

Topics in Stereochemistry, Volume 20

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**TOPICS IN
STEREOCHEMISTRY**

VOLUME 20

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TOPICS IN

STEREOCHEMISTRY

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VOLUME 20



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INTRODUCTION TO THE SERIES

It is patently impossible for any individual to read enough of the journal literature so as to be aware of all significant developments that may impinge on his or her work, particularly in an area such as stereochemistry, which knows no topical boundaries. Stereochemical investigations may have relevance to an understanding of a wide range of phenomena and findings irrespective of their provenance. Because stereochemistry is important in many areas of chemistry, comprehensive reviews of high quality play a special role in educating and alerting the chemical community to new stereochemical developments.

The above considerations were reason enough for initiating a series such as this. In addition to updating information found in such standard monographs as *Stereochemistry of Carbon Compounds* (Eliel, McGraw-Hill, 1962) and *Conformational Analysis* (Eliel, Allinger, Angyal, and Morrison, Interscience, 1965; reprinted by American Chemical Society, 1981) as well as others published more recently, the series is intended also to deal in greater detail with some of the topics summarized in such texts. It is for this reason that we have selected the title *Topics in Stereochemistry* for this series.

The series is intended for the advanced student, the teacher, and the active researcher. A background of the basic knowledge in the field of stereochemistry is assumed. Each chapter is written by an expert in the field and, hopefully, covers its subject in depth. We have tried to choose topics of fundamental importance aimed primarily at an audience of inorganic and organic chemists. Yet, many of these topics are concerned with basic principles of physical chemistry and some deal with stereochemical aspects of biochemistry as well.

It is our intention to produce future volumes at intervals of one to two years. The editors will welcome suggestions as to suitable topics.

We are fortunate in having been able to secure the help of an international board of editorial advisors who have been of great assistance by suggesting topics and authors for several chapters and by helping us avoid, in so far as possible, duplication of topics appearing in other, related monograph series. We are grateful to the editorial advisors for this assistance, but the editors and authors alone must assume the responsibility for any shortcomings of *Topics in Stereochemistry*.

E. L. ELIEL
S. H. WILEN

PREFACE

The first of the four chapters in this volume of *Topics in Stereochemistry* by William C. Ripka and Jeffrey M. Blaney, deals with applications of computer graphics and molecular modeling. This is an extraordinarily active subject whose growth has been so rapid that, as yet, there seems to be a paucity of textbooks and review articles. The topic, which at its most fundamental level probes the three-dimensional interaction between molecules and between groups and atoms within molecules, is reviewed by two outstanding practitioners of the on-screen manipulation of molecular models. This technique, and the attendant calculations required to insure that the specific conformations examined are of low energy, are increasingly applied to the analysis of biochemical phenomena at the molecular level and to the design and synthesis of new medicinal agents. The authors introduce us to the specialized language that characterizes the field and provide us with a unique overview of the major software packages and of the several modeling techniques presently in use as applied to specific examples.

The second chapter, by David A. Oare and Clayton H. Heathcock, deals with the stereochemistry of uncatalyzed Michael reactions of enamines and of Lewis acid catalyzed reactions of enol ethers with α,β -unsaturated carbonyl compounds. It is effectively a continuation of their definitive review of base-promoted Michael addition reaction stereochemistry that appeared in the preceding volume of the series.

In the third chapter, Nikolai S. Zefirov and Vladimir A. Palyulin have summarized the conformational behavior of bicyclo[3.3.1]nonanes and their hetero analogs. This review reflects a thoroughly modern viewpoint in which calculations, x-ray crystallographic results and spectroscopic data all are brought to bear on a polycyclic molecular framework that is able to support several relatively stable conformations including some in which boats figure prominently.

The final chapter in this volume deals with the chemistry of strained (bent and nonplanar) alkenes. Wolfgang Luef and Reinhart Keese have surveyed the recent literature with respect to syntheses and properties. This chapter also reflects the modern tendency to calculate the energies of interesting molecules and to use the calculated values to rationalize properties and to guide syntheses.

With the appearance of this volume we are pleased to welcome two new members to our Editorial Advisory Board: Marian M. Mikolajczyk (Polish Academy of Sciences) and Nikolai S. Zefirov (Moscow State University and Soviet Academy of Science). We also welcome Meir Lahav (Weizmann Institute of Science), who joined the editorial board with the appearance of Volume 19. We hope that these colleagues will help us keep in touch with stereochemical developments in Poland, in the Soviet Union, and in Israel, respectively. We also wish to acknowledge with thanks the advice received over the past decade from Professor Jan Michalski who is relinquishing his position on the Board.

Finally, with the appearance of Volume 20, the *Topics in Stereochemistry* series that began in 1967 marks a minor milestone. In recognition of this milestone, we are pleased to include a cumulative author index. We hope that this index will be useful to readers seeking to locate reviews by the name of the authors who are often leading researchers in the area which they have reviewed in this series.

ERNEST L. ELIEL
SAMUEL H. WILEN

Chapel Hill, North Carolina
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October 1990

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**TOPICS IN
STEREOCHEMISTRY**

VOLUME 20

Computer Graphics and Molecular Modeling in the Analysis of Synthetic Targets

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I. INTRODUCTION

X-ray crystallography and molecular modeling provide a detailed view of ligand-receptor interactions and have made possible a new, rational approach where molecules can be designed based on their fit to the three-dimensional structure of a receptor site. Initial research into this approach began in the late 1970s, with widespread application beginning in the early 1980s. The general methodology has been the subject of several recent reviews (1-13).

We survey computer-assisted molecular modeling with a discussion of the selection of receptor targets, the design of small molecule ligands to fit the selected target, computational methods for model building, docking, and energy calculations, and currently available software and hardware. We focus on the several features necessary to meet the demanding requirements of small molecule construction, the first step in most modeling problems dealing with synthetic design, and the docking and fitting of these structures to macro-molecular targets.

Consideration must be given to the target receptor at the outset of a molecular modeling study. Many protein and nucleic acid X-ray structures are available (14), and three-dimensional structures of small to medium sized proteins (< 100 residues) in solution can now be determined by NMR (15-17). These structures can be used directly or can serve as the basis for "homology model building." The amino acid sequence of the target protein can be used along with one or more X-ray structures of similar (i.e., of the same family) proteins to construct a three-dimensional model of the target protein. Although attempts have been made to predict protein structures in a completely *de novo* fashion using rule-based approaches (18), they have not been accurate enough to use for designing small molecule ligands.

Design of potential ligands can begin after a model for the target receptor becomes available. The cases discussed in this chapter deal primarily with enzymes. Enzymes usually have well-defined "active sites" or pockets, which provide the best opportunities for synthetic design of ligands, and the

effectiveness of the designed ligand can be measured accurately by inhibition of enzymatic activity.

Conceptually, the problem of molecular design seems simple: a ligand must be designed that has a complementary surface to the receptor binding site and positions functional groups so that hydrogen bonding and other electrostatic interactions can occur between the ligand and the walls of the active site. To do this effectively, it is necessary to have some understanding of the binding forces used in macromolecule–ligand interactions. The structures of several protein–ligand and DNA–ligand complexes have been solved by X-ray crystallography and detailed studies of these systems suggest the relative importance of specific intermolecular interactions. When the three-dimensional structural information is coupled with site-specific mutagenesis of the macromolecule (leading to slightly modified structures) and kinetic or binding studies, quantitative estimates can be made of the importance of specific interactions. The design process tries to take advantage of such potentially available interactions and to provide complementary functionality in the designed ligand.

There are currently several commercial molecular modeling software packages available with varying capabilities. All of them will handle simple manipulations of structures. Features beyond these quickly become important in any sophisticated modeling study and the ease with which the software handles them is important. In particular, while the current trend toward a menu-based system satisfies the needs of the beginning and “occasional use” modeler, it can become restrictive in the hands of more experienced users. On the other hand, a powerful command language based on the ability of the program to interpret sensible English language syntax can be extraordinarily powerful, although beginners may find it difficult to use. A significant advantage of a good command language is that commands can be combined and associated in extremely versatile ways to carry out operations that were not anticipated by the software developers and therefore would not be included in menus. In an environment that must meet the needs of both inexperienced and experienced users, software that has both menus and command language must be considered. Unfortunately, much of the recent modeling software has concentrated on reinventing the wheel, ignoring previous developments and experience, and does not always provide important functionality with a good user interface. We hope that in the future new software will incorporate *significant* advances and that a better educated modeling community will insist on it. State-of-the-art molecular modeling systems provide extensive computational and graphics facilities for analyzing known structures and interactions, but no currently available system is capable of designing molecules by itself, so it is clear that a well-designed system must focus on maximizing the strengths of the key design component—the user.

Currently, there are few systematic approaches to the ligand design problem. Kuntz et al. (19) search for small molecules that provide a complementary steric fit to a receptor site by using a collection of spheres to define the three-dimensional structure of the site. Goodford and co-workers (20, 21) generate probe maps to find favorable placements or "hot spots" of specific functionality (e.g., hydroxyl, amine, carbonyl) in the binding site. The most frequently employed strategy uses interactive, real-time (when you turn a knob or adjust another device, you get immediate, continuous response on the display) modeling in which molecules are designed and constructed based on visual inspection of the target site (with color-coded molecular surface and perhaps probe map displays) using the intuition, experience, and creativity of the chemist-modeler. This latter approach has the advantage that the target will probably be designed with the ease of synthesis kept firmly in mind. Although computer-assisted synthetic analysis programs (e.g., LHASA (22)) can interactively guide experienced synthetic chemists and even suggest new routes, no self-contained algorithms exist that can assess the ease of synthesis of a designed structure; this places severe restrictions on any automated approach to molecular design. Currently, the most effective method to design small molecule ligands for a known binding site appears to be combining the geometric and probe algorithms with interactive modeling to suggest synthetic targets.

Once candidate structures have been designed they must be docked into the binding site. Such docking is useful to refine the initial fit and to look for alternate modes of binding. This can be done by either "off-line" processing or "on the fly" with specialized hardware and software. Another important role of docking is to use it as an initial step to screen a database of known small molecule structures to locate complete or partial structures that fit the site and, in turn, use these structures as the basis for design (Section IX.B). Molecular mechanics (Section VI) can then be used to clean up any close contacts and to estimate the conformational energy of the bound conformation of each ligand. The conformational energies of these bound ligands can then be used to prioritize them, such that the lower energy forms would be considered to be more probable than the higher ones. Current approaches for conformational searching of flexible molecules are described in a recent review article (23). Molecular dynamics and free-energy perturbation methods (Section VI) can be used to impart more flexibility to the fit and, in special cases, to estimate binding energies. Molecular mechanics calculations comparing the conformational energies of free ligand and protein with the bound protein-ligand complex are unlikely to give reasonable estimates of the binding energies except when very close analogs are being compared (24-26).

To date there are extremely few examples of *de novo* design of ligands based on a known binding site. This suggests the difficulty of the process. However,

several examples are available where modeling has been used to improve the binding of previously known compounds by selective structural changes. Modeling has also been extremely useful in the construction and modification of enzyme substrate analogs. Several case studies, which may give some appreciation for the problems and successes that may be encountered, are discussed later.

Finally, we address some of the newer techniques of constructing three-dimensional pharmacophore maps. When target receptor structures are not available, which is usually the case, the size and shape of the binding site are completely unknown. *De novo* design of a ligand is impossible without structural details of the binding site. In these cases we must rely on the natural substrate's structure, if known, or the serendipitous discovery of structures that show binding to the target receptor. Judicious synthesis of selected, preferably conformationally restricted, analogs may then provide the basis for constructing a three-dimensional model of the receptor or active site. This model can then be used to improve the binding of the known ligands and, hopefully, design novel ones.

II. COMPUTER GRAPHICS SOFTWARE AND HARDWARE

A general and effective molecular modeling system requires capabilities for constructing and manipulating both small molecules and macromolecules and should incorporate features to study their interactions. The ability to model both types of molecule in the same system is essential. Several of the systems currently available were originally designed for handling the regular, repeating polymeric structure of proteins and nucleic acids and deal rather poorly with the more arbitrary structures found in small organic molecules. Other systems, however, were initially designed for modeling small molecules and do not handle macromolecular structures well. Few systems come close to combining the best of macromolecular and small molecule modeling and provide the essential ability to interactively design and build potential ligands directly into a macromolecular binding site. We review the requirements for these two kinds of modeling approaches and suggest benchmarks to evaluate modeling software.

A. Small Molecule Construction and Modeling

For small molecules the system should allow one to construct the molecule and generate a reasonable three-dimensional conformation quickly. The best currently available approach is CONCORD (27), which rapidly (15–30 s) generates a low-energy conformation for most classes of organic compounds from a simple alphanumeric SMILES code (28), a powerful, easily learned

language for encoding chemical structures. Other approaches include AIMB, an artificial intelligence method that rapidly assembles small molecules using rules and fragments from a three-dimensional structure database (29, 30), and those that start from a simple two-dimensional sketch followed by distance geometry (31, 32) or molecular mechanics. The molecular mechanics-based approach usually requires that great care be taken when drawing the initial two-dimensional sketch and often gets stuck in unreasonable conformations. To circumvent this problem, recent systems refine the structure with molecular dynamics (Section VI), which, although time consuming, usually escapes local minima to converge on energetically reasonable conformers.

A good approach for constructing small molecules targeted at a specific site is to design and build the developing ligand piece by piece in the binding site by combining preformed three-dimensional fragments from a library. The library may contain several hundred different ring systems, chains, and functional groups, which should be selected conveniently from within the modeling system. Small molecules can be built very rapidly in this way, and the resulting structures are usually accurate enough for initial fitting or "docking" into the site model. The Cambridge X-ray Database (33) is a particularly useful source of three-dimensional fragments from which to construct small molecules and has the advantage that bond lengths, bond angles, and torsion angles are experimentally determined and represent a local energy minimum. This is particularly useful for flexible rings in which it is difficult to avoid local minima by molecular mechanics energy minimizations. Once the small molecule is completely constructed, it is usually refined with molecular mechanics and/or dynamics (Section VI).

All the above features should be tightly coupled to the graphics display, which should permit one to easily select which parts of the structure are to be acted on by a given command and to see the results in real time.

B. Macromolecular Construction and Modeling

The complexity and size of macromolecules require sophisticated graphics software and hardware to provide real-time, interactive response along with selective display and manipulation (34). A modeling system should be capable of simultaneously handling 20 or more molecules, each with several thousand atoms and thousands of molecular surface points in depth-cued (foreground objects are brighter than background objects) color, with perspective, clipping (cross-sectional display), and stereoscopic display. Each molecule must be individually adjustable in three dimensions, while simultaneously monitoring intermolecular and intramolecular distances and adjusting multiple contiguous or noncontiguous torsion angles—all in real time.

Dials, joysticks, and/or a mouse are usually used to translate and rotate

molecules and rotate bonds. A new control device, "Spaceball" (35), provides one-hand control of all six degrees of freedom (three rotational and three translational) and is a significant improvement over the earlier interactive devices. Most new systems (36) have very fast processors that do complete "bump-checking" (checking for interatomic contacts closer than van der Waals distances), molecular mechanics energy calculations, and even molecular dynamics calculations in real time. These features provide excellent feedback during interactive modeling. Selective control of which molecules or portions of molecules (e.g., an enzyme active site) are displayed, which distances and torsions are "turned on" and can be manipulated at any given time, and so on, should be easily accessible, preferably by a powerful, easily learned command language. Atoms or groups of atoms should be easily selected by interactive "picking" (selection of specific atoms on the screen by positioning the graphics cursor over them) of atoms and bonds with a mouse or stylus. It should be possible to combine interactive picking of molecules, residues, or atoms with the command language to provide full control over specifying complex combinations of molecules, residues, bonds, surfaces, labels, and so on.

Full interactive control over the position (by translation and rotation along the *X*, *Y*, and *Z* coordinate axes) and conformation (by adjustment of torsion angles) of both the macromolecule and the ligand(s) must be independently and simultaneously available. Convenient facilities for adjustment of torsion angles are essential, since optimization of torsion angles is often the most time-consuming aspect of interactive modeling. Several current modeling systems are limited to defining only multiple *contiguous* torsion angles (i.e., defined by consecutive atoms in a backbone or side chain) and otherwise can only have one torsion angle active at a time. This is a serious limitation and makes complex modeling very slow and tedious, since one usually wishes to adjust several torsion angles in different structures (or parts of the same structure) simultaneously. There should be simultaneous control of as many torsion angles as possible (e.g., 6–24), where the torsions may involve several residues or even several molecules. Choosing bond rotations should be allowed in both a forward and backward direction along a chain and these should be permitted simultaneously. The system should be capable of handling several molecules simultaneously with independent adjustment of rotations, translations, and torsions of each one, allowing the comparison of different ligands in the binding site or of different fits of the same ligand. Molecular surface displays should associate a set of dots with each atom, so that the dots move together with the atom as the molecule is moved or bonds are rotated. Solvent-accessible molecular surface calculations (37) may require long computational times for macromolecules (minutes to hours) and usually must be precalculated for use in a later interactive modeling session. The system should

support using such a precalculated surface in the current modeling session *even if the molecule associated with the surface has been translated and rotated from its original position* used in the surface calculation. The system should also include the option to rapidly compute van der Waals surfaces (38, 39), which are useful to generate surfaces around small molecules and around small portions of a macromolecule and display these in combination with the solvent-accessible molecular surface.

Additional useful features include the ability to enter new molecules into an ongoing modeling session at any time and to "save" individual molecules at any time. Since the *conformation* of the macromolecule is usually not changed during the initial modeling, it should be necessary to store its updated coordinates along with each saved "docked" ligand. Saving each macromolecule-ligand complex eventually results in confusion due to the accumulation of multiple copies of the same macromolecule coordinate set saved in different orientations relative to the screen. It is much more convenient to store each "docked" ligand conformation in a fixed orientation relative to the initial macromolecule coordinates (some systems provide an automatic facility to do this), so that only one copy of the macromolecule needs to be saved. Finally, a facility to associate arbitrary three-dimensional graphical objects with individual molecules is very useful; such objects might be electrostatic potential maps, molecular orbital plots, and electron density maps. The ability to display a molecular dynamics simulation by animation (rapidly switching from one saved coordinate set to the next) is essential; dynamics simulations produce an enormous amount of data that are difficult to interpret without a graphics display.

For peptides and nucleic acids, the system should provide rapid generation of a model from sequence data in any of the commonly observed conformations (e.g., α -helix, β -sheet, β -turn, B-DNA, Z-DNA). For peptides, it should be possible to make insertions or deletions in the sequence easily and to mutate side chains for homology model-building applications, where the sequence of the unknown structure is mapped onto the three-dimensional structure of a sequentially homologous protein whose structure has previously been determined by X-ray crystallography.

Raster graphics (used in conventional television) is now the dominant technology in interactive molecular modeling. Raster graphics technology has advanced rapidly during the last decade to the point where its price/performance is competitive with the best calligraphic (vector) systems, as demonstrated by the latest high performance workstations. In fact, only one vector display system is still commercially available, the Evans and Sutherland PS390. Vector and dot images (on raster displays) still provide the best approach for interactive molecular modeling due to their ability to provide full transparency and clipping while displaying a complex, color-coded molecular

surface and bonds in real time. These features are essential for studying interactions deep inside a macromolecular binding site (34). Stereoscopic viewing, where the left and right eye views are alternately displayed and viewed either through a mechanical or liquid crystal shutter synchronized to the display, provides a very convincing three-dimensional illusion and is extremely helpful for modeling complex interactions (40). The best currently available stereo display system places a liquid crystal polarizing screen over the graphics scope, allowing the user(s) to wear circularly polarized plastic glasses (40). A variation of this device uses battery-powered liquid crystal glasses that communicate with the monitor via an infrared sensor.

C. Molecular Surfaces

The simultaneous development of real-time interactive color graphics (34) and Connolly's molecular surface program (37) in 1980 revolutionized macromolecular computer graphics modeling. Connolly's original program implemented Richards' definition (41) of the *molecular surface* by rolling a probe sphere (usually a radius of $1.4 \text{ \AA}$, the effective radius of a water molecule) over the surface of the macromolecule (Figure 1), resulting in a smooth surface of dots which represents the surface accessible to a water molecule, including

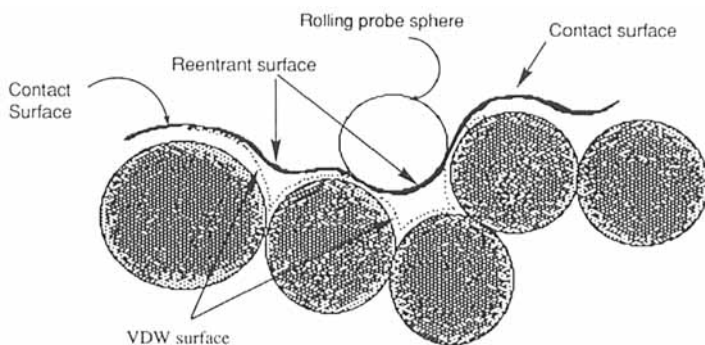


Figure 1. Schematic diagram of a molecular surface as defined by Richards (41) in which a probe sphere (water radius = $1.4 \text{ \AA}$) is "rolled" over the van der Waals (VDW) surface of the protein with dots being generated along the path traveled by the probe sphere. The molecular surface is defined by the inward-facing surface of the probe sphere and consists of two parts—the contact surface and the reentrant surface. When the probe touches a single atom, this is equivalent to the outward-facing VDW surface of that atom, and this surface is defined as the contact surface. The reentrant surface corresponds to the inward-facing surface of the probe when it simultaneously is in contact with more than one atom. The molecular surface then is an approximation of the VDW surface in which the clefts between atoms and interstices too small to accommodate the probe sphere are smoothed over.

internal cavities (see color insert, Figure 2a). Bash et al. (38) and Pearl and Honegger (39) independently developed very fast *van der Waals surface* programs that are several orders of magnitude faster than Connolly's original program. However, they are not as effective at eliminating buried surface (the surface area on each of two atoms in close proximity to each other that is inaccessible to a probe sphere) and produce a more complicated surface display (see color insert, Figure 2b). A combination of molecular and van der Waals surface calculations provides a good compromise. Thus, it is usually more advantageous to calculate the more computationally demanding molecular surface for the macromolecule before the modeling session and to quickly calculate the van der Waals surface for the ligand and any side chains which may be adjusted in the protein during the modeling session.

When surfaces are generated around both a receptor site and a ligand to be docked, it is often difficult to visually determine how well these surfaces match. Barry (42) introduced the very useful concept of "extra radius" surface, which is calculated one van der Waals radius beyond the normal surface, collapsing the surface of the binding site onto the stick model of the ligand and eliminating the need for displaying the ligand's surface. With the receptor site surface at two van der Waals radii away from the site atoms, it is only necessary to fit the stick structure of the ligand onto this surface to obtain a good fit such that the atoms of the ligand and the site are at or beyond the sum of their van der Waals radii. This simple graphics trick makes it much easier to visualize the "docking" of a ligand into a binding site. For example, the specificity of chymotrypsin for aromatic amino acid side chains is not immediately apparent from a conventional molecular surface of its active site, while the "extra radius" surface reveals an almost perfectly planar pocket (see color insert, Figure 2c) which is obviously complementary to an aromatic ring. The "extra radius" surface can also be color-coded according to hydrophobicity or electrostatic potential.

Connolly (43, 44) and Richmond (45) also developed analytical methods for calculating molecular surface area and volume, which provide nearly exact values for the surface area and enclosed volume. Richmond's method provides analytical derivatives for surface area with respect to the cartesian coordinates of the atoms, which may be useful for docking (Section V). Connolly's algorithm also produces spectacular shaded raster graphics images (46), which give a very different "feel" for a macromolecular surface than conventional space-filling displays.

Color-coded molecular surfaces can provide qualitative or quantitative displays of hydrophobic and hydrophilic regions, neutral and charged amino acid side chains, electrostatic potential, and conformational mobility of side chains (based on the temperature factors from X-ray crystallographic refinement or molecular dynamics simulation). Color-coding by hydro-

phobicity and by electrostatic potential is particularly useful in drug design applications, where the goal is to design a molecule that is complementary in shape, hydrophobicity, and charge to a binding site. Hydrophobic color-coding originally colored all surface points associated with carbon "hydrophobic" (e.g., red) and all nitrogen and oxygen surface points "hydrophilic" (e.g., blue); a more detailed approach (47) included "neutral" or "semi hydrophilic" surface (e.g., yellow) for sulfur, α -carbon atoms of amino acids, the carbon between the imidazole nitrogens in histidine, and carbonyl carbon atoms. A recent approach is based on color-coding by "hydrophobic potential" (48), calculated using partial atomic hydrophobicities (49) (analogous to partial atomic charge), and a function similar to the classical coulombic electrostatic interaction. While this approach is not based on a physically meaningful calculation, it appears to provide a qualitatively useful display of relative hydrophobicity and hydrophilicity. Electrostatic potential molecular surfaces (50) are calculated using quantum mechanically derived partial atomic charges for each atom (51, 52). The potential is typically calculated one probe sphere radius above the molecular surface, which should provide a reasonable estimate of what an incoming ligand "sees" as it approaches the macromolecule. The molecular surface is then color-coded according to the value of the electrostatic potential at each point. The electrostatic potential surface for superoxide dismutase (53) is shown in Figure 3 (see color insert). The electrostatic potential gradient can also be displayed graphically, where the gradient at each point on a grid above the molecular surface is displayed as a short vector. This method was used to locate the probable trajectory for superoxide anion as it approaches superoxide dismutase (53). More accurate estimates of electrostatic potential are available in recent methods that directly solve the Poisson-Boltzmann equation (54).

III. X-RAY CRYSTALLOGRAPHIC RECEPTOR STRUCTURE DETERMINATION

The X-ray crystallographic structure of the specific macromolecular receptor is the best starting point for designing a ligand for it. Over 300 X-ray crystal structures of proteins and nucleic acids have now been solved, including several ligand-macromolecule complexes (55); most of these are available in the Brookhaven Protein Data Bank (14). NMR is also now providing the equivalent of medium ($\sim 3 \text{ \AA}$) resolution structures for proteins up to about 100 residues (15-17, 56).

The rate-limiting step in crystallography is still the complicated art of macromolecular purification and crystallization, which may take years of effort to find conditions that produce crystals that diffract X-rays well.

Table 1

Protein	Source	Disease	Target	References
Hemoglobin Phospholipase A ₂	Human Pancreas, venom	Sickle cell anemia Inflammation	Hemoglobin S Intracellular phospholipase A ₂	180, 275-278 210-212, 279-282
Dihydrofolate reductase	Bacteria, chicken	Cancer, bacterial infection	Dihydrofolate reductase	283
Carboxypeptidase A	Bovine, bacteria	Hypertension	Angiotensin converting enzyme	284-287
Thermolysin	Bacteria	Hypertension	Angiotensin converting enzyme	220, 288-291
Aspartyl proteases	Bacteria, human	Hypertension	Renin	83, 84, 292
Elastase	Porcine	Emphysema	Leukocyte elastase	261, 293, 294
Subtilisin	Bacteria	Emphysema	Leukocyte elastase	
α 1-Proteinase inhibitor	Human	Emphysema, thrombosis	α -1-Proteinase anti-thrombin	295
Calmodulin	Rat	Psychosis	Calmodulin	296, 297
Interleukin-1	Human	Immune system	Interleukin-1	298
Interleukin-2	Human	Cancer	Interleukin-2	299
<i>c-H-ras</i> Oncogene protein	Human	Cancer	<i>ras</i> -Oncogene protein	197
Major histocompatibility complex (MHC) protein	Human	Immune system	MHC protein	300
Rhinovirus HRV14	Human	Cold, hepatitis	HRV14	102
Thymidylate synthetase	Bacteria	Cancer	Human thymidylate synthetase	301
Hemagglutinin	Human	Influenza	Hemagglutinin	302
Neuraminidase	Human	Influenza	Neuraminidase	230
RSV protease	Human	AIDS	HIV protease	303
HIV protease	Human	AIDS	HIV protease	304, 305

Fortunately, once a parent macromolecular structure has been solved, new structures of the macromolecule complexed with different ligands can often be solved very quickly (within a few days in some cases (57)). These new structures are determined by cocrystallization of the ligand–macromolecule complex or by soaking protein crystals in a solution of the ligand and allowing the ligand to diffuse into the binding site.

Although relatively few structures of pharmaceutically important enzymes or receptors have been determined (Table 1), the rate of solving these structures has increased steadily during the last few years and will continue to increase due to improvements in crystallographic and NMR methods and the availability of new proteins through recombinant DNA approaches. Unfortunately, the rate of release of the three-dimensional coordinates of newly solved, biologically important macromolecular structures to the Brookhaven Protein Data Bank is decreasing, so much of the potential benefit of X-ray crystallography for drug design is unrealized. This counterproductive situation has recently been reviewed by Richards (58).

Although X-ray crystallography represents a static, time-averaged model of a dynamic structure, crystal structures are often good starting models for the biologically active solution conformations. One reason for this is that the crystals usually have very high solvent content (30–78%) and therefore mimic the solution state quite well (59). It has, in fact, been found experimentally that many enzymes even retain catalytic activity in the crystalline state. If one suspects that a target protein has regions of high mobility, some information about the flexibility of the macromolecule is provided by the crystallographic temperature factors (*B*-values). Surface side chains are frequently very mobile, as indicated by high-temperature factors, so the X-ray positions for these atoms represent a time average. Molecular dynamics simulations (Section VI) can estimate these intramolecular motions, although the observed extent of these motions is limited by the time period over which the dynamics calculations can currently be extended (up to a few hundred picoseconds). For the above reasons and because, in practice, it is extremely difficult to hit a moving target, virtually all design efforts begin with the static X-ray model, although it should be kept in mind that limited conformational changes in the protein are possible.

Accuracy of the molecular models derived from X-ray crystallography depends on both the level of resolution and refinement (60). Refined structures with resolutions at 2.5 Å or higher will typically have uncertainties in atomic coordinates of up to 0.5 Å, although the average uncertainty is only about 0.25 Å. Resolution of 3 Å or poorer will usually be sufficient to trace the path of the peptide backbone but will reveal few details about the side chains and may contain errors. Protein structures solved by NMR currently appear to be comparable to approximately 3 Å resolution X-ray structures.

IV. PROTEIN MODEL BUILDING BY HOMOLOGY

Although the number of protein structures defined at atomic resolution has increased in the last several years from application of improved X-ray crystallographic analysis to large proteins and of two-dimensional NMR techniques to small ones, they represent only a small fraction of the total number of proteins that have been isolated and sequenced. For rational synthetic design of ligands to be successful, information about the target macromolecules is crucial. Recent advances in computer graphics, computational techniques, and database technology have allowed approximate models to be constructed based on analogies between the protein to be modeled and other proteins of known three-dimensional structure.

Protein amino acid sequences are available from the Protein Identification Resource Data Bank at the National Biomedical Research Foundation (61). Any of the several DNA sequence data banks can also be accessed and the gene sequences converted to protein amino acid sequences (62,63). Sequence homology between a target protein and a structurally related one can be determined using sequence alignment algorithms (64–66). Although it is beyond the scope of this chapter to describe in detail the methodology in comparative model building, the general approach is outlined here. First, correct alignment of the sequences of the structurally unknown target and the structurally known protein is essential for success and even minor errors can have serious consequences (67). Once the basic alignment is accomplished, insertions, deletions, and replacement corrections must be made in the known three-dimensional structure to transform it into the target protein. This is a critical step since insertions and deletions often occur in loop regions and these, in turn, are frequently at or near the active sites of interest and thus constitute the focal point of ligand design. The problems of modeling loop regions have been summarized by Blundell et al. (68). One particularly attractive approach to this problem searches a database of well-resolved protein structures to find all possible loops of the correct length using a method based on the distance between the two “end” α carbons of the loop (69). An alternate and effective method in the absence of satisfactory fits from the database search is to use distance geometry (Section VII) coupled with molecular mechanics and/or molecular dynamics (70). Once a satisfactory backbone structure has been obtained, appropriate side chain replacements are constructed using interactive computer graphics, with care being taken to avoid close contacts of adjacent groups. Finding acceptable rotamers of side chains can be aided by the library of rotamers compiled by Ponder and Richards (71). The entire structure is then energy minimized with molecular mechanics programs such as AMBER (72) or CHARMM (73, 74).

A number of homology-built protein models have been constructed,

including models of α -lactalbumin (75–77), relaxins (78,79), insulin-like growth factors (80), serine proteinases (81), HLA-DR antigens (82), aspartic proteinases, for example, renin (83–86), nicotinic acetylcholine receptor (partial model) (87), immunoglobulins (88,89), human-liver alcohol dehydrogenase (90), sorbitol dehydrogenase (91), retinol binding protein (69), dimer of sea lamprey hemoglobin (92), and frog lens β - α 1 crystallin (93). In a particularly interesting approach to the model-building problem, Jones and Thirup (69) showed that a protein can be built up from a small number of large substructures taken from unrelated proteins. The several possible techniques available for model building and the future of this approach have been summarized in a recent review (68).

While molecular mechanics can be useful to clean up bad interactions in homology-built models, care must be taken not to overinterpret the results of such calculations. Novotny et al. (94) constructed two incorrectly folded proteins and showed that energy minimizations gave potential energy values comparable to the correct structures. The analysis of the incorrectly folded structures showed no bad nonbonded contacts, which suggests that their absence is a necessary but not sufficient condition for correct folding. The modelling must be accompanied by a thorough evaluation of additional factors, such as solvent accessible surface, the fraction of nonpolar side chains exposed to solvent, and other experimentally observed packing characteristics of proteins (95).

Although one would prefer the most exact models possible, even approximate models of receptors can be useful in the design of potential ligands and inhibitors. Problematic fits of proposed inhibitors can often be recognized and eliminated and reasonable candidate structures can be suggested. Because of the approximate nature of a homology-built model, the ligand “fits” will be less precise and less reliable than in those cases where an actual X-ray structure of the enzyme or enzyme–inhibitor complex is available. Rather than immediately attempting to design novel ligands for these crude models, one might take the intermediate step of proposing binding modes of linear peptide substrates or inhibitors that are known to bind to these proteins. These fits may then suggest more rigid cyclic structures which would be entropically favored over the more flexible linear peptide ligands and these, in turn, may be useful in suggesting nonpeptide mimics. Sham et al. (96) used this approach to design inhibitors of renin. They first constructed a model of the target protein based on the amino acid sequence of renin and the known three-dimensional structures of three, structurally related, fungal enzymes and a related mammalian porcine pepsin. The resulting model was used to propose the binding mode of a known linear hexapeptide inhibitor which had been synthesized from the hexapeptide substrate for this enzyme by substituting a reduced amide for the scissile bond at the peptide’s cleavage site. Several

conformationally constrained cyclic peptide inhibitors were designed to fit the active site model based on suggested cyclized versions of the bound linear peptide inhibitor, such that the preferred bound conformation of this linear peptide was not altered. Modeling was also used to explain the lack of potency of a 10-membered ring compound; its lack of activity was traced to a *cis*-peptide bond that forced the 10-membered ring into a conformation unacceptable for binding.

V. DOCKING SMALL MOLECULES WITH MACROMOLECULES

The "docking problem" is the positioning of a target macromolecule and a ligand so that one is a geometric and electrostatic complement of the other and there is a favorable interaction energy between them. Docking is typically done interactively with molecular surface displays (e.g., "extra radius" surface) and color coding based on hydrophobic or electrostatic potential used to guide the fit. The binding site of the protein is initially treated as being completely rigid, while the conformation of the ligand is adjusted interactively.

Physically impossible models of molecular complexes are easily built with current systems, which allow molecules to collide and pass through each other; the visual cues provided by molecular surface displays are essential for realistic modeling to avoid "close contact" problems. Some current hardware is fast enough to calculate molecular mechanics energies in real time during docking and use this information to provide feedback, thus preventing collisions or high-energy conformations. A method for real-time docking using graphics and high-speed calculations of the interaction energies between a ligand and a receptor site was developed by Pattabiraman et al. (97). A three-dimensional grid enclosing the receptor site is built prior to the docking and the van der Waals and electrostatic energies, in the absence of ligand, are calculated at each grid point. As the ligand is moved within the receptor site, the interaction energy between the ligand atoms and the grid points is calculated and updated in real time. This approach requires a close grid spacing (0.25–0.50 Å), which in turn requires substantial computer memory to store the precalculated energy grid map. The much faster workstations available today can usually perform the docking calculation without resorting to this approximate grid technique.

Evans and Sutherland developed an energy coprocessor board for their PS3000 graphics system to provide real-time docking energetics (98). This coprocessor rapidly computes the pairwise steric and electrostatic interaction energies between receptor and ligand on the fly as the ligand is moved. The coprocessor handles approximately 250,000 atom pairs/s and displays the

results both visually (as color-coded vectors between interacting atoms) and as a numerical range of energies. The latest generation of graphics workstations from Silicon Graphics, Stellar, and Ardent are beginning to approach the speed of this coprocessor for this application.

Swanson and Blaney (99) developed a simple approach to provide "tactile" feedback using the instantaneous numerical derivative of the total interaction energy with respect to the translational or rotational degree of freedom being adjusted. The derivative is used to scale the responsiveness of a dial (or analogous device) so that the dial becomes less responsive as the derivative increases (more turns are required to move a fixed amount) and more responsive as the derivative decreases. The user perceives the decreased sensitivity of the dial with increasing energy as resistance, without the need for actual, physical force-feedback. This technique encourages motions that lead to improved interaction energy by increasing responsiveness and accelerating the motion, in a sort of interactive energy minimization: the molecular models follow the path of least resistance as the user adjusts them.

It is possible to minimize the energy of a ligand-macromolecule interaction very rapidly (< 30 s) by treating the ligand as a rigid body with respect to translation and rotation and docking it into a fixed macromolecule (100). To optimize the initial fits of the ligand, interactive docking typically alternates between continuous motion, possibly with real-time updates of the interaction energy, and periodic cycles of simple rigid body (plus selected torsion angle) energy minimization. Future modeling systems should be fast enough to perform this minimization with a completely flexible ligand (and possibly a flexible protein) in close to real time. Finally, energy minimization of the entire complex, where all atoms are allowed to relax (which requires large amounts of computer time and cannot be performed interactively with current systems), provides a good indication of the plausibility of the model and a rough estimate of the relative interaction enthalpy of the candidate ligand. This provides only a crude estimate of the enthalpy—not free energy—of interaction.

Solvation energy is often critical in determining the free energy of binding; specific inclusion of solvation effects is, however, orders of magnitude beyond what is now possible with interactive modeling. Without explicitly including solvent, ionic interactions and hydrogen bond energies are overestimated in the typical gas-phase molecular mechanics calculation, even when "corrected" by using reduced partial atomic charges or a distance-dependent dielectric constant. This is due to the omission of solvent hydrogen bonding competition; these effects are treated properly in the free-energy perturbation theory method (Section VI). A distance-dependent dielectric constant is often used for calculations that do not explicitly include solvent. In these cases, the dielectric

constant is set proportional to the interatomic distance (24). Alternatively, the partial atomic charges on atoms bearing formal charges are reduced to attempt to compensate for the lack of counterions or solvent in simulations.

Multiple binding modes have been observed experimentally, as illustrated by the X-ray structure of the elastase acetyl-Ala-Pro-Ala complex in which the ligand, the product from the elastase-catalyzed hydrolysis of acetyl-Ala-Pro-Ala-*p*-nitroanilide, is flipped end for end and binds backward relative to the productive binding mode required for hydrolysis (101). "Wrong-way" binding has also been observed in a series of antiviral compounds bound to human rhinovirus, where closely related analogs bind in the same site but in opposite orientations (102). In evaluating the fit of a proposed ligand, it is important to consider all possible modes of binding, a factor that becomes important when correlating experimental binding data of analogs with the modeled fit. Almost all quantitative structure-activity relationship (QSAR) approaches require that each ligand bind in the same way as the parent compound of the series.

It is very difficult with interactive methods to find the most likely binding modes, due to the many degrees of freedom (rigid body motion of the ligand, plus bond rotations) involved in docking the ligand to the receptor site. Naruto et al. (103) used a systematic search procedure to find potential chymotrypsin tetrahedral intermediate conformers with a conformational search around the covalent bond linking the ligand with the site in the acyl enzyme alkylation complex and Wodak et al. (104) used a similar approach to find the most favorable conformation of the glutathione-cysteine in glutathionyl hemoglobin. Kuntz et al. (19) developed a more general docking method for rigid ligands based on a fast sphere-matching algorithm; the approach was recently extended to flexible ligands (with only a few rotatable bonds) by docking each rigid fragment (fragments between rotatable bonds) of the ligand independently (105).

In a more specialized case, Horjales and Branden (90) determined a preferred orientation of cyclohexanol in the active site of liver alcohol dehydrogenase for what was believed to be a productive enzyme-substrate complex. By using the positions of the atoms of the bound cyclohexanol ring as a starting point, an extended diamond lattice was constructed to fill the available space in the enzyme site. Each of the lattice points could then be examined to determine the steric possibility of placing an atom at that position. This framework could then be used to design and dock additional structures.

Connolly developed a computational technique for docking two protein structures based on matching complementary patterns of knobs and holes (106). The algorithm was used to predict the association of the α and β subunits of hemoglobin to form the correct α - β dimer.

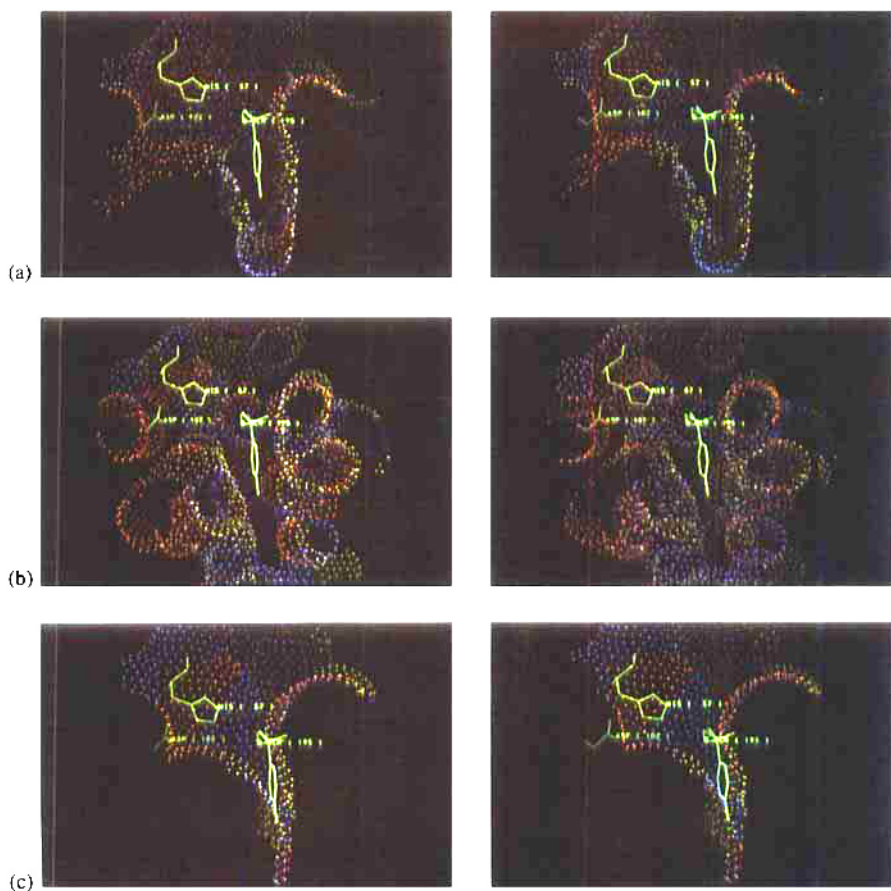


Figure 2. Molecular (a), van der Waals (b), and 'extra radius' (c) surfaces of chymotrypsin-tosyl inhibitor complex. The surface is color-coded by hydrophobicity as described in the text: red = hydrophobic, blue = hydrophilic, neutral = yellow. The tosyl group is covalently attached to the sidechain hydroxyl of Ser-195. The 'catalytic triad' of His-57, Asp-102, and Ser-195 is shown in green. (The coordinates for this and all other molecules in the following figures are from the Brookhaven Protein Data Bank (14) except where otherwise noted.)

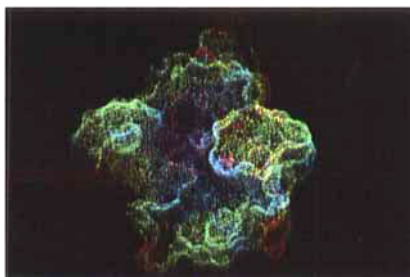


Figure 3. Cu, Zn superoxide dismutase – electrostatic potential mapped onto the enzyme's molecular surface to show the highly positive potential around the active site channel (53). The dots are color-coded by electrostatic potential: red, < -21 kcal/mol; yellow, -21 to -7 kcal/mol; green, -7 to $+7$ kcal/mol; cyan, $+7$ to 21 kcal/mol; blue, > 21 kcal/mol. The bound copper ion is shown by the purple sphere.

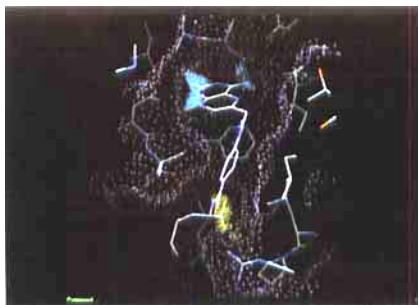


Figure 8. Probe map of *E. coli* dihydrofolate reductase-methotrexate (10) complex. The calculated minimum energy positions for an ammonium probe (blue) and carboxylate oxygen probe (yellow) closely match the experimental positions for the pteridine amino groups and the carboxyl of methotrexate (20, 21). The molecular surface of the enzyme is purple, while all bonds are color-coded by atom type: carbon = white, nitrogen = blue, oxygen = red, sulfur = yellow.

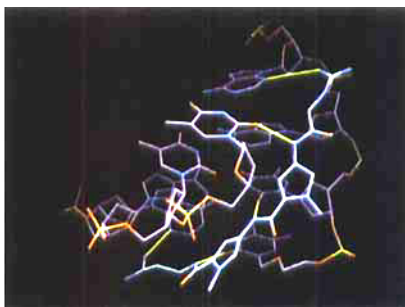
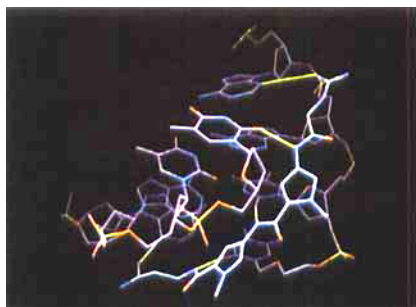


Figure 10. Netropsin (1) bound to the minor groove of DNA. Hydrogen bonds are shown in yellow, while bonds are color-coded by atom type: netropsin carbon = white, DNA carbon = purple, nitrogen = blue, oxygen = red, phosphorus = yellow.

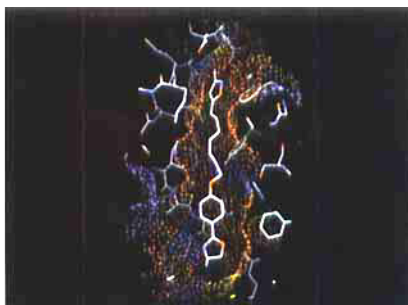
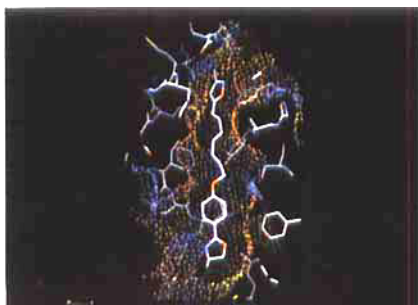


Figure 11. Human rhinovirus 14 complexed with antiviral compound WIN 52084 (2c). The molecular surface of the protein binding site is color-coded by hydrophobicity as in Figure 2 and the bonds are color-coded by atom type: carbon = white, nitrogen = blue, oxygen = red, sulfur = yellow.

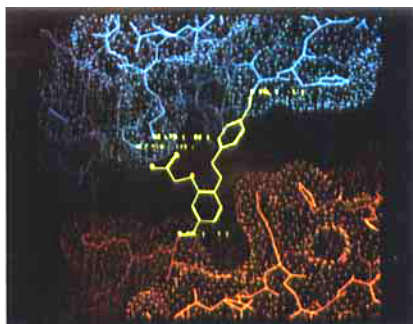
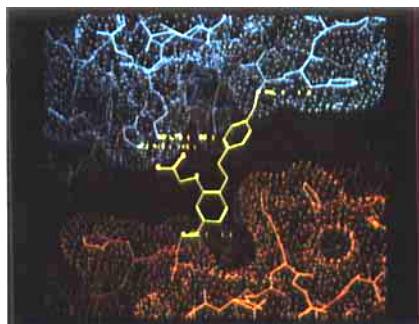


Figure 13. β -1 and β -2 subunits of human deoxyhemoglobin with a model for the binding of bibenzyl-4,4'-dialdehyde (**4**, yellow) through Schiff base formation with the amino termini of each subunit (179).

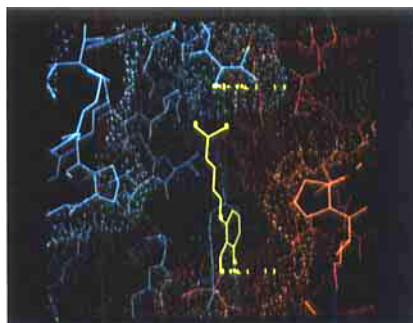
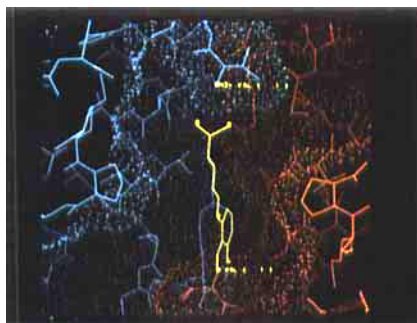


Figure 14. α -1 and α -2 subunits of human oxyhemoglobin with model for 5-(2-formyl-3-hydroxyphenoxypentanoic acid (**5**, yellow) forming a Schiff base with the α -1-amino terminus and a salt bridge with the α -2 amino terminus (180).

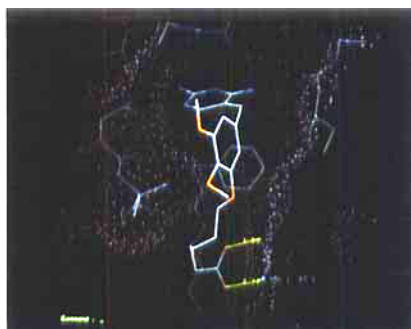
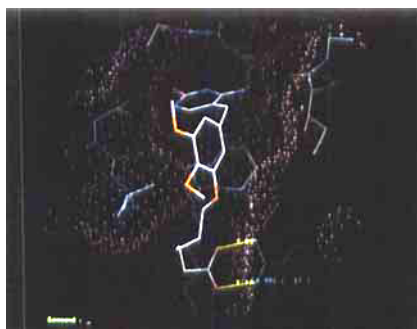


Figure 21. Model of *E. coli* dihydrofolate reductase complex with 3'-carboxyalkoxytrimethoprim analog (**11b**), shown interacting with Arg-57 (208). The same orientation and color-coding are used as in Figure 8.

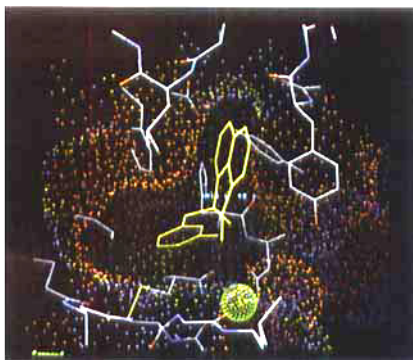
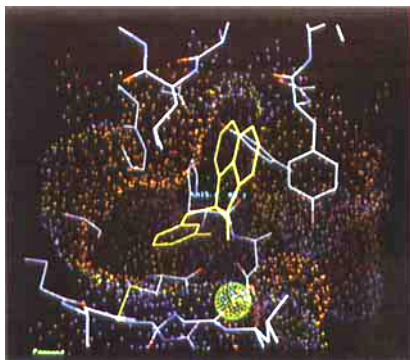


Figure 25. Bovine phospholipase A₂ with model of benzylacenaphthene (**12**, yellow) binding. The active site molecular surface is color-coded by hydrophobicity as in Figure 2 and the bonds for the enzyme are color-coded by atom type as in Figure 8. The bound Ca⁺⁺ ion is shown by the green sphere.

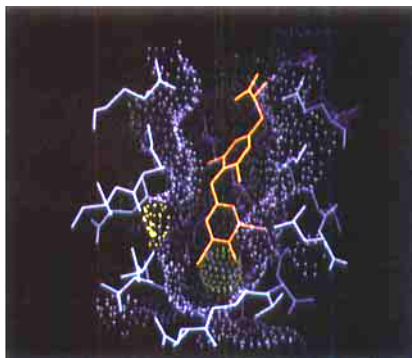
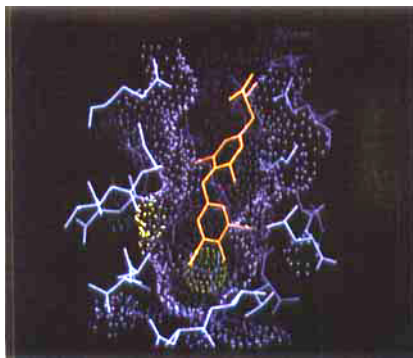


Figure 26. Prealbumin (blue) complexed with L-thyroxine (**14a**, red). The empty binding pocket is highlighted in yellow and a bound water molecule is shown in green.

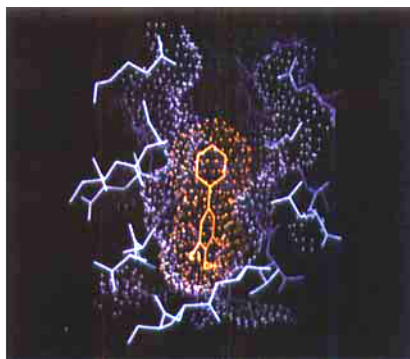
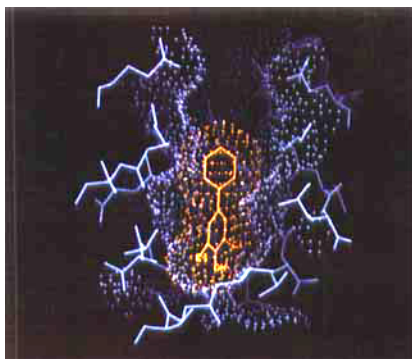


Figure 27. Prealbumin (blue) with model for binding of 3,5-dichloro-4-hydroxybiphenyl (**21**, red).

VI. ENERGY CALCULATIONS

Empirical force field methods are typically used for calculating intramolecular and intermolecular energies in macromolecules and ligand-macromolecule complexes. These methods include molecular mechanics energy minimization, in which an initial model is iteratively adjusted until its energy reaches a minimum value, molecular dynamics, which simulates the motion of the model as a function of time and temperature, and the recently introduced free-energy perturbation method, which can calculate realistic free energies for ligand-macromolecule binding.

A. Molecular Mechanics

Molecular mechanics (107-109) treats the molecular structure as a set of balls (atoms) and springs (bonds) with a potential energy function expressing the energy of the molecule. A typical energy equation is

$$E_{\text{total}} = E_{\text{stretching}} + E_{\text{bending}} + E_{\text{dihedral}} + E_{\text{van der Waals}} \\ + E_{\text{electrostatic}} + E_{\text{hydrogen bond}}$$

Each of the individual energy terms have preferred equilibrium positions (bond lengths, bond angles, dihedral angles, van der Waals interaction distances, etc.) and force constants, which are either experimentally known or theoretically estimated and used to associate energetic penalties with each individual deviation. The molecular mechanics force field consists of a set of analytical energy functions and their associated sets of numerical parameters. The electrostatic component of the energy requires the assignment of bond dipoles (108) or partial atomic charges (51, 52) to each atom, usually calculated using quantum mechanical methods.

A broadly parameterized molecular mechanics force field is necessary to handle the wide variety of atoms, bonds, bond angles, and torsion angles which occur in small organic molecules. Force field development is a tedious problem for the large variety of complex functional groups encountered in organic chemistry, each of which requires its own set of parameters. This is further complicated by the fact that not all force fields are readily transferable from one energy function to another. Force fields fall into two major categories: "united-atom" force fields implicitly include all non-hydrogen-bonding hydrogens by slightly increasing the effective size of the parent atom to which the hydrogen(s) are bonded, while "all-atom" force fields explicitly include all hydrogens. United-atom force fields are commonly used for macromolecular calculations to reduce the amount of computer time required (computer time increases with the square of the number of atoms). The best

tested force fields are MM2 (108) (all-atom; hydrocarbons plus a limited selection of simple heteroatom functional groups), AMBER (72,110,111) (united-atom; peptides and nucleic acids), and CHARMM (73) (united-atom; peptides and nucleic acids). Hybrid force fields, such as the AMBER all-atom force field (111), are usually used for calculations involving small molecule-macromolecule interactions. Molecules that contain functional groups not parameterized by the above force fields require the estimation of new parameters specific for each new bond, bond angle, or dihedral angle type (112). Features in the software which facilitate generating parameters for new functional groups are essential. Most of the major modeling systems provide facilities for automatically assigning the appropriate atom types and parameters, but there is considerable variation in the quality and quantity of the parameters available. It is always prudent to calibrate unfamiliar software with some well-known test cases.

Assuming that all the necessary parameters are available for a given molecule, relative total strain energies can be calculated for estimating rotation or inversion barriers, preferred conformations, the energy required to achieve a specific conformation, and so on. Except for special cases (e.g., estimating the enthalpy of formation of a hydrocarbon), the absolute calculated energy is of little value: *relative* energies between different conformers or isomers are important. The texts by Buckert and Allinger (108) and Clark (113) provide an excellent description of molecular mechanics and its applications.

Molecular mechanics energy minimization involves successive iterative computations, where an initial conformation is submitted to full geometry optimization. All parameters (e.g., the *X*, *Y*, and *Z* coordinates for each atom) defining the geometry of the system are modified by small increments until the overall structural energy reaches a local minimum. No minimization method guarantees finding the absolute lowest energy structure – the global minimum. Energy minimization stops at the first local minimum encountered, without realizing that much deeper, more stable minima may be accessible. The problem is analogous to a ball rolling downhill, which stops in the first valley it finds but is unable to roll over the next hill, which may lead to a deeper valley. Molecular dynamics is able to jump over small barriers (the barrier height depends on the temperature of the dynamics simulation) and is therefore much more efficient at locating deep local minima than simple minimization; short dynamics runs are now commonly used for minimization.

B. Molecular Dynamics

Molecular dynamics (114,115) simulations have had a major impact on changing the way we view molecular structures. X-ray crystal structures

represent a time-averaged structure of a continuously moving system, while molecular dynamics simulates the actual, instantaneous motion of the system. Each atom is treated as a particle responding to Newton's equations of motion, with forces calculated using the same molecular mechanics potential energy function described previously: successive integrations of these equations lead to the trajectory of the atom over time in the form of a list of positions and velocities. Analyses are made through periods of typically 1–100 ps. The calculations require considerable computational resources as well as graphics animation facilities. Animation consists of the viewing of consecutive conformations generated by molecular dynamics calculations. Animated display of molecular dynamics simulations is essential; dynamics simulations produce huge amounts of data, which are difficult to interpret without graphics.

Molecular dynamics is useful in order to identify preferred motions, to locate conformational fluctuations within a binding site that may affect ligand binding, and as an improved energy minimization approach. Restrained molecular dynamics (116) adds an artificial penalty function to restrain specific distances, angles, or dihedral angles. Restrained molecular dynamics and distance geometry (117, 118) followed by restrained dynamics have been used to generate three-dimensional structures of small molecules, proteins, and nucleic acids consistent with NMR data (15).

Conventional energy minimizations with a flexible protein or protein–ligand complex are easily trapped in local minima and thus can give deceptive results; in fact, energy minimizations in these cases rarely produce structures that are significantly different from the starting coordinates. Molecular dynamics simulations over short time spans (5–10 ps) are much better at escaping local minima and can give much lower energy structures; a good strategy is to begin with a short dynamics run and follow it with a complete energy minimization. Such short dynamics simulations provide no meaningful information about the actual motions of the structure but they do provide a more efficient method of energy minimization and a good indication of the stability of the model. Poor models tend to fly apart very quickly.

C. Free-Energy Perturbation Methods

A major problem with all design approaches is our current lack of ability to calculate even a qualitatively accurate estimate of the free energy of binding between two molecules in aqueous solution. An important advance in modeling ligand–receptor interactions is the recent application of free-energy perturbation methods. This approach calculates $\Delta(\Delta G)$, the difference in the free energy of binding of two closely related ligands to a binding site (119). The method takes advantage of the properties of a thermodynamic cycle to

simulate a physical process that is very difficult to calculate: the transfer of a ligand, **A**, from solution into a binding site, compared with the transfer of a closely related analog, **B**. It accomplishes this by calculating a thermodynamically equivalent nonphysical process: the "mutation" of ligand **A** into analog **B**, performed both in solution and in the binding site. This "mutation" is carried out by gradually changing the parameters of the initial ligand, **A**, to the parameters of the final ligand, **B**, during a molecular dynamics simulation. Molecular dynamics generates a statistical mechanical ensemble average at each point along the simulation as the properties of the initial molecule are varied. This is performed once in "solution," usually in a box of several hundred water molecules, and again in the macromolecule. The simulation starts with 100% initial ligand (**A**) properties and ends with 100% final ligand (**B**) properties; intermediate steps in the simulation have physically nonmeaningful hybrid ligand molecules (Figure 4). These simulations require large amounts of supercomputer time ($\frac{1}{2}$ –1 day on a CRAY supercomputer).

Wong and McCammon (120) described the calculation of the free-energy difference of binding benzamidine versus para-fluorobenzamidine to trypsin, while Bash et al. (121) reported calculations on free energy of binding differences for several thermolysin inhibitors and for a single thermolysin inhibitor to different mutant thermolysins. Merz and Kollman (122) recently

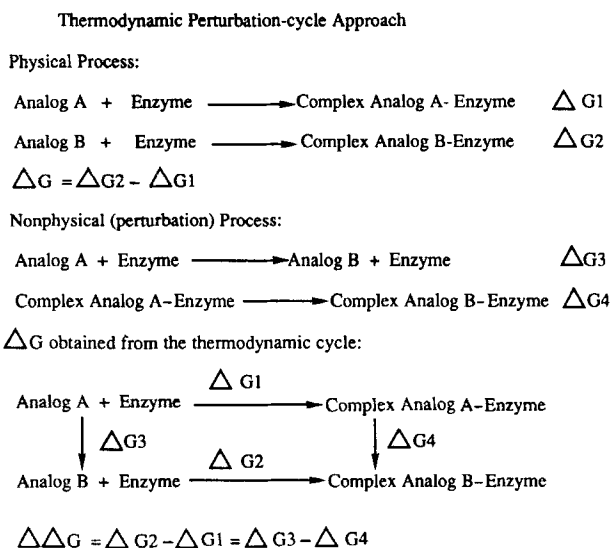


Figure 4. Free-energy perturbation cycle for determining relative free energy of ligand binding.

demonstrated the predictive ability of the approach by estimating the $\Delta(\Delta G)$ of thermolysin binding to a new inhibitor (Section IX.H).

It is not clear yet how large a structural difference between molecules can be simulated. All ligand-receptor simulations so far have involved conservative replacements, although Singh et al. (123) found excellent results with changes in entire amino acid side chains for calculating differences in solvation free energy.

Free-energy perturbation calculations offer the exciting prospect of calculating accurate differences in binding free energies between related ligands, which could make it possible to predict the binding affinity of new compounds prior to synthesis. However, recent work (124, 125) has pointed out that it is extremely difficult to verify when a simulation has converged and has shown that some of the early reports were overly optimistic and tended to overestimate the precision with which $\Delta(\Delta G)$ was calculated. It is now clear that much additional basic research is necessary before the method can routinely be applied and yield quantitatively reliable results. Current results suggest that $\Delta(\Delta G)$ for ligand-macromolecule binding can be calculated to within ± 1.5 – 2 kcal/mol (equivalent to about a factor of 10–30 in binding affinity). Van Gunsteren (124) and Pearlman and Kollman (125) recently reviewed problems and pitfalls of the approach.

VII. DISTANCE GEOMETRY AS A MODELING TOOL

Distance geometry (126) is a general method for converting a set of interatomic distance ranges into three-dimensional cartesian coordinates consistent with these ranges. In distance geometry, a molecular structure is described by the set of all pairwise interatomic distances. Since there are $(N^2 - N)/2$ distances for a structure with N atoms, at first the distance geometry representation seems wasteful compared to the typical cartesian (X, Y, Z) or internal coordinate (bond length, bond angle, dihedral angle) representations, which require only $3N$ coordinates to completely describe the structure. Cartesian and internal coordinates have been used historically primarily for mathematical convenience; for many modeling applications a distance representation is often simpler, since chemical structure information is most often described by distances. Intermolecular and intramolecular contacts are easily described by distances (hydrogen bond lengths, van der Waals contact, experimentally determined distances from NOESY spectra, fluorescence energy transfer, etc.) so that the distance representation can be used directly to specify all the known information about a molecular structure. The application of distance geometry to protein structure determination from NMR data has been reviewed recently (16). Angular information can also be converted

simply into distances, although few experimental methods provide angular data (the Karplus equation (127, 128) relating NMR coupling constants to dihedral angles is the most widely known).

The distance matrix provides an especially concise way of describing the *complete* conformation space of a molecule by entering the maximum possible distance (upper bound) between each atom pair in the upper diagonal and the minimum possible distance (lower bound) in the lower diagonal. All possible conformers therefore must lie between these upper and lower distance bounds: the task of distance geometry is to convert this imprecise distance information into accurate three-dimensional cartesian coordinates. Crippen and Havel (129) solved the problem for the case of an exact distance matrix, where actual distances are known. Much additional research effort has gone into finding efficient and practical methods for solving the general problem of an imprecise distance matrix; this still remains a very difficult problem for large molecule (> 1000 atoms).

A. Methodology

Distance geometry programs (31, 117, 118, 130–132) require the covalent structure of the molecule (connectivity plus atom types), bond lengths, and bond angles. The distance matrix is initially filled in by entering the upper and lower bounds for bonded atoms; the upper and lower bounds are set equal to the bond length. For atoms A and C, which form a bond angle A–B–C, the upper and lower bounds are set equal to the A–C distance. For atoms A and D connected by a rotatable bond B–C, the lower bound is set to the A–D distance measured when the dihedral angle A–B–C–D is 0° (some programs choose 60° depending on the surrounding environment of the dihedral angle to avoid high-energy eclipsed conformers) and the upper bound is set to the A–D distance measured when the dihedral angle is 180° . For non rotatable bonds (aromatic, alkene, amide, etc.), the A–D upper and lower bounds are both set equal to the 0° or 180° distance depending on whether A and D are cis or trans, respectively. Atoms separated by more than three bonds have lower bounds set equal to the sum of their van der Waals radii (or hydrogen bonding distance if the atom pair is capable of hydrogen bonding) and the upper bound set to the distance corresponding to the maximum length of a fully extended chain between these atoms.

The distance matrix of upper and lower bounds now describes the complete conformation space of the molecule but unfortunately cannot describe its chirality, since the distance matrix is invariant with respect to chirality. Chiral constraints are added to supply this missing information; a chiral constraint is specified as the signed volume of the tetrahedron formed by the four substituents attached to a chiral center. The volume is calculated as a vector

cross product and therefore can be positive or negative; a stereo center with the R configuration will have the same volume as the corresponding center with the S configuration but will have the opposite sign. Chiral constraints are also used to help maintain planarity of planar groups by constraining groups of four atoms to have zero volume.

All the distance and chiral constraints can be assigned automatically by the distance geometry program directly from connectivity, atom type, bond length, and bond angle data (132). Additional distance and chiral constraints can also be assigned by the user to generate specific conformations or intermolecular interactions (several molecules at a time can also be entered into a distance matrix).

Distances for each atom pair are randomly chosen between their lower and upper bounds. These distances are then converted into three-dimensional coordinates and refined against a simple error function made up of contributions from upper and lower bound violations and chiral constraint violations to ensure that the structure meets all distance and chiral constraints. The details of converting the distance matrix to three-dimensional coordinates are beyond the scope of this chapter but are provided in Crippen's text (126) and in an upcoming review article (133).

B. Generation of Conformations

Three-dimensional coordinates for small molecules are obtained from X-ray crystallography (33) in favorable cases but otherwise must be generated by a model-building approach. The simplicity of entering a structure as a simple two-dimensional sketch has made this a popular method, but classical energy minimization methods often encounter great difficulty converting the initial two-dimensional structure into a reasonable low-energy three-dimensional conformation and tend to get stuck in local minima. Distance geometry provides an elegant solution to this problem by generating upper and lower bound distance constraints from the two-dimensional structure using standard bond lengths and angles and then directly generating an approximate three-dimensional starting conformation, which provides a much better starting point for energy minimization (31). For most classes of structure it now appears that the approach used by CONCORD (27) is more efficient and provides higher quality results than distance geometry or alternative molecular mechanics approaches for converting a two-dimensional sketch to a reasonable three-dimensional conformation. However, CONCORD will generate only a single conformer, while distance geometry can be used to quickly generate a random sampling of conformation space.

Systematic search (134, 135), which increments all rotatable bonds in turn

to explore the complete conformation space of the molecule, distance geometry, and other random sampling approaches (136) attempt to locate the global minimum through complete exploration of the allowed conformations, while the ellipsoid method (137, 138) and an extension of distance geometry called energy embedding (139) can accomplish near global optimization in some cases.

Distance geometry produces a random sampling of conformation space. This approach samples conformation space rapidly but cannot guarantee that all conformation space has been searched. Systematic torsion search methods can in theory promise that all conformation space is adequately searched, but the completeness of the search is in practice limited by the angle increment used in the torsion scan. The time required for a systematic search increases exponentially with each additional rotatable bond and becomes impractical beyond 12–13 rotatable bonds. The time required for distance geometry is independent of the number of rotatable bonds and depends only on the total number of atoms; distance geometry has approximately an N^2 time dependence on the number of atoms (N) and therefore is still practical for large structures that are beyond the reach of systematic search methods. Distance geometry has also been shown to be competitive in both time and completeness with systematic search methods for small molecules (32, 140). Cyclic structures are handled naturally by distance geometry with no decrease in efficiency, but systematic search methods must deal with the ring closure problem, which further limits their efficiency and range. Both methods require molecular mechanics calculations to calculate the energy of each generated conformation.

Random sampling of distances does not ensure efficient energetic sampling of conformation space. Consider *n*-hexane as a simple example: the 1–4 distance lower bounds correspond to a gauche conformation and the upper bounds to an anti conformation, so that random sampling within this range will seldom select the anti conformer since it is at one extreme of the sampling range. The global minimum energy, all-anti conformer is sampled infrequently since all three 1–4's must be simultaneously selected anti. Therefore, it is clear that distance geometry does not preferentially sample low-energy conformers and that many random structures may need to be generated for one to be confident of locating preferred, minimum energy conformations. The problem remains of how to determine how many random structures must be generated for a given structure. While there can be no definite answer, cluster analysis methods (141) are helpful for classifying the conformers into unique families and determining when no additional unique families appear, which is a reasonable indication (but not a guarantee) that sampling is complete.

Weiner et al. (32) have described the application of distance geometry to the conformational analysis of cyclooctane, cyclododecane, 18-crown-6, and

androstanedione. For cyclooctane, they generated the major low-energy conformers with only 30 random trials and found that these structures tended to be very close to local energy minima, requiring few iterations of molecular mechanics for convergence. Distance geometry located a cyclododecane conformer that refined to a structure 0.1 kcal/mol lower in energy than the previously determined global minimum. For the crown ether, 18-crown-6, Weiner et al. (32) found a previously unidentified low-energy conformer within 0.7 kcal/mol of the global minimum.

Blaney and Ripka (140) studied the sampling behavior of distance geometry on *n*-hexane, cyclooctane, and cyclodecane to estimate how many random trials are necessary for complete sampling of all low-energy conformers (within about 3 kcal/mol of the global minimum) for these simple structures. Distance geometry (132) found *n*-hexane's global minimum four times out of 100 randomly generated conformations, seven out of 100 for cyclooctane, and two out of 100 for cyclodecane. The remaining eleven *n*-hexane and three cyclooctane conformers were found within 100 tries, while cyclodecane required 200 tries to locate all 15 minima (although the global minimum plus the next eight local minima were found within the first 100 tries). The distance geometry sampling for cyclooctane is fairly typical:

Conformer	Frequency	Relative MM2 energy
1	7/100	0.0 kcal/mol
2	5/100	0.8
3	15/100	1.5
4	73/100	3.1

The efficiency of distance geometry in conformational analysis is close to that of a systematic search in these small "test case" problems. In larger structures with more torsional freedom, distance geometry will probably visit the global and nearby local minima less frequently than in these small structures but should still give reasonable sampling statistics. Due to the approximately quadratic time dependence of distance geometry versus the exponential time dependence of systematic search, distance geometry can be used on structures that are far too large (142) for systematic search. Chang et al. (136) recently described a new Monte Carlo (random) torsion search method which appears to be one of the most efficient approaches for small molecule conformational analysis.

C. Energy Embedding

Conventional energy minimization approaches all suffer from the "local minimum" problem, since all known nonlinear minimization methods are

locally rather than globally convergent. For a flexible molecule this means that energy minimization can only be expected to clean up bond lengths and angles and then fall into the closest local minimum, usually resulting in a structure very similar to the original. The most popular approaches to date for circumventing this problem are exhaustive (systematic), random (e.g., distance geometry), or energetically biased (molecular dynamics and Monte Carlo) sampling of conformation space. Molecular dynamics and Monte Carlo simulations have frequently been used with apparent success to locate global minima for molecules up to the size of small peptides (5–10 residues). None of these approaches is likely to be of practical value for molecules much larger than this in the absence of other information which can be used to constrain the conformational search (e.g., NOE distance constraints).

Crippen (143) proposed energy embedding in 1982 as an alternate approach to finding the global minimum or relatively low-energy minima, based on reducing the number of local minima by increasing the number of dimensions. The general idea is that the “hills” and “valleys” of the potential surface are smoothed out as the system moves from three- into higher-dimensional space. For example, a triangle with vertices labeled 1,2,3 in a clockwise direction cannot be converted into the corresponding triangle with vertices labeled 3,2,1 if the triangle is constrained to lie in a plane (this is the two-dimensional equivalent of chirality). Adding a third dimension allows the triangle to move out of the plane, flip over, and move back into the plane. Energy embedding takes advantage of the smoother potential surface in the high-dimensional space to locate a deep or global minimum in this space and then chooses the projection into three-dimensional space, which keeps the energy at a minimum. Since a typical molecular mechanics potential function consists solely of pairwise interactions for N atoms, the global minimum in $N - 1$ dimensions is found by simply setting each interatomic distance to its minimum energy value. This $N - 1$ dimensional structure is then gradually compressed into three dimensions while keeping the energy at a minimum.

Few practical examples of energy embedding have been described to date. Crippen (139) showed that the five major local minima for *N*-acetyl-L-alanine-*N'*-methylamide all refine to the same high-dimensional minimum energy structure, which in turn refines uniquely to the three-dimensional global energy minimum. Purisima and Scheraga (144) used a similar approach to locate the apparent global energy minimum for the opiate pentapeptide Met-enkephalin.

D. Generation of Constrained Conformations

Distance geometry can be used as a general model-building tool, as illustrated by O'Neil and DeGrado (70) in their attempt at predicting the structure of

calmodulin based on the homologous sequences and X-ray structures of intestinal calcium-binding (ICB) protein and carp parvalbumin. The calmodulin sequence had two insertions in one of the ICB loops. Interactive modeling of this 14-residue loop so as to simultaneously bind the calcium with the proper geometry and fit the protein proved to be hopeless and was abandoned. Distance geometry was used to generate models for the loop by constraining the ends of the loop to the ICB X-ray coordinates, forcing the side chains of four polar residues and a main chain carbonyl to interact with the calcium cation in a geometry identical to that from the second ICB loop, maintaining octahedral coordination about the calcium and allowing the remainder of the loop to remain flexible. Ten unique loop conformers that satisfied the constraints were identified from 30 random trials; these 10 structures were energy refined with molecular mechanics. Only one of the refined conformers had reasonable contacts with the rest of the calmodulin model when reinserted back into the complete protein structure. Complex modeling of this sort with many rotatable bonds, which must be adjusted in a concerted fashion in order to make several specific interactions, can be nearly impossible to achieve by hand but is often simple with distance geometry.

E. Ensemble Distance Geometry

Another useful distance geometry model-building application is the elegant "ensemble" approach of Sheridan et al. (145), where multiple molecules are entered into a single distance bounds matrix. *Intramolecular* distance constraints are set as described in Section VII.A and *intermolecular* distance constraints are entered to force specific intermolecular interactions to occur, for example, to superimpose a set of molecules using common functional groups. This approach is described in more detail in Section X.B on pharmacophore modeling.

VIII. BINDING FORCES CRITICAL FOR SYNTHETIC DESIGN OF LIGANDS

Much of the early understanding of protein structures came from extrapolation of rules derived from analysis of small molecules to larger ones. Pauling et al. (146) used information from the crystal structures of individual amino acids and some dipeptides to arrive at the probable hydrogen bonding patterns in proteins, particularly those giving rise to α -helices and β -sheets. With several macromolecular structures now available, it is desirable to reverse this process and use information from protein crystallography to

assess how residues pack, how proteins bind ligands, cofactors, and metals, and to suggest the design of other molecules that might bind to these proteins.

The major interactions involved in drug receptor binding are electrostatic (including hydrogen bonding), dispersion or van der Waals forces, and hydrophobic interactions (147, 148). Hydrophobic interactions usually provide the major driving force for binding, while hydrogen bonding and electrostatic interactions mainly promote specificity and often add little to the free energy of binding in solution (149). Ligand-macromolecule binding requires desolvation of the free individual molecules with concomitant breaking of the ligand-water and macromolecule-water hydrogen bonds. Although many or all of these hydrogen bonds may be reformed between the ligand and macromolecule in the complex if the two are highly complementary, the net change in free energy is often close to zero or only slightly negative. Macromolecular hydrogen bonding groups, which are shielded from solvent, are an exception to this and therefore provide the best design targets, since they have little hydrogen bonding competition from solvent and therefore greatly stabilize the ligand-macromolecule complex relative to unshielded groups. On the other hand, hydrogen bonding mismatches destabilize the ligand-macromolecule complex relative to the free ligand and macromolecule, reducing the free energy of binding (150). Binding affinity is therefore increased primarily by optimizing hydrophobic and van der Waals interactions, achieved to a first approximation by maximizing shape complementarity between the ligand and its receptor, while simultaneously ensuring specificity by maintaining hydrogen bonding and electrostatic complementarity.

Fersht et al. (150), who used site-directed mutagenesis to remove specific hydrogen bonding groups from the enzyme in the tyrosyl tRNA synthetase-substrate complex, and Street et al. (151), who removed specific hydrogen bonding groups from the ligand in the glycogen phosphorylase-glucose complex, found that neutral hydrogen bonds contributed only 0.5–1.5 kcal/mol to the free energy of binding and that ionic hydrogen bonds contributed up to 3.8 kcal/mol. In triose phosphate isomerase, Asn-78 forms two hydrogen bonds to neighboring residues. When this is mutated to Thr-78, only one hydrogen bond can form and the protein is destabilized by 1 kcal/mol. Evidence suggesting this effect is additive comes from the mutation of Asn-78 to Ile-78, in which both hydrogen bonds are lost and the destabilization increases to 2 kcal/mol (152). Bartlett and Marlowe (153) determined a possible upper limit for intrinsic hydrogen bonding energy of 4.0 kcal/mol for an unusually favorable phosphoramidate N–H hydrogen bond to a carbonyl oxygen on the peptide backbone of thermolysin, a result that has been confirmed crystallographically (154). Hydrogen bond lengths

range from about 2.6 Å (distance between heteroatoms) for ionic interactions to 2.8 Å (strong) and 3.2 Å (weak) for neutral interactions.

Several other themes occur regularly in protein structure and protein–ligand complexes and represent other stabilizing interactions. Both side chains and the peptide backbone should be considered for possible ligand–protein interactions. In particular, the inherent polarizability of the peptide bond makes it an ideal candidate for hydrogen bonding and in fact is extensively used in proteins to stabilize buried polar side chains.

Sawyer and James (155) have found carboxy–carboxylate interactions to be an important stabilizing force in protein–protein interactions in situations where the carboxylates can share a proton at low pH. In these cases of strong hydrogen bonds, oxygen–oxygen distances as short as 2.4–2.5 Å have been observed (155). In the complex of the phosphoramidate transition state inhibitors with thermolysin, Glu-143 is protonated and forms a strong hydrogen bond to the phosphonamide oxygen (154).

In general, highly ionized groups are only found as surface residues in most proteins (95). However, in a survey of 36 protein structures (81), six completely buried salt bridges were found: proteinase A (Asp-194–Arg-138), superoxide dismutase (Asp-81–His-78 and Asp-122–His-69), β -trypsin (Asp-102–His-57), rhodanese (Arg-182–Glu-192 and Arg-182–Asp-180), and glutathione reductase (Lys-66–Glu-201). Interestingly, all these were in the active sites of their respective enzymes and clearly play a functional role. A detailed study of the hydrogen bond network stabilizing these polar groups could give some insight into similar possibilities for designing polar ligands. The importance of electrostatic interactions, especially with buried charged groups, is emphasized in the binding of L-arabinose to L-arabinose binding protein (156). A positively charged arginine in the enzyme is inaccessible to solvent in the enzyme–sugar complex and all five possible hydrogen bond donor groups of the guanidinium of the arginine are used in hydrogen bonding to the arabinose sugar and other residues (Figure 5). Similarly, in the case of a bound sulfate dianion, the sulfate is stabilized by seven hydrogen bonds (156). In any design work it is clearly necessary to ensure that buried, charged functionality with limited solvent accessibility has the maximum number of strong hydrogen bonds. Of possible importance in these proteins and a potentially complicating factor is the apparent coupling of buried ionic groups to hydrogen bond arrays that ultimately lead to bulk solvent. These binding modes result in highly polarizable bonds in the protein–ligand complex and this factor may be crucial for maximum stability.

Warshiel et al. (157) have taken a computational approach to argue that the catalytic effect in trypsin is almost exclusively due to the change in electrostatic stabilization of the ionic configuration of the transition state in the oxyanion hole of the enzyme. These electrostatic effects are not only the interaction

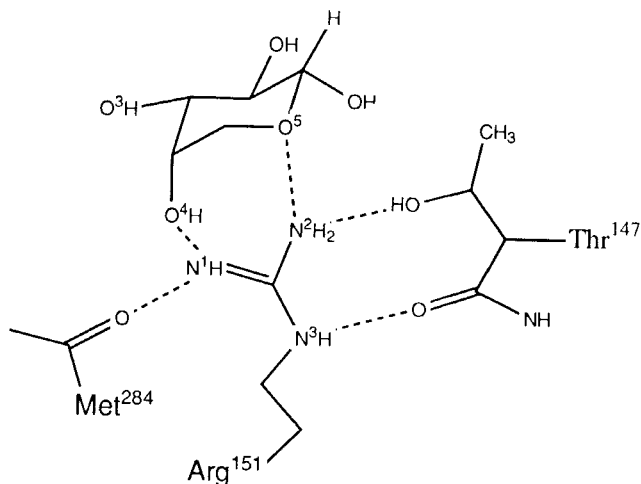


Figure 5. Extensive hydrogen-bonding interactions of Arg-151 of L-arabinose binding protein with L-arabinose. Three arrays of hydrogen bonds exist: two neutral (to the backbone) and one ionic (to charged side chains) stabilize the buried Arg-151, including hydrogen bonding to the ring oxygens of the bound L-arabinose.

between opposite charges but also between isolated charges and their polar environment. In effect, the suggestion is made that the enzyme cleft is a "better solvent" for the dipolar transition state than is bulk water, a concept that might be useful in serine protease inhibitor design.

The α -helix dipole is well known, originating from the alignment of all the individual peptide bonds and their associated dipoles in the helix, and can be described as having partial charges of $+\frac{1}{2}$ at its N terminus and $-\frac{1}{2}$ at its C terminus (158). These helix dipoles can be a means of stabilizing the charges of ionic groups in a complexed ligand (up to 4 kcal/mol) and, in fact, the N-terminal end of an α -helix is often involved in anion (e.g., phosphate) binding sites. Branden (159) has pointed out that active-site clefts in α/β proteins generally occur near the carboxyl end of a β -sheet, where the chain geometry favors cleft formation. In this position the cleft will be close to the amino ends of the α -helices and will have the potential for binding negative charges in the complexed ligand. Dipoles have also been proposed for β -sheets. Hol et al. (160) have modeled a β -sheet strand as a dipole and suggest charges of $+\frac{1}{15}$ and $-\frac{1}{15}$ at the N and C termini, respectively. This corresponds to an interaction energy with a charged atom of about 0.5 kcal/mol.

Fluorine is a popular substituent because of its unusual physico chemical properties (metabolic and oxidative stability, solubility) and the spectral properties (^{19}F NMR) it imparts to a molecule. Murray-Rust et al. (161)

analyzed 260 small molecule structures from the Cambridge database containing the C–F fragment and found nine that appeared to have C–F---H–N hydrogen bonds. Other crystallographic evidence has suggested the existence of C–F---H–O bonds in fluorinated carboxylic acids (162) and difluorinated sugars (163) and enzyme–inhibitor complexes (164). Although this is somewhat controversial, in optimal situations the C–F fragment may act as a weak proton acceptor. In a crystallographic and modeling study of the binding of thyroxine (165) and of polychlorinated biphenyls (166) with prealbumin, halogenated ligands were found to bind in a channel lined with amino acid side chains that form polarizable pockets for halogen interactions. Specifically, the halogens are in close contact with side chains from several alanines and leucines as well as the hydrocarbon chain of lysine. Polar amino acids, with long aliphatic chains (lysine, arginine, and glutamine) can stabilize both polar interactions with their functional groups (protonated amines and ionized carboxylic acids) and hydrophobic contacts with their aliphatic chains.

