M) in methylene chloride was irradiated with a 300-W Xe lamp through a Corning 3-74 ($\lambda > 400$ nm) glass filter for tetracyanoethylene and a Corning 0-51 ($\lambda > 360$ nm) glass filter for 1,2,4,5-tetracyanobenzene. The photolysate was concentrated in vacuo followed by ^{1}H NMR analysis to determine product yields. When the solutions of substrates and acceptors at the same concentrations as photoreactions were stirred in the dark, no conversions of starting materials were observed.

Aminium Salt Catalyzed Reactions. To a methylene chloride solution (1 mL) of a substrate (0.049 mmol) with or without an additive (TMB, 0.052–0.056 mmol) was added tris(*p*-bromophenyl)aminium hexachloroantimonate (0.013 mmol for **1**, and 0.0024 mmol for **2**) in methylene chloride (1 mL). The solution was stirred at room temperature. The reaction was quenched on addition of 1,4-diazabicyclooctane. The reaction mixture was concentrated in vacuo to give the residue, which was subjected to ^{1}H NMR analysis.

Registry No. **1**, 4759-04-0; $1^{\bullet+}$, 119391-88-7; **2**, 96581-96-3; $2^{\bullet+}$, 119477-45-1; **3**, 119391-87-6; **4**, 3306-02-3; TMB, 2441-46-5; NAP, 91-20-3; $NAP^{\bullet+}$, 34512-27-1; $NAP^{\bullet+}$–$TCNB^{\bullet+}$, 740-98-7; DCA, 1217-45-4; TCNE, 670-54-2; TCNB, 712-74-3; dibenzoylethane, 495-71-6; tris(*p*-bromophenyl)aminium herachloroantimonate, 78065-12-0.

Supplementary Material Available: Listings of positional parameters, thermal parameters, and bond distances and angles (7 pages). Ordering information is given on any current masthead page.

Computer-Assisted Evaluation of Oxidation Reactions†

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The scope and predictive capability of the CAMEO program have been enhanced to encompass the chemistry of 21 oxidative reagents including transition-metal acetates, metal and nonmetal oxides, hydrogen peroxide, peracids, and chromium(VI) oxidants. The implementation of the oxidation module required a strategy that deviates from the highly mechanistic approach employed by the other modules in CAMEO because of the dearth of mechanistic information on many oxidative transformations. The approach keys reactivity on the nature of the oxidant and utilizes the reaction conditions to narrow down the competing processes. This necessitated the formulation of "reactivity tables" for the featured reagents to help assess competitions among viable reactive sites. Algorithms for evaluating multipathway transformations for a specific site have also been devised based on reaction schemes that can presently account for all the observed transformations.

I. Introduction

CAMEO, an interactive computer program designed to predict the products of organic reactions, given the starting materials and conditions, is under continuous expansion. The incorporation of a reaction module that treats the chemistry of organic and inorganic oxidants into the program is addressed in this paper. Overall, the program now consists of modules that correspond to broad classes of reactions, namely, nucleophilic,[1] electrophilic,[2a,b] carbenoid,[2c] radical,[2d] thermal pericyclic,[3] heterocycle-forming,[4] and oxidative/reductive processes. The varying levels of sophistication found in these modules normally reflect the different states of knowledge in the corresponding areas. Thus, the nucleophilic module utilizes a mechanistic approach since a vast number of nucleophilic processes can be decomposed into a sequence of a few recurring fundamental mechanistic steps, whereas the pericyclic module goes beyond the usual mechanistic analysis and makes use of frontier molecular orbital (FMO) theory in predicting both the feasibility and regiochemistry of reactions.

A hierarchical approach, employing mechanistic reasoning for identifying and selecting the most reactive sites, and empirical rules, derived from literature precedents for evaluating competitions among several viable pathways, is a common key feature in most reaction modules in CAMEO. This approach, which relies on a mechanistic classification of reactions, is not generally viable when applied to oxidation reactions, for the following reasons: (a) knowledge of the mechanisms of oxidation reactions is oftentimes lacking or limited to specific reagent–substrate combinations; (b) oxidation chemistry encompasses diverse classes of reactions that involve many types of intermediates including radical ions, carbenes, and nitrenes; hence, reaction pathways are difficult to classify; and (c) the reaction pathways, and consequently the oxidation products, are highly dependent on the nature of the oxidizing agent and on the reaction conditions, such as temperature, pH of the medium, and stoichiometry. In view of these constraints, an alternative approach, which keys reactivity on the nature of the reagent, and which utilizes the reaction conditions to narrow down the potential oxidizable sites, has been adopted for the oxidation module. Importantly, this strategy permits sound predictions even for mechanistically obscure reactions. The oxidation module currently treats 21 reagents, which have been selected on the basis of their high synthetic utility. These reagents as well as the reaction conditions available to the user are listed on the menu shown in Figure 1. The major classes of oxidants that have been implemented are Cr(VI) com-

† Based on the Ph.D. Thesis of G. D. Paderes, Purdue University, 1988.

(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) Peishoff, C. E.; Jorgensen, W. L. *Ibid.* **1985**, *50*, 1056. (e) Peishoff, C. E.; Jorgensen, W. L. *Ibid.* **1985**, *50*, 3714. (f) Gushurst, A. J.; Jorgensen, W. L. *Ibid.* **1986**, *51*, 3513. (g) Metivier, P.; Gushurst, A. J.; Jorgensen, W. L. *Ibid.* **1987**, *52*, 3724.

(2) (a) McLaughlin, D. Ph.D. Thesis, Purdue, University, 1983. (b) Bures, M. G.; Roos-Kozel, B. L.; Jorgensen, W. L. *J. Org. Chem.* **1985**, *50*, 4490. (c) Helson, H. E. *J. Org. Chem.*, in press. (d) Laird, E. R. *J. Org. Chem.*, in press.

(3) (a) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1983**, *48*, 3923. (b) Burnier, J. S.; Jorgensen, W. L. *Ibid.* **1984**, *49*, 3001.

(4) Bures, M. G.; Jorgensen, W. L. *J. Org. Chem.* **1988**, *53*, 2504.

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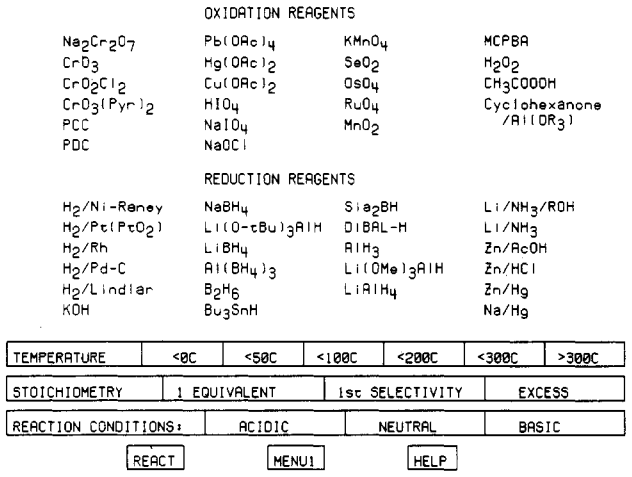


Figure 1. Reagent menu for the REDOX package.

pounds, transition-metal acetates, metal and nonmetal oxides, peracids and hydrogen peroxide, and other miscellaneous reagents such as periodic acid, potassium permanganate, sodium hypochlorite, sodium periodate, and the Oppenauer reagent (cyclohexanone/$Al(iPrO)_3$).

It must be pointed out that mechanistic analyses are specifically invoked, if possible, for those reactions where several possible oxidative transformations can operate on a given reactive site. If discrete mechanistic steps are not known, which is usually the case, multistep conversions (macrosteps) are applied to a given site. For cases where even macrosteps are unavailable, competitions among reaction pathways are dealt with by the application of heuristics based on empirical analyses that correlate the structural features of the reactants with the preferred products. Reaction schemes that aid in predicting the products of mechanistically obscure processes are sometimes proposed.

In the following, a brief overview of the general aspects of oxidation reactions is first given. The intent is not to provide a comprehensive review of all the reactions covered, but rather to consider representative reactions that illustrate the issues involved for implementation of this chemistry in CAMEO. The overview focuses on the similarities rather than the intrinsic differences or specificities of the processes, thus providing a coherent framework for systematizing the existing data in the literature. This is followed by a discussion of the methodology of implementation with emphasis on new algorithms for perception of reactive sites, proposed reaction schemes, and empirical rules for evaluating competitions. The paper concludes with examples of reaction sequences predicted by the CAMEO program.

II. Key Aspects of Oxidation Chemistry

The many facets of oxidation reactions and their synthetic applications in organic chemistry have been extensively reviewed.[5-14] The diversity and complexity of these processes stem from the specific chemical composition of the reagents, the majority of which are compounds of transition metals and nonmetals, and the interactive effects of several factors, such as temperature, pH of the medium, stoichiometry, and structure of the substrate. In order to develop an efficient program, it was necessary to break down this complexity into manageable components and to examine closely the individual contributions of the components to the overall reaction schemes. Hence, a brief summary of the key factors that affect oxidation reactions is presented here.

A. Nature of the Reagent. Reagents may be categorized according to chemical properties such as oxidation potential, electrophilicity, nucleophilicity, and the ability to form complexes with organic substrates. This categorization can help decide which functionalities in the spectrum of oxidizable sites are prone to attack by specific reagents. For example, $Hg(OAc)_2$[5] and $Pb(OAc)_4$ (LTA)[6a,9a,10a] are similarly classified since both are two-electron, electrophilic oxidants capable of forming complexes with nucleophilic sites such as carbon–carbon multiple bonds and heteroatomic sites bearing lone pairs of electrons. Likewise, OsO_4[6b,7,14] and RuO_4[6c,9c] belong to the same category since both can form similar complexes with alkenes, alkynes, and aromatic compounds.

Other reagents such as MCPBA, CH_3CO_3H, H_2O_2, SeO_2, $NaIO_4$, and HIO_4 are classified as "ambivalent" oxidants since they are capable of acting as nucleophiles or electrophiles depending on the nature of the substrates and the reaction conditions. Thus, MCPBA and CH_3CO_3H may act as electrophilic reagents in oxidizing alkenes, alkynes, allenes, heterocumulenes, imines, sulfides, amines, and azo and nitroso compounds, or as nucleophilic reagents in oxidizing sulfoxides, ketones, aldehydes, and α-dicarbonyl compounds.[5] The solvated form of SeO_2 may act as a nucleophile in its reaction with allylic sites or as an electrophile in its reaction with phosphines and sulfides. Periodate may function as an electrophile in the oxidation of α-diols and α-amino alcohols or as a nucleophile in the oxidation of α-keto acids. On the other hand, the dual nature of H_2O_2 as an oxidant is pH-dependent. In basic media, it exists as the peroxy anion and acts as a nucleophilic oxidizing agent, thus effecting transformations of aldehydes, ketones, α-diketones, nitriles, sulfoxides, phosphine oxides, and boranes. In acidic media, it functions as an electrophilic oxidant and attacks substrates such as amines, sulfides, selenides, phosphines, and azo compounds.[5]

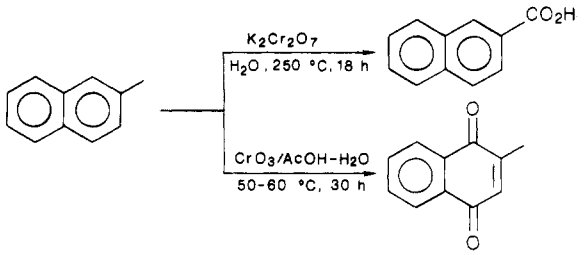
While this method of classification is useful, it is not sufficient to exhaustively identify all the possible reactive sites since a quantification of the oxidizing abilities of the

(5) Paderes, G. D. Ph.D. Thesis, Purdue University, 1988.
(6) (a) Mihailovic, M. L.; Cekovic, Z.; Lorenc, L. In *Organic Synthesis by Oxidation with Metal Complexes*; Mijs, W. J., De Jonge, C. R. H., Eds.; Plenum Press: New York, 1986; Chapter 14, p 741. (b) Singh, H. S. *Ibid.* 1986; Chapter 12, p 633. (c) Courtney, J. L. *Ibid.* 1986; Chapter 8, p 445. (d) Fatiadi, A. J. *Ibid.* 1986; Chapter 3, p 119. (e) Freeman, F. *Ibid.* **1986**; Chapter 2, p 41.
(7) Haines, A. M. In *Methods for Oxidation of Organic Compounds*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: New York, 1985; Chapter 2, p 66; Chapter 3, p 75.
(8) Cainelli, E.; Cardillo, G. In *Chromium Oxidations in Organic Chemistry*; Hafner, K., Lehn, J. M., Rees, C. W., Schleyer, P. v. R., Trost, B. M., Zahradnik, R., Eds.; Springer-Verlag: Berlin, Heidelberg, New York, Tokyo, 1984.
(9) (a) Rubottom, G. M. In *Oxidation in Organic Chemistry*; Trahanovsky, W. S., Ed.; Academic Press: New York, 1982; Part D, pp 1–45. (b) Plesnicar, B. *Ibid.* 1978; Part C, Vol. 5, Chapter 3, p 211. (c) Lee, D. G.; Van der Engh, M. *Ibid.* 1973; Part B, Chapter 4, p 177; p 147. (d) Nigh, W. G. *Ibid.* 1973; Part B, Chapter 1. (e) Crigee, R. In *Oxidation in Organic Chemistry*; Wiberg, K., Ed.; Academic Press: New York, 1965; Part A, Chapter 5, pp 277–366. (f) Bunton, C. A. *Ibid.* **1965**; Part A, Chapter 6, p 367. (g) Stewart, R. *Ibid.* 1965; Part A, Chapter 1, pp 1–68.
(10) Rabjohn, N. In *Organic Reactions*; Dauben, W. G., et al., Eds.; John Wiley & Sons, Inc.: New York, London, Sydney, Toronto, 1976; Vol. 24, Chapter 4, p 261.
(11) (a) Mihailovic, M. L.; Partch, R. E. In *Selective Organic Transformations*; Thyagaran, B. S., Ed.; Wiley-Interscience: New York, 1972; Vol. 2, p 97. (b) Jerussi, R. A. *Ibid.* 1970; Vol. 1, p 301. (c) Moriarty, R. M. *Ibid.* 1972; Vol. 2, p 183.
(12) Rinehart, K. L., Jr. In *Oxidation and Reduction of Organic Compounds*; Prentice-Hall: Englewood Cliffs, NJ, 1973; Chapter 5, p 68.
(13) Schroeder, M. *Chem. Rev.* **1980**, *80*, 187.
(14) (a) Fatiadi, A. J. *Synthesis* **1976**, 65, 133. (b) Mihailovic, M. L.; Cekovic, Z. *Synthesis* **1970**, 209. (c) Aylward, J. B. *Q. Rev., Chem. Soc.* **1971**, *25*, 407.

reagents and of the relative oxidizing susceptibilities of the substrates is presently not available. As a result, subtle nuances in the behavior of similar reagents (e.g., OsO_4 and RuO_4, and MCPBA and CH_3CO_3H), which are attributed to their innate oxidizing strengths, are not discernible. While general classification is useful, a knowledge by the program of the existing literature is indispensable for the identification of all possible reactive pathways.

B. Reaction Conditions. Reaction conditions may exert a profound effect on the viability of an oxidative process, the reactivity of a given site, and the nature of the oxidation products. The stoichiometric and temperature requirements of many oxidative transformations are well-known.[15,16] The effects of the acidity of the reaction media on the reactivity of a given site are also well-established in the literature. Variation in reactivity can oftentimes be traced to a change in the structure of the reactive site or the reagent. An example is the dramatic increase in the rate of oxidation of alcohols by potassium permanganate when solutions are made acidic or basic. The rate enhancement may be rationalized in terms of ionization of the alcohol to a more reactive alkoxide ion in alkaline solutions or of conversion of the permanganate ion to the more active permanganic acid in highly acidic solutions.[9c,g]

The nature of the oxidation products may also be affected by a variation in reaction conditions. The effects can be attributed to a change in mechanism or to further reaction of the initially formed product. An example of the former is the oxidation of polynuclear aromatic compounds by chromic acid. Oxidation may occur either in the aromatic ring or at the benzylic position, depending on the reaction conditions. Neutral conditions favor benzylic attack, whereas acidic conditions favor ring oxidation, as shown in eq 1 and 2.

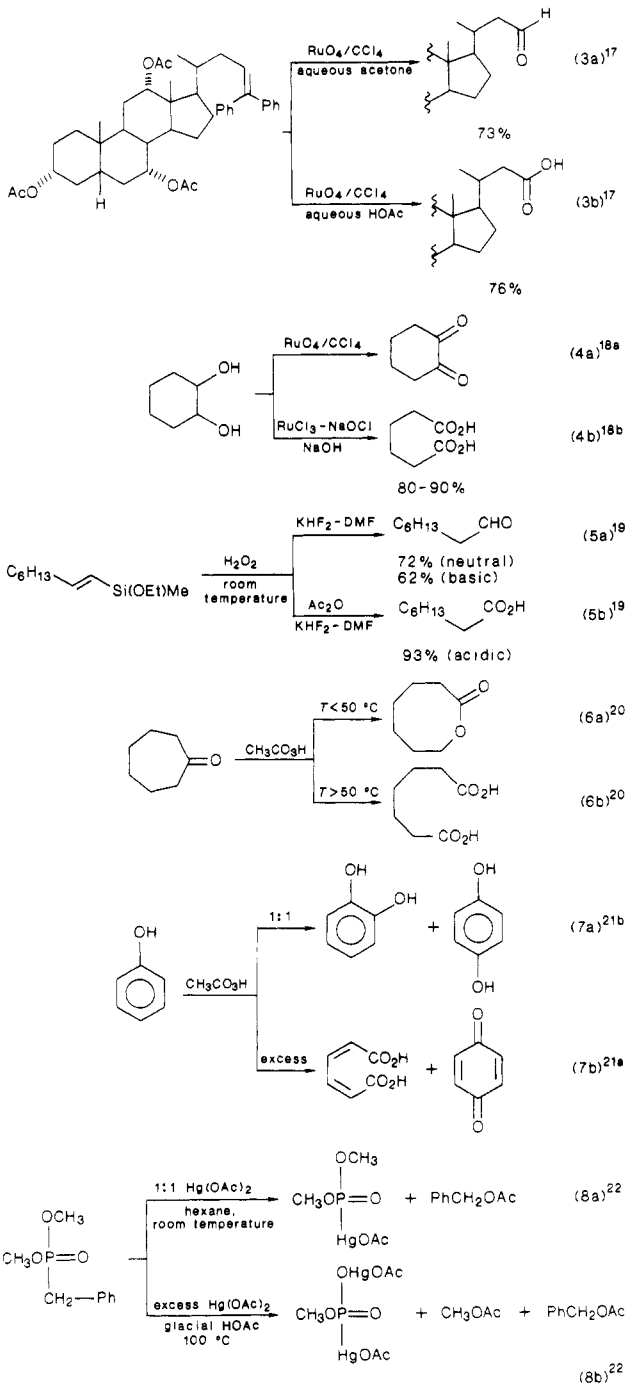


(1)

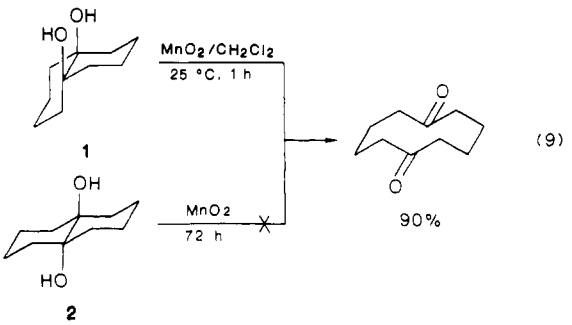
(2)

Examples of reactions where high temperatures, excess reagents, or extreme pH conditions result in further oxidations are shown in eq 3–8.

