Molecular Mechanics in Organic Synthesis

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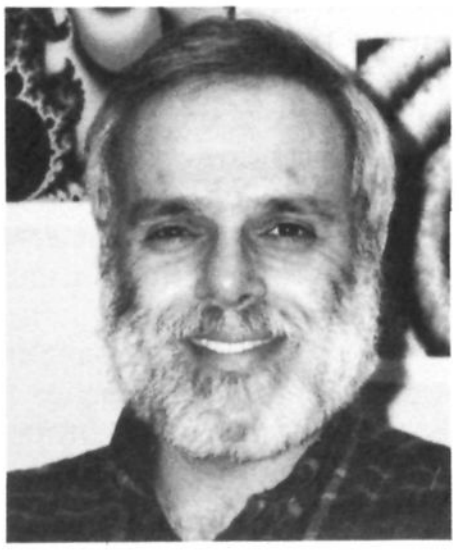

Ken Lipkowitz received his B.S. in chemistry from SUNY Geneseo in 1972 and earned his Ph.D. under the direction of Brad Mundy at Montana State University in 1975. After a postdoctoral at Ohio State University with Leo Paquette, Ken initiated his academic career in chemistry at IUPUI in 1976. Ken was one of the early faculty members at the QCPE Summer Workshops on Practical Applications of Quantum Chemical Methods in the 1980s. He organized numerous workshops on molecular mechanics and was co-founder and first co-chairman of the Gordon Research Conference on Computational Chemistry. Ken is currently on the editorial board of *Chirality* and is co-editor of *Reviews in Computational Chemistry*.

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I. Introduction

Molecular mechanics is a non-quantum mechanical way of computing structures, energies, and some properties of molecules. The method and its underlying philosophy have been reviewed by us[1] and others.[2] Molecular mechanics implements an empirical force field (EFF) as do molecular dynamics and Monte Carlo methods for simulations, but, in the organic community, the term molecular mechanics is synonymous with empirical force field. Historically, force fields were developed for simple alkanes, then branched, and then strained hydrocarbons. Other common functional groups were then included. For this reason, organic chemists have been the predominant users of molecular mechanics.

One would expect molecular mechanics to be a valuable aid to the synthetic chemist. It can provide insights about structures of reactants and stabilities of products, evaluate strain energies of synthetic pathways, and so on. However, until recently, there have been relatively few applications of molecular mechanics in organic synthesis. It is not that we are a recalcitrant lot who abhor theory, but the lack of an easy-to-use graphical interface impeded implementation of the technique. Few bench chemists were motivated to learn the theory, much less determine atom types, connectivities, coordinates, atomic charges, missing parameters, and so on needed to get the job done. The turning point was the development of menu-driven graphics programs that did much of that for the user. All that was required was to learn what molecular mechanics can and cannot do (there were innumerable workshops in the early to mid 1980s for bench chemists) and then apply molecular mechanics to the problem at hand. Since then a trickle of applications in synthesis have appeared, and within the last few years, a torrent of papers have flooded the literature.

At the outset, the reader should be cognizant of three key issues concerning molecular modeling in synthesis. These involve the hardware, the software, and the user. The computing machinery needed to be successful has been available for a long time. Most of the papers cited

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in this review concern small molecules, amenable to fast computation on minicomputers like the VAX, or PC's and workstations. By comparison, software was (is) slow in developing. Above, we mentioned that easy-to-use graphics interfaces are still relatively new. It is now fairly straightforward to model organic systems. A major concern, however, is the empirical force fields implemented in molecular mechanics along with their associated parameter sets. There is no formula for selecting the "right" potential function and every author of a force field used his or her own judgment in that process. Often the functions were selected for expediency and were justified only by the fact that they appeared to work. Many of the deficiencies in the force fields were compensated for by judicious selection of parameters, and when that failed, a new potential function was selected. By trial and error, one could usually hone in on a potential function and a parameter set that could reproduce results in a data set with some degree of precision, but it is not clear that the correct results are obtained for the right reasons. In any event, molecular mechanics, when used properly, can give valuable predictions of interest to synthetic chemists.

The third criterion for successful modeling is the user him or herself. That is to say, the user of these programs must be aware of the limitations of these programs and must be making the correct decisions about what to model. Furthermore, the user must make an informed decision about how to compare computed versus experimental results. In this regard it should be noted that many of the results cited in this review, albeit consonant with experiment, were incorrectly modeled or incorrectly interpreted. Here are several points to keep in mind when reading this review. First, although the force fields can give reasonably good heats of formation for a well-balanced, properly parameterized force field, they can be misleading especially when *ad hoc* or guessed-at parameters are used. While many parameters are thoroughly tested and well-documented, many are not; rather, they are in a preliminary form that may or may not be good. On the one hand this appears to be a serious problem, but, as will be pointed out later, most studies in synthesis involve competing reactions, e.g. the same reagent under the same conditions attacking at one face of a carbonyl or the other, and so, many of the inherent deficiencies of the force fields tend to cancel leaving reliable results. Another problem facing synthetic chemists is what to model. Until recently molecular mechanics could only compute isolated, thermally cold molecules. One can argue that the parameterization process rolls into the force field thermally averaged information, but one cannot avoid the fact that most of the calculations are of isolated, gas-phase systems, void of solvent, ions, and other materials the chemist has in his or her flask. The question to bear in mind, then, is what is the significance of the computed results when compared to experiment? On a related note it is pointed out that the molecular mechanics energies that are typically reported are internal strain energies rather than heats of formation. For some modeling purposes this is adequate, but often it is not. Another issue that synthetic chemists tend to forget when modeling synthetic reactions involves conformer reactivity. It is common to read that the most stable conformer predicted by molecular mechanics is in agreement with observed chemical selectivity. Missing from these papers is consideration of the Curtin–Hammett principle, described in nearly every graduate text on physical organic chemistry and mentioned throughout this review. Briefly, one should think of each conformer of a compound as a unique entity that undergoes a reaction at its own characteristic rate. For a very simple two-conformer distribution, then, one has the following

$$P_1 \overset{k_1}{\leftarrow} C_1 \overset{K}{\rightleftharpoons} C_2 \overset{k_2}{\rightarrow} P_2$$

where P_1 is a product derived from conformer 1 and P_2 is a product derived from conformer 2. When the conformers are in fast exchange compared to the rates of reaction the Curtin–Hammett principle promulgates that the product ratio is dependent on the conformational equilibrium constant, K, and the rate ratio of the individual conformers. This latter point, the rate ratios, is often omitted from consideration, effectively setting $k_1 = k_2$. The key issue is that the experimental product ratio need not reflect the conformer populations; it is possible to observe product from the minor conformer! This has been a major pitfall in modeling synthetic reactions. Another point to keep in mind is that molecular mechanics provides thermodynamic information. Difficulties in using thermodynamic data for kinetic purposes exist. The proclivity is to invoke the Hammond postulate which may or may not be justifiable for a given case.

The upshot of all of this is that as a reader one should adopt a position of cautious optimism. The computing machinery is fine, and the potential functions with their associated parameter sets, albeit reasonably good, are still undergoing improvement. The weak link in most of the modeling, usually offset by a gross cancellation of errors, originate from the molecular modelers themselves. It is common to find modelers using both potential functions and parameters that were not meant for the task at hand. In other words it is easy to transcend the boundary between proper and improper use of this tool. Furthermore, it is common for chemists to model only part of what is involved in their reaction and wrongly interpret the results by comparing enthalpies with free energies, neglecting the Curtin–Hammett principle and so on. In spite of these pitfalls one can, with caution, invoke molecular mechanics to explain the outcome of chemical reactions and to make valuable predictions. With this in mind, we now examine the application of molecular mechanics in synthesis.

Because so much has happened in the past few years, this review is partitioned chronologically. Part II considers work up to 1983, and part III summarizes work since then. Part III is divided into two categories: *a priori* and *a posteriori* applications of molecular mechanics. Part IV contains a summary and a look at the future of molecular mechanics in chemical synthesis. Only those papers that contain both experimental and theoretical components in their text are considered in this review even if, as is often the case, the molecular mechanics work is in a footnote. This constraint excludes situations where the synthesis is described in one paper and a theoretical assessment of the results is given in another, even if the papers were from the same group and appeared back-to-back. We adopt this

policy because there are too many published papers to consider in the space allotted here. Most of the papers we exclude are molecular mechanics studies directed toward understanding reaction mechanisms rather than assisting in synthesis. While the partitioning of papers into a "synthetic" category *vs* a "mechanistic" category is difficult, we have tried to keep the focus on applications of molecular mechanics in organic synthesis. With this clarification we apologize to some of our colleagues whose work is excluded.

II. Work Prior to 1983

Not many molecular mechanics papers appeared in the 1970s; we were working with a new tool that was limited in scope and difficult to use. Compounding this was the prevailing negative attitudes of applied quantum theorists who felt that one should do structure studies with a method based on first principles (quantum mechanics explicitly treats electrons, molecular mechanics implies they are there). While empirical force fields for molecular mechanics were being developed almost exclusively in academic laboratories, the implementation of molecular mechanics was taking place mostly in industrial laboratories. Industrial scientists realized far before academicians the potential molecular mechanics had in the realm of molecular design. Molecular mechanics was nurtured by those scientists because quick, efficient, and accurate methods for predicting molecular structure were needed.

Early applications of molecular mechanics were directed more toward *what* to synthesize than *how* to synthesize it. For example, Belanger felt that nonpeptide compounds could be designed to mimic enkephalins.[3] They derived a model of the active conformation of the enkephalins on the basis of theoretical work using the Merck Modeling System. The target molecule was then synthesized and, when tested, found to display weak binding activity. It is difficult to document industrial research, but successes of computer-aided design have been summarized.[4] Academic scientists, usually collaborating with industrial scientists, were also actively using molecular mechanics to progressively design analogs more active than known ones. A good example is from Momany[5] (who eventually became a co-founder of Polygen, now Molecular Simulations Inc., a major molecular modeling software company). Again, his studies had nothing to do with synthesis but rather focused on what to synthesize.

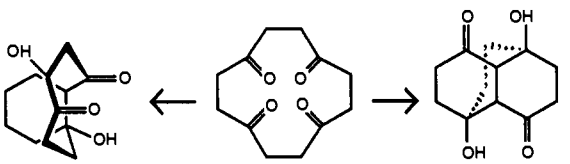
This time period was one where physical organic chemistry was reshaping what we knew about organic reaction mechanisms. We take the opportunity, then, in the context of this review, to pay tribute to four eminent scientists who are recognized as pioneers in the discipline we now call computational chemistry. These scientists, Allinger, DeTar, Osawa, and Schleyer, developed and implemented empirical force fields for the study of organic molecules.

Early on, DeTar embarked on an ambitious project to understand how steric factors accelerate or retard rates of reaction. Using an all-hydrogen force field he computed energy differences between ground-state and tetrahedral intermediates (not transition states) for ester hydrolyses.[6] Steric effects on rates of the reverse process, lactonization, were considered.[7] The work on ester hydrolysis was later improved upon,[8,9] and then steric effects on S_N2 reactions were considered.[10] Eventually the steric effects in S_N2 ring closure reactions were examined quantitatively and Ruzicka's hypothesis of ring closure updated.[11]

Concurrent with this was Schleyer's work evaluating steric effects of organic reactions. Schleyer pioneered the use of molecular mechanics in treating strain energies in solvent assisted unimolecular dissociations (solvolysis).[12,13] Other groups were likewise exploring the role of strain energies on solvolysis rates.[14-17] Solvolysis reactions involve hybridization changes from sp^3 to sp^2 carbon. A related reaction with this type of rehybridization is oxidation of secondary alcohols to ketones. These reactions were investigated by Müller's group.[18-21]

Allinger was able to correlate rates of aldol condensations with steric energy differences between 3-keto steroids and their corresponding Δ^2 alkene analogs.[22] Although his work was directed toward understanding the concept of "conformational transmission", it, like DeTar's and Schleyer's, provided a quantitative rationalization for reactivity and illustrated the predictive ability of molecular mechanics for synthesis.

In the early 1980s, Eiji Osawa was instrumental in bringing molecular mechanics to Japan. His work focused on the application of force field calculations to organic chemistry and early on delineated possible applications.[23] One of these roles is the prediction of product distributions based on computed enthalpies. Consider the following example. Osawa's colleague, Musso, intended to obtain the bicyclic ring system **2** from **1** by carrying out an intramolecular, double aldol condensation. Only two intermediates can result from the first cyclization, but there are 20 ways for the second step to take place. An analysis of the enthalpies of all possible products indicated the tricyclic dione **3** to be most stable which, indeed, was the one isolated and characterized by Musso. Osawa's statement that "If



2 **1** **3**

the calculations had been performed *before* experiments, this reaction would probably have been abandoned in favor of better ways..." was a bold one but, in retrospect, an accurate one. Osawa also applied this methodology to the study of ring openings and rearrangements of strained cage molecules.[24] Thermodynamically controlled bond scissions, homoketonizations, and cationic ring expansion reactions, which all have multiple ring opening possibilities but are found to be highly specific, were studied. Again, this is an *a posteriori* application of molecular mechanics, but it illustrates the usefulness of predicting the products of highly complex cage ring compounds undergoing a cascade of ion rearrangements.