Metals play a particularly important role in enzymes and receptor proteins and are often involved in fundamental biological processes such as electron storage and transfer (Fe, Cu) or substrate activation and catalysis (Mg, Mn, Ge, Co, Cu, Zn, Ca, Mo). It has been estimated that up to one-third of all proteins and enzymes bind metal ions and/or require them for biological activity (167). These metal ions and their associated coordination spheres, which in some cases include functionality supplied by the complexed ligand, are frequently located at the active sites of the proteins and therefore are potential targets for ligand design (Figure 6). A review of the role of coordination sites in metallobiomolecules is available (168).

The role of water in its association with protein structures may also suggest possible positions of ligand functionality in a binding site. Crystal structures of proteins often show tightly bound water molecules in internal cavities, at the surface, or bound to metal ions. These water molecules may stabilize protein structure by connecting or bridging charged or polar groups or may serve a catalytic function. It is interesting that two to three times more water hydrogen bonds are made to the main chain carbonyl oxygens than to amide–NH groups, suggesting a greater tendency for carbonyl oxygens to form hydrogen bonds (169, 170). The water structure around crambin, a hydrophobic protein, has been analyzed by X-ray crystallography and 77% of the solvent molecules were located (171). One notable feature of the water structure was the pentagonal array of 16 water molecules that occupy a hydrophobic, intermolecular cleft between adjacent protein molecules (Figure 7). This may have relevance to the role of water in hydrophobic active sites and could aid in modeling the consequences of removing these waters by ligand binding. In one study of the binding of phosphoramidates to thermolysin, a single, tightly bound water was thought to be responsible for the slow binding kinetics and



Figure 6. Types of metal coordination sites commonly found in proteins (168).

Singh and Thornton (172) and Burley and Petsko (173) investigated the geometry of aromatic interactions in protein environments using the Brookhaven Protein Data Bank. The preferred distance between aromatic ring centers of interacting aryl rings was about 4.6 Å, with the planes of the

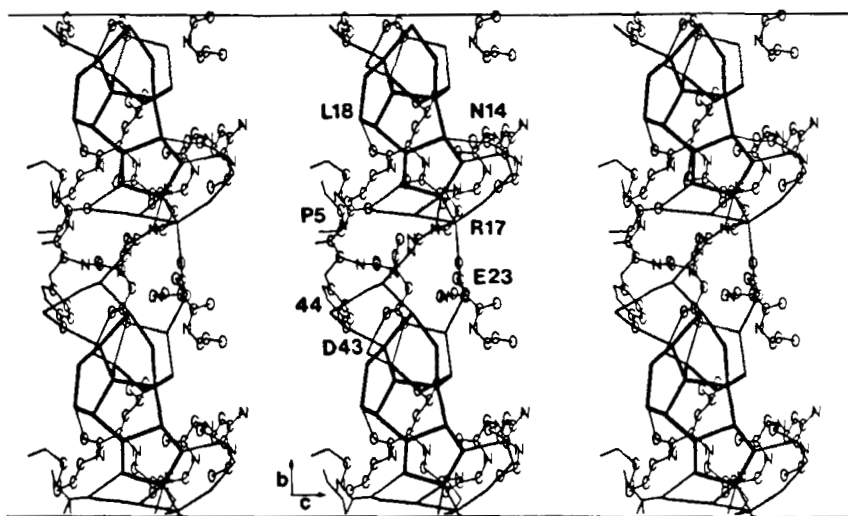


Figure 7. Stereo diagram of water pentagons, typical of those found packed to hydrophobic clefts in the protein crambin. The left-hand pair is for viewing with stereoviewers, while the right-hand pair should be viewed with the "cross-eyed" view. The pentagon cluster has the darkest lines. From ref. 171.

interacting rings nearly perpendicular, such that the edge of one ring is projected into the ring face of the second. Quantum mechanical calculations (174, 175) support these findings and suggest an electrostatic basis for the interaction between the positively charged hydrogen atoms and the π electron cloud. This concept was used as the basis for the design of novel phospholipase A_2 inhibitors (176).

Tintelnot and Andrews (55) studied the binding site environment of 40 protein-small molecule complexes in the Brookhaven Protein Data Bank. They analyzed protein preferences for binding various functional groups (phenyl, carboxyl, carbonyl, hydroxyl, amine) present in the small molecule ligands. From this study they observed a consistent chelate-like orientation between ligand carboxyl groups and arginine side chains, and between ligand guanidine or amidine groups and glutamic or aspartic acid side chains that could be useful in ligand design.

These concepts are useful to keep in mind when modeling ligand-macromolecule interactions or when attempting to design a new ligand. Excellent references for protein structure and interactions are available in the texts by Creighton (95), Cantor and Schimmel (59), and Schulz and Schirmer (177).

IX. THE SYNTHETIC DESIGN PROCESS

Computer graphics enables us to visualize ligand–receptor interactions qualitatively; docking methods suggest possible binding modes; molecular mechanics and dynamics refine the possible fits; and analysis of known ligand–protein complexes suggests important interactions. Can novel ligands be designed using this information? If the X-ray structure of a suitable lead compound complexed with the receptor is available, new compounds can be designed by analogy with the lead compound. An integrated approach combining recent developments in molecular modeling with over 20 years of quantitative structure–activity relationships (QSAR) development has proved to be especially powerful for this application (178). The QSAR can help differentiate between possible binding modes and conformations by revealing the physical nature of the surface surrounding each substituent. We have much less experience in the *de novo* design of novel molecules without such a lead compound and with only the X-ray structure of the native protein. The designs by Beddell et al. (179) of 2,3-diphosphoglycerate mimics and antisickling compounds (180) using mechanical wire models based on the hemoglobin X-ray structure are still some of the best examples of this approach. Another example is the design of novel inhibitors of phospholipase A₂ based on the X-ray structure of the native enzyme (176).

Molecular structure design is still a formidable challenge dependent on the creativity, ingenuity, and experience of the medicinal chemist. Once we overcome the initial challenge of how to model a macromolecular binding site with computer graphics and energy calculations, we are faced with the much greater challenge of what to put in the site and where to put it. Although it is tempting to speculate that all the information required for the design of an optimal ligand is present in the high-resolution structure of a binding site, no computational approaches exist yet for complete *de novo* design. There is still no systematic method to lead to an optimum design if in fact an optimum exists. Very different, apparently reasonable designs are often found by different researchers.

A. Optimal Atom Locations

Before considering a complete structure it would be useful to determine preferred locations of functionality that could later be connected together into a synthetic target. Goodford and co-workers developed a simple molecular mechanics-based approach (20,21) for predicting optimal ligand atom locations in a binding site of known structure. The method involves calculation of the molecular mechanics interaction energy for each of a variety of probes (e.g., hydroxyl oxygen, carbonyl oxygen, carboxyl oxygen, amide

nitrogen, amine nitrogen) at each point on a three-dimensional grid superimposed on the binding site. Solvation is considered in a simple way by modifying the dielectric constant based on the solvent accessibility at each grid point. The grid is then contoured by energy and the resulting contours are graphically displayed (as color-coded contour maps or dot clouds) in the binding site. The contours indicate predicted "hot spots" where a ligand atom of a given type should prefer to bind (see color insert, Figure 8). While this method provides useful visual clues for structure design, it is not a simple matter to connect these "hot spots" together into a single molecule which can be synthesized in a reasonable amount of time, contains the majority of the predicted optimum atoms in a low energy conformation, and simultaneously places these atoms near the calculated locations.

Goodford's probe method can be combined with the other previously described interactive methods, where the user fits a variety of organic fragments in a trial and error fashion into the site, attempting, eventually, to combine the fragments into a complete molecule. Alternatively, a library of fragments could be searched to determine optimal fits to the probe positions.

B. Geometric Fits of Proposed Ligands

The design of synthetic ligands to produce a geometric fit to a structurally well-defined binding site of a target receptor is a problem of surprising complexity. Molecular modeling systems give excellent visualizations of the three-dimensional architecture of macromolecules (where the X-ray structures are available), tempting us to design molecules with surfaces that are geometrically and electrostatically complementary to the binding site. There is no analytical way of representing the irregular surface characteristic of binding sites. The great variety of possible bond length and angle constraints of organic molecules makes it exceedingly difficult to design molecules with appropriate bond lengths and angles that also have the required complementary surface. Perhaps, in recognition of this difficulty, Nature also has not solved this problem, since in many of the known active site-ligand complexes the ligand does not completely fill the site pocket. This suggests that several possible solutions exist if, in fact, an exact complementary fit is not necessary. It is probably safe to assume, however, that the more completely a site is filled by the ligand the more stable the complex will be (165). Designing a molecular structure that produces a predetermined surface remains a major unsolved problem in the area of ligand design.

A novel approach for estimating the geometric requirements of a receptor site is due to Kuntz and co-workers (19). They fill the target site with spheres of varying sizes that occupy the gaps and grooves of the site (Figure 9). A second set of spheres are generated that fill the space occupied by the ligand or

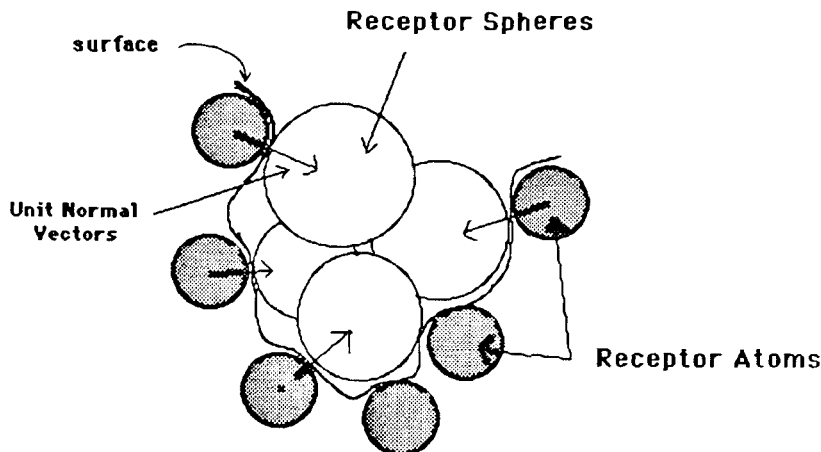


Figure 9. Sphere generation approach to determine the geometric requirements of a binding site. The binding site is formed from six atoms (filled circles). The molecular surface is shown by a thick black line. The receptor sphere (which will contain the bound ligand) are constructed with centers along the surface normals (19).

molecular fragment of interest in a fixed, rigid conformation. Each of the receptor sphere centers are then paired with each of the ligand sphere centers and a set of spheres are determined which match within some set tolerance. Pairing the sets of spheres is done by matching all the internal distances of the ligand set with the receptor set. In the limit of a perfect fit, the ligand and receptor surfaces will be in exact correspondence. If the surface and spheres are generated for the entire macromolecule, spheres are produced that can be grouped depending on whether they overlap or not. This procedure usually identifies a small number of sites scattered on the surface of the macromolecule with the largest often being the recognized binding site (e.g., active site). This technique could also suggest alternate allosteric sites (remote sites that interact with the major site to modulate its binding affinity) which could be useful for the design of potential inhibitors.

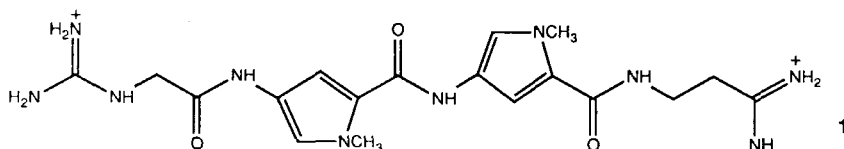
In principle, a library of rigid fragments could exist such that for each of these fragments of atom-atom distances could be matched with the receptor sphere-sphere distances to find sets of receptor spheres that would correspond to the fragment shape. The ligand would then be created by pairing fragments with correct interfragment bonding distance and angle constraints. Finally, the ligand would be energy minimized. This technique was applied to dihydrofolate reductase (DHFR) and prealbumin (105). In the case of DHFR, the fragments selected were two overlapping pieces of the known inhibitor methotrexate. With two fragments from methotrexate there were 607 initial

matches to DHFR for the two fragments, 339 unique matches, and 14 joined solutions. An acceptable joined solution is one in which fragments can be connected together with acceptable bond lengths and bond angles.

More recently, the idea of using shape complementarity as a screen to design ligands for a known protein structure has been extended to structural databases (181). Small molecules from the Cambridge Database (33) were docked to the receptor in several orientations, with each evaluated for "goodness of fit." This approach was applied to papain and carbonic anhydrase and generated several potential ligands, which could be used as a framework to design novel compounds.

C. Design of DNA-Binding drugs

The X-ray crystal structures of several drugs bound to DNA have been solved: actinomycin-D (182), daunomycin (183), triostin-A (184), *cis*-diaminedichloroplatinum(II) (185), and netropsin (186). The X-ray crystal structures of several DNA-binding proteins have also been solved: catabolite activator protein (187), lambda repressor (188), catabolite repressor operon (189), Trp repressor (190), and the restriction enzyme ECO-R1 in complex with its target DNA sequence (191). As more drug-DNA and protein-DNA structures are solved, the challenge of exploiting the information in them for the design of new sequence-selective DNA-binding drugs has become increasingly important. Current DNA-binding drugs inhibit DNA replication and/or transcription and have important clinical uses as antibiotics and anticancer agents, but they also have severe side effects, which are related to their poor sequence selectivity. These compounds recognize only a few base pairs at best; recognition of up to 17–18 base pairs will be required for a selective DNA-binding drug, based on the probability of multiple random occurrence of the same sequence in the human genome (192).



Kopka et al. (186) solved the X-ray crystal structure of netropsin (**1**) complexed with CGCGAATT^{Br}CGCG at 2.2 Å resolution. Netropsin binds to the minor groove of double helical B-DNA and is selective for four or more A–T (adenine–thymine) base pairs; a single G–C (guanosine–cytosine) pair prevents binding (see color insert, Figure 10). Netropsin's amide NH groups

hydrogen bond to adenine and thymine in the minor groove, replacing the waters that form a "hydration spine" along the minor groove in native DNA. While these hydrogen bonds determine the orientation and location of netropsin in the minor groove, the A-T specificity is due to the steric hindrance of the N₂-amino group on guanine, which would collide with netropsin's pyrrole CH groups. This observation led to modeling (193), which showed that replacing a pyrrole by imidazole should favor G-C recognition, since the imidazole nitrogen can hydrogen bond with the guanine N₂-amino group. Kopka et al. (193) suggested that this approach could provide synthetic "lexitropsins" selective for any short sequence of DNA (the amide-heterocycle unit of netropsin cannot be repeated indefinitely since its repeat distance does not exactly match B-DNA). Several lexitropsins have been synthesized with imidazole and furan replacing netropsin's pyrrole and bind in the minor groove with DNA binding affinity comparable to netropsin. These first-generation lexitropsins tolerate G-C sites but still prefer A-T, possibly since the dicationic lexitropsins favor the strong negative electrostatic potential in the minor groove of A-T-rich sequences over the more positive minor groove potential of G-C-rich sequences. A monocationic lexitropsin should have reduced electrostatic interaction with the minor groove and presumably lead to less preference for A-T-rich sequences. Second-generation monocationic lexitropsins were designed with an *N*-formyl end group and in fact were G-C selective. The design and structure-activity relationships of lexitropsins were reviewed by Lown (194). This work represents one of the best examples to date of rational design of DNA sequence-selective binding agents, combining X-ray crystallography, two-dimensional NMR, and molecular modeling techniques.

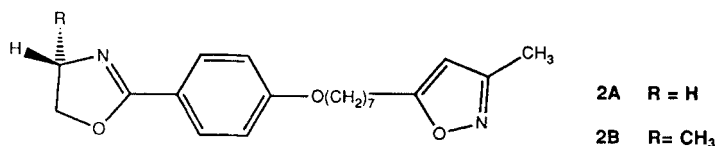
The study by Lybrand et al. (195) of DNA-actinomycin-D interactions combines molecular graphics, molecular mechanics, and two-dimensional NMR. They model-built intercalation sites into several deoxyhexanucleoside fragments with different sequences, followed by interactive computer graphics docking of actinomycin-D into each of the intercalation sites and molecular mechanics energy minimization. Their results were consistent with actinomycin-D's selectivity for binding on the 3' side of guanine, due to hydrogen bonding between threonine side chains in the cyclic pentapeptide portion of actinomycin-D and guanine. Their intercalation structure, which was model-built and energy minimized without using any NMR data, was subsequently compared with the 214 NOE distances in the complex observed by NMR. Good qualitative agreement between the model-built structure and the experimental NOE distances suggests that the model is reasonably close to the solution structure of the complex.

Pearlman et al. (196) built a model of a psoralen-DNA covalently crosslinked complex based on the crystal structure of a thymidine-psoralen-thymine complex, using computer graphics and molecular mechanics calcu-

lations to refine the model. Their proposed structure is remarkably close to the solution structure of the complex, which was determined by two-dimensional NMR and distance geometry (197).

D. Design of Compounds Against Viruses

Smith et al. (198) solved the structure of human rhinovirus 14 (HRV14), one of about 100 known rhinovirus serotypes which cause the common cold, complexed with the structurally related antivirals WIN 51711 (**2A**) and WIN 52084 (**2B**) at 3 Å resolution. These compounds inhibit viral replication by



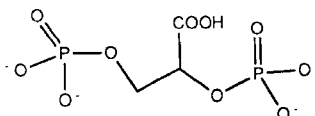
preventing uncoating of the viral RNA. This is the first description of a drug-virus complex at atomic resolution. These structures should provide a good starting point for the design of new antivirals selective against different picornaviruses due to their sequence and structural homology.

HRV14 is a member of the picornavirus family, which includes poliovirus and mengo virus, whose structures have also been solved by X-ray crystallography (199, 200). The WIN drugs bind in an extended conformation to a very deep binding site (see color insert, Figure 11), with the oxazoline end of the drugs in a hydrophilic area, probably with a hydrogen bond from the oxazoline nitrogen to an asparagine side chain. The isoxazole end binds to a buried hydrophobic pocket with no apparent hydrogen bonds to the heteroatoms of the isoxazole ring. In fact, the only proposed hydrogen bonds involve the oxazoline nitrogen and possibly a weak hydrogen bond to the ether oxygen, leaving the other polar atoms buried in hydrophobic areas. The (*S*)-methyloxazoline of WIN 52084 is 10 times more active than the *R* enantiomer, which is attributed to a hydrophobic pocket optimally available to the *S* isomer of the drug. However, more recent work with improved X-ray analytical procedures has revealed that at least one of the WIN drugs exhibits "wrong-way binding," since it binds 180° opposite from the originally proposed orientation and may bind in both orientations (102). This "wrong-way binder" is a very close analog of the original WIN compounds and was originally assumed to bind in the same way. This example clearly illustrates the difficulty in predicting the binding mode of new analogs in a closely related series with moderate binding affinities poorer than approximately 10⁻⁶ M (binding affinity is usually determined by measuring the dissociation constant,

K_d); specificity tends to increase with increasing binding affinity so that the assumption of a common binding mode for a series of analogs becomes increasingly likely.

E. Hemoglobin

Hemoglobin was one of the first proteins whose structure was determined by X-ray diffraction and ever since has been the subject of extensive investigation. Besides the interest in possible therapeutic uses of molecules that bind to the protein, it has also been proposed as a general model for receptor interactions (201, 202). Hemoglobin is a tetrameric protein with two identical α -chains (141 amino acids) and two slightly different β -chains (146 amino acids). Each chain covalently binds one heme. The α -chains contain seven helices while the β -chains have eight. The molecule can exist in two conformational states, one with high affinity for oxygen (R-state) and the other with low affinity (T-state). A natural effector molecule, 2,3-diphosphoglycerate (DPG, 3), binds to hemoglobin at a cleft that opens between the



3

β -subunits in the T-state. By altering the equilibrium between the T- and R-states, DPG increases the availability of oxygen by stabilizing the T-state and promoting the release of oxygen from oxyhemoglobin. This, in some ways, is similar to a receptor model for cell systems in which a first messenger (DPG) binds and causes the release of a second messenger (O_2) (201, 202). In this context, DPG may be considered an agonist molecule and molecules that oppose its actions could be considered antagonists. As shown later, allosteric changes in the action of DPG can also be effected by molecules that bind at sites remote from the DPG site.

Beddell et al. (179) published a remarkable paper in 1976 in which they described the design of a simple but structurally novel compound which mimicked the action of DPG on hemoglobin by selectively binding to deoxyhemoglobin and promoting oxygen release. This structure was designed using wire models of the DPG-deoxyhemoglobin complex and is the first example of a successful *de novo* design of a small molecule based on the three-dimensional structure of a specific receptor site. DPG's carboxyl and phosphate groups bind to the site through ionic interactions with the amino termini of the $\beta 1$ - and $\beta 2$ -subunits and with lysine and histidine side chains (Figure 12). Beddell et al. found that bibenzyl-4,4'-dialdehyde (4) nicely

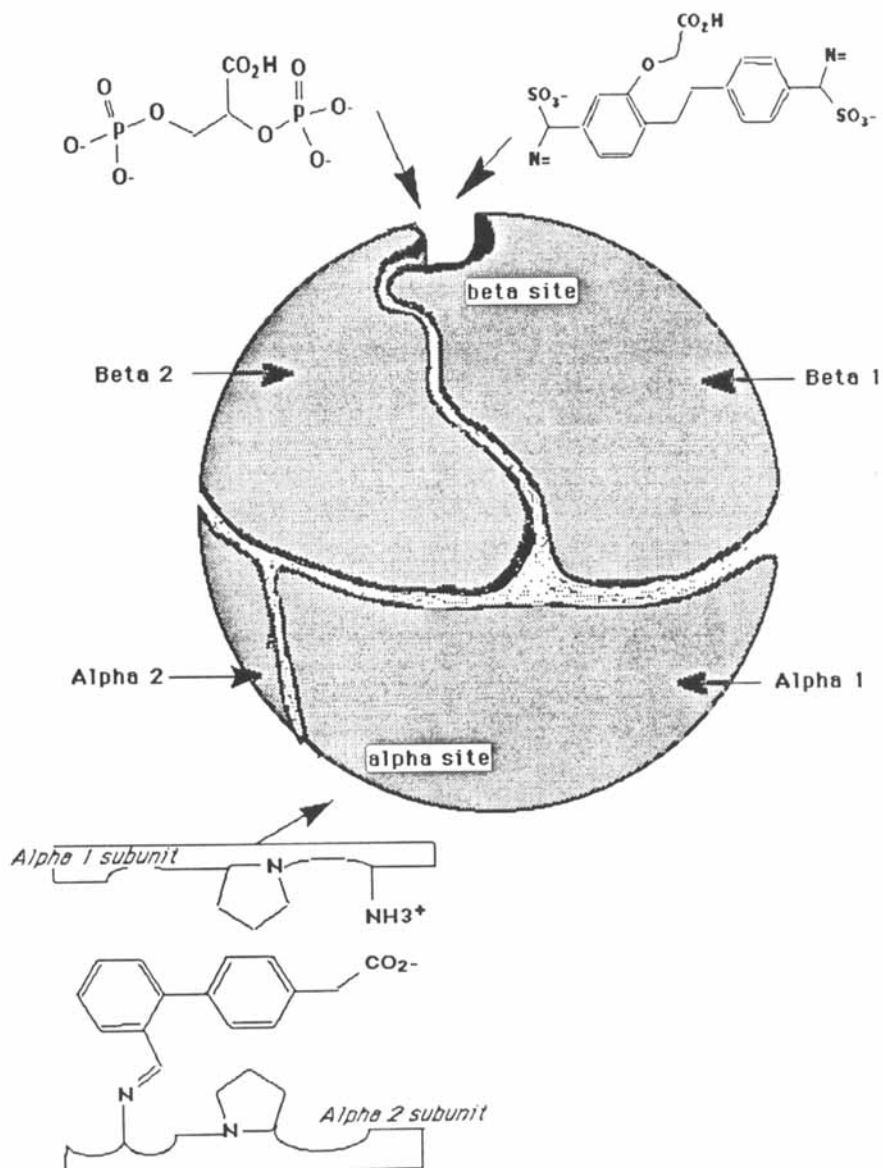
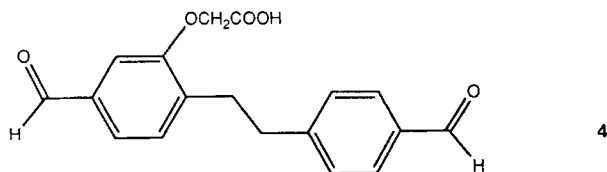
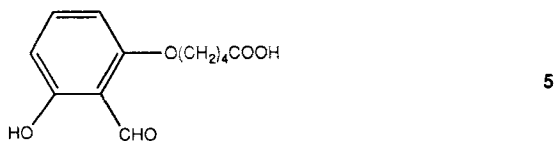


Figure 12. Hemoglobin tetramer showing the two targeted sites for synthetic design. The β -site binds DPG and 4. The α -site is also shown schematically with a potential binding ligand (179).



spanned the site and should be able to react with the amino termini by Schiff base formation (see color insert, Figure 13). They added an OCH_2COOH group at the 2 position of **4** to provide additional interaction with a lysine side chain and converted the formyl groups of **4** into their bisulfite adducts to increase solubility. This compound was as active as DPG and indirect NMR evidence (203) was consistent with its designed binding mode. While this work demonstrated the feasibility of receptor-based drug design, there is no therapeutic value in molecules that mimic DPG by right-shifting the hemoglobin–oxygen dissociation curve.

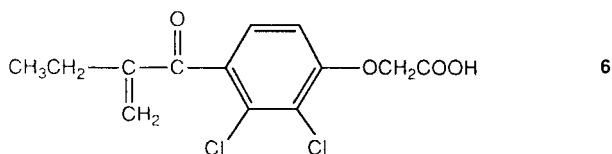
Sickle cell anemia is characterized by aggregation of deoxyhemoglobin into large insoluble fibers, resulting in the characteristic sickle erythrocyte cell shape. Beddell et al. (180) followed up their original work with the design of DPG antagonists which stabilize oxyhemoglobin, thereby left-shifting the oxy-deoxyhemoglobin equilibrium toward oxyhemoglobin and reducing sickling. This is the first description of a drug designed *de novo* by receptor-based molecular modeling which has reached clinical trials. The DPG site is nearly collapsed in the oxy conformation, so design of a compound to bind selectively to oxyhemoglobin at this site was not possible. Beddell et al. observed that another potential binding site existed at the amino termini of the $\alpha 1$ - and $\alpha 2$ -subunits, with the amino groups 20.7 Å apart in the deoxy form and 12.4 Å apart in the oxy form, suggesting that it might be possible to design compounds selective for the oxy form by placing substituents which could interact with both amino groups only at the shorter distance. Beddell et al. designed 5-(2-formyl-3-hydroxyphenoxy)pentanoic acid (**5**) to interact



with the two amino groups by forming a Schiff base and a salt bridge; the hydroxy group ortho to the formyl group was included to promote Schiff base formation (see color insert, Figure 14). This compound is indeed active in left-shifting the oxygen dissociation curve and is a potent antisickling agent *in vitro*. Although attempts to crystallize the drug–hemoglobin complex

have failed, the binding of this compound to its intended site is supported by borohydride reduction of the Schiff base formed on drug-oxyhemoglobin binding followed by tryptic digestion and localization of the covalently bound drug to the α 1-terminal amino group (204); additional weaker noncovalent and Schiff base binding at other sites was also found. On the other hand, Perutz et al. (205) have reported that their X-ray results on this Schiff base-modified hemoglobin suggest that the compound only loosely binds to the oxyhemoglobin.

In a study of drugs known to inhibit or promote the polymerization of deoxyhemoglobin-S, Perutz and co-workers (205) cocrystallized several of these compounds with human deoxyhemoglobin and determined the structures of the complexes by X-ray analysis. Significantly, their results show that the same compound can, in fact, bind to the protein at several sites, consistent with the low binding affinity (about 10^{-3} M) of these compounds. Low binding affinities translate to very weak intermolecular interactions (only about 4 kcal/mol; each order of magnitude in binding affinity is worth 1.4 kcal/mol at physiological temperature), implying that only a few specific interactions are made. The binding sites were determined by the available van der Waals space, nearby electrostatic interactions, and hydrophobic effects. An understanding of the interactions involved in binding these compounds could be useful for synthetic design.



One of the compounds in this study, ethacrynic acid (ECA, **6**), is an acrylophenone that covalently binds to deoxyhemoglobin at two different sites. ECA is irreversibly attached via Michael addition to the thiol of a cysteine and the NH of a histidine (Figures 15 and 16). The dichloroaryl group of ECA possesses a strong dipole with the positive pole between C(4)H and C(5)H and the negative pole between the two chlorines. This dipole is stabilized by placement of the negative chlorines near a protonated histidine (His-97) and the positive end of the dipole oriented toward a carboxylate group from Asp-94. The carbonyl group of ECA accepts a hydrogen bond from the NH of His-97. Several van der Waals contacts also stabilize this binding mode. Interestingly, the carboxyl group of ECA is external to the binding site and apparently solvated.

A second site of attachment of ECA involves a covalent bond with the N of His-117. In this case, the carboxylate of ECA forms a salt bridge with

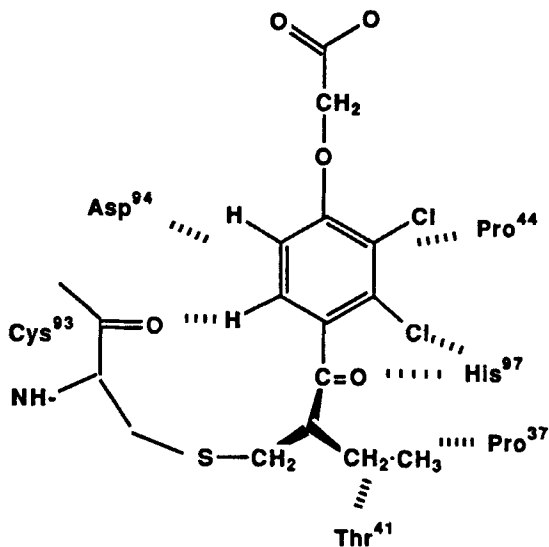


Figure 15. Schematic diagram of the contacts between ECA (6) and hemoglobin (205).

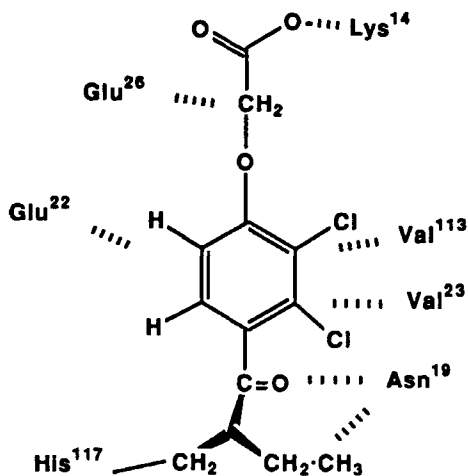
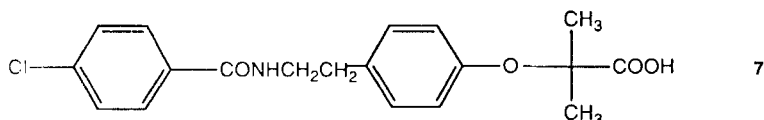


Figure 16. Schematic diagram of the contacts between ECA (6) bound to His-117 and hemoglobin (205).

the NH_3^+ of Lys-14 of a neighboring molecule in the crystal structure. The carbonyl forms a hydrogen bond with the main chain NH of Asn-19. The positive pole of the *o*-dichlorobenzene is compensated by the carboxylate of Glu-22. Again, several van der Waals contacts exist, including contact of the chlorines with aliphatic groups from Val-113 and Val-23.



A second drug, bezafibrate (BZF, 7), is known to bind to hemoglobin with a K_d of 0.11–0.89 mM (205). This molecule binds to the central cavity by contacts with one β and two α subunits. In contrast to ECA, this compound has no covalent bonds to the protein but does have several nonbonded contacts, many of them polar in nature (Figure 17). The electronegative chlorine of BZF is stabilized by the NH of His-103 and the NH_2 of Asn-108. Van der Waals contacts are made between this chlorine and the CH of Phe-36 and the side chain of Leu-100. The amide hydrogens of Asn-108 are in close

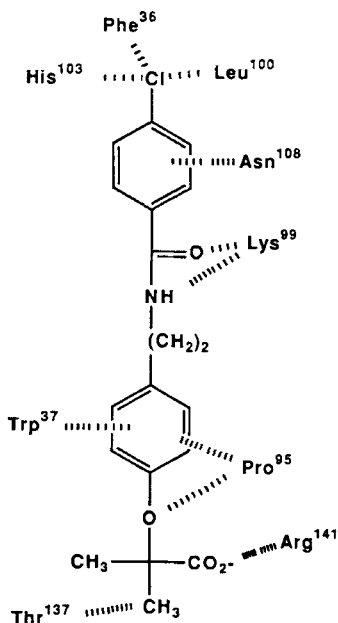
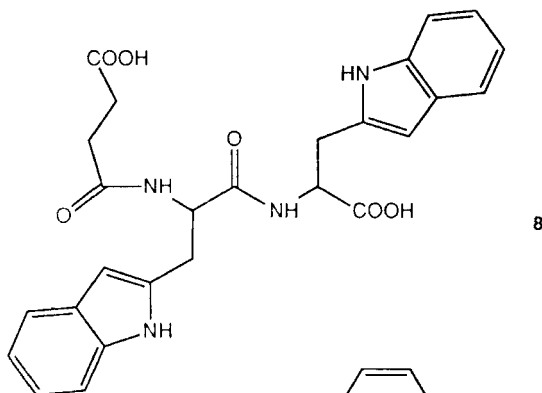
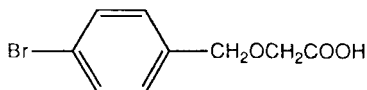


Figure 17. Schematic diagram of the contacts between BZF (7) and hemoglobin (205).

contact with the π -electrons of the aromatic ring of BZF. Several contacts are made between the amide group of BZF and the aliphatic portion of the side chain of Lys-99. Interestingly, van der Waals contacts suffice without the necessity of hydrogen bonding to this amide group. Trp-37 is in contact with the second phenyl ring of BZF, possibly suggesting a charge transfer interaction. As with the carboxy group of ECA, the terminal carboxyl of BZF appears to be solvated. In this case, however, this was somewhat surprising since there was the option of forming a salt bond with a nearby Arg-141, a positively charged group for which there appears to be only a weak interaction. The major portion of binding energy in the case of BZF apparently comes from hydrophobic contacts from displacement of three partially immobilized water molecules. Although the greatest contribution to the free energy of binding probably comes from this hydrophobic effect, the specificity of binding comes from several specific interactions between the molecule and the protein.



8



9

Succinyl-L-tryptophan-L-tryptophan (STT, **8**) and *p*-bromobenzyl-oxyacetic acid (BBA, **9**) also bind to deoxyhemoglobin at several sites. In the case of STT, four different sites are involved. The major portion of binding in the case comes from hydrophobic contacts in which 21 molecules of water are displaced. Each STT is bound to one α subunit by three hydrogen bonds and several van der Waals interactions (Figure 18). STT binds to the protein with a K_d of 3.0 mM. BBA is held in place by a salt bridge between its carboxylate and Lys-40. There are also van der Waals contacts between its bromine and the aliphatic portion of the side chain of Glu-30 (Figure 19).

From these studies several general observations can be made. The preferred "perpendicular" packing of aromatic rings observed earlier (173) is also seen in

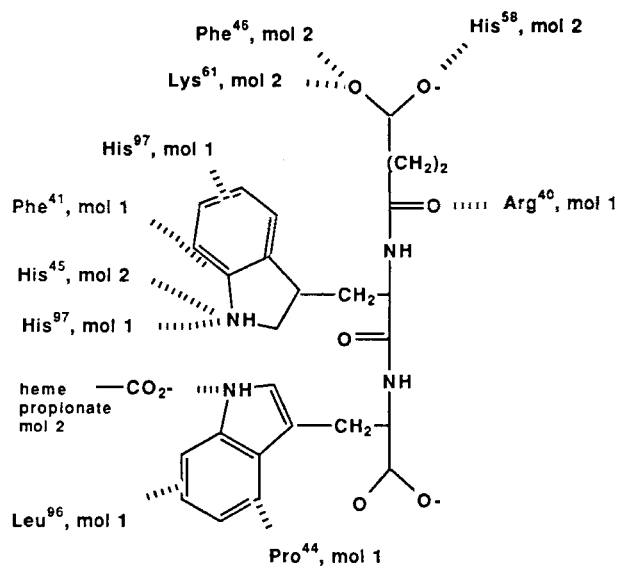


Figure 18. Schematic diagram of the contacts between STT (8) and neighboring hemoglobins (205).

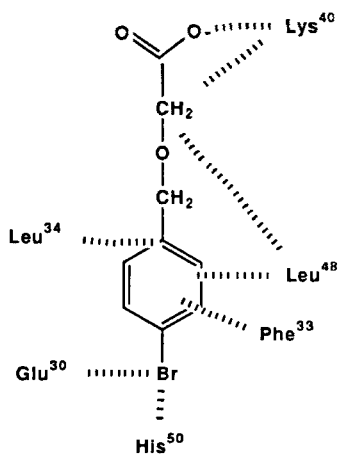


Figure 19. Schematic diagram of the contacts of BBA (9) and hemoglobin (205).

the interaction between globin and the indole ring of STT. There appears to be a tendency to maximize electrostatic interactions and in particular to orient dipoles to allow stabilization by protein side chains. Halogens appear to interact preferentially with aromatic hydrogens and somewhat with aliphatic ones. The aliphatic portions of the side chains of Lys and Glu can make important van der Waals contacts to nonpolar segments of the ligand. Hydrogen bonding is important as well as polarizability of interacting atoms.

Sheh et al. (206) used X-ray crystallographic studies to design potential compounds to block the polymerization of deoxyhemoglobin S (HbS). The $\beta 6$ mutation that occurs in this protein allows one molecule (the donor) to insert itself into a hydrophobic cavity of a second molecule (the acceptor) (Figure 20). Sheh and co-workers have designed a set of cyclic peptides that mimic the loop of the donor protein which inserts into the "acceptor" HbS. The structure of the cyclic peptides was suggested by modeling to be such that the conformation of the peptide is close to that required by the protein loop.

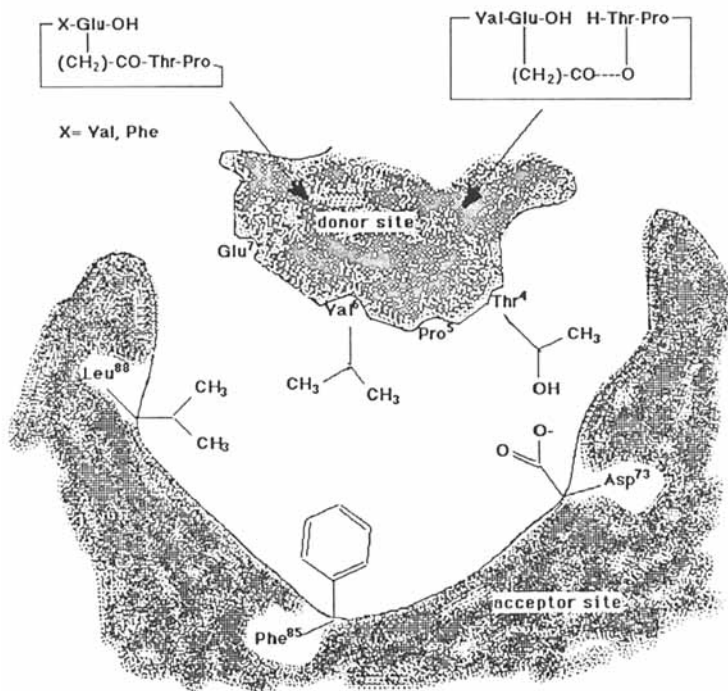
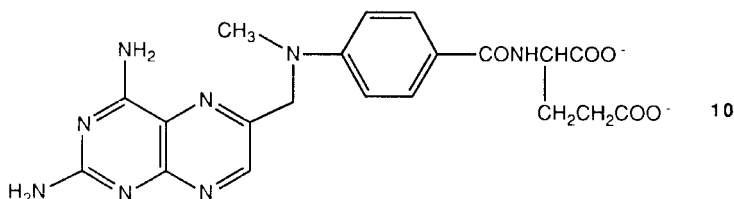


Figure 20. Schematic diagram of the donor-acceptor site interaction between two molecules of deoxyhemoglobin S with cyclic peptides designed to mimic the donor site (206).

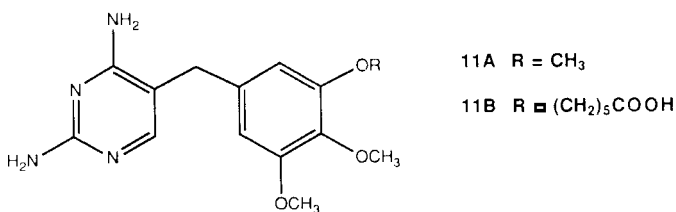
F. Dihydrofolate Reductase

Dihydrofolate reductase (DHFR) has been studied intensively ever since the discovery of methotrexate (**10**) and many other potent DHFR inhibitors in the



late 1940s and 1950s. DHFR inhibitors are used as antibiotics, antimalarials, and anticancer agents due to the crucial role DHFR plays in thymidylate and purine biosynthesis. The X-ray crystal structures of several different DHFRs have been solved by Kraut and co-workers (60, 207): those from *E. coli*, *L. casei*, chicken liver, and most recently a trimethoprim-resistant DHFR from *E. coli* R-plasmid R67. These crystal structures provided the first look at atomic resolution of a real drug–receptor complex and stimulated renewed interest in the structure–activity relationships and design of DHFR inhibitors.

Kuyper et al. (208) modeled the binding of the bacterial DHFR-selective antibiotic trimethoprim (**11A**) using the X-ray structure of the *E. coli*–methotrexate complex. They assumed that the pyrimidine ring of trimethoprim would bind analogously to the corresponding pteridine ring of methotrexate (their model was later shown to be qualitatively correct by



X-ray crystallography of the *E. coli*–trimethoprim complex). Based on their model for trimethoprim binding, they designed new trimethoprim analogs (**11B**) by adding 3'-carboxyalkoxy groups targeted to interact with an arginine side chain at the entrance of the active site (see color insert, Figure 21). The arginine–guanidinium group is almost completely buried in the active site surface and is probably poorly hydrated, suggesting that an ionic interaction between the inhibitor and this arginine might be unusually strong. The

binding mode of these new trimethoprim analogs was verified crystallographically; the best compound was 55 times more active than trimethoprim *in vitro* against *E. coli* DHFR. This work clearly demonstrated the potential for rational design of analogs with greatly improved *in vitro* activity. Unfortunately, these structures showed poor *in vivo* antibacterial activity, possibly due to the highly polar carboxy group, which may prevent entry into bacteria.

G. Phospholipase A₂

Phospholipases are crucial enzymes in the arachidonic acid pathway and appear to be primarily responsible for the esterolytic action that releases arachidonic acid from phospholipids (209). Once released, this acid is converted into several mediators of inflammation. The PLA₂'s are small (MW 14,000) stable proteins that require Ca²⁺ ions for the specific hydrolysis of the 2-acyl group of 3-*sn*-phospholipids.

The X-ray crystal structures of three PLA₂'s have been determined: bovine pancreatic (210), porcine pancreatic (211), and the crotonolus atrox (212). The highest resolution structure to date is the bovine enzyme (1.7 Å), which was used as a target for inhibitor design (176). Potential binding modes of the substrate phospholipid were first studied with the expectation that they might suggest conformationally restricted mimics. Extensive biochemical information (212) indicated His-48 was close to the 2-acyl carbonyl of the phospholipid and involved, possibly via a water molecule, in its hydrolysis (Figure 22). A phosphate oxygen of the substrate phospholipid has also been proposed to occupy one position of the coordination sphere of the calcium (213, 214). These constraints suggested a model in which the hydrated ester carbonyl intermediate was hydrogen bonded to His-48, whereas one of the phosphate oxygens was located at one of the water positions located in the coordination sphere of the calcium. Distance geometry was used to generate many potential binding modes (Figure 23) of the phospholipid using these constraints (176).

The substrate fits generated by distance geometry, particularly the frequently encountered "planar" conformations of the polyene chain threaded between Leu-2 and Tyr-69, suggested the hydrophobic "slot" in the PLA₂ structure might accommodate a naphthalene ring. This offered the possibility of building a rigid framework from which additional functionality could be directed to interact with other parts of the site (Figure 24). A consequence of this fit was that the naphthalene was approximately perpendicular to the aryl ring of Tyr-69 with a distance between the center of the aryl ring of Tyr-69 and the two rings of the naphthalene of 4.6 and 4.7 Å. Closing a five-membered ring between the 1 and 8 positions of the naphthalene was sterically allowed by the

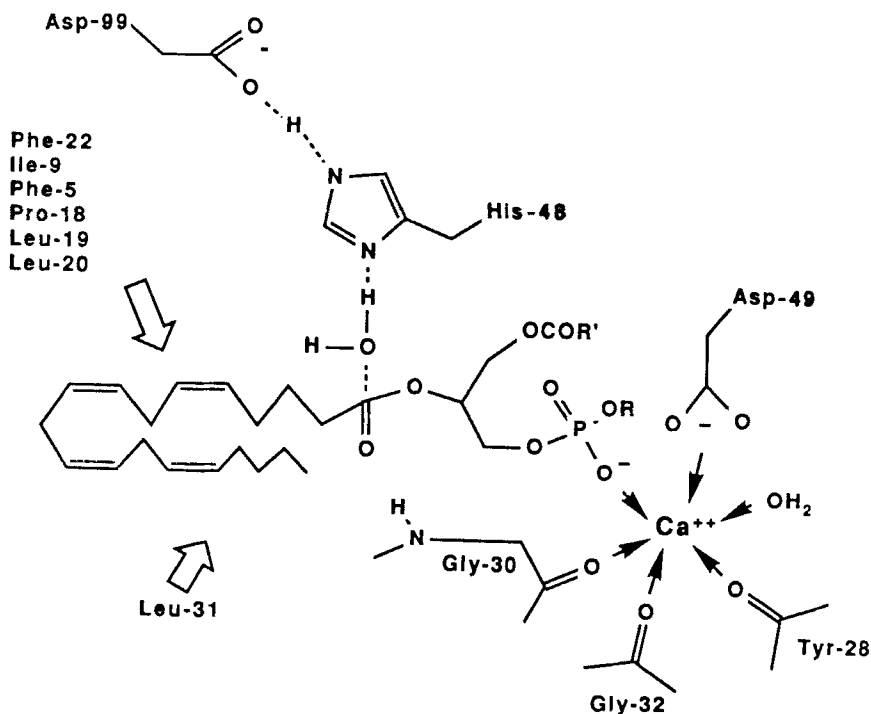


Figure 22. Schematic diagram of the active site of phospholipase A_2 with bound lecithin. From ref. 176.

enzyme and resulted in four stereochemically oriented positions to continue the design. Biochemical information had shown the importance of His-48 and interactive graphics were used to position a meta-substituted benzyl group projecting from the 1- β position of the acenaphthene such that a hydrogen bond was possible.

A second design target was the carboxyl of Asp-49 of the essential calcium (176). To reach this part of the site, a protonated amine was projected from the 2 position of the acenaphthene with the idea of creating an electrostatic interaction with the Asp-49 carboxyl or displacing the calcium. The latter case would allow the design of a bisubstrate analog. Bisubstrate analogs, which in this case would combine a ligand (the benzylacenaphthene) and cofactor (the amine that would displace the calcium) in a single molecule, can have binding constants lower than the product of the binding constants of the two independent ligands (215). Support for the concept that a protonated amine could replace the calcium ion in the enzyme comes from the finding of a class of

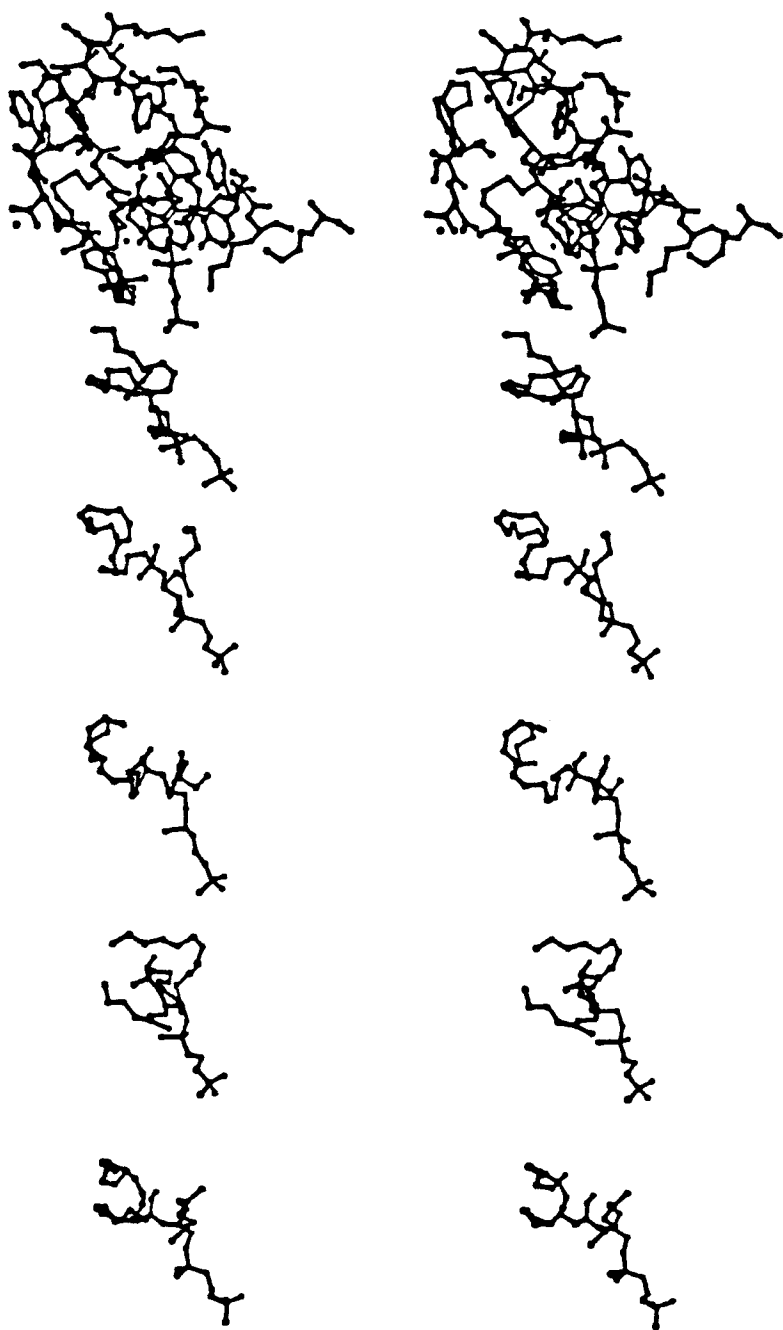


Figure 23. Stereo pairs of possible binding modes of phospholipids to PLA₂ as determined by distance geometry. From ref. 176.

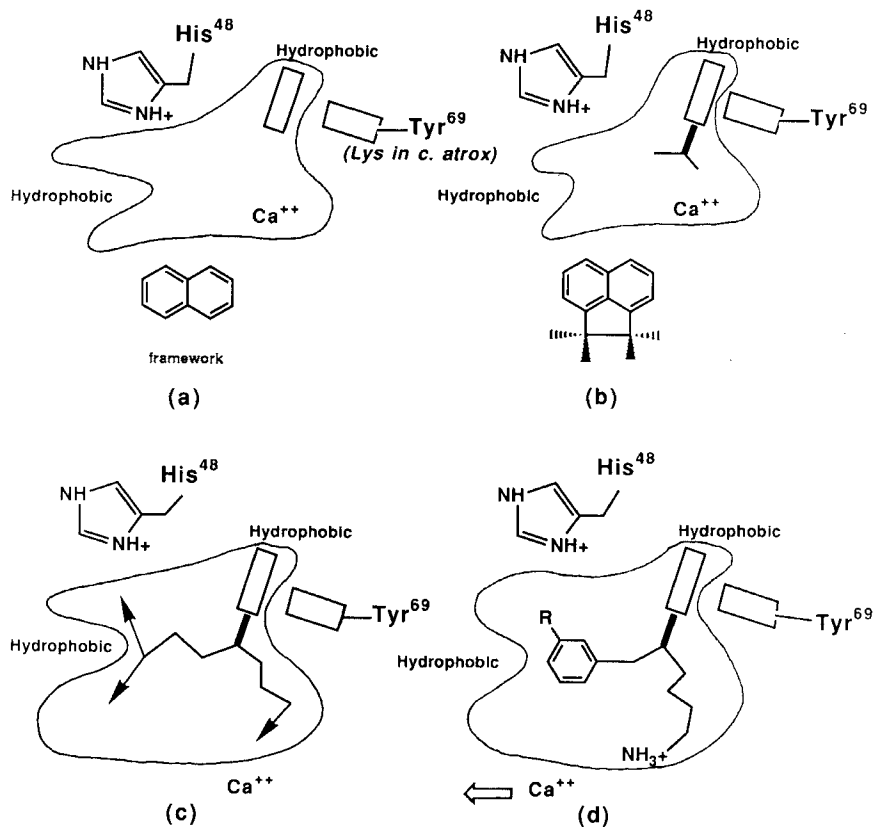
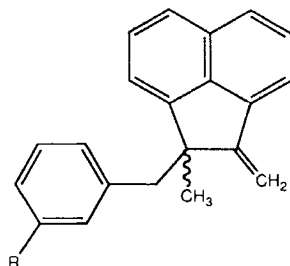


Figure 24. Strategy for the design of PLA₂ inhibitors. From ref. 218.

PLA₂'s that have a lysine at position 49 rather than the usually conserved aspartate (216). Molecular modeling of the Lys-49 enzyme based on the X-ray crystal structure of the bovine PLA₂ shows the ϵ -amino group can readily fit the calcium-binding site by occupying the calcium position((217). Additionally, in the atrox dimer, one of the interactions at the dimer interface is a water-mediated salt bridge between the carboxyl group of Asp-49 of one subunit and the ϵ -nitrogen of Lys-69 of the other (218).

Based on this modeling approach, several compounds were designed and synthesized (e.g., **12**) which showed the regioselectivity and structure-activity relationships in binding assays predicted by the modeling (176) (see color insert, Figure 25). Additionally, the modeling suggested one enantiomer should be preferred and some stereoselectivity was in fact observed (218). This

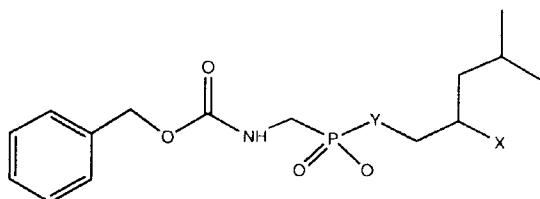


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is one of the first examples of the use of interactive computer graphics to design, in a *de novo* sense, completely novel inhibitors of an enzyme target. The best inhibitors in this series and K_i values (inhibition constants) of about 10^{-7} M.

H. Thermolysin

Bartlett and Marlowe (153) designed a series of five phosphoramidate analogs of the peptide carbobenzoxy-Gly-Leu-X ($X = \text{NH}_2$, Gly, Phe, Ala, Leu), where a $-\text{PO}_2-\text{NH}-$ replaces the Gly-Leu peptide bond, and showed that these compounds were potent transition-state analog inhibitors of the zinc endopeptidase thermolysin. They also synthesized the corresponding phosphonate analogs, where the $-\text{NH}-$ (13A) is replaced by $-\text{O}-$ (13B). The



13A Y = NH

13B Y = O

13C Y = CH_2

phosphonates were uniformly 840-fold less active than the corresponding phosphoramidates, corresponding to a 4.0 kcal/mol difference in binding free energy, a very large difference for such a small structural variation. X-ray crystallography of a phosphoramidate-thermolysin complex and the corresponding phosphonate-thermolysin complex at 1.6 Å resolution (154) showed the two inhibitors bind identically to the active site and that the phosphoramidate NH hydrogen bonds to the carbonyl oxygen of Ala-113. The corresponding phosphonate oxygen is in the same position but is unable to donate a hydrogen bond.

A molecular dynamics free-energy perturbation simulation (121) comparing the phosphoramidate and phosphonate in solution and in the enzyme

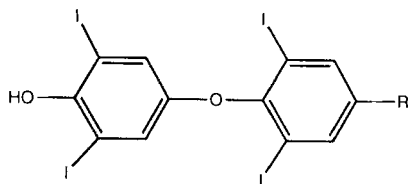
active site calculated a free-energy difference of 3–4 kcal/mol, remarkably close to the experimental value. Merz and Kollman (122) followed up on this work by performing free-energy perturbation calculations comparing the unknown $-\text{CH}_2-$ analog (**13C**) with phosphonamidate (**13A**) and phosphonate (**13B**). The $-\text{CH}_2-$ analog is calculated to interact 2 kcal/mol less well with the enzyme than the $-\text{NH}-$ analog but costs 2 kcal/mol less free energy to desolvate, so the net effect is that the $-\text{CH}_2-$ analog is predicted to bind almost as well as the $-\text{NH}-$ analog. This surprising prediction was subsequently verified by synthesis and testing of **13C**. X-ray crystallography of a thermolysin–**13C** complex showed that **13C** binds the same as **13A** and **13B** (219). Experimental verification of such a nonintuitive and unexpected prediction by theory is particularly important.

These results demonstrate how important the role of differential solvation can be in determining binding affinity differences; desolvating a hydrophilic group may cost more free energy than is gained upon binding the group to the receptor site, so that a hydrophobic group could in fact be favorable for binding. These studies provide the clearest example yet of a complete study of rational enzyme inhibitor design, followed by X-ray crystallographic determination of inhibitor binding and accurate free-energy simulations to quantify and pinpoint the differences in activity between inhibitors.

Hangauer et al. (220) used computer modeling techniques to investigate the mechanism of peptide hydrolysis by thermolysin using the crystallographic information on the enzyme, inhibitor, and substrate along with available structure–activity relationships. Using a model substrate, Z–Phe–Phe–Leu–Trp, they modeled the Michaelis complex as well as the tetrahedral intermediate complex.

I. Prealbumin

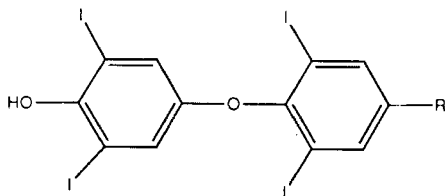
Prealbumin is a transport protein for thyroid hormones which has been used as a model for the nuclear thyroid hormone receptor. Blaney et al. (165) used a qualitative computer graphics molecular modeling approach in their work on modeling thyroid hormone–prealbumin interactions and predicting thyroid hormone analog binding affinities to prealbumin. They used interactive graphics with molecular surface displays to model the interaction of a variety of thyroid hormone analogs with prealbumin based on the 1.8 Å resolution X-ray crystal structure of the thyroxine–prealbumin complex. The molecular surface of the prealbumin–thyroid hormone binding site revealed six unusually well-defined pockets capable of binding substituents on thyroid hormones. Binding affinity correlated qualitatively with the number of filled pockets, presumably by increasing surface complementarity and promoting stronger van der Waals and hydrophobic interactions. L-thyroxine (L-T₄,



14A $R = \text{CH}_2\text{CH}(\text{NH}_3)\text{COO}^-$

14B $R = \text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$

14A) and other high-affinity analogs filled four pockets and a crystallographically well-defined water molecule filled a fifth, leaving one empty pocket (see color insert, Figure 26). This suggested that analogs which could occupy this last pocket should have increased binding affinity. The relative binding affinities of a series of α -naphthyl-thyroid hormone analogs were predicted based on modeling the number of pockets filled by each analog and their potential steric "collisions" with the binding site. The qualitative predictions were confirmed experimentally, showing that the simple concept of surface complementarity can be extremely useful for predicting relative binding affinity and the design of new compounds to fit a receptor site.



15 $R = \text{CH}_2\text{CH}(\text{NH}_3)\text{COO}^-$

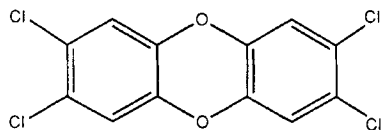
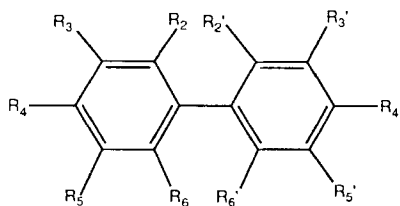
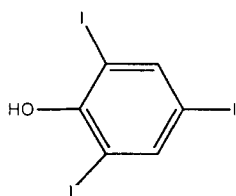
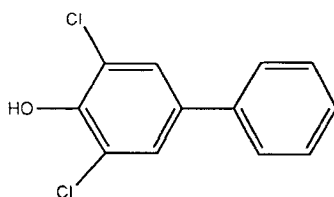
16 $R = \text{CH}_2\text{CH}_2\text{COOH}$

17 $R = \text{CH}_2\text{CH}_2\text{NH}_2$

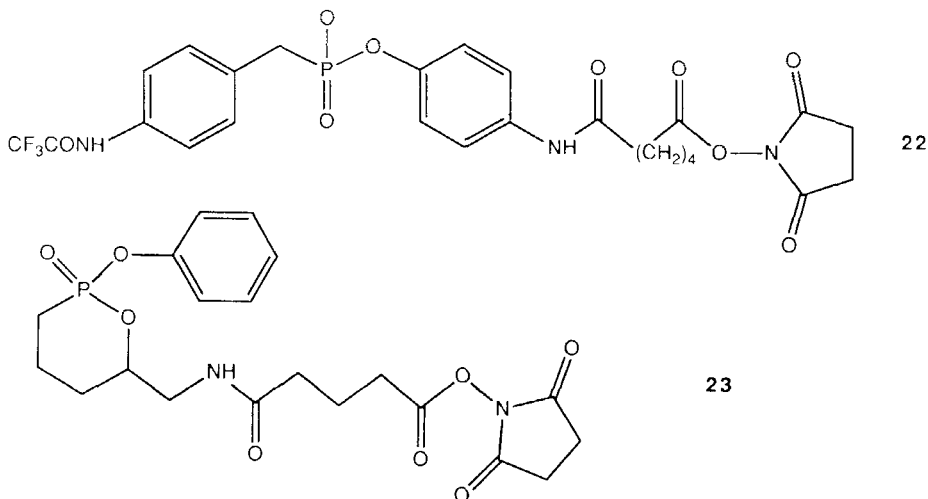
Blaney et al. (24) also used molecular mechanics to attempt to provide a more quantitative understanding of thyroid hormone–prealbumin structure–activity relationships. Calculations comparing L-T₄, D-T₄ (**15**), des-amino-T₄ (**16**), and des-carboxy-T₄ (**17**) showed that a major factor in determining the free energy of binding was desolvation of the charged thyroxine side chain, which was estimated from the gas phase–aqueous phase free energies of transfer of methylamine, acetic acid, and glycine as models for the side chains of des-carboxy-T₄, des-amino-T₄, and T₄, respectively. Although previous thyroid hormone structure–activity research focused on the apparent need for a negatively charged carboxyl-containing side chain or a zwitterionic amino acid side chain, these results suggested that a neutral side chain might also produce high binding affinity, since a neutral side chain would be much more easily desolvated. T₄ with a neutral hydroxypropyl side chain (**14B**) was synthesized and found to have a binding affinity comparable to des-amino-T₄, the most tightly bound known analog to prealbumin. A neutral side chain had never been considered before but actually produced very high binding affinity, demonstrating that molecular modeling and calculations can in fact provide

new insight and suggest valuable new ideas which might otherwise be overlooked.

McKinney et al. (166,221) discovered that dioxin and polychlorinated biphenyl (PCB) analogs also bind to prealbumin and suggested this may be related to their toxicity. They modeled the binding of several dioxin (**18**) and PCB (**19**) analogs to the prealbumin binding site and predicted their relative binding affinities with good overall success. Although the dioxin analogs do not fit the site as tightly as thyroxine, they have very high binding affinity, up to 15% the affinity of L-T₄. Even more surprising was the discovery that the simple compound 2,4,6-triiodophenol (**20**) binds nearly four times better than L-T₄ and that 3,5-dichloro-4-hydroxybiphenyl (**21**) binds 850 times better than T₄! These compounds obviously cannot fill as much of the prealbumin hormone binding site as T₄ and might be expected to have lower binding affinity due to the few possible interactions available to them. In fact, they

**18****19** $R_2-R_6, R_2'-R_6' = H, Cl, OH$ **20****21**

probably bind deep at the bottom of the binding site, where the phenolic ring of L-T4 binds, making very effective hydrophobic and van der Waals interactions. The complementarity of these *ortho*-halophenol structures to the binding site in this deep, solvent-shielded region is identical to L-T4's, so that they are almost completely buried within the site (Figure 27), while the outer portion of L-T4 is well exposed to solvent. The diphenyl ether oxygen of T4 is buried in a hydrophobic region of the site, with no hydrogen bonds to compensate for its desolvation, while **20** and **21** have hydrophobic groups (iodo and phenyl) at this site. This suggests that perhaps the critical factor in determining binding affinity is how much of the ligand's hydrophobic surface is buried by complementary portions of the receptor. The work of McKinney and co-workers (166,221) illustrates that there are still surprises and discoveries to be made even when designing molecules based on the X-ray crystal structure of a receptor site; it is not obvious what the best candidates



are and even simple molecules can easily be overlooked. Pedersen et al. (26) used molecular mechanics calculations with simple empirical solvation corrections to simulate the binding of the dioxin and PCB analogs to prealbumin; their results showed good qualitative agreement with the experimental relative binding affinities.

J. Molecular Modeling and Antibodies

In the absence of X-ray diffraction data, a combination of monoclonal antibody technology, binding assays, quantitative structure–activity relation-

ships, sequencing technology, and computer graphics model building can provide speculative models of the molecular interactions that occur between drugs and receptor proteins.

Antibody production for specific antigens is a mature technology that may be an important part of molecular modeling in the future. The binding region of immunoglobulins, which includes the portion of the molecule with the most variability in its amino acid sequence, has a surprisingly constant three-dimensional structure than can be characterized in simple, well-defined models (222). The interface forming the binding region consists of two closely packed β -sheets with cylindrical barrel geometry. Since antibodies presumably use the same "rules" as other receptor and enzyme proteins to bind ligands, knowledge of antibody–ligand molecular structures and interactions could be useful in suggesting possible synthetic variations. The general validity of this concept is supported by the success in generating antibodies toward transition-state analogs, which show stereoselective catalytic activity similar to enzymes, with rate enhancements observed up to several million-fold (223, 224).

A few X-ray crystal structures of the antigen binding Fab portion of antibodies are available (225–231). From what is known of these structures it appears that the antigen specificities shown by immunoglobulins result from a small variable region that is directly involved in ligand binding and a highly conserved invariant superstructure. For modeling purposes, this suggests using the conserved region as a framework on which to construct the variable antigen-binding loops (88, 232–237). The validity of the method has been demonstrated by comparing the predicted structure for the anti-lysozyme antibody with the actual 2.8 Å resolution X-ray studies (238). Once the desired monoclonal antibody is isolated, the amino acid sequence can be determined (by DNA sequencing) to characterize the variable region involved in antigen binding and this information can be used as the starting point for modeling studies and crystallography. X-ray crystallography of monoclonal antibodies is usually much easier than solving new protein structures due to the large quantities of pure antibody that can be prepared and its highly conserved structure, which often allows molecular replacement techniques to be used without the need for preparing and solving heavy atom derivatives.

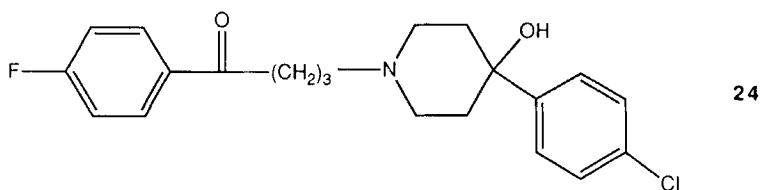
Two common approaches to immunoglobulin modeling differ in how they handle the critical binding site (hypervariable) loop structure. The first approach looks only at the amino acid sequence in deriving possible local structures (232, 239, 240). This approach suggests that these conserved hypervariable residues will have differing conformations depending on sequence. A second approach uses the idea that loops of equivalent length will have similar secondary structure independent of sequence (234). By using this strategy hypervariable segments from known structures are spliced into the

region of interest. Recent findings tend to argue for a combination of approaches. Thus, Kabsch and Sander (239) have shown that an identical five residue sequence appearing in several proteins can have several different conformations; the same sequence appears in helices, sheets, and turns. This suggests the amino acid sequence is not the sole determinant of conformation and the environment this sequence finds itself in is certainly important. In a second study, Jones and Thirup (69) found substantial conservation in protein structures beyond the typical helix and β -sheet structural units, particularly in the less-well-defined loops and turns. Thus, structural elements from one protein can be used in the construction of a second.

Feldman and co-workers used a combination of techniques to construct plausible hypervariable loops into the galactan-binding myeloma protein J539 (237) and lysozyme-binding antibody (241), using energy minimizations to optimize the structures. Because molecular mechanics shows strong dependence on the starting structures, and because of problems with local minima, molecular dynamics may be a better choice.

Recently, de la Paz et al. (242) modeled the binding sites of several antilysozyme monoclonal antibodies (mAbs) using both splicing and energy minimization techniques. Chothia and co-workers (88) used a similar approach to model their own anti-lysozyme mAb with more emphasis on preserving the orientation of the structural hypervariable residues. This model was recently confirmed by X-ray crystallography (243).

If a monoclonal antibody can be selected with a similar structure-activity profile to antigens that the target receptor shows to the same ligands, the antibody may in fact be a reasonable model for the receptor. Sherman and Bolger (244) applied the strategy of using antibodies as receptor mimics in their investigation of the binding of the dopaminergic D-2 antagonist haloperidol (24) to five different monoclonal antibodies. The amino acid sequences of these



antibodies were obtained and used to build three-dimensional models of the variable region binding sites. Their results indicate that hydrophobic, aromatic, and ionic amino acids are involved in specific interactions with the ligand molecule. From fluorescence studies the fluorophenyl ring of haloperidol was predicted to stack with the electron-rich typtophan ring of the antibody loop at a distance of about 3.3 Å. Making this association places the

positively charged piperidinyll nitrogen of haloperidol within hydrogen-bonding distance of the negatively charged Glu-95 and Asp-100 of the H3 loop. This orientation is consistent with much of the structure-activity relationships derived from binding data to the dopamine receptor, suggesting the structure of the antibody may resemble that of the receptor. Evaluation of binding of haloperidol analogs to the antibodies showed:

1. An inter-ring chain of exactly four atoms was required for good binding.
2. A narrow, sp^3 hybridized grouping was required at the keto position.
3. Small substituents were needed in the fluorine position.
4. High electron density was necessary on the substituent in the chlorine position.

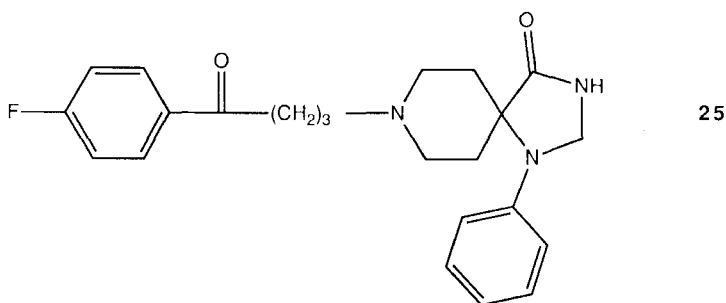
From their antibody model of the dopamine receptor these observations could be explained at a molecular level:

Points 1 and 2 above are required for ring stacking and positioning of the protonated piperidine nitrogen atom over negatively charged residues in the binding site.

Point 3 results from placing a fluorine atom in a small pocket as a result of ring stacking.

Point 4 is probably due to the presence of two residues with conjugated π systems in the vicinity of the chlorine atom (Tyr-91, Asn-32 of light chain) for which charge-transfer interactions could be imagined.

Additionally, spiperone (**25**) binding can be rationalized using this model by noting that a Tyr-32 of the heavy chain is ideally oriented for a perpendicular ring stacking interaction with the spiperone phenyl ring.



The characteristics of one of the antibodies in the structure-activity relationships of binding haloperidol analogs was quite close to what is accepted as a reasonable pharmacophore map for the dopamine receptor;

none of the antibodies, however, precisely matched the proposed receptor map. In a summary of their work, Sherman and Bolger suggest the following guidelines for the production of receptor-like antibodies:

1. The drug should be somewhat rigid to prevent the formation of antibodies that bind an inactive conformer of the drug.
2. The drug must be attached to the carrier protein in a fashion such that moieties believed to be directly involved in receptor binding are fully exposed and available for antibody recognition.
3. Antibodies with a range of affinities for a given hapten should be characterized; high-affinity antibodies do not necessarily possess the most receptor-like binding sites.

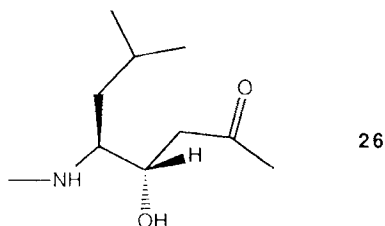
The authors also point out that there may be a limited set of amino acid residues that are capable of binding a given chemical feature, such as haloperidol's fluorophenone moiety or piperidine nitrogen. The antibody residues selected in response to these groupings therefore suggest possible receptor binding site residues.

K. Renin

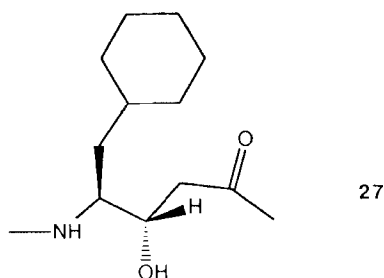
Angiotensin II(AII) is an important molecule in the regulation of blood pressure; high levels of AII lead to high blood pressure or hypertension. The enzyme renin catalyzes the cleavage of angiotension I from the inactive proenzyme angiotensinogen. Angiotensin I, in turn, is converted by angiotensin converting enzyme (ACE) into angiotensin II by cleaving the carboxyl-terminal dipeptide from AI. Inhibitors of ACE are now well known. Reducing the concentrations of AII by either an ACE or renin inhibitor should lead to a lowering of blood pressure.

Renin belongs to a class of enzymes known as the aspartyl proteases. The availability of high-resolution X-ray structures of several aspartyl proteases (pepsin (245), *Rhizopus chinensis* pepsin (246), penicillopepsin (247), endo-thiapepsin (248), complexes of rhizopuspepsin-pepstatin (246) and penicillopepsin-tetrapeptide (247)) and of the amino acid sequence of human renin (249, 250) have spurred efforts to construct, by molecular modeling and computer graphics techniques (251), three-dimensional models of renin (83–86). These models have been used to predict the modes of substrate binding and to suggest possible inhibitors (252, 253). To date most of the inhibitors suggested by these studies have been peptides, often modified with unusual amino acids (e.g., statine, **26**) to produce transition-state inhibitors and metabolically stable cyclic peptides.

The challenge is to convert these metabolically labile, poorly absorbed peptide structures into more stable organic structures (cf. enkephalins and

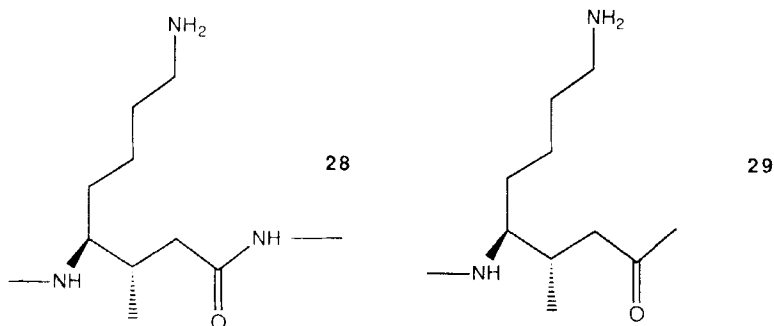


morphine (254, 255), CCK and asperlicin (256)). X-ray crystal structures of pepstatin bound to *Rhizopus* pepsin (246) and of the complex of peptide analog Iva-Val-Val-Sta-OEt with penicillopepsin (247) have served to locate binding interactions between these ligands and the active site residues of the protein. Computer graphics analysis of the binding of pepstatin to *R. chinensis* pepsin (246, 257) suggested additional binding might be obtained by the addition of alkyl groups to the statine residue **26** or by extending the isobutyl side chain of statine to a cyclohexylmethyl group (cf. **27**). It is indicative of the

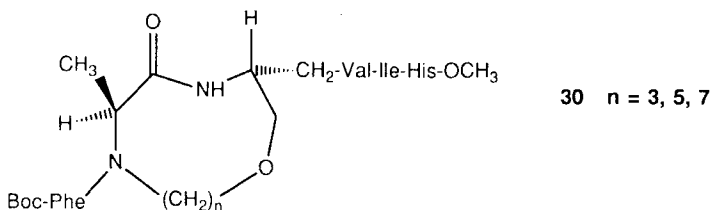


uncertainties in modeling, that whereas these compounds were found to be more active against human renin than the corresponding statine-derived inhibitors, *they were not more potent against the R. chinensis pepsin, the enzyme which was used in the modeling study!*

Salituro et al. (258), using a penicillopepsin-tripeptide complex, designed modifications to enhance interactions between ligand and enzyme. using the fact that the fungal aspartic proteinases prefer to cleave the Lys-Xxx bond, and lysine in this position enhances binding, they replaced the isobutyl side chain in statine in the inhibitor Iva-Val-Val-Sta-OEt with the 4-aminobutyl side chains of lysine (LySta, **28**) and the 3-aminopropyl group of ornithine (cf. **29**). The enhanced binding of these compounds takes advantage of an electrostatic interaction between the new LySta and the carboxyl group of Asp-77. Consistent with this, these compounds showed substantially weaker binding against the porcine pepsin, an enzyme known to prefer hydrophobic



residues at the cleavage site (e.g., Leu-Leu, Phe-Phe). X-ray analysis of the complex of Iva-Val-Val-(LySta)-OEt (247) showed that small rotations in the LySta side chain moved these atoms away from the original position of the statine isobutyl side chain and allowed the protonated amine of LySta to approach Asp-77, a result that was not foreseen in the original modeling (259). Based on their own model of renin, Sham et al. (96) designed conformationally constrained cyclic peptides ligands (30). These cyclic compounds were based



on the proposed active site binding of a known linear hexapeptide inhibitor with a reduced amide replacing the scissile bond. Modeling was done to achieve cyclization without altering the preferred conformation as suggested by the fit of the linear peptide. While the 12- and 14-membered ring compounds were active, the 10-membered one was not. This lack of potency was traced, by NMR and molecular modeling techniques (96), to the presence of a cis peptide bond that forced the 10-membered ring into a configuration unacceptable for binding.

Foundling et al. (260) determined by X-ray crystallography the three-dimensional structures of 31 and 32 complexed with endothiapepsin. These

Pro-His-Pro-Phe-His-Leu^R-Val-Ile-His-Lys 31 Leu^R = Leu with reduced peptide bond

Boc-His-Pro-Phe-His-...Sta-...Leu-Phe-NH₂ 32

P6 P5 P4 P3 P2 P1 P1' P2' P3'

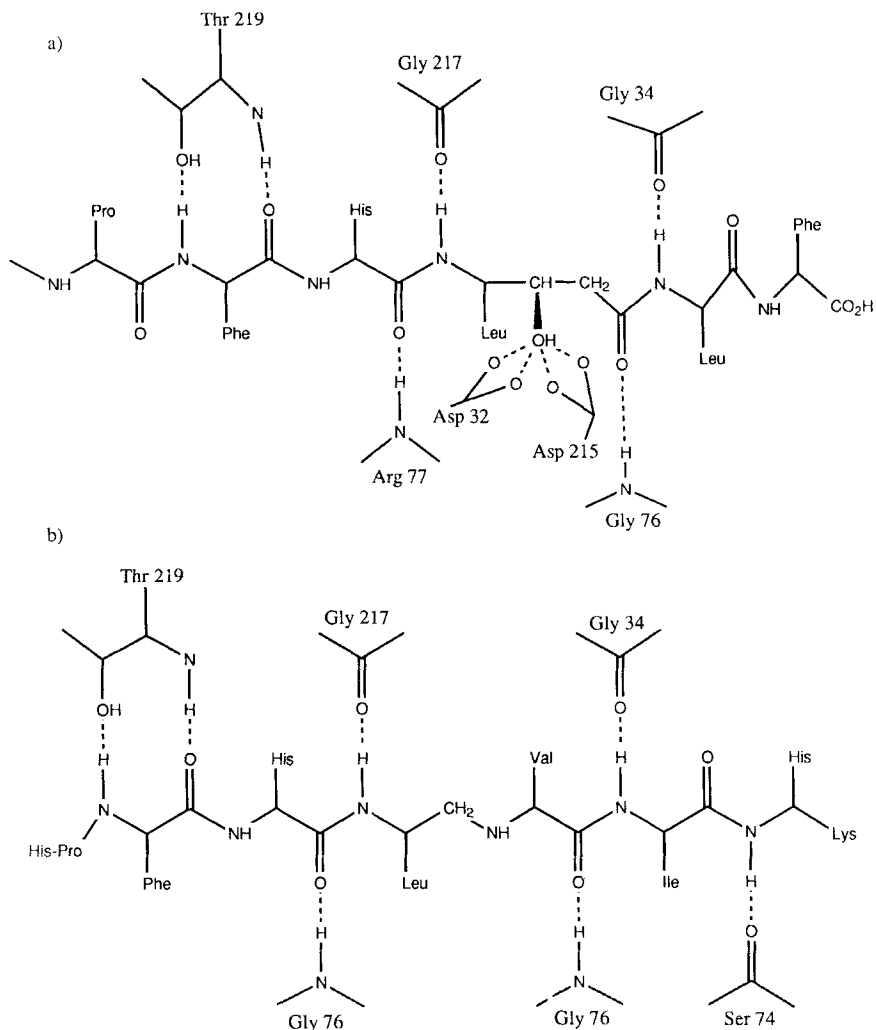


Figure 28. A schematic representation of the extensive backbone hydrogen bonding between (a) compound 32 and (b) compound 31 with the enzyme endothiapepsin. These inhibitors displace waters bound to Asp-32 and Asp-215 in the uncomplexed enzyme.

inhibitors bind in a deep cleft between the amino and carboxyl terminal lobes of the endothiapepsin. The transition-state isosteres at P1-P'' (reduced amino acids and statine) are in close proximity to the two catalytic carboxyl groups of Asp-32 and Asp-215 in the center of the cleft. The residues in P3-P1 of each inhibitor form an antiparallel β -pleated sheet with residues

219 to 217 of the enzyme through an extensive hydrogen bond arrangement (Figure 28). While the residues P3 and P4 for each inhibitor bind in a common and well-defined conformation, the residues at P2, P5, and P6 show considerable variation in their interactions. These and other observations of the binding of these compounds suggest that inhibitors tend to be somewhat "promiscuous, exploring relationships with various residues of the enzyme in their vicinity" (260). The similar hydrogen-bonding pattern and location of P4, P3, and P1 in the hydrophobic pockets of the enzyme position the inhibitors "transition-state-mimicking residues" close to the two active aspartic acid residues, Asp-32 and Asp-215. In **32** the hydroxyl of the statine displaces a water molecule and occupies its position in the active site of the native enzyme. Although few changes of the protein conformation apparently occurred on binding of these inhibitors, there was a slight repositioning of the residues in the "flap region." This is a highly flexible part of the enzyme that must open to allow access of the inhibitor to the active site cleft. This flap action ensures an environment that excludes solvent and encapsulates the substrate or inhibitor.

L. Serine Proteases

The serine proteases represent an important class of enzyme as targets for directed inhibitor design. The crystal structures of several of these enzymes are available (14) and they have been the subject of extensive studies in homologous model building (68). These proteases are involved in many biological processes including blood coagulation, complement activation, protein degradation, and chemotaxis.

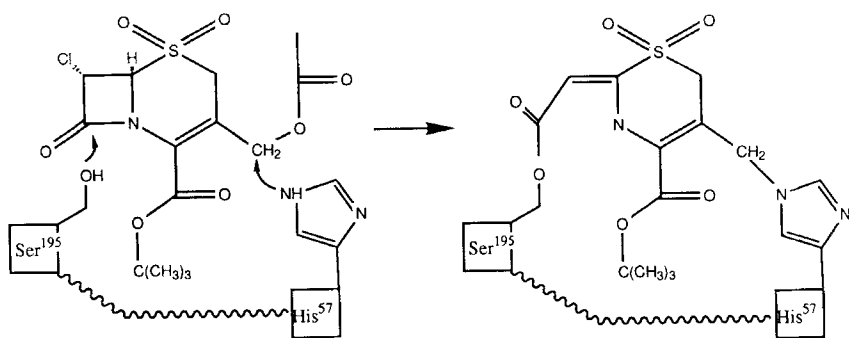
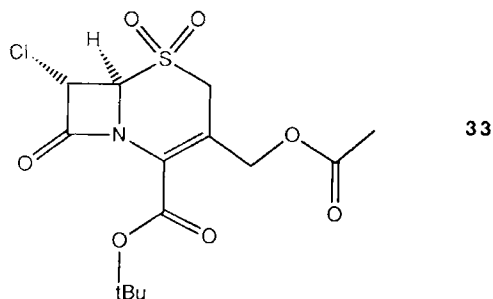


Figure 29. The reaction of haloenol lactone inhibitors of chymotrypsin with Ser-195 and His-57 (103).