C. Structural Effects. Structural variations in substrates may determine both the reactivity of a site and the products of a reaction. Specifically, reactivity can be affected by stereochemistry, molecular conformation, ring strain, steric accessibility, and substituents. A stereochemical effect is demonstrated by the relative reactivity of 9,10-*cis*- and 9,10-*trans*-decalindiols (**1** and **2**) toward manganese dioxide.[23] In general, only 1,2-*cis*-diols and



1,2-*trans*-diols in conformationally flexible and unhindered molecules are reactive toward MnO_2.



(9)

Many examples of the effects of ring strain can be cited. To illustrate, carbon–phosphorus bonds in phosphoryl systems are generally resistant to oxidizing agents; however, oxygen insertion by MCPBA occurs in phosphine

(15) Leonard, N. J.; Johnson, C. R. *J. Org. Chem.* **1962**, *27*, 282.
(16) Connon, H. A.; Sheldon, B. G.; Harding, K. E.; Letterman, L. E.; Fulton, D. G.; Nigh, W. G. *J. Org. Chem.* **1973**, *38*, 2020.
(17) Shalon, Y.; Elliott, W. H. *Synth. Commun.* **1973**, *3*, 287.
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(19) Tamao, K.; Kumada, M. *Tetrahedron Lett.* **1984**, *25*, 321.
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(22) Awad, W. I.; Ei-Deek, M.; El-Sawi, E. *J. Indian Chem. Soc.* **1978**, *55*, 662.
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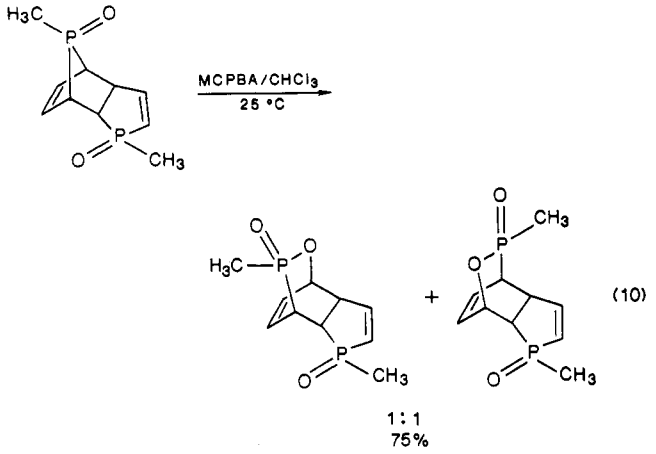
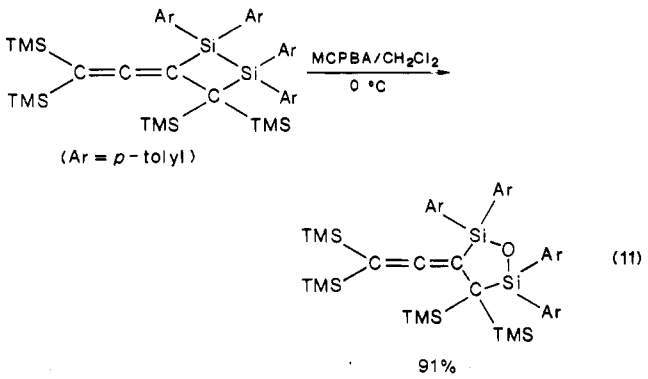
oxides with small C–P–C angles.[24] This reaction presumably results in relief of angle strain for the P(V) intermediate, as in eq 10.[24] The rate of oxygen insertion into bonds in α-disilanes by MCPBA is also enhanced for bonds in three- or four-membered rings (e.g., eq 11).[25]

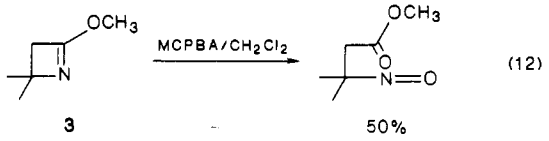


(10)



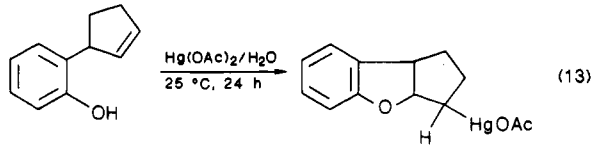
(11)

For some sites, further reactions may ensue if the sites are incorporated into three- or four-membered rings. Thus, oxidative cleavage of the initially formed oxaziridine occurs in the oxidation of imine 3 with MCPBA (eq 12).[9b]

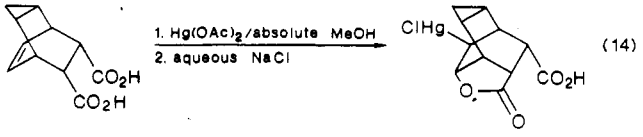


(12)

The standard course of a reaction can also be altered by the presence of geometrically accessible functionalities. For example, olefins normally undergo trans-addition reactions with mercuric acetate at room temperature; however, in the presence of suitably situated nucleophilic sites, neighboring-group participation may occur to quench the positively charged mercury complex, as in eq 13[26] and 14.[27]



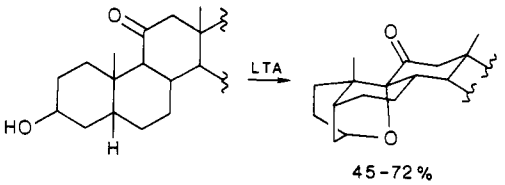
(13)



(14)

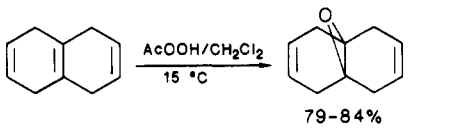
(24) Quinn, L. D.; Kisalus, J. C.; Mesch, K. A. *J. Org. Chem.* **1983**, *48*, 4466.
(25) Ishikawa, M.; Nishimura, K.; Ochiai, H.; Kumada, M. *J. Organomet. Chem.* **1982**, *236*, 7.

Remote functional groups, i.e., groups that are far removed from the actual site of attack, can also direct the course of a reaction electronically. Thus, in the oxidation of saturated alcohols by lead tetraacetate (LTA), hydrogen is preferentially abstracted by the intermediate alkoxy radical from a geometrically accessible δ-position, leading to the formation of a five-membered cyclic ether. However, the presence of an ether oxygen, a phenyl group, or a keto group on the ε-carbon considerably enhances the ease of hydrogen abstraction from the ε-carbon, resulting in the formation of a six-membered cyclic ether, as in eq 15.[28] Undoubtedly, the foregoing functional groups stabilize the intermediate ε-carbon radical, thereby increasing the likelihood of its formation.

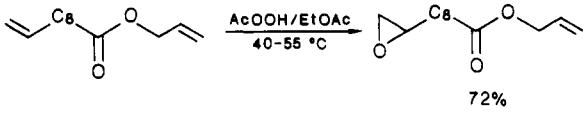


(15)

In addition, reactivity can, of course, be influenced by direct substituent effects. Thus, the reactivity of an olefinic bond toward peracetic acid is enhanced or reduced by electron-donating and electron-withdrawing substituents, respectively. This is evident in the site selectivity for the reactions depicted in eq 16[29] and 17.[30]



(16)



(17)

Different substitution patterns on a given site are another source of product variation. For example, the oxidation of enones by RuO_4 proceeds according to the following equations:[5]

$$RR'C{=}CHCOR \rightarrow RR'C{=}O + CO_2 + R''CO_2H \quad (18a)$$

$$RCH{=}CHCOR' \rightarrow RCO_2H + CO_2 + R'CO_2H \quad (18b)$$

$$RCH{=}C(R')COR'' \rightarrow RCO_2H + R'COCOR'' \quad (18c)$$

$$RR'C{=}C(R')COR'' \rightarrow RR'C{=}O + R'COCOR'' \quad (18d)$$

Apparently, the presence of a hydrogen atom at the α-position is crucial for determining the number of oxidative cleavages. These reactions are exemplified in eq 19[31] and 20.[32]

D. Competitions. Another aspect of oxidation reactions that requires explicit consideration in CAMEO is the issue of selectivity. Achieving selective transformations in polyfunctional molecules is always a concern in the design of efficient synthetic schemes. In this regard, two types of competitions may be envisioned: (a) among the different oxidizable sites in a molecule and (b) among the

(26) Hosokawa, T.; Miyagi, S.; Murahashi, S. I.; Sonoda, A. *J. Org. Chem.* **1978**, *43*, 719.
(27) Sasaki, T.; Kanematsu, K.; Kondo, A.; Nishitani, Y. *J. Org. Chem.* **1974**, *39*, 3569.
(28) Immer, H.; Mihailovic, M. L.; Schaffner, K.; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* **1962**, *45*, 753.
(29) Vogel, E.; Klug, W.; Breuer, A. *Org. Synth.* **1976**, *55*, 86.
(30) Frostick, F. C., Jr.; Phillips, B.; Starcher, P. S. *J. Am. Chem. Soc.* **1959**, *81*, 3350.
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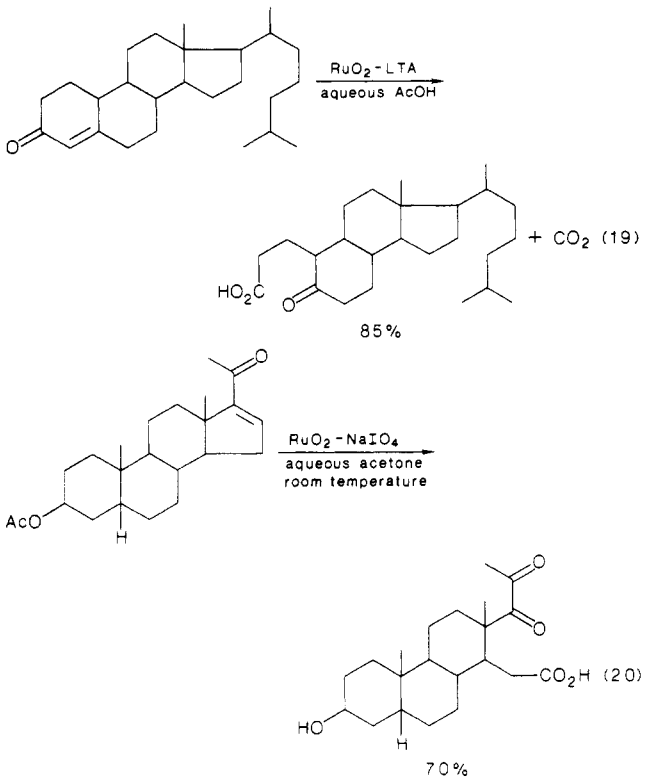
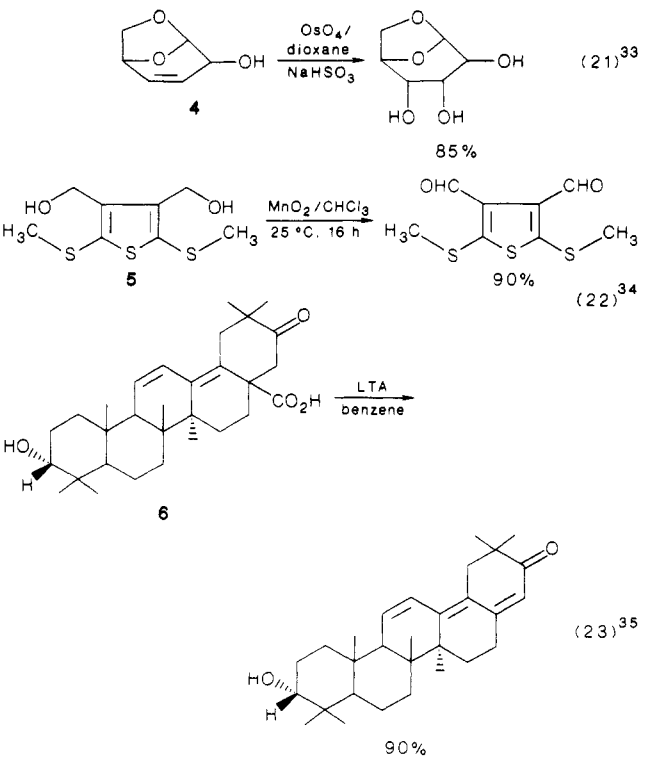
(32) Piatak, D. M.; Bhat, H. B.; Caspi, E. *J. Org. Chem.* **1969**, *34*, 112.



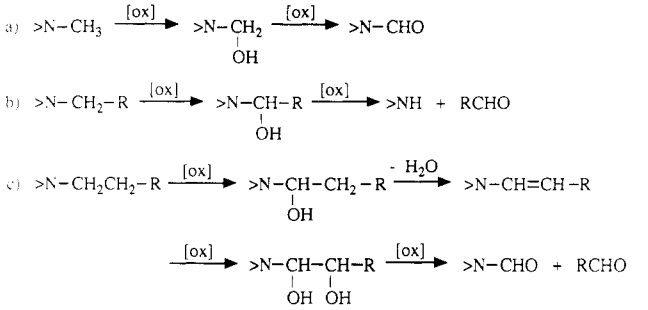
different mechanistic pathways that may be operative at a given site.

The first type of competition involves determining the preferential sites of attack by a specific reagent under a given set of conditions. Relative reactivity is controlled by chemical structure, which yields a reactivity order that is manifested in the experimentally observed products and in kinetic data. Examples of reactions showing competitions among different functional-group types are provided in eq 21–23. Competition exists between an olefinic bond

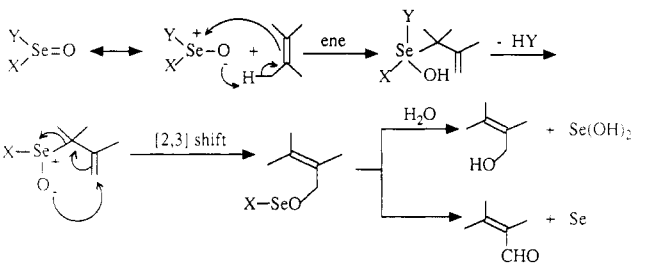


(33) Singh, U. P.; Brown, R. K. *Can. J. Chem.* **1971**, *49*, 1179.

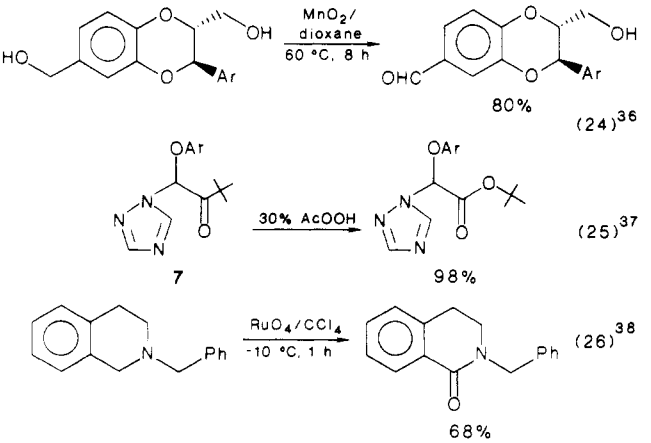
Scheme I. Proposed Mechanistic Pathways for Oxidation of Tertiary Amines by MnO_2



Scheme II. Mechanism for Oxidation of Olefins by SeO_2



and a hydroxyl group with OsO_4 in **4**, and between the sulfur atoms and hydroxyl groups toward MnO_2 in **5**. In **6**, the carboxyl group is apparently more reactive than the olefinic bonds and the keto and hydroxyl groups toward oxidation by LTA. Homoselectivity can also exist as shown in eq 24–26. In eq 24, the benzylic alcohol is selectively

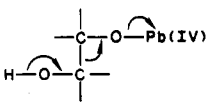
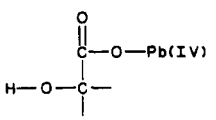
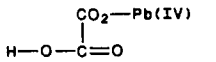
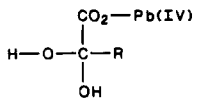
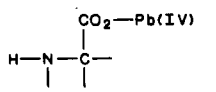
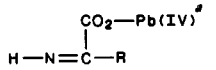
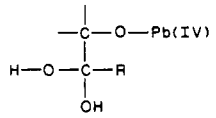
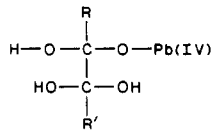
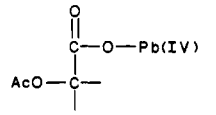
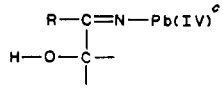
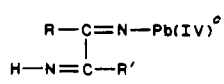


oxidized, while in eq 25, preferential migration of a quaternary alkyl group is found in the Baeyer–Villiger rearrangement of ketone **7** with peracetic acid. The relative reactivity of α-methylene groups in cyclic tertiary amines is exemplified in eq 26.

The second type of competition is normally encountered in multipathway transformations that often lead to a complex mixture of products. For example, the oxidation of aliphatic amines by MnO_2 may proceed through one or several pathways leading to the oxidation of alkyl groups α to nitrogen,[39] cleavage of carbon–nitrogen (Cα–N)[40,41] or

(34) *Chem. Abstr.* **1970**, *72*, 43323.
(35) Amagaya, S.; Takeda, T.; Ogihara, Y.; Yamasaki, K. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2044.
(36) Hansel, R.; Su, T. L.; Schultz, J. *Chem. Ber.* **1977**, *110*, 3664.
(37) *Chem. Abstr.* **1983**, *99*, 53764c.
(38) Bettoni, G.; Carbonara, G.; Franchini, C.; Tortorella, V. *Tetrahedron* **1981**, *37*, 4159.
(39) Henbest, H. B.; Thomas, A. *J. Chem. Soc.* **1957**, 3032.
(40) Curragh, E. F.; Henbest, H. B.; Thomas, A. *J. Chem. Soc.* **1960**, 3559.

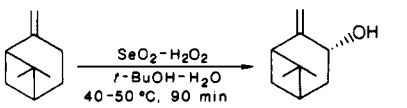
Table I. Oxidation of 1,1- and 1,2-Bifunctional Compounds by $Pb(OAc)_4$

entry	compound	intermediate	cleavage products	ref
1	1,2-diol		2>C=O	6a
2	α-hydroxy acid		CO_2 + >C=O	52
3	oxalic acid		$2CO_2$	52
4	α-keto acid		CO_2 + RCO_2H	52
5	α-amino acid		CO_2 + —N=C<	53
6	α-imino acid		CO_2 + N≡CR	52
7	α-hydroxy ketone		>C=O + RCO_2H	6a
8	1,2-diketone		RCO_2H + $R'CO_2H$	6a
9	α-acetoxy acid		CO_2 + >C=O[b]	54
10	α-hydroxy amine		RC≡N + >C=O	55
11	1,2-diamine		RC≡N + R'C≡N	56

[a] R = NHR. [b] From hydrolysis of $>C(OAc)_2$. [c] After removal of hydrogen from amino-bearing α-carbon atom.

carbon–carbon (Cα–Cβ) bonds,[40] or dehydrogenation of carbon–nitrogen[42,43] or carbon–carbon bonds.[44] A reaction scheme consisting of three major pathways (Scheme I) has been proposed by Henbest and co-workers.[45] The first step, which is common to all pathways, is the oxidation of the amine to an α-hydroxy amine. The next step can then be (a) oxidation of the α-hydroxy group to give an *N*-acyl derivative, (b) rearrangement leading to a secondary amine and an aldehyde, or (c) dehydration to give an enamine, which is oxidatively cleaved to an *N*-acyl derivative and a carbonyl compound. For most amines, a single pathway predominates and a major product is usually obtained in good yield. The preferred pathway depends on the structural characteristics of the starting materials.

