catalyzed dissociation of water, the use of carbon dioxide as a source of carbon reactant, new methods of nitrogen fixation, and the partial oxidation of methane. The surface reactions of molecules in their excited states are also being studied.

While most catalysis studies have focused on reactions that occur at the solid-gas interface, because of the available techniques, research is now being expanded to include catalysis at solid-liquid interfaces. Reactions of electrode surfaces, of colloid surfaces, and in biological systems, all of which occur at these interfaces, will benefit greatly from scrutiny at the molecular level. Laser spectroscopies and solid-state NMR spectroscopy are among the techniques that appear most promising for these studies.

A number of academic institutions now focus on surface science and catalysis research, and there is strong industrial participation in the newly formed research centers intended to educate scientists and engineers in this subdiscipline of chemistry. As catalysis-based technologies are converted to high technologies, the design and development of new catalyst systems will occur with greater frequency and the development of science and technology will continue at an accelerated pace. The future is indeed bright for surface science and for catalysis science.

References and Notes

1. G. A. Somorjai, *Chemistry in Two Dimensions: Surfaces* (Cornell Univ. Press, Ithaca, N.Y., 1981).
2. B. Davis and W. Hettinger, Eds., *ACS Monogr. 222* (1983); *Proc. Welch Conf.* **25** (1981); M. Boudart, *Kinetics of Chemical Processes* (Prentice-Hall, Englewood Cliffs, N.J., 1968).
3. G. A. Somorjai and M. A. Van Hove, *Adsorbed Monolayers on Solid Surfaces, Structure and Bonding* (Springer-Verlag, New York, 1979); J. B. Pendry, *Low Energy Electron Diffraction* (Academic Press, New York, 1974); M. A. Van Hove and S. Y. Tong, *Surface Crystallography by LEED* (Springer-Verlag, New York, 1979).
4. S. Overbury, P. Bertrand, G. A. Somorjai, *Chem. Rev.* **75**, 550 (1975).
5. J. Sinfelt, *Science* **195**, 643 (1977).
6. H. D. Shih, F. Jona, D. W. Jepsen, P. M. Marcus, *Surf. Sci.* **60**, 445 (1976); R. L. Strong, B. Firey, F. W. de Wette, J. L. Erskine, *J. Electron Spectrosc. Relat. Phenom.* **29**, 187 (1983); R. J. Behm, V. Penka, M.-G. Cattania, K. Christmann, G. Ertl, *J. Chem. Phys.* **78**, 7486 (1983).
7. J. T. Yates, T. E. Madey, Jr., J. C. Campuzano, in *Chemical Physics of Solid Surfaces and Heterogeneous Catalysis Series*, vol. 3, *Chemisorption Systems*, D. A. King and D. P. Woodruff, Eds (Elsevier, New York, in press); C. B. Duke, *Appl. Surf. Sci.* **11-12**, 1 (1982); R. J. Koestner, M. A. Van Hove, G. A. Somorjai, *Surf. Sci.* **107**, 439 (1981); H. J. Behm, K. Christmann, G. Ertl, M. A. Van Hove, *ibid.* **88**, L59 (1979).
8. M. A. Van Hove, R. J. Koestner, J. C. Frost, G. A. Somorjai, *Surf. Sci.* **129**, 482 (1983).
9. L. L. Kesmodel, L. H. Dubois, G. A. Somorjai, *J. Chem. Phys.* **7**, 2180 (1979); R. J. Koestner, M. A. Van Hove, G. A. Somorjai, *Surf. Sci.* **121**, 321 (1982); P. Skinner *et al.*, *J. Chem. Soc. Faraday Trans. 2*, **77**, 1203 (1981); L. H. Dubois, D. G. Castner, G. A. Somorjai, *J. Chem. Phys.***72**, 5234 (1980); H. Ibach and D. L. Mills, *Electron Energy Loss Spectroscopy and Surface Vibrations* (Academic Press, New York, 1982), p. 326; J. A. Gates and L. L. Kesmodel, *Surf. Sci.* **124**, 68 (1983).
10. M. Salmeron and G. A. Somorjai, *J. Phys. Chem.* **86**, 341 (1982); C. Minot, M. A. Van Hove, G. A. Somorjai, *Surf. Sci.* **127**, 441 (1982).
11. M. Mate and G. A. Somorjai, *Surf. Sci.*, in press.
12. A. J. Gellman, M. H. Farias, M. Salmeron, G. A. Somorjai, *ibid.* **136**, 217 (1984); M. H. Farias, A. J. Gellman, R. R. Chianelli, K. S. Liang, G. A. Somorjai, *ibid.* **140**, 181 (1984).
13. J. E. Crowell, E. L. Garfunkel, G. A. Somorjai, *ibid.* **121**, 303 (1982); E. L. Garfunkel, J. E. Crowell, G. A. Somorjai, *J. Phys. Chem.* **86**, 310 (1982); J. E. Crowell, W. T. Tysoe, G. A. Somorjai, in preparation; G. A. Somorjai, Plenary Lecture for International Congress on Catalysis, Berlin, July 1984; G. Ertl, *Proc. Welch Conf.* **25**, 179 (1981).
14. F. Zaera and G. A. Somorjai, *J. Catal.* **84**, 375 (1983).
15. A. L. Cabrera, N. D. Spencer, E. Kozak, P. W. Davies, G. A. Somorjai, *Rev. Sci. Instrum.* **53**, 1888 (1982).
16. N. D. Spencer, R. C. Schoonmaker, G. A. Somorjai, *J. Catal.* **74**, 129 (1982); M. Asscher and G. A. Somorjai, *Surf. Sci.* **143**, L389 (1984); M. Asscher, J. Carrazza, M. Khan, K. Lewis, G. A. Somorjai, in preparation.
17. S. M. Davis, F. Zaera, G. A. Somorjai, *J. Am. Chem. Soc.* **104**, 7453 (1982).
18. M. Salmeron, R. J. Gale, G. A. Somorjai, *J. Chem. Phys.* **67**, 5324 (1977); M. Salmeron, R. J. Gale and G. A. Somorjai, *ibid.* **70**, 2807 (1979).
19. L. M. Falicov and G. A. Somorjai, *Proc. Natl. Acad. Sci. U.S.A.*, in press.
20. F. Zaera and G. A. Somorjai, *J. Am. Chem. Soc.* **106**, 2288 (1984); B. E. Koel, B. E. Bent, G. A. Somorjai, in preparation; A. Wieckowski *et al.*, in preparation.
21. S. M. Davis, F. Zaera, G. A. Somorjai, *J. Catal.* **85**, 206 (1984); S. M. Davis, F. Zaera, G. A. Somorjai, *ibid.* **77**, 439 (1982); F. Zaera and G. A. Somorjai, *J. Phys. Chem.* **86**, 3070 (1982).
22. B. A. Sexton and G. A. Somorjai, *J. Catal.* **46**, 167 (1977); P. R. Watson and G. A. Somorjai, *ibid.* **74**, 282 (1982).
23. F. T. Wagner, S. Ferrer, G. A. Somorjai, *ACS Symposium Ser.* **146**, 159 (1981); F. T. Wagner and G. A. Somorjai, *J. Am. Chem. Soc.* **102**, 5494 (1980); Van Damme and K. Hall, *ibid.* **101**, 4373 (1980).
24. J. A. Rabo, Ed., *ACS Monograph. 171* (1976); J. Sinfelt, *Bimetallic Catalysts* (Wiley, New York, 1983).
25. For examples, see the *Journal of Catalysis*, *Surface Science*, and the *Journal of Physical Chemistry*.
26. H. Conrad, E. Ertl, J. Koch, E. E. Latta, *Surf. Sci.* **43**, 462 (1974).

