_2$NH$_2$	36. −CH=C(Me)$_2$
7. −tBu	17. −OnBu	27. −CH$_2$N(Me)$_2$	37. −Ph
8. −nC$_5$H$_{11}$	18. −OtBu	28. −CH$_2$OH	38. −CN
9. −iC$_5$H$_{11}$	19. −SiH$_3$	29. −CH$_2$F	39. −CHO
10. −NH$_2$	20. −Si(Me)$_3$	30. −CH$_2$Cl	40. −CO$_2$Me
			41. −OAc

Figure 6. Identification numbers for FG's in Figures 7–12.

for substituted ethylenes,[82] this parent was chosen as a starting point. Hydrogens are assigned a τ of 0 such that electron-donating and -withdrawing FG's have positive and negative τ's, respectively. A scale was chosen such that a change in IP of 0.5 eV is equivalent to a change in τ of 10 units. If the IP for $H_2C=CHY$ is known, the τ value for Y is defined. Unfortunately, there are many FG's for which there are no IP data available. Since CAMEO must be able to handle any FG, it was necessary to develop an algorithm that will predict the "known" τ values as closely as possible and give reasonable estimates for those that are not known. These new τ values are determined in subroutines FGTYPE and FGVAL and are discussed further in section V.C.4. The estimated τ values can then be plotted against the IP's of a variety of monosubstituted parents.[82] Figures 7-12 show plots for ethylenes, acetylenes, carbonyl compounds (Figures 9 and 10), nitriles, and butadienes, respectively. In all cases, it is the energy of the highest occupied π MO that is plotted. The data points on each plot are labeled with numbers that identify the FG's. Figure 6 matches the numbers to the corresponding FG's. A linear least-squares program finds the slopes, y intercepts, coefficients of determination, and the standard
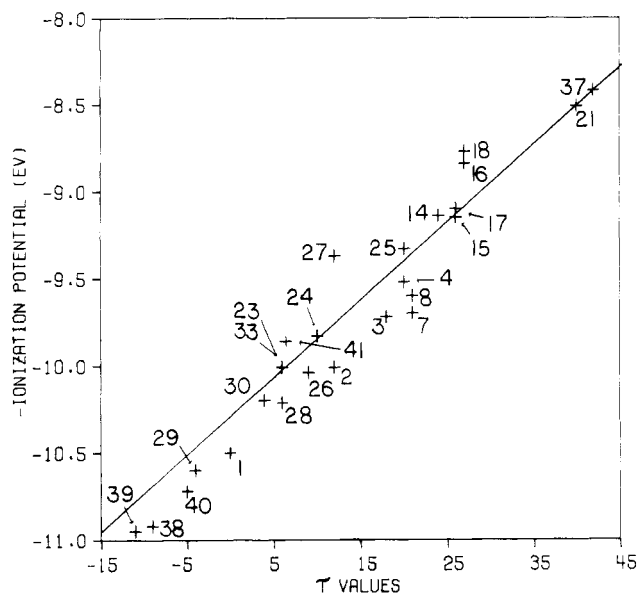
Figure 7. IP's of monosubstituted ethylenes vs. τ values.

Figure 10. IP's of monosubstituted carbonyls (excluding bulky alkyl groups) vs. τ values.

Figure 8. IP's of monosubstituted acetylenes vs. τ values.
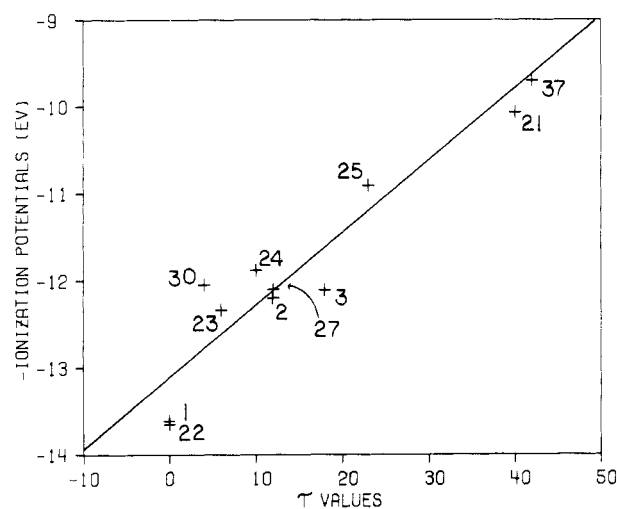
Figure 11. IP's of monosubstituted nitriles vs. τ values.
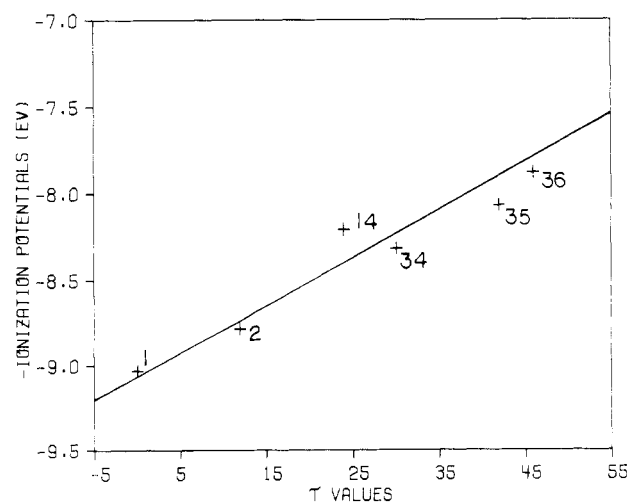
Figure 12. IP's of 1-substituted butadienes vs. τ values.

