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A Force-Field Model for Intramolecular Radical Additions

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A quantitative model based upon Allinger's MM2 force field[1] has been devised to predict relative activation energies of intramolecular radical additions leading to regioisomeric or stereoisomeric products. The new parameters for MM2 were devised from ab initio calculations on radical addition transition states and model systems. The MM2 model is "flexible", without any fixed atoms. Our model is compared to a different MM2 model for the same purpose developed by Beckwith and Schiesser,[2] which utilizes a "rigid reactant" model. Full details of the force field are given so that it can be implemented into Allinger's widely available MM2 program. The model suggests that regioselectivity and stereoselectivity can be correctly described only with the inclusion of a boat-like exo transition structure in addition to Beckwith's chair-like transition structure. Ab initio transition structures for the exo-chair, exo-boat, and endo-chair transition states have been located. These provide additional support of our model. The calculations of vibrational energies and entropies show that exo cyclization is favored enthalpically and not to any significant extent entropically. Activation energies are estimated for many reactions. Predictions of new stereoselectivities are made for several systems.

Introduction

Intramolecular additions of radicals to carbon–carbon double and triple bonds are a topic of intense current interest in synthetic organic chemistry.[3-6] Such reactions are particularly valuable techniques for the formation of five- or six-membered rings in situations where such transformations must be effected in the presence of base- or acid-sensitive functionalities. Despite the reactive nature of unstabilized carbon radicals, high regioselectivity and stereoselectivity are frequently achieved in intramolecular radical additions.

Extensive experimental studies of intramolecular radical additions have established the principal features of these reactions.[6] Beckwith has proposed qualitative guidelines to rationalize the regioselectivities and stereoselectivities of intramolecular radical additions, particularly those of substituted 5-hexenyl radicals.[7] Because these guidelines attribute selectivities to normal conformational and steric effects, we thought that these reactions would be excellent candidates for quantitative treatment by force-field models of the type that have proven to be very effective in the investigation of asymmetric hydroboration reactions and cycloadditions.[8] We have now developed a modification of Allinger's MM2 force-field,[1] using ab initio transition structures of several radical additions,[9] to determine parameters for the atoms involved in bonding changes in the transition states.

During the course of this work, Beckwith and Schiesser reported a different MM2 model for intramolecular radical cyclizations.[2] The Beckwith–Schiesser model employs MNDO transition states for exo and endo cyclizations of the 5-hexenyl, 6-heptenyl, and 7-octenyl radicals to establish the positions of the three carbon atoms involved

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in bonding changes in the transition states of these reactions. The positions of these three atoms are fixed at the MNDO transition state positions and normal MM2 optimizations of all other atomic positions, using reactant parameters, are carried out on substituted derivatives.

We have developed a flexible model that is likely to be more widely applicable for use in determining the stereoselectivities and regioselectivities of intramolecular radical cyclizations. The results of the Beckwith–Schiesser model and the model described here are qualitatively similar. There are quantitative differences in predicted product ratios and, in some cases, there are significant differences in predictions of the transition state conformations of the forming ring. Here we describe the development of this model and its application to the understanding and prediction of regioselectivity and stereoselectivity of radical cyclization reactions. Details about how the force field can be incorporated into the standard MM2 program are given in the Appendix. The scope and limitations of our model are also discussed and are compared to those of the Beckwith–Schiesser model.

The Modified MM2 Model for Intramolecular Radical Additions

General Considerations. We have developed MM2 models based upon ab initio transition structures for simple model systems for several reactions.[8] In the simplest models, the positions of the atoms involved in bonding changes from the ab initio transition structure are restricted so that they cannot move. Substituents of interest are added to this core of atoms, and geometries are optimized by using MM2. Standard MM2 force-field parameters are used, except for bonds to the core atoms. Force constants for bonds to the core atoms are fit to mimic ab initio results.

Beckwith and Schiesser devised an even simpler force field for intramolecular radical additions.[2] In their model, the positions of the three carbon atoms involved in bonding changes (the radical carbon and two alkene carbons) are fixed in space at the MNDO transition state positions. Optimization of the remaining atoms proceeds by using reactant parameters for all bonds and atoms. The transition-state model is just that of a distorted reactant, with the attacking radical carbon fixed at a distance from the alkene which is appropriate to the transition state. Energies and structures are calculated for the transition-state models, with positions of all atoms optimized except those three atoms involved in bonding changes. The van der Waals repulsion energy between the radical carbon and the alkene carbon being attacked is subtracted from the calculated energy. This gives the transition-state energy, from which the energy of the reactant radical is subtracted, to yield an energy which can be compared with the experimental activation energy. In cases where the regiochemistry is being considered, two different transition structures are utilized, based upon separate MNDO structures for the two modes of cyclization of the parent alkenyl radical. The major assumption in this model is that the transition structure of any exo or endo cyclization of substituted 5-hexenyl will not deviate much from that of the parent system and that the energy of the transition state is proportional to the energy required to distort the reactant into a geometry where the radical and alkene terminus begin to bond. The earliness of transition states for radical additions,[9] as well as the general success of the Beckwith model, indicates that these assumptions are relatively good ones.

A major drawback of this method of modeling is that the core atoms cannot move, even if a small deviation could possibly lower the overall energy of a given transition state. Energy differences between isomeric transition states are likely, therefore, to be overestimated—or perhaps predicted in the wrong order in particularly bad cases. Our procedure has been to develop a method in which all atoms are free to move and in which new parameters are developed for all unusual atom and bond types.

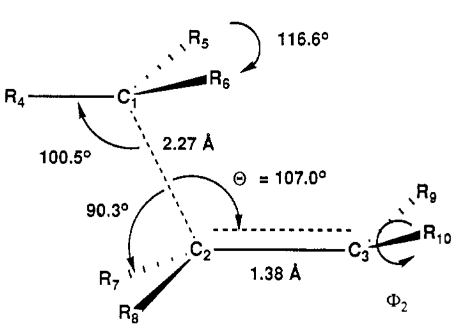

Figure 1. Normal bond lengths (Å) and angles (in deg) used in the model.

There is one potentially devastating drawback to modeling transition states in this way. The transition state is that stationary point which is an energy maximum with respect to one normal coordinate and an energy minimum with respect to all other normal coordinates. Ab initio and semiempirical calculations have been programmed to follow a reaction coordinate gradient upwards to find just such a point. Molecular mechanics could also be programmed in such a fashion, but the development of force constants appropriate to transition states and the incorporation of a normal coordinate vibrational analysis would be necessary to make this approach useful. In our models, we have searched for energy minima in the usual way, defining our minima from ab initio transition structures in model systems. In order for this technique to be successful, the transition state for the reaction being calculated must not deviate substantially from the "model" transition state used to fix normal bond lengths of the transition state. For additions of alkyl radicals to alkyl-substituted alkenes, this condition appears to be satisfied, as shown below. Alkyl groups do not have much electronic influence on the position of the transition state but can change the transition-state geometry by steric effects. Force-field models can deal with such geometry alterations quite nicely. For substituents which have large electronic effects and which change the exothermicity of the reaction and, thus, the position of the transition state along the reaction coordinate, a different force-field model will have to be devised.

Development of MM2 Parameters. Parameters for this model were developed as described in the following section. All parameters and instructions for use with Allinger's program are given in the Appendix.

Bond Lengths. The "normal" bond lengths and bond angles are obtained from the transition structure for the addition of the methyl radical to ethylene.[9] We have described the ab initio calculations in detail elsewhere, and the interested reader can find all the information about geometries and energetics in that paper. Figure 1 shows these bond lengths and bond angles. The forming bond length (C_1–C_2) is relatively constant for the addition of methyl radical to ethylene (2.27 Å), to C_2 of propylene (2.26 Å), and to C_2 of isobutylene (2.27 Å), while the partially broken double bond (C_2–C_3) is 1.38 Å in each case. The stretching force constant for the forming bond is arbitrarily set to be 10% less than the normal MM2 C_{sp^3}–C_{sp^3} value. The "double" bond (C_2–C_3) stretching force constant is set equal to that of a MM2 C_{sp^3}–C_{sp^2} single bond. Varying either of these constants has little effect on the optimized geometries or relative energies. Specifically, identical energies and structures for the 5-hexenyl radical cyclizations are obtained with the C_1–C_2 bond stretching constant set anywhere between 1.0 and 100.0 md/Å. These force constants are all sufficiently large to ensure that the forming bond length does not change, so that most adjustments occur in torsional and bending angles. Setting the forming bond constant to a very small value of 0.25 md/Å does result in significant changes of the structures and energies. However, the structures produced are not reasonable.

All bonds to C_1 and C_2 are treated as bonds to a normal C_{sp^3} atom, while those bonds to C_3 are treated as bonds to a C_{sp^2} center. This is a reasonable approximation since the ab initio bond lengths for CC bonds to C_1 and C_2 are fairly constant at 1.52 Å, and those to C_3 are 1.51 Å. The MM2 model predicts these to be 1.54 and 1.51 Å, respectively.

Bond Angles and Bending Constants. Figure 1 shows the bond angles chosen as "normal" in this model. Like the bond lengths, the angles are approximately those of the methyl radical plus ethylene transition state.

Bending force constants are obtained from standard MM2 values, assuming that C_1 and C_2 are C_{sp^3} centers and C_3 is a C_{sp^2} center. The only exception is for bending of the C_1–C_2–C_3 angle. Calculations on the transition state of hydrogen atom addition to ethylene suggest that bending in the forming angle requires about one-fourth the energy of the same distortion in the product, ethyl radical.[10] Similar distortion energies were calculated for the transition state of methyl radical addition to ethylene. One would expect, therefore, that setting the bending force constant to one-fourth of the ground-state value would allow us to reproduce this energy bending in the transition state. This is not the case. In fact, the bending constant must be *increased* to reproduce the ab initio results. MM2 uses a combination of angle deformation energy and van der Waals energies to reproduce angle bending energies. However, the van der Waals effects in the transition state are considerably smaller than those in a ground-state molecule. In order to overcome this deficiency and to reproduce the ab initio results, we must raise the angle deformation constant to 0.60 mdÅ/rad^2, which is about one-third larger than the standard MM2 value for this angle.

Torsional Parameters. Ab initio calculations on many transition states have shown that even though the transition state might be considered "early" in terms of bond length changes, torsional preferences of substituents attached to atoms undergoing bonding changes are quite product-like.[9,10] Because of this tendency, torsions about bonds to atoms directly bonded to C_1 or C_2 are set to mimic the torsions found in the products.

An exception to this is that methyl substituents at C_3 prefer to arrange themselves so as to have one hydrogen nearly eclipsed with the double bond, twisting ~9° or less. This is similar to the situation in propene. The torsional parameters for ϕ_2, Figure 1, have therefore been set so that one substituent prefers to eclipse the double bond.

A large, negative V_2 term is used to ensure that the radical enters the system in a plane perpendicular to the approximate plane of the alkene. That is, the dihedral angle C_1–C_2–C_3–R_9 in Figure 1 is preferably equal to 90°. The V_2 term of –25.0 kcal/mol is found to reproduce most accurately the exo/endo ratios of products observed for radicals 1–5 in Table VII. This parameter also serves to maintain the high rotational barrier of the partial double bond, in accord with the early transition states of these reactions. It is also necessary to maintain the orientation of substituents directly attached to the double bond. This is done by using the Imam–Allinger radical force-field torsional parameters,[11] as if the radical center is at C_3.