E. Mechanistic Considerations. Although generalizations on mechanisms of oxidations are not uniformly feasible at this time, mechanistic analyses for specific reagent–substrate combinations are utilized in the oxidation module in CAMEO. A knowledge of the mechanisms can be extremely valuable in determining the potential sites of attack by specific reagents. For example, in eq 27[46]

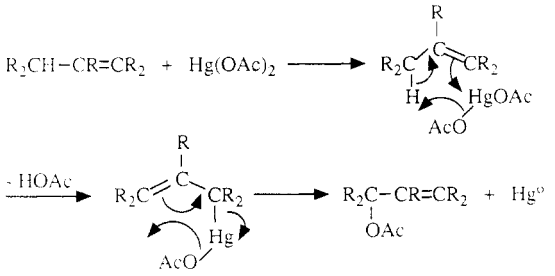


(27)

there are two possible allylic positions that are potentially available for oxidation with SeO_2. However, consideration of the currently accepted mechanism for allylic oxidation by SeO_2 (Scheme II)[47] suggests that allylic bridgehead positions in small bridged systems should be unreactive, as observed. Similarly, acetoxylation by mercuric acetate of bridgehead allylic positions that fall within the limits of Wiseman's rule should be infeasible on the basis of the proposed mechanism given in Scheme III.[48]

(41) Henbest, H. B.; Thomas, A. *Chem. Ind. (London)* **1956**, 1097.
(42) Sandhu, J. S.; Mohan, S.; Sethi, P. S. *Chem. Ind. (London)* **1970**, 1658.
(43) Field, G. F.; Zally, W. J.; Sternbach, L. H. *J. Am. Chem. Soc.* **1967**, *89*, 332.
(44) Pratt, E. F.; McGovern, T. P. *J. Org. Chem.* **1964**, *29*, 1540.
(45) Henbest, H. B.; Stratford, M. J. W. *J. Chem. Soc. C* **1966**, 995; **1964**, 711.
(46) Coxon, J. M.; Dansted, E.; Hartshorn, M. P. *Org. Synth.* **1977**, *56*, 25.
(47) Woggon, W. D.; Ruther, F.; Egli, H. *J. Chem. Soc., Chem. Commun.* **1980**, 706.

Scheme III. Mechanism for Allylic Acetoxylation by $Hg(OAc)_2$



Prior mechanistic knowledge can also be used in the evaluation of mechanistically similar reactions. Thus, a variety of oxidative transformations can be evaluated concurrently by a few mechanistic pathways. To illustrate, the different fragmentation products obtained from oxidation of a variety of 1,1- and 1,2-bifunctional compounds by LTA (Table I) can be accounted for and evaluated by a single mechanistic pathway. In the same manner, the oxidations of several nucleophilic substrates (e.g., sulfides, disulfides, thioamides,[50] thiols, selenides, amines,[49] phosphines,[51] pyridines, and azo compounds) by hydrogen peroxide to the corresponding oxo derivatives under neutral and acidic conditions can be rationalized and consequently evaluated by a single mechanistic pathway involving the attack of the nucleophilic site on the peroxy oxygen atom.[5]

Finally, mechanistic information can be utilized for evaluating competitions in some multipathway transformations. Which pathway predominates depends on the structural features of the substrate. If the mechanisms are known, the stability of the intermediates may be used to guage competitions. Multipathway transformations will be considered in detail in the subsequent section.

III. General Implementation

A. Program Flow. An executive subroutine, REDOX, oversees the processing of both oxidative and reductive processes in CAMEO. The structure of the program is modularized with the type of input reagent controlling the general program flow. Figure 1 gives the list of reagents that are available in the REDOX module. It should be pointed out that while reagents in other modules in CAMEO may be drawn alternatively via the sketch menu, the oxidative/reductive reagents may only be specified by the user from the menu in Figure 1. Introducing the redox reagent via the sketch menu is presently deemed unnecessary since the structures of the reaction intermediates are not displayed on the terminal screen. It should also be noted that code numbers are utilized by the REDOX module for storage of its reagents while atom and bond tables are used for storage of other input structures.

Upon specification of the reagent, the program branches to the proper reaction module (oxidation or reduction), which then calls the subroutine in charge of the given reagent or group of related reagents. The reagent subroutine does all the decision making and encoding of information to be used in product formation by subroutine MPROD. In MPROD, the structural commands are decoded and executed to make the actual manipulations on the atom and bond table to create the products.

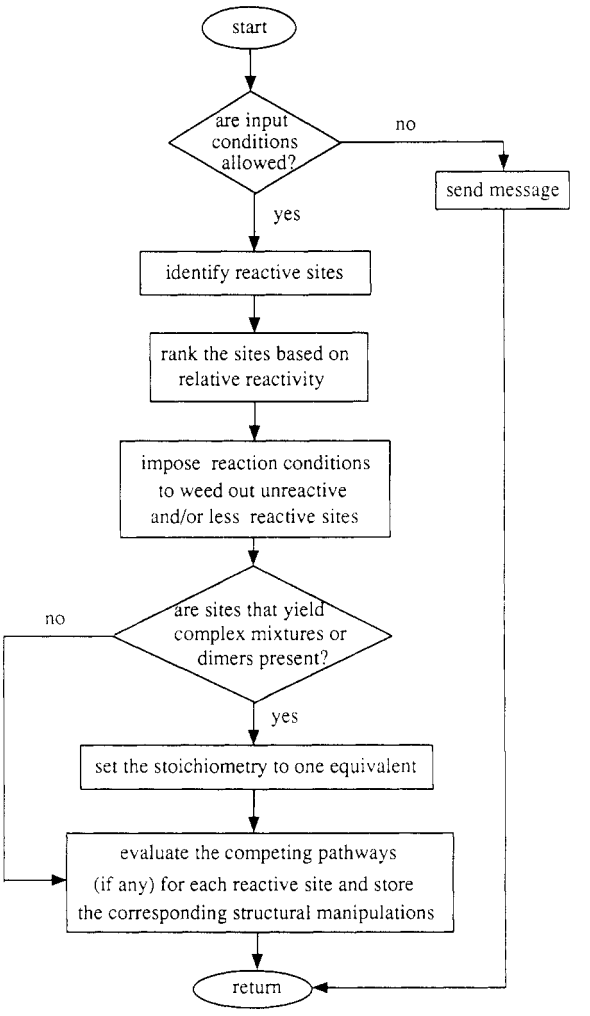


Figure 2. Simplified flow diagram of a typical reagent subroutine.

A typical flowchart for a reagent subroutine is given in Figure 2. The general procedure involves (1) perception of potentially reactive sites, (2) ranking of the sites on the basis of relative reactivity, (3) weeding out of unreactive sites on the basis of the input reaction conditions, and (4) evaluation of competing pathways, if necessary, and storage of required manipulations for product formation. These steps will now be described in detail.

B. Perception of Reactive Sites. Before perception of possible reactive sites is initiated, a preliminary screening of the viability of a reaction is performed by examining the user-specified conditions such as temperature, stoichiometry, and acidity. For example, temperatures greater than 200 °C are not allowed for reactions with $Pb(OAc)_4$ and RuO_4 since thermal decomposition of these reagents ensues at 140 °C[6a] and 108 °C,[9c] respectively. If the input conditions are unacceptable, processing of the reaction is discontinued and a message informing the user of the reasons for rejection is output on the terminal screen.

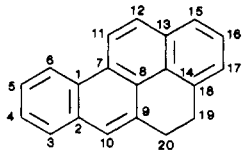
The nature of the reagent or group of reagents (in the case of chromium(VI) oxidants) dictates the types of reactive sites that have to be perceived; thus, a great reduction in the number of possible reactive sites is achieved at an early stage of processing. For some reagents, reactive sites can readily be identified (e.g., an electrophilic oxidizing agent such as $Hg(OAc)_2$ is attracted to nucleophilic sites such as multiple bonds or heteroatoms bearing electron lone pairs). For other reagents, identification of reactive sites requires more than simple intuition, and one

(48) Fielding, B. C.; Roberts, H. L. *J. Chem. Soc. A* **1966**, 1627.
(49) Calvino, R.; Gasco, A.; Serafino, A. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1240.
(50) Cashman, J. R.; Hanzlik, R. P. *J. Org. Chem.* **1982**, *47*, 4645.
(51) Yoshifuji, M.; Shibayama, K.; Toyota, K.; Inamoto, N. *Tetrahedron Lett.* **1983**, *24*, 4227.

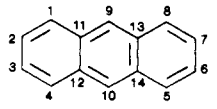
is compelled to rely on algorithms developed from literature surveys of a large number of reactions. To illustrate, even though OsO_4 and RuO_4 belong to the same group in the periodic table, these reagents elicit different chemical behavior from different oxidizable sites.

Ordinarily, perception of reactive sites is accomplished with the aid of "tool" subroutines that find the atom and bond types in various functional groups. However, specific instances arise where special algorithms have to be formulated for more sophisticated perception of reactive sites. Thus, a general algorithm that finds the aromatic bonds with the greatest double-bond character (π-bond order) in polycyclic aromatic hydrocarbons and another that identifies the sites of cleavage in aromatic degradation reactions have been implemented in the subroutines for OsO_4 and RuO_4, respectively. An algorithm based on an empirically derived set of rules for identifying the most reactive sites in allylic systems has also been established in the subroutine for SeO_2. The treatment of these and other special cases is expanded on below.

OsO_4 is essentially a "double-bond" reagent such that, for aromatic systems, the sites of attack correspond to the bonds that have the greatest double-bond contributions in the alternative resonance structures. The algorithm for identifying the most reactive aromatic bonds in polycyclic aromatic hydrocarbons is outlined as follows: (i) find the set of carbon–carbon aromatic bonds (ARBD) in six-membered aromatic systems; (ii) identify the fused carbon atoms (FUS3AR) joined by three bonds in ARBD; (iii) find the aromatic carbon atoms (FUSALF) that are adjacent to but do not include atoms in FUS3AR; (iv) the most reactive bonds (ARSITE) are then defined as the bonds connecting two atoms in FUSALF. If absent, the bonds with one atom in FUSALF, but neither in FUS3AR, are the most reactive. This algorithm has been shown to give the correct products for a variety of experimental cases.[57-59] The following examples illustrate the manner in which the algorithm works in conjunction with the aforementioned steps.



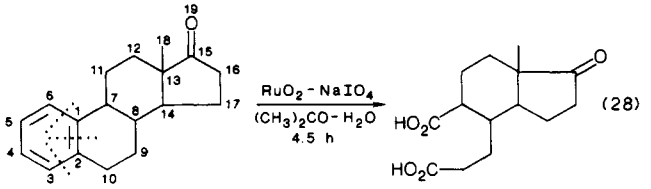
ARBD = all bonds except C_{18}–C_{19}, C_{19}–C_{20}, C_{20}–C_9
FUS3AR = 1, 2, 7, 8, 13, 14
FUSALF = 3, 6, 9, 10, 11, 12, 15, 18
ARSITE = C_9–C_{10}, C_{11}–C_{12}



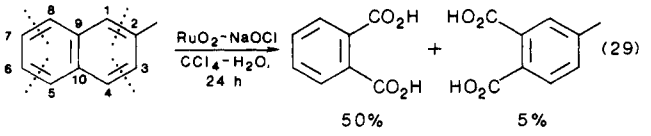
ARBD = all bonds
FUS3AR = 11, 12, 13, 14
FUSALF = 1, 4, 5, 8, 9, 10
ARSITE = C_1–C_2, C_3–C_4, C_5–C_6, C_7–C_8

Apparently, the most reactive sites toward OsO_4 generally differ from the preferred sites of attack in electrophilic aromatic substitution (EAS) reactions. In contrast to OsO_4, the most reactive sites for EAS are the positions that lead to the least loss of π-energy for the reacting aromatic system upon addition of the electrophile. Thus, the C_9 and the C_{10} positions of both anthracene and 1,2-benzanthracene are preferentially attacked in EAS reactions, whereas the C_1–C_2 bond of anthracene and the C_3–C_4 bond of 1,2-benzanthracene are attacked by OsO_4.

In perceiving aromatic sites that can undergo degradation by RuO_4, only the crucial sites for cleavages are stored as reactive sites. In general, these sites correspond to carbon–carbon aromatic bonds adjacent to carbon–carbon single bonds containing an sp^3 center.[60-65] Alternatively, the reactive sites are aromatic bonds with the greatest π-bond order.[66,67] An example illustrating the former is provided in eq 28.[63] In this example, the reactive sites are the C_1–C_2, C_2–C_3, and C_1–C_6 bonds. Equation 29 illustrates the latter case, where reactive sites correspond to bonds with the greatest double-bond character.[67]



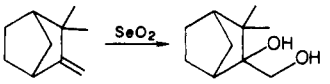
(28)



(29)

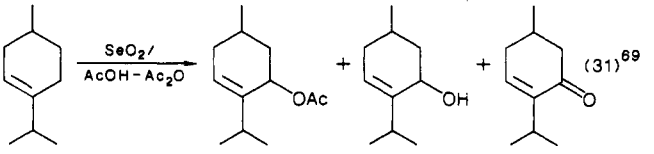
In perceiving reactive allylic sites for oxidations with SeO_2, the following set of rules was derived empirically from numerous literature precedents.

(1) Allylic bridgehead positions in small bridged systems are unreactive (recall eq 27). If nonbridgehead allylic positions are absent, oxidation occurs at the double bond (e.g., eq 30).[68a]



(30)

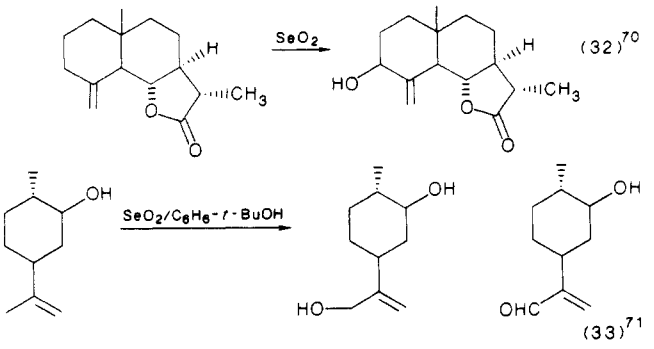
(2) For trisubstituted olefins, oxidation always occurs at the disubstituted end of the double bond. Furthermore, ring oxidation is favored over side-chain oxidation.



(31)[69]

(3) For alkenes having two or more possible allylic sites, the preferential order of attack is $CH_2 > CH_3 > CH$. However, rule 2 overrides this rule. Examples are provided in eq 32 and 33.

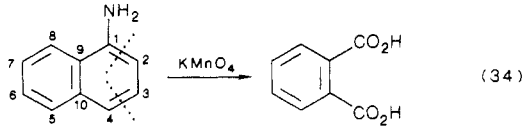
(52) Sheldon, R. A.; Kochi, J. K. *Org. React. (N.Y.)* **1972**, *19*, 279.
(53) Slates, H. L.; Taub, D.; Kuo, C. H.; Wendler, N. L. *J. Org. Chem.* **1964**, *29*, 1424.
(54) Tanabe, M.; Crowe, D. F. *J. Org. Chem.* **1965**, *30*, 2776.
(55) Parameswaran, K. N.; Friedman, O. M. *Chem. Ind. (London)* **1965**, 988.
(56) Roth, J.; Brandau, A. *Arch. Pharm. (Weinheim, Ger.)* **1960**, *293*, 27.
(57) Yagi, H.; Holder, G. M.; Dansette, P. M.; Hernandez, O.; Yeh, H. J. C.; Le Mahieu, R. A.; Jerina, D. M. *J. Org. Chem.* **1976**, *41*, 977.
(58) Jacquignon, P.; Perin-Roussel, O.; Perin, F.; Chalvet, O.; Lhoste, J. M.; Mathieu, A.; Saperas, B.; Viallet, P.; Zajdela, F. *Can. J. Chem.* **1975**, *53*, 1670.
(59) Agarwal, S. C.; Van Duuren, B. L. *J. Org. Chem.* **1977**, *42*, 2730.
(60) Caputo, J. A.; Fuchs, R. *Tetrahedron Lett.* **1967**, 4729.
(61) Guizard, C.; Cheradame, H. *J. Fluorine Chem.* **1979**, *13*, 175.
(62) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, B. K. *J. Org. Chem.* **1981**, *46*, 3936.
(63) Piatak, D. M.; Herbst, G.; Wicha, J.; Caspi, E. *J. Org. Chem.* **1969**, *34*, 116.
(64) Imajo, S.; Kuritani, H.; Shingu, K.; Nakagawa, M. *J. Org. Chem.* **1979**, *44*, 3587.
(65) Sarma, A. S.; Chattopadhyay, P. *J. Org. Chem.* **1982**, *47*, 1727.
(66) Ayres, D. C.; Hossain, A. M. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 707.
(67) Spitzer, U. A.; Lee, D. G. *J. Org. Chem.* **1974**, *39*, 2468.
(68) (a) Trachtenberg, E. N. In *Oxidation Techniques and Applications in Organic Synthesis*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1969; Chapter 3, p 119; (b) *Ibid.* Chapter 1, pp 1 ff.
(69) Suga, T.; Sugimoto, M.; Matsuura, T. *Bull. Chem. Soc. Jpn.* **1963**, *36*, 1363.



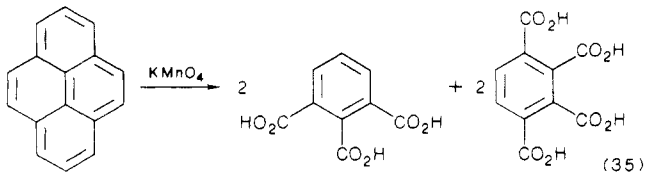
(32)[70]

(33)[71]

Another case that requires explicit treatment involves the degradation of aromatic rings by $KMnO_4$. An algorithm for identifying the possible sites of cleavage in aromatic hydrocarbons has been devised. It should be noted that the present algorithm is restricted to aromatic systems with an all-carbon framework. In this algorithm, each fused aromatic ring, r, is examined and the positions of its aromatic substituents (ARSUB) are identified. Possible cleavage sites are aromatic bonds α to ARSUB but not adjacent to any of the bonds in the rth ring. As a general rule, rings that bear electron-donating groups are preferentially attacked unless excess reagent is specified. Thus, in eq 34,[68b] the aromatic ring containing the amino group is preferentially attacked. In this case, ARSUB contains atoms 1 and 4, and the cleavage sites are the C_1–C_2 and C_3–C_4 bonds. An example of a reaction in which all the aromatic rings can undergo an oxidative cleavage with $KMnO_4$ is provided in eq 35.[68b]



(34)



(35)

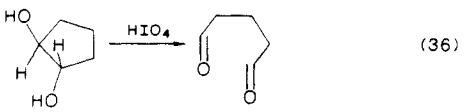
The geometric requirements for reactions that were covered in section II.C are also implemented at this point. Empirical rules have been devised that address the stereorelationships and the accessibilities of the reactive sites to specific reagents.

The rules for oxidation of α-diols with periodate are as follows.