Figure 9. IP's of monosubstituted carbonyls (including bulky alkyl groups) vs. τ values.

deviation of Y about the best fit line. These are listed in Chart III. Most of the error in the first carbonyl plot (Figure 9) originates from the fact that bulky alkyl groups have larger effects on the IP's of carbonyls than on those of ethylene. Removing alkyl substituents except methyl,

Table VI. Comparison of Literature FMO Energies and Estimated FMO Energies for 1,3-Dipoles (eV)[a]

	π-HOMO		π-NLUMO	
	literature	algorithm	literature	algorithm
Nitrilium Betaines				
HC≡N⁺CH₂⁻	−7.7	−7.3	0.9	1.0
HC≡N⁺NH⁻	−9.2	−9.3	0.1	0.5
HC≡N⁺O⁻	−11.0	−10.8	−0.5	−0.4
Diazonium Betaines				
N≡N⁺CH₂⁻	−9.0	−9.3	1.8	0.5
N≡N⁺NH⁻	−11.5	−11.3	0.1	0.0
N≡N⁺O⁻	−12.9	−12.8	−1.1	−0.9
Azomethinium Betaines				
H₂C=NH⁺CH₂⁻	−6.9	−6.8	1.4	1.0
H₂C=NH⁺NH⁻	−8.6	−8.8	0.3	0.5
H₂C=NH⁺O⁻	−9.7	−10.3	−0.5	−0.4
Oxygenated Dipoles				
H₂C=O⁺CH⁻	−7.1	−6.8	0.4	0.5
H₂C=O⁺NH⁻	−8.6	−8.8	−0.2	0.0
H₂C=O⁺O⁻	−10.3	−10.3	−0.9	−0.9
O=O⁺O⁻	−13.5	−13.8	−2.2[b]	−2.3[b]

[a] Literature values from ref 67a. [b] For ozone, the LUMO is the correct π* MO.

ethyl, and isopropyl improves the fit as shown in Figure 10. The slopes or γ values for 2π-electron parents can then be represented by eq 43.[84]

$$\gamma = 0.01N_{tb} + 0.06N_O + 0.03N_N + 0.03N_S + 0.05 \quad (43)$$

IP data for monosubstituted heterodienes are scarce but appear to deviate only slightly from butadiene's γ of 0.03. Unless future experimental data dictate otherwise, diene γ values will be set at 0.03. Note, however, that FG's attached to the inner atoms of 1,3-dienes affect FMO energies less due to the smaller MO coefficients at these positions. This point is accommodated as discussed in section V.C.6.

Effects of substitution on 1,3-dipoles have not yet been addressed. The lack of experimental and theoretical FMO energy data in this case is especially severe. The problem has been approached by first assuming that the effects of functional groups on the FMO energies should be qualitatively similar to their effects on dienes and 2π-electron systems. Then it may be noted that from perturbation theory substituent effects are proportional to the magnitude of the coefficient squared in the molecular orbital in question at the site of attachment. If the MO coefficients for ethylene and for 1,3-dipoles are known as well as the orbital energy change produced on ethylene by a substituent, the substituent effect on the 1,3-dipoles can be estimated:[67a]

$$\Delta E_{dipole} = (C^2_{dipole}/C^2_{ethene})\Delta E_{ethene} \quad (44)$$

Table VII lists the common 1,3-dipole parents with their FMO coefficients as determined from CNDO/2 calculations by Houk et al.[67a] Two trends are apparent:

(1) In the HOMO's, the "anionic" termini have the larger coefficients in absolute value, except for symmetrical dipoles.

(2) In the NLUMO's, the "neutral" termini have the larger coefficients, except for symmetrical dipoles and diazomethane, which have equal coefficients.

Since the variation in the coefficients for a given site is not large in most cases, a further simplification has been made by using average values for the coefficients. The average magnitude for each position as well as the

Table VII. CNDO/2 FMO Coefficients for 1,3-Dipoles[a]

	π-HOMO			π-NLUMO		
	a	b	c	a	b	c
Nitrilium Betaines						
HC≡N⁺CH₂⁻	−0.64	0.07	0.76	−0.52	0.70	−0.50
HC≡N⁺NH⁻	−0.59	−0.05	0.80	−0.60	0.70	−0.40
HC≡N⁺O⁻	−0.56	−0.21	0.80	−0.68	0.67	−0.30
Diazonium Betaines						
N≡N⁺CH₂⁻	−0.61	0.13	0.78	−0.50	0.70	−0.51
N≡N⁺NH⁻	−0.56	0.01	0.83	−0.58	0.71	−0.41
N≡N⁺O⁻	−0.54	−0.14	0.83	−0.65	0.69	−0.31
Azomethinium Betaines						
H₂C=N⁺HCH₂⁻	−0.71	0.00	0.71	−0.53	0.66	−0.53
H₂C=N⁺HNH⁻	−0.67	−0.07	0.74	−0.58	0.67	−0.46
H₂C=N⁺HO⁻	−0.65	−0.16	0.74	−0.62	0.67	−0.41
Oxygenated Dipoles						
H₂C=O⁺CH₂⁻	−0.71	0.00	0.71	−0.56	0.60	−0.56
H₂C=O⁺NH⁻	−0.63	−0.08	0.77	−0.64	0.61	−0.46
H₂C=O⁺O⁻	−0.56	−0.19	0.80	−0.71	0.61	−0.35
O=O⁺O⁻	−0.71	0.00	0.71	−0.53	0.67	−0.53

[a] Data from ref 67a.

Chart IV

$$a \equiv b^+ - c^-$$

|	HOMO			LUMO		
	a	b	c	a	b	c
avg coeff	0.63	0.08	0.71	0.59	0.67	0.44
$C^2_{dipole}/C^2_{ethylene}$	0.8	0.0	1.0	0.7	0.9	0.4
γ	0.04	0.0	0.05	0.04	0.05	0.02

$C^2_{dipole}/C^2_{ethene}$ ratios are tabulated in Chart IV (C_{ethene} = 0.707). These ratios have been multiplied by the γ for ethylene (0.05) to obtain the approximate γ's for the 1,3-dipoles. Note that the γ values for 1,3-dipoles depend upon where the FG is attached as well as the particular FMO in question. These values along with the parent FMO energies (eq 40 and 41) may then be used to estimate the FMO energies for monosubstituted 1,3-dipoles via eq 42.

4. Functional Group τ Values. A general program was developed to estimate τ values for FG's based on IP data for substituted ethylenes. Since IP data are not available for all FG's, it is not feasible to use a complete data base. Furthermore, it would not be efficient to do

(84) IP data for monosubstituted thiocarbonyls are scarce, while those for disubstituted ones are abundant. The γ value for C=S of 0.07 was obtained once multiple functionality was considered (section V.C.5).