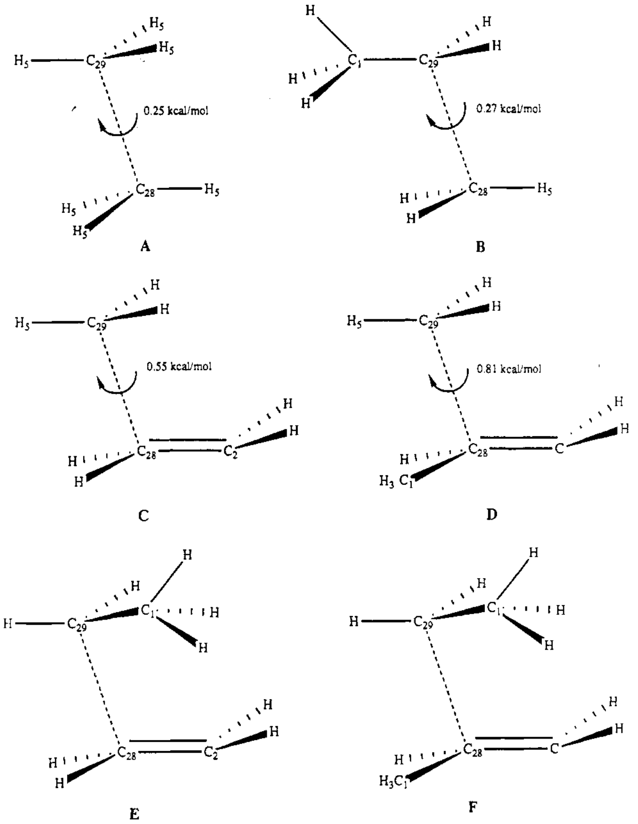

Figure 2. Model calculations and transition states used in determining rotational barrier parameters for the torsions about the forming C–C bond. The numbers on the atoms refer to the MM2 atom type being defined. (A) Model calculations of ethane with C–C set at 2.27 Å (type 5-29-28-5). (B) Same as A but with propane (type 1-29-28-5). (C) Transition states of methyl radical addition to ethylene provides type 5-29-28-2. (D) Transition states of methyl radical addition to propene provides type 5-29-28-1 parameters. (E) MP2/6-31G* calculations on four transition states of ethyl radical addition to ethylene give parameters for 1-29-28-2. (F) Ethyl radical additions to propene provide parameters for 1-29-28-1.

It is necessary to separate the energetic contributions of all the torsions involved in the rotational barrier about the forming bond, C_1–C_2. Model rotational barrier calculations at the 3-21G level[12] are combined with transition-state calculations[9] to determine these contributions. The parameters for those torsions about the C_1–C_2 bond involving hydrogens (see Figure 2a) are obtained from calculations of the eclipsed and staggered forms of ethane in which the C–C bond is elongated to 2.27 Å. The staggered form is 0.3 kcal/mol lower in energy than the eclipsed. The MM2 torsional parameters (5-29-28-5) for a similar system were set to reproduce the energy difference of the ab initio value. Similar calculations were performed on a propane molecule, in which one C–C bond was set to 2.27 Å (Figure 2b). The barrier to rotation of 0.3 kcal/mol provides the basis for the MM2 parameter 1-29-28-5, that is, for those torsions involving a carbon atom attached to C_1 and a hydrogen attached C_2 in Figure 1.

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Table I. Geometries and Energies of the STO-3G Exo Chair Transition Structure for Cyclization of the 5-Hexenyl Radical (See Figure 5)

bond length (Å)		bond angle (deg)		dihedral angle (deg)	
1–2	1.5234	1–2–3	109.3	1–2–3–4	51.3
2–3	1.5451	2–3–4	109.0	2–3–4–5	−51.9
3–4	1.5448	3–4–5	111.1	3–4–5–6	137.3
4–5	1.5296	4–5–6	122.7	2–1–5–6	−124.6
5–6	1.3857	1–5–6	105.8		
1–5	2.3421	1–5–4	92.1		

Hartree–Fock energy	−230.75582 au
E_{rel}(HF)	0 kcal/mol
zero-point energy	0.17747 au
MP2 energy	−231.03857 au
ΔS	78.4 eu
ΔG	−230.62060 au at 338 K
ΔG_{rel}	0.0 kcal/mol

Table II. Geometries and Energies of the STO-3G Exo Boat Transition Structure for Cyclization of the 5-Hexenyl Radical (See Figure 6)

bond length (Å)		bond angle (deg)		dihedral angle (deg)	
1–2	1.5232	1–2–3	109.1	1–2–3–4	−52.5
2–3	1.5445	2–3–4	109.2	2–3–4–5	49.2
3–4	1.5468	3–4–5	111.5	3–4–5–6	85.8
4–5	1.5346	4–5–6	122.2	2–1–5–6	−128.4
5–6	1.3879	1–5–6	104.8		
1–5	2.3384	1–5–4	92.6		

Hartree–Fock energy	−230.75377 au
E_{rel}(HF)	1.3 kcal/mol
zero-point energy	0.17733 au
MP2 energy	−231.03615 au
ΔS	79.0 eu
ΔG	−230.61902 au at 338 K
ΔG_{rel}	+1.0 kcal/mol

The eclipsed transition structure for methyl radical addition to ethylene is 0.6 kcal/mol higher in energy than the staggered transition structure (Figure 2c). From this, MM2 parameters for torsions about the C_1–C_2 bond involving hydrogens on C_1 and C_2 (5-29-28-2) can be fit.

In the addition of methyl radical to C_2 of propylene, the staggered transition state is 0.8 kcal/mol lower in energy than the eclipsed (Figure 2d). Type 5-29-28-1 torsional parameters are obtained from this calculation.

Contributions of a torsion of the type C_4–C_1–C_2–C_3 are obtained from ethyl radical addition to ethylene (Figure 2e) (MM2 type 1-29-28-2). Figure 3 shows four different conformations of the transition state for ethyl radical addition to ethylene. At the 3-21G level two arrangements are equal in energy, one in which the CCCC dihedral angle is 60° and one in which CCCC is 180°. The 0° and 120° rotamers are both about 0.7 kcal/mol higher in energy. Single-point calculations[9] on these structures at the MP2/6-31G* level[13] indicate, however, that the preferred conformer is now the 60° arrangement, while the 180°, 120°, and 0° conformations are 0.4, 1.1, and 0.8 kcal/mol higher in energy, respectively. Finally, three 3-21G transition structures, shown in Figure 4, for ethyl radical addition to C_2 of propylene provide the basis for the parameter for contributions of torsions such as C_4–C_1–C_2–C_3.

Table III. Geometries and Energies of the STO-3G Endo Transition Structure for Cyclization of the 5-Hexenyl Radical (See Figure 7)

bond length (Å)		bond angle (deg)		dihedral angle (deg)	
1–2	1.5268	1–2–3	113.9	1–2–3–4	−65.2
2–3	1.5499	2–3–4	113.3	2–3–4–5	60.1
3–4	1.5532	3–4–5	110.8	3–4–5–6	−75.9
4–5	1.5221	4–5–6	120.7	2–1–6–5	−53.5
5–6	1.3842	1–6–5	93.9		
1–6	2.3982				

Hartree–Fock energy	−230.75201 au
E_{rel}(HF)	2.4 kcal/mol
zero-point energy	0.17783 au
MP2 energy	−231.03406 au
ΔS	77.2 eu
ΔG	−230.61576 au at 338 K
ΔG_{rel}	+3.0 kcal/mol

Table IV. Geometries and Energies of the MM2 Exo Chair Transition Structure for Cyclization of the 5-Hexenyl Radical (See Figure 8)

bond length (Å)		bond angle (deg)		dihedral angle (deg)	
1–2	1.530	1–2–3	107.7	1–2–3–4	47.7
2–3	1.534	2–3–4	108.3	2–3–4–5	−58.4
3–4	1.536	3–4–5	109.5	3–4–5–6	147.4
4–5	1.533	4–5–6	122.4	2–1–5–6	−133.4
5–6	1.380	1–5–6	108.3		
1–5	2.273	1–5–4	90.3		

Table V. Geometries and Energies of the MM2 Exo Boat Transition Structure for Cyclization of the 5-Hexenyl Radical (See Figure 8)

bond length (Å)		bond angle (deg)		dihedral angle (deg)	
1–2	1.528	1–2–3	106.9	1–2–3–4	−50.0
2–3	1.533	2–3–4	108.2	2–3–4–5	56.8
3–4	1.535	3–4–5	110.7	3–4–5–6	77.3
4–5	1.535	4–5–6	121.5	2–1–5–6	−118.9
5–6	1.382	1–5–6	106.1		
1–5	2.275	1–5–4	90.3		

Table VI. Geometries and Energies of the MM2 Endo Transition Structure for Cyclization of the 5-Hexenyl Radical (See Figure 9)

bond length (Å)		bond angle (deg)		dihedral angle (deg)	
1–2	1.540	1–2–3	115.1	1–2–3–4	−63.3
2–3	1.546	2–3–4	115.1	2–3–4–5	58.6
3–4	1.545	3–4–5	106.7	3–4–5–6	−77.5
4–5	1.503	4–5–6	117.1	2–1–6–5	−57.4
5–6	1.378	1–6–5	96.4		
1–6	2.270				

Ab Initio Transition Structures of the 5-Hexenyl Radical Cyclization. In order to test the validity of this MM2 model, several intramolecular transition states were located with ab initio quantum mechanical calculations. Three unique transition states have been located for the 5-hexenyl radical cyclization. In all three cases, the STO-3G minimal basis set has been used. Two of these are transition states leading to formation of the exo product, cyclopentylcarbinyl radical. The third is the transition structure for the endo mode of cyclization, leading to the cyclohexyl radical. All three have been characterized by harmonic frequency analysis and possess one imaginary vibrational frequency, thus proving that all are transition states at this level. In addition, entropies and vibrational energies were calculated in order that free energies of different transition states could be calculated.

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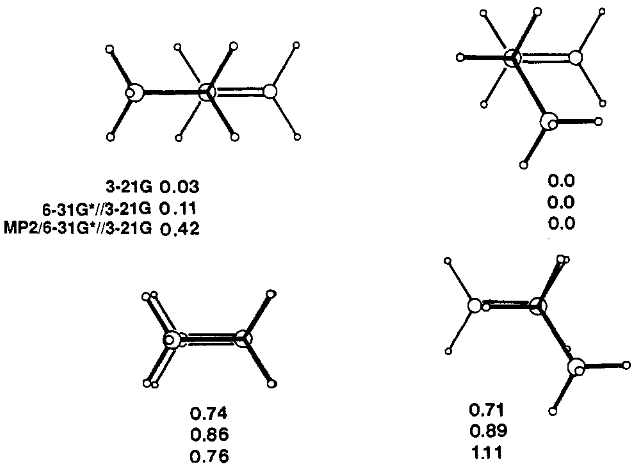


Figure 3. Transition structures and stationary points of ethyl radical addition to ethylene. Relative energies are listed for (a) 3-21G, (b) 6-31G*//3-21G, and (c) MP2/6-31G*//3-21G calculations.

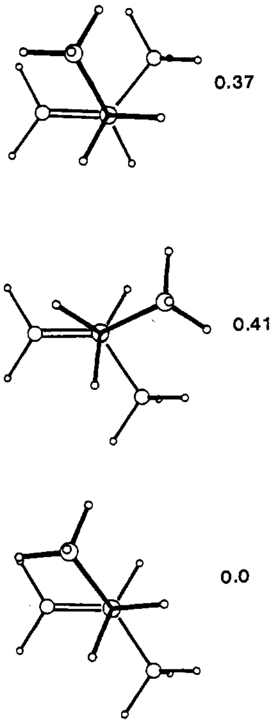


Figure 4. Transition structures and relative energies of ethyl radical addition to propylene at the 3-21G level.

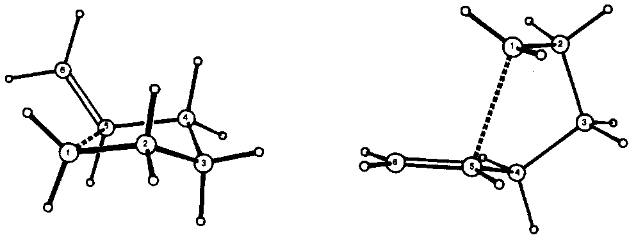


Figure 5. STO-3G-optimized transition structure of the chair exo transition state of 5-hexenyl radical. See Table I.

Geometric features of all three are given in Figures 5–7 and Tables I–III. These are compared to the MM2 structures (Figures 8 and 9, Tables IV–VI) later.