(1) All 1,2-diols in open-chain systems and all *cis*-1,2-diols in cyclic systems react with periodate to give 1,2-dicarbonyl compounds.

(2) *trans*-1,2-Diols may or may not react with periodate, depending on the structure of the substrate and the specified stoichiometric conditions.

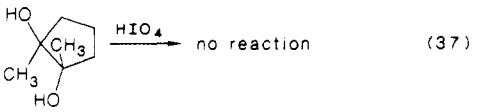
(a) *trans*-1,2-Diols in conformationally flexible molecules are considered reactive under all stoichiometric conditions (e.g., eq 36).[9f]



(36)

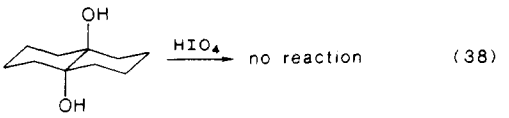
(b) *trans*-1,2-Diols in conformationally rigid molecules are considered unreactive under normal conditions. However, these sites are oxidized with excess periodate, the reactions being referred to as "overoxidations". Conformational rigidity is established if any of the following conditions is satisfied.

(i) One or both carbon atoms in a cyclic *trans*-1,2-diol are tetrasubstituted and the ring size is less than or equal to seven (e.g., eq 37).[9f]



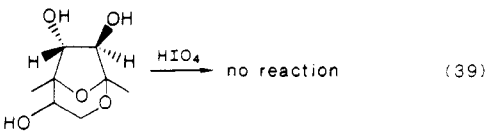
(37)

(ii) Both carbon atoms in a *trans*-1,2-diol are at ring fusions (e.g., eq 38).[9f]



(38)

(iii) Both carbon atoms in a *trans*-1,2-diol are α to bridgehead atoms in small bridged systems (e.g., eq 39).[9f]



(39)

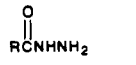
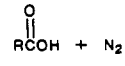
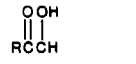
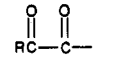
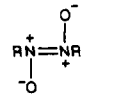
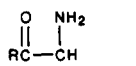
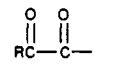
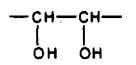
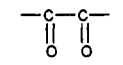
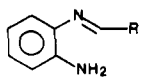
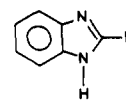
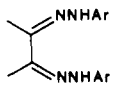
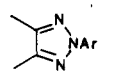
Other structural effects noted in section II.C are also taken into account at this point. Thus, oxygen insertions by MCPBA into carbon–phosphorus bonds occur only in rings or bridged systems with small C–P–C angles, e.g., the C–P–C units must be in three- or four-membered rings or in small bridged systems in which the phosphine oxide group is α to two bridgehead atoms (eq 10). Further pruning of potentially reactive sites comes from the mechanistic insights mentioned in section II.E. Thus, bridgehead allylic carbon atoms in small bridged systems are recognized as inert toward chromic acid oxidation due to their inability to achieve sp^2 hybridization in the activated complex. α-Amino alcohols and α-diols are also deemed unreactive under Oppenauer conditions since they form coordination complexes with the aluminum alkoxide reagent.[72]

C. Ranking of Reactive Sites. The predictive capabilities of the program depend not only on making a correct functional-group transformation but also on the precise determination of the relative reactivity of any competitive sites. The difficulty in achieving this task varies from reagent to reagent and is largely dependent on the data available in the literature.

For some reagents, mechanistic information is extensive, so that the determination of relative reactivity is on a firm basis. In such cases, general concepts such as stability of reaction intermediates, nucleophilicity or electrophilicity of sites, and pK_a considerations may be invoked to evaluate the competitions. To illustrate, mercuric acetate oxidations are characterized by prior complexation of Hg(II) with nucleophilic sites such as multiple bonds or heteroatoms with available lone pairs of electrons. Hence, nucleophilicity and stability of reaction intermediates form the bases for assigning the competing sites to different reactivity levels (e.g., the stabilities of Hg(II)–alkene and Hg(II)–alkyne complexes are compared). pK_a considera-

(70) Pathak, S. P.; Kulkarni, G. H. *Chem. Ind. (London)* **1968**, 1566.
(71) (a) Klinck, R. E.; De Mayo, P.; Stothers, J. B. *Chem. Ind. (London)* **1961**, 471. (b) Sakuda, Y. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 514.
(72) Warnhoff, E. W.; Reynolds-Warnhoff, P. *J. Org. Chem.* **1963**, *28*, 1431.

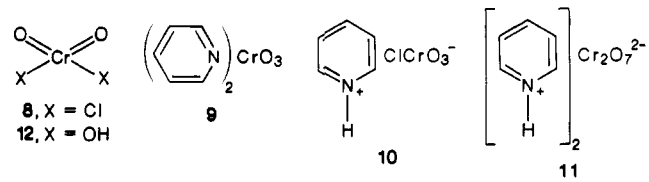
Table II. Structural Transformation and Relative Reactivity Table for $Cu(OAc)_2$

reactivity level	reactive site	reactn condtns	product
1		neutral, 25 °C	
		neutral, acidic, 25–60 °C	
	$RNHOH$	neutral	
	RSH	neutral	$RSSR$
2		basic	
	$>CHCH{=}O$	basic	$>CHCO_2H$
	$RC{\equiv}CH$	basic, neutral, acidic, 25–90 °C	$RC{\equiv}CC{\equiv}CR$
		acidic	
	$ArB(OH)_2$	neutral	$ArOAc + B(OH)_3$ or $ArAr + B(OH)_3$
	$ArNH_2$	neutral, basic	$ArN{=}NAr$
		neutral	
	NH_2NH_2	neutral	$N{\equiv}N$
	$ArNHNH_2$	acidic	$ArH + N_2$
		basic	$ArOH + N_2$
	$RNHNHR$	basic	$RN{=}NR$
		neutral	

tions are invoked in cupric acetate oxidations since the initial oxidation step in these reactions is usually preceded by abstraction of an acidic hydrogen to form an anion (e.g., the acidities of thiols and alkynes may be compared).

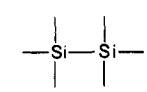
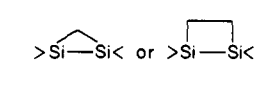
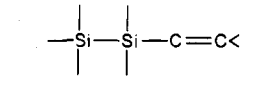
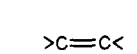
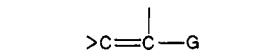
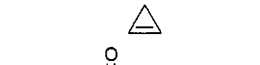
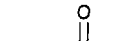
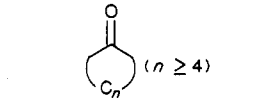
For reagents with obscure oxidation mechanisms, evaluation of reactivity is based on empirical analyses of observed product distributions for a large number of reactions that show competitions among potentially oxidizable sites. The severity of the reported reaction conditions required to effect oxidative transformations is also utilized, especially for cases where information on competitions is scarce. Reagents that fall into this category include MnO_2, SeO_2, RuO_4, $KMnO_4$, $Pb(OAc)_4$, and Cr(VI) oxidants. Competitions are dealt with by assigning the sites to different reactivity levels. Operationally, this is accomplished by storing the perceived sites in a two-dimensional array called RSITE (τ, ℓ), which contains sites of type τ (τ = 1 for atoms and τ = 2 for bonds) belonging to reactivity level ℓ. Reactivity decreases with increasing level number, and ℓ = 1 corresponds to sites with the highest reactivity. This array is then manipulated to yield two sets, ACSIT(1) and ACSIT(2), which contain all the possible reactive sites for atoms and bonds, respectively. In general, sites with a lower ℓ can be selectively oxidized in the presence of sites with higher ℓ values.

A major part of the present work was the development of the requisite reactivity tables from the literature data to address the competitions between sites. The resultant tables, which cover 19 of the 21 oxidants, are presented in Tables II–XV. In each case, the reactive site, conditions, product, and reactivity level are given. The large amount of information condensed into the tables has obvious utility for synthetic chemists, independent of the CAMEO program; the scope of the chemistry incorporated into the oxidation module is also apparent. The tables for Oppenauer oxidations, which involve only alcohols, and for NaOCl oxidations, which rely on pK_a predictions for evaluation of competitions, are not given. Furthermore, Table XIV handles both HIO_4 and $NaIO_4$ oxidations, while the oxochromium(VI) reagents referred to in Table XIII include chromium trioxide, sodium dichromate, chromyl chloride (8), dipyridinium chromium(VI) oxide (Collins'



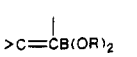
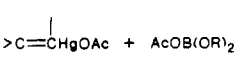
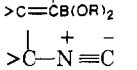
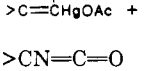
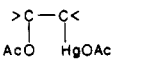
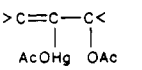
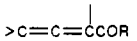
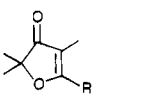
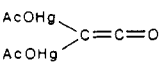
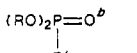
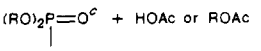
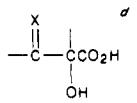
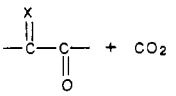
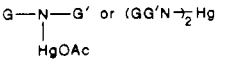
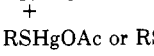
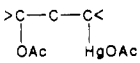
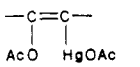
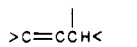
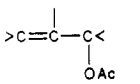
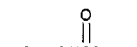
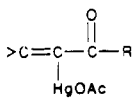
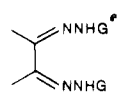
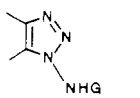
reagent, 9), pyridinium chlorochromate (PCC, 10), and pyridinium dichromate (PDC, 11). The first two reagents generate chromic acid (12) when used in acidic aqueous solutions. The last three reagents, 9–11, are specifically designed for oxidizing acid-sensitive molecules. Note that categorization of reactions with the oxochromium(VI) reagents depends on the acidity of the reaction media (Tables XII and XIII) and benefits from the similarity in chemical behavior and reactivity of the various oxidizable sites toward these reagents. Table XII is a modified and extended table derived mainly from the functional-group rankings proposed by Cainelli and Cardillo.[8] All the other tables are based mostly on available mechanistic ideas, observed product distributions for competitive cases, and rough kinetic data from reported reaction times and conditions. It was also necessary to make some assumptions, analogies, and inferences in creating these tables. Hopefully, the results presented here will spark interest and trigger further investigations on competitive reactions.

For some reactive sites, adjustments to the initially assigned reactivity levels are made for the presence of certain geometric and electronic factors. For example, some variations in reactivity for ketones, olefinic bonds, and silicon–silicon bonds with MCPBA (Table IX) can be accounted for by (a) change in ring strain resulting from oxidative cleavage of cyclopropene oxide, oxygen insertions in α-disilanes, and Baeyer–Villiger rearrangements in ketones and (b) diminished nucleophilicity of conjugated olefinic and Si–Si bonds, as summarized below.

reactive site	initial level	structure	adjustment
	3		−1
			+1
	4	 (G = COR, CO_2R, CN, etc.)	+1
			−1
	5		+2

Unfortunately, there is not always a one-to-one correspondence between reactant and product functionality, i.e., some reactive sites (e.g., acids, alcohols, and alkenes in Table IV) lead to a complex mixture of products. In these

Table III. Structural Transformation and Relative Reactivity Table for $Hg(OAc)_2$

reactivity level	reactive site	reactn condtns	product
1		neutral, 0–25 °C	
		acidic, 5–10 °C	
	$ROCH_2SCH_3$	neutral, 25 °C	$ROCH_2OAc$
2	>C=C<	neutral, acidic, 25 °C	
	>C=C=C<	neutral, 25 °C	
		acidic, 25 °C	
	>C=C=O	neutral, 25 °C	
	$ArCO_2H$	neutral, acidic, 25 °C	ArHgOAc or $(ArCO_2)_2Hg$
		neutral, 25 °C	
		neutral, 25 °C	
	$GNHG'^{e}$	neutral, acidic, 25 °C	
	$R_2NCH<^{f}$	neutral, 25 °C–reflux	
	RSH	neutral, 25–40 °C	RSHgOAc or RSHgSR
3	cyclopropyl bond	neutral, acidic, 25 °C, 1–7 days	
	—C≡C—	acidic, 25 °C or reflux	
4		acidic, 75 °C	
		acidic, 75 °C	
		acidic, 60 °C	

[a] R = H, alkyl, aryl. [b] R′ = H, alkyl, *O*-alkyl, *O*-aryl. [c] Y = HgOAc for R′ = H, alkyl; Y = OHgOAc for R′ = *O*-alkyl. [d] X = N or O. [e] G, G′ = polarized multiply bonded atoms such as SO_2Ar, $CONH_2$, OTS, etc. [f] R = alkyl or aryl.

cases, further analyses of structure and conditions are required to predict the true products, as shown in the reaction schemes in section III.E below.

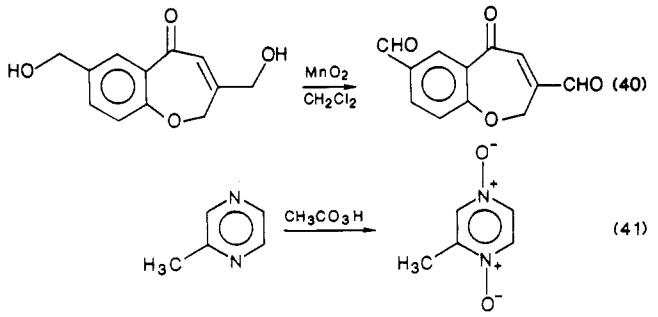
D. Selection of Sites. By imposition of the user-specified reaction conditions, product distributions can be varied and less reactive sites can be removed from consideration. The choices of conditions that are available to the user are the reagent stoichiometry (1 equiv, first selectivity, excess), reaction temperature (<0, <50, <100, <200, <300, >300 °C), and acidity of the media (acidic, neutral, basic). The default stoichiometry is first selectivity, while the default acidity is reagent dependent (e.g., acidic for MCPBA). The default temperature is <50 °C since many oxidation reactions are carried out at room temperature.

The program is designed to process sites of similar reactivity simultaneously, thus issuing, as much as possible, a smaller number of products. The simultaneous oxidation of similarly reactive sites is realized by the first-selectivity option in the reagent menu (see Figure 1). When this option is chosen, the program will automatically determine the smallest number of equivalents that is needed to effect a clean and selective reaction. Thus, both the allylic and benzylic hydroxyl groups in eq 40 are transformed by MnO_2.[73] Use of 1 equiv would yield a mixture of aldehydes, whereas only the doubly oxidized product is obtained with first selectivity. An analogous example is illustrated in eq 41.[74]

The selected temperature range is used for weeding out unreactive sites. For example, sulfoxides are oxidized by $NaIO_4$ only at temperatures greater than 60 °C;[15] hence,

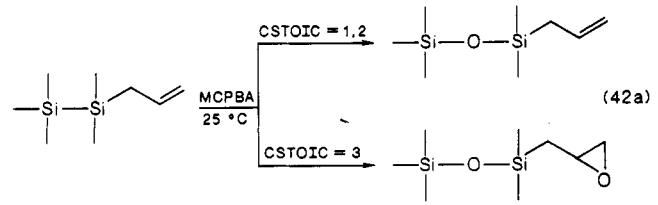
(73) Jarrah, M. L.; Thaller, V. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1719.

(74) (a) Sato, N. *J. Org. Chem.* **1978**, *43*, 3367. (b) Klein, B.; Hetman, N. E.; O'Donnell, M. E. *J. Org. Chem.* **1963**, *28*, 1682.



by specifying the reaction temperature to be <50 °C, these sites are deleted.

The stoichiometric conditions can also narrow down the possible reactive sites. With the 1-equiv (CSTOIC = 1) and first-selectivity (CSTOIC = 2) options, only the reactive sites belonging to the highest reactivity level are allowed to react. With the excess-reagent (CSTOIC = 3) option, all the reactive sites within and below the selected temperature block are considered. Thus, in eq 42a and 42b, the Si–Si bond belongs to a higher reactivity level than the C=C bond, so only the former is oxidized under the 1-equiv or first-selectivity conditions. However, both sites may be oxidized by using the excess-reagent option at room temperature.[75]

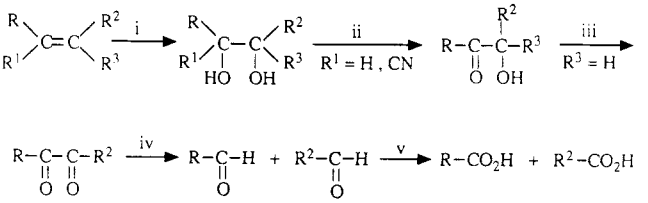


Further pruning may take place within a reactivity level if the 1-equiv or first-selectivity conditions are chosen. For example, the reactivity of alcohols toward MnO_2[6d,14a] and Cr(VI) reagents[8] follows the order benzylic, allylic > primary > secondary alcohols. Thus, if both allylic and primary alcohol groups are present in the reactant, selective oxidation of the former occurs; hence, the latter site is deleted. Other examples include the relative migratory aptitudes of α-carbon atoms in Baeyer–Villiger rearrangements of ketones with CH_3CO_3H[20,37] and MCPBA[9b] (tertiary alkyl > alkenyl > secondary alkyl > benzyl > aryl > primary alkyl > methyl), the relative reactivity of α-alkyl groups in the oxidation of ethers by RuO_4[6c,9c] (CH_2 > CH_3 > CH), and the relative reactivity of the α-methylene groups in cyclic tertiary amines toward RuO_4 (benzylic endocyclic > endocyclic > exocyclic methylene groups).[38] In addition, the stoichiometric requirement for an oxidative transformation of a site by a specific reagent is considered. This is illustrated in Table II, where the majority of the sites require at least 2 equiv of $Cu(OAc)_2$ to be oxidized; exceptions are thiols and alkynes, which require only 1 equiv. Thus, by choosing the 1-equiv condition, the former sites are not permitted to react.

Finally, the acidity requirements are examined. For example, aldehydes and keto amines are oxidized by hydrogen peroxide only under basic conditions. Once all the reaction conditions have been considered, the final selected atom and bond sites are stored in the ACSIT(1) and ACSIT(2) sets, respectively.

(75) Dixon, T. A.; Steele, K. P.; Weber, W. P. *J. Organomet. Chem.* **1982**, *231*, 299.

Scheme IV. An Analysis of Reaction Pathways for Oxidation of Olefins by $KMnO_4$



E. Generation of Products. As a preparatory step for generating the products, reactive sites that yield complex mixtures are identified. If such sites are present, they are oxidized one at a time irrespective of the stoichiometric conditions chosen by the user. Consequently, the display of products showing all possible combinations of oxidative transformations is avoided. To illustrate, if sites A and B are of similar reactivity and the corresponding numbers of oxidative transformations for these sites are two and four, respectively, then six single transformations are output one at a time instead of eight combinations of transformations. A message is also sent to the user describing the situation.

In the product-generation phase of the program, the final selected sites are examined and processed separately. The structural manipulations to be performed on each site are identified and encoded in an array using the subroutine NEWMAN. This array is later decoded by the subroutine MPROD, which executes the actual structural manipulations on a given reactant.

Three major cases may be envisaged when assessing the oxidation chemistry of a particular site with a given reagent. The site may undergo (a) a constant transformation irrespective of its environment and the reaction conditions, (b) one or more transformations via a single reaction sequence, or (c) one or more transformations via multiple reaction pathways.

