Anal. Calcd for $C_{25}H_{33}N_3O_5$: C, 65.91; H, 7.30. Found: C, 65.67; H, 7.61.

Acknowledgment. Financial support was provided by the National Cancer Institute, Grants CA-22153 and CA-24538.

Registry No. **2a**, 13910-48-0; **2b**, 29867-04-7; **3a**, 90914-08-2; **3b**, 90914-09-3; **4a**, 90914-10-6; **4b**, 90914-11-7; **4c**, 90914-12-8; **5a**, 90914-13-9; **5b**, 90914-14-0; **5c**, 90914-15-1; **6a**, 90914-16-2; **6b**, 90914-17-3; **6c**, 90914-18-4; **7**, 90914-19-5; **8**, 90914-20-8; **9**, 90914-21-9; **10**, 90914-22-0; **11**, 90914-23-1; **12**, 90914-24-2; $NH_2(CH_2)_4NH_2$, 110-60-1; PhCHO, 100-52-7; $Cl(CH_2)_3CN$, 628-20-6; $CH_2{=}CHCN$, 107-13-1; 2,3-$(MeO)_2C_6H_3C(O)Cl$, 7169-06-4; spermidine, 124-20-9; homospermidine, 4427-76-3; bis(3-aminopropyl)amine, 56-18-8.

General Treatment of Periselectivity[†]

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Procedures to treat the competitions between most thermal pericyclic reactions have been developed and implemented in the CAMEO program. The algorithms are based on analyses of a large amount of kinetic data reported in the literature for cycloadditions, electrocyclic and cheletropic reactions, and sigmatropic rearrangements. For reaction types which have been extensively studied kinetically, approximate expressions are used to estimate energies of activation. More qualitative approaches are required to gauge reactivity for less well-studied reactions. The outcome of the analyses is the assignment of each possible competing pericyclic reaction to rate ranges which may then be compared.

I. Introduction

The computer program CAMEO, which predicts the products of organic reactions given starting materials and conditions, is being continually extended and refined.[1] The original efforts on anionic chemistry[1a] were expanded to include reactions of ylides and the organometallic chemistry of lithium, magnesium, and lithium cuprates.[1b] Subsequently, the treatment of organosilicon compounds was enhanced[1c] and a comprehensive module for electrophilic processes involving carbonium ion intermediates was added.[1d] Thermal pericyclic chemistry has also now been implemented including cycloadditions, electrocyclic reactions, and sigmatropic rearrangements.[1e,f] This addition raises the important issue, addressed in the present paper, of periselectivity. That is, once all thermal pericyclic pathways available to a set of reagents are recognized by CAMEO, the program must determine which of the alternate pathways yields the predominant products that should be output.

Many obvious uses can be envisioned for a program capable of making sophisticated predictions on the outcome of organic reactions. However, as emphasized previously, the program development itself is highly beneficial because it necessitates the thorough analysis and organization of experimental data on reactivity.[1] This is well illustrated by the present work which provides a general treatment of periselectivity for all three classes of pericyclic reactions.

The CAMEO program has been set up so that the user may specify one of five temperature ranges (<0, 0–100, 100–200, 200–300, and >300 °C). The algorithms dealing with periselectivity then decide whether a particular reaction would have a rate constant above prescribed limits in the indicated temperature range. The chosen rate constant standards are $1.0 \times 10^{-5}\ s^{-1}$ for first-order reactions (e.g., electrocyclic and Cope rearrangements) and 2.2×10^{-5} L/mol s for second order reactions (e.g., cycloadditions). These values are consistent with typical experimental conditions and correspond to 75% conversion in approximately 38 h.

The relationship between the rate constant and temperature is expressed by the Arrhenius equation:

$$k = A \exp(-E_a/RT) \text{ or } E_a = RT(\ln A - \ln k)$$

where A is the preexponential factor, E_a is the energy of activation, and R is the gas constant. If log A is known, the E_a required to achieve rate constant k at temperature T can be determined. Fortunately, log A tends to be relatively constant for a reaction type. Thus, given an average log A for each reaction type, it is simple to determine the range of E_a's required to achieve rate constant k for each of the above five temperature classes.

Clearly, the development of complete algorithms to predict activation energies for pericyclic reactions is a difficult undertaking. It is particularly aggravated by the lack of kinetic data for some reaction types. Consequently, the above categorization is meant only as a framework. For reaction types which have been extensively studied kinetically, it is possible to develop approximate expressions to estimate the energies of activation. These empirical relations will of necessity contain some parameters which are approximations. A different approach must be taken for reaction types for which there are few or no kinetic data available. Characteristics of the reagents which activate or deactivate the reaction can be identified. Subsequently, the reaction can be placed into a temperature slot that reflects typical experimental conditions for the particular process. The present algorithms are intended as a starting

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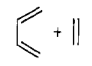
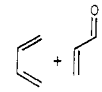
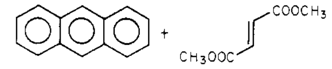
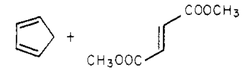
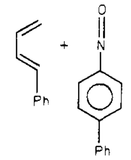
[†] Computer-assisted mechanistic evaluation of organic reactions. 8. For part 7, see ref 1e.

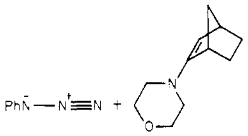
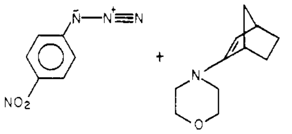
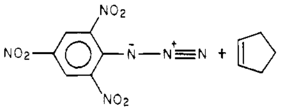
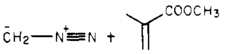
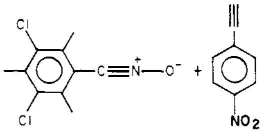
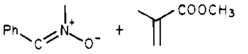
[1] (a) Salatin, T. D.; Jorgensen, W. L. *J. Org. Chem.* **1980**, *45*, 2043. (b) Salatin, T. D.; McLaughlin, D.; Jorgensen, W. L. *Ibid.* **1981**, *46*, 5284. (c) Peishoff, C. E.; Jorgensen, W. L. *Ibid.* **1983**, *48*, 1970. (d) McLaughlin, D.; Jorgensen, W. L. *Ibid.*, to be submitted. (e) Burnier, J. S.; Jorgensen, W. L. *Ibid.* **1983**, *48*, 3923. (f) Burnier, J. S. Ph.D. Thesis, Purdue University, 1984.

Table I. Activation Energies for Diels-Alder Reactions[a]

reactants	FMO gap, eV	ΔH_{rxn}, kcal/mol	exptl E_a, kcal/mol	calcd E_a, kcal/mol	T range for CAMEO, °C
	10.8	-37.3	27.5	28	200–300
	8.6	-33.0	19.6	19	100–200
	4.0	-5.8	11.0	8	<0
	8.0	-19.4	14.8	14	0–100
	4.7	-26.8	9.9	10	<0

[a] Experimental activation energies from ref 2.

Table II. Activation Energies for 1,3-Dipolar Cycloadditions[a]

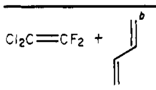
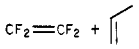
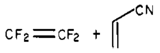
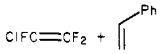
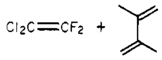
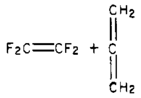
reactants	exptl E_a, kcal/mol	calcd E_a, kcal/mol	T range for CAMEO, °C
	15.3	15	0–100
	13.1	14	0–100
	12.9	15	0–100
$\mathrm{Ph{-}\bar{N}{-}\overset{+}{N}{\equiv}N + CH_3OOC{-}{\equiv}{-}COOCH_3}$	18.0	18	0–100
	8.6	13	<0
	15.1	14	0–100
	16.4	15	0–100

[a] Experimental activation energies from ref 2.

point; substantial refinements are anticipated as more kinetic data become available.

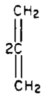
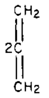
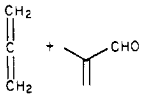
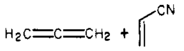
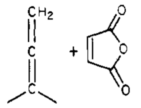
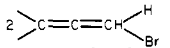
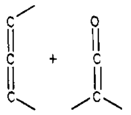
The first reactions treated here are the six-electron cycloadditions, in particular, the Diels–Alder reaction and 1,3-dipolar cycloadditions. Approximate expressions for their activation energies are derived. A more qualitative method of determining reactivities is employed for the broad range of thermal [2 + 2] reactions. The cycloaddition section is concluded by a brief discussion of the periselectivity of 10π-electron cycloadditions. Examples of cycloadditions involving more than 10π electrons are scarce and are not considered at the present time. Next, a discussion of the kinetics of electrocyclic closure reactions involving up to 10π electrons and the algorithms developed to estimate their activation energies are presented. Presently, electrocyclic reactions for systems with greater than 10π electrons and for conjugated charged systems other than allylic ions have not been incorporated into CAMEO. The more familiar sigmatropic rearrangements are then treated in the following sections. These include [3,3]- and [2,3]-sigmatropic rearrangements, and [1,*j*]-hydrogen and carbon shifts (*j* = 3, 5, or 7). Energy of activation estimates are made for all but the [1,3]-carbon shifts and the [2,3] rearrangements. The reactivities of the latter are dealt with in a qualitative fashion. The final group of reactions considered are thermal ring-opening reactions. This category includes retro-Diels–Alder reactions, cheletropic extrusions, and electrocyclic ring-opening reactions of up to 6π electrons. The major kinetic aspects of each are highlighted and the qualitative scheme designed to approximate their reactivities is then presented. Examples of electrocyclic ring-opening reactions involving greater than 6π electrons are uncommon and have not yet been incorporated into CAMEO. After a section on implementation of the reactivity algorithms, sample sequences illustrate the capabilities of the periselectivity module.

Table III. [2 + 2] Cycloadditions Involving *gem*-Difluoro Alkenes[a]

reactants	exptl T, °C	rxn time, h	% yld	RADSUM	T range for CAMEO, °C	ref
	100–125	8	90	42	100–200	11, 12
$2CF_2{=}CF_2$[c]	200	7.5		0	200–300	2, 12
	225	9	72	6	200–300	12
	150	8	84	30	100–200	12
	120	23	71	48	100–200	12
	96–115	5.5	68	48	100–200	12
	150	8	14	30	100–200	12

[a] All reactions were run without added solvent. [b] $k = 9.0 \times 10^{-6}$ L/mol s at 82 °C. [c] $k = 4.6 \times 10^{-1}$ L/mol s at 400 °C (gas phase).

Table IV. [2 + 2] Cycloadditions Involving Allenes[a]

reactants	exptl T, °C	rxn time, h	% yld	RADSUM	T range for CAMEO, °C	ref
	140–150	82	5	60	200–300	12
	400		43	60	200–300	12
	200	8	7	60	200–300	12
	200	10.5	60	60	200–300	12
	200	8	32	58	200–300	12
	60–80		42[c]	80–84	100–200	12
$2Ph_2C{=}C{=}CH_2$				228	0–100	2
	130	2		78	100–200	14b

[a] All reactions were run neat except for the third entry which was run in benzene. [b] $k = 8.5 \times 10^{-7}$ L/mol s (35 °C), E_a = 18.4 kcal/mol, log A = 6.96.[2] [c] A mixture.

II. Cycloadditions

A. The Diels–Alder Reaction. Diels–Alder reactions typically exhibit small activation energies, large negative activation entropies, high stereospecificity, and insensitivity to solvent polarity. These are all consistent with a concerted mechanism.[2] The rate constants vary over a large range at room temperature (10^{-13}–10^{-1} L/mol s).[2] However, the entropies of activation and A factors are relatively constant at −30 to −40 cal/mol deg and ca. 10^6 L/mol s.[2] Consequently, the source of the variation in rates can be traced principally to the activation energies which range from approximately 7 to 28 kcal/mol.[2]

From analyses of literature data, it appears that the major factors that affect the rates of Diels–Alder reactions are the frontier molecular orbital gap ($\Delta\epsilon$),[3,4] entropic and energetic features such as the ease with which the diene can achieve s-cis coplanarity, intramolecularity and steric effects, and, to a lesser extent, thermodynamics. The first and last factors were incorporated into eq 1 which provides

$$E_a = 27.5 - 4(10.8 - \Delta\epsilon) + 0.2(\Delta H_{rxn} + 37.3) \quad (1)$$

an estimate of activation energies using the reaction of butadiene with ethylene as a reference standard (E_a = 27.5 kcal/mol, $\Delta\epsilon$ = 10.8 eV, and ΔH_{rxn} = −37.3 kcal/mol as determined by CAMEO).[1e,f] Note that $\Delta\epsilon$ is in eV while E_a and ΔH_{rxn} are in kcal/mol so energy conversion factors are contained in the constants. Thus, as the FMO gap gets smaller and the ΔH_{rxn} becomes more negative, the E_a decreases. The other considerations may be treated as follows.