In addition to these studies Osawa was elucidating the role of conformer stability in reactions of medium and large carbocyclic systems. In contrast to others at that time who were using molecular mechanics for

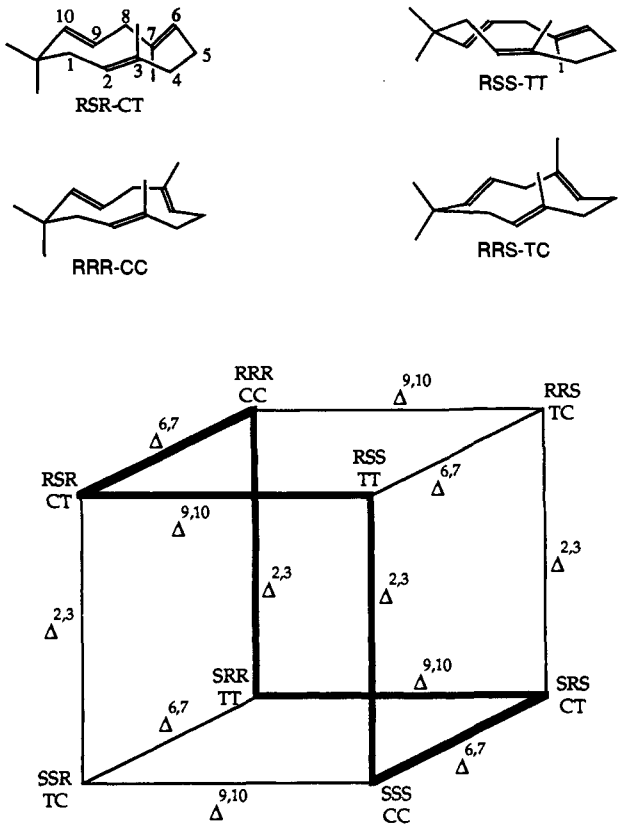


Figure 1. Four minimum energy conformations of humulene and the correlation diagram for these conformers and their enantiomeric forms. Two conformers standing on both sides of every edge of the above cube are interconvertible by a single rotation of the double bond indicated on the edge. Heavy lines show the lowest energy path for ring inversion. (Reprinted from ref 25. Copyright 1980 American Chemical Society.)

comparison with NMR and X-ray studies, Osawa's intent was to rationalize the results of transannular reactions leading to natural products. Humulene, for example, can exist as eight structures (four conformers and their mirror images) as depicted in Figure 1. The interconversion pathways among these forms were delineated, and the biosynthetic pathways leading to illudoids and hirsutanoids were rationalized.[25] More specifically, the two reacting conformers that account for the biosynthesis of humulenes and transannular reactions observed experimentally are the two most stable ground-state conformers (CT and CC in Figure 1). These calculations are in accord with experiment. This work was extended to examine the role of strain in the course of acid cleavage of humulene 9,10-epoxide[26] and the relationship of caryophyllene's 6,7-double bond reactivity with its conformational populations.[27] Another group that examined conformational control of molecules leading to stereoselective product formation was Hirota's.[28] The ratio of threo/erythro sulfoxides arising from attack of an oxidant on various alkyl 1-phenylethyl sulfides from the less sterically congested direction showed trends in accord with experiment.

The time period prior to 1983 was an era when molecular mechanics was relatively unknown to synthetic organic chemists. It was difficult to use and limited in scope. Almost all of the papers directed toward synthetic problems evaluated results after the fact. Few studies outside of the pharmaceutical industry used molecular mechanics in the design of molecules or for an *a priori* prediction of stereochemical outcome. Only recently has this been attempted, and the following section describes such studies.

III. Work after 1983

During the last decade a significant number of advances in molecular modeling allowed organic chemists to apply molecular mechanics to problems in synthesis. In addition to faster, more affordable computing machines, there were major improvements in the potential functions used in molecular mechanics, and there was a concerted effort, especially by Allinger, to include force field parameters for organic functionality. More important for synthetic chemists, however, was the creation of graphics-oriented software that significantly lowered the barrier separating the bench chemist from theory. Of particular note was the insight and creativity of Clark Still who developed and freely disseminated MODEL to the organic research community and to whom we owe a debt of gratitude.

This part of the review covers only a decade of work but encompasses 99% of existing research on molecular mechanics applied to synthesis, attesting to the "newness" of the concept. Application of molecular mechanics during this period can be divided into *a priori* and *a posteriori* applications, the latter far outweighing the former.

A. *A Priori* Applications of Molecular Mechanics in Synthesis

Ideally one would like to use molecular mechanics before a synthetic plan is initiated. The concept of using molecular mechanics to help define what to make to elicit a response and how to make it in a cost- and time-efficient manner is something the synthetic community needs but, until recently, has not widely implemented. Indeed, most molecular mechanics investigations in synthesis have been *a posteriori*, after-the-fact analyses. Relatively few applications have preceded syntheses, but these are the most enlightening because they illustrate the great potential molecular mechanics has in molecular design, stereochemistry prediction and assessment of viable reaction pathways leading to target molecules in synthesis planning.

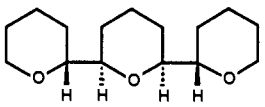
1. Computer-Aided Molecular Design (CAMD)

The first major *a priori* application of molecular mechanics in organic synthesis we consider is computer-aided molecular design. CAMD is synonymous with, although technically different from, molecular modeling. The point of CAMD is not to tell us how to make a compound but to figure out which compounds to make (or which not to make) to effect a result. Most studies to date have focused on design by comparison and *de novo* design.

Design by Comparison. By "design by comparison" we mean creating, via computer, a new molecule and comparing its structural and electronic features with one that is already known. This is usually done by determining the elements of a pharmacophore, identifying the "active" conformation(s), superimposing several molecules with their common pharmacophore and, following the inspection of the composite, to assist

the scientist in creating a new molecule to synthesize. Design by comparison, along with the use of molecular mechanics for creation of quantitative structure–activity relationships (QSARs), has revolutionized the way we discover new materials. Examples of such "rational design" from academic laboratories[29–35] and industrial laboratories[36–38] exist but, because molecular mechanics only plays an indirect role, will not be elaborated on here.

***De Novo* Design.** *De novo*, meaning "anew", is a strategy that allows molecular mechanics to play a direct role in the design process. Predictions based on computed thermodynamic stabilities or on the structural features of new molecules are directly determined by molecular mechanics. Most of these papers have appeared within the last 5 years, and much of it has been directed toward the design of synthetic receptors for guest–host complexation. For example, Still[39] prepared podands (nonmacrocyclic host molecules) that are conformationally flexible but, by virtue of their connectivity and stereochemistries, are preorganized. On the basis of molecular mechanics, the stereochemistries depicted in compounds 4 and 5 were found to be most likely to induce conformations leading to binding of alkali metals cations. These compounds were



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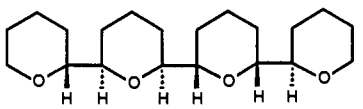

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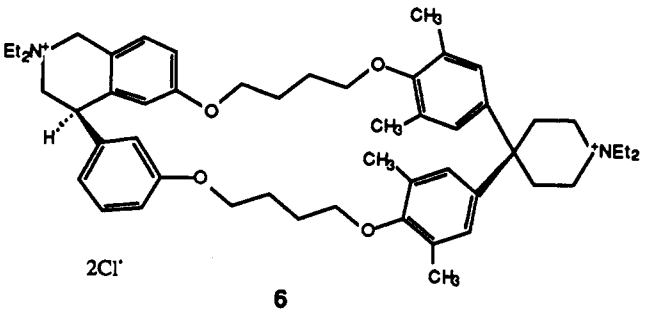
subsequently synthesized and found to have ionophoric properties comparable to dicyclohexyl-18-crown-6. Other groups focused their attention on complexation of neutral guests. The design, synthesis, and binding studies of Diederich[40] and Wilcox[41] are exemplary. Diederich decided to avoid costly errors in the design of chiral and achiral cavity-shaping aromatic building blocks. The application of MM2 to the design of 6 is described by his group. Wilcox determined that hosts related to 7 need a five- or six-atom chain rather than the overly restrictive four-atom chains to effect binding of small aromatics.

Intramolecular binding of a donor and acceptor has been the focus of attention for many groups over the years. A good example of intramolecular binding is from Beeson and Dix who decided to investigate solvent effects on conformation-based probes of electrostatic interactions.[42] Their application of molecular mechanics is clear: "The use of molecular mechanics also allowed for the screening of a large number of candidate molecules before synthesis of the best candidates was initiated; the fused bicyclohexane ring system of the *cis*-decalin skeleton is the type of structure best evaluated by these calculations." Certainly, when used properly, molecular mechanics can save a lot of time and money. In their paper they had a section on structural design. There they pointed out that the use of molecular mechanics permitted them to screen a large number of candidate molecules before synthesis of the best candidate, 8, was initiated. Selection of this bicyclic ring system as a template for their studies was straightforward. Ring system 8 allows for the interactions to be turned on or off depending on the environment. Another level of the *de novo* design was



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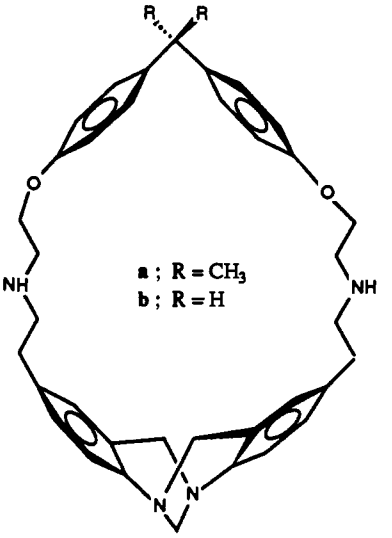

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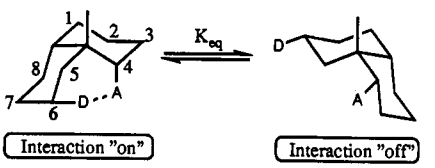
used in this study by considering the structures and energies of a large number of possible substitution patterns needed to ensure that donor and acceptor groups were in a favorable geometry to interact. Indeed, using 8 as a substructure, the authors were able to



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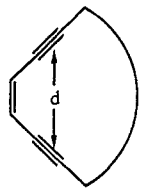
rapidly screen 32 different structural motifs of substitution patterns which yielded two candidates for synthesis. Ultimately they prepared 8 where D = CO_2^- and A = NH_3^+. For them, molecular mechanics was a qualitatively reliable "engineering tool". This molecular mechanics-based decision making process is now being applied to other systems on the basis of their success.

Enediynes in medium-sized rings, 9, serve as a fundamental substructure for a class of antibiotics that cause strand scissions in DNA. Upon binding and thiol addition, they undergo Bergman cyclization to a highly reactive arene-1,4-diradical that ultimately attacks DNA. The distance between the diyne termini, *d*, appears to control whether or not cyclization is spontaneous at physiological temperatures. Because this cyclization is the trigger that begins the cascade of hydrogen abstraction and strand scission, the design of novel enediyne cleaving reagents has been undertaken. The spontaneity of cyclization of designed model systems was undertaken by Nicolaou's group.[43] Their



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predictions, compared with experimental results, are stellar. Likewise, the design, synthesis and testing of 10-membered ring analogs of neocarzinostatin by Hirama[44] further illustrates the *de novo* design of enediynes.

Two other papers that rely heavily on molecular mechanics for the design of new materials are by Yoshikawa[45] and Chen.[46] Yoshikawa used a modified version of MM2 to make predictions about which Co^{3+} coordination compounds can be made and which cannot. Although no experimental work is presented, predictions are made, and the idea of eliminating nonproductive, unnecessary syntheses by *de novo* design with molecular mechanics is stressed and warrants citation. Chen noted that resistance to enzymatic cleavage of *N,O*-diacetylpropranolol is attributable to steric hindrance of this molecule's carbonyl group by the enzyme's nucleophilic residue. A number of structural variants of *N,O*-diacetylpropranolol were examined with MM2. A new derivative of propranolol was predicted to be reactive and, once synthesized, was indeed selectively hydrolyzed. Other syntheses that contain some component of design based on thermodynamic stability or structural motifs exist,[47-58] but most of these do not rely as heavily on *de novo* design concepts as the aforementioned studies. Fantastic applications of *de novo* design of biopolymers, especially by De Grado,[59] are to be noted.