The exo chair transition state, (see Figure 5) is the lowest in energy. The C_1–C_5 bond length is 2.34 Å, much longer than anticipated on the basis of higher level calculations.[9] The system resembles a chair cyclohexane, much as Beckwith has suggested.[7] The double bond length has stretched to 1.39 Å. All other C–C bond lengths are 1.52–1.55 Å. The angle C_1–C_5–C_6 is 105.8°, much like the C_1–C_5–C_6 angle of 104° seen in methyl radical addition to C_2 of propene. The C_1–C_5–C_4 angle is 92.1°, and C_1–C_5–H is 89.6°. The angles C_1–C_2–C_3, C_2–C_3–C_4, and C_3–C_4–C_5 are 109.3°, 109.0°, and 111.1°, respectively, which are very similar to those in cyclohexane. Finally, the radical center does prefer to attack perpendicular to the approximate plane of the double bond. The dihedral angles for C_1–C_5–C_6–H are ±87°. The dihedral angles C_1–C_2–C_3–C_4 and C_2–C_3–C_4–C_5 are and 51.3° and −51.9°, respectively.

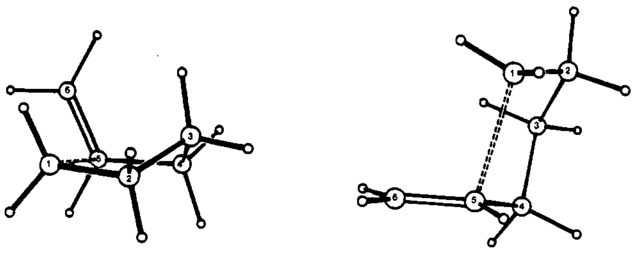


Figure 6. STO-3G-optimized transition structures of boat exo cyclization of 5-hexenyl radical. See Table II.

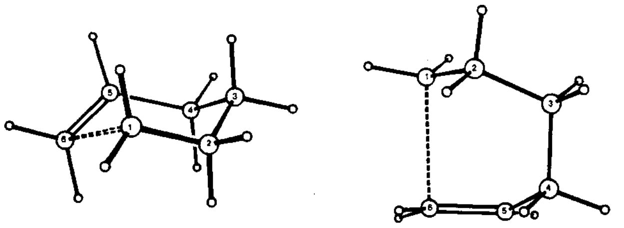


Figure 7. STO-3G transition structure for the endo transition structure of cyclizations of the 5-hexenyl radical. See Table III.

The other exo transition state is a heretofore unpostulated structure. As can be seen from Figure 6, this transition state resembles a boat cyclohexane, yet it is only 1 kcal/mol higher in energy than the exo-chair. In this transition structure, none of the "flagpole" interactions of boat cyclohexane are present. Indeed, the boat-like transition state is very similar to the chair-like transition state (see Tables I and II). The C_1–C_5–C_6 bond angle is 104.8°, and the C_1–C_5 bond length is 2.34 Å, both of which are very similar to the corresponding values for the chair-like transition state. The torsional angle C_1–C_2–C_3–C_4 is −53°, and that for C_2–C_3–C_4–C_5 is 49°. Both are similar to the chair-like transition state. The difference in free energy of 1.0 kcal/mol between the chair-like and boat-like transition structures arises mainly from a $\Delta\Delta E^{\ddagger}$ of 1.3 kcal/mol favoring the chair-like transition structure. The zero-point vibrational energy and the $T\Delta\Delta S^{\ddagger}$ at 338 K terms favor the boat-like transition structure by 0.3 kcal/mol.

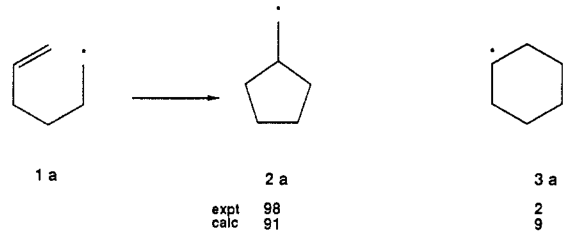
The endo transition state leading to the minor product is shown in Figure 7. The C_1–C_6 bond length is 2.40 Å, while the double bond length C_5–C_6 has stretched to 1.38 Å. The forming angle C_1–C_6–C_5 is 93.9°, very much reduced from the 108° preferred angle of attack seen in methyl radical addition to ethylene. Otherwise, this structure resembles chair cyclohexane with one bond length stretched to 2.40 Å and one shortened to 1.38 Å. The C_1–C_2–C_3 and C_2–C_3–C_4 angles are 114° and 113°. The C_3–C_4–C_5 angle is 111° and is the only one near the 110° angles found in cyclohexane. The C_1–C_2–C_3–C_4 dihedral angle is −65°, C_2–C_3–C_4–C_5 is 60°, while the C_3–C_4–C_5–C_6 dihedral is −76°. The endo transition structure is disfavored by 3.0 kcal/mol relative to the exo chair. The major component of this $\Delta\Delta G^{\ddagger}$ is the $\Delta\Delta E^{\ddagger}$ of 2.4 kcal/mol which favors the exo-chair transition structure. The zero-point energy correction of 0.2 kcal/mol favors the exo transition structure. Most interestingly, the calculated $\Delta\Delta S^{\ddagger}$ is only 1.2 eu and not 3.3 eu as estimated by MINDO/3.[19] At 65 °C this amounts to only 0.4 kcal/mol, favoring the exo transition structure. From these calculations, it can be seen that the major energetic contribution for the difference in activation energy for the exo vs. endo cyclization is *enthalpic* and not *entropic* in nature.

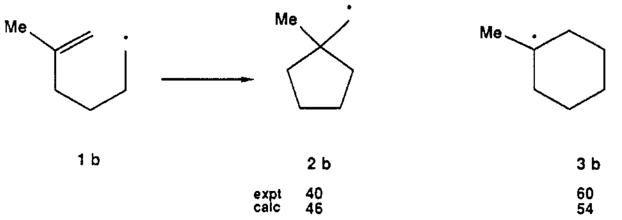
All of these structures are very similar to our MM2 model, except for the forming bond lengths. These, too, would most likely fall into line with the use of the 3-21G basis set. Therefore, we feel that our model gives accurate structures and reasonable energies.

Applications of the Transition-State Force Field to Intramolecular Radical Additions

Regiochemistry. The MM2 model predicts modest regioselectivity for simple intermolecular cases. For example, the MM2 model predicts that methyl radical addition to C_1 of propene is 1.3 kcal/mol favored over addition to C_2. For comparison, the 3-21G transition-state calculations predict a difference of 1.8 kcal/mol.[9] Likewise, our model predicts methyl radical addition to C_1 of isobutylene to be 2.6 kcal/mol favored over C_2 attack, while 3-21G transition-state calculations predict the difference to be 3.8 kcal/mol. Thus, consideration of only steric effects gives reasonable qualitative regiochemical predictions, which is in accord with conclusions by Giese and others[14] on the origin of regioselectivity in radical additions. On the other hand, the small underestimation of regiochemical preferences is also in accord with suggestions that electronic effects reinforce steric effects on regioselectivity.[15]

The regiochemical predictions of the model for intramolecular additions are compared to experiment in Table VII. The 5-hexenyl radical (**1a**) undergoes ring closure preferentially in the exo mode (98:2) to form a cyclopentylcarbinyl radical, a primary radical, (**2a**) as opposed to a cyclohexyl radical (**3**), the thermodynamically favored product. Substitution has, in some cases, a dramatic effect on regioselectivity. For example, the 5-methyl-5-hexenyl radical (**1b**) slightly prefers the endo product **3b** over the exo product **2b**, the product ratio being 60:40. Methyl substituents at other positions, however, reinforce the preference for exo cyclization.[6b,7]





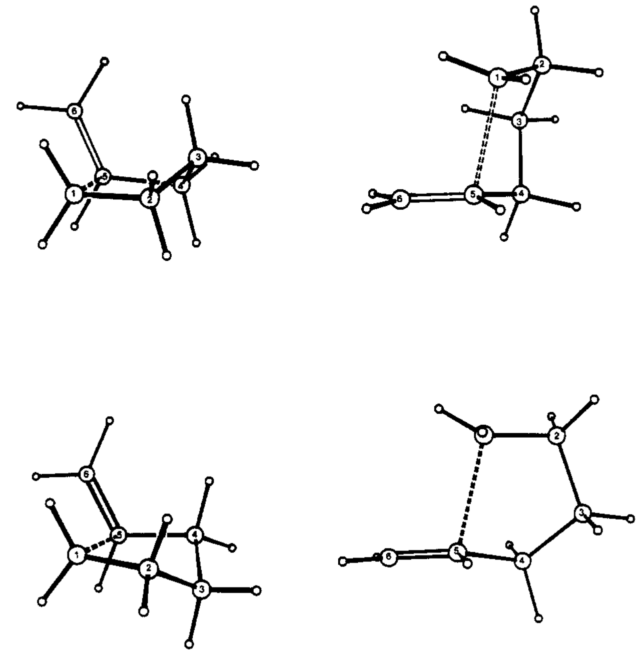


Figure 8. Two views of the MM2 model transition structure for exo cyclization of the 5-hexenyl radical. Top views are of the boat-like transition state, while the bottom view are of the chair-like cyclization. See Tables IV and V.

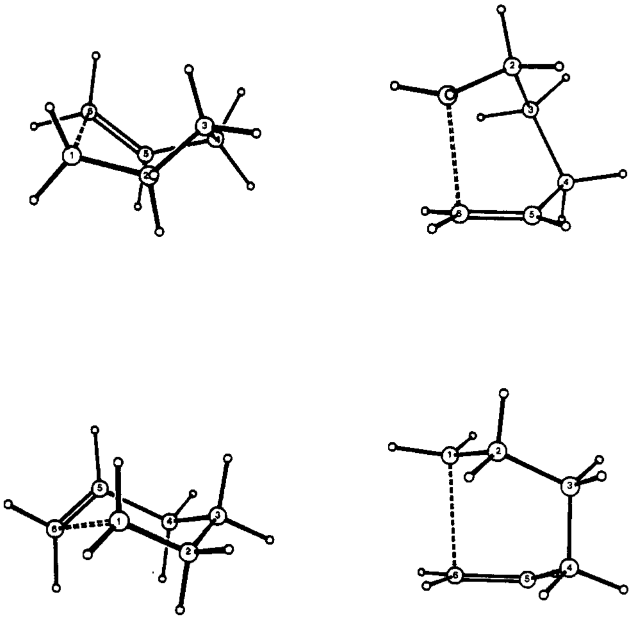


Figure 9. Two views of the MM2 model transition structure for endo cyclization of the 5-hexenyl radical. Top views are of the twist-boat transition state and the bottom views are of the chair-like transition state. See Table VI.

The MM2 transition state models for the exo and endo cyclizations are shown in Figures 8 and 9. Our model predicts that the exo cyclization of the 5-hexenyl radical can occur by either the chairlike transition state proposed by Beckwith[7] or by the boat-like transition state which is 0.5 kcal/mol higher in energy. We also find two transition structures for the endo cyclization. One resembles a chair cyclohexane in which one bond has been stretched, while the other is 2.1 kcal/mol higher in energy and resembles

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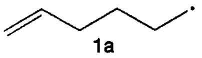
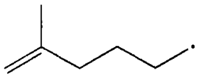
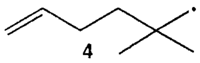
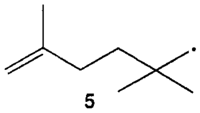
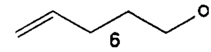
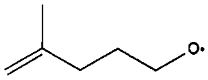
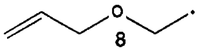
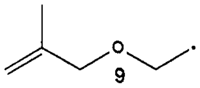
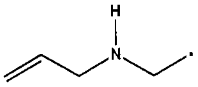
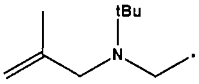
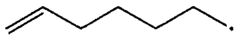
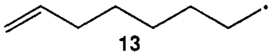
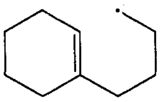
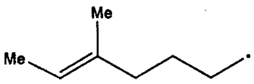
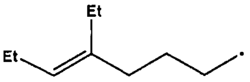
[14] Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753. Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553.

