

# Transition-State Modeling with Empirical Force Fields

John E. Eksterowicz and K. N. Houk\*

Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California 90024-1569

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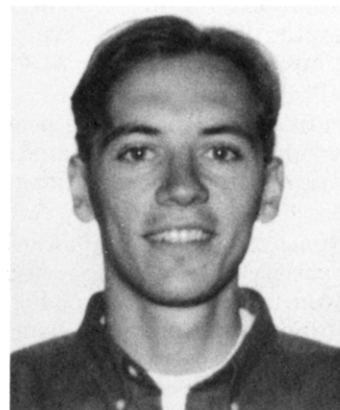
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## I. Introduction, History, and Definitions of Models

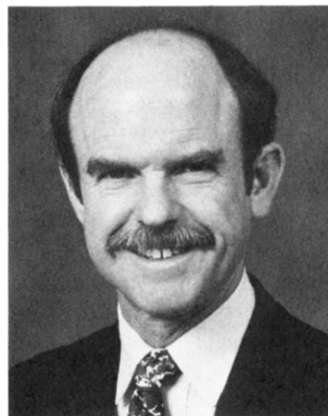
Empirical force fields, or molecular mechanics methods, have been developed for the investigations of structures and conformations of molecules. Extensions to molecular dynamics and solution simulations have enlarged the scope and utility of these methods. Many such applications are thoroughly reviewed in this volume. The use of force fields for the modeling of transition states has also developed as a method to study chemical reactivity and selectivity. This review describes the applications of force field methods, mostly modified versions of Allinger's MM2 force field, to model the geometries and energies of transition states. Literature coverage is up to the beginning of 1993.

The review begins with an introduction to the different methods which have been developed for transition-state modeling. Next, the important early developments up to a decade ago are reviewed. Finally, all the literature is reviewed by means of summary tables with accompanying explanatory text.

The transition states involved in conformational equilibria can be studied using the ground-state parameters developed from geometries and heats of formation of stable molecules. Indeed, one of the earliest applications of empirical force fields to organic chemistry was Westheimer's study of rotational barriers in biphenyls, begun in the 1940s and reviewed in the 1950s.<sup>1,2</sup> This study gave a good account of the rates of racemization of optically active halobiphenyls and required the development of appropriate nonbonding



John E. Eksterowicz was born in Philadelphia, PA, and received his B.S. in chemistry in 1989 from the University of Delaware. He is currently completing his Ph.D. in physical organic chemistry with Professor Houk at UCLA. His research involves the development and application of computational methods to study organic and biochemical problems such as stereoselectivity in radical reactions and photocycloadditions, conformational preferences in C-glycosides, and radical generation and reactions from enediyne cyclizations.



Kendall N. Houk is Professor of Theoretical and Organic Chemistry and Chair of the Department of Chemistry and Biochemistry at UCLA. He received his undergraduate and graduate training at Harvard and has served on the faculties at Louisiana State University, the University of Pittsburgh, and UCLA. He was the Director of the Chemistry Division of the National Science Foundation from 1988 to 1990. His group studies chemical reactions with experimental and computational methods.

potentials. The calculations of energies as a function of geometry were performed without the aid of computers at that time.

In the subsequent half century, there have been many studies of rates of conformational processes in organic systems. Ground-state parameters are fully appropriate to such studies; transition states have more torsional and nonbonded strain than energy minima, but have the same types of bonds.

However, when bonds are being made or broken, the parameters suitable for ground states are no longer appropriate. Consequently, parameters must be developed to model partial bonds in a quantitative way. This review covers the modeling of transition states of reactions in which bonds are made or broken.

Theoretical studies on transition structures of several classes of reaction have shown that bond lengths and other geometrical parameters in transition structures have a relatively narrow range of values. For example, in pericyclic reactions, forming CC single bonds generally have lengths of 1.95–2.28 Å, even though some of these reactions are very exothermic and others are thermoneutral.<sup>3</sup>

Radical additions to alkenes have been studied for a variety of carbon- and oxygen-centered radicals. The angles of attack and forming bond lengths are quite constant at  $105 \pm 3^\circ$  and  $2.25 \pm 0.01$  Å, respectively.<sup>4</sup>

Hydroborations of alkenes and alkynes have been studied for a variety of alkylboranes and substituted ethylenes. Even in the presence of high steric hindrance, the forming and breaking bond lengths are relatively constant.<sup>5</sup>

These examples support one critical procedure often used in simple force field transition-state modeling, namely the breaking and forming bonds are either fixed at some lengths, or these values are treated as energy minima. The energy is actually a maximum for the reaction coordinate, but the simple expedient of calculating transition states as minima has been used in many cases.

The transition state is a saddle point along the free-energy surface. This saddle point has negative curvature in only one direction. The negative force constant corresponds to motion along the reaction coordinate. All other vibrational motions have positive force constants, exactly like energy minima on potential surfaces. This one negative force constant causes transition structures to have unique properties different from energy minima.

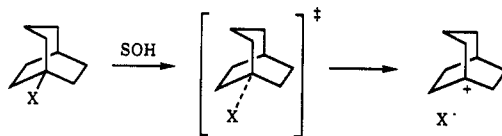
Some force field programs allow the calculation of first and second derivatives of the energy with respect to coordinates, and thus have the capability of locating saddle points on the potential surface. However, to apply a force field directly to transition-state location requires a potential energy function which is suitable not only for stable molecules, but for partially-bonded systems as well. This requires more complex functions than are ordinarily used. Such parameters would have to be highly anharmonic, and parameters such as torsional parameters, would be quite dependent on values of others in the molecule, such as bond stretching and angle bending.

Jensen has developed such a method based upon locating the seam where reactant and product potential surfaces intersect.<sup>6,7</sup> The lowest point on this seam is an approximation to the transition structure. For this to be accurate, the parameters must be reasonable, even for regions of the transition state. Later in the review, the approach by Jensen will be described in more detail.

One of the first applications of force field modeling of rates of a reaction involving extensive bonding changes was due to Garbisch et al.<sup>8</sup> They created a complete force field for the diimide reduction of alkenes, involving use of a variety of experimental data to deduce

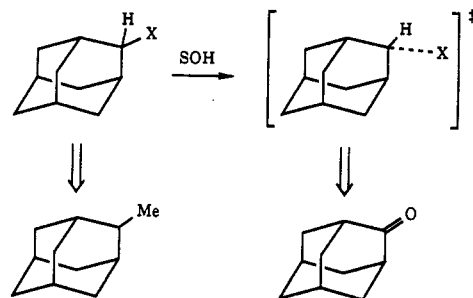
force constants, references to earlier force fields, and some judicious choices for bond lengths.

For the most part however, simpler expedients have usually been applied to the choice of force field. The simplest transition-state model involves the assumption that the geometry and force constants of the transition state are very similar to those of some molecule for which a force field has been developed. For example, in the study of solvolysis reactions, Schleyer et al. investigated bridgehead reactivity by assuming reactant strain was related to that present in the analogous hydrocarbon, and transition state strain was proportional to that of the carbocation.<sup>9–11</sup> In effect, the



geometry and force constants developed for cations were used to model the solvolysis transition state. The differences between hydrocarbon and cation strain energies correlated very well with solvolysis rates. Smith and Harris<sup>12</sup> and Lenoir and Frank<sup>13</sup> applied the same method to investigate secondary derivatives. This technique is of excellent generality for substrates and solvents which react by the limiting solvolysis mechanism.

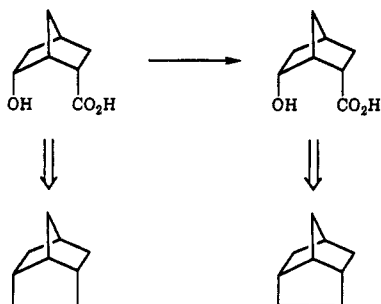
Schneider and Thomas<sup>14</sup> and Muller and Perlberger,<sup>15</sup> on the other hand, used the ketone force field to mimic the solvolysis transition state and a methylalkane to calculate the strain of ground-state tosylate. Such



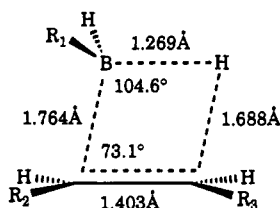
analog TS models are easy to use, since the analogs are normal energy minima. They break down only when the molecules being studied exceed the range of structures for which the force field has been parameterized.

In other cases, a more complex analogy has been adopted. For example, in a study of lactone formation from hydroxycarboxylic acids, DeTar and Tenpas used simple alkanes<sup>16</sup> and ortho esters,<sup>17</sup>  $RC(OH)_3$ , to mimic the transition state for acid-catalyzed hydrolysis of esters. Furthermore, alkane carbon parameters were used for the oxygens, since oxygen parameters were not available. In another study, DeTar calculated the rate of acid-catalyzed lactone formation in polycyclic hydroxy acids.<sup>18,19</sup> He used the strain energies of hydrocarbons to estimate those for reactant and transition-state analog.

The newer generation of transition-state models used the predictions of quantum mechanics to provide the geometry of a transition state. The simplest version of this technique involves the so-called rigid TS model.



This involves fixing the positions of atoms involved in bonding changes at values obtained from transition state calculations of some type. A good example of this technique comes from an early study of hydroboration reactions. Houk et al. located the *ab initio* transition state for the reaction of  $\text{BH}_3$  with ethylene, and for a number of analogs.<sup>20,21</sup> In the rigid TS model, the positions of the atoms involved in bonding changes are fixed at the TS geometry, as shown, and the geometries of all attached groups are optimized:



The transition-state atoms are special atom types, and some force constants may have to be developed in the creation of a rigid TS model. For the hydroboration, no parameters existed for tetracoordinated boron, and all parameters for boron were set equal ("equivalenced" in our jargon) to those of  $\text{sp}^3$  carbon.<sup>22</sup> Bond lengths and angles were taken from *ab initio* calculations.

The next level of complexity involves the so-called flexible TS model, in which the positions of all atoms, including those involved in bonding changes, are optimized. This requires the development of new parameters, and often a large number at that. The applications of this technique have generally involved one assumption which at first seems drastic—that the transition state has all positive force constants.

This is an assumption which has brought the most attention and criticism to the area of transition-state modeling. As described earlier in this review, evidence from quantum mechanical calculations indicates that the transition-state geometries are relatively constant for a given type of reaction, so this assumption is not as drastic as it seems.

It would of course be better to treat the transition state in the correct way, as a saddle point on the potential surface. This has been done in a few cases. In the mid 1980s, Still and co-workers set out to develop an empirical transition-state model using experimental stereoselectivity data.<sup>23</sup> For enolate alkylations by  $\text{MeI}$ , they assumed that the transition-state parameters would be a linear combination of the parameters of reactants and products. They then undertook a least-squares fitting of calculated to experimental stereoselectivities for enolate alkylations, by varying a parameter defining the position of the transition state. Although they achieved excellent agreement between the calculations and experiment, in general the amount

of experimental data necessary to optimize parameters in such a force field is not available, and so this technique has not been pursued.

The program MMX,<sup>24</sup> by Gilbert and Gajewski adopts the clever expedient of making force constants and bond lengths of partial bonds a function of bond order. The transition-state equilibrium bond lengths are determined by the input bond order according to Badger's rule using Pauling bond order terms, eq 1. The force constants are calculated by the simple relationship shown in eq 2.

$$R_{\text{TS}} = R_0 - 0.6 \ln(\text{BO}) \quad (1)$$

$$k_{\text{TS}} = k_0 \text{BO} \quad (2)$$

Several possible weaknesses of this method are that the partial bond orders of transition states are not generally known and force constants may not be proportional to bond order. Few quantitative applications of such an approach have been reported.