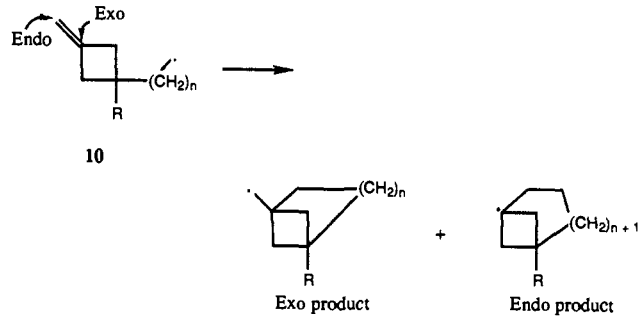
2. Predicting Stereochemistry

The second major *a priori* application of molecular mechanics in organic synthesis we consider is the prediction of stereochemistry. Once the target molecule has been designed (*vide supra*), several synthetic pathways are evaluated (*vide infra*) where the stereoselectivity of each reaction along that pathway is estimated or computed. Most studies to date have focused on transition-state modeling and understanding conformational control of stereoselectivity.

Transition-State Modeling. A transition state is a minimum-energy structure with respect to all but one degree of freedom. With respect to other atomic motions then, the transition state can be treated as an energy minimum. By defining unique atom types for those nuclei most involved in bond making and bond breaking and having some knowledge about the transition structure (usually from quantum theory), it is possible to construct a crude molecular mechanics model of the transition structure. While the early work of DeTar was described above, most of the developmental work based on transition structures derived from *ab initio* SCF molecular orbital theory has been done by Houk who provides a review on this topic in this journal issue.

For synthetic chemists the accuracy of these crude models is not very important because we are usually concerned with *relative* reaction rates. For most reactions leading to diastereomeric products, the reaction trajectories are so similar that, by cancellation of errors inherent in the force field method, one can qualitatively, and often times quantitatively, determine the preferred pathway. The reader should be aware that only a handful of *a priori* transition-state applications exist; most are *a posteriori* rationalizations described later in this review or are purely theoretical studies with no synthetic component.

One of the most useful synthetic reactions involves nucleophilic attack on a carbonyl group. The stereochemical outcome depends upon whether the nucleophile attacks from the *si* or the *re* face of the trigonal planar carbon. The simplest reaction is hydride attack. Using a previously defined force field model for nucleophilic attack of lithium aluminum hydride (LAH) to ketones, Houk predicted the distribution of axial *vs* equatorial alcohols from reductions of benzocycloheptanones.[60] After synthesis, LAH reduction gave alcohol products fully commensurate with prediction. These predictive models need not be limited to bimolecular reactions; unimolecular additions can be treated similarly. For example, two trajectories for radical addition to **10** are possible giving rise to the exo and endo intermediates. Pigou[61] determined the MM2 transition structure strain energy for ring closure and predicted the exo isomer would predominate. This prediction was then verified experimentally.



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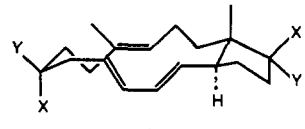
Cycloaddition reactions have been modeled, both with and without Lewis acid catalysis. Marshall used molecular mechanics to predict the diastereoselectivity of intramolecular Diels–Alder reactions leading to octahydronaphthalenecarboxaldehydes.[62] Rather than use a true transition structure model, he computed structures resembling products (late TS) to predict stereochemical outcome. This product-oriented approach gave a distinct preferred isomer and the ensuing synthesis confirmed the prediction. Other intramolecular Diels–Alder reactions were studied *a priori* with molecular mechanics. The macroring contraction methodology of Takahashi[63] used Houk's synchronous butadiene–ethene transition structure to predict that the trans stereochemistry at C_{13} and C_{14} would control the conformation of triene **11** which, in turn, would provide a highly stereoselective cycloaddition. Another suc-



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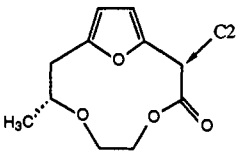
cessful prediction of stereochemistry by Takahashi based on MM2 transition structure modeling was later published.[64]

Conformational Control. Protecting one of two faces of a trigonal planar carbon from attack is one way of inducing stereoselectivity. Steric congestion inhibits attack so that reagents approach from the less encumbered direction. In rigid systems it is easy to predict the product. For conformationally flexible systems, however, one needs to know the population of each conformer, and with an understanding of the Curtin–Hammett principle, one may then predict the outcome of the reaction. Rings can be constructed which, by virtue of their preferred conformation, promote stereoselectivity. *A priori* applications of molecular mechanics to decide which systems to use for directing attack have been published.

Large Ring Systems. Conformational control in large ring systems is different from that in small rings and acyclics. In large rings, conformations exist where olefins are perpendicular to the mean plane of the macrocycle. The origin of this is the minimization of transannular nonbonded repulsions. Consequently the in-plane alignment of olefin π lobes results in one face of the alkene exposed to external attack while the other face is shielded by the remainder of the hydrocarbon loop. Macrocyclic reactions are thus anticipated to give a high degree of facial selectivity.

The first person to seriously use this concept was Still.[65] He went so far as to purposefully construct a macrocyclic system from acyclic materials, conformationally control the stereochemical outcome of reaction, and then spawn stereochemically complex acyclic products containing distant, planned stereocenters from the designed macrocyclic intermediate.[66] In Still's synthesis of nonactic acid, for example, lactones **12** and **13** were analyzed with MM2. The conformational



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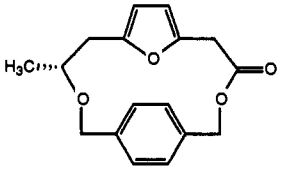
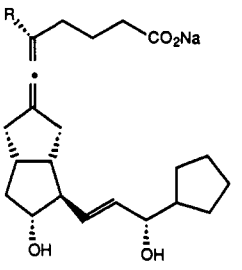


13

orientation of the furan with respect to the macrocycle has a major influence on the stereochemistry at C2. For **12**, it was found that the energetic differences between conformers was so small that alkylation would proceed without useful stereoselection. The xylene-spaced macrocycle **13**, in contrast, was predicted to exist with the furan nearly perpendicular to the ring's mean plane so that a single diastereomer would form. The use of **12** was abandoned, **13** was prepared, and upon alkylation, a 70:1 product distribution was found as expected. Still was not the only synthetic chemist to use molecular mechanics to make *a priori* predictions of conformationally controlled stereoselection. Of particular note is the work by Takahashi. Using MM2 he decided that changing functionality would enhance the C2–C3 epoxidation stereoselection in his synthesis of periplanone B.[67] Mori also used molecular mechanics to examine the distribution of conformers in 10-membered ring skeletons that would lead to high diastereoselection in their synthesis of periplanone B.[68] Takahashi has further used molecular mechanics to design key synthetic intermediates in the total synthesis of bicyclohumulenone[69] and sarcophytol A.[70] Other papers exist where molecular mechanics was used *a priori* to predict stereochemical outcome in macrocyclic reactions.[71–76]

Acyclic and Small–Medium Rings. Conformational control in small–medium rings and acyclics is different from that in large rings. In small- and medium-sized rings the reacting π lobes are perpendicular to the mean plane of the ring, and both faces are subject to attack. Thus, these systems are expected to have a much lower degree of facial selectivity.

The search for prostacyclin mimics led Djuric[77] to use some of the aforementioned strategies to design allene–carbacyclin **14**. It was thought that the critical stereochemistry could be introduced by addition of an acetylide to bicyclic ketone **15**. MM2 indicated two



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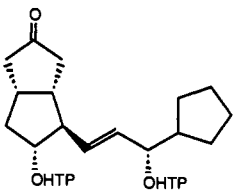
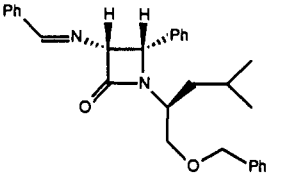


15

things; first, that the direction of nucleophilic attack would be favored from the requisite *si* face and, second, that the diastereoselectivity would be high enough to warrant pursuit of this synthetic plan. The ensuing synthesis was fully in agreement with theory. Not all *a priori* predictions of stereochemical outcome are consonant with experiment, however. For example, Ojima was interested in the asymmetric [2 + 2] cycloaddition of azido ketene to **16** and **17**.[78] MM2 calculations indicated that the 4-phenyl group in **16** would have an influence on the stereoselection because it is close to the reacting 3-imino group, while in the trans isomer **17**, the phenyl group is distant for all conformations. It was reasonable for Ojima to assume



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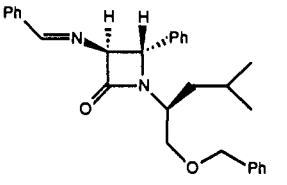
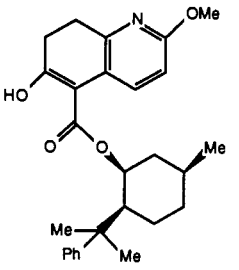


17

16 would be highly stereoselective while **17** would not. It was found that lactam **16** showed high diastereoselection. But, so did **17**, leading Ojima to conclude that steric hindrance is not the single critical factor giving such high diastereomeric excess in these reactions.

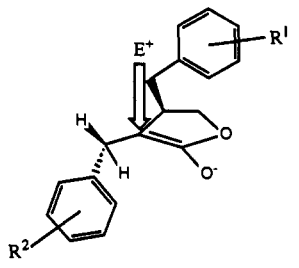
By comparison, Kozikowski[79] chose to introduce the absolute stereochemistry into his (–)-huperzine A synthesis at the stage of a Michael/aldol reaction. Prior to the laboratory work Kozikowski's group speculated that the menthol ester derivative **18** would have the required stereodirecting effects. Relying heavily on molecular mechanics, they predicted a 4:1 ratio of

desired product. With that favorable prediction in hand they proceeded with their synthetic plan and obtained the expected 4:1 distribution exactly.



18

An important, yet subtle, influence on conformation is allylic strain. Allylic strain is a conformational effect that molecular mechanics handles very well and has played a role in the *a priori* prediction of stereochemistry in several studies. For example, diastereofacial differentiation in the electrophilic attack on metal enolates of α,β-dibenzyl-γ-butyrolactones (**19**) was expected by Iwasaki to be controlled by allylic strain.[80] He reasoned with molecular mechanics that shielding on the bottom face by the phenyl group of the α-benzyl moiety, due to 1,3-allylic strain, would force addition from the top face in spite of the γ-benzyl group's presence. Another example is Comins' synthesis of pumiliotoxin C that required conjugate addition to enone **20**.[81] MMX calculations on the conformations



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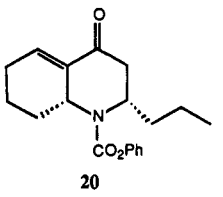
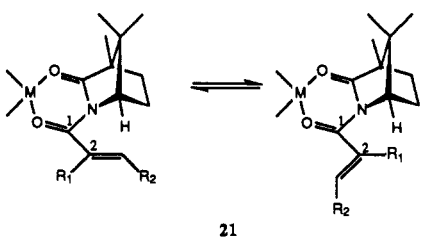


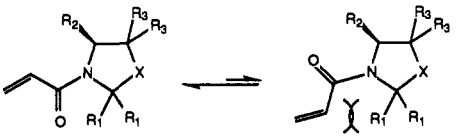
20

of **20** indicated preferential axial attack of a methyl nucleophile would take place, as needed, because 1,3-allylic strain locks the ring into the correct conformation. This analysis was proved correct by the ensuing synthesis. In Boeckman's goal to develop a general chiral auxiliary for the construction of quaternary centers via cycloaddition reactions,[82] he settled on camphor lactams **21**, where rotation around C1–N would be restricted by metal chelation and rotation around C1–C2 is restricted by allylic strain. Furthermore, the



21

preponderance of the s-trans rotamer would depend on the substituents used. The crotonate dienophile that was predicted to exist in the syn conformation gave product arising from the trans rotamer. This is a complete failure of an *a priori* prediction and is one of interest because Kanemasa[83] has predicted the syn conformation and s-cis geometry of **22** should result in high diastereoselection of 1,3-dipolar cycloadditions.



syn anti

22

A successful application by Boeckman should be noted and is described in his review on the solution of complex stereochemical problems with the aid of molecular mechanics.[84] Additional studies that use molecular mechanics to predict stereochemistry of synthetic transformations have appeared.[85–87]

There are other papers that use molecular mechanics as a predictive tool. In these studies the relative rates of competing reaction pathways are analyzed. Examples include Baker's prediction of Dieckman cyclization pathways to diastereomeric quinuclidines,[88] Ojima's assessment of metal catalyzed amidocarbonylation of lactams,[89] and Shibasaki's determination of strain energies to predict stereochemical products of hydrindans.[90]

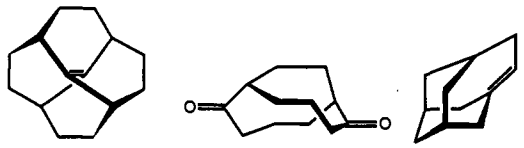
3. Synthesis Planning

The third major *a priori* application of molecular mechanics in organic synthesis we consider is synthesis planning. Given a target molecule, there are several pathways that can be followed to successfully achieve the synthetic goal. Deciding which pathway to follow involves consideration of several factors, one of which is whether or not key intermediates are isolable. Furthermore, it is desirable to address the relative strain energies of intermediates along a synthetic pathway to decide, for example, if a high-energy photochemical transformation is better than a lower energy, thermally driven one. This type of *a priori* analysis has been used in synthesis planning, especially in the design of multiple ring systems where a large number of synthetic routes to product can be envisaged. It has also been used for strained ring systems where *a priori* knowledge of stabilities are desirable.