Entropic factors and steric effects may affect log A, though it is easier for our purposes to keep the log A values constant and vary E_a. Several molecular features are being taken into account at this time. If the diene is held rigidly in a planar s-cis conformation, the [4 + 2] reaction is more facile.[5] For CAMEO's purposes, the presence of a diene in

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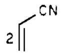
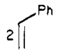
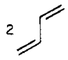
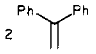
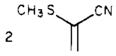
(2) Bamford, C. H.; Tipper, C. F. H. "Comprehensive Chemical Kinetics"; Elsevier Scientific Publishing Co.: New York, 1973; Vol. 9, Section 4.

(3) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.

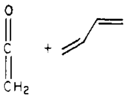
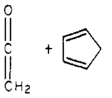
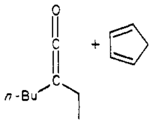
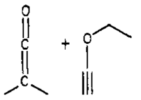
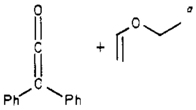
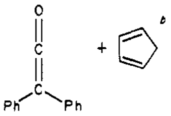
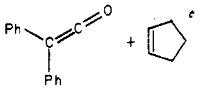
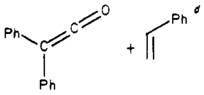
(4) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie: Weinheim/Bergstr., 1970.

Table V. [2 + 2] Diradical Cycloadditions between Olefins[a]

reactant	exptl *T*, °C	rxn time, h	% yld	RADSUM	*T* range for CAMEO, °C	ref
	195–300	1–24	3–7	60	>300	12, 15a
	150	24	<5	84	200–300	12, 15b
	150	18	4–5	60	>300	12
	50–55	2–5	2–5	168	100–200	12
	room temp	48	65	136	100–200	12

[a] All reactions were run neat except for the fourth entry which was run in dimethoxy sulfone. [b] E_a = 26.1 kcal/mol, log A = 5.37. [c] E_a = 17.9 kcal/mol, log A = 2.8.

Table VI. [2 + 2] Cycloadditions between Ketenes and Olefins or Acetylenes

reactants	exptl *T*, °C	rxn time, h	% yld	Δε, eV	*T* range for CAMEO, °C	ref
	100	2	1	9.4	0–100	12
	100	2	17	9.1	0–100	12
	120	1	82	9.3	0–100	18
	−20	170		10.3	0–100	12
	60	24	80	7.9	<0	12
	room temp	24–48	69–92	7.4	<0	2, 12
				7.7	<0	2
				7.1	<0	2

[a] $k = 4.5 \times 10^{-3}$ L/mol s (40 °C), E_a = 9.3 kcal/mol, $\Delta S^{\ddagger}$ = −40 eu.[1,17] [b] $k = 2.8 \times 10^{-4}$ L/mol s (30 °C). [c] $k = 1.25 \times 10^{-6}$ L/mol s (40 °C). [d] $k = 7.0 \times 10^{-4}$ L/mol s (120 °C).

a five-membered ring or diexo to a four- or five-membered ring lowers the E_a by 5 kcal/mol. If the diene is in a six-membered ring, it is lowered by 2 kcal/mol. Steric hindrance at the reacting termini is accounted for by incrementing the E_a by 0.3 kcal/mol for each disubstituted terminus and by 2.0 kcal/mol for each saturated tertiary, quaternary, or phenyl substituent attached to the terminal positions. If the diene or dienophile is part of a five- or six-membered ring, the ring atoms are not counted as substituents in the above algorithm. If the cycloaddition is intramolecular, the E_a is decreased by 5 kcal/mol in CAMEO. Although the changes in activation parameters in going from inter to intramolecular Diels–Alder reactions have not been established, it has been noted that the enthalpies of activation do not differ significantly for comparable systems whereas the $\Delta S^{\ddagger}$ is less negative by about 20 cal/mol deg.[6] A comparable rate effect is obtained by a reduction in E_a of 4–5 kcal/mol.

The unusual behavior of electron-deficient alkynes with nucleophilic reagents should also be considered. Because of molecular distortions which occur in the transition state, they behave as if they were considerably more electron deficient than the corresponding alkenes, a fact not explicable by FMO theory.[7] This factor will be taken into

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

(6) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63.

(7) Houk, K. N. *Top. Curr. Chem.* **1979**, *79*, 1.

Chart I

reactivity order	$H_2C{=}\overset{+}{N}H{-}\overset{-}{C}H_2$ ≈	$HC{\equiv}\overset{+}{N}{-}\overset{-}{C}H_2$ >	$H_2C{=}\overset{+}{N}H{-}\overset{-}{N}H$ ≈	$HC{\equiv}\overset{+}{N}{-}\overset{-}{N}H$ >	$HC{\equiv}\overset{+}{N}{-}\overset{-}{O}$ ≈	$N{\equiv}\overset{+}{N}{-}\overset{-}{C}H_2$ >
$-\epsilon_{HOMO}$, eV	6.9	7.7 (6.9)	8.6	9.2 (8.4)	11.0 (9.0)	9.0

$H_2C{=}\overset{+}{N}H{-}\overset{-}{O}$ >	$N{\equiv}\overset{+}{N}{-}\overset{-}{N}H$ >	$N{\equiv}\overset{+}{N}{-}\overset{-}{O}$
9.7	11.5	12.9

account by adjusting the LUMO energy for the parent acetylene from 2.8 eV to that of ethylene, 1.8 eV. Since the sensitivity to functionality is slightly greater for acetylene than for ethylene, this change makes electron-deficient acetylenes more reactive than the corresponding alkenes. This applies to all reaction types for which the FMO gap is used to gauge reactivity.

In Table I, the FMO gaps, ΔH_{rxn}, and E_a's calculated by CAMEO are tabulated along with the literature E_a's for a few Diels–Alder reactions. Also included for each reaction is the lowest temperature range in which the reactions are allowed by CAMEO. The latter are determined from straightforward manipulations of the Arrhenius equation using the standard rate constant, 2.2×10^{-5} L/mol s (section I), and log $A = 6.0$.

B. 1,3-Dipolar Cycloadditions. Like the Diels–Alder reaction, small activation energies, large negative activation entropies, stereospecificity, and little sensitivity to solvent polarity are all consistent with a concerted mechanism for 1,3-dipolar cycloadditions.[8] Reported rate constants for these reactions vary over 4 orders of magnitude, ranging from 10^{-6} to 10^{-2} L/mol s, while activation energies range from 8.6 to 18.0 kcal/mol.[2] This corresponds to the low end of the range of activation energies for Diels–Alder reactions. However, the entropies of activation for the 1,3-dipolar cycloadditions (−24 to −40 cal/deg mol) are very similar to those for the Diels–Alder reaction.[2]

The estimation of activation parameters for 1,3-dipolar cycloadditions is particularly difficult for several reasons. Not only are experimental kinetic data relatively scarce, but published values are often inaccurate.[2] In addition, Houk et al. have noted that "... the perturbation treatment often performs poorly in the comparison of relative reactivities of quite widely different 1,3-dipoles, e.g., the low reactivity of nitrous oxide in an absolute sense is not predicted, while the relative rates of reactions of different types of dipolarophiles with nitrous oxide are... These difficulties are in part due to the crudeness of FMO energy estimates, neglect of electrostatic interactions, closed-shell repulsions, and steric effects. An additional factor which must be taken into account is the stability of products and reactants."[9] The Coulombic (electrostatic) effects are undoubtedly of special importance because of the highly polar nature of 1,3-dipoles. When the dipolarophile is also very polarized as in electron-deficient species, enhanced rates are observed.[9] Another difficulty is that the CAMEO program is limited in its ability to accurately predict heats of reaction for such polar species. In short, any prediction of activation energies will be crude at best. Nevertheless, the following controlling factors can be identified and accommodated: (1) the FMO gap, (2) the inherent reactivity of the 1,3-dipole, (3) the Coulombic effect. Algorithms have already been developed to predict the FMO gap.[1e] In addition, an index on the inherent reactivity of 1,3-dipoles has previously been recognized by noting an approximate correlation with HOMO energies[10] (Chart I).

With the exception of the nitrile betaines, the correlation is quite good. If we correct the values by subtracting 0.8 eV for nitrile ylides and imines and 2.0 eV for nitrile oxides, the pattern can be used to help gauge reactivity. Adjusted energies are shown in parentheses in Chart I.

For the Diels–Alder reaction, a measure of the "goodness" of the FMO gap was made by comparing the FMO gap for a reaction with the worst allowed case, butadiene plus ethylene. For 1,3-dipoles, the standard is not obvious. Since the largest gap in the general schemes in Houk's summary of 1,3-dipolar cycloadditions is 10.8 eV,[9] the same gap as for butadiene plus ethylene, this value also makes a convenient standard for 1,3-dipolar reactions. In a similar fashion, the inherent reactivity of 1,3-dipoles will be gauged by the difference between the HOMO energy of the least reactive dipole (−12.9 eV) and the HOMO energy of the 1,3-dipole in question. The relative importance of these two effects was determined empirically by trying to most closely match the available literature E_a's. The resultant expression for E_a is given in eq 2 where again

$$E_a = 27.5 - 2(10.8 - \Delta\epsilon) - 3(12.9 + \epsilon_{HOMO}) \qquad (2)$$

the $\Delta\epsilon$ is in eV and E_a is in kcal/mol. In addition, to account for the Coulombic effect noted above, the dipolarophile's electron deficiency is measured by comparison of its HOMO energy with that of ethylene. Specifically, the difference between the HOMO energies of ethylene and of the electron-deficient dipolarophile is subtracted from the calculated E_a. Furthermore, as with Diels–Alder reactions, if the reaction is intramolecular, the E_a is taken to be lowered by 5 kcal/mol. Table II lists a few 1,3-dipolar cycloadditions with their experimental and calculated E_a's and the lowest temperature at which the reaction is allowed to proceed in CAMEO.

C. Thermal [2 + 2] Cycloadditions. Before the reactivity of [2 + 2] thermal cycloadditions can be discussed, these reactions must be categorized into mechanistic types which include diradical, dipolar, and concerted processes. The reactions can be complex and the kinetic data are limited so a qualitative approach is necessitated. Thus, the aim is to develop simple algorithms to place the reactions into temperature blocks after they have been categorized mechanistically.

Diradical Processes. In CAMEO, functional groups (FG's) and other substituents are examined to determine a number reflecting the approximate radical-stabilizing ability of each attachment. The index has been developed in part by considering C–H bond dissociation energies.[1f] Values for the following common FG's are shown in parenthesis: F (0), Cl (3), Br (5), Me (6), Et (9), *t*-Bu (10), OMe (24), CHO (24), $CH{=}CH_2$ (30), CH (30), and Ph (42). In considering [2 + 2] diradical cycloadditions, the sum of the numbers for the groups on both radical centers in the diradical intermediate will be referred to as the "RADSUM". The chosen temperature limits attempt to

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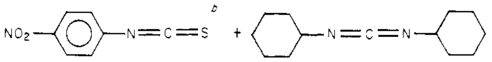
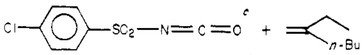
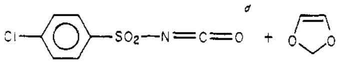
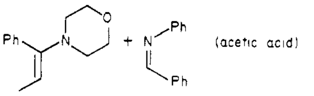
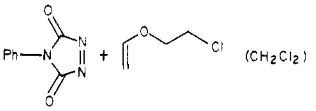
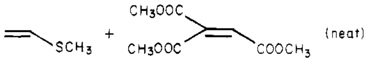
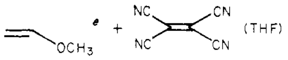
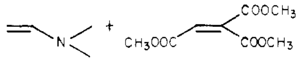
(8) Gilchrist, T. L.; Storr, R. C. "Organic Reactions and Orbital Symmetry", 2nd ed.; New York: Cambridge University Press, 1979.

(9) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301.

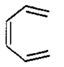
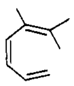
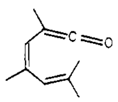
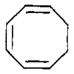
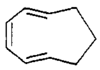
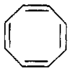
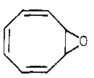
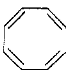
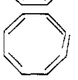
(10) Houk, K. N.; Sims, J.; Duke, R. E., Jr.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287.

Table VII. [2 + 2] Dipolar Cycloadditions

reactants	exptl *T*, °C	rxn time, h	% yld	$\Delta\epsilon$, eV[a]	*T* range for CAMEO, °C	ref
 [b]	50			10.4	0–100	19
	70	12	90	9.3	0–100	23
 [c]	25			5.0	<0	2
 [d]	20			4.6	<0	2
	*f*	7	60–65	5.8	<0	25a
	*f*		100	7.8	0–100	25b
				DIPSUM		
	28	3 days	47	48	>300	21
 [e]	*f*			84	0–100	26
	-55	1	88	80	0–100	21

[a] $\Delta\epsilon$ is the effective HOMO – LUMO energy difference (see text). [b] 1.3×10^{-3} L/mol s (50 °C, CCl_4); 3.0×10^{-3} L/mol s (50 °C, CH_3CN). [c] $1.2–1.5 \times 10^{-5}$ L/mol s (25 °C, CCl_4); $5–10 \times 10^{-1}$ L/mol s (25 °C, CH_3NO_2). [d] 1.2 L/mol s (20 °C, CH_2Cl_2). [e] 5.54×10^{-2} L/mol s (25 °C, CH_2Cl_2);[26] 1.85×10^{-2} L/mol s (25 °C, CH_3CO_2Et).[19b] [f] Room temperature.