[15] Poblet, J. M.; Canadell, E. *Can. J. Chem.* **1983**, *61*, 2068. See also, Delbecq, F.; Ilavsky, D.; Anh, N. T.; Lefour, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1623.

Table VII. Regiochemical Ratios for Intramolecular Radical Cyclizations

compd	calcd exo/endo [ΔE]	exptl exo/endo [$\Delta\Delta G^{\ddagger}$]	T (°C)	ref
 1a	91:9 [1.55]	98:2 [+2.61]	65	26
 1b	46:54 [−0.11]	40:60 [−0.27]	65	26
 4	98:2 [2.61]	>99:<1 [>+2.86]	40	31
 5	82:18 [1.02]	68:32 [+0.47]	40	31
 6	98:2 [2.61]	100:0 [>+2.86]	35	21
 7	98:2 [2.61]	100:0 [>+2.86]	35	21
 8	100:0 [+4.82]	100:0 [>+2.86]	40	22
 9	97:3 [2.33]	98:2 [+2.42]	40	22
 10	99:1 [+3.09]	100:0 (>2.86]	80	23
 11	96:4 [2.22]	100:0 [>2.86]	80	23
 12	100:0 [3.0]	89:11 [+1.55]	65	26
 13	14:86 [−1.22]	0:100 [−2.66]	65	2, 26
 14	63:37 [0.36]	55:45 [+0.13]	65	25
 15	80:20 [0.92]	100:0 [>+2.86]	25	17
 16	89:11 [1.40]		25	

a twist-boat cyclohexane with one stretched bond.

In the preferred exo transition state, C_1 to C_5 of 5-hexenyl occupy the positions of C_1 to C_5 of a chair cyclohexane. The double bond is rotated away from the ring. The forming bond length of 2.27 Å is slightly shorter than the corresponding C_1–C_5 distance of 2.53 Å observed in cyclohexane. The torsion about the forming bond places the four carbons C_1, C_2, C_4, and C_5 nearly coplanar, as in cyclohexane. The angle C_1–C_5–C_6 is 108.3°, and the double bond is stretched to 1.38 Å. The carbon being attacked is slightly pyramidalized. The angle C_1–C_5–C_4 is 90.3°, and that of C_1–C_5–H is 91.2°. The hydrogens on C_6 remain coplanar with the double bond carbons. The remaining bond lengths and bond angles resemble those of cyclohexane. The torsional angles are similar to those of cyclohexane, also. Angle C_1–C_2–C_3–C_4 is 48° in the transition state and −56° in cyclohexane, while C_2–C_3–C_4–C_5 is −58° and −56° in these two situations, respectively.

The analogy of the exo transition state to chair cyclohexane has become very prominent. In actuality, the lower energy exo transition state resembles an envelope cyclopentane with the C_1–C_5 bond stretched to 2.27 Å. The double bond is then placed on C_5 in the position anti to the C_3 methylene (Beckwith's chair) or syn to the C_3

methylene (our "boat"). It is then easier to understand that the energy difference between these structures should not be as great as in cyclohexane, but diminished, as these two positions are similar. We will, however, continue to use the Beckwithian nomenclature.

Our model suggests a transition state slightly later than the exo chair STO-3G structure, based upon the C_1–C_5 bond length of 2.27 vs. 2.34 Å. Both of these are earlier than the MINDO/3[16] or MNDO[2] methods, which predict a C_1–C_5 distance of 2.20 Å. The C_1–C_5–C_6 bond angle is 108° in our model, 104° by MNDO, and 106° by STO-3G. Our model more closely reproduces the ab initio structure than does either of the MNDO or MINDO/3 methods. These methods suggest a quite flat structure, with the dihedral angles C_1–C_2–C_3–C_4 and C_2–C_3–C_4–C_5 equal to 35° and 40° *less* than our model predicts. This is typical of these methods which underestimate torsional effects in general. Of course, the boat-like transition structure has not been investigated by these means.

As Figure 8 shows, the second exo transition structure has the appearance of a boat cyclohexane. As in the exo-chair transition state, atoms C_1 to C_5 occupy the same positions as five atoms in boat cyclohexane. The final atom, C_6, has been rotated outward from the position occupied by C_6 in cyclohexane. That this structure is only 0.5 kcal/mol higher in energy than the chair transition state is a result of the positioning of C_6 away from the C_3 methylene unit, which would be the cause for large steric interactions. The chair–boat energy difference is 6.5 kcal/mol in cyclohexane and is directly attributable to "flagpole" interactions which are *not* present in this transition state. The forming angle (C_1–C_5–C_6) is 106.1° while the remaining angles are unchanged from the chair transition state. Again, our model predicts a structure very similar to the STO-3G transition structure although slightly later (C_1–C_5 = 2.27 Å by MM2 vs. 2.34 Å by STO-3G). The difference between the exo-chair and the exo-boat is larger in the STO-3G structures than in the MM2 structures by about 0.8 kcal/mol.

Figure 9 shows the geometrical features of the chair-like transition state leading to the minor product. This transition state is 1.4 kcal/mol higher in energy than the chair exo transition state. As can be seen from Figure 9, the endo transition state resembles a chair cyclohexane with one bond length elongated and one bond length compressed. Like cyclohexane, there is no eclipsing about the C–C bonds. The forming bond and double bond lengths are unchanged from the exo transition state at 2.27 and 1.38 Å, respectively. The forming bond angle (C_1–C_6–C_5) has been reduced from the natural 107° angle to 96.4°. The carbon being attacked is considerably less pyramidal than in the other transition states calculated, due to the decreased angle of attack. Unlike any intermolecular transition structure, the endo cyclization has one terminal substituent very much noncoplanar with the double bond. Carbon 4 of the connecting chain is pulled 20° out-of-plane in order to place the radical into a geometry suitable for reaction. The hydrogen attached to C_5 remains coplanar with the double bond.

Once again, our model predicts that the endo–chair transition structure is amazingly similar to the STO-3G structure. (See Figures 7 and 9 and Table III and VI). The STO-3G structure is the earliest, with the C_1–C_6 bond length at 2.40 Å, while the MINDO/3[16] C_1–C_6 distance is 2.27 Å and that of MNDO/2 is 2.20 Å. The double bond by all four methods is 1.38 Å. The STO-3G C_1–C_6–C_5 angle is 94°, our MM2 model predicts 96°, and MNDO predicts 98°. Again, the MINDO/3 structure is flatter than our MM2 or STO-3G structures.

Since we have located a boat-like exo transition structure, we searched for an endo-twist boat-like transition structure with our MM2 model. This transition state is 2.1 kcal/mol higher than the chair-like endo transition state. While this is still significantly less than the cyclohexane chair vs. twist-boat energy difference, it is large enough to exclude this pathway as an appreciable contributor to the overall product ratio. The forming bond length is 2.27 Å, and the double bond is stretched to 1.38 Å. The angle C_1–C_6–C_5 is 97.8°, still quite different from the 107° angle assumed as ideal. There is no eclipsing of atoms in this transition structure. The dihedral angle C_1–C_6–C_5–C_4 is –73° and C_6–C_5–C_4–C_3 is 39°, while C_2–C_1–C_6–C_5 is 31°.

Several hypotheses have been put forward concerning the origin of the preference for exo closure of the 5-hexenyl radical (**1a**). Beckwith has outlined and critically evaluated these in his excellent review of intramolecular radical cyclizations.[6b] Beckwith's hypothesis is, "...the strain engendered in accommodating the mandatory disposition of reactive centers within the 1,6-ring closure outweighs those steric and thermochemical factors expected to favor the formation of the more stable possible product".[2,6b] Julia, upon the basis of a discussion with LeBel,[17] has suggested that there is a nonbonded interaction between the axial hydrogen on C_2 and the syn hydrogen on C_6 in the endo cyclization. Because there is no such interaction in the exo cyclization, this causes the endo cyclization to be disfavored. Finally, Capon and Rees[18] have suggested that the activation entropy controls the formation of the five-membered ring rather than the six-membered ring. This concept has been perpetuated through the application of energy partitioning schemes using semiempirical techniques.[19]

Intramolecular radical cyclizations should be governed by the same electronic and steric influences operating in the intermolecular counterparts if geometric constraints allowed. The strain engendered in the endo cyclization of 5-hexenyl more than overcomes the usual steric and electronic preference for the endo mode. In the absence of geometrical constraints, the endo cyclization would be preferred by as much as 1.8 kcal/mol, the calculated difference in energy between C_1 and C_2 addition of methyl radical to propylene. In 5-hexenyl radical, torsional effects favor the endo transition states by 1.9 kcal/mol. As can be seen in Figure 9, the lower energy transition state is in a chair conformation in which all bonds are staggered. This is in contrast to the exo cyclization transition states in which there is some eclipsing. These torsional preferences for endo cyclization are, however, overcome by a 3 kcal/mol preference in the bending values for the exo cyclizations. The forming angle is 11° less in the exo transition structures than in the endo transition structures, accounting for a 2 kcal/mol preference for exo cyclization. In addition, the angles C_2–C_3–C_4 and C_4–C_5–C_6 in the endo structure are larger than the normal 109° found in a chair cyclohexane, while all angles in the exo structures are nearly normal (See Figures 8 and 9 and Tables IV–VI).

Steric interactions cause the 5-methyl-5-hexenyl radical (**1b**) to cyclize predominantly in the endo mode rather than

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(16) Bischof, P. *Helv. Chim. Acta* **1980**, *63*, 1434.

(17) Julia, M.; Descoins, C.; Baillarge, M.; Jacquet, B.; Uguen, D.; Groeger, F. A. *Tetrahedron* **1975**, *31*, 1737. LeBel had suggested this hypothesis in a discussion with Julia, as mentioned in this paper.

(18) Capon, B.; Rees, C. W. *Ann. Rep. Chem. Soc.* **1964**, *61*, 221.

(19) Canadell, E.; Igual, J. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1331.

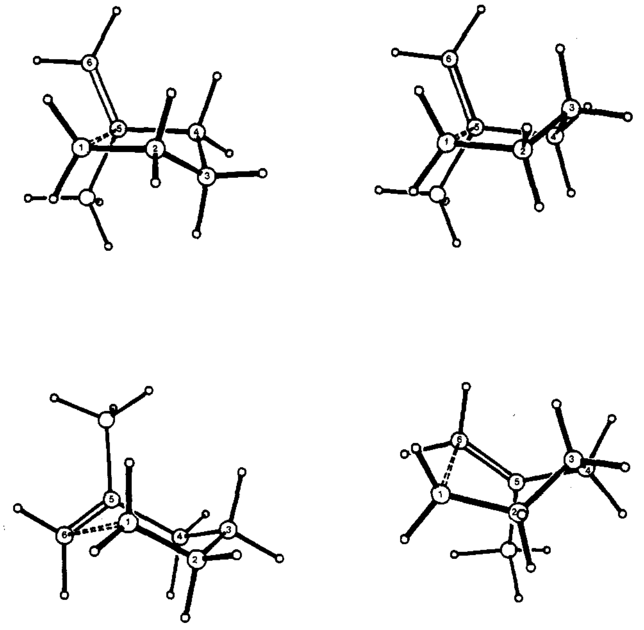

Figure 10. Views of the exo and endo transition structures of 5-methyl-5-hexenyl (**1b**) radical cyclization.

the exo mode of the unsubstituted case. The calculated ratio of 54:46 agrees with the 60:40 ratio observed experimentally. The structural features of the substituted and unsubstituted transition states are similar. (See Figures 8–10). Two substituents, the methyl group and the connecting chain, increase the steric repulsion present at the substituted end, thereby forcing the reaction to proceed via the endo mode. This follows the guidelines set forth by Beckwith, which state the endo preference in this reaction is "mainly steric in nature".[7] Our results would indicate that the Julia–LeBel[17] hypothesis is incorrect. There is little interaction between the syn hydrogen at C_6 and the axial hydrogen at C_2, as they are 2.7 Å apart in the endo transition state. The same atoms in the exo transition state are 4.3 Å apart. This is much too large a distance over which to have any significant steric repulsion.