Olefin Strain. The evaluation and prediction of the stability of bridgehead olefins was placed on a firm basis by Maier and Schleyer who, in a seminal paper, founded the concept of olefin strain (OS).[91] OS is calculated by subtracting the total strain energy of the most stable conformer of the parent hydrocarbon from that of the olefin in its most stable conformation. Since OS values are obtained by differences, many of the inherent errors of a given force field tend to cancel. An empirical set of rules derived from comparison of OS values computed with molecular mechanics with experimental data allows classification of bridgehead alkenes into three categories: isolable (OS $\leq$ 17 kcal mol^{-1}), observable (17 $\leq$ OS $\leq$ 21 kcal mol^{-1}) and unstable (OS $\geq$ 21 kcal mol^{-1}). Schleyer further came to realize that some systems had negative OS values because they resisted reactions that change their

hybridization from sp^2 to sp^3. To describe these he coined the term hyperstable olefin.[92]

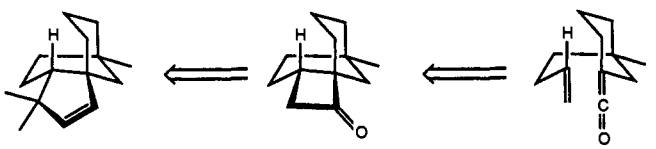
Several applications of OS to synthesis planning include: the assessment of whether or not orthogonalene (**23**) is isolable,[93] the regiochemistry of cage openings,[94] and the question of kinetic stability of bridgehead alkenes directed toward taxane synthesis.[95] In the latter study by Swindell, all olefins related to the taxane skeleton were predicted to be hyperstable, giving the authors insight about synthetic strategies needed to build such diterpenes.



23 **24** **25**

An early study that used molecular mechanics to help determine relative stabilities of intermediates was done by House[96] who, based on MM2, decided that isolation of several bicyclo[3.3.1]enones would require unusual conditions. In another study of olefin stability, diketone **24** was expected to exist as one of several tautomers.[97] One of them was predicted to be a hyperstable olefin that, if isolated, would be the first nonconjugated aliphatic enol more stable than its isomeric ketone. The hyperstability of this enol was confirmed and, ultimately, a quadrone analog was made. Finally, the prediction that the bishomoadamantene (**25**) would be stable and isolable (OS = 1.2 kcal mol^{-1}) was made by Murray who then synthesized and characterized it.[98]

Cage and Ring Strain. In terms of synthesis planning, other types of strain have been considered. For example, prior to his total synthesis of clovene (**26**), Funk[99] anticipated **28** would produce only stereoisomer **27** rather than its epimer because MM2 predicted less ring strain. Rosenfeld[100] relied on molecular mechanics



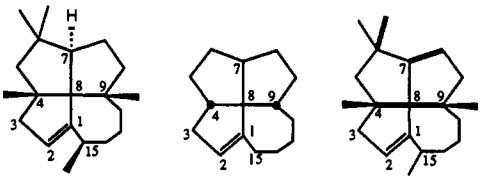
26 **27** **28**

to determine the feasibility of isolation small cyclophanes and, using MMX, determined the distortions and strain energies of 9,10-anthracenophanes before he synthesized them. Finally, the fascinating prediction by Saunders[101] that the minimum energy isomer of $C_{60}H_{60}$ will have 10 hydrogens pointed inside the cage awaits experimental confirmation.

When planning a synthesis, especially of strained ring molecules, it is desirable to estimate how much strain is associated with the product or with key intermediates so that an energy-compatible strategy is followed. For example, before synthesis of the 1,7-cyclobutanonorbornane ring skeleton **29** was undertaken, Eaton[102] compared its MM2 strain energies with the three-carbon homolog **30**. The relatively low strain energy of **30** allows accessibility through acid-catalyzed rearrangement of propellanes, but the high strain energies of **29** implied an alternative route should be pursued. Indeed, Eaton then intentionally selected a strategy where a photochemical Wolff contraction would provide sufficient energy to access the desired system.

29 **30**

Another example of applying molecular mechanics *a priori* to help plan a synthetic strategy for a strained ring system is by Itô.[103] Before his attempt at synthesizing the natural product **31**, molecular mechanics calculations were carried out on a series of hypothetical fenestrenes to reveal the origin of steric strain and estimate its magnitude. His group found that the introduction of a methyl group in a near-eclipsed orientation (near-eclipsed C–C bonds are indicated by thick lines in **33**) causes far more strain than a noneclipsed one and that the increase in strain when going from **32** to **33** originates from near-eclipsing interactions rather than transannular methyl–methyl repulsions. They also found the fusion of a 7-membered



31 **32** **33**

ring onto the triquinene localizes the strain into that ring rather than over the whole system and that fenestrene is less flexible than its polyquinene precursor. These results provided clues to forming a synthetic strategy. First, since triquinene is more flexible than fenestrene, the construction of all quaternary carbons should be completed before the fenestrane system is formed. Second, two crucial steps for which to plan were the formation of quaternary carbon C9, due to two sets of near-eclipsing interactions, and formation of the 7-membered ring. Taking these molecular mechanics data into account, Itô's group elaborated an eight-step plan that would, on the basis of theory, provide the natural product. That plan was successful.

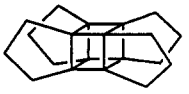
Most of the *a priori* application of molecular mechanics in synthesis planning has not been directed toward natural products, but non-natural products containing complex and/or multiple strained rings. For example, diene **34** can exist in several conformations, the most stable of which has the olefins directed inward. Musso realized that the distances between olefins together with their parallel alignment would ensure [2 + 2] photochemical ring closure to **35**.[104]

34 **35**

This kind of ring closure plays a key role in the synthesis of caged and strained-ring molecules. For example, the [2 + 2] photoclosure approach toward heptaprismane analogs (not heptaprismane itself) was

studied by Mehta and Osawa.[105] Feasibility of intramolecular photocage formation depends on two features: the strain energy change, ΔSE, and the distance between olefins. All possible [2 + 2] photoclosures leading to [7]-prismanes were considered. Of the 39 possibilities, 15 had ΔSE < 55 kcal mol^{-1}, a cutoff they find gives product. One ring closure was pursued because it had a ΔSE > 55 kcal mol^{-1}. It should not and did not cyclize. A second system pursued did not cyclize because the computed distance between olefins was excessively long. A third molecule studied had suitable distances and strain energies and did cyclize as anticipated.

Osawa and Mehta continued studying the implications of strain in evaluating synthetic strategies for hexa- and pentaprismanes.[106] Again, ring closures described by MM2 as having ΔSE > 55 kcal mol^{-1} were not pursued or were unsuccessful. They concluded that, considering the various synthetic options open to these highly catenated polycyclobutanes, it is advantageous to place the methylene bridge in the position at which key cyclobutane bond formation is created early in the synthetic sequence rather than later. Finally, these same authors analyzed the factors that influence intramolecular [2 + 2] ring closure leading to propellaprismane **36**. Although no experimental work is given, the impact of molecular mechanics on synthetic pathways is clear.[107]



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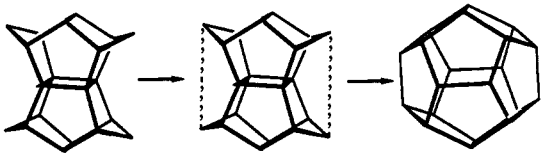
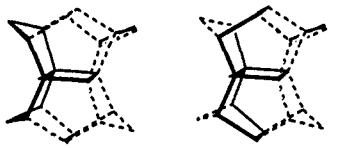
The best application of molecular mechanics for synthesis planning is, in our opinion, the elegant series of papers by Prinzbach who conceived the idea of transforming pagodane (**37**) to dodecahedrane (**38**).[108-117]

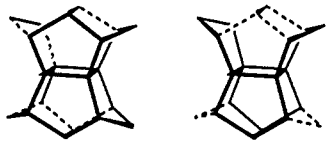


37 **38**

Before pagodane can be transformed, it must be synthesized. One can view this complex ring system as linked propellanes or fenestranes as in **37A-D**. The



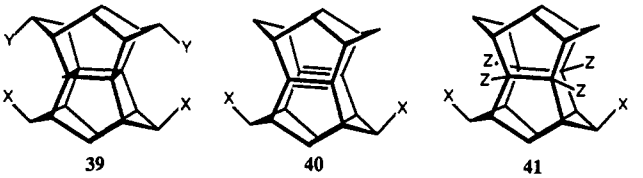
37A **37B**



37C **37D**

total number of subsidiary rings in this system, derived by graph theory, is 865. How best to make pagodane is indeed a complex issue but a challenge met by Prinzbach.[108] Pagodane was estimated to be ~42 kcal mol^{-1} less stable than dodecahedrane by their MM2 calculations. Most of the strain energy is localized on the central cyclobutane suggesting that hydrogenolytic cleavage of two cyclobutane bonds and dehydrogenative bond formings between the methylene groups (central structure between **37** and **38** above) are strategies to pursue. Three pathways were considered. For each pathway, molecular mechanics analyses of strain energies (especially olefin strain), heats of formation, and distances between key reaction sites were carried out. The three routes and the energy changes along paths B and C are presented in Figure 2. Route A was not pursued. Route B involves transformation of **37** to the bissecododecahedradiene. This diene was predicted to have negative olefin strain and to be hyperstable.[109] Indeed, only monohydrogenation could be achieved and alternative strategies had to be taken.

Similar *a priori* molecular mechanics calculations were used as a guide by Prinzbach's group in synthesis planning of tetra-substituted pagodanes.[110-111] In their first study MM2 revealed OS values in the positive, "isolable" range suggesting a synthetic route involving hydrogenation pathways to be feasible. In the second study MM2 strain energies suggested a synthetic methodology where variation in the X residues required for the Y function **39** is not possible at the bisseco stages, **40** or **41**, but must be brought about at an earlier stage of synthesis. Two ensuing papers on the design and synthesis of polyfunctionalized pagodanes, where olefin strain and thermodynamic calculations implicated viable pathways, are to be noted.[112-114] Recent back-to-back papers summarizing earlier work from Prinzbach's group and extending their application of pagodane → dodecahedrane transformations guided by molecular mechanics have appeared,[115-117] and others, no doubt, shall be forthcoming.



39 **40** **41**

B. *A Posteriori* Applications of Molecular Mechanics in Synthesis

Most applications of molecular mechanics in synthetic organic chemistry have, for the last decade, been *a posteriori*, after-the-fact assessments rationalizing results. These studies are valuable because they often provide working models of what transpired so that future work is more predictable and better focused. In this part of the review we again limit the number of citations by considering only those papers that contain both experiment and theory. In contrast to above, however, we spend less time on each application. In this regard a disproportionate allocation of space is made for *a priori vs a posteriori* applications. This section is partitioned into two major categories. First, we consider unimolecular reactions, and second, we consider bimolecular reactions. These are followed by several smaller sections on photochemistry and macromolecular syntheses.