Table VIII. Activation Energies for Electrocyclic Closures

reactant	exptl E_a, kcal/mol	log *A*	calcd E_a, kcal/mol	*T* range for CAMEO, °C	ref
	29.9	11.85	29	100–200	29
	31.8	10.50	31	100–200	29
	13.9		21	0–100	29
	26.0	13.0	22	0–100	2
	23.6	12.2	24	0–100	2
	28.0	13.0	22	0–100	2
	24.6		22	0–100	29
	17.0	11.0	19	<0	2, 29
	23.3	10.5	23	0–100	2

match typical experimental conditions as closely as possible.

For [2 + 2] reactions involving *gem*-difluoro compounds: if RADSUM < 30, *T* > 200 °C and if RADSUM ≥ 30, *T* > 100 °C.

In [2 + 2] reactions involving allenes, the intermediate diradical will always yield a resonance stabilized allylic radical. Thus allenes are treated as if they contain a vinylic group for determining the RADSUM.[1f] Thus the following limits are used for allenes: if RADSUM < 70, *T* > 200 °C, if 70 ≤ RADSUM ≤ 200, *T* > 100 °C, and if RADSUM > 200, *T* < 100 °C.

Diradical [2 + 2] reactions between olefinic components generally give low yields and require relatively high temperatures. The limits in CAMEO are as follows: if RADSUM < 60, no reaction occurs, if 60 ≤ RADSUM < 80, *T* > 300 °C, if 80 ≤ RADSUM ≤ 120, *T* > 200 °C, and if RADSUM > 120, *T* > 100 °C.

Tables III, IV, and V give examples of the three types of [2 + 2] diradical cycloadditions mentioned above. Rates constants and activation parameters are included if available along with experimental reaction conditions. The lowest temperature range in which CAMEO allows the reaction to proceed is also listed.

Concerted Processes. The reaction of ketenes with olefins or acetylenes is the only [2 + 2] cycloaddition which is generally believed to be concerted.[4,15] The exceptions are cases in which a particularly stable intermediate can be formed as in the reaction between ketenes and enamines. Ketene itself is the least reactive and requires heating even with cyclopentadiene. Dialkylketenes are of intermediate reactivity and usually react well only with fairly nucleophilic olefins or acetylenes. However, diarylketenes are very labile and react with dienes at room temperature.[16]

The FMO gap gives a rough indication of the favorability of [2 + 2] reactions with ketenes, though it is not an infallible guide. In particular, donating groups such as ethers

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(11) Bartlett, P. D.; Montgomery, L. K. *J. Am. Chem. Soc.* **1964**, *80*, 628.

(12) Roberts, J. D.; Sharts, C. M. *Org. React.* (*N.Y.*) **1962**, *12*, 1.

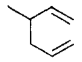
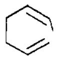
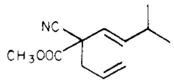
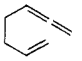
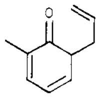
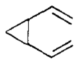
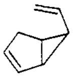
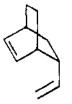
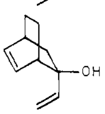
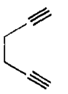
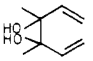
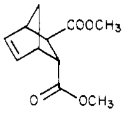
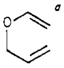
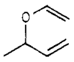
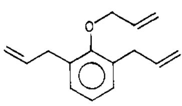
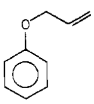
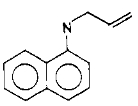
(13) Bertrand, M.; Maurin, R.; Gras, J. L.; Gil, G. *Tetrahedron* **1975**, *31*, 849.

(14) (a) Shuraeva, V. N.; Katsobashvili, V. Y., *Zh. Org. Khim.* **1975**, *11*, 923. (b) Shuraeva, V. N.; Katsobashvili, V. Y. *Ibid.* **1975**, *11*, 1870.

(15) Holder, R. W. *J. Chem. Educ.* **1976**, *53*, 81.

(16) Martin, J. C.; Gott, P. G.; Goodlett, V. W.; Hasek, R. H. *J. Org. Chem.* **1975**, *30*, 4175.

Table IX. Activation Energies for [3,3]-Sigmatropic Rearrangements

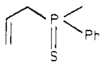
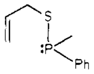
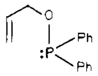
reactant	exptl E_a, kcal/mol	log A	calcd E_a, kcal/mol	T range for CAMEO, °C	ref
	34.2	10.55	34	100–200	2, 29
	36.7	10.66	37	200–300	2, 29
	28.6	10.38	28	0–100	2, 29
	28.5	9.97	29	100–200	2, 29
	26.8	11.81	25	0–100	2
	25.4	11.18	24	0–100	29
	22.9	11.67	24	0–100	2, 29
	44.2	12.8	44	>300	2, 29
	41.8	12.5	40	200–300	29
	34.4		35	100–200	29
	25.0		25	0–100	29
	21.0–24.3	10.94–11.96	28	0–100	29
	10.4	15.7	9	<0	2
 [a]	30.6	11.7	30	100–200	2, 29
	25.3–29.1	10.78–11.32	29	100–200	2, 27
 [b]	30.5		32	100–200	2
 [c]	33.1		32	100–200	2
 [d]			40	200–300	2

[a] $k = 1.2 \times 10^{-4}$ s^{-1} (157 °C). [b] $k = 7.0 \times 10^{-5}$ s^{-1} (170 °C). [c] $k = 7.0 \times 10^{-6}$ s^{-1} (170 °C). [d] Rearranges at 260 °C.

or amines are more rate enhancing than would be predicted based on the calculated FMO energies. Also, alkyl substituted ketenes are more reactive than ketene itself, even though they should have higher LUMO energies. In order to accomodate these considerations, two modifications are required. (1) If the ketene is alkyl substituted, the LUMO energy is considered to be lowered by 0.3 eV per alkyl group. (2) If the olefin or acetylene is substituted with a donating FG containing a saturated heteroatom, the FMO gap is decreased by 1.0 eV. Once these adjustments have been made, the reactions are classified as follows: if $\Delta\epsilon > 11.0$ eV, no reaction occurs, if $\Delta\epsilon \leq 11.0$ eV, reaction is allowed at <200 °C, if $\Delta\epsilon \leq 10.5$ eV, reaction is allowed at <100 °C, and if $\Delta\epsilon \leq 9.0$ eV, reaction is allowed at <0 °C. Table VI lists a few examples with their experimental reaction conditions and the temperature range in which the reaction can occur in CAMEO.

Dipolar Processes. A variety of reagent combinations yield [2 + 2] dipolar cycloadditions. These include the reactions of heterocumulenes with other heterocumulenes

Table X. Activation Parameters for [2,3]-Sigmatropic Rearrangements (Ref 32)

reactant	E_a, kcal/mol	log A	ΔS^*, eu	T (°C) for $k = 1 \times 10^{-5}$ s^{-1}
	33 ± 2	9.6	−18	221
	20	10.8		3
	23.0	10.4	−14	55

or double bonds containing one or more heteroatoms, the reactions of heterocumulenes and double bonds containing one or more heteroatoms with olefins or acetylenes, and the reactions between olefins of widely different polarity. Some reactions between heterocumulenes have been shown to be concerted with some degree of polarity in the transition state.[17] These reactions fit better into the algorithms developed for dipolar [2 + 2] reactions and for our purposes are considered as such.

The available kinetic data on true dipolar [2 + 2] processes show that their rate constants are highly dependent upon the polarity of the solvent.[2] A typical example is the rate study at 25 °C of *cis*-1-methoxypropene with tetracyanoethylene.[19b] In CCl_4 and CH_3CN, the rate constants are 4.85×10^{-5} L/mol s and 4.96×10^{-1} L/mol s, respectively. At this time, the user does not have the option of choosing a particular solvent for pericyclic reactions. Since the primary concern is with the competition between different pathways, and since the choice of solvent has little effect on the rate constants of most pericyclic processes, all pericyclic reactions are currently considered to be run in nonpolar solvents. Refinements will be made in the future.

For all but the dipolar [2 + 2] reactions between unsaturated carbon–carbon bonds, the FMO gaps give a rough idea of the favorability of a reaction. It should be mentioned that the wide range of reactivities displayed by heterocumulenes is difficult to predict because the effects of substituents involve a subtle interplay between sterics and electronics. Nevertheless, Ulrich gives an approximate order of inherent reactivities:[18] C=C=O > N=C=O > N=C=N > N=C=S > N=S=O > inert heterocumulenes such as CO_2 and SO_2. So that these inherent reactivities are taken into account, heterocumulenes are now being classified as parent systems[1e] and their LUMO energies are being set relative to ketene's. Ab initio molecular orbital calculations with the 3-21G basis set yield a LUMO energy of 3.74 eV for ketene. This number is adjusted to 0.4 eV as for other parent systems as described previously.[1e] In the above series, the LUMO energies are incremented by 0.4 eV at each step in going from left to right. The HOMO energies are calculated by the same algorithm used for 2π systems,[1e] but 1.0 or 0.5 eV is added if the unreactive cumulene terminal atom is an oxygen or nitrogen, respectively.

Once these adjustments have been made, the reactions are classified into different temperature blocks depending upon the perceived effective FMO gap. Larger FMO gaps must be allowed for the reactions of heterocumulenes with other heterocumulenes or with compounds containing hetero double bonds because of the additional Coulombic attraction between the two reagents. In these two cases the following rules are used: if $\Delta\epsilon \le 8.5$ eV, reaction is allowed at <0 °C, if $\Delta\epsilon \le 10.5$ eV, reaction is allowed at <100 °C, if $\Delta\epsilon \le 12.5$ eV, reaction is allowed at <200 °C, if $\Delta\epsilon \le 14.5$ eV, reaction is allowed at <300 °C, and if $\Delta\epsilon \le 15.0$ eV, reaction is allowed at >300 °C. Much more stringent requirements are needed for reactions between heterocumulenes or multiple bonds containing heteroatoms with olefins or acetylenes. If the reaction has a $\Delta\epsilon \le 7.6$ eV, it is allowed at <0 °C. If $\Delta\epsilon \le 8.8$ eV, the reaction is allowed at <100 °C. No reaction is allowed for larger gaps.

The reactivity of [2 + 2] dipolar cycloadditions between olefins of widely different polarity is strongly influenced by the stability the 1,4-dipolar intermediate. The Hammett equation and its many variations correlate the effects of functionality with reactivity.[20] Numerous σ constants have been devised to represent the effect of substituents on particular reaction rates. Along these lines, for the development of an algorithm to estimate FMO energies, substituents have been assigned τ values reflecting their π-donating or π-withdrawing abilities.[1e] Positive and negative τ's correspond to π-donating and π-withdrawing FG's, respectively. The larger the absolute value of τ, the stronger the electronic effect of the FG. The numbers are derived from the effects of FG's on the ionization potentials of substituted ethylenes and are utilized in empirical expressions to estimate frontier molecular orbital energies.[1e] These values can be modified somewhat to correlate better with σ^+ and σ^- values for use in CAMEO to estimate the stability of 1,4-dipoles. σ^+ and σ^- values cannot be used directly since they have only been determined for a limited number of substituents. Thus, in CAMEO, the greater the sum of the revised τ's for substituents on an olefinic atom, the better an incipient positive charge will be stabilized. Conversely, the more negative the sum of the τ's, the better an incipient negative charge will be stabilized. The following adjustments are made to the original τ values: (1) Conjugating substituents (e.g., vinyl $\tau = 30$, phenyl $\tau = 42$) have large positive τ values.[1e] First, since they can stabilize either a positive or a negative charge, the sign of τ must be reversed when approximating their effect on the stability of an anionic site. In addition, the values are halved to more accurately reflect their relative stabilizing effect on a charged atom. (2) Since π donating FG's have more pronounced effects on HOMO energies than withdrawing FG's, the absolute values of τ for the former are significantly larger than the latter (e.g., –OMe $\tau = 24$, –CHO $\tau = -12$). If the τ values for π-withdrawing groups are tripled, except for those groups that already have very negative τ's such as a nitro group or a sulfone, they correlate much better with σ^- values. (3) The original τ values for saturated sulfur groups are much too large (–SH $\tau = 32$) in the present context. They are divided by three to reflect more closely their ability to stabilize a carbocation. (4) The halogens, except for fluorine, slightly stabilize and destabilize anionic and cationic centers, respectively. The τ's for the Cl, Br, and I are adjusted to −6. The effect of fluorine appears to be small and no adjustment is made at this time.