27. This work was supported by the director, Office of Energy Research, Office of Basic Energy Sciences, Materials and Chemical Sciences Divisions of the U.S. Department of Energy under contract number DE-AC03-76SF00098.

Sculpting Horizons in Organic Chemistry

Barry M. Trost

The quality of our lives today has benefited from successes in organic chemistry. Our food, clothing, shelter, and health care have been significantly improved by the creation of new materials based on carbon compounds. Safer and more effective agrichemicals such as pesticides and herbicides enhance the quality and quantity of our food supply. The miraculous polymers have been the basis of new materials that have increased the durability, versatility, and beauty of the clothes we wear and the homes we live in. New drug discoveries contribute significantly to life preservation and extension and an improved quality of living. Can we expect such contributions to continue at the same or perhaps an even greater rate in the future?

In order to address such a question, we must look at the present in order to extrapolate to the future. At a fundamental level, where do the challenges lie and what methods are being developed to meet these challenges? Four general areas may be recognized: structures, reactions, techniques, and concepts. In highlighting some of the specific advances in these areas in a field as broad as organic chemistry in a very brief overview, only a few of the many different exciting developments can be treated. There are undoubtedly developments not included that are as significant as the few illustrations presented here.

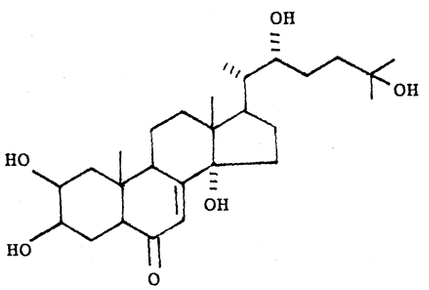
Structures

Historically, organic chemistry focused on isolating compounds from nature. Structure determination became the first step in understanding. However, the methods available, which relied on systematic degradation and correlations, required relatively large amounts of material; thus only abundantly occurring natural products were accessible. With

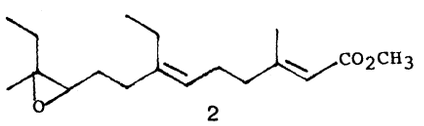
Barry M. Trost is Vilas and Helfaer Professor of Chemistry, McElvain Laboratories of Organic Chemistry, Department of Chemistry, University of Wisconsin, Madison 53706.

the great advances that have been made in spectroscopy and separations science, a whole new world has begun to emerge. As it has become possible to detect, isolate, and characterize ever smaller components in nature, the importance of small organic molecules for a myriad of purposes has become evident.

Understanding the control mechanisms for the maturation of insects and for their behavior has led to an entire area called insect chemistry. Probing the physiology of insects revealed the presence of microgram amounts of hormones that regulate the maturation process. The availability of the new separations and spectroscopic techniques allowed the identification of two simple molecules—ecdysone, **1** (*1*), and juvenile hormone, **2** (*2*)—and led to the idea of using insect growth regulants as an approach



1



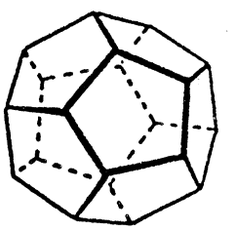
2

to control of insect populations. Present in even smaller quantities are constituents that control insect behavior. These organic molecules, called pheromones (*3*), regulate behavior ranging from sex to defense and offer opportunities for defense against insect infestations ranging from early warning devices to terminating the populations.

New directions continue to emerge. Studies of mammalian physiology have revealed the role in metabolism of the arachidonic acid cascade (see Fig. 1A) (*4*). The role of the leukotrienes in control of human metabolism suggests pharmaceutical applications, such as in the control of inflammation. Another branch of the same metabolic cascade involves a family of human hormones, the prostaglandins (*5*). The pervasive influence of these hormones on the action of cells remained undiscovered until recently because of the limits of detection in analytical instrumentation. As instruments become still more refined, new factors will be discovered.

Our analytical tools allow precise definition of molecules of enormous complexity. In the life sciences, biomacromolecules such as the enzymes and polynucleic acids come to mind. Their primary structure is not a major problem today. However, other molecules from nature can constitute a major challenge. Palytoxin (see Fig. 1B), a highly toxic metabolite from algae, is a molecule of this type that is now in the realm of approachable problems (*6*). This molecule, with its 64 asymmetric centers and 7 double bonds, has so many possible geometric and stereoisomers that if a single molecule of each permutation were present in a flask, nearly 1 mole of compound would be present. In seeking to define the precise structure of this compound, we need to pick out a single molecule from the entire mole of molecules. The weaknesses of our current tools are also highlighted by this compound. The secret of its structure was not revealed by any combination of spectroscopic tools. It ultimately required chemical synthesis. Development of structural tools for noncrystalline, conformationally mobile molecules is a challenge.

Organic chemistry is not restrained by the limits of nature. Only man's imagination defines the limits of the structural varieties that can be created. What factors influence the choice from among these almost unlimited possibilities? Esthetics is clearly one. The beauty of the diamond led to the design of adamantane—a hydrocarbon model for a small unit of the diamond carbon lattice (*7*). Besides stimulating much fascinating fundamental understanding of bonding and reactivity, its design also had practical consequences. A simple analog of adamantane, amantidine, has proved to be one of the first effective antiviral agents and a beneficial treatment for parkinsonism (*8*). The platonic solids capture the imagination because of their beauty. Dodecahedrane (*9*) and tetrahedrane (*10*) are the chemists' versions of these geometric figures which have recently yielded to synthesis. What properties such beautiful lattices possess remain to be discovered.



Dodecahedrane

Highly unsaturated compounds appeal to chemists because of their unusual electronic properties. The evolution of such compounds into organic conductors may have broad applications in the electronics industry. Molecular switches, as well as having obvious weight advantages, promise to open up a new time domain.

Even the world of enzymes may be simplified into small organic fragments. The active sites of enzymes may be viewed as surfaces or cavities that influence a reacting substrate. While rate factors associated with enzymatic reactions capture a great deal of attention, perhaps more significant are the stereochemical consequences of enzymatic reactions. Crown compounds (*11*) and cavitands (*12*) are simple analogs of these surfaces and cavities in what is referred to as host-guest chemistry. Figure 2 de-

Summary. Organic chemistry as a discipline derives from and impacts on the biological and abiological world in which we live. Its challenges lie in the areas of structure, reactivity, techniques, and concepts. Powerful structural tools reveal structures from biology that range from control of insect development and behavior to whole new metabolic pathways in humans. Unnatural products create beautiful new molecular shapes whose properties cannot be predicted as well as catalysts that function with enzyme-like control. From structure flows reactivity. Exploration of known reactions points to new directions, and development of new reactions offers the opportunity of streamlined synthetic design. Emerging new techniques offer new dimensions for performing and studying reactions as well as the hope for developing new ones. Merging disparate facts into unified concepts increases predictive capabilities. The extraordinary difficulty of finding the resultant of many small effects may obscure the presence of general theories, creates the art in the practice of the science, and challenges the practitioner. From these general themes derives the quest for selectivity—chemo-, regio-, diastereo-, and enantio-. An examination of the fundamental underpinnings of the applications of organic chemistry reveals that, while impressive strides have been made, the science is best described as being between infancy and childhood. The cross-fertilization between organic chemistry and molecular biology vividly illustrates a merging of chemistry and biology.

picts a chiral crown compound which begins to approach the behavior of enzymes (*13*). It is capable of selective recognition of (D)-amino acids to a sufficient extent that their preferential complexation allows a racemic mixture to be resolved. More significantly, it serves as a chiral surface for the formation of a carbon-carbon bond in a conjugate addition (also depicted in Fig. 3) and led to a 99 percent enantiomeric excess at −78°C in a partially catalytic reaction. Are we at the very early stages of designing "unnatural enzymes"?