The ideal achievement would be the development of a simple empirical force field capable of accurately reproducing the geometries and energies of a broad range of stable molecules and transition states. The versatility of the force field would be such that reasonable predictions could be made about the activation energies of reactions not yet investigated.

With a highly parameterized force field using sufficient examples, it is possible to develop a force field based upon potentials and constants that do not correspond to any physical process. This is not highly probable, however, and it becomes less and less likely as more data are collected. While it is difficult to prove this statement, it is clear from extensive development of semiempirical quantum mechanical methods that the only way to reproduce the Schrödinger equation is by solutions of the Schrödinger equation itself! Parameterized semiempirical approximations invariably fail at some point, although the less approximate they become, the closer they get to the correct answer.

In order that the force field be used to analyze the origin of reactivity and substituent effects, it is necessary that the various potentials and force constant parameters are reasonable. The ability of force field to reproduce the force constants as judged from vibrational spectra as well as thermochemistry and geometry, will be a measure of its utility for interpretive purposes. Interpretations can be made in terms of various energy terms (bond or angle distortions, torsions, nonbonded repulsions, and electrostatic effects) which are a function of the potentials used in the parameterization, rather than the more fundamental electron-nuclear, nuclear-nuclear, and electron-electron interactions which are the quantum mechanical origins of chemical effects. Nevertheless, the language of force fields is in general the language used by chemists to discuss chemistry.

Another method being explored in various laboratories is to use quantum mechanics for the atoms involved in bond-making and bond-breaking processes, and to use force fields for all the remaining atoms. Warshel has applied such ideas for some years to the study of reactions in solution and catalyzed by enzymes. These methods have been introduced and reviewed in his recent book.<sup>25</sup> The quantum mechanics is applied to bond-making and bond-breaking processes through

the use of an empirical valence bond (EVB) scheme. Here the reaction center is treated by a valence bond formalism, and parameters are adjusted in order to fit experimental data available on bond dissociation energies, ionization potentials, and related experimental quantities. The interactions of the reacting molecule with the solvent or the enzyme are treated by various empirical methods such as the consistent force field (CFF) of Warshel and Lifson or the method of Langevin dipoles (LD). This approach has been widely applied by Warshel to study a variety of organic and biological reactions.<sup>25</sup>

Karplus, Field, and Bash<sup>26,27</sup> have combined semiempirical quantum mechanics (AM1 and MNDO) with empirical force fields (CHARMM),<sup>28</sup> while Kollman et al.<sup>29</sup> use *ab initio* calculations plus AMBER.<sup>30</sup> Specific examples of the applications of such techniques will be described later.

## II. Survey of Literature

We have used a table format to help illustrate reactions studied and methods employed. For each section of the review, there is a table which indicates the reaction studied, the method, the main authors, the year, and the references. Also depicted are transition structures or other graphical representations of the reaction for ready reference to the reaction being studied. The method column generally lists the program used, the origin of the transition structure (*ab initio* calculations, etc.), whether or not parameters were developed, and a classification of the type of TS model used. The text provides further detail when necessary. We have not attempted to tabulate all of the results in each article, but rather to provide a guide to what can be found in the article.

### A. Pioneering Work

Table I summarizes the early work in empirical modeling of transition states. In addition to the examples described in the previous section, DeTar and Tenpas developed a model to study ester hydrolysis using a tetrahedral intermediate (ortho acid) as an approximation for the transition structure.<sup>17</sup> DeTar used this model to determine enzyme-substrate specificities for chymotrypsin by predicting relative substrate reactivities.<sup>31,32</sup>

Perlberger and Muller modeled sodium borohydride reductions of ketones.<sup>33</sup> The hydride attack was simulated by placing a hydrogen atom 2.30 Å away from and perpendicular to the reacting center. The product alcohol was simulated with a methyl group. The structures were partially optimized with the forming bond length and angle of attack fixed.

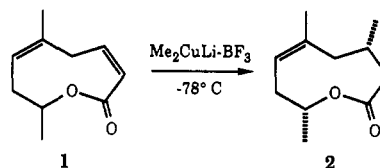
The S<sub>N</sub>2 reaction transition state was studied as early as 1946 by Ingold and co-workers.<sup>34</sup> Geometries were assumed, and some guesses about geometries and parameters had to be made. Later studies of the S<sub>N</sub>2 reaction with this approach and more information upon which to base parameters, have given excellent results.<sup>35</sup>

DeTar, Luthra, and McMullen<sup>36,37</sup> investigated steric effects in S<sub>N</sub>2 reactions with a flexible model developed with a modified Schleyer 1973 force field.<sup>16,38</sup> A trigonal bipyramidal model was assumed for the S<sub>N</sub>2 transition state for amine attack on an alkyl halide. The relative

enthalpies and entropies of activation for cyclization of bromoamines were calculated.<sup>36</sup> Similar models were used to study steric effects in S<sub>N</sub>2 reactions.<sup>37</sup> The model calculations gave excellent correlation with experimental rate effects, and the DeTar work outlines a detailed prescription for development of such force fields.

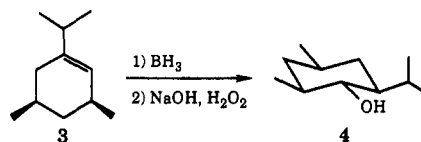
Muller, Blanc, and Lenoir studied chromic acid oxidation of alcohols, assuming that the transition state resembled the product ketone.<sup>39</sup> A good correlation was obtained.

Still and Galynker predicted the stereochemistry of dimethyl cuprate addition to **1**, a key step in the synthesis of a palytoxin segment.<sup>40</sup> The method involved locating all low-energy conformers of **1**, adding a methyl from the periphery (rather than from the inside of the ring) and reoptimizing the product structures from the same geometry. The product energies were then used to predict *cis/trans* ratios successfully.



### B. Hydroborations

Table II summarizes various molecular mechanics methods that have been employed to study hydroboration reactions. White and Bovill applied the SACF method (summed atomic congestion factors) of Wipke and Gund<sup>41</sup> to study hydroborations of hindered cycloalkenes.<sup>42</sup> This algorithm generates a cone of



preferred approach for each atom of an alkene and calculates the "congestion" caused by each sterically hindering atom. The total congestion is given by the sum of these terms and is determined for both the top and bottom faces of the molecule. From this the effective weighted-mean product averages are calculated.

White and Bovill optimized the geometry of a number of alkylcyclohexenes with the White-Bovill force field<sup>43</sup> and then used the SACF method to calculate the product ratios. Excellent correlation with experiment was observed for some cases. They concluded that steric congestion was the key factor controlling stereoselectivity in these reactions.

However, the observance of some discrepancies prompted them to try another method.<sup>42</sup> The transition structures for the addition were approximated by placing BH<sub>3</sub> 1.5 Å above or below the plane of the double bond. With the transition structure atoms fixed, the geometries of the substituents were optimized and the energy differences determined. From this the product ratios were calculated. This method greatly improved on the results from the SACF method. In the case of **3**, for example, only one alcohol is observed experimentally, **4**.<sup>44</sup> The SACF method predicted a mixture

Table I. Pioneering Force Field Modeling of Transition States

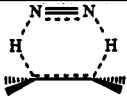
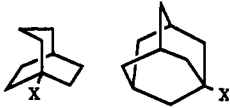
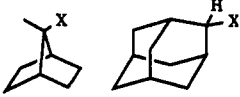
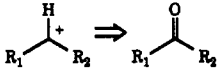
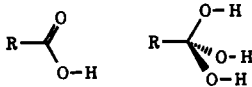
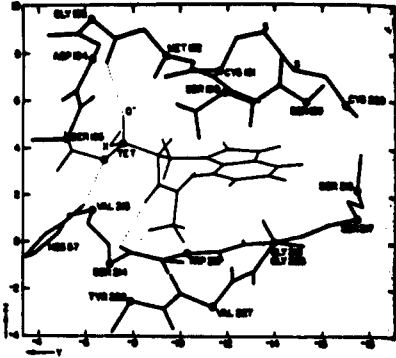
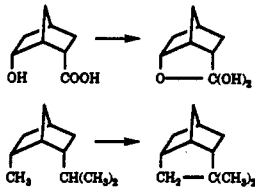
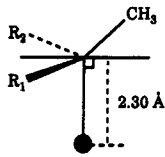
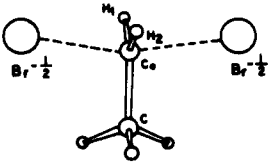
reaction studied		method	author(s)	ref(s)
diimide reduction of olefins		developed force field for the transition state of diimide reduction	Garbisch et al. (1965)	8
solvolysis rates: reactivity at bridgehead positions		Schleyer 1973 force field; carbonium ion as model for transition state; parameter development; analog TS model	Schleyer et al. (1971, 1972, 1974)	9-11
solvolysis rates: polycyclic secondary derivatives		Schleyer 1973 force field; carbonium ion as model for transition state; analog TS model	Smith, Harris (1978); Lenoir, Frank (1981)	12, 13
solvolysis rates: secondary derivatives		MM2; ketone used to approximate transition state; analog TS model	Schneider, Thomas (1978); Muller, Perlberger (1982)	14, 15
ester hydrolysis		MOLMEC program; Schleyer 1973 force field; tetrahedral intermediate (ortho acid) as model for TS; parameter development; analog TS model	DeTar, Tenpas (1976)	17
ester hydrolysis: chymotrypsin and prediction of relative substrate reactivities		MOLMEC program; tetrahedral intermediate as model for TS; protein X-ray data; parameter development; analog TS model	DeTar (1981)	31, 32
ester hydrolysis and lactone formation: inter- and intramolecular reactions		Schleyer 1973, and Allinger MM1 force fields/MOLMEC; simple hydrocarbons as models for tetrahedral intermediates; analog TS model	DeTar (1974, 1976)	16, 18, 19
sodium borohydride reduction of aliphatic ketones		BIGSTRN program; Schleyer (1973) force field; oxygen approximated with methyl group; bond length and attack angle frozen	Perlberger, Muller (1977)	33
steric effects in S <sub>N</sub> 2 reactions: inter- and intramolecular reactions		modified Schleyer 1973 force field; parameter development using "reasonable estimates"; flexible model	DeTar, Luthra, McMullen (1978, 1980)	36, 37

Table I (Continued)

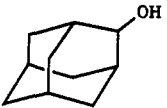
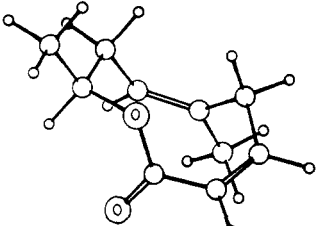
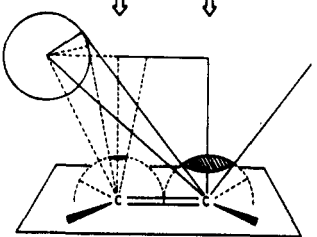
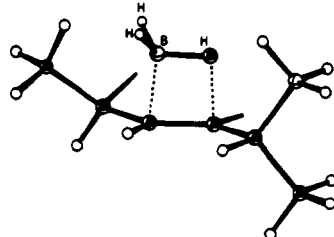
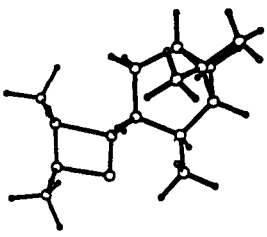
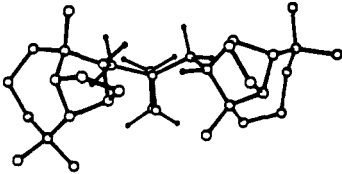
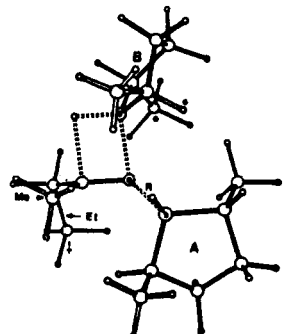
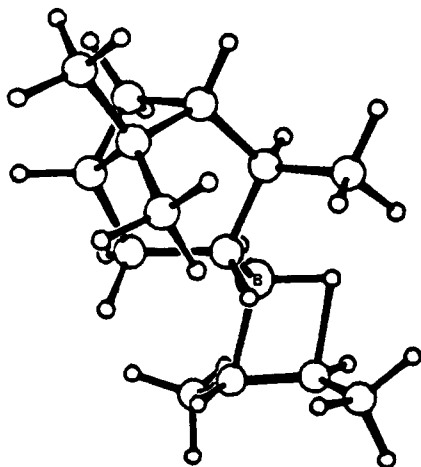
reaction studied		method	authors(s)	ref(s)
chromic acid oxidation of alcohols		MM1; ketone as model for TS; analog TS model	Muller, Blanc, Lenoir (1982)	39
stereospecific synthesis of the C <sub>30</sub> -C <sub>43</sub> segment of palytoxin		MM2; predicted reaction pathway based on product and reaction energies	Still, Galynker (1982)	40