An interesting feature of this reaction is that the exo-boat transition state for **1b** is 0.4 kcal/mol lower in energy than the exo-chair transition state. Placing a methyl group on the double bond syn to the C_3 methylene unit causes some steric interactions between the methyl group and the C_3 methylene. These are relieved somewhat by reversing the positions of the double bond and the methyl group (i.e., flipping the chair). This places the double bond syn to the CH_2 group. As we have seen, this does not require a significant amount of energy and is therefore favored over the chair-like transition structure in this case.

Canadell and Igual[19] and Bischof[16] have located the transition states for exo and endo cyclizations of **1a** by the MINDO/3 method. They find the activation enthalpy for both transition states to be identical at 16.5 kcal/mol. Both studies predict that the activation entropy favors exo cyclization by 3.3–3.6 cal mol^{-1} K^{-1}. The $\Delta\Delta G^{\ddagger}$(exo–endo) difference is, therefore, about 1 kcal/mol. While this predicts the correct product, it "seems to be insufficient to explain the degree of regioselectivity."[19] Canadell and Igual have also located the transition states for cyclization of the 5-methyl-5-hexenyl radical. They find the enthalpy of activation favors the endo transition structure by 7.7 kcal/mol, while the entropy of activation favors the exo transition state by 3.8 cal mol^{-1} K^{-1}. Clearly, these results are in poor agreement with the experimental values[7] of $\Delta\Delta G^{\ddagger}$(exo–endo) of 2.8 kcal/mol for the 5-hexenyl radical and −0.3 kcal/mol for the 5-methyl-5-hexenyl radical. However, the authors conclude that enthalpic and entropic factors determine the outcome of the reaction.

Our model, which incorporates only enthalpic factors, disagrees with the MINDO/3 results. Even though our model is relatively simple, we estimate an energy difference of 1.5 kcal/mol in favor of the exo mode. While this is modest, it is obviously superior to the semiempirical techniques, which predicts a ΔE of zero! It is also obvious that some entropic effects are present in this system. Experimental results for other systems support the fact that steric effects are the dominant effects governing regioselectivities of these reactions[20–23] and that entropic factors are less significant.

In order to assess the entropic effects at a reliable level of theory, we have located three transition states of the cyclization of 5-hexenyl radical at the STO-3G level. As was mentioned previously, the exo-chair structure is the lowest in energy and is 1.0 kcal/mol lower than the exo-boat form and 3.0 kcal/mol lower than the endo form. These values are in quite good agreement with the experimental value of 2.8 kcal/mol preference for exo cyclization. Entropy effects favor the exo-boat transition state over the exo-chair mode by only 0.2 kcal/mol and by 0.6 kcal/mol relative to the endo cyclization at 65 °C.

Intermolecular additions of oxygen-centered radicals follow the same pattern of intermolecular addition of the carbon-based analogues. In contrast, the intramolecular cyclization of 1-oxa-5-hexenyl (**6**) and 1-oxa-5-methyl-5-hexenyl (**7**) radicals both follow the exo pathway exclusively.

We have used our model with no modifications, save for redefining the radical as an oxygen, to investigate these reactions. The assumption is that the transition structures for the oxy-centered radicals are not too different from those of the carbon-based systems. While this is an overly simplistic assumption, very extensive calculations would be necessary to determine all the parameters for these radicals. It is of interest, therefore to attempt this modeling technique first.

Our model predicts a 98:2 ratio for both **6** and **7** in good agreement with experiment. Analysis of the MM2 results from these two cyclizations shows that it is the shorter C–O single bonds, relative to C–C bonds, interior to the ring which impose greater restrictions on the endo cyclization than it does on the exo, even though the transition states are similar to the carbon-based systems. This is also the case for the 1-oxa-5-methyl-5-hexenyl radical (**7**). The shorter C–O bond decreases the forming angle in the endo cyclization to 93°, manifesting itself in increased torsional and bending energies relative to the cyclization of the unsubstituted radical. Therefore, the endo transition state is disfavored, even though the parent system undergoes endo cyclization.

Further evidence as to the extent of steric control of intramolecular radical cyclizations can be seen in radicals with a heteroatom in the connecting chain. The 3-oxa-5-hexenyl radical (**8**) and its 5-methyl derivative (**9**) both undergo predominantly exo cyclization, as reported by Smith and Butler.[22] The transition states for 3-oxa-5-hexenyl radical cyclization are similar to those of the parent system. Our model accurately predicts the exo product to be the only product from cyclization of **8** and

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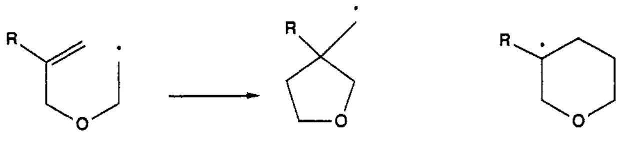
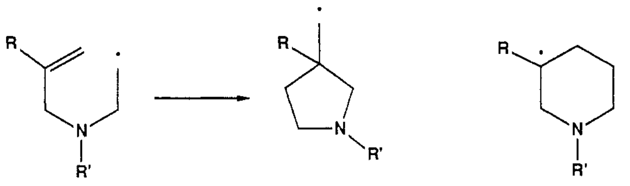


8 R=H	expt	100	0
	calc	100	0
9 R=Me	expt	100	0
	calc	97	3

a 97:3 ratio from cyclization of **9**. Very few differences exist between the exo chair transition states of **1a** and **8** and **9**. However, unlike the 5-hexenyl cyclizations in **8**, the boat transition state is 0.1 kcal/mol lower in energy than the chair. This is due to the lack of steric interactions between the double bond and the substituents on atom 3. In the 5-hexenyl radical, this interaction accounts for the 0.5 kcal/mol destablization of the boat. In the transition states for **9**, the boat is only 0.2 kcal/mol lower than the chair, as compared to 5-methyl-5-hexenyl, where the boat is 0.4 kcal/mol lower in energy than the chair. Again, since the oxygen is a smaller group than the methylene, steric interactions between the methyl group at C_5 and the oxygen are diminished in the chair exo transition states for **9**. Some small but very significant differences exist in the endo structures. The C_2–O_3–C_1 angle of 114.6° in **8** and **9** is similar to the 115.4° C–C–C angle in **1a**. The normal MM2 values for COC and CCC angles are 106.8° and 109.5°, respectively. The energy to deform the COC angle to 114.6° is, subsequently, greater by 1 kcal/mol than the energy required to deform the same CCC angle to 115.4°. Shorter C–O bonds and this slightly smaller internal angle combine to pull the radical center attack angle further from the normal value of 107° to 91.6°, adding another 1 kcal/mol relative to the exo cyclization. Replacement of the carbon by an oxygen also changes the torsional energy in the ring system, so that the endo is now preferred by slightly over 1 kcal/mol as opposed to 2 kcal/mol in **1a**.

A further consequence of placing the smaller oxygen at the 3-position is that the twist boat endo transition state for **8** is only 1.2 kcal/mol higher than the endo chair transition state and 1.3 kcal/mol higher in **9**, as compared to the 2.1 kcal/mol difference in 5-hexenyl and 2.0 kcal/mol in 5-methyl-5-hexenyl.

Similar arguments hold for the 3-aza-5-hexenyl (**10**) and 3-aza-5-methyl-5-hexenyl radicals (**11**). Padwa et al.[23] have shown that 3-aza systems, with a large SO_2Ph group on N, produce exclusively exo product, regardless of substitution of the double bond. They attribute this to increased stereoelectronic effects due to the shortened C–N bonds with respect to C–C bonds. Our calculations on the unsubstituted radical also predict exo product to be favored but not by as large a difference as in **8** and **9**. Our calculations predict exo to be the major product of cyclization of **10** (99:1). The product ratio of **11** is predicted to be 71:29 in favor of exo when R′ = H but increases to 96:4 when R′ = *t*-Bu. In these systems, the C–N bond lengths are 1.46 Å, and the C_2–N_3–C_4 normal angle is 107.7°. These are smaller than the corresponding C–C bond lengths and C_2–C_3–C_4 angle in **1a** but larger than the C–O and C_2–O_3–C_4 angles in **8** and **9**. The energy required to deform angle C_2–N_3–C_4 in the endo cyclization is, therefore, less than that required to deform the C_2–O_3–C_4 angle, and the forming angle is more like **1a** and **1b** at 92.6°. These systems, therefore, should show some endo product in the absence of larger substituents. Indeed, if a *t*-Bu group is substituted on the nitrogen in **11**, the exo cyclization is preferred in a 96:4 ratio. The large groups apparently place greater strain on the endo transition states than on the exo, causing the exo to be favored. This effect is generally observed in the hexenyl radicals.[6]



10 R=H	expt	R′=SO_2Ph	100	0
	calc	R′=H	99	1
11 R=Me	expt	R′=SO_2Ph	100	0
	calc	R′=H	71	29
		R′=^{t}Bu	96	4

Increasing the size of the forming ring should make it easier for more endo product to be formed. The endo preference could be even larger in large ring intramolecular cases than in intermolecular reactions, since the radical center in the endo transition state attains the more favorable 107° attack angle as the system increases in size, but the same angle is smaller in the exo transition state. Beckwith observed this trend in the MNDO transition states used in his model.[2] Our model follows this same trend. While the forming bond length remains constant, the MNDO attack angle increases from 98° in 5-hexenyl (**1a**) to 100° in 6-heptenyl (**12**) to 106° in 7-octenyl (**13**), for the endo transition states. We calculate 96°, 103°, and 106° attack angles for the same systems. Likewise, the attack angle decreases from 104° to 101° to 99° in the MNDO exo transition states, and we calculate 109°, 107°, and 106° respectively. As the ring size increases, the attack angle approaches that of the normal value found in ab initio calculations of intermolecular cases. Consequently, the larger alkenyl radicals should be able to cyclize in the thermodynamically favored mode.

Even though the exo and endo attack angles are predicted to be almost the same in the 6-heptenyl radical (**12**), the exo product is still favored experimentally by 89:11.[24] Both models predict too large an exo/endo product ratio in the 6-heptenyl cyclization. Beckwith's model predicts a 95:5 mixture, and our's predicts exclusively exo cyclization. One would expect the 7-octenyl radical (**13**) to cyclize in a predominantly endo fashion. Both Beckwith's model and our's predict that the endo mode is the favored pathway with endo/exo ratios of 100:0 and 86:14, respectively. This is contrary to early reports[24] of this cyclization in which the products were said to arise exclusively from the exo transition state. Beckwith reexamined this cyclization with preliminary results supporting the endo preference predicted by both models.[2]

In the 5-hexenyl radicals, additional substitution at C_6 increases the steric hindrance in carbon-based systems, causing these radicals to undergo exo cyclization. The 4-(1-cyclohexenyl)butyl radical (**14**), formally a 5,6-disubstituted 5-hexenyl system, undergoes cyclization in the exo mode, forming the spiro[4.5]decalyl and bicyclo[4.4.0]decalyl radicals in a ratio of 55:45.[25] Our calculations predict exo attack to be preferred by 1.0 kcal/mol to give a ratio of 63:37.

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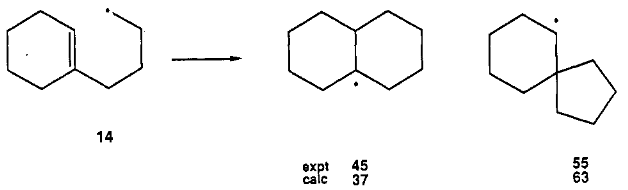


14

expt 45 55
calc 37 63

In a set of calculations on the related radicals, 5-methyl-5-heptenyl (**15**) and 5-ethyl-5-octenyl (**16**), the exo/endo ratio is found to be approximately the same as that of the 4-(1-cyclohexenyl)butyl radical. Julia et al.[17] found that **15** cyclizes exclusively in the exo fashion, although the yields were low, and mainly the products of hydrogen abstraction were observed.

