Computer-Assisted Analysis of Reactions Involving Organic Free Radicals and Diradicals[1]

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Recent extensions to the CAMEO program include a mechanistic model for free radical chain reactions. The controlling algorithm treats all reactions as a series of fundamental radical processes, i.e., abstractions, additions, and fragmentations. Chain propagating steps are mimicked by automatic resubmission of selected intermediates. Refinements for integration of biradical processing are described. Several prominent examples that demonstrate the synthetic utility of free radical reactions and the success of the CAMEO program in predicting complex sequences are presented.

INTRODUCTION

CAMEO is an interactive computer program that mimics mechanistic logic to predict the products of organic reactions. Given graphical input of starting materials and conditions, the program arrives at its conclusions by application of a series of rules designed to consider structural features for the determination of reactivity. The approach avoids the use of large databases and topological simplifications; reaction modules correspond to and are designed for the evaluation of reactions by the type of intermediate involved. The program is presently capable of analyzing base-catalyzed and nucleophilic,[2] acid-catalyzed and electrophilic,[3] pericyclic,[4] oxidative,[5] reductive,[6] free radical,[7] and carbenoid[8] reactions.

An overview of the processing by the CAMEO program is presented in Figure 1. The user enters structures in a sketch menu plotting box with a mouse and selects various options through a series of menus. Commonly used reagents and special conditions are available through menus associated with each mechanistic class. Upon submission of the structure for processing, a generalized perception phase establishes a connectivity table of atom numbering, type, charge, coordinates, and bonding and stereochemical information. Erroneous structures are returned to the user for correction before processing may continue. Following successful perception, the structure is submitted to the chosen mechanistic module for analysis and product formation. Products issued by the program are perceived to assure structural integrity, and offending products are removed. The heat of reaction is also estimated at this point. Products are displayed in a "starting material → products" format, and are accompanied by brief mechanistic notes describing the transformations, as well as the previously selected conditions. A "tree" menu displays the relationship between products and allows the selection of individual structures for examination or further reaction. Detailed comments concerning the decisions made by the mechanistic phase are also available on this menu.

The goals of the project are twofold. From a practical standpoint, the utility of a program for analyzing the feasibility of a proposed synthetic pathway is evident. Awareness of potential side-products is invaluable to the practicing organic chemist. Academically, the program acts to accumulate and integrate the fundamental principles that govern organic reactivity. The earliest implementations, therefore, focused upon well-established heterolytic reactions, which lent themselves to stepwise treatment without the explicit creation of intermediates other than proton transfer structures. However, growth of the program has required incorporation of algorithms for processes involving reactive intermediates. In particular, the introduction of a module for analysis of free radical reactions poses significant challenges, because several intermediate radical species must be formed and evaluated even for reactions resulting in relatively simple overall transformations. The self-propagating nature of radical reactions also requires control to prevent excessive product formation. This paper describes the general implementation for mechanistic analysis of free radical reactions and provides representative reaction sequences for illustration of the program's capabilities. After a brief review focusing on the processing of monoradicals,[7] the recent extensions that have enabled the treatment of diradicals are summarized.

IMPLEMENTATION

The principles governing organic free radical reactivity are condensed here in the context of their translation into algorithms for the CAMEO program; several excellent reviews and monographs are available for the interested reader.[9] Mechanistically, radical processes may be divided into three discrete phases, as outlined below and portrayed schematically in Figure 2.

1. Initiation: Neutral → Radical + Radical. Free radicals are usually generated from closed shell species via homolysis of a σ bond possessing a bond dissociation energy (BDE) $\leq$75 kcal/mol. Alternatively, cycloaromatization of enediynes and eneynecumulenes can lead to diradical formation.[10]

2. Propagation(s): Radical (+Neutral) → New Radical (+Neutral). Propagation steps involve relocation of the unpaired electron, either by rearrangement or by reaction with a neutral molecule. Since a new radical intermediate is always generated by these propagations, they comprise the most synthetically significant transformations.

3. Termination: Radical + Radical → Neutral. These processes end reaction sequences by failing to produce another radical fragment. Radical–radical reactions occur at diffusion-controlled rates, but do not compete effectively under chain reaction conditions (i.e., when initiator species are present in low concentrations). For diradical processes, however, products of recombination and disproportionation become prominent.

Figure 2 illustrates the unique challenges inherent to the portrayal of these phases. For chain reactions, only the propagation phase results in products of sufficient yield. In addition, while the overall equation gives the illusion of 1:1 stoichiometry of reactants, the initial production of R-X requires *two* molecules of X-X. It is therefore necessary to construct the algorithm such that (1) input of closed-shell starting materials results in output of closed-shell products, (2) the important chain-transferring propagation (step c of Figure 2) occurs without requiring explicit entry of a chain-transferring agent, and (3) intermediates must be permitted to continue propagating without spurious generations.

An overview of the processing is presented in Figure 3 and encompasses *four* major reaction phases, i.e., radical initiation,