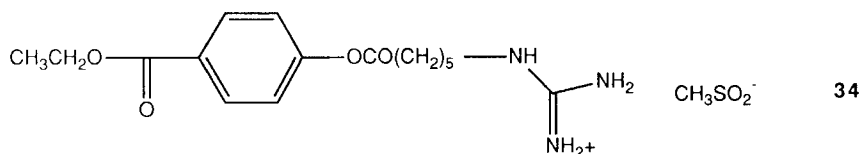
Computer graphics and molecular mechanics have been used to study the inhibition of chymotrypsin by three haloenol lactone enzyme-activated irreversible inhibitors (103). These inhibitors transfer the lactone acyl group to Ser-195 with subsequent alkylation of His-57 by the halomethyl ketone (Figure 29). Calculations of the inhibitor-enzyme complex were useful in proposing a detailed mechanism of action and guiding further synthetic efforts. In the mechanistic study, three stages of binding were evaluated in atomic detail: the non covalent substrate complex (Michaelis complex), the acyl enzyme alkylation complex, and the "suicide complex." This work is a useful study in one possible strategy for attacking a general modeling problem. Interestingly, the van der Waals stabilization energy (ΔE before and after docking the substrate in the active site) paralleled the inhibition constants (K_i).

In a similar case, Navia et al. (261) solved the structure of the complex of the irreversible inhibitor **33** with porcine pancreatic elastase at 1.84 Å resolution.



Study of this protein-inhibitor complex provides a good model for the action of β -lactams and could lead to additional synthetic design.

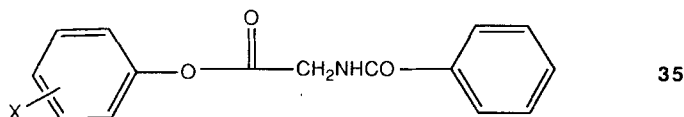
Gabexate mesylate (ethyl 4-(6-guanidino hexanoyl oxy)benzoate methane sulfonate), **34**, is a synthetic inhibitor of serine proteases that has been used



therapeutically for pancreatitis and intravascular coagulation. Molecular modeling was used to predict the binding of this inhibitor to bovine β -trypsin and to porcine pancreatic β -kallikrein-B (262) as prototypical serine proteases. It was modeled into the active site of these proteins with the ϵ -guanidino group, making an ionic interaction with the negatively charged Asp-189. A second site, taken into account in the modeling, was the oxyanion site where

the carbonyl oxygen of the central ester group hydrogen bonds to amide hydrogens of Ser-195 and Gly-193. In this orientation the inhibitor occupies a position similar to the crucial peptide bond of other proteinase inhibitors with respect to His-57 and Ser-195. In fact, gabexate mesylate must bind in a very similar way since it is cleaved by human pancreatic proteases. From the measured enzyme--gabexate mesylate affinities to different serine proteases the following order was found: human urinary kallikrein, porcine pancreatic β -kallikrein-B $\ll$ bovine β -trypsin, bovine factor Xa, human Lys-77-plasmin, human urokinase, bovine α -thrombin. These differences in affinities for these proteases may reflect structural differences at their primary specificity subsites and could allow alterations of the gabexate mesylate framework to tailor inhibitors for specific proteases.

Morgenstern and co-workers (263) used interactive computer graphics to analyze the binding of a set of substituted phenylhippurates **35** to chymotrypsin. A model of these substituted phenylhippurates in the active site of



chymotrypsin was constructed based on the X-ray crystallographic coordinates for chymotrypsin. These models were constructed by adding substituents to the known phenylhippurate coordinates using standard geometries. The fit of these substituted hippurates was done with interactive computer graphics with the aid of both rigid-body energy minimization and limited, conformationally flexible fitting. The resultant fit predicts expected activity of different analogs and was consistent with the experimental structure-activity relationships found for this series. Interestingly, from a design viewpoint, when polar substituents have the option of binding to hydrophobic space or remaining in solvent, this study (and others on the cysteine proteases papain and actinidin (178)) has shown they prefer to remain in solvent. This can be important when substituents are added for purposes other than to improve binding, for example, to improve solubility or to block metabolism.

X. THREE-DIMENSIONAL PHARMACOPHORE MODELING

A frequent problem facing one interested in ligand design is that in which the structure of the receptor is unknown and must be deduced from systematic variation of the structure of some lead compound, often found by randomly screening compounds from a large database in biological or biochemical test

systems. Such a study frequently suggests substructures (functional groups or individual atoms) that are important for binding or activity and the three-dimensional orientation of these critical molecular features describe what is known as the *pharmacophore*. After defining the pharmacophore, the problem is then to determine how the individual molecules can be superimposed to align the common pharmacophoric groups and thereby indirectly define a model for the receptor. This superimposition is usually a very difficult problem since the molecules may be structurally different and conformationally flexible.

An important problem shared by all the current approaches is the difficulty in determining a unique, well-defined binding model that includes conformationally flexible ligands; this is usually a very underdetermined problem.

A. The Active Analog Approach

The "active analog" method of Marshall and co-workers (10, 134, 264, 265) uses the composite volume of a set of superimposed, active compounds to define the volume and shape of the binding site. The approach uses a systematic search (performed by incrementing each rotatable bond a small amount until all possible combinations are exhausted) to search through all possible combinations of rotatable bonds in each molecule to find every allowed conformer, and then find conformational subsets that align the pharmacophoric groups. Multiple sets may be reduced to a single unique site by consideration of the maximum distortion energy of any member of this set to adopt the required "binding conformation." The "unique site" is then used to examine inactive compounds to ensure that they are consistent with the model, for example, compounds with the prerequisite pharmacophoric groups that can be oriented correctly but are inactive since they require large distortion energies to adopt the required conformation. The volume of the "bound" set of active analogs also determines the minimum available space for binding. One possible explanation for inactive compounds is the occupancy of volume outside that defined by the set of bound active compounds. Extensions and applications of this approach have been reviewed (10). While the primary use of pharmacophore models has been to explain the binding characteristics of different classes of known ligands to their respective receptors, novel antidepressants (266) and diuretics (267) have been designed based on such maps.

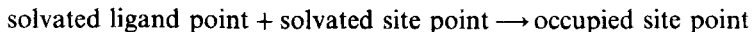
B. Ensemble Distance Geometry

The "ensemble" distance geometry pharmacophore modeling approach of Sheridan et al. (145) provides the most direct and efficient method for

generating three-dimensional pharmacophore models. Distance geometry provides a simple solution to the problem by entering all the molecules simultaneously into a single distance bounds matrix and then specifying intermolecular constraints to force the common pharmacophoric groups to become superimposed. No time is wasted searching conformations that cannot fit the pharmacophore; instead, only those conformations that fit the pharmacophore are sampled. This approach determines rapidly if any solutions exist and, if so, provides a unbiased, random sampling of solutions which indicates how uniquely determined the model is. Additional advantages of this approach are that it handles rings naturally without the ring closure difficulties encountered in dihedral search methods and that chirality can be allowed to vary for any stereo centers of unknown absolute configuration (simply by omitting the chiral constraint for that center). Sheridan et al. (145) used the ensemble method to generate models for the nicotinic receptor pharmacophore. The method is implemented in the distance geometry program DGEOM (132).

C. Distance Geometry QSAR

Crippen applied distance geometry to the problem of three-dimensional receptor mapping (268). QSAR techniques had been known since the early 1960s as a means to quantitatively correlate compound functionality with biological binding data (178). Crippen's approach allowed a similar correlation of binding data with the added advantage that three-dimensional geometric details of the binding site could be inferred. His mapping procedure deduces the geometric requirements of the receptor site based on the experimental data of binding affinities of a series of ligands and hypothesized binding modes (i.e., pharmacophore model) for each ligand. It is important that this applies even to conformationally flexible ligands. All ligands were assumed to bind to the same site on the receptor and any free-energy input due to conformational changes on binding was assumed to be small compared to the free energy of binding. The site itself was allowed limited flexibility. The free energy of binding was taken to be approximately equal to the sum of the "interaction energies" in all instances where the site points (regions on the receptor) were occupied by ligand points (regions on the ligand). Not considered were the conformational changes of the ligand upon binding, nor its loss in translational energy and degrees of rotational freedom. The point to point interaction energy, however, could be considered to be the ΔG for the process:



The overall procedure involved the following steps:

1. Free energy of binding values are experimentally determined for a series of ligands.

2. Each ligand is represented by a collection of points, called ligand points, which correspond to atoms or groups of atoms. This simplifies the calculations and is necessary for larger ligands to make the problem computationally feasible. Careful selection of these points is clearly important since the outcome of the analysis depends on them. Conformational flexibility of the ligands is accounted for by using the upper and lower bounds of the interatomic distances over all sterically allowed conformations.

3. Site points are proposed, representing several empty or filled site pockets, which must interact with specific ligand points. These were originally chosen after an analysis of the way the collection of ligands could possibly bind to a receptor and were suggested by common features of the ligand molecules. An empty site point provides an opportunity for binding if a suitable ligand point is placed in the immediate vicinity (within some small range). A filled site point, however, is used to indicate the location of a steric blocking group, which prevents a coincident ligand point. Because of the qualitative way in which site points are chosen, there is no guarantee the site chosen is unique.

4. All possible geometrically allowed binding modes are generated, in which each possible binding mode consists of a case in which ligand points coincide with empty site points.

5. For each possible binding mode, including the proposed mode, an "energy table" is created by regression analysis versus the observed binding free energies to estimate the interaction energy of ligand points with site points. The calculated free energy of binding is obtained by adding the contributions from each constant between a ligand point and a site point for each binding mode. Each point-point interaction energy is taken to be the ΔG for the binding process and incorporated solvation, enthalpy, and entropy. The final model is chosen to be that which best fits the observed binding free energies. The binding calculation avoids the temptation to bias the fits and avoids preconceptions on how a particular ligand might bind.

Two cases were studied by Crippen (268). The first was a set of eight phenoxyacetone inhibitors of chymotrypsin. A set of site points was developed that rationalized the experimental binding data. Although the X-ray crystal structure of α -chymotrypsin was known, no structures of a complex with the phenoxyacetone inhibitors were available and therefore a direct comparison of Crippen's site points with the X-ray structure was not possible. It was possible, however, to fit these site points and the ligand into the chymotrypsin X-ray coordinates and show they were compatible.

The second case used the binding of a series of quinazoline inhibitors to *S. faecium* dihydrofolate reductase (269). In this case, six site points were used to represent the binding site of the dihydrofolate reductase and the data for 22 inhibitors were correlated. Again the site points and ligand were compared with the only available crystal study at the time, a methotrexate complex of *E. coli* dihydrofolate reductase, and shown to be consistent.

This analysis generates a three-dimensional geometric representation of an active site (given a collection of known ligands) that involves both energetic and steric features. Since it predicts the mode of binding as well as the energies, it offers the opportunity to suggest conformationally restricted analogs that might maximize binding to the site.

A weak point in the above analysis is clearly the determination of the site points. It is necessary to guess the number and kinds of site points and assign specific ligand points for them to interact with. To improve this, Crippen developed algorithms to aid in these decisions (270). A decomposition algorithm was used to determine the points that were common to all the ligand molecules. At this point a unique set of substituent groups, needed to account for all the remaining points of the ligands, was determined. Since site points were eventually based on the location of these substituent points, inherent to this method is that a plausible binding mode for each ligand must be selected in advance. One site point was chosen for each of the points common to all the ligands, as well as for each geometrically distinct substituent group. The geometries of the "common points" and the substituent groups were helpful in deciding on the number of different site points required. On the basis of these specified binding modes, the site point distance bounds and their coordinates were evaluated. The set of proposed binding modes implies constraints on the arrangement of the site points in space, and distance geometry produced a sampling of allowed site point coordinate sets. In the last stage, the energy parameters were determined. A few were explicitly fixed at a large positive value to represent severe steric constraints, while the others were determined by an optimization routine that fit the observed binding energies to the occupancy of empty site points.

A quick check on the consistency of the data and the assumption of a constant binding mode was undertaken by doing a least-square fit of the observed free energies of binding (estimated from the IC_{50} , the concentration required to produce 50% inhibition) to the sum of the contributions of each component group (substituent points) for each of the ligands in the experimental set. If the constant binding mode assumption gave a satisfactory fit to the observed binding data, the site and energy parameters could be produced directly. If this assumption were not valid, however, it suggested certain ligands were not fitting the general pattern. Comparison of these deviant ligands with the "normal" ones suggested alternate modes of binding.

An expanded analysis of 68 quinazoline inhibitors of DHFR using this improved technique gave a RMS (root mean square) difference between observed and calculated fits of 1.33 kcal (experimental error about ± 1 kcal) (271). In addition to this correlation, the possibility of a variable binding mode of some inhibitors was noted and some suggestions were made to modify these quinazolines to make tighter binding ligands.

Further improvements were made with the introduction of methods to deal with chiral ligands (272). In a distance matrix there is no way to distinguish between enantiomers (both give the same distance matrix). They can, however, be distinguished by calculating a "signed volume" of the tetrahedron formed by the four atoms attached to the asymmetric center. Using this technique, Crippen analyzed the binding data for 27 chiral analogs of thyroxine interacting with human prealbumin (272). The receptor site incorporated the observed stereospecificity of the bound ligands and the calculated free energies compared well with the observed (RMS = 0.5 kcal/mol). The binding of three additional analogs, not included in the original data set, were accurately predicted. The geometry of the proposed binding site was consistent with the X-ray crystal structure of the T4-prealbumin complex.

D. Comparative Molecular Field Analysis (COMFA)

Cramer et al. (273) described a new approach to three-dimensional QSAR. A pharmacophore model must be proposed and used to superimpose all the ligands (in a fixed conformation) to define the binding mode. Cramer et al. then calculate the interaction energies for a variety of probes on a three-dimensional grid surrounding each ligand (similar to Goodford's approach (20, 21)), followed by partial least-squares regression analysis to correlate the probe energies at specific grid points with the observed free energy of binding. Those grid points included in the final correlation are presumed to map critical regions of the receptor. While the technique looks very promising for rigid ligands (the initial example was on steroids), it is not clear how unique the resulting correlations and their implied three-dimensional receptor models will be for conformationally flexible ligands. Even for rigid ligands, it is not certain that a unique correlation will be generated that can differentiate between different possible choices of the pharmacophore.

XI. SUMMARY

Molecular modeling approaches to ligand design based on the three-dimensional structures of macromolecular receptors are still very new; research in this area began in the 1970s and has continued at a rapidly

increasing rate as more receptor structures become available due to advances in X-ray crystallography, and computer hardware and software improves and becomes less expensive. Most pharmaceutical companies and many universities now have research groups in molecular modeling; the number of publications in this area has increased dramatically in the last several years. Guidelines suggesting publication standards for molecular modeling research were recently proposed (274).

Early on, we believed that once we had the detailed three-dimensional structure of a receptor in hand that it would be easy to design an optimum drug; after all, much of classical medicinal chemistry and drug design is oriented toward defining a model of the receptor site based on the structures and activities of the compounds that interact with it. We have now had this opportunity with several different receptor structures and found that there are still formidable challenges to overcome, but that receptor-based design and the variety of powerful modeling and QSAR methods that can be used with it undoubtedly provide the best possible chance for success in rational drug design.

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Acyclic Stereocontrol in Michael Addition Reactions of Enamines and Enol Ethers

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I. INTRODUCTION

Conjugate addition of a nucleophile to an activated olefin is generally referred to as a Michael addition reaction (1). Of particular interest is the addition of delocalized carbanions to unsaturated acceptors, a process resulting in the construction of a carbon–carbon bond, often stereoselectively (2). However, the addition of metal enolates to unsaturated acceptors is not completely general and two major modifications have been developed wherein covalently bound enolate equivalents are added to unsaturated acceptors.

The first of these modifications was developed by Stork and co-workers, who explored the synthetic utility of enamines as enolate equivalents (3). One class of electrophiles that react with enamines are “electrophilic olefins,” α,β -unsaturated aldehydes, ketones, esters, amides, and nitriles.

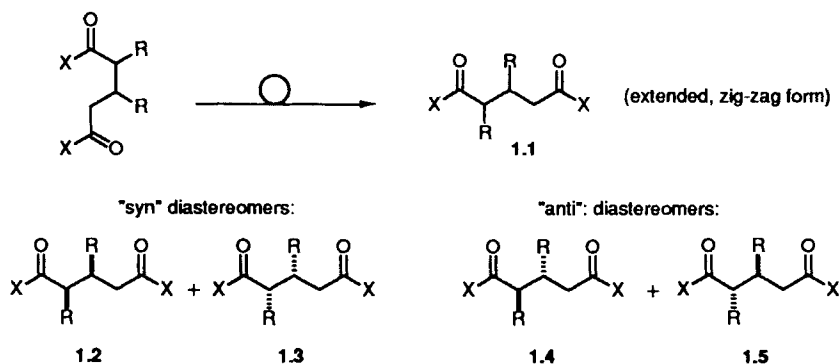
The second major modification was developed by Mukaiyama and co-workers (4) and Hosomi and Sakurai (5). These workers found that weakly nucleophilic silyl enol ethers and allylsilanes add to α,β -unsaturated ketones that have been precomplexed with a Lewis acid. This process formally mimics the protic-acid-catalyzed Michael addition but allows for regiocontrol over enol generation.

Thus, present technology permits conjugate addition of stabilized carbon nucleophiles under formally basic (enolate), neutral (enamine), or acidic (Lewis acid) conditions. In general, the softer enamine and enol ether additions show a greater preference for 1,4- over 1,2-addition than do isosteric metal enolates.

The focus of this chapter is on the stereoselectivity of the conjugate addition of the Lewis acid and enamine Michael additions. Only donors that are formally enol equivalents are considered. Selectivity that results from preferential addition to one of the faces of an endocyclic enamine or enol ether as a result of the influence of a stereocenter in the ring is not emphasized. In general, the factors that control the stereochemistry in these instances are analogous to those active in the reactions of other electrophiles with such compounds.

II. TERMS AND NOMENCLATURE

Concerning the relative configuration of stereocenters in the products, the nomenclature used here is (usually) the syn/anti convention currently used for acyclic aldols and related compounds (6–8). To apply this convention, the carbon backbone is drawn in its longest extended (zigzag) form such as for **1.1** (Scheme 1). If both substituents on the chain project in the same direction from the plane of the carbon backbone as in **1.2** or **1.3**, then the descriptor is syn. If the two substituents project in opposite directions from the plane of the carbon backbone as in **1.4** or **1.5** the descriptor is anti.[†]



Scheme 1

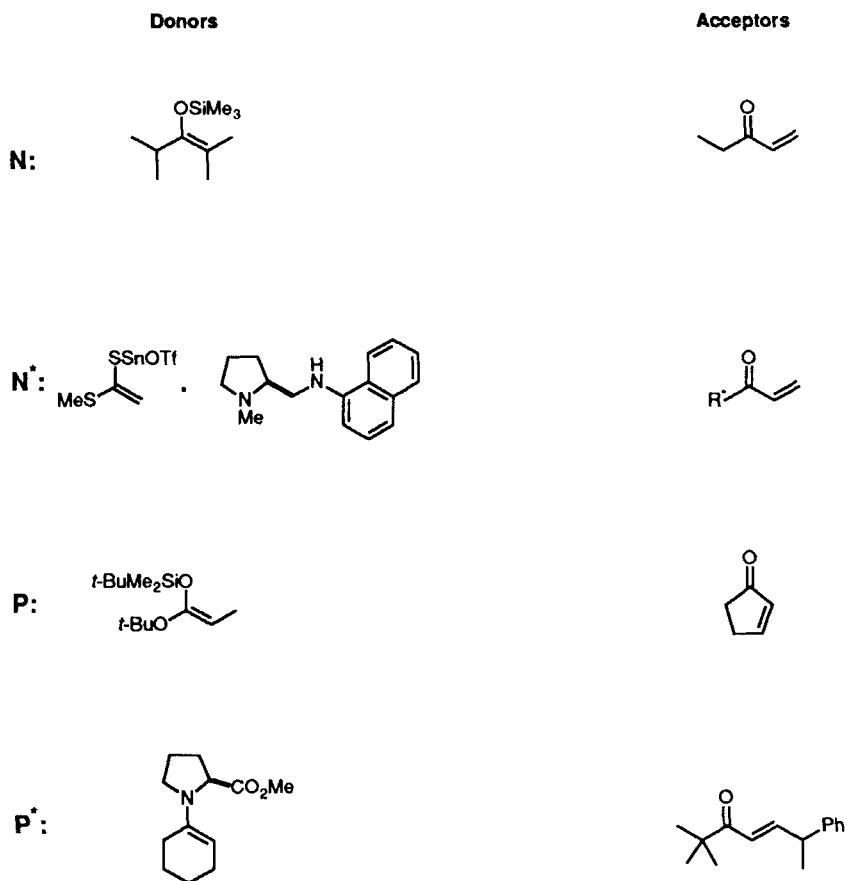
In any bimolecular reaction, four different types of component can be combined in 16 different ways.[‡] The four general types of substrate are (Scheme 2):

1. An achiral donor or acceptor where reaction occurs at a center that is not prostereogenic (**N**).
2. A chiral donor or acceptor where reaction occurs at a center that is not prostereogenic (**N***).
3. An achiral donor or acceptor where reaction occurs at a center that is prostereogenic (**P**).

[†]For a brief discussion of the limitations of the syn–anti nomenclature system with respect to assigning structures of products from Michael additions see ref. 2 pages 236–237. Here, we again define the "longest linear chain" as the chain of the adduct that includes both the donor and acceptor portions of the reactants.

[‡]For a somewhat more expanded discussion, the reader is referred to ref. 2, pages 237–242.

Examples of Reaction Components



Scheme 2

4. A chiral donor or acceptor where reaction occurs at a center that is prostereogenic (**P***).

(The term "chiral compound" also applies to an achiral compound in a chiral, non-racemic medium.)

Here, reactions are classified by the types of component that are combined. Hence, addition of a **N*** donor to a **P** acceptor is denoted [**N***, **P**]. Similarly, reactions of **P*** donors and **N** acceptors are labeled [**P***, **N**].

The stereoselection process that occurs in the [P,P] union is called simple diastereoselection. In [P*,N] and [N,P*] fusions, diastereofacial selection can occur. Situations in which both selection processes (simple and diastereofacial) are operative are [P*,P], [P,P*], and [P*,P*]. Furthermore, in [N*,P] and [P,N*] cases, the possibility of diastereofacial and pseudo-simple diastereoselection[†] exists.

III. ENAMINES

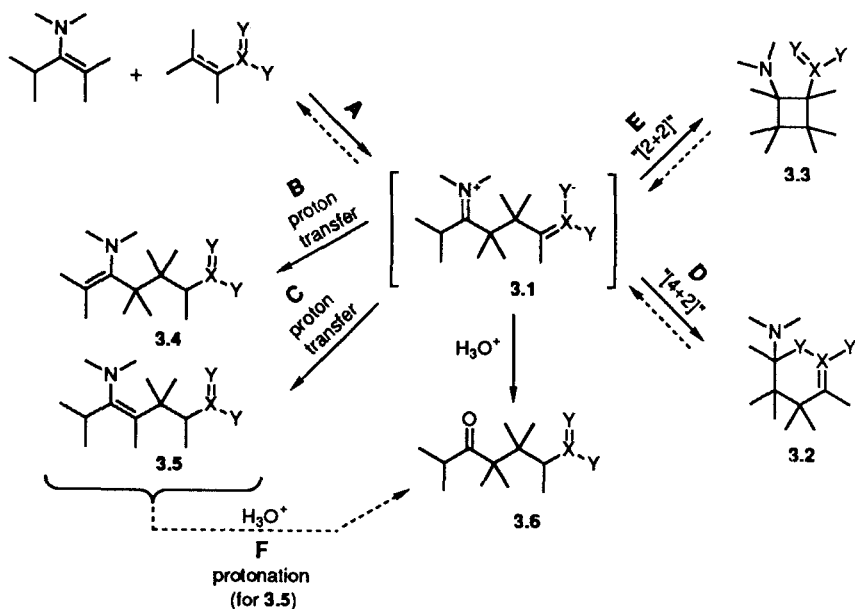
A. Preparation and Regiochemistry

Enamines (3) are usually prepared from secondary amines and ketones or aldehydes under dehydrating conditions. Removal of water is usually facilitated by azeotropic distillation or by the addition of a dehydrating agent. In the solid state, enamine nitrogens often exhibit some degree of pyramidalization (10), the precise amount of which depends on the substrate (11). The regiochemistry and stereochemistry of enamine preparation and the reactivity of the enamines produced depends strongly on structure, with allylic strain and electronic considerations being particularly important. Additionally, isomeric enamines are often easily interconvertible under mildly acidic conditions. Consequently, it is sometimes found that the product distribution depends not only on the relative stability of various enamine isomers but also on their relative reactivity.

In addition to steric considerations, a factor that profoundly influences the reactivity of enamines is the ability of the nitrogen lone pair to achieve conjugation with the olefinic π -system. As enamine additions usually lead to zwitterionic intermediates (*vide infra*), coulombic considerations are often vital and fairly subtle changes in structure can result in striking changes in reactivity. As a complete discussion of the factors controlling both the generation and reactivity of enamines is beyond the scope of this discussion, readers are directed to recent discussions (12).

Reactions of enamines with activated olefins can give several possible products (Scheme 3). The exact composition of the adducts formed depends critically on the substrates employed and the reaction conditions utilized. An initial zwitterionic adduct (3.1) is believed to be the first intermediate formed. Intermediate 3.1 is usually unstable under the reaction conditions and undergoes one of four possible transformations. Cyclization of 3.1 can occur in two ways. Intramolecular closure can occur by addition of the acceptor-stabilizing substituent (Y) to the carbon of the immonium ion to provide 3.2

[†]The term pseudo-simple diastereoselectivity is defined in ref. 2, page 391.



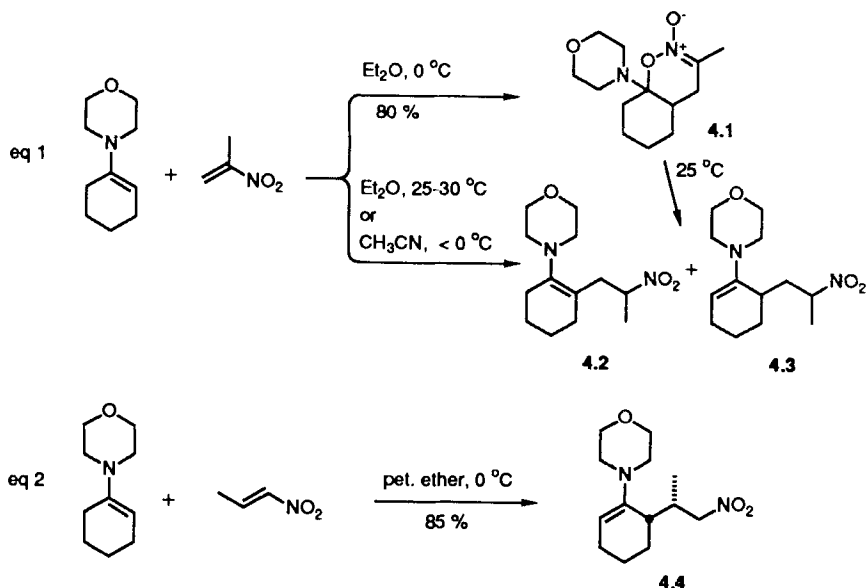
Scheme 3

(path D). Note that addition in this manifold corresponds to a formal reverse-electron-demand Diels–Alder cycloaddition. Alternatively, **3.1** can yield cyclobutane **3.3** by joining of the enolate carbon of the acceptor with the carbon of the immonium ion of the donor (path E) (13). Reaction through this pathway is formally a $[2+2]$ cycloaddition. Either **3.2** or **3.3** may be in equilibrium with **3.1**.

Proton transfer, either intermolecular or intramolecular, can serve to stabilize **3.1**. In this manner, enamines **3.4** or **3.5** can be produced as initial products (paths B and C). Production of **3.5** is particularly worrisome in stereoselective versions of the reaction with **P** donors because the configuration at the stereocenter derived from the prostereogenic center of the donor is established in the hydrolysis and not in the initial conjugate addition. Upon acidic hydrolysis, **3.1**–**3.5** all produce **3.6**.

Intermediates **3.1**, **3.4**, and **3.5** are capable of further addition to the electrophilic olefin. Generation of 2:1 or higher adducts depends on the substrates and the stoichiometry employed.

The subtle nature of the factors that influence the type of product(s) (**3.2**–**3.5**) that are produced is illustrated in Eqs. [1] and [2] (Scheme 4) (14).

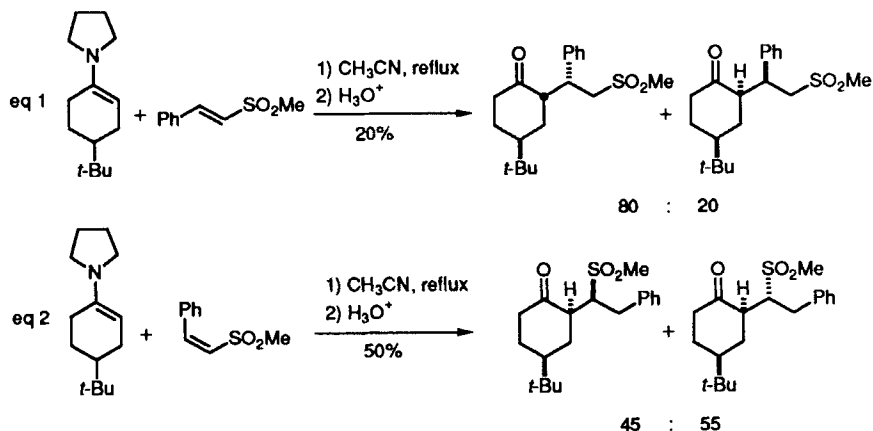


Scheme 4

With 2-nitropropene as the acceptor, the enamine derived from cyclohexanone and morpholine at 0°C in ether gives heterocycle **4.1**. If **4.1** is warmed to $25\text{--}30^\circ\text{C}$ or if the reaction is carried out in acetonitrile ($< 0^\circ\text{C}$) a mixture of the regioisomeric enamines **4.2** and **4.3** is formed. Addition of the same enamine to 1-nitropropene in petroleum ether at 0°C gives the product with the less substituted enamine (**4.4**, Eq. [2]).

B. Addition to α,β -Unsaturated Sulfones

[P*, P] Risaliti and co-workers examined the addition of the pyrrolidine enamine of 4-*tert*-butylcyclohexanone to β -styryl sulfones (Scheme 5)(15). The stereoisomeric sulfones exhibit divergent behavior in the reaction (cf. Eqs. [1] and [2]). With the *E* sulfone, syn conjugate addition products are obtained as a 80:20 (trans/cis) mixture in low yield. In contrast, the *Z* styryl sulfone gives products from addition to the α -position, presumably through the intermediacy of a benzylic anion. Note that fairly vigorous reaction conditions are required for the addition and this may allow the addition to proceed through such an unusual pathway.

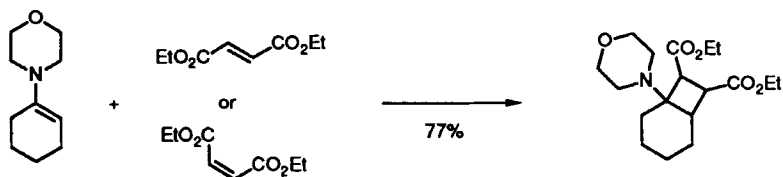


Scheme 5

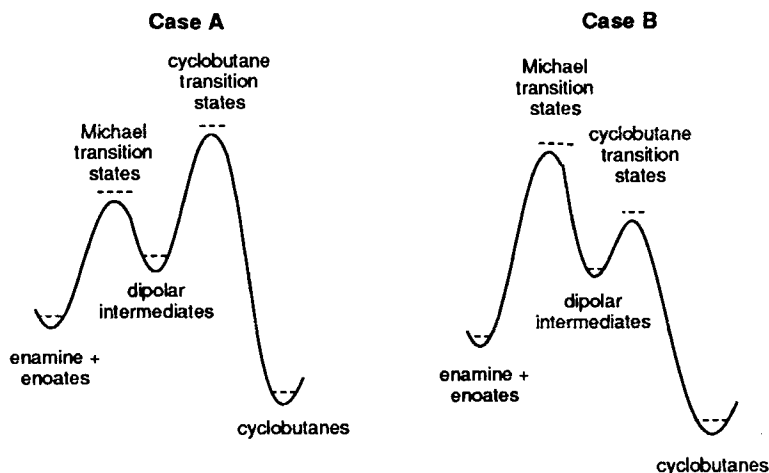
C. Addition to Enoates

[P, P] The cyclohexanone morpholine enamine reacts with both diethyl maleate and diethyl fumarate to give the same cyclobutyl adduct, of undefined stereochemistry (Scheme 6) (16). When the reaction is carried out in the presence of a large excess of diethyl maleate, the unreacted enedioate is recovered in the more stable *trans* (fumarate) configuration. However, under the lower temperature reaction conditions employed, diethyl maleate by itself was found to be stable to isomerization. These observations suggest that the initial conjugate addition to yield a dipolar intermediate is reversible under the reaction conditions and that the subsequent closure to create the cyclobutane is reversible at higher temperatures. The loss of the stereochemical integrity of the acceptor in the cycloaddition process suggests that bond rotation occurs at a significant rate in the dipolar intermediate.

A reaction coordinate diagram for this process is illustrated in Case A in Scheme 7. The product-determining step is the collapse of the dipolar intermediate to yield the cyclobutane. As the initial addition to produce the dipolar intermediate is freely reversible and the Michael addition transition



Scheme 6

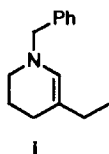


Scheme 7

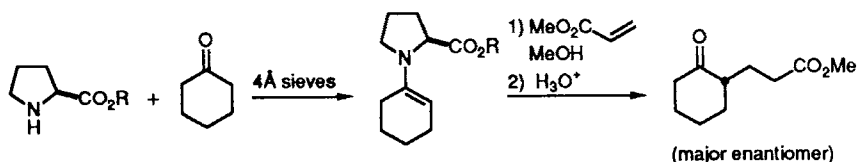
state is lower in energy than the cyclobutane-forming pathway, the product ratio should be determined by the relative energies of the diastereomeric cyclobutane transition states (Curtin-Hammett principle (17)).

An alternative process can be imagined where the Michael addition is the product-determining step (Case B, Scheme 7). In this circumstance, collapse of the dipolar intermediate is more rapid than retro-Michael addition and thus a kinetically controlled process is responsible for determining the relative configuration of the stereogenic centers that result from the conjugate addition.[†]

[†] Preliminary results (18) indicate that the high-pressure induced conjugate addition of enamine *i* to *cis*- and *trans*-crotonates yields stereoisomeric cyclobutanes. Isolation of isomeric cyclobutanes contrasts Risaliti's results (*vide supra*) and suggests that *cis*-*trans* interconversion of the acceptor does not occur to an appreciable extent under the reaction conditions. It is important to note that high pressure is necessary to induce addition in this case, potentially influencing the course of the reaction. Under these conditions, collapse of the dipolar intermediate to the cyclobutane appears to be more rapid than retro-Michael addition and the stereochemistry is determined in the initial conjugate addition.



[P*, N] Some of the earliest examples of asymmetric Michael additions were reported by Yamada and co-workers, who used enamines derived from cyclohexanone and proline esters (19). The results of this study are summarized in Scheme 8 and Table 1. Although yields were generally poor, enantiomeric excesses as high as 59% were found using the *tert*-butyl ester of proline at low temperature (entry 5). Asymmetric induction was also observed with acrylonitrile, but no enantiomeric purities were reported. The enantiomeric purities of the methyl acrylate products were determined by measurement of optical rotations.

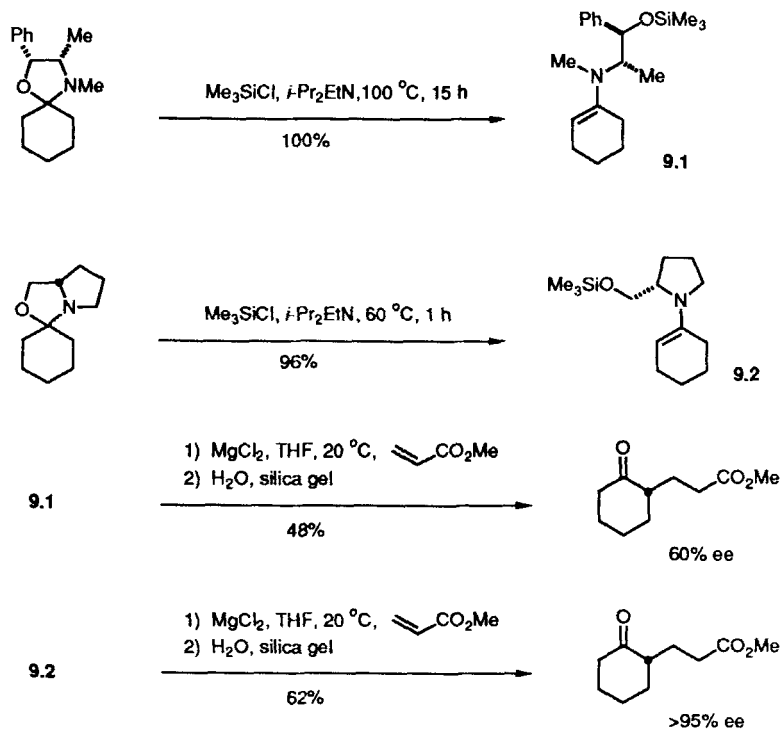


Scheme 8

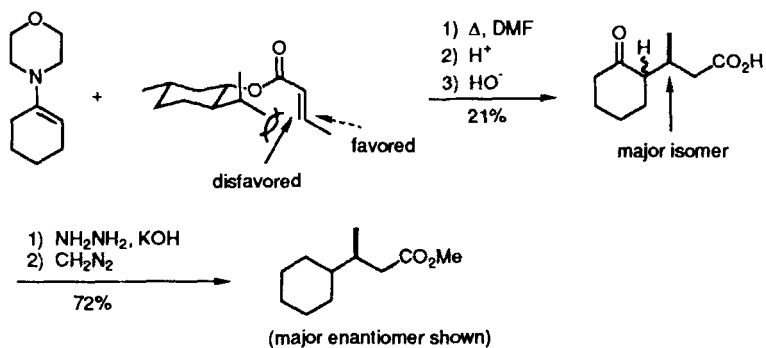
Analogous additions were later reported by Ito and co-workers (Scheme 9) (20). The enamines for these additions were prepared from the corresponding aminals using a mild base in the presence of trimethylsilyl chloride. In turn, the aminals used are available from (–)-ephedrine and (*S*)-prolinol. The by-product amine hydrochloride was removed either by distillation or by precipitation from a benzene solution. Enamines prepared by this method were found to be unreactive toward unsaturated carbonyl compounds in a variety of solvents. Importantly, it was found that use of a mild Lewis acid such as anhydrous MgCl_2 or ZnCl_2 in THF promoted the reactions. Thus, the addition of enamines **9.1** and **9.2** to methyl acrylate is achieved. Of the two enamines, the proline-derived **9.1** is the more effective auxiliary. The

Table 1
Addition of Proline Ester Enamines to Methyl Acrylate
(Scheme 8)

Entry	Ester R	Temperature	Yield (%)	ee (%)
1	Me	Reflux	32	15
2	Et	Reflux	38	21
3	<i>t</i> -Bu	Reflux	33	43
4	<i>t</i> -Bu	40°C	22	53
5	<i>t</i> -Bu	20°C	17	59



Scheme 9



Scheme 10

stereochemical results obtained by this method compare favorably with other chiral enamine methods that have been reported (*vide infra et supra*).

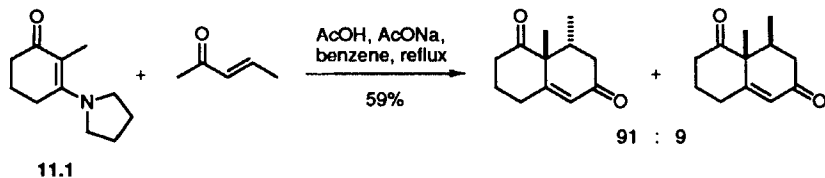
[P,P*] Inouye and co-workers documented that the addition of the morpholine enamine of cyclohexanone to (–)-menthyl crotonate proceeds with detectable asymmetric induction (Scheme 10) (21). Although the level of face selection was not determined, degradation indicated that the *S* enantiomer is the preferred product.

D. Addition to Enones

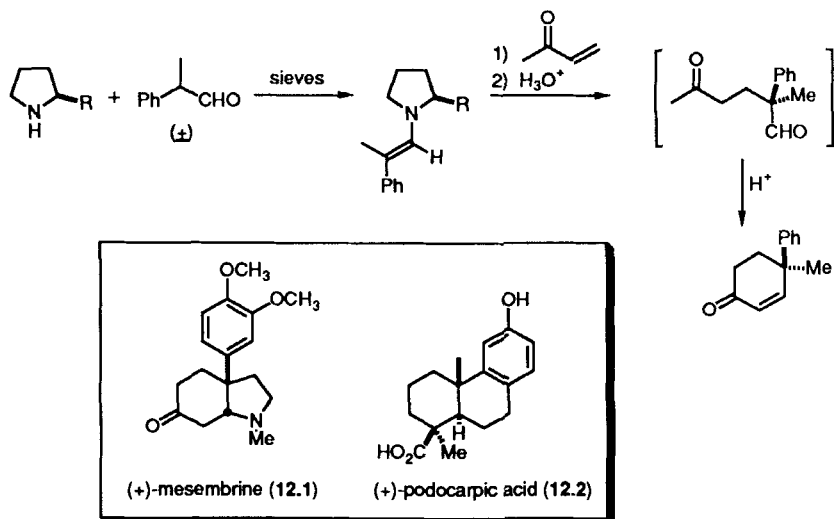
When an α,β -unsaturated ketone is the acceptor, subsequent ring closure to yield a six-membered ring can occur, in two modes. As shown in Scheme 3, the initially formed enolate oxygen can add to the immonium ion of the dipolar intermediate to generate a dihydropyran (e.g., **3.2**, Y = O, X = C). Alternatively, proton transfer from the initially formed enolate and subsequent carbon-carbon bond construction between the enolate and the immonium ion can produce a new cyclohexanone ring. Elimination of the amine usually ensues to generate the corresponding cyclohexenone. This amine-promoted Robinson annelation is commonly referred to as a Stork annelation (3, 22).

[P,P] Although the stereochemistry of the process was not fully elucidated, Risaliti and co-workers examined the addition of the enamine derived from morpholine and cyclohexanone to *cis*- and *trans*-chalcone (23). In general, this process leads initially to dihydropyrans and the same product is obtained from either isomer of chalcone. Furthermore, *cis*-chalcone is converted to the *trans* isomer under the reaction conditions, even though such *cis*-*trans* isomerization does not occur in the presence of a tertiary amine alone. Thus, the initial conjugate addition of the enamine to form the dipolar intermediate appears to be freely reversible under the reaction conditions.

Coates and Shaw found that vinylogous amide **11.1** reacts with *trans*-3-penten-2-one to provide a 91:9 (*trans*/*cis*) mixture of diastereomers (Scheme 11) (24). Choice of solvent is critical; in formamide, a 50:50 mixture of diastereomers is produced.



Scheme 11



Scheme 12

[P*,N] The addition of the enamines derived from α -phenylpropionaldehyde and chiral amines to methyl vinyl ketone was the subject of an early investigation by Yamada and co-workers (Scheme 12, Table 2). Three types of chiral amine were used. The first set (entries 1–17) were derived from proline (25, 26). Additionally, some diamines derived from proline (entries 18–23) (27) and alkylamine “mimics” of proline were later examined (entries 24–27) (28).

It was most convenient to isolate the products after acidic conversion to cyclohexenones. Structures of the products were assigned by chemical correlation and circular dichroism and the enantiomeric purities were based on optical rotations. The selectivities obtained, although impressive for the era, are moderate at best, despite significant attempts to optimize the substrates and reaction conditions. Use of substituted cyclohexanones (29) and other aldehydes (30) lead to optically active products but the extent of enantiomeric induction in these products was not determined. This technology was used for the partial asymmetric synthesis of (+)-mesembrine (12.1) (29) and (+)-podocarpic acid (12.2) (31).

Better results for similar cyclizations were obtained later by Ito and co-workers (Scheme 13) (20). The enamines for this study were obtained from the corresponding aminor, trimethylsilyl chloride, and Hünig's base (see also

Table 2
Addition of Proline-Derived Enamines of Phenylpropionaldehyde to Methyl Vinyl Ketone (Scheme 12)

Entry	Enamines R	Solvent	Temperature (°C)	Yield (%)	ee (%)
1	<i>t</i> -BuO ₂ C	MeOH	0	43	6
2	Me ₂ N(O)C	MeOH	0	42	31
3	Et ₂ N(O)C	MeOH	0	53	27
4	C ₄ H ₈ N(O)C ^a	MeOH	0	48	37
5	C ₄ H ₈ N(O)C ^a	MeOH/THF (10:3)	0	^b	37
6	C ₄ H ₈ N(O)C ^a	EtOH/THF (10:3)	0	^b	28
7	C ₄ H ₈ N(O)C ^a	<i>t</i> -BuOH/THF (10:3)	0	^b	22
8	C ₄ H ₈ N(O)C ^a	MeOH/DMSO (1:9)	0	^b	14
9	C ₄ H ₈ N(O)C ^a	MeOH/CHCl ₃ (1:9)	0	^b	41
10	C ₄ H ₈ N(O)C ^a	MeOH/CCl ₄ (1:9)	0	^b	47
11	C ₄ H ₈ N(O)C ^a	MeOH/C ₆ H ₆ (1:9)	0	^b	49
12	C ₄ H ₈ N(O)C ^a	MeOH	−20	35	36
13	C ₄ H ₈ N(O)C ^a	MeOH	−10	41	32
14	C ₄ H ₈ N(O)C ^a	MeOH	0	40	37
15	C ₄ H ₈ N(O)C ^a	MeOH	20	49	32
16	C ₄ H ₈ N(O)C ^a	MeOH	40	41	26
17	C ₄ H ₈ N(O)C ^a	MeOH	64	47	20
18	Me ₂ NCH ₂	MeOH	15–20	55	33
19	Et ₂ NCH ₂	MeOH	15–20	54	31
20	C ₄ H ₈ NCH ₂ ^c	MeOH	15–20	82	37
21	C ₄ H ₈ NCH ₂ ^c	MeOH/C ₆ H ₆ (1:9)	5	40	45
22	C ₄ H ₈ NCH ₂ ^c	MeOH/MeC ₆ H ₅ (1:9)	−15	32	51
23	3-Pyridyl ^d	MeOH/MeC ₆ H ₅ (1:9)	−15	28	54
24	Me	MeOH	15–20	29	19
25	<i>i</i> -Pr	MeOH	15–20	27	26
26	PhCH ₂ ^e	MeOH	15–20	43	31 ^f
27	<i>i</i> -Pr ^e	MeOH	15–20	14	29 ^f

^aPyrrolidine amide.

^bNot reported.

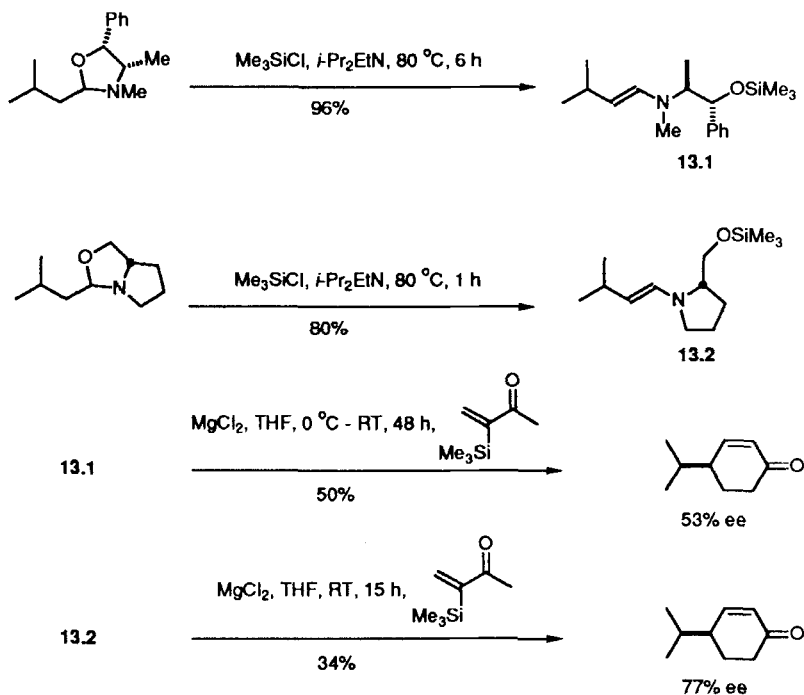
^cPyrrolidine amine.

^d75% optically pure.

^eThe chiral amine used has the opposite configuration.

^fThe product obtained has the *S* configuration; all others have the *R* configuration as shown in scheme (see note *e*).

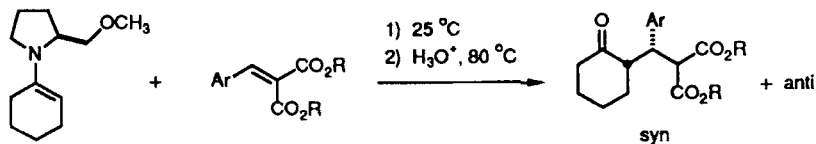
Scheme 8). Conjugate addition of the resulting enamine–silyl ether to methyl α -trimethylsilylvinyl ketone in the presence of MgCl₂ provided the cyclohexenones. Using the prolinol-derived enamine, the annelated product was obtained with 77% ee.



Scheme 13

E. Addition to Arylidenemalonates

[P*, P] Seebach and Blarer examined the addition of the enamine derived from proline methyl ether and cyclohexanone to arylidene malonates (Scheme 14, Table 3) (32, 33). The process is uniformly selective for the syn, *S,S* diastereomer. Diastereoselectivities from 88% to > 95% and enantiomeric excesses (for the syn product) of 80–92% were observed. The results were



Scheme 14

Table 3
Addition of the Proline Methyl Ether Enamine of Cyclohexanone to Arylidene Malonate (Scheme 14)

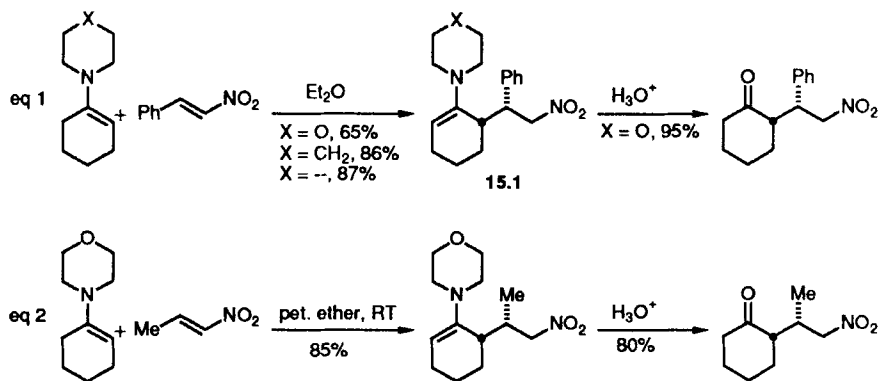
Entry	Acceptor		Yield (%)	Syn/Anti	ee ^a (%)
	Ar	R			
1	Ph	Me	76	>95:5	92
2	Ph	Et	70	>95:5	95
3	4-Cl-C ₆ H ₄	Me	53	88:12	80
4	4-O ₂ N-C ₆ H ₄	Me	35	88:12	83
5	3,4-(OCH ₂ O)C ₆ H ₃	Me	55	95:5	82

^aMajor diastereomer.

rationalized in terms of kinetic stereoselection in the conjugate addition, although actual experimental proof that stereoselection occurs at this stage has not yet been presented.

F. Addition to Nitroolefins

[P,P] Risaliti and co-workers in 1966 reported the stereoselective additions of enamines derived from cyclohexanone and morpholine, piperidine, and pyrrolidine to β -nitrostyrene (Eq. [1], Scheme 15) (34). The less-substituted enamines of the general structure **15.1** were isolated prior to hydrolysis. The location of the double bond of **15.1** was established by ¹H-NMR spectroscopy and by addition to diethyl azodicarboxylate. The

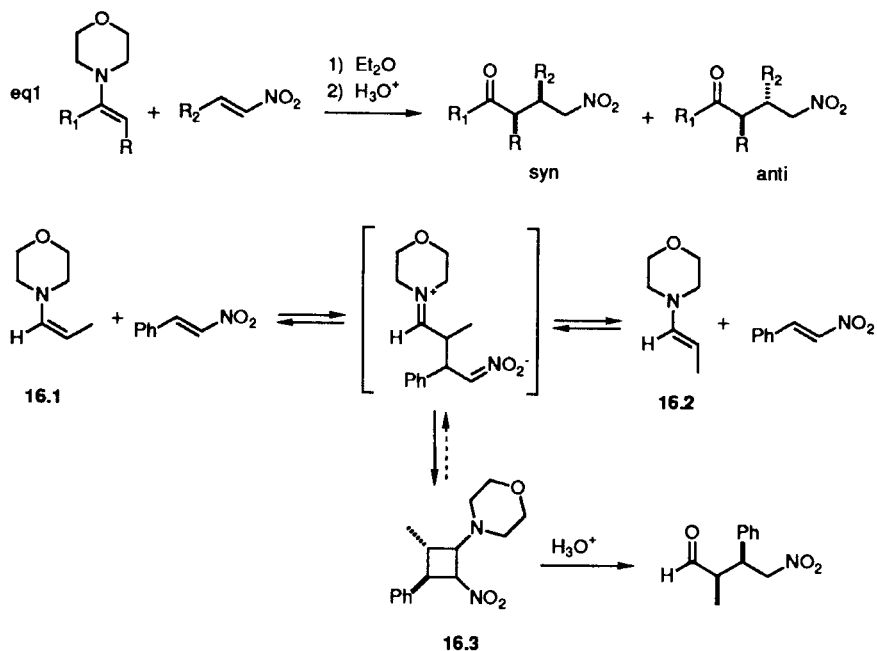


Scheme 15

configuration of the product was determined by single crystal X-ray analysis of the nitro ketone derived from addition of the enamine to *p*-bromo- β -nitrostyrene followed by hydrolysis.

Similar results were found with 1-nitropropene (Eq. [2] and *vide supra*) (14). The addition process again provided only one detectable diastereomer, which was assigned *syn* configuration by analogy to the results with β -nitrostyrenes. Piperidine and pyrrolidine enamines gave similar results, although the corresponding intermediate enamine adducts could not be isolated.

Seebach and Golinski further examined the Michael addition of the enamines derived from ketones and morpholine to nitroolefins, as shown in Scheme 16 and Table 4 (33, 35, 36). The structure of the major product of entry 1 (Table 4) was assigned by chemical correlation. The remaining structures were assigned by analogy to entry 1. High levels of *syn* selectivity were uniformly observed. Control experiments revealed that the geometry of neither the enamine nor the nitroolefin influences the stereochemistry. Indeed, observation of the reaction of isomeric nitrostyrenes and the morpholine



Scheme 16

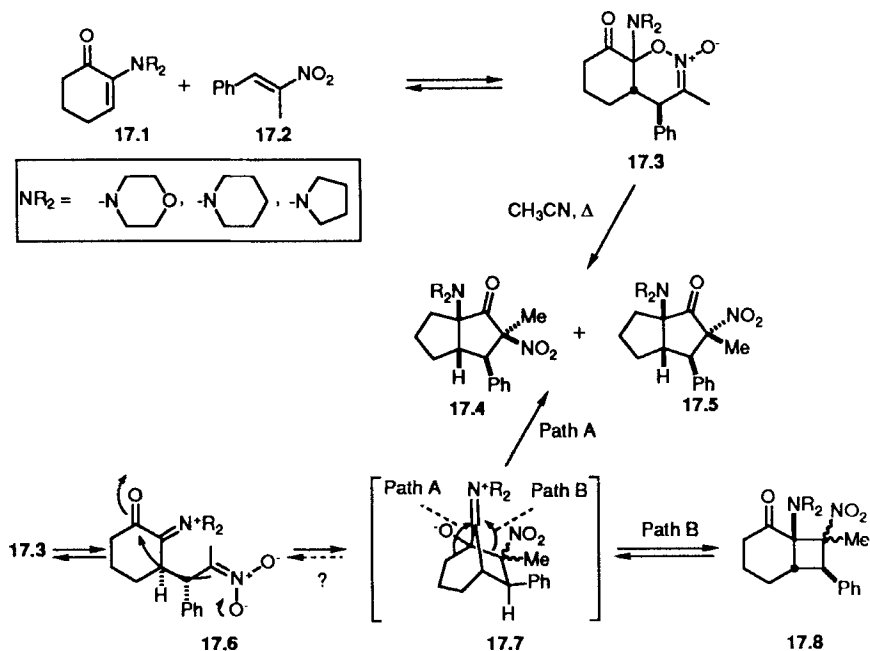
Table 4
Addition of *E* Enamines to *E* Nitroolefins (Eq. [1],
Scheme 16)

Entry	Enamine		Nitroolefin R ₂	Yield (%)	Syn/Anti
	R	R ₁			
1	Me	Et	Me	88	96:4
2	Me	Et	Et	75	92:8
3	Me	Et	<i>i</i> -Pr	24	90:10
4	Me	Et	Ph	77	98:2
5	Et	<i>n</i> -Pr	Me	^a	93:7
6	Et	<i>n</i> -Pr	Ph	^a	97:3
7	Me	Ph	Me	^a	93:7

^aNot reported.

enamine of cyclohexanone by NMR revealed that the *Z* nitrostyrene is converted (at least partially) under the reaction conditions to the *E* isomer. Because the nitro olefins are only slowly interconverted when the enamine is replaced by a tertiary amine, this suggests that the initial Michael addition is reversible and that the stereochemistry may not be determined at the Michael addition stage. Indeed, with enamines **16.1** and **16.2** and nitrostyrenes, an initial, stereochemically homogeneous product consistent with **16.3** is observed by NMR spectroscopy. Hydrolysis of **16.3** leads to the observed products.

A diversion of the normal enamine–nitroolefin reaction pathway has been reported by Valentin and co-workers (37, 38). α -Acylenamines **17.1** were combined with (*E*)-(2-nitro-1-propenyl)benzene (**17.2**) to give, after heating in acetonitrile, nitro- α -amino ketones **17.4** and **17.5** in undisclosed yields (Scheme 17). Compounds **17.4** and **17.5** were found to be isomeric at the nitro-substituted stereocenter; the remaining stereocenters have the same relative configuration in **17.4** and **17.5**. This reaction presumably occurs through an initial stereoselective Michael addition to generate **17.3**. The stereochemistry of this addition is consistent with analogous reactions (*vide supra*). A reasonable explanation for the production of **17.4** and **17.5** is that the initially created **17.3** opens up to **17.6**. Migration of the carbon–carbon bond perpendicular to the immonium π -system (path A, **17.7**) serves to neutralize the formal charges and results in construction of **17.4** and **17.5**. Alkoxide accelerated migrations of this sort are well precedented (39). Alternative migration (path B) would result in the establishment of strained cyclobutane **17.8**. Cyclobutane adducts are known to be produced reversibly in enamine Michael additions (*vide supra*); hence, **17.8** may be a transient intermediate in the reaction manifold.

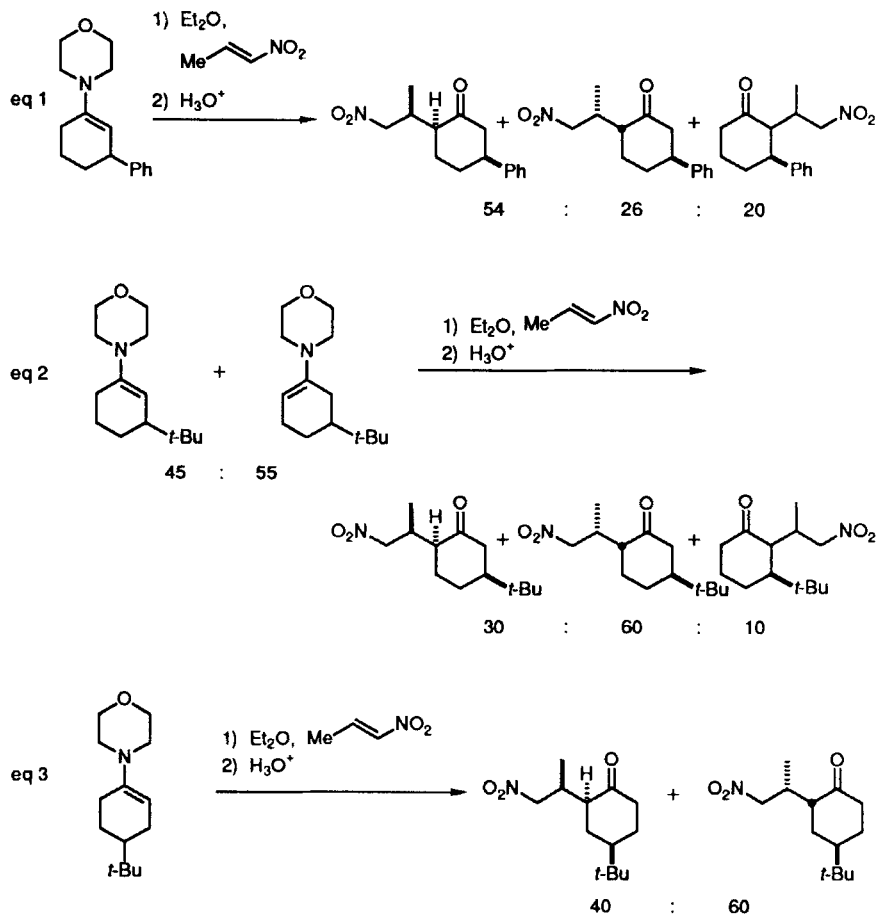


Scheme 17

[P*,P] Risaliti and co-workers examined the addition of enamines derived from substituted cyclohexanones to nitropropene (Eqs. [1]–[3], Scheme 18) (40). In all cases, only syn addition products were obtained. The facial selectivity with respect to the preexisting stereocenter in the cyclohexane ring is poor with this acceptor; a very slight preference for the products of axial attack is seen. As can be seen in Eqs. [1] and [2], the regiochemical integrity of the enamines is not maintained in the addition process. In Eq. [1], almost complete isomerization occurs while a similar regioisomeric mixture of products is seen in Eq. [2]. The preferred products in both cases are those from addition distal to the ring substituent.

A similar loss of the regiochemical integrity of the enamines is seen in the addition to nitrostyrenes (Eq. [1], Scheme 19, Table 5) (41). In contrast to nitropropene, nitrostyrenes give exclusively products from axial addition with enamines **19.2** and **19.5** (Eq. [2]). With the products derived from enamine **19.1**, only the syn adducts from equatorial addition are generated.

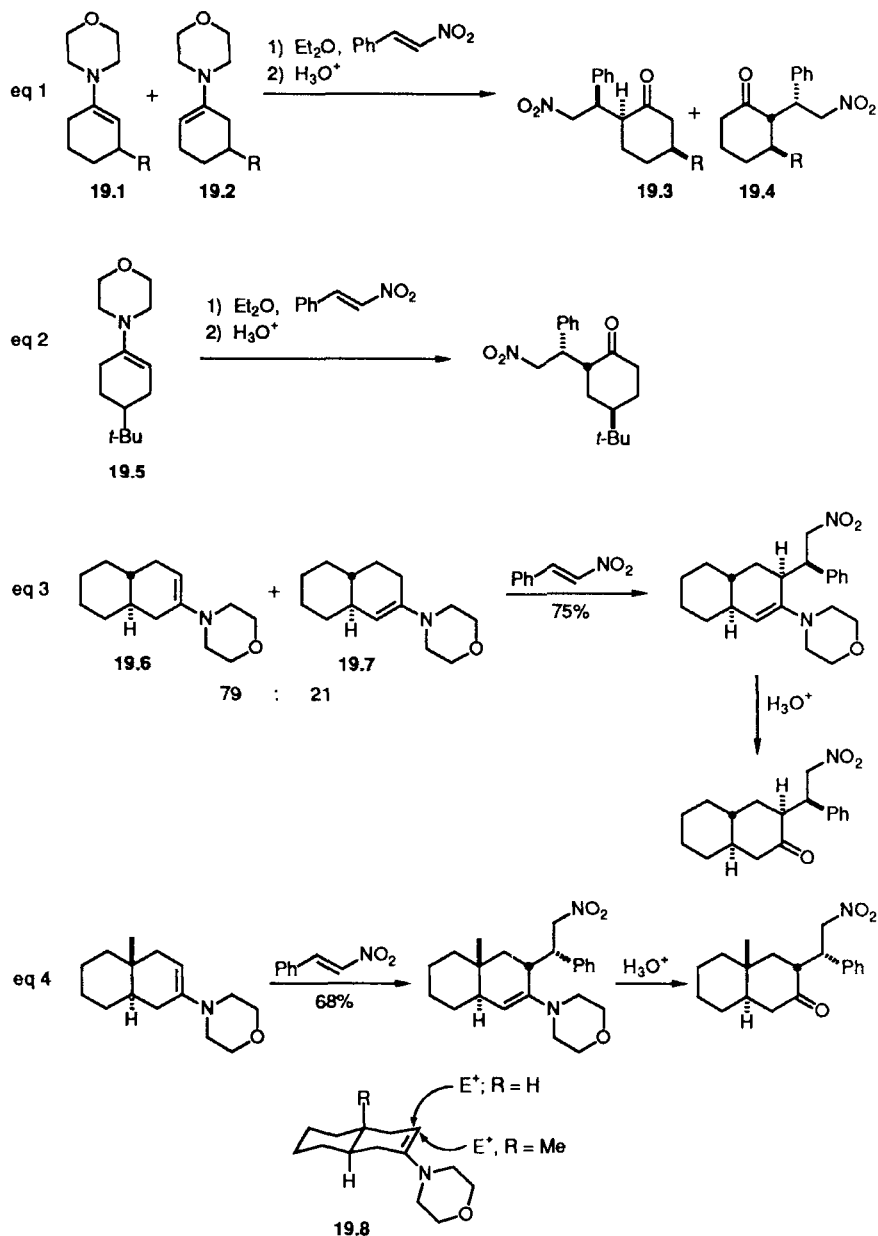
Nitrostyrene also undergoes axial addition with the enamines derived from *trans*-decalin-2-one (Eq. [3]) (42). In this case, only enamine regioisomer **19.6**



Scheme 18

Table 5
Addition of Nitrostyrenes to Substituted Cyclohexanone
Morpholine Enamines (Eq. [1], Scheme 19)

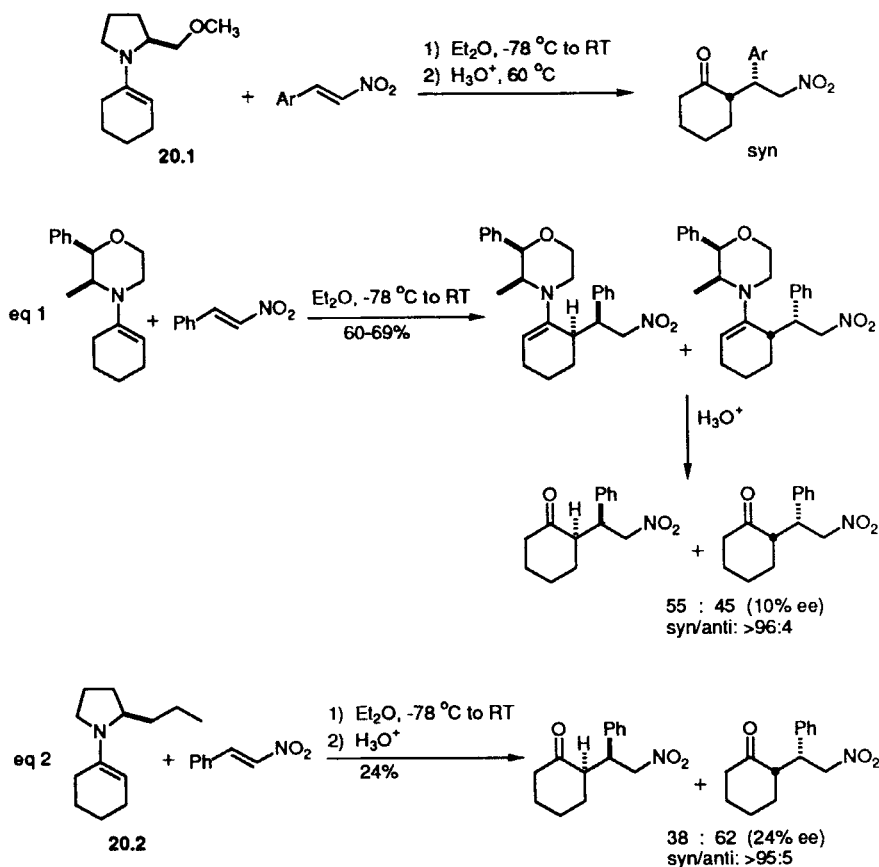
Entry	Enamine		Product 19.3:19.4
	R	19.1:19.2	
1	Me	45:55	20:80
2	Ph	~100:0	20:80
3	<i>t</i> -Bu	55:45	15:85



Scheme 19

reacts; after hydrolysis the parent ketone is recovered in equal proportion to the amount of **19.7** present in the starting material. The morpholine enamine of the methyl decalone in Eq. [4] is produced and reacts only (> 90%) in the regioisomeric form depicted. With this enamine, only products from equatorial addition are formed, presumably due to steric hindrance by the methyl substituent at the ring juncture (see structure **19.8**). Again, the enamines in Eqs. [3] and [4] exhibit syn stereoselectivity in this system.

The structures of the products shown in Scheme 19 were established by X-ray analysis (43) and $^1\text{H-NMR}$ spectroscopy in conjunction with equilibration experiments. In cases where a less stable axial addition product is observed, equilibration to the more stable equatorial products is usually



Scheme 20

possible. Note that this also changes the relative configuration of the addition products from syn to anti.

Reactions of the enamine derived from cyclohexanone and prolinol methyl ether with β -nitrostyrenes have been described by Seebach and co-workers (Scheme 20, Table 6) (33,44). This procedure uniformly provides the syn diastereomer as the exclusive detectable product. With the exception of the 2-bromo- β -nitrostyrene in entry 4, enantiomeric excesses of $>92\%$ are observed.

The methyl ether of **20.1** is crucial for achieving high levels of enantioselection. With the enamines in Eqs. [1] and [2] (32), which lack the methyl ether of **20.1**, virtually no prochiral recognition is achieved. These reactions (eqs. [1] and [2]) still show a strong syn preference, suggesting that there has not been a gross change in the mechanism of the reaction. The importance of the alkoxy group is shown especially by Eq. [1]; replacement of methoxymethyl by the nearly isosteric propyl side chain of **20.2** results in essentially no discrimination between the heterotopic faces of the double bond.

As shown in Eq. [1], the less-substituted enamines are detected by $^1\text{H-NMR}$ prior to hydrolysis. Whether the relative rates of proton transfer from the diastereomeric dipolar intermediates (*vide supra*) influences the stereochemistry in this case remains to be elucidated.

The enantioselective Michael addition of enamines derived from β -tetralone and proline methyl ether to nitrostyrenes has been described by Blarer and Seebach (33,45). Enamines of β -tetralone have two potential sites of nucleophilicity, C-1 and C-3 in **21.1** and **21.2** (Scheme 21). For the substrates studied, attack occurs preferentially at C-3. The results of this study are summarized in Table 7 and Scheme 21.

Table 6
Addition of the Proline Methyl Ether Enamine of Cyclohexanone (**20.1**) to Nitrostyrenes (Scheme 20).

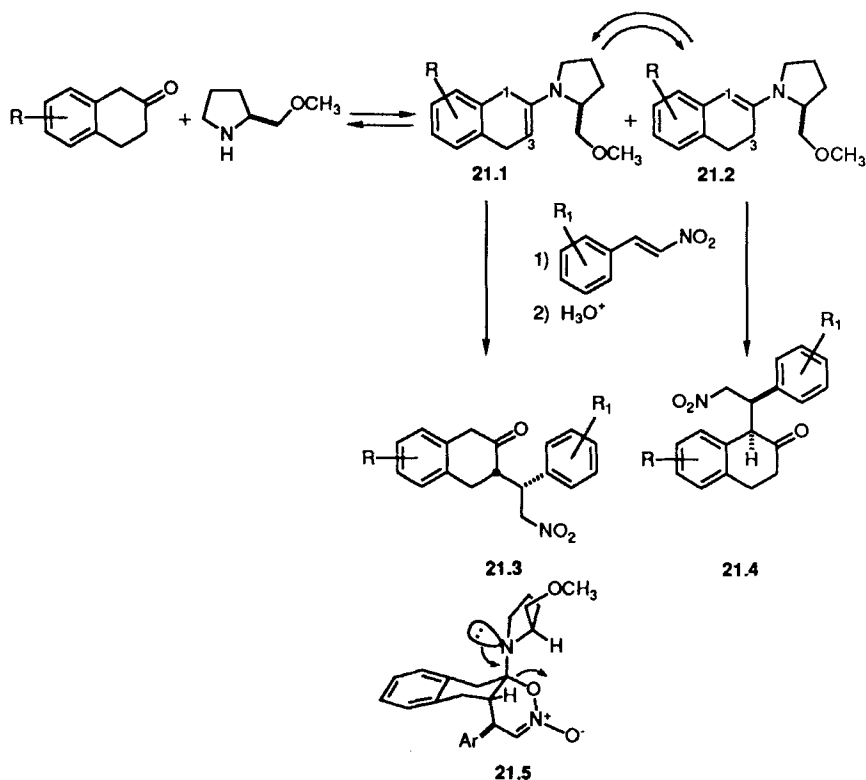
Entry	Acceptor Ar	Yield (%)	Syn/Anti	ee ^a (%)
1	Ph	80	>96:4	97
2	4-Cl-C ₆ H ₄	56	>95:5	97
3	3,4-(OCH ₂ O)-C ₆ H ₃	80	>95:5	92
4	2-Br-4,5-(OCH ₂)-C ₆ H ₂	63	>95:5	44
5	3,4-(CH ₃ O) ₂ -C ₆ H ₃	70	>95:5	93
6	3-O ₂ N-C ₆ H ₄	75	>95:5	98
7	2-Naphthyl	81	>95:5	92

^aMajor diastereomer.

Table 7
Addition of Proline Methyl Ether Enamines of β -Tetralone to Nitrostyrenes (Scheme 21).

Entry	Enamine R	Nitrostyrene R ₁	Solvent	Temperature (°C)	Yield (%)	21.3:21.4	ds (%)	ee (%)
1	H	H	Toluene	20	50	90:10	>95	89
2	H	H	Toluene	-18/0	39	89:11	>95	97
3	H	H	Ether	20	54	90:10	>95	75
4	H	H	Ether	-18/0	45	80:20	>95	96
5	H	3-NO ₂	Toluene	0	34	90:10	>95	98
6	H	3,4-(OCH ₂ O)	Toluene	20	53	90:10	>95	95
7	5-OCH ₃	H	Toluene	0	28	83:17	>90	^a
8	6-OCH ₃	H	Toluene	0	40	90:10	>95	89
9	8-OCH ₃	H	Toluene	0	44	95:5	>95	99
10	7-NO ₂	H	Toluene	0	38	95:5	>90	^a
11	6-Cl	H	Toluene	0	52	90:10	>95	>90

^aNot reported; retro-Michael addition occurred during recrystallization.



Scheme 21

After optimization of the reaction conditions, excellent diastereomeric and enantiomeric excesses were obtained. The structures of the major products were assigned by analogy with the previously observed results (*vide supra*). Additional support for the structural assignment was obtained by circular dichroism and $^1\text{H-NMR}$ spectroscopy.

The point at which stereodifferentiation occurs in these reactions is not obvious (*vide infra*). If the asymmetric induction is the result of thermodynamic considerations or kinetically preferred cyclization, then an additional organizational consideration such as the exo-anomeric effect in **21.5** may be important.

IV. IMINES

A. Addition to Enoates and Enones

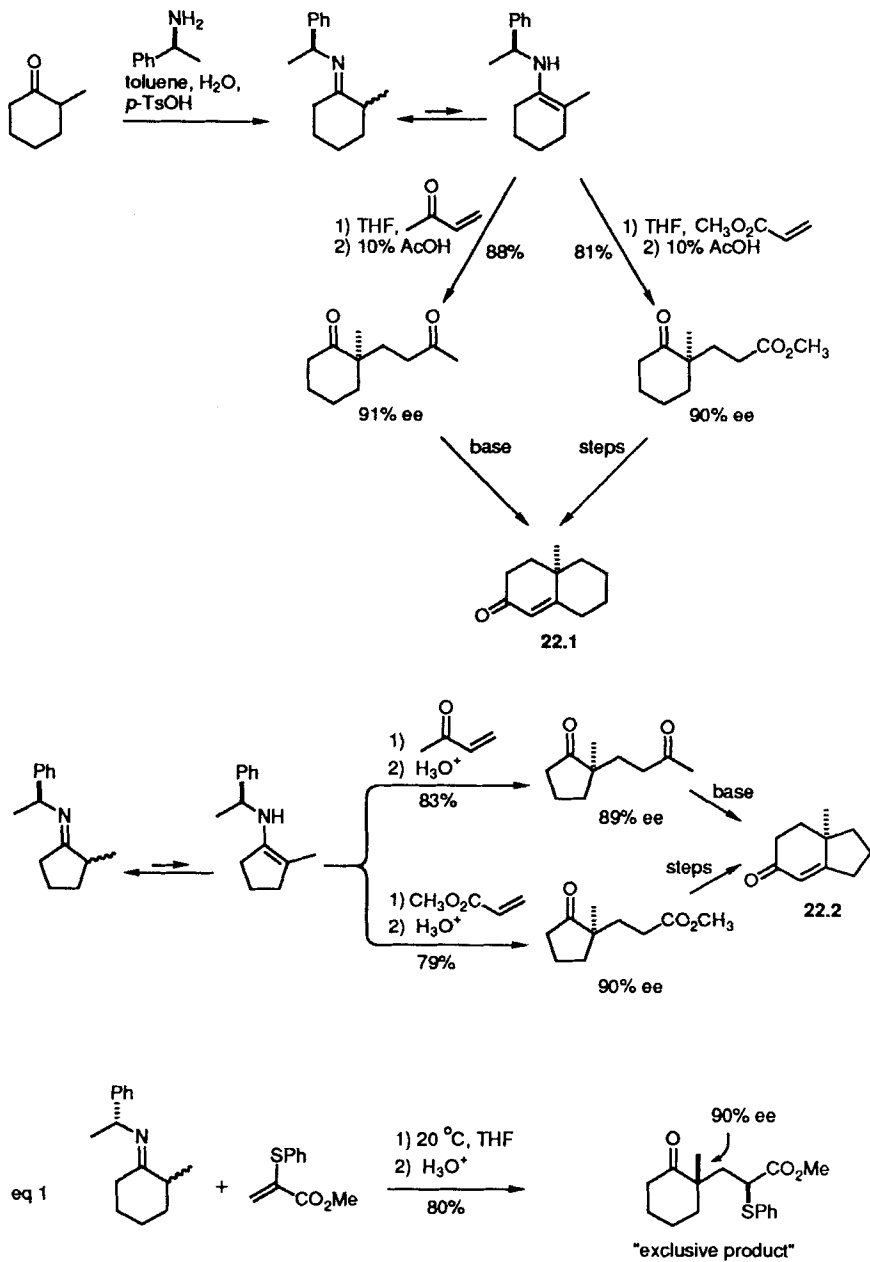
[P*, N] Imines can add, through their enamine tautomers, to activated olefins. Pfau and co-workers extended this approach to asymmetric Michael additions of 2-methylcycloalkanones to methyl vinyl ketone and methyl acrylate (46). Reaction occurs preferentially at the more substituted position of the ketone, leading through 1,4-asymmetric induction to a quaternary stereocenter (Scheme 22). In all cases high levels (~ 90% ee) of asymmetric induction and good chemical yields were realized. Because both enantiomers of the amine are relatively cheap and readily available, this is an attractive method for the synthesis of this class of compounds. The structure assignment of the products was based on conversion into enones **22.1** and **22.2**. These conversions occur with complete retention of stereochemical integrity of the stereocenter. The chiral auxiliary is easily recyclable, with no loss of optical purity.

Using the more reactive α -phenylthioacrylate as an acceptor, good selectivity for the construction of two stereogenic centers is observed (Eq. [1], Scheme 22) (47). The mechanism for the enantioselection in the establishment of the quaternary center is likely to be similar to the other examples in Scheme 22. For the formation of the thiophenyl-substituted stereocenter, intramolecular proton transfer from the immonium ion of the dipolar intermediate to the enolate is probably responsible for the stereoselection observed.

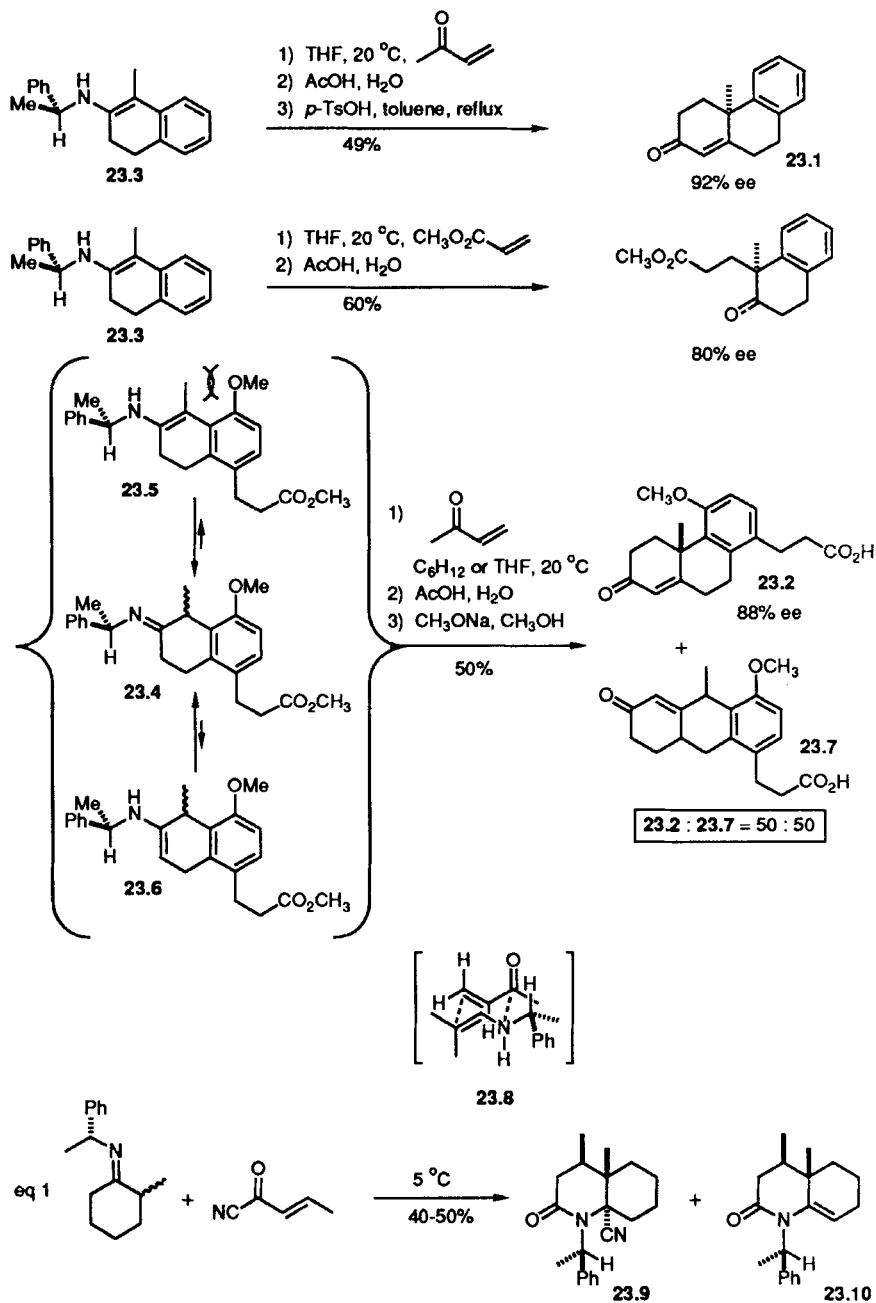
The Pfau methodology has been applied to the preparation of phenanthrones **23.1** and **23.2**, which are key intermediates for the synthesis of several compounds of interest (Scheme 23) (48). For **23.1**, enamine **23.3** results directly from the condensation of the amine and the ketone. With methyl vinyl ketone, **23.1** is created with 92% ee after hydrolysis and cyclization. Slightly lower optical purities are found with methyl acrylate. Note that the regiochemistry of the attack contrasts that obtained from *N,N*-dialkyl enamines (*vide supra*) where products from attack at the less-substituted carbon often predominate.

Imine **23.4** is prepared by combination of the ketone and the amine. In this instance, generation of the enamine is inhibited as a result of allylic strain with the methoxy group on the aromatic ring. Indeed, products **23.2** and **23.7** resulting from attack on the isomeric enamines **23.5** and **23.6** are formed in equal molar quantities. Note that enone **23.2** is produced with excellent enantioselectivity.

[P*, P] Crotonates are unreactive toward these imine nucleophiles. Use of the reactive (*E*)-crotonyl cyanide as an acceptor results in the construction



Scheme 22



Scheme 23

of a moderate yield of addition products, however (Eq. [1], Scheme 23) (47). In this case, the initial Michael adducts cyclize to a mixture of lactams **23.9** and **23.10**. Although the exact diastereomeric purities of the products were not reported, apparently, **23.9** and **23.10** are each formed as essentially one isomer.