Stereochemistry. Table VIII gives a comparison of predictions with experimental results for a variety of substituted 5-hexenyl radicals. Table IX compares the predictions of our model with those of Beckwith and Schiesser.[2] With the exception of the cyclic substrates, **25** and **29**, our model gives astonishingly good agreement with experiment.

The stereochemical outcome of the cyclizations of most substituted 5-hexenyl radicals can be rationalized quite readily, as Beckwith has shown,[7] by using the chair-like exo transition state. The major product arises when the substituent occupies an equatorial conformation, while the minor product arises when the substituent is axial (see Figure 11). Equatorial substitution at C_2 and C_4 leads to products with substituents trans to C_6, while equatorial substitution at C_3 would lead to products with substituents cis to C_6. Although not discussed by Beckwith, placing a substituent at C_1 in the equatorial conformation gives a cis product, which is found to be favored experimentally.

Beckwith and Schiesser have assumed major and minor products arise from substitution of the chair-like transition state shown in Figure 11. The major product arises from equatorial substitution at C_2, C_3, or C_4, while the axial substitution leads to the minor product. Their model seriously overestimates the product ratios for C_2, C_3, or C_4 substitution but underestimates the cis preference for C_1 substitution, as shown in Table IX.

Our model predicts that the minor products of these reactions arise from the transition states which have the substituents in pseudoequatorial positions of boat-like transition states, not in axial positions of chairs. Figure 12 shows the chair-like and boat-like transition states of the parent system. The boat transition state is only 0.5 kcal/mol higher than the chair, unlike cyclohexane itself, for which the boat is 6.5 kcal/mol higher in energy than the chair, according to MM2 calculations. Figure 13 shows a Newman projection down the C_5–C_4 bond in both the chair and boat transition states. Unlike boat cyclohexane, there are no "flagpole" interactions present in the boat transition state, and there is considerably less eclipsing in the radical transition state than in the boat cyclohexane. The 0.5 kcal/mol difference is, however, a consequence of increased steric interaction between the double bond and the now closer CH_2 unit. An interesting feature in both of these transition states is that the double bond is rotated outward from the ring. This places the substituent in the axial position on the radical in a more sterically crowded position than the equatorial, even though the equatorial position eclipses the double bond, while the axial eclipses a hydrogen.

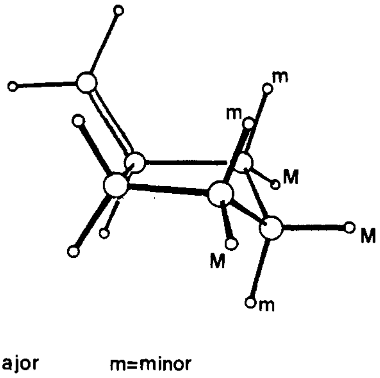


Figure 11. Chair transition state showing positions of substituents giving rise to major and minor products in 5-hexenyl radicals as expected from Beckwith's model.

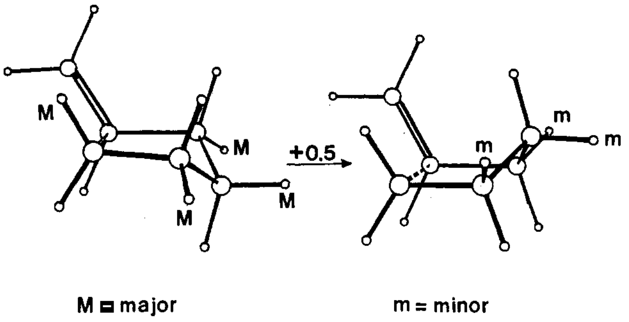


Figure 12. Views of chair and boat transition structures showing positions of substituents giving rise to major and minor products in our model.

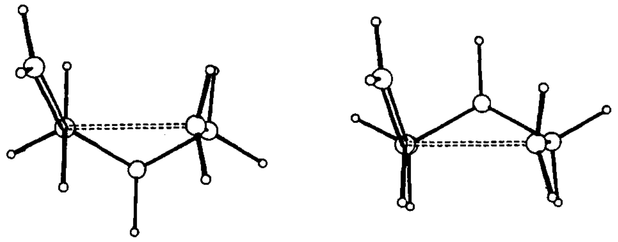
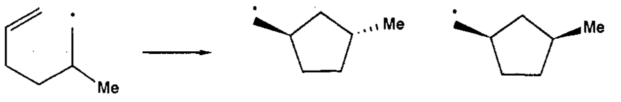


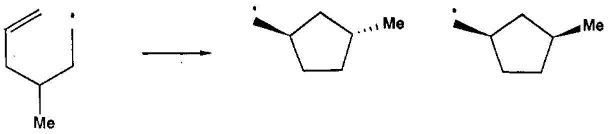
Figure 13. Views of the chair and boat transition structures showing Newman projections down the C_5–C_4 bond.

Whereas the chair–boat energy difference in cyclohexane is large enough so that axial-alkyl chair cyclohexane is more stable than the equatorial-axial boat, the opposite is true in the transition state for cyclization of substituted 5-hexenyl radicals. This is demonstrated by the 3-methyl-5-hexenyl radical (**19**), which cyclizes to form a cis-disubstituted cyclopentane preferentially. Figure 14 shows the axial and equatorial chair and boat transition states for cyclization. The equatorial-methyl chair and axial-methyl



18 21 22

expt 64 36
calc 61 39



19 21 22

expt 29 71
calc 36 64

Table VIII. Stereochemical Ratio for Substituted 5-Hexenyl Radical Cyclizations

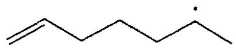
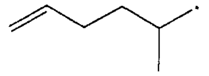
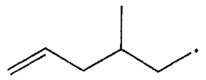
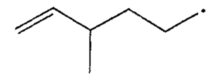
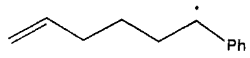
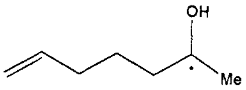
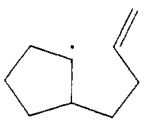
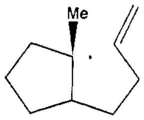
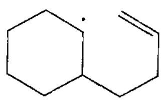
compd	calcd cis/trans [ΔE]	exptl cis/trans [$\Delta\Delta G^{\ddagger}$]	T (°C)	ref
17 	66:34 (+0.45)	67:33 (+0.48)	65	26
18 	40:60 (−0.27)	36:64 (−0.40)	80	7
19 	63:37 (+0.36)	71:29 (+0.63)	80	7
20 	19:81 (−0.97)	17:83 (−1.11)	80	7
23 	14:86 (−1.22)	0:100 (>−2.72)	80	32
24 	71:29 (+0.60)	59:41 (+0.22)		6b
25 	52:48 (+0.05)	89:11 (+1.40)	65	27
28 	37:63 (−0.32)			
29 	86:14 (1.22)	78:22 (0.85)		33

Table IX. Comparison of Experimental Cis/Trans Ratios and Relative Activation Energies with Those Predicted with Our Model and the Beckwith-Schiesser Model[2]

compd	trans/cis [$\Delta\Delta G^{\ddagger}$] exptl	this work	Beckwith model
17	67:33 [+0.48]	66:34 [+0.45]	58:42 [0.2]
18	36:64 [−0.40]	40:60 [−0.27]	16:84 [−1.0]
19	71:29 [+0.63]	63:37 [0.36]	94:6 [+1.6]
20	17:83 [−1.11]	19:81 [−0.97]	5:95 [−1.7]

chair (A and B, Figure 14) differ in energy by 1.7 kcal/mol, predicting product ratio of 95:5. However, the equatorial-methyl boat is only 0.5 kcal/mol higher in energy. Using all the transition states gives a trans/cis ratio of 64:36 in excellent agreement with the experimental value of 71:29.[7]

Similar results are found for 2- and 4-substituted derivatives. In all cases, ignoring the boat transition state leads to overestimation of the product ratios. Only upon inclusion of the boat transition state, which is considerably lower in energy for the minor product than an axially-substituted chair transition state, do we obtain good agreement with experiment. All of the ratios and calculated $\Delta\Delta G^{\ddagger}$'s in Table VIII were calculated from a Boltzmann distribution including all four transition states.

The 1-methyl-5-hexenyl radical (**17**) cyclizes preferentially via the equatorial, albeit apparently sterically more crowded, transition state, A, giving cis-1,2-dimethylcyclopentane rather than trans. Beckwith suggested that since the cis product must arise from the sterically disfavored transition state, shown as A in Figure 15, then interaction of the methyl parent of a singly occupied orbital with the remote terminus of the π^* orbital[26] must lower the energy of transition-state A enough to compensate for what appear to be the higher steric interactions in transition-states B, C, and D. In order to determine the origin of the cis preference and to test Beckwith's hypothesis, we have performed ab initio transition-state calculations, at several

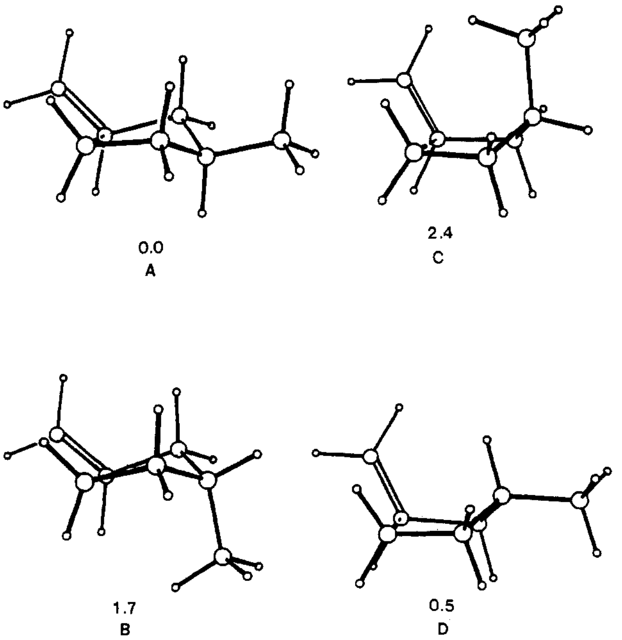
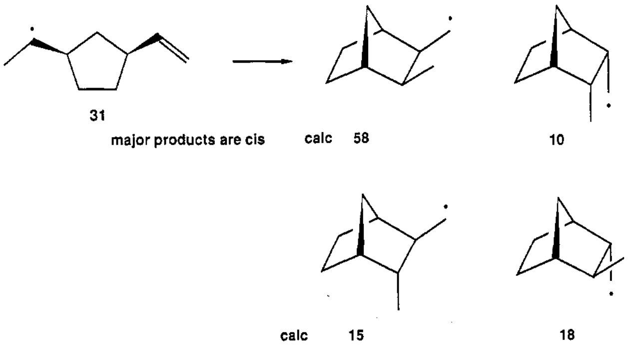


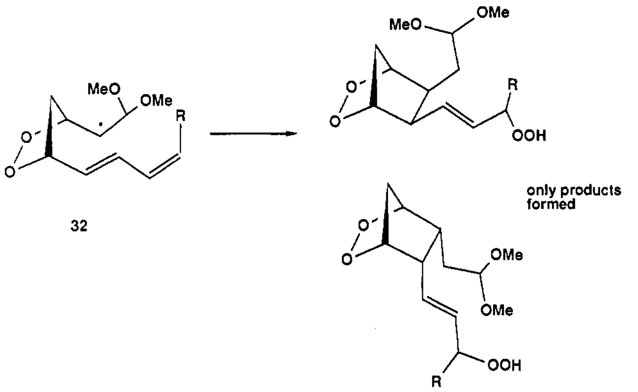
Figure 14. Views of four possible transition states of cyclization of the 3-methyl-5-hexenyl radical: (A) chair-to-cis; (B) chair-to-trans; (C) boat-to-cis; (D) boat-to-trans.

levels, for ethyl radical addition to ethylene.[9] These results were summarized earlier in Figure 3.