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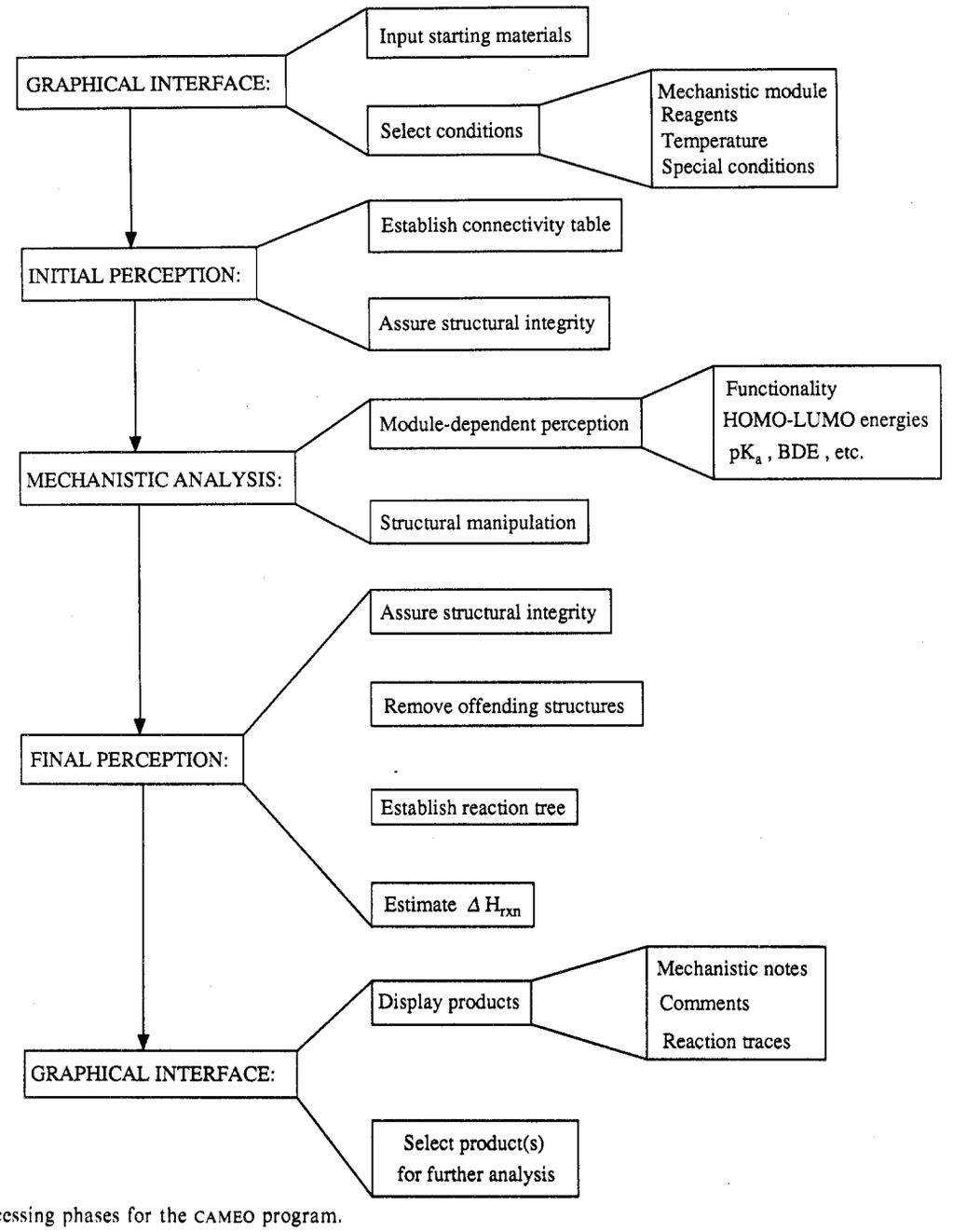


Figure 1. Processing phases for the CAMEO program.

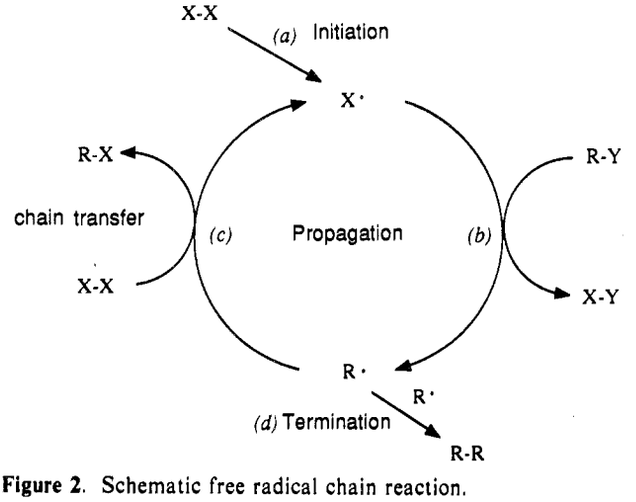


Figure 2. Schematic free radical chain reaction.

primary propagation (intermolecular abstraction), secondary propagation (all remaining chain-propagating steps), and radical trapping, which generates closed-shell products via implicit chain transfer or, for diradicals, recombination and disproportionation. The operational premise of the module is that complex interconversions may be explained and predicted by reducing processes to a series of fundamental steps, as illustrated in Figure 4. Successful predictions are made because each radical intermediate is explicitly generated and submitted to a series of mechanistic algorithms. This iterative resubmission process mimics the self-propagating nature of radical reactions. The mechanistic phases are described briefly below. A full description of the algorithms for monoradicals is available;[7] summaries of the rules pertaining to chain processes are given to provide a perspective for the discussion on the treatment of diradicals.

Phase I: Radical Initiation. Initiator molecules are sought according to relative decomposition rates.[11] Simple homolysis of the weakest available bond is insufficient for subsequent processing, since initiators may double as chain transfer agents or may act only as catalysts, and relative trapping rates must be known for the assessment of competitions between trapping and propagation.