An alternative mechanism is possible with crotonyl cyanide as an acceptor. Switching the order of the steps, N-acylation of the imine followed by cyclization would provide the observed products. With this manifold, the origins of the diastereoselectivity in the reaction could be substantially different from the Michael addition-acylation pathway.

The course of these reactions was studied by *ab initio* SCF calculations using the 3-21G basis set (49). Although several pathways were found to be energetically accessible, the authors preferred a chair like transition state such as **23.8**. The facial discrimination was reasoned to arise from a preferred conformation of the enamine where the C-H bond of the phenethylamine lies in the nodal plane of the conjugated system. In this configuration, selective attack occurs on the face occupied by the smaller methyl group, away from the phenyl ring.

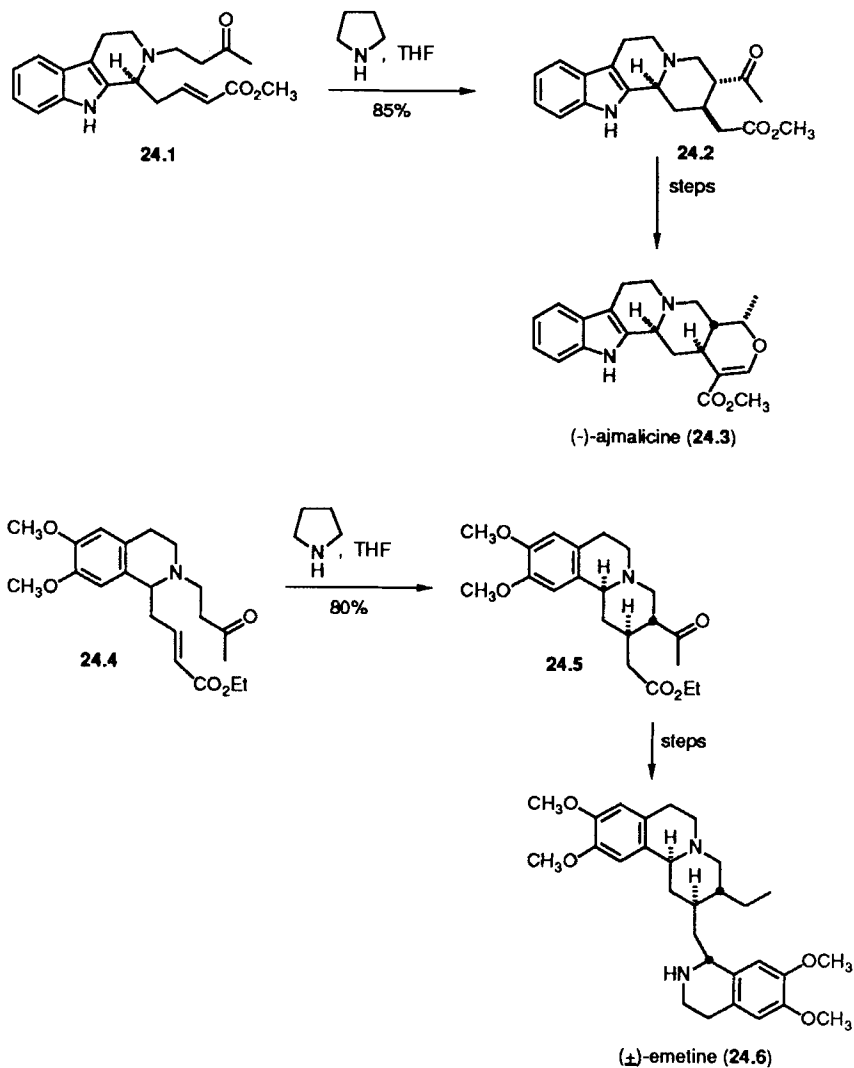
The possibility that the stereoselectivity arises from either a thermodynamic preference or a subsequent process (cyclization) is less likely with imines as conjugate addition leads to an N-protonated immonium ion, which should rapidly undergo proton transfer. The resulting neutral product should be substantially less likely to undergo reversal to starting material than the dipolar intermediate involved in enamine Michael additions.

V. INTRAMOLECULAR ENAMINE MICHAEL ADDITIONS

Stereoselection can also occur in the intramolecular Michael addition. Factors other than those operative in the acyclic additions may influence the stereochemistry. In particular, certain stereoelectronic preferences are important in cyclizations that are not considerations in acyclic examples. In this respect, enamine and enolate cyclizations often exhibit similar behavior.[†]

A stereoselective intramolecular Michael addition was reported by Massiot and Mulamba (50,51). In this example, optically active **24.1** was cyclized with pyrrolidine in THF to **24.2** with no loss of optical purity and complete stereoselectivity (Scheme 24). Use of sodium hydride in THF, sodium methoxide in methanol, and Triton B in dimethoxyethane rather than pyrrolidine lead to products from further condensation of **24.2**. The configuration of Michael adduct **24.2** was assigned by ¹H-NMR and conversion into (–)-ajmalicine (**24.3**).

[†]See ref. 2, pages 355–374.



Scheme 24

Hirai and co-workers reported that **24.4** similarly cyclizes to **24.5** (Scheme 24) (52). Once again, the addition occurs with complete selectivity as **24.5** is obtained as one isomer. Further manipulations of **24.5** lead to (±)-emetine (**24.6**).

Strikingly high levels of asymmetric induction were found by Hirai and co-workers for the intramolecular Michael additions of **25.1** and **25.2** promoted by either *R* or *S* phenylethylamine (Scheme 25) (53). By varying the amine, either enantiomer of products **25.3** and **25.4** can be obtained in approximately 90% enantiomeric excess. Under similar conditions, the cyclization of **25.2** to yield pyrrolidine **25.5** occurs in 62% ee. The use of molecular sieves in the reaction of **25.1** increased the optical purity from 80 to 90% ee.

The stereochemical assignments for the cyclization of **25.1** were based on conversion into synthetic intermediates for the synthesis of (–)-ajmalicine (**25.6**), (–)-tetrahydroalstonine (**25.7**), and (–)-(10*R*)-hydroxydihydroquinine (**25.8**). No details of the stereochemical assignment of **25.5** were reported. These results can be rationalized by transition state **25.9**, which allows for association of the donor and acceptor portions of the substrate. Attack occurs from the face of the enamine opposite to the phenyl group. As in the intermolecular reactions of similar imines, these reactions are probably under kinetic control.

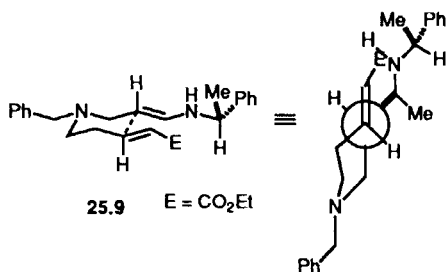
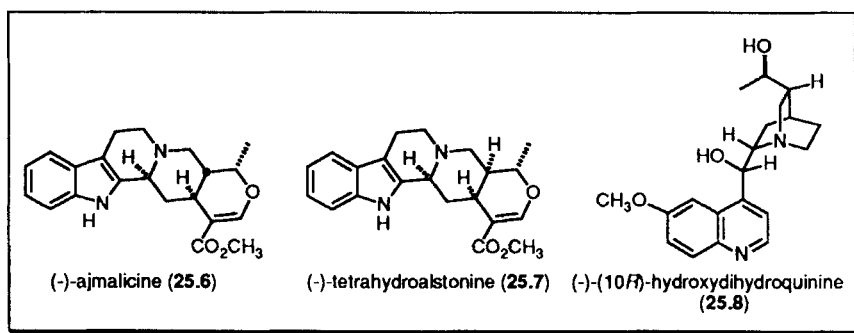
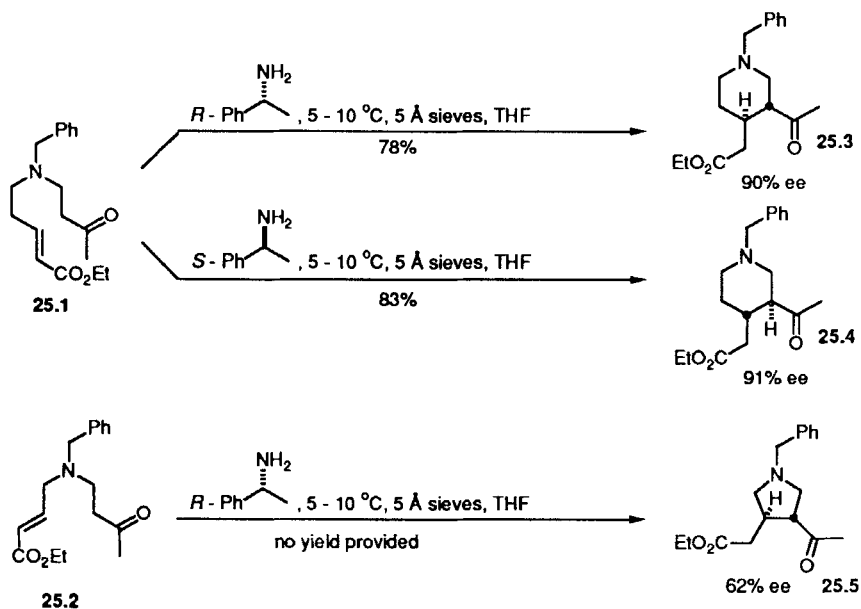
In connection with the synthesis of (±)-patchouli diol (**26.1**), Yamada and co-workers have examined the cyclization of the aldehyde derived from **26.2** (Scheme 26) (54). This ring closure provides **26.3** in 40% overall yield. Although no information has been provided to indicate whether **26.3** is the only diastereomer produced, the yield suggests that the process occurs with reasonable efficiency.

VI. SEQUENTIAL ENAMINE MICHAEL ADDITIONS

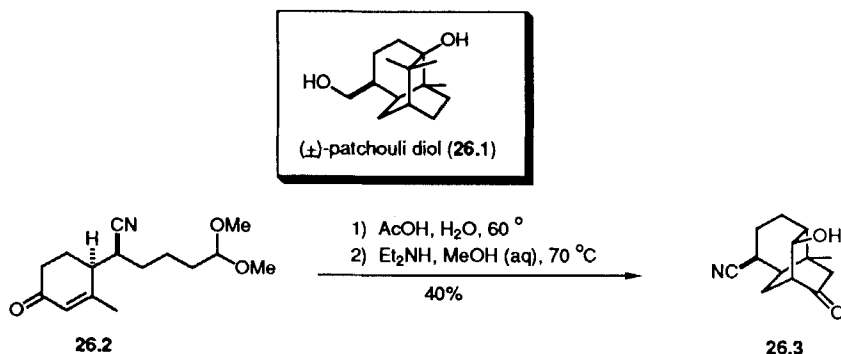
Addition of a cross-conjugated enamine to an activated olefin can give products that correspond to net [4 + 2] cycloaddition. The process can be viewed as occurring either through a concerted Diels–Alder mechanism or through a sequential Michael addition pathway. At this point, is not possible to unambiguously discriminate between these mechanisms and, hence, additions of cross-conjugated enamines are not treated in the following discussion.

A. Addition to Nitroolefins

[P, P] and **[P*, P]** Seebach and co-workers reported a stereoselective annelation scheme that does not have the possibility of proceeding through a concerted pathway (Schemes 27 and 28) (33, 55, 56). Presumably, the initial adduct of the Michael addition (**27.2**) eliminates pivalate anion, yielding



Scheme 25



Scheme 26

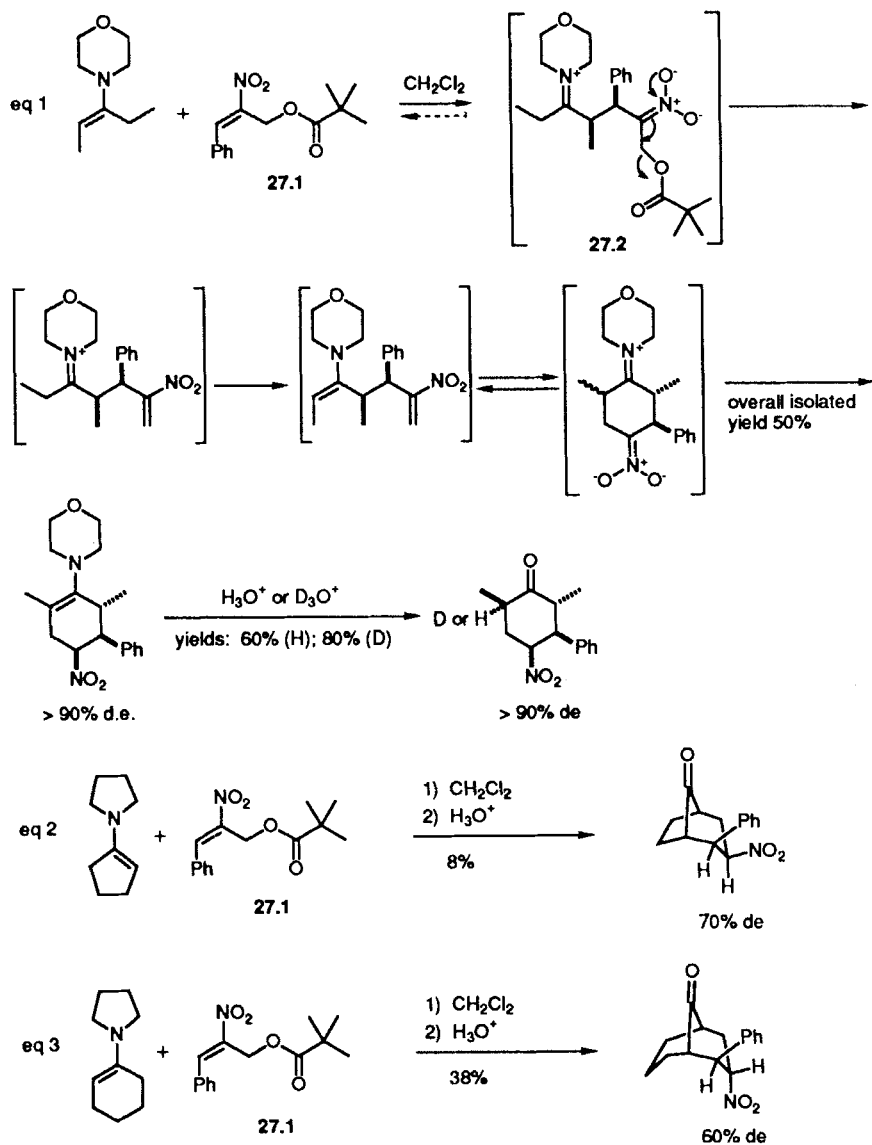
another nitroolefin, which undergoes further conjugate addition to provide a cyclic product. The initial addition occurs with good-to-excellent selectivity. Mechanistically, the stereoselectivity can occur at several points in the reaction pathway (see Eq. [1], Scheme 27). The high selectivity observed for the stereocenters that are established in the protonation steps is also striking. Only poor stereoselection relative to a preexisting stereocenter in the cyclohexane ring of the enamine is observed (Eq. [2], Scheme 28).

An asymmetric annelation sequence analogous to the foregoing achiral version has been reported (Scheme 29) (55a). Although only moderate yields were achieved, the diastereoselectivity and discrimination between heterotopic faces achieved in the process are both excellent.

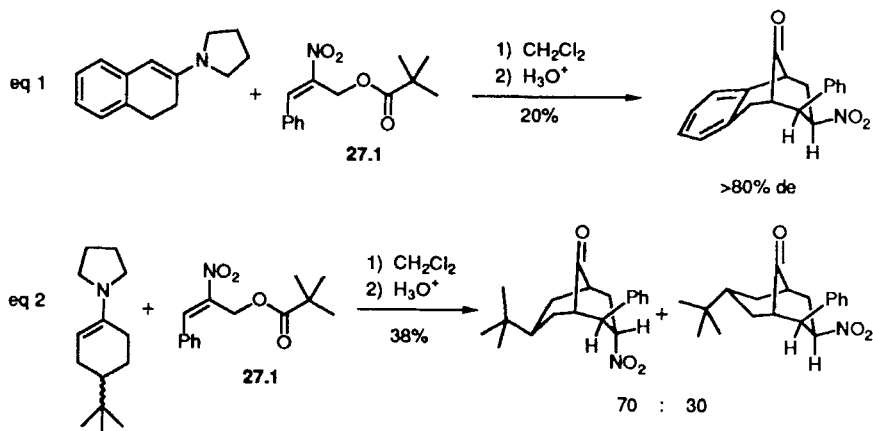
Particularly intriguing is the selectivity observed in Eqs. [3] and [4] (Scheme 29). In these cases, an enamine that probably exists as a 1:1 diastereomeric mixture yields products whose diastereomeric and enantiomeric excesses exceed 67%. This suggests that the isomeric enamines exist in a rapid equilibrium prior to the conjugate addition and/or the conjugate addition is at least partially reversible.

VII. DISCUSSION OF MECHANISM: ENAMINE REACTIONS

On first inspection, the enamine Michael addition appears to be a mechanistically simple reaction where neutral starting materials go to neutral products. Stereochemical studies have revealed, however, that the process is exceedingly complex. Initially, at least four different types of product (not counting stereoisomers!) can be obtained prior to hydrolysis (see Scheme 3). The point at which stereochemical differentiation occurs has yet to be convincingly



Scheme 27



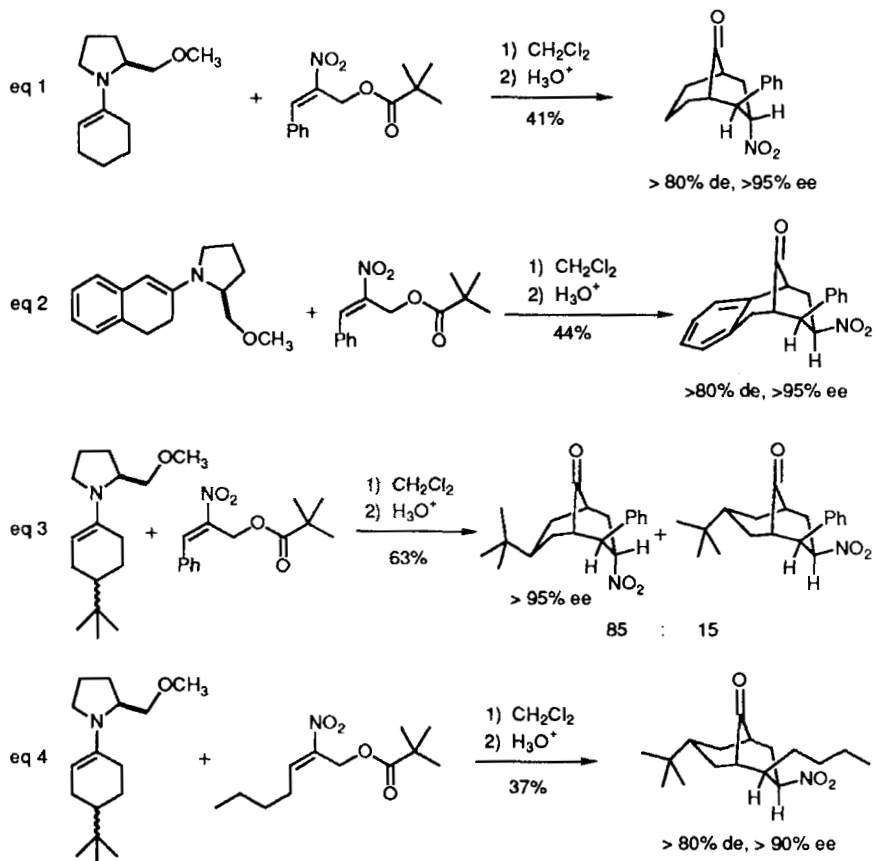
Scheme 28

demonstrated in all cases and, in fact, is likely to differ from substrate to substrate. All told, there are at least six points (A–F in Scheme 3) at which stereochemistry can be induced under kinetic control.

If the initial addition (A, Scheme 3) is essentially irreversible, the net stereoselectivity can be controlled by interactions that exist in the transition state for the Michael addition. However, if there is not a rapid intervening process (cyclization or proton transfer), the initial dipolar adducts would be expected to reform starting materials at an appreciable rate (*vide supra*). Based on the reports described previously, a significant possibility exists that this initial addition is reversible, at least in most cases. If indeed step A is reversible or if the configuration of **3.1** is not stable to reaction conditions, then the net stereoselectivity can be determined by the relative stability of the diastereomers of **3.1** or by the relative rates of the diastereomeric transition states for some subsequent reaction (e.g., B–F).[†] For example, selectivity could be induced by preferential cyclization (paths D and E) or by selective proton transfer (path B) from one of the components of the initial diastereomeric mixture (**3.1**). Also, it is possible that selective protonation (path F) of enamine **3.5** could give the observed products. This prospect is less likely as the generation of enamine **3.5** is disfavored by allylic strain considerations.

Seebach and Golinski advanced a topological rule to account for the stereochemistry of enamine Michael additions along with many other

[†] Note that products **3.2**–**3.5**, resulting from pathways B, C, D, and E, have all been observed in enamine Michael additions prior to hydrolysis, either as stable entities or as transient intermediates (*vide supra*).

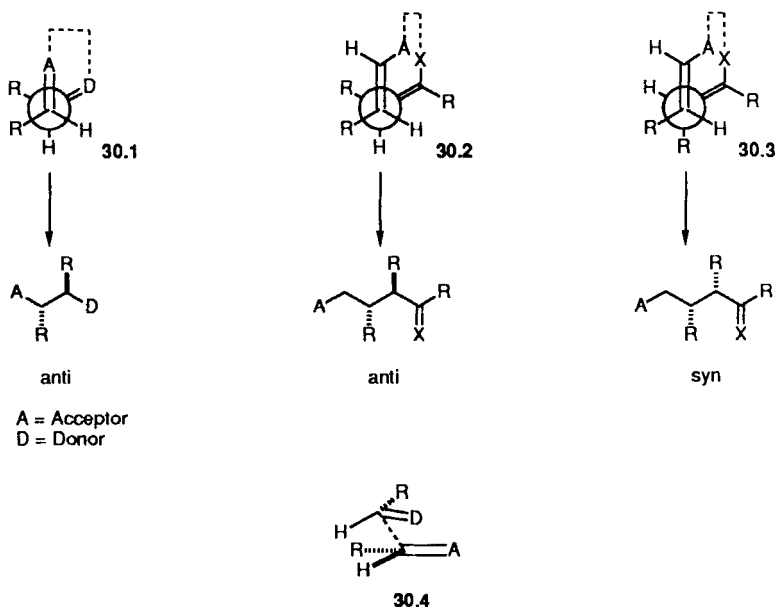


Scheme 29

combinations of two prostereogenic components (33,35). This model, illustrated in Scheme 30 (A = electron acceptor, D = electron donor), is applied by placing the two prostereogenic centers in a staggered conformation. It is assumed that some associative phenomenon (such as chelation or coulombic attraction) results in the gauche orientation of the donor (D) and acceptor (A) portions of the reactants (**30.1**, Scheme 30). With an enamine or enolate, the products are favored that result from the closest association of the donor atom (in this case X in **30.2** and **30.3**) and the acceptor (A) are preferred. Additionally, products are favored that arise from pathways where the smaller substituent of the donor (H in **30.1**) is placed between R and the H in the acceptor. This

pathway is believed to be preferred as a result of attack along the Bürgi–Dunitz trajectory (57), which results in a nonperpendicular approach of the two components (30.4). In this orientation, the effective size of the donor substituent between the R and the H of the acceptor is increased. The combination of these factors leads to prediction that *E* enamines/enolates should give syn products while *Z* enamines/enolates should give anti products and that *Z* enamines (through pathway 30.2) should be more selective than *E* enamines (through pathway 30.3).

Seebach and Golinski are careful to pose this analysis as a topological rule, which does not necessarily reflect the actual course of the reaction. With modifications, this tenet appears to crudely describe the course of enolate Michael additions (2, 58). While Seebach's rule was originally used to account for the "kinetically controlled" conjugate addition of enamines to nitroolefins, it now appears that in many enamine 1,4-additions the conjugate addition is not the product-determining step. Thus, the rule only can reflect the course of the reaction in examples where the conjugate addition is the product-determining step.



Scheme 30

VIII. LEWIS-ACID-MEDIATED REACTIONS

Protic-acid-catalyzed Michael additions (59) are subject to most of the limitations of base-catalyzed Michael additions (regioselectivity and stereoselectivity of enol generation, polyaddition, etc.), and hence, the stereochemistry has been little studied (60). At low temperatures silyl and stannyl enol ethers,[†] ketene acetals, and allyl species are unreactive to all but the most reactive activated olefins. However, it was discovered by Mukaiyama and co-workers that enol ethers and ketene acetals react with α,β -unsaturated carbonyl compounds in the presence of certain Lewis acids (4, 61, 62). Sakurai, Hosomi, and co-workers found that allylsilanes behave similarly (5, 63, 64).

Lewis-acid-promoted Michael additions complement the enolate (2) and enamine reactions (*vide supra*). Since a variety of methods exist for the generation of enol ethers and ketene acetals, often with good stereochemical and regiochemical control (*vide infra*), the Mukaiyama–Michael reaction often permits a degree of stereochemical and regiochemical control that is not easily possible in enolate and enamine reactions. Additionally, the reaction occurs under formally acidic conditions, so it can be used with base-sensitive substrates.

Although the reaction can be envisaged as catalytic in the Lewis acid, in practice only certain Lewis acids are effective in a catalytic sense. Notable among these are triphenylmethyl (trityl) cation (65), trimethylsilyl triflate (66), and trimethylsilyl chloride–tin(II) chloride (61a), which efficiently promote the reaction using as little as 2–3 mol% catalyst.

In general, competing 1,2-addition is less of a problem under the Mukaiyama conditions than with corresponding lithium enolates (2). This allows for good yields of conjugate addition products with substrates that give large proportions of 1,2-adducts with enolates.

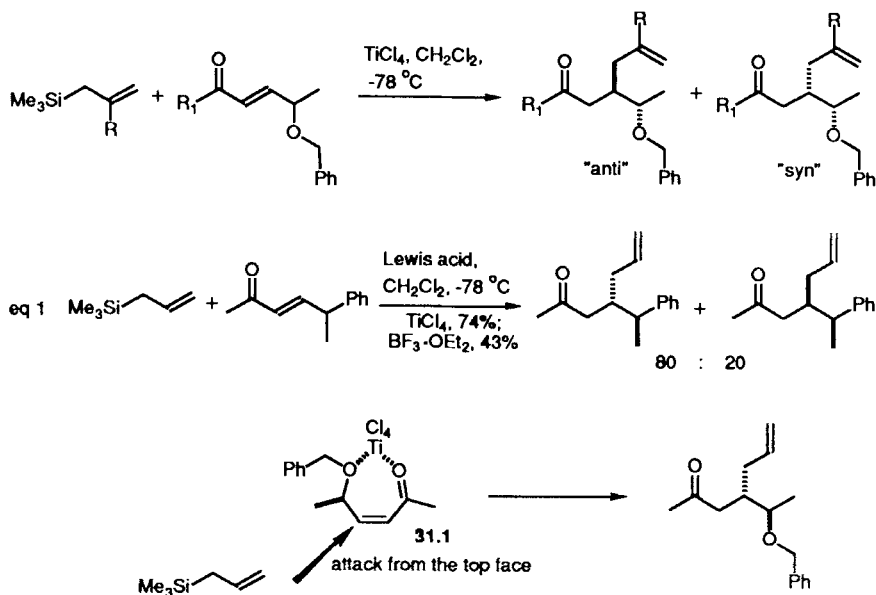
A. Allylsilanes and Stannanes

1. Addition to Enones

[N,P*] The Lewis-acid-promoted additions of allylsilanes and methallylsilanes to several chiral α,β -unsaturated ketones (Sakurai reaction) are summarized in Scheme 31 and Table 8 (67).[‡] The most effective catalyst for the

[†]Other enol and enolate species that are unreactive on their own towards conjugate addition can be induced to undergo conjugate addition by use of Lewis acid. For the purposes of this review, however, the discussion is limited to the Lewis-acid-promoted Michael additions of stannyl and silyl enol ethers.

[‡]The “longest linear chain” for the syn–anti nomenclature in this case is defined as the segment that contains both stereogenic centers.

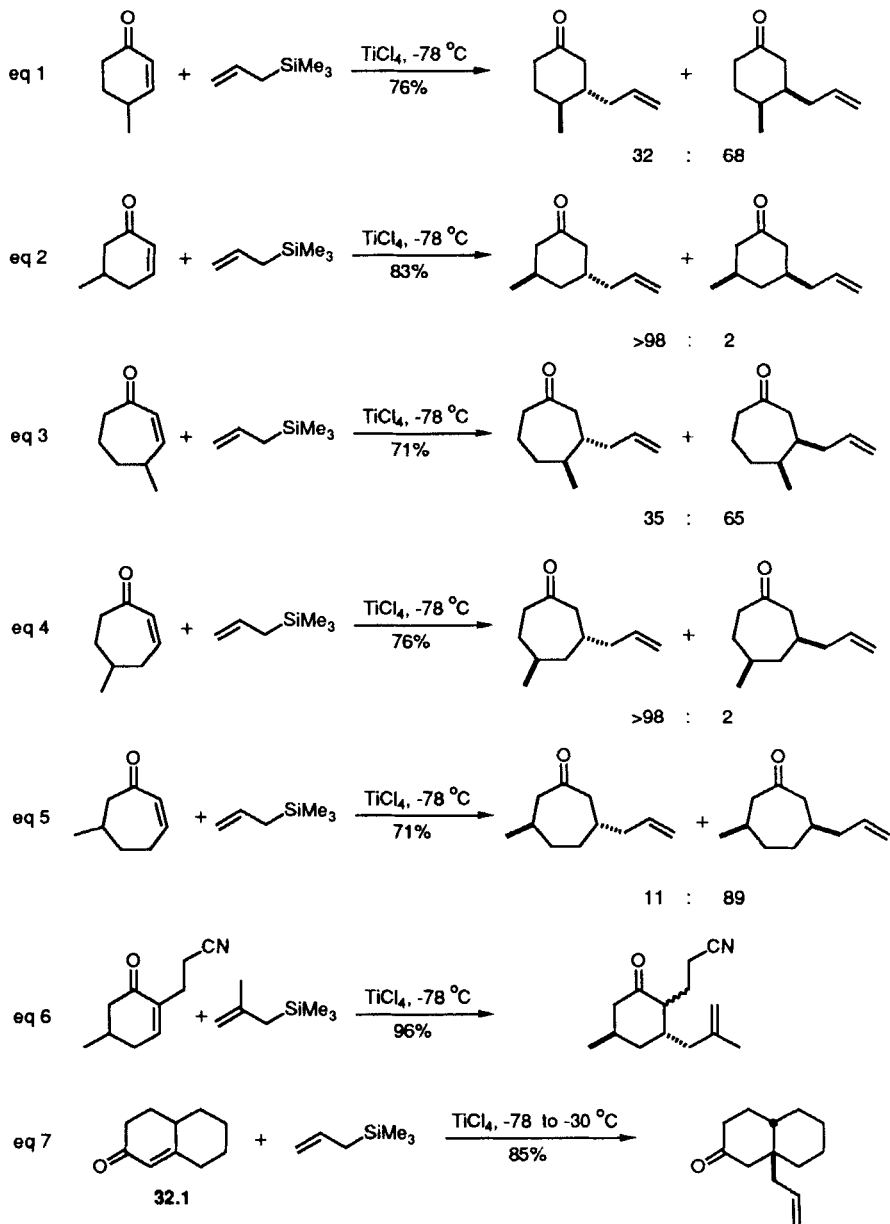


Scheme 31

Table 8
Addition of Allylsilanes to Chiral α,β -Unsaturated Ketones (Scheme 31)

Entry	Allylsilane R	α,β -Unsaturated Ketones		Yield (%)	Anti/Syn
		R ₁	E/Z		
1	H	Me	<i>E</i>	83	88:12
2	H	Me	<i>Z</i>	70	9:91
3	H	Ph	<i>E</i>	82	89:11
4	Me	Me	<i>E</i>	80	80:20
5	Me	Me	<i>Z</i>	78	50:50

reaction is TiCl_4 ; $\text{BF}_3 \cdot \text{OEt}_2$ results in similar selectivity but lower yields. Other Lewis acids (BF_3 , BCl_3 , $\text{BF}_3 \cdot \text{OEt}_2/\text{CuBF}_4$, ZnCl_2 , and $\text{CF}_3\text{CO}_2\text{H}$) are less effective. Good facial selectivity was found with the enones examined and γ -benzyloxy is more effective than γ -phenyl as a stereodifferentiating group (cf. Eq. [1], Scheme 31 with entry 1, Table 8). Interestingly, methallylsilane is less



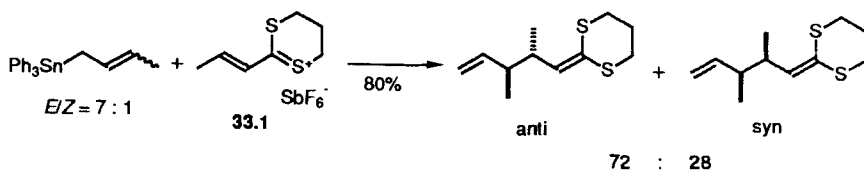
Scheme 32

selective than allylsilane (cf. entries 1–3 with entries 4 and 5). A striking reversal in selectivity is apparent with the *Z* enones (cf. entry 1 with 2 and 4 with 5). This reversal is rationalized by the chelated intermediate **31.1** (Scheme 31) where addition occurs in a manner analogous to the allylation of 4-methyl-2-cycloheptenone (Eq. [3], Scheme 32).

The titanium tetrachloride-promoted addition of allyltrimethylsilane to methylcyclohexenones and methylcycloheptenones has been explored (68, 69); results are summarized in Eqs. [1]–[6] of Scheme 32. With the exception of 4-substituted cyclohexenones and cycloheptenones, good to excellent facial selection is observed (Eqs. [2], [5], and [6], Scheme 32). The major products obtained are those predicted by “axial” attack of the nucleophile on the more stable conformer of the acceptor. Although there are some similarities, the results show some significant deviations from the corresponding cuprate additions. Addition to the bicyclic enone **32.1** occurs from the convex face, producing exclusively the *cis*-fused decalone (Eq. [7], Scheme 32) (5). In this case, the product is formally the result of equatorial attack of the allylsilane on the α,β -unsaturated ketone.

2. Addition to α,β -Unsaturated Thionium Ions

[**P**, **P**] The addition of (triphenyl)crotylstannane to vinylthionium ion **33.1** (Scheme 33) has been reported (70).[†] Only low levels of selectivity were observed.



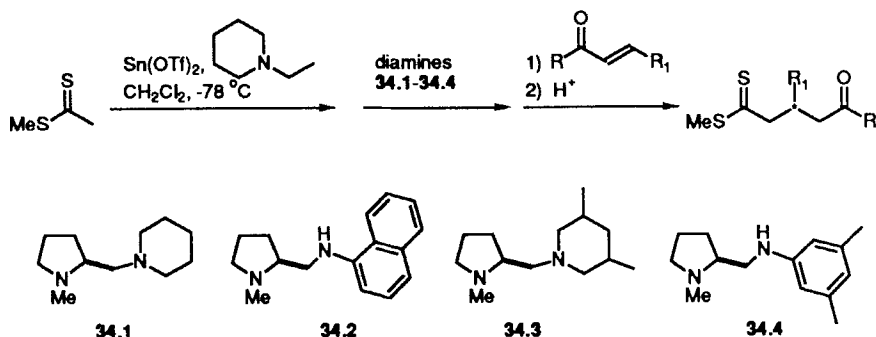
Scheme 33

B. Dithioesters

1. Addition to Enones

[**N***, **P**] Mukaiyama and co-workers explored the addition of methyl dithioacetate to enones under the influence of tin(II) triflate, a chiral, nonracemic diamine (**34.1**–**34.4**), and trimethylsilyl triflate (Scheme 34,

[†]The α,β -unsaturated thionium ion was generated by method A in Scheme 40.



Scheme 34

Table 9
Addition of Methyl Dithioacetate to α,β -Unsaturated Ketones in the Presence of
Chiral, Non-racemic Diamines (Scheme 34)

Entry	α,β -Unsaturated Ketone		Diamine	Yield (%)	ee ^a (%)
	R	R ₁			
1	Me	Ph	34.1	73	26
2	Me	Ph	34.2	82	70
3	Me	Ph	34.3	67	46
4	Me	Ph	34.4	65	36
5	Ph	Ph	34.2	75	40
6	Me	2-furyl	34.2	79	60
7	Ph	<i>i</i> -Pr	34.2	79	60
8	Ph	Me	34.2	62	15
9	-CH ₂ CH ₂ -		34.2	44	30

^aThe absolute configuration of the products was not determined.

Table 9) (71). Although the absolute stereochemistry of the products was not determined, it is apparent that reasonable levels of asymmetric induction are possible using this procedure. Amine **34.2** gives the highest levels of enantioselection and the degree of stereoselectivity is strongly dependent on the enone used.

It is likely that the chiral diamine complexes the tin of the enolate, thus enhancing the nucleophilicity and differentiating the faces of the enethiolates.

Enhanced reactivity of a diamine–tin(II) enolate complex suggests that the reaction could be made catalytic. Indeed, this has proved to be the case (*vide infra*). An alternative mechanism where a chiral Lewis acid is formed from the diamine and tin(II) triflate appears less likely as complexation with the diamine would be expected to attenuate the reactivity of the enone–Lewis acid complex.

Two fundamental conditions must be met to achieve the levels of enantioselectivity observed in this reaction; the diamine must preferentially shield one of the faces of the dithioacetate enolate and the resulting complex must react with a large degree of pseudo-simple diastereoselectivity (*vide supra*). The strong dependence of the stereoselectivity of this method on the choice of enone is suggestive of a breakdown of pseudo-simple selectivity in the less selective cases. Also note that the highest levels of selection occur only when the β -substituent (R_1) is aromatic.

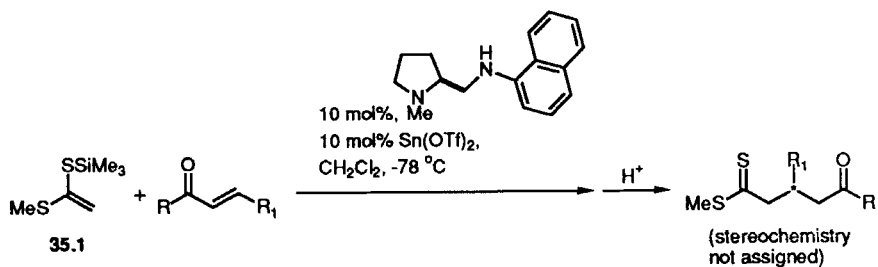
A catalytic version of this reaction has also been developed by Mukaiyama and co-workers (Scheme 35) (72). Addition of the trimethylsilyl dithioketene acetal **35.1** to the enone in the presence of the amine–tin(II) triflate complex gives nearly identical yields and optical purities as the stoichiometric procedure.

Products with lower optical purities are obtained when the tin(II) enethiolate of methyl dithioacetate is used, apparently as a result of competing direct nucleophilic addition of this species to the enone. Use of the silyl dithioketene acetal minimizes direct conjugate addition and permits a catalytic, asymmetric procedure as TMSOTf is generated *in situ*. Again, complexation of the tin enethiolate with the diamine should serve to activate this species toward nucleophilic addition. Although the enantioselectivities obtained so far are not optimal, it is clear that this strategy shows excellent promise as a general method of catalytic, asymmetric induction.

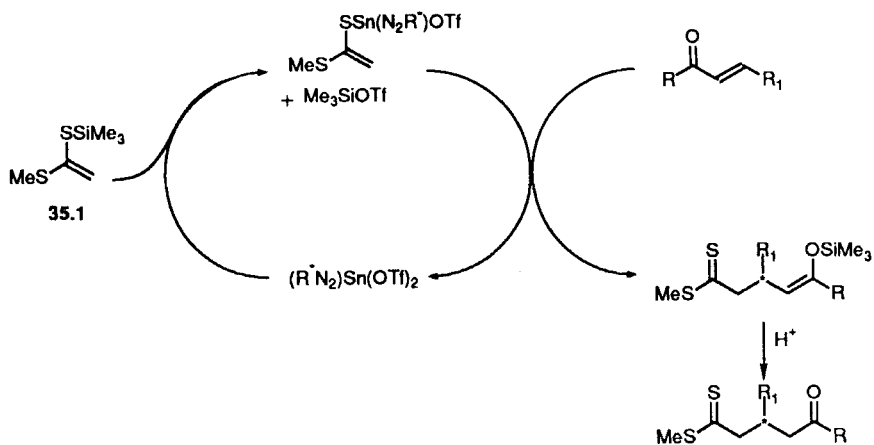
C. Silyl Enol Ethers

Ketone enolates and silyl enol ethers are generally interconvertible. In practice, silyl enol ethers are usually generated from ketones using a strong base followed by a silylating agent or a weak base (usually an amine) in the presence of a silylating agent. Although these methods can be limited by regiochemical and stereochemical considerations (73–75), a substantial variety of silyl enol ethers can be prepared by these methods.

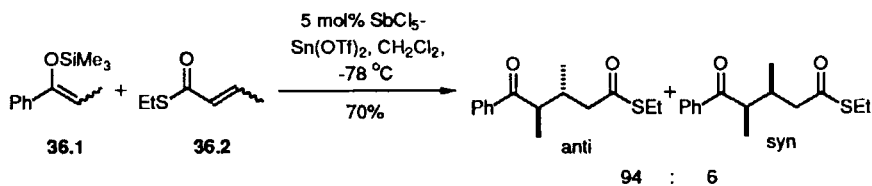
As will be shown, the stereochemistry of Mukaiyama–Michael additions is in many instances insensitive to the stereochemistry of the silyl enol ether used. This method is potentially advantageous relative to the direct conjugate addition of ketone enolates when it is impossible to obtain the enolate or silyl enol ethers in a stereoisomerically pure form.



R	R ₁	% yield	% ee
Me	Ph	80	70
Me	2-furyl	82	60
Ph	Ph	79	40



Scheme 35



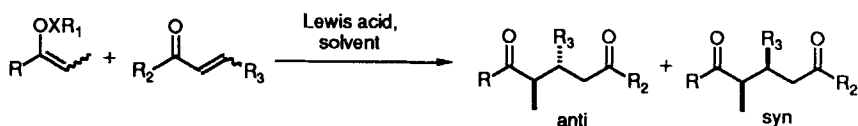
Scheme 36

1. Addition to α,β -Unsaturated *S*-Alkyl Monothioester

[P, P] A single example of a stereoselective, Lewis-acid-assisted addition of silyl enol ether to an α,β -unsaturated thioester has been reported by Mukaiyama and co-workers (76). In this report, silyl enol ether **36.1** was added to thioester **36.2** under the influence of an antimony(V) chloride–tin(II) triflate mixture to give a 94:6 (anti/syn) mixture of diastereomers in 70% yield (Scheme 36).

2. Addition to Enones

[P, P] Additions of silyl enol ethers derived from ketones to α,β -unsaturated ketones under Lewis acid catalysis are summarized in Scheme 37 and Table 10 (77–80). Although the question has not been systematically explored, the data in Table 10 suggest that there is no strong influence of the nature of the Lewis acid. The role of the Lewis acid in most cases is formally catalytic. In practice, however, a full equivalent of the Lewis acid is needed when TiCl_4 or SnCl_4 are used as Lewis acids (entries 1–33, Table 10). With clay montmorillonite (entries 34, 35, and 57) and trityl salts (entries 36–56), only catalytic amounts of the Lewis acid are needed. Use of trityl salts presents the disadvantage of the removal of trityl alcohol after the quench. With clay, the Lewis acid can be removed by filtration through celite.



Scheme 37

The geometry of the silyl enol ether has only a slight influence on the stereochemistry of the Mukaiyama–Michael addition. For example, the *Z* silyl enol ether in entry 5 (Table 10) provides a 35:65 (syn/anti) mixture of diastereomers. With the corresponding *E* silyl enol ether (entry 25), a 23:77 (syn/anti) mixture of diastereomers results.

An increase in the size of the silyl group from trimethylsilyl to *tert*-butyldimethylsilyl results in an increase in the amount of the anti diastereomer (entries 41–44, Table 10), at least with *E* silyl enol ethers.

In all instances, the Mukaiyama–Michael addition of silyl enol ethers is anti selective. For the most part, however, the selectivity is only modest. A

Table 10
Addition of Enol Silanes and Stannanes to α,β -Unsaturated Ketones (Scheme 37)

Entry ^a	Enol Ether		Enone ^b			Lewis Acid	Temperature (°C)	Yield (%)	Syn/Anti	Reference
	R	R ₁ X	E/Z ^c	R ₂	R ₃					
1	Et	Me ₃ Si	Z	<i>t</i> -Bu	Me	SnCl ₄	-78	74	12:88	79
2	Et	Me ₃ Si	Z	<i>t</i> -Bu	Me	TiCl ₄	-78	52	12:88	79
3	Et	Me ₃ Si	Z	<i>i</i> -Pr	Me	SnCl ₄	-78	52	24:76	79
4	<i>i</i> -Pr	Me ₃ Si	Z	Et	Me	SnCl ₄	-78	42	41:59	79
5	<i>i</i> -Pr	Me ₃ Si	Z	<i>i</i> -Pr	Me	SnCl ₄	-78	87	35:65	79
6	<i>i</i> -Pr	Me ₃ Si	Z	<i>t</i> -Bu	Me	SnCl ₄	-78	63	15:85	79
7	<i>i</i> -Pr	Me ₃ Si	Z	Ph	Me	SnCl ₄	-78	78	40:60	79
8	<i>i</i> -Pr	Me ₃ Si	Z	<i>t</i> -Bu	Et	SnCl ₄	-78	68	17:83	79
9	<i>i</i> -Pr	Me ₃ Si	Z	<i>t</i> -Bu	<i>i</i> -Pr	SnCl ₄	-78	24	9:91	79
10	<i>i</i> -Pr	Me ₃ Si	Z	<i>t</i> -Bu	<i>t</i> -Bu	SnCl ₄	-78	0	—	79
11	<i>i</i> -Pr	Me ₃ Si	Z	<i>t</i> -Bu	Ph	SnCl ₄	-78	91	15:85	79
12	<i>t</i> -Bu	Me ₃ Si	Z	<i>i</i> -Pr	Me	SnCl ₄	-78	37	41:59	79
13	<i>t</i> -Bu	Me ₃ Si	Z	<i>t</i> -Bu	Me	SnCl ₄	-78	10	31:69	79
14	Ph	Me ₃ Si	Z	<i>i</i> -Pr	Me	SnCl ₄	-78	50	9:91	79
15	Ph	Me ₃ Si	Z	<i>t</i> -Bu	Me	SnCl ₄	-78	69	<5:95	79
16	Ph	Me ₃ Si	Z	Ph	Me	SnCl ₄	-78	75	5:95	79
17	Ph	Me ₃ Si	Z	<i>t</i> -Bu	Et	SnCl ₄	-78	95	<5:95	79
18	Ph	Me ₃ Si	Z	<i>t</i> -Bu	<i>i</i> -Pr	SnCl ₄	-78	89	<5:95	79
19	Ph	Me ₃ Si	Z	<i>t</i> -Bu	<i>t</i> -Bu	SnCl ₄	-78	0	—	79
20	Ph	Me ₃ Si	Z	<i>t</i> -Bu	Ph	SnCl ₄	-78	81	32:68	79
21	<i>p</i> -MeOC ₆ H ₄	Me ₃ Si	Z	<i>t</i> -Bu	Me	SnCl ₄	-78	94	7:93	79
22	Me ^d	Me ₃ Si	Z	<i>t</i> -Bu	Me	TiCl ₄	0	68	7:93	79
23	Et	Me ₃ Si	<i>E</i>	<i>t</i> -Bu	Me	SnCl ₄	-78	59	13:87	79

24	<i>i</i> -Pr	Me ₃ Si	<i>E</i>	Et	Me	SnCl ₄	-78	42	31:69	79
25	<i>i</i> -Pr	Me ₃ Si	<i>E</i>	<i>i</i> -Pr	Me	SnCl ₄	-78	69	23:77	79
26	<i>i</i> -Pr	Me ₃ Si	<i>E</i>	<i>t</i> -Bu	Me	SnCl ₄	-78	81	33:67	79
27	<i>i</i> -Pr	Me ₃ Si	<i>E</i>	Ph	Me	SnCl ₄	-78	82	19:81	79
28	<i>i</i> -Pr	Me ₃ Si	<i>E</i>	<i>t</i> -Bu	Et	SnCl ₄	-78	73	24:76	79
29	<i>i</i> -Pr	Me ₃ Si	<i>E</i>	<i>t</i> -Bu	<i>i</i> -Pr	SnCl ₄	-78	26	11:89	79
30	<i>i</i> -Pr	Me ₃ Si	<i>E</i>	<i>t</i> -Bu	<i>t</i> -Bu	SnCl ₄	-78	0	—	79
31	<i>i</i> -Pr	Me ₃ Si	<i>E</i>	<i>t</i> -Bu	Ph	SnCl ₄	-78	46	37:63	79
32	Ph	Me ₃ Si	<i>E</i>	<i>t</i> -Bu	Me	SnCl ₄	-78	77	27:73	79
33	Mes ^d	Me ₃ Si	<i>E</i>	<i>t</i> -Bu	Me	TiCl ₄	0	87	18:82	79
34	Et	Me ₃ Si	<i>E</i> ^e	Me	Ph	Clay ^f	-78	98 ^g	29:71	78
35	Et	Me ₃ Si	<i>E</i> ^e	Me	Ph	Clay ^f	-30	81 ^{g,h}	21:79	78
36	Ph	<i>t</i> -BuMe ₂ Si	<i>i</i>	Ph	Me	TrCl/SnCl ₂	-78	84	<5:95	80
37	Ph	<i>t</i> -BuMe ₂ Si	<i>i</i>	-CH ₂ CH ₂ CH ₂ -	Me	TrCl/SnCl ₂	-78	84	17:83	80
38	Ph	<i>t</i> -BuMe ₂ Si	Z	-CH ₂ CH ₂ CH ₂ -	TrClO ₄	TrClO ₄	-45	63/	23:77	77
39	Ph	<i>t</i> -BuMe ₂ Si	Z	-CH ₂ CH ₂ CH ₂ -	TrPF ₆	TrPF ₆	-45	66/	22:78	77
40	Ph	<i>t</i> -BuMe ₂ Si	Z	-CH ₂ CH ₂ CH ₂ -	TrSnCl ₅	TrSnCl ₅	-45	62/	21:79	77
41	Et	Me ₃ Si	<i>E</i>	Ph	Me	TrClO ₄	-45	51 ^g	41:59	77
42	Et	PhMe ₂ Si	<i>E</i>	Ph	Me	TrClO ₄	-45	44 ^g	30:70	77
43	Et	Et ₃ Si	<i>E</i>	Ph	Me	TrClO ₄	-45	70 ^g	29:71	77
44	Et	<i>t</i> -BuMe ₂ Si	<i>E</i>	Ph	Me	TrClO ₄	-45	81 ^g	23:77	77
45	Et	<i>t</i> -BuMe ₂ Si	Z	Ph	Me	TrClO ₄	-45	75 ^g	17:83	77
46	Et	<i>t</i> -BuMe ₂ Si	Z	Ph	Me	TrClO ₄	-78	81 ^g	23:77	77
47	Et	<i>t</i> -BuMe ₂ Si	Z	Me	Me	TrClO ₄	-78	54 ^{g,k}	16:84	77
48	Ph	<i>t</i> -BuMe ₂ Si	Z	Me	Me	TrClO ₄	-78	64 ^g	<5:95	77
49	Et	<i>t</i> -BuMe ₂ Si	Z	Ph	Me	TrClO ₄	-78	84 ^g	15:85	77
50	Ph	<i>t</i> -BuMe ₂ Si	Z	Ph	Me	TrClO ₄	-78	81 ^g	<5:95	77
51	Et	<i>t</i> -BuMe ₂ Si	Z	Ph	Ph	TrClO ₄	-78	81 ^g	26:74	77
52	Ph	<i>t</i> -BuMe ₂ Si	Z	Ph	Ph	TrClO ₄	-45	75 ^g	<5:95	77

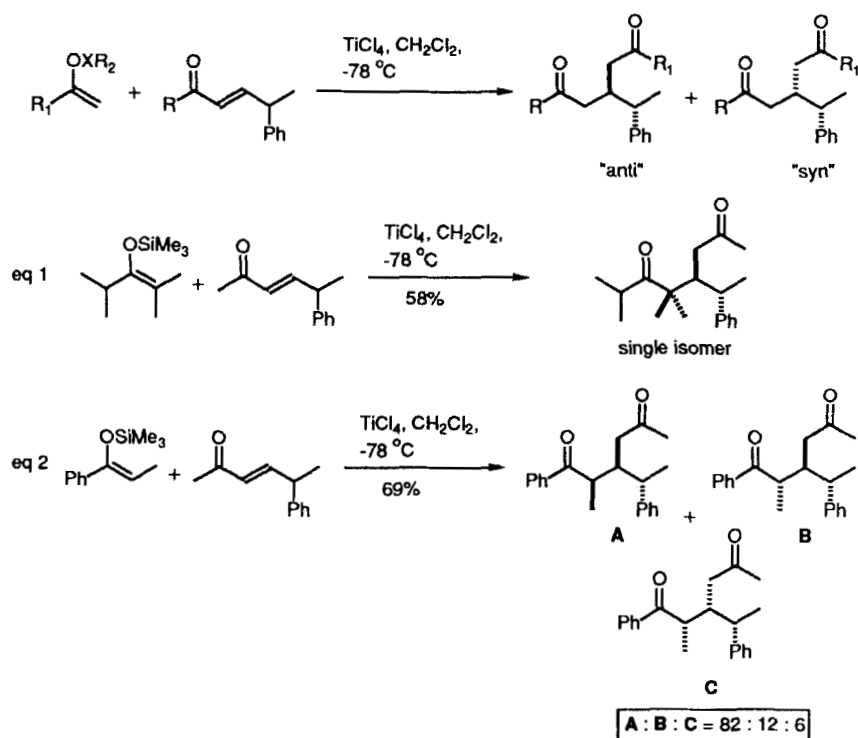
Table 10 (Continued)

Entry ^a	Enol Ether		Enone ^b			Lewis Acid	Temperature (°C)	Yield (%)	Syn/Anti	Reference
	R	R ₁ X	E/Z ^c	R ₂	R ₃					
53	Et	<i>t</i> -BuMe ₂ Si	Z	Me	Ph	TrClO ₄	-78	75 ^g	27:73	77
54	Ph	<i>t</i> -BuMe ₂ Si	Z	Me	Ph	TrClO ₄	-78	81 ^g	<5:95	77
55	Et	<i>t</i> -BuMe ₂ Si	Z	-CH ₂ CH ₂ CH ₂ -	Ph	TrClO ₄	-78	68 ^g	46:54	77
56	Ph	<i>t</i> -BuMe ₂ Si	Z	-CH ₂ CH ₂ CH ₂ -	Ph	TrClO ₄	-78	68 ^{g,k}	17:83	77
57	Et	Me ₃ Si	<i>E</i>	-CH ₂ CH ₂ CH ₂ -	CH ₂ CH ₂ CH ₂ -	Clay ^j	-78	83 ^{g,k}	38:62	78

^aAll reaction performed in CH₂Cl₂, unless otherwise noted.^bAll the enones have the *E* configuration except for the cyclic cases.^cThe major isomer is shown; unless otherwise indicated, the exact ratio was not reported.^d2,4,6-Trimethylphenyl.^eAn 83:17 *E/Z* mixture was used.^fAluminum-cation-exchanged clay montmorillonite was used as a Lewis acid.^gYield is for the enol silane obtained as a product.^h1,2-Dimethoxyethane was used as solvent.ⁱNot reported.^jThe initial enol silanes were hydrolyzed with acid.^kCH₃CN/CH₂Cl₂ (1.7:1) was used as a solvent.

notable exception is for the *Z* silyl enol ether of propiophenone, which reacts with a variety of acyclic enones with excellent anti selectivity (see entries 14–18, 36, 48, 50, 52, and 54, Table 10). Selectivity is also enhanced, in general, by increasing the steric demand at either the α or β positions of the enone or by decreasing the bulk of the alkyl group of the silyl enol ether. Neither of these changes by themselves are sufficient to raise the selectivity above 95%.

[N, P*] and [P, P*] Aldehydes with an α -stereocenter exhibit unusually high diastereofacial preferences for the addition of silyl enol ethers and ketene acetals with Lewis acid assistance (81). Heathcock and Uehling found good levels of facial discrimination in the addition of silyl enol ethers to chiral enones (Scheme 38, Table 11) (82). With the more substituted silyl enol ether, only one diastereomeric addition product is obtained (Eq. [1], Scheme 38). Use of a prostereogenic silyl enol ether allows control over the relative



Scheme 38

Table 11
Addition of Enol Silanes to Chiral Enones (Scheme 38)

Entry	Enol Silane		Enone R	Yield (%)	Ratio "Syn"/"Anti"
	R ₁	XR ₂			
1	<i>t</i> -Bu	Me ₃ Si	Me	69	11:89
2	<i>t</i> -Bu	<i>t</i> -BuMe ₂ Si	Me	59	5:95
3	Ph	Me ₃ Si	Me	60	8:92
4	Ph	Me ₃ Si	<i>t</i> -Bu	64	7:93
5	<i>t</i> -Bu	Me ₃ Si	Ph	62	16:84
6	<i>t</i> -Bu	<i>t</i> -BuMe ₂ Si	Ph	46	16:84

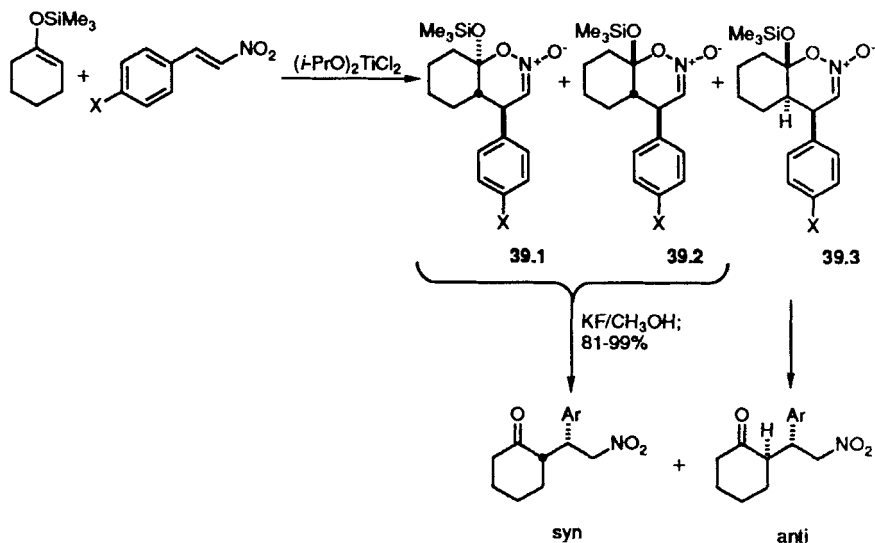
configurations of three contiguous stereocenters (Eq. [2]). Note that 12% of the product results from syn simple diastereoselectivity.

3. Addition to Nitroolefins

[P,P] Seebach and Brock reported the dichlorodiisopropoxytitanium-mediated addition of the trimethylsilyl enol ether of cyclohexanone to β -nitrostyrenes (83). The initial products generated are nitronic esters **39.1**–**39.3**. Separation followed by fluoride-induced desilylation of these intermediates yields the corresponding syn and anti nitroketones. The results of this study are summarized in Scheme 39 and Table 12. Anti isomers are obtained in moderate diastereomeric excess. Moreover, the method is complementary to the additions of similar substrates by way of their lithium enolates (2) or enamines (*vide supra*), which provide the syn diastereomers. Further reactions of the intermediate nitronic esters were briefly explored. For example, addition of aldehydes and activated olefins provides stereoselectively the products from nitroaldol and [3 + 2] cycloadditions.

4. Addition to α,β -Unsaturated Thionium Ions

[P,P] Vinylthionium ions such as **40.1** are potent Michael acceptors. Additions of silyl and stannyl enol ethers to vinylthionium ions such as **40.1** have been reported by Mukaiyama and co-workers (84–86). Two methods were employed for generation of the Michael acceptors; elimination of ethyl sulfide from **40.2** under the action of a cationic trityl species (method A) and hydride abstraction from **40.3** and **40.4** by a trityl salt (method B) to give **40.1**. Although both procedures use a strong Lewis acid to promote reaction, they differ substantially from the prior examples because an acceptor–acid



Scheme 39

Table 12
Lewis-Acid-Promoted Addition of Enol Silanes to Nitro-
styrenes (Scheme 39)

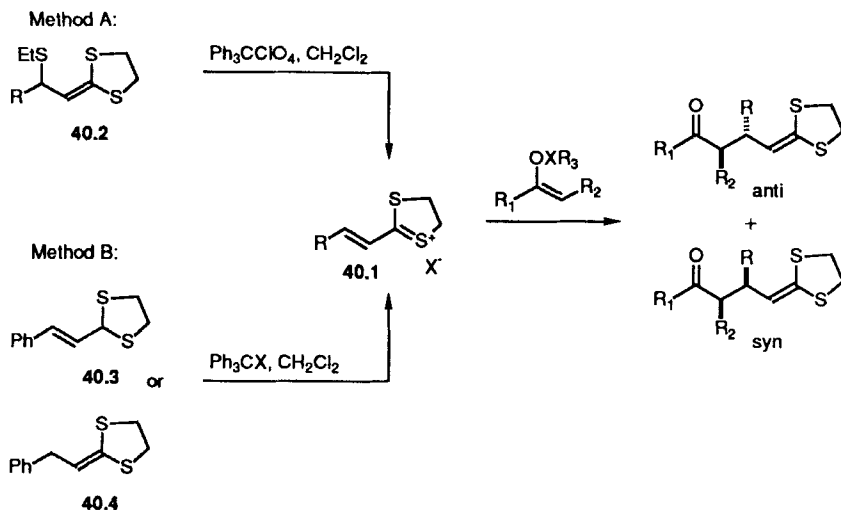
Entry	Nitrostyrene X	Yield ^a (%)	Anti/Syn ^b
1	H	62	75:25
2	Me	47	80:20
3	MeO	42	67:23
4	CN	27	73:27

^aIsolated yields for the anti diastereomer only.

^bFor the hydrolyzed product with no epimerization.

complex does not appear to be involved as the species to which conjugate addition occurs. The results of the addition of a variety of enol ethers to **40.1** are summarized in Scheme 40 and Table 13.

Vinylthionium ions are at the same oxidation state as α,β -unsaturated esters. They are much more reactive than the corresponding enoates, however, reacting readily with silyl and stannyl enol ethers.



Scheme 40

The stereochemistry observed is similar to that observed for the corresponding addition of silyl enol ethers to α,β -unsaturated ketones (*vide supra*), suggesting a similarity in the factors controlling the stereochemistry in the two cases. With the exception of the *tert*-butyldimethylsilyl ligand, a rough trend relating the bulk of the silyl group to the proportion of the anti diastereomer produced is apparent (entries 8–14, Table 13). With the triphenylsilyl group the reaction requires higher temperatures and the selectivity drops (entry 14).

D. Imides

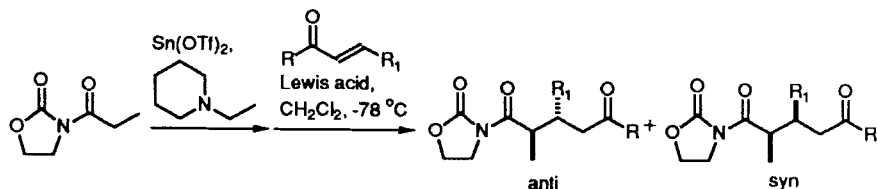
1. Addition to Enones

[P, P] Tin(II) enolates of propionyl imides do not undergo uncatalyzed reactions with enones. Lewis acid catalysis results in the construction of 1,4-addition products. The stereoselectivity of this reaction has been examined by Mukaiyama and co-workers (87, 88) and is summarized in Scheme 41 and Table 14. The tin(II) enolates were generated by the action of tin(II) triflate with *N*-ethylpiperidine on the propionyl imide. Although not examined, it is likely that this procedure results in the generation of a *Z* enolate (89). A process can be envisioned whereby transmetalation occurs to yield a silyl ether and a tin(II) species capable of Lewis acidic behavior. Hence, either direct conjugate addition of the tin enolate to a silyl-activated acceptor or transmetalation to

Table 13
Addition of Enol Silanes and Stannanes to Vinylthionium Ions (Scheme 40)

Entry	Vinylthionium			Enol Ether				Temperature (°C)	Yield (%)	Anti/Syn
	R	Method	Catalyst	R ₁	R ₂	R ₃ X	E/Z			
1	Me	A	Ph ₃ CBF ₄	Ph	Me	Me ₃ Si	Z ^a	-78	85	96:4
2	Me	A	Ph ₃ CBF ₄	-(CH ₂) ₄ -	Me	Me ₃ Si	E	-78	54	71:29
3	<i>n</i> -Pr	A	Ph ₃ CBF ₄	Ph	Me	Me ₃ Si	Z ^a	-78	87	93:7
4	Ph	A	Ph ₃ CBF ₄	Ph	Me	Me ₃ Si	Z ^a	-78	89	97:3
5	Me	A	Ph ₃ CClO ₄	-(CH ₂) ₄ -	Me	Bu ₃ Sn	E	25	85	30:70
6	Me	A	Ph ₃ CClO ₄	Et	Me	Bu ₃ Sn	^a	25	78	50:50
7	Me	A	Ph ₃ CClO ₄	Ph	Me	Bu ₃ Sn	^a	25	81	75:25
8	Ph	B	Ph ₃ CBF ₄	-(CH ₂) ₄ -	Me	Me ₃ Si	E	-78	84	65:35
9	Ph	B	Ph ₃ CBF ₄	-(CH ₂) ₄ -	Me	Et ₃ Si	E	-78	89	78:22
10	Ph	B	Ph ₃ CBF ₄	-(CH ₂) ₄ -	Me	<i>t</i> -BuMe ₂ Si	E	-78	86	40:60
11	Ph	B	Ph ₃ CBF ₄	-(CH ₂) ₄ -	Me	PhMe ₂ Si	E	-78	88	84:16
12	Ph	B	Ph ₃ CBF ₄	-(CH ₂) ₄ -	Me	Ph ₂ MeSi	E	-78	83	88:12
13	Ph	B	Ph ₃ CO ₃ SCF ₃	-(CH ₂) ₄ -	Me	Ph ₂ MeSi	E	-78	74	91:9
14	Ph	B	Ph ₃ CBF ₄	-(CH ₂) ₄ -	Me	Ph ₃ Si	E	-78 to 0	84	85:15
15	Ph	B	Ph ₃ CO ₃ SCF ₃	-(CH ₂) ₃ -	Me	Ph ₂ MeSi	E	-78	86	92:8
16	Ph	B	Ph ₃ CO ₃ SCF ₃	Ph	Me	Ph ₂ MeSi	E	-78	74	92:8
17	Ph	B	Ph ₃ CO ₃ SCF ₃	Et	Me	Ph ₂ MeSi	E ^a	-78	90	53:47
18	Ph	B	Ph ₃ CO ₃ SCF ₃	Et	Me	Ph ₂ MeSi	E ^a	-78	85	51:49

^aExact isomer ratio not reported.



Scheme 41

Table 14

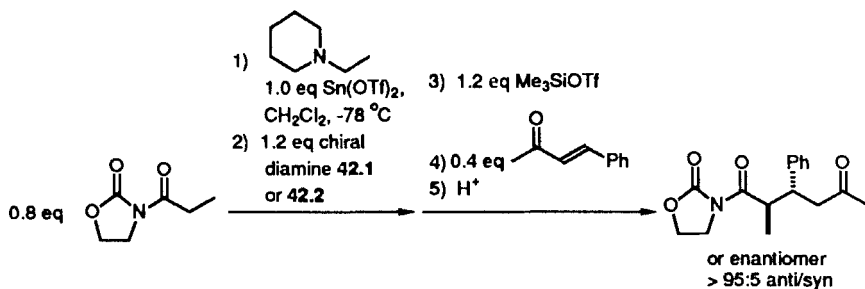
Addition of Tin Enolates of Propionyl Imides to α,β -Unsaturated Ketones (Scheme 41)

Entry	Enone		Catalyst	Yield (%)	Anti/Syn
	R	R ₁			
1	$-\text{CH}_2\text{CH}_2\text{CH}_2-$		Me_3SiCl	84	62:38
2	Me	Ph	Me_2SiCl_2	77	8:92
3	Me	Ph	Me_3SiCl	78	71:29
4	Me	Me	Me_2SiCl_2	56	95:5
5	Me	Me	Me_3SiCl	56	71:29
6	Ph	Me	Me_2SiCl_2	85	75:25
7	$-\text{CH}_2\text{CH}_2\text{CH}_2-$		BF_3OEt_2	28	69:31
8	$-\text{CH}_2\text{CH}_2\text{CH}_2-$		Ph_2BCl	17	53:47

form a silyl ether followed by addition to a tin-activated acceptor is possible. Control experiments, however, reveal that at -78°C addition of preformed silyl enol ethers to tin-activated acceptors does not occur to an appreciable rate. Thus, tin(II) enolates are implicated as the reactive species in this process.

The stereoselectivity of the reaction shows interesting dependence on the Lewis acid and the enone. For example, in the reaction with 4-phenylpent-3-en-2-one, dimethylsilyl dichloride and trimethylsilyl chloride give opposite stereoselectivity (entries 2 and 3). Depending on which substrate is used, both syn- and anti-stereoselectivity can be obtained (entries 2 and 4).

[P*, P] An enantioselective version of the foregoing reaction has been reported by Mukaiyama and co-workers (71). In this procedure, a tin(II) enolate prepared in an analogous manner to the above was complexed with chiral, nonracemic diamines **42.1** and **42.2** (Scheme 42). Addition of the resulting undefined complexes to benzalacetone in the presence of a Lewis acid results in exclusive formation of the anti diastereomer. Although the absolute configuration of the products has not been established, products with optical purities of 80% when amine **42.1** and 93% when **42.2** are used are constructed.



chiral amine	% yield	% ee
 42.1	70	80
 42.2	72	93

Scheme 42

The reaction is not promoted by trimethylsilyl chloride and is critically dependent on stoichiometry of the reagents employed.

The reactive species in these additions has not been fully elucidated. It is likely that considerations similar to those involved in the addition of dithioester enethiolates to enones are involved (*vide supra*).

E. S-Alkyl, O-Silyl Ketene Acetals

1. Generation

S-Alkyl, O-silyl ketene acetals can be derived from the corresponding thioesters in a manner analogous to the generation of dialkoxy ketene acetals (*vide supra*).[†]

[†]Because of the higher priority given to sulfur, the *Z* monothioketene acetal derived from the corresponding monothioester is mechanistically equivalent to the *E* ketene acetal derived from an ester. Care must be taken when comparing the results from monothioketene acetals with the results from ketene acetals to avoid confusion as a result of the nomenclature inversion.

2. Addition to Enones

[P,P] Mukaiyama and co-workers explored the trityl-salt-catalyzed addition of *S*-alkyl, *O*-silyl ketene acetals to α,β -unsaturated ketones (80, 90, 91). In general, these additions are more selective than the corresponding additions of the alkoxy silyloxy ketene acetals (*vide supra*). The results of this study are summarized in Scheme 43 and Table 15. High anti selectivity results from addition of the *E* monothioketene acetal (silyloxy and methyl groups *cis*) to the acyclic enones that were examined (entries 4, 12, and 13, Table 15). With the corresponding *Z* monothioketene acetal, slightly lower selectivity is observed (entry 5). Contrary to what was found with the dialkoxyketene acetals (*vide infra*), good anti selectivity (92%) was obtained with cyclopentenone after optimizing the thioalkyl and silyloxy groups (entry 11).

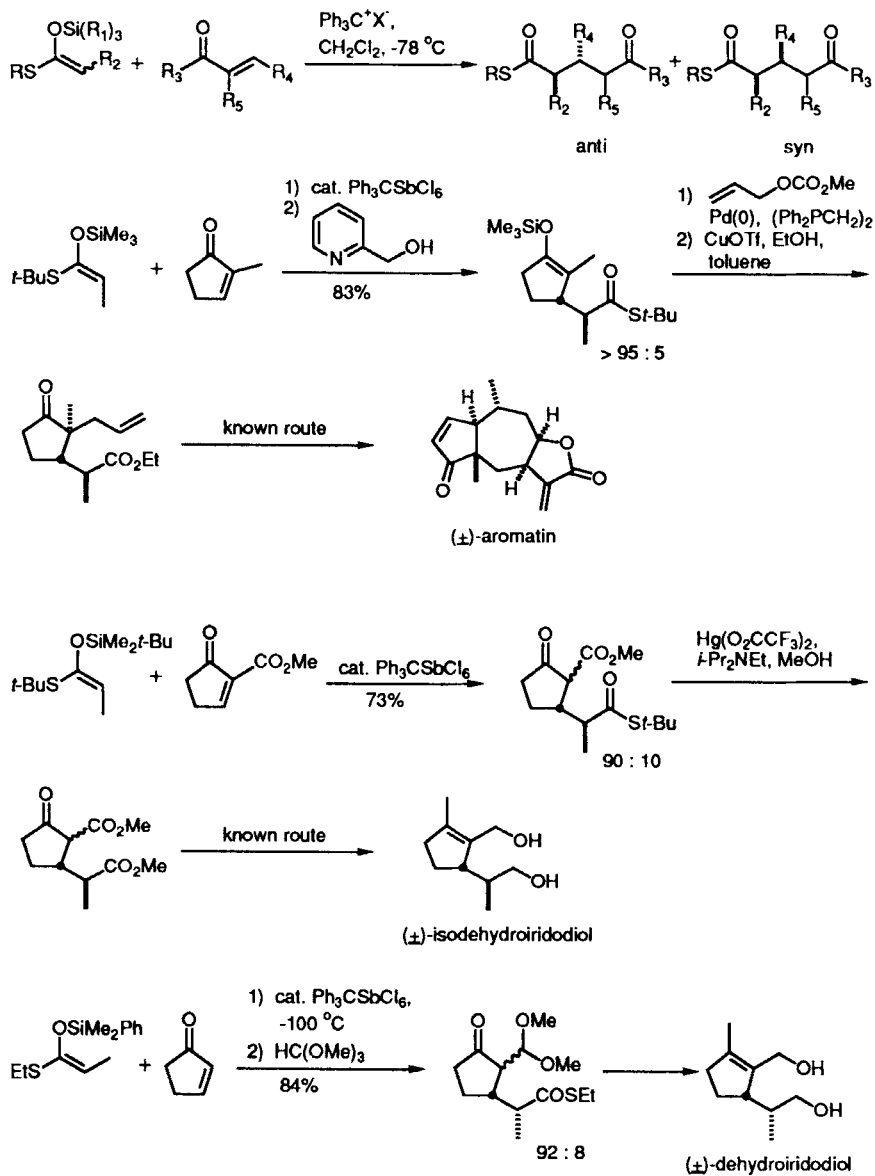
Notable is the exceptionally high syn selectivity seen in the reactions of the 2-substituted-2-cycloalkenones with the *Z* monothioketene acetals (silyloxy group and the methyl groups *trans*, entries 19–25, Table 15). Note that good proportions of the anti diastereomer can be obtained with no substituent at the 2-position, whereas high syn selectivity can be obtained with 2-substituted cyclopentenones.

Variation of the thioalkyl group, silyloxy group, counterion of the trityl group, or the geometry of the thioketene acetals influences the stereochemistry of the Michael addition. The optimal substituents depend on the nature of the acceptor. In most instances, however, more bulky silyl groups result in higher selectivity.

The stereochemical assignments of the products were confirmed and the technology developed was demonstrated by the synthesis of (+)-aromatin, ($\pm$)-isodehydroiridodiol, and ($\pm$)-dehydroiridodiol. These synthetic pathways are shown in Scheme 43.

3. Addition to Enethioates

[P,P] By using antimony(V) chloride and tin(II) triflate, monothioketene acetals can be induced to add to α,β -unsaturated thioesters (76). Interestingly, neither antimony(V) chloride nor tin(II) chloride by themselves effectively promote the reaction, implying that the combination of Lewis acids produces a new species. The stereochemistry of these additions is summarized in Scheme 44 and Table 16. For all cases studied, the reaction uniformly provides the anti diastereomers with good selectivity. The selectivity observed is somewhat lower than the optimized results observed with thioketene acetals and enones (*vide supra*).



Scheme 43

Table 15
Addition of *S*-Alkyl, *O*-Silyl Ketene Acetals to α,β -Unsaturated Ketones (Scheme 43)

Entry	<i>S,O</i> -Ketene Acetal			Enone			Catalyst	Yield (%)	Anti/Syn
	R	R ₂	(R ₁) ₃ Si	E/Z	R ₃	R ₄	R ₅		
1	Et	Me	<i>t</i> -BuMe ₂ Si	<i>E</i> ^a	Ph	Me	H	66 ^b	80:20
2	Ph	Me	<i>t</i> -BuMe ₂ Si	<i>E</i> ^a	Ph	Me	H	84 ^b	89:11
3	<i>t</i> -Bu	Me	Me ₃ Si	<i>E</i> ^a	Ph	Me	H	73 ^b	71:29
4	<i>t</i> -Bu	Me	<i>t</i> -BuMe ₂ Si	<i>E</i> ^a	Ph	Me	H	82 ^b	95:5
5	<i>t</i> -Bu	Me	<i>t</i> -BuMe ₂ Si	<i>Z</i> ^a	Ph	Me	H	66 ^b	80:20
6	<i>t</i> -Bu	Me	<i>t</i> -BuMe ₂ Si	<i>E</i> ^a	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	H	43	66:34
7	<i>t</i> -Bu	Me	Me ₃ Si	<i>Z</i> ^a	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	H	70	21:79
8	<i>t</i> -Bu	Me	Me ₃ Si	<i>Z</i> ^a	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	H	56	23:77
9	Et	Me	<i>t</i> -BuMe ₂ Si	<i>E</i> ^a	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	H	58	82:18
10	Et	Me	PhMe ₂ Si	<i>E</i> ^a	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	H	76	88:12
11	Et	Me	PhMe ₂ Si	<i>E</i> ^a	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	H	84	92:8 ^c
12	<i>t</i> -Bu	Me	<i>t</i> -BuMe ₂ Si	<i>E</i> ^a	Me	Me	H	67 ^b	>95:5
13	<i>t</i> -Bu	Me	<i>t</i> -BuMe ₂ Si	<i>E</i> ^a	Ph	Ph	H	80 ^b	92:8
14	Et	Me	PhMe ₂ Si	<i>E</i> ^a	-(CH ₂) ₃ -	-(CH ₂) ₃ -	H	94 ^b	88:12 ^c
15	Et	Me	PhMe ₂ Si	<i>E</i> ^a	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	Me	71 ^b	67:33
16	Et	Me	PhMe ₂ Si	<i>Z</i> ^a	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	Me	80 ^b	12:88
17	Et	Me	<i>t</i> -BuMe ₂ Si	<i>E</i> ^a	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	Me	77 ^b	17:83
18	Ph	Me	<i>t</i> -BuMe ₂ Si	<i>E</i> ^a	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	Me	83 ^b	16:84
19	<i>t</i> -Bu	Me	PhMe ₂ Si	<i>Z</i> ^a	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	Me	58 ^b	<5:95
20	<i>t</i> -Bu	Me	<i>t</i> -BuMe ₂ Si	<i>Z</i> ^a	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	Me	73 ^b	<5:95

21	<i>t</i> -Bu	Me	Me ₃ Si	Z ^a	-CH ₂ CH ₂ -	Me	Ph ₃ CSbCl ₆	83 ^b	<5:95
22	<i>t</i> -Bu	Me	<i>t</i> -BuMe ₂ Si	E ^a	-CH ₂ CH ₂ -	Me	Ph ₃ CSbCl ₆	57 ^b	5:95
23	<i>t</i> -Bu	Me	<i>t</i> -BuMe ₂ Si	Z ^a	-(CH ₂) ₃ -	Me	Ph ₃ CSbCl ₆	78 ^b	<5:95
24	<i>t</i> -Bu	Me	<i>t</i> -BuMe ₂ Si	Z ^a	-CH ₂ CH ₂ -	PhS	Ph ₃ CSbCl ₆	85 ^b	<5:95
25	<i>t</i> -Bu	Me	<i>t</i> -BuMe ₂ Si	Z ^a	-CH ₂ CH ₂ -	MeO ₂ C	Ph ₃ CSbCl ₆	73 ^b	10:90
26	<i>t</i> -Bu	Me	<i>t</i> -BuMe ₂ Si	^d	Ph Me	H	Ph ₃ CCl + SnCl ₂	90	84:16
27	Et	Me	PhMe ₂ Si	^d	-(CH ₂) ₃ -	H	Ph ₃ CCl + SnCl ₂	86	81:19
28	Et	Me	PhMe ₂ Si	^d	-CH ₂ CH ₂ -	H	Ph ₃ CCl + SnCl ₂	88	85:15

^aExact ratio not reported; corresponds to the configuration of the Z alkoxysilyloxy ketene acetal.

^bIsolated as silyl enol ether.

^cThis reaction was performed at -100°C; all others were done at -78°C.

^dNot reported.

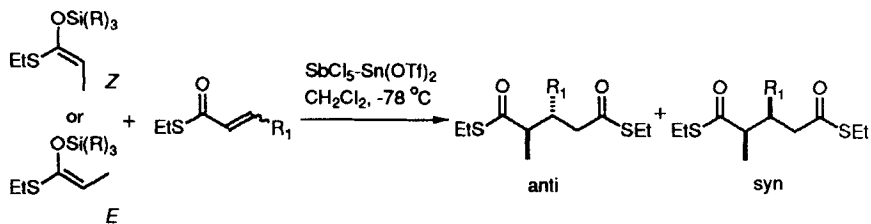


Table 16
Addition of Thioketene Acetals to α,β -Unsaturated Thioesters (Scheme 44)

Entry	Thioketene (R) ₃ Si	Acetal <i>E/Z</i> ^a	Thioenoate		Yield (%)	Anti/Syn
			R _t	<i>E/Z</i>		
1	Me ₃ Si	<i>E</i>	Me	^b	75	87:13
2	<i>t</i> -BuMe ₂ Si	<i>E</i>	Me	^b	78	88:12
3	<i>t</i> -BuMe ₂ Si	<i>Z</i>	Me	^b	84	81:19
4	Me ₃ Si	<i>E</i>	Ph	<i>Z</i> ^a	65	85:15
5	<i>t</i> -BuMe ₂ Si	<i>E</i>	Ph	<i>Z</i> ^a	75	87:13

^aExact ratio not reported.

^bNot indicated.

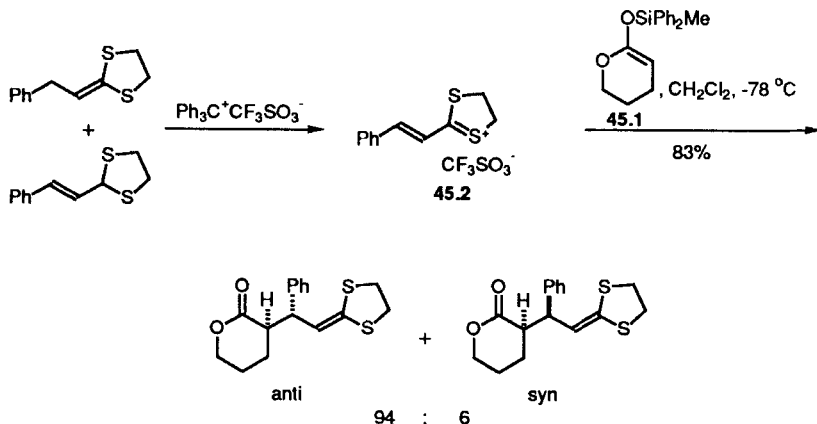
F. Ketene Acetals

1. Generation

Silyl ketene acetals are generally prepared from the corresponding ester enolates and a silylating agent, generally in the presence of HMPA. Because *n*-alkyl esters can be deprotonated to give either enolate geometry (92, 93), both ketene acetal diastereomers are readily available. It was initially reported that silylation of ester enolates with trimethylsilyl chloride leads to significant amounts of the C-silylated products (94). It now appears that the O-trimethylsilyl ketene acetals can be produced efficiently by using very low temperatures (-100°C), avoiding aqueous work-ups, and carrying out distillations at the lowest possible temperature (95). Ketene acetals derived from more substituted silylating agents (particularly *tert*-butyldimethylsilyl chloride) are often more convenient to use because of their enhanced stability and their relative ease of synthesis (higher O- to C-silylation ratios) (94).

2. Addition to Vinylthionium Ions

[P, P] Only one example of the addition of a silyl ketene acetal to a vinylthionium ion has been reported (84). The addition of ketene acetal **45.1** to vinylthionium ion **45.2** provides a 94:6 (anti/syn) mixture of diastereomers in good yield.

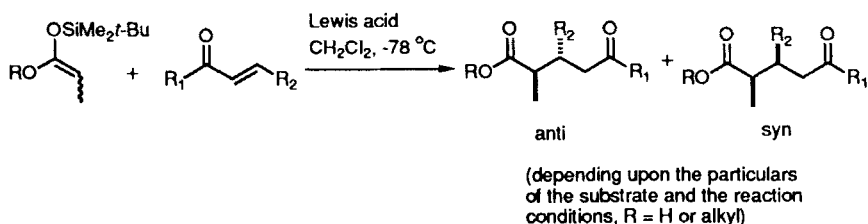


Scheme 45

3. Addition to Enones

[P, P] The diastereoselectivity of the addition of silyl ketene acetals to α,β -unsaturated ketones has been examined by three research groups (78–80, 96). The results of this study are summarized in Scheme 46 and Table 17.