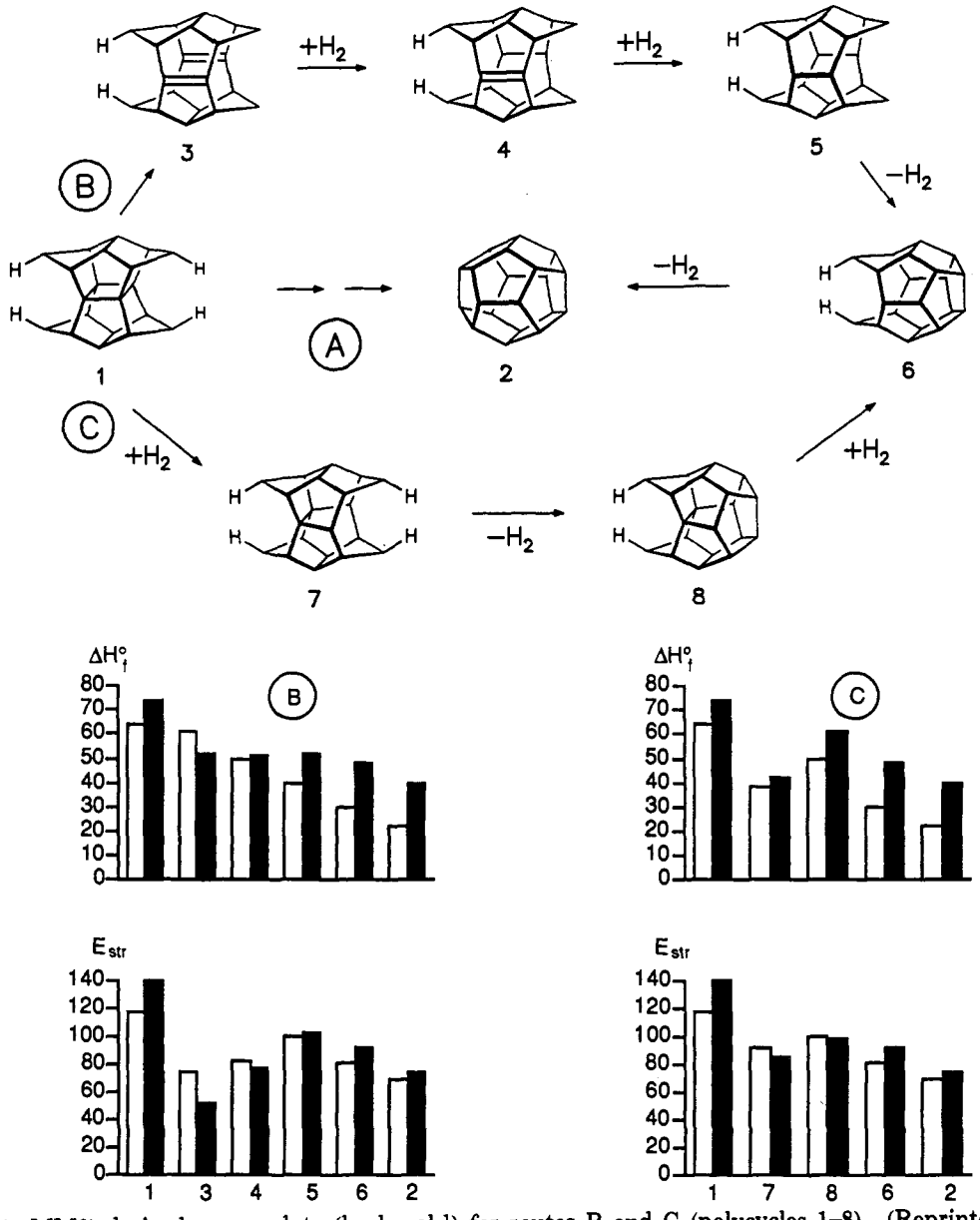


Figure 2. MM2 (MM3)-derived energy date (kcal mol^{-1}) for routes B and C (polycycles 1–8). (Reprinted from ref 115. Copyright 1992 VCH Verlagsgesellschaft.)

1. Unimolecular Reactions

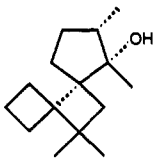
Dissociations. Unimolecular dissociation would appear to be the antithesis of what synthetic chemists do, but bond breaking is an integral component of organic synthesis. The molecular mechanics investigations of bond breaking, or lysis, is divided into two categories: solvolysis and thermolysis.

As a synthetic methodology, solvolysis is not often used. However, the unimolecular, heterolytic bond cleavage to make cations which undergo Wagner–Meerwein 1,2-shifts can be useful to generate expanded ring systems that are otherwise difficult to access. The ratio of rearrangement products and the rates of reaction are often correlated with molecular mechanics energies as exemplified by Adams[118] and Kirmise.[119] Another good example of explaining the results of solvolytic ring expansion with molecular mechanics is by Crumrine.[120] A molecular mechanics investigation by Jarvis[121] of the chair–boat equilibrium of a modified trichothecene ring system (trichothecenes inhibit protein synthesis) showed that the boat form was more stable than chair. This places an otherwise remote alkene proximal to an epoxide. Double-bond participation in the spontaneous solvolysis of the epoxide gave an undesired, albeit unique, caged product. Most molecular mechanics studies of solvolyses, however, are more focused on explaining reaction rates due to steric or electronic effects.[122,123] The studies by Müller[124] and Schneider[125–127] are also noted. Some work on hydrolysis of sugars to explain the ALPH (antiperiplanar lone pair hypothesis) exists.[128,129]

Thermolysis (pyrolysis) is more of a synthetic mainstay than is solvolysis. Some of these studies involve unimolecular dissociations that are symmetry allowed. These include pericyclic reactions like the retro-Diels–Alder fragmentation by Czarnik[130] and retro-aldol by Seeman.[131] Other studies involve symmetry-forbidden dissociations like the disrotatory electrocyclic ring opening of Berson,[132] the thermal [$2\pi + 2\pi$] cyclobutane cycloreversions of Nishimura[133] and the thermolysis of 1,2-dioxetanes by Baumstark.[134] Many thermolyses analyzed by molecular mechanics are those that give

rise to radicals by homolytic cleavage. Of special note in this regard are the studies by Lomas,[135] Beckhaus,[136] and Rüchardt.[137] Other types of fragmentation reactions during the course of synthesis that have been rationalized via molecular mechanics are the diastereoselective C–O bond fission of metal-chelated acetals by Iwata[138] and Heathcock's explanation of bond scission in a key intermediate in the total synthesis of daphnilactone A.[139]

Isomerizations. As expected, many of the molecular mechanics studies of isomerizations involve rearrangements that are pericyclic reactions of one sort or another. These mostly include sigmatropic shifts, but other types are included in this review. Generation of a cation followed by [1,2] shift of an adjacent carbon is the Wagner–Meerwein rearrangement. An interesting *a posteriori* application of molecular mechanics focusing on this rearrangement was done by Fitjer.[140] Beginning with **42**, acid-promoted formation of a cation gives a mixture of modephene, **43**, and isocomene, **44**, via a cascade of [1,2] shifts. Fitjer described the complexity



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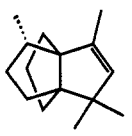

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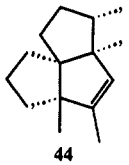
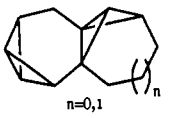


44

of these rearrangements by evaluating the heats of formation of all possible intermediates and products. Another application of molecular mechanics to [1,2] shifts is Overman's rationalization of the high stereochemical fidelity associated with his ring-enlarged tetrahydrofuran annulation reactions.[141] Other applications of molecular mechanics to [1,2] shifts in natural product syntheses have appeared,[142] but a large number have been focused on [1,2] reorganization in caged molecules.

Caged molecules containing 3-, 4- and 5-membered rings have considerable strain. They can undergo one or more [1,2] shifts to afford either kinetic or thermodynamic products. For example, the bisbicyclo-[1.1.0]butanes, **45**, studied by Paquette[143] undergo electrophilic bond scission at only one of the 10 strained bonds. Reconciliation of products from bond migration was assisted with MM2. Another example is the electrophilic attack on the double bond of homocubylidenehomocubane (**46**) that was anticipated by Marchand to result in Wagner–Meerwein rearrangement.[144] Marchand found rearrangement could not compete with 1,2-addition in this system and a rationalization based on MM2 was given. In another paper, dimerization of trishomocubanone to the *dl* and *meso* stereoisomers, **47** and **48**, was accomplished.[145] Marchand found the *dl* pair underwent electrophilic additions like **46**, but **48** rearranged by two consecutive Wagner–Meerwein rearrangements to a complex, spirocyclic product. Of the four possible products, MM2 indicates the observed one to be the thermodynamically most stable. Molecular mechanics explanations of other [1,2] shifts involving caged or polycyclic systems have been reported by Nelson[146] and Fry.[147] We also point out that the stereochemical course of ring expansion of bridged bicyclic ketones to spirocyclic products reflect a kinetic



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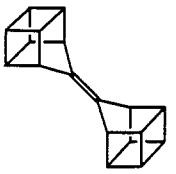

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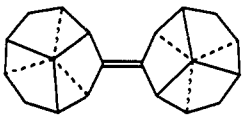
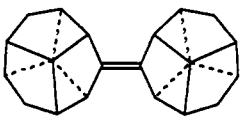


(*dl*)

47

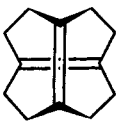


(*meso*)

48

preference rather than a thermodynamic one based on MMX calculations by Paquette.[148]

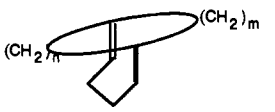
By far, most unimolecular pericyclic rearrangements studied by molecular mechanics involve Cope, anionic oxy-Cope, Claisen, and related [3,3] sigmatropic shifts. Using the previously described tetraone **1**, McMurry felt that a titanium-induced cyclization would lead to **49**.[149] Cope rearrangement to an isomer prevailed,



49

however, in accordance with force field analysis. Similar topologically interesting dienes had already been studied by Shea.[150] He found divinyl groups in bicyclo-[*n.m.*0]alkenes (**50**) underwent Cope rearrangement to the bridgehead diene **51**. A rough correlation between rates of isomerization and MM2 strain energies was noted. Further work by Shea addressed the preference for chair *vs* boat transition states.[151]

50



51

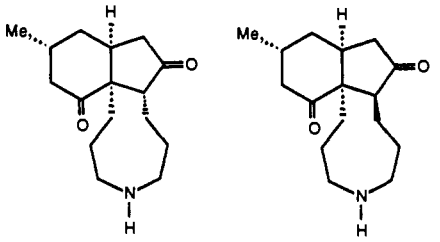
Chair–boat topographic stereoselection during anionic oxy-Cope rearrangements have been exhaustively studied experimentally and theoretically by Paquette[152–154] who also evaluated related oxy-Cope[155] and other rearrangements[156] with molecular mechanics. The chair *vs* boat transition structures in Claisen-mediated ring contraction studies was addressed in detail by Funk.[157] Other *a posteriori* applications of molecular mechanics to understand [3,3] sigmatropic shifts in organic synthesis exist.[158–160] Interesting applications to [1,3],[161,162] [1,5],[163] and higher[164] sigmatropic rearrangements are noted.

In comparison to sigmatropic rearrangements, few other pericyclic reactions have been studied by molecular mechanics as part of a synthesis paper. The electrocyclic studies by Houk[165] and Liu[166] are exceptions that complement the previously described pyrolysis studies of Berson.[132] Force field analysis of dyotropic rearrangements by Howard[167] and Marchand[168] which assess steric and strain effects during hydrogen migration have been published. Nonpericyclic, unimolecular isomerizations that have relied on

molecular mechanics interpretations include cis–trans isomerization in alkenes[169] and sterically congested alkenes.[170,171] Other nonpericyclic rearrangements involving a series of bond-breaking and bond-making steps have also used molecular mechanics to rationalize products.[172,173]

Epimerization. Another type of isomerism is epimerization. Epimers are stereoisomers that differ at only one of several possible stereocenters, and accordingly, they are diastereomers. Epimerizations are usually acid- or base-promoted, and the distribution of products usually represents thermodynamic equilibria. One of the advantages of using molecular mechanics to address epimer ratios is that these molecules, like other diastereomers, have identical molecular connectivities and differ only in the spatial positions of atoms. Consequently, many of the errors in the empirical force field method tend to cancel.

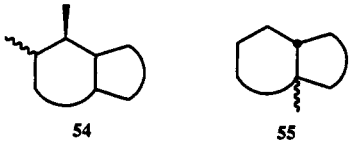
An *a posteriori* application of molecular mechanics in natural products chemistry is given by Heathcock in his total synthesis of fawcettimine.[174] In this study molecular mechanics was used to clarify the behavior of fawcettimine with respect to epimerization. The strain energies of intermediates **52** and **53** were computed with the idea of determining the likelihood of forming 4-epifawcettimine. These strain energies were compared with the *N*-acetyl derivatives of **52** and **53**.



52 **53**

It was found that while fawcettimine and its epimer have nearly the same strain energies, the *N*-acetyl derivatives behave differently. The *N*-acetylfawcettimine is more stable than its epimer. This type of analysis, along with Heathcock's assessment of site selectivity during carbinolamine formation, fully supports the presence of product suggested by NMR and anomalous IR data.

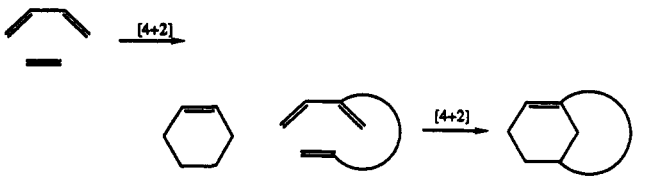
Another interesting application of molecular mechanics involves the epimerization study of the methyl cinnamate dimer in a basic medium.[175] Robinet's epimerization scheme for creation and depletion of products over time is fully consonant with MM2 results. Many other reconciliations of epimer distributions exist. They can be divided into two categories, the first being systems whose stereochemistry involves pendant groups attached to a ring, **54**, and the second involving the stereochemistry at the ring juncture of fused ring systems, **55**. In the former category, studies on



54 **55**

5-membered,[176,177] 6-membered,[178–182] 8-membered,[183,184] and larger ring systems[185] exist. In the latter category the stereochemistries of 6/4-,[186] 6/5-,[187–189] 6/6-,[190,191] 8/4,[192] 8/5-,[193,194] and 10/5-fused[195] ring junctures have been addressed as part of synthetic studies.