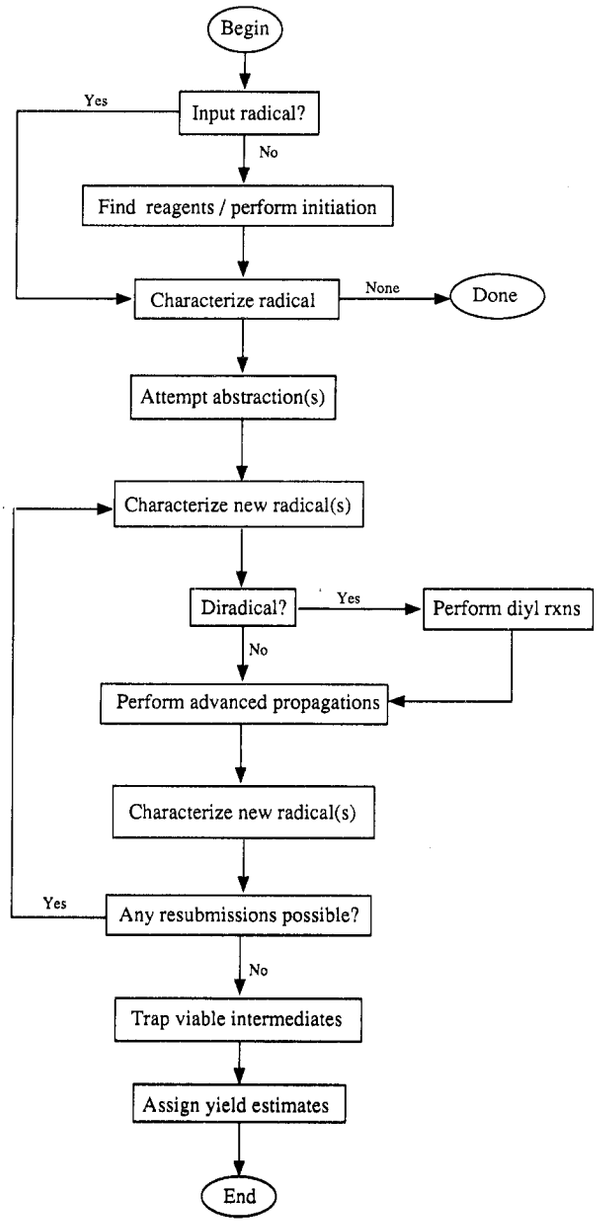


Figure 3. Flowchart for free radical processing.

Radicals generated in all phases are submitted for brief characterization to store information regarding, for example, electronic nature and relative stability. For diradicals, cognizance of the geometrical relationship between the radical sites is also necessary.

Phase II: Primary Propagations. This phase of processing is segregated from remaining propagations to prevent indiscriminant abstraction by resubmitted intermediates, as described subsequently. This is the only time that explicit intermolecular abstractions are considered. The general rules for abstraction are the following: (1) Abstraction is always limited to mono- or divalent atoms. (2) Monovalent atoms are generally abstracted in preference to divalent atoms. (3) Abstractions are dependent upon a balance between bond dissociation energy and electronic effects. For example, electrophilic heteroatom radicals prefer to abstract hydrogen atoms from relatively electron-rich sites, even if slightly weaker bonds are available, while nucleophilic radicals prefer abstraction of heteroatoms from electron-deficient sites.

Identification of a chain-transferring fragment may occur during phase I if the initiating fragment is recognized as noncatalytic. For example, Bu_3SnH is generally present in slight excess and may perform the dual role of initiator and chain-transfer agent. However, initiators such as peroxides or AIBN are used as catalysts only, and chain transfer is assumed to occur via abstraction from a duplicate of the phase II abstraction target. In either event, the program performs chain transfer by abstraction from an *implicit* duplicate reagent.

Phase III: Advanced Propagations. The bulk of free radical processing occurs during this phase. Fragmentations, ring closures, additions, and intramolecular abstraction reactions are executed. The implemented algorithm is based on experimental kinetic data and product distributions[12] and is organized by reaction rates into the following subphases.

Subphase 1: intramolecular processes with rate constants $\geq 10^5$
1. α-scissions
2. intramolecular abstractions (H-shifts to heteroradicals and heteroatom migrations)
3. 1,6-C=O and 1,5-C=C additions
4. β-scissions
5. 1,5-C=O additions

Subphase 2: intramolecular processes with rate constants $\geq 10^3$
1. 1,6-C=C, and 1,5- and 1,6-C≡N additions
2. 1,5- and 1,6-hydrogen shifts to reactive σ carbon radicals (e.g., aryl, vinyl)

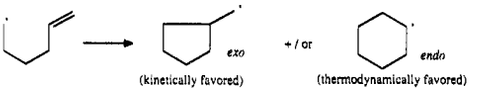
Subphase 3:
1. 1,7-C=C and 1,3-C=O or C≡N additions
2. intermolecular additions and large (>10-membered) ring closures

Subphase 4:
1. 1,3-C=C additions
2. 1,5- and 1,6-hydrogen migrations to alkyl radicals

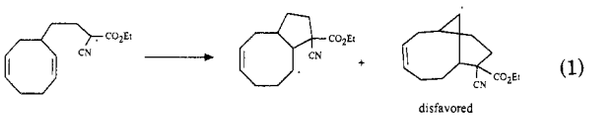
Only processes in the subphase with the highest rate are performed to avoid formation of spurious products, e.g., intermolecular additions are not considered if 5- or 6-membered ring closures are possible. Generalized rules for analyzing the feasibility of various propagations are described below.

Alpha fragmentations are considered when loss of small stable fragments (e.g., CO, SO_2) result. The relative yield is dependent upon the trapping rate. β-Scissions occur when analysis reveals the possibility for (1) relief of ring strain, (2) formation of C=O and C≡N π bonds, and (3) fragmentation of weak (i.e., BDE $\leq$ 70 kcal/mol) σ bonds. When more than one bond is available for scission, those with the lowest BDE are selected.

Rules governing ring closures are extensive. Eligible sets of bonds are found according to the reactivity hierarchy outlined above. The selected bonds are then analyzed individually with a specialized algorithm that determines the relative feasibility of exo and endo ring closure. Structural



information is accumulated such as the size of the new ring, the cis/trans relationship of the joining termini, and the types of atoms and bonds residing in the intervening path. A series of restrictive rules prevents ring formation when it is considered geometrically poor, highly reversible, or noncompetitive with an alternative. For example, a trans double bond or an acetylene linkage in the path usually renders the termini incapable of coupling. Furthermore, if both exo and endo closures are permitted, a series of ranking rules determines which products are "major", "minor", or "disfavored". These designations appear when the trapped product is displayed at the graphics terminal, and they are also used for determining the relative competitions between subsequent progeny. The restrictive rules take precedence over ranking rules when conflicts arise. For example, in eq 1[13] the uncyclized radical is stabilized by two electron-withdrawing groups; ring closure should



(1)

therefore be reversible and favor the endo mode (ranking rule). Endo closure would, however, result in a bridged ring when a more stable fusion is possible via exo closure, and the product of endo bridge formation is therefore labeled disfavored upon display (restrictive rule).