As was mentioned previously, MP2/6-31G* single-point calculations on the 3-21G stationary points show a 0.4 kcal/mol difference between the 0° and 120° conformations (See Figure 3). These results are significant for the 1-methyl-5-hexenyl case in that transition states leading to the cis, or major product, have a similar relative orientation of the methyl group and the double bond as the 0° transition-state conformation. The 1-methyl-5-hexenyl cyclization transition state leading to the trans product has a similar methyl–alkene orientation to the model 120° conformer. Transition states A and C are favored over B and D by 0.4 kcal/mol. This finding supports the Beckwith assumption that there is a stabilization of a seemingly crowded transition state, A. It does not, however, support his hypothesis of hyperconjugative stabilization.[26] If the SOMO interaction with the π^* interaction stabilizes A, one would expect the HF level calculations at the 3-21G and 6-31G* levels to show a significant difference in energy between the 0° and 120° stationary points. They do not. Only upon inclusion of electronic correlation is there any significant difference between the 120° and 0° rotamers. Nevertheless, there is some electronic preference for the transition states A and C relative to B and D. It is probably the result of a van der Waals attraction, since it appears only upon inclusion of electron correlation. The Beckwith MM2 calculations did not include this preference and consequently predict a rather low 58:42 cis/trans ratio. Our model, on the other hand, predicts a ratio of 66:34 in excellent agreement with the experimental value of 67:33.



31



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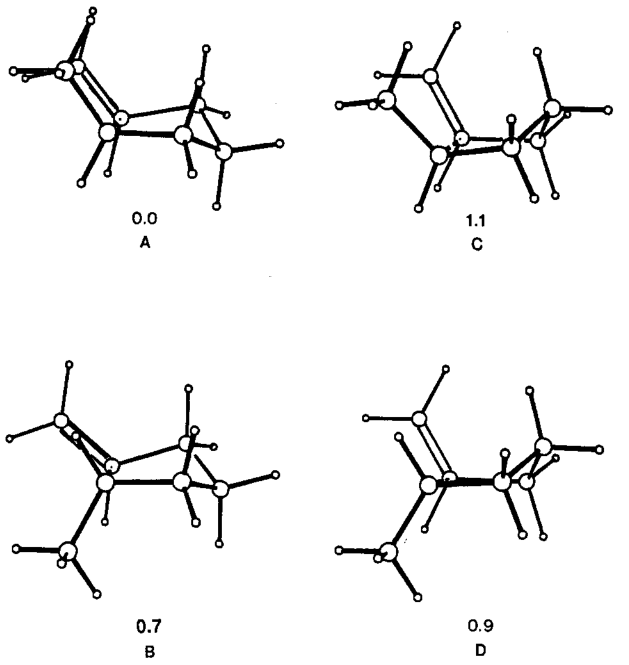

Figure 15. Views of four possible transition structures of cyclization of the 1-methyl-5-hexenyl radical.

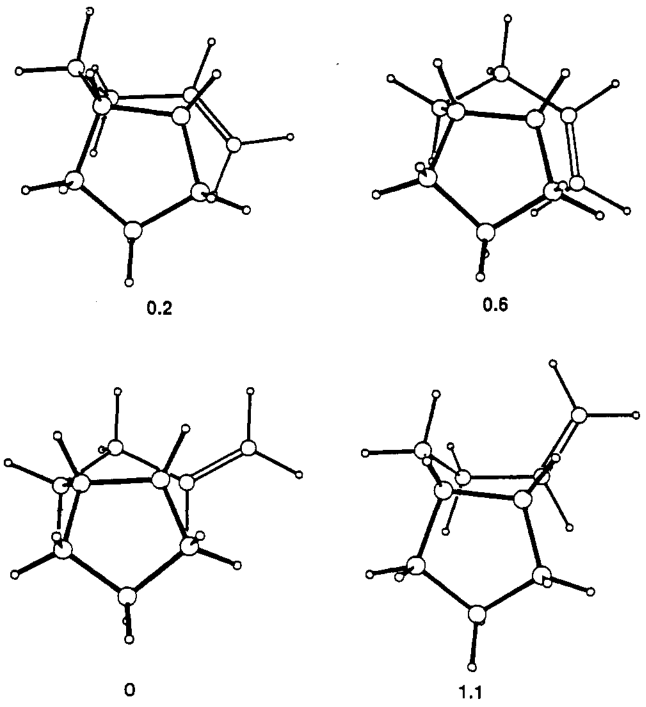

Figure 16. Views of four transition structures of the closure of the 2-(3-butenyl)cyclopentyl radical.

The cyclization of radical **31** is related. Beckwith reports that **31** cyclizes to form predominantly cis products.[6b] Our model predicts that cis products predominate over trans but that the cis-exo product is favored. Corey et al.,[28] in an attempt to mimic a biosynthetic route to form prostaglandins, such as **32**, observed that only cis products are formed. The *exo*/*endo* ratio is dependent upon solvent.

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(28) Corey, E. J.; Shimoji, K.; Shih, C. *J. Am. Chem. Soc.* **1984**, *106*, 6425.

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(31) Beckwith, A. L. J.; Lawrence, T. *J. Am. Chem. Soc., Perkin Trans. 2* **1979**, 1535.

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Table X. Comparison of Calculated and Experimental Activation Energies (kcal/mol) of Regioisomeric Cyclizations

cmpd	E_{gs}	exo chair[a] E_{act}	exo boat[a] E_{act}	endo chair[a] E_{act}	endo boat[a] E_{act}	exo exptl[b] E_{act}	endo exptl[b] E_{act}
1a	3.0	6.8	7.3	8.2	10.0	6.8	8.5
1b	3.3	8.3	7.9	7.5	9.5	8.5	7.9
4	6.8	5.0	5.5	7.3	8.8	5.4	
5	7.2	6.3	6.0	6.7	8.8	6.9	7.2
12	3.6	4.3		10.4		7.9	8.8
13	4.5	11.1		9.8			9.6

[a] Activation energies are calculated by using the formula $E_{act} = E_{TS} - E_{gs} + 51.7$ kcal/mol, where the constant 51.7 is chosen to reproduce the activation energy of **1a** (see text for details). [b] Experimental activation energies are found in ref 2 and 31.

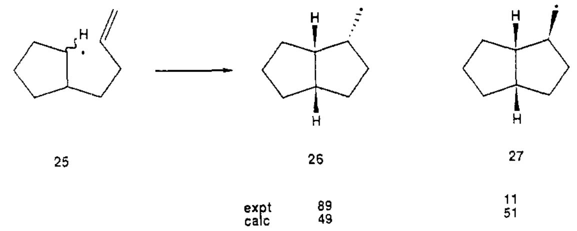
Table XI. Comparison of Calculated and Experimental Activation Energies (kcal/mol) of Stereoisomeric Cyclizations

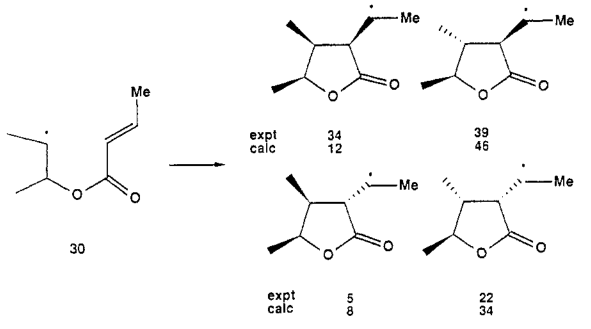
cmpd	E_{gs}	cis chair[a] E_{act}	cis boat[a] E_{act}	trans chair[a] E_{act}	trans boat[a] E_{act}	cis exptl[b] E_{act}	trans exptl[b] E_{act}
17	3.2	6.3	7.4	7.0	7.3	6.9	7.6
18	4.9	6.4	5.6	5.2	7.1	6.5	6.1
19	4.4	5.7	8.1	7.4	6.1	6.0	6.4
20	4.4	7.9	6.8	5.7	7.7	7.7	6.6

[a] Activation energies are calculated by using the formula $E_{act} = E_{TS} - E_{gs} + 51.7$ kcal/mol, where the constant 51.7 is chosen to reproduce the activation energy of **1a** (see text for details). [b] Experimental activation energies are found in ref 2.

Our model, as applied to the similar radical **31**, suggests that there is no electronic preference for the cis products as Corey has suggested. Rather, the cyclization of **32** follows the cis preference found in the 1-methyl-5-hexenyl radical.

Unfortunately, our model is a poor predictor in cases such as that shown below. When the radical center is part of a ring, our model tends to underestimate the cis preference observed experimentally. For example, **25** cyclizes to give an 89:11 ratio of anti (**26**) to syn (**27**) product.[27] Our model predicts only a 49:51 anti/syn ratio. Figure 16 shows the four transition states of the cyclization of **25**. There is no apparent reason for failure of our model in these systems. The cyclopentane ring system does apparently place greater strain on the forming ring in the transition state than in the unsubstituted case. This distorts the transition states with relative energies of 0 and 0.6 kcal/mol from a chair-like or boat-like structure to an envelope-like structure. Subsequently, there is less of a steric difference between the syn or anti position in the transition state leading to a predicted syn to anti ratio much lower than experiment.



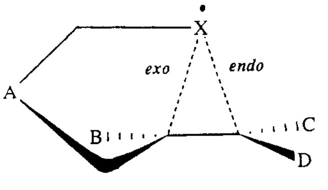


Our model is generally limited, of course, by the current lack of parameters in MM2 for many types of systems. For example, Clive and Beaulieu[29] have shown that radical **30** undergoes cyclization to form four products as shown. Our model does not provide very accurate quantitative predictions of the product ratio. This is related to the fashion in which MM2 handles esters and conjugated systems and to the possibly modified transition structure involved in the system. Nevertheless, the prediction could be qualitatively useful in that it predicts that selectivity is low, and the major product is predicted correctly.

Prediction of Activation Energies. Our model can be used to predict activation energies, also. Table X and XI give the calculated and experimental activation energies for several molecules. Note that in only one case (**12**) does the calculated activation energy fall more than 1 kcal/mol from the experimental value. In all other cases, our model does surprisingly well in predicting the activation energies of these reactions.

Activation energies are calculated as follows: the ground-state energy, E_{gs}, as calculated using the Imam–Allinger radical force field,[11] is subtracted from the transition-state energy. This provides a large negative number, due to the larger, negative torsional parameters used in our force field. To this is added a constant, in this case 51.7 kcal/mol, which places the activation energy for the chair-exo cyclization of **1a** at the experimental value of 6.8 kcal/mol. All other activation energies are calculated with this constant.

Predictions. The results presented here indicate that our model can be used to predict the regiochemical and stereochemical outcomes of cyclizations in many types of systems. The model is most accurate when applied to reactions of molecules summarized in structure **33**. We



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have explored cases where X = C or O and A–D are alkyl groups or heteroatoms N or O, where parameters are available. The formation of five to eight-membered rings have been studied successfully. The only cases which give problems are those in which the radical carbon is part of a ring. We also expect to have problems when substituents B–D have large electronic effects and consequently alter the position of the transition state. Obviously, the model

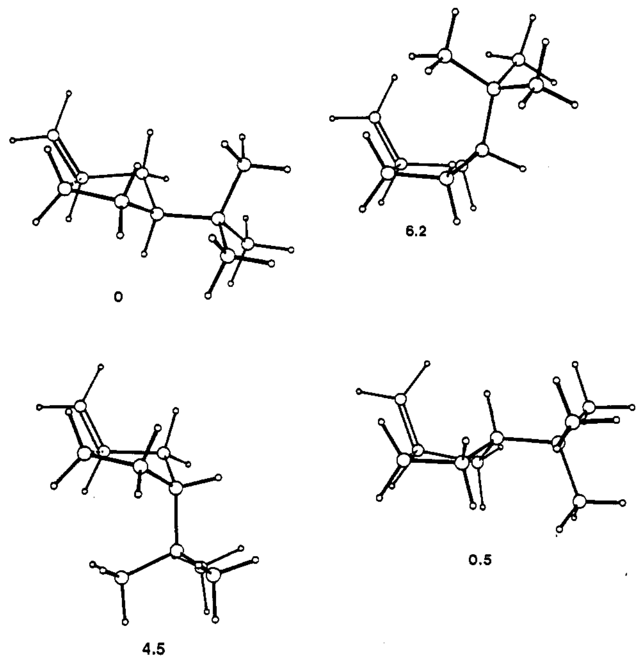


Figure 17. Transition structures of 3-*tert*-butyl-5-hexenyl radical cyclization.