When R_1 of the enone is a sterically demanding *tert*-butyl group, *tert*-butyldimethylsilyl ketene acetals provide the syn keto acids (after saponification) as essentially one diastereomer (entries 1–3 and 6, Table 17). With other



Scheme 46

Table 17
The Addition of Silyl Ketene Acetals to α,β -Unsaturated Ketones (Scheme 46)

Entry	Ketene R	Acetal E/Z	Enone		Lewis Acid	Yield (%)	Syn/Anti	Reference
			R ₁	R ₂				
1	<i>t</i> -Bu ^a	Z ^b	<i>t</i> -Bu	Me	TiCl ₄	88	99:1	79
2	<i>t</i> -Bu ^a	Z ^b	<i>t</i> -Bu	<i>i</i> -Pr	TiCl ₄	87	96:4	79
3	<i>t</i> -Bu ^a	Z ^b	<i>t</i> -Bu	Ph	TiCl ₄	77	98:2	79
4	<i>t</i> -Bu ^a	Z ^b	Me	Me	TiCl ₄	74 ^c	50:50	79
5	<i>t</i> -Bu ^a	Z ^b	-CH ₂ CH ₂ CH ₂ -	-CH ₂ CH ₂ CH ₂ -	TiCl ₄	78	75:25	79
6	<i>t</i> -Bu ^a	E ^b	<i>t</i> -Bu	<i>i</i> -Pr	TiCl ₄	76	98:2	79
7	<i>t</i> -Bu ^a	E ^b	-CH ₂ CH ₂ CH ₂ -	-CH ₂ CH ₂ CH ₂ -	TiCl ₄	78	62:38	79
8	Me	Z ^b	Ph	Me	TrClO ₄	65	38:62	91
9	Et ^d	80:20	-CH ₂ CH ₂ CH ₂ -	-CH ₂ CH ₂ CH ₂ -	Clay ^e	91	57:43	78

^aThe initial products, a mixture of *tert*-butyl and *tert*-butyldimethylsilyl esters, are saponified with NaOH to form the keto acids (R = H).

^bThe exact ratio was not reported.

^cThe reaction gave 35% of 1,2-addition products and 65% of 1,4-addition products.

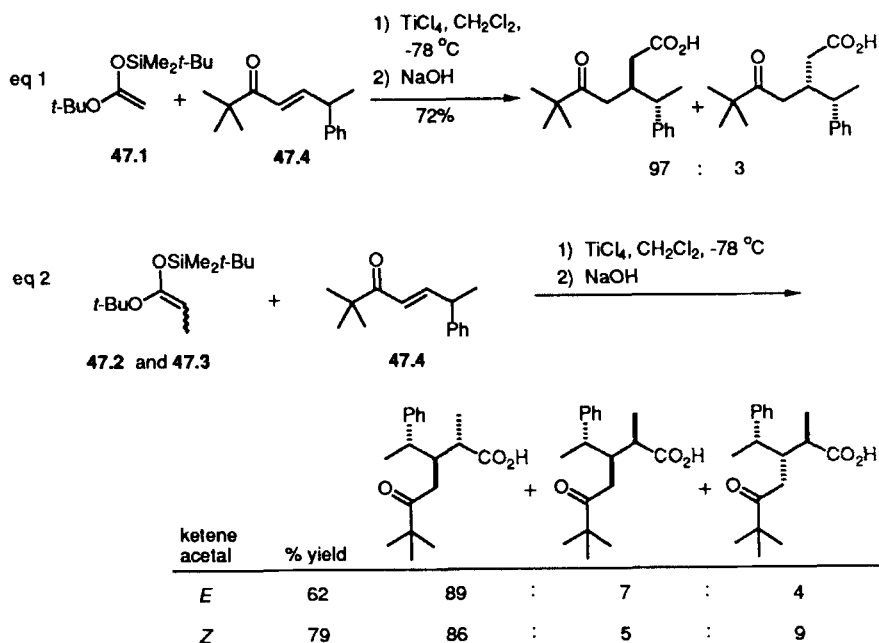
^dThe trimethylsilyl ketene acetal was used.

^eAluminum cation-exchanged clay montmorillonite.

enones, the selectivity observed is moderate, despite the variation of Lewis acids and the alkoxy group of the ketene acetals.

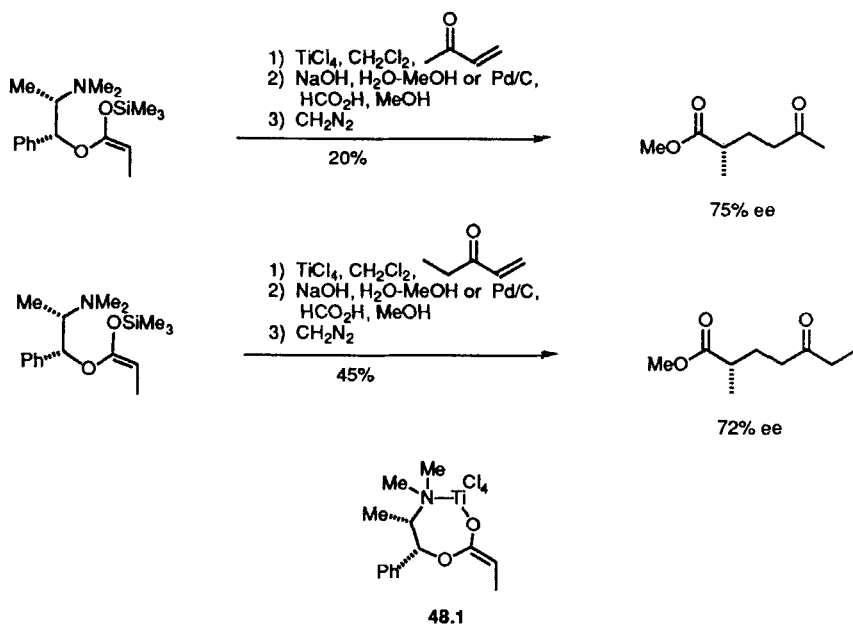
[N, P*] and [P, P*] Heathcock and Uehling examined diastereofacial discrimination in the addition of achiral silyl ketene acetals to chiral, racemic α,β -unsaturated ketones (82). The addition of ketene acetals **47.1–47.3** to enone **47.4** occurs with good selectivity (Scheme 47). For example, the addition of **47.1** gives essentially one diastereomeric 1,4-addition product, along with 8% of 1,2-addition product (Eq. [1]). With the prostereogenic ketene acetals in Eq. [2], the same 1,4-adduct predominates. In these cases, the selectivity shows a curious decrease relative to the addition of the same ketene acetals to simple prostereogenic enones (entry 2, Table 17) and relative to the less substituted **47.1**.

[P*, N] Gennari and co-workers reported the asymmetric Michael addition of the silyl ketene acetal derived from *N*-methylephedrine propionate ester to methyl and ethyl vinyl ketones (Scheme 48) (97). Premixing the ketene



Scheme 47

acetal and TiCl_4 prior to the addition of the acceptor results in enantiomeric excesses in the range 72–75%. The absolute configurations of the products were not rigorously assigned but were inferred from the facial selectivity observed in related reactions. $^1\text{H-NMR}$ studies suggest that a titanium enolate is generated in this case (*vide infra*). The presumed facial bias can be rationalized by a chelated enolate such as **48.1** where attack occurs away from the phenyl and methyl substituents. The yields of the products obtained after saponification and treatment with diazomethane are low, apparently as a result of competing polymerization of the enone during the Michael addition. Control experiments revealed that saponification occurs without epimerization.



Scheme 48

4. Addition to Enoates

[P, P] The Michael addition of silyl ketene acetals to enoates requires more strongly Lewis acidic conditions. Both aluminum triflate (**98**) and clay montmorillonite (**78**) have been used to catalyze stereoselective reactions (Table 18, Scheme 49). In general, the selectivities obtained for ketene acetals

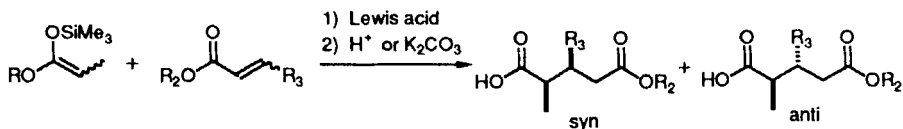
Table 18
Lewis-Acid-Assisted Addition of Silyl Ketene Acetals to α,β -Unsaturated Esters (Scheme 49)

Entry	Ketene Acetal			Enoate		Lewis Acid	Temperature (°C)	Yield (%)	Anti/Syn	Reference
	R	R ₁	E/Z	R ₂	R ₃					
1	Me	Me	61:39	Me	Me	Clay ^a	-78	84	73:27	78
2	Me	Me	61:39	Me	<i>i</i> -Pr	Clay ^a	-60	90	45:55	78
3	Me	Me	61:39	Me	Ph	Clay ^a	-50	91	39:61	78
4	Me	Me	61:39	Me	CH ₃ CH=CH	Clay ^a	-50	96 ^b	61:39	78
5	Me	Et	80:20	Et	EtO ₂ C	Clay ^a	-78	85	58:42	78
6	Me	Ph	5:95	Me	Me	Al(OTf) ₃	-78	84	60:40	98
7	Me	Ph	5:95	PhCH ₂	Me	Al(OTf) ₃	-78	74	50:50	98
8	Me	Ph	5:95	<i>t</i> -Bu	Me	Al(OTf) ₃	-78	65	75:75	98
9	Me	Ph	5:95	Menthyl	Me	Al(OTf) ₃	-78	82	80:20 ^c	98

^aAluminum cation-exchanged clay montmorillonite.

^b2% of the 1,6-addition adduct was formed.

^cIsomer ratio was determined on diol produced by LiAlH₄ reduction.



Scheme 49

and enoates are lower than for the addition of ketene acetals to α,β -unsaturated ketones (*vide supra*). As shown by entries 6–9, selectivity in the aluminum triflate reactions is dependent on the nature of the alkoxy group of the enoate. Using clay montmorillonite as catalyst, filtration followed by distillation allows for isolation of the product as the sensitive trimethylsilyl ketene acetal.

Of interest also is the regiochemistry of the addition to the dienolate in entry 4. Despite relatively similar steric environments, addition occurs preferentially in the 1,4- rather than 1,6-manner (98:2).

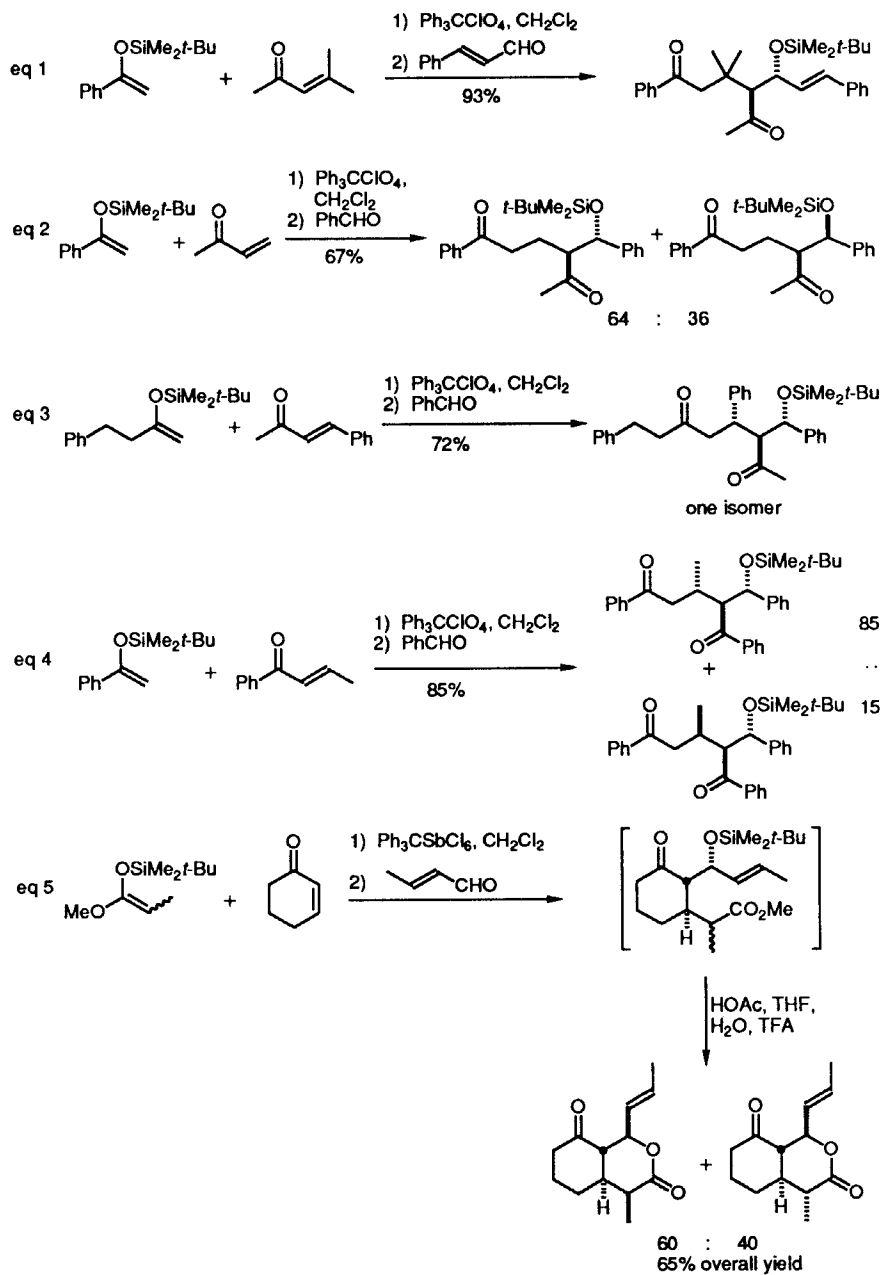
IX. SEQUENTIAL MICHAEL–ALDOL REACTIONS

[N,N; P,P] and [N,P; P*,P][†] When trityl perchlorate, clay montmorillonite, or HgI_2 is used to catalyze a Michael addition to an enone, a silyl enol ether is produced in a group transfer process. This silyl enol ether can be used in subsequent reactions. For example, Kobayashi and Mukaiyama exploited the silyl enol ether produced in such a process in an aldol addition (99).[‡] Some examples of this approach are shown in Scheme 50. The more substituted the enone is at the β -position, the higher the selectivity observed in the aldol process (cf. Eqs. [1] and [2]). In fact, with β,β -disubstituted enones, only one isomer is produced. Additionally, good selectivity for the establishment of three adjacent stereocenters is seen with prostereogenic enones (Eqs. [3] and [4]). Note that in the examples in Eqs. [1]–[4] the stereoselectivity occurs not at the Michael addition stage but rather at the aldol stage.

[P,P; P*,P] Danishefsky and Audia reported similar additions using a prostereogenic donor (Eq. [5], Scheme 50) (100). In this case, the conjugate

[†]In this case, the first set (N,N or N,P) refers to the donor and acceptor in the Michael addition; the second group (P,P or P*,P) refers to the aldol process with a P or P* donor (from the conjugate addition) and a P acceptor (the aldehyde).

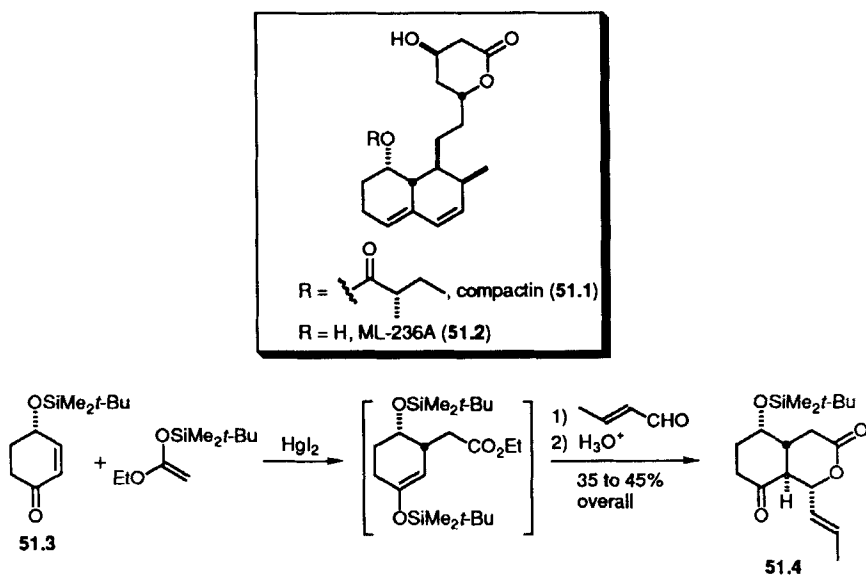
[‡]Kawai, Onaka, and Izumi also demonstrated a sequential Michael–aldol addition using aluminum cation exchanged clay montmorillonite as catalyst; however, the stereochemistry of the product was not ascertained (78).



Scheme 50

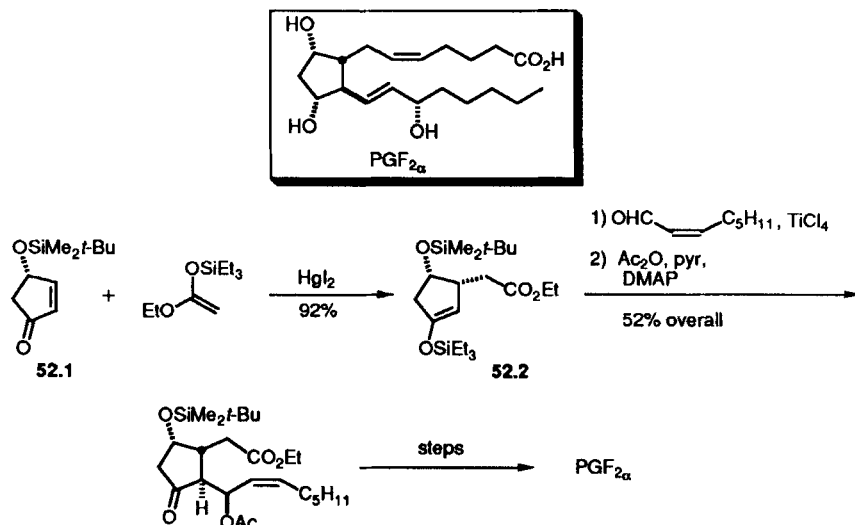
addition occurs with little selection and the aldol trap occurs with high stereoselection.

[N,P*;P*,P] Danishefsky and Simoneau utilized the sequential Michael–aldol reaction for the synthesis of compactin and ML-236A (**51.1** and **51.2** in Scheme 51) (101). In this context, the HgI_2 -promoted addition of the *tert*-butyldimethylsilyl ketene acetal derived from ethyl acetate to cyclohexenone **51.3** followed by reaction with crotonaldehyde and acidic work-up produces 35–42% of lactone **51.4** as one stereoisomer. As enone **51.3** is available in optically pure form from quinic acid (102), the naturally occurring enantiomer of compactin can be obtained.



Scheme 51

The sense of facial selectivity in the addition to enone **51.3** is noteworthy. In particular, the addition of lithium dimethylcuprate to **51.3** produces the anti adduct with high selectivity. The authors report that the Diels–Alder addition of butadiene and the Hosomi–Sakurai addition of allyltrimethylsilane promoted by Lewis acids (AlCl_3 and TiCl_4 , respectively) to the same acceptor also give syn addition products. In contrast, the TiCl_4 -promoted addition of allyltrimethyl silane to 4-methyl-2-cyclohexenone gives only a 2:1 preference for the syn adduct (see Scheme 32). Although the factors responsible for the syn



Scheme 52

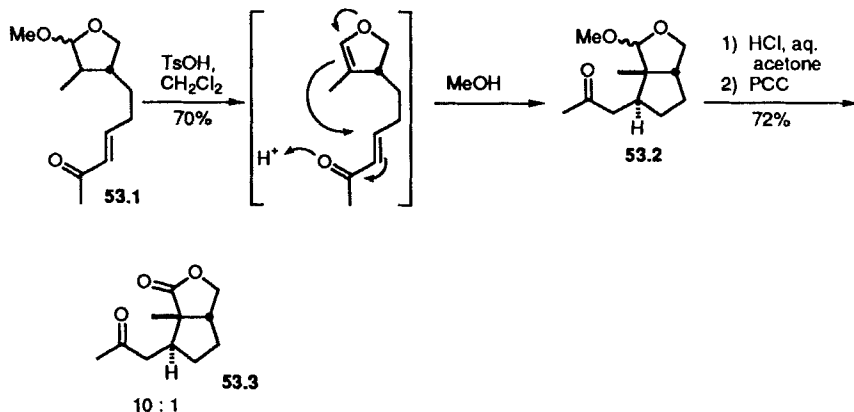
selectivity in the Danishefsky reactions remain to be completely elucidated, it is clear that the effect is not completely steric in origin.

A similar conjugate addition–silyl group transfer process was reported later by Danishefsky and co-workers for the synthesis of PGF_{2α} (Scheme 52) (103). In this case, the silyl ketene acetal adds, under HgI₂ promotion, *cis* to the OTBS group in the optically pure enone **52.1** to provide silyl enol ether **52.2** as the exclusive product. The indicated aldol products are obtained from **52.2** in subsequent reactions with (*E*)- and (*Z*)-octenal using TiCl₄ catalysis.

X. LEWIS-ACID-CATALYZED INTRAMOLECULAR MICHAEL ADDITIONS

Stork and Atwal reported an intramolecular Michael addition of **53.1** that proceeds with protic acid catalysis (Scheme 53) (104). After hydrolysis and oxidation of ketal **53.2**, a 10:1 mixture of lactones of the general structure **53.3** was produced. Proof that the major isomer is **53.3** followed from conversion into a compound of known configuration. Use of optically enriched acetals **53.1** resulted in products with no loss of optical purity.

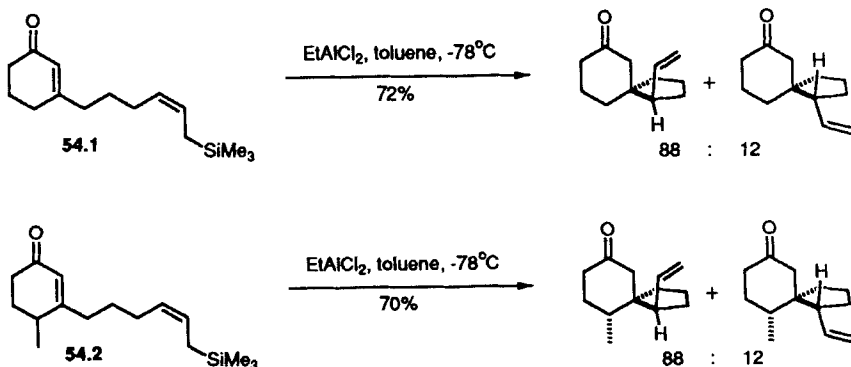
The intramolecular version of the Lewis-acid-promoted conjugate addition of allylsilanes to α,β -unsaturated ketones (Hosomi–Sakurai reaction) has



Scheme 53

been explored by Schinzer (105–107) and others (*vide infra*). In this study, *Z* allylsilanes **54.1** and **54.2** undergo intramolecular addition to the α,β -unsaturated ketone if the reaction is catalyzed by ethylaluminum dichloride in toluene (Scheme 54). Other Lewis acids (BF₃, SnCl₄, and TiCl₄) did not provide cyclization products. Additionally, the highest selectivities were found at low temperature using toluene rather than methylene chloride as solvent.

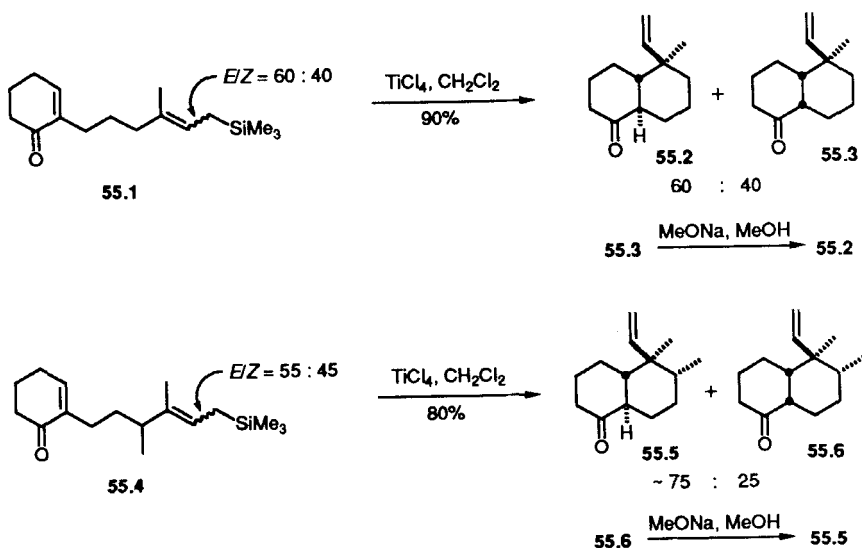
Note that the preferred products have the olefin *syn* to the carbonyl group. If the initial adduct of the conjugate addition (the silyl-stabilized cation/Lewis



Scheme 54

acid enolate) generates products more rapidly than reversing to starting materials, then the stereochemistry implies that the donor and acceptor have a synclinal orientation in the transition state. Alternatively, the conjugate addition might be reversible with the product-determining step being loss of the silyl group from the silyloxonium ion. If this transfer involves the Lewis acid enolate, then a synclinal geometry could be preferred.

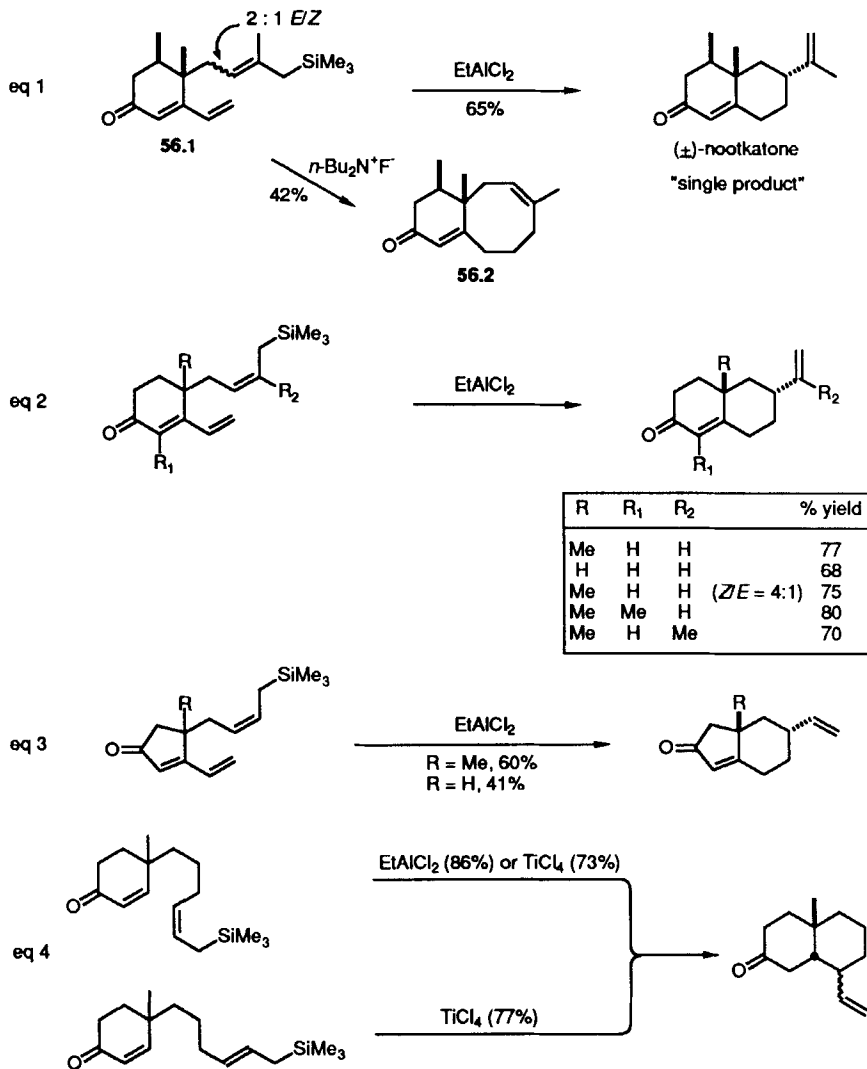
For the synthesis of clerodane diterpenoids, Tokoroyama and co-workers examined another version of the intramolecular Hosomi–Sakurai reaction (108). Substrates **55.1** and **55.4** were cyclized to yield adducts **55.2–55.3** and **55.5–55.6**, respectively (Scheme 55).



Scheme 55

Even when isomeric mixtures of the allylsilane are used, complete stereochemical control is observed for all the stereocenters established in the conjugate addition. The only breakdown in selectivity in the process occurs with the stereocenters adjacent to the carbonyl carbon, which result from protonation on work-up. The less stable *cis*-fused decalone is readily converted to the *trans*-fused isomer by treatment with base. Hence, with two steps, complete control over the relative configuration of four contiguous stereogenic centers is achieved.

Majetich and co-workers examined the cyclization of trimethylsilyl trienone **56.1** under both Lewis-acid- and fluoride-promoted conditions



Scheme 56

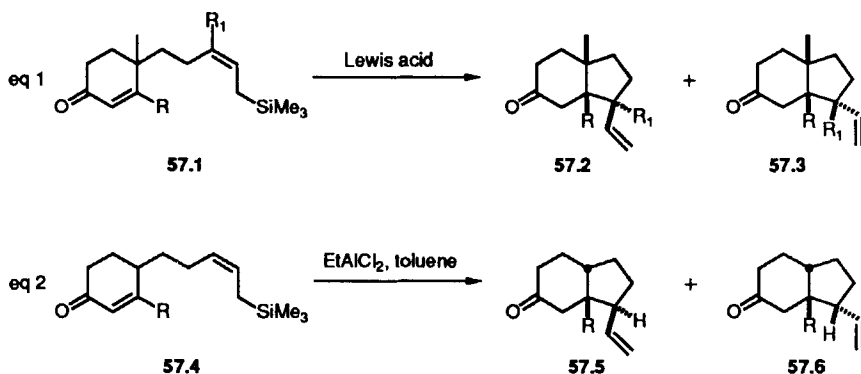
(Eq. [1], Scheme 56)(109). When fluoride is the catalyst, cyclooctene **56.2** is the major product. Interestingly, if the choice is between producing a five- or a seven-membered ring, the fluoride-induced cyclization (2) leads to a higher ratio of five- and seven-membered rings than does the EtAlCl₂ (110). In agreement with Schinzer's observations, Majetich and co-workers found the

best Lewis acid for cleanly promoting the reaction to be ethylaluminum dichloride. Under these conditions, ($\pm$)-nootkatone was obtained as a single product in reasonable yield.

Further exploration of this cyclization with the substrates in Eqs. [2] and [3] (Scheme 56) has been reported (110). In each of these examples, only one isomer is observed. Although the relative stereochemistries of the products have not been reported, it seems likely on analogy to the nootkatone example that the products have a trans relationship between the R group and the exocyclic olefinic appendage as depicted in the scheme.

Fluoride-promoted reaction of the substrates in Eq. [4] (Scheme 56) gives only desilylated products (111). Lewis acidic conditions, however, lead to cis-fused products in good yields. The stereochemistry at the vinyl stereocenter was not established, but "remarkable" diastereoselection is claimed.

Substrates with prostereogenic allylic silane segments (**57.1** and **57.4**) can be cyclized using EtAlCl_2 or TiCl_4 (111,112). Only cis-fused products were detected (Eqs. [1] and [2], Scheme 57, Tables 19 and 20). The stereochemistry at the vinyl-substituted stereocenter in Eq. [1] depends strongly on whether the reaction is carried out under Lewis-acid- or fluoride-promoted conditions (2). Under Lewis acid conditions, products in which the vinyl group is trans to the ring fusion substituents are favored, albeit in low selectivity. A similar outcome is achieved with the less substituted substrates of the general structure **57.4** (Eq. [2], Scheme 57, Table 20) (113). The slight decrease in the selectivity as the size of the R group increases is likely the result of higher temperatures needed to induce reaction as the β -position of the acceptor becomes more hindered.



Scheme 57

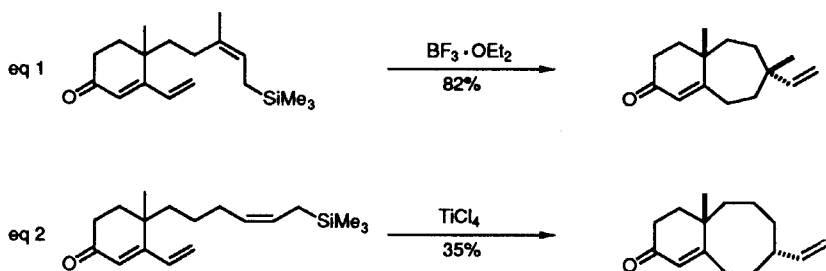
Table 19
Lewis-Acid-Promoted Cyclization of **57.1** (Eq. [1],
Scheme 57)

Entry	Substrate		Lewis Acid	Yield (%)	57.2:57.3
	R	R ₁			
1	H	H	EtAlCl ₂	62	25:75
2	H	Me	EtAlCl ₂	71	17:83
3	Me	H	TiCl ₄	77	20:80
4	Me	Me	TiCl ₄	78	20:80

Table 20
EtAlCl₂-Promoted Cyclization of **57.4** (Eq. [2],
Scheme 57)

Entry	Substrate R	Temperature (°C)	Yield (%)	57.5:57.6
1	H	-78	92	20:80
2	Me	-30	77	25:75
3	Et	-30	86	29:71

The Lewis-acid-promoted intramolecular 1,6-addition of the trienones in Eqs. [1] and [2] (Scheme 58) also result in the preferential construction of products with the trans disposition of the vinyl substituent and the methyl group at the ring fusion (114). Reasonable efficiency for the generation of 7- and 8-membered rings is achieved.



Scheme 58

XI. DISCUSSION OF MECHANISM: LEWIS-ACID-MEDIATED REACTIONS

In general, Lewis-acid-mediated conjugate additions show a preference for formation of the anti diastereomer. Enol ethers with the *Z* configuration (*E* monothioketene acetals) have a slightly higher propensity to give anti products than do the *E* enol ethers (*Z* monothioketene acetals). With both reagents, however, anti products are generally favored with α -unsubstituted acceptors. In contrast, silyl ketene acetals in certain instances produce the syn diastereomers with high selectivity. Selectivity with dioxoketene acetals is strongly dependent on the acceptor, the Lewis acid, and the silyloxy and alkoxy groups of the donor.

As with protic-acid-catalyzed additions, the Lewis-acid-promoted additions are believed to occur by attack of an enol species on a Lewis acid complex (protonated) form of the acceptor. Complexation of the acceptor with the Lewis acid serves to lower the energy of the acceptor LUMO and polarize the π -system. Neutral or anionic nucleophilic species with high HOMOs will then combine with the acceptor–Lewis acid complex to yield products.

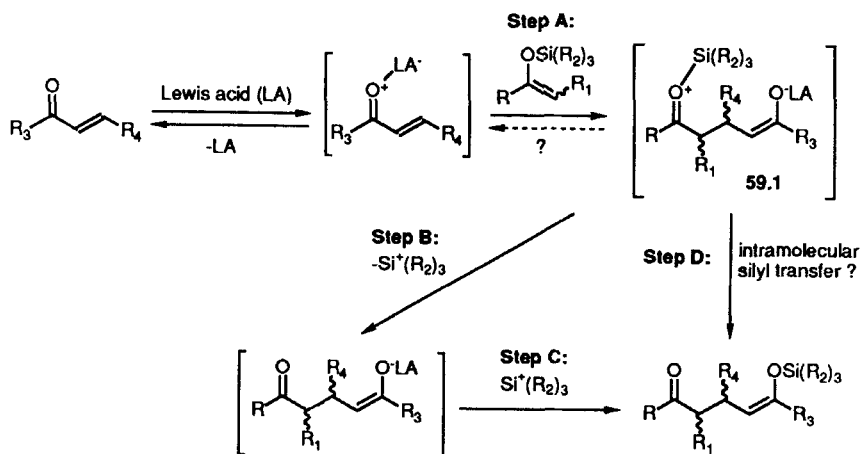
What is the reactive donor species in the reaction? The possibility exists that, in the presence of the Lewis acid, the silyl enol ether is transformed into an alternative reactive species. For example, the Mukaiyama–Michael addition of a trimethylsilyl enol ether promoted by TiCl_4 could proceed first by transmetallation to produce a trichlorotitanium enolate and TMSCl . This species could then undergo conjugate addition to either an activated or unactivated acceptor. However, the best results in the addition have usually been obtained by precomplexation of the acceptor and the Lewis acid followed by addition of the donor. This strongly suggests that an acceptor–Lewis acid complex is the important intermediate and not a Lewis acid metal enolate (115). Furthermore, the similarity of the stereochemistry of the addition irrespective of the Lewis acid used also suggests that an enolate species is not important. Indeed, the stereoselectivity of the reaction often contrasts with the results found in the enolate reactions (2), implicating a nonenolate reactive species.[†] Although the circumstantial evidence presented hints that the enol

[†]Gennari and co-workers have concluded that, at least for the Mukaiyama aldol condensation, a titanium enolate is involved in the addition of *N*-methylephedrine-derived trimethylsilyl ketene acetals (97). The behavior of the ephedrine ketene acetals in the aldol reaction shows substantial deviations from that shown by the silyl ketene acetals from ethyl propionate (115b) both in terms of stereoselectivity and in the effect of the order of addition of the TiCl_4 . Thus, although a titanium enolate could be involved with the ephedrine ketene acetals, Gennari's work does not necessarily imply the intermediacy of titanium enolate in nonamino silyl ketene acetals. Parenthetically, the addition of the basic dimethylamino substituent in Gennari's work would be expected to favor the formation of a titanium enolate through an associative phenomenon.

ether is the reactive donor, further work at the mechanistic level would be helpful to definitely rule out the possibility that Lewis acid enolates are intermediates in these reactions.

As in the uncatalyzed reactions with enamines (*vide supra*), there is potentially more than one point where stereochemical differentiation can occur (Scheme 59). Selectivity can occur if the initial addition of the enol ether to the Lewis acid complex of the α,β -unsaturated acceptor (step A) is the product-determining step. Reversion of the initial adduct **59.1** to the neutral starting acceptor and the silyl enol ether is possible, at least in some cases. If the Michael-retro-Michael manifold is rapid, then selectivity in the product generation would be determined by the relative rates of the decomposition of the diastereomers of the dipolar intermediate (**59.1**). For example, preferential loss of the silyl cation (or *tert*-butyl cation for *tert*-butyl esters; step B) from one of the isomers could lead to selectivity in product construction. Alternatively, intramolecular transfer of the silyl cation from the donor to the acceptor (step D) could be preferred for one of the diastereomeric intermediates. If the Michael-retro-Michael addition pathway is rapid and an alternative mechanism (silyl transfer) is product-determining, then the stereochemistry of the adducts formed should show little dependence on the configuration of the starting materials employed, as is observed.

The relative rates in this manifold should be dependent on the substitution pattern of the substrates. For example, a substituent R capable of electron donation (i.e., an alkoxy group) should stabilize the oxonium intermediate **59.1**, thereby slowing the reverse Michael addition and potentially the rate of



Scheme 59

silyl cation loss (Scheme 59). Hence, the factors operative in determining by which pathway product stereoselection occurs can be subtle and can vary from system to system. Similar considerations can be evoked for the intramolecular Hosomi–Sakurai addition (114b).

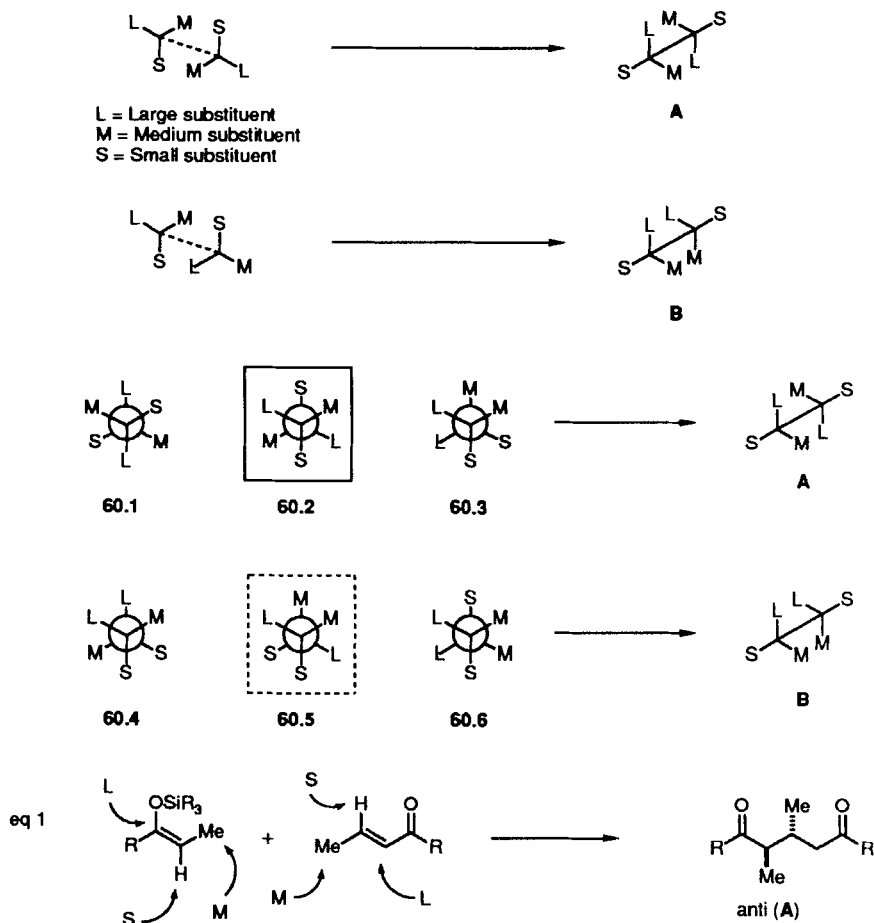
In some instances, particularly when a dependence of the stereochemistry on the double-bond geometry of either the acceptor or donor is observed, it appears likely that the stereochemistry-determining step is the initial conjugate addition. The stereochemical consequences of Lewis-acid-mediated additions of silyl enol ethers (116) and allylsilanes (117, 118) have frequently been rationalized by open-extended transition states. Similar pathways seem likely with the Mukaiyama–Michael addition (*vide infra*) (77, 79).

The preference for the open-extended transition state and thus the anti product can be visualized as follows. If two prostereogenic centers with groups that are effectively large, medium, and small (Scheme 60) are combined, two possible diastereomeric products are possible (A and B). Assuming that no associative phenomenon exists, then the stereochemistry of the reaction should be determined solely by the steric demand of the substituents. If it is further assumed that the reaction proceeds only through staggered transition states, the elimination of detrimental eclipsing interactions results in only six possible transition structures (60.1–60.6, Scheme 60).

Considering the substituents on the prostereogenic centers as perfect spheres, then model transition structure 60.2 appears superior because it minimizes adverse gauche-type interactions (the large groups are between the medium and small groups; the small groups are between the medium and large ligands). If one assigns relative sizes to the various groups as shown in Eq. [1],[†] then this simplistic model predicts that the anti diastereomer should be produced preferentially. This first-order model predicts that the geometry of both the silyl enol ether and the enone should not affect the sense of selectivity observed in the reactions.

In certain instances, however, Lewis-acid-mediated Michael additions show a slight dependence on the geometry of both the donor and acceptor (*vide supra*). Hence, the first-order analysis must be modified to include the differential effects induced by the double-bond substitution patterns. By consideration of these effects and by minimization of the adverse gauche-type interactions, trends in Lewis-acid-mediated additions where the conjugate addition is likely to be the actual product-determining step can be rationalized.

[†]The assignment of the relative sizes for the groups is debatable. However, the same result is obtained if the olefinic linkage for both the donor and acceptor is assigned the same size (usually either medium or large).



Scheme 60

XII. CONCLUSIONS

Enamine and Lewis-acid-catalyzed Michael additions provide a useful complement to the enolate Michael addition. These variants allow for the reaction to be carried out under nearly neutral or formally acidic conditions. In terms of the stereochemistry, the enolate Michael addition appears at this point to be more versatile in that both stereoisomers are often obtainable from a given set of substrates. However, in particular cases, the enamine or the

Mukaiyama–Michael addition is the method of choice for providing a specific stereochemistry.

Mechanistically, enamine and Lewis-acid-mediated conjugate additions are complex. The opportunity exists for the product-determining step to occur at a number of points and, without further study, the precise nature of the manifold is not entirely clear. In some enamine cases where the stereoselectivity likely results from the conjugate addition, a synclinal type transition state seems to be involved. With the Mukaiyama–Michael addition, some processes implicate an open-extended pathway. Despite the mechanistic uncertainties that remain, sufficient data are now available so that the stereochemistry in many cases can be anticipated by extrapolation.

ACKNOWLEDGMENTS

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Conformational Analysis of Bicyclo[3.3.1]nonanes and Their Hetero Analogs

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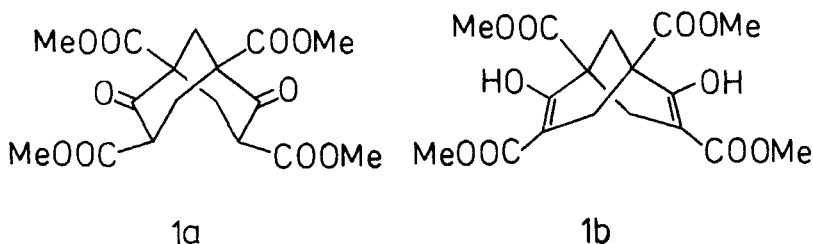
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I. INTRODUCTION

The conformational analysis of organic compounds constitutes one of the most fruitful concepts in modern organic chemistry. The foundations of conformational analysis are based primarily on studies of cyclohexane derivatives and their hetero analogs. Most conformational studies on six-membered rings have concerned themselves with the orientation of substituents in the chair conformations of the ring and with the relative energies of these conformations. The significant energy difference between chair and boat conformations precludes the study of model compounds bearing a variety of substituents that can adopt the boat conformation. However, in some bicyclic molecules, conformations of this type are realized more easily.

The study of derivatives and hetero analogs of bicyclo[3.3.1]nonane are

of interest in this connection. The systematic study of the conformational behavior of this system began in the 1960s (1–5). However, a number of important results, including the conformational study of bicyclo[3.3.1]nonane itself, were not obtained until the decade just past. One of the first bicyclo[3.3.1]nonanes to be studied in a conformational context (in 1922) (6) is the “Meerwein’s ester” **1**, which was believed at the time to exist in the chair–chair conformation **1a**. Only in 1984 was it established by means of spectroscopy and by means of single-crystal X-ray diffraction that **1** exists as a dienol (**1b**) that adopts a twisted double envelope conformation in solution and in the solid state (7).



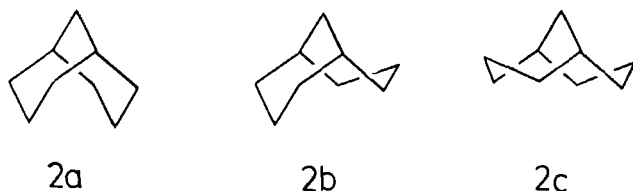
Significant progress in conformational studies of bicyclo[3.3.1]nonanes in the past two decades have revealed the main conformational features of carbocyclic compounds bearing different substituents, including the ways in which both chair–boat and boat–boat conformations could be stabilized. The conformational behavior of some heterobicyclo[3.3.1]nonanes was interpreted in terms of conformational effects (8). Naturally occurring compounds that include the bicyclo[3.3.1]nonane moiety in their structure have also been studied extensively (9–15).

There are hundreds of publications on virtually all conceivable aspects of the conformational analysis of bicyclo[3.3.1]nonanes. The most fundamental of these studies have been reviewed by Zefirov in 1975 (1) and, for the 3-azabicyclo[3.3.1]nonanes, by Jeyaraman and Avila in 1981 (2). Reviews on the synthesis of bicyclo[3.3.1]nonanes (16–18) also have been published.

In the present chapter, the basic principles of the conformational analysis of substituted bicyclo[3.3.1]nonanes and their hetero analogs are considered. These principles are illustrated with experimental and computational data with attention concentrated on those results believed most important to the understanding of the conformational behavior of bicyclo[3.3.1]nonanes. Some results previously reviewed in references 1 and 2 are not discussed here. Conformational studies of polycyclic compounds that incorporate the bicyclo[3.3.1]nonane skeleton as part of their structure are generally beyond the scope of this chapter.

II. CONFORMATIONAL ANALYSIS OF BICYCLO[3.3.1]NONANES: GENERAL PROBLEMS

The following conformations, free from angular strain, can be postulated for bicyclo[3.3.1]nonane itself: chair–chair, CC (**2a**), chair–boat, CB (**2b**) boat–boat, BB (**2c**). Although conformations **2a–2c** are free from angular strain, none is free from strong destabilizing interactions between nonbonded atoms. In order to discuss the experimental and computational data more systematically, it is necessary to consider the factors that stabilize and destabilize conformation **2a–2c**.



Varying terminology is used for the designation of substituent positions in the bicyclo[3.3.1]nonane skeleton (1, 19, 20). To specify the substituent positions, mostly *endo*-, *exo*- and α,β -descriptors are used in the literature, although in some papers the authors prefer nautical nomenclature for the boat rings (20). The designations are shown in Figure 1.

In the chair–chair conformation **2a**, the steric repulsion of *endo*-3 and *endo*-7 substituents is the main destabilizing factor (3). If these positions are occupied by hydrogen atoms, their repulsion is insufficient to destabilize the CC conformation (1). However, the introduction of any substituent more bulky than the hydrogen atom even in one of these positions will cause a sharp

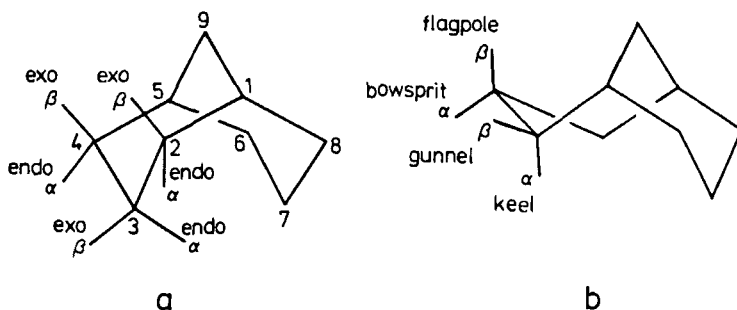
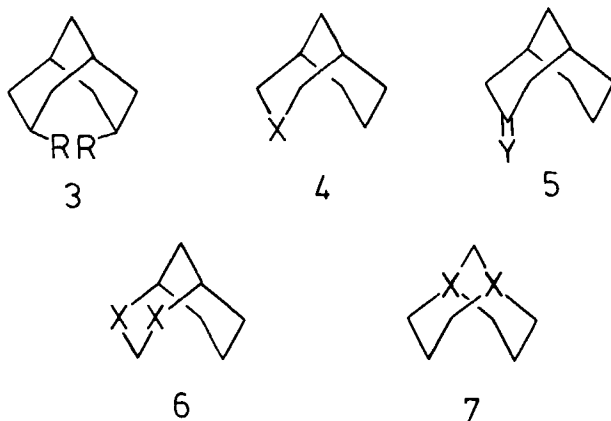
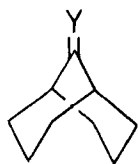


Figure 1. The designations of substituents' positions for the rings in a chair (a) and in a boat (b) conformation in the substituted bicyclo[3.3.1]nonanes.

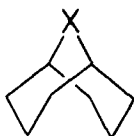
increase of the steric repulsion. As a result, the CC conformation usually becomes less preferable than the CB one. Even in bicyclo[3.3.1]nonane itself, the distance between *endo*-3 and *endo*-7 hydrogen atoms in an undistorted chair-chair conformation would have the physically impossible value of 0.75 Å (21), so the "wings" of the bicyclo[3.3.1]nonane molecule must be inevitably flattened and the angles H-(C-3)-H and H-(C-7)-H somewhat decreased. Evidently any further flattening is so unfavorable that the chair-boat conformation **2b** becomes preferable to CC conformation **2a**. The introduction of a heteroatom (as in **4**) or of a trigonal atom (as in **5**) in the 3-position has the opposite effect, namely, of decreasing the 3...7 repulsion, thus stabilizing the chair-chair conformation (1, 22, 23). The introduction of heteroatoms in the 2- and 4-positions (**6**) or in the 1- and 5-positions (**7**) can either decrease or increase the 3...7-repulsion depending on the C-X bond lengths as compared with C-C bond lengths and the values of the C-X-C and X-C-C angles.



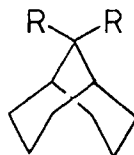
In the chair-boat conformation **2b** the destabilization is due to the same factors that operate in the boat conformation of cyclohexane, namely, the presence of eclipsed ethane conformations and the flagpole-flagpole repulsion between the hydrogen atoms. However, the ring in the boat part of a CB conformation cannot be deformed appreciably to give the twist form, owing to the rigidity of its junction with the second ring. This conformation could be somewhat stabilized by the removal of the flagpole-flagpole interaction, for example, by the introduction in the 9-position of a trigonal atom (as in **8**) or of a heteroatom (as in **9**). Obviously, the presence of substituents at the 9-position increases the flagpole-flagpole repulsion and destabilizes the CB conformation (in favor of conformation **10**).



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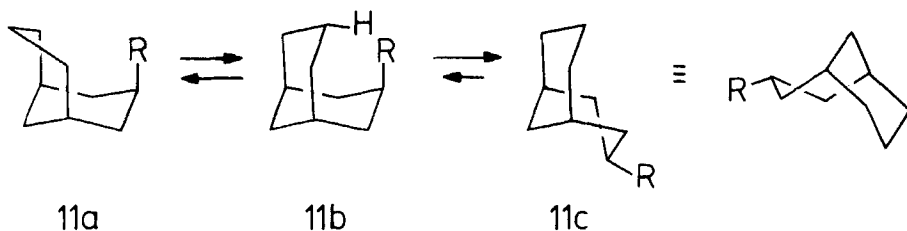


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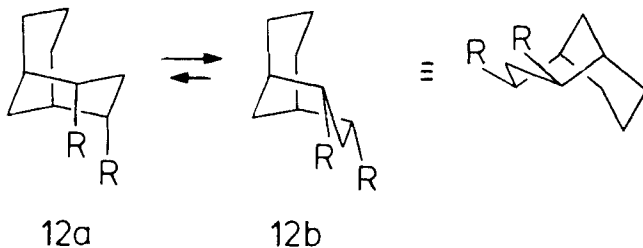


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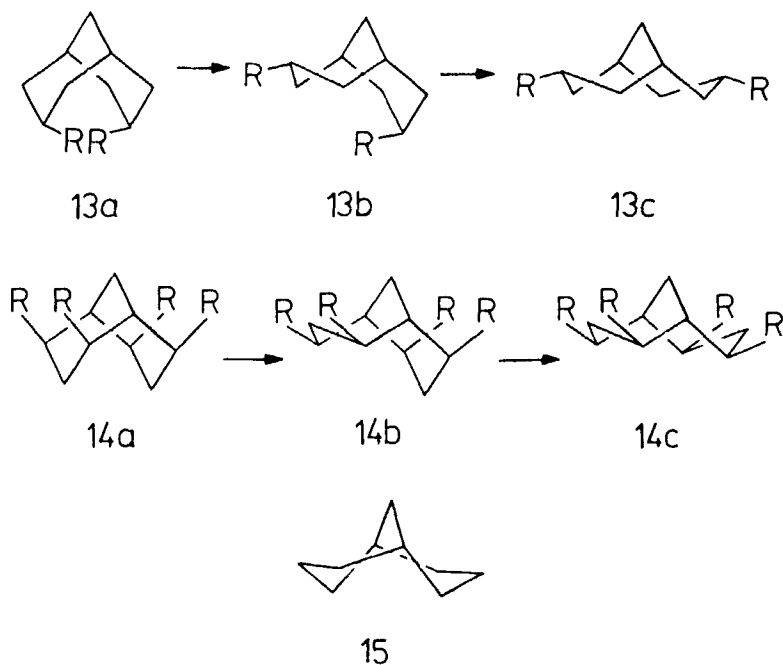
Considering the factors favoring the CB conformation, it should be taken into account that the introduction of an *endo*-3 substituent (**11**) causes one of the CB forms (**11a**) to be destabilized by the resulting extra 1,3-diaxial interactions. Indeed, for each six-membered ring in the bicyclo[3.3.1]nonane skeleton, the second ring is equivalent to two axial substituents, the introduction of an *endo*-3 substituent being equivalent in this case to a third axial one. It leads not only to the absence in the equilibrium of the chair–chair conformation **11b** (which is mostly destabilized by the 3...7 repulsion) but also to the minor content of the chair–boat form **11a**. The alternative boat–chair conformation **11c** with the substituent in the bowsprit position dominates in this case (24, 25).



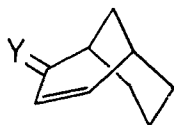
Another way to use the 1,3-diaxial repulsion for the destabilization of a chair–chair conformation is the introduction of two bulky substituents in *exo*-2 and *exo*-4 positions (**12**), which should and does lead to a preference for the chair–boat conformation **12b** (26).



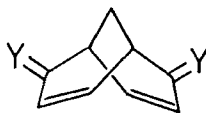
From the analysis of the factors thus far considered, boat–boat conformation **2c** should be stabilized by 1,3-diaxial repulsion. The introduction of bulky substituents both in *endo*-3 and *in* *endo*-7 positions (**13**) leads to the predominance of the double boat conformation **13c** in the equilibrium (27, 28). Analogously, the introduction of four bulky substituents in *exo*-2, 4, 6, and 8 positions (**14**) could lead to the destabilization of the chair form for each of the six-membered rings and to a preference for boat–boat conformation **14c** because of the strong 2...4 and 6...8 repulsion of the substituents. However, compounds of this kind have not been studied yet. It is necessary to mention that the boat–boat conformation should correspond in fact to a maximum on the energy curve, while a twist–twist, TT, form approximated by **15** would be expected to correspond to a minimum. In the TT conformation the flagpole and eclipsed interactions are diminished (the BB conformation is significantly more flexible than the CB one and is easily twisted).



The introduction of three trigonal atoms in a wing of the bicyclo[3.3.1]nonane skeleton leads to the planarity of the wing. Such molecules tend usually to adopt envelope–chair conformations exemplified by **16**. In the case of six such trigonal atoms, the envelope–envelope form **17** would be expected to become the only stable one.



16



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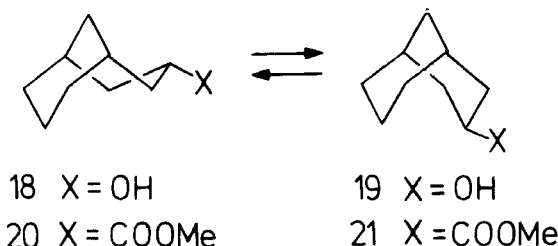
The factors thus far considered determine the conformational behavior of alkyl-substituted bicyclo[3.3.1]nonanes and their hetero analogs in molecules in which the interaction of heteroatoms is approximately the same in different conformations. In other cases, the interaction of heteroatoms or functional groups, especially at 3-, 7-, and 9-positions, may lead to significant deviations from that of the conformational behavior of alkyl-substituted carbocyclic analogs (*vide infra*). Thus, not only the dipole-dipole interactions but also lone pair interactions must be taken into account. In molecules bearing several substituents and heteroatoms in different positions, a very careful analysis is necessary in making predictions since different factors can cause opposite effects and the overall conformational behavior will be determined by their balance.

III. CONFORMATIONAL ANALYSIS OF CARBOCYCLIC BICYCLO[3.3.1]NONANE SYSTEMS: EXPERIMENTAL AND COMPUTATIONAL DATA

A. Bicyclo[3.3.1]nonane

Despite significant progress in the conformational analysis of substituted bicyclo[3.3.1]nonanes and their hetero analogs, reliable experimental data on the conformational behavior of bicyclo[3.3.1]nonane itself appeared only toward the end of the 1970s and at the beginning of the 1980 decade. Electron diffraction studies (29–32) have shown that for bicyclo[3.3.1]nonane in the gas phase the chair-chair conformation with flattened “wings” is predominant, the content of the chair-boat conformation **2b** in the equilibrium being estimated as approximately 5% at 65°C and 25% at 400°C. From the data at the two temperatures, the thermodynamic parameters of the $CC \rightleftharpoons CB$ equilibrium could be roughly estimated: $\Delta H^\circ = 2.5 \text{ kcal mol}^{-1}$, $\Delta S^\circ = 1.5 \text{ cal mol}^{-1} \text{ deg}^{-1}$. These values are in good agreement with the results of molecular mechanics calculations (MM2; Schleyer force field), which give a CC – CB energy difference in the range of 2.3–2.5 kcal mol^{-1} (24, 30, 33, 34). The same 2.3 kcal mol^{-1} value was obtained from *ab initio* STO-3G and 4-31G calculations (5). Similar values were found earlier in studies of epimerization

equilibria in substituted bicyclo[3.3.1]nonanes assuming that *exo*-3 substituents in chair-chair conformations and *endo*-3 substituents in chair-boat conformations make equal contributions to the strain energy. Epimerization experiments for bicyclo[3.3.1]nonan-3-ols **18** and **19** (35) gave the value $\Delta G^\circ_{367} = -2.5 \text{ kcal mol}^{-1}$, and for esters **20** and **21** $\Delta G^\circ_{298} = -2.7 \text{ kcal mol}^{-1}$ (36). Since ΔG is nearly independent of the nature of the substituent, the difference between the free energies can be attributed to conformational changes of the skeleton.



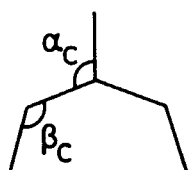
The potential surface for the conformational transition $CC \rightleftharpoons CB$ in bicyclo[3.3.1]nonane calculated using the MM1 molecular mechanics program has also been published (37).

The BB conformation is predicted by *ab initio* calculations to be located 10–11 kcal mol^{-1} above the CC one and optimizations of twist-twist forms with C_2 symmetry led to a boat-boat conformer of C_{2v} symmetry for all starting deformations chosen (5). This result is in contradiction with molecular mechanics calculations predicting the energy of the BB form of bicyclo[3.3.1]nonane to be 10.7 kcal mol^{-1} and the TT form 8.2 kcal mol^{-1} above that of the CC conformer (24,33).

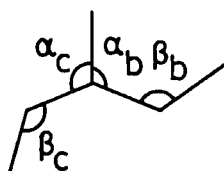
The geometry of bicyclo[3.3.1]nonane has been determined by the electron diffraction method (29–32) and has been calculated by molecular mechanics (24, 30, 33, 34, 38) and *ab initio* methods (5). Table 1 shows some experimental and calculated geometric parameters of bicyclo[3.3.1]nonane. The values of the dihedral angles demonstrate the significant flattening of the “wings” of bicyclo[3.3.1]nonane skeleton in a CC conformation. According to the ED data (29), the distance $C3 \cdots C7$ is equal to 3.10 Å, while the corrected X-ray diffraction data give a value in the range 3.11–3.13 Å (21, 39, 40). The distance *endo*-H3...*endo*-H7 in bicyclo[3.3.1]nonane obtained from the corrected X-ray diffraction data for substituted compounds (21, 38–40) is equal to 1.85–1.89 Å. The best calculated value of this distance (1.97 Å) was obtained using molecular mechanics (White and Bovill force field) (38); other molecular mechanics methods lead to a value in the range 2.03–2.11 Å (24, 34). The *ab initio* study gave the value 1.96–1.97 Å (5) for this distance in good agreement with the White–Bovill molecular mechanics calculations.

Table 1
Experimental (ED at 65°C (29) and 400°C (30)) and Calculated (MM2 (30), *ab initio* (5))
Geometry of Bicyclo[3.3.1]nonane

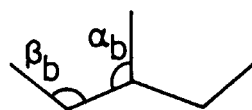
Angles (degrees)	ED ^a		MM2		<i>Ab Initio</i>		
	65°C	400°C	CC	CB	CC	CB	BB
α_c	122.8(1.7)	123.4(1.5)	116.5	115.6	122.7	122.0	—
α_b			—	120.1	—	125.8	123.7
β_c	140.0(3.0)	135.3(2.3)	137.8	129.8	141.9	134.2	—
β_b			—	132.1	—	136.8	137.2



CC



CB



BB

^aThe ED data were obtained assuming $\alpha_c = \alpha_b$ and $\beta_c = \beta_b$; the estimated errors of 3σ are given in parentheses.

B. 3- and 3,7-Substituted Bicyclo[3.3.1]nonanes

The substituents at the *endo*-3 and *endo*-7 positions have a dramatic influence on the conformational behavior of bicyclo[3.3.1]nonanes and determine in many cases the preference for CC, CB, or BB conformations.

Most of the calculated data available for the comparison of different conformations of substituted bicyclo[3.3.1]nonanes were obtained using the molecular mechanics method (Schleyer force field) (24, 33). Figure 2 shows the strain energy levels for bicyclo[3.3.1]nonane **2**, *exo*-3-methyl- (**22**), *endo*-3-methyl- (**23**), *endo*-3-*tert*-butyl- (**24**), and *endo*-3-*tert*-butyl-*endo*-7-methyl- (**25**) bicyclo[3.3.1]nonanes. The molecular mechanics data reveal that the minimum points on the strain energy surface of unsubstituted bicyclo[3.3.1]nonane **2** correspond to the CC conformation (absolute minimum), CB and BC conformation (2.5 kcal mol⁻¹ above CC), and TT conformation (5.7 kcal mol⁻¹ above CB). The BB conformation corresponds to a saddle point (2.5 kcal mol⁻¹ above TT) and is a transition state between two TT conformations. The introduction of substituents in different positions changes the energies of the conformers and in the case of unsymmetrical substitution leads to the nonequivalence of the CB and BC conformations. The introduc-

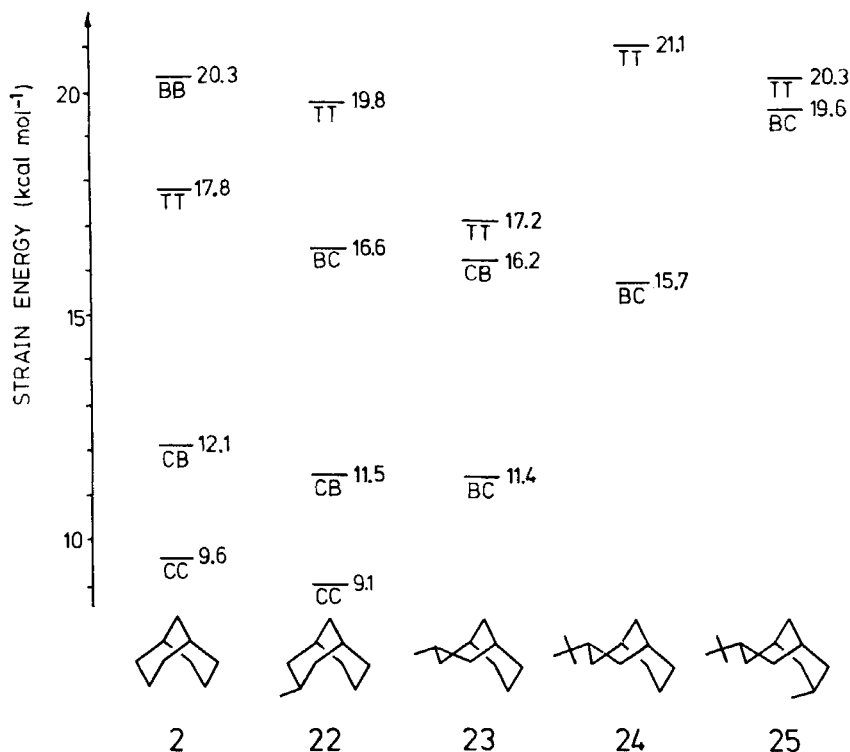
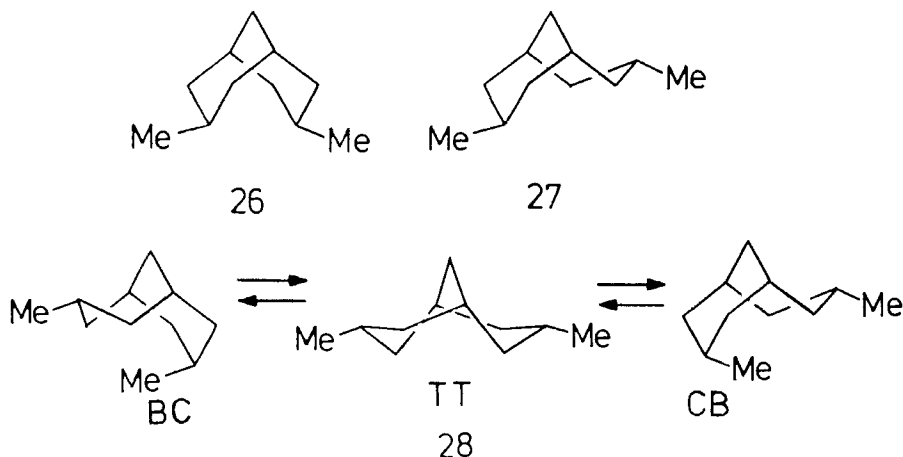


Figure 2. Strain energies of conformers of substituted bicyclo[3.3.1]nonanes **2** and **22–25** calculated using the Schleyer force field (24, 33).

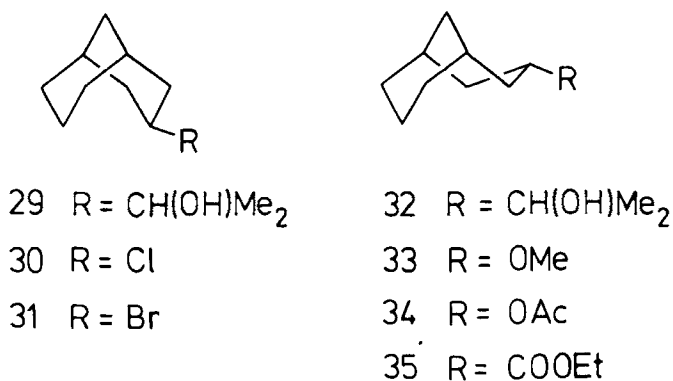
tion of an *endo*-3-methyl group (compound **23**) makes the BC conformation the lowest in energy, while the CB conformation is 4.8 kcal mol⁻¹ above being close to a TT conformation ($\Delta E_{TT-CB} = 0.9$ kcal mol⁻¹); the CC conformation becomes the most unfavorable one in this case. The presence of an *endo*-3-*tert*-butyl group (compound **24**) excludes the CB and CC conformers from the equilibrium, and if a methyl group is present additionally at the *endo*-7 position (compound **25**) the TT conformer is calculated to be only 0.7 kcal mol⁻¹ above the energy of the BC conformer (Figure 2) and should easily be detected in the equilibrium.

Some interesting results have been obtained for 3,7-dimethylbicyclo[3.3.1]nonanes **26–28** (41). The ¹³C-NMR spectrum indicates that compound **26** exists in solution as a single CC conformer, while replacement of one of the *exo*-methyl groups by an *endo*-methyl forces the molecule (**27**) into a CB conformation. For compound **28** the situation is more complex.



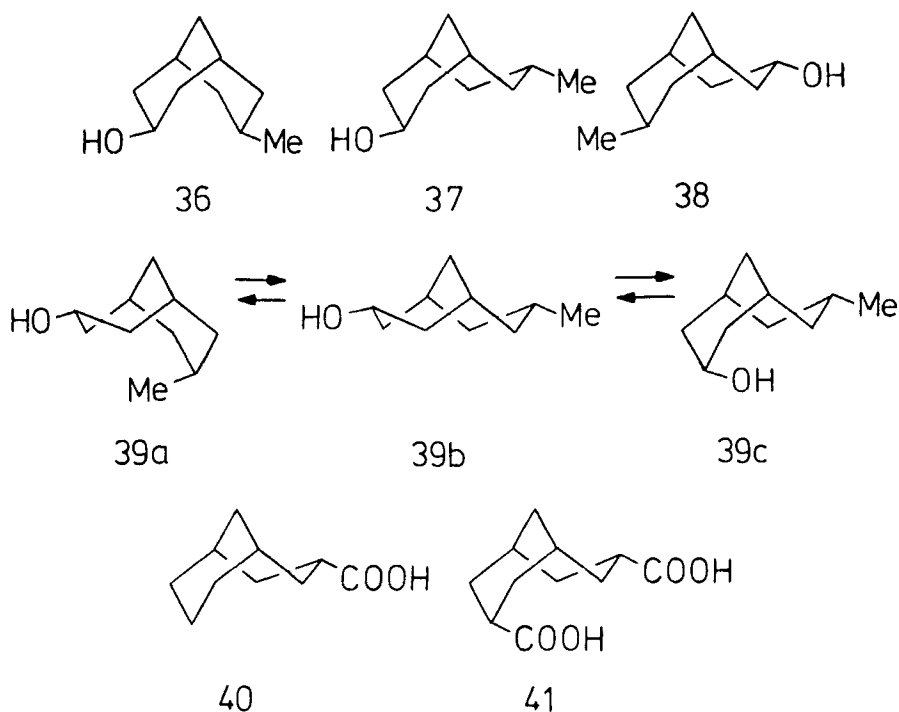
There are three conformers in the equilibrium: CB, TT, and BC. Analysis of the temperature dependence of the ^{13}C -NMR chemical shifts of **28** permitted the thermodynamic parameters of the $\text{CB} \rightleftharpoons \text{TT}$ equilibrium to be roughly estimated: $\Delta H = 0.4\text{--}1.3 \text{ kcal mol}^{-1}$, $\Delta S = 4.8\text{--}15.8 \text{ cal mol}^{-1} \text{ deg}^{-1}$, $\Delta G_{293} = -1.0 \text{ to } -2.0 \text{ kcal mol}^{-1}$. The unexpectedly large value of ΔS (a value of $0.7 \text{ cal mol}^{-1} \text{ deg}^{-1}$ is calculated by means of molecular mechanics (41)) contributes to the preference for the TT conformation at room temperature. On the other hand, molecular mechanics calculations predict a slight preference for the CB and BC conformations at room temperature ($\Delta G_{293} = 0.02\text{--}0.7 \text{ kcal mol}^{-1}$ (41)).

Studies of other derivatives have shown similar trends. Compounds **19**, **21**, **22**, and **29–31** adopt CC conformations and compounds **18**, **20**, **23**, and **32–35** adopt CB conformations (from the analysis of ^{13}C -NMR chemical



shifts) (4, 42, 43). The CC conformation for compound **36** and the CB conformation for compounds **37** and **38** (determined on the basis of ^{13}C -NMR data) are also as expected (4). However, interpretation of the chemical shift for C-9 of compound **39** shows that it exists to the extent of 70–80% in BB conformation **39b** (4) (earlier it had been reported on the basis of ^1H -NMR spectral studies that **39** exists preferentially in the CB conformation (44)).

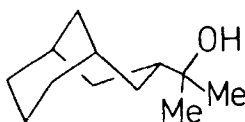
Single-crystal X-ray diffraction studies of the compounds with carboxy groups at the *endo*-3 and *endo*-7 positions have shown that both acid **40** (25) and diacid **41** (45) adopt the chair–boat conformation in the crystalline state. ^1H -NMR studies of diacid **41** and its dimethyl ester at room temperature indicate that, in solution, the CB and BC conformers predominate and that the proportion of the TT conformation in the equilibrium is negligible (42, 46).



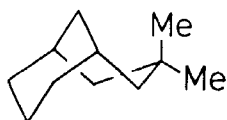
The only compound having two bulky substituents at *endo*-3 and *endo*-7 positions that has been studied is compound **42**. According to the ^1H -NMR study with the aid of shift reagents, the only conformer found to be present in solution was TT (27). The ^{13}C -NMR data are in agreement with this result (42). In the crystalline state, this compound also exists in a twist–boat/twist–boat conformation (28) as ascertained by X-ray diffraction techniques. For



42



43

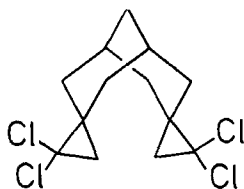


44

compound **43** containing one bulky substituent at the *endo*-3 position, the chair-boat conformation is predominant in solution according to the ^1H -NMR data (46).

Molecular mechanics calculations for 3,3-dimethylbicyclo[3.3.1]nonane predict that chair-boat conformation **44** has the lowest strain energy (47).

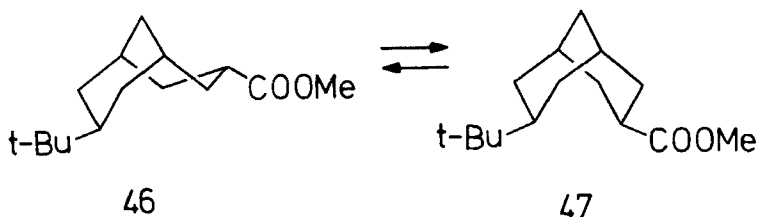
Unique results were obtained for compound **45** (48). In the crystalline state it exists in a chair-chair conformation despite the presence of the spiro-substituents at the 3- and 7-positions. The stability of the CC conformation can be explained by the small values of the bond angles in the cyclopropane



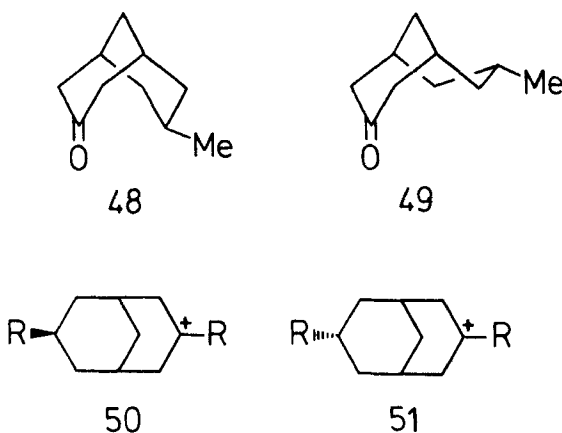
45

rings (60°) such that the "wings" of the bicyclo[3.3.1]nonane skeleton can be flattened enough to make the (C-3)- CH_2 and (C-7)- CH_2 bonds in the three-membered rings nearly parallel, thus decreasing the repulsion.

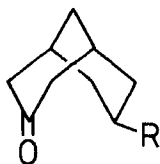
The introduction of bulky substituents at the *exo*-3 position decreases the energy difference between the chair-chair and the chair-boat conformations. The data on the epimerization of compounds **46** and **47** give a value of $\Delta G_{298} = -1.3 \text{ kcal mol}^{-1}$ for the equilibrium (compare this value with that for **20** and **21**; *vide supra*). Molecular mechanics calculations lead to the same conclusion (24).



As previously mentioned, introduction of a trigonal atom at the 3-position decreases the 3...7 repulsion. In this connection the question arises whether the CC conformation would be the most stable one in the presence of an *endo*-7 substituent. X-ray diffraction studies of ketones **48** and **49** containing *exo*-7 and *endo*-7 methyl groups, respectively, show that the *exo*-isomer **48** exists in a chair-chair conformation, as expected, while in the *endo*-isomer **49** the nonketone ring is forced into a boat conformation (**49**). (This study was undertaken in connection with the preparation of carbocations of types **50** and **51** (**49**) and the fast proton migration between 3- and 7-positions in the former.) These results are in agreement with ^{13}C -NMR studies of compounds **48** and **49** (4).



Similarly, the CC conformation was found for compounds **52** and **53** in the solid state (X-ray data) (50). Compound **52** was found by variable temperature ^1H -NMR spectroscopy to undergo a rapid base-induced intramolecular 3,7-hydride shift (the associated activation energy is $\Delta G^\ddagger = 19.4 \pm 0.2 \text{ kcal mol}^{-1}$ at 113°C) (51). The CC conformation of compounds **54** (52) and **55–58** (4) and the CB conformation of compound **59** (4) found in solution by analysis of ^{13}C -NMR spectra are as expected. However, the preference for the CC conformation was discussed on the basis of ^{13}C -NMR data for the

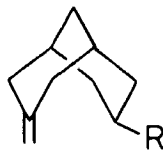


52 R = OH

53 R = OMe

54 R = COOMe

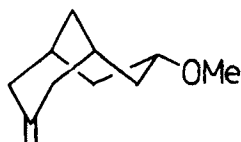
55 R = H



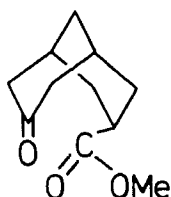
56 R = H

57 R = OH

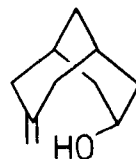
58 R = OMe



59



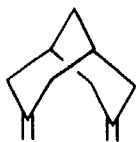
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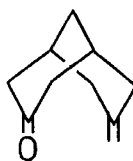
61

compounds **60** (52) and **61** (4) having *endo*-7 substituents. Thus, the absence of an *endo* hydrogen at C-3 in **60** allows the cyclohexane ring bearing even the *endo*-7 ester group to assume a chair conformation (52). The stability of a CC conformation for compound **61** was explained by possible hydrogen bonding of the hydroxy group with the π -orbital (the hydroxy group stretching band of **61** in the IR spectrum appears at 3520 cm^{-1} , while that of *exo*-3 compound **57** appears at 3630 cm^{-1} , the latter value indicating a free hydroxy group). The hydroxy group could be twisted about the connecting carbon–oxygen bond to relieve the van der Waals repulsion (4).

The CC conformation was found for 3,7-dimethylenebicyclo[3.3.1]nonane (**62**) and 7-methylenebicyclo[3.3.1]nonan-3-one (**63**) by analysis of the ^{13}C -



62



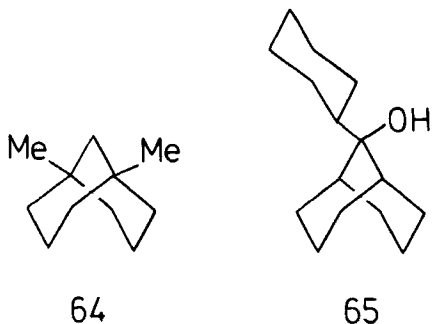
63

NMR chemical shifts (4). The through space interaction of π -orbitals in **62** and **63** was discussed.

For the complex compound **62**.AgNO₃ single-crystal X-ray diffraction has demonstrated that the organic molecule exists in the CC conformation with the Ag⁺ ion being coordinated with two π -bonds (53).

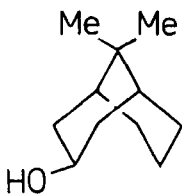
C. Influence of 1,5- and 9-Substituents on the Conformational behavior of Bicyclo[3.3.1]nonanes

The introduction of 1- and 5-substituents usually does not influence significantly the conformational behavior of bicyclo[3.3.1]nonanes. Molecular mechanics calculations (39) show that the presence of two methyl groups at the 1- and 5-positions (compound **64**) leads to some decrease (of approximately 0.03 Å) of the C3...C7 distance as compared with bicyclo[3.3.1]nonane itself. The substituents in these positions decrease the possibility of the "wings" flattening and could somewhat increase the interaction between substituent groups or lone electron pairs at *endo*-3 and *endo*-7 positions.



A substituent at the 9-position causes some flattening of the ring to which it is directed and in which it occupies an axial position. This conclusion follows both from calculations (39) and from experimental data (21,39) (for a discussion of this effect, see the X-ray diffraction results on compound **65** (21) in which molecule the ring with the axial cyclohexyl group is more flattened than that bearing the axial hydroxy group).

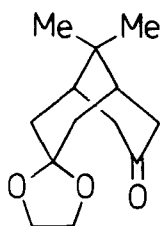
The most important role of 9-substituents is the inhibition of chair-to-boat interconversions. Forcing the two cyclohexane rings in bicyclo[3.3.1]nonanes to remain in chair conformations results in compounds in which the through space *endo*-3 and 7-substituent interaction can be maintained even under severe steric hindrance (54). When the *gem*-dimethyl groups are introduced at position 9, computation with the MM2 force field shows that the boat form is no longer a stable conformation. For compounds **66–69** a single chair–chair



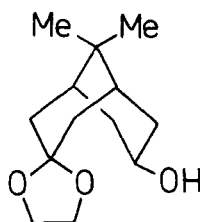
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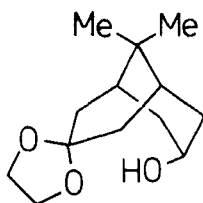


68

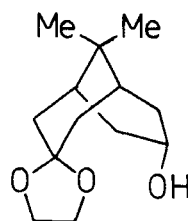


69

conformation was assumed to be present, while for compound **70** two conformations (chair–envelope and envelope–chair) differing by 1 kcal mol^{-1} were found (54). The lowest energies obtained for **66** (26.30), **67** (29.30), **68** (39.35), **69** (45.77), **70** (a, 49.99; b, 48.90 kcal mol^{-1}) show that the introduction of an OH *endo* substituent raises the total steric energy of the molecule by approximately 3 kcal mol^{-1} . Without the 9,9-*gem*-dimethyl substituents, the *endo* isomers would exist in the boat–chair form. In all these compounds the distance between *endo*-3 and *endo*-7 substituents remains at a similar value close to $2 \text{ \AA}$ (54). The steric compression imposed on carbons 3 and 7 by this double chair conformation is found to displace their ^{13}C chemical shifts to high field (54).



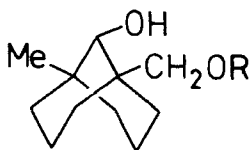
70a



70b

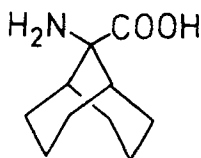
The conformational properties of 9,9-disubstituted bicyclo[3.3.1]nonanes does not allow reactants to approach from the *endo* side of the molecule. Depending on the molecule, it leads to reactions with complete stereospecificity or to complete lack of reactivity. For example, the alcohol formed by hydride reduction of **68** was identified as the *endo*-compound **70**, owing to attack by the reagent from the less hindered *exo* face of the molecule, while the reduction of **68** by sodium in ethanol, which is expected to give the thermodynamically more stable alcohol, gave the *exo*-epimer **69** as the only product. Unsuccessful attempts at the hydrolysis of **70** even under drastic chemical conditions confirms the high degree of steric hindrance in this compound (54).