Intermolecular additions are controlled by a balance of electronic, resonance, and steric effects. The general priority for bond selection is polarized C-hetero π bonds > C–C π bonds of complementary polarity > resonance-stabilized C–C π bonds > unactivated π bonds. The chosen set of bonds is then further refined to allow addition to the least hindered site available. Furthermore, addition to olefins generally is preferred over similarly substituted acetylenes, and additions that disrupt conjugation are avoided.

Intramolecular abstraction (S_H2) reactions are dependent upon the reactivity of the radical, the strength of the forming and breaking bonds, and the propinquity of reacting sites. 1,5 abstractions are favored, even if 1,6 sites with slightly lower (ca. 3 kcal/mol) BDEs are available. The algorithm seeks abstraction sites within the appropriate BDE range for the given radical type, rejects those which are in geometrically poor positions, and finally refines the remaining candidate sites to those with the lowest BDE.

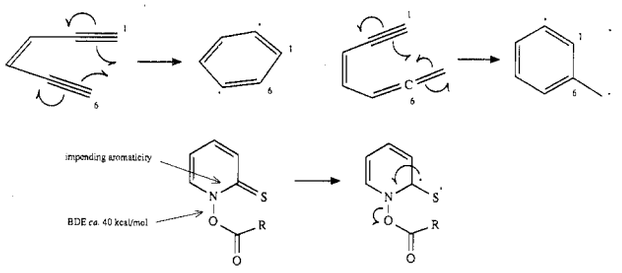
Resubmission. Each intermediate generated by an advanced propagation is considered for resubmission and analysis for subsequent reactions. Intermediates are briefly scanned for (1) fast ring closure sites, (2) rapid fragmentations, (3) intermolecular additions, and (4) 1,5 and 1,6 atom migration sites. If any of these possibilities exist, the radical is resubmitted and subjected to the detailed analysis discussed above.

Phase IV: Radical Trapping. When resubmission yields no new intermediates, the fourth phase of processing is invoked to generate closed-shell products. For chain-reaction sequences, this comprises enacting the implicit chain-transfer step described previously. The atom or fragment designated during phase I or phase II is created and bonded to the radical species. This simulated abstraction step circumvents the need to enter or recreate an explicit chain-transfer agent. Certain intermediates are prevented from trapping, e.g., structures capable of rapid fragmentation. When diradicals or radical pairs are present, implicit chain transfer may compete with recombination and/or disproportionation, as discussed below.

Integration of Diradicals. The original implementation of radical chemistry focused upon chain-reaction processes, where intermediates are generated in sufficiently low concentrations and radical–radical processes may be neglected. Successful integration of diradical and radical pair chemistry requires control of *two* unpaired electrons, and the recognition of possible interactions between them. Implementation has concentrated on extending the foundation of the existent algorithm to accommodate thermal unimolecular rearrangements.

The radical initiation phase has been updated for inclusion of classical thermal methods of diradical generation, i.e., homolysis of cyclic species containing weak σ bonds, such as diazene and peroxide thermolyses and pyrolyses of strained rings. In addition, specialized implementations have been made for synthetically significant diradical-forming reactions, including enediyne and eneynecumulene cycloaromatizations[10] and decomposition of thiohydroxamates.[14] Prototypical examples of these are shown below.

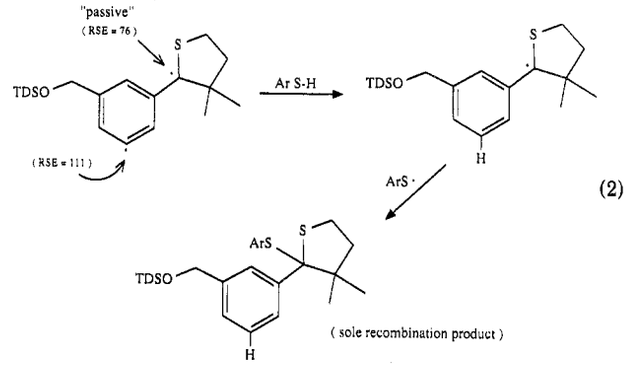
Formation of diradicals by cycloaromatization is considered by seeking pairs of sp hybridized atoms that meet three essential criteria: (1) the atoms must be in a 1,6 relationship,



(2) they must have no saturated atoms in the intervening path, and (3) a cis orientation must exist to allow bond formation. If these requirements are satisfied, the 1,6 sp pair is further analyzed for the appropriate thermal range of the reaction. Since the activation energy and, consequently, the requisite temperature decrease with smaller distances between the 1,6 sp pair, any additional connections are examined for length of the connecting chain, bridging, and multiple bonds. The results determine the temperature at which cyclization is expected to occur.[10b,c]

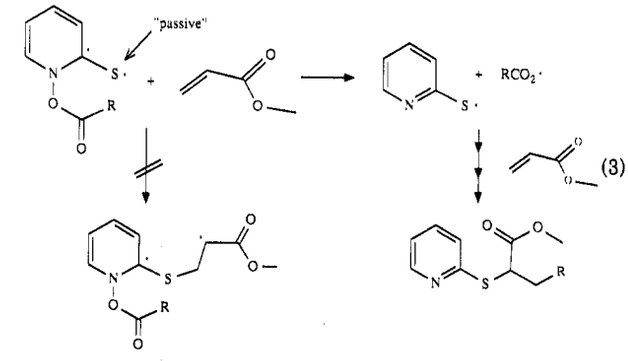
Thione decomposition is also driven by impending aromaticity, and candidates for diradical formation therefore meet two requirements: (1) increasing the bond order of a bond α to the thione carbon must result in aromaticity, and (2) the subsequent β bond must be of sufficiently low BDE (75 kcal/mol) to permit scission, as shown.