Table II. Force Field Modeling of Hydroboration Reactions

reaction studied		method	authors	ref(s)
hydroboration of hindered cycloalkenes <sup>a</sup>		White-Bovill force field; SACF method (summed atomic congestion factors)	White, Bovill (1983)	42
hydroboration of hindered cycloalkenes <sup>b</sup>		approximate TS; rigid TS model	White, Bovill (1983)	42
stereoselective hydroborations: chiral boranes		MM2; <i>ab initio</i> TS calculations (3-21G); rigid TS model	Houk et al. (1984, 1986)	20, 21
hydroborations of alkenes by alkylboranes		MM2; <i>ab initio</i> TS calculations (3-21G); parameter development; flexible TS model	Wang, Houk (1989)	46
asymmetric reduction of dialkyl ketones with (R,R)-2,5-dimethylborolane		MM2; <i>ab initio</i> TS calculations (3-21G); rigid TS model	Masamune, Houk et al. (1986)	47

<sup>a</sup> Reprinted from ref 42. Copyright 1983 the Royal Society of Chemistry. <sup>b</sup> Reprinted from ref 42. Copyright 1983 the Royal Society of Chemistry.

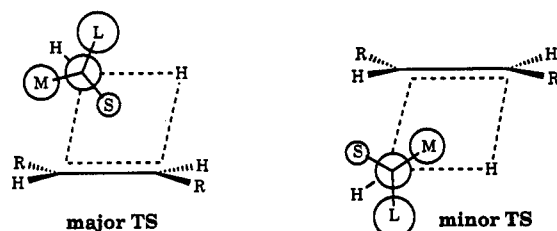


**Figure 1.** The preferred conformation of the transition structure for mono-3-pinanylborane hydroboration of *trans*-2-butene to form the *S* (major) alcohol. (Reprinted from ref 20. Copyright 1984 by Pergamon Press Ltd.)

of products, 53:47, but the rigid TS method correctly predicted only one product.

Houk, Rondan, and Paddon-Row located 3-21G transition structures for the hydroboration reactions of ethylene and propene with borane and methylborane.<sup>20,21</sup> Incorporating these structures into MM2,<sup>45</sup> Metz and Rondan constructed a rigid TS model where the core transition structure atoms were frozen and the substituents were optimized. This method was used to predict the product ratios for a variety of reactions including asymmetric hydroborations with isopinocampheylborane, diisopinocampheylborane, pinanylborane, and dipinanylborane.

These calculations gave good agreement with experimental hydroboration-oxidation ratios, indicating that steric effects govern stereoselectivity. A qualitative model, shown, was devised to rationalize the observed and calculated stereoselectivities.



The example is shown for the reaction of a *trans*-alkene with a monoalkylborane such as monoisopinocampheylborane. The specific transition state is shown in Figure 1.

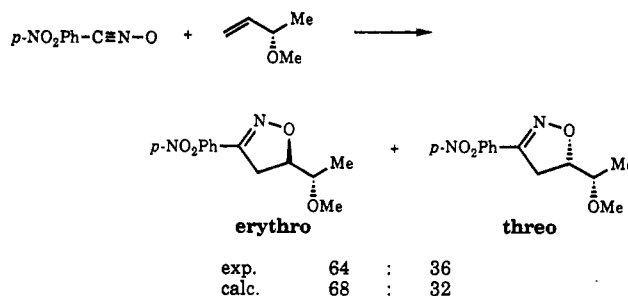
Wang and Houk later improved on this approach and developed a flexible model for MM2 in which all of the transition structure atoms were capable of moving.<sup>46</sup> This study was extended to other boranes, such as dilongifolylborane, and was used to predict stereoselectivities with a number of yet unknown chiral boranes.

Masamune, Houk, Wu and co-workers used a combination of *ab initio* molecular orbital and molecular mechanics methods to study the asymmetric reductions of prochiral dialkyl ketones with (*R,R*)-2,5-dimethylborolane.<sup>47</sup> The transition structure for the reaction of diborane with formaldehyde was optimized at the 3-21G

level. This geometry was incorporated into MM2, and parameters were developed to form a completely flexible model. This model was then used to study the larger experimental systems, and successfully explained the observed high asymmetric induction of the reaction.

### C. Nitrile Oxide Cycloadditions

A summary of the calculations on nitrile oxide cycloadditions is presented in Table III. Houk, Jager, and co-workers studied the stereoselectivities of a variety of chiral allylic ether and alcohol substituted alkenes.<sup>21,48</sup> They concluded that allylic ethers preferred the inside position (the "inside alkoxy effect") while alkyl substituents preferred the anti position as indicated in the model TS for HCNO plus  $\text{CH}_2=\text{CHCHCH}_3\text{OMe}$  shown in Table III. An MM2 model was devised in which the core atoms were frozen in the 3-21G transition-structure geometry, and the substituents were optimized. The results, as shown in the example below, compared well with experiment.



Quite recently, Raimondi, Wu, Brown, and Houk continued the study of the "inside alkoxy effect" by determining the 6-31G\* transition structure for the cycloaddition of fulminic acid and allyl alcohol.<sup>49</sup> The results are much improved over the 3-21G results. They were used to revise the MM2 parameters, and the resulting flexible model successfully reproduced experimental observations for a number of intramolecular reactions.

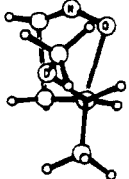
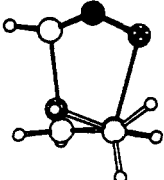
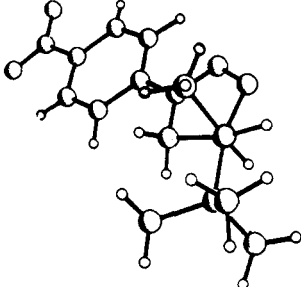
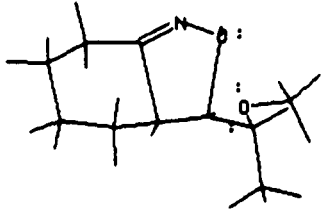
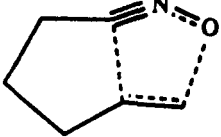
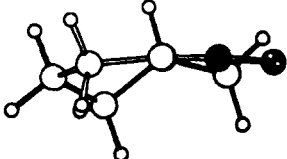
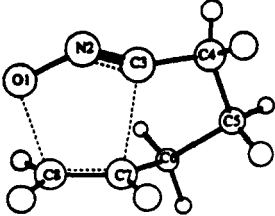
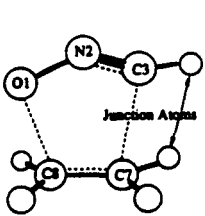
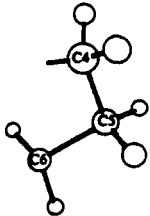
Houk, Duh, Wu, and Moses subsequently applied the fixed transition-structure geometry approach to the cycloadditions of nitrile oxides and chiral alkenes.<sup>21,50</sup> Table IV shows the excellent agreement between calculated and experimental data. This study led to the proposal of a new transition-state model: a staggered arrangement with the largest group anti to the carbon-oxygen bond and the medium-sized group inside.

Cozzi, Gennari, and co-workers used the same method in their study of stereoselectivity of intramolecular nitrile oxide additions to *Z* and *E* chiral alkenes and achieved good correlations with experimental results.<sup>51</sup>

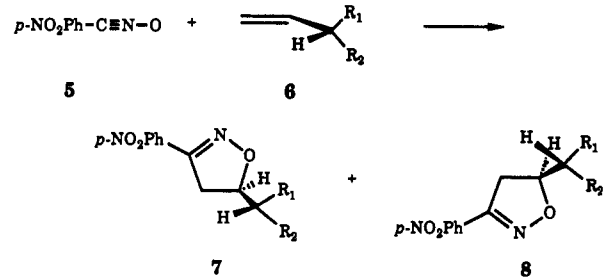
Brown, Raimondi, Wu, and Houk calculated the 3-21G transition structures for several intramolecular nitrile oxide cycloadditions.<sup>52</sup> With this information, and the parameters developed from the "inside alkoxy effect" work,<sup>49</sup> a flexible model for MM2 was developed and applied to the study of larger systems. Excellent correlations with experimental results were observed.

The most recent work, by Brown et al., in the area of nitrile oxide cycloadditions is the use of a tandem quantum mechanics-molecular mechanics method to study the transition structures.<sup>53</sup> QUEST<sup>29</sup> couples G80(UCSF)<sup>54</sup> with AMBER 3.0.<sup>30</sup> The portion of the

Table III. Force Field Modeling of Nitrile Oxide Cycloadditions

reaction studied		method	authors	ref(s)
chiral allylic ethers and alcohols: the "inside alkoxy effect"		MM2; <i>ab initio</i> TS calculations (3-21G); rigid TS model	Houk, Jager et al. (1984, 1986)	21, 48
chiral allylic ethers: the "inside alkoxy effect" revisited <sup>a</sup>		MM2; <i>ab initio</i> TS calculations (6-31G*); parameter development; flexible TS model	Raimondi, Wu, Brown, Houk (1992)	49
chiral alkenes		MM2; <i>ab initio</i> TS calculations (3-21G); rigid TS model	Houk, Duh, Wu, Moses (1986)	21, 50
Intramolecular nitrile oxide cycloadditions to chiral (Z)- and (E)-alkenes		MM2/MODEL; <i>ab initio</i> TS structure (HCNO plus ethylene); rigid TS model	Cozzi, Gennari et al. (1987)	51
intramolecular nitrile oxide cycloadditions <sup>b</sup>	 	MM2; <i>ab initio</i> TS calculations (3-21G); parameter development; flexible TS model	Brown, Raimondi, Wu, Houk (1992)	52
intramolecular nitrile oxide cycloadditions	 A: Pull System  B: QM Atoms  C: MM Atoms	QUEST (tandem QM/MM method); <i>ab initio</i> method (3-21G) for TS atoms; molecular mechanics method (AMBER) for other atoms; flexible TSmodel	Brown et al. (1992)	53



**Table IV. Ratios of Isoxazoline Diastereomers from *p*-Nitrobenzonitrile Oxide Cycloadditions (25 °C, CH<sub>2</sub>Cl<sub>2</sub>)**


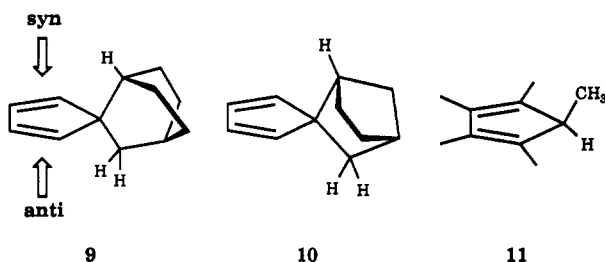
3-R-1-butene			total yield (%)	7:8	
	R <sub>1</sub>	R <sub>2</sub>		exptl	calcd
a	Et	Me	72	50:50	50:50
b	Ph	Me	70	59:41	53:47
c	<i>i</i> -Pr	Me	50	65:35	72:28
d	C(OMe)Me <sub>2</sub>	Me	93	80:20	87:13
e	<i>t</i> -Bu	Me	82	77:23	97:3
f	Me	OMe	63	64:36	68:32
g	<i>t</i> -Bu	OMe	64	>97:3	96:4

molecule undergoing bonding changes is calculated with quantum mechanics, while the remainder of the molecule is calculated with molecular mechanics. The resulting intramolecular transition structures optimized with this method compare with the 3-21G-optimized transition structures.