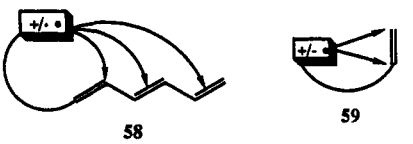
Cyclizations. By virtue of both addends belonging to the same molecule, intramolecular cyclization reactions give rise to more complex ring systems than their simple bimolecular complement. This is an obvious advantage that can be exploited for synthesis of multiple ring systems as illustrated by comparing **56** with **57**. Molecular mechanics has been used to



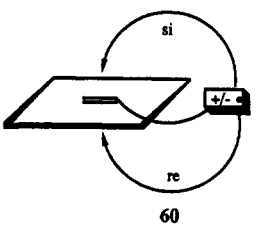
56 **57**

understand a substantial number of intramolecular cyclocondensations and cycloadditions of synthetic significance. These are described below as radical cyclizations, ionic cyclizations, and, finally, intramolecular cycloaddition reactions.

Radical Cyclizations. Three key issues must be addressed in unimolecular cyclizations: site selectivity, i.e., which of one or more double bonds will be attacked (**58**); regioselectivity, the decision of which end of the olefin to attack once the alkenes is selected (**59**); facial selectivity, either top-side or bottom-side attack (**60**) that ultimately controls the stereochemical outcome of the cyclization. Usually a single alkene is involved so



58 **59**



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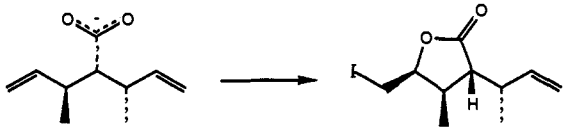
there are few concerns about site selectivity. Questions concerning regioselectivity and facial selectivity have been addressed with empirical force fields. The regioselection, depicted in **59**, is determined by stereoelectronic effects, and a general set of empirical rules has been defined by Baldwin.[196] The question of facial selectivity, however, is difficult to determine but is amenable to force field study because, again, cancellation of errors can give reliable results.

Many of the molecular mechanics investigations of radical cyclizations involve transition-state modeling (see Houk's chapter in this issue). Of special note is the work by Beckwith[197–199] who carried out experimental and theoretical studies on the regio- and stereoselectivity of various ring closures. Other transition-state modeling studies to explain unpredicted stereoselection of radical-mediated cyclizations in synthesis have been carried out by Gennari et al.[200,201] as part of their long-term studies aimed at investigating

stereodirecting effects of allylic stereocenters. The diastereoselection of ring closures in syntheses of natural products have also been addressed by molecular mechanics.[202-204] Finally, rates of intramolecular radical cyclizations have been correlated with structural features computed with empirical force fields.[205-206]

Ionic Cyclizations. Acid- and base-promoted cyclizations are a mainstay of organic synthesis. As above, concerns about site, regioselectivity and facial selectivity need to be considered. A good example of these cyclizations involves the nucleophile-selective iodocyclizations by Kurth.[207] Of the four possible products possible from **61**, iodolactone **62** formed almost exclusively. The high site selectivity and face selectivity



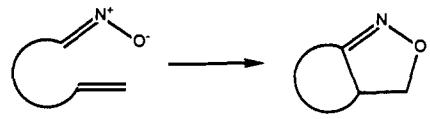
61 **62**

was impressive, and the idea that the reaction could distinguish the two diastereotopic olefins due to ground-state conformational biases was presented. Kurth extended this idea to 3-hydroxy-2-(2′-methylenecyclohexan-1′-yl)butyric acids and used molecular mechanics to demonstrate that ground-state conformational control can qualitatively predict nucleophilic additions. A second example of nucleophilic addition involves the regiospecific and stereoselective cyclizations of substituted 5-hexen-1-yllithiums by Bailey who used transition-state modeling with Wiberg to explain his results.[208] Molecular mechanics has been exploited to rationalize other ionic, intramolecular cyclizations of natural[208-216] and nonnatural[217] products.

Pericyclic Cyclizations. The majority of intramolecular pericyclizations studied by molecular mechanics are Diels–Alder reactions. These reactions usually involve carbocycles, but intramolecular hetero-Diels–Alder reactions have been studied.[218] The intramolecular Diels–Alder cyclizations of 2,8,10-undecatrienals by Marshall[219] and 1,7,9-decatrien-3-ones by Roush[220] illustrate the complexity of these cyclizations. In the latter study Roush anticipated, from mechanical models and conventional wisdom, that the desired diastereomeric adduct required for nargenicin synthesis would arise through a chair transition state. The products formed, however, clearly implied cyclization via a boatlike transition state. A detailed MMX analysis of the eight possible transition structures available to these trienes indicated that in the absence of overriding nonbonded interactions, a boatlike decatrienone cyclization pathway is favored in lieu of the traditional chair pathway.

In other intramolecular Diels–Alder reactions, unexpected products were rationalized by molecular mechanics strain energies.[221] In van der Plas' synthesis of pyrimidines, the lack of reactivity was found to originate from the reacting centers being too far apart.[222] In contrast with this is Prinzbach's force field analysis of Domino *vs* Pincer cycloadditions.[223] MM2 showed a perfect colinear alignment of π orbitals (and a compressed state of diene with dienophile) leading to a second, fascile cyclization that is so fast it precludes isolation of an intermediate in the reaction. In another study, though, high activation barriers based on unfavorable distances between adducts computed by MM3 were found by Prinzbach to be the cause of retarded ring closure in [4 + 2] cyclization to caged systems.[224]

Other [4π + 2π] electron systems that undergo cycloadditions are 1,3-dipoles, especially nitrile oxides. They react with alkenes to form 5-membered heterocycles, **63** → **64**. Extensive experimental and transition-



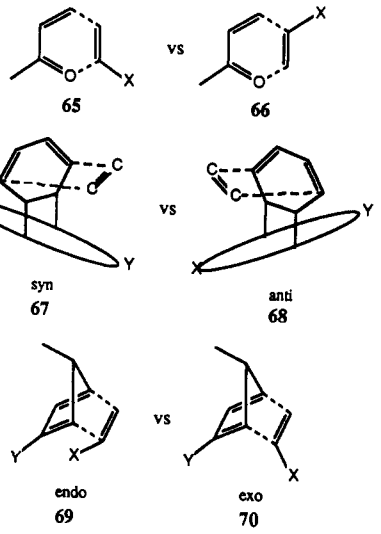
63 **64**

state modeling studies have been done by Hassner and Padwa to understand the stereochemical course of these pericyclic reactions.[225-229] An extension to intramolecular oxime–olefin cycloadditions by these authors has also appeared.[230] Transition-state analysis of intramolecular addition of nitrile oxides to *Z* and *E* chiral alkenes has been published by Gennari,[231] and Potts[232] has investigated the regio- and stereochemistry of intramolecular thiocarbonyl ylide dipole additions. Other reactions include Wender's nickel-catalyzed, intramolecular [4 + 4] cycloaddition,[233] Nakamura's intramolecular ene reaction in his synthesis of cortisone,[234] the thermochemical studies of Martin[235] on [2π + 2π] cycloadditions, and Overman's intramolecular *N*-(acyloxy)iminium ion–alkene cycloadditions.[236]

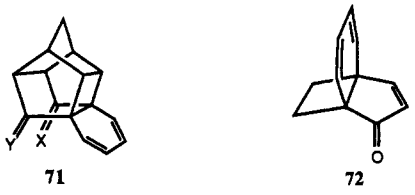
2. Bimolecular Reactions

From a computational perspective, bimolecular reactions are less tractable problems to model than unimolecular ones because they have more degrees of freedom. The same issues raised in the previous section are considered in this section. Our partitioning of material into unimolecular and bimolecular reactions is, hence, completely subjective and is done only to divide the large quantity of post-1983 papers into manageable sections. In this part of the review we consider molecular mechanics studies of bimolecular reactions involving cycloadditions, nucleophilic additions, radical and electrophilic additions and, finally, elimination reactions. Again, only those papers containing both experiment and theory are considered.

Cycloadditions. A large number of ring building protocols invoke cycloadditions. Cycloadditions have, and remain, a cornerstone of synthetic methodology. Most of these reactions are Diels–Alder reactions using $4\pi + 2\pi$ electron components to make unsaturated rings. When carrying out such reactions we usually have a well-defined diene and dienophile, so site selectivity is not important. Regioselectivity, facial selectivity and exo/endo selectivity, however, are important in dictating which ring systems form. An example of regioselectivity is shown in **65** *vs* **66**. Here constitutional isomers are formed. Regioselection is dominated by orbital interactions which are less amenable to force field analysis than by quantum mechanics. However, facial selectivity, **67** *vs* **68**, and exo/endo selectivity, **69** *vs* **70**, that give rise to diastereomeric isomers are prone to steric as well as electronic influences, and they have been studied with force fields. For example, the facial differentiation in Diels–Alder reactions of dissymmetric dienes like **71**, were investigated by Steel.[237] Molecular



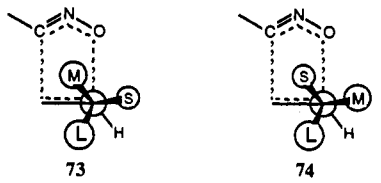
mechanics calculations of the two possible stereoisomeric products showed that product stability does not account for observed facial selectivity. This is consistent with the idea of an early (reactant-like) rather than late (product-like) transition state. The π-facial selectivity of Diels–Alder reactions of propellanones like **72** were studied by Tsuji.[238] His molecular mechanics studies revealed that facial differentiation in propellanes is founded on steric grounds.



The π-facial selectivity of dienes adding to sugar-derived dihydropyranones[239] and the anomeric *vs* allylic facial selection of dieno-pyranosides[240] have also been examined in detail. Other *a posteriori* rationalization of Diels–Alder facial selectivity include the *si vs re* attack in tandem cycloadditions carried out by Denmark[241] and others.[242,243] An example of exo *vs* endo transition states has been addressed by Vedejs[244] in his studies of thioaldehyde cycloadditions to cyclopentadiene. Another example of exo/endo selectivity is the transition-state modeling of functionalized indoles by Pindur[245,246] who revealed clear preferences for endo selectivity in accordance with Alder's endo rule.

Several applications of molecular mechanics have focused on issues of [4 + 2] cycloadditions other than the selectivities described above. For example, a bis-(phenyl sulfonyl) diene prepared by Padwa underwent rearrangement to a new diene before cycloaddition.[247,248] The rearranged diene was computed to prefer the reactive s-cis isomer. In contrast, its progenitor favors the unreactive trans orientation. Mayr has addressed the relative rates of [4 + 2] cycloadditions[249] and the equilibrium between reactants and products have been evaluated by Weiss with empirical force fields.[250] Molecular mechanics-assisted explanations of other Diels–Alder reactions in synthesis are known.[251,252]

Another type of [4π + 2π] cycloaddition that has received considerable experimental and theoretical scrutiny are 1,3-dipolar cycloadditions. An interesting example is the nitrile oxide cycloaddition to chiral alkenes studied by Houk.[253] He found that attack takes place on the more hindered face of the preferred conformation of the isolated alkene. Houk used molecular mechanics to model transition structures **73** *vs* **74** to rationalize his results. Padwa's synthesis of



heterocycles by 1,3-dipolar addition of nitrones to activated allenes[254] and his assessment of steric control of regiochemistry in these additions have been addressed with molecular mechanics.[255] Explanations for facial selectivity in nitrile oxide additions to sugars,[256] exo *vs* endo preferences of nitrile oxides and nitrone diastereoselection to chiral crotonates[257] and the influence of torsionally strained double bonds on azide additions[258] have also been addressed.