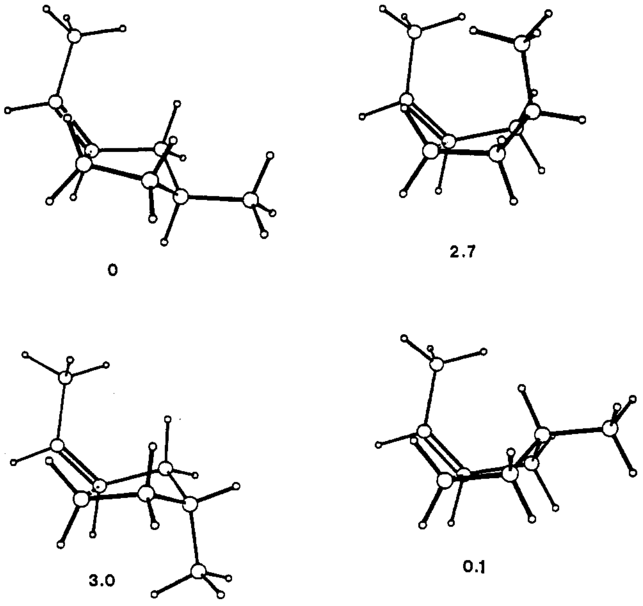


Figure 18. Transition structures of (*Z*)-3-methyl-5-heptenyl radical cyclization.

cannot be applied to systems for which MM2 parameters do not exist.

Predictions can be made with our model if we stay within the "high-confidence" realm described above. As yet, there has been no evidence to support our hypothesis that the major product arises from a chair-like transition state while the minor product arises from the boat. Calculations suggest that a 3-*tert*-butyl-substituted 5-hexenyl radical would give 100% cis product if only the chair transition state is considered. As shown in Figure 17, it is clear that an axial *tert*-butyl is very unfavorable. However, including the boat transition states leads to a prediction of a 68:32 mixture of cis and trans products. This is about the same as that of a 3-methyl substituent.

Similarly, our calculations predict that the (*Z*)-3-methyl-5-heptenyl radical will cyclize with little selectivity, a 54:46 cis/trans ratio. If only the chair transition states were included in the calculations, a very high cis selectivity is expected (Figure 18). The (*E*)-3-methyl-5-heptenyl radical, however, would give about the same cis/trans ratio (64:36) as that of the 3-methyl-5-hexenyl radical (see Figure 19).

An interesting consequence of placing a methyl group at C_5 is that the boat-like exo transition state is lower in energy than the chair exo transition state. Utilizing this feature, we predict that the 3-methyl-5-ethyl-5-hexenyl radical (**34**) will undergo cyclization to form 1-ethyl-1,3-dimethylcyclopentane (**35**), in which the methyl groups are anti rather than syn in a 71:39 ratio. This product is of the opposite stereochemistry than the 3-methyl-5-hexenyl,

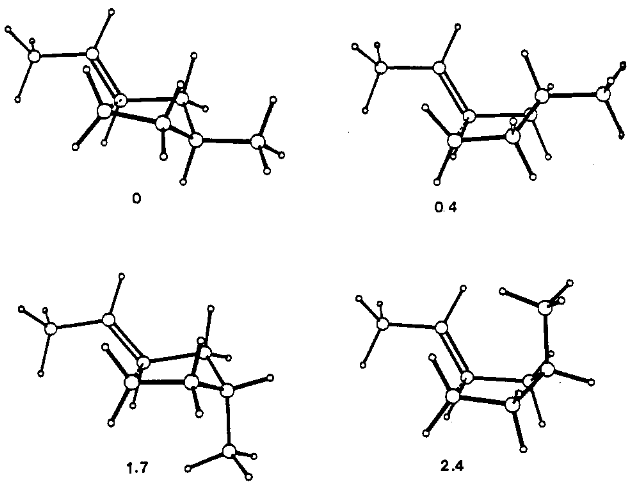


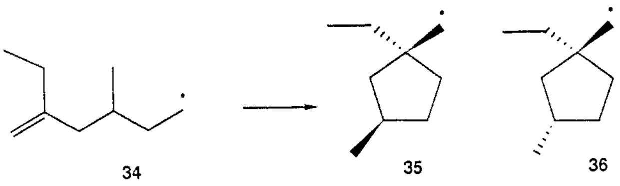
Figure 19. Transition structures of (*E*)-3-methyl-5-heptenyl radical cyclization.

Table XII. Parameter List for Radical Addition Reactions[a]

14	02	0	17			
29	28	2	1	0.0	−25.0	0.0
29	28	2	5	0.0	−25.0	0.0
5	2	28	5	0.0	0.0	0.25
5	2	28	1	0.0	0.2	0.2
1	2	28	5	0.0	0.0	0.34
1	2	28	1	0.4	0.03	0.5
5	29	28	5	0.0	0.0	0.0267
1	29	28	5	0.0	0.0	0.0273
5	29	28	2	0.0	0.0	0.0405
5	29	28	1	0.0	0.0	0.0646
1	29	28	2	−0.241	0.241	0.399
1	29	28	1	1.364	−1.103	0.339
5	1	2	28	0.0	0.0	−0.24
1	1	2	28	−0.44	0.24	0.06
29	28		4.0	2.27		
28	2		4.4	1.375		
5	29	5		0.32	116.6	
5	29	28		0.36	100.5	
29	28	5		0.36	90.3	
29	28	2		0.60	107.0	
5	28	2		0.36	120.3	
5	28	5		0.32	115.8	
28	2	5		0.36	121.4	
5	2	5		0.32	117.0	
1	29	5		0.36	116.6	
1	29	1		0.45	116.6	
1	29	28		0.45	100.5	
29	28	1		0.45	90.3	
1	28	2		0.45	120.3	
1	28	5		0.36	115.8	
1	28	1		0.45	115.8	
28	2	1		0.45	121.4	
5	2	1		0.36	117.0	

[a] Spellmeyer and Houk, 1986. Atom types are as follows: type 29 is the radical center; type 28 is the atom being attacked. All remaining parameters are defined from the internal MM2 parameter list just as if atom types 28 and 29 are equivalent to atom type 1. For instance, the bond length parameters for a 28-1 bond are identical with a type 1-1 bond.

in which the methyl groups are syn. It should be noted that the endo product will also be formed in about 24% yield.



calc 39 71

Conclusions. The model described here is an accurate predictor of regioselectivity and stereoselectivity of alkyl radical cyclization reactions. There are some limitations, as described here. Nevertheless, this model can be used to aid in design of syntheses involving intramolecular radical cyclizations, and the force-field should be extendable to related systems following the techniques described here.

Acknowledgment. We are grateful to the National Science Foundation and the National Institutes of Health for financial support of this research, the Andrew Mellon Foundation for a Fellowship to D.C.S., Professor Dennis P. Curran for encouragement and helpful comments, and Dr. John Yates and Dr. K. K. Sunil for the Harris versions of the GAUSSIAN 80 and 82 series of programs. We would also like to thank the Harris Corporation for grants of Harris H800 computers at Pittsburgh and UCLA and the National Science Foundation for equipment grants and for supercomputer time used in this research.

Appendix

New MM2 Parameters. Our model can be reproduced with the parameters described here. The incoming radical center is defined as MM2 type 29, while the alkene atom being attacked is type 28. The remaining carbon of the double bond remains type 2. The van der Waals parameters for all carbons are identical with those for any other carbon in MM2 as are stretch-bend an out-of-plane bending of the terminal carbon of the olefin. Our version of MM2 has an atom type equivalence property which allows a user to equivalence two atom types. This enables one to redefine one or two parameters of an atom type without having to duplicate numerous definition cards. For example, to redefine just one C–C bond length in propane, one carbon is defined as type 30, equivalenced to type 1, and then only *one* redefinition card is read in. Otherwise, the parameter list to be read in would be several cards long. The equivalence mechanism, therefore, provides all of these extra definitions internal to the program. The radical center, type 29, is equivalenced to type 1 as is the atom being attacked, type 28. The parameter list, remarkably small, is then as follows:

Torsional Definitions. Fourteen torsional definition cards are read into the program. The first two, types 29-28-2-1 and 29-28-2-5 have $V_1 = V_3 = 0$ and $V_2 = -25.0$. Definitions for rotations about the double bond are as follows (V_1, V_2, and V_3): 5-2-28-5, 0, 0, 0.25; 5-2-28-1, 0, 0.2, 0.2; 1-2-28-5, 0, 0, 0.34; 1-2-28-1, 0.4, 0.03, 0.5. Rotations about the forming bond are as follows: 5-29-28-5, 0, 0, 0.0267; 1-29-28-5, 0, 0, 0.0273; 5-29-28-2, 0, 0, 0.041; 5-29-28-1, 0, 0, 0.065; 1-29-28-2, –0.241, 0.241, 0.399; 1-29-28-1, 1.364, –1.103, 0.339. The remaining parameters are as follows: 5-1-2-28, 0, 0, –0.24; 1-1-2-28, –0.44, 0.24, 0.06.

Bond Stretching and Compression Parameters. The stretching parameters for this model define the forming bond length and the double bond length. Type 29-28 has $l_0 = 2.27$ and $K_s = 4.0$, while 28-2 has $l_0 = 1.375$ and $K_s = 4.4$.

Angle-Bending Parameters. Seventeen bending parameters are used in our model. The K_B and θ_0 parameters for the radical are as follows: 5-29-5, 0.32, 116.6; 5-29-28, 0.36, 100.5; 5-29-1, 0.36, 116.6; 1-29-1, 0.45, 116.6; 1-29-28, 0.45, 100.5. Bending parameters for angles about the central carbon are as follows: 29-28-5, 0.36, 90.3; 29-28-2, 0.60, 107.0; 5-28-2, 0.36, 120.3; 5-28-5, 0.32, 115.8; 1-28-1, 0.45, 115.8; 29-28-1, 0.45, 90.3; 1-28-2, 0.45, 120.3; 1-28-5, 0.36, 115.8. Finally, angle definitions about the terminal carbon of the double bond are as follows: 28-2-5, 0.36, 121.4; 5-2-5, 0.32, 117.0; 28-2-1, 0.45, 121.4; 5-2-1, 0.36, 117.0. Note: if two double bonds are present in the molecule, care *must* be taken to redefine these last parameters for *only* the double bond involved in the transition state. A complete list is given in Table XII as it appears in an MM2 input.

On the Regio- and Stereoselectivity of $Bu_4N[Fe(CO)_3NO]$-Catalyzed Allylic Alkylation

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$Bu_4N[Fe(CO)_3NO]$ has been found to catalyze the alkylation of allylic carbonate with malonate anion. The reaction proceeds with good regioselectivity, the nucleophile attacking predominantly at the carbon where the leaving group was attached. Retention of configuration of the double bond during the course of reaction was observed. Alkylation of methyl (*Z*)-5-carbomethoxy-1-cyclohexen-3-yl carbonate with sodium salt of dimethyl malonate yielded dimethyl ((*Z*)-5-carbomethoxy-1-cyclohexen-3-yl)malonate in a highly stereoselective fashion, and a net retention of configuration at the center undergoing substitution is thus established. On the basis of regio- and stereochemical results, a reaction pathway involving an σ-allyliron complex has been suggested.

Nucleophilic substitution reactions of carbon nucleophiles on allylic esters represents one of the most important carbon–carbon bond-forming reactions promoted or catalyzed by transition-metal complexes. Extensive studies

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