Once these adjustments have been made, one further restriction is placed upon the two reacting olefins. One reagent must be nucleophilic and the other electrophilic. This is easily determined by comparing their HOMO en-

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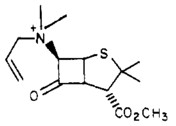
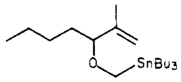
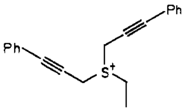
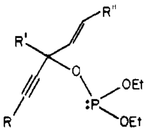
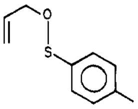
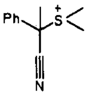
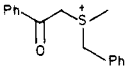
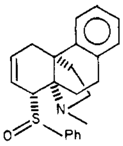
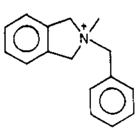
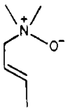
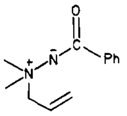
(17) Dondoni, A.; Battaglia, A. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1475.

(18) Ulrich, H. "Cycloaddition Reactions of Heterocumulenes"; Academic Press: New York, 1967.

(19) (a) Huisgen, R.; Mayr, H. *Tetrahedron Lett.* **1975**, 2965. (b) Huisgen, R.; Steiner, G. *Ibid.* 1973, 3763.

(20) (a) Jaffe, H. H. *Chem. Rev.* **1953**, *53*, 191. (b) Wells, P. R. *Ibid.* 1963, *63*, 171. (c) Stock, L. M.; Brown, H. C. *Adv. Phys. Org. Chem.* **1963**, *1*, 35. (d) Ritchie, C. D.; Sager, W. F. *Prog. Phys. Org. Chem.* **1964**, *2*, 323.

Table XI. [2,3]-Sigmatropic Rearrangements[a]

reactant	exptl conditions	PV for CAMEO	T range for CAMEO, °C	ref
	NaH, room temp, 30 min	4	0–100	33
	n-BuLi, 30 min, −78 °C	5	<0	34
	n-BuLi, THF, −70 °C	5	<0	35
	−10 °C	5	<0	36
	0 °C, fast	5	<0	37
	n-BuLi, THF, 0 °C	5	<0	38
	5% Na, 10 equiv NaOMe, 60–65 °C, 2 h	4	0–100	39
	70 °C, 24 h	4	0–100	40
	10% PhLi, ether, 25–37 °C	3	100–200	41a
	80–150 °C	4	0–100	41b
	120–140 °C	3	100–200	41c

[a] 15% of the product from a Stevens rearrangement. The ratio is temperature dependent.

ergies with that of ethylene. In addition, if only conjugating groups are present, a diradical process tends to predominate and a [2 + 2] dipolar mechanism is not considered (e.g., the dimerization of 1,1-diphenylethylene).

For the nucleophilic olefin, the adjusted τ's are added on each terminus. The larger sum is stored and corresponds to the ability of the functionality on that terminus to stabilize a positive charge. Similarly, the τ's for FG's on electrophilic olefins are added for each terminus and the most negative sum is stored and reflects the ability of the functionality on that terminus to stabilize a negative charge. The absolute values of the stored sums are then added to yield DIPSUM which is used to gauge the reactivity of [2 + 2] dipolar cycloadditions. The following rules are used by CAMEO: if DIPSUM < 35, no reaction occurs, if $35 \leq$ DIPSUM < 55, $T > 300$ °C, if $55 \leq$ DIPSUM < 65, 200 °C $< T <$ 300 °C, if $65 \leq$ DIPSUM < 75, 100 °C $< T <$ 200 °C, if $75 \leq$ DIPSUM < 85, 0 °C $< T <$ 100 °C, and if DIPSUM $>$ 85, $T <$ 0 °C.

For example, the reaction of N,N-dimethylisobutenylamine and tricyanoethylene (DIPSUM = 104) is explosive at 0 °C.[21] The less electrophilic trimethylethylenetricarboxylate reacts quantitatively with N,N-dimethylisobutenylamine (DIPSUM = 80) at room temperature after 1 day.[21] The same nucleophilic olefin with methylethylenecarboxylate requires heating for 2 h at 170 °C[21] (DIPSUM = 62). 1-Methoxyethylene reacts with tricyanoethylene at room temperature in a few hours[21] (DIPSUM = 84).

This algorithm is particularly useful in dealing with the competition between [4 + 2] and [2 + 2] processes when one or both reagents is a 1,3-diene. Each process is considered separately. Only one restriction on the competition is presently incorporated into CAMEO. If a Diels–Alder reaction is estimated to occur two or more temperature blocks (see section I) below a [2 + 2], or vice versa, only the lower temperature reactions are displayed by the program. Thus, for the Diels–Alder reaction between

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[21] Hall, H. K.; Ykman, P. *J. Am. Chem. Soc.* **1975**, *97*, 800.

Table XII. Activation Parameters for [1,5] H and C Sigmatropic Migrations

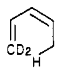
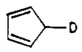
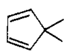
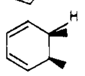
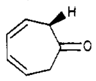
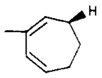
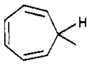
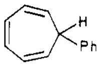
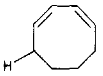
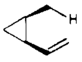
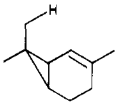
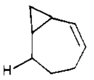
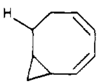
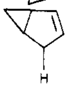
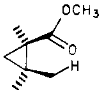
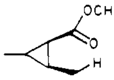
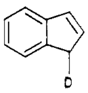
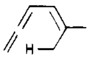
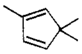
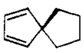
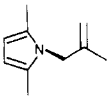
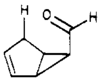
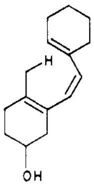
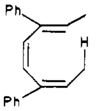
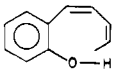
reactant	exptl E_a, kcal/mol	log *A*	calcd E_a, kcal/mol	*T* range for CAMEO, °C	ref
	36.3	11.45	36	200–300	2, 27
	24.3	12.11	24	0–100	2
	21.7	11.88	21	0–100	42a
	34 (32.1)	11.7	33	100–200	2 (42a)
	26.5	11.5	30	100–200	2
	29.5	11.4	30	100–200	27
	33.3 (32.3)	12.6	33	100–200	2 (42a)
	27.6 (26.9)	10.8	30	100–200	2 (42a)
	30 (29.3)	11	30	100–200	2 (42a)
	33.5	11.41	36	200–300	2
	28	9.5	30	100–200	2
	38.6	12.76	39	200–300	2
	28	11.4	32	100–200	2
	>44		46	NR	2
	37.5		36	200–300	42a
	32.5		36	200–300	27
	36	12	32	100–200	2
	24		26	0–100	42a
	44.2	13.9	41	200–300	42a
	34.6	13.3	34	100–200	42a
	48.0		41	200–300	42a

Table XIII. Activation Parameters for [1,7] H Sigmatropic Migrations

reactants	exptl E_a, kcal/mol	log *A*	calcd E_a, kcal/mol	*T* range for CAMEO, °C	ref
	25.5	9.9	22	0–100	27
	20.9		19	0–100	42a
	18.5	9.5	19	0–100	42a
	26.1		27	100–200	42a

1,1-dimethoxy-3-((trimethylsilyl)oxy)-1,3-butadiene with diethyl acetylenedicarboxylate, the program estimates an E_a of 11 kcal/mol (<0 °C).[22] The DIPSUM for the best dipolar [2 + 2] is 68 units, corresponding to the 100–200 °C temperature range. Therefore, the [2 + 2] reaction is not shown. In the reaction of 1-methylbutadiene with TCNE, the E_a for the [4 + 2] process is approximated at 13 kcal/mol (<0 °C), and the [2 + 2] dipolar cycloaddition has a DIPSUM of 76 (0–100 °C). The products of both processes are displayed by CAMEO.

Table VII lists some [2 + 2] dipolar cycloadditions, their experimental reaction conditions, and the lowest temperature at which each reaction is allowed to proceed in CAMEO.

III. Larger Cycloadditions

Cycloadditions involving greater than 6π electrons are much less common than the smaller cycloadditions. Yet generally, the ends of a conjugated polyene have the largest coefficients in the frontier molecular orbitals and therefore a pericyclic reaction could be expected to use the longest part of a conjugated system compatible with the Woodward–Hoffmann rules.[23] Of course, this is only true if the reactants can attain the required geometry. Spacial, entropic, and steric factors are all crucial. Thus, concerted cycloadditions involving open chain polyenes leading to large ring systems are unlikely due to entropic reasons.[8] The dimerization of *cis*-hexadiene, for example, leads exclusively to the [4 + 2] adducts because the triene is rarely in the required planar conformation.[8] Cyclic polyenes are more likely to be involved in a large cycloaddition, but if they are in equilibrium with their valence tautomer, the latter often reacts in a smaller cycloaddition. However, those cyclic polyenes which do not tautomerize, such as tropone and azepines, do participate in [6 + 4] cycloadditions.

Presently, only larger cycloadditions involving 10π electrons are dealt with in CAMEO, namely the [${}_\pi 8_s + {}_\pi 2_s$] and the [${}_\pi 6_s + {}_\pi 4_s$] reactions. Still larger cycloadditions become progressively rarer.[8] Certain geometrical restrictions are placed on the acceptable 8π and 6π polyenes. Namely, all the bonds comprising the polyene must either be part of a ring or exo to a ring. In addition, if more than two rings are involved, they must be fused to one another.

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[22] Danishefsky, S.; Singh, R. K.; Gammill, R. B. *J. Org. Chem.* **1978**, *43*, 379.

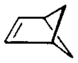
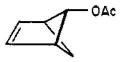
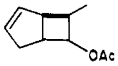
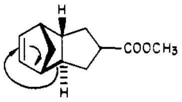
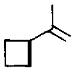
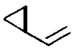
[23] Fleming, I. "Frontier Orbitals and Organic Chemical Reactions"; Wiley: New York, 1976.

[24] Aue, D. H.; Thomas, D. *J. Org. Chem.* **1975**, *40*, 2552.

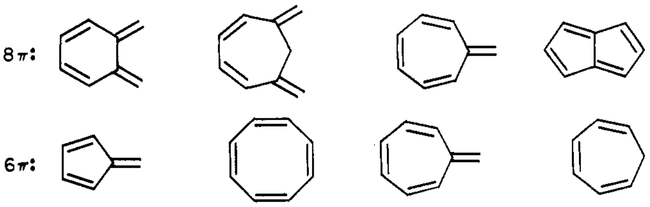
[25] (a) Nomura, Y.; Muneak, K.; Shibata, T.; Yoshito, T.; Shuji, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3343. (b) Herbert, H. J.; Jones, M. L. *J. Org. Chem.* **1983**, *48*, 822.

[26] von Jouanne, J.; Kelm, H.; Huisgen, R. *J. Am. Chem. Soc.* **1979**, *101*, 151.

Table XIV. Activation Parameters for [1,3] sp^3 Carbon Sigmatropic Migrations

reactant	exptl E_a, kcal/mol	log A	T range exptl, °C	point value	T range for CAMEO, °C	ref
	34.29	13.95	150–190	3	100–200	42a
	27.5		85–105	4	0–100	42a
	34.9		227–237	2	200–300	42a
			290	2	200–300	42a
			220–230	2	200–300	42a
	51			1	>300	2
	50.0	13.7		1	>300	2
	50.2	14.09		1	>300	2
	49.5	14.47		1	>300	2

The following systems illustrate the most typical 8π- and 6π-electron polyenes used in 10π-electron cycloadditions.



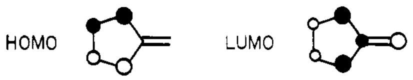
Since the larger cycloadditions are uncommon, they have received limited mechanistic and kinetic study. However, Houk and co-workers have recently examined some [8 + 2] and [6 + 4] cycloadditions.[27] The reactions appear to be concerted and the stereochemistries observed are in agreement with the Woodward–Hoffmann rules.[27] Though no systematic kinetic studies have been done on the larger cycloadditions, they are generally run at temperatures between 0 and 100 °C and the reaction times range from a few hours to a few days.[27]

The reactivities of thermally allowed [8 + 2] and [6 + 4] cycloadditions should be controlled by the same factors as the 6π-electron reactions, namely, the FMO gap and coefficients, entropic features, intramolecularity, and steric effects. Equation 3, a modified form of eq 1, is used in

$$E_a = 25 - 4(10.8 - \Delta\epsilon) \qquad (3)$$

CAMEO as a highly empirical gauge of their reactivity. Since conjugation has the effect of raising the HOMO and lowering the LUMO, the E_a's calculated for larger cycloadditions are competitive with those of the [4 + 2] reactions. The base value is lowered to 25 kcal/mol because the recognized 6π- and 8π-electron systems are all held in rigid conformations due to the framework restrictions mentioned above. In addition, as with Diels–Alder reactions, 0.3 kcal/mol is added to the E_a for each disubstituted terminus and E_a is incremented by 2.0 kcal/mol for each terminal substituent that is a saturated tertiary, quaternary, or phenyl group. If the reaction is intramolecular, the E_a is considered to be lowered by 4 kcal/mol.