Table VIII. Recognized Atoms or Groups

no.	atom or group	no.	atom or group
1	H	16	C≡CH
2	O	17	CH=NH
3	N	18	N=CH₂
4	C	19	N=NH
5	F	20	CH=S or N=S
6	Cl	21	anion: not part of 1,3-dipole
7	Br	22	anion: 1,3-dipole terminus
8	I	23	cation: 1,3-dipole terminus
9	B	24	central 1,3-dipole atom
10	Si	25	cation: not part of 1,3-dipole
11	P	26	C≡N
12	S	27	C=O or P=O
13	Se	28	N=O
14	aromatic	29	SO₂
15	olefinic	30	S=O

Table IX. τ Values for Common Functional Groups (FG)

| FG	τ	FG	τ	FG	τ
C₆H₅-p-OMe	51	OH	18	CCl₃	0
N(CH₃)₂	44	Et	18	CONH₂	−3
C₆H₅	42	C≡CH	18	NF₂	−6
SCH₃	38	CH=S	16	COOMe	−6
NH₂	36	SCl	16	COOH	−8
CH=CHMe	36	OOCH₃	14	P(O)Me₂	−8
SH	32	CH₃	12	COEt	−8
SSCH₃	31	SCN	12	COMe	−9
CH=CH₂	30	SiMe₃	11	C≡N	−10
O-i-Pr	27	Br	10	S(O)Me	−10
OMe	24	CH=NH	9	CHO	−12
N=CH₂	21	Cl	6	CF₃	−12
t-Bu	21	N=NH	4	COCl	−14
n-Pr	20	SiH₃	1	N=O	−17
NHCl	20	F	0	SO₂Me	−27
I	20	H	0	NO₂	−36

so because it would require the recognition of hundreds of specific FG's. A much simpler approach has been taken: a set of atoms and groups of atoms, shown in Table VIII, has been selected such that almost any FG can be constructed from them. For instance, a CF₃ FG is a carbon with three fluorine atoms, an ester is a carbonyl with an attached alkoxy group. FG's can be thought of as layers of atoms, where each atom of each layer influences the origin to which it is attached. An atom's effect on the FG origin decreases the farther it is from this origin. A maximum of three layers is examined. For example: in **14**, the sulfur's donating ability toward the ethylene moiety
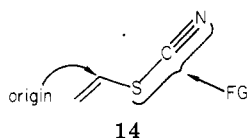
14

is decreased by the cyano group. Note that S–CN is not a recognized unit, rather it is made up of the units S and CN.

τ values are estimated in subroutine FGTYPE. It initially subdivides the atoms of an FG into layers as shown in **15**.
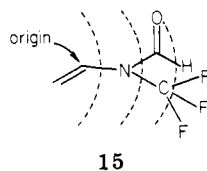
15

Starting from a specific origin, as each unit is encountered, FGVAL is called to find the atom or group of atoms to which it corresponds (see Table VIII). When the first unit is encountered, FGTYPE assigns a τ value that reflects the IP change the unit produces on a π system. As each subsequent unit is encountered, the τ value is adjusted such that both the inductive and/or the resonance effects are taken into account. In **15**, the nitrogen's donating ability is dampened by both the carbonyl group and the trifluoromethyl group. Naturally, the farther an atom is from the origin, the smaller its effect on the overall donating or withdrawing ability of the FG. Table IX lists τ values obtained for a variety of common FG's. Some of these, especially the electron-withdrawing FG's, are subject to change if warranted by further experimental data.

5. Polysubstituted Systems. An added complication in the calculation of FMO energies is that the effect of functionality is not additive. A simple algorithm has been developed that yields reasonable predictions for the IP's of polysubstituted systems. It is based on a collective τ value (τ_C), which represents the total effect of all FG's attached to the parent system. If all FG's on a parent are

Chart V

compound	IP	$-E_{HOMO}$ (predicted)
H₂C=CH₂	10.5	10.4
H₂C=CHMe	10.0	9.8
H₂C=CMe₂	9.4	9.5
MeHC=CHMe	9.3	9.5
MeHC=CMe₂	8.9	9.2
Me₂C=CMe₂	8.4	9.1
	9.0	9.1
	8.9	8.9
	8.8	8.7
	8.6	8.8
	8.1	8.5
	7.8	8.3
H₂C=CH₂	10.5	10.4
H₂C=CHCl	10.0	10.1
H₂C=CCl₂	10.0	9.9
ClHC=CHCl	9.8	9.9
ClHC=CCl₂	9.7	9.8
Cl₂C=CCl₂	9.3	9.7
H₂C=CH₂	10.5	10.4
H₂C=CHCN	10.9	11.1
NCHC=CHCN	11.2	11.5
H₂C=C(CN)₂	11.4	11.5
NCHC=C(CN)₂	11.6	11.7
(NC)₂C=C(CN)₂	11.8	11.8

electron donating or all are electron withdrawing, the FG with the largest absolute τ value (τ_{max}) will exert its full effect. The sum of the τ values for the remaining FG's (τ_{sum}) is divided by a factor dependent upon the total number of FG's (NFG) plus 1 to yield τ_C via eq 45. The

$$\tau_C = \tau_{max} + 2\tau_{sum}/(1 + \text{NFG}) \qquad (45)$$

resultant τ_C's can then be inserted in eq 42 to obtain the FMO energies.

The four series in Chart V show that each added substituent changes the IP by a varying amount.[82,85] The IP's predicted by eq 42 and 45 are shown for comparison. However, if there is a mixture of donating and withdrawing functionality, the τ values of the most donating and most withdrawing FG's are added together and the sum of the remaining τ values are factored. Some examples of calculated HOMO energies are compared with literature IP's

(85) K. N. Houk and L. L. Munchausen, *J. Am. Chem. Soc.*, 98, 937 (1976).

Table X. Sample FMO Energy Calculations

$\tau_C = 18 + (2 \times 18)/(1 + 2) = 30$
HOMO = $(0.05) \times (30) - 10.5 = -9.0$ eV
experimental IP = 9.0 eV

$\tau_C = 20 + (2 \times 42)/(1 + 4) = 36$
HOMO = $(0.05) \times (36) - 10.5 = -8.7$ eV
experimental IP = 8.1 eV

$\tau_C = 11 + (2 \times 6)/(1 + 2) = 15$
HOMO = $(0.06) \times (15) - 11.5 = -10.6$ eV
experimental IP = 9.7 eV

$\tau_C = 24 + (2 \times 18)/(1 + 2) = 36$
HOMO = $(0.11) \times (36) - 14.5 = -10.6$
experimental IP = 11.1 eV

HOMO = $(0.08) \times (18) - 13.5 = -12.1$ eV
experimental IP = 12.1 eV

$\tau_C = 38 + (2 \times 38)/(1 + 2) = 63$
HOMO = $(0.03) \times (63) - 9.0 = -7.2$ eV
experimental IP = 7.5 eV

$\tau_C = 12 + (2 \times 12)/(1 + 3) = 20$
HOMO = $(0.03) \times (20) - 9.0 = -8.4$ eV
experimental IP = 8.4 eV

$\tau_C = -10 + 6 = -4$
HOMO = $(0.05) \times (-4) - 10.5 = -10.7$ eV
experimental IP = -10.7 eV

$\tau_C = -12 + (2 \times (-12 - 10 - 10))/$
$(1 + 4) = -24$
HOMO = $(0.05) \times (-24) - 10.5 = -11.7$ eV
experimental IP = 11.9 eV (ref 85)

in Table X. The agreement is generally within 0.5 eV.