Reactions

The availability of organic substances to serve our needs depends critically on the repertoire of reactions available for synthesis. The obvious interdependence of structure and reactivity determines the advances that are possible. The legendary Diels-Alder reaction illustrates the evolutionary aspect of reaction development. Although the reaction was extensively described in the early part of this century and its impact was recognized by a Nobel Prize in 1950, the 1970's became the decade of recognition of its power in complex synthesis (see Fig. 3). Nevertheless, new faces of this classical reaction continue to be revealed. A most recent one is the reaction of heteroatom unsaturated molecules with certain dienes, especially in the presence of lanthanides as catalysts. This makes the designed synthesis of some carbohydrates, especially those which are attached to other molecules by C–C bonds, a simpler procedure. Practical targets of this approach are antibiotics and antitumor agents, exemplified by vineomycin B_2 (see Fig. 3) (*14*) and, even more important, analogs of such molecules designed for improved therapeutic properties.

The power of the Diels-Alder reaction is due to its chemo-, regio-, and diastereoselectivity and its rapid creation of molecular complexity. The development of cycloadditions to rings of other than six members may extend these benefits to the synthesis of other ring sizes. Five-membered rings are of particular interest from both a biological and a theoretical point of view. An attractive possibility is the cycloaddition of trimethylenemethane (TMM), which conceptually is conveniently designated as a 1,3-dipole as in Fig. 4 although it exists as a 1,3-diradical. The resultant methylenecyclopentanes possess a useful array of functionality with which to mold the initial adducts into the ultimate targets. Chemistry involving such a reactive intermediate appears feasible with the use of transition metal templates (*15*). This leads to a strategy for synthesis of the antitumor, antiviral, and antifungal compound brefeldin A which resolves the stereochemical problems (*15b*).

Research on transition metal templates in catalytic reactions has suggested that these easily tailored templates may become the "chemists' enzymes." However, organotransition metal complexes are also useful stoichiometric templates. The "esoteric" carbene complexes of tungsten and chromium show remarkable behavior in joining an aromatic ring, an acetylene, and carbon monoxide to form naphthoquinones (see Fig. 5) (*16*). The use of chromium complexes in this way allows facile elaboration of the therapeutically important antitumor compounds of the anthracyclinone variety such as daunomycin (*17*).

The wealth of unusual chemistry revealed by merging carbon with the other hundred or so elements has only recently begun to be appreciated. The maturing of this field is not even in sight. Nevertheless, it will not be the only mechanism for discovering new reactions. The means by which nature creates complex molecules, discovered through studies of biosynthesis and metabolism, suggest new pathways which we refer to as biomimetic. One of the most dramatic illustrations of this approach evolved from the discovery of squalene as the precursor of the tetracyclic steroids (*18*). The enzyme system responsible for squalene cyclization creates an electrophilic initiator, an epoxide, and then folds the linear chain to generate the beautiful steroid

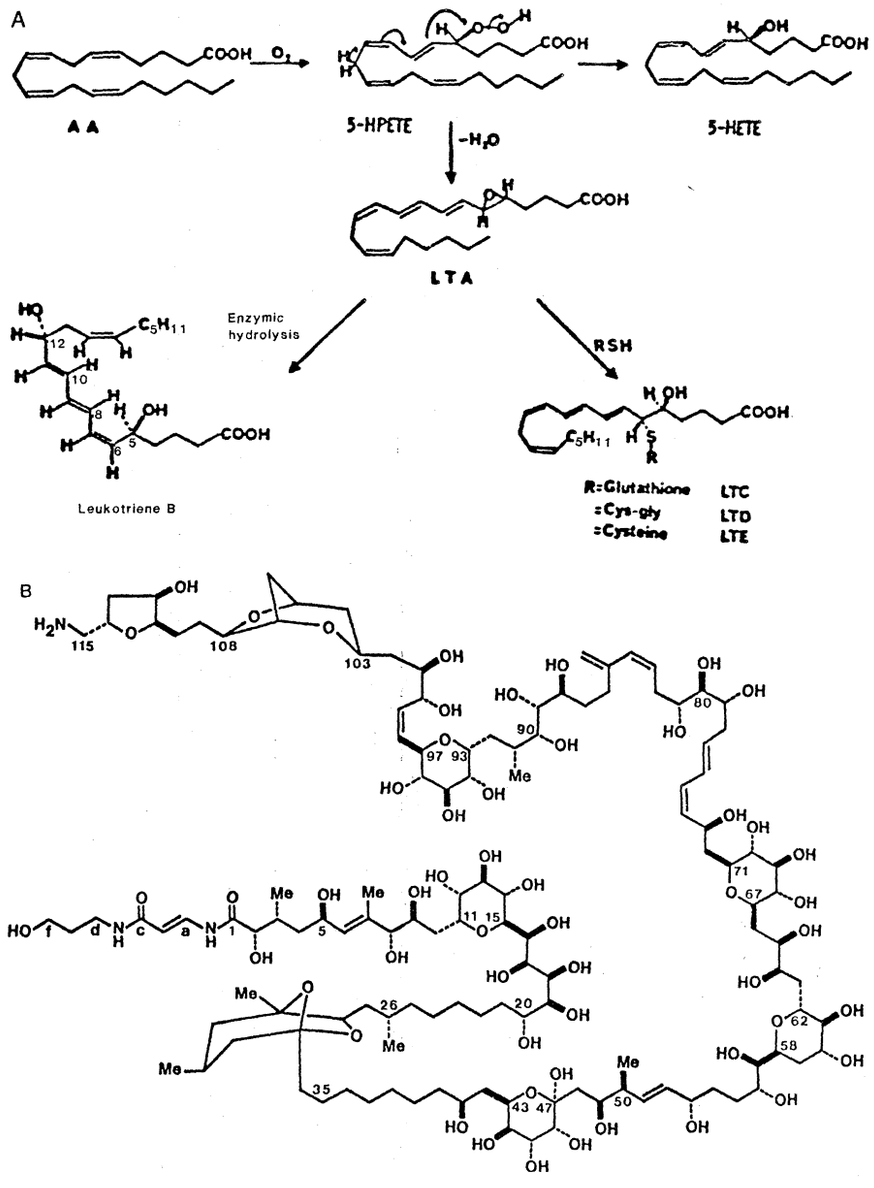


Fig. 1. New structures: (A) biosynthesis of leukotrienes; (B) palytoxin.

framework. Figure 6 shows that, with a proper initiator and a suitable terminator, a simple proton successfully promotes the polyolefin cyclization and translates a biosynthetic notion into a practical synthesis of the anti-inflammatory corticosteroids (*19*). As our understanding of how nature does things increases, new opportunities for reaction design will undoubtedly arise.

Techniques

Advances in a science closely parallel the development of new tools. Separations science, specifically chromatography, has had a great effect on the practice of organic chemistry and the types of problems that can be broached, such as the study of bioregulators present in very small amounts in complex mixtures. There will be further advances in designing selective absorbents and improved detection systems, and new concepts in separations science undoubtedly remain to be discovered which will make it possible to tackle problems that are now unapproachable.

Related to separation techniques for stable molecules is the development of methodology for isolating reactive intermediates. Matrix isolation permits the encapsulation of an unstable species in a frozen matrix at temperatures approaching absolute zero (*20*). Species which have been postulated as intermediates on the basis of indirect methods cannot only be generated but also directly observed. Direct study of these intermediates will lead to better control of their reactivity and thus to improved reactions and even new ones. The possibility of detecting previously unknown types of reactive intermediates is particularly exciting.