Case a obviates the need for mechanistic analysis since the fate of the site is constant. Case b is normally encountered in oxidative processes that are condition-dependent (e.g., eq 3–8 in section II.B). Case c usually leads to a complex mixture of products via two or more competing pathways. Typically in this case, the alternate reaction pathways arise from structural features of the reactive sites in question, which include neighboring groups and other functionalities that may be far removed from the actual site of attack (see section II.D). Thus, the routine searches for key features in the reactants and/or intermediates that trigger the selection of a pathway or combination of pathways.

The process of structural correlation is greatly facilitated by analyses of intermediates when the reaction mechanisms are known. In situations where the mechanisms are unknown, ad hoc schemes consisting of macrosteps can sometimes be proposed to account for as many observed results as possible. Otherwise, empirical rules for observed trends must be used to gauge competitions. In the remainder of this section, representative examples of reaction schemes that were developed to facilitate the evaluations for cases b and c are presented. It must be borne in mind that the proposed schemes are subject to modifications and extensions as more mechanistic data become available.

An Analysis of Olefinic Oxidation by $KMnO_4$. In assessing the products of oxidations of alkenes by potassium permanganate, an algorithm based on Scheme IV has been implemented in the pertinent subroutine. This scheme seems to account for all the products obtained experimentally.[76] As already mentioned, the nature of the

Table IV. Structural Transformation and Relative Reactivity Table for $Pb(OAc)_4$

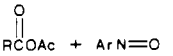
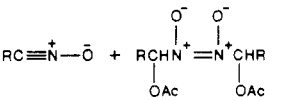
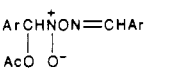
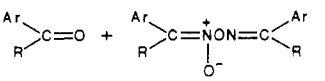
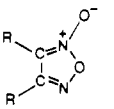
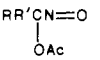
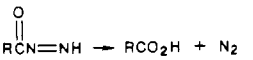
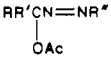
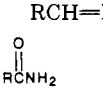
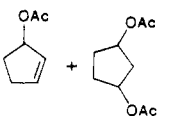
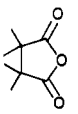
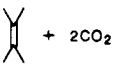
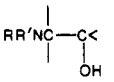
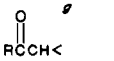
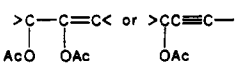
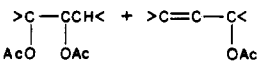
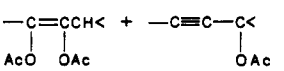
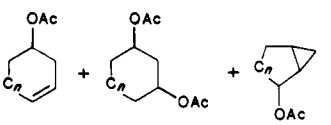
reactivity level	reactive site[a]	reactn condtns	products
1		acidic, −60 to −20 °C	
	$RR'NNH_2$	neutral, −60 to 25 °C	$RR'NN{=}NNRR'$
2	$GNHNHG'$[b]	neutral, −30 to 25 °C	$GN{=}NG'$
	$RCH{=}NOH$	neutral, −30 °C	
	$ArCH{=}NOH$	neutral, 0 °C	
	$ArRC{=}NOH$	neutral, 0 °C	
		neutral, 0 °C	
		neutral, 0 °C	
	$RR'C{=}NOH$	acidic	$RR'C(OAc)_2 + HNO$
		neutral	
		neutral	
		neutral	$RCO_2H + RN{=}NR'$
	$ArNHNH_2$		$ArN{\equiv}N{:}$
3	$>C{=}N{=}N$	neutral, 2 °C	$>C(OAc)_2 + N_2$
	$(RCO)_2CH{-}$	neutral, acidic, 10–20 °C	
		neutral, 25 °C	
	$(RO)_3P$	neutral, 20 °C	$(RO)_3P{=}O$
	RSH	neutral, 25–30 °C	$RSSR$
	$H_2NCH_2CH_2NH_2$	acidic, 20 °C	$N{\equiv}CC{\equiv}N$
4		acidic, 25 °C	$>C{=}O + O{=}C<$
	RSR'	neutral, 25 °C	$RR'S{=}O$
	$RCH(SR)_2$	neutral, 25 °C	$RCH(OAc)_2 + RSSR'$
	$RR'C{=}NNH_2$[c]	neutral	$RR'C{=}N{=}N{-} + RR'C(OAc)_2 + N_2$
		acidic, 25 °C	$RR'CHOAc$
	$RR'C{=}NNHR''$	neutral, 25 °C	
	$RCH{=}NNHR'$	neutral, 25 °C	$RC{=}N{=}NR'$
		acidic, 25 °C	$RN{=}C{=}O$
		neutral, 80–130 °C	$RN{=}C{=}O$
		acidic, 29 °C	
	$p\text{-}RC_6H_4X$[d]	acidic, 20–30 °C	$p\text{-}C_6H_4O_2$
5		acidic, neutral, 20–80 °C	complex mixture[e]

Table IV (Continued)

reactivity level	reactive site	reactn condtns	products
			
6	RCH_2NH_2	neutral, 80 °C	RC≡N
	$RR'ArCNH_2$	neutral, 80 °C	RR′C=NAr
		neutral, 80 °C	>C=O + RC≡N
	RR′CHNHR″	neutral, 80 °C	RR′C=NR″ + RR′C=O + R″NH_2
	RR′NCH<	neutral, acidic, 20–80 °C	RR′NH + >C=O
			RR′N=C< + >C=O
7	ROH	neutral, acidic, 25–80 °C	cyclization products[f]
		basic	>C=O
8		neutral, acidic, 80–100 °C	
	ArCH<	acidic, 60–100 °C	
9	>C=C=C<	acidic, 20–55 °C	
	>C=CCH<[h]	acidic, neutral, 20–80 °C	
10	>CHOR	neutral, 55–70 °C	
	$>CHCO_2R$	neutral, 80 °C	
	—C≡CCH<	acidic, 80 °C	
	$RP(OR)_2$, $R_2P(OR)$, R_3P	neutral, 80 °C	
	$ArNH_2$	neutral, 80 °C	ArN=NAr
		acidic, 25 °C	quinone
11		acidic, 118 °C	
	($n \geq 1$)		

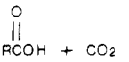
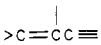
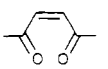
[a] R, R′, R″ = alkyl or aryl. [b] G, G′ = alkyl, aryl, COR, SO_2R, >C=C<. [c] R′ may be a hydrogen atom. [d] X = OH, NH_2, NHG. [e] See Scheme VI. [f] See Scheme VII. [g] R may be an olefinic carbon. [h] See Scheme VIII.

products is found to be highly dependent on the acidity of the reaction medium. In the proposed scheme, products emanating from each oxidative step in succession may be formed, depending on the specified acidity level. If basic conditions are chosen and the temperature is less than 0 °C, oxidation stops at step i, giving α-diols as the major products. However, if neutral or acidic conditions are chosen, further oxidations (steps ii–v) may occur and a mixture consisting of α-ketols, α-diones, and cleavage products is formed. The ultimate oxidized products, i.e., carboxylic acids, may also be formed under basic conditions if the selected temperature range in CAMEO is <50 °C or <100 °C. Scheme IV is a good example of case b in which macrosteps are applied to a given site.

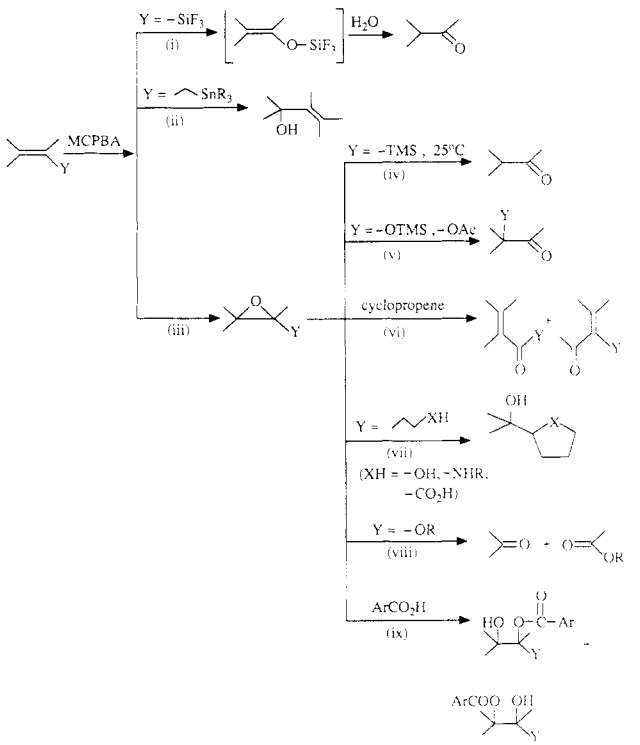
An Analysis of Olefinic Oxidation by MCPBA. The algorithm for determining the products of oxidation of olefinic bonds by MCPBA is based on Scheme V. In this algorithm, a reaction path is selected if the required structural features are present. Thus, the presence of a trifluorosilyl substituent or an allylic tin functionality causes the selection of paths i or ii in the scheme. If path iii is appropriate, the product that is formed depends on the nature of the substituents, the specified reaction temperature, and the structural features of the reacting olefins. The epoxide is not displayed as a product if (a) a TMS group is present and the temperature is greater than 0 °C; (b) the olefinic bond is incorporated in a three-membered ring, in which case oxidative ring opening occurs; and (c) OTMS, OAc, or OR groups are present as olefinic substituents. If a geometrically accessible nucleophilic site such as a hydroxyl, carboxyl, or amino group is available, then a cyclic product resulting from intramolecular nucleophilic attack on the epoxide is formed in addition to the epoxide. Addition products resulting from acidolysis of epoxides by MCPBA are presently not shown by the

(76) (a) Nelson, W.; Sherwood, B. E. *J. Org. Chem.* **1974**, *39*, 183. (b) Tanaka, H.; Torii, S. *J. Org. Chem.* **1975**, *40*, 462. (c) Srinivasan, N. S.; Lee, D. G. *Synthesis* **1979**, 520. (d) Jensen, H. P.; Sharpless, K. B. *J. Org. Chem.* **1974**, *39*, 2314. (e) Sharpless, K. B.; Lauer, R. F.; Repic, O.; Teranishi, A. Y.; Williams, D. R. *J. Am. Chem. Soc.* **1971**, *93*, 3303. (f) Lee, D. G.; Chang, V. S. *J. Org. Chem.* **1978**, *43*, 1532. (g) Birchall, J. M.; Clarke, T.; Haszeldine, R. N. *J. Chem. Soc.* **1962**, 4977.

Table V. Structural Transformation and Relative Reactivity Table for OsO_4

reactivity level	reactive site	reactn condtns	product
1	RC≡CR′	neutral, basic, 25 °C	
	RC≡CH	neutral, basic, 25 °C	
2	>C=C<	neutral, basic, 25 °C	
		neutral, basic, 25 °C	
3	RCH_2OH	neutral, acidic, 25 °C	RCH=O
	RR′CHOH	neutral, acidic, 25 °C	RR′C=O
4	>C=C< (aromatic)	basic, 25 °C, several days	
			
5		basic, 35 °C	2>C=O
		basic, 35 °C	>C=O + CO_2

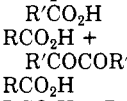
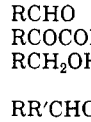
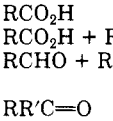
Scheme V. Possible Mechanistic Pathways for Olefinic Oxidation by MCPBA



oxidation module since these are products of secondary reactions which may be obtained by resubmitting the initial products to the ACIDIC package of the CAMEO program.

A Mechanistic Analysis of Oxidations of Carboxylic Acids by LTA. Oxidations by lead tetraacetate (LTA) are particularly complex, as indicated in the following three subsections. Scheme VI forms the basis of the algorithm that determines the products of oxidations of carboxylic acids by LTA. In this scheme, the major

Table VI. Structural Transformation and Relative Reactivity Table for RuO_4

reactivity level	reactive site	reactn condtns	products
1	RSR′	neutral, <0 °C	RR′S=O or $RR'SO_2$
	RR′S=O	neutral, <0 °C	$RR'SO_2$
	RR′S=NR″	neutral, <0 °C	
	$(RO)_2S$=O	neutral, <0 °C	$(RO)_2SO_2$
	RC≡CR′	neutral, 0 °C	
	RC≡CH	neutral, 0 °C	$RCO_2H + CO_2$
2[a]	RR′C=CRR′	neutral, acidic, basic	2RR′C=O
	RR′C=CHR″	neutral, acidic	RR′C=O + R″CHO
		basic	RR′C=O + $R''CO_2H$
	RCH=CHR′	neutral, acidic	RCHO + R′CHO
		basic	$RCO_2H + R'CO_2H$
	$RR'C=CH_2$	neutral, acidic, basic	RR′C=O + HCO_2H
	$RCH=CH_2$	neutral, acidic	RCHO + HCHO
		basic	$RCO_2H + HCO_2H$
	RR′C=CHCOR″	neutral, acidic	RR′C=O + CO_2 + $R''CO_2H$
	RCH=CHCOR′	neutral, acidic	$RCO_2H + CO_2$ + $R'CO_2H$
	RCH=CR′COR″	neutral, acidic	RCO_2H + R′COCOR″
	RCHO	neutral	RCO_2H
	RCOCOR′	neutral	$RCO_2H + R'CO_2H$
	RCH_2OH	neutral, basic	$RCHO + RCO_2H$
	RR′CHOH	neutral, basic	RR′C=O
	$ArCH_2OR$	neutral	$ArCO_2R$
		neutral	2>C=O
		acidic	$2-CO_2H$
	$>NCH_2-$[b]	neutral	
3[a]	RCH_2OR	neutral	RCO_2R'
	RR′CHOCHRR′	neutral	2RR′C=O
4[a]	—CH=CH— (aromatic)	neutral	
		neutral	
5[a]		neutral	

[a] 0–50 °C. [b] Secondary and tertiary. [c] X = H, OH, NH_2.

reaction pathway[6a] is represented by steps a–d, each of which gives rise to intermediates which, in turn, can be transformed to products. The algorithm looks for some key features of the reactive site that trigger the selection of a path or group of paths.

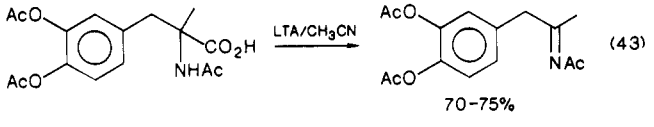
The initially formed lead carboxylate intermediate usually undergoes homolytic cleavage to form an acyloxy radical (step b). However, in the presence of suitable α-functionalities such as hydroxy, keto, amino, imino, and acetoxy groups, the initial intermediate decarboxylates

Table VII. Structural Transformation and Relative Reactivity Table for SeO_2

reactivity level	reactive site[a]	reactn condtns	products
1	$RR'NNH_2$	neutral, −10 °C	RR'NN=NNRR'
2	RSH	neutral, 25 °C	RSSR
	RSR'	neutral, 25 °C	RR'S=O
	RR'S=O	neutral, 25 °C	$RR'SO_2$
3	>C=C(|)−CHOH		>C=CC=O
	−C≡CCHOH		−C≡CC=O
4	>C=CCH$_2$−	neutral, acidic, 25–115 °C	>C=C−CHOH + >C=C−C=O
	>C=CCHRCH<	neutral, acidic, 25–100 °C	>C=CCRCH< (OH) + >C=CCR=C<
	−C≡CCH$_2$−	neutral, acidic, 25–100 °C	−C≡CCHOH + −C≡CC=O
	−C≡C−	acidic, 40–110 °C	−C(=O)−C(=O)−
5	RCCH$_2$− (=O)	neutral, acidic, 65–120 °C	RC(=O)−C(=O)−
	RC(=O)−CHCH<	neutral, acidic	RC(=O)−C=C−
	R_3P	neutral, 80 °C	R_3P=O
	$HetArCH_2OH$[b]	neutral, 80–90 °C	HetArCH=O
	$HetArCH_3$[b]	neutral, acidic, 100–135 °C	HetArCH=O
	$HetArCH_2R$[b]	neutral, acidic, 98 °C	HetArCOR
	HetArCHRR'[b]	neutral, acidic	HetArCRR'OH
	HetArCH=O[b]	neutral, acidic, 100 °C	$HetArCO_2H$
	GCH_2G'[c]	neutral, acidic, 90–180 °C	GCG'(=O)
	GCH_2−[c]	neutral, acidic, 130–180 °C	GC=O
	CH_2=CH_2	neutral, 110–120 °C	HC(=O)−CH(=O)
	RCH=CHR'	neutral, 110–240 °C	RC(=O)−CR'(=O)
	RCH=CRR', RR'C=CRR'	neutral, ≥100 °C	>C(HO)−C(OH)<
	GCH_2CH_2G'[c]	neutral, acidic, 170 °C	GCH=CHG'
	GCHCHG'[c]	neutral, acidic	GC=CG'
6	RCH_2OH[d]	neutral, 200 °C	RCH=O
	RCH=O	neutral, 200 °C	RCO_2H
	$ArCH_3$	neutral, acidic, 235–250 °C	ArCH=O

[a] R, R' = aryl or alkyl unless specified otherwise. [b] Heteroaromatic. [c] G, G' = CO_2R, CO_2H, CN, CHO, CONHR, $CONR_2$, COOCOR, Ar. [d] Alkyl or aromatic hydrocarbons.

(path i; see entries 2, 4–6, and 9 in Table I). This tendency is exemplified by eq 43.[87]



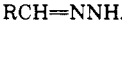
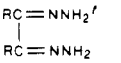
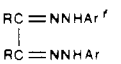
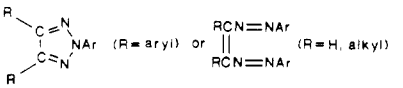
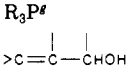
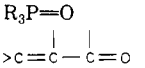
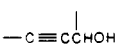
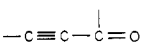
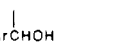
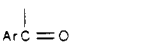
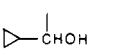
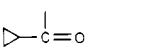
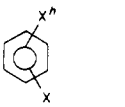
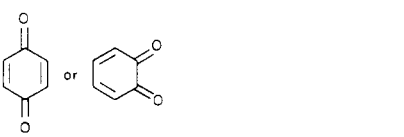
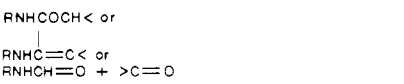
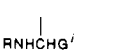
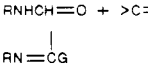
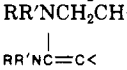
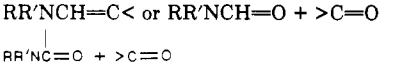
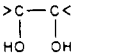
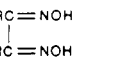
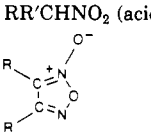
(43)

The acyloxy radical, in turn, normally undergoes rapid decarboxylation to produce a carbon radical (step c).[6a] However, intramolecular quenching of the former (paths ii–iv) takes place when geometrically accessible functionalities such as olefinic bonds and ortho positions in phenyl rings are present in the reacting system. Examples of reactions involving these pathways may be found in Table XVI as follows: entries 4, 8, and 9 for path ii; entry 12 for path iii; and entry 13 for path iv. The carbon radical intermediate and products resulting from paths ii–iv can coexist.