6. LUMO Energies of Substituted Systems. The estimation of LUMO energies for substituted systems is more difficult due to the paucity of accurate theoretical and experimental data as discussed in section V.C.2. In view of this, it has been decided to develop a simple algorithm for LUMO energies based upon the known general trends in the relationships between the effects of FG's on HOMO energies and their effects on LUMO energies.[6] From ab initio results, it appears that, in general, a donating FG raises the HOMO energy of a parent about twice as much as it raises the LUMO energy. Conversely, a withdrawing FG lowers the HOMO energy about a third as much as it lowers the LUMO energy. Olefinic, acetylenic, and aromatic groups lower the LUMO energies about one-third to one-half as much as they raise the HOMO energies. To accommodate these trends, we find it convenient to leave the γ's for parents constant and modify the τ values. Thus, the τ's for calculating LUMO energies are obtained by adjusting the τ values in Table IX in the following manner: positive τ values, except those for conjugated hydrocarbons, are divided by 2, negative values are multiplied by 3, and τ's for conjugated hydrocarbons are divided by 3. The sign for the latter is also reversed. Also, the resultant τ's are divided by 2 for the 2 and 3 positions in dienes due to the smaller FMO coefficients at these sites. Although these are crude approximations, they nevertheless reveal correct trends and have been found to be good enough to predict the regioselectivities and reactivities of cycloaddition reactions.

A detailed calculation of both the HOMO and LUMO energies of a disubstituted 1,3-dipole is shown in Chart VI. In section V.C.3, we noted that the γ for 1,3-dipoles varies depending upon the point of attachment of the FG. Again, we find it more convenient to vary the τ values and leave

Chart VI

	HOMO	
τ	FG(a) = -6	FG(b) = -6
adjusted τ	$(0.8)(-6) = -5$	$(1.0)(-6) = -6$
τ_C (eq 45)	$-6 + (2)(-5)/(1 + 2) = -9$	
HOMO (eq 42)	$(0.05)(-9) - 6.8 = -7.3$ eV	
lit. HOMO[67b]	-7.4 eV	

	LUMO	
τ	FG(a) = -18	FG(b) = -18
adjusted τ	$(0.7)(-18) = -12$	$(0.4)(-18) = -7$
τ_C (eq 45)	$-12 + (2)(-7)/(1 + 2) = -17$	
LUMO (eq 42)	$(0.05)(-17) + 1.0 = 0.2$ eV	
lit. LUMO[67b]	-0.6 eV	

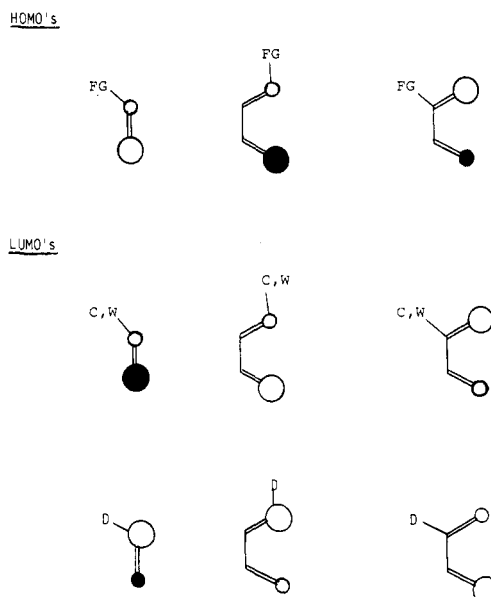**Figure 13.** Polarization of FMO's for ethylene and butadiene by substituents; C, W, and D refer to conjugated hydrocarbon, π-withdrawing and π-donating groups, respectively, while FG is any of these.

γ constant. Therefore, 0.05 is taken as the γ for 1,3-dipoles and the τ values are correspondingly adjusted by using the dipole/ethylene coefficient ratios tabulated in section V.C.3.

D. Prediction of Regiochemistry. Once the FMO energies for two reactants have been estimated, one can predict the controlling pair of molecular orbitals. But before regiochemical predictions can be made, the relative magnitudes of the MO coefficients at the reacting termini must be determined. This function is performed by subroutine REGIO.

1. Carbon Parents. The effects of FG's on the FMO coefficients for 1,3-butadiene and ethylene are well-known. Houk provides a concise pictorial summary.[86] The results can be further condensed as follows. For the HOMO's, all FG's attached to terminal positions increase the magnitude of the coefficient on the opposite termini. For 2-substituted dienes, all FG's increase the coefficients at position 1 of the diene. For LUMO's, the same relationships hold, except for donating FG's, which are opposite. These patterns are summarized in Figure 13. Of course, the extent of polarization of the coefficients depends upon how donating or withdrawing the FG is.

(86) K. N. Houk, *J. Am. Chem. Soc.*, **95**, 4092 (1973).

Fortunately, all attached FG's have been perceived and their electronic nature has been stored conveniently as τ values. For the HOMO's, if the sum of the absolute values of the τ's for FG's on positions 1 and 3 of dienes (position 1 for dienophiles and dipoles) is greater than the sum on positions 2 and 4 (position 2 for dienophiles and 3 for dipoles), the largest coefficient is on position 4 of the diene (2 of dienophile, 3 of dipole). Otherwise, the largest coefficient is on position 1. For estimation of the relative coefficients in the LUMO's, account must be taken of the opposite effect of donating FG's. In this case, if the sum of the absolute values of FG's with negative τ's on positions 1 and 3 of dienes (1 for dienophiles and dipoles) plus the sum of FG's with positive τ's on positions 2 and 4 of dienes (2 for dienophiles, 3 for dipoles) is greater than the equivalent sums on the other corresponding positions, then the largest coefficient in the LUMO is on position 4 of the diene (2 for dienophiles, 3 for dipoles). Otherwise, it is on position 1 of the diene (1 for dienophiles and dipoles). For example:

HOMO

$|24| + |6| > |-10|$
largest coefficient: position 4

LUMO

$|0| < |-30| + |12| + |3|$
largest coefficient: position 1
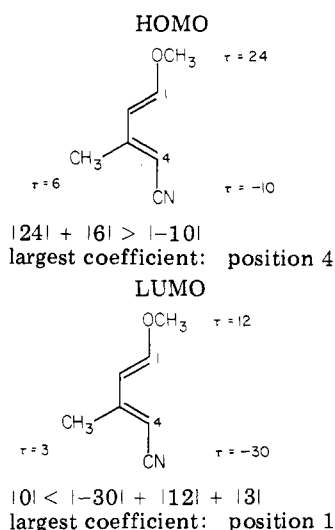
When the differences in the above sums are less than about 12 units, a significant amount of the minor regioisomer (>10%) begins to be observed experimentally. When a mixture is expected, the major isomer is displayed on the graphics terminal before the minor one. A typical case, that of 2-substituted dienes, is indicated in eq 46.[87]


R = CN	84%
R = CF₃	55%
R = CH₃	69.5%

$$(46)$$

	16%
	45%
	30.5%
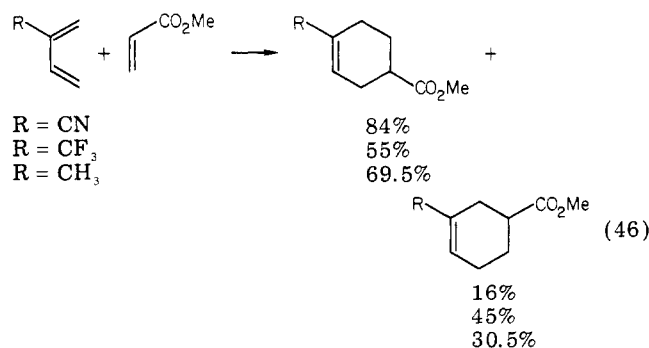
2. Unsymmetrical Parents. When unsymmetrical hetero parents are used as one or both components in a Diels–Alder reaction (1,3-dipolar reactions have been treated in section V.B.2), the concerted nature of the reaction becomes questionable and thus the regiochemical outcome is not necessarily governed by the frontier orbitals. Nevertheless, the algorithms developed thus far can be utilized to predict correct regiochemistries, albeit with

---

(87) T. Inukai and T. Kojima, *J. Org. Chem.*, **36**, 924 (1971).

some restrictions. It is well-known that for 2π-electron unsymmetrical parents, the π HOMO's and LUMO's are polarized such that the largest coefficients reside on the most and least electronegative terminal atoms, respectively. Ab initio calculations for hetero dienes also show the LUMO's are polarized in a similar fashion, but the polarization in the HOMO's is unpredictable. Thus, the coefficient magnitudes for the FMO's of hetero parents (except for the HOMO's of hetero dienes) will be determined by a comparison of the electronegativities of the terminal atoms. If a heteroatom occupies the 2 position of a diene, as in **16**, the largest coefficient in the LUMO will be on the terminal atom adjacent to the most electronegative atom.


16
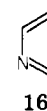
For prediction of the correct regiochemistry, four possible combinations of reactants must be considered.

(1) Hetero diene + electron-rich or conjugated olefin. These reactions are LUMO diene controlled, and the algorithm works without modification (eq 47). (Note: the atoms with asterisks in the examples indicate the largest terminal coefficient in the specified FMO.)

$$(47)^9$$
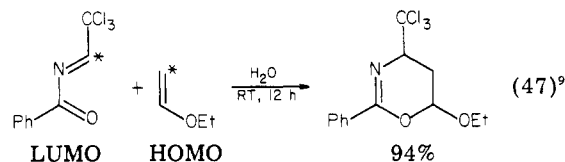
(2) Hetero diene + electron-poor olefin. This combination is not very reactive, yet is quite regioselective. The algorithm yields the correct prediction if the hetero diene is considered to be the LUMO component (eq 48 and 49).
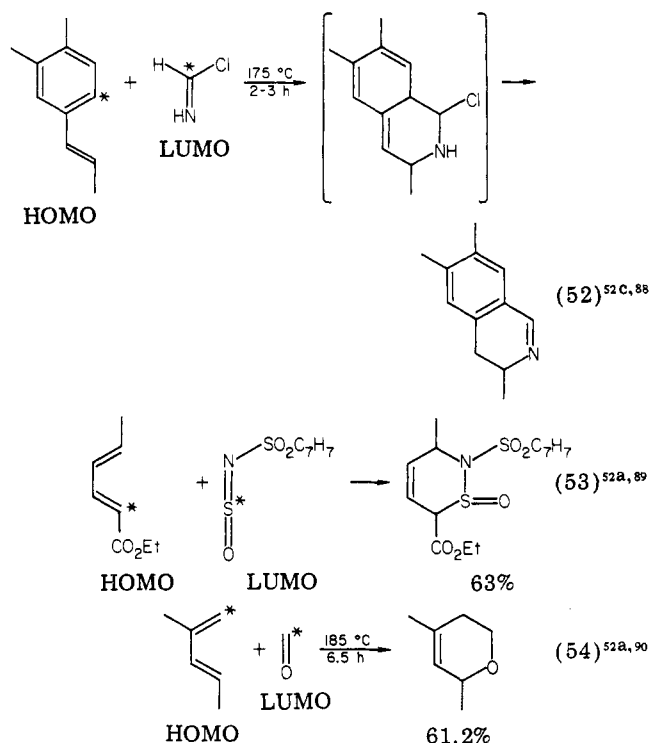

$$(48)^8$$

$$(49)^9$$
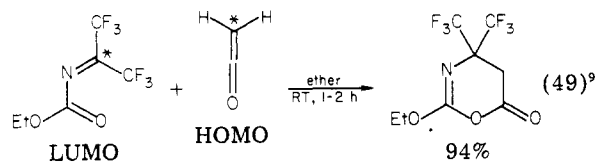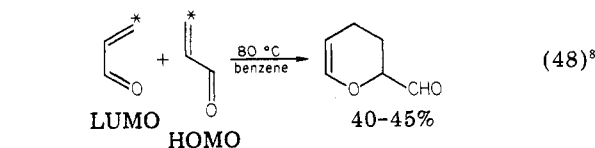
(3) Hetero diene + hetero dienophile. The algorithm yields the correct prediction if the reaction is assumed to be diene LUMO controlled (eq 50 and 51).