Organic chemistry has largely relied on thermal reactions for synthesis. The electronically excited state offers another dimension of reactivity and another world of reactions. Thermally forbidden reactions are sometimes photochemically allowed. Thus, while cycloaddition of two olefins to give a four-membered ring fails thermally, it succeeds photochemically, and this is one of the few synthetically important photochemical processes (*21*). Controlling photoreactions appears to constitute one of the difficulties. The therapeutically important vitamin D metabolites rely on photoconversion of the previtamin to the provitamin form, as shown in Fig. 7 for 1-α-hydroxy series. The use of lasers with precisely tuned wavelengths of incident radiation generates the specific excited state to effect

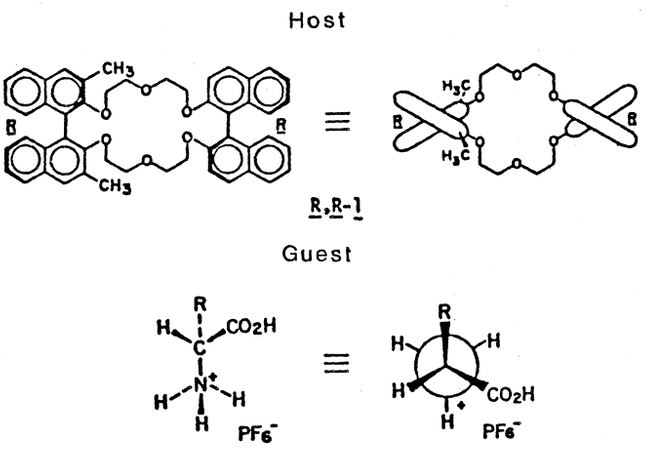
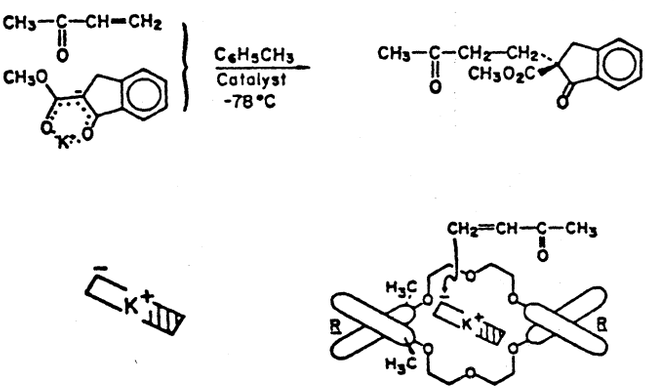


Fig. 2. New structures: chiral crown compounds.



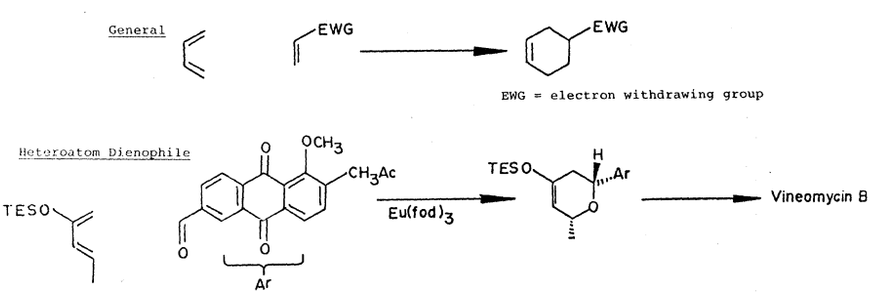


Fig. 3. Diels-Alder reaction: new faces.

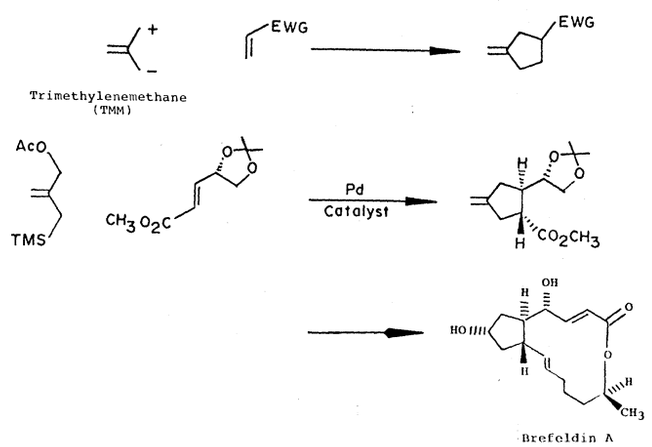


Fig. 4. Catalysis: cycloaddition to cyclopentanes.

this transformation and minimizes undesired side reactions (*22*). The enhanced control doubled the efficiency of this commercially important process.

At times, the obvious appears to have been overlooked. Much of synthesis involves condensing two reacting species and forming one molecule from two. A decrease in the volume and normally a negative volume of activation accompanies such a process. The simple mechanical operation of high pressure should and does facilitate such condensations, as shown in Fig. 8 in a projected synthesis of the antitumor quassinoids (*23*). The absence of any additional reactants and the lower temperatures frequently possible prevent decomposition pathways from superseding, as happens with acid or base catalysis. Greater accessibility of equipment for ultrahigh pressure and better reactor design will enhance the role of this technique in synthesis.

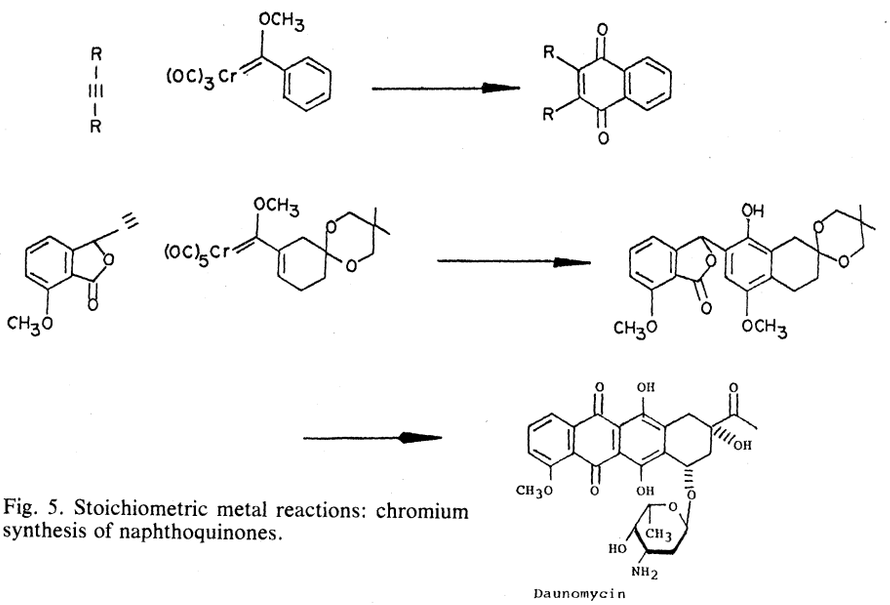


Fig. 5. Stoichiometric metal reactions: chromium synthesis of naphthoquinones.