The perception algorithm has been augmented to characterize both radical atoms with regard to philicity and relative stabilization. In addition, 1,2-, 1,3-, and 1,4-diradicals are noted as such. Large differences in stability (≥15 kcal/mol) are used to gauge the relative reactivity of radical sites. If such a disparity exists, the more stable radical is considered "passive" and is permitted to undergo only radical–radical reactions, e.g., eq 2.[15] Disparate reactivity is also recognized



(2)

when rapid fragmentation is imminent for one site, as in eq 3.[14]



(3)

Attempted propagation of diradicals is preceded by some specialized considerations. 1,2-Diradicals formed by previous propagation steps are recombined, and the diradical is overwritten. 1,3-Diradicals may undergo a variety of 1,2-hydrogen or halogen shifts, and 1,4-diradicals are subject to cleavage

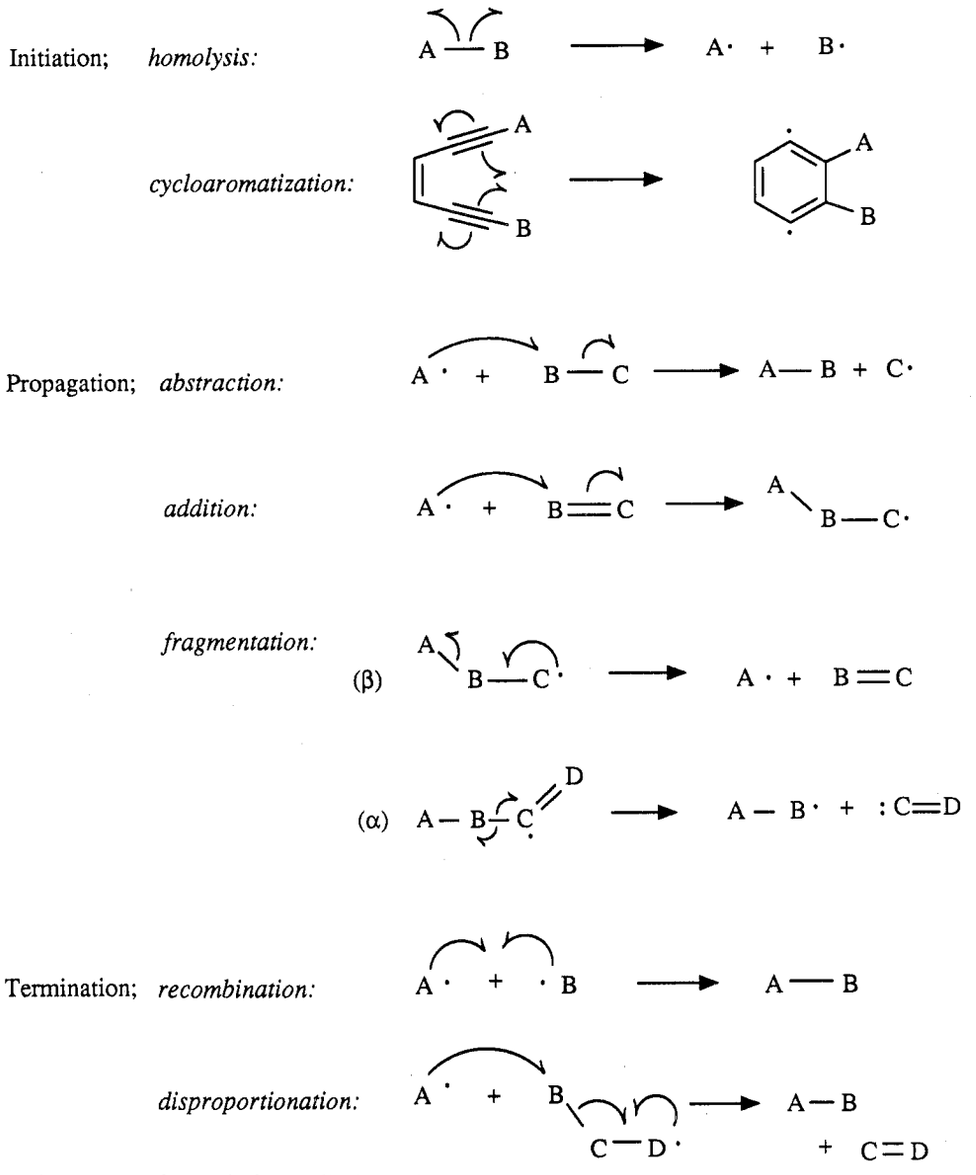
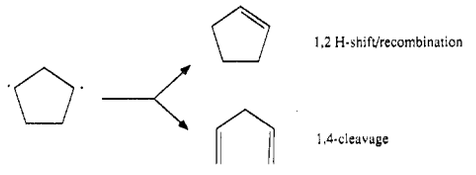


Figure 4. Fundamental processes of organic free radical reactions.

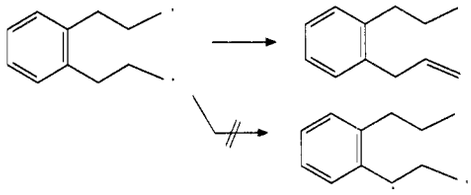
of the intervening β bond. Radical pairs are also examined for possible intermolecular disproportionation reactions (Figure 4). As throughout the program, these processes are governed by rules prohibiting structurally infeasible interactions.



The remainder of the propagation phase treats each reactive radical site in turn, i.e., one radical site is held fixed while the other is submitted for propagation analysis. As described above, sites labeled "passive" are not subjected to this phase. At this time, all propagation analyses are performed as described previously, with the following exceptions.

For monoradical chain reactions, the intermolecular abstraction phase simply assesses the availability of a chain-transfer agent. For diradicals, however, chain transfer must compete with fast diyl termination reactions such as disproportionation, recombination, or 1,4-cleavage. Accordingly, the intermolecular abstraction phase gauges the reactivity of any available atom donors. When abstraction by a diyl occurs with an atom donor that has a BDE $\leq$70 kcal/mol, trapping by abstraction is considered competitive with other diyl trapping reactions.