$$(50)^9$$

$$(51)^9$$
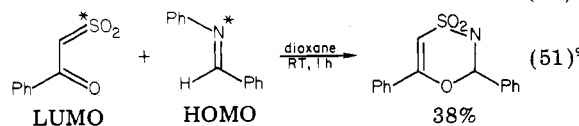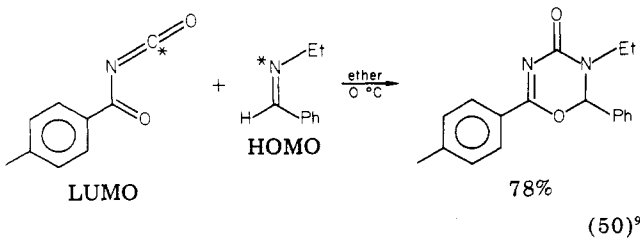
(4) Carbon diene + hetero dienophile. In general, the algorithm works without modification such that the diene HOMO controlled reaction leads to the correct regioadduct (eq 52–54).

(52)[52c,88]

(53)[52a,89]

63%

(54)[52a,90]

61.2%

Shown in eq 55 and 56 are two cases where a substituted hetero dienophile yields regiochemical mixtures. In each example, the algorithm only predicts the second isomer. Clearly, for only slightly polarized hetero parents, the algorithm will have to be refined to include substituent effects.

(55)[52a]

major   72%   minor

(56)[52a]

mixture
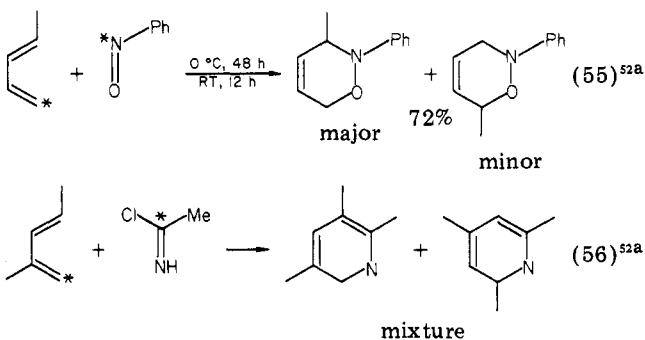
3. Intramolecular Six-Electron Cycloadditions. In the intramolecular Diels–Alder reaction, the diene may be connected to the dienophile at the 1-position (Type I) or at the 2-position (Type II). Type I reactions are much more common, and, although exceptions have been reported, the large majority have bridge sizes between diene and dienophile of two to four atoms. Furthermore, model studies indicate no product formation in bridges of from 5 to 12 atoms.[91a,b] Type II reactions generate strained compounds with bridgehead double bonds and require much higher temperatures.[91c] Reactions with bridge sizes of three or four atoms have been attempted successfully. Steric constraints dictate that most reactions occur in a quasi-"ortho" rather than a quasi-"meta" sense. With in-

(88) M. L. Tamayo, G. G. Muñoz, and R. Madroñero, *Bull. Soc. Chim. Fr.*, 1331 (1958).

(89) G. Kresze, A. Maschke, R. Albrecht, K. Bederke, H. P. Patzschke, H. Smalla, and A. Trede, *Angew. Chem.*, **74**, 135 (1962).

(90) T. L. Gresham and T. R. Steadman, *J. Am. Chem. Soc.*, **71**, 737 (1949).

(91) (a) G. Brieger and J. N. Bennett, *Chem. Rev.*, **80**, 63 (1980); (b) W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, **16**, 10 (1977). (c) K. J. Shea, S. Wise, L. D. Burke, P. D. Davis, J. W. Gilman, and A. C. Greeley, *J. Am. Chem. Soc.*, **104**, 5708 (1982).


ortho   meta

tramolecular 1,3-dipolar cycloadditions, the situation is less straightforward. Although quasi-"ortho" products still predominate, the occurrence of quasi-"meta" products appears to be much more common than in the Diels–Alder reaction (eq 57).[92]

(57)

~50:50
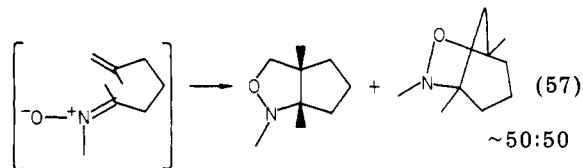
Presently, the program will allow intramolecular six-electron cycloadditions with bridges of two to four atoms for Type I reactions and of three to five atoms for Type II reactions. Only the quasi-"ortho" products will be displayed for intramolecular Diels–Alder reactions, but for 1,3-dipolar reactions both regio products will be formed. For formation of the quasi-"ortho" adduct, the terminal atoms of the reaction components that are connected by the shortest chain of atoms will be bonded in the product.
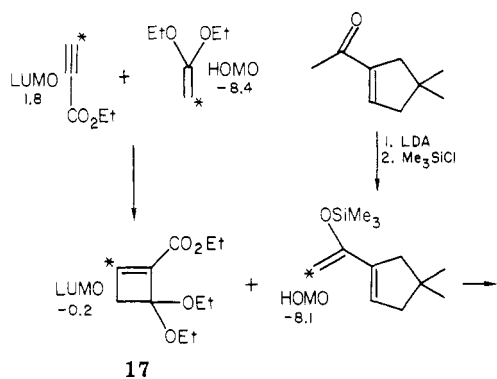
E. Stereochemistry. Subroutine PROD forms the necessary bonds and determines the stereochemistry of the substituents in the product(s). One well-established aspect of stereochemistry is the preservation of configuration in the diene and dienophile in Diels–Alder reactions and in the dipolarophile in 1,3-dipolar cycloadditions.[7,19,33] Most 1,3-dipoles, however, are not isolable and their geometry and regiostability are uncertain. CAMEO, therefore, does not indicate any stereochemistry for substituents attached to 1,3-dipoles. Endo selectivity, which can be attributed to secondary orbital interactions, is another aspect to be considered in cycloadditions. It is well documented for Diels–Alder reactions[19] but rare in 1,3-dipolar cycloadditions. The program presently displays endo stereochemistry only for Diels–Alder reactions with dienophiles containing conjugated electron-withdrawing groups, excluding derivatives of conjugated hydrocarbons. The first example (eq 58) yields an endo adduct,[93] and this is correctly predicted by CAMEO. In the second example (eq 59),
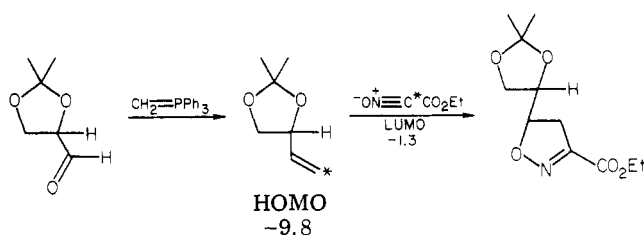