#### D. Diels–Alder Reactions

The models developed for Diels–Alder reactions are summarized in Table V. Brown and Houk carried out the first modeling of this reaction in a study of stereoselectivity in isodicyclopentadiene cycloadditions.<sup>55</sup> The transition structures for top and bottom attack of ethylene on isodicyclopentadiene were located using MNDO and a *C<sub>s</sub>* symmetry constraint. The positions of the core transition structure atoms were fixed in the MM2 calculations. The substituents were added and geometries were optimized fully with MM2. This model was used to predict the product ratios for a number of reactions of isodicyclopentadienes with ethylene and maleic anhydride.

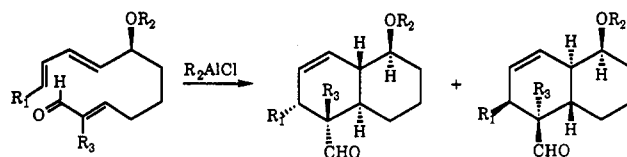
Brown, Houk, Burnell, and Valenta used this rigid TS model to study cycloadditions of unsymmetrically substituted cyclopentadienes, 9–11.<sup>56</sup> For the reaction



of maleic anhydride with 10, the experimental anti to syn ratio was 72:28. In the calculations, the dienophile was approximated by ethylene, and the calculated ratio was 70:30. Such examples are particularly amenable to modeling of this type, because stereoselectivities are likely to be determined exclusively by steric effects.

Marshall, Grote, and Audia used MM2 in Still's MODEL<sup>57</sup> program to predict the outcome of Lewis

acid-catalyzed intramolecular Diels–Alder reactions shown.<sup>58</sup>



The calculations were performed on the boat conformations of the cyclohexenes formed in the reaction. The major stereochemical trends are correctly reproduced by these calculations.

Tucker, Houk, and Trost investigated the question of  $\pi$ -stacking in Diels–Alder reactions of the chiral diene 1,3-butadienyl *O*-methylmandelate with benzoquinone.<sup>59</sup> The geometry of the 3-21G transition structure for the addition of butadiene plus acrolein<sup>60</sup> was fixed and incorporated into MM2. Substituents were added to this structure, and the geometries were optimized. Torsional parameters were also developed for  $\alpha$ -alkoxy esters and vinyl esters. The calculations predicted that in both the reactants and products, the phenyl ring is perpendicular to the plane of the diene, as shown in Table V. Thus it was not necessary to invoke special  $\pi$ - $\pi$  interactions to explain the stereoselectivity of the reaction.

Takahashi and co-workers have studied transannular Diels–Alder reactions of 14-membered (*E,E,E*)-macrocyclic trienes<sup>61</sup> and trienones,<sup>62</sup> and the intramolecular reaction of an *o*-quinodimethane.<sup>63</sup> In each case they took the frozen STO-3G transition-structure geometry for the reaction of butadiene plus ethylene<sup>64</sup> and incorporated it into MM2. Substituents were then added and optimized. This method was successful in predicting the stereochemical outcome of these reactions.

Pindur, Otto, Molinier, and Massa investigated the Diels–Alder reactions of 1*H*-indol-3-yl enamides with a variety of carbo- and heterodienophiles.<sup>65</sup> They used MMX<sup>24</sup> to study approximate endo and exo transition states for these cycloadditions and concluded that there was no special steric hindrance present in either orientation of the reactants. Thus, the reaction is a HOMO (diene)–LUMO (dienophile) controlled process.

Using the STO-3G transition structure for butadiene plus ethylene<sup>64</sup> and MM2, Brown and Houk studied the Diels–Alder reactions of 1,3,9-nonatriene and 1,3,8-decatriene.<sup>66</sup> A twist asynchronous model was developed for substituted nonatrienes such that incorporating a 10° twist of the vinyl moiety into the transition structure relieved strain in the developing cyclopentane rings.

Raimondi, Brown, Gonzalez, and Houk used the 3-21G transition structures for the Diels–Alder reactions of butadiene plus ethylene, acrolein, and acrolein coordinated to BH<sub>3</sub>, to develop flexible MM2 models for both thermal and acid-catalyzed reactions.<sup>67</sup> Transition-state calculations were used to explain the diastereoselectivity for a variety of intramolecular Diels–Alder cycloadditions of nonatrienes and decatrienes. The parameters were also tested with MM3<sup>68</sup> and provided satisfactory results for unactivated hydrocarbon cases.

Table V. Force Field Modeling of Diels-Alder Reactions

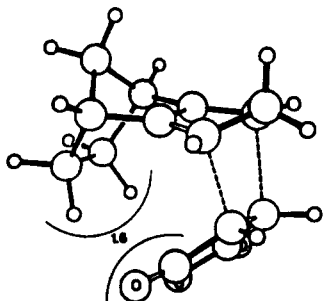
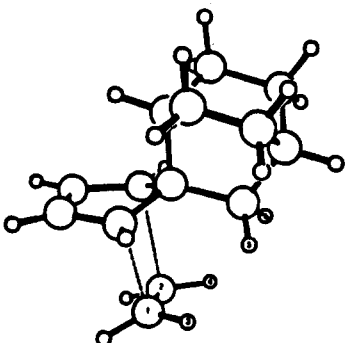
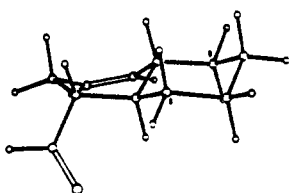
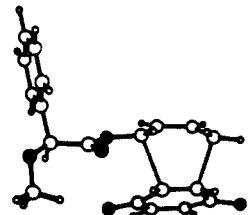
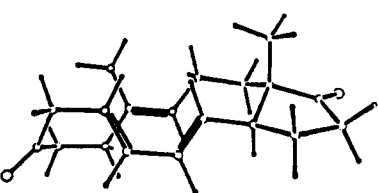
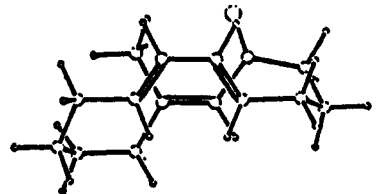
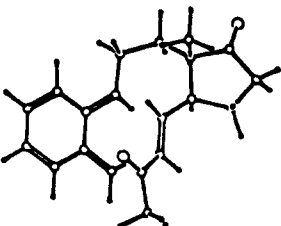
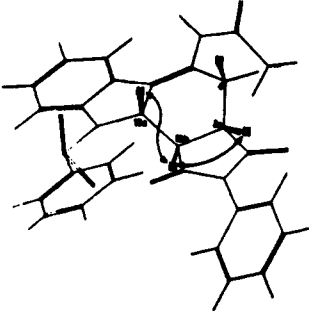
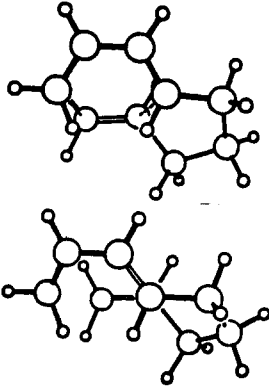
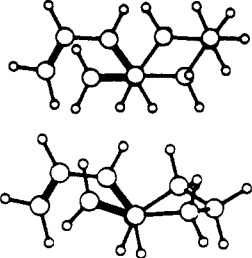
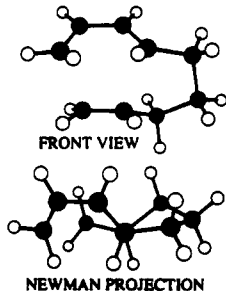
reaction studied		method	authors	ref
facial stereoselectivity in isocyclopentadiene cycloadditions		MM2; semiempirical TS calculations (MNDO); rigid TS model	Brown, Houk (1985)	55
unsymmetrically substituted cyclopentadienes		MM2; semiempirical TS calculations (MNDO); rigid TS model	Brown, Houk, Burnell, Valenta (1987)	56
intramolecular Diels-Alder cyclizations leading to octahydronaphthalenecarboxaldehydes		MODEL; TS approximated as product in boat cyclohexene conformation	Marshall, Grote, Audia (1987)	58
dienol esters of <i>O</i> -methylmandelic acid: the question of $\pi$ -stacking		MM2; <i>ab initio</i> TS structure (butadiene plus acrolein, 3-21G); developed MM2 parameters for $\alpha$ -alkoxy esters and vinyl esters; rigid TS model	Tucker, Houk, Trost (1987)	59
transannular Diels-Alder reactions of a 14-membered macrocyclic triene		MM2; <i>ab initio</i> TS structure (butadiene plus ethylene, STO-3G); rigid TS model	Takahashi et al. (1988)	61
transannular Diels-Alder reactions of a 14-membered trienone <sup>a</sup>		MM2; <i>ab initio</i> TS structure (butadiene plus ethylene, STO-3G); rigid TS model	Takahashi et al. (1992)	62
intramolecular Diels-Alder reactions in the synthesis of estrone methyl ether <sup>b</sup>		MM2; <i>ab initio</i> TS structure (butadiene plus ethylene, STO-3G); rigid TS model	Takahashi et al. (1990)	63

Table V (Continued)

reaction studied		method	authors	ref
formation of amino-function- alized carbazoles <sup>c</sup>		MMX; TS geometry approximated; flexible TS model	Pindur, Otto, Molinier, Massa (1991)	65
intramolecular Diels-Alder reactions of 1,3,9-nonatriene and 1,3,8-decatriene <sup>d</sup>		MM2; <i>ab initio</i> TS structure (butadiene plus ethylene, STO-3G); rigid TS model	Brown, Houk (1985, 1986)	66
intramolecular Diels-Alder reactions of nonatrienes and decatrienes: new force fields for substituted cases and Lewis acid-catalyzed reactions		MM2 and MM3; <i>ab initio</i> TS calculations (3-21G); parameter development; flexible TS model for unactivated, activated, and acid-catalyzed	Raimondi, Brown, Gonzalez, Houk (1992)	67
intramolecular Diels-Alder reactions of 1,3,9-nonatriene and 1,3,8-decatriene		QUEST (tandem QM/MM method); <i>ab initio</i> method (3-21G) for TS atoms; molecular mechanics method (AMBER) for other atoms; flexible TS model	Brown et al. (1992)	53

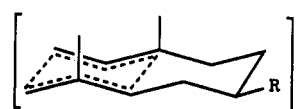
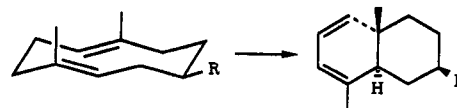
<sup>a</sup> Reprinted from ref 62. Copyright 1992 Pergamon Press Ltd. <sup>b</sup> Reprinted from ref 63. Copyright 1990 Pergamon Press Ltd.  
<sup>c</sup> Reprinted from ref 65. Copyright 1991 Neue Schweizerische Chemische Gesellschaft. <sup>d</sup> Reprinted from ref 66. Copyright 1985 Pergamon Press Ltd.