X-ray diffraction data have been reported for yet other 9-substituted bicyclo[3.3.1]nonanes that adopt the chair-chair conformation. In these (**71** (55), **72** (39), **73** (56), **74** (57)), the CC conformation is not destabilized by the bulky *endo*-3 or *endo*-7 substituents.

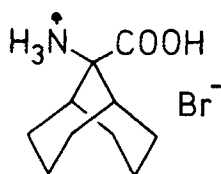


71 R = Bs

72 R = Ts



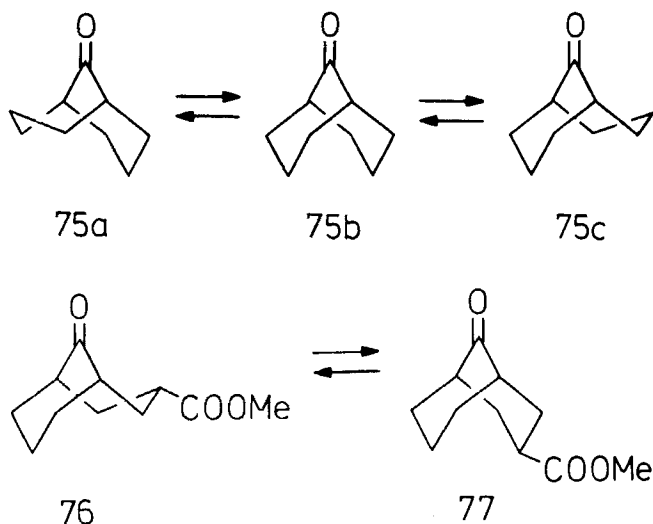
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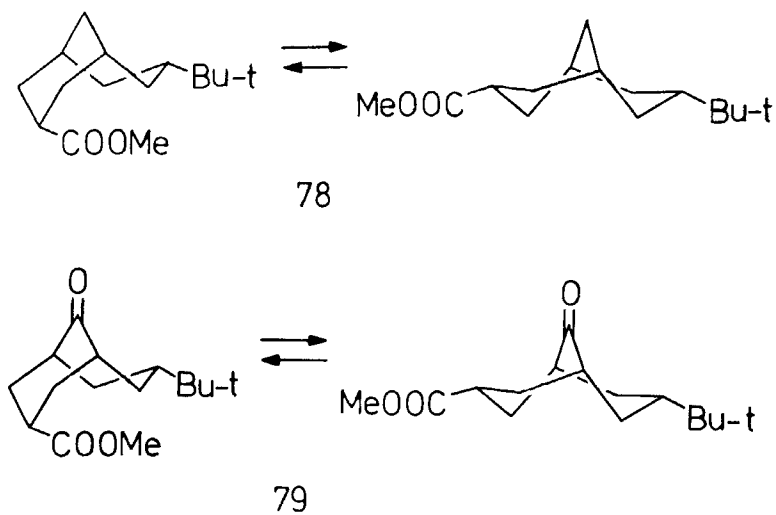
In contrast, introduction of a trigonal atom at the 9-position should decrease the flagpole-flagpole repulsion and thus increase the content of a CB conformer in the equilibrium. The study of the conformational equilibrium of bicyclo[3.3.1]nonan-9-one (**75**) at room temperature using shift reagents and ^1H -NMR techniques made it possible to determine the content (22%) of conformations CB + BC (**75a**, **75c**) (58).

A similar conclusion was reached from the results of epimerization experiments on **76** and **77**: $\Delta G_{298} = -1.6 \text{ kcal mol}^{-1}$ (24); that is, the energy



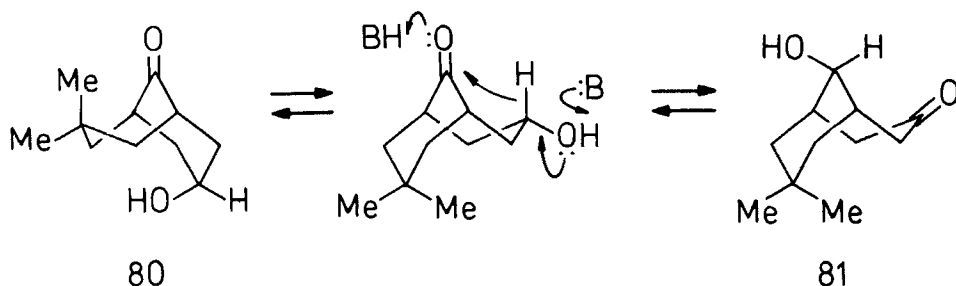
difference between the CC and CB conformers was found to be $1.1 \text{ kcal mol}^{-1}$ less than for the corresponding compounds devoid of the keto group (**20**, **21**).

The same trend was observed in the CB $\rightleftharpoons$ TT equilibrium. For compound **78**, $\Delta H_{\text{equil}} = 1.8 \text{ kcal mol}^{-1}$, while for ketone **79**, $\Delta H_{\text{equil}} = 1.0 \text{ kcal mol}^{-1}$ (24); that is, for the latter compound, the content of the TT conformation in the equilibrium would be expected to be higher.



Thus, for compounds having a trigonal atom at the 9-position, the energy difference between the CC, CB, and TT conformations is decreased relative to bicyclo[3.3.1]nonanes containing a methylene group at the 9-position. Compounds of this kind would always be expected to have an increased content of CB and TT conformations in the conformational equilibrium.

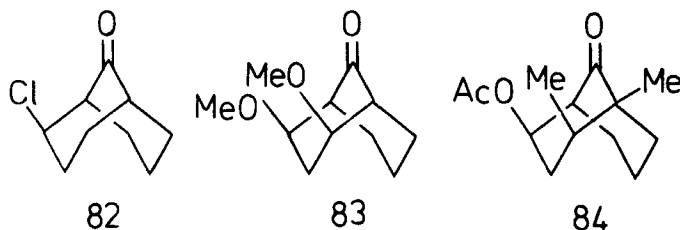
For studies of the conformations of other 3- and 7-substituted bicyclo[3.3.1]nonan-9-ones, see references 24, 42, and 59.

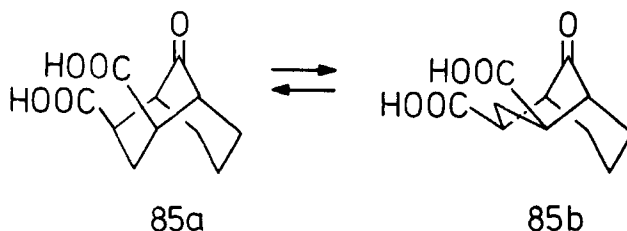


An interesting example of a reaction involving conformational equilibria in 3,7,9-substituted bicyclo[3.3.1]nonane systems is the base-induced rearrangement of *endo*-7,7-dimethylbicyclo[3.3.1]nonan-3-ol-9-one (**80**) into **81**. The rearrangement is rationalized by a reversible intramolecular transfer of hydride from the carbinol methine to the carbonyl carbon (60). The reacting centers at C-3 and C-9 are only placed in proximity when the cyclohexanol ring adopts a boat conformation. The resulting ketol **81** is 2.7 kcal mol⁻¹ more stable than its isomer **80** (60).

D. 2-, 4-, 6-, and 8-Substituted Bicyclo[3.3.1]nonanes

Comparatively few data are available on the conformational behavior of bicyclo[3.3.1]nonanes devoid of skeletal heteroatoms and containing substituents at the 2-, 4-, 6-, or 8-positions. Compounds containing an *exo*-2-chlorine (compound **82**, X-ray diffraction data (61)), two *exo*-methoxy-groups or one *exo*-acetoxy and one *exo*-methyl-group at the 2- and 4-positions (compounds **83** (62, 63) and **84** (64), respectively, ¹H- and ¹³C-NMR

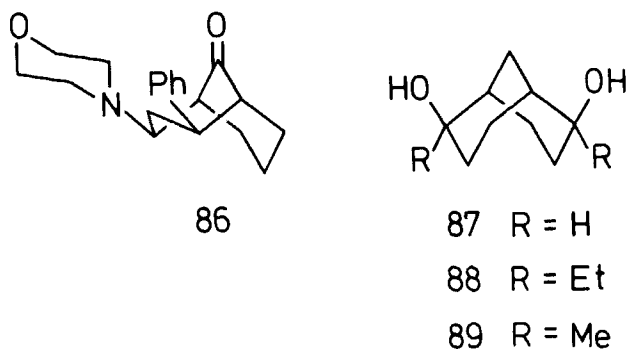




spectroscopy data) preferentially adopt the chair–chair conformation.

However, *exo,exo*-2,4-dicarboxylic acid **85** exists almost exclusively in the boat–chair conformation, in DMSO-*d*₆ or alkaline D₂O solution (according to ¹H- and ¹³C-NMR spectroscopy) (26).

Compound **86** having two rather bulky *exo,exo*-2,4 substituents also adopts the chair–boat conformation in the crystalline state (65). This conformation occurs because of steric reasons (*exo*-2- and *exo*-4-substituents in a chair–chair conformation would occupy the axial positions).

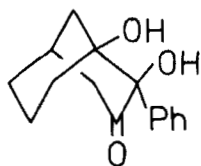


Compounds **87–89** containing *gem*-substituents at each of the 2- and 6-positions adopt a noticeably twisted chair–chair conformation as found by X-ray crystal structure analysis (66–69). The crystal structure of compound **89** belongs to a new family of “helical tubuland inclusion crystals,” the shape and the capacity of whose guest cavity in the crystal have been analyzed in detail (69).

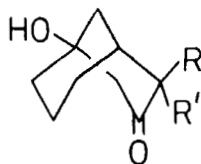
Other compounds with substituents at the 2-position that preferentially adopt the chair–chair conformation are compounds **90** (70) (X-ray crystal structure analysis data), **91**, and **92** (71) (NMR data).

E. Bicyclo[3.3.1]nonanes with Trigonal Atoms in the “Wings”

The introduction of trigonal atoms at the 2,3,4- and/or the 6,7,8-positions of bicyclo[3.3.1]nonane skeleton leads as previously mentioned (see **16** and **17**)



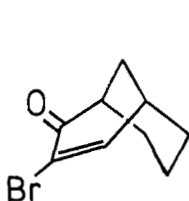
90

91 $R = H$, $R' = (CH_2)_{15}Me$ 92 $R = (CH_2)_{15}Me$, $R' = H$

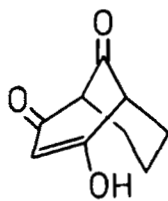
to the envelope conformation of both six-membered rings or of one of them.

Compounds **93** (72), **94** (73), and **95** (74) are examples of those having chair-envelope conformations in the crystalline state. The envelope part of the skeleton is rather rigid. It should be mentioned that the *endo*-7 substituent does not destabilize the chair part of the bicyclic system enough to convert it into the envelope-boat conformation. Both in solution (^1H -NMR data) and in the solid state (X-ray data) **95** exists in the chair-envelope conformation (74).

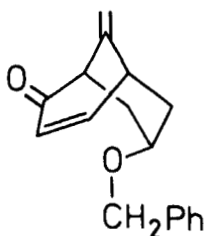
The presence of only two trigonal atoms at the 2- and 3-positions leads to a significantly twisted envelope conformation of the ring, the conformation of such a ring being in fact intermediate between envelope and half-chair forms. Compound **96** is an example (from a single crystal X-ray diffraction study (75)).



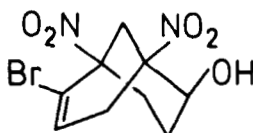
93



94



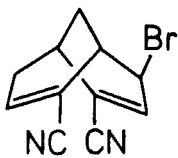
95



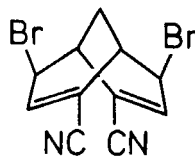
96



97



98

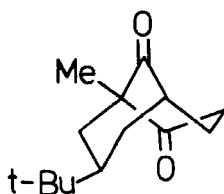


99

The presence of double bonds in both rings leads to a strongly twisted double envelope conformation for compounds **97–99** (76) found in the crystalline state.

The introduction of trigonal atoms at both 2- and 9-positions results in a preference for the chair–boat conformation for compound **100** (77).

The presence of a double bond at a bridgehead position (as in **101** and **102**) leads to strained olefins. From molecular mechanics (MM1) calculations (Z)-bicyclo[3.3.1]non-1-ene (**101**) should exist preferentially in a chair–boat conformation (the alternative boat–boat conformation is 1.18 kcal mol⁻¹ higher in energy) while (E)-bicyclo[3.3.1]non-1-ene (**102**) would be expected to adopt a chair–chair conformation (the strain energy of **102** is 29 kcal mol⁻¹ higher than of **101** and the chair–boat conformation is 3.34 kcal mol⁻¹ above the chair–chair one) (78).



100



101



102

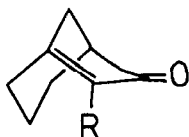


$$\text{Fp} = (\eta^5\text{-C}_5\text{H}_5)(\text{CO})_2\text{Fe}$$

103

A single-crystal X-ray diffraction of a π -complex of **101** (compound **103**) has shown that its bicyclo[3.3.1]non-1-ene skeleton exists in a chair-boat conformation (79).

The conformations of highly reactive bicyclo[3.3.1]non-1-en-3-one derivatives **104**–**107** were computed using a molecular mechanics method (MMP1) for conjugated systems. In all cases, the calculated inherent strain energy was less for a structure incorporating a chair conformation in the non-enone relative to that incorporating a twist-boat conformation. The enone ring in the structure is suggested as being intermediate in shape between boat and envelope forms and rather twisted (70,80) (for the UV spectra of **104** and a



104 R = H

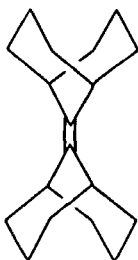
105 R = Me

106 R = Ph

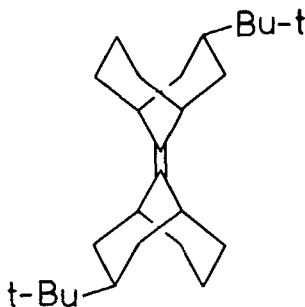
107 R = t-Bu

discussion of the distortion of its C=C bond, see references 80 and 81). X-ray diffraction data have been published for the adducts and dimers of bicyclo[3.3.1]non-1-en-3-one (80, 82, 83).

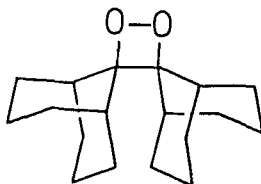
We conclude this section with a description of results on the interesting bis compounds **108**–**110** (84, 85). All rings in these compounds adopt the chair conformation.



108



109



110

In this section we have described the conformational behavior only of compounds containing the carbocyclic bicyclo[3.3.1]nonane skeleton; their behavior is governed mainly by steric interactions.

IV. CONFORMATIONAL STUDIES OF HETERO ANALOGS OF BICYCLO[3.3.1]NONANE

The conformational behavior of heterobicyclo[3.3.1]nonanes is determined not only by the steric factors discussed in the previous sections. In some cases it is strongly influenced by specific interactions involving the heteroatoms.

The conformational preferences for 3-heterobicyclo[3.3.1]nonanes, in general, are similar to those for their carbocyclic analogs. As previously mentioned (see Section II), the introduction of a heteroatom at the 3-position can somewhat stabilize the CC conformation. Molecular mechanics (MM1) calculations for 3-oxabicyclo[3.3.1]nonane (**111**) (22) show that the CC conformation is $4.5 \text{ kcal mol}^{-1}$ lower in energy than that for the CB form. Preference for the CC form in the case of **111** was demonstrated by ^1H - and ^{13}C -NMR techniques (23, 86); analysis based on the use of shift reagents suggests that in **111** the tetrahydropyran ring is less flattened than the corresponding ring in the carbocyclic system (23).



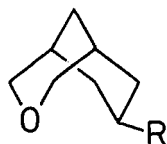
111 X = O

112 X = S

113 X = NR

The preferred conformation of 3-thia- and 3-aza-compounds **112** and **113**, respectively, was found to be the CC form as well (2, 87).

On the basis of ^1H - and ^{13}C -NMR spectral data, the *exo*-7-alkyl derivatives of 3-oxabicyclo[3.3.1]nonane, **114**–**116**, exist in the chair–chair conformation



114 R = Me

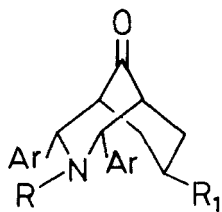
115 R = *i*-Pr116 R = *t*-Bu

117 R = Me

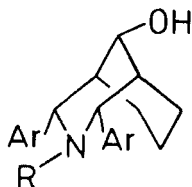
118 R = *i*-Pr119 R = *t*-Bu

in solution, as expected (23). The *endo*-7-alkyl substituted compounds **117–119** predominantly occur in the CB conformation (23).

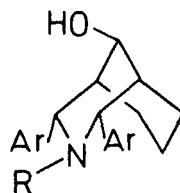
The influence of substituents on the conformational behavior of 3-aza-bicyclo[3.3.1]nonanes is generally similar to that observed for carbocyclic analogs. ^{13}C -NMR data on 41 compounds of types **120–123** demonstrate a



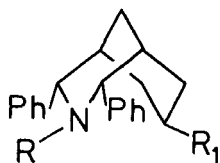
120



121



122

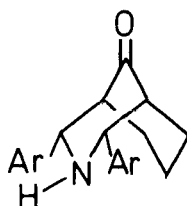
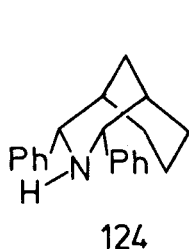


123

preference for the chair-chair conformation (88), which is additionally stabilized by diequatorial 2- and 4-aryl groups and by *exo*-7 R_1 substituents.

Single-crystal X-ray diffraction studies of compounds **124–127** (89, 90), **129** (91), **130** (92), **131** (93), **132**, **133** (89), **134** (94), **135** (95), **136** (96), **137** (97), and nitroxyl radical **138** (98) demonstrate their preference for the CC conformation. In the case of compounds **125** and **128**, this preference (in solution) was

confirmed by dipole moment measurements (99,100). Studies of 9-aza-3-oxabicyclo[3.3.1]nonan-9-ones with and without various substituents at the 2- and 4-positions have shown that even the presence of two *exo,exo*-2,4-substituents, as in compound **139**, does not destabilize the chair-chair conformation (from X-ray data) (101, 102), and a similar chair-chair conformation was found in the solid state for compound **140** (103). It should be mentioned that compounds of this type lack the 3...7 repulsion of hydrogen atoms in a typical CC conformation. Compound **141** also adopts a CC conformation in the solid state (104). X-ray diffraction studies show that endo-substituted compounds **142–144** (89), **145**, and **146** (105) adopt the chair-boat conformation.

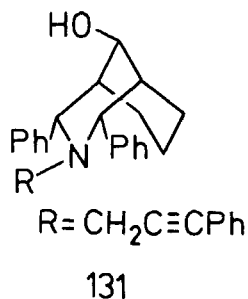
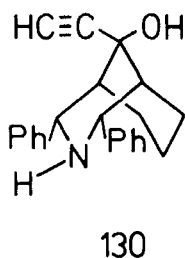
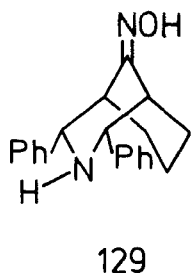


Ar = Ph

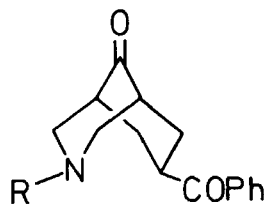
126 Ar = C₆H₄Me-p

127 Ar = C₆H₄OMe-p

128 Ar = C₆H₄Me-o

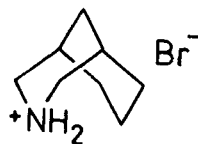
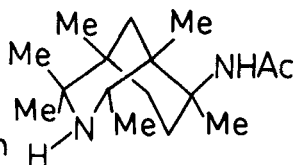


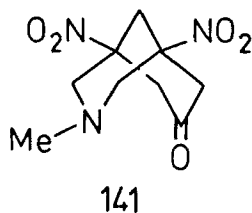
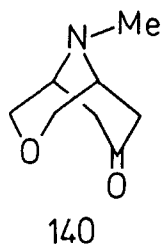
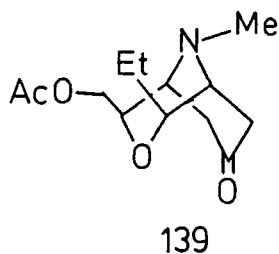
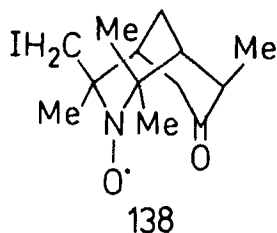
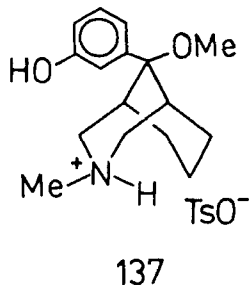
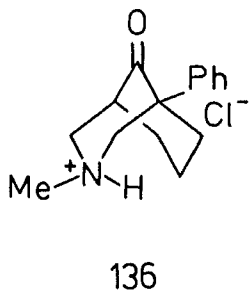
R = CH₂C≡CPh



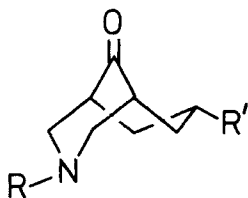
R = Ms

133 R = Bs





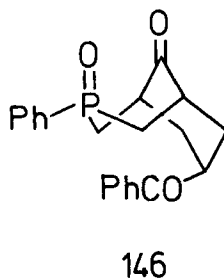
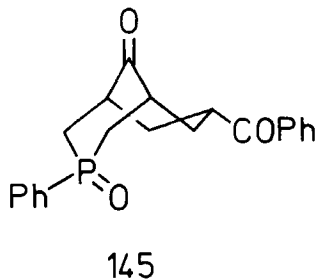
The *exo*-2-methyl- and ethyl-substituted 3-benzyl-3-azabicyclo[3.3.1]-nonanes were shown to adopt the CC conformation in solution (from ^{13}C -NMR data), while for the *exo*-2-isopropyl compound the CB conformation is predominant (106).



142 R = Ts, R' = COPh

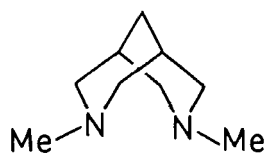
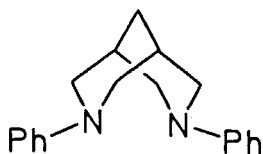
143 R = Bs, R' = COPh

144 R = Ts, R' = COOEt



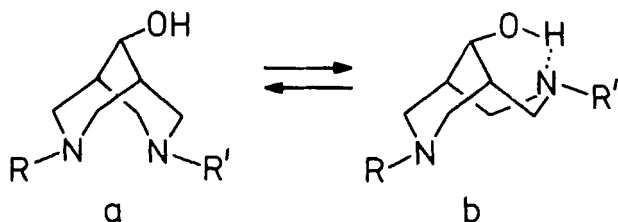
While replacement of two methylene groups at the 3- and 7-positions by heteroatoms removes the repulsion between *endo*-3 and *endo*-7 hydrogen atoms, it introduces two new kinds of interaction: dipole–dipole repulsion and the overlap of lone pair orbitals.

The 3,7-diazabicyclo[3.3.1]nonanes (bispidines) are among the most thoroughly investigated hetero analogs of bicyclo[3.3.1]nonane (1,2). Conformational studies of 3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonane (**147**) in solution by the dipole moment method, and by ^1H - and ^{13}C -NMR spectroscopy (107, 108), have shown a preference for the chair–chair conformation. Semiempirical calculations (EH, CNDO/2) (109) and analysis of the photoelectron spectrum of **147** in combination with three sets of other MO calculations (MINDO/3, MNDO, and *ab initio* at the STO-3G level) lead to the conclusion that, in the gas phase, **147** exists in the chair–chair conformation (108).

**147****148**

Compound **148** adopts a chair–chair conformation both in solution (87) (according to ^1H -NMR data) and in the solid state, as shown by a single-crystal X-ray diffraction study (110), significant flattening of the “wings” being found in the latter case.

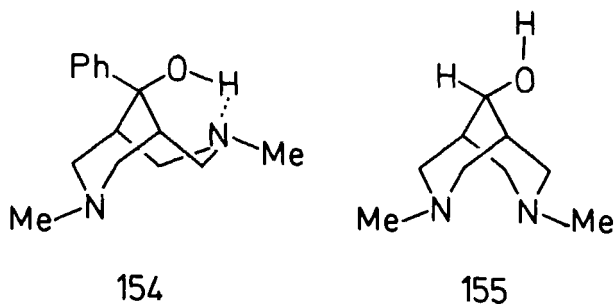
The introduction of substituents at the 9-position of 3,7-diazabicyclo[3.3.1]nonane can drastically change the conformational behavior. Studies of a series of 9-hydroxy derivatives **149**–**153** using ^1H - and ^{13}C -NMR, IR, and Raman spectroscopy reveal that, for these compounds, the bicyclic system adopts the chair–boat conformations **149b**–**153b** in nonpolar solvents and that these conformations are stabilized by intramolecular O–H...N bonding (111). Only a small proportion of free OH groups was found in dilute solutions of **149** in CCl_4 and CS_2 . However, the IR spectra in $(\text{CD}_3)_2\text{SO}$ solution indicate that there is solute–solvent interaction causing a change from the CB to the CC conformations **149a**–**153a**. An X-ray diffraction study of **149**·2H₂O·EtOH shows that it exists in a chair–chair conformation stabilized by water and ethanol molecules (111). A strong preference by the 9-phenyl-substituted analog **154** for the CB conformer in solution was also found earlier (112).

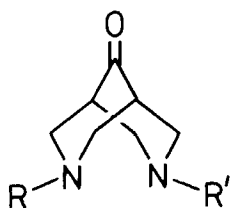


- 149 $R = \text{Me}, R' = \text{Me}$
 150 $R = \text{Me}, R' = \text{CH}_2\text{Ph}$
 151 $R = \text{Me}, R' = \text{CH}_2\text{CH}_2\text{Ph}$
 152 $R = \text{CH}_2\text{Ph}, R' = \text{Me}$
 153 $R = \text{CH}_2\text{CH}_2\text{Ph}, R' = \text{Me}$

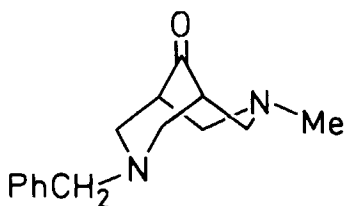
A study of compound **149** using CNDO/2 calculations in combination with the "electronic population"— ^1H -NMR chemical shift relationship permitted the assignment of the conformation of the hydroxy-group hydrogen in $(\text{CD}_3)_2\text{SO}$ solution as being *cis* to the methine hydrogen at C-9 (**155**) (113). From a study of infrared spectra, a water-free crystal form of **149** has the intramolecular $\text{O}-\text{H}\cdots\text{N}$ bonding within a chair-boat conformation **149b** (111).

A flattened CC conformation has been assigned for the 3,7-diazabicyclo[3.3.1]nonan-9-ones **156–159** in $(\text{CD}_3)_2\text{SO}$ and in CDCl_3 on the basis of ^1H - and ^{13}C -NMR, IR, and Raman spectral data (111, 114). ^1H - and ^{13}C -NMR studies of compounds **156** and **160–162** in CDCl_3 solution have confirmed for **156** and shown for **160–162** a flattened chair-chair conformation with the *N*-substituents in the equatorial position. Additionally, an increase in distortion of the *N*-alkylpiperidine ring was observed as the size of the *N*-substituent was increased (115).

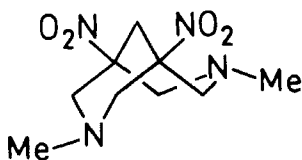




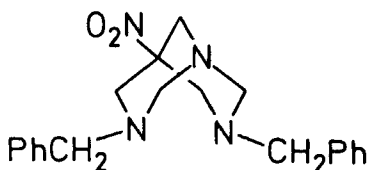
- 156 $R = \text{Me}, R' = \text{Me}$
 157a $R = \text{Me}, R' = \text{CH}_2\text{Ph}$
 158 $R = \text{Me}, R' = \text{CH}_2\text{CH}_2\text{Ph}$
 159 $R = \text{CH}_2\text{Ph}, R' = \text{CH}_2\text{Ph}$
 160 $R = \text{Me}, R' = \text{Et}$
 161 $R = \text{Me}, R' = n\text{-Pr}$
 162 $R = \text{Me}, R' = i\text{-Pr}$



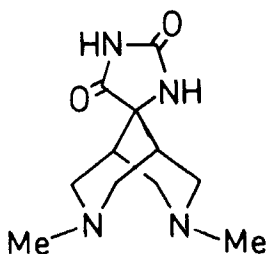
157b



163



164



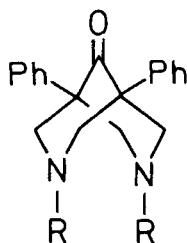
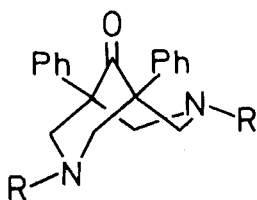
165

Compound **157** has a chair-boat conformation **157b** in the solid state as revealed by a single-crystal X-ray diffraction study (116).

According to the X-ray data, dinitro compound **163** exists in a CB conformation (117). In contrast, the 1,3,7-triaza system **164** adopts a CC conformation in the solid state (118). A CC conformation was also found for the 9-spiro-substituted compound **165** (X-ray study) (119).

X-ray studies of a series of 1,5-diphenyl *N,N'*-disubstituted derivatives of 3,7-diazabicyclo[3.3.1]nonan-9-one have shown that their conformation depends on whether the lone-pair electron density is delocalized away from the

nitrogen atoms (120–124). The presence of phenyl substituents at the 1- and 5-positions does not permit a noticeable increase in the (C-2)–(C-1)–(C-8) and (C-4)–(C-5)–(C-6) bond angles. Hence, the phenyls prevent a significant flattening of the wings in a chair–chair conformation, thus increasing 3...7 interactions in compounds **167–173**. Compounds **166–169** with alkyl and tosyl groups at the 3- and 7-positions have pyramidal nitrogen atoms; repulsion of their endo-oriented lone electron pairs in CC conformations destabilizes them to such an extent that the CB conformations become preferable (123, 120, 121, 124). The sp^2 hybridization of nitrogen atoms decreases the endo–endo repulsion of lone electron pairs and leads to a preference for CC conformations for compounds **170–173** (122, 123).



166 R = Me

167 R = CH₂Ph

168 R = CH₂CH=CH₂

169 R = Ts

170 R = COCH₃

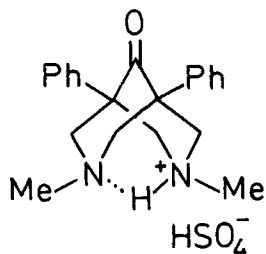
171 R = COCF₃

172 R = COOEt

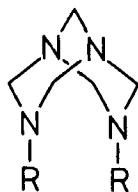
173 R = NO

Similar conformational preferences were found in solution. For compound **166**, variable temperature ¹³C-NMR measurements in CS₂-CD₂Cl₂ solution (coalescence temperature –63°C) yielded $\Delta G^\ddagger = 9.7 \text{ kcal mol}^{-1}$ for the CB $\rightleftharpoons$ BC degenerate interconversion (125). However, in subsequent measurements, a coalescence temperature of $-83 \pm 3^\circ\text{C}$, corresponding to $\Delta G^\ddagger = 8.7 \text{ kcal mol}^{-1}$ was found for compound **166** (117). The latter value corresponds to that for nitrogen inversion in piperidines (126). One may conclude that the BC $\rightleftharpoons$ CB interconversion and nitrogen inversion may take place synchronously (117). A coalescence temperature of -91°C has been reported for **167** corresponding to $\Delta G^\ddagger = 8.4 \text{ kcal mol}^{-1}$; this value is in better agreement with the remeasured $\Delta G^\ddagger$ value for **166**.

The protonation of one nitrogen atom in compound **166** stabilizes the chair–chair conformation (compound **174**; from X-ray data (127)) owing to the formation of N–H...N hydrogen bonding.



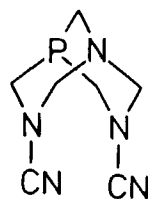
174



175 R = Ac

176 R = NO₂

177 R = NO

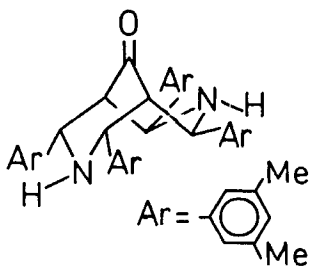


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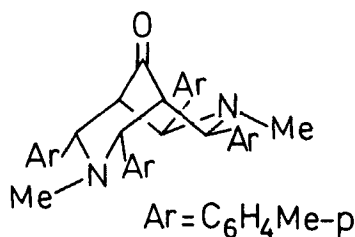
In a manner similar to that found for compounds **170–173**, tetraaza and phosphatriaza compounds **175–178** adopt CC conformations in the solid state (based on X-ray diffraction studies) (128–131). From dipole moment and ¹H-NMR measurements, **175–177** exist in a CC conformation in solution (132, 133).

Substituents at the 2-, 4-, 6-, and 8-positions of the 3,7-diazabicyclo[3.3.1]nonane skeleton usually determine the conformational preferences. X-ray studies and ¹H-, ¹³C-, and ¹⁵N-NMR spectroscopy have shown that tetraaryl compounds **179–181** adopt the chair–boat conformation both in the solid state and in solution (134–136). The alternative chair–chair conformation is destabilized by the presence of two phenyl groups at the *exo,exo*-2,4-positions. Analogously, compound **182** exists in a chair–boat conformation according to an X-ray study (137).

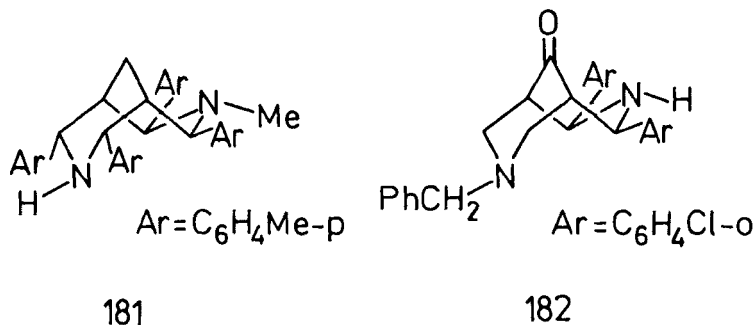
Cooperative effects in the restricted rotation of aryl groups in 2,4,6,8-tetraaryl-3,7-diazabicyclo[3.3.1]nonanes have been described; it was concluded on the basis of the large, negative value of $\Delta S^\ddagger$ for rotation of the 2(4)



179



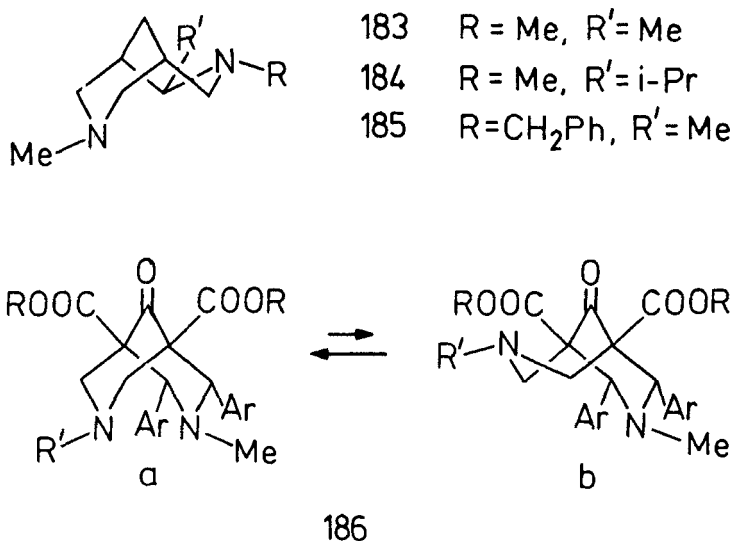
180



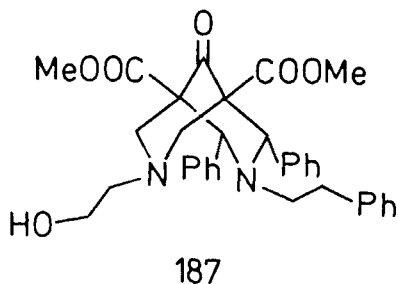
aryl group that this rotational process is correlated with rotation of the 8(6) aryl group (138).

The significant influence of even one *exo*-2 substituent was demonstrated for compounds **183–185** (139); according to ^1H -NMR measurements, these compounds exist in solution preferentially in the chair–boat conformation.

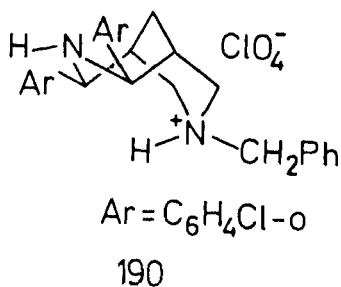
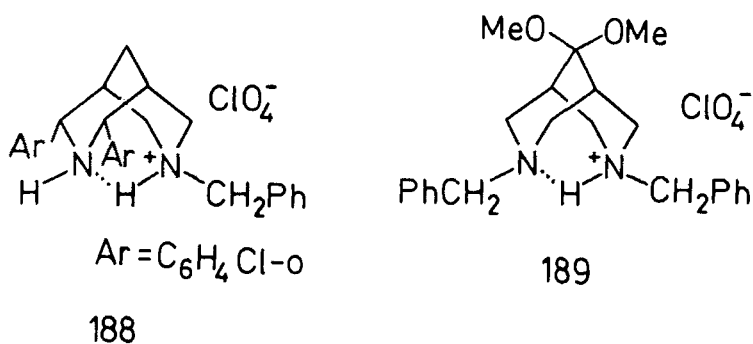
^1H - and ^{13}C -NMR studies of a series of ten 3,7-diazabicyclo[3.3.1]nonan-9-ones of type **186** have shown that in all cases the CC conformation is predominant in solution although the percentage of a CB conformation increases with the increased bulkiness of the *N*-7-substituent (34% of the CB **186b** for $\text{R}' = \text{adamantyl}$) (140).



A conformation very close to the ideal chair–chair was found in the solid state for compound **187** (X-ray data) (141).

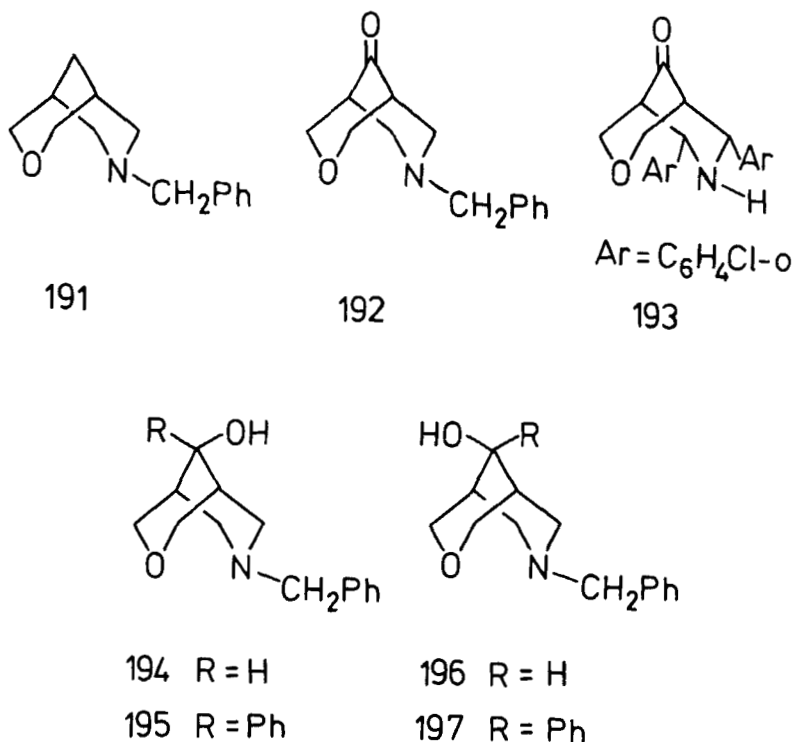


The CC conformations of perchlorates **188** and **189** (from X-ray studies) are quite predictable; however, salt **190** adopts a CB conformation in the solid state as a result of the destabilization of the CC conformation by the steric interaction of two aryl groups (137). The surprising observation was made in the ^{15}N -NMR spectrum of **190**. Protonation in solution takes place at the secondary nitrogen rather than at the tertiary nitrogen in salt **190** (137).



There are significantly fewer data available on the conformational behavior of 3-oxa-7-azabicyclo[3.3.1]nonanes than for the 3,7-diaza compounds described above.

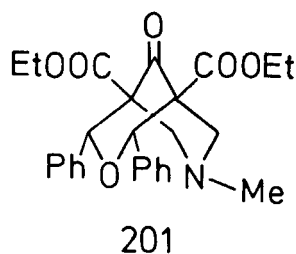
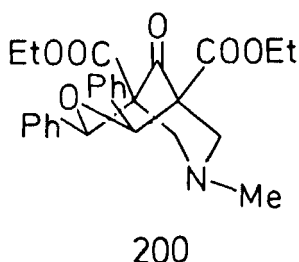
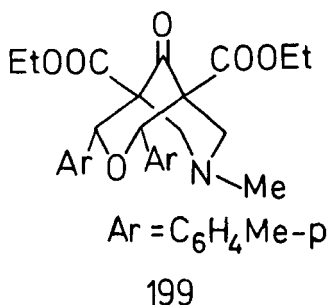
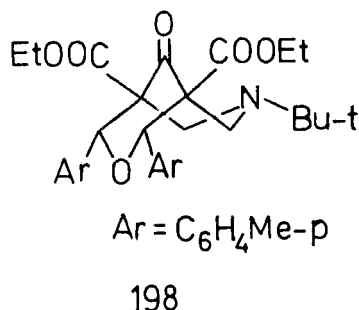
A CC conformation, possibly with ring flattening, was assigned as the probable conformer of compounds **191**–**193** in solution on the basis of $^1\text{H-NMR}$ (142). An X-ray study of compound **193** revealed that it adopts a CC conformation in the solid state with a slight flattening of the oxygen-containing ring (142). A CC conformation was suggested as also being preferred in a series of 9-hydroxy derivatives **194**–**197** (142) on the basis of $^1\text{H-NMR}$ and IR spectral data.



The influence of a bulky substituent at nitrogen on the conformational behavior of 3-oxa-7-azabicyclo[3.3.1]nonan-9-ones is illustrated by X-ray studies of compounds **198** and **199**: the compound having a *tert*-butyl group at nitrogen adopts a CB conformation (143).

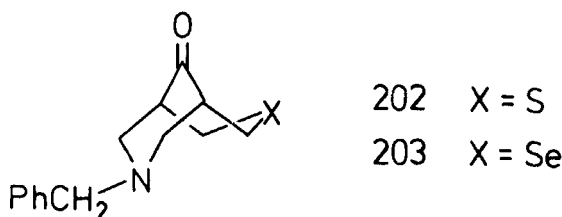
The preferred conformation of compounds **200** and **201** (from X-ray data) is determined by the configurations of the 2- and 4-phenyl groups: the *exo,exo* arrangement of these groups destabilizes a CC conformation and leads to a CB conformation (**200**) (144).

The solution conformations of compounds analogous to **200** and **201** and of the corresponding 9-hydroxy analogs, and the role of hydrogen bonding in the



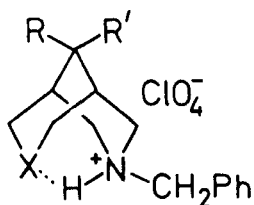
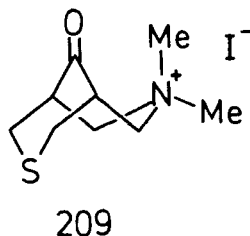
latter, have also been discussed on the basis of IR, ¹³C- and ¹H-NMR data (145–147).

Single-crystal X-ray diffraction studies of 3-thia-7-aza- and 3-selena-7-azabicyclo[3.3.1]nonan-9-ones **202** and **203**, respectively, have shown that

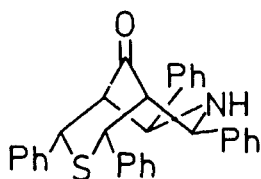


they adopt a chair–boat conformation in the solid state (148,149). NMR studies have confirmed the same conformation to be that preferred in solution (148–150).

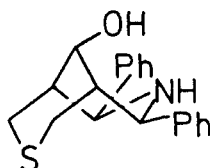
As demonstrated by X-ray diffraction studies, salts **204–208** adopt the chair–chair conformation in the crystal state. This conformation is stabilized by intramolecular N–H...X bonding (148,149,151). However, for steric reasons, compound **209** having two methyl groups at nitrogen adopts the CB conformation in the crystal state (from X-ray data) (152). The alternative BC conformation would be destabilized by 1,3-diaxial repulsion.

204 $R = R' = H, X = S$ 205 $R = R' = H, X = Se$ 206 $R = R' = OH, X = S$ 207 $R = R' = OH, X = Se$ 208 $R = OH, R' = Ph, X = S$ 

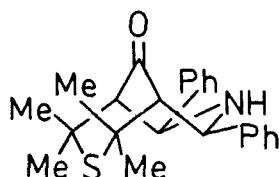
209



210



211

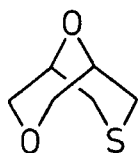


212

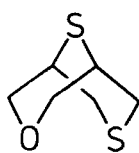
The conformational behavior of compounds **210**–**212** is determined mainly by the *exo*-phenyl groups; the CB conformation was found for them both in the solid state (from X-ray data) and in solution (from ^1H -NMR spectroscopy) (153–155). Dipole moment measurements have confirmed the CB conformation of **210** (99) and suggest the existence of a $\text{CC} \rightleftharpoons \text{BC}$ equilibrium for the *trans*-2,4-diaryl analog of **210** (100).

Earlier references on the conformational behavior of azabicyclo[3.3.1]nonanes can be found in two previous reviews on the subject (1,2).

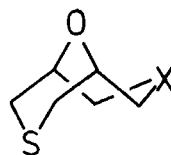
Specific interactions of heteroatoms can strongly affect the conformational behavior. Interesting results have been obtained for a series of 3,7,9-triheterobicyclo[3.3.1]nonanes. For compounds **213** and **214** with oxygen and sulfur atoms at the 3- and 7-positions, the CC conformation is the most stable one both in the solid state and in solution (87, 156–158). In contrast, the presence of two sulfur atoms, or one sulfur and one selenium atom, at the 3- and 7-positions of compounds **215** and **216** destabilizes the chair–chair conformation (87, 156, 159, 160). This phenomenon was explained by the destabilizing



213



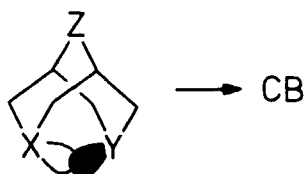
214



215 X = S

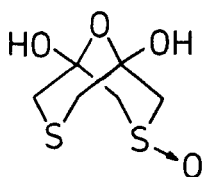
216 X = Se

through-space interaction of lone electron pairs of heteroatoms found in the lower periods of the periodic table when they occupy the 3- and 7-positions in a CC conformation (**217**) ("hockey-sticks" effect (8)). The overlap of oxygen and sulfur atom lone pairs was insufficient for the destabilization of a chair-chair conformation. Subsequently, attention was called to the operation of through-bond interactions in these systems (161).

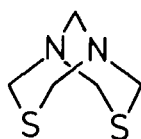


217

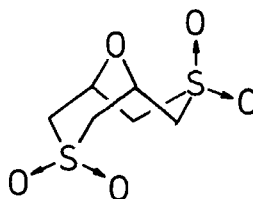
Sulfoxide **218** exists both in solution (from ^1H -NMR data) and in the solid state (from X-ray data) in a chair-chair conformation (162, 163); that is, the change in valence state of one sulfur atom stabilizes the CC conformation. The chair-chair conformation was unexpectedly found for compound **219** despite the strong interaction of lone-pair orbitals of the sulfur atoms demonstrated by photoelectron spectroscopy (164, 165). The $\text{S}3 \cdots \text{S}7$ distance is equal to 3.37 Å. Thus, the presence of sulfur atoms solely at the 3- and 7-positions is insufficient to destabilize a CC conformation; heteroatoms must be present at other positions. The chair-boat conformation of compound **220** (from X-ray data) was explained by steric and dipole-dipole interactions (166).



218

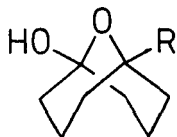
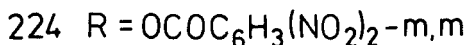
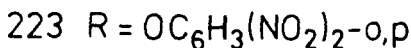
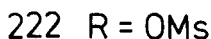
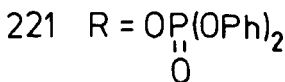
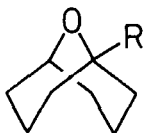


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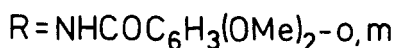
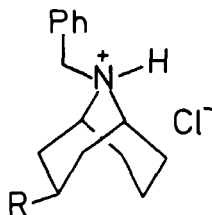


220

The conformational behavior of 9-heterobicyclo[3.3.1]nonanes usually follows the regularities found for carbocyclic systems. For a series of 9-oxa derivatives **221**–**225**, X-ray studies revealed the CC conformation in the solid state (167–171). The CC conformation was also found for salt **226** (from X-ray data) (172).



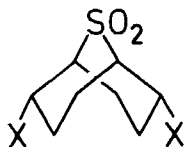
225



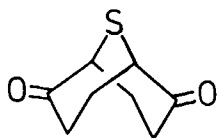
226

The 2,6-disubstituted compounds **227**–**229** adopt a chair–chair conformation with significant twisting of both rings (from X-ray data) (38, 40, 173). However, the boat rings in compounds **230** and **231** that adopt a CB conformation are not considerably twisted (from X-ray data) (174, 175). The CC conformation was found for nitroxyl radical **232** in the solid state; **232** was found to crystallize as a dimer (176).

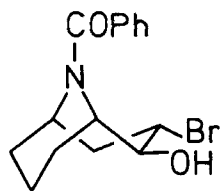
In solution the *endo*-3 and *exo*-3 substituted compounds **233** and **234** adopt CB and CC conformations, respectively, according to ^{13}C -NMR data (177). A variable temperature ^{13}C -NMR study of 9-methyl-9-azabicyclo[3.3.1]nonane has shown that the nitrogen inversion barrier is $\Delta G^\ddagger = 8.1 \text{ kcal mol}^{-1}$ at -90°C (178). For some other 9-heterobicyclo[3.3.1]nonanes studied using ^{13}C -NMR data, the conformational behavior was shown to be governed by steric interactions (177–180).



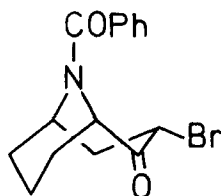
227 X = Cl

228 X = ONO₂

229

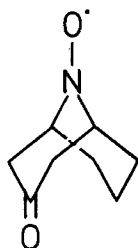


230

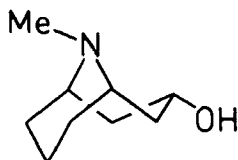


231

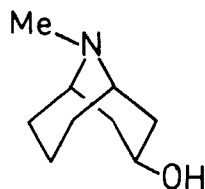
Unusual results have been obtained for compound **235** (181). In the solid state, the bicyclic system adopts a distorted CC conformation **235a** despite the presence of an *endo*-3 substituent (from X-ray data). The C-3 apex is flattened due to a strong steric interaction between the *endo*-3 hydroxy group and the *endo*-7 hydrogen, which is reflected in the interatomic distance C-3...C-7, 3.305 Å. The molecules are held together in crystals by two hydrogen bonds. On the other hand, in CDCl₃ solution, **235** preferentially adopts a flattened chair-boat conformation (**235b**) according to IR and ¹H- and ¹³C-NMR spectral data. In **235b**, the substituent at N-9 has the opposite orientation to



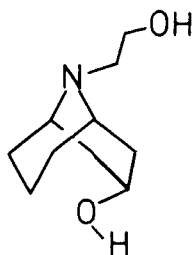
232



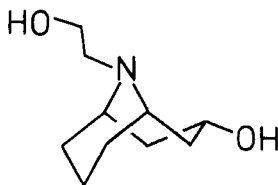
233



234



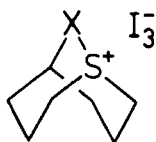
235a



235b

that found in **235a**. This example demonstrates that the solid state conformation can sometimes differ significantly from the conformation preferred in solution.

Compounds **236–238** having heteroatoms at the 1- and 9-positions adopt a CC conformation in the solid state (182–184).



236 X = O

237 X = NH

238 X = NMe

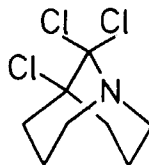
The CC conformation was found in the solid state (from X-ray data) for phospho compounds **239** and **240** (185, 186) and for 1-aza compound **241** (187); in solution compound **241** and some its analogs also adopt a CC conformation (187).



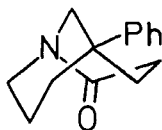
239



240



241



242

The important role of a heteroatom at the 1-position is demonstrated by the CB conformation of compound **242** in the solid state (188). The presence of a N-1, C-2 amide bond makes it somewhat similar to bridgehead olefins of type **101**.

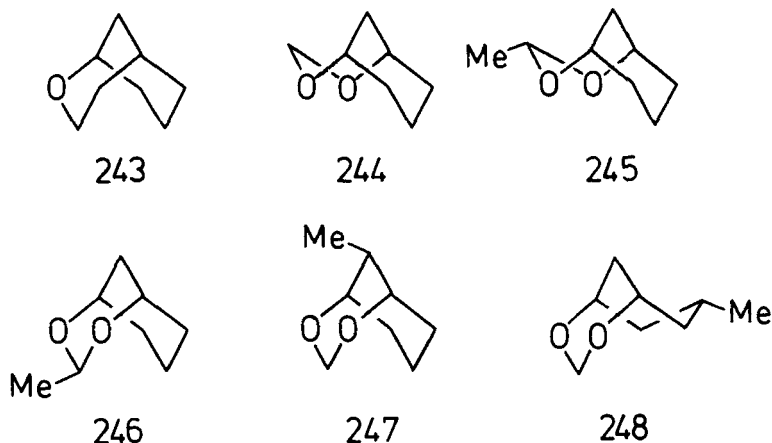
The introduction of heteroatoms at 2- and 4- and/or 6- and 8-positions can lead to steric effects due to the difference between C–C and C–heteroatom bond lengths and the resultant change in van der Waals interactions.

In the case of oxygen atoms at these positions the C–O bond is shorter than the corresponding C–C bond and 3...7 repulsion should be increased. In Table 2, the relative energies of CC, CB, BC, and TT conformations for compounds **243–248** calculated using the MM1 molecular mechanics method are given (22). Comparison of the data in Table 2 with those for substituted carbocyclic bicyclo[3.3.1]nonanes described in this chapter (*vide supra*) reveals that replacement of the 2- and 4-methylene groups in bicyclo[3.3.1]nonane by ether oxygen atoms strongly destabilizes the CC conformation as a result of increasing 3...7 repulsion. For 2-oxabicyclo[3.3.1]nonane **243** the CC and BC conformers are about equally populated while for 2,4-dioxo-compound **244** the CC conformation is 2 kcal mol⁻¹ less stable than the corresponding BC conformation. The introduction of methyl groups at various positions allows one to change the conformational behavior of 2,4-dioxabicyclo[3.3.1]nonanes (compounds **245–248**) (22).

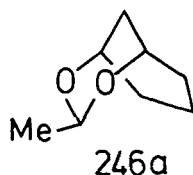
The calculational data are in general agreement with the experimental results. The conformation of 2,4-dioxabicyclo[3.3.1]nonane **244** was investigated with the use of ¹H-NMR spectroscopy and this compound was found to occur predominantly in the BC conformation (19). The preferred conformations of **243**, **245**, **247**, and **248** found using ¹H- and ¹³C-NMR techniques are also in agreement with the results of the calculations shown in Table 2 (189, 190). A study of compounds **245** and **246** with the help of proton chemical shifts, proton–proton geminal, vicinal, and long-range indirect coupling

Table 2
Relative Energies (in kcal mol⁻¹) of the CC, BC, CB, and
TT Conformations of Compounds **243–248** Calculated
Using the Molecular Mechanics (MM1) Method (22)

Compound	CC	BC	CB	TT
243	0	0.1	2.0	4.2
244	2.0	0	2.3	3.9
245	—	0	8.3	3.7
246	0	—	0.3	—
247	0	2.7	5.7	5.4
248	—	0.8	0	1.5



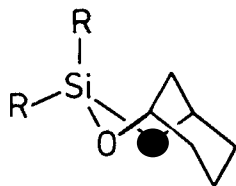
constants at 400 MHz as well as ^{13}C and ^{17}O chemical shifts leads to the conclusion that the *endo*-epimer is more stable than its *exo*-isomer. Compound **245** exists in a boat–chair conformation and it exhibits a rather strong 3...9 repulsion in the heterocyclic ring, which causes a torsion of the dihedral angle between the protons at carbon 9. The less stable *exo*-isomer **246** is in a chair–envelope conformation **246a**. No signs of separate minimum energy conformations were detected for **246**, even at low temperatures (190).



2,4-Dioxa-3-silabicyclo[3.3.1]nonanes **249** and **250** occur predominantly in the BC conformation as established by ^{13}C - and ^1H -NMR spectroscopy (189). For 2,4-dioxa-3-phospha compounds **251** and **252**, the BC conformation was also found in the solid state (from X-ray data) (191, 192) with a flattened boat–ring while diphospha compounds **253** and **254** exist in the chair–chair conformation (193).

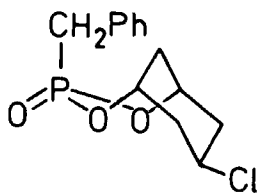
An interesting result was obtained for compound **255** bearing an *endo*-7 hydroxy group. In the solid state, it adopts an envelope–flattened chair conformation (from X-ray data) (194).

In bis compounds **256**, **256⁺**, and **257** (9-borabicyclononane, BBN), the bicyclo[3.3.1]nonane system adopts a chair–chair conformation according to X-ray studies (195, 196). The CC conformation was also found for some other BBN derivatives (197–199).

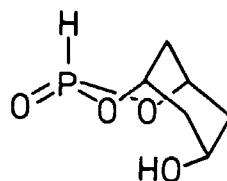


249 R = Me

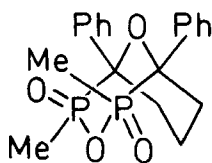
250 R = Ph



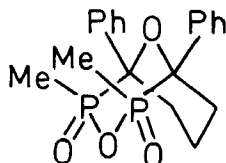
251



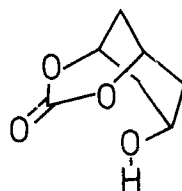
252



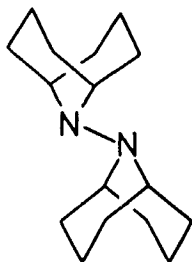
253



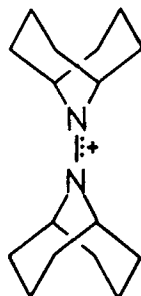
254



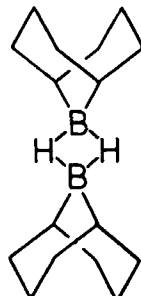
255



256



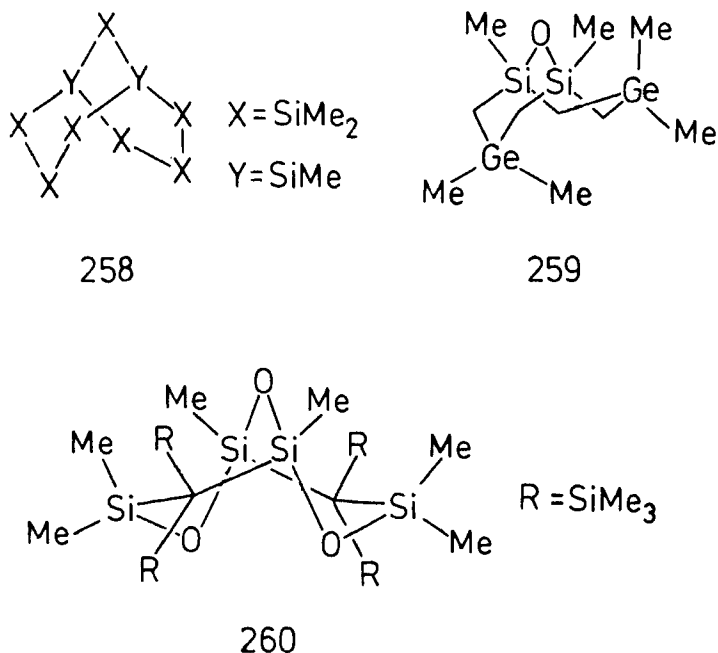
256*



257

Single-crystal X-ray diffraction data for a number of sila compounds have been reported in the literature. Nonasila compound **258** containing 16 methyl groups adopts a chair-envelope conformation (200), while compound **259** exists in a chair-boat conformation (201). In **258**, two steric factors principally determine the conformation: the flagpole-flagpole repulsion of methyl groups in a CB conformation and the 3...7 repulsion of *endo*-methyl groups in a CC conformation. As a result, both the CC and the CB conformations are destabilized. In compound **259**, the flagpole-flagpole repulsion is absent from

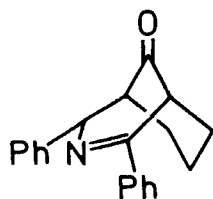
the CB conformation and this conformation becomes preferable owing to the destabilization of the alternative CC conformation by the *endo*-3....*endo*-7 repulsion of methyl groups. Compound **260** represents an interesting example



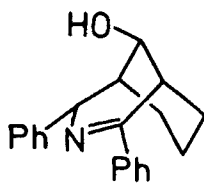
of destabilization of both CC and CB conformations due to the presence of *gem*-dimethyl groups at the 3- and 7-positions and to bulky substituents at the 4- and 8-positions. In addition, some factors disfavoring the TT conformation have been removed owing to the presence of oxygen atoms in the skeleton. As a result, **260** adopts the rare TT conformation in the solid state (202).

The introduction of a double bond at the 2-position of the heterobicyclo[3.3.1]nonane system leads to the chair-envelope conformation. Since the envelope part is rather twisted, as in the case of the corresponding carbocyclic analogs, it can be close in shape to the half-chair form. Conformations of this kind were found for compounds **261** (203), **262** (204), **263** (205), and **264** (206) (from X-ray data).

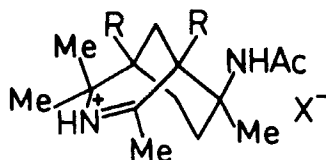
The carbocyclic six-membered rings in molecules of compound **265** adopt an envelope conformation (the ring having three sp^2 atoms), while the heterocyclic ring exists in a somewhat twisted chair conformation (the ring having amide fragment) which is significantly flattened (from X-ray data) (207). Compounds **266** (from X-ray data) (208) and **267** (from $^1\text{H-NMR}$ data) (209) exist in the distorted envelope-chair conformation despite the presence of an



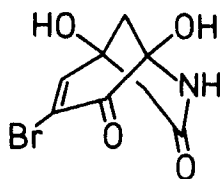
261



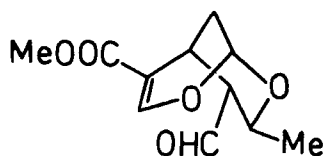
262

263 R = H, X = ClO₄

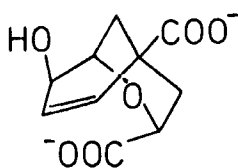
264 R = Me, X = Br



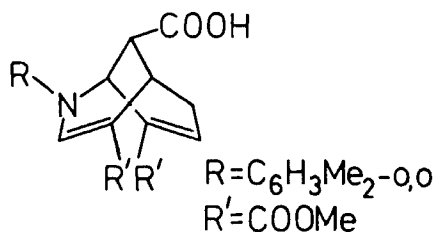
265



266



267



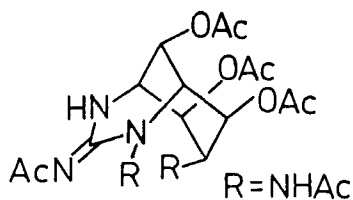
268

R = C₆H₃Me_{2-0,0}
R' = COOMe

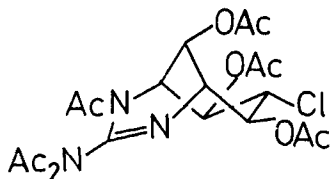
endo-3 substituent in the latter, while **268**, having two double bonds, adopts the twisted double envelope conformation in the solid state (from X-ray data) (210).

Interestingly, for compounds **269** and **270** (211), the envelope-chair and envelope-boat conformations were found, respectively, in the solid state though both compounds contain *exo*-6 and *exo*-7 acetoxy groups as well as an *endo*-7 substituents.

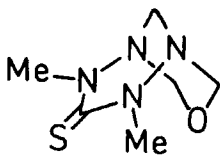
Compounds **271** (212) and **272** (213) were found to exist in the solid state in a conformation close to the envelope-chair form. Hexaaza compound **273** adopts the chair-boat conformation (214) and diimide **274** (215) exists in the envelope-envelope form according to the X-ray data. Interesting results were



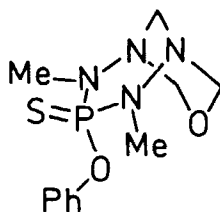
269



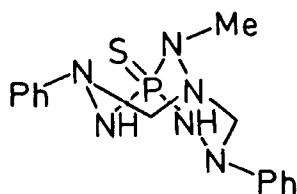
270



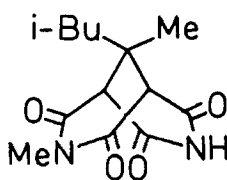
271



272



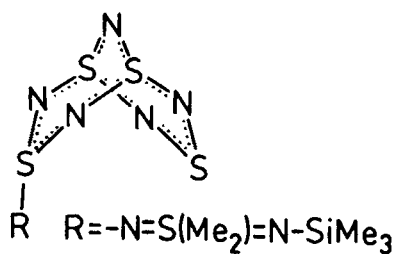
273



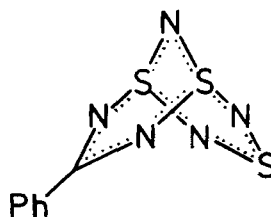
274

obtained for compounds having a S_4N_5 skeleton. Compound **275** adopts a very flattened chair–chair conformation with a $S3 \cdots S7$ distance of 3.8 Å (216) in the solid state. In earlier studies it was shown that the cations $[S_4N_5]^+$ adopt the envelope–envelope conformation with a $S3 \cdots S7$ distance of 4.0 Å (217) while the anions $[S_4N_5]^-$ exist in the chair–chair form with a very short $S3 \cdots S7$ distance, 2.6–2.7 Å (218, 219). Compound **276** was found to adopt the envelope–envelope conformation (220).

Envelope–envelope conformation (in some cases a little twisted) have been found for compounds with P_4N_5 (221, 222), $C_3P_2N_4$ (223), $C_2P_2N_4O$ (224), $C_2B_2O_5$ (225), and $C_2B_2N_2O_3$ (226) bicyclo[3.3.1]nonane skeletons bearing various substituents (from single-crystal X-ray diffraction data).



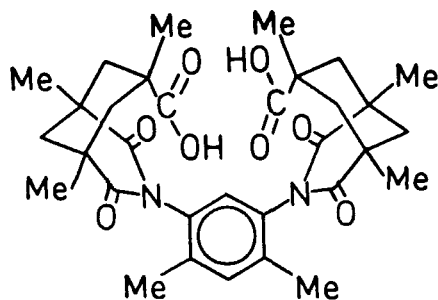
275



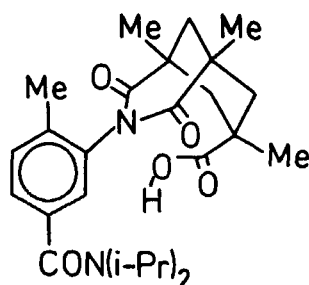
276

A series of *Z*-isomers of bridgehead olefins—9-oxa-, 9-thia-, 9-azabicyclo[3.3.1]non-1-enes—was studied using IR, UV, and ^1H -NMR spectral data (227–229). In the case of 9-thiabicyclo[3.3.1]non-1-ene 9,9-dioxide, the formation of the less stable *E*-isomer was confirmed by the X-ray data for its Diels–Alder adduct (230). For *Z*- and *E*-isomers, the CB and CC conformations, respectively, were believed to be preferred.

In recent years, a number of complexation agents have been developed that incorporate the bicyclo[3.3.1]nonane skeleton. In a series of publications, selective model receptors consisting of two substituted 3-azabicyclo[3.3.1]nonane fragments interconnected with various aromatic bridges were described (231–242 and references therein). The X-ray study of one of them (compound 277) revealed a chair–envelope conformation for the bicyclo[3.3.1]nonane fragments (231); a similar conformation was found in the monomeric compound 278 (231) and in the salts of compounds analogous to 277 (237, 238).



277



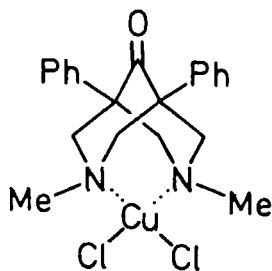
278

A number of complexes were obtained with the 3,7-diazabicyclo[3.3.1]nonane derivatives. Single-crystal X-ray diffraction data were reported for

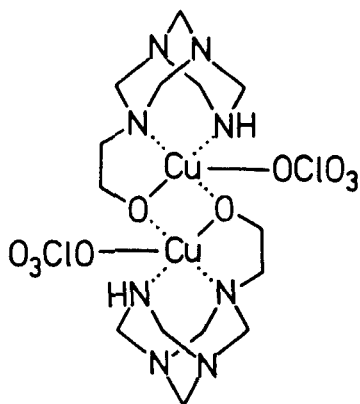
copper(II) complex **279** (243), for complex **280** and for three of its analogs (244), and nickel(II) complex **281** (245). It is necessary to mention that during the formation of complex **279**, the ligand changes its conformation from a chair-boat form (**166**) into the nearly ideal chair-chair conformation.

In the nickel(II) and cobalt(II) complexes of phosphabicyclo[3.3.1]nonanes **282** (246) and **283** (247), respectively, the bicyclo systems exist in a CC conformation according to X-ray data. Some complex compounds incorporating the bicyclo[3.3.1]nonadienes as ligands have been studied; for example, X-ray data were reported for the platinum(II) complex **284** (248).

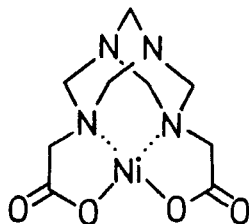
The synthesis of optically active crown ethers incorporating a bicyclo[3.3.1]nonane fragment has been reported recently (compound **285**) (249).



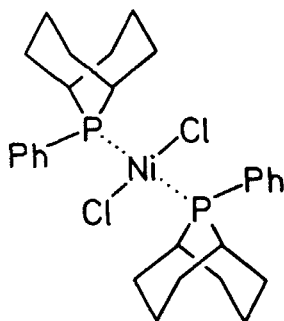
279



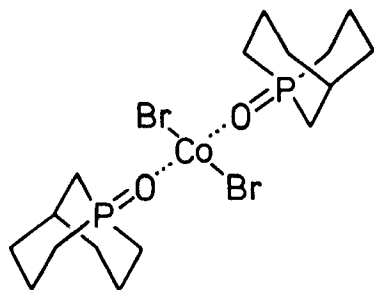
280



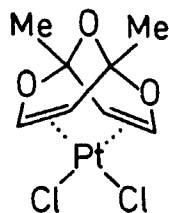
281



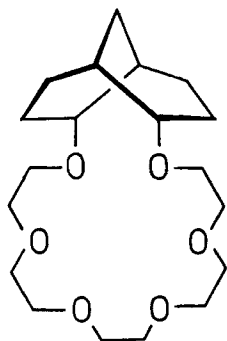
282



283



284



285



286

The heterobicyclo[3.3.1]nonane skeleton is imbedded in a great many naturally occurring compounds such as sparteine **286** and the isosparteines (for a review, see reference 9). For many of these, the conformational behavior has been studied using ^{13}C -NMR spectroscopy, single-crystal X-ray diffraction, as well as other methods. However, their consideration is beyond the scope of the present chapter.

V. CONCLUSION

The data considered here demonstrate that, despite occasionally unusual conformational behavior, the preferred conformation of the bicyclo[3.3.1]nonane system can be predicted following the analysis of intramolecular interactions and a comparison with the conformational behavior of molecules already described. In many cases, the preferred

conformation can be predicted by molecular mechanics methods. Such predictions are rather reliable if the conformational behavior is determined principally by steric factors. However, for compounds containing heteroatoms in the skeleton and skeletal functional groups, it should be taken into account that for some of them the conformational behavior can strongly depend not only on intramolecular interactions but also on the polarity and the nature of the solvent (e.g., see references 111 and 112). Moreover, the conformation in the solid state can differ from that preferred in solution.

A knowledge of the regularities in the conformational behavior of the comparatively simple bicyclic systems discussed in this chapter allows one to consider the factors that may be responsible for the conformational preferences of more complex polycyclic molecules including a great variety of biologically active naturally occurring compounds such as alkaloids and antibiotics (9–15). Medicinal agents incorporating the bicyclo[3.3.1]nonane system as a structural component have been extensively developed in recent years. A knowledge of the conformational regularities in this system can be important in understanding the mechanism of their action.

Moreover, these conformational regularities are important in the study of reaction mechanisms, including intramolecular migrations, rearrangements, and solvolyses of bicyclo[3.3.1]nonane systems (e.g., see references 60, 250, and 251).

The conformational analysis of bicyclo[3.3.1]nonanes continues to develop. Despite the publication of a great many experimental and calculational results, as evidenced in this chapter, at present, the conformational behavior of many comparatively simple structures has not yet been investigated.

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Strained Olefins: Structure and Reactivity of Nonplanar Carbon–Carbon Double Bonds*

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*This chapter is dedicated to Professor V. Prelog

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I. INTRODUCTION

The development of organic stereochemistry rests on the fundamental recognition by van't Hoff and Le Bel that a tetrasubstituted carbon atom prefers tetrahedral coordination (1). This hypothesis has led to the systematic development of the chemistry and stereoisomerism of carbon compounds.

The strong preference for tetracoordinated carbon atoms to arrange its four ligands into a tetrahedral array seemingly found its limitation in small rings. In order to incorporate the structure of small rings into the framework of van't Hoff's hypothesis, von Baeyer postulated that deformations from regular tetrahedral bond angles lead to an increase in energy, which was discussed in terms of strain and used for evaluating reactivity (2). With a regular tetrahedron as structural element, he evaluated the geometrical deformations to be expected for *trans*-cyclohexene and concluded that its strain must be exceptionally "strong." He therefore considered it as unlikely that cyclohexene could be transformed into the *trans* isomer (2b). Using mechanical models, Bredt later analyzed the extent of deformations in bicyclic bridgehead olefins and surmised that in camphane, pinane, and similar bicyclic structures a regular double bond cannot be located at bridgehead (3).

It was thus early recognized that structural deformations of double bonds are related to instability and enhanced reactivity. It is this relationship that induced extensive studies of strained carbon compounds and distorted olefins. Moreover, it is evident that even today, the inherent chemical information potential of strained olefins has only been partially explored (4-6).

Quantum-chemical concepts were used at an early stage for describing the carbon-carbon bonds. The sigma/pi dichotomy introduced by Hückel was and still is highly successful for interpretation and rationalization of structure and reactivity of double bonds (7). Although distortions can be incorporated into this bonding model, more elaborate quantum-chemical methods are preferable for detailed analyses of highly distorted and twisted double bonds (8). Molecular mechanics calculations, which provide structure-energy relationships of unstrained and strained carbon compounds, complement efficiently the quantum-chemical analyses (9).

In this chapter, structural and chemical features of nonconjugated, nonpolar carbon-carbon double bonds are surveyed. Starting with a systema-

tic analysis of the deformation space available to ethylene, the chemistry of the various classes of olefins with distorted double bonds is outlined. The wealth of experimental and computational results dealing with alkenes contributes to a better understanding of the nature of the olefinic double bond (10).

II. GEOMETRY AND STRUCTURE

A. Normal Coordinates of Ethylene

An unstrained olefinic double bond in the ground state is described by six atoms lying in a plane with bond angles near 120° and bond lengths of about 134.0 pm. Two classes of deformations can be distinguished: in nonplanar or out-of-plane (oop) distortions, substituents move perpendicular to the molecular plane, whereas planarity is maintained with the planar or in-plane (ip) distortions of substituents. For a systematic approach, these static distortions can be derived from the normal vibrations of ethylene.

The total deformation space of ethylene and hence of any olefin can be described in a systematic manner by group theory. This approach has competently been elaborated by Ermer (11). From the irreducible representation of ethylene (I) with its D_{2h} symmetry, twelve normal coordinates are obtained, three of which are related to out-of-plane and nine to the in-plane

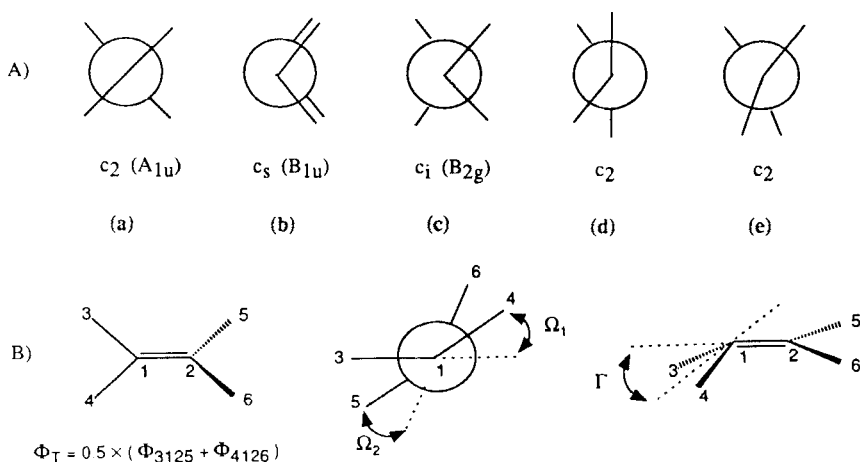
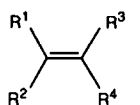
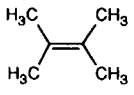
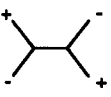
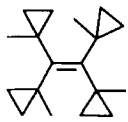
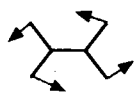
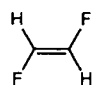
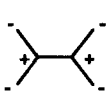
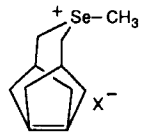
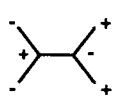
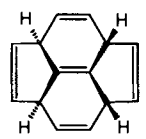
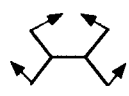
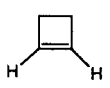
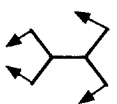
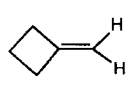


Figure 1. (A) Nonplanar double bond deformations and possible combinations. Specification of symmetry element and class. (a) twisting, (b) symmetric out-of-plane bending, (c) antisymmetric out-of-plane bending, (d) combination of twisting and symmetric oop bending, (e) combination of twisting and antisymmetric oop bending (11). (B) Definition of the torsion angle Φ_T and the two possibilities to measure the oop bending (see text).

Table 1
Bond Angle Deformations in Ethylene (1) and Examples of Molecules
with Main Distortion in One Symmetry Class (20)

	Symmetry class	Example	Formulae- No.	Ref.
	D_{2h}	 $R^1=R^2=R^3=R^4=H$	1	12
	A_{1g}		2 ^a	13
	A_{1g}	 H_3C	3	14
	A_{1u}		4	15
	B_{1g}	 H	5 ^b	16
	B_{1u}	 $Se-CH_3$ X^-	6	17
	B_{2g}		7 ^c	11
	B_{2u}		8	18
	B_{3u}		9	19

^a *Ab initio* result (13).

^b MNDO calculation (16).

^c Not yet prepared.

distortions. For ethylene (1) the conventional assignment of the eight symmetry classes to the appropriate vibrations, which involve bond angle distortions, are given in Table 1. These symmetry classes are used to describe the static deformations of distorted olefins.

As our primary interest is in bond angle distortions, we consider only the six in-plane bond angles and in particular the three out-of-plane (oop) deformations. The oop deformations are represented by the symmetry classes A_{1u} , B_{1u} , and B_{2g} (20). The A_{1u} -type distortion or twist is due to the torsion of the CH_2 groups against each other. The amount of twist is normally given by the angle Φ_T , which is the mean value of the dihedral angles Φ_{3125} and Φ_{4126} (11) (Figure 1). In several cases the twist was defined as the dihedral angle Θ_T between the two least-squares planes through the atoms 1-2-3-4 and 1-2-5-6. In the case of ethylene (1) ($\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$) the angle between the p orbitals of the double bond coincides with the twist angle $\Phi_T = 0$.

The B_{1u} -type distortion represents symmetrical, whereas B_{2g} represents antisymmetrical out-of-plane bending. To characterize these deformations (in a local perspective also called pyramidalization), Ermer used the out-of-plane bending parameters Ω_1 and Ω_2 , which are the dihedral angles between the planes through the atoms 2-1-3 and 2-1-4 (in the case of Ω_1) and 1-2-5 and 1-2-6 (in the case of Ω_2) (11, 21) (Figure 1B). The extent of this distortion can also be defined through the angle Γ , which measures at each center the difference between the $\text{C}(\text{sp}^2)\text{--}\text{C}(\text{sp}^2)$ vector and the plane through $\text{C}(\text{sp}^3)\text{--}\text{C}(\text{sp}^2)\text{--}\text{C}(\text{sp}^3)$ (atoms 1-3-4 in Figure 1). Typical examples of olefins in which the double bond is distorted with respect to one specific out-of-plane or in-plane bond angle distortion are given in Table 1.

In general, bond angle deformations of most nonplanar double bonds can be analyzed in terms of the three oop distortions, given by the symmetry classes A_{1u} , B_{1u} , and B_{2g} . Examples of molecules containing fragments with twist (A_{1u}) are given in Table 2 and structures with distorted double bonds, where all three oop bond angle deformations have to be taken into account, are shown in Table 3. For double bonds with one or three different substituents or different geometrical constraints on both sides of the doubly bonded carbon atoms, pyramidalization and twist lead to a structure in which the angle of the two sp^x hybrid orbitals of the partial double bond is only approximately given by the angle Ω .

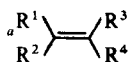
B. Structures

1. X-ray, Electron Diffraction, and Microwave Results

a. Twist (A_{1u}) as Main Distortion. Torsionally distorted double bonds are apparent in olefins with several sterically demanding substituents and in *trans*-

Table 2
Lengths of Double Bonds and Twist Angles Φ_T in Substituted Olefins

Formulae No.	Substituents ^a				C=C [pm]	Twist- angle Φ_T [°]	Ref.
	R ¹	R ²	R ³	R ⁴			
1	H	H	H	H	133.5	0.0	12
3	CH ₃	CH ₃	CH ₃	CH ₃	135.3	0.0	14
4	Mcp ^b	Mcp	Mcp	Mcp	135.3	19.7	15
10	Ip ^c	Ip	Ip	Ip	134.7	0.0	22
11	Ph ^d	Ph	Ph	Ph	135.6	8.5	23a
12	CH ₃	H	H	H	133.6	0.0	24
13	CH ₃	CH ₃	H	H	134.2	0.0	14,25
14	Tl ^e	Tl	H	H	133.8	0.9	26
15	CH ₃	H	H	CH ₃	134.7	0.0	27
16	Ph ^d	H	H	Ph	133.8	0.0	28a
17	CH ₃	H	CH ₃	H	134.6	-	27
18	Ph ^d	H	Ph	H	133.4	0.0	28b
19 ^f					135.3	16.0	29
20 ^g					136.0	24.0 ^g	30



^bMcp, 1-methyl-cyclopropyl.

^cIp, isopropyl.

^dPh, phenyl.

^eTl, *p*-tolyl.

^fSee page 239.

^gTwist angle Θ_T .

cyclooctene. A few selected examples are given in Table 2. With the exception of 1,1-di-*p*-tolylethene (**14**), all mono-, di-, and trisubstituted olefins are locally planar around the double bond. In such molecules deviations from standard geometry occur exclusively in the molecular plane and affect bond angles as well as bond lengths.