The carbon radical intermediate is always oxidized to carbenium ions (step d). In addition, other products may result from paths v–vii in Scheme VI, depending on the nature of the substrates. Path v is favored by the presence of geometrically disposed aromatic rings which are prone to free-radical attack by either an alkyl radical (entry 11, Table XVI) or an aryl radical (entry 14, Table XVI). Intramolecular addition to a suitably placed double bond (path vi) may also occur, as in the case of transannulation reactions (entry 10, Table XVI). For a primary alkyl

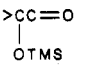
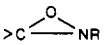
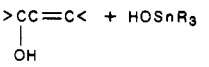
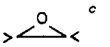
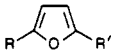
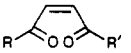
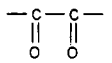
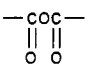
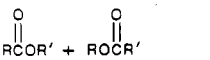
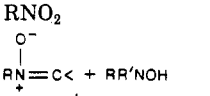
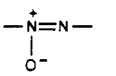
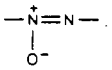
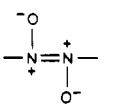
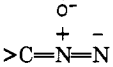
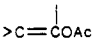
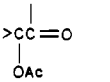
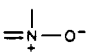
(77) Shirahata, K.; Kato, T.; Kitahara, Y. *Tetrahedron* **1969**, *25*, 3179.
(78) Cimarusti, C. M.; Wolinsky, J. *J. Am. Chem. Soc.* **1968**, *90*, 113.
(79) (a) Crandall, J. K.; Colyer, R. A.; Hamptoa, D. C., unpublished results. (b) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1980**, *21*, 1819.
(80) McCoy, L. L.; Zagalo, A. *J. Org. Chem.* **1960**, *25*, 1824.
(81) Bacha, J. D.; Kochi, J. K. *J. Org. Chem.* **1968**, *33*, 83.
(82) Moriarty, R. M.; Walsh, H. G.; Gopal, H. *Tetrahedron Lett.* **1966**, 4363.
(83) Cope, A. C.; Park, C. H.; Scheiner, P. *J. Am. Chem. Soc.* **1962**, *84*, 4862.
(84) Davies, D. I.; Waring, C. *J. Chem. Soc. C* **1968**, 1865.
(85) Davies, D. I.; Waring, C. *J. Chem. Soc. C* **1967**, 1639.
(86) Davies, D. I.; Waring, C. *Ibid.* **1968**, 2337.
(87) See ref 53.

Table VIII. Structural Transformation and Relative Reactivity Table for Active MnO_2

reactivity level	reactive site[a]	reactn condtns[b]	product
1	$ArNH(CH_2)_3NHAr$	−20 °C	
	$RNHNHR'$[c]	−15 °C	$RN{=}NR'$
2	RNHOH[d]	0 °C	RN=O
	$RNHNH_2$	0–25 °C	$RH + RR + N_2$
	$RCONHNH_2$	0–25 °C	$RCO_2H + N_2$
	$RR'NNH_2$	0–25 °C	$RR'NN{=}NNRR'$ or $RR' + N_2$
	$RR'C{=}NNH_2$[e]	0–25 °C	$RR'C{=}\overset{+}{N}{=}\overset{-}{N}$ or $RR'C{=}O + N_2$
	RCH=NNHAr	25 °C	
	RR'C=NNHAr	25 °C	$RR'C{=}O + N_2 + ArH$
		≥25 °C	$RC{\equiv}CR' + 2N_2$
		≥25 °C	
	RR'C=NNHCOR	25 °C	$RR'C{=}O + N_2 + RCO_2H$
3	$RCH(NH_2)CO_2H$	25 °C	$RCH{=}O + CO_2 + NH_3$
	ArNHNHAr	25 °C	ArN=NAr
	ArNHNHCOR	25 °C	$ArH + N_2 + RCO_2H$
4	RSH	25 °C	RSSR
	RSeR'	25 °C	RR'Se=O
	R_3P[g]	25 °C	$R_3P{=}O$
		25 °C	
		25 °C	
		25 °C	
		25 °C	
	$ArNH_2$	25 °C	ArN=NAr
		25 °C	
5	RSR'	25 °C	RR'S=O
	RCH_2OH	25 °C	RCH=O
	RR'CHOH	25 °C	RR'C=O
	RCH_2NH_2	25 °C	$RCH{=}O + NH_3$
	$RR'CHNH_2$	25 °C	$RR'C{=}O + NH_3$
	$RNHCH_3$	25 °C	RNHCH=O
	$RNHCH_2CH<$	25 °C	
		25 °C	
	$RR'NCH_3$	25 °C	RR'NCH=O
	$RR'NCH_2R''$	25 °C	$RR'NCOR'' + RR'NH + R''CH{=}O$
	$RR'NCH_2CH<$	25 °C	$RR'NCH{=}C<$ or $RR'NCH{=}O + >C{=}O$
		–	
	—NHCH=CHNH—	–	
		25 °C	$2{>}C{=}O$
	$RC{\equiv}N$	25–150 °C	$RCONH_2$
6	RR'C=NOH	≥25 °C	$RR'C{=}O$ + NO (neutral) $RR'CHNO_2$ (acidic)
			
	>C=NN=C<	≥25 °C	$2{>}C{=}O + N_2$
	RR'S=O	–	$RR'SO_2$
	RCH=O	≥25 °C	RCO_2H
	$ArCH_2$—	125 °C	ArC=O

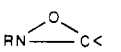
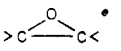
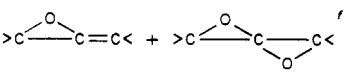
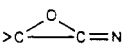
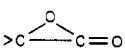
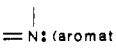
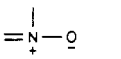
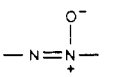
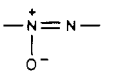
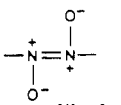
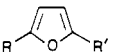
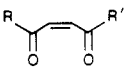
[a] R, R', R'' = alkyl or aryl unless specified otherwise. [b] Neutral and acidic media. [c] R, R' = alkyl in bicyclic compounds. [d] R may be an olefinic carbon. [e] R, R' may be a hydrogen, >C=O, >C=N, $—SO_2—$. [f] R may be a hydrogen. [g] R may be an olefinic carbon or an alkoxy group. [h] X = OH, NH_2, NHG where G is a polarized, multiply bonded atom. [i] G = aryl, olefinic carbon or any polarized, multiply bonded atom.

Table IX. Structural Transformation and Relative Reactivity Table for MCPBA

reactivity level	reactive site	products	reactn condtns[a]
1	RSeR′	RR′Se=O	−78 °C
	>C=NNH$_2$	>C=$\overset{+}{N}$=$\overset{-}{N}$	−63 °C
	>C=$\overset{+}{N}$=$\overset{-}{N}$	>C=O + N_2	−63 °C
	>C=NNR$_2$	>C=O	−63 °C
	>C=CSiF$_3$	>CHC=O + HOSiF$_3$	−50 °C
2	RSH	RSOH	−30 °C
	RSOH	RSO$_2$H	−30 °C
	RSR′	RR′S=O	−20 °C
	RR′S=O	RSO$_2$R′	−20 °C
	RSSR′	RSO$_3$H + R′SO$_3$H	−20 °C
	>C=S	>C=S=O	<0 °C
	>C=S=O	>C=O	−
	>C=COTMS		−15 to 25 °C
3	>C=NR		0–20 °C
		>C=O + O=NR	−
	>C=CSiR$_3$	>CHC=O + HOSiR$_3$	0–25 °C
	>C=CCSnR$_3$		0–25 °C
	R$_3$SiSiR$_3$[b]	R$_3$SiOSiR$_3$	0–25 °C
	RI	ROH + alkene	0–27 °C
	R$_3$P=O	R$_2$P(=O)OR	25 °C
4	>C=C<[b]		0–25 °C
			0 °C
			−
5			25 °C
	ArCHO	ArCO$_2$H + ArOH	25 °C
	RSiR$_3$	ROH + HOSiR$_3$	25 °C
	(>N)$_3$P=O	>NOP(N<)$_2$	25 °C
	RNH$_2$	RNHOH	−
	RNHOH	RN=O	−
	RN=O	RNO$_2$	−
	RR′NH		−
	RR′R″N	RR′R″N—O	25 °C
	—N=N—		−
			−
			25 °C
	>C=$\overset{+}{N}$=$\overset{-}{N}$	>C=O + N_2	25 °C
	>C=NOH	>CHNO$_2$	25 °C
6			30 °C
	—N=[d]		25–60 °C
7	ArNH$_2$	ArNHOH	>25 °C
	ArNHOH	ArN=O	>25 °C
	ArN=O	ArNO$_2$	>25 °C

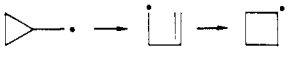
[a] Acidic conditions. [b] Reactivity level may be adjusted on the basis of the nature of substituents or molecular configuration. [c] See Scheme V. [d] Aromatic.

Table X. Structural Transformation and Relative Reactivity Table for CH_3CO_3H

reactivity level	reactive site	product[a]	reactn condtns[b]
1	RN=C<		<0 °C
		RN=O[c] + O=C<	–
2	RSR′	RR′S=O	0–<50 °C
	RR′S=O	RSO_2R'	0–<50 °C
	RSSR′	RSOSR′ + RSSOR′	–
	RSOSR′, RSSOR′	RSO_2SR' + $RSSO_2R'$	–
	RSO_2SR', $RSSO_2R'$	RSO_3H + $R'SO_3H$	–
	RCHO	RCO_2H	–
3	>C=C<[d]		–
	>C=C=C<		–
	>C=C=NR		–
		>C=O + C≡NR	–
	>C=C=O		–
		>CHOAc + CO_2	–
		>C=O + CO_2	–
	RNH_2	RNHOH	–
	RNHOH	RN=O	–
	RN=O	RNO_2	–
	RR′NH	RR′NOH	–
	RR′R″N	$RR'R''^{+}N-O^{-}$	–
	Ar_3P=C<[g]	Ar_3P=O + dimer	–
4			0–<50 °C
		RCO_2H + $R'CO_2H$	–
	$ArNH_2$	ArNHOH	–
	ArNHOH	ArN=O	–
	ArN=O	$ArNO_2$	–
	$-CH(OR)_2$	$-CO_2R$ + ROH	–
5			>50 °C
	–N=N–		–
			–
	ArOH, ArH	*o*-, *p*-dihydroxy aromatic	–
	o-, *p*-dihydroxy aromatic	*o*-, *p*-quinones	–
	o-, *p*-quinones	dicarboxylic acids	–
			–

[a] CSTOIC = 1 for 1 equiv of reagent; CSTOIC = 2 for first selectivity; CSTOIC = 3 for excess reagent. [b] Acidic conditions. [c] Dimerizes under reaction conditions. [d] Reactivity level of olefins may be raised or lowered, depending on the nature of olefinic substituents. [e] May undergo ring-opening reactions. [f] See Scheme IX. [g] Weakly basic phosphoranes.

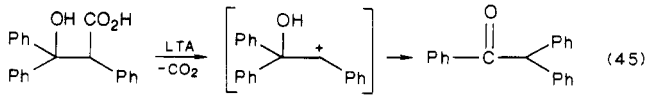
radical, alkane formation is always a side product (path vii). Certain alkyl radicals are prone to undergo rearrangement to other radicals. For example, eq 44 shows the possible rearrangements of a cyclopropylmethyl radical. These rearranged radical intermediates are likely to produce acetates in the oxidation of their corresponding carboxylic acids.



(44)

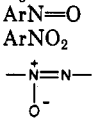
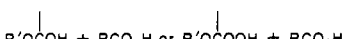
The carbenium ion intermediate is oftentimes converted into alkenes and acetates (paths viii and ix, respectively), which are the major products of carboxylic acid oxidation. Path viii is disallowed if the incipient alkene is formed in a small fused ring or if Wiseman's rule is violated. Path x is prevalent in 1,2-dicarboxylic acids (entries 2 and 3, Table XVI) while path xi is undertaken by 1,3- and 1,4-dicarboxylic acids (entries 5 and 6, Table XVI).

An added complexity in the overall reaction scheme for carboxylic acids is the possibility of rearrangements involving the carbenium ion intermediate. The program permits 1,2-shifts, and the rearranged carbenium ions are subject to the same mechanistic analysis that is applied to the parent ion in addition to the direct formation of other oxidation products such as the one shown in eq 45.[88]



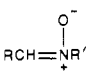
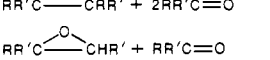
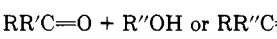
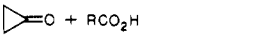
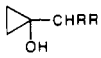
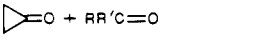
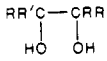
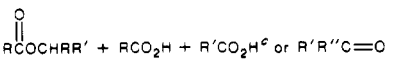
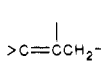
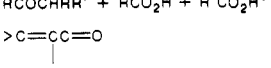
(45)

Table XI. Structural Transformation and Relative Reactivity Table for H_2O_2

reactivity level	reactive site[a]	product	reactn condtns[b]
1			A; 0 °C
		$RCO_2H + R'CO_2H$	B, N; ≤20 °C
2	RSH	RSSR	B, N
	RSR′	RR′S=O	B, N, A
	RSeR′	RR′Se=O	B, N, A
	RR′S=O	$RR'SO_2$	B, N, A
		ArC≡N	B, N
	$(>N-)_2C=S$	$(>N-)_2C=S=O$	N, A
	$(>N-)_2C=S=O$	$(>N-)_2C=SO_2$	N, A
			A
			B, N, A
			B, A
			N
	RC≡CCOR′	$RCO_2H + CO_2 + R'CO_2H$	B
	R_3N		N, A
	$ArNH_2$	ArN=O	N, A
	ArN=O	$ArNO_2$	N, A
	—N=N—		N, A
			N, A
	R_3P	$R_3P=O$	N, A
	$ArPH_2$	$ArPH_2=O$	N, A
	>PH=O		B, N
	$RSeO_2H$	$RSeO_3H$	A
	R_3COH	R_3COOH	A
	RB<	ROH + HOB<	B
	ArOH	*o*- or *p*-dihydroxybenzene	N, A
		$CO_2 + H_2O + RCO_2H$	B, A
		$>C=O + RCO_2H$	B
		$>C=N- + RCO_2H$	B
			B
3	RCHO[f]	RCO_2H	B, N
	ArCHO	$ArCO_2H$ and/or ArOH	A, B; 40–50 °C
	RR′C=O	$RCO_2R' + R'CO_2R$[g]	A, N, B; 65 °C
	RCO_2H	RCO_3H	A; 40–55 °C
	RC≡N	$RCONH_2$	B, N; 40–50 °C
			B, N, A; 60 °C
			B, N, A; 60 °C
	RNH_2	RNO_2	N, A; 40–70 °C
	CN=C (aromatic)		N, A; 35–50 °C
	RSSR′	$RSO_3H + R'SO_3H$	N, A
	—NHNH—	—N=N—	N, A; 40–55 °C

[a] R, R′ = alkyl, aryl. [b] Room temperature unless specified otherwise; A = acidic, B = basic, C = neutral. [c] R = alkyl. [d] R = aryl, SiR_3. [e] G = CHO, COR, CO_2H, CO_2R, CN. [f] R = alkyl or hydrogen. [g] Esters are hydrolyzed into acids and alcohols under basic conditions.

Table XII. Structural Transformation and Relative Reactivity Table for CrO_3 and $Na_2Cr_2O_7$ in Acidic Media

reactivity level	temp range	reactive site[a]	reagent	product (CSTOIC)
1	<0 °C	RNHOH	$Na_2Cr_2O_7$	RN=O
		$RCH_2NR'OH$	$Na_2Cr_2O_7$	
2	<50 °C	RCH_2OH	CrO_3, $Na_2Cr_2O_7$	RCHO (1) or RCO_2H (>1)
		RR'CHOH	CrO_3, $Na_2Cr_2O_7$	RR'C=O
			CrO_3	$RCO_2R' + R''OH + RCO_2R'' + R'OH$
		RSR'	CrO_3, $Na_2Cr_2O_7$	RR'S=O (1) or RSO_2R' (>1)
		RR'S=O	CrO_3, $Na_2Cr_2O_7$	RSO_2R'
		RCHO	CrO_3, $Na_2Cr_2O_7$	RCO_2H
3	<50 °C	RR'C=CRR'	CrO_3, $Na_2Cr_2O_7$	
		RR'C=CHR'	CrO_3, $Na_2Cr_2O_7$	
		RR'R''COH[b]	CrO_3	RR'C=O + R''OH or RR''C=O + R'OH or R'R''C=O + ROH
			CrO_3	
			CrO_3	
			CrO_3	2RR'C=O
		RR'C=NOH	CrO_3	RR'C=O
		RCH_2OCH_3	CrO_3	RCH_2OCHO
		$RCH_2OCHR'R''$	CrO_3	
			CrO_3, $Na_2Cr_2O_7$	
		ArH (polynuclear)	CrO_3, $Na_2Cr_2O_7$	quinone
4	<100 °C	$ArCH_3$	CrO_3	$ArCO_2H$ (>1)
		$ArCH_2R$	CrO_3	ArRC=O
		ArCHRR'	CrO_3	ArCRR'OH or ArCOR + R'OH
			$Na_2Cr_2O_7$	ArCOR' + ROH
		$RCH_2CHR'R''$[d]	CrO_3, $Na_2Cr_2O_7$	$RCH_2CR'R''OH$ or $RCO_2H + R'R''C=O$
		$RCOCH_2R'$	CrO_3	$RCO_2H + R'CO_2H$
5	<100 °C	RCH_2X[e]	CrO_3	RCHO
		RR'CHX[e]	CrO_3	RR'C=O
		$ArCH_2CH_2Ar'$	CrO_3	$ArCO_2H + Ar'CO_2H$

[a] R, R', R'' = alkyl or aryl. [b] Tertiary bridgehead alcohols. [c] R'' = H. [d] Nonbenzylic tertiary alkyl group. [e] X = halogen.

A Mechanistic Analysis of the Oxidation of Alcohols by LTA. The determination of products for the LTA oxidation of alcohols is based on Scheme VII. If basic conditions are specified, formation of carbonyl compounds becomes the predominant reaction pathway. Otherwise, all oxidation products emanating from paths i–iv in Scheme VII, in addition to the carbonyl compounds, are shown by CAMEO since they all evolve from a common intermediate, an alkoxy radical.

Internal competition exists if more than one β-branching possibility exists. For example, in β-fragmentation reactions (path i), only those cleavages resulting in the formation of the more stable radicals (e.g., benzyl, allyl, tertiary radicals or radicals that are adjacent to an ether oxygen or a carbonyl group) are performed. In cases of similar radical stability, all possible Cα–Cβ cleavages are allowed by the program.

Another example of internal competition is exhibited by alcohols which can undergo more than one 1,6-cyclization reaction. As a rule, activated ϵ-positions are favored over unactivated ones. Functional units that are considered activating include aryl rings, ethers, and carbonyl groups. Recalling the example given in eq 15, only the ϵ-position activated by the carbonyl group undergoes 1,6-cyclization. The present algorithm also shows 1,5-cyclization products, which are normally preferred. Geometric factors such as molecular conformation and accessibility also play a crucial role in the product determination. The following rules[6a,9a,11a,14b] are utilized by the subroutine in determining the feasibility of cyclic ether formation (path ii, Scheme VII).

(a) δ- or ϵ-positions that are at bridgehead atoms or α to two bridgehead atoms in small bridged systems (e.g., [2.2.1] and [2.2.2] bicyclic systems) are considered unreactive.

(b) Cycloalkanols with ring sizes less than or equal to six are excluded since 1,5-abstraction or cyclization is geometrically infeasible; e.g., cyclohexanol is not converted to 7-oxanorbornane.