Finally, while [2 + 2] cycloadditions are formally disallowed ground-state pericyclic reactions, Pasto has fastidiously examined the cycloaddition reactions of allenes.[259] Product distributions were interpreted on the basis of favored conformations of diradical intermediates. Work on chiral allenes was also investigated. Molecular mechanics calculations on the orientation of the reactants leading to the activated complexes for diradical intermediate formation and the conformational preferences of these structures leading to regioselective ring closure have been scrutinized.[260,261]

Nucleophilic Additions. Most bimolecular nucleophilic addition reactions studied with molecular mechanics involve site or facial selectivity of organometals adding to carbonyl groups. In Mundy's synthesis of modephen,[262] methyllithium was observed to add to only one of two nearly identical ester groups located on a bicyclo[3.3.0]octane ring juncture. One of the 5-membered rings had a methyl group at the C2 position that was found to induce a twist to the molecule. The ester distal to the methyl group maintained an orientation which allowed the incoming nucleophile to approach unimpeded while the proximal ester group was ensconced in a cavity formed by the bicyclic ring and the C2 methyl group. Other studies of organolithium additions examined facial selectivity rather than site selectivity.[263–265]

The venerable Grignard reaction has also been studied *a posteriori* to rationalize facial selectivity. In Hansen's synthesis of daunomycinone and isodaunomycinone,[266] 2 molar equiv of the magnesium reagent were tied up chelating to a key intermediate and the third equivalent of reagent was found to add to a distant ketone with very high diastereoselectivity. A rationalization for this was made by comparing the two diastereotopic faces of the ketone whose structure was determined by MM2. Similarly, Comins[267] was able to rationalize the major diastereomer found in his studies of Grignard additions to chiral 1-acylpyridinium salts, and the nature of the Grignard reagent itself was addressed in a synthetic study by Gawley.[268] Other molecular mechanics studies on the facial selectivity of

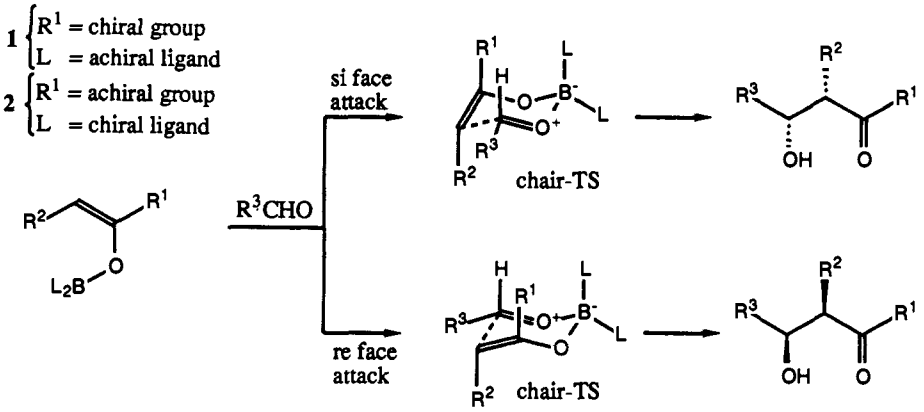


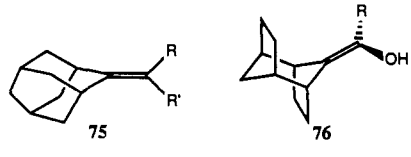
Figure 3. Competing chairlike structures in the boronate aldol reaction. (Reprinted from ref 275. Copyright 1992 Pergamon.)

organometals containing copper,[269,270] cerium,[271,272] and titanium[273] have been published.

The aldol reaction, an important method for stereocontrolled synthesis of acyclic molecules, has been carried out with boronates. The transition-state modeling by Hoffmann[274] substantiated earlier interpretations for the course of asymmetric induction promoted by chiral aldehydes. Most of these reactions, like their alkali metal counterparts, are modeled as competing chairlike structures as depicted in Figure 3. Here, the *si vs re* preference, usually determined by steric effects, dictates the stereochemical outcome. A detailed assessment of these boronate transition-state models is provided by Gennari.[275] A related study of Lewis acid mediated aldol condensations by Gennari's group is also noted.[276]

Yet another type of bimolecular nucleophilic attack that has been examined with empirical force fields involves hydride addition. These reactions include $NaBH_4$ and $LiAlH_4$ additions to simple cyclohexanones,[277] $LiAlH_4$ and L-Selectride additions to complex cyclohexanones,[278] $ZnBH_4$ reductions of β-keto esters containing chiral auxiliaries,[279] and an assessment of stereoselective reductions of cyclohexanones by a chiral rhodium bis(oxazolinyl)pyridine catalyst.[280] Finally, we point out that a molecular mechanics based rationalization for the inability of several benzisoquinolines to form Wittig-type intermediates for the conversion of amides to thioamides with Lawesson's reagent has been published by Wrobel,[231] and the diastereoselection of hydroxide attack on homochiral *vs* heterochiral peptide *p*-nitrophenyl esters in micelles has been studied by Moss.[282]

Electrophilic Additions. Protonation and halogenation of alkenes are representative electrophilic addition reactions that have been studied by molecular mechanics to understand rates of reactions as well as product distributions. Most of these studies involve sterically congested alkenes like adamantylidenealkanes **75** studied by Ruasse[283] or the tricyclic enols **76** examined by Zimmerman.[284] In the latter study, MM2



75 76

energy profiles for exo *vs* endo approach revealed the large kinetic preference for the less stable endo product to arise from steric hinderance by methylene groups.

A similar type of energy profiling was carried out by Marchand.[145] The differences in reactivity of *dl*- and *meso*-trishomocubylidenetrishomocubanes, **47** and **48**, were described earlier in this review. The *meso* stereoisomer was noted to undergo Wagner–Meerwein rearrangement while the *dl* pair underwent simple addition.[145] A molecular mechanics analysis of a pseudoproton approaching these congested alkenes revealed that the sharp increase in energy of the *meso* isomer arises from a sudden increase in torsional energy at a critical alkene-proton distance. This energetic feature is lacking in the *dl* isomer. A follow-up paper by Osawa on this has appeared.[285]

Another type of electrophilic reaction is oxidation, especially epoxidation by *m*-chloroperbenzoic acid (MCPBA). In Little's total synthesis of hypnophilin and coriolin,[286] the highly unusual, energetically less stable, trans-fused bicyclo[3.3.0]octane ring system was formed when a quinane was epoxidized. MM2 energies of products indicated to Little that attack by MCPBA must be assisted by a neighboring hydroxyl such that the energetically less favorable α-face of the π system is approached. The MCPBA oxidation of a benzazonine was found by Maryanoff[287] to give an *N*-oxide with high stereoselectivity. His molecular mechanics analysis indicated that attack on the exocyclic nitrogen lone pair must arise from a high energy, unpopulated conformation of the 9-membered ring. What sets this paper apart from most others is the authors' acknowledgement of the Curtin–Hammett principle. Another heteroatom oxidation was the conversion of cephalosporins to their corresponding sulfoxides. Hatanaka[288] found that accessibility to the cephalosporin's α-face, along with product stability, favored the observed stereoisomer. A very detailed analysis of MCPBA epoxidations of torsionally strained alkenes has been carried out by Shea.[289] He found that rates of epoxidation correlate better with differences in strain energies of alkene and epoxide (ΔSE) than with olefin strain (OS) values. Finally, the stereoselectivity of epoxidation of *cis- vs trans*-stilbenes and styrenes by congested hypervalent oxo porphyrins was modeled by Bruice.[290] The distance and angle of alkene approach to the electrophile, based on molecular mechanics docking studies, helped him rationalize the preferential cis *vs* trans stereoselectivity. Other oxidations including the relative stabilities of allylic alcohols from singlet

oxygenation of a steroid,[291] and the relative stabilities of two intermediate peroxy radicals of cyclohexadienes[292] have been reported.

Hydroboration reactions involve four-center, electrophilic attack on alkenes and have been studied with empirical force fields. The reversal in stereoselectivity between small electrophiles, like BH_3 or $BrBH_2$, and large ones, like 9-BBN and thexylborane, led Bryson to carry out transition-state modeling to reconcile the changeover.[293] Sibi explained the regioselectivity and facial selectivity of hydroborations of chiral allyl amines as arising from ground-state conformer populations,[294] and the asymmetric reduction of dialkyl ketones with a chiral dimethylborolane has been explained by Masamune and Houk[295] with transition-state modeling.

Finally, although hydrogenation reactions are not easily defined as electrophilic, we include them here. The stereoselective hydrogenation of *N*-benzoyltrifluorodehydroleucine and its esters was shown by Ojima[296] to result from the lower energy conformation residing on the palladium surface. A similar conformational analysis by Haviari of chiral dihydropyrroles reduced over Raney nickel indicated the presence of only a single conformer, the backside of which was sterically crowded resulting in frontside reduction.[297] An explanation for the all-cis-fused stereoisomer of ufolane from catalytic reduction of acenaphthene was deduced from MM2 stabilities by Boldt et al.[298]

Other bimolecular electrophilic addition reactions that have been analyzed by molecular mechanics include the addition of PhSeCl with erythrinanes[299] and the insertion of chlorodicarbonylrhodium dimer into strained bonds of 1,3-dihomocubanes.[300] Finally, we point out the molecular mechanics investigations on the observed diastereofacial selectivity of substituted radicals by Giese.[301]

Eliminations. Bimolecular elimination reactions following an E2 pathway are controlled by stereoelectronics. In these mechanisms a syn- or antiperiplanar arrangement of orbitals enhances reaction rates. Most molecular mechanics assessements of elimination reactions have focused on this orientational aspect by evaluating the dihedral angles of atoms involved in the elimination. For example, Haider[302] found that elimination of pyrrolidene from dihydroisoquinolines was fast for some examples studied and slow for others. In the fast elimination the leaving group's dihedral angle was closer to synperiplanar (30°) compared to the slow example which was closer to a synclinal orientation (50°). In Liebeskind's synthesis of benzoabikoviromycin,[303] the final step required formation of an *E* rather than *Z* ethylidene from the dehydration of a benzylic alcohol. Holding the H–C–C–OH torsion angle fixed at the 180°, antiperiplanar geometry, the energies of two conformations that would lead to two different products were found to be nearly equal in energy. The dehydration would be expected to form a 1:1 mixture of *Z*/*E* stereoisomers which was found experimentally. Yet another example of this type of analysis is given by Brown[304] who found that electrochemical reductions of *meso*- and *dl*-dibromohexanes resulted in cis/trans ratios of elimination products that depend on the precursor molecules' ability to achieve an antiperiplanar conformation. Other examples of conformational studies to assess orientations of leaving groups have been published.[305,306] Finally, we note Paquette's use of molecular mechanics to compute strain energies of possible caged products to explain why double elimination reactions could not be induced.[307]

3. Photochemical Reactions

Photochemically driven reactions that have been studied by molecular mechanics can be divided into four basic categories. These include reactions involving [2 + 2] cycloaddition, photoinduced rearrangements, hydrogen abstractions, and reactions of singlet oxygen. In most studies molecular mechanics was used *a posteriori* to address stereochemical outcome. In other studies molecular mechanics was used to explain relative rates of reactions or to rationalize why some systems react while others do not.

[$2\pi + 2\pi$] cycloadditions are photochemically allowed processes and serve as a main source of cyclobutane formation in synthesis. A compelling example for why one should use molecular mechanics in synthesis planning is given by Mehta in his synthesis of secohexaprismane.[308] Photoring closure of several important precursor molecules could not be induced by Mehta's group even though the olefins maintained a favorable distance and good alignment with respect each other. In their research, molecular mechanics was used to explore strain energies involved in photoclosure. For the synthetic pathway they initially pursued, a prohibitive 75 kcal mol^{-1} strain was found. In another pathway, however, where photocyclization was carried out first (strain <55 kcal mol^{-1}), the authors were able to make the secoprismane. In a follow-up study a large number of [2 + 2] cage closure reactions were analyzed.[309] Two variables controlling ring closure were found. These are differences in strain energy between diene and cycloadduct (ΔSE) and the dihedral angle between double-bond planes. This *a posteriori* analysis led to the conclusion that prismanes could form if ΔSE < 55 kcal mol^{-1} and dihedral angles < 50°.

Other intramolecular cycloadditions studied by molecular mechanics involve the multibridged cyclophane syntheses of Nishimura. In one report he suggested that selectivity of cyclization arises from preferred ground-state geometries of reacting divinylbenzene moieties which are held in anti orientations.[310] In another report he provided a molecular mechanics based explanation for why distal *vs* proximal cyclobutanes formed in three-bridged cyclophanes.[311] Other molecular mechanics studies of intramolecular [2 + 2] ring closures include Schultz' studies on regio- and diastereoselectivity in butenyl-2,5-cyclohexadiene-1-ones,[312] and Schriver's ring closure of a highly symmetric tetrathiadiene macrocycle to a thermodynamically less stable valence isomer.[313] Intermolecular cycloaddition studies that used molecular mechanics to evaluate product stabilities have been reported by Schuster[314] and Robinet.[175] Finally, analysis of topochemically controlled, solid state [2 + 2] photocyclizations have been reported.[315,316]

The second major use of molecular mechanics in the analysis of photochemically driven reactions involve molecular rearrangements. Most of these papers originate from Zimmerman. In one study the factors controlling steric effects on triplet di-π-methane rearrangements were examined,[317] and the preference for radical conformations leading to products was ad-

dressed.[318] In another study, the relative migratory aptitudes of α- *vs* β-naphthyl groups was understood by determining the conformations of the reactants and their photoexcited states. The relevance of these conformations to observed photochemical stereochemistry was highlighted.[319] Finally, the stereochemistry of 4,4-diphenylcyclohexenone rearrangement was evaluated by computing "half-migrated" exo and endo diradicals.[320] Unfavorable steric interactions were found by Zimmerman to preclude phenyl migration along one pathway but not the other. Rearrangements analyzed by other groups include the six-electron photocyclizations of enamides by Eguchi[321] and 1,3-acyl shifts by Suginome.[322] In the latter study, correlations between stereochemistry of photoproducts and ground-state conformer populations implicated tight biradical intermediates.