Brown et al. have used QUEST<sup>29</sup> to further investigate the intramolecular Diels-Alder reactions of 1,3,9-nonatriene and 1,3,8-decatriene.<sup>53</sup> The structures obtained with this method compare well with the 3-21G transition structures, and the calculated stereoselectivities agree with experiment.

### E. Cope and Claisen Rearrangements

Terada and Yamamura used transition-state modeling to study Cope rearrangement stereochemistry in the germacrenes,<sup>69</sup> such as shown in Table VI. They assumed that bond lengths for forming and breaking single bonds were the average of those in the reactant

and product. They were able to rationalize the preferred stereochemistry in three different cases studied.



Funk, Abelman, and Munger utilized MMPM,<sup>70</sup> a modified version of MM2, to study Claisen rearrange-

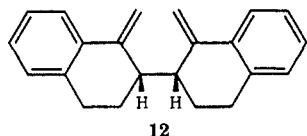
Table VI. Force Field Modeling of Claisen and Cope Rearrangements

reaction studied	method	authors	ref
stereochemical studies on germacrenes <sup>a</sup>	MM1; TS bond lengths average of those in reactant and product; flexible TS model	Terada, Yama- mura(1979)	69
claisen rearrangement- mediated ring contraction of macrocyclic lactones <sup>b</sup>	MMPM; TS geometry approximated; all carbon model used for TS calculations; flexible TS model	Funk, Abelman, Munger (1986)	71
cope rearrangement: preference for the chain conformation	MM2/MACROMODEL; TS geometry approximated; forming and breaking single bond lengths fixed	Shea, Stoddard, England, Haffner (1992)	72

<sup>a</sup> Reprinted from ref 69. Copyright 1979 Pergamon Press Ltd. <sup>b</sup> Reprinted from ref 71. Copyright 1986 Pergamon Press Ltd.

ments in macrocyclic lactones.<sup>71</sup> Calculations were performed on the all-carbon Cope transition states, since there were no parameters for oxygen transition-state atoms. The calculated product ratios compared well with experiment.

The chair conformational preference in the Cope rearrangement was probed by Shea, Stoddard, England, and Haffner for reactions ranging from the parent to that of **12**.<sup>72</sup> The forming and breaking bond lengths



were frozen at 2.0 Å, and all other parameters were kept at reactant values. MM2/MACROMODEL<sup>73</sup> calculations were performed on the boat and chair transition structures. Shea et al. compared the calculated energy differences of transition states to experiment and concluded that secondary orbital interactions play a minor role. They inferred that nonbonded steric interactions are more important in determining the transition-state conformations and energies.

## F. Hydrogen Transfers

Table VII summarizes the force field modeling of hydrogen transfer and lactonization reactions. Green, Allinger, et al.<sup>74</sup> analyzed intramolecular hydrogen transfers in the Barton reaction using MM2. To

develop parameters for the transition state, they varied OH force constants and made comparisons to the experimental results. They also calculated deuterium isotope effects as a function of the linearity of the hydrogen transfer.

Dorigo and Houk investigated the preferred transition structures for intramolecular hydrogen abstractions by alkoxy radicals.<sup>75-78</sup> This force field was developed by a relatively unbiased technique in which *ab initio* calculations were used to obtain transition-state geometries and energies required to distort from ideal geometries. The force field was applied to six-membered ring selectivity observed in the Barton reaction, and was also compared with the yields of intramolecular hydrogen abstraction products formed in oxidations of polycyclic alcohols by Pb(OAc)<sub>4</sub>. The C...H...O angle often deviates from the ideal 180°. This distortion requires little energy. By contrast, deviation of the C-C...H and H...O-C angles causes the transition state to be destabilized. This force field and *ab initio* calculations were used to calculate enthalpies and entropies of activation for different ring sizes. The activation energies calculated with the flexible MM2 force field model agreed qualitatively with available experimental data.

White and Breslow studied intramolecular hydrogen abstractions by chlorine atoms in steroids.<sup>79</sup> Using approximated transition structures in MM2/MACROMODEL<sup>80</sup> they developed a flexible model which was able to account for the experimentally observed stereoselectivities.

Table VII. Force Field Modeling of Hydrogen-Transfer Reactions

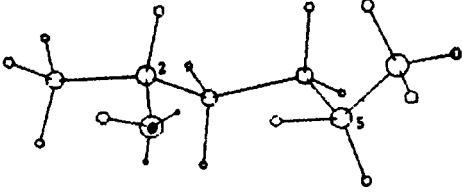
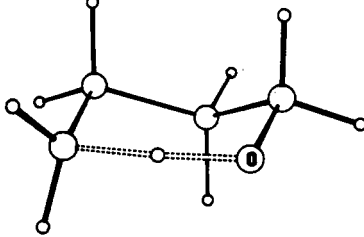
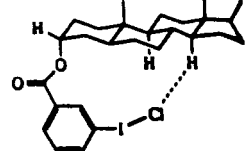
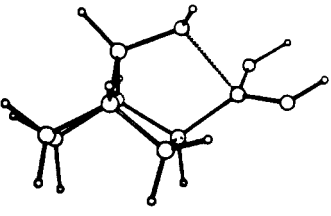
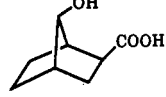
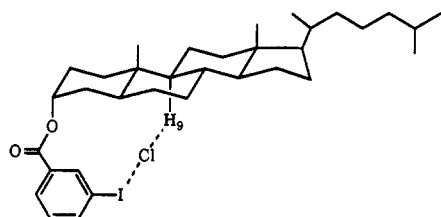
reaction studied		method	authors	ref(s)
intramolecular hydrogen abstractions by alkoxy groups: the Barton reaction		MM2; TS geometry approximated; parameter development; flexible TS model	Green, Allinger et al. (1986)	74
alkoxy hydrogen abstractions: study of proximity effects on organic reactivity		MM2; <i>ab initio</i> TS calculations (6-31G*); parameter development; flexible TS model	Dorigo, Houk (1987, 1988, 1990)	75-78
intramolecular hydrogen abstractions by complexed chlorine atoms: template-directed steroid chlorinations		MM2/MACROMODEL; TS geometry approximated; parameter development; flexible TS model	White, Breslow (1990)	79

Table VIII. Force Field Modeling of Lactonization Reactions

reaction studied		method	authors	ref(s)
acid-catalyzed lactonizations of hydroxy acids: study of proximity effects on organic reactivity		MM2; <i>ab initio</i> TS calculations (3-21G); parameter development; flexible TS model	Dorigo, Houk (1987, 1988, 1990)	75, 78, 81
acid-catalyzed lactonizations		MODEL; <i>ab initio</i> TS calculations; parameter development (FUDGIT); flexible TS model	Menger, Sherrod (1988, 1990)	82, 83

The best results were obtained when the C...H...Cl...I transition state was held linear. This required the



bending force constants for the TS atoms to be set to values equal or greater than those of single bonds. The authors concluded that the "apparent strict angular requirement in order for the calculations to agree with experiment may reflect the need for an almost linear collision rather than a glancing blow, to achieve energy transfer into the modes needed for reaction".<sup>79</sup>

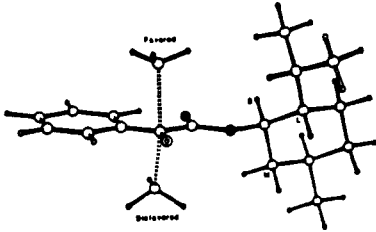
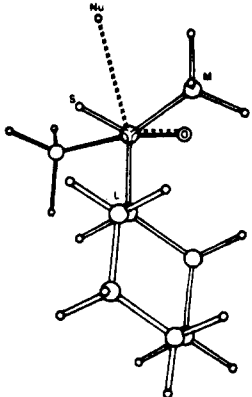
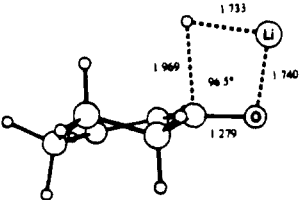
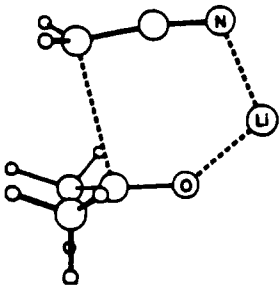
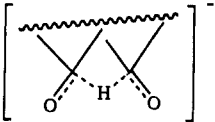
### G. Acid-Catalyzed Lactonizations

Dorigo and Houk studied the acid-catalyzed lactonizations of hydroxy acids to determine the role of

functional group proximity and orientation on reactivity.<sup>75,78,81</sup> (Table VIII). They used 3-21G *ab initio* calculations for the attack of water on protonated formic acid to develop a flexible transition-state model for MM2. This model reproduced experimental activation energies, when the breakdown of the tetrahedral intermediate is taken as the rate-determining transition state. On the basis of the calculations Houk concluded that "there is no relationship between (i) the angle of nucleophilic attack and the reactivity of an hydroxy acid or (ii) the distance between reacting atoms in the starting material and the rate of reaction".<sup>81</sup>

This conclusion proved offensive to Menger and Sherrod since they had studied these reactions and concluded that the rates of reaction were proportional to the proximity of reactant functional groups. To emphasize this point of view, they also investigated acid-catalyzed lactonizations.<sup>82,83</sup> They used FUDGIT to develop "nonsense" force field parameters for MODEL<sup>84</sup> and achieved better correlation with experimental reaction rates than Houk.<sup>75,78,81</sup> The program FUDGIT works as follows: First a correlation coefficient is determined between the observed reaction rate and the

Table IX. Force Field Modeling of Nucleophilic Additions to Carbonyls

reaction studied		method	authors	ref(s)
1,4-asymmetric induction: Prelog's rule <sup>a</sup>		MM2; model <i>ab initio</i> calculations (methyl anion plus glyoxylic acid), located approximate TS; rigid TS model	Houk, Honcharich (1986)	21
metal hydride reductions of ketones: Grignard reactions <sup>b</sup>		MM2; <i>ab initio</i> TS calculations (3-21G); parameter development; flexible TS model	Houk, Wu et al. (1986, 1987)	21, 85-87
metal hydride reductions of cyclohexenones		MM2; <i>ab initio</i> TS calculations (3-21G); parameter development; flexible TS model	Wu, Houk, Florez, Trost (1987, 1988, 1991)	88, 89
ketenimine additions to cyclohexanones and cyclohexenones		MM2; <i>ab initio</i> TS calculations (3-21G); parameter development; flexible TS model	Wu, Houk, Florez, Trost (1991)	89
intramolecular hydride transfers		MODEL; <i>ab initio</i> TS calculations (3-21G); parameter development (FUDGIT); flexible TS model	Menger, Sherrod (1989, 1990)	90, 94