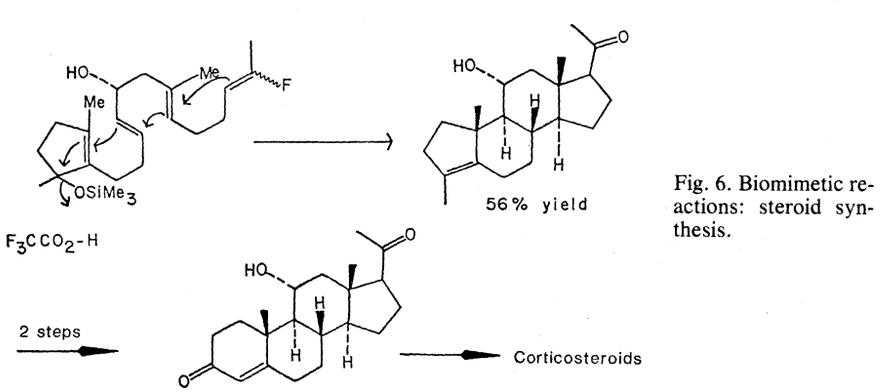


Fig. 6. Biomimetic reactions: steroid synthesis.

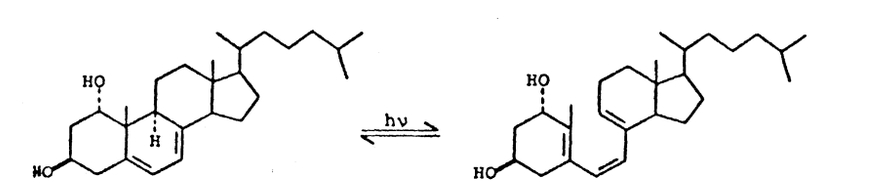


Fig. 7. Photolysis with lasers.

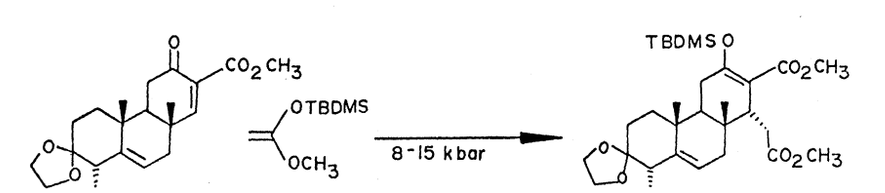


Fig. 8. Reaction under ultrahigh pressure.

Clearly, other techniques remain to be explored. Effects of magnetic fields (*24*), of solid states, of molten salts, and of weightlessness, to name a few, can only be speculated upon. Such unexplored techniques may open up new dimensions in performing and studying reactions.

Concepts

The correlation of a vast number of observations into unified concepts or theories not only provides a better basis for understanding the existing facts but also serves as a basis for making predictions. The concepts of aromaticity that evolved in the 1930's are still sources of animated debate and of inspiration for research directions. The concepts of orbital symmetry and frontier orbital control of reactions, enunciated less than 20 years ago, almost immediately profoundly changed the thinking of chemists. An avalanche of new ideas resulted and will continue to grow as further experimental data develop. Most important, our ability to rationally propose and experimentally implement the synthesis of unusual unsaturated molecules or the generation of new reactions has moved large steps forward.

Most areas in experimental organic chemistry have not enjoyed the benefits of such sweeping theories. In part, this may be due to the extremely small effects that we attempt to correlate. In this sense, organic chemistry is an exercise in perturbation theory. We must concern ourselves with many small effects and deduce the ultimate resultant. Defining and quantifying these small effects is a major endeavor.

A good illustration is provided by the idea of stereoelectronic effects as applied to saturated systems. The ability of saturated single bonds to transmit electronic information has usually been ignored. The "anomeric" effect, a propensity for an alkoxy group to prefer the normally less favorable axial position in a tetrahydropyran ring, appeared to be restricted to carbohydrates (Eq. A in Fig. 9 (*25*). The tendency to attribute its behavior to the special properties of the carbohydrate system delayed the development of a fundamental understanding. An appre-

ciation of the general implications of this basic phenomenon has arisen from the observation that a *t*-butyl group, long considered to be an immovable object, an anchor, in terms of its propensity to be equatorial in a six-membered ring, can be forced into an axial position (Eq. B in Fig. 9) (*26*). The transmission of the electronic effects of the lone pairs on the ring heteroatoms to the axial C–O bond in Eq. A, a stabilizing effect, and the axial C–Li bond in Eq. B, a destabilizing effect, account for such observations. A growing understanding of this unusual effect and the uncovering of many related examples led to its predictable application in reaction design (*25*). It has already been applied in the preparation of important highly oxygenated natural (ionophores) and unnatural (crown and cryptand) products.

Almost any reaction reveals additional areas of little or no understanding. This primitiveness is revealed by the fact that as central and widely used (sometimes confused with understood) a reaction as the addition of nucleophiles to a carbonyl group remains a mystery. The observation that acetylide anions add preferentially in the normally "sterically more hindered" axial fashion (Fig. 10) (*27*) suggests the existence of unrevealed but significant concepts.

One strategy for trying to evaluate the resultant of many small effects is exemplified by the field of conformational analysis. The orientation of parts of molecules to each other which vary by only simple bond rotations that form different isomers (conformers) frequently determines the chemical or biological behavior of the molecules. In certain systems, such as six-membered rings, the molecules are relatively rigid and well understood. However, noncyclic systems and large ring molecules, of particular practical importance, are conformationally mobile.

Molecular mechanics, the empirical computation of conformational energy, combined with computer graphics constitutes molecular modeling (*28*). This technique has greatly enhanced our ability to perceive the exact shapes of molecules. Nevertheless, it is not the panacea. Using such models in a synthesis of the polyether antibiotic lysocellin, as depicted in Fig. 11, the prediction suggests formation of the *cis* alkylated product; experimentally, alkylation of **3**, Fig. 11, produces **4** with one alkylation proceeding as predicted but the second one not (*29*). Obviously, refinements are required before this approach becomes more generally useful. Nevertheless, the beginnings offer a great deal of anticipation that an impasse in structural analyses may be removed by such computer-based techniques.

Selectivity

Underlying the major challenges in designing and creating more complex molecules for a multitude of uses is selectivity. In defining strategies and reactions to construct complex molecules we require synthetic methods that can (i) perform a wanted structural change and none other (that is, be chemoselective), (ii) orient the reacting partners in a correct fashion (be regioselective), (iii) create the correct orientations of the various parts of the molecule with respect to each other (be diastereoselective), and (iv) enable the formation of a molecule of one-handedness or a mirror image isomer (be enantioselective). Such extraordinary demands are exciting challenges. Some recent examples demonstrate that such challenges can be met but also demonstrate how far we have to go.

Chemoselectivity. If you have a target

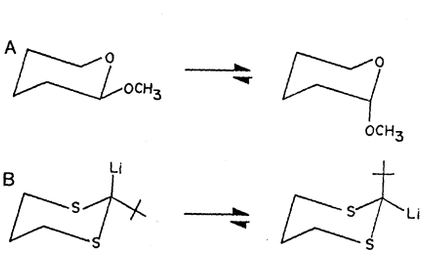


Fig. 9 (left). Stereoelectronic factors.

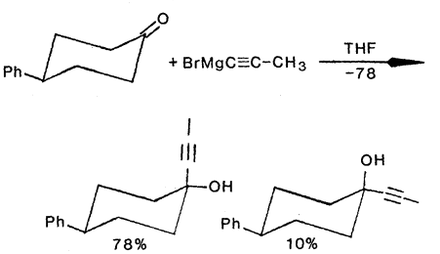


Fig. 10 (right). Stereoelectronics: axial selectivity.