(58)

60%

(59)

95:5 (61%)
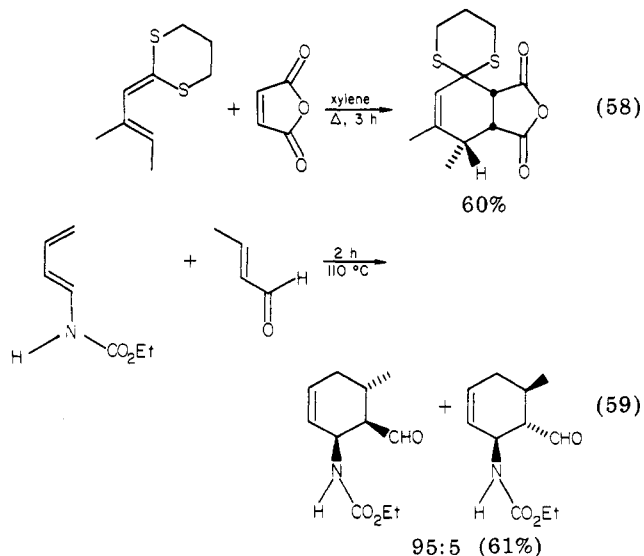
a mixture of stereoadducts is formed with the endo isomer

(92) A. Padwa, *Angew. Chem., Int. Ed. Engl.*, **15**, 123 (1976).

Scheme I

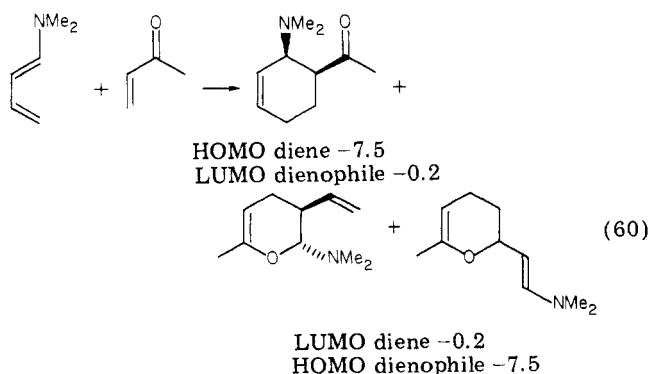LUMO 1.8 + CO₂Et   EtO OEt HOMO -8.4

1. LDA
2. Me₃SiCl

LUMO -0.2   CO₂Et OEt OEt

OSiMe₃ HOMO -8.1

17

OSiMe₃ ... CO₂Et OEt OEt   KF →   O H ... CO₂Et OEt OEt

Scheme II

CH₂=PPh₃ →   ⁻O⁺N≡C*CO₂Et LUMO -1.3 →   CO₂Et

HOMO -9.8

Scheme III

OMe Me₃SiO   +   NO₂ CF₃

HOMO (-8.1)   LUMO (-1.3)

Me₃SiO ...CF₃ OMe NO₂   +   Me₃SiO CF₃ OMe NO₂

18   **19**

Scheme IV

NH₂ NC   +   O   →

LUMO

HOMO

NH₂ NC O O

20
HOMO diene -7.5 eV
LUMO dienophile -0.4 eV

O N NH₂ O

21
HOMO dienophile -10.2 eV
LUMO diene -0.4 eV

NH₂ NC O

22
HOMO diene -7.5 eV
LUMO dienophile 1.6 eV

predominating, though the minor product may result from equilibration.[94] In any event, the program only predicts the major, presumably kinetic, product.

F. Ordering of Products. It is desirable to output products in order from most to least likely. Continuing with the frontier orbital approach, the FMO gaps already calculated provide a measure of relative reactivities:[60] the smaller the FMO gap, the more facile the cycloaddition. If several products have comparable FMO gaps, a comparison of the enthalpy changes for the competing reactions often reveals a clear thermodynamic preference that may also be reflected in the transition states. For example, when a diene reacts with a dienophile which is itself a diene, such as the α,β-unsaturated carbonyl compound in eq 60, there are several alternative pathways that have the

NMe₂   +   O   →   NMe₂ O   +

HOMO diene -7.5
LUMO dienophile -0.2
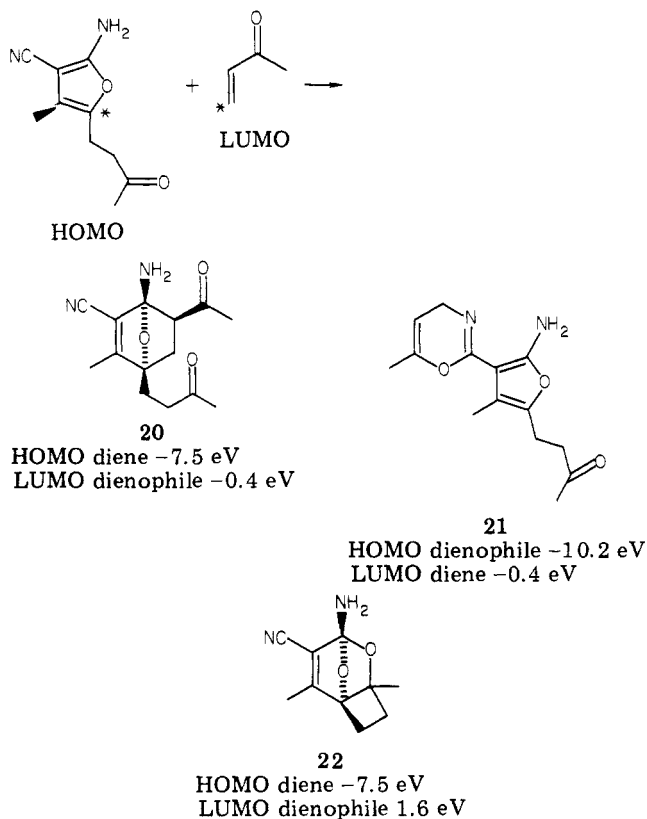
O NMe₂   +   O NMe₂   (60)