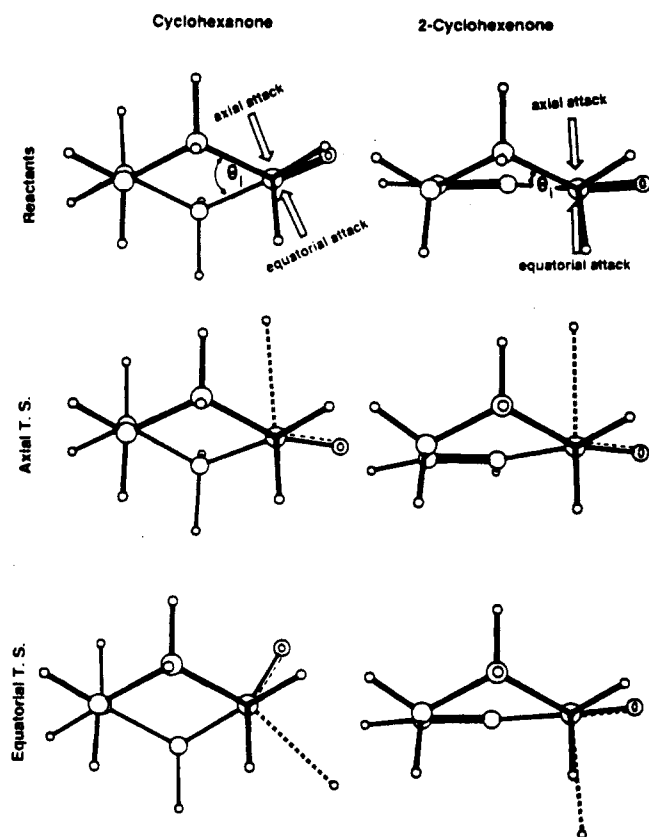
<sup>a</sup> Reprinted from ref 21. Copyright 1986 the AAAS. <sup>b</sup> Reprinted from ref 21. Copyright 1986 by the AAAS.

calculated activation energy for an initial set of parameters. Then, certain parameters are varied by small increments, and the correlation coefficient is calculated again. If the correlation improves, the changes are kept, and the additional parameters are further varied to achieve a higher correlation. They concluded that it was "not necessary to 'model' a transition state accurately to achieve high correlations", and advised caution in "deducing from transition-state modeling any notions about chemical reactivity including transition-state structure and the relationship between rate and distance".<sup>83</sup>

## H. Nucleophilic Additions to Carbonyls

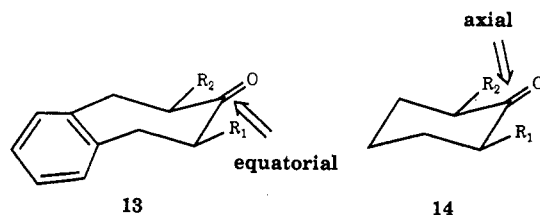
In an early application of force field modeling, Houk and Loncharich used an approximate transition structure for the attack of methyl anion on glyoxylic acid to develop an MM2 model to study 1,4-symmetric inductions.<sup>21</sup> The calculations on menthyl phenylglyoxylate confirm Prelog's rule, as the methyl anion prefers to attack from the sterically less hindered side, as shown in Table IX.

Houk and Wu developed a flexible MM2 force field model to predict quantitatively the stereoselectivity of



**Figure 2.** Newman projections along the C<sub>2</sub>-C<sub>1</sub> bonds for cyclohexanone and 2-cyclohexenone and for the transition structures for the axial and equatorial attack of hydride on cyclohexanone and 2-cyclohexenone.

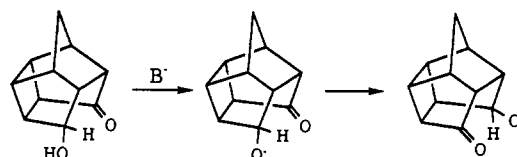
nucleophilic additions to carbonyls.<sup>21,85-87</sup> Parameters were developed from 3-21G transition structures for the reaction of sodium hydride with propionaldehyde, and from the reaction of LiH with acetone. A variety of stereoselectivities of acyclic and acyclic chiral compounds were studied; the force field gave excellent agreement with experiment and provided strong support to the Felkin model. The force field was used to make the nonintuitive conclusion that equatorial rather than axial attack would occur on benzocycloheptanones (13) in spite of the obvious similarity to cyclohexanones (14). This was verified experimentally for LAH reductions.



Wu, Houk, Florez, and Trost<sup>88,89</sup> studied nucleophilic additions to cyclohexanones using a modified MM2 for hydride additions. The flexible model reproduces the high experimentally-observed stereoselectivities and provides good support for the torsional explanation of stereoselectivity. As in Figure 2, axial attack on cyclohexanone occurs with slightly less torsional strain than equatorial attack. The difference is much larger for 2-cyclohexenones, as shown qualitatively in Figure 2.

A similar flexible model was devised to study metal ketenimine reductions of ketones.<sup>89</sup> Wu, Houk, Florez, and Trost explained the large difference in experimentally-observed stereoselectivities between cyclohexanones and cyclohexenones and were also able to understand the stereoselectivity for attack on chiral alkenes.

A controversial analysis of transition-state modeling was reported by Sherrod and Menger.<sup>90</sup> They employed several ground-state-like force field models to accurately reproduce a series of experimental data obtained by Watt and co-workers<sup>91,92</sup> for hydroxy ketone hydride transfers, such as that shown:



They reported that a transition-state model developed by the method of Houk from 3-21G *ab initio* geometries failed drastically, however, to reproduce the experimental activation energy trends. This led Sherrod and Menger to reject the basic precepts of transition-state modeling. Closer analysis of the data reveals that the reactivity of only one compound fails to be reproduced by the Menger-Sherrod transition-state modeling. This deviation is the result of an unnaturally large oxygen van der Waals parameter that Sherrod and Menger employed (2.20 vs 1.70 Å). If standard van der Waals parameters are used for oxygen, the poor reported correlation ( $R = 0.89$ ) becomes a near-perfect 0.99!<sup>93</sup>

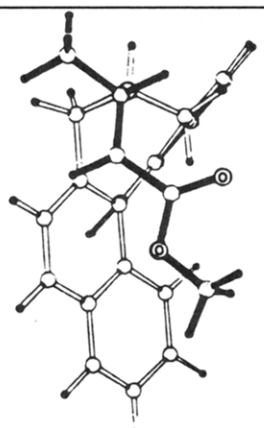

Sherrod later subjected their transition-state bond- and angle-stretch parameters to optimization with the cutely-named program FUDGIT<sup>83</sup> and was able to increase correlation to 0.96.<sup>94</sup> "Optimization" of these parameters resulted in only one substantial change: the oxygen-carbon bond length stretched from 1.26 to 1.42 Å. Clearly, FUDGIT forced the offending oxygen further from the reaction site in order to alleviate the strain that the abnormal van der Waals parameter imposed. Sherrod and Menger's results on hydride-transfer transition-state modeling show that excellent correlation can be obtained if physically meaningful parameters are used. The use of random parameters obtained with FUDGIT is not likely to give insight into chemistry, even if it happens to give a high correlation.

## I. Michael Additions

Table X summarizes force field modeling of Michael additions. Rudolph, Hawkins, Loncharich, and Houk investigated Michael additions of a chiral amine and its corresponding lithium amide to methyl crotonate.<sup>96</sup> The flexible MM2 model was developed on the basis of the approximated transition structures and rationalized the experimentally-observed stereoselectivities.

Bernardi, Capelli, Gennari, and Scolastico incorporated the 6-31++G transition structure for the addition of fluoride ion to acrylic acid<sup>96</sup> into MM2/MACRO-MODEL and developed a flexible model to study Michael additions to  $\alpha,\beta$ -unsaturated carbonyl com

Table X. Force Field Modeling of Michael Additions

reaction studied		method	authors	ref
Michael additions of an optically active amine and lithium amide to acrylates		MM2; TS geometry approximated; developed MM2 parameters for binaphthyl; flexible TS model	Rudolph, Hawkins, Loncharich, Houk (1988)	95
1,4-addition to $\alpha$ , $\beta$ -unsaturated carbonyl compounds bearing a $\gamma$ -stereocenter <sup>a</sup>		MM2/MACROMDEL; <i>ab initio</i> TS structure (F <sup>-</sup> addition to acrylic acid, 6-31++G): parameter development; flexible TS model	Bernardi, Capelli, Gennari, Scolastico (1990)	97

<sup>a</sup> Reprinted from ref 97. Copyright 1990 Pergamon Press Ltd.

pounds bearing a  $\gamma$ -stereocenter.<sup>97</sup> This model provided results that agreed qualitatively with experiment.

## J. Radical Additions to Alkenes

One of the most successful applications of force field transition-state modeling has been in the area of radical additions to alkenes. This is illustrated in Table XI. It is perhaps not surprising, since these reactions have relatively early transition states and have little polarity.

Beckwith and Schiesser performed semiempirical MNDO calculations to determine the transition structures for intramolecular radical additions to alkenes.<sup>98,99</sup> They developed an MM2 model in which the radical center and alkene carbons were fixed at the MNDO geometry, and the positions of the remaining atoms were optimized. This was implemented into MM2. Reactant parameters were used, so this model had no adjustable parameters. In order to obtain the strain energy components of the activation energies, the strain energy arising from the close approach of C<sub>1</sub> and C<sub>5</sub>, the energy from the stretching of the C<sub>5</sub>–C<sub>6</sub> bond (see illustration in Table XI), and the energy of the hexenyl radical in its open-chain form were subtracted from the total energy. This permitted the elimination of the spurious severe nonbonded interactions in this model, which became partial bonds in the actual transition state. This model successfully reproduced relative rates and regio- and stereochemistries for a variety of alkenyl, alkenylaryl, alkenylvinyl, and other radicals.

About the same time, Spellmeyer and Houk developed a flexible MM2 model to predict intramolecular regio- and stereoselectivities in radical addition reactions.<sup>100</sup> *Ab initio* 3-21G transition structure calculations for methyl radical plus ethylene,<sup>101</sup> as well as various substituted analogs, were used to develop the

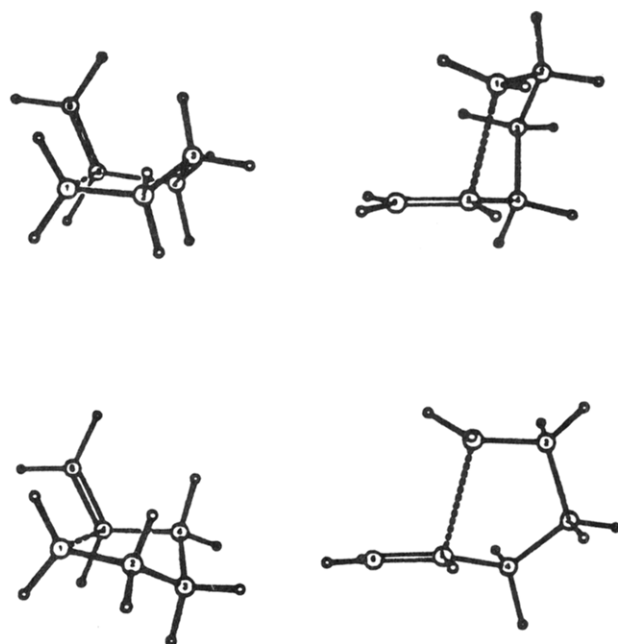


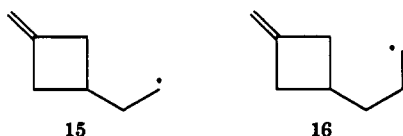
Figure 3. Two views of the MM2 model transition structure for exo cyclization of the 5-hexenyl radical. Top views are of the boatlike transition state, while the bottom views are of the chairlike transition state.

parameters. For a large number of radical cyclizations, excellent stereochemical results were obtained, as compared to experiment. Several improvements over the Beckwith–Schiesser model resulted, including the location of an additional boat-like transition structure for the cyclization of the 5-hexenyl radical (Figure 3). *Ab initio* calculations confirmed that the boat transition structure is only about 1 kcal/mol over the chair. This led to a prediction about the stereoselectivities of cyclizations of 3-alkyl-5-hexenyl radicals. Recently,

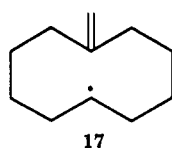


Beckwith has confirmed this prediction experimentally.<sup>102</sup>

Pigou used the method of Beckwith and Schiesser<sup>98</sup> to investigate the reaction pathways of 3-(3'-methylenecyclobutyl)propyl and 2-(3'-methylenecyclobutyl)ethyl radicals (15 and 16, respectively).<sup>103</sup> The MM2 results generally reproduced the experimental results, showing a preference for *exo* closure, due to the higher strain energies of the *endo* transition states.