Advanced propagations (phase III reactions) are conducted for each active radical site presuming the same reactivity hierarchies developed for monoradicals, except that intramolecular abstractions that lead to disproportionations are favored. For example, the diyl in eq 4[16] prefers 1,7-hydrogen



(4)

abstraction leading to disproportionation over the 1,6-hydrogen abstraction from a benzylic position. In addition, when subphase 1 reactions are performed, the structure under scrutiny is prevented from trapping and diyl reactions are rejected. This is discussed further in the context of a sample reaction sequence provided in the next section.

For diradicals, the trapping phase must discern between possibilities for implicit chain transfer or recombination

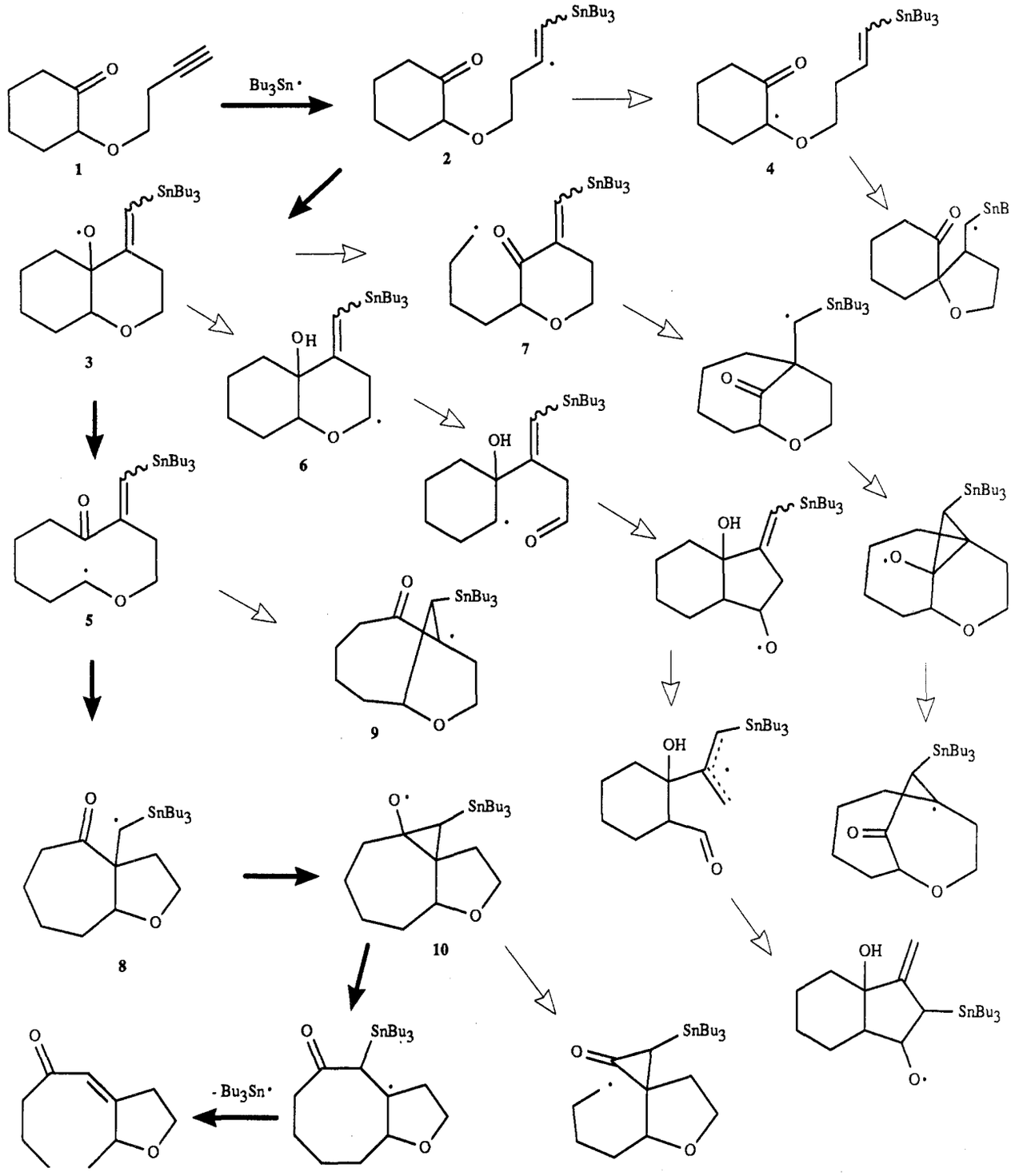


Figure 5. CAMEO analysis of a multistep ring expansion. Faint arrows indicate spurious paths that are considered and rejected.

(disproportionations are considered during the abstraction analyses). Recombinations are preferred unless atom donors with BDEs ≤70 kcal/mol are encountered during the abstraction phase; in this event, equal competition is assumed. When recombination is structurally infeasible, chain transfer is enacted regardless of the nature of the atom donor.

EXAMPLE SEQUENCES

The hallmark of the free radical module in CAMEO is its simulation of chain processes with full mechanistic detail. The philosophy dictates that each radical be submitted to each of the algorithms described, thus mimicking a self-propagating chain. The repetitive nature of the algorithm suggests that an excessive number of intermediates could be generated. The analysis in Figure 5 of a ring expansion[17] illustrates control of this problem in detail. The initiation and primary abstraction steps have been performed, and the figure enters the chain with stannyl radical addition to **1**. Vinyl radical adduct **2** prefers 1,6-C=O ring closure (subphase 1) over the thermodynamically favorable 1,5-hydrogen migration (subphase 2), and formation of **3** is the sole process. Three subphase 1 propagations are available to oxy radical **3**: β-scission of a ring fusion, β-scission to a primary alkyl radical, or a 1,5-hydrogen shift. Cleavage of ring fusions is generally rejected unless the fusion is activated by an electron-withdrawing or -releasing substituent, i.e., the ether oxygen in **3**. Since β-scission to a primary radical is rejected when other propagations are available, and the 1,5-hydrogen abstraction is geo-