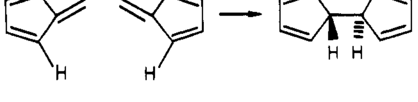
Many interesting studies on larger cycloadditions have involved fulvenes. Their varied reactivity with other systems provide good tests of frontier molecular orbital theory. The patterns of MO coefficients for the frontier orbitals of fulvene itself are illustrated below.[8] Thus, if



fulvene reacts via its HOMO, it should react as a 4π-electron or a 2π-electron component but not as a 6π system. [6 + 4] reactions with fulvene as the 6π-electron component should only occur if the fulvene is reacting via its LUMO. These modifications have been incorporated into CAMEO. The chemistry of fulvenes is further complicated by the fact that strong donating or withdrawing functional groups can raise the NHOMO above the HOMO or lower the NLUMO below the LUMO. These adjacent orbitals have different symmetries and can alter the selectivities mentioned above.[8] This factor is not yet handled by CAMEO.

IV. Electrocyclic Ring Closure Reactions

An electrocyclic ring closure results in the formation of a single bond between the terminal atoms of a conjugated molecule. The processes are concerted, intramolecular, and insensitive to both solvent polarity and catalysis.[2] They are also stereospecific; $4n + 2$ and $4n$ π systems close in disrotatory and conrotatory fashions, respectively. Most commonly, electrocyclic closures involve 6π and 8π systems, although closures of larger π systems with restricted geometries, such as in the pentafulvalene below, undergo rapid thermal cyclizations.[28] 1,3-Butadienes can also close



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[27] (a) Gupta, Y. N.; Doa, M. J.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7336. (b) Houk, K. N.; Luskus, L. J.; Bhacca, N. S. *Ibid.* 1970, *92*, 6392. (c) Houk, K. N.; Luskus, L. J. *Tetrahedron Lett.* **1970**, 4029. (d) Houk, K. N.; Watts, C. R. *Ibid.* **1970**, 4025. (e) Houk, K. N.; Woodward, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 4143. (f) Houk, K. N.; Woodward, R. B. *Ibid.* **1970**, *92*, 4145. (g) Tegmo-Larsson, I.-M.; Houk, K. N. *Tetrahedron Lett.* **1978**, 941. (h) Dunn, L. C., Houk, K. N. *Ibid.* **1978**, 3411.

[28] Sauter, H.; Gallenkamp, B.; Prinzabach, H. *Chem. Ber.* **1977**, *110*, 1382.

Table XV. Activation Parameters for Ring-Opening Reactions

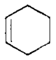
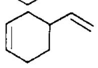
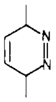
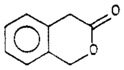
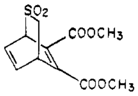
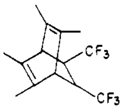
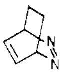
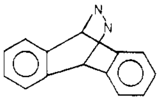
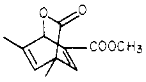
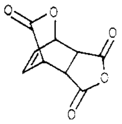
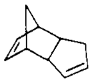
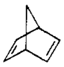
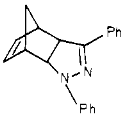
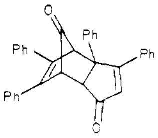
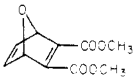
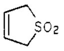
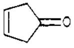
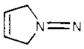
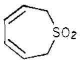
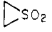
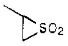
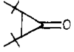
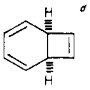
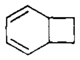
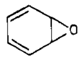
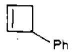
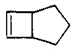
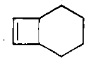
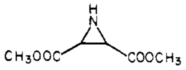
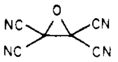
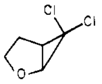
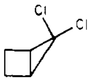
reactant	exptl E_a, kcal/mol	log A	exptl T, °C	point value CAMEO	T range for CAMEO, °C	ref
	55.1–72.7	12.1–17.1	485–750	−1	NR	47a
	62.0	15.2	750	0	NR	47a
			25	4	0–100	47b
			500	0	NR	48
			220	2	200–300	48
			250	2	200–300	47a
			−10	6	<0	49
			80	1	>300	47a
			110	3	100–200	48
	33.2	13.9	130	3	100–200	47a
	42.8	13.8		2	200–300	47a
	33.7	13.0	185	3	100–200	47a
	50.5	14.72	350	1	>300	47a
			135	3	100–200	47a
			200	3	100–200	47a
			195–400	3	100–200	47b
	30.1		125	3	100–200	45
 [a]				2	200–300	45
				4	0–100	50
	29.7		128	3	100–200	45
 [b]	27.8		93	4	0–100	45
	ca. 18			5	<0	45
 [c]				4	0–100	45
 [d]	25.0			5	<0	29

Table XV (Continued)

reactant	exptl E_a, kcal/mol	log A	exptl T, °C	point value CAMEO	T range for CAMEO, °C	ref
	24.7–25.5			4	0–100	29
	7.2–9.1			5	<0	29
	32.5	13.08		3	100–200	29
	26	12.4		4	100–200	29
			380	1	>300	51
	43		230–260	2	200–300	52
			100 (rev)	3	100–200	53
			130–150	3	100–200	53
			126	3	100–200	54
			60	4	0–100	55
			<0	4	0–100	55

[a] $k = 3\text{–}12.5 \times 10^{-9}$ s^{-1} at 100 °C. [b] 15 times faster than extrusion of SO_2 from five-membered ring sulfolene. [c] $k = 2 \times 10^{-4}$ s^{-1} at 150 °C. [d] The following are electrocyclic ring openings.

to cyclobutenes, but, except in rare cases, the equilibrium lies strongly in favor of the diene. At this time, the largest π system recognized by the program includes 10 electrons. When either a 10π-, 8π-, or 6π-electron system is found, the restriction is made that all inner double bonds must be cisoid unless they are exo to a ring. Fulvene type systems and those in fully conjugated rings such as the 8π system in cyclooctatetraene or in pentalene are not considered. Naturally, the program displays the product stereochemistry, reflecting the disrotatory or conrotatory nature of the reaction.

The loss of rotational freedom in the transition state of an electrocyclic closure dictates substantial negative entropies of activation.[2] The average log A value for acyclic 6π-electron closures is about 11, for acyclic 8π-electron closures about 10, and for conjugated systems incorporated within rings, about 12.[2] An average log A of 11 is used for electrocyclic closures to estimate the E_a's allowed for each temperature range (see section I). The E_a's for cyclic cases and for 8π-electron acyclic closures are artificially modified to take the above data into account.

Analysis of the available literature data reveals certain patterns of use in predicting the E_a's.[2,29] These trends have been incorporated into the following algorithms:

(1) The E_a for closure of *cis*-hexatriene (29.0 kcal/mol) and *cis,cis*-octatetraene (17.0 kcal/mol) are taken as the base values for 6π- and 8π-electron closures. The base value for 8π-electron systems is incremented by 2 kcal/mol and for π systems within rings it is decremented by 2 kcal/mol to correct for the log A differences mentioned above.

(2) Cis substituents on the terminal positions of the conjugated system raise the E_a, possibly by forcing the system to be nonplanar. For each cis substituent on the terminus of an acyclic conjugated system, the E_a is raised by 2.0 kcal/mol.

(3) A terminal atom that is part of a cumulene lowers the E_a by 10 kcal/mol.

(4) The E_a's for cyclic π systems can be substantially lower than for analogous acyclic systems. If a triene is part of a ring of more than six members, the E_a is lowered by 10/(ring size − 6) kcal/mol.

(5) If closure of a π system not fully within a ring generates a three- or four-membered ring, the E_a is raised by 10 kcal/mol.

(6) If closure destroys or generates aromaticity, the E_a is raised or lowered by 8 kcal/mol, respectively.

Data for some electrocyclic closures are presented in Table VIII including experimental activation parameters, the calculated E_a, and the lowest temperature range at which the reaction is allowed to proceed in CAMEO.

V. Sigmatropic Rearrangements

A. [3,3]-Sigmatropic Rearrangements. The Cope and Claisen rearrangements exhibit first order kinetics, high stereospecificity, and reaction rates which are similar in the gas phase and in polar and nonpolar solvents (a small solvent effect is observed for Claisen rearrangements).[2] They are characterized by low activation energies and large negative entropies of activation which are highly suggestive of a concerted mechanism. Average log A values are about 11.[2]

Since a large amount of kinetic data is available for these reactions,[2,29] the E_a's may be estimated using 1,5-hexadiene as a standard (E_a = 35 kcal/mol). This base value is adjusted according to the presence of activating or deactivating factors as listed below.

(1) The presence of heteroatoms in the 1,5-diene affects the E_a. If one of the inner atoms is an oxygen (Claisen), the E_a is lowered by 5 kcal/mol. If, on the other hand, the inner atom is nitrogen or sulfur, the E_a is raised by 3 kcal/mol. If the termini of the 1,5-diene are heteroatoms, the system is less reactive. Each nitrogen and oxygen terminus raises the E_a by 4 and 8 kcal/mol, respectively.

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[29] Wilcott, M. R.; Cargill, R. L.; Sears, B. A. *Prog. Phys. Org. Chem.* **1972**, *9*, 25.

Table XVI. Activation Limits for Pericyclic Reactions

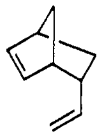
reaction type:	[8 + 2] and [6 + 4]	[4 + 2] and [3 + 2]	electrocyclic ring closure [3,3]-sigmatropic and [1,5]-sigmatropic	[1,7]-sigmatropic	[2 + 2] diradical (gem-di F)	[2 + 2] diradical (allene)	[2 + 2] diradical (2 olefins)	[2 + 2] concerted (ketene + olefin)	[2 + 2] dipolar (hetero + hetero)	[2 + 2] dipolar (hetero + olefin)	[2 + 2] dipolar (olefin + olefin)	reverse [4 + 2] and ring-opening reactions, [2,3]-sigmatropic and [1,3]-sigmatropic
avg log *A*		6.0	11.2–11.3	9.5								
activation parameter	E_a	E_a	E_a	E_a	RADSUM	RADSUM	RADSUM	FMO gap	FMO gap	FMO gap	DIPSUM	point value
>300 °C	30	30	45	40	0	0	60	11.0	15.0	8.8	35	1
200–300 °C	28	28	43	38	0	0	80	11.0	14.5	8.8	55	2
100–200 °C	23	23	35	31	30	70	120	11.0	12.5	8.8	65	3
0–100 °C	18	18	28	25	200	200	200	10.5	10.5	8.8	75	4
<0 °C	13	13	20	18	200	250	200	9.0	8.5	7.6	85	5

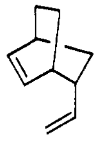
(2) A terminus which is part of a cumulene lowers the E_a by 6 kcal/mol. This reflects increased resonance energy for the product.[2]

(3) If either double bond of the 1,5-diene is aromatic, the E_a is raised by 2 kcal/mol. Conversely, if the reaction creates an aromatic ring, the E_a is lowered by 13 kcal/mol.

(4) If the central bond is part of a three- or four-membered ring and the vinyl groups are cis, the E_a is lowered by 11 kcal/mol. This reflects the release of ring strain during the reaction. If the divinyl groups are trans, however, the 1,5-diene is not allowed in the set of viable 1,5-dienes. These compounds cannot achieve the required transition state for a concerted process and more than likely proceed via diradical intermediates.

(5) A fixed orientation of the 1,5-diene into a bicyclic structure can affect the rate considerably. If the central bond is part of a [2.2.1] or a [2.2.2] bridged system in the manner of 1 and 2 below, the E_a's are lowered and raised by 15 and 9 kcal/mol, respectively.


1


2

(6) Substituents on the 1,5-diene can also affect the E_a, although only limited study has been done to gauge their effects on the reaction rates.[30a] Alkyl groups and unsaturated groups on the 1 or the 6 position raise the E_a about 1 kcal/mol. If any of these is cis with respect to the 1,5-diene, one more kcal/mol is added to the E_a. In the Claisen rearrangement, functionality on the 2- or the 5-position increases the reactivity such that alkyl groups lower the E_a by 1 kcal/mol and another functionality lowers the E_a by about 2 kcal/mol. An anionic substituent on the 2-position has a very large effect.[30b] For CAMEO's purposes, the E_a is lowered by 10 kcal/mol. For both Cope and Claisen rearrangements, unsaturated functionality and hydroxyl groups on the central atoms of the 1,5-diene lower the E_a by 4 kcal/mol. Alkyl groups on the central atoms only lower the E_a by about 1 kcal/mol. Reported rate enhancements for the Cope rearrangement when the substituent is anionic range from 10^{10} to 10^{12}.[31] This is handled in CAMEO by decreasing the E_a by 20 kcal/mol. It should be noted that if one of the double bonds in the 1,5-diene is part of an aromatic ring, substituents attached to the aromatic ring are not considered in the current algorithm. Likewise, if the 1,5-diene is in a ring, the ring atoms are also not treated as substituents.