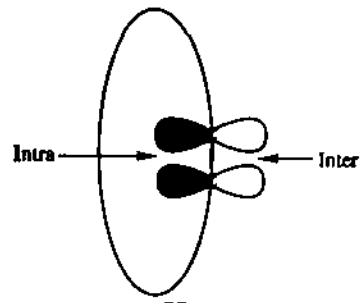
The third category of photochemical reactions that implements molecular mechanics to explain product formation are those reactions where hydrogen abstraction takes place. Two detailed studies come from Wagner's group. In one study, photocyclization of o-alkyl phenyl ketones formed 5-membered rings by δ-hydrogen abstraction.[323] The relatively slow reactivity of several molecules was found to reflect conformational factors. More specifically, it was established with MMX that there is an unfavorable syn–anti equilibrium for rotation around the benzene–ether oxygen bond such that in the preferred syn form there is no C–H bond near the carbonyl. In the second example from Wagner's group, the conformational effects on δ-hydrogen abstraction in sterically congested α-arylacetophenones was thoroughly examined. They found that α-mesityl ketones must be reacting from their ground-state conformations and that hydrogen abstraction can occur from nonideal geometries.[324] The relationship between the dihedral angle formed by the reacting hydrogen and the nodal plane of the carbonyl is discussed from a molecular mechanics perspective as are structural effects on α-cleavage and 1,3-mesityl migrations.

Heathcock has recently extended Breslow's idea of using a benzophenone template to direct the remote oxidation of fused 6-membered ring systems.[325] Differences between remote oxidations by template-directed hydrogen abstractions in Heathcock's trans–anti–trans perhydrophenanthrene and Breslow's steroid were found by molecular mechanics to involve differences in curvature of these fused ring systems. The phenanthrene system is cupped, with concave and convex faces, and some hydrogens are shielded by this topography. Other hydrogen abstraction studies whose results have been aided by molecular mechanics involve work by Sauers, who developed a force field for excited state hydrogen abstractions[326] and then addressed the stereoelectronics of Norrish type II reactions in caged ketones;[327] the work of Lahav and Leiserowitz[328] who mapped the photoaddition pathway of acetophenone guests in deoxycholic acid hosts; and the intramolecular hydrogen-transfer reactions of substituted cyclopropenes carried out by Padwa.[329]

Finally, we emphasize that molecular mechanics interpretation of singlet oxygen [2 + 2] additions and ene reactions, especially by Clennan[330–332] and Brosa,[333] are published. Other molecular mechanics-assisted interpretation of photogenerated systems exist.[334,335]

4. Macrocycle Reactions

We pointed out earlier that unsaturated, large ring compounds tend to adopt conformations where the π lobes lie in the mean plane of the ring **77**, rather than orthogonal to it as in small rings. Accordingly, one



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face of the π system is exposed to the exterior of the macrocycle so that intermolecular attack takes place from that direction while intramolecular attack can be induced from the other direction. Facial differentiation may be conformationally controlled, and an emphasis in large-ring chemistry, initiated by Still, is to modulate these conformations to effect stereocontrol at distant centers. Because these rings have unique conformational properties and special reactivities, we reserve a special discussion of them here. Some aspects of synthesis with macrocyclic rings have already been discussed earlier in this review.

Carbocycles. The polyunsaturated carbocycles which have been prepared or used in synthesis and studied with empirical force fields span the range from 10-m (10 membered) to 18-m rings. Most of these syntheses and their *a posteriori* force field analyses have been directed toward natural products. A particular emphasis has been placed on using and understanding the site selectivity, regioselectivity, and facial selectivity of germacrene, humulene, and related sesquiterpenes. For example, Fransen and Buck,[336] who generated conformational correlation diagrams for 8-hydroxygermacrene B, were able to correlate some of their unusual diimide reductions, asymmetric inductions and chemical reactivities with ring conformation. An extensive literature on biomimetic and synthetic reactions of epoxygermacrene D, another 10-m ring, has appeared because of its relationship to periplanones, which are cockroach pheromones.[337–339] A conformational analysis of germacrene D and periplanone analogs has revealed the inherent flexibility of these molecules.[340]

Many other 10-m ring system studies involve transannular cyclizations. An interesting example of how substituents can induce regio- and stereochemistry of 10-m ring cyclizations to give steroid and secosteroids is provided by Dosen-Micovic who used transition-state modeling to rationalize her results.[341] Another example of 10-m ring closures is provided by Beckwith, but the transition-state modeling inexplicably fails.[342] Ten-membered ring templates for stereoselective radical cyclizations have been shown by Winkler to depend on alkene geometry,[343] and the consequences of ring strain release in the Weiss–Cook condensation of an α-diketo cyclodecene has been illustrated by Paquette.[344]

Eleven- and 12-m rings have likewise been used and studied. The conformational analysis of a dolabellane diterpenoid was carried out by Matsuo where the distribution of epoxidation products was rationalized

in terms of the cycloundecadiene's conformer populations.[345] The conformational analysis and transannular cyclization of (*Z,E,E*)-humulene, another 11-m ring, showed that products arose from TT or CC conformations of an epoxide intermediate.[346] In Nishimura's synthesis of 12-m paracyclophanes, precursor exo and endo conformations were of nearly equal energy reflecting the final exo/endo ratios observed from synthesis.[347]

Thirteen-membered ring transformations have been a focal point of Takahashi's group. They proposed that the stereochemistry of [2,3] Wittig rearrangements, where all five atoms participating in the sigmatropic shift were incorporated into a ring, could give a different sense and degree of diastereoselectivity than traditional acyclic rearrangements. Indeed, the stereoselective synthesis of costunolide with trans stereochemistry was rationalized by considering possible transition states available during sigmatropy.[348] In a following paper a six-step synthesis of costunolide and the remote stereocontrolled synthesis of haageanolide, along with transition-state modeling of the transannular [2,3] Wittig rearrangement, was presented.[349]

Fourteen-membered carbocyclic rings have been a synthetic target of Marshall's group for many years. In one example of their work on cembranolides, the conjugate addition of lithium dimethylcuprate to a 14-m, cyclic, ynone yielded a single stereoisomer that was shown to arise by a distinct bias for attack anti to an acetic acid side chain.[350] In another study they reported that the stereoselective conversion of a precursor alcohol to a cembratrienediol tumor inhibitor relied heavily on stereodirecting transformations of 14-m macrocyclic intermediates.[351] Finally, in their synthesis of anisomelic acid, Marshall's group used molecular mechanics to help rationalize how conformational preferences of 14-m rings influence elimination of alkoxyphosphonate intermediates in Horner–Emmons cyclizations.[352] Carbocycles larger than 14 have been examined also. An example is Macomber's synthesis and molecular mechanics study of the stereoisomers of bicyclo[8.8.2]icos-19-ene.[353]

Finally, we again mention that 10-m and 12-m rings, which serve as core structures of enediyne antibiotic and antitumor agents, have been synthesized and analyzed with molecular mechanics.[354-356]

Heterocycles. Most of the heterocyclic systems considered are macrolides. These are large-ring lactones found in a variety of antibiotics. In terms of conformational control, the lactone moiety prefers a trans geometry and behaves like an (*E*)-alkene. One of the most enlightening and enjoyable articles to read about conformational control in natural products synthesis is by Still who outlines synthetic strategies and molecular mechanics studies directed toward baccharin and roidin E.[357] He presents concepts of synthesizing complex macrocyclic lactones where remote diastereomeric relationships are established, and he discusses strain energy criteria for macrolactonization.

The idea that conformations can control alkene facial selectivity was also being explored by Vedjes who argued that one need not know all of the conformational states of large-ring systems to determine stereochemical outcome.[358] His "local conformer" approach for predicting epoxidation selectivity of alkenes considered only the immediate environment of the olefin. In a study of local conformer effects in unsaturated macrolides he considered epoxidation and osmylation selectivities of (*Z*)- and (*E*)-alkenes.[359] Information from molecular mechanics clarified some of the observed trends and confirmed the generalizations about conformer preferences. Other groups have compared local conformer approaches with full conformational analysis. As part of Weiler's work aimed at studying the stereoselective reactions of macrolides, he proposed a local conformer model to rationalize conformationally controlled reactions in 14-m lactones. Full conformational analysis as well as a proposed local conformer model were both able to rationalize the direction of $NaBH_4$ reduction of ketones.[360] Weiler extended these studies to other reductions in similar ring systems where again MM2 calculations correctly predicted the stereochemistry of product.[361] Finally, Weiler found the stereochemical alkylation of 16-m lactones to proceed with high diastereoselectivity. He proposed a simple local conformer model to rationalize the results but made note of the shortcomings of such models.[362]

The synthesis of 16-m macrolide aglycones by Yonemitsu involved stereoselective epoxidations and reductions that were based on conformational control of macrolide rings with protecting groups.[363] The shapes of these molecules and their populations were assessed by molecular mechanics. The preferred direction of reagent attack during the syntheses was made clear from these studies. In a following paper Yonemitsu described two conformational isomers of a 16-m epoxyenone that serve as key intermediates of maridonolides.[364] The direction of hydride attack leading to the desired (*R*)-alcohol was explained by Yonemitsu using molecular mechanics. Finally, in Baker's attempt to find acid-stable erythromycin A analogs, a novel series of compounds were envisioned. The synthesis of these analogs involved intramolecular Michael reaction that was dictated by macrocycle conformations.[365]

Other heterocyclic systems beside lactones that have been studied with molecular mechanics to understand stereochemical outcome include the diastereofacial selectivity of hydrogenation reactions of 9-m amines by Maryanoff,[366] the role of atropisomerism in ring closure to macrocyclic lactams by Bringmann,[367] ring closures driven by steric strain in 10-m diketolactams by Boeyens,[368] and a rationalization by Marshall of unusual furan reactions that are facilitated by ring strain.[369]

IV. Summary and Prospectus

The work described above is a representative slice of the use of molecular mechanics in organic synthesis. There are other categories of synthetic studies that have likewise implemented molecular mechanics. These include, among others, *a posteriori* studies of olefin strain,[268,269,370-375] and studies of enols[376] and enolates.[177,362,380-390]

Several review articles that focus on the application of molecular mechanics in the design of natural products have appeared,[391-393] but they are limited in scope. The examples described in this review reflect how synthetic organic chemists in general have used this computational tool for their studies to date. Prior to 1983 there were relatively few applications of molecular mechanics

in organic synthesis. Outside of the pharmaceutical community, the reluctance of organic chemists to adopt these tools, compounded with the difficulty of using these programs, resulted in a long induction period before molecular mechanics was deemed acceptable. Menu-driven, graphic front-ends catalyzed the use of molecular mechanics in synthetic chemistry laboratories, and today it is becoming a standard tool for the bench chemist.

Most of the publications in synthesis which implemented molecular mechanics did so sparingly and only within the past decade. These studies were mostly *a posteriori* applications. There have been excellent and poor applications. Most of the papers reviewed here neglected the Curtin–Hammett principle, did inadequate conformational searches, were oblivious to medium effects, made unsound approximations, and often transcended the boundary between judicious and native use of the methodology altogether. On the other hand, many of the scientists whose work is described here were fully cognizant of what they were doing. They recognized that, for most applications, especially for stereochemical studies, cancellation of errors would occur, or they were simply curious about how far one could push the method. A need clearly exists, however, to incorporate this and related computational methods into the undergraduate curriculum so that novice modelers are aware of what molecular mechanics can do and what it cannot do.[394]

So, what is the future of molecular mechanics in synthesis, and where do we go from here? Molecular mechanics is only beginning to emerge as a tool that synthetic chemists will routinely use in an *a priori* manner. The applications will include predicting *what* to make (CAMD) and *how* to make it (synthesis planning). The way we will implement empirical force fields into synthetic chemistry in the forthcoming decade will be substantially different than our current *modus operandi*. Noteable changes include use of new generation force fields that treat polarization[395] and electrical properties[396] more reasonably, consideration of the medium by inclusion of counterions and solvent with explicit or implicit methods,[397] and use of potentials that treat bond making and bond breaking for probes of reaction mechanism.[398] In this last regard there will be a more detailed assessment of bond making and breaking with hybrid molecular mechanics/quantum mechanics techniques.[399,400] The bond-making/bond-breaking potentials are called reactive potentials. Also, with the exception of determining energies and structures of nonflexible systems, the days of simple energy minimizations are limited. We shall see statistical thermodynamics come to the fore where ensemble averaging is done from full-scale simulations. A prelude of what can be expected in this regard is given by Whitnell and Wilson.[401] Finally, the development of empirical force fields for inorganics and organometallics[402] will allow us to consider the full range of reagents and synthetic methodology currently being developed by synthetic chemists. The application of empirical force fields in organic synthesis looks promising.

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Addendum

Since this paper was written several other reports on the use of molecular mechanics in synthesis have appeared. These are listed in alphabetical order by first author in references 403–449.

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