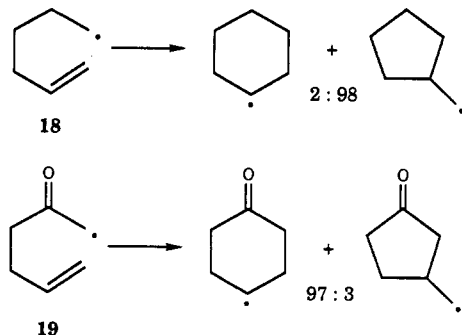
Beckwith, Bowry, and Schiesser used the MM2/MNDO<sup>98</sup> method to study the ring closure of the 6-methylenecyclodecyl radical (17).<sup>104</sup> Experimentally,



*cis*-fused products are favored, but calculations predict the *trans*-fused system as the major product. This is a significant failure of the method, but extensive tests have uncovered the origin of this discrepancy.<sup>104</sup> Beckwith and Gerba used the MM2/MNDO method to study the ring closure of *o*-(butyl-3-enyl)phenyl radicals, and the calculated reactivities and diastereoselectivities agree qualitatively with experiment.<sup>105</sup>

Beckwith and Raner have applied the MM2/AM1 method to study the radical cyclization of  $\omega$ -formylalkyl radicals.<sup>106</sup> Good correlation with experiment was achieved for the cyclization of substituted formylpentyl radicals, but not for substituted formylbutyl radicals. The authors point out that at low concentrations, the *cis*/*trans* product ratio is thermodynamically controlled.

Broeker and Houk modified the radical addition force field to include transition-structure parameters for acyl-substituted radicals.<sup>107</sup> Of particular interest is the difference in regioselectivity found for cyclization of 5-hexenyl and 2-oxo-5-hexenyl radicals, 18 and 19, respectively.

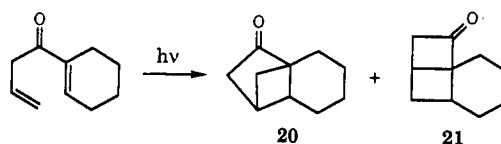


The difference arises from the conjugation of the radical with the carbonyl group, and the resulting tendency for the methylene group to remain coplanar. The predicted regio- and stereochemistries correlated well with experimental data for a variety of molecules.<sup>107</sup>

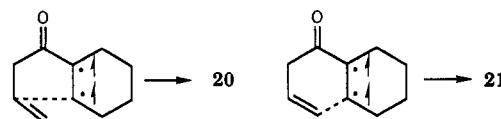
Giese, Zipse, et al. have applied the radical addition MM2 force field study the stereoselectivities of alkyl-

substituted cyclohexyl radical addition to alkenes.<sup>108</sup> The calculated results reproduced the experimentally observed stereoselectivities, indicating that steric and torsional effects account nicely for the experimental results.

Broeker, Eksterowicz and Houk, in collaboration with Agosta have developed a flexible model MM2 force field for the addition of enones to alkenes.<sup>109</sup> This model has its basis in the alkyl radical and the acyl-substituted radical addition force fields. In the example below, the cross closure product 20 is favored experimentally over the straight closure product 21 by a ratio of 93:7. The



force field model calculates that the attack of the alkenyl radical terminus of the perpendicular enone triplet is favored in the 5-*exo* rather than the 6-*endo* fashion.



Both of these are favored over the 4-*exo* or 5-*endo* attacks of the acyl substituted radical. The calculated ratio of 20:21 is 99:1 using the force field.

The force field provides a good prediction of product ratios when the formation of the biradical is followed only by bicyclic product formation. However, the biradical may also revert to the reactants, and a study of this process is underway in order to extend the application of the force field to all enone-alkene systems.

Another extension of Spellmeyer-Houk<sup>100</sup> transition-state force field for intramolecular radical additions is to 1,4-diene intramolecular, triplet-sensitized [2 + 2] photocycloadditions.<sup>110</sup> The first step of the [2 + 2] photocycloaddition is the addition of one carbon of a triplet excited olefin to the second olefinic moiety. This transition state is remarkably similar in geometry to that for alkyl radical additions to olefins. The second carbon of the triplet excited olefin is not involved in the addition and parameters describing this carbon had to be developed. MM2 parameters were developed from calculations on triplet ethylene addition to ground-state ethylene. This force field accurately reproduces *ab initio* transition structures and energy trends reported by Morokuma<sup>111</sup> and successfully predicts other transition structures not found in the *ab initio* studies.

Recently, Meyers and Condroski have used the flexible MM2 model developed by Spellmeyer and Houk to study transannular radical cyclizations in the synthesis of (+)-7,8-epoxy-4-basmen-6-one.<sup>112</sup> The calculations correctly predict the outcome of two intramolecular radical cyclizations, with radicals adding to both an alkene and an allene.

## K. Boron Enolate Aldol Reactions

Gennari, Paterson, and co-workers used 3-21G transition-structure calculations to develop a flexible MM2/MACROMODEL model to predict the stereochemical

Table XI. Force Field Modeling of Radical Additions to Alkenes

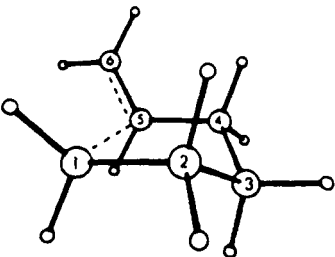
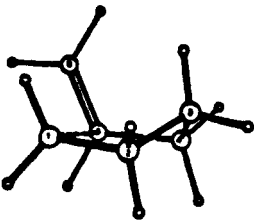
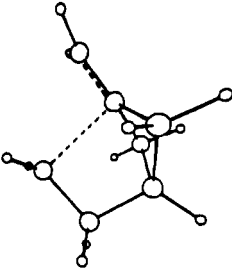
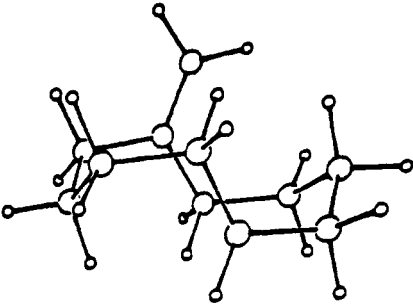
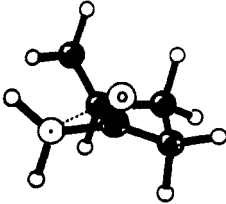
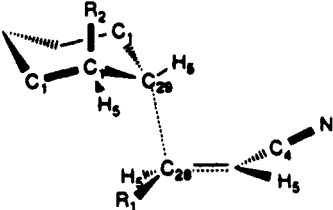
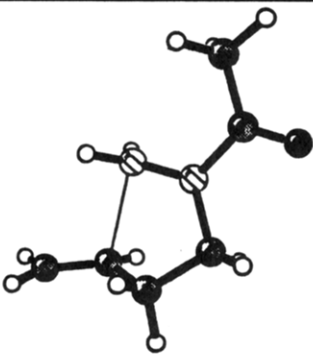
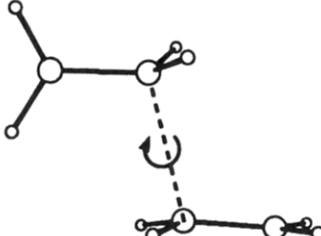
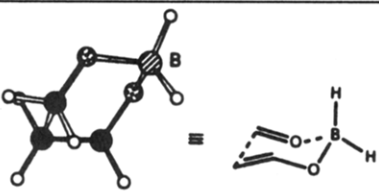
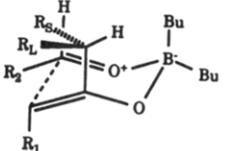
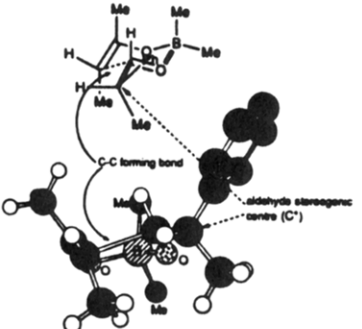
reaction studied		method	author(s)	ref(s)
intramolecular alkyl radical addition to alkenes <sup>a</sup>		MM2; semiempirical TS calculations (MNDO); reactant parameters; rigid TS model	Beckwith, Schiesser (1985)	98, 99
intramolecular radical additions to alkenes		MM2; <i>ab initio</i> TS calculations (3-21G); parameter development; flexible TS model	Spellmeyer, Houk (1987)	100
radical cyclizations of 3-(3'-methylenecyclobutyl) propyl and 2-(3'-methylenecyclobutyl) ethyl radicals		MM2/MNDO method (Beckwith and Schiesser, ref 98); rigid TS model	Pigou (1989)	103
ring closure of the 6-methylenecyclodecyl radical <sup>b</sup>		MM2/MNDO method (ref 98); rigid TS model	Beckwith, Bowry, Schiesser (1991)	104-106
intramolecular additions of acyl-substituted radicals to alkenes		MM2; TS structure adapted from methyl radical addition to ethylene (3-21G); parameter development; flexible TS model	Broeker, Houk (1991)	107
substituted cyclohexyl radical addition to alkenes		MM2; <i>ab initio</i> TS calculations (3-21G); parameter development; flexible TS model	Giese, Zipse et al. (1992)	108

Table XI (Continued)

reaction studied		method	author(s)	ref(s)
intramolecular [2 + 2] photocycloadditions: 1,5-hexadien-3-ones and acyl-1,5-hexadienes		MM2; <i>ab initio</i> TS calculations (3-21G); parameter development; flexible TS model	Broeker, Eksterowicz, Houk, Agosta (1993)	109
intramolecular [2 + 2] cycloadditions: 1,4-pentadienes and 1,5-hexadienes		MM2; <i>ab initio</i> TS calculations (MP2/6-31G*); parameter development; flexible TS model	Eurenius, Houk (1993)	110

<sup>a</sup> Reprinted from ref 98. Copyright 1985 Pergamon Press Ltd. <sup>b</sup> Reprinted from ref 104. Copyright 1991 Pergamon Press Ltd.

Table XII. Force Field Modeling of Boron Enolate Aldol Reactions

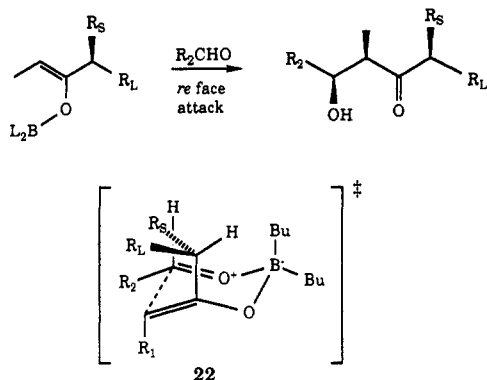
reaction studied		method	authors	ref
simple <i>Z</i> and <i>E</i> substituted enol borinates		MM2/MACROMODEL; <i>ab initio</i> TS calculations (3-21G); parameter development; flexible TS model	Gennari, Paterson et al. (1990)	113
chiral enolates and chiral ligands on boron		MM2/MACROMODEL; TS geometry from ref 113; flexible TS model	Gennari, Paterson et al. (1991)	114
chiral $\alpha$ -methyl aldehydes <sup>a</sup>		MM2/MACROMODEL; TS geometry from ref 113; parameter development; flexible TS model	Gennari et al. (1992)	116

<sup>a</sup> Reprinted from ref 116. Copyright 1992 Pergamon Press Ltd.

outcome of aldol reactions of boron enolates,<sup>113</sup> shown in Table XII. The calculated results correlated well with experiment for reactions of simple *Z* and *E* substituted enol borinates, and reproduced the observed aldehyde *si/re* face selectivity for the reaction of chiral *Z* enol borinates.