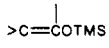
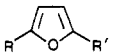
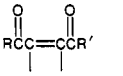
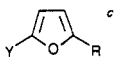
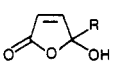
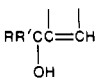
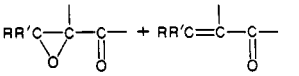
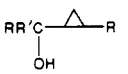
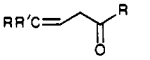
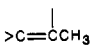
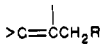
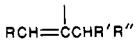
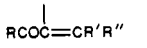
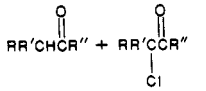
In the evaluation of ring cyclization of unsaturated alcohols (path iii, Scheme VII), the following rules are employed:[6a]

(a) In Δ^4-olefinic alcohols, both 1,6- and 1,5-cyclizations leading to the formation of six-membered and five-membered cyclic ethers, respectively, are considered.

(b) In Δ^5-, Δ^6-, and Δ^7-olefinic alcohols, addition of the alkoxy radical is directed to the olefinic carbon which is nearest the hydroxyl oxygen, thus yielding the cyclic ether with the smaller ring (i.e., six-, seven-, and eight-membered ring, respectively).

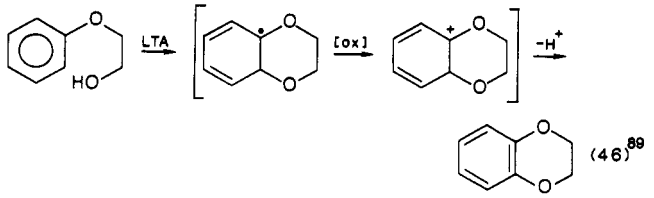
(88) Corey, E. J.; Casanova, J., Jr. *J. Am. Chem. Soc.* **1963**, *85*, 165.

Table XIII. Structural Transformation and Relative Reactivity Table for Cr(VI) Reagents in Neutral and Slightly Basic Media

reactivity level	temp range	reactive site[a]	reagent	product
1	<0 °C		CrO_2Cl_2	
		>C=C<	CrO_2Cl_2	
2	<50 °C		PCC	
			PCC	
3	<50 °C	RCH_2OH	CrO_3, PCC, PDC, $CrO_3(pyr)_2$, $Na_2Cr_2O_7$	RCH=O
		RR'CHOH	CrO_3, PCC, PDC, $CrO_3(pyr)_2$, $Na_2Cr_2O_7$	RR'C=O
		RCH=O	PDC	RCO_2H
			PDC	RCO_2H
4	<50 °C		$CrO_3(pyr)_2$, PCC	
			PCC	
		$RC{\equiv}CCH_2R'$	$CrO_3(pyr)_2$	
		>C=NOH	PCC, $CrO_3(pyr)_2$	>C=O + HNO
		>C=CHOR	PCC	$>CCO_2R$
			$CrO_3(pyr)_2$	
			$CrO_3(pyr)_2$	
			$CrO_3(pyr)_2$	
		p-$(OSiR_3)_2C_6H_4$	PCC	p-$C_6H_4O_2$
		C_6H_5OH or p-RC_6H_4OH	CrO_2Cl_2	p-$C_6H_4O_2$
5	<100 °C	RR'R''CH	CrO_2Cl_2	RR'R''COH + RR'R''CCl
		$RR'CHCH_2R''$[e]	CrO_2Cl_2	
		$ArCH_3$	CrO_2Cl_2	$ArCH{=}O + ArCH_2Cl + ArCO_2H$
		$ArCH_2R$	CrO_2Cl_2	
6	<300 °C	$ArCH_3$	$Na_2Cr_2O_7$	$ArCO_2H$
		$ArCH_2R$	$Na_2Cr_2O_7$	

[a] R, R', R'' = alkyl or aryl. [b] May undergo rearrangement or cleavage to carbonyl compounds. [c] Y = halogen, OTS. [d] Rearrangement to isomeric α,β-unsaturated carbonyl compound may occur. [e] R'' = H, alkyl.

β-, γ-, or δ-aryl-substituted alcohols are searched for and processed separately to yield cyclic ethers fused to aromatic rings (path iv). The subroutine currently allows only saturated atoms such as carbon and oxygen to be present along the path connecting the hydroxyl oxygen to the aromatic atom. An example of free-radical aromatic substitution is provided in eq 46.



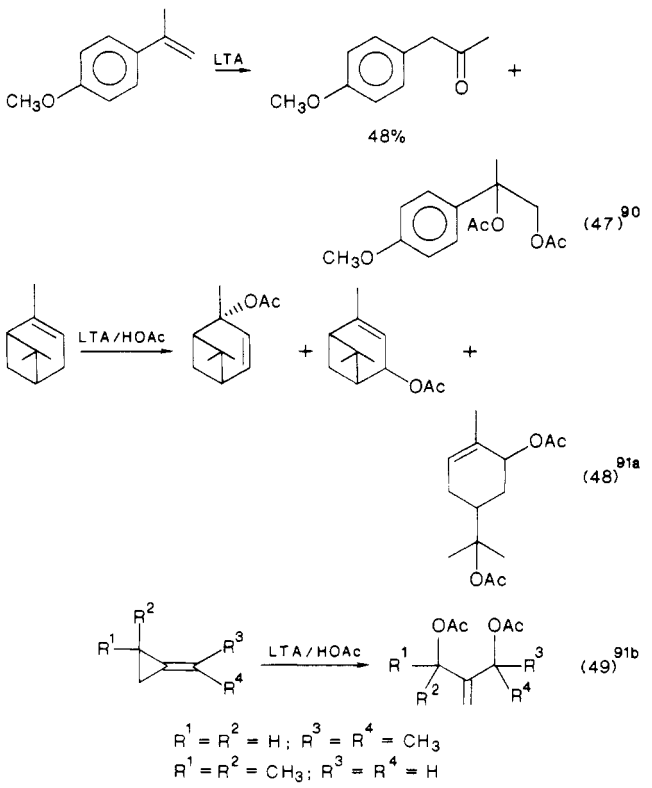
(46)[89]

A Mechanistic Analysis of the Oxidation of Olefins by LTA. The algorithm for evaluating the products of oxidation of olefins by LTA is based on Scheme VIII. The algorithm executes both 1,2-acetoxylation and allylic acetoxylation on cyclic and acyclic alkenes with allylic rearrangement being executed only for the former. Aryl migration is prevalent only with acyclic double bonds (e.g., eq 47). Carbon–carbon bond cleavage is effected in cyclic olefinic systems bearing an adjacent three- or four-membered ring bond as shown in eqs 48 and 49.

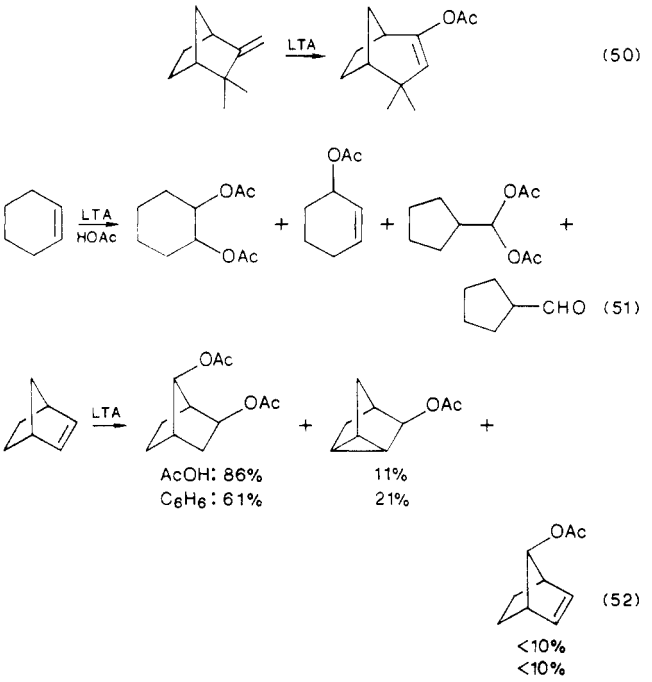
If reactive allylic positions are absent, or if the olefinic bond is part of a six-membered ring, then alkyl migration is performed. Thus, both the ring enlargement and ring contraction illustrated in eq 50[92] and 51[93] can be accounted

(89) Mihailovic, M. L.; Cekovic, Z. *Synthesis* **1970**, 209.

(90) Yukawa, Y.; Hayashi, N. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2255.
(91) (a) Whitham, G. H. *J. Chem. Soc.* **1961**, 2232. (b) See ref 11c.



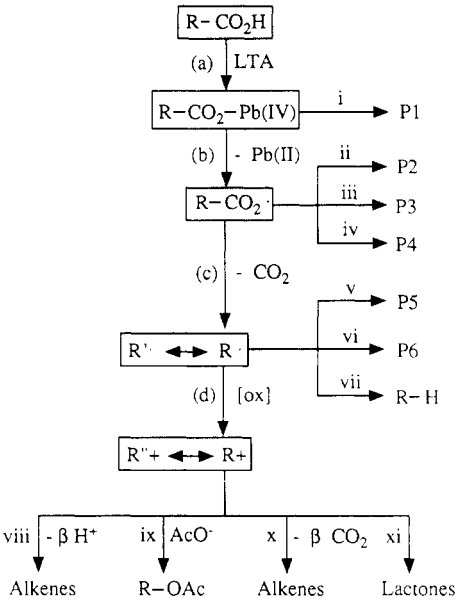
for by path iii in Scheme VIII. If the olefinic bond in question is part of a norbornyl system, then oxidation products arising from norbornyl rearrangements are shown by the program (e.g., eq 52).[94]



An Analysis of the Oxidation of Allenes by CH_3C-O_3H. Scheme IX is utilized in evaluating the products of oxidation of allenes by peracetic acid. Two sets of products emanating from paths i and ii may be obtained, depending on the specified stoichiometry. It should be noted that an epoxide is not displayed as a product if the allene is exo

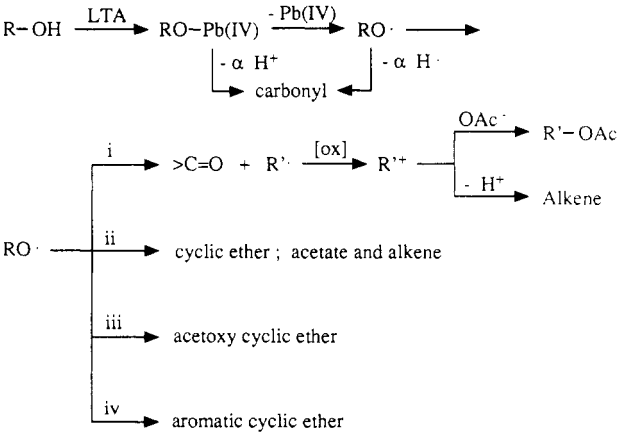
(92) Huckel, W.; Kirschner, H. G. *Chem. Ber.* **1947**, *80*, 41.
(93) Anderson, C. B.; Winstein, S. *J. Org. Chem.* **1963**, *28*, 605.
(94) Alder, K.; Flock, F. H.; Wirtz, H. *Chem. Ber.* **1958**, *91*, 609.

Scheme VI. Overview of Mechanistic Pathways for LTA Oxidation of Carboxylic Acids



Path i intramolecular oxidative cleavage
ii intramolecular free radical addition to olefinic bond
iii intramolecular free radical aromatic substitution with RCO_2·
iv [1,5] - and [1,6] - free radical cyclization
v intramolecular free radical aromatic subtitution with R · or Ar ·
vi intramolecular free radical addition to olefinic bond
vii alkane formation by H-abstraction from the solvent
viii oxidative elimination of β -hydrogen
ix oxidative substitution by acetate
x oxidative β - decarboxylation
xi intramolecular electrophilic quenching by a nearby carboxyl group

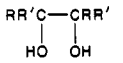
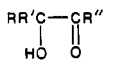
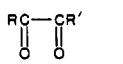
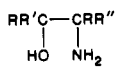
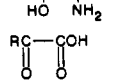
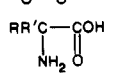
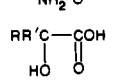
Scheme VII. Simplified Scheme for Evaluating LTA Oxidation of Alcohols



Path i fragmentation reaction or Cα−Cβ cleavage
ii [1,5]- and/or [1,6]- free radical cyclization; oxidative substitution and elimination
iii intramolecular addition of alkoxy radical to olefinic bonds
iv intramolecular free radical aromatic substitution

to a three-membered ring. Although allenic epoxides and diepoxides are considered to be unstable and prone to acidolysis and other rearrangements, their isolation has been reported under buffered conditions. Hence, these products are created by the program. Acidolysis products may be obtained by resubmitting the resulting mono- and

Table XIV. Structural Transformation and Relative Reactivity Table for Periodate Oxidation in Neutral and Acidic Media

reactivity level	temp range	reactive site[a]	product
1	<50 °C	$RSeR'$[b]	$RR'Se{=}O$
		RSR'[b]	$RR'S{=}O$
		$RSSR'$[b]	$RSOSR' + RSSOR'$
		$RSOSR'$	RSO_2SR'
			$2RR'C{=}O$
			$RR'C{=}O + R''CO_2H$
			$RCO_2H + R'CO_2H$
			$RR'C{=}O + RR'C{=}O + NH_3$
			$RCO_2H + CO_2$
			$RR'C{=}O + CO_2 + NH_3$
			$RR'C{=}O + CO_2$
		GCH_2G'[c]	$GG'C{=}O$
		o-, *p*-$C_6H_4(OH)_2$[d]	*o*-, *p*-$C_6H_4O_2$
2	50–100 °C	$RR'S{=}O$	$RR'SO_2$
		$ArNH_2$	$ArN{=}NAr$

[a] R, R′, R″ = hydrogen, alkyl, aryl. [b] R, R′ = alkyl, aryl, or olefinic carbon. [c] G, G′ = polarized multiply bonded functionalities such as CHO, COR, CO_2R, CO_2H, CN, etc. [d] Other substituted *o*- or *p*-dihydroxybenzene compounds are also oxidized to quinones.

diepoxides to the ACIDIC package of CAMEO. However, rearrangements of the epoxides and diepoxides to cyclopropanones and oxetanones, respectively, are always carried out.

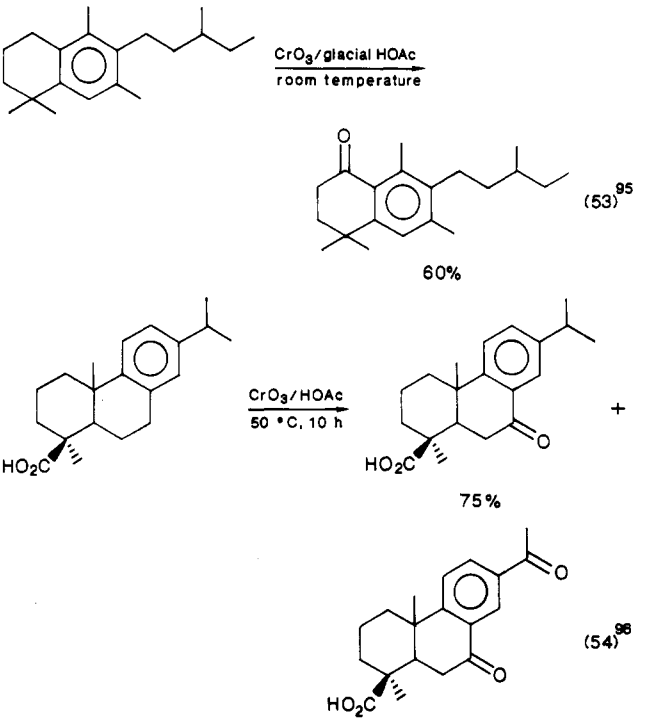
The utility of the foregoing schemes in facilitating structure–pathway correlation and consequently product formation is evident. In addition, more examples of the application of these newly proposed schemes are available elsewhere.[5] For oxidation reactions whose mechanisms are largely unknown, empirical rules derived from extensive analyses of literature data were formulated to facilitate the prediction of products. A few examples are provided below.

(1) In determining the products of oxidations of aromatic compounds by CrO_3 or $Na_2Cr_2O_7$ in acidic media, the following rules are imposed.

(a) Isolated benzene rings with hydroxyl or amino substituents situated para to each other or para to a hydrogen, halogen, alkyl, or sulfonic acid group are oxidized to quinones.[8]

(b) Alkyl benzenes that do not fall under rule 1.a are generally resistant to ring oxidation and are oxidized exclusively at the benzylic positions. The order of reactivity of benzylic positions is secondary > tertiary > primary. Oxidation of cyclic benzylic positions is favored over that of acyclic ones (eg., eq 53 and 54).

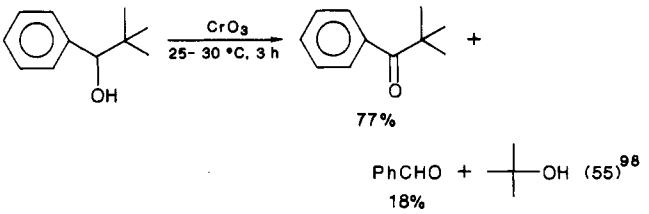
(c) Polynuclear aromatic compounds are generally converted to quinones. Reactive aromatic positions are always α to fused atoms joining at least two aromatic rings and are either ortho or para to each other, as in eq 2.



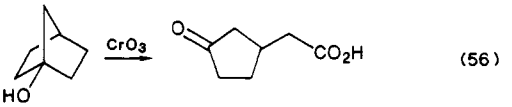
(2) Rules for evaluating the products of oxidation of alcohols by CrO_3 or $Na_2Cr_2O_7$ in acidic media are as follows.

(a) Primary alcohols are selectively oxidized in the presence of secondary and tertiary alcohols. The products are either aldehydes or, if excess reagent is used, carboxylic acids.[97]

(b) Secondary alcohols are always oxidized to ketones. Cleavage to carbonyl compounds is performed only for sterically hindered alcohols (e.g., eq 55) or highly strained cyclic alcohols.[8]



(c) Tertiary alcohols are oxidized only if they are cyclopropanols, α-diols, or bridgehead alcohols in small bridged systems (e.g., eq 56).[99]



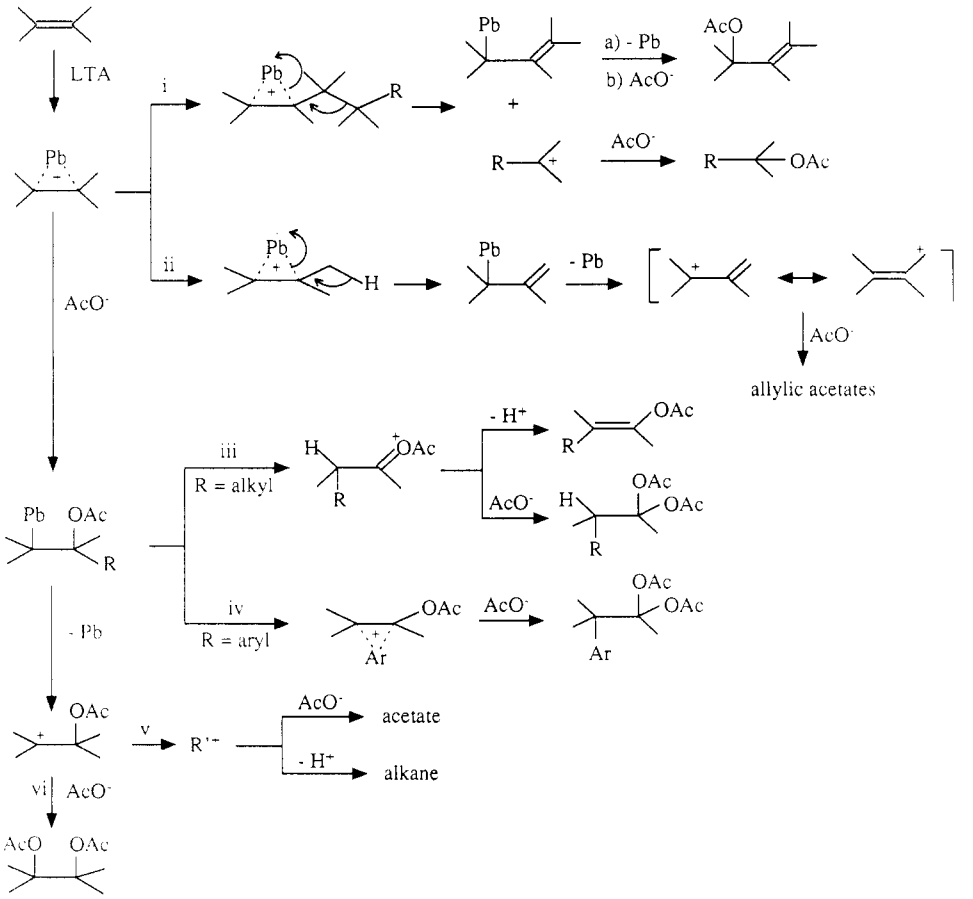
(3) The following rules are utilized in the algorithm that evaluates allylic oxidation with $CrO_3(pyr)_2$.[100]

(a) Allylic methyl groups are oxidized to allylic aldehydes.