(7) Homotropilidene and its derivatives undergo degenerate valence tautomerisms via [3,3] shifts. These reactions are extremely fast owing to the relatively high energy of the reactants and, for bridged systems, to favorable orbital alignment. They are characterized by large log *A* values and very low E_a's. Consequently, the E_a is lowered for CAMEO by 5 kcal/mol if the termini of the *cis*-divinyl three-membered ring are joined by an atom and by an additional 10 kcal/mol if the system is appropriately bridged. These adjustments place these reactions well into the <0 °C temperature category. Table IX lists some

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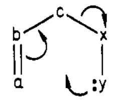
(30) (a) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983. (b) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972.

(31) (a) Miyashi, T.; Hazato, A.; Mukai, T. *J. Am. Chem. Soc.* **1982**, *104*, 891. (b) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765. (c) Evans, D. A.; Baillargion, D. J.; Nelson, J. V. *Ibid.* **1978**, *100*, 2242. (d) Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *Ibid.* **1980**, *102*, 3972.

[3,3]-sigmatropic rearrangements with their experimental activation parameters, the calculated E_a, and the lowest temperature at which the reaction is allowed to proceed in CAMEO.

B. [2,3]-Sigmatropic Rearrangements. [2,3]-Sigmatropic shifts are six electron, concerted, intramolecular rearrangements of the general form shown in **3** below



3

where Y has a lone pair of electrons and X can accept a pair of electrons. Although these processes are frequently used by synthetic chemists, precise kinetic data are very scarce. Table X summarizes the activation parameters for three systems. Under the circumstances, it is not possible to estimate the activation parameters and one is forced to use a very qualitative approach. In CAMEO, each reaction is assigned a point value from 1 to 5 corresponding to the five temperature ranges. Systems with a rating of 5 are highly reactive and rearrange below 0 °C. Most [2,3] shifts are quite fast; generation of an ylide by proton abstraction is followed by in situ rearrangement. A few features which decrease or increase the rate of rearrangement can be identified and the point value (PTS) is modified accordingly.

(1) The initial value for PTS is set equal to 5.

(2) If X in **3** is a doubly bonded sulfur as in a sulfoxide or a quaternary nitrogen, PTS is decremented by 1.

(3) If X in **3** is a doubly bonded phosphorus, as in a phosphorus ylide, PTS is decremented by 3.

(4) If Y in **3** is a singly bonded phosphorus or nitrogen, PTS is decremented by 1.

(5) If Y in **3** has two electron-withdrawing or conjugating functional groups attached, the reactant is stabilized and PTS is decremented by 1.

(6) If the a═b bond in **3** is a carbonyl bond, PTS is decremented by 1.

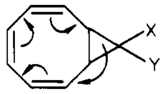
(7) If the a═b bond in **3** is part of an acetylene or an allene, PTS is increased by 1.

(8) If the a═b bond in **3** is part of an aromatic ring, PTS is decremented by 1.

Although this scheme is very crude, it correctly places most [2,3]-sigmatropic rearrangements into the most reactive temperature category in CAMEO. Table XI lists a few [2,3]-sigmatropic rearrangements with their experimental reaction conditions, the PTS assigned by CAMEO, and the lowest temperature block in which the reaction proceeds in CAMEO.

C. [1,5] and [1,7] Hydrogen and Carbon Sigmatropic Migrations. According to orbital symmetry rules, thermal [1,5] migrations occur suprafacially, and [1,3] and [1,7] migrations need an antarafacial component. Due to the minimal geometrical constraints of the [1,5] shift, many examples can be found in the literature. The mechanism is concerted, involving a six-membered transition state which necessitates a cis geometry about atoms 3 and 4 of the diene. [1,7]-Hydrogen migrations are observed much less frequently because two double bonds in the triene must be cisoid and, since the migration is antarafacial, the migration is not possible if the triene is incorporated within a small- or medium-size ring. It should also be noted that cyclopropyl bonds can replace double bonds in the reactants for these processes.

A summary of the activation parameters for sigmatropic migrations is provided in a review by Spangler.[42a] The entropies of activation for [1,5]-hydrogen shifts are around −10 eu, and the E_a's range from 30 to 36 kcal/mol for acyclic molecules, and from 25 to 35 kcal/mol for cyclic systems. [1,7]-Hydrogen migrations exhibit more negative entropies of activation (−15 to −25 eu) and E_a's ranging from 15 to 27 kcal/mol. In general, if there are no geometrical constraints, studies indicate that the [1,7] shift is favored over the [1,5] shift.[42a] The E_a's for homodienyl and homotrienyl systems in which the unsaturated chain is not in a ring do not differ significantly from those of acyclic dienyl and trienyl systems. However, if the vinyl cyclopropane is within a ring, geometrical constraints are introduced for [1,5]-hydrogen shifts in five- and seven-membered rings. It should also be noted that, in general, the E_a's for [1,5]-methyl migrations (41–50 kcal/mol) are approximately 20 kcal/mol higher than for similar [1,5]-hydrogen migrations. Only a single example of a [1,7]-carbon migration appears to have been reported; the circumambulation for **4** was determined to have an E_a of 29 kcal/mol.[42a]



4

For CAMEO's purposes, the E_a's of [1,5] and [1,7] shifts are being estimated by using the hydrogen migrations for *cis*-1,3-pentadiene (E_a = 36 kcal/mol) and *cis*,*cis*-1,3,5-heptatriene (E_a = 22 kcal/mol) as starting points. These values are then adjusted taking the following factors into account.

(1) The nature of the migrating group is clearly important. Therefore, for sp^3 carbons, sp^2 carbons, and aryl migrations, the E_a is incremented by 20, 10, and 5 kcal/mol, respectively. If the migrating carbon is in a five-membered ring and the other atom of the migrating bond is spiro, the E_a is decremented by 7 kcal/mol. If an aromatic ring is generated or destroyed during the course of the reaction, the E_a is lowered or raised by 8 kcal/mol. For hydrogen migrations to an oxygen atom, the E_a is decreased by 4 kcal/mol.

(2) If the 1,3-diene is part of a ring of size five or greater than size six, the E_a is decremented by 12 and 6 kcal/mol, respectively.

(3) If a vinylcyclopropyl unit is part of a ring of five or seven members, the E_a is incremented by 10 and 3 kcal/mol, respectively. Vinylcyclopropyl systems in rings of other sizes cause decrements of 4 kcal/mol.

(4) If the atom to which the group is migrating is part of a cumulene, the E_a is decreased by 10 kcal/mol.

(5) Substituent effects must also be considered. Alkyl groups on C1 or C5 of a pentadienyl system or on C1 or

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(32) Herriott, A. W.; Mislow, K. *Tetrahedron Lett.* **1968**, *25*, 3013.

(33) Kaiser, G. V.; Ashbrook, C. W. *J. Am. Chem. Soc.* **1972**, *93*, 2342.

(34) Still, W. C.; Abhijit, M. *J. Am. Chem. Soc.* **1978**, *100*, 1927.

(35) Baldwin, J. E.; Hackler, R. E., Kelly, P. D. *Chem. Commun.* **1968**, 1083.

(36) Huche, M.; Cresson, P. *Tetrahedron Lett.* **1973**, *44*, 4291.

(37) Rayner, D. R.; Miller, F. G.; Bickart, P.; Gordon, A. J.; Mislow, K. *J. Am. Chem. Soc.* **1966**, *88*, 3138.

(38) Morel, G.; Khamsitrthideth, S.; Foucaud, A. *J. Chem. Soc., Chem. Commun.* **1978**, 274.

(39) Oda, R.; Hayashi, Y. *Tetrahedron Lett.* **1968**, *51*, 5381.

(40) Evans, D. A.; Bryan, C. A.; Sims, C. L. *J. Am. Chem. Soc.* **1972**, *94*, 2891.

(41) (a) Hayashi, Y.; Oda, R. *Tetrahedron Lett.* **1968**, *51*, 5381. (b) Kleinschmitt, R. F.; Cope, A. C. *J. Am. Chem. Soc.* **1944**, *66*, 1929. (c) Brindle, I. D.; Gibson, M. S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 517.

(42) (a) Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187. (b) Roth, W. R.; Konig, J. *Liebigs Ann. Chem.* **1965**, *688*, 28.

C7 of a hexatrienyl system decrease the E_a by about 3 kcal/mol each. Hydroxyl and unsaturated substituents on C5 or C7 lower the E_a by 6 kcal/mol. If an anionic substituent is attached to the atom bearing the migrating group, the rate of the reaction is enhanced by 10^5 to 10^6.[31c] This rate acceleration is taken into account by lowering the E_a by 15 kcal/mol. It should be noted that if the diene or triene is part of a ring, the ring atoms are not counted as substituents in the above algorithm.

Tables XII and XIII contain a sampling of [1,5] and [1,7] shifts with their literature activation parameters, the calculated E_a's, and the lowest temperature range in which the reaction is allowed in CAMEO.

D. [1,3]-Carbon Migrations. Orbital symmetry rules predict that thermal [1,3]-hydrogen shifts should occur antarafacially and that migration of sp^3 carbons should occur either suprafacially with inversion of configuration at the migrating center or antarafacially with retention of configuration at the migrating center. The migration of hydrogen is not feasible geometrically, but some carbon shifts are known and typically exhibit inversion of the migrating group. Overall, these processes are generally not facile thermally.

The molecular frameworks that are most disposed to [1,3]-carbon migrations are [*i.j.k*] bicyclic or fused ring systems such that $i + j + k$ is less than or equal to 6 and at least *i*, *j*, or *k* is 1 or 0. [1,3] Migrations also occur with methylene- or vinylcyclobutanes and cyclopropanes. However, studies on vinylcyclopropanes indicate that the mechanisms for these are diradical rather than concerted.[42b]

For most bridged systems, the choice of the migrating bond is straightforward. First of all, the ring double bond must be adjacent to a bridgehead (I). The possible migrating bonds are those bonds next to I that are not bonds adjacent to the double bond. When the two possible migrating bonds are in bridges of equal length, such as in [4.1.1] systems, the most highly branched bond usually migrates preferentially. In the [3.2.1] and the [2.2.1] bridged systems, migration of the bond in the larger bridge is generally favored probably because the product is less strained.

The reactivity of [1,3] shifts is gauged in CAMEO by once again assigning a point value to each reaction. The following set of rules determine the point value (PTS) for the particular reaction.

(1) Three- or four-membered rings with an exocyclic double bond or a vinylic attachment are assigned a PTS of 1.

(2) Allowed bridged systems are assigned a PTS of 2 except for the particularly reactive [2.1.1] bridged system which is given a PTS of 3.

(3) All allowed fused systems are assigned a PTS of 1. PTS is incremented by 1 for the more reactive [3.2.0] systems.

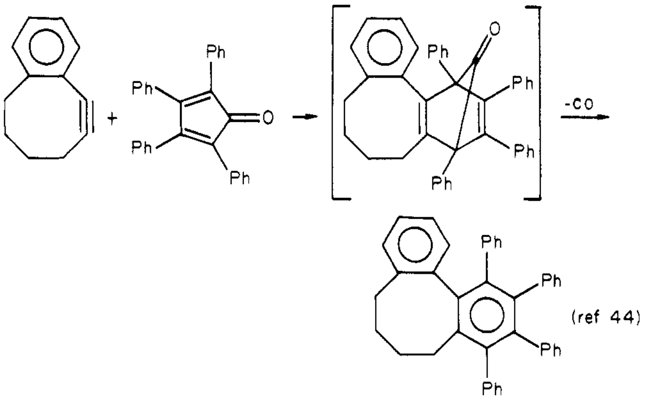
(4) If the migrating center has an attached donating or conjugating functional group, the PTS is incremented by 1. [1,3]-Carbon shifts have been shown to be dramatically accelerated if the migrating bond has an anionic group attached.[43] 2-Vinylcyclopropanols typically require high temperatures to rearrange to the cyclopentene product, but if the alcohol is deprotonated, the reaction proceeds smoothly at room temperature.[43a,b] This factor is taken into account by incrementing PTS by 3 units.

Table XIV lists a few [1,3]-carbon migrations with their literature activation parameters, the PTS value assigned by CAMEO, and the lowest temperature range in which the reaction is allowed to proceed.

VI. Ring-Opening Reactions

The ring-opening reactions that are presently considered by CAMEO are the retro-Diels–Alder reaction, cheletropic extrusion reactions, and the electrocyclic ring-opening reactions of 1,3-cyclohexadienes, cyclobutenes, and three-membered ring compounds. Electrocyclic ring-opening reactions involving more than 6π electrons have apparently not been observed. The key reactivity features for each reaction type are described below. The presence or absence of these features form the basis for the algorithms used to predict reactivity.