In some tetrasubstituted olefins with bulky substituents—also called overcrowded olefins—twist has been found with C₆H₅- and 1-methyl-cyclopropyl as substituents (cf. Table 2). Other examples are given by **19** and

Table 3
Amount of Twist, Bend, and Length of Double Bonds in Some Selected Olefins

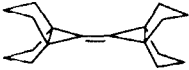
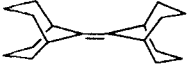
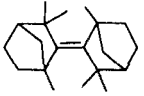
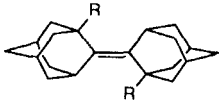
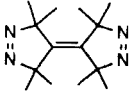
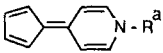
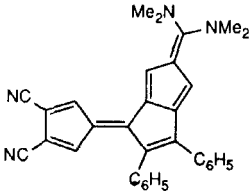
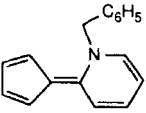
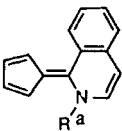
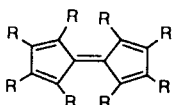
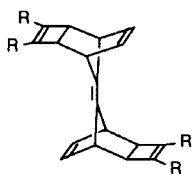
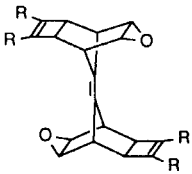
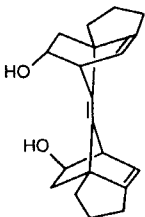
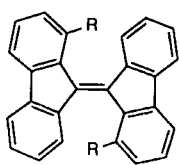
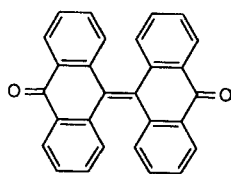
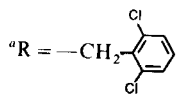
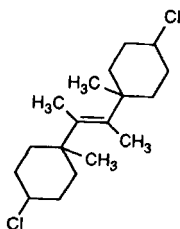
	Formulae No.	Twist Φ_T [°]	Bent Γ [°]	C=C [pm]	Ref.
	21	0.0	-	130.7	31
	22	0.0	-	132.4	32
	23	11.8	-	134.9	33
	24a R = H b R = C ₂ H ₅ c R = CH ₃	0.0 12.3	0.5 8.9	133.6 135.8	34a 34b
	25	0.0	-	135.6	35
	26	2.6 ^b	0.8	138.8	36
	27	14.6 ^b	-	139.8	37
	28	18.6 ^b	4.5	141.0	36
	29	31.2 ^b	1.9	141.2	36

Table 3 (Continued)

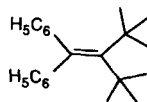
	30a R = Cl	34.5 ^b	4.0	136.5	38
	30b R = Br	37.1 ^b	3.0	138.5	38, 39
	31 R = COOCH ₃	5.4	-	131.3	40
	32 R = COOCH ₃	5.4	-	131.4	40
	33	8.3	-	130.2	41
	Formulae No.	Twist Φ_T [°]	Bent Γ [°]	C=C [pm]	Ref.
	34a R=H	- 33.0	10.0 -	133.0 138.0	42a,b 43b
	34b R=COO-CH(CH ₃) ₂	40.0 38.0	- -	139.0 139.0	36,43a 43b
	35	40.0	-	131.0	44



^bTwist angle Θ_T .



19



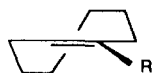
20

20 where the torsional angles are $\Phi_T = 16^\circ$ and $\Theta_T = 24^\circ$, respectively. Comparison of bond lengths with the size of the torsional angle suggests that increasing twist Φ_T is related to increasing bond lengths (cf. Table 2).

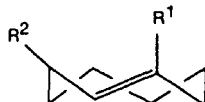
Significant torsional angles are also found in the olefins **23**, **24b**, and **26–30b** (Table 3). In these structures ring substituents in the α -position to the double bond interfere with each other. If large substituents are absent, as in **21**, **22**, and **24a**, no torsion is observable. In the highly crowded bispyrazolinyldiene **25**, steric repulsion is exclusively released by in-plane opening of the bond angle. Large torsional angles are observed in the derivatives of fulvalene **26–29**.

Concomitant with the increase of the torsional deformation from **26** to **29**, the C–C bond distances increase from 138.8 to 141.2 pm. Repulsive interactions between the chlorine and bromine substituents in **30a** and **30b**, respectively, give rise to torsional angles Θ_T of 34.5° and 37.1° , respectively, the out-of-plane bending being small in both molecules ($\Gamma = 4^\circ$ and 3° , respectively). In **31** and **32**, twist at the 7, 7' double bond, albeit rather small, might be due to long-range interactions between the substituted cyclobutene ring and the opposite ethylidene bridge, whereas in **33**, the *exo*-hydroxy group might interfere with the opposite hydroxy group. Structure elucidation of the bifluorenylidenes **34a** and **34b** revealed significant torsion in **34b**, whereas it is smaller in the unsubstituted **34a**. In **35** interactions of the protons in the 1, 1' and 8, 8' positions of opposite aromatic rings lead to a torsional angle of 40° .

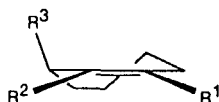
The deformation of the double bond in medium-sized *trans*-cycloalkenes like **37a**, **39a**, and **41** is due to twist and some pyramidalization. An early electron diffraction study suggests that the structure of *trans*-cyclooctene (**37a**) is best described by a distorted chair conformation (45). Later, it was concluded that *trans*-cyclooctene (**37a**) assumes a twist or crown conformation with a twist angle Φ_T of 20° and an oop bending angle Ω of 23° (46). X-ray as well as a neutron diffraction study of **37b** gave bond angles and lengths for the carbon skeleton and the total structure, respectively, which are in good agreement with the twist conformation (21).



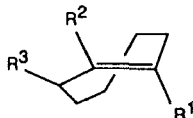
- 36a $R=H$
 b $R=CH_3$
 c $R=C_6H_5$



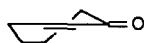
- 37a $R^1=R^2=H$
 b $R^1=H$, $R^2=3',5'$ -dinitrobenzoyloxy
 c $R^1=CH_3$, $R^2=H$
 d $R^1=C_6H_5$, $R^2=H$



- 38a $R^1=R^2=R^3=H$
 b $R^1=C_6H_5$, $R^2=R^3=H$
 c $R^1=R^2=tert.-C_4H_9$, $R^3=H$
 d $R^1=R^2=H$, $R^3=OCH_3$



- 39a $R^1=R^2=R^3=H$
 b $R^1=C_6H_5$, $R^2=R^3=H$
 c $R^1=R^2=tert.-C_4H_9$, $R^3=H$
 d $R^1=R^2=H$, $R^3=OCH_3$



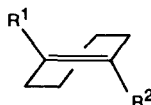
40



41



- 42a $R=H$
 b $R=C_6H_5$
 c $R=CH_3$

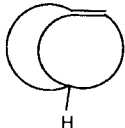
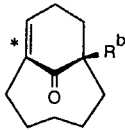
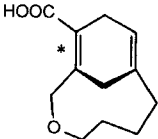
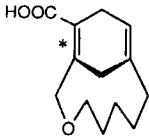
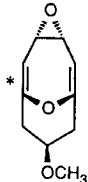


- 43a $R^1=R^2=H$
 b $R^1=C_6H_5$, $R^2=H$
 c $R^1=C_6H_5$, $R^2=CH_3$

Due to its thermal instability, the ring structure of *trans*-cycloheptene (39a) has only been characterized in *trans*-2-cycloheptenone (41) by its IR spectrum and by trapping experiments (47). To date, no direct structural evidence has been found for *trans*-cyclohexene (43a). It seems likely, however, that *trans*-1-phenylcyclohexene (43b) is the species detected by pulsed time-resolved photoacoustic calorimetry (cf. Section III. B) (48).

Twist as well as pyramidalization are the typical deformations of bridgehead double bonds in bicyclic compounds of type 44 (Table 4). Structures of the type 44 comprise Bredt-olefins (formerly called anti-Bredt-olefins) and bridgehead olefins. In Bredt-olefins, the double bond is located at the bridgehead of a bicyclo[m.n.o]alkane skeleton with $m, n, o \geq 1$, whereas

Table 4
Twist, Bend, and Length of the Olefinic Double Bond in Bicyclic Systems
of Type **44**

	Formulae No.	Twist ΦT [°]	Bent ^a [°]	C=C [pm]	Ref.
	44				
	45	22 ^c	10	129.0	49, 50
	46	10	6.1/1.4		51
	47	3.1	1.6/1.7		51
	48	11.6	20.1/7.9	131.1	52

^aPyramidalization angles Ω_1 and Ω_2 ; the first value is the bend angle at the bridgehead carbon atom of the marked (*) double bond.

^bR = *p*-Cl-C₆H₄-NHCO-.

^cThe average deviation from planarity of the double bond (32°) is combined by about 22° twist and 10° bend (50).

bridgehead olefins comprise Bredt-olefins and those with a bicyclic skeleton for which $m, n \geq 1$ and $o = 0$.

The size of the torsional angle in the Bredt-olefins **45–48** increases with decreasing ring size and by substitution of a CH₂ group with an oxygen atom. This may be due to the observation that the average C–O–C bond

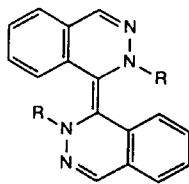
angle in unstrained ethers is smaller and the C–O bond length shorter than the corresponding values in R–CH₂–R fragments. In **48** the deformation of the bridgehead double bond is due to twist ($\Phi_T = 11.6^\circ$) and a symmetrical oop bending of 20.1° (Ω_1) and 7.9° (Ω_2) at the two double bond atoms (52).

b. Symmetrical Out-of-Plane Bending (B_{1u}). Dominant if not exclusive symmetrical out-of-plane bending of the double bond is found in the polycyclic compounds **49–56** (Table 5). It was argued that the origin of the oop bending in the *anti*-sesquinorbornene derivative **49** is due to the molecular frame as such. The constraints of the carbon skeleton of norbornene lead to C(*sp*³)–C(*sp*²)–C(*sp*²) bond angles that are significantly smaller than those at a *cis*-disubstituted double bond. Fusion with a second norbornene unit would consequently give rise to large extra-ring bond angles (54). The corresponding strain is partially released by out-of-plane bending. Whether the symmetrical oop bending in the *syn*-sesquinorbornenes **51–54** is exclusively caused by steric repulsion between the methylene bridges is a matter of conjecture. Due to the geometrical constraints imposed by the cyclohexane rings in **55** and **56**, the large pyramidalization at the bridgeheads appears reasonable.

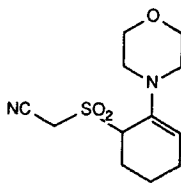
A further example of this type of deformation is given by the tetracyclic compound **6** (Table 1). The pyramidalization Γ at the bridgehead syn to the methyl group is larger (20.3°) than that at the other carbon atom (12.3°) (17).

It was mentioned earlier that the overall distortion of a C=C double bond is in most cases a combination of more than one type of deformation. Comparison of **24a** with **24b** (Table 3) reveals that introduction of an ethyl group in both adamantylidene moieties leads to twist as well as symmetrical oop bending. Also, the contribution of oop bending to the overall deformation of the double bond in the *trans*-cyclooctene derivative **37b** should be mentioned here.

c. Antisymmetrical Out-of-Plane Bending (B_{2g}). B_{2g} -type deformation has been discussed for the structure of **7** (Table 1), which hitherto has not been prepared. The antisymmetrical out-of-plane bending reported for the C=C double bond of the bifluorenylidene **34a** has more recently been rejected (42b,

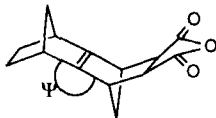
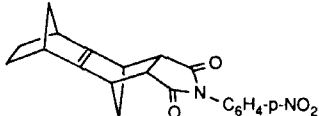
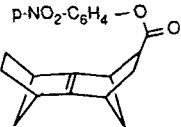
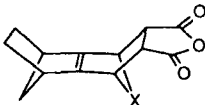
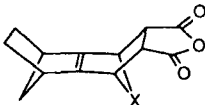
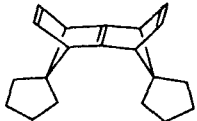
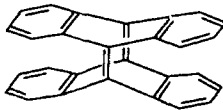
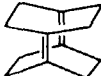


57 R = C₆H₄-p-Br



58

Table 5
Symmetrical oop Bending in Some Polycyclic Olefins

	Formulae No.	Bent ^a [°]	Ψ^b [°]	C=C [pm]	Ref.
	49	2.1	143.8	132.6	53
	50	13.2	142.3	134.0	54
	51	15.9	138.2		54
	52a X=CH ₂	16.4	140.1	133.2	53
	52b X=O	16.8	142.1	133.5	55
	53	18.0	139.8	133.0	53
	54	22.7 32.4 ^c		—	56
	55	19.7 ^c		135.0	57a
	56	27.3 ^c		135.4	57b
	6	20.3/12.3 ^c		—	17

^aMean value of Ω_1 and Ω_2 .

^bAngle between C(sp³)-C(sp²)-C(sp³).

^cPyramidalization angle given by Γ .

43b). At present, **57** is the only bona fide compound that contains a C=C double bond with an antisymmetrical oop bending deformation (58). The steric interactions are minimized by the combination of a pyramidalization of 8.9° and a slight puckering of the phenyl rings. It might be argued that the oop deformation is not caused by nonbonded interaction of the opposite *p*-bromophenyl rings but by the adjacent nitrogen atoms, because pyramidalization has also been observed at the central carbon atom of several enamines (59, 60). Although this oop bending is small, it is consistently in the opposite direction to that of the nitrogen atom. A corresponding oop bending of a few degrees at the terminal carbon atom of enamines like **58**, which all carry a hydrogen atom at this carbon atom, cannot be excluded (60).

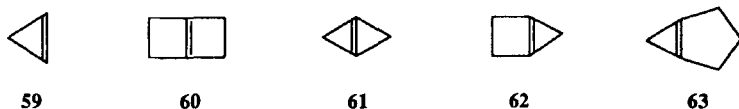
2. Results from Force Field and Quantum-Chemical Calculations

Computational methodology has been used to accompany or to anticipate experimental results for many classes of compounds. Such results are particularly helpful for transient species, for rationalization of physical and structural properties, and for simulation of reaction pathways and transition states. Semiempirical valence electron (CNDO/MNDO), *ab initio*, and nonquantum mechanical force field (molecular mechanics) calculations have mainly been used for the examination of structure and stability of moderately strained olefins, whereas many-electron quantum-chemical methods have been used for detailed discussion of electronic aspects. Excellent reviews of molecular mechanics calculations, the principal method used to describe geometrical and energy features in distorted double bond systems, have been written by Ōsawa and Musso (61).

The consistent force field (CFF) method developed by Ermer and Lifson (62, 63) and the molecular mechanics method described by Allinger (MM1 and MM2) (64) have been used widely for computational investigations of strained hydrocarbons. Other force fields have been developed and their merits have been critically evaluated (65, 66).

a. In-Plane Deformations. The geometries of cyclobutene (**8**) and of cyclopropene (**59**) have been studied by *ab initio* methodology (4-31G) (67, 68). In both cases calculated bond lengths as well as bond angles are in good agreement with those determined by electron diffraction (Table 6) (18a, 69).

In both structures no out-of-plane distortion has been found. Although bicyclo[2.2.0]hex-1(4)-ene (**60**) is calculated as being planar, its oop bending force constant is very weak (68, 70). In contrast, bicyclo[1.1.0]but-1(3)-ene (**61**) and similar compounds (such as **62** and **63**) have been calculated as being bent (67, 68, 70). Model (*ab initio*) calculations have been performed for distorted ethylenes to elucidate the origin of the oop bending in these olefins (70, 71). The



analysis of relevant MOs reveals why the transformation from a planar structure with small bond angles to a pyramidalized structure has a stabilizing effect (Figure 2) (70).

In ethylene with bond angles $\text{H}-\text{C}=\text{C} > 100^\circ$ the overlap between the four hydrogen orbitals and the appropriate carbon orbitals as well as that between the carbon orbitals forming the π -bond favor a planar structure ($\text{I}_{\text{A,B}}$) (Figure 2). As the angle $\text{H}-\text{C}=\text{C}$ is decreased, the $\text{H}-\text{C}$ overlap diminishes in the planar form ($\text{II}_{\text{A,B}}$). Upon pyramidalization at each carbon center, the II_{A} MO mixes with the originally pure π -MO (II_{B}). The consequence of this mixing is the generation of a new set of MOs ($\text{III}_{\text{A,B}}$), one of which (III_{A}) has much better $\text{C}-\text{H}$ bonding. The other MO (III_{B}) of this combination is only marginally destabilized in comparison with I_{B} or II_{B} . The result is a substantial lowering in energy on going from planar to nonplanar forms when $\text{H}-\text{C}=\text{C} < 100^\circ$.

b. Out-of-Plane Deformations. Numerous calculations have been performed for torsionally distorted double bonds in olefins with bulky substituents, in *trans*-cycloalkenes, and in bridgehead olefins. Model studies with distorted ethylenes clearly indicate that the strain (cf. Section V) imposed by torsion can be reduced by allowing some pyramidalization at each carbon center (Figure 3) (72, 73).

If ethylene (I) is twisted by 10° energy minimization leads to structure II, with an energy 7.1 kcal/mol above that of I. Upon distortion of one pair of synplanar (or synperiplanar) hydrogens out of the original plane each by 10° and optimization of all other parameters, the relaxed structure III, with a

Table 6
Calculated (68) and Experimental (18a, 69) Length of the
Double bond and $\text{C}=\text{C}-\text{H}$ Bond Angle in Cyclobutene
(8) and Cyclopropene (59)

Alkene	8		59	
	calc.	exp.	calc.	exp.
$\text{C}=\text{C}$ [pm]	132.6	134.2	128.2	128.6-130.0
$\text{C}=\text{C}-\text{H}$ [$^\circ$]	133.5	133.5	150.2	149.5-152.0

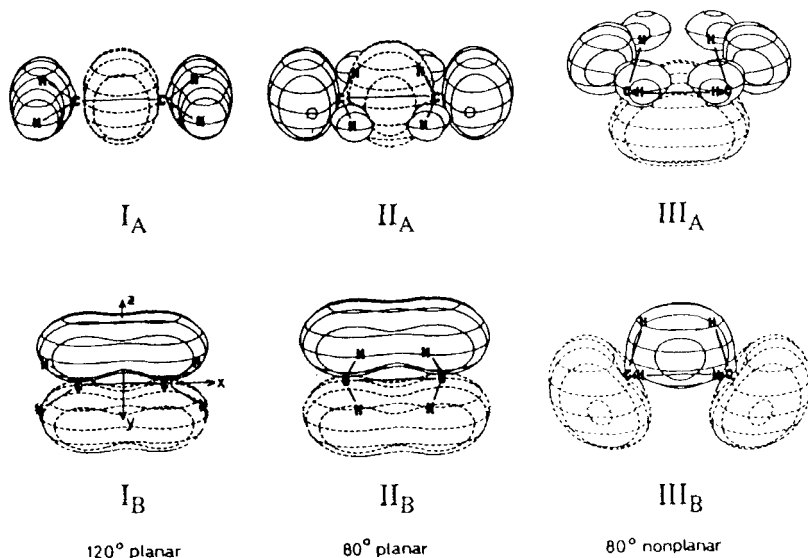


Figure 2. Three-dimensional molecular orbital drawings of normal and distorted ethylene (I). Adapted from ref. 70 with permission of the American Chemical Society.

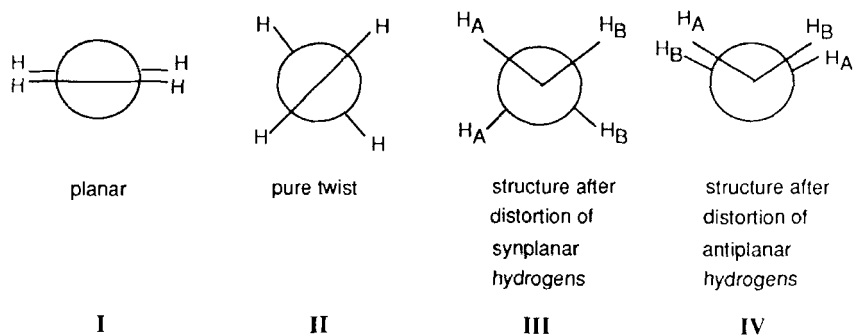


Figure 3. Twist, cis, and trans distortion of ethylene (I).

strain energy relative to I of only 2.5 kcal/mol, is obtained. Structure IV was obtained by distortion of one pair of antiplanar (antiperiplanar) hydrogens out of the plane of ethylene each by 10° and full optimization of all other parameters. In structure IV, where H_B 's have "followed" the distortions of H_A 's the energy is only 3.0 kcal/mol above that of I. In several theoretical investigations, the electronic states of ethylenes with torsion up to 90° and

inclusion of appropriate pyramidalization have been discussed (74, 75) (see Section IV.E).

Crowded Olefins. Force field calculations have mainly been used for exploring structural details of olefins with bulky substituents. The parameters of the CFF, SFF, MM1, and MM2 force fields have been adjusted to reproduce the geometry of several crowded olefins with errors in bond angles less than 2.0° and in lengths of the double bond less than 0.1 pm (62, 64, 66).

According to several computational studies, the distortion in the elusive tetra-*tert*-butylethene (**64**) is exclusively due to twist, with out-of-plane deformations being absent.

Using the CFF method, a torsional angle of 75° has been found, which upon improvement of the torsional potential by Ermer decreased to 43.3° (11). The latter value is very similar to the MM1 and MM2 results, which gave 45.2 – 44° (76, 77). Nevertheless, the parameterization of force fields for highly distorted olefins such as **64**–**66** would become more reliable if the elusive olefin **64** could be prepared and its structure elucidated.

For *E*-dimethyl-di-*tert*-butylethene (**65**), torsional angles of 22° (63) and of 11.9° (76) have been reported; for the dinorbornylidene **23** (78), MM2 results agree well with the structural details found by X-ray analysis (33) (cf. Section II.B.1).

trans-Cycloalkenes. It appears that the CFF method is better adjusted than the original MM1 force field to reproduce the experimentally determined deformations in small *trans*-cycloalkenes. Although the MM1 method seems to underestimate the extent of twist at the expense of pyramidalization, both methods gave the crown or twist conformation as the most stable structure of *trans*-cyclooctene (**37a**). According to MM1, the chair conformation of **37a** is less stable by 2.4 kcal/mol than the crown conformation. The difference in strain energy between *cis*- (**36a**) and *trans*-cyclooctene (**37a**) was estimated to be 11.27 kcal/mol (11, 21a, 64a). This value can be compared with differences of 9.6 and 9.2 kcal/mol found for the heats of hydrogenation of these two cyclooctenes in the gas phase and in the liquid state, respectively (62, 64).

Based on MM2 results, predictions have been made for the structure of *trans*-cyclohexene (**43a**) and *trans*-cycloheptene (**39a**). *trans*-Cyclohexene

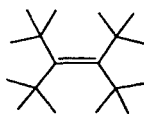
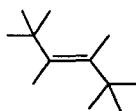
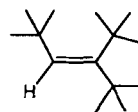
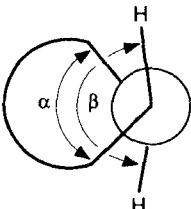
**64****65****66**

Table 7
MM2-Calculated (64a) and Experimental Dihedral Angles in
trans-Cycloolefins

	43a	39a	37a	67	
	calc. α [°]	85.1	125	149	164
	β [°]	166.6	166	171	179
	exp. α [°]			136 ^a	138.3 ^b
	β [°]			177.5	--

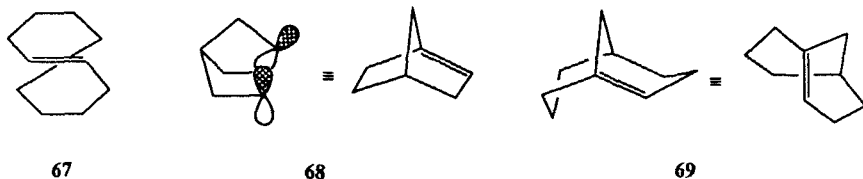
^aElectron diffraction study (46).

^bX-ray study of silver nitrate adduct (62, 64a).

(43a) should be a highly distorted species with dihedral angles of 85.1° for C-C=C-C and 166.6° for H-C=C-H (Table 7) (64). Similar results for 39a and 43a were obtained by Ermer (11). With an increase in the ring size, the dihedral angles approach the normal values of 180° in *trans*-cyclodecene (67) (64a).

Bridgehead Double Bonds. Typical bridgehead olefins represented by 44 (cf. Table 4) have been extensively discussed by Bredt (3). Inspection of molecular models, which do not allow for rehybridization at the carbon atoms of the double bond, suggest that structure 68 should prefer extensive torsional deformations. Extended Hückel calculations showed, however, that the structure of a bridgehead double bond is best described by the overlap of a sp^x hybridized orbital at the bridgehead with an orbital at the adjacent carbon atom of high p character. This type of π bond is favored over a structure with two strongly pyramidalized carbon atoms (79).

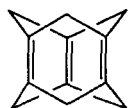
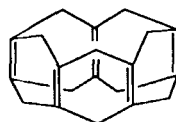
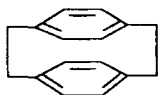
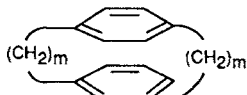
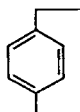
The bridgehead double bond of bicyclo[3.3.1]non-1-ene (69) is pyramidalized to only a slightly greater extent than that of *trans*-cyclooctene (37a) (64a). This supports the proposition that *trans*-cycloalkenes, preferentially with a methyl-substituted double bond, can be used as chemical models



for Bredt-olefins (80). Increasing the length of all carbon chains in bicyclic structures of type **44** leads to bridgehead olefins with double bonds, the reactivity of which should be quite reduced in comparison with the above mentioned Bredt-olefins (cf. Section VI) (81).

Sesquinorbornenes and Norbornenes. Deviations from planarity have been observed for *syn*-sesquinorbornenes and norbornene derivatives (82–84). The origin of this pyramidalization has been attributed to torsional effects of the type that cause alkanes to be staggered. The arrangement of the bonds at the bridgeheads adjacent to the double bond is hardly flexible and the structure accommodates the strain by oop bending of the double bond (82). This explanation, which is based on a thorough analysis of the MOs obtained from *ab initio* calculations, is consistent with results of the force field methodology, parameterized to reproduce classical torsional effects. *Ab initio* results were also used for interpretation of the highly stereoselective thermal and photochemical reactions of sesquinorbornenes (84).

Superphanes, Cyclophanes, and Betweenanenes. The simplest member of the "superphanes," tricyclo[4.2.2.2^{2,5}]dodeca-1,5-diene (**56**) (cf. Table 5) has been experimentally and theoretically described by Wiberg and co-workers (57b, 85). *Ab initio* as well as molecular mechanics calculations reproduce the structural features and the pyramidalization in **56** as observed in X-ray analysis rather well. Due to the small distance between them, the two pyramidalized double bonds interact with each other (85). Using the CCF method, Ermer has discussed the structure of columnenes **70–72** (11). *Ab initio* studies gave, for these columnenes pyramidalization angles Γ of 18.2°, 29.3°, and 47.3°, respectively; strong through-space π – π interactions were found in all three (86).

**70****71****72****73****74** $m = 6 - 12$ **75****76**

Pyramidalization is not limited to superphanes. Suitably short para and meta bridges induce significant departures from planarity also in cyclophanes. Typical examples, where the deformation is spread over more than one formal double bond, are given by the highly strained [2.2]paracyclophane (**73**) and the [m]paracyclophanes ($m = 6-12$) (**74**) (87). Evidence for a still smaller member of this family of compounds, [4]paracyclophane **75**, has recently been reported (88). Essentially no structural or computational results have been reported for betweenanenes. These are bicyclic compounds of type **76**, in which formally two *trans*-cycloalkenes share the double bond. This structural relationship suggests a A_{1u} -type deformation for the highly shielded double bond, similar to that found in overcrowded olefins (89).

III. SYNTHESIS OF MOLECULES CONTAINING NONPLANAR DOUBLE BONDS

The wealth of publications on strained olefins over the last 40 years demonstrates a high interest in the generation and study of molecules with nonplanar double bonds. From the plethora of methods tried and used for the synthesis of strained olefins, only a few are mentioned here. The successful transformations contain information about reactions which are sufficiently exergonic and have "reaction channels" available to allow the generation of highly strained olefins. In this way, they form an important part of our knowledge about the scope and limits of many chemical reactions. In this section our aim is to give an overview of the major methods used for the synthesis of molecules containing nonplanar double bonds with an emphasis on the more recent results. Several reviews and a monograph on strained

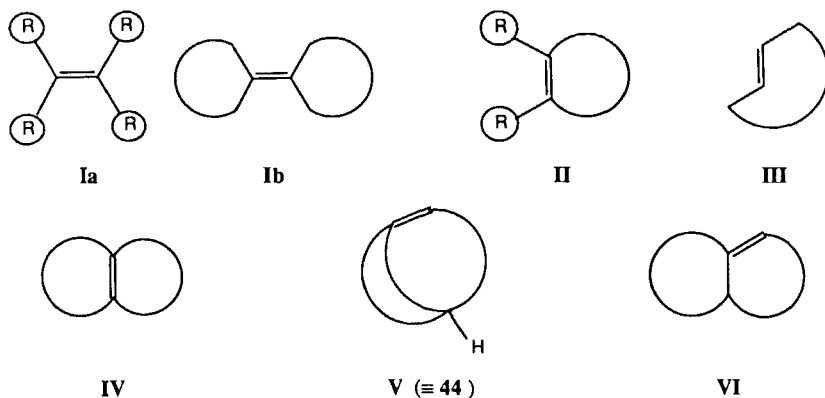
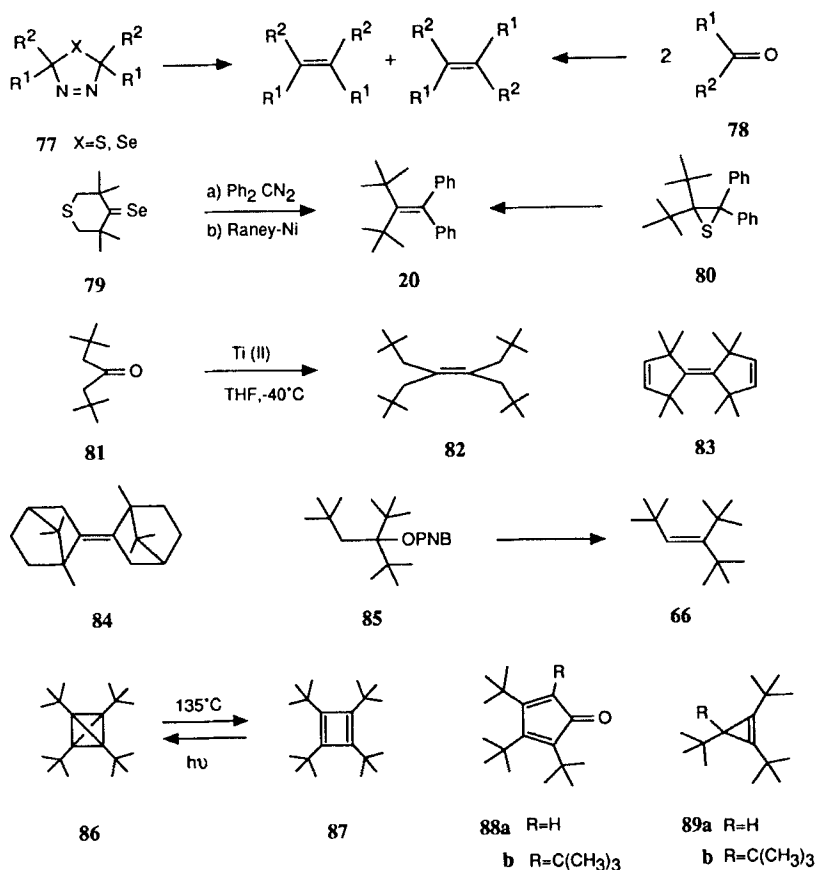


Figure 4. Basic structures used for generation of distorted double bonds.

organic molecules, which contain a survey of many strained olefins, have appeared (87, 90–97). The families of strained olefins are discussed in the order I–VI (Figure 4).

A. Sterically Crowded Olefins

The twofold extrusion of nitrogen and sulfur and selenium and sulfur from 1-thia- and 1-selena-3,4-diazolines(77), readily available from the reaction of diazoalkanes with thio- and selenaketones, respectively, as well as from the reductive coupling of carbonyl compounds such as **78**, is the preferred method for preparation of olefins of type I and II (98, 99). Examples of the extrusion method, developed by Barton (100), and the McMurry reaction (101) are given in Scheme 1.



Scheme 1

Although olefins like **20** and **82** and **83** could be prepared in reasonable yield by the Barton method and the McMurry reaction, respectively, the elusive tetra-*tert*-butylethene (**64**) could not be obtained using either of these methods (100a, 102–104). However, the sterically hindered olefins *syn*-2,2'-bifenchylene (**23**) and bi-2,2,5,5-tetramethylcyclopentylidene (**83**), which closely approximate the steric hindrance of tetra-*tert*-butylethene (**64**), have been prepared (102, 104). They may be considered to be derivatives of tetra-*tert*-butylethene (**64**) where the methyl groups are tied back, thus decreasing the steric interactions between the *cis* substituents of the double bond.

An optically active and sterically crowded olefin **84**, with similar structural features, has been prepared from (+)camphor (105). Other methods, which have been used for the generation of distorted olefins, are illustrated in the following examples. Heating di-*tert*-butylneopentylcarbinyl-*p*-nitrobenzoate (**85**) gave tri-*tert*-butylethene (**66**) in 30% yield (106).

Several *tert*-butylsubstituted cycloalkenes have been prepared in the course of the synthesis of tetra-*tert*-butyltetrahedrane (**86**) (107). Upon heating, tetra-*tert*-butyltetrahedrane (**86**) is transformed into its sterically crowded valence isomer **87**, which itself reacts to form **86** upon irradiation (107, 108). The preparation of tetra-*tert*-butylcyclopentadienone (**88**) and tri-*tert*-butylcyclopropene (**89**) are also mentioned here (108).

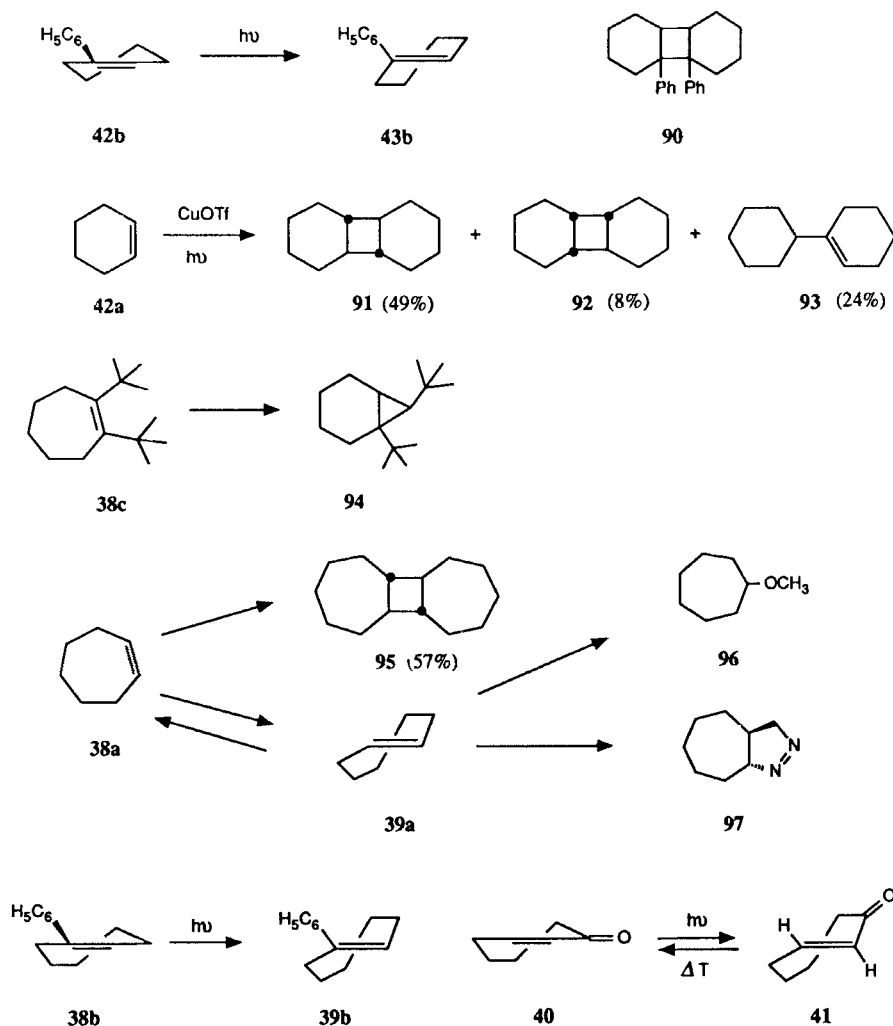
B. *trans*-Cycloalkenes

Irradiation with UV light is the key step for the generation of transient *trans*-cyclohexenes (**43**) and *trans*-cycloheptenes (**39**). Laser photolysis of 1-phenylcyclohexene (**42b**) in methanol at room temperature gave a species with a life time of 9 μ s (48, 109) (Scheme 2).

The spectral data and the chemistry of this intermediate are attributed to *trans*-1-phenylcyclohexene (**43b**) containing a highly twisted double bond with partial singlet diradical character rather than an orthogonal triplet state or an orthogonal zwitterionic phenylcyclohexene (109). Isomerization to *cis*-1-phenylcyclohexene (**42b**) occurs with an activation energy of $E_A = 12.0$ kcal/mol ($\log A = 14.1$), which is lowered in the tetrasubstituted **43c** (110) (Table 8). Apparently, cleavage to ethylene and a butadiene does not occur in these highly strained cyclohexenes.

Low-temperature studies of the photocatalyzed addition of methanol to 1-phenylcyclohexene (**42b**) also indicated that **43b** is the intermediate (111). Evidence for the existence of a free *trans*-1-phenylcyclohexene (**43b**) is found in the structure of a [4 + 2]dimer **90** formed in irradiation of **42b** in methanol at -75°C (111) (Scheme 2).

The copper(I) trifluorosulfonate catalyzed photoisomerization of cyclohexene (**42a**) leads to a mixture of three products, **91–93** (112, 113). The



Scheme 2

stereoselective formation of the major product **91**, the structure of which has been established by X-ray structure analysis, is suggestive of a photoinduced [2 + 2]cycloaddition with a copper(I)-stabilized *trans*-cyclohexene (**43a**) as intermediate. Unsubstituted *trans*-cyclohexene (**43a**) has hitherto not been detected. On the basis of quantum-chemical studies by the generalized valence bond method, it has been argued that it is not an energy minimum (48).

Table 8
Activation Energies for *trans* → *cis* Isomerization of Some
Substituted Cycloolefins (110b)

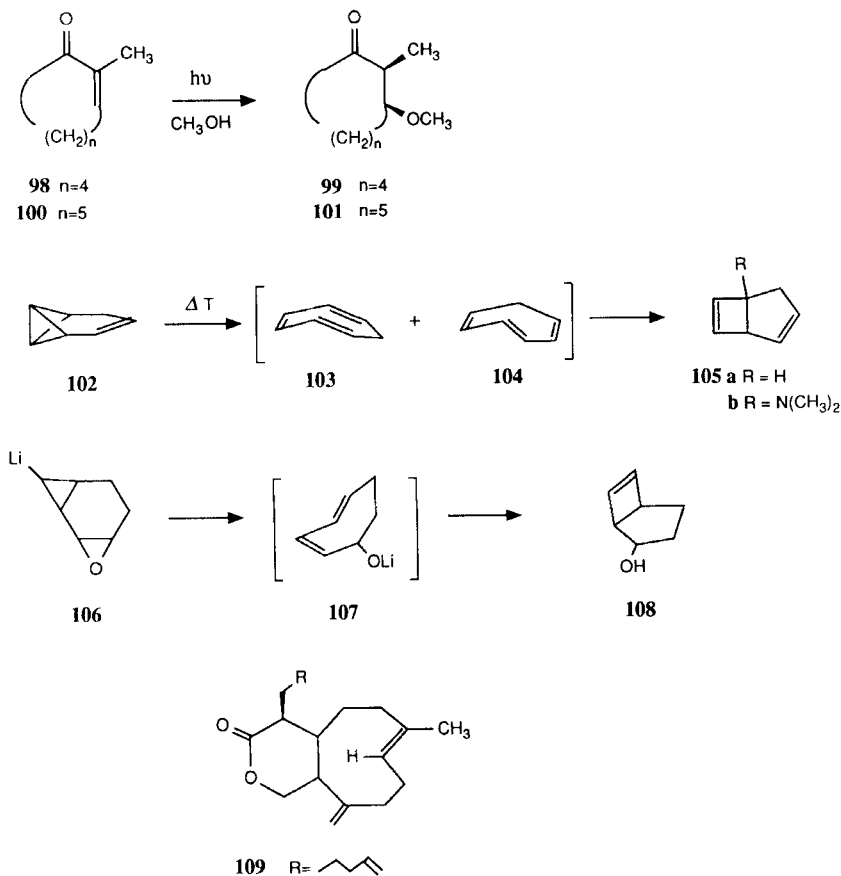
	E_A [kcal/mol]	log A
43b → 42b	12.0	14.1
43c → 42c	9.82	14.1
39b → 38b	18.54	12.2

trans-Cycloheptene (**39a**) as well as the 3-methoxy derivative **39d** has been generated by photoisomerization (114, 115). Not unexpectedly, **39a** is more stable than **43a**, and it isomerises to *cis*-cycloheptene (**38a**) more slowly. Upon irradiation of 1,2-di-*tert*-butylcycloheptene (**38c**), it might have been expected that the eclipsing of the two bulky substituents would favor formation of *trans*-1,2-di-*tert*-butylcycloheptene (**39c**) in the same way as 1,2,5-tri-*tert*-butyl-Dewar-benzene is favored over 1,2,4-tri-*tert*-butylbenzene (116). However, only the norcarane derivative **94** could be obtained. The formation of the endo product is attributed to a hydrogen shift on the exo face, requiring the *tert*-butyl group to move inward.

The copper(I) trifluorosulfonate catalyzed photoreaction of cycloheptene (**38a**) leads to the dimer **95** (114c). Formation of the latter was taken as support for the generation of *trans*-cycloheptene (**39a**) as an intermediate. However, isomerization of free *trans*-cycloheptene (**39a**) seems to be faster than its cyclodimerization. *Trans*-cycloheptene (**39a**), obtained by photoreaction with methyl benzoate as sensitizer, isomerizes to *cis*-cycloheptene (**38a**) at 0°C (114b) but reacts at low temperature with acidified methanol to form **96** or with diazomethane to form **97** (114a). The stereochemistry of the pyrazoline **97** is *trans*, in accord with the stereospecific addition to *trans*-cycloheptene (**39a**).

Flash photolysis of *cis*-1-phenylcycloheptene **38b**, as well as of *cis*-cyclohept-2-enone (**40**), gives rise to the corresponding *trans* species **39b** and **41**, respectively (117, 118). *trans*-2-Methyl-cyclohept-2-enone **98**, as well as the higher analog **100**, reacts with methanol under acid catalysis in a stereospecific *syn* addition to yield *cis*-substituted **99** and **101**, respectively (119) (Scheme 3).

The stereoisomers of *cis-cis-cis*-cycloheptatriene **103** and **104** have been postulated as intermediates in the thermal rearrangement of the homobenzvalene **102** to *cis*-bicyclo[3.2.0]hepta-2,6-diene (**105a**) (120). The *cis-trans*-cycloheptadiene derivative **107** is considered to be the intermediate in the butyllithium-induced rearrangement of the β -bromocyclopropyloxirane **106** to *cis*-bicyclo[3.2.0]hept-6-en-2-ol (**108**) (121). Evidence of the intermediacy of **107** was obtained by trapping with 1,3-diphenylbenzoisofuran.



Scheme 3

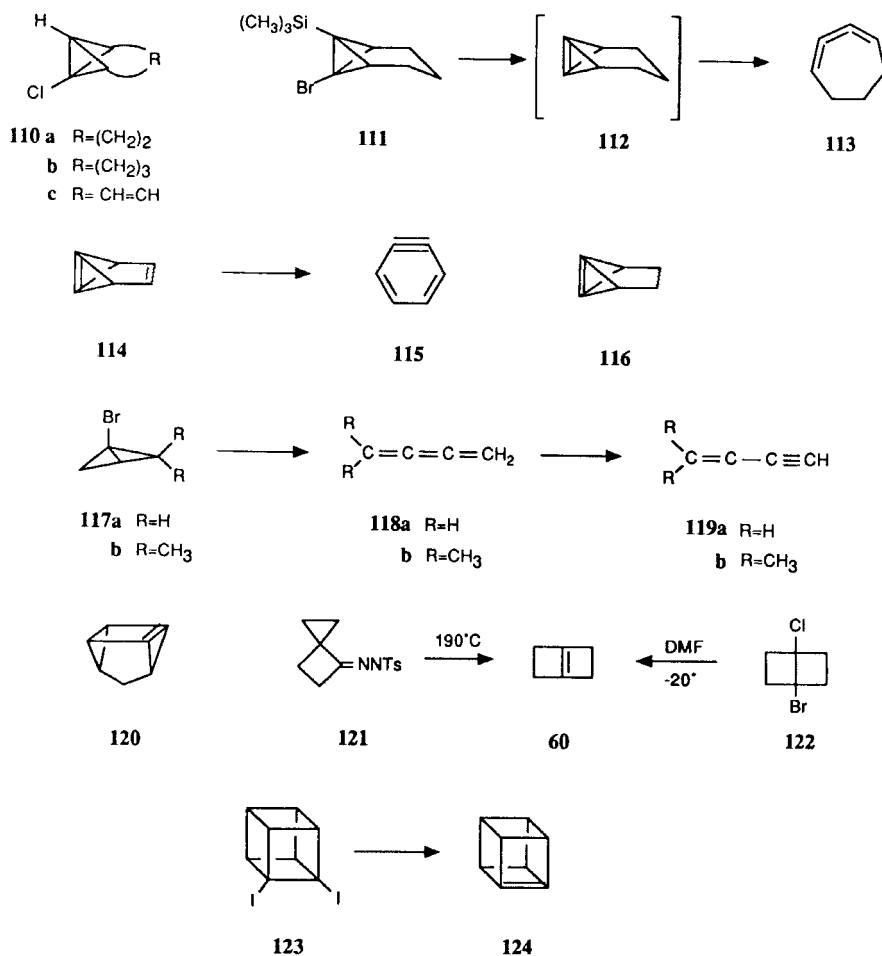
In view of the abundance of publications of *trans*-cyclooctene (**37a**) and higher homologs and derivatives, their preparation is not discussed here (122). The synthesis of the biologically active diterpene acalcixenolide **109**, which contains a *trans*-cyclononene subunit, has not yet been reported (123).

C. Bicyclo[m.n.0]alk-1,(m + 2)-enes

The generation of 2,4-alkylidene bridged bicyclo[1.1.0]but-1(3)-enes became possible when the acidity of the bridgehead proton in compounds of type **110** was detected (124–127). The deprotonation by lithium diethylamide and similar bases is reminiscent of the formation of 1,2-dehydrobenzene from

halobenzenes (128). In this way, bridgehead olefins such as **112**, **114**, and **116** could be generated as short-lived intermediates from the appropriate precursors **110a–c** by base-induced dehydrohalogenations (Scheme 4). The bridgehead olefin **112** can be trapped by furan and some of its derivatives. If generated by fluoride-induced fragmentation above room temperature, compound **112** forms 1,2,3-cycloheptatriene (**113**) (124, 127).

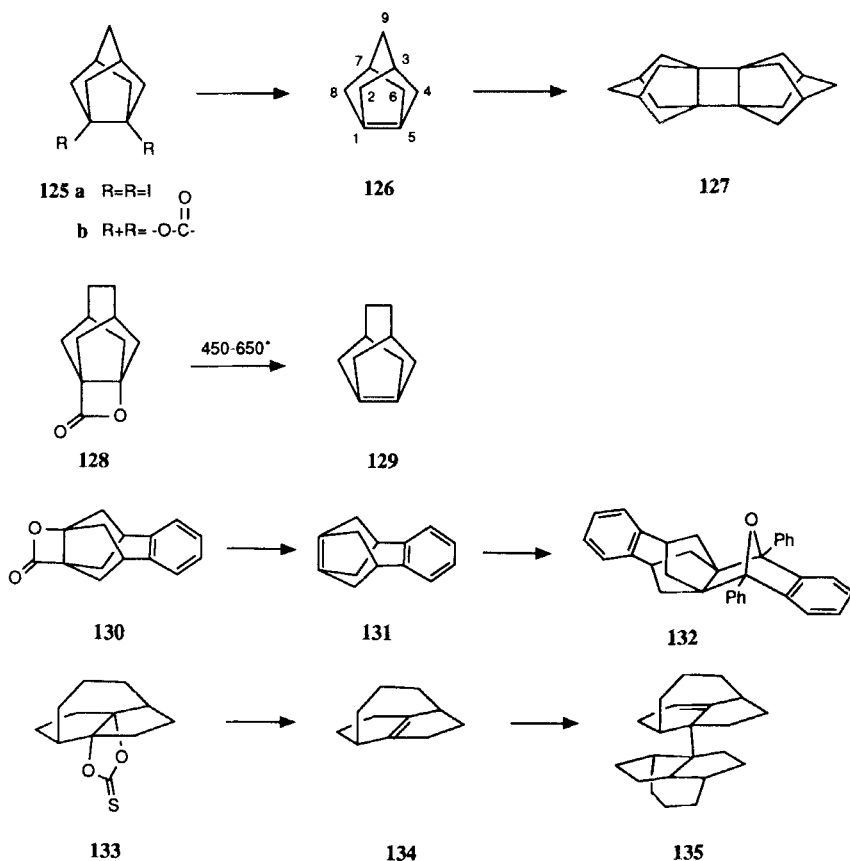
Dehydrobenzvalene **114** rearranges to 1,2-dehydrobenzene (**115**); the latter reacts with the butyllithium used for deprotonation of **110c** (126). The bicyclobutene **116** does not rearrange readily and is trapped by 1,3-



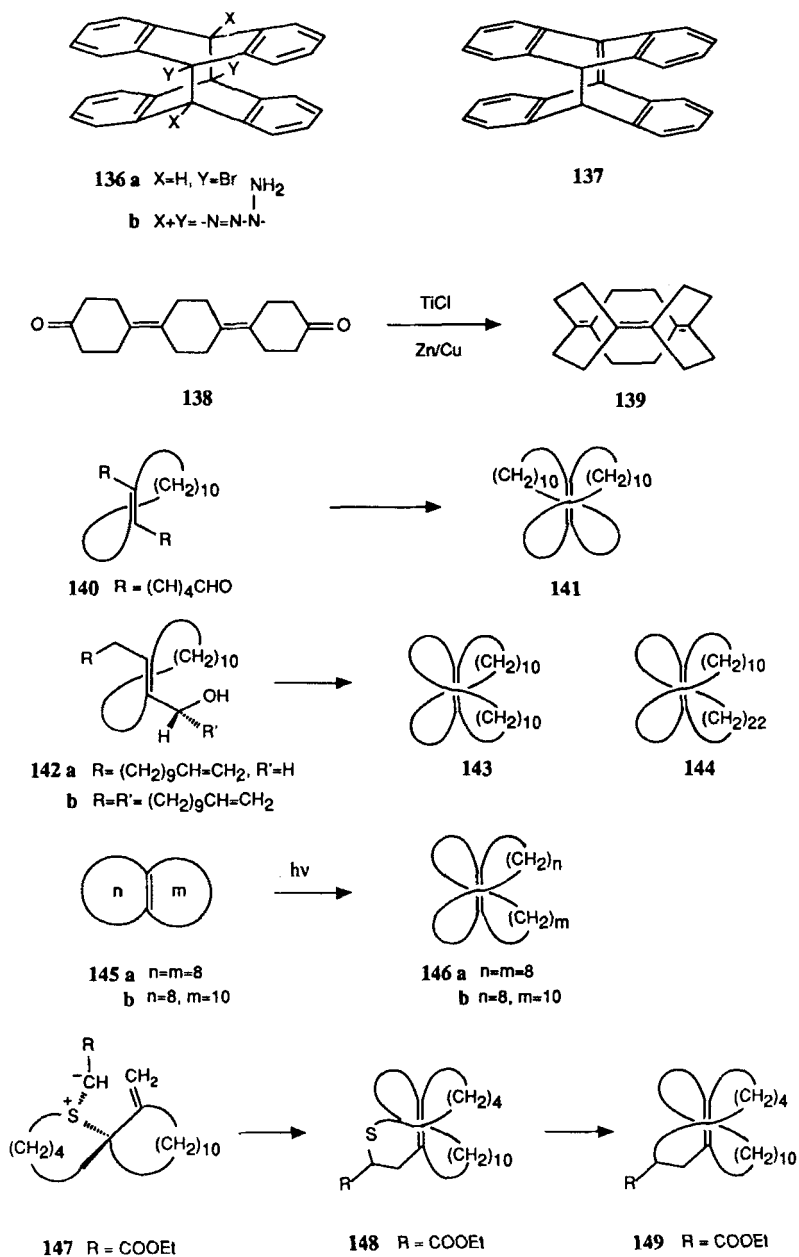
Scheme 4

diphenylisobenzofuran directly (127). In contrast, up to now all attempts to generate bicyclo[1.1.0]but-1(3)-ene (**61**) itself or derivatives without a 2,4-alkylene bridge by the same methodology have failed (127, 129). When **117a** and **117b** are treated with lithium diethylamide in the presence of trapping agents at -40°C , only the alkynes **119a** and **119b**, respectively, which are formed via **118a** and **118b**, respectively, are isolated (130). Labeling experiments with **117a** lead to the conclusion that the intermediate formed by base-induced removal of the bridgehead proton rearranges directly to the alkyne **118a** (130a).

Similarly, no experimental evidence for the detection of bicyclo[2.1.0]pent-1(4)-ene (**62**) even as a short-lived intermediate has been published, whereas the bridged analog **120** could be trapped by anthracene (124, 131). The next higher



Scheme 5



Scheme 6

homolog, bicyclo[2.2.0]hex-1(4)-ene (**60**), can be prepared via ring expansion of a carbene generated from **121** or by reductive dehalogenation of **122** (132). The neat olefin is highly reactive and polymerizes even at low temperature; under high dilution it dimerizes to **56** (cf. Table 5). 1,2-Dehydrocubene (**124**), which can be considered a derivative of **60**, has recently been generated from **123** as a highly reactive intermediate (133). Other bridgehead olefins that have been detected as short-lived intermediates are shown in Scheme 5.

The common feature of compounds **126**, **129**, and **131** is a bicyclo[3.3.0]oct-1(5)-ene skeleton tied back by a one- or two-carbon bridge between centers C(3) and C(7) (Scheme 5, **126**). Reductive bisdehalogenation of **125a** leads to the hydrocarbon **127**, which is formally the [2 + 2]cycloadduct of **126** (134a). In the presence of 1,3-diphenylisobenzofuran, the expected [2 + 4]cycloadduct was isolated in 90% yield. This has to be taken as evidence for the intermediacy of **126**. The β -lactone **125b** proved to be very resistant to pyrolytic loss of CO₂. Loss of CO₂ from **125b** was observed only at temperatures above 550°C. A small amount of the dimer **127** was isolated with 2,6-dimethylenebicyclo[2.2.1]heptane being the major product (134a). The homologous β -lactone **128** readily yielded CO₂ and the bridgehead olefin **129**, which upon deposition onto a window at 10 K was detected by IR spectroscopy (134b). Similarly, pyrolysis of **130** leads to the benzo derivative **131**, which can be trapped by 1, 3-diphenylisobenzofuran to give **132** (135). The distortion in **134**, a bicyclo[3.3.0]oct-1(5)-ene with a 2,6-propylene bridge, might be of A_{1u} rather than of B_{1u} type. When prepared by pyrolysis of **133**, **134** gives **135**, the product of an ene-type reaction of two molecules of **134** (136).

One of the early examples of a bridgehead olefin with exclusive oop bending is given by the 9,9',10,10'-tetrahydrodianthracene (**55**) (cf. Table 5) (57a). It has been isolated by oxidative cleavage of the bis-*N*-aminotriazoline (**136b**) as a crystalline compound (Scheme 6). An analogous synthesis of 9,9'-didehydrodianthracene (**137**) has been described. The structure and chemistry of the parent compound **56**, obtained by controlled dimerization of bicyclo[2.2.0]hex-1(4)-ene (**60**), has been mentioned above (137). The "columnane" **139**, formally a trimer of **60**, has recently been prepared from the diketone **138** by McMurry reaction in a yield of 24% (138).

D. [a.b]Betweenanenes

Compounds of type **76** in which a pair of *trans*-cycloalkenes shares the double bond, were first discussed by Cahn, Ingold and Prelog as hypothetical molecules possessing planar chirality (139). The deformation of the double bond in this class of compounds appears to be twist (A_{1u} -type deformation), perhaps modified by pyramidalization. Members of this class of compounds, which contain a highly shielded unreactive double bond, have been prepared by several groups (140–143).

The key step in the synthesis of [10.10]betweenanene (**141**) is the McMurry reaction of an appropriately disubstituted *trans*-cyclodecene (**140**) (**140**). Starting with optically active *trans*-cyclododecenyl-carbinols **142a** and **142b**, the optically active (*R*)(+)-[10.10]- (**143**) and (*R*)(+)-[22.10]betweenanenes (**144**), respectively, could eventually be prepared (**141**). Other [m.n]betweenanenes with $m, n \leq 10$ (**146**) have been prepared by photoisomerization of the corresponding *cis*-bicycloalkenes **145** (**142**). The derivative of [10.6]betweenanene **149** was prepared from a spirocyclic sulfonium ylide **147**, which gave the desired thiabetweenanene **148** via [2, 3]-sigmatropic rearrangement (**143**). The sulfur could be extruded to give the [10.6]betweenanene (**149**) by a variant of the Ramberg-Baeklund reaction (**143**).

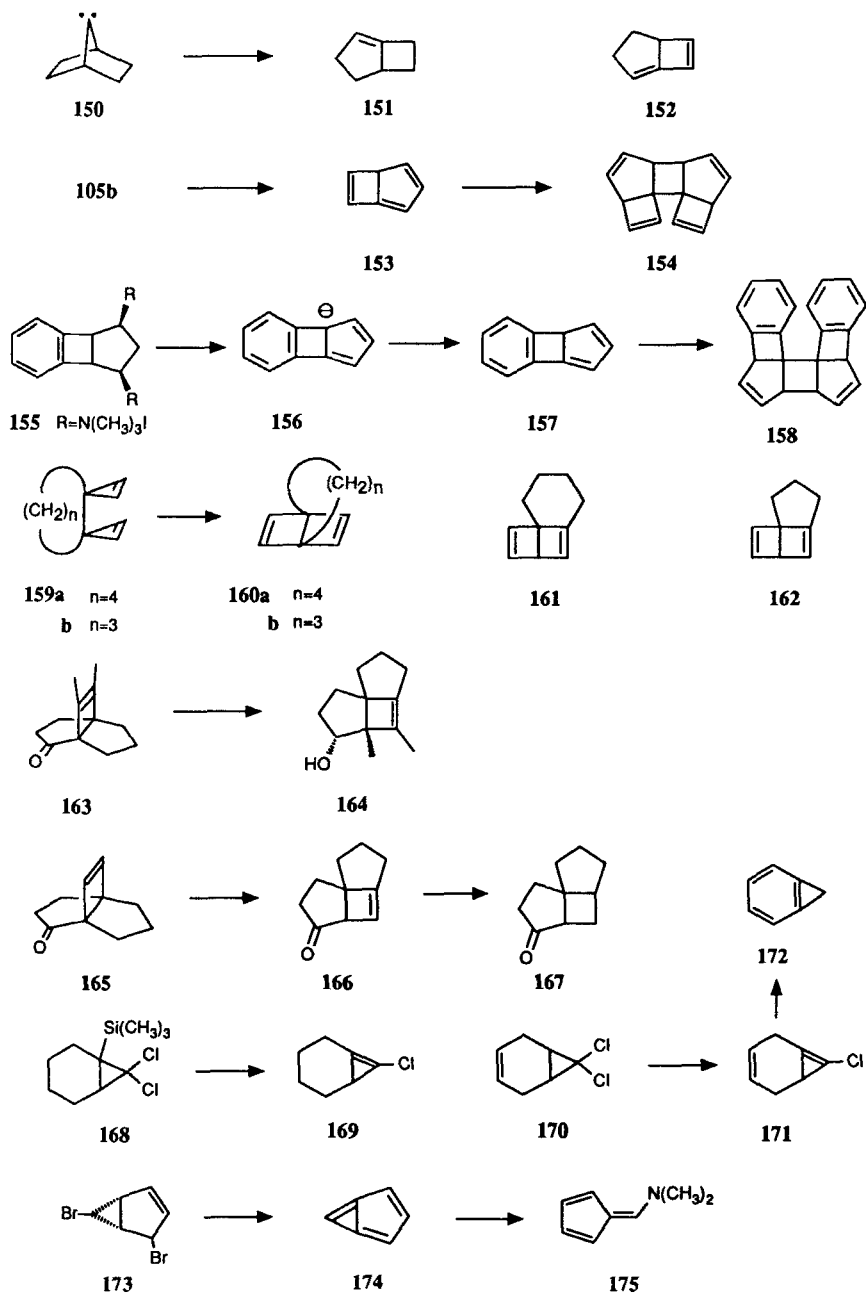
E. Bicyclo[m.n.0]alkenes with Bridgehead Double Bonds

Apart from in-plane distortions, bridgehead olefins of type **44** (Table 4) show torsion and oop bending. Typical examples and the precursors from which they are prepared are given in Scheme 7.

Bicyclo[3.2.0]hept-1-ene (**151**) can be prepared from the tosylhydrazone of norbornan-7-one via norbornan-7-ylidene **150** in 74% as a stable olefin (**144**). Similarly, **152** has been obtained from norborn-2-en-7-one in a yield of 67% (**144a**). Introduction of a further double bond leads to the strained triene **153**, which has been prepared from **105b** (Scheme 3). Compound **153** dimerizes readily at room temperature to a 1:1 mixture of hydrocarbons **154** (**145**). The most likely structures of these dimers arise from a formal [2 + 2]cycloaddition of the bridgehead double bonds of **153** with each other. Support for the intermediacy of **153** comes from trapping experiments with 1,3-diphenylisobenzofuran, which yield a mixture of stereoisomers via reaction with the bridgehead double bond of **153**.

When the bistrimethylammonium iodide **155** is treated with the dimethylsulfoxide anion, a stable deep brown solution is obtained (**146**). Addition of water leads to two dimers, one of which was identified as **158**. This result is consistent with the formation of the norbiphenylene anion **156**, which upon protonation gives **157** and eventually the two dimers.

1,2-Bridged Dewar-benzenes such as **161** and **162** contain a bridgehead double bond in the smaller ring of the bicyclic substructure. Potential precursors for the synthesis of the 1,2-bridged Dewar-benzenes are the 1,1'-tetramethylene and 1,1'-trimethylene bicyclopropenyls **159a** and **159b**. On treatment with AgClO_4 in different solvents at -20°C , **159a** rearranges to a mixture of 1,2- and 1,4-bridged Dewar-benzenes **160a** and **161** (**147**). The tricyclic diene **161** is thermally unstable and, at 20°C , rearranges quantitatively with $\tau_{1/2} = 58$ min to tetralin. When **159b** was treated with AgClO_4 at -20°C , only the 1,4-bridged Dewar-benzene **160b** was detected; the expected



Scheme 7

162, certainly being more strained than **161**, aromatizes to indane even at low temperatures (148).

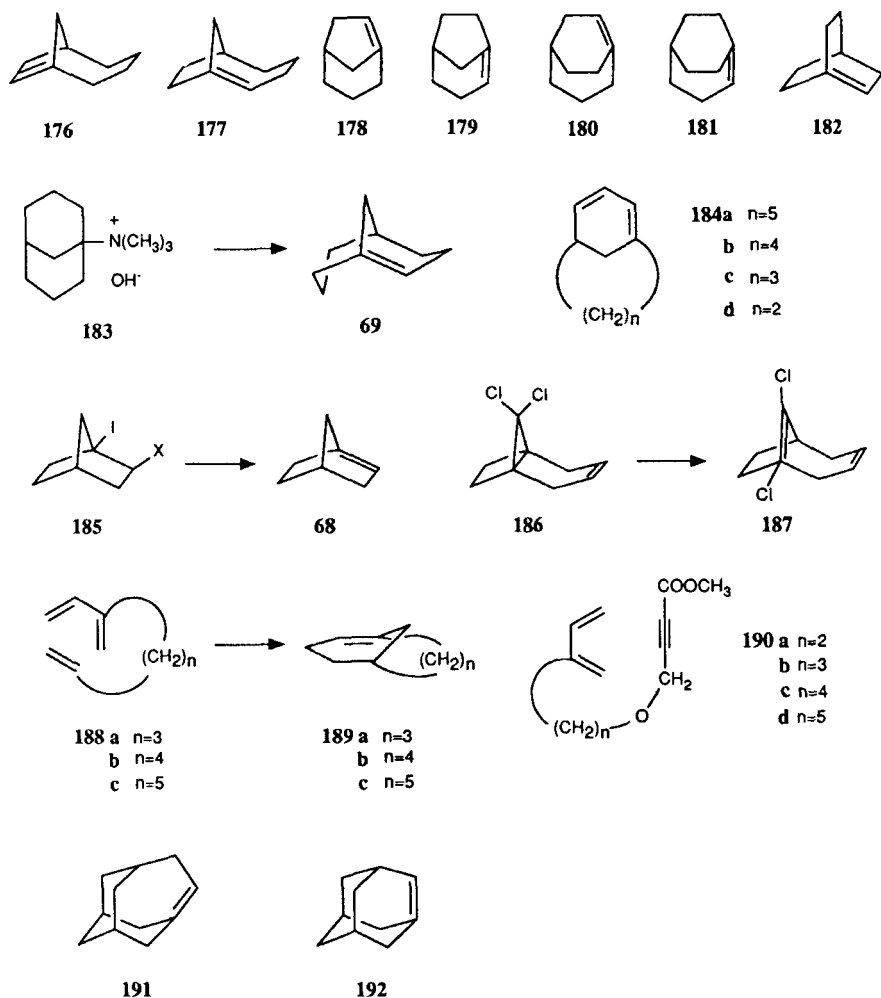
A less reactive bicyclo[3.2.0]hept-1(7)-ene substructure has been found in **164** (149). This compound was prepared from propellane **163** by photolysis and subsequent reduction. In contrast to **163**, irradiation of the parent tricyclic ketone **165** in ethanol gives the saturated ketone **167**. The formation of **167** is taken as evidence for the intermediate formation of the ketone **166**. When **168** was treated with CsF in the presence of 1,3-diphenylisobenzofuran, an adduct was isolated, which was assigned the structure of the expected [2 + 4]cycloaddition product of **169** (150).

Based on mechanistic considerations, **171** has been suggested as an intermediate in the base-induced transformation of **170** to benzocyclopropene (**172**) (150). On treatment of **173** with lithium dimethylamide at -75°C , the fulvene derivative **175** could be isolated (151). The mechanism by which the fulvene arises was elucidated by several isotope labeling experiments. These results require the formation of triene **174** as an intermediate in the base-induced elimination reaction of **173** (151).

F. Bicyclo[m.n.o]alkenes ($o \geq 1$) with Bridgehead Double Bonds

Two classes of bridgehead olefins with the basic skeleton of a bicyclo[n.m.o]alkene can be recognized: the Bredt-olefins (for a definition see Section II.B.1.a) of type **44**, which formally contain a *trans*-cyclooctene or smaller *trans*-cycloalkene ring system and an additional methylene, or ethylene bridge and the "hyperstable" bridgehead olefins, one group of which can structurally be related to larger *trans*-cycloalkenes with an additional ethylene or larger alkylene bridge (see below). Typical examples of Bredt-olefins are given in Scheme 8.

Bredt-olefins such as **69**, **176**, and **177**, which are formally derived from *trans*-cyclooctene, have in all cases been isolated, whereas those with a *trans*-cycloheptene skeleton, such as **178–181**, are detectable intermediates at low temperature. Bredt-olefins with a formal *trans*-cyclohexene substructure, such as **68** and **182**, have hitherto only been implied by their trapping products. Since Bredt's rule and general and synthetic aspects of Bredt-olefins have frequently been reviewed (90–93, 96), only some of the typical and more recent methods are presented here. Eliminations under a variety of mechanistic pathways, fragmentations, and rearrangements are typical types of reaction used for generation of bridgehead olefins. The recent period of activity in the field of bridgehead olefins started when Wiseman and co-workers reported the pyrolysis of the quaternary ammonium hydroxide **183** to produce bicyclo[3.3.1]non-1-ene (**69**) in 35% yield (49, 152). The Wittig reaction was the key step in the preparation of the bicyclo[n.3.1]



Scheme 8

alkadienes **184a–d** ($n = 2–5$) and bridgehead olefins such as **178** and **179** (153).

Conclusive evidence has been given for the formation of $\Delta^{1,2}$ -norbornene (**68**) in reductive bisdehalogenations of diastereomeric dihalides **185** (154a). The perfluoro analog of **68** had been obtained by base-induced elimination of appropriate precursors (154b). Solvolytic cyclopropyl-allyl-cycloreversions of compounds such as **186** have extensively been studied for formation of bridgehead olefins like **187** (155).

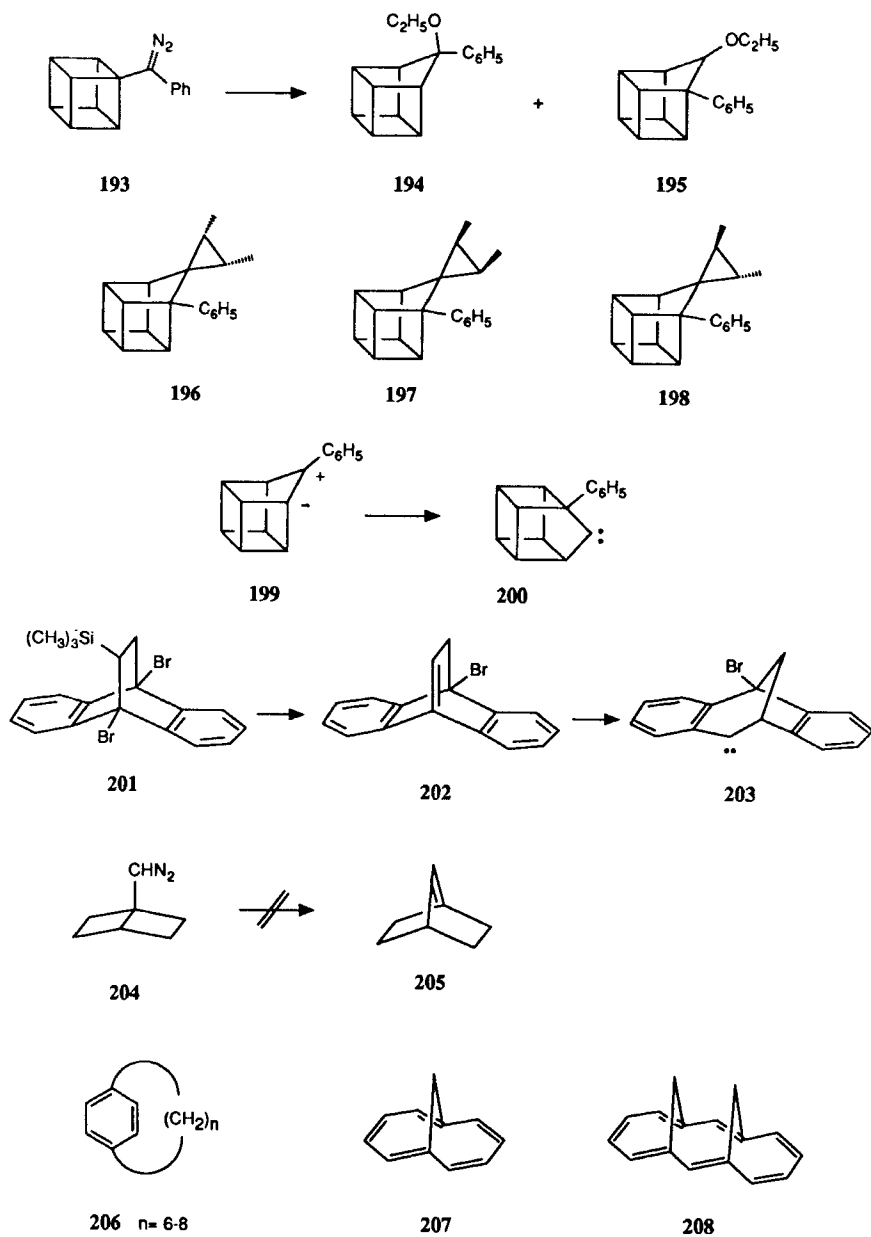
Intramolecular Diels–Alder cycloadditions provide another highly effective route for the synthesis of a wide variety of bridgehead alkenes (95, 156). After short contact times, gas-phase pyrolysis of the trienes **188a–c** provide the bridgehead olefins **189a–c** in substantial quantities. The synthetic potential of the intramolecular Diels–Alder cycloaddition has further been exploited in the synthesis of bridgehead dienes such as **46**, and **47** (Table 4) starting from the precursors **190c** and **190d** (51, 157). Rearrangements of alkylcarbenes have been used for the generation of bridgehead alkenes such as homoadamantene (**191**) and adamantene (**192**) itself (158, 159). A more recent example of a ring expansion reaction comes from a study of cubylphenyldiazomethane (**193**) (160) (Scheme 9).

Photolysis of **193** in ethanol gives a mixture of two ethoxyethers, **194** and **195**, derived from the phenylhomocubane skeleton. Irradiation of **193** in neat *cis*- or *trans*-2-butene leads to the spiroadducts **196** and **197** and to **198**, respectively. Topologically, the reaction sequence requires ring expansion and a 1,2-shift of the phenyl groups. The energetics are discussed in terms of 9-phenyl-1(9)-homocubene (**199**), which rearranges on the time scale given by the reaction rate of the trapping reagents to 1-phenyl-homo-9-cubylidene (**200**) (160). An earlier example, where a Bredt-olefin rearranges to a carbene, has been observed with **201** (161): fluoride-ion-induced elimination at temperatures above 100°C leads to the bridgehead olefin **202**, which could be trapped with *C,N*-diphenyl nitron in a [2 + 3]cycloaddition. The carbene **203** underwent a [1 + 2]cycloaddition with nitriles. Attempts to generate the parent bicyclo[2.2.1]hept-1(7)-ene (**205**) by photolysis of bicyclo[2.2.0]hex-1-yl diazomethane (**204**) have been unsuccessful (162).

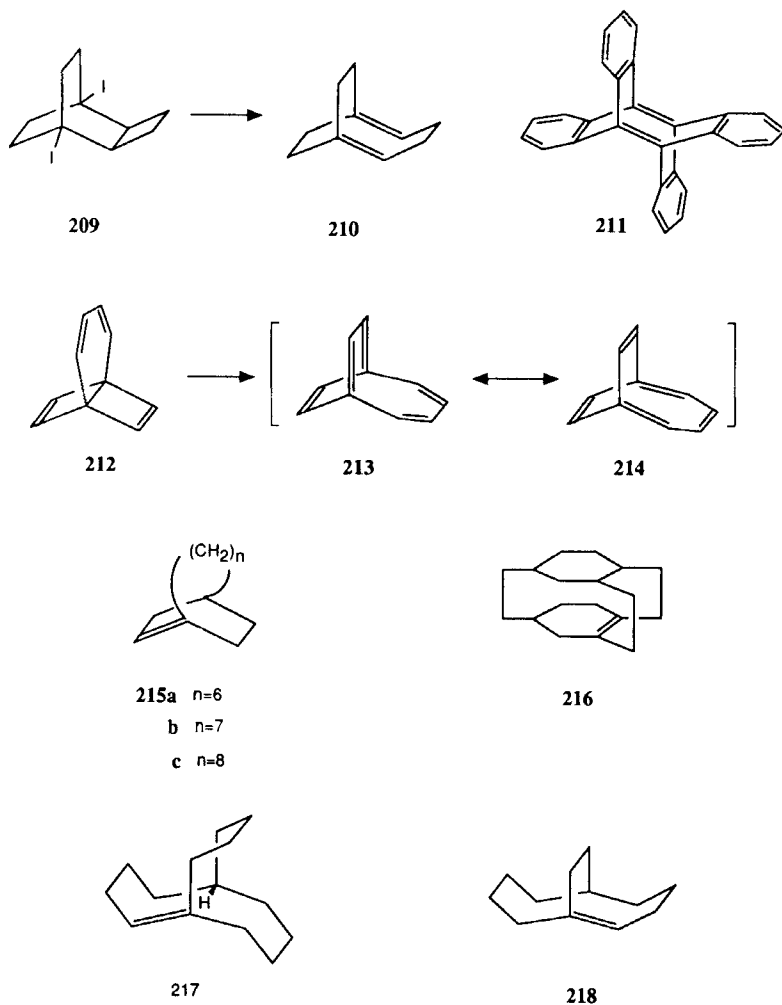
Whereas the chemistry of cyclophanes **206** (88, 163) and bridged annulenes such as **207** and **208** (164) is well known and has been reviewed several times, only a few members of these bridgehead dienes, where aromatization is not a stabilizing factor, have been prepared.

The bridgehead diolefins **210** and **211**, which, like **55**, are formally alkylene-bridged derivatives of *trans*, *trans*-cycloalkenes, have been reported (165) (Scheme 10). The stability of **211** toward heat, air, and moisture is in contrast to that of the unsubstituted bicyclo[4.2.2]deca-1,5-diene (**210**). The latter diene was obtained by a kinetically controlled reductive deiodination of **209**, which leads to the cleavage of the cyclobutano bridge in preference to the ethano bridge, despite the greater thermodynamic stability of the monocyclic diene to be expected from the latter reaction.

Recently, the formation of bicyclo[4.2.2]decapentaene (**213**) as a highly unstable intermediate in the photolysis of the propellane **212** has been reported (166). Classical formulae are used to interpret the spectroscopic and trapping results in terms of the valence isomer **213** rather than **214**. It remains to be seen whether **213** and **214**, the π system of which is apparent in the tetrabenzannulated derivative **211**, are true valence isomers.



Scheme 9



Scheme 10

Systematic experimental studies of “hyperstable” (cf. Section V.B) bridgehead olefins are lacking. Hydrogenation of polyunsaturated bicyclic precursors is the common route to the few “hyperstable” bridgehead alkenes hitherto prepared. In all cases studied, the rate of hydrogenation of the bridgehead olefin formed is sufficiently slow to allow its isolation. Typical examples prepared from cyclophanes by catalytic hydrogenation are **215a–c** and **216** (167, 168). The bridgehead double bond of **216** resisted further hydrogenation

under a variety of conditions. Addition to hydrogen to the bridgehead double bond of "in"-bicyclo[4.4.4]tetradeca-1-ene (**217**) and of bicyclo[4.4.2]dodeca-1-ene (**218**) is remarkably slow (169, 170).

G. Transition Metal Complexes

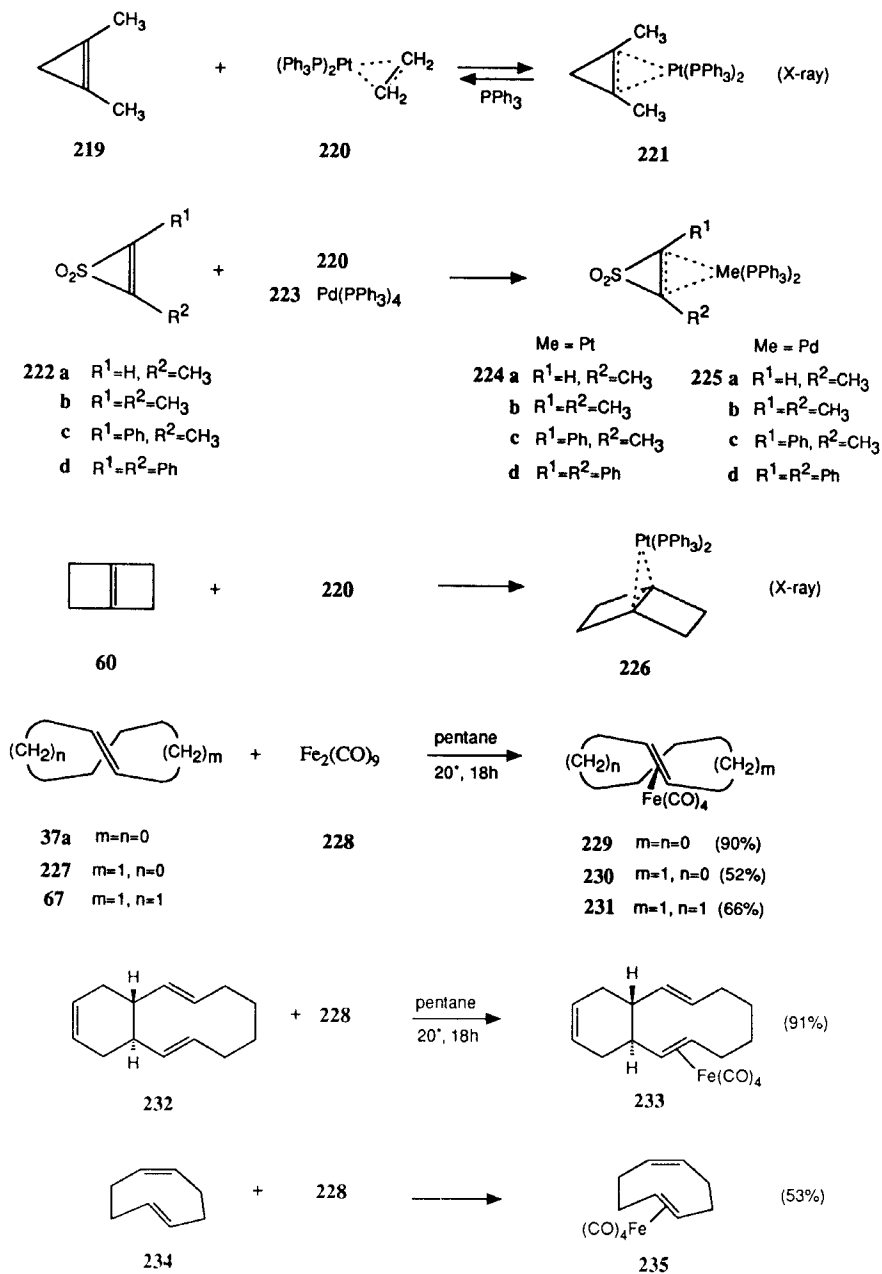
Whereas transition metal complexes of alkenes and their chemistry have been well explored, comparatively little is known about the structure and reactivity of π complexes obtained from strained olefins. The stability of transition metal complexes of alkenes in general is preferably discussed in terms of the Dewar–Chatt–Duncanson model (171). A mutual σ -type donor–acceptor interaction accounts for the bonding: overlap of the bonding π -MO of the olefin with vacant orbitals of the metal together with interaction of filled d orbitals with the π^* -MO of the double bond (back bonding) leads to a partial transfer of electron density in both directions (172). The major contribution to the stabilizing interaction is due to back-bonding.

In twisted double bonds, the energy of the bonding π -MO is raised and that of the antibonding π^* -MO is lowered. This may lead to stronger interactions and hence to π complexes with greater stability than that found in π -complexes of unstrained olefins (173). In general, back-donation of electron density from the transition metal to the strained double bond has a similar effect on strain as the transformation into a C—C single bond: with the exception of "hyperstable" olefins, strained olefins are thermodynamically but not necessarily kinetically stabilized by complexation with transition metals. The general experience that ethylene complexes of transition metals readily undergo ligand exchange with a strained double bond and the preferential complexation of the bridgehead double bond in dienes, such as **184b** and **236**, is compatible with this stabilizing effect.

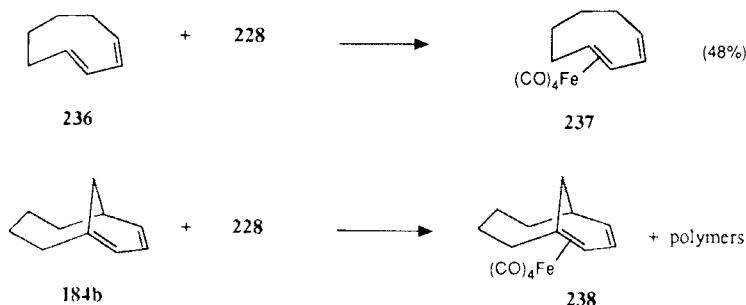
Transition metal complexes of strained olefins have preferentially been prepared by two methods: ligand exchange (Scheme 11) and rearrangement of appropriate transition metal complexes of polycyclo-alkyl-carbenes (Scheme 11).

The highly reactive and thermally labile 1,2-dimethylcyclopropene (**219**) has reversibly been stabilized by bis(triphenylphosphine) Pt(0) (**220**) (174). The X-ray structure of **221** reveals that complexation of **219** leads to significant changes. The C=C double bond lengthens from 130 pm reported for the free ligand to 150 pm in the complex. The methyl groups are bent out of the plane of the cyclopropene ring, away from the metal with 112° ; the angle between the ring and the plane defined by Pt and the P atoms is 116° .

Thiiren-1,1-dioxides **222a–d** are strong bonding ligands for zero-valent metals such as Pt(0) and Pd(0) (175). Complexation readily occurs with $(\text{PPh}_3)_2\text{PtX}$ ($\text{X} = \text{C}_2\text{H}_2$, CS_2 , or PPh_3) (**220**) and $\text{Pd}(\text{PPh}_3)_4$ (**223**), leading to



Scheme 11



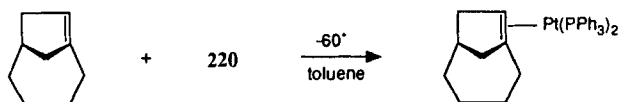
Scheme 11 (Continued)

the π complexes **224a–d** and to **225a–d**; *trans*-Ir(CO)Cl(PPh₃)₂ coordinates only with **222a**. The NMR spectra of these complexes are indicative of complexation at the C=C double bond. The chemical shifts and heteroatom–hydrogen spin–spin couplings are similar to those of **221**. Additional structural evidence is based on the absence of an infrared absorption band in the C=C stretching frequency region of the complexes of **222a–d**.

Displacement of ethylene in **220** by bicyclo[2.2.0]hex-1(4)-ene (**60**) was used to prepare the Pt(0) complex **226** (176). Its stability makes it a convenient way to store **60**, since it can be recovered by addition of carbon disulfide. The X-ray structure analysis of **226** revealed a C(1)–C(4) bond length of 155 pm and an angle between the two four-membered rings of approximately 123°. In planar **60**, the C=C bond distance was calculated (*ab initio*, 4-31G) to be 130.3 pm (68).