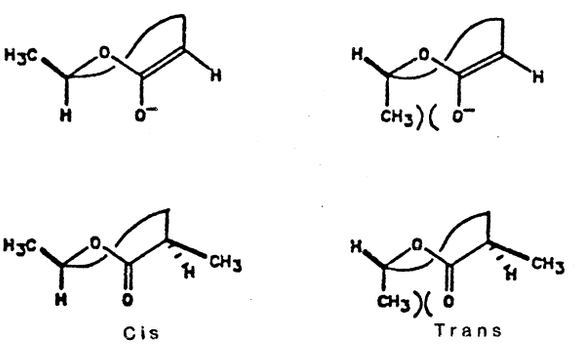
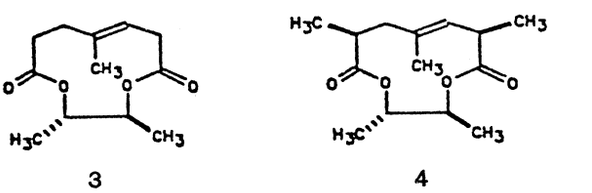


Fig. 11. Computer modeling—conformational analysis.



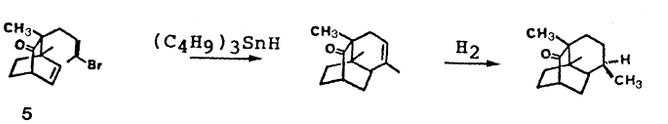


Fig. 12. Chemoselectivity: radical intermediates.

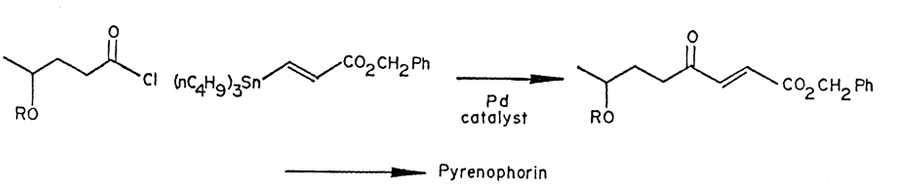


Fig. 13. Chemoselectivity: transition metal catalysts.

consisting of a hundred moving parts of similar size and shape, how can you hit a single preselected part without harming any of the others? Trying to carry out a reaction involving a hundred atoms is a similar problem and defines the challenge of chemoselectivity. An approach involves rediscovery of existing knowledge to offer new insight and applications. A renaissance in radical chemistry beautifully illustrates this concept. Radicals, extremely important reactive intermediates because of their role in polymer synthesis, have the property of being compatible with most polar functional groups such as hydroxyl and carbonyl groups. In contrast, carbanion chemistry, a more commonly employed synthetic technique for forming C–C bonds, is incompatible with such groups—a fact which has led to the idea of "protecting" these functional groups. Unfortunately, protection results in synthetic inefficiency. Consider the cyclization of **5** in Fig. 12 (*30*). Any type of carbanion reaction would (i) lead to carbonyl rather than olefin addition or (ii) require protection of the carbonyl group. Quite the contrary is true for radical reactions. Indeed, direct cyclization with C–C bond formation and, most important, without recourse to protecting groups occurs upon exposure of **5** to a radical-generating agent. A particularly efficient synthesis of the fragrance ingredient seychellene results.

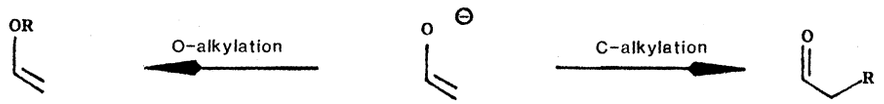


Fig. 14. Regioselectivity: O versus C alkylation.

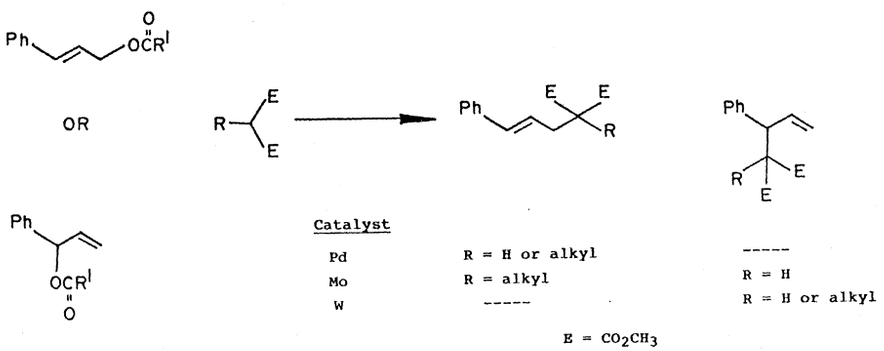


Fig. 15. Regioselectivity: allylic alkylation.

Transition metal complexes, which we referred to earlier as the chemists' enzymes, represent a tremendous stride in our quest for chemoselectivity. An important example is the catalyzed cross-coupling reaction, illustrated in Fig. 13 in a synthesis of the antifungal antibiotic pyrenophorin (*31*). Here, in contrast to the classical approaches, we adjust the reactivity of our carbanion chemistry to make it compatible with carbonyl groups. Clearly, we must avoid the use of "crutches" such as protecting and activating groups if we are to achieve full synthetic efficiency. Whether such a goal is practical remains to be determined.

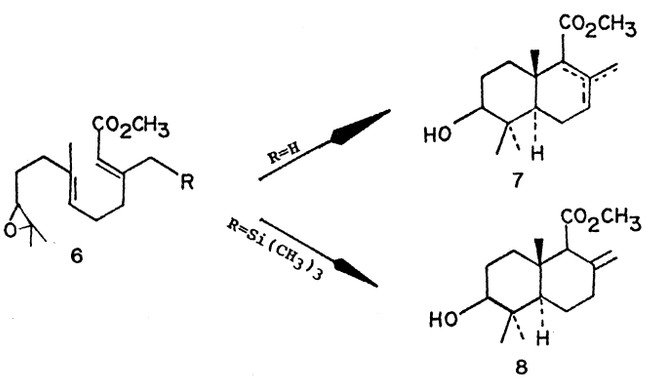


Fig. 16. Regioselectivity control element: silicon.

Regioselectivity. An ability to adjust the orientation in which two reacting partners approach one another can increase our synthetic flexibility, although sometimes it is not so important. For example, in O versus C alkylation of enolates (Fig. 14), C alkylation usually dominates but it is also normally the desired product. In contrast, directing allylic alkylation to give either of the two regioisomeric products at will is desirable and important (Fig. 15). The transition metal complexes reveal their versatility in allowing us to titrate the reaction with full control by varying the electronic and steric nature of the catalyst template (*32*).

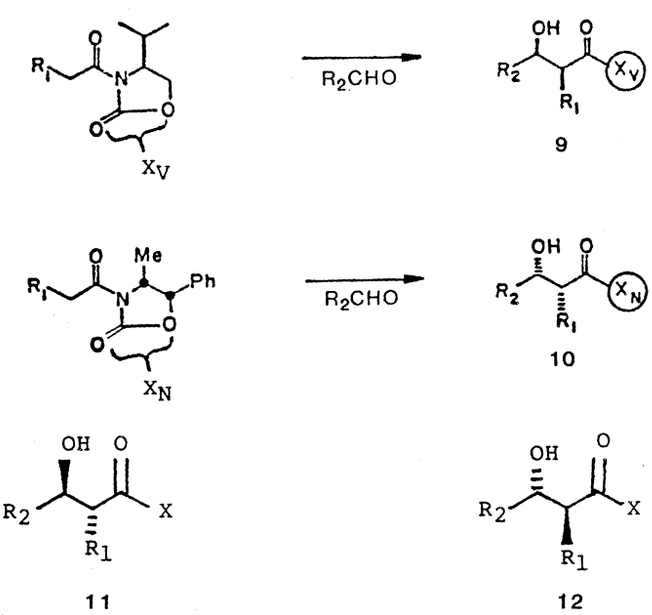


Fig. 17. Diastereoselectivity: aldol-type reaction.