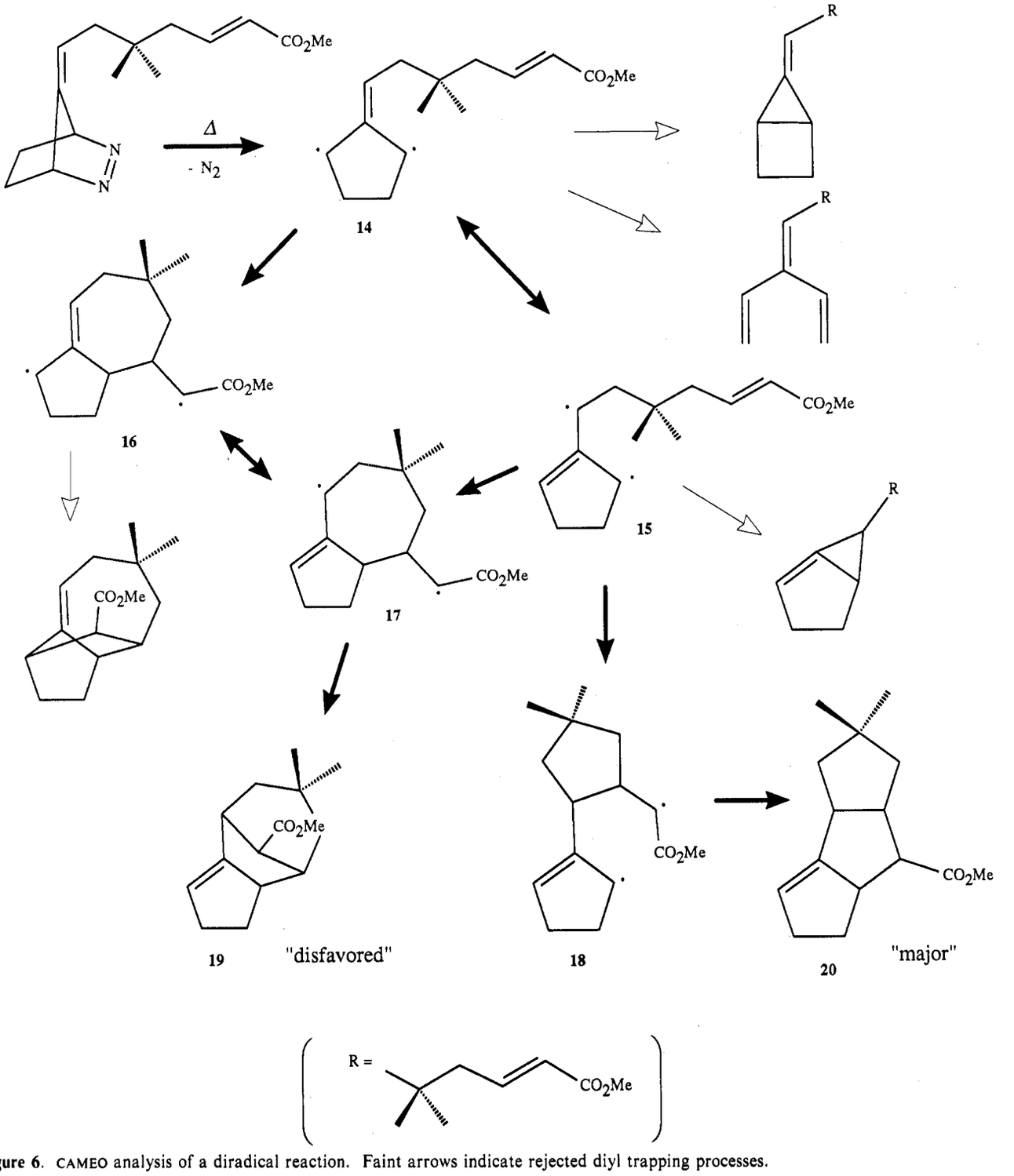


Figure 6. CAMEO analysis of a diradical reaction. Faint arrows indicate rejected diyl trapping processes.

metrically poor, formation of **7** and **6** are rejected in favor of ring opening to give **5**. Expanded ring **5** also chooses among three subphase 1 processes: a fragmentation forming a primary alkyl radical (not shown) is rejected due to the available ring-closure site. Endo and exo ring closures are considered for hexenyl radicals such as **5**; however, bridge formation giving **9** is rejected for the more stable ring fusion closure in **8**. Upon resubmission, **8** resorts to the subphase 3 small ring closure giving **10**; possible subphase 4 hydrogen shifts are not considered. Oxy radical **10** in turn selects small ring cleavage over primary alkyl radical formation. Fragmentation of the weak C–Sn bond of **11** gives doubly expanded cyclooctenone **13**, and the released stannyl radical proceeds to another propagation.

The reaction analysis ends with the trapping of selected intermediates by an implicit stannane chain-transfer agent. **3**-H, **8**-H, and **13** are considered major products, **5**-H is considered minor due to formation of its favorable progeny, and **2**-H is disfavored due to the reversibility of the original addition. Experimentally, **8** is obtained in 62% yield, although reaction of several analogues resulted in cyclooctenone yields up to 50%.[17] In addition, yields of alcohols such as **3**-H are known to be competitive with ring opening. The remaining intermediates in Figure 5 would result from propagations of radicals **4**, **6**, and **7**; these are *not* considered since **4**, **6**, and **7** themselves are rejected. Their inclusion in the figure emphasizes the need for selectivity at all stages of processing.