(b) Allylic methylene groups are oxidized to allylic ketones. Oxidative rearrangement to an isomeric α,β-unsaturated carbonyl compound is performed only if the

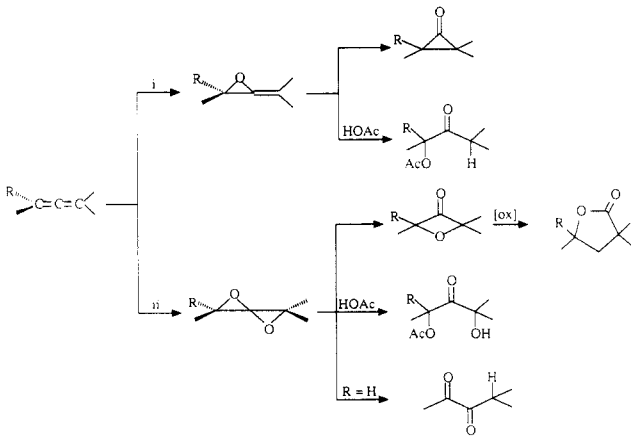
(95) Nasipuri, D.; De Dalal, L.; Roy, D. N. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1754.
(96) Ritchie, P. F.; Sanderson, T. F.; McBurney, L. F. *J. Am. Chem. Soc.* **1954**, *76*, 723.
(97) a) Parish, E. J.; Shroepfer, G. J. *Chem. Phys. Lipids* **1980**, *27*, 281; (b) *Ibid.* **1979**, *25*, 381. (c) Yoshii, E.; Oribe, T.; Tumura, K.; Koizumi, T. *J. Org. Chem.* **1978**, *43*, 3946. (d) Savona, G.; Piozzi, F.; Marino, M. L. *Gazz. Chim. Ital.* **1977**, *107*, 511. (e) Beugelmans, R.; Lee Goff, M. T. *Bull. Soc. Chim. Fr.* **1969**, 335.
(98) Cawley, J. J.; Westheimer, F. H. *J. Am. Chem. Soc.* **1963**, *85*, 1771.
(99) Cawley, J. J.; Spaziano, V. T. *Tetrahedron Lett.* **1973**, 4719.
(100) Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587.

Scheme VIII. Detailed Mechanistic Analysis of LTA Oxidation of Nonconjugated Olefinic Sites

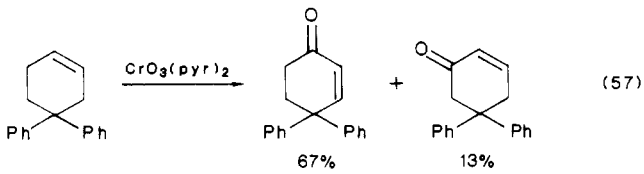


Path i C-C cleavage of adjacent three- or four-membered ring bond
ii C-H cleavage with allylic rearrangement
iii oxidative rearrangement involving alkyl migration
iv oxidative rearrangement involving aryl migration
v norbornyl rearrangement
vi 1,2-addition of acetoxy groups

Scheme IX. Stoichiometric Dependence of Reaction Pathways for Oxidation of Allenes by Peracetic Acid

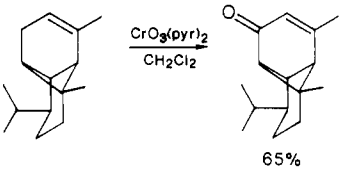


methylene carbon is benzylic or sterically hindered (e.g., eq 57).[100]



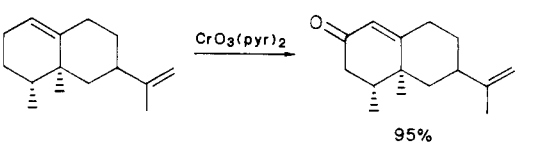
(57)

(c) Allylic methine groups are converted to rearranged ketones. Oxidative rearrangement is not allowed when a bridgehead double bond would be formed in small bridged systems or when a double bond would be formed exo to a ring (e.g., eq 58).[100]



(58)

(d) Allylic positions α to a fused olefinic carbon atom are unreactive (e.g., eq 59).[100] Otherwise, the order of reactivity is tertiary > secondary > methyl allylic groups.



(59)

(4) Rules governing the formation of products of oxidation of olefins by SeO_2 are provided below.

(a) Allylic, nonbridgehead, hydrogen-bearing sp^3 carbon atoms may be oxidized to allylic alcohols and/or allylic keto compounds.[10,11b,68]

Table XV. Structural Transformation and Relative Reactivity Table for $KMnO_4$

reactivity level	temp range	substrate	reactn condtns	product
1	<0 °C	>C=CCN	basic	>C(HO)—C(=O)—
		>C=C<	basic	>C(HO)—C(OH)<
		—CR=CR′—	neutral, acidic	—CR(OH)—CR′(OH)— + —C(=O)—CR′(OH)—[e] + —C(=O)—C(=O)—[b] + 2 —C(=O)—H[b] + 2 —C(=O)—OH[b]
2	0–<50 °C	RC≡CH	basic, acidic, neutral	$RCO_2H + CO_2$
		RC≡CR	acidic, basic	$2RCO_2H$
			neutral	RC(=O)—CR(=O)
		RCH=CHR	basic	$2RCO_2H$
		RCH_2OH	acidic, basic	RCO_2H
		RR′CHOH	acidic, basic	RR′C=O
		RCHO	acidic, basic, neutral	RCO_2H
		RSH	acidic, basic, neutral	RSO_3H
		RSO_2H	acidic, basic, neutral	RSO_3H
		RSR′	acidic, basic, neutral	RSO_2R'
		RSOR′	acidic, basic, neutral	RSO_2R'
		$>CHNO_2$	basic, neutral	>C=O
3	50–<100 °C	RR′R″CH[c]	basic	RR′R″COH
		ArR[d]	acidic, basic	$ArCO_2H$
4	50–<100 °C	$RCOCH_2R'$	acidic, basic	$RCO_2H + R'CO_2H$
5	50–<100 °C	—CH=CH—[e]	neutral, basic	$2—CO_2H$

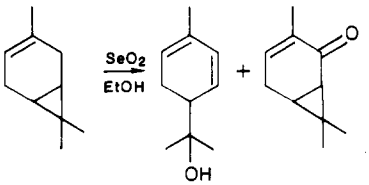
[a] R = H. [b] R, R′ = H. [c] R, R′, R″ = alkyl or aryl groups. [d] R = methyl or secondary alkyl. [e] Aromatic double bond in polycyclic hydrocarbons.

(b) Allylic ethers always undergo oxidative cleavage to form alcohols and allylic carbonyl compounds.[101]

(c) Tetrasubstituted alkenes and alkenes with tertiary allylic positions give dienes in addition to the normal allylic oxidation products.[68]

(d) Allylic rearrangement occurs whenever possible.[68,102]

(e) Skeletal rearrangement occurs if the allylic position is adjacent to a cyclopropyl or a quaternary carbon atom (e.g., eq 60).[68]



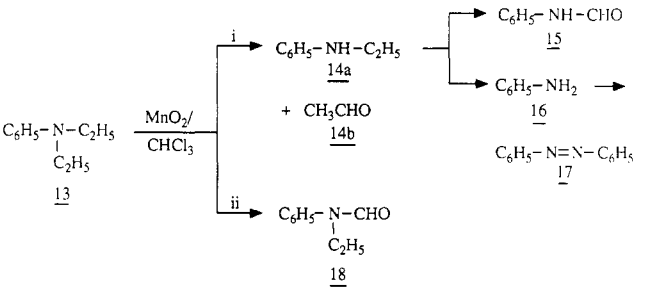
(60)

IV. Sample Sequences

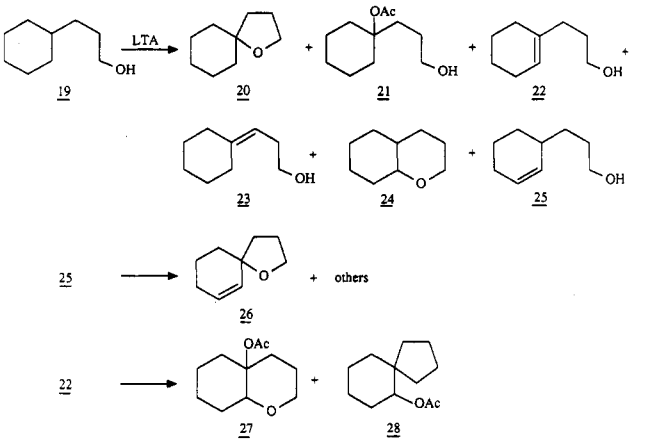
Currently, the oxidation module of the CAMEO program is capable of making accurate predictions for over 1000 known reactions, including the ones depicted in eq 1–60. In many cases, side products are also predicted, which explains in part the less than quantitative yields that are typically reported. The following sample sequences further illustrate the current capabilities of the program.

In Scheme X, oxidation of *N*,*N*-diethylaniline (**13**) by MnO_2 gives predominantly *N*-ethylaniline (**14a**) and acetaldehyde (**14b**) in 54% yield.[6d,39,41] Minor quantities of **15**, **17**, and **18** have also been obtained experimentally. Compounds **15** and **18** are formed via the corresponding enamines of **14a** and **13**, respectively. All these products are given in the first pass by the CAMEO program, with the exception of **17**, which may be obtained by resubmitting **16** to the oxidation module. In addition, CAMEO also gives the α-keto derivative of **13** as another side product. Note that all structures are stored in a synthetic tree and may be retrieved by the user for further processing.

Scheme X. Oxidation Products of *N*,*N*-Diethylaniline by MnO_2 As Predicted by CAMEO



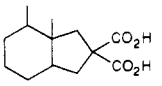
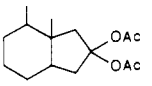
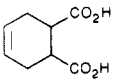
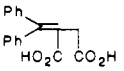
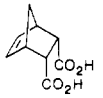
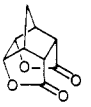
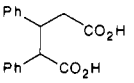
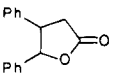
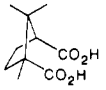
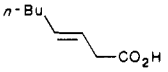
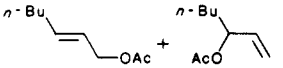
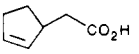
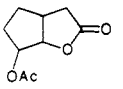
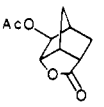
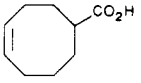
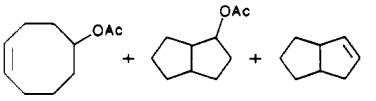
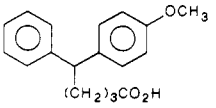
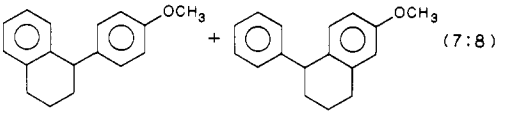
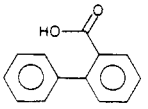
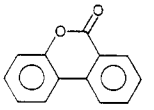
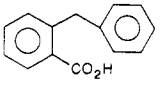
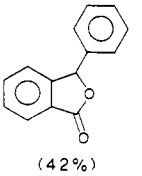
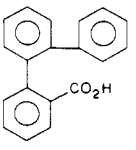
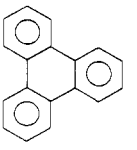
Scheme XI. Oxidation Products of an Alicyclic Alcohol by LTA As Predicted by CAMEO



Scheme XI shows the products of oxidation by LTA of a simple alicyclic alcohol, **19**. A mixture consisting of **20**–**24**, **26**, and **27** in minor yields is observed.[6a,103] The CAMEO program predicts structures **20**–**25**. Resubmission of **25** yields **26** whereas resubmission of **22** results in the

(101) Kariyone, K.; Yazuwa, H. *Tetrahedron Lett.* **1970**, 2885.
(102) Pan, H. L.; Cole, C. A.; Fletcher, T. L. *Synthesis* **1980**, 813.
(103) Mihailovic, M. L.; Konstantinovic, S.; Milovanovic, A.; Jankovic, K.; Cekovic, Z.; Jeremic, D. *J. Chem. Soc. D* **1969**, 236.

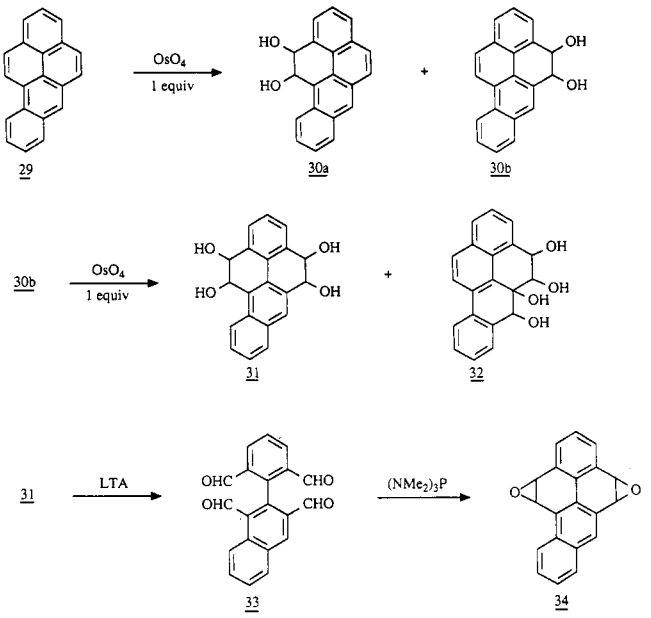
Table XVI. Oxidation of Carboxylic Acids by $Pb(OAc)_4$

entry	carboxylic acid	reactn condtns	product (yield)	ref
1		dry HOAc–pyridine; Δ	 (60%)	77
2		pyridine; 67 °C	 (76%)	78
3				79a
4			 (99%)	79b
5		C_6H_6–pyridine; 50 °C		80
6		C_6H_6–pyridine; 50 °C	 (70%)	80
7		HOAc; 81 °C	 (30%) (21%)	81
8			 (35-70%)	82
9			 (65-80%)	82
10		HOAc; 70 °C		83
11			 (7:8)	84
12		C_6H_6, N_2; Δ		85
13		C_6H_6, N_2; Δ	 (42%)	86
14				85

formation of **27** and **28**. Six products in addition to **26** are also predicted from compound **25**.

The synthesis of the "K-region" diepoxide, **34**, from benzo[*a*]pyrene (**29**) is outlined in Scheme XII.[59] The program predicts the formation of diols **30a** and **30b** from compound **29** by using 1 equiv of OsO_4. The selectivity choice, in this case, is based on the greater reactivity of aromatic bonds with the highest π-electron density (see section III.B). Resubmission of **30b** under the same conditions yields the experimentally reported tetraols **31** and

Scheme XII. Synthesis of the "K-Region" Diepoxide, 4,5:11,12-Diepoxy-4,5,11,12-tetrahydrobenzo[*a*]pyrene



32. Treatment of **31** with LTA using the first-selectivity conditions gives the tetraaldehyde **33**, which is the precursor of the desired diepoxide, **34**.

V. Conclusion

A reaction module that treats the chemistry of organic and inorganic oxidants has recently been incorporated into the CAMEO program. Clearly, the development of this module is a difficult undertaking, considering the current state of knowledge in the area. Nevertheless, its implementation has been successfully carried out by employing a technique that analyzes the problem in terms of the nature of the reagent, the interactive effects of reaction conditions, and traditional structure–reactivity correlations. Selectivity for the potential reactive sites is dealt with by using reactivity tables derived from extensive empirical analyses of product distributions as well as mechanistic and kinetic data. Fortunately, the evaluation of products is simplified by the constancy of oxidative transformations for most reagents. Consequently, mechanistic analyses have been confined to reactive sites that undergo more than one possible transformation. Grand reaction schemes that establish structure–pathway correlations have been utilized to assess competitions among viable reaction paths. For the mechanistically less well defined reactions, empirical rules have been employed to evaluate multistep transformations.

So far, the oxidation module has been shown to make reliable predictions for a wide range of reactions. However, significant extensions and refinements are anticipated as more information, especially mechanistic data, becomes available.

Acknowledgment. Gratitude is expressed to the National Science Foundation for support of this work. The assistance of Dr. Pascal Metivier is also gratefully acknowledged.

Preparation of Optically Active 2-Furylcarbinols by Kinetic Resolution Using the Sharpless Reagent and Their Application in Organic Synthesis

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The kinetic resolution of 2-furylcarbinols **1** by the Sharpless reagent proceeds highly efficiently, thus providing a general method for the synthesis of homochiral **1**. The reaction can be applied to compounds **1** possessing various types of substituents, although compound **1d**, which has a sterically demanding tertiary alkyl group, is a poor substrate. The kinetic resolution of 3-furylcarbinol **3** also proceeds efficiently. Various homochiral **1** thus obtained have been successfully converted into α-alkoxy acids **4** by oxidative cleavage of the furan ring after protection of the hydroxyl group. The compound (*R*)-**1b** has been converted into the naturally occurring γ-lactone **5**.

After the discovery of the highly efficient kinetic resolution of secondary allylic alcohols by asymmetric epoxidation using *tert*-butyl hydroperoxide (TBHP) in the presence of chiral titanium/tartrate catalyst,[1] Sharpless has pointed out that this asymmetric oxidation reaction is applicable to the kinetic resolution of other substrates, that possess a hydroxyl group for coordination to the metal center, and a proximate locus capable of accepting an oxygen atom. On the basis of this idea, several substrates were investigated, and it was revealed that β-hydroxy amines[2] are good substrates, while β-hydroxy sulfides[3] and α-acetylenic alcohols[3] are poor substrates.

2-Furylcarbinols **1** can be oxidized to 2*H*-pyran-3-(6*H*)-ones **2** by TBHP in the presence of an early transition metal catalyst (eq 1),[4] and we were, therefore, interested in the possibility of the kinetic resolution of **1** using the Sharpless reagent. Herein we describe our finding that the kinetic resolution proceeds highly efficiently, thus pro-

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