This group continued their studies in this area by investigating aldol reactions with chiral enolates and chiral ligands on boron.<sup>114</sup> Using the parameters from

the earlier model<sup>113</sup> they were able to reproduce experimental stereoselectivities. For chiral ligands the authors concluded that conformational factors involving the ligands themselves are important in determining the stereoselectivity. In the case of chiral ketones they propose a new general transition-state model 22, where the hydrogen on the  $\alpha$ -stereogenic center is directed toward the boron ligand and the large group is anti to the incoming aldehyde.



Quite recently, Gennari et al. have used their flexible model<sup>113</sup> along with some newly developed parameters, including vinyl torsional parameters from Broeker, Hoffmann, and Houk<sup>115</sup> to study chiral  $\alpha$ -methyl aldehydes.<sup>116</sup> The calculations reproduce the experimental results implying that nonbonded steric interactions control diastereofacial selectivity in additions to chiral aldehydes.

### L. Additional Work in Transition-State Modeling

There are additional reactions which have been studied that do not fit neatly into the previous categories. These are discussed in this section and summarized in Table XIII.

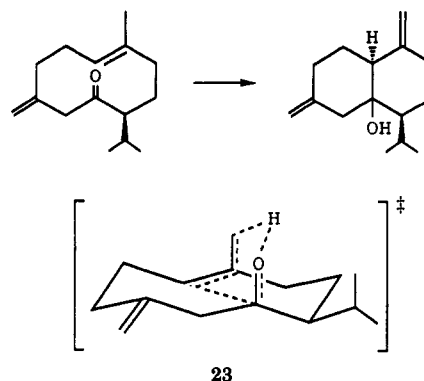
Wang and Houk developed an MM2 model to predict the reactivity and stereoselectivity in intramolecular ketene cycloadditions.<sup>46</sup> This rigid TS model was based upon an MP2/6-31G\* optimized ketene-ethylene transition structure.<sup>117</sup> The central ketene carbon, the ketene oxygen, and the terminal olefinic carbon were fixed, and the rest of the atoms were allowed to vary. About a dozen reactions were studied, and successful predictions of experimental stereoselectivities and regiochemistries were made. An MM3 version of this force field is now under development.<sup>118</sup>

Sauers and Krogh-Jespersen studied Norrish type II reactions.<sup>119</sup> They performed STO-3G calculations on the excited triplet states of model systems and developed MM2 parameters for a flexible transition-state model. The transition-state parameters were related to those developed earlier to study the Barton reaction.<sup>75-78</sup> In the meantime, high-level *ab initio* calculations have been performed which show the large similarities between transition states for Barton and Norrish type II hydrogen abstractions.<sup>120</sup> Sauers and Huang used the Norrish type II MM2 model to help explain the preferred product formation for photochemical reactions of cyclodecanone.<sup>121</sup>

Dosen-Micovic, Lorenc, and Mihailovic developed a MM2 transition-state model with a fixed forming bond length to study the acid-catalyzed transannular electrophilic attack of a protonated ketone on an alkene.<sup>122</sup> They achieved reasonable correlations with experiment for the reactions of normal and 19-nor-5,10-secosteroidal cyclodecanone systems.

An intramolecular ene reaction was investigated by Terada and Yamamura using Allinger's MM1 force field.<sup>123</sup> Various assumptions were made about the bond lengths and force constants for the transition-state model. The lowest energy transition-state conformer

23 was found to correspond to the stereochemistry observed experimentally.



Thomas and Houk have used 3-21G *ab initio* transition-structure calculations to develop a MM2 model for the study of intramolecular ene reactions.<sup>124</sup> The geometries of the core transition-structure atoms were frozen, and the substituents were optimized. The predicted stereochemistries compare well with experiment for reactions with unactivated enophiles, but gave poor results for activated enophiles. They concluded that the geometry must change significantly in the reactions of activated enophiles.

Wu, Wang, and Houk investigated the dihydroxylations of alkenes by chiral diamine complexes of osmium tetroxide.<sup>125</sup> Using MM2, they developed a fixed, symmetrical five-membered ring transition structure geometry, which was based on X-ray data and *ab initio* calculations on smaller systems. This model reproduced experimentally observed stereoselectivities for some cases and predictions were made for others.

Peyman and Beckhaus studied the dimerization of carbon radical and developed a MM2 variable force field model to investigate the entire reaction path.<sup>126</sup> They included distance-dependent switch functions to account for the change in hybridization in the bond-forming process. The model provided excellent agreement with experiment for the rate of dimerization of di-*tert*-butylmethyl radicals and 1-phenylneopentyl radicals.

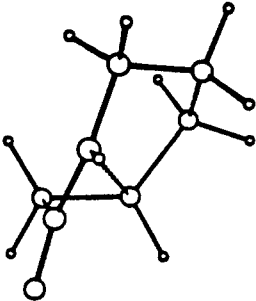
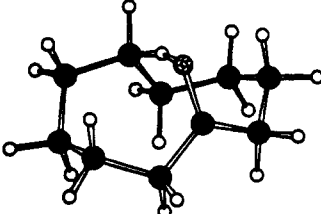
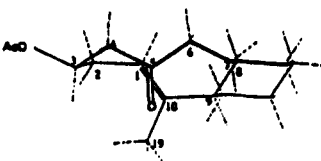
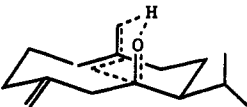
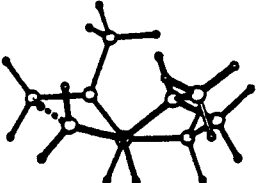
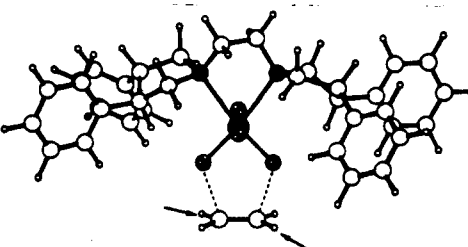
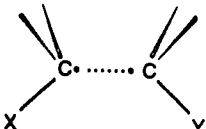
From the early days of molecular mechanics, Osawa has been involved in pioneering studies using molecular mechanics methods. Among recent applications, he studied [2 + 2] cycloadditions, predicting whether a reaction might proceed or not based on the basis of product strain energies. This has proven a useful guide to experiment.<sup>127-129</sup>

### III. Transition Structure Modeling by Intersecting Potential Energy Surfaces

As noted in the introduction, the empirical transition-state modeling techniques in common use employ the a simple expedient of treating the transition state as an energy minimum, and developing parameters specifically for the transition state.

Jensen has described an alternative method to find the point where the reactant and product surfaces intersect.<sup>6,7</sup> He used the MM2 force field and various modified values of the cubic stretch term in order to produce parameters which are accurate in regions of highly-stretched bonds. The method was applied to

Table XIII. Other Reactions Studied by Transition-State Modeling

reaction studied		method	authors	ref(s)
intramolecular ketene cycloadditions		MM2; <i>ab initio</i> TS calculations (3-21G); parameter development; rigid TS model	Wang, Houk (1989)	46
Norrish type II photochemical hydrogen abstraction reactions <sup>a</sup>		MM2; <i>ab initio</i> TS calculations (STO-3G); parameter development; flexible TS model	Sauers, Krogh-Jespersen (1989, 1990)	119, 121
acid-catalyzed transannular electrophilic attack of protonated ketone on alkene <sup>b</sup>		MM2; TS geometry approximated; forming bond length fixed	Dosen-Micovic, Lorenc, Mihailovic (1990)	122
thermal isomerization of preisocalamendiol: intramolecular ene reaction		MM1; TS geometry approximated; flexible TS model	Terada, Yamamura (1979)	123
intramolecular ene reactions		MM2; <i>ab initio</i> TS calculations (3-21G); parameter development; rigid TS model	Thomas, Houk (1992)	124
dihydroxylations of alkenes by chiral diamine complexes of osmium tetroxide		MM2; approximated TS from X-ray data and <i>ab initio</i> structures of smaller systems; parameter development; rigid TS model	Wu, Wang, Houk (1992)	125
dimerization of carbon-free radicals <sup>c</sup>		MM2; distance-dependent switch functions and variable force field; parameter development; flexible TS model	Peyman, Beckhaus (1992)	126

<sup>a</sup> Reprinted from ref 121. Copyright 1990 Pergamon Press Ltd. <sup>b</sup> Reprinted from ref 122. Copyright 1990 Pergamon Press Ltd.

<sup>c</sup> Reprinted from ref 126. Copyright 1992 by John Wiley and Sons Inc.

the study a wide variety of organic reactions, including, the Cope rearrangement, the Diels–Alder reaction of butadiene with ethylene, the [1,5]-hydrogen shift in 1,3-pentadiene, the cyclobutene ring opening, S<sub>N</sub>2 reactions of alkyl halides, the hydride transfers studied by Menger and Sherrod, dihydrogen transfers, and lactonization of hydroxy acids.

The geometries of the transition states are reasonable, although they differ from the *ab initio* in some cases.<sup>6</sup> A new parameterization has improved the agreement.<sup>7</sup> Relative reactivities in several reaction series were studied; comparisons with experimental data were mixed.<sup>6</sup> Of special note is the fact that the geometries of the transition structures in each series are nearly

constant; this is the major assumption of most transition-state modeling procedures.

A technique like that advocated by Jensen is capable of excellent results if appropriate care is taken to develop parameters suitable for the geometrical region of the transition structure.

#### IV. Summary

In this review, the various methods of empirical transition-state modeling have been described, and the literature has been reviewed up to 1993. To date, many different methods have been applied to individual reactions. It is clear that excellent accord between calculations and experiment can be achieved by appropriate parameterization. The degree to which force fields can be used for prediction is not well-established, although successes have been reported in a few cases.

The force fields for some of the most common reactions are becoming available in common programs such as MACROMODEL.<sup>73</sup> Nevertheless, the barrier to the general application of such techniques is the time required to develop a force field from experimental data and ab initio calculations, regardless of the assumptions made about the force field. It is likely that future programs will make parameter development more routine.

More general approaches to the location of transition states using force fields are likely to be developed. This may be a refinement of the methods for development of parameters specific to transition states, as in Gajewski and Gilbert's MMX, or further refinements of Jensen's method of locating transition states by searching for intersection of reactant and product potential surfaces.

The continuous development of rapid quantum mechanics methods will not eliminate the importance of empirical force field methods for the study of transition states, since there will always be molecules or collections of molecules too large to be studied practically with quantum mechanics.

The future is likely to bring force fields which are highly refined for accurate predictions, and others sufficiently complex to deal simultaneously with stable molecules and transition states, and to study transition states more generally.

**Acknowledgement.** The development of transition-state force field modeling in the Houk laboratories at Pittsburgh was the result of the tireless efforts of Nelson G. Rondan (Dow) and James Metz (Lilly), who developed the first hydroboration force field. Over the years, many members of the group contributed enormously to force field development, but the pioneering efforts of David Spellmeyer (Chiron), Yundong Wu (HKUST), Andrea Dorigo (Erlangen), and Yi Li (Bristol-Meyers Squibb) should be singled out. Our research has been generously supported by the National Institutes of Health and the National Science Foundation.

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