Figure 6 provides a representative diradical analysis[18] and

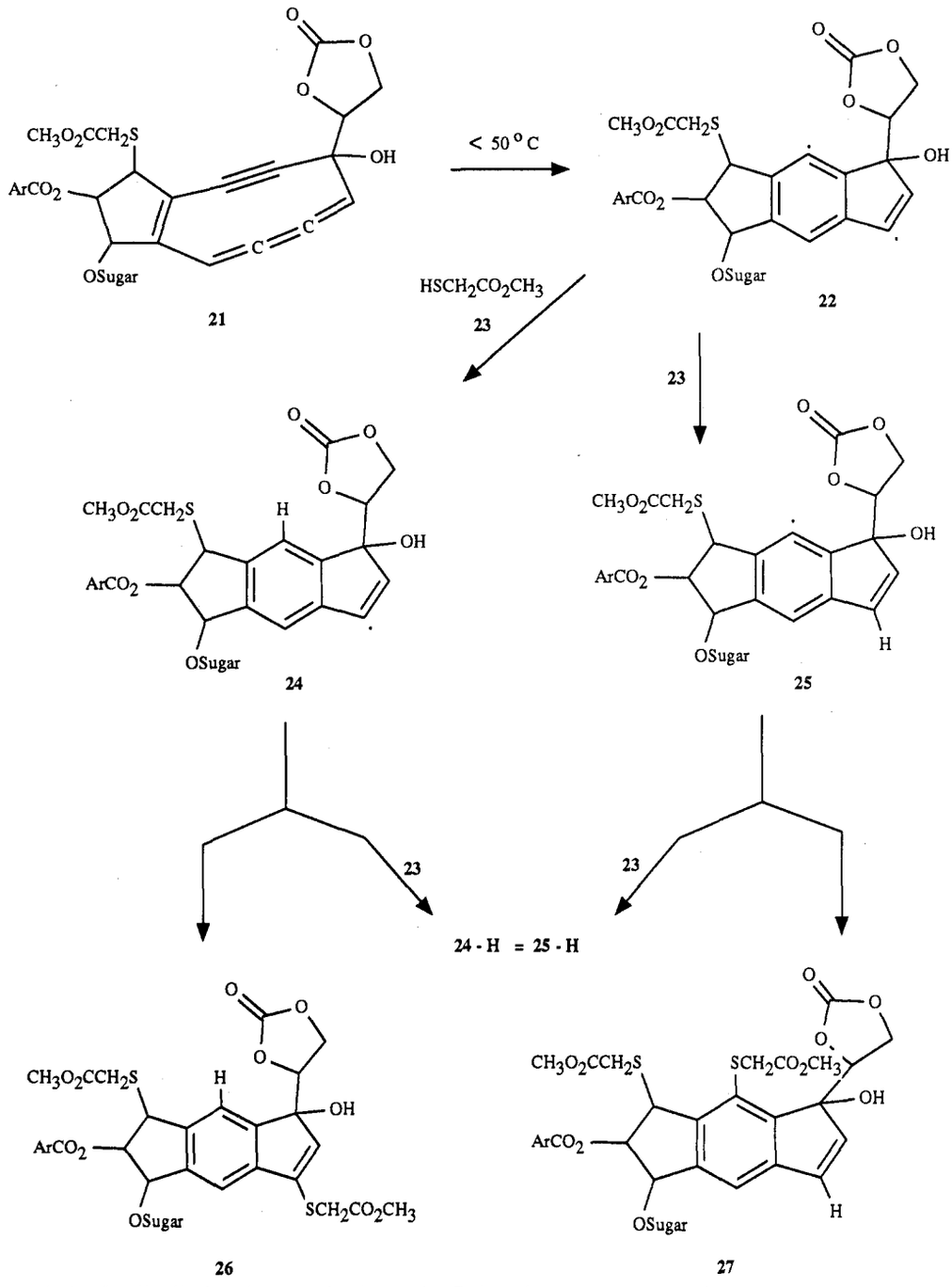


Figure 7. CAMEO analysis of a diradical cycloaromatization path. Rejected processes are not shown.

is suggestive of the additional problems associated with analyzing two reactive sites per intermediate. Diazene thermolysis produces both diyl **14** and its resonance form **15**. Propagation analysis is performed as if these are separate diyls: exo cyclization to **16** is the only reaction available for **14**, while **15** undergoes a similar 1,7 exo closure at one radical site as well as a subphase 1 exo hexenyl closure for the alternate radical atom. In addition, exo closure to the stabilized **18** precludes endo cyclization to the unstabilized cyclohexyl radical. As alluded to in the previous section, the indicated diyl trapping reactions of **14** and **15** are rejected since the favorable subphase 1 formation of **18** is detected. The awkward recombination of **16** is also rejected. Diyls **17** and **18** *are* permitted to recombine since no further subphase 1 propagations can occur, and the product yield estimates are as indicated in the figure. Recombination product **19** is disfavored as the descendent of a 1,7-cyclization (**14** → **16** or **15** → **17**). Such subphase 3 cyclizations are disfavored if rival intermediates undergo higher ranking cyclizations, i.e., the 1,5 exo cyclization **15** → **18** in this case. The diazene thermolysis reportedly resulted in an 85% yield of tricyclic **20**.[18]

Current interest in the chemistry of esperamicin, neocarzinostatin, and related analogues has been accommodated as reflected in analyses such as in Figure 7.[19] Eneynecumulene **21** is recognized during the initiation phase as an unencumbered cycloaromatization precursor and undergoes closure to dehydroindene **22** at or below ambient temperature. In the presence of atom donor methylthioglycolate **23**, the equally reactive σ radicals alternately abstract hydrogen. During this abstraction phase, donor **23** is recognized as a fast trapping agent allowing implicit chain transfer for **24** and **25** to compete with recombination. Three products are generated by the program; in practice **27** is not observed, and an alternative addition/cyclization chain mechanism is also proposed for formation of **26** when thioglycolate **23** is present in low concentrations.[19]

CONCLUSION

An iterative resubmission algorithm based upon kinetic hierarchies has been successfully implemented for the mechanistic evaluation of radical reactions. The algorithms have been refined with a rigorous test base of over 1000 multistep reactions to assure program integrity throughout development. The philosophy of treating reaction analysis by applying a series of fundamental precepts is shown to be successful, even when reactive intermediates are involved and permitted to propagate.

COMPUTATIONAL DETAILS

CAMEO is a FORTRAN program developed on Digital Equipment Corporation computers using the VMS operating system; UNIX and AIX versions have also been created. The graphics interface requires a Tektronix 4010, 4208, or 4100 Series terminal or emulation.

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