The retro-Diels–Alder reaction has found synthetic utility because it may yield products that are different from the original reactants. Although the mechanism of the reverse Diels–Alder is still somewhat controversial, a concerted process is generally favored.[2] It is unimolecular, has high log *A* values (10–15), and $\Delta S^{\ddagger}$'s near 0 eu. The retention of sterochemistry in the product also supports a concerted mechanism.



In general, any factor which destabilizes a Diels–Alder product tends to ease fragmentation. Thus, adducts of cyclic dienes and adducts which are sterically hindered decompose more readily than less strained compounds. The E_a's for the retro-Diels–Alder reactions of norbornene, norbornadiene, and cyclohexene are quite high, about 43, 50, and 66 kcal/mol, respectively.[29] However, the reaction can be greatly facilitated if the products have increased resonance energy (especially through formation of an aromatic ring), if there is relief of ring strain (commonly from destruction of three- or four-membered rings), or by extrusion of a particularly stable fragment, such as CO_2, SO_2, or N_2.

Cheletropic reactions are defined as those processes in which two σ bonds to the same atom are ruptured in a concerted process. Most typically, the reactions involve extrusion of SO_2, CO, and N_2. The stereochemistries observed for cyclopentenyl and cycloheptadienyl sulfolenes are as expected for retro $[{}_{\pi}4_{s} + {}_{\omega}2_{s}]$ and $[{}_{\pi}6_{a} + {}_{\omega}2_{s}]$ processes, respectively. Furthermore, the extrusions of SO_2 from episulfones are cleanly suprafacial with respect to the olefin formed even though the concerted retro $[{}_{\pi}2_{s} + {}_{\omega}2_{s}]$ process is forbidden on orbital symmetry grounds. Rate studies on episulfones are ambiguous and the mechanism is still not established with certainty.[45]

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(43) (a) Danheiser, R. L.; Martinez-Davila, C.; Auchus, R. J.; Kadonaga, J. T. *J. Am. Chem. Soc.* **1981**, *103*, 2443. (b) Danheiser, R. L.; Martinez-Davila, C.; Morin, J. M., Jr. *J. Org. Chem.* **1980**, *45*, 1341. (c) Zoeckler, M. T.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 7661.

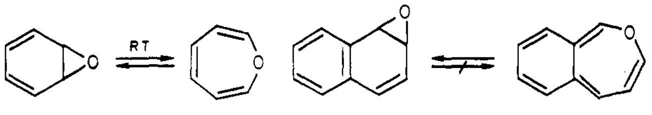
(44) Meier, R.; Layer, M.; Zetzche, A. *Chem. Ztg.* **1974**, *98*, 460.

(45) Mock, W. L. "Pericyclic Reactions"; Academic Press: New York, 1977; Vol. 2, p 141.

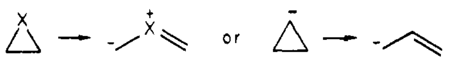
A review of the kinetics of sulfolene extrusion reactions can be found in ref 45. Episulfone itself has an E_a of 27.8 kcal/mol. Phenyl substitution lowers the activation energy dramatically to about 18 kcal/mol and may accompany a switch from a forbidden concerted to a stepwise mechanism. The E_a's for 3-sulfolene and its alkylated derivatives range from 26.5 to 31.9 kcal/mol. A cyclopropane ring can replace the double bond in 3-sulfolene with virtually no change in activation parameters. The 1,6-extrusion of SO_2 from a seven-membered ring sulfolene, if geometrically unconstrained and proceeds at a similar rate as the 1,4-extrusion (E_a = 29.7 kcal/mol).

Cheletropic extrusions of CO are quite facile for 2,3-di-*tert*-butylcyclopropanone but much more difficult for cyclopenten-4-one.[45] Extrusion of N_2 from five-membered ring diazines is spontaneous at room temperature.[8]

Several types of electrocyclic ring-opening reactions, along with the correct product stereochemistries, are now handled by CAMEO. The equilibrium between acyclic conjugated trienes and 1,3-cyclohexadienes usually favors the latter. However, if the triene is cyclic, and the closure generates a strained three- or four-membered saturated ring, both forms are in equilibrium. Some well known examples are the norcaradiene–tropilidene and cyclooctatetraene–bicyclo[4.2.0]octa-2,4,7-triene equilibria in which the open forms are favored. On the other hand, if the electrocyclic-opening reaction reduces aromaticity, the equilibrium can lie completely in favor of the closed form even when a three-membered ring is created.[8]



Four-electron electrocyclic ring openings include reactions of cyclobutenes and three-membered ring compounds containing either a saturated heteroatom or an anionic center. Because the openings are conrotatory, ring fusion of the above systems renders the reactions more difficult because a trans double bond is generated in a ring. Therefore, the concerted reaction does not occur at low temperature for bicyclic systems with fewer than eight ring atoms. At elevated temperatures diradical ring openings may take place. In the case of cyclobutenes, conjugating substituents on the 3- or 4-positions lower the E_a for ring opening. It should also be noted that ring openings of three-membered rings generate either a 1,3-dipole or an allylic anion. Any functionality which stabilizes the incipient charges speeds up these reactions.



Lastly, the 2π-electron dirotatory ring openings of cyclopropyl cations or of cyclopropanes with leaving groups such as halogens are facilitated by substituents which can stabilize the incipient positive charge. If the system is bicyclic, the reactions provide useful routes to ring expanded products. Furthermore, the disrotatory nature of the opening requires that the leaving group be endo for the reaction to proceed smoothly.[46] This effect is most prominent in small bicyclic systems for obvious stereochemical reasons.

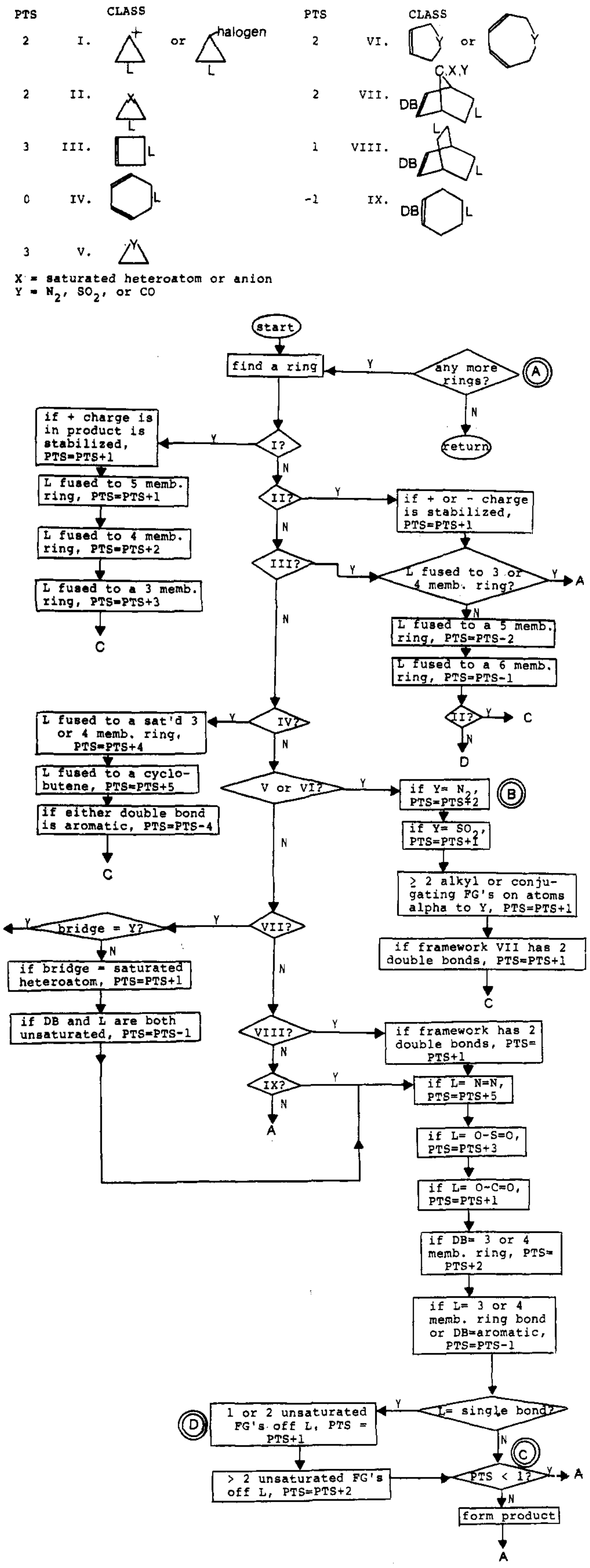


Figure 1. Definition of classes and flowchart for ring-opening reactions.

The ring-opening reactions are treated in CAMEO by using a point assignment system. Nine general classes are recognized and assigned an initial point value (PTS) as shown on the top of Figure 1. Points are added or subtracted from the base value depending upon the presence of the structural features described above. Table XV lists several reactions from each general type along with literature activation parameters if available and/or experimental

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(46) Berson, J. A. *Acc. Chem. Res.* **1968**, *1*, 33.

temperature conditions, the point value assignment in CAMEO, and the lowest temperature range in which the reaction is allowed to proceed in CAMEO.

VII. Implementation

A. Program Flow. It is appropriate at this point to summarize the overall flow of the pericyclic phase in CAMEO. A simplified flowchart is shown in Figure 2. In addition, the names of the subroutines responsible for the various functions are given in parentheses on the figure. In general, electrocyclic-closure reactions and cycloadditions are processed first, followed by sigmatropic rearrangements, and finally by ring-opening reactions.

The pericyclic executive, PREXEC, oversees the entire pericyclic module. CYCLST, DIENE, and DFINFO are responsible for the perception of all π systems capable of being involved in electrocyclic or cycloaddition reactions. The parent FMO energies are estimated by FMO and refined by REGIO, which takes into account the functionality attached to each parent system. The task of perceving functional groups and assigning τ values is performed by FGTYPE and FGVAL. These have all been described in greater detail previously.[1e] Once all this information is garnered, PREXEC proceeds to consider electrocyclic-closure reactions and cycloadditions. Energies of activation are estimated and stored for all but the [2 + 2] reactions. For these, either RADSUM, DIPSUM, or the smallest FMO gap is stored, depending upon the mechanistic class into which they have been categorized. PROD is responsible for forming the products with the correct regio and stereochemistry, and DRAW reconstructs intermolecular products more aesthetically.

At this point, PREXEC calls SIGMA, the executive for sigmatropic rearrangements. SIGMA in turn calls SIGM33, SIGMHC, and SIGM23, the subroutines responsible for the perception and storage of suitable components for [3,3]-sigmatropic rearrangements, [1,*j*]-hydrogen and carbon migrations (*j* = 3, 5, and 7), and [2,3]-sigmatropic rearrangements. The bonds that will decrease or increase in bond order and the termini that will be bound in the products are also stored. Actual product formation is performed by SIGMA.

The ring-opening reactions are the last group of reactions considered in the pericyclic module. Subroutine REVERS finds the systems capable of ring-opening reactions, estimates their PTS values, and forms the products. The logic followed is illustrated in detail in Figure 1.

Finally, the subroutine SELECT, flowcharted in Figure 3 and described in detail in the next section, is responsible for the incorporation of periselectivity. The energies of activation and PTS values stored throughout the pericyclic module for each reaction are used to order the products from most to least favorable.

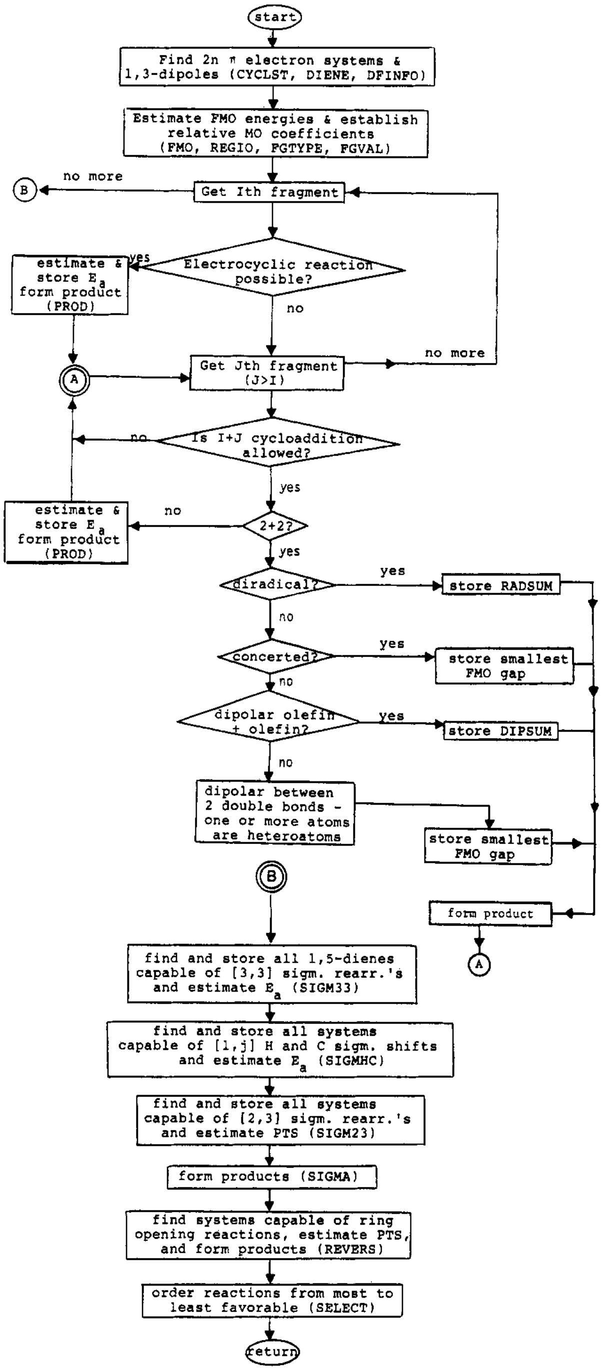

Figure 2. Simplified flowchart for pericyclic reactions.