LUMO diene -0.2
HOMO dienophile -7.5

same FMO gap. The latter two products, however, are approximately 20 kcal less favorable than the first and thus
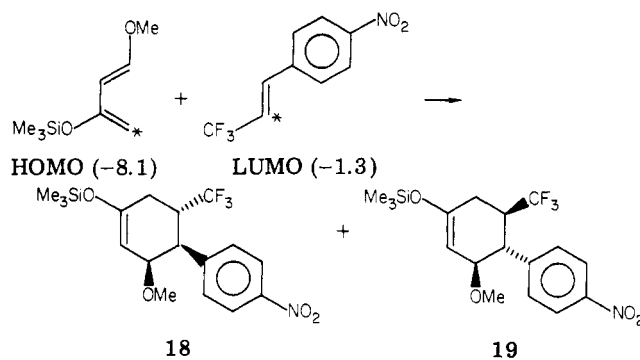
would not be expected to be competitive. It should be noted that the program displays the ΔH for each reaction along with the product. The computation includes changes in bond energies, ring strain, aromaticity, and ion stabilities.[95] For cycloadditions, the HOMO and LUMO energies are also displayed.

VI. Sample Sequences

Some sample sequences are shown in Schemes I-IV. For each cycloaddition the controlling HOMO-LUMO pair and their estimated energies in eV are indicated. In addition, the positions with asterisks indicate the predicted site with the largest coefficient in the appropriate controlling FMO.

Scheme I illustrates that dipolar (nonconcerted) [2 + 2]'s follow the FMO rules, so **17** is formed regioselectively. A Diels-Alder reaction with endo selectivity is next and goes cleanly, as observed.[96] The regioselectivity is also correctly predicted in the 1,3-dipolar cycloaddition with

(93) F. A. Carey and A. S. Court, *J. Org. Chem.*, **37**, 4474 (1972).
(94) L. E. Overman and P. J. Jessup, *Tetrahedron Lett.*, 1253 (1977).

(95) J. Gao, D. McLaughlin, and W. L. Jorgensen, to be submitted for publication.
(96) M. F. Semmelhack, S. Tomoda, H. Nagaoka, S. D. Boettger, and K. M. Hurst, *J. Am. Chem. Soc.*, **104**, 747 (1982).

a nitrile oxide shown in Scheme II.[97] In Scheme III, CAMEO properly finds the p-nitrophenyl group is dominant for the regiochemistry, though no stereoselectivity is indicated. Experimentally, both 18 and 19 are found, with 18 predominating.[98] In Scheme IV, 20 is observed but with exo stereochemistry.[99] Although furans form endo adducts initially, the reaction is reversible and the more thermodynamically stable exo adduct eventually predominates. More detailed analyses of reactants and reaction conditions are needed before CAMEO can properly handle this point. The program also yields two other products, 21 and 22, though the enthalpy change computed for these reactions is much less favorable.

VII. Conclusion

The capabilities of CAMEO have been broadened to include six-electron cycloadditions as the first part of a general module for pericyclic chemistry. The frontier molecular orbital method was chosen as the framework for predictions of the likelihood and regiochemistry of cycloadditions. This required the development of comprehensive algorithms for the estimation of the energies and relative coefficients of the frontier orbitals by using empirical relationships based on experimental and theoretical data. Sophisticated regiochemical predictions are now possible for a broad range of systems including 1,3-dipoles

and cumulenes. The pericyclic phase of CAMEO will soon be extended to include electrocyclic and sigmatropic rearrangements as well as other cycloaddition reactions.

(97) A. P. Kozikowski and A. K. Ghosh, *J. Am. Chem. Soc.*, **104**, 5788 (1982).

(98) I. Ojima, M. Yatabe, and T. Fuchikami, *J. Org. Chem.*, **47**, 2051 (1982).

(99) N. A. Vaidya, W. J. Nixon, Jr., A. A. Fatmi, and C. D. Blanton, Jr., *J. Org. Chem.*, **47**, 2483 (1982).

Metabolites from the Marine Sponge *Tedania ignis*. A New Atisanediol and Several Known Diketopiperazines[1]

Francis J. Schmitz,* David J. Vanderah, Keith H. Hollenbeak, Carol E. L. Enwall, and Yalamanchili Gopichand

Marine Chemistry Laboratory, Department of Chemistry, University of Oklahoma, Norman, Oklahoma 73019

P. K. SenGupta, M. B. Hossain, and Dick van der Helm*

X-ray Crystallography Laboratory, Department of Chemistry, University of Oklahoma, Norman, Oklahoma 73019

Received November 29, 1982

A new hydroxylated atisane, atisane-3β,16α-diol (5), has been isolated from the Caribbean sponge *Tedania ignis*, and its structure has been determined by single-crystal X-ray diffraction. The absolute configuration was assigned from circular dichroism data for the derived ketone 6. Also identified in the extracts were batyl and chimyl alcohol, the diketopiperazines *cyclo*-(L-Pro-L-Leu) (1), *cyclo*-(L-Pro-L-Val) (2), and *cyclo*-(Pro-Ala) (3), and epiloliolide (4).

Tedania ignis is an abundant Caribbean sponge also known as the fire sponge[2] because it reputedly causes varying degrees of dermatitis upon contact.[2,3] Whether

the dermatitis is caused by sponge metabolites or is due to mechanical irritation by sponge spicules is not known. Our own interest in this sponge was stimulated by the fact that extracts showed cytotoxicity and in vivo tumor inhibition. In the course of a bioassay-guided search for the tumor-inhibitory principles we have isolated a number of inactive or mildly cytotoxic components which are described in this paper. One of the marginally cytotoxic

(1) Presented in part at the 3rd International Symposium on Marine Natural Products, Brussels, Belgium, Sept *1980*; see: Schmitz, F. J.; Gopichand, Y.; Michaud, O. P.; Prasad, R. S.; Remaley, S.; Hossain, M. B.; Rahman, A.; Sengupta, P. K.; van der Helm, D. *Pure Appl. Chem.* **1981**, *53*, 853.

(2) See, for example: de Laubenfels, M. W. *Trans. Zool. Soc. London* **1950**, *No. 27*, Pt. 1, 1.

(3) Yaffee, H. S.; Stargardter, F. *Arch. Dermatol.* **1963**, *87*, 601.