The *trans*-cycloalkenes **37a**, **67**, and *trans*-cyclononene **227** react with diironnonacarbonyl **228** to form the tetracarbonyliron(0) complexes **229–231** with the *trans*-cyclooctene complex **229** being significantly more stable than that of *trans*-cyclodecene **231** (177). The bicyclic triene **232** reacts with **228** preferentially at one of the *trans* double bonds of the *trans, trans*-cyclodecadiene substructure. In line with the expected stability, the *trans, cis*-cycloocta-1,5-diene **234** and *trans, cis*-cycloocta-1,3-diene **236** react with **228** exclusively at the *trans* double bond to give the complexes **235** and **237**. In the complex **238**, tetracarbonyliron(0) is bonded to the bridgehead double bond of bicyclo[4.3.2]deca-7,9-diene (**184b**) (177).

Smaller bridgehead olefins, which react with **220** by ligand exchange to form the appropriate complexes **239** and **240**, are the isomeric bicyclo[4.2.1]nonenes **176** and **177** (178) (Scheme 12). The X-ray structure analysis of **239** revealed that the bis(triphenylphosphine) Pt(0) is bonded to the *exo* side of the bridgehead double bond. Comparison of the geometry in **239** with that calculated for the uncomplexed olefin **176** leads to the conclusion that back-bonding of Pt(0) plays an important role for relaxation: The torsional angle C(2)–C(1)–C(8)–C(7) found in the complex **239** (124°) is smaller



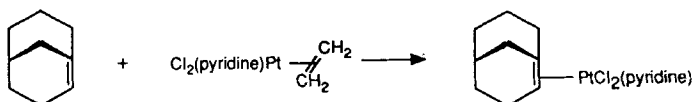
176

239 (52%)



177

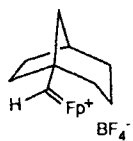
240



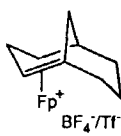
69

241

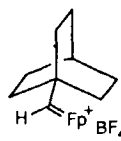
242



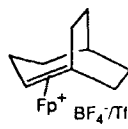
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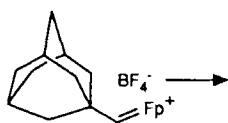
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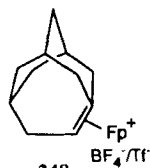
245



246 (X-ray)

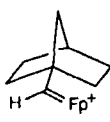


247

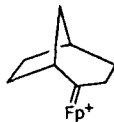


248

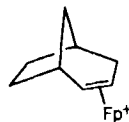
(X-ray)



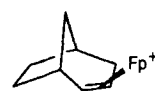
249



250



251



252

Scheme 12

than that calculated for **176** (136.5°) and pyramidalization at the bridgehead carbon atom C(1) is larger (39°) than in the olefin **176** (33.3°) itself (178b).

When the Pt(0) complex **239**, prepared from isomerically pure olefin **176**, was recrystallized from refluxing ether, a 7:3 mixture of **239** and **240** could be obtained. The relevance of this and complementary experiments to the transition metal catalyzed isomerization of olefins has been discussed (178a). Although smaller bridgehead alkenes could be generated and trapped at low temperature, attempts to stabilize bicyclo[2.2.1]hept-1-ene (**68**) by complexation with transition metals have hitherto failed (179). The Pt(II) complex of bicyclo[3.3.1]non-1-ene (**69**) has been prepared by displacement of ethylene in **241** (180). Whereas **69** dimerizes at room temperature with a half-life time of about 3 days, the complex **242** is stable for several months. In reactions of **69** with Pd(II)-acetate or (CH₃CN)₂PdCl₂, only bicyclo[3.3.1]non-2-ene rather than appropriate complexes could be detected.

Rearrangement of polycycloalkyl methylidenes bonded to dicarbonyl-(μ^5 -cyclopentadienyl)-Fe(II) (Fp⁺) provides an efficient route to Fe(II)⁺ complexes of bridgehead olefins (181). In this way the carbene complexes **243**, **245**, and **247**, readily available from corresponding bridgehead carboxylic acids, are converted at low temperature to the π complexes **244**, **246**, and **248**. The rearrangement involves a 1,2-shift of one alkyl group with concomitant stabilization of the incipient bridgehead carbenium ion by the adjacent Fp⁺ group. In the case of carbene complex **249**, ring expansion is followed by hydride shifts to give the carbene complex **250**, which eventually leads to the diastereomeric π complexes **251** and **252** (182).

IV. SPECTROSCOPIC PROPERTIES

Spectroscopic methods are indispensable tools for the ready identification of the molecular structure of noncrystalline compounds and for the detection of unstable intermediates. Beyond the gross structural features, spectroscopic results contain essential information about structural details. Earlier results in this area have been summarized by Zefirov and Sokolov (183). In this section, the more recent features of distorted double bonds apparent in NMR, IR, UV, and PE spectroscopy are presented.

A. Nuclear Magnetic Resonance Spectroscopy

Nuclei with magnetic moments are probes for the electronic environment in which they are located and may thus reflect structural details. With advanced NMR methods, the positions of such nuclei and their neighbors in a molecule can be located. However, despite many efforts to interpret the observed nuclear shielding and spin-spin coupling constants in terms of geometrical

distortions, the explanations have for most purposes remained qualitative. Nevertheless, it is of interest to discuss some of the ^1H - and ^{13}C -NMR results relevant to distorted olefins.

In the presence of alkyl groups, the vinylic proton in open chain and cyclic olefins resonates in the range of $\delta = 4.7\text{--}5.7$ ppm with the exception of cyclopropene (**59**) and cyclobutene (**8**) (**59**: $\delta = 7.01$; **8**: $\delta = 5.97$ ppm) (Table 9). Even the oop distortions in the bridgehead olefins **69**, **176**, **177** affect the chemical shift of the vinylic proton only to a small extent. Noteworthy is the small shift difference between *trans*-1-methylcyclooctene (**37c**) and 1-methylcyclohexene (**42c**) (Table 10).

The vicinal and geminal coupling constants $J_{\text{H,H}}^{\text{cis}}$, $J_{\text{H,H}}^{\text{trans}}$, and $J_{\text{H,H}}^{\text{gem}}$ have been determined for many undistorted mono- and disubstituted olefins (184). Whereas $J_{\text{H,H}}^{\text{cis}}$ is in many cases close to 10 Hz, $J_{\text{H,H}}^{\text{trans}}$ is larger and reaches 19.1 Hz in ethylene (185). In terminal olefins $J_{\text{H,H}}^{\text{gem}} \approx 0\text{--}4$ Hz and is thus much smaller than the vicinal coupling constants. Theory predicts that $J_{\text{H,H}}$ (vicinal) in olefins should decrease with an increase of the $\text{H}\text{--}\text{C}=\text{C}$ bond angle (186, 187) and hence with an increase of *s*-character in the carbon hybrid orbitals.

In cyclic olefins the range of $J_{\text{H,H}}^{\text{cis}}$ is very similar for six- to eight-membered rings (Table 9). The larger coupling constant of *trans*-cyclooctene (**37a**) is in accord with the general rule, that $J_{\text{H,H}}^{\text{trans}} > J_{\text{H,H}}^{\text{cis}}$ and hardly reflects its oop distortion (bend and twist). Significantly smaller vicinal coupling constants, which are related to in-plane distortions with bond angles much larger than 120° , are only found in cyclopropene (**59**) and cyclobutene (**8**). This may be interpreted in terms of an increase of *s* character in the orbitals, which the trisubstituted carbon atoms use for $\text{C}\text{--}\text{H}$ bonding. Attempts to predict CH_2 bond angles in terminal olefins have remained inconclusive (184, 186).

^{13}C Chemical shifts of olefinic C atoms in typical alkenes without heteroatoms fall into the range of $\delta = 100\text{--}160$ ppm (191, 192). With *Z*- (**17**) or *E*-2-butene (**15**) as standards ($\delta(^{13}\text{C}) = 124.2$ and 125.4 ppm, respectively) the signal of the less substituted C atom in mono-, geminal-di-, and trisubstituted ethylenes is shifted to higher field, whereas the higher substituted C atom resonates at lower field. The bridgehead olefins **69**, **176**, and **177** are no exception to this rule, although the downfield shift of the bridgehead C atom is larger than in *trans*-1-methylcyclooctene (**37c**) and 1-methylcyclohexene (**42c**) (Table 10).

In view of the limited number of known examples, it is questionable whether this small difference in ^{13}C chemical shifts is an indication of the oop distortions at the bridgehead carbon atom. In methyldene-cycloalkenes and similar olefins the dependency of the relative chemical shift on the number and kind of substituents (for alkyl groups parameterized in terms of steric corrections) has been related to charge differences between the two olefinic C atoms (195).

Table 9
 ^1H and ^{13}C Chemical Shifts (δ in ppm Relative to $(\text{CH}_3)_4\text{Si}$) and Selected Coupling
 Constants in Cyclic Olefins (183, 188)

Ringsize	3	4	5	6	cis-7	trans-7	cis-8	trans-8
	59	8	253	42a	38a	39a	36a	37a
$\delta\ ^1\text{H}[\text{ppm}]$	7.01	5.97	5.60	5.59	5.71		5.56	5.35 ^a
$J^{\text{cis}}[\text{Hz}]^{\text{b}}$	0.5-	2.5-	5.1-	8.8-	9.0-		10.0-	16.0 ^c
H,H	1.5	3.7	7.0	11.0	12.5		13.0	
$\delta\ ^{13}\text{C}[\text{ppm}]$	108.7	137.2	130.8	127.4	133.4	139.7/135.7	131.0	134.8
$J_{\text{C,H}}[\text{Hz}]$	228.2	168.6	161.6	158.4	155.0	158.0 ^d	155.0	151.0 ^c

^aReference 92.

^bThe range of vicinal coupling constants for substituted cycloolefins is given (185).

^cReference 189.

^dCoupling constant for the 139.7 ppm peak at -80°C (190).

Table 10
 Spectral Properties of the Bridgehead Olefins **69**, **176**, and **177**, *trans*-1-
 Methylcyclooctene (**37c**) and 1-Methylcyclohexene (**42c**) (152a, 153a)

		69	176	177	37c^a	42c^b
$^1\text{H-NMR}$	=C-H	5.65	5.40	5.30	5.26	5.31
δ [ppm]						
$^{13}\text{C-NMR}$	=C-H	125.1	127.4	124.9	127.4	122.3 ^c
δ [ppm]	=C	146.8	147.2	147.3	137.6	134.2 ^c
IR-spec-	C=C	1620	1618	1656	1654	1672
trum	=C-H	3022	3047	3020	--	3043
[cm^{-1}]		(811)	(781)	(838,811)	(880)	(791)
UV-spectrum						
λ_{max} [nm]		206	186,200	206	--	188 ^d
lg ϵ		3.8	3.8,3.7	3.9	--	3.85

^aReference 193.

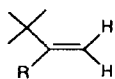
^bReference 194b.

^cReference 194a.

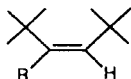
^dReference 92.

With the exception of cyclopropene (**59**) and cyclobutene (**8**), the ^{13}C chemical shift of the doubly bonded carbon atoms in cycloolefins with ring size 5–8 is centered around $\delta = 130$ ppm (Table 9). Comparison of *cis*-cycloheptene (**38a**) to the *trans*-isomer **39a** and of *cis*- (**36a**) and *trans*-cyclooctene (**37a**) reveals a small downfield shift of the olefinic ^{13}C signal in the *trans*-isomers. This observation is compatible with the general tendency that the ^{13}C chemical shift in *Z*-alkenes is smaller than in *E*-alkenes (196). A strong correlation with the oop distortions is not apparent.

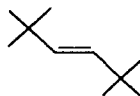
It was early recognized that the $^1J(^{13}\text{C}, \text{H})$ coupling constant that is dominated by the Fermi contact term increases linearly with the *s* character of the hybrid orbital, which the carbon atom uses for the C–H bond (197). In olefins such as ethylene (**1**), propene (**12**), and *tert*-butylethene (**254a**), $^1J(^{13}\text{C}, \text{H})$ ranges from 150 to 157 Hz, with the value for the substituted C atom being closer to 150 Hz. The $^1J(^{13}\text{C}, \text{H})$ coupling constants in distorted olefins should be compared to this range of 150–157 Hz, which is indicative of sp^2 hybridization. In 1,1-di-*tert*-butylethene (**254b**), the coupling constant



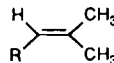
254 a R=H
b R=C(CH₃)₃
c R=CH₃



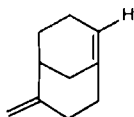
255 a R=H
b R=CH₂C(CH₃)₃



256



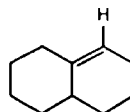
257 a R=CH₃
b R=C(CH₃)₃



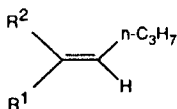
258



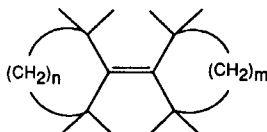
259



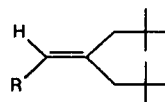
260



261 a R¹=H, R²=n-C₃H₇
b R¹=n-C₃H₇, R²=H



262 a n = m = 1
b n=1, m=2
c n=1, m=3
d n = m = 2
e n=2, m=3



263 a R=H
b R=C(CH₃)₃
c R=CH₃

($^1J(^{13}\text{C}, \text{H}) = 151.9 \text{ Hz}$) is compatible with hybridization at the $=\text{CH}_2$ carbon atom which is unaffected by the in-plane distortion at the substituted C atom.

The difference of coupling constants in *Z*- and *E*-1,2-di-*tert*-butylethene (*Z* (**255a**): 159.0 Hz; *E* (**256**): 149.4 Hz) is suggestive of reduced *s* character in the hybrid orbital of **256**. In **255a** the steric crowding of the two substituents leads to an increase of the C–C=C bond angles ($\sim 135^\circ$) and a corresponding decrease of *s* character in the hybrid orbitals used for C–H bonding.

In trisubstituted ethylenes such as trimethylethene (**257a**; $^1J(\text{C}, \text{H}) = 148.4 \text{ Hz}$) and 1,1-dimethyl-2-*tert*-butylethene (**257b**; $^1J(\text{C}, \text{H}) = 148.0 \text{ Hz}$), the coupling constants are surprisingly similar. This may indicate a similar and possibly slightly decreased *s* character in the hybrid orbital used for C–H bonding.

The smaller coupling constant found in tri-*tert*-butylethene (**66**; $^1J(\text{C}, \text{H}) = 143.2 \text{ Hz}$) must be discussed in terms of the in-plane bond angle opening and the twist angle Φ_T of 16° (198). Despite the oop distortions and a twist angle Φ_T of $\sim 21^\circ$ observed in the derivative of *trans*-cyclooctene (**37b**) (cf. Section II.B), the $^1J(\text{C}, \text{H})$ coupling constant in **37a** is only 4 Hz smaller than that of *cis*-cyclooctene (**36a**) (Table 9). The large $^1J(\text{C}, \text{H})$ coupling constants found in cyclopropene (**59**) and cyclobutene (**8**) are related to the increased *s* character in the hybrid orbital used for the C–H bond. It should be noted that the ^{13}C –H coupling constants in cycloalkenes with ring size 5–8 are very similar and centered around 157 Hz. Despite great differences in the $=\text{C}(\text{C})_2$ bond angle, the coupling constants ($^1J(\text{C}, \text{H}) = 154.2 \pm 0.7 \text{ Hz}$) in methyldene cycloalkenes with ring size 4–7 lack variation. This may indicate that these olefins are free of the effects of steric compression (198).

It may be concluded that the ^1H - and ^{13}C -NMR spectra of many distorted olefins have chemical shifts and coupling constants similar to those of standard alkenes. Noticeable exceptions are cycloalkenes with small rings and considerable in-plane bond angle distortions as well as double bonds with sterically demanding substituents, which give rise to considerable oop distortions. It remains to be seen whether the ^{13}C – ^{13}C coupling constants of doubly bonded C atoms, which correlate linearly with the product of the *s* character in the carbon hybrid orbitals and with the π -bond order in conjugated π systems (199), can be used for at least qualitative estimates of C–C bond distance and bond angle deformations in distorted double bonds.

B. Infrared and Raman Spectra

For simple molecules with *n* atoms, the vibrational spectra may be analyzed in terms of the $3n - 6$ normal vibrations. According to the relevant symmetry point group, the number of IR- and Raman-active as well as the inactive

frequencies can be determined (200). For planar ethylene of D_{2h} symmetry, there are five IR-, six Raman-active, and one inactive normal vibrations (Table 11, cf. also Section II.A) (201).

Three of the five IR-active vibrations are related to two in-plane and one oop (B_{1u}) bond angle distortions. The corresponding bands appear in the "fingerprint" area. The remaining two IR-active vibrations with frequencies around 3000 cm^{-1} are due to the in-plane symmetrical (B_{3u}) and antisymmetrical (B_{2u}) bond length deformations. Partially deuterated ethylenes were used for assignment of these nonplanar vibrations and to locate the twisting frequency at 1027 cm^{-1} (cf. Table 11). The 1623.2 cm^{-1} Raman-active frequency of ethylene (**1**) has been assigned to the C=C double bond stretching vibration.

In distorted olefins, the normal vibrations are coupled to other vibrations and hamper the analysis of the infrared spectra. It is therefore not surprising that little work has been done to analyze the vibrational frequencies—particularly those of the fingerprint area—with respect to the in-plane and the more interesting out-of-plane bond angle distortions in strained olefins. Most correlations between infrared spectroscopic properties and structural details

Table 11
Assignment of the Fundamental Vibrational Frequencies
for Ethylene (**1**) (200, 201)

Frequency [cm^{-1}]	Assignment		Activity ^a
	Symmetry	Label	
3019.3	A_{1g}	ν_1^b	R,p
1623.3		ν_2	R
1342.4		ν_3	R
1027	A_{1u}	ν_4	IN ^c
3272.3	B_{1g}	ν_5^b	R,d
1236		ν_6	R
946.2		ν_7	IR
943	B_{2g}	ν_8	R,d
3105.5	B_{2u}	ν_9^b	IR
810.3		ν_{10}	IR
2989.5		ν_{11}	IR
1443.5	B_{3u}	ν_{12}	IR

^aR = Raman, IR = infrared, p = polarized, d = depolarized.

^bBond length deformation.

^cIR and Raman inactive.

around distorted double bonds are based on the C=C double bond stretching and the adjacent =C-H bond vibration. We shall briefly discuss some pertinent results.

In 1,1- and 1,2-disubstituted olefins the stretching frequencies of the C=C double bond lie between 1635 and 1690 cm^{-1} . The frequencies of the symmetrical and antisymmetrical =C-H stretching vibrations are found at 3010–3095 cm^{-1} . In tri- and tetrasubstituted olefins with little distortion, the C=C double bond vibrations may be located at 1670–1680 cm^{-1} and 1650–1690 cm^{-1} , respectively. In cycloolefins the stretching frequency of the C=C double bond decreases, whereas the =C-H stretching vibration increases (202) (Table 12).

The fact that cyclopropene (**59**) absorbs at a higher frequency than cyclobutene (**8**) is due to coupling with the adjacent C-C single bonds, which are stretched concomitant with the C=C double bond in **59**, but not in **8**.

In view of the C=C and =C-H stretching frequencies of the *Z*- and *E*-isomers of 4-octene, the isomeric *cis/trans*-cyclooctenes **36** and **37a** differ surprisingly little. Similarly, the C=C frequencies of the bridgehead olefins **177** and **260** differ little from *trans*-1-methylcyclooctene (**37c**) (Table 10).

The rather low frequencies for C=C bond stretching in the Bredt-olefins **69**, **176**, **258**, and **259** may be an indication of reduced π -bond order (96). Whereas the in-plane distortions of the trisubstituted olefins **257a** and **257b** hardly affect

Table 12
IR Frequencies $\nu(\text{cm}^{-1})$ for C=C and =C-H Stretching Vibrations in Various Olefins (183, 202)

Alkene	ν (C=C)	ν_{as}^a (=C-H)	Ref.	Alkene	ν (C=C)	ν_{as}^a (=C-H)	Ref.
59	1641	3076	183	69	1620	3022	153a
8	1570	3060	183	176	1618	3047	153a
253	1615	3060	183	177	1656	3020	153a
42a	1654	3024	183	258	1633	--	96
38a	1650	3020	183	259	1620	--	96
36a	1664	3010	183	260	1666	3048	153a
37a	1658	3000	92,183	37c	1645	--	153a,193
261a	1670	3010	183				
261b	1650	3027	183				

^aAsymmetric stretching frequency.

Table 13
Raman Frequencies $\nu(\text{cm}^{-1})$ of the C=C Stretching Vibration
in Selected Olefins

Alkene	ν	Ref.	Alkene	ν	Ref.
257a	1678	106	263b	1636	103,106
257b	1663	106	66	1583	103,106
3	1675	203			
10	1638	103	24a	1658	76
82	1607	103	24b	1572	76
262a	1670	77	24c	1592	76
262b	1619	77			
262c	1545	77			
262d	1540	77			
262e	1490	77			

the stretching vibration, twist and pyramidalization in tri-*tert*-butylethene (**66**) may be the cause for the considerable shift to the lower frequency (Table 13).

Analogous structural changes have to be considered for the analysis of the decreasing double bond frequencies in the tetrasubstituted ethylenes of Table 13. However, it has been pointed out that twisting in the tetraisopropyl compound **10** is essentially absent (204). Comparison of the bisadamantylidenes **24a** and **24b** (Table 13) shows a considerable lower stretching frequency in the latter. This difference is almost certainly related to the changes in twist (**24a**: $\Phi_T = 0^\circ$; **24b**: $\Phi_T = 12.3^\circ$). The strong dependency of the C=C stretching frequency in **262a–e** also must be the result of twist caused by increasing steric repulsion between the juxtaposed methyl groups in the two rings (77).

In summary, infrared and Raman stretching frequencies of the C=C double bond are affected by in-plane as well as out-of-plane distortions. For an assessment of how the different distortions affect the stretching frequency of the C=C double bond, the coupling of vibrations cannot be ignored. The general importance of force constants determined experimentally from stretching frequencies or obtained from *ab initio* calculations for force field calculations of undistorted and distorted saturated and unsaturated carbon compounds can only be mentioned here (9, 11).

C. Ultraviolet Spectra

The ultraviolet spectra of ethylene (**1**) and its alkyl derivatives provide another source of information about the properties of the olefinic double bond. In order to discuss the spectra and correlate substituent effects with molecular structure, some aspects of theory are given first. According to LCAO-MO theory, the π -MO and π^* -MO of ethylene are obtained from the in-phase and out-of-phase combination of the $2p$ -AOs orthogonal to the σ -bonding system of the C=C double bond. The Hückel-MO energies, given by $\pi = \alpha + 1.0\beta$ and $\pi^* = \alpha - 1.0\beta$, lead to a π - π^* excitation energy of $\Delta E = 2\beta$. The substitution of alkyl groups for hydrogen on ethylene leads to a bathochromic shift. This is due to hyperconjugation (205) and the σ -donating property of the alkyl substituents (10), which may raise preferentially the energy of the π -MO and hence decrease the π - π^* excitation energy ($\Delta E_\pi < 2\beta$). Out-of-plane deformations at one or both C atoms of the double bond lead to a decrease of overlap and hence also to a π - π^* excitation energy $\Delta E < 2\beta$. Twist or rotation will similarly lead to decreasing overlap between the two 2σ -AOs and decreasing excitation energy. At a twist angle Φ_T of 90° a pair of degenerate orbitals is formed from which a singlet and a triplet state are derived (cf. Figure 5a). The energy levels for the appropriate configurations and electronic states as a function of the twist angle are given in Figure 5b and 5c. At $\Phi_T = 90^\circ$, the energy of the triplet state $^3B_{1u}$ has an energy minimum and is slightly lower than the maximum of the singlet ^1A_g state. The minimum energy of the singlet state $^1B_{1u}$ is again found for a twist angle Φ_T of 90° . For a more complete discussion of the ultraviolet spectrum of ethylene and its alkyl-substituted derivatives, a Rydberg state and the doubly excited state $(\pi^*)^2$ (see Section IV.E) have to be taken into account (207). The intense absorption band of ethylene (**1**) at 7.66 eV has been assigned to the electronic transition $^1B_{1u} \leftarrow ^1A_g (V \leftarrow N)$, whereas the 4.6 eV band of weak intensity is due to the excitation of an electron from the ground (^1A_g) to the triplet state $^3B_{1u} (T \leftarrow N)$ (cf. Table 14). The absorption band at 7.11 eV has been assigned to an electronic transition to a Rydberg state (207).

The ultraviolet spectra of a series of substituted ethylenes and sterically crowded olefins have been determined (Table 15).

The position of the absorption band is shifted slightly to the red with an increasing number of alkyl substituents. The maxima at 174–184.5 nm found for *Z*-1,2-disubstituted olefins are shifted to the red in *E*-isomers by 3–4 nm and reach 186–189 nm in 1,1-disubstituted olefins. Maxima of absorption bands are observed at 177–191 nm for trisubstituted and at 187–191 nm for tetrasubstituted olefins. The position of the maximum of the $V \leftarrow N$ band is further shifted to the red by a few nanometers in olefins with sterically demanding substituents like **66**, **255b**, and **263b**.

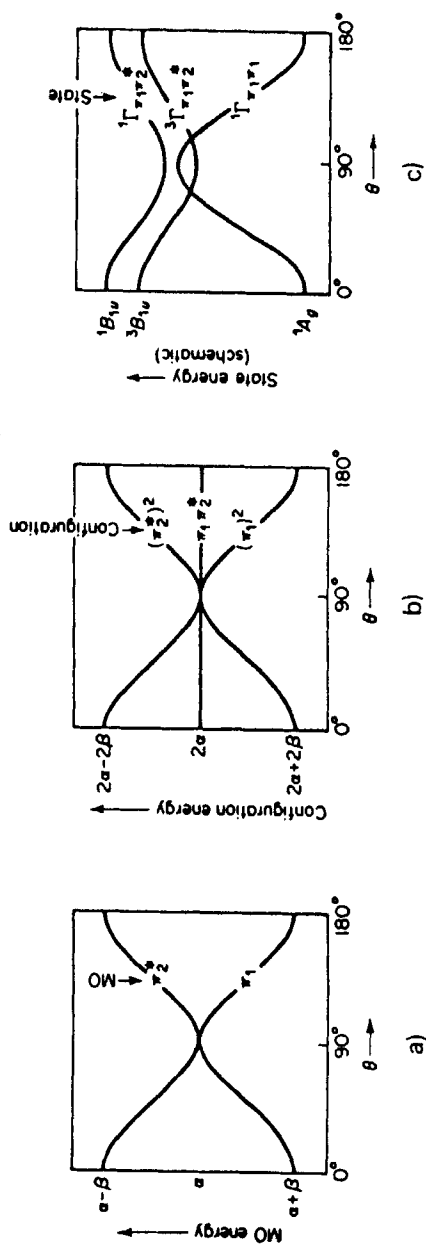


Figure 5. Schematic MO energies, configuration and state energies of ethylene as functions of the twist angle Φ_T . Adapted from ref. 206 with permission of Prentice-Hall Inc., Englewood Cliffs, New Jersey.

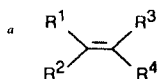
Table 14
Excitation Energies of Ethylene (**1**) (207) According to (a)
Symmetry Point Group and (b) Valence Bond Notation

$\Delta E[\text{eV}]$	$\lambda[\text{nm}]$	excitation	type of assignment	
			a)	b)
4.6		$\pi_2^* \leftarrow \pi_1$	$^3B_{1u} \leftarrow ^1A_g$	$T \leftarrow N$
7.11		$3s \leftarrow \pi_1$	$^1B_{3u} \leftarrow ^1A_g$	$R \leftarrow N$
7.66	163	$\pi_2^* \leftarrow \pi_1$	$^1B_{1u} \leftarrow ^1A_g$	$V \leftarrow N$

Table 15
Excitation Energies of Ethylene (**1**) and its Alkyl-Substituted Derivatives:
(A) in the Gas Phase (207a) and (B) in Cyclohexane (208)

A)					Observed excitation maxima E (eV, λ_{max})		Ionization Potential [eV]
Alkene	Substituents ^a				V $\rightarrow$ N ^b	R $\rightarrow$ N ^b	
	R ¹	R ²	R ³	R ⁴	($^1B_{1u} \leftarrow ^1A_g$)	($^1B_{3u} \leftarrow ^1A_g$)	
1	H	H	H	H	7.66	7.15	10.51
12	CH ₃	H	H	H	7.15	6.72	9.73
13	CH ₃	CH ₃	H	H	6.68	6.19	9.23
17	CH ₃	H	CH ₃	H	7.10	6.03	9.13
15	CH ₃	H	H	CH ₃	6.97	6.09	9.13
257a	CH ₃	CH ₃	CH ₃	H	6.75	5.74	8.68
3	CH ₃	CH ₃	CH ₃	CH ₃	6.61	5.40	8.30

B)					V $\leftarrow$ N	
					λ_{max}	ϵ^c
13	CH ₃	CH ₃	H	H	188.2	11300
254c	t-Bu	CH ₃	H	H	186.0	10850
254b	t-Bu	t-Bu	H	H	189.0	11650
263a	Np	Np	H	H	196.5	7900
257b	CH ₃	CH ₃	t-Bu	H	192.0	10050
66	t-Bu	t-Bu	t-Bu	H	194.5	13300
255b	t-Bu	Np	t-Bu	H	197.5	10500
263b	Np	Np	t-Bu	H	200.0	9650



^bFranck-Condon maxima, corresponding to vertical transitions.

^cWith the exception of **13** (vapor) and **263b** (vapor), the spectra were measured in cyclohexane solutions.

Table 16
UV Absorption (nm) (209, 210) and Ionization Potentials (eV) of Cycloalkenes (211)

				cis		trans		cis		trans		cis	trans
	55	8	253	42a	42b	43a	43b	38a	38b	39a	39b	36a	37a
$\lambda_{\max}$	<185	<185	<185/200	<190	248	--	385 ^c	--	248 ^c	--	300 ^c	185 ^c	196 ^c
			<194									208	
$IP_a(\pi)^a$	9.70	9.43	9.01	8.94				8.87				8.82	8.53
$IP_v(\pi)^b$	9.86	9.43	9.18	9.12				9.04				8.98	8.69

^a $IP_a(\pi)$ = adiabatic IP for π -ionization corresponding to the oop bond.

^b $IP_v(\pi)$ = vertical IP for π -ionization corresponding to the most intensive band (highest Franck–Condon factor).

^cReference 110b.

The ultraviolet spectra of cyclopentene (**253**) and cyclohexene (**42a**) and *cis*-cyclooctene (**36a**), structurally comparable to *Z*-but-2-ene (**17**) and similar *Z*-1,2-dialkylsubstituted olefins, have absorption maxima in the range of 183–185 nm (Table 16).

An additional shoulder at 200–220 nm observed in **253** and **42a** has been interpreted as $R \leftarrow N$ excitation (207a). The considerable shift of the UV absorption to longer wavelengths (compared with the *cis*-isomers) found in *trans*-cyclooctene (**37a**) and in phenyl-substituted *trans*-cyclohexene (**43b**) and *trans*-cycloheptene (**39b**) must be analyzed with respect to the oop bending in these olefins, which reduces the overlap between the $2p$ -AOs of the C=C double bond. Comparison of the ultraviolet spectra reported for the Bredt-olefins **69**, **176**, and **177** with the $V \leftarrow N$ band of trimethylethene (**3**) at 6.61 eV (207) may be an indication of slightly more distorted bridgehead double bonds. More experimental and theoretical work is needed before the spectra of these distorted olefins can be analyzed in terms of the in-plane, out-of-plane bond angle and bond length deformations and their impact on structure can be assessed.

D. Ionization Potentials

Ionization potentials, which can be determined by a variety of methods, are a valuable source of information about occupied orbitals and hence of molecular structure. Photoelectron spectroscopy has been a particularly sensitive probe for the sequence of occupied orbitals. By using Koopman's method, the ionization potentials can be assigned to valence orbital energies

Table 17
Vertical Ionization Potentials of Selected Olefins (213a)

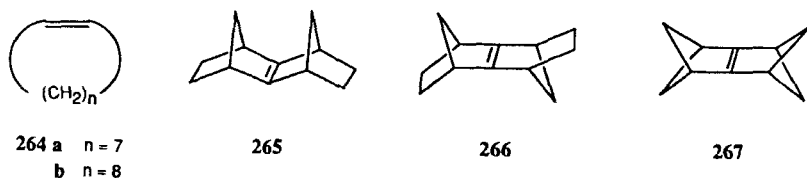
Alkene	IP _v [eV]	Alkene	IP _v [eV]
1	10.515		
13	9.239	254b	8.795
17	9.124	255a	8.695
15	9.122	256	8.741
3	8.271	66	8.169
10	8.13 ^a	24a	7.84 ^a
264b	8.98 ^b	265	8.12 ^c
67	8.92 ^b	266	7.90 ^c

^aReference 204.

^bReference 211.

^cReferences 212 and 213b.

obtained by MO methodology (212). The IP values of olefins strongly depend on substituents (Table 17) (213).



Increasing the number of alkyl groups leads to a rapid decrease of the ionization potentials from 9.7–9.4 eV in $\text{RCH}=\text{CH}_2$ to 9.3–8.7 eV in $\text{RCH}=\text{CHR}$ and to 8.6–8.25 eV in $\text{R}_2\text{C}=\text{CHR}$, while those of $\text{R}_2\text{C}=\text{CR}_2$ appear in the range of 8.3–8.0 eV. *E*- and *Z*-isomers of disubstituted olefins differ surprisingly little in their ionization potentials (ΔE for *E/Z*-2-butene = 0.002, ΔE for *E/Z*-*tert*-butylethene = 0.046 eV). Similar results have been obtained for the *E/Z*-isomers of diisopropyl-dimethylethene ($\Delta E = 0.03$ eV) (204).

A more detailed analysis has to take into account the number of carbon atoms in the substituents and their branching. The σ -donating and hyperconjugative interaction of the alkyl substituents appears to play an important role in the dependency of the IP values on substitution pattern. With a few exceptions, the out-of-plane particularly twist distortions of tetrasubstituted ethylenes appear to be too small for a shift in ionization potential (213).

(Table 17). Only in tetrasubstituted olefins with *tert*-butyl groups and in *trans*-cyclooctene (**37a**), are the IP values slightly shifted to lower energies. With the exception of cyclopropene (**59**) and cyclobutene (**8**), the ionization potentials of the cycloolefins with ring size 5–8 fall in the range observed for disubstituted ethylenes (Table 16).

The difference of the ionization energy $\Delta E = 0.29$ eV between *cis*- (**36a**) and *trans*-cyclooctene (**37a**) has been discussed in terms of twist and oop bending distortions (214). By ignoring the oop bending, a rough estimate gave a twist angle Φ_T of about 20° , which is to be compared with that observed in **37b** (21°) (21). The difference of ionization potential $\Delta E = 0.08$ eV found for the bridgehead olefins **176** and **177** is too small for any acceptable analysis of the modes of distortions; both IP values fall within the range expected for trisubstituted, planar ethylenes (214). The difference $\Delta E = 0.2$ eV in the ionization of *syn*- (**265**) and *anti*-sesquinorbornene (**266**) is larger than those of **37a** and **1**. The higher value has been attributed to the oop bending in the *syn*-isomer, which should reduce the overall electron repulsion and increase the *s* character in the C orbital used for π bonding. Both factors contribute to the increase in the ionization potential relative to that of the *trans*-isomer.

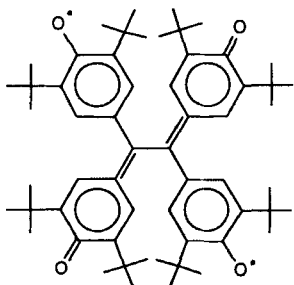
E. Sudden Polarization

For a more complete discussion of the electronically excited states of planar and twisted ethylene and alkenes, four rather than the three different electronic states shown in Figure 5 have to be considered (Table 18) (74, 75).

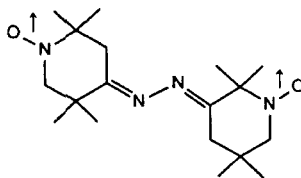
The $Z(^1A_1)$ state, hitherto ignored, correlates with a doubly excited state of planar ethylene. At a torsional angle of 90° , the $N(^1B_1)$ and $T(^3B_{1u})$ states have biradical character. Typical examples of a singlet and triplet biradical are given by bisgalvinoxyl (**268**) and the nitroxide (**269**).

Table 18
The Calculated Four π^2 ($2e^2$) States (74a), Double Bond Lengths, and Energies of Ethylene (**1**) with 90° Twist Relative to the Planar Ground State (74b)

State	Electron configuration	Energy rel. to planar ethene [eV]	Type of state	C=C [pm]	Symmetry type of orbital
N	$(1\sigma_g)^2 1\Sigma_g^+$	2.6	biradical	149	$^1B_1$
T	$(1\sigma_g)(1\sigma_u) 3\Sigma_u^+$	2.7	biradical	149	$^3A_2$
V	$(1\sigma_g)(1\sigma_u) 1\Sigma_u^+$	5.9	zwitterion	140	$^1B_2$
Z	$(1\sigma_u)^2 1\Sigma_g^+$	5.8	zwitterion	140	$^1A_1$



268



269

Salem recognized that the $V(^1B_2)$ and $Z(^1A_1)$ states are highly polarizable and zwitterionic (74, 75). The energy separation between these two states is very small and they can easily "borrow" ionic character from each other. None of the four different electronic states of ethylene with a twist angle Φ_T of 90° develops a dipole moment. Perturbation of these states by pyramidalization of one CH_2 group or by an external electric field leads to dipole moments. This computational result has been named "sudden polarization" by Salem and co-workers (74, 75). According to a detailed analysis, the dipole moments of these states increase rapidly with pyramidalization with twisting angles Φ_T from 75° to 90° (74c). It has been suggested that such zwitterionic excited states play a key role in the photochemistry of vision (215, 216).

V. STRAIN

The concept of strain, originally based on bond angle distortions, has been extended and today it is discussed in terms of bond length and bond angle deformations as well as torsional and nonbonded interactions (217, 218). The deformations exerted by nonbonded interactions or bond angle distortions lead to an overall adjustment of a structure. Nevertheless, it is desirable to identify domains of preferential deformations and analyze, for instance, the strain of a bridgehead olefin in terms of the strain of the double bond and the residual strain associated with the carbon skeleton (219). The strain energy, associated with geometrical distortions, has provided valuable information about carbon compounds and the predisposition for their reactivity. Its origin has recently been discussed by Wiberg (218).

A. Strain Energy

The strain energy is defined as the difference between the observed heat of formation and that calculated for a strainless structure with the same number

Table 19
Group Increments for the Calculation of Heats of Formation of
Strainless Model Hydrocarbons

Group	Increment [kcal/mol]		Group	Increment [kcal/mol]	
	a)	b)		a)	b)
CH ₃	-10.12	-10.12		+15.00	+14.87
CH ₂	-4.926	-4.92		+18.80	+17.30
CH	-10.9	-1.75		+20.19	
	+0.8	-0.06		+20.19	+18.40
				+24.57	+24.57

^aReference 220.

^bReference 221.

and arrangement of atoms (218). Whereas the heat of formation of a compound from the elements is well defined, the energies of bond or group increments needed for estimation of the energy of the corresponding strainless structure depend on certain assumptions. Given reasonable and self-consistent definitions, the consequences of the different approaches are negligibly different, because strain energies are only used for comparisons. In many cases, the group increments of Franklin have been used (220) (Table 19).

Table 20
Experimentally Determined Differences in Strain Energies (kcal/mol)

17/15	255a/256	36a/37a	264a/227	264b/67	69
cis/trans	cis/trans	cis/trans	cis/trans	cis/trans	
-1.13 ^a	-9.37 ^d	9.26 ^c	2.87 ^c	3.34 ^c	12 ^c
-1.20 ^b	-9.34 ^c				
-1.0 ^c					

^a $\Delta\Delta H_f^0(g)$, reference 221.

^b ΔH (equilibrium at 400°C), reference 222.

^c ΔH (hydrogenation), reference 223.

^d $\Delta\Delta H_f^0(l)$, reference 221.

^eCalculated from heat of reaction with CH₃COOH relative to **257a**, reference 219.

In suitable cases such as *cis/trans*-isomers, the difference in strain energies can be determined from equilibrium constants or heats of hydrogenation. It is apparent from Table 20 that both methods give similar results. The strain energy of the *Bredt*-olefin **69** has been estimated from the heat of reaction with acetic acid, with the calculated ΔH_R of the corresponding reaction of 2-methyl-2-butene (**257a**) as standard (219).

For many strained hydrocarbons and alkenes, heats of formation are not known. In these cases, computational methodology may be used. For a number of molecules, the total energies determined by *ab initio* calculations and transformed into heats of formation by special group equivalents may be used (81b). Strain energies have also been obtained via isodesmic reactions, which measure deviations from the additivity of bond energies (224).

The force field methodology is of particular interest for alkanes and alkenes, because they provide strain energies as well as structural features (9, 61).

B. Olefinic Strain

Schleyer introduced the concept of olefinic strain (OS) (225, 226) for interpreting the stability of bridgehead olefins. Based on an earlier proposition by Turner (219), that the strain energy of a bridgehead alkene can be approximated by the strain of the double bond and the residual strain of the carbon skeleton, it was argued that the change in strain energy upon hydrogenation of a bridgehead olefin might be used as an index of its stability. The specific structural features around the bridgehead double bond are thus related to those of the corresponding substructure of the alkane.

Olefinic strain energies are obtained as a difference between the total strain energy of the olefin in the most stable conformation and the total strain energy of the most stable conformer of the parent saturated hydrocarbon. Olefinic strain energies (OS) and heats of hydrogenation (ΔH_H^0) are related by a constant difference, 26.1 kcal/mol, which corresponds to the heat of hydrogenation ΔH_H^0 for a hypothetical unstrained trisubstituted olefin to the hypothetically unstrained alkane (225). Transformation of the two tricoordinated carbon atoms of a strained double bond into tetracoordinated carbon atoms may be associated with a reduction or increase of strain. Positive values of OS, associated with ΔH_H^0 values larger than 26.1 kcal/mol, are an indication of the reduction of strain upon hydrogenation. Typical examples are given in Table 21.

Negative OS energies reduce the calculated ΔH_H^0 values and indicate that the parent alkanes are more strained than the corresponding olefins. This class of strained alkenes are considered "hyperstable" and less reactive.

It has been mentioned earlier that *Bredt* attempted to correlate the stability of bridgehead olefins with that of the appropriate *trans*-cycloalkenes. Other

Table 21
Olefinic Strain (OS) (kcal/mol) of Bridgehead Olefins (225)

68	69	176	177	180	181	215a	218
34.9	15.2	9.1	14.1	19.5	20.6	-10.6	-13.0
	13.8 ^a						
	16.1 ^b	11.0 ^b	16.2 ^b	21.8 ^b			

^aReference 227.

^bReference 228.

similar propositions have been reported (90, 91, 152a, 229). A more reliable parameter for evaluation of the stability of Bredt-olefins and the prospects of their isolation is given by the olefinic strain: compounds with $OS \leq 17$ kcal/mol should be stable at room temperature, whereas those with $17 \text{ kcal/mol} \leq OS \leq 21$ kcal/mol may be observed at low temperature and those with $OS > 21$ kcal/mol should be unstable and may only be formed as transients (231a). While bicyclo [2.2.1] hept-1 (2)-ene (**68**) (79) and bicyclo [2.2.2] oct-1 (2)-ene (**182**, $OS = 40.4$ kcal/mol) have been trapped but not observed directly (230), the isomeric bicyclo [3.2.2] non-1-enes **180** and **181** have been detected at -80°C (231). The olefinic strain indicates that the known bicyclo [3.3.1] non-1-ene (**69**) should prefer a chair/half-boat to a chair/half-chair structure (225).

Two examples of hyperstable bridgehead olefins, which have been prepared and for which negative OS values have been calculated, are also given in Table 21. The double bond of bicyclo [4.4.2] dodeca-1-ene (**218**) (170) resisted hydrogenation and, due to the slow rate of hydrogenation, the heat of hydrogenation of **215a** could not be determined (232).

The relation between the experimentally determined strain and structure is illustrated with the *Z/E*-isomers of 2-butene. Electron diffraction (27) and microwave analysis (233) of *Z*- (**17**) and *E*-2-butene (**15**) reveal that the strain in **17** (~ 1 kcal/mol, cf. Table 20) is distributed over several parameters. Most significant is the opening of the $\text{C}-\text{C}=\text{C}$ (**17**: 125.4° ; **15**: 123.8°) and the inner $\text{H}-\text{C}-\text{C}$ angles (**17**: 114.5° ; **15**: 121.5°). In *Z*-2-butene (**17**) (which has C_{2v} symmetry) the contribution of twisting of the double bond for removal of the short inner $\text{H} \cdots \text{H}$ distance is insignificant (233).

Since the structural parameters obtained by consistent force field calculations reproduce the experimental data rather well, a similar structure-strain analysis for *Z*- (**255a**) and *E*-1,2-di-*tert*-butylethene (**256**) is appropriate (Table 22). The structure of the *E*-isomer **256** most likely has C_{2h} symmetry. The $\text{C}=\text{C}$ bond length corresponds to that calculated for *Z*- (**17**) and *E*-2-butene (**15**), whereas the $\text{C}-\text{C}=\text{C}$ bond angle is 2.4° larger than that of **15**.

Table 22
Experimental Bond Angle and Bond Length Data for
Z/E-2-Butene (**17/15**) and *Z/E*-1,2-di-*tert*-Butylethene
(**255a/256**)

bond angle				
(C-C=C) [°]	17	15	255a	256
a)	125.4	123.8		
b)	126.7			
c)	127.6	123.5	135.2	125.9
bond length				
(C=C) [pm]	17	15	255a	256
a)	134.6	134.7		
b)	135.0			
c)	133.3	133.4	133.2	133.3

^aReference 27.

^bMicrowave spectrum (233).

^cErmer/Lifson CFF (62, 63).

The structure of the *Z*-isomer **255a** is significantly different. The nonbonded interaction between two hydrogen atoms of the two *tert*-butyl groups caused a calculated opening of 12.9° relative to the reference value of 122.3° for ethylene (**1**). Due to the torsion of the double bond (C-C=C-C dihedral angle = 5.1°), the *tert*-butyl groups avoid their unfavorable staggered orientation with

Table 23
Calculated Strain Energy and Structural Parameters of Some
Olefins (77)

	64	262a	262d	262e
ΔH_f° [kcal/mol]	-10.43	-13.18	-34.16	-21.18
Strain [kcal/mol]	97.23	76.04	53.74	72.46
Torsion [°]	44	0.05	5.5	4.9
oop bend [°]	0.0	1.1	0.0	0.6/0.5
C=C length [pm]	137.9	133.6	137.1	137.9

respect to the double bond and make more room for the inner hydrogens. According to these calculations, the relief of steric compression in **255a** is achieved to a large extent by bond angle opening. As for *Z*-2-butene (**17**), the extra strain in **255a**, which is 2.23 kcal/mol larger than the experimental value, is distributed over several deformation modes with bond angle opening as dominant factor. Hence, the dominant modes for accommodation of strain in a given molecule depends critically on its carbon skeleton and the constraints imposed by the latter (Table 23).

According to MM2 calculations, the highly strained tetra-*tert*-butylethene (**64**) prefers a large torsional angle (cf. Section II.B). The biscycloalkylidenes **262a** and **262d–e** behave quite differently (77). The strain in these compounds is related to an increase in C=C bond length, an adjustment of bond angles with only a small torsion, and negligible oop bend.

It was mentioned earlier that the strain of a molecule is distributed over various degrees of freedom. Nevertheless, it is possible to distinguish olefins with preferential if not exclusive in-plane distortions from those with out-of-plane bending and torsional deformations.

In cycloolefins of decreasing ring size $6 \rightarrow 3$, the strain increases with a concomitant decrease of the C=C–C bond angles. For a more detailed analysis, it is of advantage to consider the olefinic strain (Table 24).

The excess of strain in cyclopropene (**59**) over cyclopropane (**8**) is related to the different changes in intra-ring bond angles. The decrease of the bond angle at a trigonal center from 120° to 60° should lead to a larger increase in strain than the bond angle contraction upon formation of cyclopropane. The larger bond angle in cyclobutane should reduce the excess strain upon introduction of two trigonal centers. The negative strain calculated for cyclopentene (**253**) is due to the torsional strain in cyclopentane, which is reduced upon dehydrogenation (218). For the larger rings like cycloheptane and cyclooctane, torsional as well as transannular strain and their decrease in the *trans*-cycloolefins **39a** and **37a** have to be considered.

Computational comparison of the estimated strain energy in *trans*-cycloheptane (**39a**) with that of the corresponding *cis*-isomer **38a** indicates **39a** to be less stable by 27 kcal/mol (64). According to the difference in heats of hydrogenation, *trans*-cyclooctene (**37a**) is more strained by 12.2 kcal/mol than the *cis*-isomer (**36a**). In both cases, oop bending and twist may account for the additional strain in the *trans*-isomers. With increasing ring size, the difference in strain energies between *trans*- and *cis*-isomers decreases, with *trans*-cycloundecene and *trans*-cyclododecene being more stable than their *cis*-isomers (218).

Analyses of strain-related structural features of olefins with symmetrical out-of-plane deformations are essentially based on computational results. For the chemistry of this family of strained olefins see Section VI.

Table 24
Experimental Heats of Formation $\Delta H_f^0(g)$ (kcal/mol), Strain Energies (SE), and
Olefinic Strain Energies (OS) of Cycloalkenes (218)

a)					38a	39a	36a	37a
	59	8	253	42a	cis	trans	cis	trans
ΔH_f	66.2	37.45	8.23	-1.08	-2.19	--	-6.45	4.70
SE ^a	55.2	28.40	4.10	-0.30	3.60	--	4.20	16.40
OS ^b	27.7	1.9	-2.1	-0.30	-2.70	--	-5.50	6.70
b)								
	60	61	62	63	70^c	71^c	72^c	
ΔH_f	92	145	136	91	125	109	108	
SE ^a	87	130	126	86	101	78	69	
					33.7 ^d	19.3 ^d	13.8 ^d	
OS ^b	35	66	71	55	73	24	--	

^aStrain energies (SE) are obtained as difference of heats of formation between the olefins indicated and the sum of bond increments for their strainless counterparts.

^bFor definition of the olefinic strain (OS), see Section V.B.

^cMM₂ calculation, reference 234.

^dPer C₄H₄ unit.

The rooflike structures of **61** and **62** have been analyzed in terms of orbital interactions (cf. Section II.B.2) and with respect to minimization of the strain in the σ bonds: concomitant with the reduction of the C(*sp*³)–C(*sp*²)–C(*sp*³) bond angle of 237° in the planar form of **61** to 214°, the strain energy decreases by 13 kcal/mol (218). Similarly, the oop bending in **62** reduces the strain by 16 kcal/mol. The higher olefinic strain of **62** may be attributed to increasing 1, 3-interactions between the hydrogen atoms. The isomeric bridgehead olefins **60** and **63** have essentially the same ΔH_f and the same strain energy. The large difference in olefinic strain is largely due to the strain in the corresponding alkanes, with bicyclo[2.2.0]hexane being more strained by 20 kcal/mol (Table 24b) (218).

The columnenes or [n]beltenes such as **70–72** (n = 3–5) are attractive molecules by virtue of their intriguing structures and the cavity to be expected for larger systems (86,234). The strain energy per –CH₂–C=C–CH₂ unit, which decreases monotonically from [3]beltene to [12]beltene, is related to the decrease in oop bending. Hydrogenation of **70** and **71** is accompanied by relief of strain. The decrease of strain upon hydrogenation of **71** is

considerable smaller, because in the perhydro compound the cyclohexane rings exist as flattened boats.

With the exception of sesquinorbornenes such as **49–54** and **265–267**, strained olefins with symmetrical oop bending like **55** and **56** and the columnenes ([*n*]beltenes) **70–72** have a fixed geometry. The possible hingelike bending motions about the double bond in the sesquinorbornenes **265**, **266**, and **267** have been explored using a force field approach (84). Although the angle of bending of 27° about the double bond in **266** is much larger than that observed in **49** (see Table 5), the transition state for topomerization lies only 1.7 kcal/mol above the ground state. For **265**, where the calculated bending angle is in good agreement with the experimental value of **53**, a minimum structure with 2.9 kcal/mol above the ground state which is bent 35° in the opposite direction from planarity has been found. Both structures are linked by a transition state 4.2 kcal/mol above the ground state. For **267**, a sesquinorbornene yet to be prepared, a planar transition state 6.2 kcal/mol above the ground-state structure with a bond angle of 35° was obtained. This possible dynamic behavior of sesquinorbornenes needs further investigation and experimental verification.

The chemical consequences of strain are of key importance for our understanding of structure and reactivity (235–237). The use of *trans*-cycloolefins as model systems for the reactivity to be expected for corresponding bridgehead olefins has already been mentioned. The olefinic strain has been proposed as a parameter to interpret stability and also to predict the reactivity of bridgehead olefins. Although experimental evidence in support of the argument is scarce, a linear correlation of OS with rates might be expected for reactions provided that linear free-energy relationships are applicable.

Based on a comparative analysis of results obtained for the structure of bridgehead olefins, it has been proposed that the total energy of the oop deformations (V_{oop}) of a bridgehead double bond might provide a more quantitative reactivity criterion. A rough estimate leads to $V_{oop} \approx 15$ kcal/mol, which is at least necessary for a bridgehead olefin to dimerize at room temperature (238).

VI. STRAIN AND REACTIVITY

Early in the history of chemistry it was suggested by Baeyer that strained compounds might be more reactive than unstrained ones (2). While it is true that ground-state destabilization may lead to enhanced reactivity, a more detailed analysis of reactivity has at least to consider electronic and steric factors in ground and transition states.

The structural and energy features of strained compounds have been

discussed earlier. Important aspects of the transition state to be considered are the position of the activated complex along the reaction coordinate and its energy. In an early transition state, the activated complex will structurally resemble the reactants and little strain energy will be released.

The relation between strain and reactivity may be illustrated with electrophilic reactions of cyclopropane and cyclobutane (218). The decrease in strain is essentially equal in both compounds, but cyclopropane is highly reactive, whereas cyclobutane is essentially inert. Acid-catalyzed ring opening, for example, is controlled by the basicity of the two cycloalkanes. The latter are only slightly deformed by protonation and little strain is therefore released.

Sterically demanding substituents, which give rise to distortions, may also reduce reactivity. Examples are given by the strained olefins tri-*tert*-butylethene (**66**) and tetraeneopentylethene (**82**); the former reacts only slowly and the latter not at all with bromine (103, 239). Tetra-*tert*-butylcyclobutadiene (**87**) and betweenanenes **141**, **144**, and **146** also belong to this class of highly strained compounds where reactions are prevented by steric hindrance (95, 240).

In this section mechanistic aspects of some typical reactions performed with strained olefins are discussed and the possible implications of computational results obtained for the transition-state geometry are indicated.

A. Rotational Barriers

In simple alkenes, thermal *Z/E*-isomerizations have a free-energy barrier of 60–65 kcal/mol (241, 242). The reaction profile for rotation around a double bond requires that at 90° the triplet state is more stable than the singlet state (cf. Figure 5). Thus, a temporary *S* → *T* crossing might be considered. However, the high Arrhenius factors observed for the gas-phase isomerization of 1,2-*cis*-²H₂-ethylene **270** and **17** indicate that thermal isomerizations proceed exclusively via the singlet state (243).

The rotational barriers of the olefins **17**, **255a**, and **271** decrease with increasing strain energy (244) (Table 25). A more detailed analysis suggests that ground-state destabilization is an important factor for the reduction of the activation energy, but strain is still apparent in the transition state (245). It has been shown that the rotational barriers, which vary over a range of nearly 30 kcal/mol, can be described by a unique torsional potential (65 ± 0.9 kcal/mol) if corrections are made for the perturbation, exerted in the ground and transition states, by the substituents.

Likewise, the *trans/cis*-isomerization of the more strained *trans*-cycloheptene (**39a**) is faster than that of *trans*-cyclooctene (**37a**) (114a, 246). It should be mentioned that a negative entropy of activation has been found for the isomerization of **39a**.

progress from the two sp^2 -hybridized carbon atoms toward sp^3 -hybridized centers is small in the transition state and electrophilic additions to alkenes are expected to be rather insensitive to strain effects. An *ab initio* analysis for the addition of electrophiles to ethylene (**1**) leads to the conclusion that, in the transition state, the double bond is stretched slightly, but little pyramidalization and other geometrical deformations are apparent (247).

The effects of *cis*/*trans*-isomerism on electrophilic additions to 1,2-disubstituted alkenes are illustrated by examples shown in Table 26 (94).

It is apparent that release of strain and steric hindrance to attack of the proton are negligible for these isomers. Similar results have been obtained in the protonation of 1-methylcyclopentene (**274**) and 1-methylcyclobutene (**275**), where the small rate difference leads to the conclusion "that little change in alkene structure at the transition state has occurred" (237).

Oxymercuration and bromination, which occur by way of bridged transition states, show large k_Z/k_E ratios for *Z*-(**255a**) and *E*-1,2-di-*tert*-butylethene (**256**). Steric hindrance of attack may account for the exceptionally high k_Z/k_E value in the reaction of arylsulfenyl chloride with **255a** and **256** (94). The formation of an *S*-phenyl-episulfonium cation (**276**) with a pyramidal sulfonium atom is less hindered in the *Z*- than in the *E*-isomer (248).

In contrast to the protonation of the disubstituted alkenes mentioned above, high k_{trans}/k_{cis} ratios of 9×10^8 and 3×10^3 , respectively have been observed in the acid-catalyzed addition of methanol to the *trans*- and *cis*-isomers of cycloheptene (**39a** and **38a**) and cyclooctene (**37a** and **36a**) (114a). The rate constants reflect partially the release of strain in the transformation of the cyclic olefins to the appropriate cycloalkyl cations. Comparison of the relative activation energies for these addition reactions with the difference of strain release leads to the estimate that the response to strain effects is about 60%. In a more recent study of the acid-catalyzed hydration of *cis*- (**36b**) and *trans*-1-methylcyclooctene (**37c**), it was concluded that two conformationally different 1-methyl-carbocationic intermediates are

Table 26
Rate Ratios k_Z/k_E for Electrophilic Attack on Isomeric *Z/E*-Alkenes
 $R-CH=CH-R$ (94)

R=		H ₃ O ⁺	ArSCl	Hg(OAc) ₂	Br ₂
tert-Bu.	(255a/256)	3.8	1.6×10^5	>100	52
i-C ₃ H ₇	(272b/273b)	0.5	0.5	0.42	0.42
C ₂ H ₅	(272a/273a)	1.2	9.2	6.2	1.2
CH ₃	(17/15)	2.1	3.1	3.4	1.6

formed (249). The *trans*-isomer leads to an unstable crown or twist cation, whereas the *cis*-isomer forms the cation in a boat-chair conformation. If the acid-catalyzed addition of methanol to *cis*- (**36a**) and *trans*-cyclooctene (**37a**) gives rise to cations in two different conformations, the linear correlation cited above is all the more surprising.

For the hydronium-ion-catalyzed *hydration* of bicyclo[4.2.1]non-1-ene (**177**) and bicyclo[4.2.1]non-1(8)-ene (**176**), appreciable solvent isotope effects have been observed. Since these correspond to those found for reactions of unstrained olefins, it was concluded that the hydration proceeds as with unstrained alkenes by a two-step mechanism: protonation of the double bond is followed by addition of the nucleophile (152b). The strained olefin with its distorted double bond is higher in energy and more reactive than an unstrained alkene. Hence, the transition state for protonation of Bredt-olefins is expected to be an early one (95).

The rates of hydration of the Bredt-olefins **69** and **176** (Table 27) have been used to estimate strain effects in electrophilic reactions of these strained olefins. It was estimated that the 10^5 -fold rate increase of **69** over 2-methyl-but-2-ene (**257a**) is due to about 50% strain release in the transition state of protonation.

The three Bredt-olefins **69**, **176**, and **177** added acetic acid without catalysis of mineral acid to give exclusively the corresponding bridgehead acetates (250). The rates of addition were used together with the solvolyses rates of the two isomeric bridgehead bromides for an evaluation of the strain differences in the olefins **69**, **176**, and **177**. On the assumption that the transition states of protonation resemble the carbenium ions and that solvation effects are negligible, it was estimated that **176** and **177** are less strained than **69** by 4 and 3 kcal/mol, respectively. With an absolute value of strain of 12 kcal/mol for **69** (cf. Table 20), the strain energy in bicyclo[4.2.1]-non-1(8)-ene (**176**) and bicyclo[4.2.1]non-1-ene (**177**) is calculated to be 8 and 9 kcal/mol, respectively. Thus, the two isomeric olefins have strain energies similar to that of *trans*-cyclooctene (**37a**) (250).

Strain-related features in *epoxidation* of strained olefins by peracids were first discussed for the *cis/trans*-isomers of cyclooctene (189). The rate

Table 27
Relative Rates of Electrophilic Addition to Bredt Olefins (152b)

Reagent	69	176	177	257a
H ₃ O ⁺ (25°C)	1.24×10^5	1.12×10^3	--	(1)
CH ₃ COOH (25°C) ^a	2.32×10^{-3}	8.43×10^{-6}	3.33×10^{-5}	--

^aRate of the addition of acetic acid in 0.1 M solution (250).

Table 28
Relative Rates of Epoxidation by Metachloroperbenzoic Acid in CH_2Cl_2 at 0° (227) and Strain (SE) and Olefinic Strain Energies (OS) (kcal/mol): In Dienes **277a,b** and **278a,b**, the Rate and Strain Energies for the First Double Bond are Given

	69	189b	277a	278a	277b	278b
k_{rel}	4570	135	570	9650	53.8	23200
SE	31.7	25.0	29.4	24.2	36.1	31.2
OS	13.8	0.5	-2.1	2.9	2.7	6.7

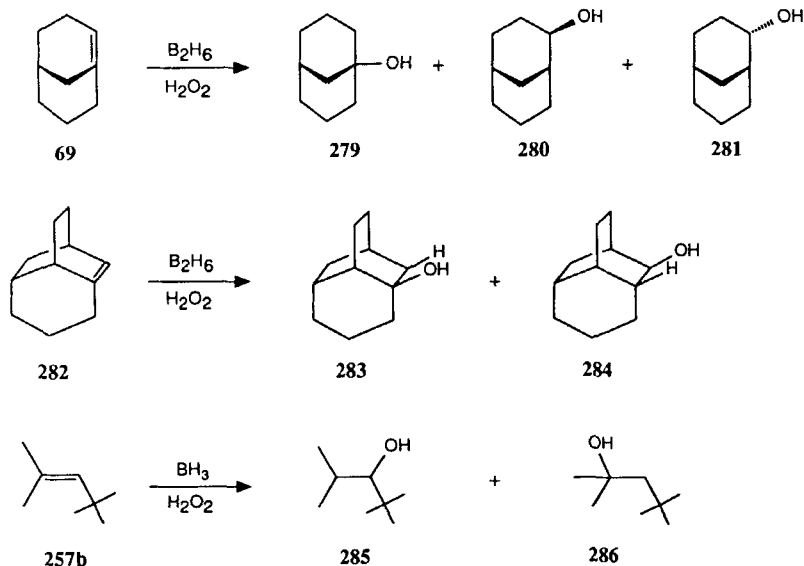
acceleration (by a factor of 90) was explained in terms of an epoxide-like transition state and the possible strain release in the reaction of olefins with oop bending and twist distortions.

In a recent study, Shea discussed the rate acceleration in epoxidations of bridgehead olefins with respect to strain effects (227) (Table 28). Significant rate ratios are observed for these strained olefins. While a relationship between the kinetic results and strain-related properties like strain or olefinic strain energies could not be established, a reasonable correlation between $\log k_{\text{rel}}$ and the ionization potentials of the strained olefins was found. The absence of a rate-strain relationship might be due to the structural features of the transition state in epoxidation. According to the generally accepted mechanism for epoxidation by peracids, the oxygen is transferred in a concerted process. A simulation of the oxygen transfer to ethylene revealed that the elongation of the carbon-carbon double bond is small in the transition state (251).

Little work has been carried out to probe the reactivity of the double bond of strained olefins by *hydroboration*. In an early investigation it was found that hydroboration of bicyclo[3.3.1]non-1-ene (**69**) occurs with low regioselectivity but with reasonable stereospecificity (**279:280:281** $\approx$ 30:64:6) (252) (Scheme 13). However, it remains to be seen whether **281** is a primary product of the reaction with borane.

Similarly, 4-homoisotwist-2-ene (**282**) is hydroborated to give **283** and **284** with low regioselectivity (**283:284** = 23:77) and high stereoselectivity (253a, 253b). These results may be compared to the reaction of 1-*tert*-butyl-2,2-dimethylethene (**257b**), which upon hydroboration-oxidation yields **285** and **286** in a ratio of 98:2 (253c).

It is well established that hydroboration of alkenes proceeds preferentially, if not exclusively, by syn-addition with high regioselectivity: the boron



Scheme 13

becomes attached to the less substituted carbon atom with high stereoselectivity. In comparison to electronic effects, steric effects are of minor importance in hydroborations with borane.

According to MNDO and *ab initio* results for the addition of BH_3 to ethylene (**1**), the reaction is highly exothermic and proceeds via a reactant-like transition state with the double bond elongated to 138–140 pm and little pyramidalization (254). It therefore seems unlikely that release of strain will be noticeable in hydroborations of distorted double bonds. The low regioselectivity observed in hydroboration of **69** and the structurally related **282** may therefore reflect similar hybridizations of both carbon atoms of the double bond.

Product distribution in *hydrogenations* is affected by steric interactions between substituents of the substrate and the surface of the metal and by the strain within the adsorbed species (255). The effect of steric hindrance on substrate–surface interactions is illustrated by the hydrogenation of methylallene on palladium, where the thermodynamically less stable *cis*-butene (**17**) is formed preferentially (255), and by the fact that betweenanene **146b** cannot be hydrogenated (95). In order to elucidate the effect of strain in the substrate on product selectivity, the catalytic hydrogenation of *Z*- (**255a**) and *E*-di-*tert*-butylethene (**256**) over palladium and platinum has been investigated (255). With both catalysts, *Z/E*-isomerization dominates over hydrogenation with

Table 29
Distribution of Deuterium in 1,2-di-*tert*-Butylethane and **256** at 33% Conversion (255)

metal	D-distribution				
	d ₄	d ₃	d ₂	d ₁	d ₁ (256)
Pd	0	2.1	89.0	8.8	2.0
Pt	0	1.8	85.8	12.2	2.0

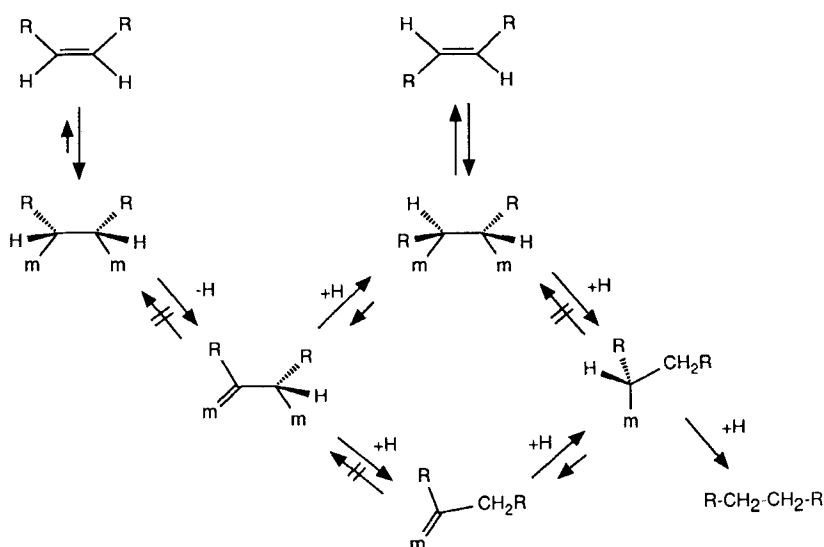


Figure 6. Mechanism of hydrogenation of *Z/E*-1,2-dialkylethene (*m* = Pd, Pt of surface) (255).

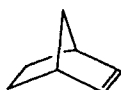
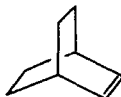
the product ratio being independent of conversion to give at least 90% of **256** and only 10% of di-*tert*-butylethane. The comparatively low rate of hydrogenation is attributed to the strong steric hindrance of adsorption of the *E*-isomer **256**. Reaction of *Z*-di-*tert*-butylethene (**255a**) with deuterium gave after ~ 39% conversion partially monodeuterated **256** (Pd: 13.4%; Pt: 64%) and di-*tert*-butylethane with an average number of 0.85 and 1.34 deuterium atoms, respectively.

Reaction of *E*-di-*tert*-butylethene (**256**) with deuterium gave the dideuterated alkane as the major product [Pd(Pt):d₁:d₂:d₃ = 8.8:89:2.1 (12.2:85.8:1.8)] (Table 29). A mechanism has been proposed that accounts for

the exchange reaction in the conversion of **255a** to **256** as well as in the formation of the alkane with special reference to steric features (255) (Figure 6).

C. Addition of Radicals

The intra- and intermolecular addition of carbon centered radicals to carbon-carbon double bonds is currently of great synthetic interest and much work has been done for control of regioselectivity (256, 257). Comparatively little work has been done to investigate the reactivities of strained olefins. The rates of gas-phase additions of $\text{HO}^\bullet$ and $\text{NO}_3^\bullet$ radicals to the cyclic olefins with ring size 5–7, norbornene (**287**) and bicyclo[2.2.2]octene (**288**), showed little variation ($k_{\text{rel}} < 1.8$ and $k_{\text{rel}} < 5$, respectively) and were insensitive to the ring strain energies (258).

**287****288**

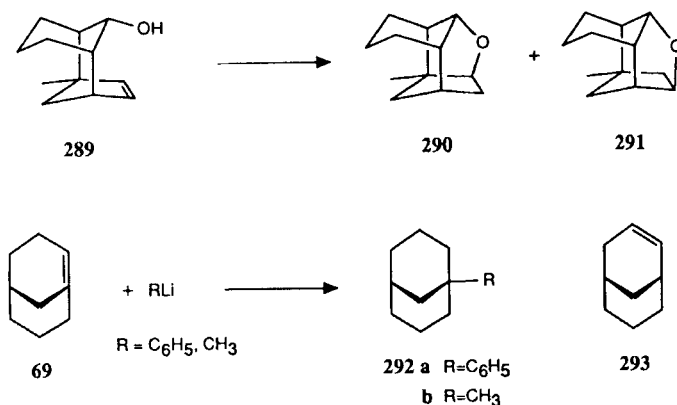
In another analysis of structure-reactivity relationships in free radical addition reactions of cycloalkenes with ring size 5–8, it was concluded that strain effects as well as the electronegativity of the attacking radical affect the reactivity (259). The rate constants for the addition reactions of the *p*-chlorophenylthiyl radical to cycloalkenes of ring size 5–8 and 10 have been discussed in terms of released strain energy and the polar nature of the transition state (260).

In a more detailed analysis of the structural and strain-related features of radical additions to alkenes, transition states should be taken into account (261, 262). According to *ab initio* calculations, the elongation of the carbon-carbon double bond and the pyramidalization at both centers in the transition state for the addition of a hydrogen atom to ethylene (**1**) are small and compatible with an early transition state. Thus, effects of strain release are expected to be small.

D. Nucleophilic Additions

Unactivated double bonds do not react readily with nucleophiles. However, additions are observed if the olefin is coordinated to a transition metal; many organometallic complexes are known which induce such reactions (263). While this aspect has not been explored with strained olefins, a few examples of direct nucleophilic additions to distorted double bonds have been reported.

The base-catalyzed addition of the hydroxyl group of **289** to the carbon–carbon double bond which occurs at 150°C has been attributed to high steric compression (264). The ready addition of carbanions to bridgehead olefins such as **112** has been reported (124). The addition of phenyllithium to the bridgehead of bicyclo[3.3.1]non-1-ene (**69**) gives exclusively **292a**, whereas **292b** and **293** are formed with methylolithium in a ratio of 54:39 (152a, 252) (Scheme 14). The high regioselectivity corresponds to the orientation expected as a result of formation of the more stable carbanion at the secondary carbon atom (152a).



Scheme 14

Since no strain-related kinetic data are available, it would be premature to discuss nucleophilic additions in terms of strain release during the addition step. However, the elongation of the carbon–carbon double bond in the computed transition state for addition of hydride to ethylene appears to be small (265).

E. Cycloadditions

Numerous examples of unstable bridgehead olefins trapped by dienes such as 2,5-diphenyl-3,4-isobenzofuran, furan, and similar compounds have been reported (96). However, systematic studies for probing the reactive double bond and strain effects are rare.

[2 + 2]Cycloadditions. The Bredt-olefins **69**, **176**, and **177** and *trans*-1-methylcyclooctene (**37c**) react with 1,1-dichloro-2,2-difluoroethene at elevated temperature with low regioselectivity and high stereoselectivity favoring the

Table 30
1,2-Cycloadducts from Reaction of **69**, **176**, **177**, and **37c**
with (a) 1,1-Dichloro-2,2-Difluoroethene (266) and (b)
Diphenylketene (268), and 1,3-Cycloadducts Formed with (c)
Phenyl Azide, (d) Diazomethane, and (e) Mesitonitrile (270)

	ratio	294	295	296	297
a)	a:b	66:33	75:25	77:22	100:0
b)	c:d	100:0	100:0	0:100	100:0
	ratio	300	301	302	303
c)	a:b	33:67	45:55	67:33	100:0
d)	c:d	70:30	67:33	40:60	7:93
e)	e:f	10:90	23:77	64:36	0:100

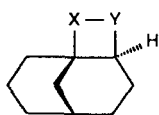
exoadducts. Norbornene (**287**) requires 3 days at 120°C for completion of this reaction and *cis*-1-methylcyclooctene (**36b**) gave a low yield of a cycloadduct only after 15 days at 150°C (266) (Table 30).

The formation of regioisomers is explained in terms of a stepwise diradical mechanism, found for [2 + 2]cycloadditions of Cl₂C=CF₂ (267). Because a chloro substituent stabilizes an alkyl radical more efficiently than a fluoro substituent, only two diradicals like **298** and **299** have to be considered as intermediates. The formation of regioisomeric products is taken as evidence for small energy differences between the tertiary (bridgehead) and secondary radical in the bicyclic systems studied. Although the data indicate a rate-enhancing effect in these cycloadditions, a crude evaluation of the relationship between olefinic strain of norbornene and **69** leads to the conclusion that the olefinic strain difference contributes little to the rate ratio (237).

Diphenylketene reacts fast with **69**, **176**, **177**, and **37c** at room temperature to give the adducts **294c**, **295c**, **296c**, and **297c** as single isomers, whereas the addition to *cis*-1-methylcyclooctene (**36b**) is much slower (268). The high regioselectivity and *syn*-stereoselectivity are compatible with the mechanism established for the concerted [2 + 2]cycloaddition reactions of ketenes to olefins (269).

Other [2 + 2]cycloadditions are observed when bridgehead olefins such as **182** or norborn-1-ene (**68**) are generated in the absence of dienes. The facile formation of mixtures of dimeric products is suggestive of stepwise reactions (268). Polymerization of unstable bridgehead olefins is not competitive under these reaction conditions.

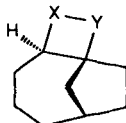
1,3-Dipolar Additions. Low regioselectivity but high stereoselectivity have been observed in the 1,3-dipolar addition of phenyl azide, diazomethane, and



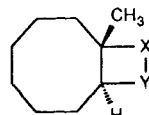
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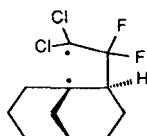
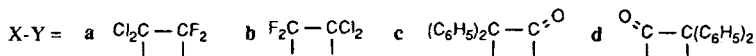
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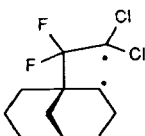
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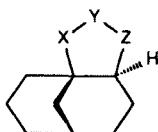
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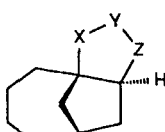
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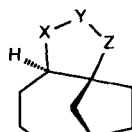
299



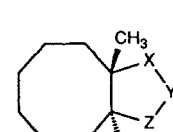
300



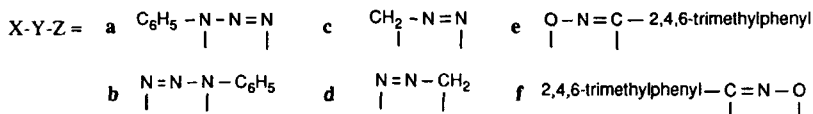
301



302



303



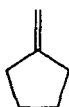
mesitronitrile oxide to the Bredt-olefins **69**, **176**, and **177**, whereas *trans*-1-methylcyclooctene (**37c**) reacts fairly regioselectively (**270**) (Table 30). An attempt to interpret these results in terms of frontier molecular orbital theory leads to the conclusion that factors associated with rehybridization may give rise to the low regioselectivity.

The rates of 1,3-dipolar addition of mesitronitrile oxide to *cis*- (**36a**) and *trans*-cyclooctene (**37a**) and some other cyclic olefins have been discussed with respect to strain effects (**271**). It was concluded that frontier orbital energies of the alkenes and differences in olefinic strain energies do not correlate with the observed reactivities. The relative rates for addition of phenyl azide to several alkenes and the olefinic strain energies are shown in Table 31 (**272**).

It has been estimated that about 20–25% of strain release contributes to the

Table 31
Addition of Phenyl Azide to Alkenes (272a) and Strain
Relieved on Hydrogenation (S_H) in kcal/mol

	304	305	253	287	306
k_{rel}	0.005	0.23	1	101	580
S_H	-0.9	13	-0.3	9.6	26



304



305



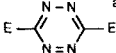
306

rate enhancement (272). Huisgen and co-workers have investigated cycloaddition reactions of norbornene (**287**) with respect to strain effects (Table 32) (273).

In contrast to the reaction with phenylsulfenyl chloride, 1,3-dipolar reagents react much faster with norbornene (**287**) than with cyclohexene (**42a**). It appears as if the rate ratio is correlated with the differential olefinic strain energies.

Six-Center Reactions. Apart from the [2 + 4]cycloadditions used for trapping highly strained olefins, systematic studies for probing the nature of distorted double bonds and strain-related features are scarce. The relative rates

Table 32
Relative Rates ($10^6 \text{ mol}^{-1} \text{ s}^{-1}$) and Strain Energies (kcal/mol) for Reaction of
Cyclohexene (**42a**) and Norbornene (**287**) with Various Reagents

	Alkene-alkane strain energy $\Delta \text{ strain}^a$	$\text{C}_6\text{H}_5\text{SCl}^b$	$\text{C}_6\text{H}_5\text{C}\equiv\text{N}^+-\text{O}^-^a$	$\text{C}_6\text{H}_5\text{N}_3^c$	CH_2N_2^d	
42a	-0.15	0.15	1.2	0.33	4	1.27
287	-4.74	12.3	3150	1880	20200	11700

^aReference 237.

^bReference 273a.

^cReferences 273b and 273c.

^dReference 273d.

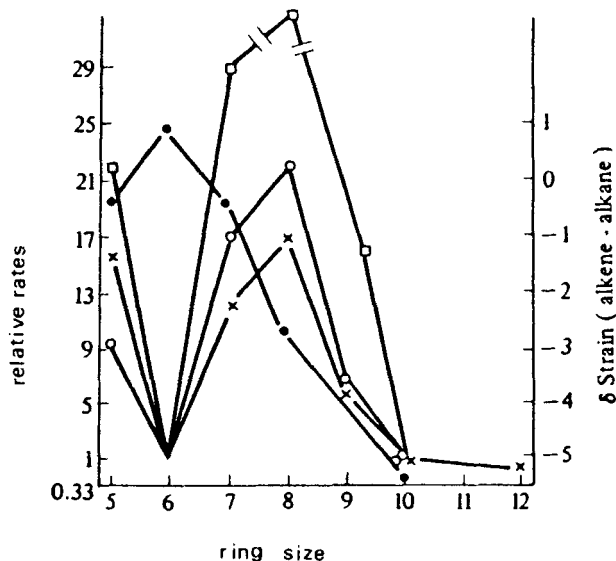


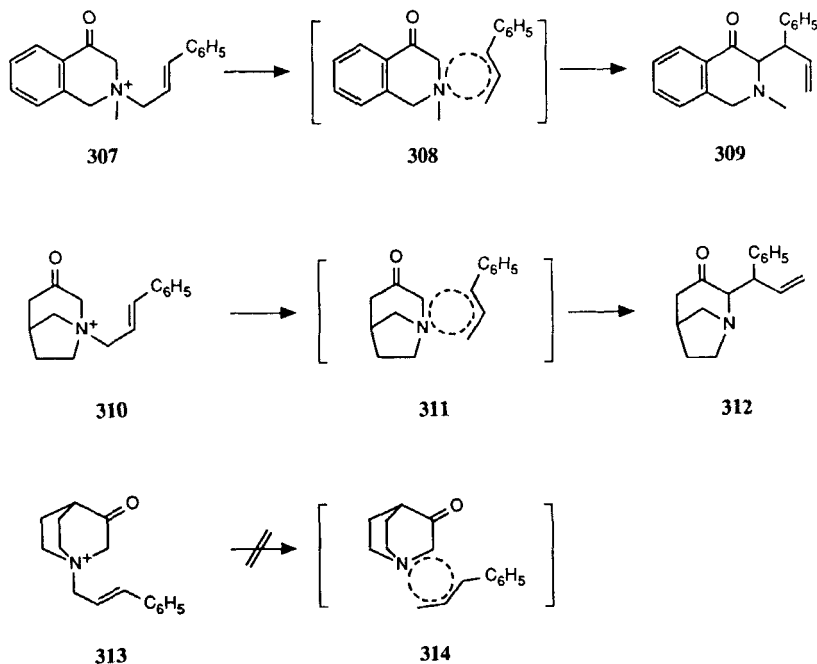
Figure 7. Relative rates for reaction of *cis*-cycloalkenes with diethylaluminum hydride (○) and hexachlorocyclopentadiene at 78°C (□) and diimide at 80°C (×) as a function of ring size, δ strain (kcal mol⁻¹) (●). Adapted from ref. 237 with permission of Pergamon Press Ltd., Great Britain.

measured for diimide reductions of cycloalkenes with ring size 5–12 do not follow either their strain energies or their olefinic strains (cf. Figure 7).

The rates of addition of hexachlorocyclopentadiene to *cis*-cycloalkenes with ring size 5–10 shows a 70-fold variation. Again, no simple relationship between the relative rates and the olefinic strain energies of these cycloolefins is apparent (237). The lack of a simple correlation between these rate values and strain energies may be rationalized with reference to the transition-state geometry. According to *ab initio* (3-21G) calculations for the Diels–Alder reaction of butadiene with ethylene (1), the double bond of the latter is elongated only to a small extent in the transition state (274). If this computational result is relevant for the [2 + 4]cycloadditions of the cycloolefins mentioned, it may be argued that the transition state is early and little affected by strain release.

Although formally a five-center reaction, the $6e^-$ [2 + 3]sigmatropic rearrangement should be mentioned here. Whereas the reaction of **307** occurs readily at -50°C , it is slow for **310** and does not occur with **313** (275).

This strong dependency of the rearrangement on the specific structure is related to strain differences in the transition state in which the π system of the iminium cation interacts with an allylic moiety. In **310** and **313**, the double



Scheme 15

bond of the iminium cation is formed at the bridgehead and is thus highly distorted by twist and other oop deformations (Scheme 15).

In summary, the reactivity of strained olefins is different from that of simple alkenes. The wealth of transformations initiated by strained double bonds has recently been reviewed in great detail (276). In this chapter some structural and strain-related features of reactivity observed for olefins with nonplanar double bonds have been presented. It is apparent that in polar reactions as well as cycloadditions of these molecules the release of strain may contribute to enhanced rates, but it is certainly not the controlling factor. In view of the operation of microscopic reversibility, it may be questioned whether the build-up of strain in reverse reactions—eliminations and cycloreversions—is the controlling factor.

The regioselectivity in reactions of Bredt-olefins has been studied. Typical electrophilic and nucleophilic reactions, the latter supported by only two examples, show high regioselectivity and syn-stereoselectivity. With the exception of diphenylketene, the [2 + 2] and [2 + 3] cycloadditions of Bredt-olefins have negligible regioselectivity.

VII. CONCLUDING REMARKS

Structural features of olefins with distorted double bonds have been discussed within the deformation space defined by the eight bond angle deformations. The out-of-plane bond angle distortions are of particular interest because they are involved in addition reactions of the double bond. The symmetrical B_{2g} -type deformation is related to concerted anti-additions, whereas the B_{1u} -type distortion (cf. Table 1) is appropriate for concerted syn-addition and those reactions that involve three-center intermediates and the formation of transition metal complexes. Twist or torsion is due to the A_{1u} -type oop distortion and may be related to addition reactions, which in principle would lead—in the extreme case of a 90° twist angle—to an eclipsed rather than a staggered arrangement.

More than one of the three possible oop bond angle deformations are usually apparent in the distorted olefins. Nevertheless, it is possible to detect in most cases the dominant type of distortion. The kinetic stability of olefins with distorted double bonds is enhanced by steric shielding. Hence, distorted double bonds in bicyclic and polycyclic structures may not display the reactivity to be expected if the dominant type of the oop distortion is the selectivity-controlling factor. The strong preference of syn- over anti-addition in Bredt-olefins may be due to this steric shielding.

In many examples the reactivity has been discussed in terms of strain release. Whereas it is apparent that some strain is released in addition reactions, other factors have to be considered. Thus, a linear correlation between the rate of epoxidation and the ionization potential of bridgehead olefins has been observed (227). Other factors such as the polarizability and hyperpolarizability, which are associated with the outer region of the electronic structure of molecules as well as with intermolecular forces and chemical reactivity have not yet been considered (277).

It is to be expected that further experimental and theoretical results will lead to a more detailed understanding of how the geometrical dispositions of strained double bonds are related to their reactivity (278).

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