At times, introduction of an easily removed substituent permits regiocontrol. The discovery of the other elements of the periodic table by organic chemists has revealed a number of elements which are of value in such a task. Silicon, so far, appears to be a very powerful one.

We discussed the biomimetic polyolefin cyclization as a useful approach to forming complex molecules from simple ones (Fig. 6). Figure 16 discloses a limitation, the lack of regioselectivity in the termination by proton loss, in which every possible olefin results (**6**→**7**). The simple expedient of employing an allyl silane as the terminator gives a unique product (**6**→**8**), even though it is the thermodynamically unfavorable one (*33*). Our ability to control regioselectivity remains highly limited. Nevertheless, the idea that we are powerless to do so must be put aside.

Diastereoselectivity. Nature has evolved elaborate mechanisms for molding the shape of its objects. Man does not share nature's success. Molding the shape of organic molecules, or stereocontrol, remains a formidable challenge for the chemist. Our limited success is understandable if we realize that the delicate interplay of many opposing forces, few of which can be quantified at present, determines the experimental outcome. Even so, impressive studies have recently been made.

The aldol reaction, one of the classical reactions in organic chemistry, reveals new faces in its ability to serve the chemist. As Fig. 17 discloses, with an appropriate choice of reaction conditions, such as metal reactant and substrate, *syn*-type products such as **9** and **10** dominate over *anti*-type products such as **11** and **12** (*34*). Such diastereoselectivity easily translates into enantioselectivity. In the examples of Fig. 17, X_V and X_N are optically active and transfer their stereochemistry to the products **9** and **10** in such a way that (ignoring the parts that correspond to X_V and X_N) these two compounds are mirror image or optical isomers or enantiomers. By simple hydrolysis, we obtain enantiomerically pure products. We refer to X_V and X_N as chiral auxiliaries.

Another facet of this approach derives from the expanding world of organoboranes. While the use of such compounds for formation of C–H and C–O bonds is well recognized, their role in forming C–C bonds may ultimately be even more important. The conformational rigidity associated with the transition states for boron-mediated additions to carbonyl groups serves to enhance stereochemical control.

The aldol reaction, already discussed, is one reaction that is susceptible to the use of boron chemistry for such a purpose (*35*). Replacement of the magnesium of allyl Grignard reagents with boron (Fig. 18) is another example (*36*). The fact that the two stereochemical centers in the product **13** are not directly bonded to each other permits their separation by simple hydrolysis to the fragrance ingredient artemesia alcohol, **14**, in enantiomerically pure form. Thus, the diastereoselectivity of the carbonyl addition translates into enantioselectivity in the final product. A great deal of progress in diastereoselectivity still results from the empirical or "try and see" approach. The transition to rational design will become possible only with better understanding.

Enantioselectivity. If you take a glove from a box containing equal numbers of right-handed and left-handed gloves, you

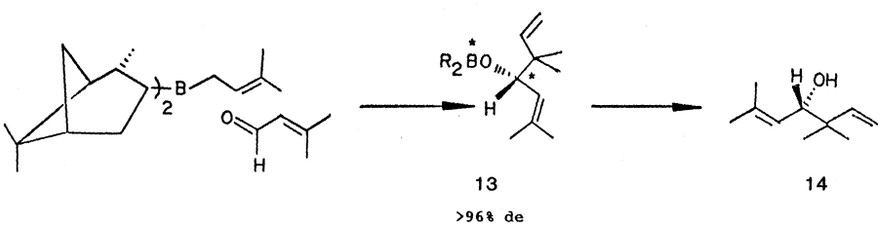


Fig. 18. Diastereoselectivity: allylboranes (de, diastereomeric excess).

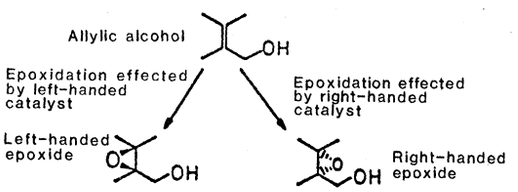
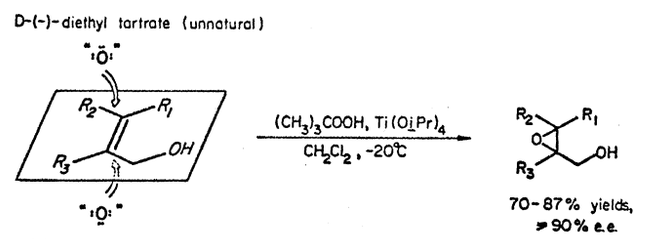


Fig. 19. Enantioselectivity: abiological catalysts.



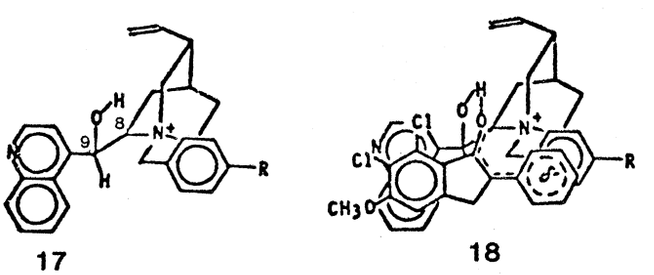


Fig. 20. Enantioselectivity: phase transfer catalysis.

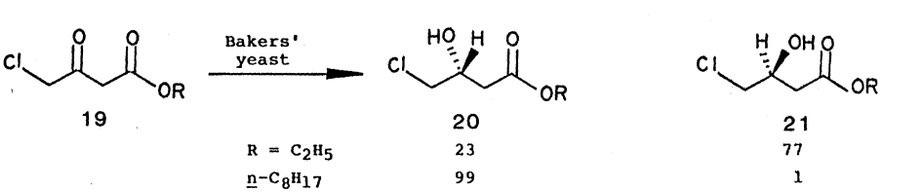


Fig. 21. Enantioselectivity: microbial methods.

have a 50:50 chance of drawing a right-handed glove. Is there a way to increase that probability to 100 percent? This is the type of problem that the chemist confronts in trying to control enantioselectivity.

Once again, transition metal templates come into use. Previously, control of stereochemistry appeared to be possible only in the realm of enzymes. Now, however, abiological catalysts for asymmetric induction are beginning to emerge. Figure 19 illustrates a benefit of wine other than the obvious physical one. The metal titanium, in an environment of tartarates, constituents of wine, selectively delivers an oxygen atom to one of the enantiotopic faces of the olefin of an allyl alcohol (*37*). Unfortunately, very few cases of asymmetric metal catalysts exist and only the formation of C–O or C–H bonds has so far succumbed to asymmetric induction.

Transition metal catalysts need not be the only substances used for this purpose. Figure 20 depicts a sculpted host used for asymmetric induction. In examining the source of chiral recognition at the active site of enzymes, we discuss many small effects such as hydrogen bonding and π stacking. By use of an optically active phase-transfer catalyst (**17**), a dramatic asymmetric alkylation is achievable (**15**→**16** in Fig. 20) in a process directed toward the uricosuric agent indacrinone (*38*). In retrospect, enzyme-like interactions such as that depicted in **18** may account for this extraordinary result. The simplicity of the catalyst but the enzyme-like experimental result begin to strip away some of the mysticism we associate with enzymes.