B. Periselectivity. At the end of the pericyclic mechanistic phase of CAMEO, each reaction product has associated with it either an estimated energy of activation or the point value, PTS, as a qualitative gauge of reactivity. Before the products are displayed, they must pass structural approval in CAMEO's perception phase and a subroutine SELECT is called to implement periselectivity. The reason SELECT is invoked at this point is because for the Diels–Alder reaction the ΔH_{rxn} is needed to calculate the E_a (eq 1) and the former is determined during perception of the product. Thus, the first step in SELECT is the adjustment of the E_a for Diels–Alder reactions.

A flowchart for SELECT can be found in Figure 3. The routine follows the logic described below:

(1) The range of activation parameters required for the five temperature ranges by each reaction type is stored in an array as summarized in Table XVI. The numerical value stored for each product is compared with the appropriate entry in the array to find the temperature range

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(47) (a) Kwart, H.; King, K. *Chem. Rev.* **1968**, *68*, 415. (b) Berson, J. A.; Olin, S. S. *J. Am. Chem. Soc.* **1969**, *91*, 777.

(48) Ripoll, J. L.; Rouessac, A.; Rouessac, F. *Tetrahedron* **1978**, *34*, 19.

(49) Rieber, N.; Alberts, J.; Lipsky, J. A.; Lemal, D. M. *J. Am. Chem. Soc.* **1969**, *91*, 5668.

(50) Lemal, D. M.; McGregor, S. D. *J. Am. Chem. Soc.* **1966**, *88*, 1335.

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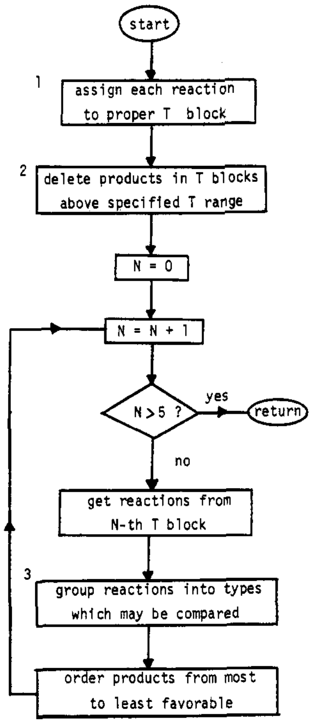


Figure 3. Flowchart for SELECT.

in which the reaction can achieve a rate constant of approximately 1×10^{-5} (see Section I). The products are then placed into one of five temperature blocks.

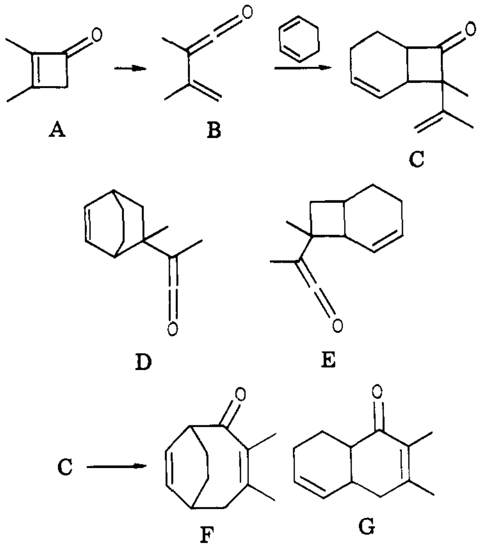
(2) Next, the program removes all products which can only achieve the standard rate above the specified temperature range.

(3) At this stage, the products within each temperature block are reordered from most to least favorable wherever possible. This is feasible only for reactions for which an actual E_a has been calculated and which have approximately known log A values. Thus, before any reordering is done, the reactions are grouped into categories as follows: (i) cycloadditions involving greater than or equal to 6π electrons (average log A for 6π-electron cycloadditions is 6.0); (ii) electrocyclic ring closures, [3,3]-sigmatropic rearrangements, and [1,5]-sigmatropic shifts (average log A = 11.25), and [1,7]-sigmatropic shifts (average log A = 9.5); (iii) free radical [2 + 2] reactions of *gem*-difluoro compounds; (iv) free radical [2 + 2] reactions of allenes; (v) free radical [2 + 2] reactions between olefins; (vi) concerted [2 + 2] reactions between ketenes and olefins; (vii) dipolar [2 + 2] reactions between heterocumulenes and a double bond containing a heteroatom or another heterocumulene; (viii) dipolar [2 + 2] reactions between olefins; (ix) [2,3]-sigmatropic rearrangements; (x) [1,3]-sigmatropic shifts; (xi) reverse Diels–Alder reactions; (xii) electrocyclic ring-opening reactions.

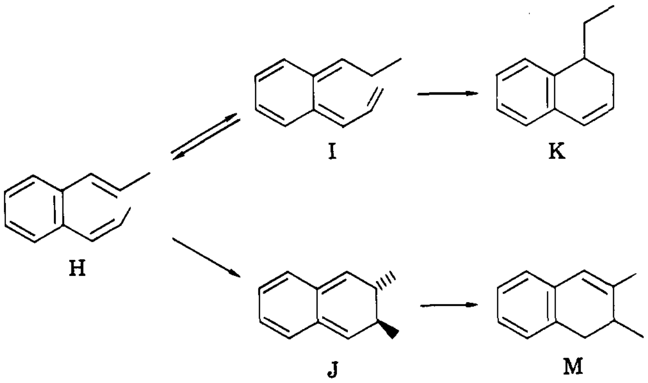
The log A values for [1,7] migrations are smaller than for the other reactions in category ii above. In order to compare the reactions, the E_a limits for the [1,7] shifts must be adjusted. Appropriate modifications have been made as shown in Table XVI.

The reactivity parameters for reactions within each category are ordered from smallest to largest for categories i, ii, and vi–viii and from largest to smallest for the remaining categories by using a subroutine REORDR. Thus, the reactions are first grouped in terms of the temperature blocks (from the lowest to the user-specified temperature block). Then, the reactions within each category in each temperature block are also ranked and displayed from most to least favorable. Naturally, the user must keep in mind the approximate nature of the analyses of periselectivity.

Scheme I



Scheme II



VIII. Sample Sequences

In concluding this presentation on the treatment of periselectivity, three examples are presented that compare CAMEO's predictions with experimental findings.

In Scheme I, when the cyclobutenone A is heated at 120 °C for four days, the adduct F is formed in 81% yield.[56] This is the result of a [2 + 2] cycloaddition that generates C, followed by a Cope rearrangement. CAMEO's predictions are as follows: A should open to B below 100 °C. Submission of B along with 1,3-cyclohexadiene yields not only the reported [2 + 2] product C (<0 °C), but also the Diels–Alder adduct D (100–200 °C), degenerate [1,5]-hydrogen shifts for cyclohexadiene (200–300 °C), and a diradical [2 + 2] adduct E (200–300 °C). The predicted temperature ranges clearly indicate a strong preference for the ketene [2 + 2] reaction. The Cope rearrangement of C to generate compound F is predicted in the 0–100 °C temperature range with an estimated E_a of 23 kcal/mol. The [1,3]-carbon shift product G is also displayed, but the high temperature required (200–300 °C) shows that its rate is not competitive with that of the Cope rearrangement.

The competitions between electrocyclic closure reactions and sigmatropic hydrogen migrations are nicely illustrated

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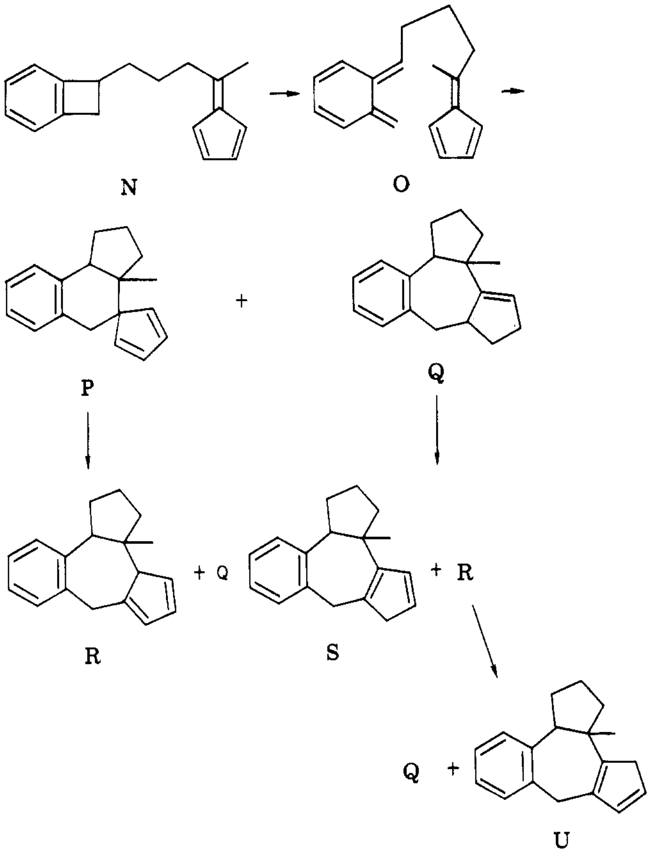
Scheme III



in Scheme II.[57] When compound H is heated at 225 °C for about 6 days, adducts K and M are formed in 11% and 3% yields, respectively. I is formed via a reversible [1,7]-hydrogen shift and can close to K by a 6π-electron electrocyclic closure. Another pathway available to H is the disrotatory 6π-electron closure to produce J, which in turn can generate the aromatic compound M by a [1,5]-hydrogen shift. CAMEO predicts that I and J could form in the 100–200 °C and 200–300 °C temperature ranges, respectively. Submission of I regenerates H (<0 °C), illustrating the reversibility of the reaction, and the 6π-electrocyclic closure product K (0–100 °C). The [1,7]-hydrogen migration is predicted to proceed at 100–200 °C, and the ring closures at 0–100 °C, with K predominating. If J is resubmitted, the [1,5]-hydrogen shift adduct M is produced in the 0–100 °C range. The E_a for the conversion of H to M is reported to be 32.3 + 0.3 kcal/mol, with the closure to J being rate determining.[57] CAMEO estimates the E_a to be 35 kcal/mol. The program also considered the 8π-electrocyclic closure of J to form a tricyclic fused product, but conrotatory closure generates a highly strained trans fused cyclobutane and the adduct is removed in the final preception phase of CAMEO.

In Scheme III, when compound N is heated at 195 °C for 12 h, adduct P is formed in 26% yield, and a mixture of S and U is formed in 44% yield.[27a] N first undergoes a 4π-electron ring opening to compound O. Product P presumably results from a [4 + 2] cycloaddition, and S and U by a competitive [6 + 4] cycloaddition to form Q followed by [1,5]-hydrogen shifts. CAMEO predicts the cyclobutene ring opening (N → O) at 100–200 °C. If O is resubmitted, both P and Q are displayed and predicted to form below 0 °C. The [1,5]-hydrogen shifts leading to S and U are facile reactions (0–100 °C). Interestingly, resubmission of P results in a [1,5]-carbon migration (100–200 °C) that can also lead to the reported products via [1,5]-hydrogen shifts. This particular example illustrates very nicely the capability of the CAMEO program to point out a variety of mechanistic pathways.

IX. Conclusion

The treatment of thermal pericyclic reactions in CAMEO has been much enhanced by the addition of procedures to treat periselectivity. This required extensive analyses of literature data and the development of methods to effectively calculate approximate rates for a wide range of reactions. When this study was initiated, it was hoped that simple, pedagogically attractive rules might emerge for periselectivity. Unfortunately, the enormous rate variations for pericyclic reactions due to substituent effects and to details of molecular structure for unimolecular reactions make simple generalizations elusive. However, for the time being, the data and semiquantitative procedures presented here can provide a useful guide to periselectivity.

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