Nevertheless, enzymes, modified enzymes, or whole cells will undoubtedly play an increasing role in synthesis. The challenge of manipulating an enzyme by using biotechnology to modify enzyme selectivity or create new types of reactivity is exciting. However, potential pitfalls must be recognized. In a synthesis of L-carnitine, a compound with therapeutic use as an antihyperlipoproteinemic agent, the yeast reduction of the β-ketoester **19** was expected to give **20** but, surprisingly, gave a mixture of **20** and **21** (see Fig. 21). Careful investigative work showed that this lack of enantioselectivity was due to the presence of multiple oxidoreductases with opposing stereochemical effects (*39*). Substrate manipulation by changing the nature of an ester modifies the relative activity of the competing enzymes and restores high enantioselectivity.

Enantiocontrol remains most primitive. The fact that the world we live in is chiral and nature is particularly sensitive to enantioisomerism stresses the importance of the challenge.

Conclusion

At what stage of development does organic chemistry stand? Its successes of the past have led some to believe that it is mature. The idea persists that we can synthesize anything. The major flaw in this view is that it fails to recognize effectiveness and practicality. Clearly, we cannot synthesize with the directness with which nature manipulates polyfunctional molecules. In fact, there is considerable evidence that we are still in our infancy and only beginning to learn to walk. The advances that have been made, although they are impressive, reveal how much further we need to go.

The relationship between chemistry and biology must enter any discussion of the future. Almost by definition, molecular problems of the life sciences are integral parts of organic chemistry. Some of the discussion in this article shows the prominent position such problems have in contemporary organic research and surely will have in the future. With the development of molecular biology as a subdiscipline of biology, the boundaries between these sciences have begun to vanish. While some speak of interdisciplinary research between these areas, perhaps we should speak of co- or even unidisciplinary research as the objectives of the researchers seem to merge. Regardless of tradition, the best definition of any science is what the individuals who call themselves practitioners of that science are doing.

References and Notes

1. K. Nakanishi, *Pure Appl. Chem.* **25**, 167 (1971).
2. B. M. Trost, *Acc. Chem. Res.* **3**, 120 (1970).
3. J. M. Brand, J. C. Young, R. M. Silverstein, *Fortschr. Chem. Org. Naturst.* **37**, 1 (1979); B. A. Leonhardt and M. Beroza, *ACS Symp. Ser. 190* (1982).
4. B. Samuelsson, *Pure Appl. Chem.* **53**, 1203 (1981); E. J. Corey, *Experentia* **38**, 1259 (1982); T. Scheinman and J. Ackroyd, *Leukotriene Syntheses. New Class of Biologically Active Compounds Including SRSA* (Raven, New York, 1984).
5. B. Samuelsson, *Recent Prog. Horm. Res.* **34**, 239 (1978); K. C. Nicolaou, G. P. Gasic, W. E. Barnette, *Angew. Chem. Int. Ed. Engl.* **17**, 293 (1978).
6. Y. Kishi, in *Selectivity—a Goal for Synthetic Efficiency*, W. Bartmann and B. M. Trost, Eds. (Verlag Chemie, Weinheim, 1984), pp. 99–119.
7. R. C. Fort, Jr., and P. V. R. Schleyer, *Chem. Rev.* **64**, 277 (1964).
8. W. L. Davis *et al.*, *Science* **144**, 862 (1964).
9. L. A. Paquette, *Proc. Natl. Acad. Sci. U.S.A.* **79**, 4495 (1982).
10. G. Maier, S. Pfriem, U. Schafer, K.-D. Malsch, R. Matusch, *Chem. Ber.* **114**, 3965 (1981).
11. D. J. Cram, *Science* **219**, 1177 (1983).
12. J. M. Lehn, *Stud. Phys. Theor. Chem.* **24**, 181 (1983); *Pure Appl. Chem.* **52**, 2441 (1980).
13. D. J. Cram and J. M. Cram, in *Selectivity—a Goal for Synthetic Efficiency*, W. Bartmann and B. M. Trost, Eds. (Verlag Chemie, Weinheim, 1984), pp. 43–64.
14. S. J. Danishefsky, B. J. Uang, G. Quallich, *J. Am. Chem. Soc.* **106**, 2453 (1984).
15. (a) B. M. Trost, *Chem. Soc. Rev.* **11**, 1419 (1982); (b) _____, J. Lynch, P. Renaut, D. Steinman, unpublished results.
16. K. H. Dotz, *Angew. Chem. Int. Ed. Engl.* **23**, 587 (1984).
17. W. D. Wulff and P. C. Tang, *J. Am. Chem. Soc.* **106**, 434 (1984).
18. E. E. van Tamelen, J. D. Willett, R. B. Clayton, K. E. Lord, *ibid.* **88**, 4752 (1966); E. J. Corey and W. E. Russey, *ibid.*, p. 4750.
19. W. S. Johnson, T. A. Lyle, G. W. Daub, *J. Org. Chem.* **47**, 161 (1982).
20. G. C. Pimentel, *Angew. Chem. Int. Ed. Engl.* **14**, 199 (1975); I. R. Dunkin, *Chem. Soc. Rev.* **9**, 2 (1980).
21. P. Margaretha, *Top. Curr. Chem.* **103**, 1 (1982); S. W. Baldwin, *Org. Photochem.* **5**, 123 (1980).
22. W. G. Dauben and R. B. Phillips, *J. Am. Chem. Soc.* **104**, 5780 (1982).
23. C. H. Heathcock, C. Mahaim, M. F. Schlecht, T. Utawanit, *J. Org. Chem.* **49**, 3264 (1984).
24. N. J. Turro, *Proc. Natl. Acad. Sci. U.S.A.* **80**, 609, (1983).
25. P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry* (Pergamon, Oxford, 1983).
26. E. L. Eliel, A. A. Hartmann, A. G. Abatjoglou, *J. Am. Chem. Soc.* **96**, 1807 (1974).
27. I. Fleming and N. K. Tenett, *J. Organomet. Chem.* **264**, 99 (1984); G. Stork and J. M. Stryker, *Tetrahedron Lett.* **24**, 4887 (1983).
28. U. Burkert and N. L. Allinger, *ACS Monogr. 177* (1982).
29. W. C. Still, in *Selectivity—a Goal for Synthetic Efficiency*, W. Bartmann and B. M. Trost, Eds. (Verlag Chemie, Weinheim, 1984), pp. 263–279.
30. G. Stork, *ibid.*, pp. 281–298.
31. J. W. Labadie, D. Tueting, J. K. Stille, *J. Org. Chem.* **48**, 4634 (1983).
32. B. M. Trost and M.-H. Hung, *J. Am. Chem. Soc.* **106**, 6837 (1984).
33. R. J. Armstrong and L. Weiler, *Can. J. Chem.* **61**, 214 (1983); *ibid.*, p. 2530.
34. D. A. Evans, M. D. Ennis, T. Le, N. Mandel, G. Mandel, *J. Am. Chem. Soc.* **106**, 1154 (1984).
35. S. Masamune *et al.*, *ibid.* **103**, 1566 (1981).
36. H. C. Brown and P. K. Jadhav, *Tetrahedron Lett.* **25**, 1215 (1984).
37. K. B. Sharpless, S. S. Woodard, M. G. Finn, in *Selectivity—a Goal for Synthetic Efficiency*, W. Bartmann and B. M. Trost, Eds. (Verlag Chemie, Weinheim, 1984), pp. 377–390.
38. U.-H. Dolling, P. Davis, E. J. Grabowski, *J. Am. Chem. Soc.* **106**, 446 (1984).
39. C. J. Sih and C.-S. Chen, *Angew. Chem. Int. Ed. Engl.* **23**, 570 (1984).

40. I thank the National Science Foundation and the National Institutes of Health for their generous support of our programs. I thank Professor Samuel J. Danishefsky for providing a copy of his address to the AAAS on 25 May 1984 on an overview of organic chemistry, which contributed some of the examples used here.